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REVIEW

Nutritional assessment in patients with liver cirrhosis

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Abstract

Malnutrition is a liver cirrhosis complication affecting more than 20%-50% of patients. Although the term can refer to either nutrient deficiency or excess, it usually relates to undernutrition in cirrhosis settings. Frailty is defined as limited physical function due to muscle weakness, whereas sarcopenia is defined as muscle mass loss and an advanced malnutrition stage. The pathogenesis of malnutrition in liver cirrhosis is multifactorial, including decreased oral intake, maldigestion/malabsorption, physical inactivity, hyperammonemia, hypermetabolism, altered macronutrient metabolism and gut microbiome dysbiosis. Patients with chronic liver disease with a Body Mass Index of < 18.5 kg/m^2 and/or decompensated cirrhosis or Child-Pugh class C are at the highest risk of malnutrition. For patients at risk of malnutrition, a detailed nutritional assessment is required, typically including a history and physical examination, laboratory testing, global assessment tools and body composition testing. The latter can be done using anthropometry, cross-sectional imaging including computed tomography or magnetic resonance, bioelectrical impedance analysis and dual-energy X-ray absorptiometry. A multidisciplinary team should screen for and treat malnutrition in patients with cirrhosis. Malnutrition and sarcopenia are associated with an increased risk of complications and a poor prognosis in patients with liver cirrhosis; thus, it is critical to diagnose these conditions early and initiate the appropriate nutritional therapy. In this review, we describe the prevalence and pathogenesis of malnutrition in liver cirrhosis patients and discuss the best diagnostic approach to nutritional assessment for them.

Key Words: Malnutrition; Cirrhosis; Nutritional assessment; Sarcopenia; Nutrition; Frailty

Core Tip: Malnutrition is a common complication of liver cirrhosis that is not often addressed by physicians. Due to its association with poor outcomes, it is important to identify patients at risk of malnutrition in order to treat them early. We herein describe the mechanism of malnutrition in cirrhosis and discuss the best diagnostic approach.

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INTRODUCTION

Malnutrition is defined as nutrient imbalance (deficiency or excess) with adverse effects on the body's form, function or outcome. According to the European Association for the Study of Liver Disease (EASL), the term "malnutrition" refers to "undernutrition"[1]. Frailty is defined as limited physical function due to muscle weakness and diminished muscle contractility, while sarcopenia is defined as the generalized loss of muscle mass. Malnutrition is a common complication of liver cirrhosis, with a prevalence rate of 5-92%[2]. The prevalence of malnutrition increases with worsening liver disease[3]. It has been reported that one-fifth of patients with compensated cirrhosis and more than half the patients with decompensated cirrhosis have malnutrition[4]. Additionally, even patients with chronic liver disease who are not cirrhotic can have malnutrition. In this group of patients, malnutrition may be masked by obesity[5]. Due to the increasing prevalence of non-alcoholic fatty liver disease, overweight and obesity are becoming more common in cirrhotic patients. In this review, we describe the pathophysiology of malnutrition in liver cirrhosis and discuss the best diagnostic approach to assess the nutritional status of patients in clinical practice.

METHODS

A PubMed web-based search was conducted to review the literature published from its inception until January 1, 2022, using the keywords 'malnutrition', 'nutritional assessment,' 'liver cirrhosis,' and 'sarcopenia.' All relevant articles published in the English language were reviewed, and data on epidemiology, pathogenesis, diagnosis and prognosis were extracted.

PATHOGENESIS

There are multiple factors that contribute to the development of malnutrition and sarcopenia in liver cirrhosis (Figure 1). First, the principal cause of malnutrition is reduced oral intake, and this can be due to anorexia, early satiety, nausea and cognitive impairment in the setting of hepatic encephalopathy. Patients with liver cirrhosis often have altered taste and smell, which can cause anorexia due to changes in the oral flora, use of antibiotics, dry mouth, zinc or magnesium deficiency[6]. Additionally, imbalances between orexigenic and anorexigenic hormones and chronic elevations in cytokines like tumor necrosis factor (TNF)-α can also trigger anorexia[7,8]. Early satiety can be explained by abdominal distension secondary to ascites or altered intestinal motility, which is common in cirrhosis[9]. Furthermore, unpalatable low-salt diets followed by the patients with ascites, alcohol abuse, and frequent tests requiring fasting for hours can all contribute to decreased oral intake[8]. Second, nutrient maldigestion and malabsorption can occur due to reduced bile production, altered intestinal motility with subsequent small bowel bacterial overgrowth, portal hypertensive gastropathy/ enteropathy and long-term lactulose use[8]. Furthermore, pancreatic insufficiency frequently coexists with alcoholic liver cirrhosis, contributing to decreased nutrient uptake. Third, alteration in macronutrient metabolism is an important factor affecting nutritional status in cirrhosis. Carbohydrate metabolism is characterized by increased gluconeogenesis, elevated fasting serum insulin levels, insulin resistance, decreased glycogen synthesis and storage and the early use of lipids and proteins as substrates for energy production and gluconeogenesis[7]. It has been observed that the rate of fat and protein catabolism after a short overnight fast in patients with liver cirrhosis is similar to that of healthy individuals who underwent 2-3 d of starvation[10]. Abnormal protein metabolism manifests itself as more protein catabolism and less synthesis, low levels of branched-chain amino acids (BCAA), and higher levels of aromatic amino acids (AAA), resulting in a lower Fischer's ratio (BCAA/AAA ratio) which has been associated with complications such as hepatic encephalopathy[11]. Hyperammonemia promotes muscle breakdown and

Figure 1 Factors contributing to malnutrition and sarcopenia in liver cirrhosis.

sarcopenia by upregulating myostatin which inhibits protein synthesis[12]. Testosterone levels are decreased in cirrhotic males and this further contributes to decreased protein synthesis and loss of muscle mass[13].

Lipid metabolism exhibits increased lipolysis, lipid oxidation and ketogenesis[14]. Fourth, hypermetabolism affecting one-third of cirrhotic patients, contributes to malnutrition. It is defined as having a resting energy expenditure > 120% of the predictive value, and it can be caused by infections or chronic inflammation and is not associated with sex, underlying cause or severity of liver disease [15]. Fifth, an imbalance of gut microbiota (dysbiosis) in liver cirrhosis has been suggested as a contributing factor in malnutrition. Short-chain fatty acid-producing bacteria such as Bacteroides are reduced in patients with cirrhosis, and there is a higher abundance of Campylobacterales in moderately malnourished cirrhotics; findings have been associated with malnutrition in children[16-19]. The alteration in gut microbiome composition leads to increased intestinal permeability, bacterial translocation and infectious complications like spontaneous bacterial peritonitis[20]. This results in increased protein catabolism and muscle mass loss mediated by inflammation. Finally, physical inactivity, which is common in patients with significant ascites or hepatic encephalopathy may contribute to reduced muscle mass[21].

Beta blockers have been suggested as a possible external factor contributing to malnutrition in cirrhosis. However, a recent study found that patients who received non-selective beta blockers had actually better skeletal muscle index and improvement in sarcopenia[22].

The role of portal hypertension in malnutrition and sarcopenia is not clear. There is very limited literature about the prevalence of malnutrition and sarcopenia in non-cirrhotic portal hypertension. A study by Lattanzi *et al*[23] found that the prevalence of sarcopenia in non-cirrhotic portal hypertension was similar to that in patients with compensated cirrhosis. This could suggest that portal hypertension per se may play a role in the development of malnutrition and sarcopenia given the fact that those patients have less liver damage compared to cirrhotic patients. This theory could be supported by the fact that nutritional status improves after transjugular intrahepatic portosystemic shunt (TIPS) and resolution of portal hypertension[24,25].

DIAGNOSIS

Malnutrition screening tools

The EASL released clinical practice guidelines in 2019 on nutritional assessment and management in chronic liver disease patients[1]. They recommended the screening of all patients with chronic liver disease for the risk of malnutrition using two tests: The body mass index (BMI) and Child-Pugh classification. Patients with a BMI < 18.5 kg/m^2 and/or those with Child-Pugh class C or decompensated cirrhosis are considered at higher risk for malnutrition. On the other hand, patients with BMI 18.5-29.9 kg/m^2 and are Child-Pugh class A or B should undergo nutritional screening using one of the following liver disease-specific malnutrition screening tools: The Royal Free Hospital-nutritional prioritizing tool (RFH-NPT) or the liver disease undernutrition screening tool. Those who are at low risk for malnutrition need follow-up and re-assessment every year, while patients with moderate or high risk for malnutrition should have a detailed nutritional assessment. In addition, patients with a high risk for malnutrition need to be assessed for sarcopenia as well (Figure 2).

RFH-NPT uses simple clinical questions that take less than 3 minutes to complete and can be used by non-specialist staff. It classifies patients into low (0 points), medium (1 point), or high risk (2-7 points) for malnutrition. It considers the patient's nutritional history (unplanned weight loss, dietary intake, BMI) and the presence or absence of fluid overload (ascites and/or peripheral edema). Although it has been validated in a multicenter trial in the United Kingdom, it requires further testing[26]. RFH-NPT was reported to correlate with clinical deterioration, the severity of liver disease, and complications of liver cirrhosis and was found to be an independent predictor of clinical deterioration and transplant-free survival. Furthermore, improvement in RFH-NPT score was associated with improved survival[27]. RFH-NPT is recommended by the European Society of Parenteral Enteral Nutrition guidelines as the best available tool for malnutrition screening in liver disease[28].

The liver disease undernutrition screening tool uses six patient-directed questions about nutritional intake, weight loss, subcutaneous fat loss, muscle mass loss, fluid accumulation and decline in functional status. Its limitation is that it is entirely dependent on the patient's subjective judgment and has a low negative predictive value[29]. As with RFH-NPT, it needs further validation.

Detailed nutritional assessment

Patients who are at risk of malnutrition during screening should undergo comprehensive nutritional evaluation for confirmation of malnutrition and characterization of their nutritional status. This should ideally be done by a registered dietician or nutritionist. The evaluation process includes history taking, physical examination, laboratory tests, subjective global assessment and specialized methods for body composition assessment.

HISTORY

Patients should be asked about their dietary intake; recent weight loss; use of supplements; alcohol consumption; any eating barriers such as anorexia, nausea, altered taste or smell, abdominal distension or pain, or any socioeconomic barrier; and symptoms of nutritional deficiency such as dermatitis (zinc, niacin, vitamin A), sore tongue (folate, vitamin B12), or paresthesia (thiamine, pyridoxine, vitamin B12). Dietary intake can be assessed using 24-h dietary recall, which is simple to use and does not require a high level of literacy. However, one significant disadvantage is that it is dependent on the patient's recall skills and may not be representative of daily meal selection or eating behavior[30]. Another option is a 3-d food diary, which requires patients to cooperate and follow standardized instructions; however, it may be burdensome for patients and difficult to implement in those with advanced disease. It is the preferred method because it relies the least on patient recall[31]. Repeated 24-h dietary recalls are another option[32]. At a minimum, the patients should be asked if their relative food intake has changed over time and, if so, how much.

PHYSICAL EXAMINATION

It should include measuring the BMI; examination for ascites and edema; muscle wasting, which is usually done by assessing the temporalis muscle, quadriceps and deltoids; and loss of subcutaneous fat which can be assessed in the chest, eye sockets and triceps areas. The BMI divides patients into four categories: Underweight, normal weight, overweight, and obese. In cirrhotic patients, it can be used to diagnose obesity in the absence of fluid retention. In the case of fluid retention, the patient's dry weight should be used, which can be estimated using the documented patient's weight prior to the development of fluid retention if available, the patient's weight post paracentesis, or by subtracting a percentage of weight based on the severity of ascites (5% for mild, 10% for moderate and 15% for severe) with an additional 5% subtracted if bilateral lower limb edema is present[33,34]. This has not

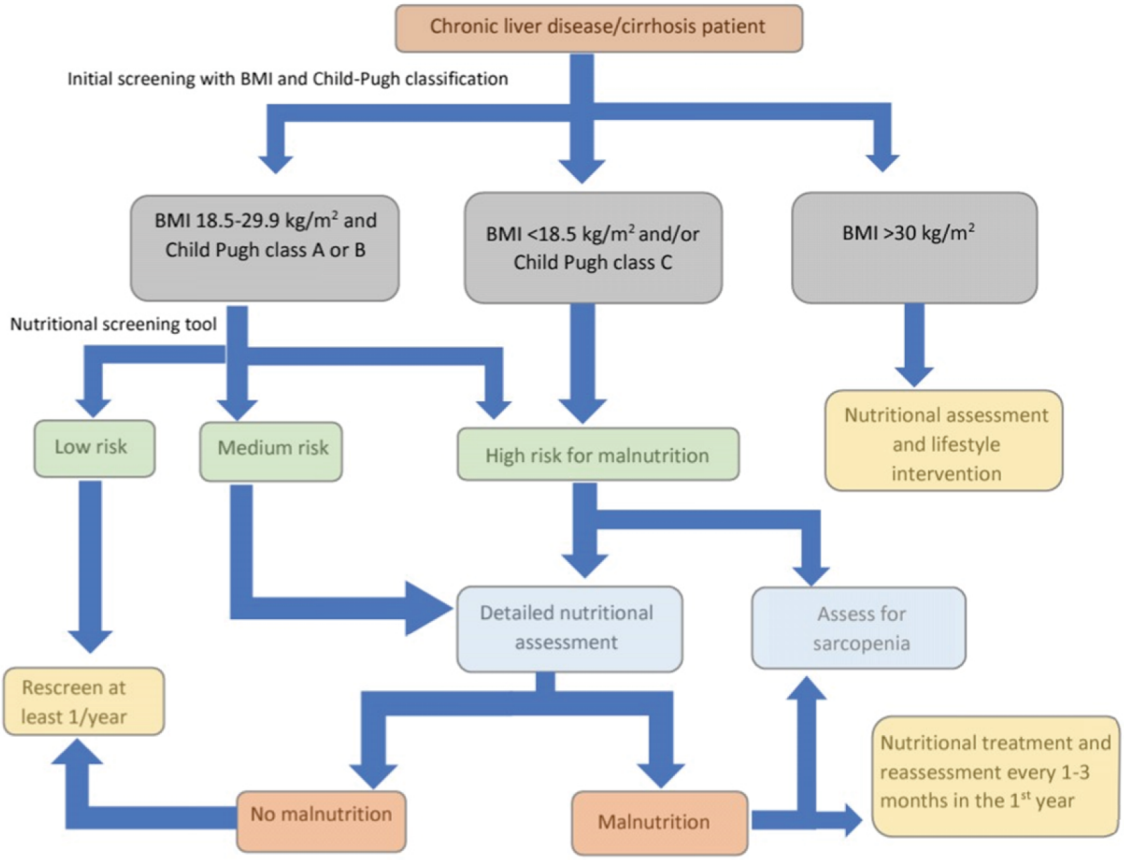

Figure 2 Algorithm for nutritional screening and assessment in liver cirrhosis. Adapted from the European Association for the Study of the Liver (EASL) clinical practice guidelines (with permission from Elsevier). Citation: European Association for the Study of the Liver. EASL Clinical Practice Guidelines on nutrition in chronic liver disease. *J. Hepatol*. 2019, 70, 172-193. Copyright© 2018 European Association for the Study of the Liver. Published by Elsevier. BMI: Body mass index (Supplementary material).

been validated yet but has demonstrated excellent inter-observer agreement.

LABORATORY TESTS

The use of serum biomarkers for the diagnosis of malnutrition is controversial and currently they only complement the nutritional assessment[35]. Complete blood count; serum creatinine; serum albumin, C-reactive protein (CRP); levels of vitamins and minerals like zinc, phosphorus, magnesium and iron are included in laboratory tests. Serum protein measurements may be limited in patients with advanced liver cirrhosis and synthetic dysfunction because they do not always reflect nutritional status. CRP may be useful in assessing catabolism and interpreting the results of nutrient levels. It is important to tailor testing according to the patient's underlying liver disease and comorbidities.

GLOBAL ASSESSMENT TOOLS

Subjective global assessment

It consists of five historical parameters (weight loss, dietary changes, gastrointestinal symptoms, functional capacity and metabolic demand associated with the underlying disease) and three physical examination parameters (loss of subcutaneous fat, muscle wasting and edema/ascites)[36]. Based on the results of these parameters, the patient gets a rating of A (well-nourished), B (moderately malnourished) or C (severely malnourished). Although subjective global assessment (SGA) is simple to administer, has fair to good interobserver reproducibility[37] and correlates with post-operative outcomes in patients without liver cirrhosis, it underestimates the prevalence of sarcopenia and has a low agreement with other methods of nutritional assessment[34,38].

Royal free hospital-SGA

Due to the limitations of the SGA, the royal free hospital-SGA (RFH-SGA) was developed[39]. It consists of dietary intake, BMI based on dry weight and mid-arm muscle circumference. Patients are stratified into three groups: adequately nourished, moderately malnourished and severely malnourished. The RFH-SGA is reproducible, correlates with other measurements of body composition and has shown promise in predicting survival and post-transplant outcomes[40,41]. However, it takes a longer time than SGA and requires additional validation.

Assess for frailty

There are currently no standardized criteria for diagnosing frailty in cirrhosis. There are several geriatric measures that have been used to assess frailty in cirrhotic patients. The Liver Frailty Index measures hand grip strength, balance, and timed chair stands and has been found to be correlated with mortality [42]. The Fried frailty criteria include unintentional weight loss, self-reported exhaustion, grip strength, slow walking speed and low physical activity. An increase in the Fried frailty score was found to be associated with an increased risk of waiting list mortality[43]. The short physical performance battery measures repeated chair stands, balance, and timed 13-foot walk and has been shown to predict transplant waiting list mortality[43].

BODY COMPOSITION TESTING

Body composition testing is summarized in Table 1.

Anthropometry

These are simple and quick bedside methods for determining body fat and muscle mass that are unaffected by fluid retention. Triceps skin fold (TSF) and mid-arm muscle circumference (MAMC) are the most commonly used measurements [MAMC = mid-arm circumference - (TSF × 0.314)]. Both MAMC and TSF have been found to correlate with survival in cirrhotic patients, with MAMC having higher prognostic power than TSF[44]. These tests have interobserver variability and low accuracy.

Bioelectrical impedance analysis

It determines the water content of the body by measuring the resistance to electrical current flow within the body which is then used to estimate muscle mass. Bioelectrical impedance analysis (BIA) is measured with a special scale or by attaching electrodes to an arm and a leg. It is inexpensive, portable and simple to use; however, the results are influenced by the patient's volume status which can change in cirrhosis[45].

Computed tomography

The gold standard for sarcopenia assessment is the quantification of muscle mass using cross-sectional imaging[46]. The skeletal muscle index (cm^2/m^2) is calculated by analyzing the abdominal skeletal muscles at the L3 vertebral level. Cut-off values based on an American study (50 cm^2/m^2 in males and 39 cm^2/m^2 in females) that correlated best with outcomes have been proposed, though ethnicity-specific criteria may be required given the fact that Asians have lower lean body mass compared to Western populations[47]. A meta-analysis of the impact of computed tomography (CT-assessed muscle mass on clinical outcomes in liver transplant patients showed an association between low muscle mass and mortality that was independent of the Model for End-Stage Liver Disease Score[48]. Obviously, the routine and multiple CT scans to diagnose sarcopenia are limited by the cost, availability, radiation and contrast exposures; however, since it is often used for other purposes in liver cirrhosis like evaluation of hepatocellular carcinoma and liver transplantation assessment, thus it can be used at least once for assessment of sarcopenia.

Magnetic resonance imaging

The use of magnetic resonance imaging for the assessment of sarcopenia has been suggested with the advantages of high accuracy and lack of ionizing radiation. It is only used for research purposes due to limitations of high cost and lack of cut-off values.

Ultrasonography

It has been more than two decades that the use of ultrasound for skeletal muscle mass estimation in the context of fluid retention has been proposed[49]. The biceps, anterior forearm flexors and quadriceps muscles correlated best with lean body mass. The test is radiation-free and allows bedside assessment at a low cost. A previous study showed that combining BMI with thigh muscle thickness measured by ultrasound is significantly correlated with sarcopenia diagnosed *via* cross-sectional imaging[34]. However, a more recent study found that ultrasound muscle thickness had no advantage over other bedside techniques (namely MAMC and BIA)[50].

Table 1 Comparison between body composition testing modalities

Modality	Accuracy	Advantage	Disadvantage
Anthropometry	Low	Simple, rapid, not affected by fluid retention	Interobserver variability
BIA	Moderate	Easy, portable, relatively inexpensive	Influenced by volume status, requires special equipment
Ultrasound	Moderate to high	Inexpensive, radiation-free, bedside	Interobserver variability
DEXA scan	High	Suitable for repeat testing	Radiation exposure & high cost (but less than CT scan)
CT scan	High	Allows direct assessment of muscle mass	Radiation and contrast exposure, high cost
MRI	High	No radiation exposure, allows direct assessment of muscle mass	Expensive, lacks cut-off values

BIA: Bioelectrical impedance analysis; DEXA: Dual energy X-ray absorptiometry; CT: Computed tomography; MRI: Magnetic resonance imaging.

Dual-energy X-ray absorptiometry

It allows regional and whole-body assessment of bone mineral density, fat mass and lean mass. Even though it is less precise compared to a CT scan, it has a lower cost and radiation exposure which makes it more suitable for repeat testing during follow-up[51]. The major limitation is its validity in the case of fluid retention which can lead to the underestimation of sarcopenia. To overcome the confounding effect of ascites, use of appendicular lean mass that excludes the abdominal compartment has been proposed [52]. Other studies proposed the use of arm lean mass to further reduce the effect of lower limb edema and it was found to be superior to appendicular lean mass in terms of mortality[53,54].

IMPACT OF MALNUTRITION, SARCOPENIA AND FRAILTY ON LIVER CIRRHOSIS

Malnutrition has a negative impact on cirrhosis progression and outcome[55]. For example, patients with cirrhosis who are malnourished were found to have twice the rates of hospitalizations and mortality as compared to well-nourished patients[56]. It has also been shown that malnutrition is a predictor of other complications of cirrhosis, such as infections, hepatic encephalopathy and ascites[57-59]. Malnutrition and sarcopenia are independent predictors of poor outcomes in patients with liver cirrhosis and in those undergoing liver transplantation[60-62]. In addition, sarcopenic obesity and myosteatosis are independently associated with long-term mortality in liver cirrhosis[63]. Furthermore, it has been demonstrated that the diagnosis of frailty in cirrhosis is associated with an increase in mortality[64]. Given the significant impact on morbidity and mortality, it is critical to screen all patients with liver cirrhosis for malnutrition and provide nutritional therapy to those who require it in order to improve their quality of life and survival. A multidisciplinary approach is the best way to accomplish this.

CONCLUSION

Malnutrition is a common complication of liver cirrhosis with complex pathophysiology that adversely affects the clinical outcome. A stepwise diagnostic approach should be followed for early recognition and management.

FOOTNOTES

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MINIREVIEWS

Non-alcoholic fatty liver disease: Is surgery the best current option and can novel endoscopy play a role in the future?

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Abstract

Over the last decade, non-alcoholic fatty liver disease (NAFLD) has overtaken alcohol as the leading cause of cirrhosis in the Western world. There remains to be a licensed pharmacological treatment for NAFLD. Weight loss is advised for all patients with NAFLD. Many patients however, struggle to lose the recommended weight with lifestyle modification alone. Many drugs have either failed to show significant improvement of steatosis or are poorly tolerated. Bariatric surgery has been shown to reduce liver steatosis and regress liver fibrosis. The patho-physiology is not fully understood, however recent evidence has pointed towards changes in the gut microbiome following surgery. Novel endoscopic treatment options provide a minimally invasive alternative for weight loss. Randomised controlled trials are now required for further clarification.

Key Words: Obesity; Metabolic associated fatty liver disease; Non-alcoholic fatty liver disease; Non-alcoholic steatohepatitis; Bariatric endoscopy; Bariatric surgery

Core Tip: The overstitch endoscopic suturing system (Overstitch; Apollo Endosurgery, Austin, Tex) which was first reported in 2013, allows sleeve gastropexy to be performed by placing full-thickness sutures through the gastric wall from the pre-pyloric antrum to the gastro-oesophageal junction. Performed using flexible endoscopy, it has the advantage of being less invasive with no permanent visible scar and evidence suggestive of fewer complications compared to laparoscopic sleeve gastrectomy. There is now mounting evidence not only showing benefits in terms of weight loss but also improvements in other metabolic markers including Hemoglobin A1c, blood pressure and alanine aminotransferase, making endoscopic sleeve gastroplasty potentially a viable treatment option for non-alcoholic fatty liver disease in the future.

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INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is an umbrella term used to describe a range of conditions characterised by accumulation of fat in the liver[1]. NAFLD ranges from steatosis through non-alcoholic steatohepatitis (NASH), fibrosis, to cirrhosis and possible hepatocellular cancer (HCC)[1]. Fibrosis is sub-classified into F0-F4: (F0-F1) representing no or mild fibrosis respectively, (F2) – moderate fibrosis, F3 –severe fibrosis and F4 as cirrhosis[1]. Steatosis is defined by the presence of > 5% of hepatic fat hepatic steatosis (HS), whereas NASH is defined by the presence of > 5% of HS with hepatic inflammation and hepatocyte injury[2]. Patients with NASH have a significantly increased risk for disease progression to fibrosis and cirrhosis, which may ultimately lead to HCC.

There is an increasing evidence-base showing the parallel association between NAFLD and metabolic syndrome. Insulin resistance (IR), often defined as the failure of insulin to stimulate glucose transport into its target cells, is a key factor linking NAFLD and metabolic syndrome[3]. However, the exact pathophysiological factors connecting these conditions are unclear, which is a problem as they embody a growing healthcare problem[4]. Metabolic syndrome is often defined as a collection of metabolic risk factors including hypertriglyceridemia, impaired glucose tolerance, abdominal obesity, decreased high density lipoprotein cholesterol and hypertension. Each component of the metabolic syndrome has the potential to raise the severity of cardiovascular disease including microvascular and cardiac dysfunction, coronary atherosclerotic plaques, myocardial infarction, and heart failure[5].

In recent literature, a group of experts have questioned the acronym NAFLD and decided to integrate the current understanding of the condition to suggest a different term which they felt more accurately describes the underlying pathogenesis[6-10]. It has been investigated that NASH is closely associated with metabolic syndrome[6]. Due to lack of clarity of the association between NAFLD with metabolic syndrome, the acronym 'MAFLD' (metabolic associated fatty liver disease) was suggested as a more appropriate description[7]. MAFLD is a concept which proposes to be a more practical acronym for the identification of patients with hepatic steatosis with a high risk of disease progression[8]. This term however remains controversial and has not been universally adopted.

EPIDEMIOLOGY

The prevalence and overall global incidence of NAFLD is increasing exponentially and is now the leading cause of chronic liver disease in the West, as well as being more recognised in all parts of the world[11]. The global prevalence of NAFLD was estimated to be over 1 billion in 2013[11], about 25% of the global population. NAFLD is recognised in Western countries to be the most common liver disorder [1,12], affecting 17%-46% of adults. The differences in percentages include ethnicity, age and gender[1]. A recent study in 2020 has shown that the overall prevalence of NAFLD in Asia may have surpassed the Western populations, with an estimated prevalence to be 29.6%[13]. The prevalence of NAFLD in Middle Eastern and European populations range from 20% to 30%[14,15]. Studies conducted in the past decade have shown the prevalence of NAFLD in Asia, measured in countries such as Japan and China, are similar to countries in Europe (20%-30% in Japan and 15%-30% in China)[16,17]. NAFLD is associated with the similar spectrum of metabolic syndrome, which has the progressive tendency to increase the risk of more advanced disease, across the range of age groups from children to adults[1].

NAFLD AND OBESITY

Obesity is defined by the WHO as 'abnormal or excessive fat accumulation that may impair health'. The most commonly used index to measure weight is the body mass index (BMI) which is defined as the person's weight in kilograms divided by the square of their height in meters. A BMI ≥ 25 is considered as being overweight, and > 30 is defined as obese. BMI should not be used as an independent marker of obesity as a person's muscle mass can also affect the weight and may be ethnically affected. Waist circumference has been shown to be another reliable marker of obesity.

Estes *et al*[18] built a dynamic Markov model for eight countries, including China, France, Germany, Italy, Japan, Spain, UK and the US. The results of this study suggested that if obesity and diabetes continue to increase at the current rate, in parallel, both NAFLD and NASH prevalence are also expected to increase[18]. Conclusively, they have shown that efforts used to mitigate disease burden should be linked to strategies that slow the growth of the current obesity pandemic[18].

PATHOPHYSIOLOGY OF NAFLD

The pathophysiology of NAFLD has evolved over the last few years; however, it is still not clearly understood. Previously, the 'two-hit hypothesis' proposed that hepatic triacylglycerol accumulation sensitized the liver to secondary insults such as oxidative stress, which resulted in the development of NASH[19]. More recently our understanding has moved beyond this hypothesis, and we now know that the natural history of the disease is much more complex. NAFLD should be viewed as part of a metabolic disorder and management should take this into account.

One of the main events in the pathogenesis of NAFLD is a dysregulation between adipose tissue and hepatocytes[20]. Expansion of the adipose tissue results in reduced response to insulin which leads to increased lipolysis and free fatty acids production[21]. This increasing adiposity results in chronic low-grade systemic inflammation, and essence obesity may lead to the development of NASH[20].

The ''Western diet'' which consists of high calories including high fructose content is thought to have contributed significantly to the increasing prevalence of NAFLD. Previous studies in animal models looking at high fructose diets in animals were found to stimulate hepatic de novo lipogenesis and lead to hepatic steatosis[22]. It has now also become more apparent that genetic factors play a key role in the development of NAFLD. Liu *et al*[23] demonstrated that carriage of the TM6SF2 rs58542926 variant is strongly associated with the presence of NAFLD. Furthermore, carriage of this variant was associated with a significantly greater risk of developing advanced hepatic fibrosis/cirrhosis[23]. Moreover, carriage of the 1148M PNPLA3 variant has been found to be the major common genetic determinant of NAFLD.

The gut-liver axis has long been known to play a key role in the development of NASH. Intestinal derived products which can reach the liver are thought to lead to multiple effects on liver physiology [24]. The role of the gut microbiota in patients with NAFLD is still not clearly understood however many hypotheses have been postulated. Patients with NASH have been found to have increased levels of microbial products, ethanol and altered bile acid profiles[24].

HISTOPATHOLOGICAL FEATURES OF NAFLD

Liver biopsy is currently the only method to reliably grade NAFLD. It is also beneficial in excluding other causes for abnormal liver enzymes and liver disease.

Hepatic steatosis without inflammation often carries a benign course whereas NASH can progress to significant fibrosis and cirrhosis[12]. In most cases, hepatic steatosis is diagnosed on imaging such as ultrasound, computerised tomography (CT) or MRI. Magnetic resonance elastography (MRE) can detect hepatic fat fraction, however it cannot differentiate between steatosis and steatohepatitis[25].

A ''fatty liver'' is defined by > 5% macrovesicular steatosis[26]. However, NAFLD is defined as predominantly macrovesicular steatosis with the presence of visible steatosis in > 5% of hepatocytes [27]. For the diagnosis of NASH, there is a > 5% macrovesicular steatosis, inflammation and hepato-cellular ballooning which is predominantly centrilobular distributed seen on biopsy[25-29]. Patients found to have zone 3 accentuation of macrovesicular steatosis and the features of ballooning and lobular inflammation are defined as having definite steatohepatitis[26]. Apoptotic bodies may also be seen which may also be associated with Mallory-denk bodies[26].

Kleiner *et al*[27] devised the NAFLD activity score (NAS) which is a sensitive and reproducible scoring system for the histological diagnosis of steatohepatitis.

This scoring system comprises histologically of 4 main groups, each score as shown Steatosis (0-3), lobular inflammation (0-3), hepatocellular ballooning (0-2) and fibrosis (0-4) (26) (Table 1). A score greater than or equal to 5 is defined as correlating with a diagnosis of NASH[21,27].

Table 1 illustrates the non-alcoholic fatty liver disease activity scoring system

Group	Definition	Scoring
Steatosis	< 5%	0
	5%-33%	1
	> 33%-66%	2
	> 66%	3
Lobular inflammation	No foci	0
	< 2 foci per 200× field	1
	2-4 foci per 200× field	2
	> 4 foci per 200× field	3
Hepatocyte ballooning	None	0
	Few	1
	Many	2
Fibrosis	No fibrosis	0
	Zone 3 mild perisinusoidal fibrosis	1a
	Zone 3 moderate perisinusoidal fibrosis	1b
	Periportal/portal fibrosis only	1c
	Zone 3+ periportal/portal fibrosis	2
	Bridging fibrosis	3
	Cirrhosis	4

Overview of the components of the non-alcoholic fatty liver disease activity score scoring system.

DIAGNOSIS AND CURRENT GUIDELINES

Commonly, the diagnosis of NAFLD is usually suspected following the findings of abnormal liver function on routine laboratory tests or incidental findings on radiological imaging. Although imaging may be used to investigate NAFLD, the gold standard for diagnosis and assessment of NAFLD is a liver biopsy. However, the accuracy of the biopsy result is dependent on many factors including the size of the biopsy and remains observer dependent. Given that this is an invasive procedure with risks of complications, including bleeding, other modalities have been developed for the assessment of hepatic fibrosis.

Diagnostic tools using direct and indirect markers [Albumin, Bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), prothrombin time] such as fibrosis-4, ALT/AST ratio serum markers and the NAFLD fibrosis score have been developed and utilised to provide non-invasive markers of hepatic fibrosis. The NAFLD fibrosis score is a non-invasive scoring system that is calculated by the measurement of six variables; age, BMI, platelet count, blood glucose, albumin and AST:ALT ratio. Direct serum marker of liver fibrosis such as type IV collagen and glycoproteins such as hyaluronic acid, laminin, YKL-40 have been also shown to be useful non-invasive modalities for the assessment of hepatic fibrosis[30].

A previous study in 79 patients with histologically confirmed NAFLD, had serum hyaluronic acid measured at the same time of liver biopsy[31]. The positive and negative predictive values were found to be 51% and 96% respectively and concluded that measurement of serum hyaluronic acid was a useful serum marker to identify significant fibrosis in patients with NAFLD[31]. More recently there has been a development of transient elastography (Fibroscan®), which is used to assess liver fibrosis by measuring the liver stiffness using low frequency amplitudes.

The Fibroscan allows rapid assessment of liver fibrosis which can be made safely and accurately at the bedside. Unfortunately, as many patients with NAFLD are also obese, interpretation of transient elastography may not be a reliable tool for patients undergoing bariatric surgery. A study performed by Sandrin *et al*[32] concluded that in patients with obesity, measurements ''can be difficult or even impossible'' as there is attenuation of the ultrasound waves by the fatty tissue.

Ultrasonography has been shown to be a reliable and cost-effective form of imaging with a sensitivity and specificity of 84.8% and 93.6% respectively[33]. Given that it is a cheaper and an easily accessible diagnostic tool, ultrasonography is the preferred initial screening modality for most centres. However, a

limitation is that given it is user dependent, the findings may be subjective.

A previous study looking at radiologic evaluation of NAFLD concluded that CT has a poor sensitivity for detecting mild steatosis. However, it was found to be reasonably accurate in detecting moderate to severe hepatic steatosis[34]. Given that it is more expensive than ultrasonography, with the added concern of radiation, guidelines do not recommend the use of CT for screening or evaluation of hepatic steatosis. Lee *et al*[35] performed a prospective comparison of four imaging examinations: Ultrasonography, CT, dual gradient echo magnetic resonance imaging (DGE-MRI) and proton magnetic resonance spectroscopy (1H-MRS). They came to the conclusion that DGE-MRI was the most accurate form of imaging, with a sensitivity and specificity greater than 90%. To add to DGE-MRIs clinical superiority in this study, it was also found to have had 76.7% sensitivity and 87.1% specificity in detecting all degrees of hepatic steatosis[35].

The liver multiscan can be considered as an alternative option for patients who do not want or are unable to tolerate liver biopsy. Using patented technology, the liver multiscan is a software used to process MRI Liver data for quantitative characterisation of liver fibrosis and inflammation.

EASL (EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER) RECOMMENDATIONS AND CURRENT MANAGEMENT OF NAFLD

EASL currently recommends that the incidental finding of steatosis should ''prompt a full assessment and evaluation, including metabolic work-up''[1]. They also advise that the presence of obesity, type 2 diabetes (T2DM) or incidental abnormal liver function tests in patients with metabolic risk factors should undergo non-invasive screening to predict steatosis, NASH and fibrosis[1]. All patients found to have steatosis should undergo surrogate markers of fibrosis in order to exclude significant fibrosis which is defined as >F2[1]. Patients found to have significant fibrosis on non-invasive screening should be referred to a specialist clinic and have the diagnosis confirmed on liver biopsy[1]. In terms of obesity, the current recommendation is that these patients should be referred for a structured weight loss program or an obesity specialist[1].

Current treatment regimens recommended by EASL are limited. For patients without NASH or significant fibrosis, lifestyle modification is strongly recommended with a view to achieving a 7%-10% weight loss target. This target weight loss range has been proven to be associated with improvement of liver enzymes and histology[1]. This is supported with a study from Petersen *et al*[36] that showed moderate weight loss of 8 kg or 8% of body weight was associated with normalization of fasting plasma glucose concentration and a 10% decrease in plasma cholesterol. Petersen *et al*[36] also found a significant improvement in hepatic insulin sensitivity which was associated with an 80% reduction in hepatic triglyceride content.

Pharmacotherapy is currently only advised for patients with NASH or significant fibrosis (>F2)[1]. EASL does state however that patients without significant disease but are at high risk for disease progression, with other components of the metabolic syndrome or persistently elevated ALT ''could also be candidates to prevent disease progression''[1]. Currently only two drugs have been approved for the treatment of NASH by regulatory agencies and EASL do not recommend any specific drug for the treatment of NAFLD[1]. The use of all treatments discussed would be off-label and many of the previous medications trialed have been poorly tolerated. Insulin sensitizers such as metformin and Thiazolidinediones such as pioglitazone peroxisome proliferator-activated receptor agonists have been used. However, the effect of metformin was found to be weak and the side-effect profile of glitazones were of a particular concern.

Moreover, treatment with Vitamin E has been shown to induce show histological improvement in patients with NASH. However, these results were not reciprocated in the paediatric and adolescent population[37,38]. A further randomized controlled trial published in the NEJM in 2010 compared vitamin E, Pioglitazone or placebo for NASH[39]. The primary outcome was improvement in histological features of NASH. The study showed that Vitamin E was superior to a placebo for the treatment of NASH in patients without T2DM[39]. When comparing pioglitazone over placebo, no benefit was observed for the primary outcome. However, unfortunately the trial showed that pioglitazone use was associated with weight gain which continued throughout the trial.

EASL AND BARIATRIC SURGERY

Many studies have shown that weight reduction and improvement in metabolic risk factors lead to a marked improvement of hepatic steatosis. Consequently, EASL currently recommends that in patients who do not respond to lifestyle changes or pharmacotherapy, bariatric surgery can be considered. Therefore, it is imperative to outline the most efficacious lifestyle interventions and medical regimens to increase the chances of successful reduction in hepatic steatosis.

AASLD (AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES) DIAGNOSIS & MANAGEMENT

Similar to EASL, AASLD currently recommend that patients with hepatic steatosis detected on imaging should have a follow-up if they present with abnormal liver biochemistry or have metabolic risk factors [2]. AASLD also advocates for routine screening for patients in primary care who are deemed to be at high risk for NAFLD such as patients with T2DM or obese patients[2]. Although some studies have previously suggested ''familial clustering'' of NAFLD, AASLD do not currently recommend screening of family members for NAFLD[2].

All patients with suspected NAFLD should be screened for other causes of chronic liver disease, including genetic disease such as genetic haemochromatosis and autoimmune liver disease[2]. Parallel to previous studies with EASL, non-invasive markers of fibrosis such as diagnostic tools using serum markers and transient elastography (Fibroscan®) are advocated for identifying patients with significant fibrosis and cirrhosis[2]. Unlike EASL, AASLD also considers MRE to be a clinically useful tool for identifying advanced fibrosis in patients with NAFLD[2].

In terms of liver biopsy, current guidance is that this should be considered in patients with NAFLD who ''are at increased risk of having steatohepatitis and/or advanced fibrosis''[2]. AASLD also recommends liver biopsy for patients in whom other underlying aetiology contributing to hepatosteatosis cannot be excluded[2]. Similar to EASL, lifestyle modification including a hypocaloric diet and increased activity is recommended for patients with NAFLD[2]. Pharmacological treatment is currently only advised for patients with biopsy proven NASH and fibrosis[2]. Metformin is currently not recommended for treating NASH by AASLD[2]. With Pioglitazone, given that there is evidence that shows histological improvement in patients with or without T2DM with biopsy proven NASH, AASLD currently only advocate its use in patients with biopsy proven NASH[2]. However, given the complication risk of biopsy, both the risks and benefits should be taken into consideration and discussed with all patients so that they are able to make an informed decision[2].

Other pharmacotherapies include the glucagon-like peptide-1 agonist Liraglutide (GLP-1 agonist) which work by stimulating insulin secretion and inhibiting glucagon secretion from pancreatic islet cells. GLP-1 agonists are not currently recommended by AASLD for the treatment of patients with NAFLD or NASH[2]. In addition, vitamin E is also not currently recommended for the treatment of NASH in patients with T2DM, NASH or cryptogenic cirrhosis or without biopsy proven NASH[2].

AASLD AND BARIATRIC SURGERY

Given the strong evidence base showing improved liver histology in patients with NASH who underwent bariatric surgery, AASLD state that bariatric surgery can be considered in patients with obesity and NAFLD or NASH who are eligible for surgery[2]. There is currently no published literature on randomised controlled trials (RCT) of the effects of bariatric surgery on patients with NASH. Although bariatric surgery can be considered, AASLD do not recommend bariatric surgery as an established option to specifically treat NASH[2]. Interestingly, AASLD do not consider cirrhosis as an absolute contraindication for bariatric surgery and state in patients with compensated NASH or cryptogenic cirrhosis ''bariatric surgery may be considered on a case-by-case basis''[2].

BARIATRIC SURGERY AND NAFLD

In essence, bariatric surgery aims to achieve weight loss by one of three means. Either ''restrictive surgery'' such as a laparoscopic sleeve gastrectomy (LSG) which aims to reduce the amount the patient is able to eat by gastric volume reduction or ''malabsorptive surgery'' such as biliopancreatic diversion (BPD) which leads to weight loss by inducing malabsorption. However, this procedure is now less commonly performed due to the risk of significant nutritional deficiencies. Lastly, Roux-en-Y gastric bypass (RYGB) is a form of ''combined surgery'' which aims to achieve weight loss by both volume reduction and malabsorption.

IFSO (International federation for the surgery of obesity and metabolic disorders)

Position statement & recommendations: A position statement from IFSO in 2016 concluded that 'comprehensive, sustainable, and proactive strategy to deal with the challenges posed by the obesity epidemic is urgently needed'[40]. Weight loss induced by surgery has proven to be highly efficacious in treating obesity and its comorbidities[40]. With regards to NAFLD the consensus was that this may be improved after surgery for obesity[40]. Weight loss after surgery for obesity and weight-related diseases provide improvement or resolution of NAFLD and NASH[40].

Given the current lack of medical therapies available to manage NAFLD, bariatric surgery at present remains the only proven effective treatment. However, it is imperative for further studies, including RCTs, to assess the long-term benefit.

Systematic reviews and post-surgical improvements in NAFLD

Bariatric surgery has been shown to be associated with a significant improvement in both histological and biochemical markers of NAFLD[41]. There have been several previous systematic reviews which have studies the improvement of NAFLD with different types of bariatric surgery[41-44]. Lee *et al*[42] conducted a systematic review which has analysed data from 32 cohort studies comprising of 3093 biopsy specimens, observed a significant improvement in steatosis, inflammation, balloon degeneration and fibrosis in patients with NAFLD. Patients' mean NAFLD activity score was reduced significantly after bariatric surgery (mean difference, 2.39; 95%CI, 1.58-3.20; $P < 0.001$). However, 12% of patients (95%CI, 5%-20%) had worsening features of NAFLD, such as fibrosis. There are a variety of different types of bariatric surgery and Baldwin *et al*[43] conducted a systematic review and meta-analysis of RYGB compared with LSG for improving liver function in patients with NAFLD. They compared the efficacy of both surgical interventions using four criteria: Liver enzymes (AST and ALT), NAFLD fibrosis score, and NAS. Although, both RYGB and LSG significantly improved the 4 criteria, the comparisons of both surgical interventions proved equal efficacy.

Moreover, there have been several studies analysing the post-surgical improvements with other types of bariatric surgery such as gastric bypass, gastric banding, biliopancreatic diversion and jejunal bypass. Bariatric surgery has the potential to cause substantial and sustained weight loss and weight loss is the primary factor which initiates the treatment of NAFLD. One study reflected on the effect of gastric bypass and sleeve gastrectomy on liver function[45]. Liver enzymes, including ALT, AST, and ALP, were the main determinants of liver function. Patients which had undergone gastric bypass surgery had raised ALT at 6 mo and raised AST and ALP at 6 and 12 mo. Patients which had undergone LSG showed significantly lower ALT at 12 mo and AST and ALP levels at 6 and 12 mo. Although both cohorts were comparable 24 mo post-operatively, conclusively sleeve gastrectomy showed more favourable liver biochemistries within the first 12 mo post-surgery.

Keshishian *et al*[46] studied the effects of duodenal switch surgery on hepatic function and steatohepatitis 6 mo post-operatively. Although there was a worsening of the liver enzymes AST ($P < 0.02$) and ALT ($P < 0.0001$) levels found at 6 mo after the surgery, normal levels the enzymes were achieved after 12 mo. More promisingly, there was an improvement with the severity of NASH with up to three grades and a 60% improvement in hepatic steatosis was seen 3 years post-operatively.

Another form of bariatric surgery is adjustable gastric band, where an inflatable device is placed around the superior aspect of the stomach with the intendment to decrease food consumption and ultimately lead to sustained weight loss. Although there has been very limited literature found on the effects of gastric banding on NAFLD, weight loss is a significant factor which contributes to the reduction of hepatic steatosis. A systematic review has been conducted to demonstrate the amount of weight loss in cohorts of patients with gastric banding, gastric sleeve, and gastric bypass[47]. Extracted from 24 studies and a total of 29 surgical subgroup populations, all types of bariatric surgery have caused short term weight loss. The short-term weight loss, measured as mean absolute change in BMI (kg/m^2) at 6 mo, was –5.4 (-3.0, -7.8) after gastric band, -11.5 (-8.8, -14.2) after gastric sleeve, and -18.8 (-10.9, -26.6) after gastric bypass. Weight loss at 36 mo, also measured as mean absolute change in BMI (kg/m^2), was -10.3 (-7.0, -13.7) after gastric band, -13.0 (-11.0, -15.0) after gastric sleeve, and -15.0 (- 13.5 - 16.5) after gastric bypass. Bariatric surgery has shown to be efficacious in achieving short-term weight loss at 36 mo, although it is imperative for more research to be established on long-term weight loss to understand the long-term efficacy of bariatric surgery[47].

BPD and Jejunal bypass are both types of malabsorptive surgery. A recent study by Yu *et al*[48] demonstrated the effects of duodenal-jejunal bypass surgery on ameliorating NASH in diet-induced obese rats. It was found that duodenal-jejunal bypass improved NASH particularly by altering insulin sensitivity, inflammatory responses, HSC activity, and hepatocyte autophagy. Duodenal-jejunal bypass has shown to have a promising role of reducing NAFLD severity and preventing NASH progression. However, further trials on human subjects would be necessary to make more appropriate evidence-base conclusions.

Biliopancreatic diversion alters the normal mechanisms of digestion by making the stomach smaller and diverting the course of food to bypass part of the small intestine with the desired outcome of patients absorbing fewer calories to achieve sustained weight loss. Kral *et al*[49] studied liver biopsies on a cohort of 104 patients who have had a biliopancreatic diversion procedure to correct their metabolic syndrome. As expected with sustained weight loss, in this study steatosis grades decreased, although 40% of the patients had a post-operative increase in mild fibrosis, 27% had a decrease in severe fibrosis, and no change in the remaining 33%. Hence, although 27% patients had a decrease in liver fibrosis, the majority (40%) had an increase. Many factors affected fibrosis levels such as low serum albumin, low alcohol intake and menopausal status.

ENDOSCOPIC TREATMENTS OF NAFLD

For some patients, significant weight loss can be difficult to achieve or maintain through lifestyle measures alone. Invasive interventions, such as bariatric surgery, may be contraindicated due to anaesthetic and/or surgical risks or patients may not meet BMI criteria for bariatric surgery. There are limited effects of pharmacotherapy on weight loss and no drug currently universally approved for the treatment of NAFLD, hence for some patients, less invasive interventions such as endoscopic treatments may be an ideal option to achieve weight loss. Innovative endoscopic procedures can also be used as a bridge to surgery by bringing the BMI within the accepted threshold for anaesthetic and/or bariatric surgery or for patients emphatically who do not want bariatric surgery.

Intra-gastric balloon

In 2015, both Obera (manufactured by Apollo endosurgery) and the ReShape Integrated Dual Balloon System (manufactured by ReShape medical) were approved by the FDA for use in the United States. However, in April 2020, the FDA updated its recommendations following post-approval studies on these liquid filled intra-gastric balloons (IGB). Currently, the FDA recommends that all healthcare providers are aware of rare adverse effects such as acute pancreatitis secondary to hyperinflation and death. All patients should be made aware of these risks prior to undergoing IGB placement, so that they can make an informed decision.

A meta-analysis by Popov *et al*[50] studied the effect of IGBs on liver enzymes. 9 observational studies and one randomized trial were identified (n = 468) and showed overall improvement in liver function tests[50]. The duration of treatment with the IGB was 6 mo in all the studies. The ALT decreased by -10.02 U/L (95%CI, -13.2, -6.8) with the BMI decreasing by -4.98 kg/m^2 (95%CI -5.6, -4.4)[50]. This was associated with improvement of hepatic steatosis, which was assessed with both fat fraction on MRI and histological NAS which was found to be lower after 6 mo of IGB *vs* control with sham endoscopy and diet (2 ± 0.75 *vs* 4 ± 2.25, P = 0.03)[50]. Six of the studies reported adverse events, with vomiting being a feature in 6%-10% of patients and in some of the patients this led to removal of the balloon[50]. However, the studies in this meta-analysis have some limitations. Firstly, only one study was an RCT with diet/sham endoscopy being the control arm. Secondly, in all the studies, dietary recommendations were given to the participants, therefore it is difficult to ascertain how much of an effect lifestyle change contributed to the improvement in weight and liver enzymes.

A paper published in clinical Gastroenterology and Hepatology (2020) looked at 21 patients (BMI > 30) with early hepatic fibrosis, who underwent IGB placement[51]. This was an open-label prospective study and all patients underwent MRE and endoscopic ultrasound with core liver biopsy at the time of IGB placement. Follow up was after 6 mo with mean total body weight loss being 11.7% ± 7.7% with NAS improved in 90% of patients[51]. Fibrosis was found to have improved in 50% of the patients by 1.5 stages with 42% of patients being found to have had normal liver stiffness. Improvements were also seen in glycated haemoglobin (HbA1c) and waist circumference[51]. Interestingly, in this paper they applied the FDA criteria for NASH pharmacological endpoints at 6 mo and found that 50% of patients reached endpoints approved by the FDA. Furthermore, these findings surpass those found with pharmacotherapies including Liraglutide, Vitamin E, Pioglitazone and Obeticholic acid which reached NASH resolution and fibrosis improvement endpoint at 18 mo in 12% and 23% of patients[51,52]. In this study however, patients were prescribed a diet and exercise program over the 6 mo study period which again may act as a cofounder.

These studies do suggest that IGBs may have a role to play in the endoscopic management of NAFLD with short-term weight loss. However, with no clear long-term data available and evidence to suggest ''rebound'' weight gain after the removal of these balloons the evidence to support its use as a definitive treatment for NAFLD remains inadequate.

Endoscopic sleeve gastroplasty

The overstitch endoscopic suturing system (Overstitch; Apollo Endosurgery, Austin, TX, United States) which was first reported in 2013 allows sleeve gastroplasty to be performed by placing full-thickness sutures through the gastric wall from the pre-pyloric antrum to the gastro-oesophageal junction[53]. Performed using flexible endoscopy, it has the advantage of being less invasive with no permanent visible scar and evidence suggestive of fewer complications. It also has the added benefit of a shorter hospital stay with same day discharge possible when compared to LSG. As a novel procedure, further studies are still needed to ascertain benefit for NAFLD however there is now mounting evidence to support its use for obesity. Some studies have also shown improvement of HbA1c, reduction in blood pressure and improvement of gastroesophageal reflux disease (GERD) following endoscopic sleeve gastroplasty (ESG)[54].

With regards to hepatic steatosis, liver enzymes and ESG, there is limited literature. A study by Sharaiha *et al*[55] collected data from 91 patients who underwent ESG. All patients had a BMI > 30 and had failed non-invasive weight loss measures or had a BMI > 40 and were not considered candidates for surgery[55]. At 12 mo after ESG, patients were found to have statistically significant reductions in ALT (P < 0.001) and metabolic components including HbA1c (P = 0.01), systolic blood pressure (P = 0.02),

waist circumference ($P < 0.001$) and serum triglycerides ($P = 0.02$)[47]. No significant change was found in low density lipoprotein after *vs* before ESG ($P = 0.70$)[55].

Although there are no results from RCTs looking at ESG and hepatic steatosis or NASH are available, two RCTs (NASH-APOLLO and TESLA-NASH) started in 2018 and 2019 respectively. NASH-APOLLO involves two parallel arms, placebo (sham endoscopy + lifestyle modification) or ESG with OverStitch® system (Apollo Endosurgery, Austin, TX, United States) + lifestyle modifications in patients with biopsy proven [NCT03426111]. TESLA-NASH is looking at comparing the efficacy and safety of ESG *vs* LSG in subjects with obesity and NASH [NCT04060368].

COMPARISON BETWEEN BARIATRIC SURGERY AND BARIATRIC ENDOSCOPY

A case matched study comparing 54 ESG with 83 LSG patients showed that although at 30 d patients who underwent ESG achieved a greater % TBWL than LSG (9.8% ± 2.5% *vs* 6.6% ± 2.4%, $P < 0.001$), at 6 mo, patients who underwent ESG achieved a lower %TBWL (17.1% ± 6.5% *vs* 23.6% ± 7.6%, $P < 0.01$) compared to LSG[56]. However, patients in the ESG group were found to have significantly less adverse events (5.2% *vs* 16.9% $P < 0.05$) compared to LSG. The patients in the ESG group were healthier with less diabetes, hypertension, and obstructive sleep apnea than the LSG group[56]. Interestingly, new-onset GERD was also found to be significantly lower in the ESG group (1.9% *vs* 14.5%, $P < 0.05$)[56]. This is likely since these patients had lost weight. A limitation to this study was that patients in the ESG group underwent a weight management program post procedure, which may have induced a confounding bias.

Novikov *et al*[57] performed a similar study comparing ESG with LSG and laparoscopic band for weight loss. Similar results were seen with LSG achieving the greatest %TBWL (29.28 *vs* 13.30 *vs* 17.57%, $P = 0.01$) compared to the LAGB and ESG respectively[57]. In patients with a BMI < 40 kg/m^2, %TBWL at 1 year were similar between ESG and LSG[57]. Adverse effects were the lowest in ESG group and ESG having the shortest stay[57].

BARIATRIC SURGERY IN CIRRHOSIS

With no current approved pharmacological therapies available for the treatment of NAFLD, bariatric surgery is an option that should be considered. Klebanoff *et al*[58] assessed the cost-effectiveness of bariatric surgery in patients with NASH and compensated cirrhosis and concluded that bariatric surgery could be highly cost-effective. Unfortunately, there is a high risk of morbidity and mortality post-surgery which has been reported to be as high as 30% post operatively with an 11.6% 30-d mortality in patients with cirrhosis. Hepatologists and Bariatric surgeons remain reluctant to consider surgery as a treatment option[59]. Not only are patients with cirrhosis at an increased risk of complications post-surgery, but it has also been reported that this group of patients are associated with a longer hospital stay[59]. Portal hypertension as a consequence of cirrhosis leads to specific risks of morbidity and mortality. Thrombocytopenia secondary to splenomegaly increases the risks of bleeding and a hyperkinetic circulation with hypolbuminaemia leading to ascites. This impairs wound healing and increases the risk of complications, including infection.

A case matched study published in 2013 evaluated the morbidity related to laparoscopic sleeve gastrectomy (LSG) in patient with established cirrhosis compared with non-cirrhotic patients[60]. Over a 9-year period, 13 patients with established cirrhosis undergoing LSG were included and matched with 26 non-cirrhotic patients[60]. The aetiology of cirrhosis in 93% of patients was NASH. Weight loss was found to be similar between the two groups[60]. The overall complication rate in both groups was 7.7% *vs* 7.7% ($P = 1$). However, a limitation to the study was that all 13 patients in the cirrhosis group had Child-Pugh A cirrhosis[60]. The paper concluded that LSG can be performed in patients with Child-Pugh A cirrhosis with no increased risk of post-operative complications[60].

Similar results were observed in a multicentre, retrospective study conducted by GOSEEN (Obesity group of the Spanish society of endocrinology and nutrition)[61]. 41 patients of which all but 1 had Child-Pugh A cirrhosis underwent bariatric surgery (68.3% sleeve gastrectomy)[61]. Total weight loss (%TWL) was 26.33% ± 8.3% and 21.16% ± 15.32% at 1 and 5 years[61]. Improvements were seen in liver enzymes, blood pressure and glycaemic control with 17% of patients having early postsurgical complications[61]. No patients died in the study. Although, there is some evidence to support bariatric surgery in patients with early (Child-Pugh A) cirrhosis if the benefits outweigh the risks there is currently lack of consensus among surgeons regarding the safety of bariatric surgery and the best bariatric procedure in these patients. A systematic review was carried out and showed an acceptably higher overall risk of complications and perioperative mortality with bariatric surgery in cirrhotic patients[44].

Bariatric surgery in patients with advanced cirrhosis is associated with higher than usual risk of complications and mortality. In patients with NASH or significant fibrosis undergoing bariatric surgery, these overall risks highlight that surgeons must discuss the possibility of unexpected intraoperative findings of cirrhosis and agree on a course of action.

UPCOMING PHARMACOLOGICAL AGENTS

Although there remains to be any licenced pharmaceutical treatments for NAFLD or NASH, some drugs are currently in clinical trials which do appear promising.

Semaglutide

In a 72-wk double-blind phase 2 clinical trial patients with biopsy confirmed NASH and fibrosis were treated with Semaglutide *vs* placebo[62]. 320 patients were randomly assigned to different doses of Semaglutide *vs* 80 patients who received placebo[62]. The results showed that treatment with Semaglutide resulted in a significantly higher percentage of patients with NASH resolution compared to placebo however the trial did not show a significant difference in terms of improvement of fibrosis stage [62].

Resmetirom

Resmetirom (MGL-3196) is a selective thyroid hormone receptor-β agonist which is liver directed and designed to improve NASH by reducing lipotoxicity and enhancing liver fat metabolism[63]. In a 36-wk, phase 2, multicentre randomised, double-blind, placebo-controlled trial, treatment with Resmetirom showed a significant reduction in hepatic fat on both MRI-PDFF and liver biopsy after 12 and 36 wk compared to placebo[63]. The drug was well tolerated although there was a higher incidence of transient mild diarrhoea and nausea, in the Resmetirom group[63].

Tirzepatide

Tirzepatide is a 39-amino acid synthetic peptide which has agonist activity at glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptors and is administered once weekly by subcutaneous injection[64]. In phase 2 clinical trials, treatment with Tirzepatide has been shown to reduce HbA1c and lead to weight loss[64]. There is currently a phase 2 clinical trial in progress to assess impact on non-alcoholic fatty liver disease.

OUR EXPERIENCE WITH METABOLIC ENDOSCOPY

In a previous publication by Nguyen *et al*[65] we showed that intragastric balloon (IGB) therapy is an efficacious non–surgical method of achieving weight loss in the short term. We retrospectively examined the outcome in 135 IGB patients with obesity and NAFLD who had received 1 to 3 IGBs Clinical and anthropometric data were analysed at 6 mo. There were significant improvements in ALT, GGT and HOMA-IR, the latter as a measure of insulin resistance, a key component of NAFLD. The mean reduction in weight and BMI was 11.3 kg and 4.1 kg/m^2 respectively, ($P < 0.01$). The greatest amount of weight loss was seen at 6 mo. We found minor benefit from repeated IGB insertions.

More recently we have been able to analyse data from all patients who underwent IGB insertion at St Thomas' hospital, London, from 2014 to 2018. We separated the data into 2014-2016 *vs* 2017-2018. The characteristics are available in Table 2. Following our previous study, which showed little benefit from repeated IGB insertions, most patients only received one IGB. 127 patients underwent a total of 172 IGB insertions between 2014 and 2016. In comparison 60 patients underwent a total of 67 IGB insertions from 2017 to 2018.

Patients undergoing IGB insertions between 2014 and 2016 had a mean weight loss of 8.9 kg, (95%CI 7.4-10.4kg), $P < 0.0001$. Mean weight loss as %BW was 7.9% (95%CI 6.6-9.2%), $P < 0.0001$.

In comparison, more weight loss was observed in patients undergoing IGB insertions between 2017 to 2018, with a mean weight loss of 10.2 kg, (95%CI 7.5-11.9 kg), $P < 0.0001$. Mean weight loss as %BW was 9.1% (95%CI 7.5-10.6%), $P < 0.0001$ (Table 3).

Our data show that IGB can be a useful adjunct to dietary and lifestyle modification for achieving weight loss, in managing NAFLD.

CONCLUSION

With the global rise in obesity, NAFLD will continue to rise and poses a significant burden on healthcare systems. Liver fibrosis and cirrhosis associated with NAFLD is predicted to continue to increase over the next decades and become the commonest cause for liver transplantation. This poses a challenge. There is currently no licensed pharmacological treatment for NAFLD. There is mounting evidence that bariatric surgery not only provides histological improvement in patients with NASH, but improvements are seen in other components of the metabolic syndrome including blood pressure and diabetes. Moreover, with the lack of pharmacological treatments, bariatric surgery remains a proven and viable option for all patients at risk of developing significant fibrosis. The involved numbers globally, however, mean that not all patients can be offered bariatric surgery. Metabolic endoscopy is an

Table 2 Characteristics of patients who underwent intra-gastric balloons insertion

Variable	2014-2016, *n* (%)	2017-2018, *n* (%)
Total IGBs	172	67
Total number of patients	127	60
Age (yr) (mean; min-max)	46.8 (11.9;19-73)	46.6 (11.7;21-67)
Sex		
Male	56 (27)	17 (25)
Female	126 (73)	50 (75)
Baseline weight (kg) (mean; min-max)	110.0 (19.5;67-173.3)	114.6 (21.6;70-165)
Balloon number		
1	102 (59)	41 (61)
2	46 (27)	14 (20)
3	19 (11)	5 (7)
4	5 (3)	3 (4)
5	-	2 (3)
6	-	2 (3)

IGB: Intra-gastric balloons.

Table 3 Comparison weight loss

Variable	2014-2016	2017-2018
Baseline weight (kg) (mean)	110.0 (19.5)	114.6 (21.6)
Weight at removal (kg) (mean)	101 (19.8)	103.5 (21.2)
Weight loss (kg) (mean)	8.9 (8.6)	10.2 (6.8)
Weight loss as %BW (%) (mean)	7.9 (7.5)	9.1 (6.1)

evolving treatment option that may provide an alternative for patients who are either contraindicated to have surgery or who do not wish to undergo surgery. It can also be used as a ''bridge'' to surgery. Innovative metabolic endoscopic procedures such as IGB and endoscopic sleeve gastroplasty may be ideal for patients with obesity and NASH or with significant liver fibrosis who do not meet criteria for bariatric surgery. Randomised control trials are now required to further identify the overall benefits of both bariatric surgery and metabolic endoscopic procedures.

FOOTNOTES

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MINIREVIEWS

Therapies for non-alcoholic fatty liver disease: A 2022 update

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Abstract

The incidence of non-alcoholic fatty liver disease (NAFLD) is rapidly increasing and lifestyle interventions to treat this disease by addressing the underlying metabolic syndrome are often limited. Many pharmacological interventions are being studied to slow or even reverse NAFLD progression. This review for hepatologists aims to provide an updated understanding of the pathogenesis of NAFLD, current recommended therapies, and the most promising treatment options that are currently under development.

Key Words: Non-alcoholic fatty liver disease; Non-alcoholic steatohepatitis; Treatment

Core Tip: Non-alcoholic fatty liver disease (NAFLD) is a rapidly growing epidemic with high morbidity and mortality. Although lifestyle modifications will remain a cornerstone of disease management, a multitude of therapies are under development that target different aspects of NAFLD pathogenesis.

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INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is an epidemic affecting 20%-30% of the global population, paralleling the rise of type 2 diabetes (T2DM) and obesity[1-4].

Unfortunately, about one in five patients with NAFLD progress to non-alcoholic steatohepatitis (NASH). Of those patients with NASH, 10% develop cirrhosis. NAFLD is now the second leading cause of liver transplantation in the US[5,6]. In patients diagnosed with NASH, cardiovascular events are the leading cause of morbidity and mortality. These patients are also at higher risk of developing hepatocellular, pancreatic, and colorectal carcinoma[6]. The rapid rise in disease burden, increased utilization of healthcare resources, morbidity, and mortality mandates early and effective therapies for NAFLD.

The past decade has seen a variety of new medications targeting novel physiological pathways undergoing evaluation. They purport to halt, and in some cases, even reverse the fibrosis seen in NAFLD. In this review we provide the present pathophysiological understanding and therapeutic options for NAFLD, with a preview of medications on the horizon.

UNDERSTANDING THE SPECTRUM OF NON-ALCOHOLIC FATTY LIVER DISEASE

Definitions

NAFLD is a clinical diagnosis that requires the presence of lipids in ≥ 5% hepatocytes as seen on liver imaging or biopsy, without secondary causes of hepatic fat accumulation such as alcohol use. It consists of the clinical spectrum of disease, which ranges in severity from simple steatosis to cirrhosis. Simple steatosis, or non-alcohol fatty liver (NAFL), is defined as the presence of fat without hepatocellular injury or inflammation, and while it was initially defined as a benign disease, recent evidence suggests that almost 25% of these patients can develop fibrosis[7,8]. As there is an increase in disease activity, NAFL can progress to NASH, which is defined as evidence of hepatocellular injury through detection of lobular inflammation and hepatocellular ballooning, with varying degrees of fibrosis[9]. Recent consensus statements argue that NAFLD is more accurately described as MAFLD, or "metabolic associated fatty liver disease" and is the interplay of genetic, environmental, and metabolic factors that manifest in multiple ways[10], requiring a definition of inclusion rather than exclusion.

Patients with NAFLD including fibrosis are at the highest risk of adverse outcomes (*e.g.* progress to cirrhosis and hepatic decompensation)[11,12]. The presence and extent of fibrosis is the strongest predictor of many liver-related outcomes such as liver-related death and overall mortality[13].

The need for a noninvasive clinical marker that can measure disease progression and prognosis is still present. The current gold standard to diagnose NAFLD is liver biopsy, which is invasive and can result in complications. Scoring systems to measure disease activity include the FIB-4 score have high negative predictive value, but have overall moderate accuracy[14].

Measuring disease activity

The scoring systems used for patients with NAFLD are the NAFLD Activity Score (NAS), developed by the NASH Clinical Research Network (CRN), and the Steatosis Activity Score (SAF), proposed by the European-based Fatty Liver Inhibition of Progression consortium[9,15].

Both NAS and SAF look at hepatocyte ballooning, lobular inflammation, and steatosis. However, the NAS reports disease activity as a composite score, with breakdown as shown in Table 1. In the cases where NAS is used, fibrosis stage is then reported separately. Alternatively, the SAF includes fibrosis as part of its score.

It is important to note that while both scores are used to grade disease severity and quantify the efficacy of interventions in clinical trials, they do not replace the analysis of histological patterns and subsequent diagnosis of the disease by a pathologist[2,9,16]. Furthermore, both scores have limitations in their ability to fully assess patient response to treatment, due to inter- and intra-observer variability and "sampling error," due to the regional variability of disease activity within the liver itself[15].

PATHOGENESIS OF NAFLD

Hepatic lipid homeostasis is maintained through a variety of pathways. The main source of lipid uptake for the liver is *via* triglyceride lipolysis in adipose tissue, which releases fatty acids into the blood that are then taken up by the liver *via* membrane proteins called fatty acid transporters[17]. The liver also performs de novo lipogenesis (DNL), through acetyl-coenzyme A, and DNL is regulated by enzymes such as sterol regulatory element binding protein 1c (SREBP-1c), a nuclear transcription factor, and peroxisome proliferator-activated receptor α (PPARα).

In the liver, fatty acids undergo either beta oxidation in the mitochondria to produce ketone bodies, which are then exported to the rest of the body as fuel, or undergo fatty acid esterification with glycerol to form inert triglycerides, which is released as VLDL or stored in hepatocytes as lipid droplets[18,19].

The complex pathophysiology of NAFLD is driven by multiple hits. The major drivers include increased insulin resistance and impaired lipid metabolism. Other factors such as hormonal influences, gut-liver interactions, and genetics also play a significant role.

Table 1 The non-alcoholic fatty liver disease activity score reports disease activity as a composite score, with breakdown

NAS		SAF	
Component	Scoring range	Component	Scoring range
Steatosis	0-3	Steatosis	0-3
Lobular Inflammation	0-3	Activity (lobular inflammation + ballooning)	0-8
Hepatocyte ballooning	0-3		
Fibrosis (separate from NAS)		Fibrosis (uses the same fibrosis staging as NAS)	
F0	None		
F1	Perisinusoidal or periportal		
F1A	Mild, zone 3, perisinusoidal		
F1B	Moderate, zone 3, perisinusoidal		
F1C	Portal/periportal		
F2	Both perisinusoidal and portal/periportal		
F3	Bridging fibrosis		
F4	Cirrhosis		

NAFLD: Non-alcoholic fatty liver disease; NAS: NAFLD activity score; SAF: Steatosis activity score.

Insulin resistance

Insulin resistance plays a key role in the development of NAFLD, and is a nearly universal feature of the disease[2]. In hepatocytes, insulin inhibits gluconeogenesis, activates de novo lipogenesis, and promotes glycogen storage to decrease plasma glucose levels. In adipocytes, insulin promotes fatty acid esterification and lipid droplet storage while also

Insulin resistance is a defective metabolic response of target cell (hepatocyte, adipocyte inhibiting lipolysis[17], skeletal muscle) to insulin, and develops mainly due to acquired factors such as obesity [18]. It manifests as the ineffective suppression of lipolysis in adipose tissues, decreased glucose uptake by skeletal muscle due to the disruption of the translocation of the GLUT4 receptor to the surface membrane, and disturbed insulin mediated suppression of hepatic gluconeogenesis[18,20].

In NAFLD, hyperinsulinemia is combined with inappropriately increased levels of peripheral lipolysis and de novo lipogenesis, contributing to increased circulating levels of free fatty acids and hepatic lipid burden. Furthermore, hormones that increase insulin sensitivity such as glucagon-like peptide-1 (GLP-1) have been reported to be decreased in patients with NAFLD[21].

Lipid metabolism

Impaired intestinal permeability leading to increased translocation of intestinal toxins like lipopolysaccharides and ethanol has been reported in NAFLD. This can result in activation of hepatic macrophages releasing hepatotoxic factors like tumor necrosis factor (TNF)-alpha[22].

The farnesoid X receptor (FXR) is a nuclear receptor located in the liver and small intestine that plays a key role in glucose metabolism, triglyceride synthesis, and bile acid flow regulation[19,23,24]. Within the liver, FXR regulates hepatic triglyceride synthesis *via* inhibition of SREBP-1c, thus decreasing lipogenesis. It also promotes free fatty acid oxidation and represses gluconeogenesis[24]. Within the gut, FXR and its ligand, fibroblast growth factor 19 (FGF19), regulate bile acid synthesis by repressing CYP7A1, the enzyme for the rate limiting step in converting cholesterol to bile acids. Via the inhibition of CYP7A1 and de novo bile acid synthesis in the liver, the FXR/FGF19 pathway is an important component of bile acid synthesis and overall lipid metabolism[23,25].

Gut microbiota

There is increasing evidence that gut microbiome alteration and dysfunction contributes to NAFLD, T2DM, and obesity[26]. Patients with these comorbidities have increased proportions of ethanol producing, Gram-negative microbes such as *Proteobacteria* and *Escherichia coli*, resulting in increased ethanol levels[27,28]. Both bacteria itself and the ethanol activate production of Toll-like receptors (TLRs) and TNF in the liver, which may drive NAFLD progression.

Furthermore, altered microbiota may contribute to inflammasome dysfunction, which has been associated with insulin resistance and obesity[29]. Inflammasomes are protein complexes which sense damage-associated molecular pattern (DAMP) or PAMPs and process pro-inflammatory cytokines such as IL-1B and IL-18[30]. Unbalanced activation of these cytokines are associated with hepatic steatosis

through increased TLR entry into the portal system[29].

Epigenetics

Genetics also plays a role in NAFLD, as familial aggregation, twin studies, and genome-wide association studies (GWAS) provide strong evidence NAFLD is an inheritable condition[31]. Several genetic polymorphisms have been associated with NAFLD risk and severity, most notably the single nucleotide polymorphism I148M of the PNPLA3 gene. Other genetic loci such as neurocan, PPP1R3B, and glucokinase regulator have also been associated with steatosis in various GWAS[32,33]. More research is needed to determine the exact mechanism of how epigenetic modifications can influence NAFLD pathogenesis.

Hepatic inflammation

Insulin resistance, impaired intestinal motility, and impaired bile acid regulation, with underlying genetic alterations, all lead to a disruption of hepatic lipid homeostasis. Increased free fatty acid delivery to the liver results in increased VLDL secretion and generation of lipotoxic species[34] and decreased lipid removal. This sustained metabolic dysregulation maintains the ongoing low-grade systemic inflammation seen in NAFLD patients[18]. This lipotoxicity causes DAMP release that activates Kupffer cells and hepatic stellate cells, two of the resident hepatocyte immune cells. This triggers an immune system cascade that results in hepatic inflammation[17,35].

This hepatic inflammation characterizes NASH, which can eventually progress to liver fibrosis, cirrhosis, and hepatocellular carcinoma. However, the pathophysiology behind how some patients simply develop steatosis while others progress to fibrosis and cirrhosis remains to be determined.

CURRENT RECOMMENDED INTERVENTIONS FOR NAFLD

There are no current FDA-approved medications for NAFLD. Lifestyle modifications of 5%-10% weight loss through hypocaloric diets, aerobic exercise, and resistance training have been strongly advocated for by the AGA, AASLD, and EASL guidelines[9,36]. A weight loss of ≥ 5% of TBW can decrease hepatic steatosis, and ≥ 10% weight loss has been shown to stabilize or even reverse fibrosis from NAFLD[36]. This weight loss has been advocated through methods such as a hypocaloric diet, intermittent fasting, and aerobic exercise.

The Mediterranean diet (MD) has been the most extensively studied for patients with NAFLD. It is made up of a diet high in vegetables, fruit, legumes, minimally processed whole grains, fish, and nuts, with avoidance of dairy and red meat. In a study of twelve non-diabetic patients with NAFLD, the MD was found to reduce hepatic steatosis as measured on localized magnetic resonance H-spectroscopy [37]. Furthermore, in a prospective analysis of 1521 participants in the Framingham Heart Study, increased incorporation of the MD was found to be associated with reduced liver fat accumulation and odds of fatty liver incidence[38].

UPDATE ON THERAPIES UNDER EVALUATION

The present therapies under evaluation for NAFLD target the various stages of disease, with some having the possibility of reversing underlying fibrosis. Below we categorize therapies based on their role in the pathophysiological process of NAFLD.

Therapies targeting insulin resistance

Since insulin resistance is one of the main drivers of NAFLD, obesity, and T2DM, and these diseases often coexist in the same patient, there have been several clinical trials to assess the efficacy of antidiabetic therapies. Currently, semaglutide and dapagliflozin are under phase 3 trials.

GLP-1 receptor agonists: One promising therapy are GLP-1 receptor agonists (GLP-1RA), which stimulate fatty acid oxidation and gluconeogenesis, cause weight loss in diabetic and non-diabetic patients[39], improve glycemic control in patients with diabetes, and are associated with decreased cardiovascular risk. Exenatide, semaglutide, and liraglutide have all been studied.

Exenatide was initially studied in 44 obese patients with T2DM, who were initially given 5 μg twice daily and increased to 10 μg twice daily if well-tolerated. Compared to the placebo group, exenatide was found to reduce hepatic triglyceride content on MRI (-23.8 ± 9.5% *vs* +12.5 ± 9.6%, $P = 0.007$), most likely due to its weight loss effect ($r = 0.47$, $P = 0.03$)[40]. When GLP-1RA showed benefit in weight loss and HgbA1c, further studies were conducted to assess their effect in patients with NASH.

Liraglutide was then studied in the LEAN trial, where 9/23 (39%) of patients with NASH who received subcutaneous liraglutide 1.8mg daily were found to have histological resolution of their disease, compared to 2/22 (9%) who received placebo (RR 4.3, 95%CI 1.0-17.7, $P = 0.019$). Furthermore,

only 2/23 (9%) who received liraglutide had fibrosis progression, *vs* 8/22 (36%) in the placebo (RR 0.2, 95%CI 0.1-1.0, $P = 0.04$). However, gastrointestinal side effects affected up to 31%-81% of patients who received liraglutide[41].

Semaglutide is a GLP-1RA with more metabolic effects than liraglutide. In a recent multicenter phase 2 study of 320 patients with NASH, where 230 had stage F2-F3 fibrosis, those who received semaglutide 0.4 mg weekly had a significantly higher rate of NASH resolution with no worsening of liver fibrosis (59% in 0.4-mg group *vs* 17% in placebo group, OR 6.87, $P < 0.001$) compared with those who received placebo. The authors also noted deceases in inflammatory biomarkers and weight loss in the semaglutide 0.4mg group. The main side effect was gastrointestinal disorders, but only 7% of the total study population discontinued the medication due to these side effects.

In the patients with F2 or F3 fibrosis, the confirmatory secondary endpoint of improvement in liver fibrosis with no NASH worsening was not met. It is postulated that this study may not have been long enough of a duration to truly assess fibrosis improvement, and since the patients in this study already had moderate-severe fibrosis, their condition would be harder to reverse[39]. Further studies should also be conducted to assess for other factors as to why there were non-responders to this therapy, as genetics could also play a role. Currently, ESSENCE, a phase 3 trial involving patients with NASH, is assessing efficacy of semaglutide for steatohepatitis resolution and/or fibrosis improvement. The estimated trial completion date is in 2028 (NCT04822181)[42].

SGLT-2 inhibitors: SGLT-2 inhibitors act in the kidney to promote urinary glucose excretion, causing improved insulin resistance in patients with T2DM. Canagliflozin, dapagliflozin, and empagliflozin are all SGLT-2 inhibitors that are in widespread use among patients with T2DM, and empagliflozin is also used for patients with cardiovascular disease.

In 37 patients with NAFLD and T2DM, canagliflozin 100mg daily was found to decrease hepatic fat content on MRI-PDFF (-6.9% [-9.5; -4.2] *vs* -3.8% [-6.3; -1.3] in placebo, $P = 0.05$), which correlated with weight loss ($r = 0.69$, $P < 0.001$). It also increased hepatic insulin sensitivity ($P < 0.01$)[43]. Dapagliflozin 10 mg daily has been shown to decrease hepatic fat content on transient elastography in patients with T2DM and NAFLD and decrease fibrosis in patients with significant liver fibrosis, defined as LSM values ≥ 8.0 kPa (14.7 ± 5.7 to 11.0 ± 7.3, $P = 0.0158$). It has not yet been shown to increase insulin sensitivity of any organ[44,45]. This suggests that canagliflozin could be utilized in patients with steatosis, while dapagliflozin may be more beneficial for patients with more fibrosis. Currently, a phase 3 trial is underway to assess dapagliflozin in patients with NAFLD, with an estimated completion year in 2023 (NCT 05308160)[46].

Empagliflozin was also studied in the phase 2 E-LIFT trial, where 50 patients (power ≥ 90%) with NAFLD and HgbA1c < 10% received either empagliflozin 10 mg daily or placebo. It is interesting to note that 40% of the study were women, and all were of Indian origin. The trial found that liver fat was significantly reduced in the empagliflozin group compared with the control (4.0% difference, $P < 0.0001$) [47]. A subsequent phase 4 trial further confirmed that patients on empagliflozin had decreased hepatic fat on MRI compared to placebo (relative decrease -22% [-36 to -7], $P = 0.009$), but this was in patients with well-controlled T2DM (HgbA1c 6.6 ± 0.5%)[48]. Further multicenter studies are needed to assess the effectiveness of empagliflozin on patients with less-controlled T2DM and NAFLD.

Insulin sensitizers: MSDC-0602K is a second-generation thiazolidinedione (TZD) insulin sensitizer. It targets the mitochondrial pyruvate carrier (MPC) with minimal PPARγ gonist binding, minimizing side effects seen with the original TZDs (*e.g.* edema and decreased bone density). MSDC-0602K was assessed in a phase 2b trial on patients with NASH and F1-F3 fibrosis, with the primary endpoint of achieving ≥ 2-point reduction in NAS. While histological effects were not statistically significant, it did improve glucose metabolism and liver enzymes, and patients were able to tolerate the drug with minimal side effects[49]. Mice treated with combination MSDC-0602K and liraglutide therapy were found to have improved liver histology along with glucose tolerance, suggesting that this may be a suitable combination for patients with T2DM and NASH[50].

Therapies targeting lipid metabolism

Impaired lipid metabolism with resultant lipotoxicity is a key driver of hepatic inflammation and subsequent fibrosis. Key therapies that are currently in phase 3 trials include obeticholic acid, aramchol, and resmetirom.

Farnesoid X receptor agonist: Obeticholic acid (OCA) is a farnesoid X receptor agonist, and has also been shown to reduce steatosis, liver weight, hepatic inflammation, and fibrosis in animal models, suggesting anti-inflammatory and anti-fibrotic effects. As a result, it is a promising therapy pending additional investigation of its side effects and tolerability. Other FXR agonists under investigation include cilofexor, which has been shown to decrease hepatic fat *via* MRI-PDFF, and tropifexor[24].

The FLINT trial, a multicenter double-blind, placebo-controlled, 72-wk phase 2 trial assessed the effect of OCA in 283 patients with NAFLD with an NAS of 4, with a score of 1 or more in each component, with 225 patients with definite NASH at study entry[51]. Study participants received either OCA 25 mg or placebo, with 220 patients included in the primary outcome analysis, with both groups receiving standardized recommendations on lifestyle modifications. It demonstrated a statistically

significant decrease in NAFLD activity score between the obeticholic acid *vs* placebo group, with higher rates of improvement in all three categories of the score. It also found a higher rate of improvement in hepatic fibrosis in patients receiving OCA *vs* placebo[24]. The success of FLINT[23] led to REGENERATE[52], an ongoing phase 3 multicenter, randomized, placebo-controlled study that evaluated patients with non-cirrhotic NASH. This was defined as patients with biopsy-proven steatohepatitis, and NAS ≥ 4, with at least one point in each category. Their fibrosis stage was rated as F2 or F3, or F1 with at least one comorbidity (Body mass index ≥ 30, type 2 diabetes, or alanine transaminase > 1.5 ULN), indicating that they had advanced fibrosis. Study participants received placebo, 10 mg OCA, or 25 mg OCA.

The 18-mo interim analysis of the REGENERATE trial evaluated liver histology at month 18 as a prognostic indicator for clinical outcomes in a sample size of 750 patient and had 98% power. The intention to treat group analyzed for the primary analysis also included patients with more advanced fibrosis (F2-F3), and the group who received 25 mg OCA met the primary endpoint of achieving a statistically significant improvement of fibrosis (reduction of at least one stage) with no worsening of NASH compared to placebo (23% in OCA 25 mg *vs* 12% in placebo, $P = 0.0002$)[52]. This was the first positive phase 3 study in patients with NASH fibrosis.

The main concerning side effects include elevated LDL-C and decreased HDL-C levels in the OCA 25 mg *vs* placebo group. The CONTROL trial was a phase 2, double blind, 16-wk trial that then evaluated the effects of gradual up titration of atorvastatin on 84 patients with NASH receiving OCA 25 mg, 10 mg, or placebo, starting from week four of OCA therapy. It found that with doses of atorvastatin 10 mg, patients receiving OCA had increased LDL levels that decreased to below baseline[53]. There was no clinical benefit seen with doses higher than atorvastatin 10 mg. However, it is important to note that HDL-C and apolipoprotein A levels in OCA 25 mg group remained unchanged between initiation of atorvastatin therapy and the end of the trial. Furthermore, 26% of these patients had compensated cirrhosis, and larger study sizes are needed to evaluate this medication regimen with a clear delineation between those with NASH *vs* cirrhosis.

There were also higher rates of pruritus (51%, 28%, and 19% in OCA 25 mg, OCA 10 mg, and placebo respectively), causing treatment discontinuation in 9% of those receiving OCA 25 mg (compared to < 1% in the OCA 10 mg and placebo group). Other studies currently evaluating OCA include REVERSE, a phase 3 trial that is currently underway to evaluate the effect of obeticholic acid on patients with compensated cirrhosis due to NASH, which is expected to be completed in 2022 (NCT03439254).

PPAR agonists: Peroxisome proliferator-activated receptors are nuclear receptors that have been shown to be central for fatty acid metabolism, with pleiotropic effects on glucose metabolism and fibrogenesis. The three different isotypes include PPARα (expressed in tissue with a high rate of fatty acid oxidation), β/δ (expressed in hepatocytes, Kupffer cells, hepatic stellate cells, and skeletal muscle), and γ (expressed in adipose tissue)[54].

Within the liver specifically, PPARα plays a key role in lipid metabolism, as it acts on hepatocytes and stellate cells to aid in beta-oxidation, thus reducing triglyceride levels in the liver and ameliorating hepatic lipotoxicity. It has also been shown to increase HDL levels. PPARβ/δ has systemic anti-inflammatory activity, as it regulates the expression of genes involved in innate immunity. PPARγ modulates fibrosis, as it prevents hepatic stellate cell activation, which is a key step in fibrogenesis, along with regulating insulin sensitivity. PPAR agents that have been evaluated include pioglitazone, one of the original therapies that were evaluated in a clinical trial; elafibranor, of which its phase three trial was terminated; and lanifibranor, which is currently in a phase three trial.

Pioglitazone, a PPARα/γ agonist and TZD, was one of the first drugs studied as a potential NASH therapy. The PIVENS trial was a 96-week study that compared NASH resolution in patients who received pioglitazone, vitamin E, or placebo[55]. The study found that vitamin E was superior to placebo, and there was no benefit of pioglitazone over placebo for steatohepatitis improvement. This study suggests some benefit with using vitamin E as an adjunctive medication. It is also rarely prescribed due to multiple side effects such as weight gain, cardiac decompensation in patients with pre-existing conditions, and fluid retention.

A more promising drug is lanifibranor, a pan-PPAR agonist that was evaluated in the NATIVE trial (NCT 03008070), a multicenter, double-blind, placebo controlled 24-wk trial with 247 participants who had NASH, SAF score ≥ 3, demonstrating that patients had high disease activity, and SAF steatosis score ≥ 1. Its primary endpoint was NASH improvement without worsening in fibrosis, as defined by a decrease from baseline of at least 2 points in the SAF and a stable or decreased CRN-F score, in patients through evaluation of biopsies at baseline and at the end of the 24 wk period[54].

Patients were exposed to placebo, lanifibranor 800 mg/d, or lanifibranor 1200 mg/d. Based on the initial results, by the end of week 24, 63.9% of those receiving 1200 mg lanifibranor met the primary endpoint, compared to 32.1% in the placebo group (RR 1.82, $P = 0.004$). Common side effects included gastrointestinal complaints, headache, and dizziness[56]. A phase three trial to evaluate lanifibranor (800 mg and 1200 mg once daily) *vs* placebo in patients with NASH and F2/F3 fibrosis has already been initiated with a primary composite endpoint of patients experiencing both NASH resolution and fibrosis improvement after a 72-wk period.

The RESOLVE-IT trial (NCT 02704403) was a phase three trial which evaluated the effect of elafibranor, a PPARα/δ agonist, on histological improvement and all-cause mortality and liver-related outcomes in patients with NASH and fibrosis did not meet primary or secondary endpoint on its interim analysis and was terminated[57].

Fibroblast growth factor agonist: As discussed early, the FXR/FGF19 pathway is a key regulator of energy metabolism. FGF19 has been shown to improve insulin sensitivity and increase adiponectin concentration in healthy obese patients with type 2 diabetes.

Pegbelfermin is an FGF19 analogue with a prolonged half-life that can allow for weekly dosing, which could also improve patient adherence, but its subcutaneous administration may also serve as a detracting factor. In a phase 2 trial evaluating 75 patients treated with subcutaneous injections of pegbelfermin 10 mg daily, 20 mg weekly, *vs* placebo daily, there was a significant effect of pegbelfermin on decreasing hepatic fat fraction in both groups during the interim analysis, as seen on MRI-PDFF (-6.8% in the 10-mg and -5.2% in the 20-mg group, compared to -1.3% in the placebo group). The study also found significant increases in adiponectin after pegbelfermin treatment (P = 0.0030), decreased LDL, and increased HDL[58]. The study was terminated early due to these greater than expected results, so larger studies with longer therapy duration are needed to assess efficacy in possible fibrosis improvement and monitor safety profile and side effects.

NGM282 is another FGF19 analogue that was studied in a randomized, double blind, placebo-controlled, 12-wk long trial (NCT02443116) in 166 patients with NASH and an NAS ≥ 4, stage 1-3 fibrosis, and at least 8% fat content. The primary endpoint was absolute change from baseline to week 12 in liver fat content, with a responder being categorized as someone with ≥ 5% absolute liver fat content reduction as seen on MRI-PDFF. NGM282 were associated with significant reductions in liver fat content (74% in the 3 mg group, 79% in the 6 mg group, *vs* 7% in the placebo, P < 0.0001 for both comparisons). While these results warrant further study, it is also important to note the subcutaneous need for these injections, as the most commonly (≥ 10%) reported adverse events were injection site reactions (34%), along with diarrhea (33%), abdominal pain (18%), and nausea (17%)[59].

Efruxifermin, another long-acting FGF21 fusion protein, was also studied in a phase 2a trial of patients with NASH and F1-F3 fibrosis to assess its efficacy in hepatic fat reduction on MRI-PDFF. Patients in all treatment groups had a statistically significant decrease in hepatic fat content compared to placebo (-12% to -14%, P < 0.0001)[60]. 78% of patients also had ≥ 2 point reduction in NAS without worsening fibrosis, which is comparable to aldafermin, and this drug was generally tolerated.

Stearoyl-CoA desaturase inhibitors: Stearoyl-CoA desaturase (SCD1) converts saturated fatty acids into monosaturated fatty acids and is key for hepatic lipogenesis. SCD1 downregulation has been shown to cause not just reduced hepatic lipogenesis, but also obesity resistance, enhanced insulin sensitivity, protection from steatosis, and enhanced lipid oxidation.

In the 12 mo, global phase 2b randomized placebo-controlled ARREST trial, Aramchol, a stearoyl-CoA desaturase inhibitor[61], was studied in 247 patients with NAFLD (defined as NAS ≥ 4), liver fat concentration of 5.5% or more as measured on MRS, and known T2DM (mean HgbA1c 6.6%) or pre-diabetes. Of the study population, 64.8% were women, and 63.2% were white. Patients received either Aramchol 400 mg, 600 mg, or placebo, and the primary endpoint evaluated absolute reduction in liver fat *via* mean absolute change from baseline and ≥ 5% absolute reduction from baseline as seen on MR spectroscopy. While only patients on 400 mg aramchol demonstrated a statistically significant mean absolute change from baseline in liver fat (400 *vs* placebo, P = 0.045; 600 *vs* placebo, P = 0.0655), patients on aramchol 600 mg did demonstrate a ≥ 5% absolute reduction from baseline compared to placebo (47% *vs* 24.4%, P = 0.0279), and aramchol was found to be weight neutral without effects on lipid levels. The secondary endpoints of fibrosis improvement without worsening of NASH demonstrated an non-statistically significant improvement in those on aramchol 600 mg *vs* placebo (29.5% *vs* 17.5%, P = 0.211), prompting the initiation of a phase 3 study, ARMOR (NCT 04104321), that is powered to evaluate NASH Resolution without worsening of liver fibrosis; or vice versa[62].

Thyroid hormone receptor β agonist: Thyroid hormones also act in lipid metabolism. Thyroid hormone receptor (THR) α and β are distributed throughout the body, with β being the major one expressed in the liver. Thyroid hormone receptor beta is a key player in many of the pathways that regulate the pathogenesis of NASH. THRβ activation has been associated with reduction in triglycerides and cholesterol, improvement of insulin sensitivity, promotion of liver regeneration, and reduction of apoptosis. Resmetirom is a liver-selective, orally activated THR agonist, and is specifically uptaken by the liver. This is beneficial as its sole site of action will be on the liver, avoiding more systemic side effects of thyroid hormone receptor activation[62].

116 patients with biopsy proven NASH, NAS ≥ 4, fibrosis stage 1-3, and hepatic fat levels > 10% as measured on screening MRI-PDFF were enrolled in a trial to study the effect of resmetirom on hepatic fat levels as measured with MRI-PDFF[62]. However, it also important to note that up to 10% of patients could have either fibrosis stage 0, or hepatic fat levels at least 9% but less than 10%. All resmetirom patients were given 80 mg doses for the first four weeks, and 24-h area under the curve (AUC) exposures were calculated at week 2 and 4. At week 4 the AUC aided in titration of resmetirom dosing. The treatment group was subdivided into a high exposure (resmetirom AUC ≥ 2700 ng*h/mL) and low

exposure (AUC < 2700 ng*h/mL, but still associated with lipid lowering effects in phase 1 studies) subgroup. The study found that at week 12 and 36, resmetirom therapy was associated with significant reductions in relative and absolute hepatic fat fraction from baseline (-36.3%, P < 0.0001). They also found that patients in the high exposure subgroup had greater relative hepatic fat reductions from baseline at week 12. Furthermore, the resmetirom group demonstrated reduced NASH features on liver biopsy, with a greater proportion of patients with ≥ 2 point reduction in NAS in the resmetirom group compared to placebo (46% *vs* 19% respectively, P = 0.017), and reduction in LDL, apolipoprotein B, and triglycerides. This suggests that along with improvement in hepatic fat, resmetirom may also decrease cardiovascular risk factors and improve histological features of NAFLD with minimal side effects of diarrhea and nausea that were mainly associated with therapy initiation. The phase three trial, MAESTRO-NASH, is currently underway in studying the effect of resmetirom on patients with NASH and F2-F3 fibrosis (NCT03900429)[63].

COMBINATION THERAPIES

Due to the complex pathophysiology of NAFLD, it is unlikely that there will be a single therapy for this disease.

A phase 2 of 108 patients with NASH evaluated safety of semaglutide 2.4 weekly only, *vs* in combination with cilofexor (30 or 100 mg daily) and/or firsocostat 20 mg daily. Patients had NASH based on biopsy with F2-F3 fibrosis or MRI-PDFF ≥ 10% and transient elastography (TE) liver stiffness ≥ 7 kPa[64]. Although 73%-90% of patients experienced adverse effects (mainly gastrointestinal), only 41%-48% had ≥ grade 2 adverse events and only 8 (7.4%) discontinued their study drug. Exploratory endpoints found increased relative (-55.7% to -59.4% *vs* -46.2%) and absolute reductions (-9.8% to -11% *vs* -8%) in hepatic fat on MRI-PDFF in combination *vs* semaglutide groups. Based on liver stiffness assessment on TE, there was also potential reduction in hepatic fibrosis (mean change -2.29 to -3.74 kPa). A phase 2b trial with histologic endpoints is planned to further assess safety and efficacy of these combination medications in patients with compensated NASH cirrhosis (NCT04971785)[65].

The TANDEM study was a phase 2b trial of 200 patients with biopsy-proven NASH and fibrosis F2-F3 to assess safety of tropifexor, an FXR agonist, and cenicriviroc, a chemokine receptor type 2/5 antagonist, compared to monotherapy (NCT03517540)[66]. Results from this study have not yet been published.

Recently, an investigational combination therapy of ervogastat, a diacylglycerol acyltransferase 2 inhibitor, and clesacostat, an acetyl-coenzyme A carboxylase inhibitor, has been shown to be well-tolerated with a promising safety profile. It is currently being studied in a phase 2 trial of patients with biopsy-proven NASH with F2-F3 fibrosis (NCT04321031)[67].

CONCLUSION

Currently, a multitude of NAFLD therapies are in phase 3 trials including dapagliflozin, semaglutide, resmetirom, obeticholic acid, and aramchol, with more in development. The current trajectory likely involves tailoring drug therapies for different phases of NAFLD, such as utilizing aramchol or NGM282 for reduction of hepatic fat in patients with simple steatosis *vs* dapagliflozin in patients with fibrosis. Furthermore, combination therapies are also being studied in phase 2 trials. Due to the complex pathophysiology of NAFLD, these regimens will likely also be effective, but their safety, tolerability, and optimal drug combination must be assessed.

NAFLD is a disease with increasing prevalence and high rates of morbidity and mortality. Although lifestyle modifications remain an essential part of therapy, new and exciting drug regimens are on the horizon.

FOOTNOTES

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MINIREVIEWS

Bile acids as drivers and biomarkers of hepatocellular carcinoma

Santo Colosimo, Jeremy W Tomlinson

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Abstract

The prevalence of hepatocellular carcinoma (HCC) is rapidly increasing, driven not least in part by the escalating prevalence of non-alcoholic fatty liver disease. Bile acid (BA) profiles are altered in patients with HCC and there is a developing body of evidence from *in vitro* human cellular models as well as rodent data suggesting that BA are able to modulate fundamental processes that impact on cellular phenotype predisposing to the development of HCC including senescence, proliferation and epithelial-mesenchymal transition. Changes in BA profiles associated with HCC have the potential to be exploited clinically. Whilst excellent diagnostic and imaging tools are available, their use to screen populations with advanced liver disease at risk of HCC is limited by high cost and low availability. The mainstay for HCC screening among subjects with cirrhosis remains frequent interval ultrasound scanning. Importantly, currently available serum biomarkers add little to diagnostic accuracy. Here, we review the current literature on the use of BA measurements as predictors of HCC incidence in addition to their use as a potential screening method for the early detection of HCC. Whilst these approaches do show early promise, there are limitations including the relatively small cohort sizes, the lack of a standardized approach to BA measurement, and the use of inappropriate control comparator samples.

Key Words: Bile acid; Liver cancer; Screening; Cirrhosis; Serum metabolites; Urine metabolites

Core Tip: The rapidly increasing prevalence of hepatocellular carcinoma (HCC) highlights the unmet clinical need to develop and enhance early diagnostic strategies. Evidence from rodent and *in vitro* models suggests that bile acids may have a crucial role in the pathogenesis of HCC. Changes in circulating bile acid profiles are observed in patients with HCC. Serum and urine bile acid profiles may predict HCC risk and may have potential as a non-invasive screening tool.

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INTRODUCTION

The increasing prevalence of hepatocellular carcinoma (HCC) in recent years has focused the need not only to develop better treatment strategies, but also to identify and validate accurate, non-invasive early detection strategies with the aim of improving clinical outcome. In 2018, HCC was ranked as the sixth most common incident cancer and fourth highest for mortality outcome by the World Health Organization[1]. Much of the increase in incidence is driven by the epidemic of non-alcoholic fatty liver disease (NAFLD), which is rapidly becoming the most prevalent etiology for cirrhosis, HCC and liver transplant[2].

Currently, screening strategies for HCC detection are based on regular interval ultrasound scanning (US) (usually 6 moly) while diagnosis is often confirmed by computerized tomography (CT) scan or magnetic resonance imaging (MRI). The performance of US in early detection of HCC is dependent upon both the expertise of the operator and the quality of the equipment[3]. CT scanning is not recommended for surveillance due to radiation exposure and MRI is expensive and not as widely available. Alpha-fetoprotein (AFP) is a the most widely available serum biomarker test for HCC. Despite being tested as a diagnostic tool, only two studies have investigated its performance as a stand-alone screening method for early-stage HCC[4,5]. The data are mixed and to some extent conflicting; whilst one study suggested that AFP screening can miss many incident HCCs, the other reported improved early detection, although there was no impact on clinical outcome. Importantly, in both studies, the major underlying chronic liver disease was either hepatitis B virus (HBV) or hepatitis C virus (HCV) infection related cirrhosis. AFP accuracy to detect early-stage HCC remains sub-optimal even when combined with US, increasing the accuracy by only 6%-8%[4,6]. AFP levels may also vary in patients with HBV and HCV-related cirrhosis following flares of viral replication or disease progression with further fluctuations being observed in patients with cirrhosis whenever the underlying liver disease exacerbates[7]. Moreover, early-stage HCCs express AFP in only 10%-20% of cases[8].

Bile acids (BA) include a variety of lipid compounds that are synthesized in hepatocytes, secreted into the biliary tree and stored in the gall bladder. The primary bile acids (cholic (CA) and chenodeoxycholic acid (CDCA)) are dehydroxylated to secondary bile acids by gut microbiota, reabsorbed in the intestine and conjugated in the liver (Figure 1). The amount of BA recirculating within the enterohepatic circulation is constant (approximately 3 g). As little as 0.5 mg of BAs spill over into the systemic circulation and are subsequently excreted into urine. Bile acid composition in serum and urine is thought to be proportional to concentration in the gallbladder.

The biochemical modifications that BAs undergo during this cycle reflect their functions as dietary fat emulsifiers. Importantly however, it is now widely recognized that BAs have a diverse array of functions to regulate cellular metabolic, inflammatory and proliferative phenotypes, mediated through a series of discrete BA receptors.

Farnesoid X receptor (FXR) is a nuclear receptor expressed in hepatocytes and enterocytes and is most potently activated by CDCA. FXR activation within the liver downregulates lipogenesis and enhances lipolysis preventing liver fat accumulation whilst in the intestine, it promotes inflammation and insulin resistance. Takeda G protein-coupled receptor 5 (TGR5) is a bile acid-specific G protein-coupled receptor that activates various intracellular signaling pathways. Pregnane X receptor (PXR) and constitutive androstane receptor (CAR) are BA nuclear receptors involved in the regulation of drug metabolism and BA conjugation[9].

In this review, we will discuss the evidence supporting the role of BAs and their receptors in the pathogenesis of HCC focusing largely on human models. In addition, we discuss the potential utility of BA profiling as a risk stratification and early diagnostic tool in the management of patients at risk of developing HCC.

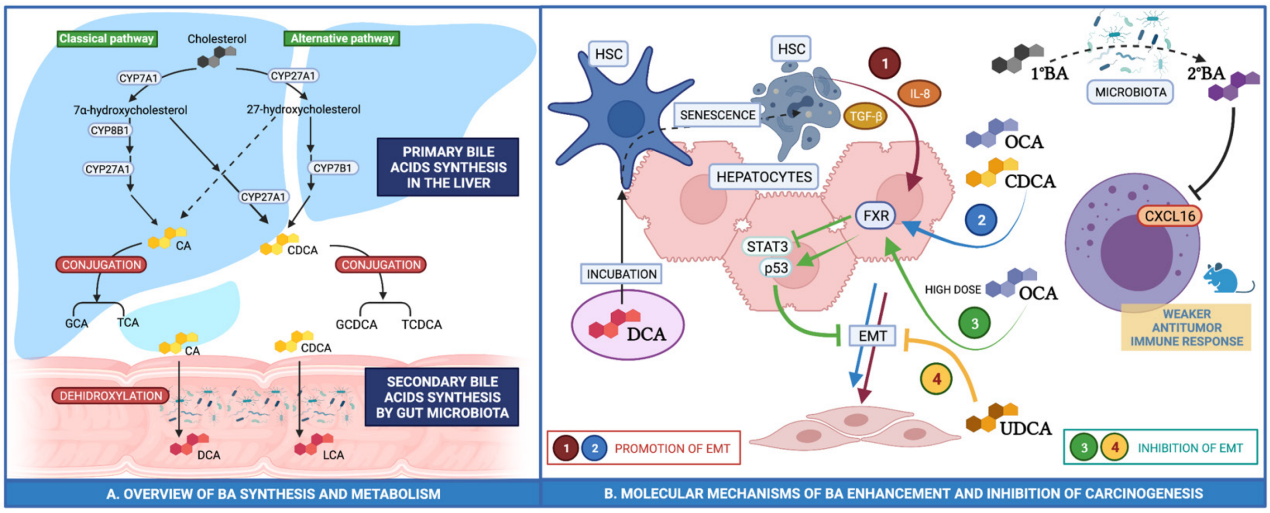

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Figure 1 The primary bile acids are dehydroxylated to secondary bile acids by gut microbiota, reabsorbed in the intestine and conjugated in the liver. A: Primary bile acids cholic acid and chenodeoxycholic acid are dehydroxylated into deoxycholic acid and lithocholic acid, respectively, by the gut microbiota. Bile acids (BA) are reabsorbed by the intestine and reach the liver through the portal circulation. Primary BA and secondary BA are conjugated to either glycine or taurine in the liver; B: Regulation of epithelial-mesenchymal transition by primary (1°) and secondary (2°) BA in human hepatocytes. GCA: Glycocholic acid; TCA: Taurocholic acid; GCDCA: Glycochenodeoxycholic acid; TCDCA: Taurochenodeoxycholic acid. OCA: Obeticholic acid; DCA: Deoxycholic acid; UDCA: Ursodeoxycholic acid; EMT: Epithelial-mesenchymal transition; HSC: Hepatic stellate cells.

BILE ACIDS AND THE PATHOGENESIS OF HCC

Evidence from rodent models

FXR-null mice accumulate BAs and develop spontaneous HCC in approximately 90% of cases[10]. In addition, liver-specific FXR-knockout mice also develop spontaneous HCC in 20% of cases whilst intestine-specific FXR-knockout only develop HCC in 5% of cases. The rate of HCC onset increases with diethylnitrosamine (DEN) treatment, a well-recognised driver of the development of HCC, as well as treatment with cholic acid[11]. Conversely, in a humanized rodent model of NASH-associated HCC induced by DEN and high fat choline-deficient diet, activation of FXR *via* administration of obeticholic acid (OCA), a synthetic bile acid FXR potent agonist, upregulated p53 and downregulated STAT3, a regulatory pattern that limits apoptosis and cancer promotion[12].

The anti-tumor immune response is also modulated by BA. Increased conversion of primary to secondary bile acids by an altered gut-microbiota has been associated with CXCL16 downregulation in Natural Killer T-cells (NK) and this has been proposed to exert a weaker antitumor immune response [13].

In addition to FXR, other BA receptors have been implicated in the pathogenesis of HCC, although they have been studied in less detail. TGR5 activation may be involved in the anti-tumor immune response. In a tumor-bearing murine model, administration of ursodeoxycholic acid restrained T-reg Cell activation working through the TGR5-AMPK-PKA (AMP-kinase, protein kinase A) axis, resulting in carboxyl terminus of Hsc70-interacting protein mediated ubiquitination and subsequent degradation of TGF-beta[14].

To date there are currently no studies that have specifically examined the role of CAR and PXR in the pathogenesis of HCC and this is clearly an area where further research is required. PXR is expressed in the intestine and has been suggested to have a role in the pathogenesis of colon cancer[15]. However, the specific pathways maybe different between colon and liver and therefore dedicated studies in HCC models are warranted.

Evidence from rodent studies would therefore suggest that BA accumulation alongside suppression of FXR expression may act synergistically in promoting carcinogenesis. However, it is important to note that there are fundamental differences in BA synthesis and metabolism between rodents and humans (exemplified by the exclusive generation of muricholic acids and their metabolites in rodents) and this may limit the interpretation of rodent derived data.

Evidence from human in vitro models

The data from human *in vitro* models are complex but do suggest a potential role for BA in HCC pathogenesis. In Huh-7 and Hep3B cell models, physiological doses of OCA and CDCA promote epithelial-mesenchymal transition (EMT) through the expression of TGF-Beta[16]. EMT is a process that entails changes in the shape of cells with loss of polarity, cell-cell adhesion, and gain of spindle shape, migratory and invasive potential and may be critical for the malignant transformation of hepatocytes.

Furthermore, in human hepatoma HepG2 cells, CDCA promotes cellular proliferation and reduces sensitivity to the chemotherapeutic agent 5-fluorouracil[17]. These data would suggest that BA may promote HCC development, however, there may also be a dose-dependency of effect. When administered in higher doses, OCA suppresses cell growth and induces cell death[16].

Hepatic stellate cells (HSC) are a subgroup of hepatic cells that account for 10% of the total cell mass of the liver and are fundamental in driving hepatic fibrosis. They maintain a quiescent phenotype in normal liver and transdifferentiate to myofibroblasts after a liver injury. There is evidence to suggest that DCA may indirectly promote hepatocellular carcinogenesis through initiation of HSC senescence. Incubation of HSC with DCA drives inflammation through the release of TGF-beta and IL-8 and both of these cytokines are able to modify the expression of adhesion molecules promoting EMT and subsequent HCC risk[18].

Ursodeoxycholic acid, a secondary BA produced by the gut microbiota causes a dose- and time-dependent increase in HepG2 cell apoptosis by activating the mitochondrial cell death pathway[19]. In addition, taurocholic acid (TCA) has an antiproliferative effect on HepG2 increasing the expression of adhesion molecules and promoting apoptosis, that may inhibit or even reverse EMT[20].

Taken together, all these data would suggest that BAs may play a role in the regulation of cellular phenotype that may predispose to the development of HCC (Figure 1), but the mechanisms are complex and currently poorly understood.

USING BILE ACID AS A CLINICAL TOOL IN PATIENTS WITH, OR AT RISK OF HCC

Based on the preclinical evidence, it has been proposed that specific patterns of serum and urine BAs concentrations may predict HCC risk or facilitate the early detection of HCC. There are many potential benefits of such approach. Firstly, this may reduce the number of percutaneous liver biopsies needed. Secondly, it may enhance the rate of early diagnosis with the potential to improve clinical outcome.

Bile acids as predictors of HCC incidence

Based upon *in vitro* and preclinical observations, BA profiling has been used as a tool to predict the subsequent development of HCC. Wang *et al*[21] reported the results of a retrospective study and showed that elevated total serum bile acids (TBA) levels were an independent risk factor for the future development of HCC. After adjusting for liver fibrosis using a non-invasive risk stratification tool (AST to platelet ratio index, APRI) and the presence of ascites, total BA levels were found to be elevated in those patients who later developed HCC on a background of HBV-related cirrhosis.

More recently, a further study has reported an increased of risk of developing HCC in cirrhotic patients with increased total BA. In addition, after adjustment for potential confounders, the taurochenodeoxycholic acid/glycochenodeoxycholic acid (TCDCA/GCDCA) and the taurodeoxycholic acid/glycodeoxycholic acid (TDCA/GDCA) ratios were both associated with a higher risk of developing HCC four years later. In contrast, a decrease in the TCA/CDCA ratio was associated with a reduction in the risk of HCC[22].

In a multi-centre, prospective observational cohort study, Stepien *et al*[23] defined the metabolic perturbations that precede the diagnosis of HCC. Among fourteen metabolites identified in the study, elevated serum levels of glycocholic acid (GCA) and GCDCA were associated with an increased risk of developing HCC. However, it is important to note that in this study, comparison was made against healthy controls matched to patients with HCC at the time of case occurrence. A comparison to patients with established cirrhosis was not made and therefore this limits the interpretation of their findings. However, these results are consistent with those of previously reported studies suggesting that elevated TBA, and specifically primary bile acid levels, are associated with an increased risk of developing HCC.

The mechanisms that underpin these observations remain poorly understood. Detailed studies examining the role of BA conjugation in the development of HCC have not been performed. However, diets high in saturated and milk-derived fats specifically increase serum levels of taurine-conjugated bile acids in rodents[24]. Increased taurine-conjugated bile acids levels may therefore be a surrogate marker providing a reflection of dietary composition that could drive HCC risk through the progression to advanced NAFLD.

Bile acids and the early detection of HCC

Current screening strategies for the early detection of HCC in patients with advanced liver disease are heavily reliant on US imaging. However, several studies have tried to use measurements of serum (and in some cases urine) BA profiles as an early detection strategy.

Han *et al*[25] measured selected BAs (CDCA, GCA and GCDCA) in 3 distinct patient groups: One group with HCC, one group with cirrhosis but not HCC and a third group of healthy controls. In both the HCC and cirrhosis groups, levels of GCDCA and GCA were found to be higher than in healthy controls. CDCA levels were reduced in patients with HCC compared to both patients with cirrhosis and healthy control subjects, suggesting a potential protective effect against tumorigenesis[25]. In the same study, samples of HCC tumor tissue were also analyzed. Levels of all three bile acids were reduced and

it is possible that this may provide an environment which allows HCC to develop by increasing inflammation and disrupting the efficacy of the immune response (Figure 1).

In a retrospective, case-control study that incorporated an analysis of the serum metabolome to identify potential markers for HCC, total BA concentrations were higher in patients with HCC [with and without diabetes mellitus type 2 (T2DM)] compared to patients with T2DM but without HCC and to healthy controls[26].

Several other studies have also confirmed higher levels of specific bile acids (most frequently GCA, but also taurodeoxycholic acid, taurocholate, glycocholate, CDCA and cholic acid) in the serum or plasma of patients with HCC when compared to healthy controls[27-33]. However, there is some variability as to the underlying etiology of chronic liver disease predisposing to HCC in these cohorts and direct comparison of BA profiles amongst these etiologies has not been made. Some of the published data are not entirely consistent and highlight the critical importance of matching, clinically relevant comparator cohorts. GCA and GDCA were found to be significantly decreased in a cohort of patients with HCC when compared to those with cirrhosis, whilst they were increased with respect to healthy volunteers[34]. Another study using samples mainly from patients with HCV and HBV related cirrhosis and HCC has shown that GCA, GCDCA, TCA, and TDCA were decreased in patients with HCC compared to those with cirrhosis[35]. Taken together, these data would seem to suggest that the changes in GCA and GDCA are the most consistent in the majority, although not all, of the published studies and could offer biomarker potential. However, on their own in isolation and without additional biomarkers (or the use of machine learning strategies) they are unlikely to offer sufficient specificity or sensitivity as an early detection test. A summary of findings from all the published studies is presented in Table 1.

Familial intrahepatic cholestasis is a group of rare genetic disorders involving bile acid transport and synthetic defects characterized by BA accumulation in liver parenchyma. Although available data are limited, there is some evidence to suggest, a risk of early onset HCC in these groups of patients[36]. Specific bile acids are found predominantly in fetal life or in rare genetic disorders of bile acid synthesis. 7α-hydroxy-3-oxochol-4-en-24-oic acid and 3-oxochol-4,6-dien-24-oic acid are not normally secreted in adults, but have been identified in plasma and urine of patients with cirrhosis and HCC[37,38]. An additional study has also suggested that Delta(4)- and/or allo-bile acids levels in urine are increased in patients with HCC[39]. Other chronic liver conditions are also associated with changes in BA levels that can predispose to malignancy. In cases of primary biliary cholangitis and primary sclerosing cholangitis, BA accumulation enhances necrosis and apoptosis of hepatocytes through mitochondrial damage, membrane disruption and ROS production. The chronic damage with oxidative stress and pro-inflammatory microenvironment can promote carcinogenesis[9].

Rather than focusing on individual BA levels, machine learning algorithms applied to BA profiles have been used successfully to differentiate benign from malignant hepatobiliary strictures[40]. Combining BAs and machine learning has not been applied to the diagnosis of HCC diagnosis but may offer a strategy to improve diagnostic and prognostic performance.

There are important inconsistencies and limitations in the published data that make direct comparisons challenging and limit the interpretation of study results. Most studies used liquid chromatography mass spectrometry to quantity bile acids and their metabolites. However, the methodology is not standardized and therefore results from different laboratories may not be completely reproducible or comparable. Race, age, gender, diet, medication, circadian rhythm are factors that can influence BAs basal concentration. Therefore, BA pool composition rather than absolute BA concentrations should be considered to overcome or adjust for individual differences. Furthermore, since the composition of BA profiles are not consistent, it is difficult to find consensus over the definition of a standard pool[41]. Study designs are also heterogeneous. Some of the reports are case-control studies designed to detect differences in the risk of development of HCC, whilst others are cross-sectional studies or retrospective studies aiming to identify differences in the concentration of specific biomarkers between patients with HCC and subjects at high risk or healthy control participants. Since most cases HCC develops on a background of cirrhosis (of differing aetiologies), it is essential that a biomarker is accurate enough to discriminate patients with disease-specific cirrhosis from those with HCC. Head-to-head comparisons of BAs measurements against the standard screening approaches of US+/-AFP have not been performed. However, these studies would be crucial next step in order to assess the potential clinical advantage of using BA profiles in replacement or addition to US+/-AFP as screening strategy.

CONCLUSION

In conclusion, there is a growing body of evidence detailing a role for BAs and their signaling in the pathogenesis of HCC. It is likely that this translates to clinical alterations in BA profiles that have been measured in serum and urine from patients with HCC and those with cirrhosis. What remains uncertain is how these observations may translate to the development of meaningful biomarkers that might help guide clinical management or predict clinical outcome. Adopting a standardized approach to the measurement of BAs, combined with innovative approaches to the analysis and interpretation, perhaps

Table 1 Summary data of clinical studies examining the utility of bile acid profiling in the diagnosis and screening for hepatocellular carcinoma

	Ref.	Type of study	Clinical cohort (No.)	Control cohort	Underlying chronic liver disease	No. of subjects (Male)	Samples	Outcome *vs* control	Outcome *vs* cirrhosis
1	Wang *et al*[17], 2016	Retrospective	Cirrhosis without HCC (1082)	NA	HBV	2262 (1710)	Serum	Increased TBA	Increased TBA-> risk factor for HCC
2	Thomas *et al*[22], 2021	Case-Control	HCC (100)	Healthy Match (age, gender, dialect group)	MAFLD/ Cryptogenetic	200 (150)	Serum	Increased TBA and CPBA	Increased TBA and CPBA -> risk factor for HCC
3	Stepien *et al*[23], 2020	Case-Control	Cirrhosis without HCC (129)	Healthy Match (age, sex, centre *etc*.)	Any	258 (176)	Serum	Increased TBA and CPBA -> risk factor *vs* healthy control	Increased TBA and CPBA
4	Han *et al*[25], 2019	Cross-Sectional	HCC (30)	Healthy (30) Cirrhosis (30)	HBV	90 (58)	Serum	Serum GCDCA reduced in HCC	Serum GCDCA reduced. GCDCA, CDCA, GCA in HCC tissue are reduced.
5	Sun *et al*[26], 2020	Cross-Sectional	HCC (16) HCC-T2DM (10)	Healthy (27) T2DM (27)	NAFLD/ Cryptogenetic	80 (50)	Serum	Increased TBA in HCC +/- T2DM *vs* T2DM and healthy	
6	Hsu *et al*[27], 2017	Case Control	HCC (121)	HBV positive non-cirrhotic	HBV	242 (242)	Serum	Increased TDCA, CA, TC, GC	
7	Li *et al*[28], 2017	Case Control	HCC (14)	Healthy	NA	28	Plasma/ Urine	Urine and Plasma GCA 3-24 times increased in HCC	
8	Luo *et al*[29], 2018	Cross-Sectional	HCC (516)	Cirrhosis Healthy	NA	1448 (1076)	Serum	GCA and Phe-Trp validated for HCC prevention and detection	GCA (increased) and Phe-Trp validated for HCC prevention and detection
9	Ikegami *et al*[30], 2016	Case Control	HCC (11)	Healthy	NASH	79	Serum	Increased PBA in NASH-HCC *vs* NASH	
10	Ressom *et al*[35], 2012	Prospective	HCC (78)	Cirrhosis	HCV	262 (165)	Serum		Metabolites of PBA are downregulated in HCC (GCDCA, GCA)
11	Xiao *et al*[34], 2012	Cross-Sectional	HCC (40)	Cirrhosis	HCV	89 (64)	Serum	GCA, GDCA increased	GCA, GDCA reduced
12	Banales *et al*[31], 2019	Cross-sectional	PSC (20), CCA (20), HCC (20)	Healthy	NA	80 (55)	Serum	GCA elevated in HCC *vs* control	
13	Patterson *et al* [38], 2011	Case Control	HCC (30)	Healthy (6), Cirrhosis (7), AML (22)	NA	53 (35)	Plasma	Fetal BAs increased in HCC *vs* AML	
14	El-Mir *et al*[39], 2001	Cross-sectional	HCC (27)	Cirrhosis (49), Viral Hepatitis (11), Liver Metastasis (19), Healthy (26)	NA	132 (91)	Urine		Increased Delta(4)- and/or allo-bile acids in urine
15	Changbumrung *et al*[30], 1990	Cross-sectional	CCA (25), HCC (75)	Healthy (21)	NA	121 (121)	Serum	Glyco-BA:Tauro-BA increased in	

								CCA and HCC *vs* control
16	Stepien *et al*[33], 2021	Case Control	HCC (233)	Healthy (233)	Any	466 (306)	Plasma	Increased total BAs and TC in HCC *vs* control

TBA: Total bile acids; CPBA: Conjugated primary bile acids; GCDCA: Glycochenodeoxycholic acid; CDCA: Chenodeoxycholic acid; GCA: Glycocholic acid; TDCA: Taurodeoxycholic acid; CA: Cholic acid; TC: Taurin-conjugated bile acids; GC: Glycin-conjugated bile acids; PBA: Primary bile acids; HCC: Hepatocellular carcinoma; CCA: Cholangiocarcinoma; T2DM: Type 2 diabetes mellitus; NASH: Non-alcoholic fatty liver disease; PSC: Primary sclerosing cholangitis; AML: Acute myeloid leukemia: MAFLD: Metabolic associated fatty liver disease; Phe: Phenylalanine; Trp: Tryptophane.

including the use of artificial intelligence and machine learning, may facilitate their meaningful clinical use to enhance patient care.

FOOTNOTES

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MINIREVIEWS

Approach to persistent ascites after liver transplantation

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Abstract

Persistent ascites (PA) after liver transplantation (LT), commonly defined as ascites lasting more than 4 wk after LT, can be expected in up to 7% of patients. Despite being relatively rare, it is associated with worse clinical outcomes, including higher 1-year mortality. The cause of PA can be divided into vascular, hepatic, or extrahepatic. Vascular causes of PA include hepatic outflow and inflow obstructions, which are usually successfully treated. Regarding modifiable hepatic causes, recurrent hepatitis C and acute cellular rejection are the leading ones. Considering predictors for PA, the presence of ascites, refractory ascites, hepatorenal syndrome type 1, spontaneous bacterial peritonitis, hepatic encephalopathy, and prolonged ischemic time significantly influence the development of PA after LT. The initial approach to patients with PA should be to diagnose the treatable cause of PA. The stepwise approach in evaluating PA includes diagnostic paracentesis, ultrasound with Doppler, and an echocardiogram when a cardiac cause is suspected. Finally, a percutaneous or transjugular liver biopsy should be performed in cases where the diagnosis is unclear. PA of unknown cause should be treated with diuretics and paracentesis, while transjugular intrahepatic portosystemic shunt and splenic artery embolization are treatment methods in patients with refractory ascites after LT.

Key Words: Liver transplantation; Liver transplantation complications, Ascites; Hepatic graft inflow obstructions; Hepatic graft outflow obstructions; Acute cellular rejection

Core Tip: Despite being relatively rare, persistent ascites after liver transplantation is associated with worse clinical outcomes. Therefore, it is of primary concern to promptly diagnose and treat modifiable causes of ascites. Early evaluation should include ultrasound with Doppler and diagnostic paracentesis. Common treatable causes include hepatic inflow and outflow obstruction, recurrent hepatitis C infection, and acute cellular rejection. Ascites of unknown cause should be treated with diuretics and paracentesis, while transjugular intrahepatic portosystemic shunt and splenic artery embolization can be used in patients with refractory ascites. The latter option represents a novel treatment modality with promising results.

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INTRODUCTION

Ascites represents the most common manifestation of decompensated cirrhosis[1]. About 5% to 10% of patients with compensated cirrhosis develop ascites annually[1]. The presence of ascites in a patient with cirrhosis is associated with a poor prognosis, as transplant-free survival is about 50% at 1 year and 20% after 5 years after decompensation[2,3]. Splanchnic arterial vasodilation secondary to nitric oxide that results in reduced effective circulatory volume and renal sodium retention is the principal cause of ascites formation in cirrhotic patients[4,5]. Portal hypertension and an increase in hepatic lymph formation also contribute to these complications of cirrhosis[4,5]. Liver transplantation (LT) is the best treatment option for patients with decompensated cirrhosis and ascites, as it induces resolution of ascites by reversing hemodynamic derangements and functional renal impairment. However, small to moderate ascites after liver transplantation is frequent in the early postoperative period and usually resolve within 2 to 4 wk after transplantation[5]. Persistent ascites after LT, commonly defined as ascites lasting more than 4 wk after LT, is an infrequent complication with a reported incidence of 5-7%[6,7]. Despite being relatively rare, it is associated with worse clinical outcomes, including higher morbidity and reduced 1-year survival[6,7].

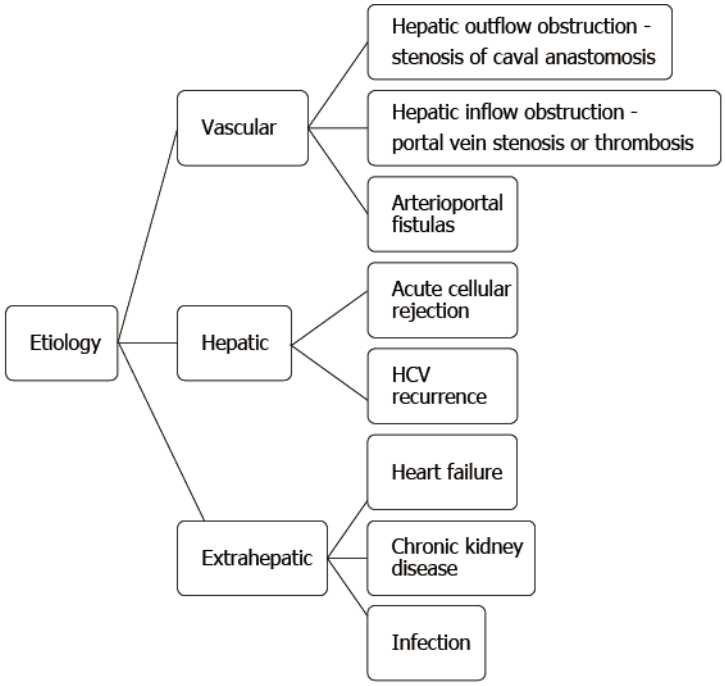
ETIOLOGY

The etiology of persistent ascites after LT can be divided into vascular, hepatic, and extrahepatic causes (Figure 1).

Vascular causes

Vascular causes of persistent ascites (PA) include hepatic outflow and inflow obstructions[8]. Inferior vena cava stenosis is a rare complication after LT, with a reported incidence of 1%[9]. This commonly iatrogenic complication is usually located at the anastomosis site or just superior to it[9]. According to the results of Cirera *et al*[6], the principal mechanism for massive ascites formation after LT is postsinusoidal portal hypertension secondary to hepatic vein outflow difficulty. In their work, from the hemodynamic data, the gradient between free hepatic vein pressure and right atrial pressure was significantly greater in patients who developed ascites than in patients who did not. However, ascites only was detected when the wedged hepatic venous pressure that mirrors sinusoidal pressure overcomes the threshold of 12 mmHg. Because evident stenosis or thrombosis in the studied population was detected in just 1 patient with ascites, hepatic vein outflow difficulty was probably due to a kinking of inferior caval vein or graft malposition. This explanation is supported by the resolution of ascites after reconstruction of caval anastomosis in some patients. Furthermore, in the same study, inferior vena cava preservation with the piggyback technique was performed more frequently in patients with PA after LT (72% *vs* 41%; $P = 0.01$)[6]. After analysis of these results, they changed the piggyback technique that previously included the origin of the left and medium hepatic veins to all three hepatic veins to ease venous graft drainage. Following this change, massive ascites in their patients have become extremely rare. The study by Nishida *et al*[10] confirmed that outflow obstruction due to stenosis of caval anastomosis is the cause of PA after LT, regardless of the type of vena cava anastomosis piggyback or caval anastomosis.

Portal vein stenosis and portal vein thrombosis are rare causes of PA after LT, with an incidence of 1%-2%[11]. Bonnel *et al*[12] showed that portal vein thrombosis after LT is more common in patients with prior PVT history. Hepatic artery to portal vein fistula is an infrequent complication after LT, and according to published case reports, patients with this type of vascular abnormality can present with ascites[8]. Arterioportal fistulas are associated with percutaneous transhepatic procedures such as



Risk factors	
Pretransplant	Perioperative
Ascites	Prolonged cold ischemic time
Refractory ascites	Spleen/graft ratio, graft recipient weight ratio
Hepatorenal-syndrome type 1	
Spontaneous bacterial peritonitis	
Hepatic encephalopathy	

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Figure 1 Etiology and risk factors of persistent ascites after liver transplantation.

percutaneous liver biopsies and percutaneous transhepatic cholangiograms with or without percutaneous biliary drain placement[13].

Hepatic causes

Acute cellular rejection with decreased liver vascular compliance during the rejection episode is one of the proposed mechanisms of ascites formation after LT[14,15]. This theory is supported by the results of the study by Gadano *et al*[16], where patients with severe acute rejection had a higher hepatic venous pressure gradient than those with moderate or mild rejection. Following the treatment of acute cellular rejection, ascites usually resolves[17].

Stewart *et al*[5] demonstrated that cirrhosis induced by hepatitis C as well as recurrent hepatitis C contribute to PA after LT. Based on histologic findings, most patients with recurrent hepatitis C and PA had cirrhosis or bridging fibrosis, well-known factors associated with portal hypertension and ascites. However, it should be emphasized that PA can develop in patients with recurrent hepatitis C without significant fibrosis[18-20].

In the study by Lan *et al*[18] among 173 hepatitis C virus (HCV) transplants, 18 patients (10%) developed posttransplant ascites, with two-thirds of ascites episodes occurring without significant fibrosis. In the retrospective study of 82 liver transplant recipients with HCV recurrence, 17% of patients developed refractory ascites, and in some patients, refractory ascites occurred in the absence of advanced fibrosis[19]. In the same study, positive cryoglobulinemia that was systematically tested (P = 0.02) and perisinusoidal fibrosis at 1 year (P = 0.02) were independently associated with posttransplant ascites[19]. These results indicate that liver microangiopathy is involved in the development of ascites in patients with recurrent HCV after LT. Nevertheless, this cause of PA will most likely become uncommon in the era of widespread use of direct-acting antivirals.

Considering pretransplant predictors for PA, the presence of ascites, refractory ascites, hepato-renal syndrome type 1, spontaneous bacterial peritonitis, and hepatic encephalopathy significantly influence the development of PA after LT[5,7,19]. Male sex was also found to be a strong risk factor for PA after LT[6]. However, data on sex as a risk factor for this complication are conflicting[18]. Factors associated

with the surgical procedure, such as cold ischemic (CI) time and size of the graft, contribute to PA after LT[5,21]. Several studies have shown that prolonged CI significantly influences PA development after LT[5,6,18]. Considering that CI time plays a significant part in the ischemic injury of the liver that primarily damages sinusoidal endothelium and results in increased hepatic resistance, PA can be expected if CI is prolonged[17,18]. A retrospective study involving 439 patients after living donor liver transplantation found that recipient spleen to graft volume ratio > 1.3, left lobe graft and graft recipient weight ratio < 0.8 were risk factors for persistent massive ascites after LT[22]. In the same study, pretransplant serum creatinine > 1.5 mg/dL and more than 1000 mL ascites at laparotomy were also risk factors for PA after LT. These five perioperative risk factors were used to develop the clinical scoring system (range from 0 to 7) for predicting PA after LT. Based on their internal validation, a cut-off of 4 points might be used as decision-changing, but only in cases of liver donor transplantation[22]. Finally, based on published case reports, PA after LT can occur due to sinusoidal obstruction syndrome, or it can be tacrolimus-induced[23,24].

Extrahepatic causes

The workup of patients with PA after LT should be directed to exclude extrahepatic causes of ascites, such as heart failure, chronic renal disease, malignancy, or infection[17]. Finally, the etiology of PA after LT can remain unknown. One hypothesis is that this type of ascites result from persisting collateral circulation and large splanchnic blood volume resulting from a disproportion between portal venous blood volume and liver uptake[25-27].

PROGNOSIS

The major negative impact of persistent ascites after LT is reduced patient survival[7,18]. In a retrospective study including 585 patients, PA was associated with reduced 1-year survival (92.3% *vs* 75.8%, $P = 0.05$)[7]. Nishida *et al*[10] showed that the mortality rate was nearly 8.6 times higher in patients with refractory ascites after LT while it was ongoing. However, the additional risk of death disappeared if the refractory ascites disappeared. In the same study, patients with an unknown reason for refractory ascites after LT had a significantly higher rate of RA disappearance[10]. Furthermore, persistent ascites after LT is associated with renal impairment, increased incidence of peritonitis and prolonged hospitalization[6].

EVALUATION

Blood analysis should be performed to evaluate liver and renal function, including complete blood cell counts, liver enzymes, albumin level, immunosuppressant level, and renal parameters. There should be a low threshold to evaluate for viral causes, primarily hepatitis C, due to relatively high incidence and available treatment options. In cases where cardiac etiology is clinically possible, N-terminal pro B-type natriuretic peptide (NTproBNP) level should be measured. The next step should be a diagnostic paracentesis, primarily to evaluate for infections such as bacterial peritonitis. A serum to ascites albumin gradient should be determined. However, its use for the assessment of portal hypertension is limited in post-transplantation settings[17].

As proposed earlier, the next step in the evaluation should be an ultrasound of the abdomen with included Doppler to assess for mechanical obstructions (vascular pathology). During the examination, it is recommended to measure liver graft and spleen size and calculate spleen to graft volume ratio as it might influence the treatment modalities, depending on the final diagnosis[8,17,28]. Angiography and invasive hemodynamic evaluation should be performed as a confirmation method for suspected mechanical obstruction[8]. In most common cases of hepatic vein stenosis, an invasively measured gradient greater than three mmHg is considered significant[8,29]. An echocardiogram should be done when a cardiac cause is suspected or in cases of elevated NTproBNP levels.

A percutaneous or transjugular liver biopsy should be per-formed in cases where the diagnosis is unclear, when there is a high probability of rejection, or when the presence of hepatitis and fibrosis should be assessed[8,17]. Despite both available options, in our opinion, the transjugular approach is more relevant due to the additional information regarding invasive pressure gradients[8,10,30].

TREATMENT

As aforementioned, the etiology of PA can be divided into vascular, hepatic, and extrahepatic. That being said, the primary goal of therapy should be directed toward the initial cause when one is known and it is modifiable. However, during diagnostic evaluation or when the cause of PA is unknown, the treatment approach to ascites after LT should follow the same principles as those in the pretransplant

Table 1 Overview of etiology, diagnosis, and treatment options for persistent ascites after liver transplantation

Etiology		Diagnosis	Treatment option[1]
Vascular	Hepatic outflow obstruction	Ultrasound of the abdomen with Doppler; Angiography and invasive hemodynamic evaluation	Balloon angioplasty +/- stent implantation; Surgical reconstruction
	Hepatic inflow obstruction		
	Arterioportal fistulas		
Hepatic	Acute cellular rejection	Evaluate liver function; Biopsy	Modify immunosuppressive therapy
	HCV recurrence	HCV serology; Biopsy	Antiviral drugs
Extrahepatic	Heart failure	NTproBNP; Echocardiogram	Treatment according to specialist recommendations
	Chronic kidney disease	Evaluate kidney function; Ultrasound	
	Infection	Paracentesis; Determine site of the infection	Antibiotics
Unknown cause or refractory ascites		Preform all above mentioned diagnostic procedures	Transjugular intrahepatic portosystemic shuntSplenic artery embolization[2]

[1]All patients should be treated with diuretics, antimineralocorticoid drugs or furosemide, in conjunction with a moderate restriction of sodium intake.
[2]Consider splenic artery embolization as the first treatment option when the initial spleen to liver volume ratio is > 0.5.
HCV: Hepatitis C virus; NTproBNP: N-terminal pro B-type natriuretic peptide.

setting. Patients with moderate ascites should be treated with diuretics, anti-mineralocorticoid drugs or furosemide, in conjunction with a moderate restriction of sodium intake[4]. Large-volume paracentesis followed by plasma volume expansion is indicated in patients with large ascites or the case of refractory ascites[4]. Transjugular intrahepatic portosystemic shunt (TIPS) and splenic artery embolization (SAE) are treatment methods in patients with refractory ascites of unknown cause after LT. In a retrospective study by Saad *et al*[31], transplantation did not pose a technical challenge to TIPS creation. However, data on TIPS success in managing refractory ascites after LT are variable[31]. Nevertheless, most studies report 16% to 58% success, which is lower than in the pretransplant population[8]. This lower success of TIPS after LT can be due to the different pathophysiology of ascites after LT[8].

SAE is an emerging option for the treatment of PA after liver transplantation. The procedure itself has been widely used in multiple pathologies, including hematologic disorders and splenic trauma, just as in settings of chronic liver disease[32-34]. The idea behind the procedure is to cause a splenic infarction, which leads to decreased flow through the spleen with a consequent reduction in portal vein flow, portal pressure and hepatic congestion[28,35,36]. Based on published reports, the procedure is effective when the initial spleen to liver volume ratio is > 0.5[28,35,37,38]. Efficacy of the SAE can be almost immediately observed as the reduction in portal vein velocities. The procedure is considered relatively safe. In the largest report presented by Presser *et al*[38], only 1 of 54 patients developed post-splenectomy syndrome. However, severe complications have been described, including splenic abscess and perforation or pancreatitis[35]. It has been recommended to perform proximal rather than distal SAE, as it induces a reduction of the flow while allowing distal revascularization, minimizing the risk of complications[8].

Vascular complications causing stenosis are considered completely curable when diagnosed and treated promptly[17]. The most common of those, stenosis of the hepatic vein, is easily treated with plain balloon angioplasty. Successful procedure results in immediate resolution of pressure gradient followed by early clinical resolution of ascites[8,29]. However, a stent should be placed in cases who are irresponsive to balloon angioplasty or those who develop "restenosis" due to recoil[39,40]. The procedure is safe without significant complications and can be performed irrespective of the type of surgical anastomosis made. The same approach is used in the case of portal vein stenosis with a similar success rate. A somewhat higher risk of primarily bleeding complications relates to the transhepatic approach. However, they can be successfully treated with embolization[41]. On the other hand, stenosis of the inferior vena cava is usually iatrogenic or connected to scar formation. Because of this, larger balloons with multiple inflations are needed to achieve adequate results. For the same reason, stent placement is more common than other types of stenosis[8].

Hepatic causes, including recurrent hepatitis C and acute cellular rejection, should be treated following the latest guidelines. In the case of peritonitis, empirical intravenous antibiotics should be started immediately as the prognosis of patients with bacterial peritonitis as a cause of ascites after LT is associated with poor outcomes[10]. A brief overview of etiology, diagnosis and treatment options is summarized in Table 1.

CONCLUSION

In summary, persistent ascites after LT is an infrequent complication associated with higher morbidity and mortality. The PA can result from vascular complications, or hepatic and extrahepatic diseases can cause it. The initial approach to the patient with PA should be directed to diagnose a modifiable cause and treat accordingly. If the etiology of PA remains unknown, treatment of ascites includes diuretics and paracentesis. TIPS or SAE should be offered when conservative treatment fails. TIPS in posttransplant settings is less effective for the treatment of ascites, while SAE is emerging as a potential alternative treatment option that is considered relatively safe.

FOOTNOTES

Author contributions: Ostojic A contributed to the literature review, analysis, and interpretation of the data, drafting of the initial manuscript, and final approval of the manuscript; Petrovic I, Silovski H, Kosuta I, and Sremac M contributed to the analysis and interpretation of the data, and final approval of the manuscript; Mrzljak A contributed to the conception and design of the manuscript, critical revised the initial manuscript, and approved the final manuscript.

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ORIGINAL ARTICLE

Case Control Study

Alcohol intake is associated with a decreased risk of developing primary biliary cholangitis

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Abstract

BACKGROUND

Primary biliary cholangitis (PBC) is a chronic progressive liver disease of unknown aetiology characterised by immune-mediated destruction of small and medium-sized intrahepatic bile ducts. There are few well-established risk factors and epidemiological studies are needed to further evaluate the pathogenesis of the disease.

AIM

To evaluate the relationship between alcohol intake, smoking and marijuana use with PBC development.

METHODS

We conducted a prevalent case control study of 200 cases and 200 age (within a five year age band) and sex-matched controls, identified from the Victorian PBC prevalence study. We assessed lifetime alcohol intake and smoking behaviour (both tobacco and marijuana) prior to PBC onset and used conditional logistic regression for analyses.

RESULTS

Alcohol intake consistently showed a dose-dependent inverse association with case status, and this was most substantial for 21-30 years and 31-40 years (P_{trend} < 0.001). Smoking was associated with PBC, with a stronger association with a longer duration of smoking [*e.g.*, adjusted OR 2.27 (95%CI: 1.12- 4.62) for those

who had smoked for 20-35 years]. There was no association between marijuana use and PBC.

CONCLUSION
Alcohol appears to have an inverse relationship with PBC. Smoking has been confirmed as an environmental risk factor for PBC. There was no association between marijuana use and PBC.

Key Words: Primary biliary cholangitis; Autoimmune liver disease; Epidemiology; Alcohol

Core Tip: Given the paucity of knowledge regarding the aetiology of this disease and that there are likely to be other environmental and lifestyle factors yet to be identified that are related to disease development, we designed this study to address the association of primary biliary cholangitis and lifestyle factors. We have identified, from a case control study, that alcohol intake is associated with a decreased risk of developing primary biliary cholangitis. This is a significant finding in a disease for which very little is known regarding its aetiology.

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INTRODUCTION

Primary biliary cholangitis (PBC) is a chronic progressive liver disease of unknown aetiology characterised by immune-mediated destruction of small and medium-sized intrahepatic bile ducts. It predominantly affects women in the fourth or fifth decade of life. The aetiology of PBC remains largely unknown but is thought to involve a complex interaction between genetic and environmental factors. Genetic factors are considered to play a role in disease onset due to higher concordance rates in monozygotic than dizygotic twins[1], and population studies that have shown higher incidence in first degree relatives of those with PBC[2]. Recurrent urinary tract infections[2-5] and smoking[2,3,5,6] have been the only risk factors that have been found to be consistently associated with disease development. However, these environmental factors combined appear insufficient to explain the pathogenesis, and it is likely that other environmental factors play a role in disease onset.

In this population-based case-control study, we examined whether alcohol intake, smoking tobacco and marijuana use were associated with the development of PBC.

MATERIALS AND METHODS

Participants

Cases: Cases were diagnosed with either definite or probable PBC. Definite PBC was defined as the presence of liver histology compatible with PBC, cholestatic liver function tests (elevation of serum alkaline phosphatase), and an anti-mitochondrial antibody titre of at least 1:40. Probable PBC was defined as patients fulfilling two of these three diagnostic criteria.

All gastroenterologists in the Australian state of Victoria were sent letters notifying them of the study and inviting them to ask their patients to participate. In addition, cases identified from the Victorian PBC prevalence study[7] were invited to participate (response rate 91%, 160/176). In total, 205 cases were recruited for this study, of which 200 were included in the final analysis. Three cases were excluded as they were not living in Victoria at the time of the study. Two cases were excluded as their histology revealed features of PBC/autoimmune hepatitis overlap syndrome.

Controls: Age and sex-matched controls were recruited from the electoral roll (12%) and *via* an advertisement in Victorian newspapers and community-based websites (88%). The latter was utilised because the electoral role alone was unsuccessful in obtaining the required number of controls. Potential participants from the electoral roll were sent a letter of invitation and a consent form. Participants who responded to advertisements were sent a copy of the consent form prior to the appointment being made. Subjects were screened *via* telephone for a history of any liver disease, and seven potential

participants were excluded for this reason. Two hundred controls were recruited for this study. Controls were matched 1:1 to the cases based on sex and age (within a 5-year age band) and linked by their grouping identification number for statistical analysis. French JA and Ng J conducted all interviews and measurements between 01 January 2015 and 31 October 2017.

Measures of alcohol intake

Pre-onset alcohol behaviours were queried by questionnaire, including frequency of alcohol intake per week (didn't drink at all, < 1 d/wk, 1-2 days per week, 3-4 days per week, 5-7 days per week) as well as an average number of drinks per session (didn't drink, 1-2 drinks, 3-4 drinks, ≥ 5 drinks) over the age periods 16-20 years, 21-30 years and 31-40 years. The frequency and average number of drinks were combined by using the mid-point value of each category and multiplying the two values to estimate average number of drinks consumed per week; these were categorised as 0, 1-5, 6-10, 11-20, and > 20 drinks/wk. A standard drink was defined as 10 g of alcohol content. Cases who had been diagnosed during the defined age periods, as well as their linked controls, were not included in the analysis of that specific age period or age periods that followed.

Measures of smoking and marijuana use

History of smoking (never smoked, ex-smoker), age of commencement, quantity of cigarettes smoked, smoking duration, and periods of non-smoking were queried by questionnaire prior to PBC diagnosis. Controls were given the age of PBC diagnosis of their matched case. History of marijuana use (never used, ex-user and current user) and frequency of marijuana use was also queried.

Other measures

Participants had their height and weight measured, and their body mass index (BMI) calculated. The questionnaire also included country of birth, self-reported ethnicity, level of education completed, history of urinary tract infection (if yes, number of urinary tract infections and at what age), past surgical history, other medical comorbidities and personal, and family history of liver disease and autoimmune diseases.

Statistical analysis

Differences in categorical characteristics between cases and controls were evaluated by Chi-square test, while differences in continuous variables between cases and controls were evaluated by *t*-test.

The associations of alcohol intake with case status were evaluated by conditional logistic regression, estimating an odds ratio (OR). Adjusted models were adjusted for country of residence, education, vitamin D supplement use, and smoking status. Further adjustment for current alcohol intake was undertaken to assess whether pre-onset alcohol associations were independent of subsequent alcohol behaviour, as these can be correlated. Tests for interactions were undertaken by including a product term of the predictor and interaction term. All analyses were done using STATA/SE 15.0 (StataCorp, College Park, TX, United States).

RESULTS

There was a female to male ratio of 10.8:1 and the mean age was 63.6 years for cases and 61.5 years for controls (Table 1). Average BMI was in the overweight range for both groups.

As would be expected given matching, there were no significant differences between cases and controls in either age or sex. As is typical for control groups, controls had a higher proportion with a higher educational level ($P < 0.001$), and they were more likely to be Australian-born ($P < 0.001$). Therefore, models were adjusted for educational level and whether the participant was born in Australia. There was no difference in ethnicity between cases and controls (Table 1). The mean time from PBC diagnosis to time of study was 12.6 years.

Alcohol intake

Alcohol intake, both frequency per week and average number of drinks per session, was significantly lower amongst cases throughout their life course. Alcohol intake consistently showed a dose-dependent inverse association with case status, which was strongest for the 21-30 age group and 31-40 age group ($P_{trend} < 0.001$) (Table 2). PBC cases were also more likely to be non-drinkers (age group 21-30 years: OR 5.05 (95%CI: 2.53-10.09), age group 31-40 years: OR 3.64 (95%CI: 1.34-9.90), persisting on adjustment. The inverse associations between alcohol intake and case status remained upon adjustment for alcohol intake at the time of questionnaire, demonstrating that pre-onset alcohol intake is independently associated with PBC development. For patients with PBC and cirrhosis at the time of the analysis, the pre-PBC alcohol intake in each 10-year band for both total drinks per week and drinks per session did not impact Child-Pugh score at the time of analysis (Supplementary Tables 1 and 2).

Table 1 Cohort characteristics of cases and controls

	Controls (*n* = 200)	Cases (*n* = 200)	Test for difference
Age, yr [mean (SD; range)]	61.5 (11.6; 29.1-95.1)	63.6 (11.6; 28.1-94.3)	*P* = 0.073
Sex			
Male	18 (9.0)	17 (8.5)	
Female	182 (91.0)	183 (91.5)	*P* = 0.86
Country of birth			
Australia	157 (78.5)	122 (61.0)	
Overseas	43 (21.5)	78 (39.0)	*P* < 0.001
Self-reported ethnicity			
Caucasian	180 (90.0)	175 (87.5)	
Asian	11 (5.5)	14 (7.0)	
Other	3 (1.5)	4 (2.0)	
Mixed race	1 (0.5)	0 (0)	
Unspecified	5 (2.5)	7 (3.5)	*P* = 0.75
Education completed			
Up to some secondary	3 (1.5)	18 (9.0)	
Yr 10/11	33 (16.5)	56 (28.0)	
Yr 12	21 (10.5)	26 (13.0)	
TAFE/Trade	32 (16.0)	43 (21.5)	
University	111 (55.5)	57 (28.5)	*P* < 0.001
Family history of PBC?			
No	200 (100.0)	194 (97.0)	
Yes	0 (0)	6 (3.0)	
BMI (kg/m^2) mean	26.8	27.1	*P* = 0.49

Results presented as *n* (%) unless otherwise specified. Differences in categorical terms between cases and controls assessed by Chi-square test. Differences in continuous terms between cases and controls assessed by *t*-test. Results in boldface denote statistical significance. Results in italics are *P* values. BMI: Body mass index; PBC: Primary biliary cholangitis; TAFE: Technical and Further Education.

Tobacco/marijuana

In the unadjusted analysis, smoking was significantly more common among cases, but the effect size reduced after adjustment [aOR1.42 (95%CI: 0.88-2.30)] (Table 3). The association was stronger for those who smoked for longer [aOR 2.27 (95%CI: 1.12-4.62) for those who had smoked for 20-35 years] [aOR 1.90 (95%CI: 0.68-5.30) for those who had smoked > 35 years].

In contrast to tobacco, there was no association with marijuana use and cases status, and this remained after adjustment for birthplace and educational level, as well as further adjustment for tobacco smoking. Small numbers precluded effective examination of the associations of the duration of marijuana use or the age of marijuana debut.

DISCUSSION

PBC is an increasingly common[7] potentially life-threatening cholestatic liver disease with a poorly defined aetiology. We identified a modest association with PBC for past smoking with an aOR of 1.42 (95%CI: 0.88-2.30), which did not quite reach significance. Our effect size is close to the pooled OR of 1.67 (95%CI: 1.4-1.92) identified in a meta-analysis of five case-control studies examining the association with PBC and smoking[8]. Importantly, our associations were stronger for those who smoked for longer [*e.g.*, aOR 2.27 (95%CI: 1.12- 4.62) for those who had been smoking for 20-35 years]. This was also the case in a study in the United Kingdom, where an OR of 3.5 (95%CI: 1.9-6.3) was found for those who smoked for 20 years or more[6]. A more robust way of assessing dose-response would be to measure the

Table 2 Odds ratios for primary biliary cholangitis and alcohol intake (frequency per week, drinks per session, drinker per week) for different age spans

	Controls, *n* (%)	Cases, *n* (%)	Univariable	Adjusted[1]	Further adjusted for current alcohol consumption
16-20 yr[2]					
Frequency per week					
Didn't drink	70 (35.5)	91 (46.2)	1.34 (0.84, 2.13)	1.36 (0.79, 2.35)	1.32 (0.74, 2.36)
< 1 d per week	71 (36.0)	68 (34.5)	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
≥ 1 d per week	56 (28.4)	38 (19.3)	0.65 (0.37, 1.15)	0.59 (0.31, 1.15)	0.71 (0.36, 1.43)
Trend			P = 0.015	P = 0.022	P = 0.088
Drinks per session					
Didn't drink	68 (35.4)	89 (46.1)	1.34 (0.81, 2.22)	1.28 (0.71, 2.31)	1.04 (0.55, 1.95)
1-2 drinks	67 (34.9)	63 (32.6)	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
≥ 3 drinks	57 (29.7)	41 (21.2)	0.61 (0.33, 1.15)	0.54 (0.26, 1.09)	0.46 (0.21, 0.99)
Trend			P = 0.010	P = 0.023	P = 0.055
Drinks per week					
Didn't drink	68 (35.4)	89 (46.1)	1.50 (0.95, 2.37)	1.53 (0.89, 2.62)	1.35 (0.76, 2.41)
1-5 drinks per week	87 (45.3)	79 (40.9)	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
≥ 6 drinks per week	37 (19.3)	25 (13.0)	0.67 (0.35, 1.27)	0.71 (0.35, 1.48)	0.85 (0.40, 1.82)
Trend			P = 0.014	P = 0.065	P = 0.26
21-30 yr[2]					
Frequency per week					
Didn't drink	19 (9.9)	64 (33.5)	3.11 (1.59, 6.08)	3.11 (1.42, 6.79)	2.81 (1.26, 6.29)
< 1 day per week	65 (33.9)	69 (36.1)	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
1-2 days per week	69 (35.9)	43 (22.5)	0.49 (0.27, 0.86)	0.48 (0.25, 0.92)	0.51 (0.26, 1.00)
≥ 3 days per week	39 (20.3)	15 (7.9)	0.26 (0.11, 0.57)	0.18 (0.07, 0.47)	0.22 (0.09, 0.57)
Trend			P < 0.001	P < 0.001	P < 0.001
Drinks per session					
Didn't drink	18 (9.6)	63 (33.9)	5.57 (2.76, 11.22)	4.81 (2.18, 10.65)	3.99 (1.76, 9.01)
1-2 drinks	102 (54.6)	67 (36.0)	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
≥ 3 drinks	67 (35.8)	56 (30.1)	1.03 (0.61, 1.77)	0.78 (0.41, 1.46)	0.89 (0.46, 1.71)
Trend			P < 0.001	P < 0.001	P = 0.003
Drinks per week					
Didn't drink	18 (9.6)	63 (33.9)	5.05 (2.53, 10.09)	4.77 (2.16, 10.53)	3.89 (1.73, 8.76)
1-5 drinks per week	98 (52.4)	75 (40.3)	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
6-10 drinks per week	47 (25.1)	37 (19.9)	0.86 (0.49, 1.53)	0.82 (0.42, 1.58)	0.84 (0.43, 1.65)
≥ 11 drinks per week	24 (12.8)	11 (5.9)	0.52 (0.23, 1.18)	0.31 (0.12, 0.83)	0.42 (0.15, 1.14)
Trend			P < 0.001	P < 0.001	P = 0.001
31-40 yr[2]					
Frequency per week					
Didn't drink	14 (9.2)	47 (31.1)	3.60 (1.28, 10.11)	3.60 (1.10, 11.81)	3.57 (1.09, 11.72)
< 1 day per week	49 (32.2)	52 (34.4)	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
1-2 days per week	53 (34.9)	35 (23.2)	0.56 (0.27, 1.18)	0.64 (0.28, 1.47)	0.69 (0.30, 1.60)

≥ 3 days per week	36 (23.7)	17 (11.3)	0.28 (0.11, 0.70)	0.29 (0.10, 0.84)	0.36 (0.12, 1.08)
Trend			$P < 0.001$	$P < 0.001$	$P = 0.002$
Drinks per session					
Didn't drink	13 (8.8)	46 (31.1)	5.12 (1.92, 13.67)	4.48 (1.48, 13.59)	3.94 (1.27, 12.27)
1-2 drinks	94 (64.0)	71 (48.0)	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
≥ 3 drinks	40 (27.2)	31 (21.0)	0.85 (0.42, 1.73)	0.71 (0.33, 1.55)	0.81 (0.36, 1.81)
Trend			$P = 0.002$	$P = 0.006$	$P = 0.034$
Drinks per week					
Didn't drink	13 (8.8)	46 (31.1)	3.65 (1.34, 9.91)	3.51 (1.13, 10.93)	3.00 (0.95, 9.54)
1-5 drinks per week	78 (53.1)	72 (48.7)	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
6-10 drinks per week	38 (25.9)	18 (12.2)	0.37 (0.15, 0.89)	0.38 (0.14, 1.01)	0.39 (0.15, 1.03)
≥ 11 drinks per week	18 (12.2)	12 (8.1)	0.51 (0.19, 1.38)	0.48 (0.16, 1.40)	0.66 (0.20, 2.15)
Trend			$P < 0.001$	$P = 0.001$	$P = 0.008$

Associations with case status assessed by conditional logistic regression, grouped on the linkage identifier for matched cases and controls.
[1]Adjusted models adjusted for whether participant was born in Australia, education completed, and whether participant had ever smoked.
[2]Cases (and their linked controls) who had been diagnosed prior to each age span were excluded from analysis, including 1 case/control pair for 16-20 yr, 8 case/control pairs for 21-30 yr, and 47 case/control pairs for 31-40 yr.
PBC: Primary biliary cholangitis.

history of smoking in pack years, which, unfortunately we were not able to perform in our study. We did not identify an association with marijuana use and the development of PBC.

This is the first study that has thoroughly evaluated the intake of alcohol in PBC cases from adolescence until the age of PBC diagnosis. Surprisingly, we found that alcohol has an inverse association with the development of PBC. Our study found that cases reported significantly less alcohol intake prior to PBC onset with dose-response associations, and compared to controls, cases were more likely to report that they never drank. For example, by age 21-30 years, a third of the cases said they never drank, and this was true for only 10% of the controls aOR 3.93 (95%CI: 1.74-8.89). Our associations remained after adjustment for country of birth, education level, and smoking, and remained after a further adjustment for current alcohol intake. The big question is whether this is a true finding or whether this could have resulted from recall bias due to the stigma surrounding the intake of alcohol. Those with established liver disease may be even more likely to underreport alcohol intake prior to disease onset. However, if this is a true observation, it has important implications with respect to modifiable risk factors.

There is minimal data in the literature on the association between alcohol and PBC. There have only been two previous case-control studies where this has been evaluated and alcohol was not the primary outcome measure in either of these studies. Gershwin *et al*[2] found no significant difference in alcohol intake between 1032 cases and 1041 controls when they evaluated those who had consumed ≥ 12/wk standard drinks over a lifetime. However, as this is a very rudimentary measure of lifetime alcohol intake, a more detailed lifetime assessment of alcohol intake is required to evaluate this further. They also found that 28% of prevalent cases were likely to have had ≥ 12/wk standard drinks in the year prior to interview compared with 50% of controls (unadjusted $P < 0.0001$)[2]. However, it is difficult to make a meaningful assessment of this data, as the alcohol intake period was after disease onset, where cases would have been advised to minimise alcohol intake.

Prince *et al*[3] compared data from more than 2400 controls with two groups of prevalent PBC cases; cases from a geographically defined epidemiology study (epidemiological cases $n = 318$) and from a survey of the national patient support group (foundation cases, $n = 2258$). They found that PBC cases from both groups were less likely to have regularly consumed alcohol over their lifetime compared with controls [OR 0.57 (95%CI: 0.39-0.83), OR 0.73 (95%CI: 0.61–0.79) for epidemiological and foundation cases respectively]. When males were excluded from the analysis, the significant difference did not persist for the foundation cases but did persist for the epidemiological cases[3]. Thus, there was a need for a more detailed study of alcohol intake prior to PBC onset.

Alcohol is thought to protect against autoimmune diseases such as rheumatoid arthritis[9,10], SLE[11,12], autoimmune thyroid disease[13], and Type I diabetes mellitus[14]. It has been suggested that moderate alcohol intake may have a protective effect on the immune system, compared with alcohol abuse or abstinence, and this may explain the protective effect on subsequent autoimmune disease development[13,15]. The mechanism as to how moderate alcohol prevents subsequent autoimmune disease development remains unclear. Potential mechanisms to explain the beneficial effects of

Table 3 Odds ratios for the association between tobacco and marijuana intake and primary biliary cholangitis development

	Controls (*n* = 200), *n* (%)	Cases (*n* = 200), *n* (%)	Univariable	Adjusted[1]	Adjusted[2]
Ever smoked tobacco prior to PBC diagnosis					
No	116 (58.0)	89 (44.5)	1.00 [Reference]	1.00 [Reference]	
Yes	84 (42.0)	111 (55.5)	1.73 (1.15, 2.59)	1.42 (0.88, 2.30)	
			P = 0.008	*P* = 0.15	
Age started smoking tobacco					
Never smoker	115 (57.8)	88 (44.2)	1.00 [Reference]	1.00 [Reference]	
10-15	19 (9.6)	24 (12.1)	1.66 (0.79, 3.47)	1.16 (0.49, 2.74)	
> 15-17	30 (15.1)	35 (17.6)	1.59 (0.87, 2.91)	1.15 (0.57, 2.31)	
> 17-19	19 (9.6)	26 (13.1)	1.66 (0.87, 3.16)	1.72 (0.79, 3.73)	
> 19-38	16 (8.0)	26 (13.1)	2.23 (1.10, 4.53)	2.16 (0.97, 4.83)	
Trend			*P* = 0.008	*P* = 0.022	
Years smoking tobacco prior to PBC diagnosis					
Never smoker	115 (57.8)	88 (44.2)	1.00 [Reference]	1.00 [Reference]	
0-10	28 (14.1)	23 (11.6)	1.15 (0.63, 2.09)	1.07 (0.54, 2.13)	
> 10-20	26 (13.1)	32 (16.1)	1.63 (0.89, 3.00)	1.18 (0.58, 2.38)	
> 20-35	22 (11.1)	41 (20.6)	2.46 (1.33, 4.55)	2.27 (1.12, 4.62)	
> 35-59.9	8 (4.0)	15 (7.5)	2.47 (1.01, 6.06)	1.90 (0.68, 5.30)	
Trend			*P* = 0.001	*P* = 0.018	
Ever smoked marijuana prior to PBC diagnosis					
No	184 (92.0)	179 (89.5)	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Yes	16 (8.0)	21 (10.5)	1.36 (0.68, 2.71)	1.45 (0.66, 3.20)	1.27 (0.56, 2.87)
			P = 0.39	*P* = 0.36	*P* = 0.56
Marijuana smoking status (constrained to starting smoking marijuana prior to PBC diagnosis)					
Never smoker	184 (92.0)	179 (89.5)	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Ex-smoker	16 (8.0)	19 (9.5)	1.21 (0.60, 2.46)	1.23 (0.55, 2.79)	1.10 (0.48, 2.55)
Current smoker	0 (0)	2 (1.0)	-	-	-

Associations with case status assessed by conditional logistic regression, grouped on the linkage identifier for matched cases and controls.
[1]Adjusted models adjusted for whether participant was born in Australia and education completed.
[2]Adjusted models adjusted for whether participant was born in Australia, education completed, and whether participant had ever smoked tobacco.
PBC: Primary biliary cholangitis.

moderate alcohol intake on the immune system function are; loss of natural killer cell activity[16], changes in immunoglobulin levels[17] and alterations in T helper 1 (Th1) and Th2 mediated immunity [18]. Thus, there is the possibility that alcohol could also be protective for PBC.

This study has several strengths. The demographic characteristics of our case cohort were similar to other published PBC cohorts in Europe[19], and the United States[2], and the participation rate of the cases was high (91%). Therefore, it is likely that our cohort is representative of other PBC populations worldwide. Our control group was matched on age (within a five-year band), and sex and was obtained from the same geographical location as cases. A limitation of our study is the selection of controls – only 12% were recruited from the electoral roll, our intended source of recruitment for all controls, but this was not possible due to this limited response to invitation. Another potential limitation of our study is possible measurement error due to respondents summarising their frequency and quantity of alcohol intake over 10 year age intervals (except for the four-year interval of 16-20 years old). It is also possible that fatigue, a symptom in up to 80% of PBC patients[20], was significant enough prior to diagnosis to reduce or even prevent alcohol intake in PBC cases.

CONCLUSION

Overall, we did not find that alcohol intake was a risk factor for PBC. Instead, we found that it was inversely associated, which raises the possibility that alcohol intake may be associated with a reduced risk of PBC, an important finding for a disease with few established risk factors. Due to the limitations of this study, this association requires replication in other PBC studies, preferably in cohort studies where the exposure is measured prior to disease onset.

ARTICLE HIGHLIGHTS

Research background

Primary biliary cholangitis (PBC) is a chronic progressive liver disease of unknown aetiology characterised by immune-mediated destruction of small and medium-sized intrahepatic bile ducts. There are few well-established risk factors and epidemiological studies are needed to further evaluate the pathogenesis of the disease.

Research motivation

Recurrent urinary tract infections and smoking have been the only risk factors that have been found to be consistently associated with PBC development. However, these environmental factors combined appear insufficient to explain the pathogenesis, and it is likely that other environmental factors play a role in disease onset.

Research objectives

To analyze environmental factors such as smoking, marijuana and alcohol use, and the role they play in PBC development.

Research methods

A prevalent case control study of 200 cases and 200 age (within a five year age band) and sex-matched controls, identified from the Victorian PBC prevalence study. The associations of alcohol intake with case status were evaluated by conditional logistic regression, estimating an odds ratio.

Research results

For PBC development alcohol intake consistently showed a dose-dependent inverse association with case status, and this was most substantial for 21-30 years and 31-40 years. Smoking was associated with PBC, with a stronger association with a longer duration of smoking while there was no association between marijuana use and PBC.

Research conclusions

Our study found that alcohol intake may be associated with a reduced risk of PBC, an important finding for a disease with few established risk factors.

Research perspectives

The association of alcohol and risk reduction of PBC requires replication in other PBC studies, preferably in cohort studies where the exposure is measured prior to disease onset.

FOOTNOTES

Author contributions: French JA, Gow P, Angus PW and van der Mei IAF conducted the research design; French JA conducted the data acquisition; French JA, Simpson-Yap S and van der Mei IAF conducted the data interpretation and all authors were involved with the manuscript preparation; French JA, Simpson-Yap S, Ng J, van der Mei IAF, Angus PW and Gow P approved the final submitted draft; Collins K assisted with submission; Nil other authors/institutions other than those listed were involved with this study; all authors have approved the final version of this manuscript, including the authorship list.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Positive autoantibodies in living liver donors

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Abstract

BACKGROUND

There is a nationwide shortage of organs available for liver transplantation. Living donors help meet this growing demand. Not uncommonly, donors will have positive autoantibodies. However, it is unclear whether donor positive autoantibodies are correlated with worse outcomes following living liver donor transplantations.

AIM

To analyze the significance of positive autoantibodies in donors on post-transplant outcomes in recipients.

METHODS

We performed a retrospective review of living liver donors who had undergone liver transplantation between January 1, 2012 and August 31, 2021. Demographic characteristics and pre-transplant data including antinuclear antibodies (ANA) and anti-smooth muscle antibody titers were collected in donors. Outcomes of interest were post-transplantation complications including mortality, biliary strictures, biliary leaks, infection, and rejection. Pediatric recipients and donors without measured pre-transplant autoantibody serologies were excluded from this study.

RESULTS

172 living donor liver transplantations were performed during the study period, of which 115 patients met inclusion criteria. 37 (32%) living donors were autoantibody-positive with a median ANA titer of 1:160 (range 1:80 to 1:1280) and median anti-SMA titer of 1:40 (range 1:20 to 1:160). There were no significant

differences in baseline demographics between the autoantibody positive and negative donors. Post-transplantation rates of death (P value = 1), infections (P value = 0.66), and overall rates of complications (P value = 0.52) were similar between the autoantibody positive and negative groups. Higher incidences of anastomotic strictures and rejection were observed in the autoantibody positive group; however, these differences were not statistically significant (P value = 0.07 and P value = 0.30 respectively).

CONCLUSION

Isolated pre-transplant autoantibody positivity is not correlated to worse post-transplant outcomes in living liver donor transplants.

Key Words: Antinuclear antibodies; Anti-smooth muscle antibody; Liver transplantation; Treatment outcome; Transplant donors

Core Tip: This was a retrospective study designed to analyze the significance of positive autoantibodies in donors on post-transplant outcomes in recipients in living donor liver transplantations. Post-transplantation rates of complications including mortality (P value = 1), infections (P value = 0.66), anastomotic strictures (P value = 0.07), and rejection (P value = 0.30) were found not to be statistically significant between the autoantibody positive and negative groups. These results suggest that isolated pre-transplant autoantibody positivity is not correlated to worse post-transplant outcomes in living liver donor transplants and should not preclude donors from donating.

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INTRODUCTION

There is a nationwide shortage of organs available for liver transplantation with more than 1700 patients dying annually while on the waitlist. Living donors help meet this growing demand. Of the 10109 liver transplantations performed in the United States in 2021, 568 were living-donor liver transplantations (OPTN, 2022).

Donors often undergo extensive screening prior to being approved. Transplant centers vary in their specific protocols for donor evaluation and selection, but general principles include ensuring that the donor has normal liver function and structure and is not a risk to the recipient with respect to disease transmission. It has been estimated that less than half of the candidates who complete transplant evaluation will be accepted for donation[1].

In the work-up of potential donors, positive autoantibodies are common and have been reported in up to 25% of healthy and asymptomatic individuals in the general population[2]. Positive autoantibodies are found in even higher prevalence in post-liver transplant populations with estimates ranging from 64%-80%[3-7]. Most studies evaluating autoantibodies in liver transplantations have focused on the significance of post-transplant positive autoantibodies, which have been correlated to the development of graft dysfunction, de novo hepatitis, and increased risk of death[4,6-10]. It is thought that the development of autoantibodies post-transplant represents a nonspecific marker of liver injury rather than a predictor of post-transplant outcomes[8,11].

In the liver transplantation literature, few studies have evaluated the effect of pre-transplant positive autoantibodies on graft outcomes. While traditionally graft rejection has been associated with antibodies specific to organ donor HLA, there is mounting evidence supporting the association of non-HLA antibodies with rejection and decreased graft survival in kidney, heart, and lung transplantations[12,13]. It is hypothesized that tissue damage associated with ischemia-reperfusion, vascular injury, and rejection creates permissive conditions for autoantigens and allows for autoantibodies to bind to antigenic targets to further cause vascular inflammation and organ dysfunction[14].

However, it is unknown if donor autoantibody positivity in liver transplants predisposes to increased rates of post-transplantation complications and whether it should preclude donors from donating. In our retrospective study, we aimed to analyze the significance of positive donor autoantibodies on recipient post-transplant outcomes in living liver donor transplantations.

MATERIALS AND METHODS

This was a retrospective study designed to compare post-transplantation outcomes between recipients who received transplants from positive autoantibody donors to those who received transplants from negative autoantibody donors. Data was collected by chart review. The study population consisted of patients that underwent a living liver donor transplantation between January 1, 2012 and August 31, 2021. Transplantations in recipients less than 18 years old and in those who received a transplant from a donor that did not have autoimmune markers checked during the pre-transplantation evaluation were excluded. Serum autoantibodies including antinuclear antibodies (ANA), antimitochondrial antibody (AMA), and anti-smooth muscle antibody (ASMA) were detected by indirect immunofluorescence. A positive antibody screen was defined by an ANA titer greater than or equal to 1:40 or anti-smooth muscle antibody greater than 1:20. Post-transplantation complications including rejection, biliary strictures, infection, post-transplantation lymphoproliferative disorder, bleeding, thrombosis, and portal vein stenosis were collected manually with chart review. Rejection was confirmed with a liver biopsy. The study was approved by our site's Institutional Review Board.

Statistical analysis

Differences among post-transplant liver recipient outcomes between positive and negative autoantibody groups were assessed by a Fisher's exact test to compare the dichotomous variables. Continuous variables were compared using independent unpaired *t*-tests. A Mantel-Haenszel chi-squared test with continuity correction was used to check for interaction between the cause of transplantation and post-transplant outcomes. Data analysis was performed with R statistical package, version 3.6.2.

RESULTS

Study population

During the study period, a total of 172 living donor liver transplantations were performed at our center (Figure 1). There were 20 pediatric recipients and 37 did not have donor autoantibodies checked during the pre-transplantation evaluation and were excluded. Of the remaining 115 individuals, 78 (68%) donors had no detectable autoantibody titers while 37 (32%) donors had a positive autoantibody titer including 23 with a positive ANA, 11 with a positive ASMA, and 3 donors with both a positive ANA and ASMA. As shown in Figure 2, the median ANA titer was 1:160 (range 1:80 to 1:1280). The median ASMA was 1:40 (range 1:20 to 1:160). No donors were found to have a positive AMA.

Recipient demographics

Baseline characteristics were similar between the patients in both groups (Table 1). 59 (51%) were female. 103 (90%) of the recipients were Caucasian, 6 (5%) were Hispanic, 4 (3%) were Black, and 2 (2%) were Asian. The average age of recipients was 51 ± 15 years. The average recipient body mass index at time of transplantation was 28 ± 6 and the average listed model for end-stage liver disease sodium of the recipients at time of transplantation was 14 ± 5.

Transplantation indications

Indications for transplantation were similar between groups and included malignancy 8 (7%), alcoholic cirrhosis 14 (12%), viral hepatitis 9 (8%), nonalcoholic steatohepatitis 36 (31%), autoimmune hepatitis 6 (5%), primary biliary cholangitis 4 (3%), and primary sclerosing cholangitis 21 (18%). Of the 6 (5%) recipients that had autoimmune hepatitis, 3 (3%) also had overlapping primary sclerosing cholangitis, and 1 (1%) had overlapping primary biliary cholangitis. The types of malignancies included metastatic colon cancer 3 (3%), cholangiocarcinoma 2 (2%), metastatic rectal cancer 1 (1%), hepatocellular cancer 1 (1%), and metastatic neuroendocrine cancer 1 (1%). Other less common causes for transplantation included biliary atresia 2 (2%), congenital hepatic fibrosis 2 (2%), cryptogenic 6 (5%), common variable immunodeficiency 1 (1%), cystic fibrosis 1 (1%), polycystic liver disease 2 (2%), sarcoidosis 1 (1%), telomere syndrome 1 (1%), and portal vein thrombosis 1 (1%). One recipient underwent a simultaneous liver-kidney transplant.

Immunosuppression regimens

Initial immunosuppressive regimens were similar for both groups. The standard immunosuppression protocol consisted of induction with thymoglobulin followed by the initiation of tacrolimus, mycophenolate, and prednisone. Mycophenolate was not started in 12 patients due to the development of bacteremia following transplant. Five were started on cyclosporine instead of tacrolimus due to a history of seizures or witnessed neurological changes after starting tacrolimus. One was switched from tacrolimus to cyclosporine after developing acute tubular necrosis requiring the initiation of hemodialysis. One individual was started only on prednisone as her liver donor was also her donor for her prior bone marrow transplant.

Table 1 Demographics and characteristics of living donor liver transplant recipients

	Recipients of transplants from autoantibody positive donors (*n* = 37), No. (%)	Recipients of transplants from autoantibody negative donors (*n* = 78), No. (%)	*P* value
Race/Ethnicity			0.61
Caucasian	33 (89)	70 (90)	
Hispanic	3 (8)	3 (4)	
Black	0 (0)	4 (5)	
Asian	1 (3)	1 (1)	
Gender			0.23
Male	15 (41)	39 (50)	
Female	22 (59)	39 (50)	
Cause for transplantation			0.11
Alcoholic cirrhosis	6 (16)	8 (10)	
Non-alcoholic steatohepatitis	16 (43)	19 (24)	
Hepatitis B	0 (0)	1 (1)	
Hepatitis C	4 (11)	4 (5)	
PSC	8 (22)	13 (17)	
PBC	1 (3)	3 (4)	
AIH	1 (3)	5 (6)	
With PBC	0	1	
With PSC	1	2	
AIH only	0	2	
Malignancy	0 (0)	7 (9)	
Other[1]	1 (3)	17 (22)	
Age at transplantation	55 ± 15	50 ± 14	0.13
Average BMI	28 ± 6	27 ± 6	0.22
Average MELD at transplantation	15 ± 5	14 ± 5	0.71

[1]Other includes biliary atresia 2 (2%), congenital hepatic fibrosis 2 (2%), cryptogenic 6 (5%), common variable immunodeficiency 1 (1%), cystic fibrosis 1 (1%), polycystic liver disease 2 (2%), sarcoidosis 1 (1%), telomere syndrome 1 (1%), and portal vein thrombosis 1 (1%). AIH: Autoimmune hepatitis; BMI: Body mass index; MELD: Model for end-stage liver disease; PBC: Primary biliary cholangitis; PSC: Primary sclerosing cholangitis.

Post-transplantation donor complications

As seen in Table 2, a total of 21 (18%) donors developed complications related to liver donation with the most common being symptomatic incisional hernias (6) and wound infections (6). Other less common complications of donation included chronic abdominal or incisional pain (3), portal vein stenosis requiring balloon angioplasty or an exploratory laparotomy (3), duodenal ulceration (1), pneumothorax requiring chest tube placement (1), and wound hematoma requiring exploratory laparotomy (1).

Post-transplantation recipient complications

Recipients were followed on average for 2.6 years with a standard deviation of 1.8 years. Acute rejection occurred in 21 (18%) individuals. Two (2%) developed plasma cell rich rejection. The remaining 19 (17%) developed acute cellular rejection. 15 individuals had a single episode of rejection, 5 had 2 episodes, and 1 had 3 episodes. Most of the episodes of rejection were mild (15) with fewer cases of mild-moderate (2), moderate (4), or severe (2). Acute cellular rejection occurred on average 7.3 mo after transplantation with a standard deviation of 10.1 mo and range of 6 days to 13.8 mo. Two had developed allograft rejection in the setting of medication non-adherence. All patients were admitted for episodes of rejection. Of the 21 patients that developed rejection, 17 were treated with 1000 mg of IV methylprednisolone followed by an oral prednisone taper and adjustment in their long-term immunosuppression regimen. One patient was treated with a prednisone and immunosuppression dose

Table 2 Donor complications in the Autoantibody Positive and Negative Groups

	Autoantibody positive (*n* = 37), No. (%)	Autoantibody negative (*n* = 78), No. (%)
Chronic abdominal or incisional pain	2 (5)	1 (1)
Diaphragmatic or incisional hernia		6 (8)
Duodenal ulcer		1 (1)
Pneumothorax requiring chest tube		1 (1)
Portal vein stenosis	1 (3)	2 (3)
Wound hematoma requiring exploration		1 (1)
Wound infection	2 (8)	4 (5)
Total	5 (14)	16 (21)

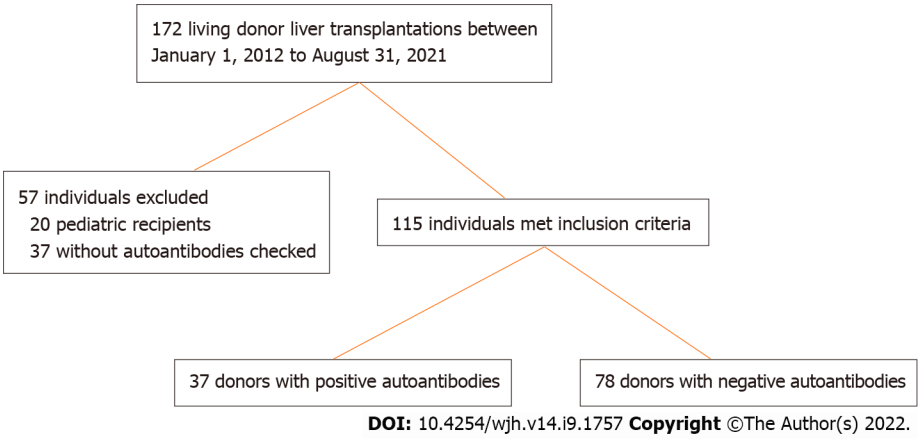

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Figure 1 Exclusion and inclusion criteria.

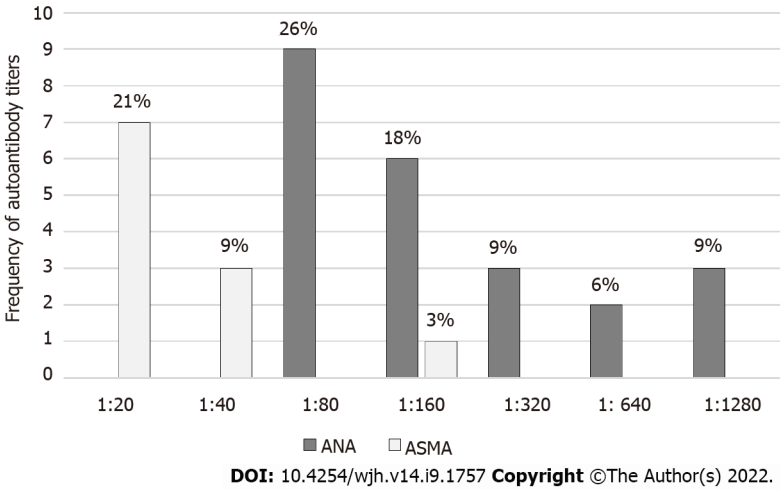

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Figure 2 Histogram of individual antinuclear antibodies and anti-smooth muscle antibody titers (Three donors had both a positive antinuclear antibodies and anti-smooth muscle antibody and are not included in the above histogram). ANA: antinuclear antibodies; ASMA: Anti-smooth muscle antibody.

increase, two were treated with lower doses of IV methylprednisolone, and one was switched to different immunosuppression agents. No patients included within the study timeframe developed chronic rejection.

Anastomotic biliary strictures developed in 48 patients (42%). Twenty-six (23%) recipients had strictures that resolved with serial ERCPs and stent placement. Sixteen (14%) underwent percutaneous transhepatic cholangiograms (PTHC). Six (5%) patients had recurrent episodes of biliary strictures

despite PTHC placement and required surgical revision of the biliary anastomosis with a Roux-en-Y heptaticojejunostomy. Four (3%) had cholangitis and 20 (17%) developed bile leaks.

Infections post-transplantation occurred in 32 (28%) of individuals. Twelve had developed cytomegalovirus and were treated with valganciclovir, 13 developed bacterial infections requiring intravenous antibiotics, 4 developed fungal infections, and 3 developed coronavirus disease 2019 (COVID-19) pneumonia.

Twelve (10%) recipients died following transplantation. Causes of death included septic shock (4), COVID-19 pneumonia (1), recurrent cirrhosis in the setting of medication non-adherence and pneumocystis jiroveii pneumonia (1), malignancy (3), intracranial hemorrhage (1), massive PE (1), and unknown (1). Of these, two recipients died during the index admission. The median length of survival of those who died was 1.3 years (range 4 d to 4.9 years).

A total of 26 recipients experienced other complications as shown in Table 3. These included gastric or bowel perforation (2), kidney rupture (1), and diaphragmatic hernia requiring urgent exploratory laparotomy (1), hematoma (2), splenic artery bleeding (1), splenic artery aneurysm (1), hepatic artery or portal vein thrombosis (9), hepatic artery or portal vein stenosis (4), portal steal syndrome (2), small for size syndrome (1), and post-transplant lymphoproliferative disorder (1). Four recipients required re-transplantation. Two had developed hepatic artery thrombosis, one developed portal vein thrombosis, and one developed ischemia.

Post-transplantation rates of death (P value = 1), infections (P value = 0.66), and any post-transplantation complication (P value = 0.52) were similar between the autoantibody positive and negative groups (Table 4). Higher incidences of anastomotic strictures (P value = 0.07) and rejection (P value = 0.30) were observed in the positive autoantibody group; however, these differences were not statistically significant.

DISCUSSION

The principal findings of this study are that positive autoantibodies commonly associated with liver disease in donors are not correlated to higher rates of complications including rejection or stricture development.

In lung, kidney, and heart transplants, various non-HLA antibodies have been associated to worse graft outcomes. Proposed mechanisms of injury include the induction of cell lysis *via* activation of the complement cascade upon antibody binding and tissue damage associated with ischemia-reperfusion, vascular injury, and rejection creates permissive conditions for autoantigens and allows for autoantibodies to bind to antigenic targets to further cause vascular inflammation and organ dysfunction. However, these findings have largely not been replicated in liver transplantations[14].

In a single center study in a pediatric population, ANA, ASMA, and angiotensin II receptor type-1 (AT1R) positivity was not associated with increased risk of fibrosis[15]. In a larger population consisting of adults, O'Leary *et al*[16] evaluated autoantibodies that had been previously correlated to worse outcomes in renal transplants including AT1R and endothelin type A receptor autoantibodies and found that these patients did not have an increased risk of rejection or fibrosis progression. In an autoimmune hepatitis population, Dbouk *et al*[9] found no difference in post-transplant outcomes between those with high and low antibody titers. Autoantibodies in living donor liver transplantations have also been studied and observed post-transplantation with several studies finding a high prevalence of autoantibody titers post-transplantation. It has been proposed that the development of autoantibodies post-transplantation represents a nonspecific marker of liver injury rather than a predictor of post-transplant outcomes[8,10,11]. Fewer studies have examined the effect of pre-transplant autoantibody titers in adults on post-transplant outcomes.

Our results corroborate and expand upon the existing body of literature. We did not find any significant difference in rates of mortality, post-transplantation infection, or overall rates of post-transplantation complications among the autoantibody positive and negative groups. Mortality rates following transplantation were low in both groups and largely did not appear to be related to graft dysfunction. Interestingly, higher incidences of anastomotic strictures (P value = 0.07) and rejection (P value = 0.30) were observed in the positive autoantibody group though these differences were not statistically significant. Overall, there was also no significant difference in rates of complications (P value > 0.05) when comparing higher and lower titers of autoantibody positivity suggesting that isolated autoantibody positivity in asymptomatic donor is not correlated to an increased rate of post-transplantation complications.

There is some data suggesting that autoantibodies are correlated to the development of *de novo* autoimmune hepatitis or plasma cell rich rejection. Autoimmune hepatitis has been estimated to recur in 17%-42% of patients post transplantation with a median time to recurrence of approximately 4.6 years [17]. In our experience, the 2 (2%) individuals that developed plasma cell rich rejection received livers from autoantibody negative donors. No recipients developed a reoccurrence of autoimmune hepatitis. Re-transplantation indications in our study were predominately related to thrombotic events.

Table 3 List of post-transplantation complications other than death, rejection, stricture, or infection

	Number of recipient complications in positive autoantibodies group, *n* = 37 (%)	Number of recipient complications in negative autoantibodies group, *n* = 78 (%)
Bowel perforation	0	1 (1)
Gastric perforation	1 (3)	0
Kidney rupture	0	1 (1)
Diaphragmatic hernia requiring urgent exploratory laparotomy	1 (3)	0
Intraabdominal hematoma	0	1 (1)
Retroperitoneal hematoma	1 (3)	0
Splenic artery bleeding	0	1 (1)
Splenic artery aneurysm s/p embolization	1 (3)	0
Hepatic and splenic vein thrombosis	1 (3)	0
Hepatic artery thrombosis	1 (3)	2 (3)
Hepatic artery stenosis	2 (5)	1 (1)
Hepatic artery-portal vein fistula s/p embolization	0	1 (1)
Portomesenteric thrombosis	0	1 (1)
Portal vein thrombosis	1 (3)	2 (3)
Portal vein stenosis	0	1 (1)
Portal vein thrombosis and stenosis, bleeding from exploratory laparotomy	0	1 (1)
Portal steal syndrome	1 (3)	1 (1)
Small for size syndrome	0	1 (1)
Post-transplant lymphoproliferative disorder	1 (3)	0
Total	**11 (30)**	**15 (19)**

Table 4 Comparison of recipient outcomes in those who received living liver transplants from autoantibody positive versus autoantibody negative donors

	Positive autoantibody (*n* = 37)	Negative autoantibody (*n* = 78)	Odds ratio (95%CI)	*P* value
Death	4 (11)	8 (10)	1.06 (0.22-4.31)	1
Strictures	20 (54)	28 (36)	2.09 (0.88-5.02)	0.07
Rejection	9 (24)	12 (15)	1.76 (0.58-5.16)	0.30
Infection	9 (24)	23 (29)	0.77 (0.28-2.02)	0.66
Other complications	11 (30)	15 (19)	1.77 (0.64-4.77)	0.24

The positive autoantibody group in this study consisted of those with positive ANA and ASMA. ANA is a nonspecific marker with estimated sensitivity and specificity of 0.65 and 0.75 for autoimmune hepatitis[18]. Up to 75% of ANA-positive individuals have no identifiable disease and ASMA can be present in up to 43% of normal healthy individuals, whereas AMA is estimated to be present in less than 1%17. None of the donors in our study were found to have a positive AMA, which would have been a more specific marker of disease. The presence of autoantibodies in healthy individuals is common with an estimated prevalence of 25%-28% in the general population[2,20]; however, the presence of an autoantibody does not necessarily indicate the presence of an autoimmune disease or its severity. The prevalence of pre-transplant autoantibodies in donors in our study was 34%, similar to that of the general population. In disease, autoantibodies are considered pathological although the mechanism in which they result in disease is poorly understood[19]. It remains unclear whether they are primary or secondary consequences of the underlying process. As none of the donors with positive autoantibodies in this study were found to have liver disease, it is possible that the autoantibodies in these individuals

are not pathogenic in of themselves.

Several limitations of our study must be acknowledged. This study was retrospective in nature and included a single center allowing a risk of type II error. Whether the results would be generalizable to a broader population would require a multi-center prospective study. Furthermore, due to the timeframe of the study, it is possible that some patients might develop strictures, rejection, or other complications that were not yet diagnosed over the duration of this study. The mean time to recurrence of autoimmune hepatitis has been reported to be 4.5 years, but may occur as early as 45 d after liver transplantation with the rate increasing with postsurgical interval. On average, patients were followed for 2.6 years following transplantation. In their study, Dbouk *et al*[9] examined the impact of age, race, sex, and autoimmune titer levels on recurrence rates or death, and found that African Americans were at a higher risk of, recurrence and death compared to other ethnic groups. Due to the predominantly Caucasian patient population skew in our cohort, we were unable to factor in race into our analysis. We also acknowledge that some donors were excluded due to lack of measurement of pre-transplant autoantibody titers. Despite this limitation, we believe our results provide a foundation for subsequent prospective multicenter studies.

CONCLUSION

In conclusion, we presented data on post-transplantation outcomes for 115 patients who received living liver donor transplants at our center. Patients were followed for an average of 2.6 years with patient survival of 90%. We found that patients who received transplants from autoantibody positive donors had similar rates of complications including strictures, death, and rejection to patients who received transplants from autoantibody negative donors. Our results expand upon existing literature suggesting that autoantibody positivity in asymptomatic donors is not correlated to worse transplant outcomes and should not preclude donation. Larger prospective studies with longer lengths of follow-up are needed to identify whether these results can be broadly applied to a wider population and whether other factors such as ethnicity or socioeconomic status may play a role in long-term transplantation outcomes.

ARTICLE HIGHLIGHTS

Research background

Positive pre-transplant autoantibodies in donors are common and of unclear significance. There is a lack of data on the significance of positive donor autoantibodies on post-transplant outcomes in living liver donor transplantations.

Research motivation

The donor pool for liver transplantations remains limited and living liver donors help bridge the gap. It is therefore important to know whether positive autoantibodies in living donors have an effect on post-transplant outcomes and whether they should pose a barrier to transplantation.

Research objectives

The objective of this study was to analyze the significance of positive autoantibodies in donors on post-transplant outcomes and complications in recipients including rates of mortality, mortality, biliary strictures, biliary leaks, infection, and rejection.

Research methods

This retrospective study included all patients above the age of 18 who underwent living liver donor transplantations at our center over a nine-year period (2012-20201). Demographic data and auto-antibody titers were collected and analyzed to determine if they were associated with worse post-transplantation outcomes, including higher rates of mortality, biliary strictures, biliary leaks, infection, or rejection.

Research results

Positive autoantibodies commonly associated with liver disease in donors were not correlated to higher rates of post-transplantation complications.

Research conclusions

Our results expand upon existing literature suggesting that autoantibody positivity in asymptomatic donors is not correlated to worse transplant outcomes and should not preclude donation in living donor liver transplantations.

Research perspectives

Larger prospective studies with longer lengths of follow-up are needed to identify whether these results can be broadly applied to a wider population and whether other factors such as ethnicity or socioeconomic status may play a role in long-term transplantation outcomes.

FOOTNOTES

Author contributions: Loh J designed, performed the research and analysis of the data and wrote the paper; Hashimoto K, Kwon CD, and Masato F helped with critical revisions of the study; Modaresi Esfeh J supervised, helped design the study, made critical revisions to the manuscript and gave final approval.

Institutional review board statement: This study was reviewed and approved by the Cleveland Clinic Foundation Institutional Review Board.

Informed consent statement: This study qualified by a Waiver of Informed Consent as determined by our hospital's IRB as it was a retrospective study that involved no more than minimal risk to the subjects, could be reasonably carried out without the waiver, and was not a threat to the rights or welfare of the subjects.

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ORIGINAL ARTICLE

Retrospective Study

Decrease in liver cancer incidence rates in Bamako, Mali over 28 years of population-based cancer registration (1987-2015)

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Abstract

BACKGROUND

Primary liver cancer is common in West Africa due to endemic risk factors. However, epidemiological studies of the global burden and trends of liver cancer are limited. We report changes in trends of the incidence of liver cancer over a period of 28 years using the population-based cancer registry of Bamako, Mali.

AIM

To assess the trends and patterns of liver cancer by gender and age groups by analyzing the cancer registration data accumulated over 28 years (1987-2015) of activity of the population-based registry of the Bamako district.

METHODS

Data obtained since the inception of the registry in 1987 through 2015 were stratified into three periods (1987-1996, 1997-2006, and 2007-2015). Age-standardized rates were estimated by direct standardization using the world population. Incidence rate ratios and the corresponding 95% confidence intervals (CI) were estimated using the early period as the reference (1987-1996). Joinpoint regression models were used to assess the annual percentage change and highlight trends over the entire period (from 1987 to 2015).

RESULTS

Among males, the age-standardized incidence rates significantly decreased from 19.41 (1987-1996) to 13.12 (1997-2006) to 8.15 (2007-2015) per 10^5 person-years. The incidence rate ratio over 28 years was 0.42 (95%CI: 0.34-0.50), and the annual percentage change was -4.59 [95%CI: (-6.4)-(-2.7)]. Among females, rates dropped continuously from 7.02 (1987-1996) to 2.57 (2007-2015) per 10^5 person-years, with an incidence rate ratio of 0.37 (95%CI: 0.28-0.45) and an annual percentage change of -5.63 [95%CI: (-8.9)-(-2.3)].

CONCLUSION

The population-based registration showed that the incidence of primary liver cancer has steadily decreased in the Bamako district over 28 years. This trend does not appear to result from biases or changes in registration practices. This is the first report of such a decrease in an area of high incidence of liver cancer in Africa. This decrease may be explained by the changes and diversity of diet that could reduce exposure to aflatoxins through dietary contamination in this population.

Key Words: Hepatocellular carcinoma; Hepatitis B infection; Aflatoxin; West Africa; Cancer registration; Annual percentage change

Core Tip: Epidemiology of liver cancer is limited in West Africa. This study investigated incidence trends of liver cancer over 28 years of the population-based cancer registry in Bamako, Mali. Findings showed a significant decrease in liver incidence rates in both males and females. This is the first study reporting a decrease in the incidence rates of liver cancer in an urban population in West Africa. Evidence points to a reduction of exposure to aflatoxin caused by lifestyle and dietary changes. The magnitude of this effect suggests that reduction of aflatoxin exposure may achieve major protective effects in West Africa.

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INTRODUCTION

Evidence shows that global trends of the incidence of primary liver cancer are undergoing contrasting changes in different parts of the world[1-5]. Primary liver cancer includes hepatocellular carcinoma (HCC), intrahepatic cholangiocarcinoma, and several rare forms of mesenchymal or lymphoid origin. Globally, HCC is by far the most common diagnosed liver cancer, representing 80%-90% of the cases in most regions, with the exception of defined regions of Southeast Asia where intrahepatic cholangiocarcinoma is predominant owing to infections by endemic liver flukes. Analysis of cancer registration data collected by Cancer Incidence in Five Continents (International Agency for Research on Cancer, IARC, CI5V-XI, and CI5plus) and the NORDCAN database revealed that the incidence of liver cancer between 1978 and 2012 in high-risk countries, mostly in Eastern and Southeastern Asia, remained high but decreased for the most recent period. In contrast, in low-risk countries, such as India and some countries in Europe, America, and Oceania, the incidence rate is rising[4].

A projection of the future burden of liver cancer in 2030 in 30 countries predicts an increase in the incidence rates in most countries, with the exception of some Asian countries (China, Japan, and Singapore) and European countries (Estonia, Czech Republic, and Slovakia) where declines in rates are foreseen[3,5]. Liver incidence rates in sub-Saharan Africa are high though data are scarce. Africans are more likely to develop liver cancer at a younger age and to be diagnosed at an advanced stage, resulting in poorer outcomes than in patients from countries with a high development index[6-9].

Worldwide, primary liver cancers are mostly HCC (> 90%)[10], and in West Africa it is the most fatal malignancy in males and the third most fatal malignancy in females[11]. The main risk factor is the synergistic effect of chronic infection by hepatitis B virus (HBV), which is endemic in these populations, and dietary exposure to the carcinogenic mycotoxin aflatoxin, a widespread contaminant of traditional diets[12-16]. In 2020 in West Africa, age-standardized rates (ASR) for liver cancer were estimated to range between 21.8 (Guinea) and 4.9 (Togo) ASR p-100000 persons[17,18] (Figure 1; https://gco.iarc.fr/). Recent changes in dietary patterns and lifestyles, in awareness and prevention of the main risk factors, and the introduction of neonatal and infant vaccination against HBV are raising expectations that the incidence of chronic liver diseases and liver cancer may significantly decrease in the coming years[9].

However, until now, the only two studies on trends of liver cancer in sub-Saharan Africa, in Uganda (Kyadondo) and in the Gambia have observed a relative stability or only a limited decrease in incidence rates among males, whereas among females a significant increase was observed[19,20]. Understanding the reasons for these variations is crucial for the correct interpretation of ongoing changes in the prevalence and population impact of the main risk factors for liver cancer in this region.

Population-based cancer registration is limited in Africa. Maintaining a registry in a low-resource context is complex from an operational viewpoint. Furthermore, variations in clinical procedures, in patterns of patient referral, and in diagnostic practices are often insufficiently documented, making it difficult to distinguish between biological effects and cancer registration biases when analyzing observed variations in incidence. Mali (Bamako district, also covering the city of Kati) and the Gambia (National cancer registry) are among the rare countries of the sub-region of West Africa to have operational population-based cancer registries. In this study, we have used cancer registration data accumulated over 28 years of activity of the population-based registry of the Bamako district to assess the trends and patterns of liver cancer by sex and age-groups.

MATERIALS AND METHODS

Study population

Cancer data from 1987 to 2015 of the cancer registry of the Bamako district, Mali were used. Mali (surface area: 1246238 km²) had an estimated population of 18343000 in 2016, with life expectancy of 60 years for females and 59 years for males[21]. Bamako district, the capital city, had a population estimated at 2529328 in 2019[22]. Mali is one of the poorest countries in the world. It has few resources for health care, and child and infant mortality rates are among the highest in the world. Education services are poorly developed, particularly at the primary level and in rural areas. The expected years of schooling in 2019 was 7.5 years. Despite improvements in medical care, Mali is still challenged by a lack of personnel, facilities, resources, and supplies. However, over the past 20 years, Mali has defined several policies that have served as a reference framework for all social and health development programs in order to strengthen the health system, to provide equitable access to health care, and to prevent, detect, and respond effectively to epidemics and public health emergencies[23,24].

The healthcare system in Mali comprises local community health centers delivering primary health care, secondary referral centers, six of which are located in the Bamako district and which provide specialized care in, among others, gynecology and obstetrics, general surgery, pediatrics, stomatology, and oto-rhino-laryngology, and tertiary referral centers represented by the three university hospitals of Mali, namely the hospitals of Point G and Gabriel Touré (both localized in Bamako city) and of Kati (15 km southeast of Bamako).

On behalf of the ministry of health, the regional cancer registry for the Bamako district created in 1987 was used to support cancer surveillance activities. It is an official authoritative source of information on cancer incidence and survival in Mali. Relevant policies, regulations, and laws are strictly implemented to guide the handling of information in cancer registries. These procedures protect the confidentiality and privacy of both cancer patients and healthcare professionals. After declassifying the patient information, with no identifiers for cancer patients, the regional cancer registry provides access to the data for researchers in the form of databases. This registry records information on cancer cases from all possible sources within the district of Bamako. Every month an active collection of all cases diagnosed in all medical services (public or private) in the Bamako district is recorded. Information is collected through pathology files, patient clinical files, hospital-based registries (such as chemotherapy, endoscopy, and surgery registries), and through death certificates managed by a non-governmental Malian organization, the Center for Information, Counselling, Care and Support for People Living with HIV/AIDS. After collection, all data are computerized using the software CanReg 4[25]. Tumors are coded according to the ICD-O third edition.

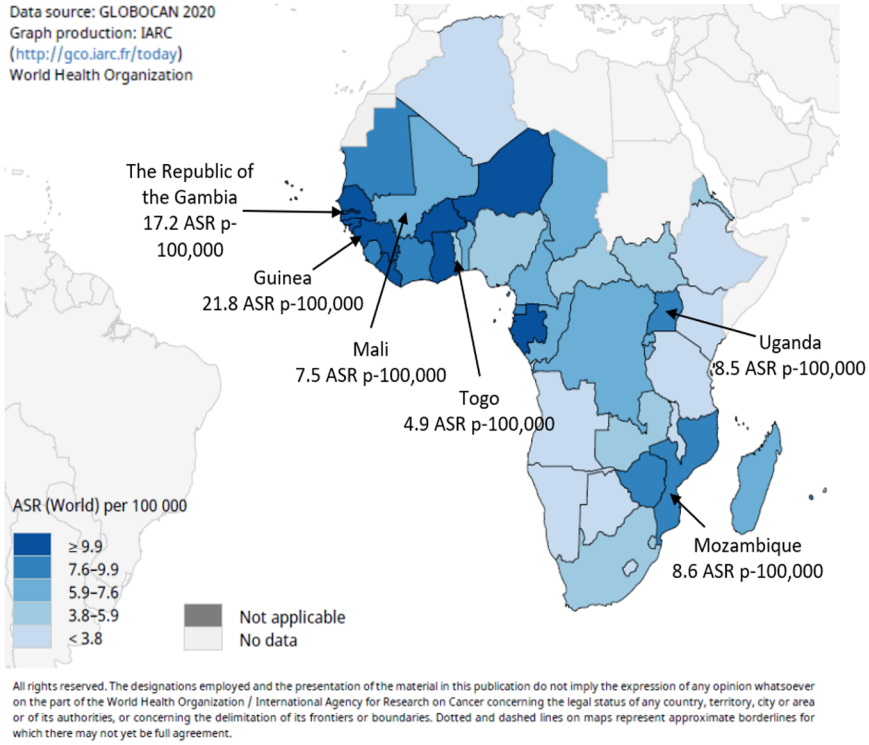

Figure 1 Estimated age-standardized rates (world) in 2020 for liver cancer in both sexes of all ages[17,18]. Figure produced with the help of the Global Cancer Observatory web site (International Agency for Research on Cancer, World Health Organization, http://gco.iarc.fr/today). ASR: Age-standardized rates.

Patients who were resident from locations outside of the Bamako district were excluded from the incidence data analyses. Bamako residents are defined as being in residence for the previous 3 mo in the district[26]. Demographic data for Bamako district in person-years (p-years) from 1987 to 2015 were obtained by the interpolation of data extracted from the national censuses of 1976, 1998, and 2009.

Statistical analysis and data modelling

ASRs were estimated by direct standardization, with rates adjusted to the world population by 5-year age groups. Incidence data were calculated for three arbitrarily defined periods: 1987-1996, 1997-2006, and 2007-2015. The incidence rate ratio (IRR) and the corresponding 95% confidence intervals (CI) were calculated using the early period as reference (1987-1996), using STATA software version 14 (College Station, TX, United States). Temporal trends over the whole period of 28 years were assessed using Joinpoint regression analyses [program version 3.3 (https://www.cancer.gov/joinpoint)]. Data for the year 2005 were excluded because of an apparent unexplained registration bias.

Liver cancer cases diagnosed by endoscopy were further excluded to avoid potential overestimation of liver cancer cases since endoscopy is not one of the standard methods for liver cancer diagnosis. As for most parts of Africa, Mali and the Bamako district have a population structure characterized by a strong representation of younger age groups, with only 2.5% of the population aged 65 years and over. This distribution causes a bias when evaluating incidence rates in the older age groups because of the small population denominators. Therefore, instead of expressing the age-specific rates per 100000, we modelled the expected number of cases in a standard population in which the age-specific rate is adjusted to the world standard population[27]. This approach minimizes the tendency to overestimate cancer incidence in older age groups and thus provides a more accurate picture of the distribution of common cancers across the different age groups. For the sake of comparison with liver cancer, we additionally analyzed the most frequent cancers (breast, bladder, stomach, prostate, and cervix uteri). All statistical tests were two-sided, and P values < 0.05 were considered statistically significant.

RESULTS

Characteristics of the cancer cases and liver diagnostic criteria

Table 1 shows the characteristics of the study subjects for all cancers and according to the three periods of diagnosis. From 1987 to 2015, the cancer registry of Bamako, Mali registered 19553 cancer cases including 8553 (44.0%) in males and 10950 (56.0%) in females. The median age of the study subjects at the time of cancer diagnosis was 49 years. Overall, diagnosis of all cancers was based on histopathology

Table 1 Characteristics of the cancer cases overall and according to the three periods of cancer diagnosis from the cancer registry of Bamako, Mali

Characteristics	Period			
	Overall	1987-1996	1997-2006	2007-2015
All cancer cases, *n* (%)	19553	3838	4681	11034
Males	8603 (44.0)	1942 (50.6)	2137 (45.6)	4524 (41.0)
Females	10950 (56.0)	1896 (49.4)	2544 (54.4)	6510 (59.0)
Age in year, median	49	48	49	50
Method for diagnostic of liver cancer, *n* (%)				
Biopsy/cytology	429 (26.3)	33 (5.7)	99 (18.9)	297 (55.6)
Clinical signs	422 (25.8)	265 (45.9)	112 (21.4)	45 (8.4)
Ultrasonography	418 (25.6)	128 (22.2)	169 (32.4)	121 (22.7)
Death registry	186 (11.4)	74 (12.8)	93 (17.8)	19 (3.6)
Unknown	178 (10.9)	77 (13.3)	49 (9.4)	52 (9.7)

for 58.2% of the cases in males and 70.2% in females, with an increase in this trend over the years.

There were 634 primary liver cancer cases (11.2% of the total cases) after exclusion of those diagnosed by endoscopy. The diagnosis of primary liver cancer mainly relied on the biopsy/cytology (26.3%), the classical triad of clinical signs (hepatomegaly, icterus, and ascites) (25.8%), and ultrasonography (25.6%). Diagnosis based on biopsy/cytology increased from 5.7% in the earlier period (1987-1996) to 55.6% in the later period (2007-2015), whereas diagnosis based only on clinical signs decreased from 45.9% in the earlier period (1987-1996) to 8.4% in the later period (2007-2015). A review of clinical bases of diagnoses at the two tertiary referral centers of Bamako city (Hospital Gabriel Touré; Department of Gastroenterology and Point G Hospital; Department of Internal Medicine) indicated that the most common clinical signs were hepatomegaly and icterus and the presence of ascites, and the main symptoms were pain, nausea, vomiting, and weight loss. Alpha-fetoprotein levels were ≥ 400 ng/mL in 45.0% of the cases.

Incidence rates and trends of liver cancer

Table 2 compares the incidence of the four most common cancers among males and females over the three periods. These cancers are liver, stomach, bladder, and prostate in males and liver, stomach, cervix uteri, and breast in females. In males, a total of 426 cases of liver cancers were diagnosed during the early period (1987-1996), representing 21.93% of all cancers compared to 378 cases in the middle period (1997-2006) (17.69%) and 405 cases in the later period (2007-2015) (8.95%). In females, the total number of liver cases diagnosed in the early period (1987-1996) was 151 (7.96% of all cancers) compared to 144 (5.66%) in the middle period (1997-2006) and 129 cases (1.98%) in the later period (2007-2015).

ASR for liver cancer significantly decreased over the three periods in both sexes. For males, rates dropped from 19.41 per 10^5 p-years for the period 1987-1996 to 13.12 for the period 1997-2006 [33% decrease; IRR: 0.67 (95%CI: 0.59-0.76)] and 8.15 for the period 2007-2015 [58% decrease over period 1987-1996; IRR: 0.42 (95%CI: 0.34-0.50)]. Among females, rates decreased from 7.02 per 10^5 p-years for the period 1987-1996 to 5.15 in the period 1997-2006 [27% decrease; IRR: 0.73 (95%CI: 0.56-0.91)] and 2.57 for the 2007-2015, representing a decrease of 63% compared to the period 1987-1996 [IRR: 0.37 (95%CI: 0.28-0.45)] (Table 2).

It is noteworthy that variations in incidence were also observed for several other common cancers in males and females over the entire registration period (Table 2). Namely, a significant increase was observed for prostate, breast, and cervical cancers. When comparing earlier (1987-1996) and later (2007-2015) periods, incidence rates of prostate and breast cancers increased by 2.57 and 2.99-fold, respectively. In contrast, rates of bladder cancer remained stable in males, whereas rates of stomach cancer showed a decrease of 33.0% and 38.0% in males and females, respectively.

Trend analyses of liver cancer covering the 28 years of registration data (encompassing the three periods) showed that incidence rates steadily and progressively declined in both sexes. The annual percentage change was -4.59 [95%CI: (-6.4)-(-2.7)] in males (Figure 2A) and -5.63 [95%CI: (-8.9)-(-2.3)] in females (Figure 2B). When analyzing age specific curves, we observed that for the three periods and for both sexes, curves were similar and showed peaks in approximately the same age group (Supplementary Figures 1 and 2).

Table 2 Comparison of the incidence (age-standardized rate) of the four most common cancers among males and females over three periods in Bamako, Mali from the cancer registry of Bamako)

Site	1987-1996			1997-2006			2007-2015			1997-2006 *vs* 1987-1996	2007-2015 *vs* 1987-1996
	Cases	ASR	%	Cases	ASR	%	Cases	ASR	%	IRR (95%CI)	IRR (95%CI)
	Males										
Stomach	287	16.86	14.78	416	19.24	19.47	583	11.36	12.89	1.14 (0.93-1.36)	0.67 (0.53-0.82)
Liver	426	19.41	21.93	378	13.12	17.69	405	8.15	8.95	0.67 (0.59-0.76)	0.42 (0.34-0.50)
Prostate	71	4.81	3.66	189	9.54	8.84	479	14.41	10.59	1.98 (1.30-2.67)	2.99 (1.99-4.00)
Bladder	159	8.49	8.19	158	6.13	7.39	357	8.10	7.89	0.72 (0.54-0.89)	0.95 (0.78-1.13)
	Females										
Cervix uteri	515	21.60	27.16	660	20.43	25.94	1732	35.54	26.61	0.95 (0.86-1.02)	1.64 (1.37-1.92)
Breast	236	10.16	12.45	421	13.03	16.55	1408	26.14	21.63	1.28 (1.01-1.56)	2.57 (2.10-3.05)
Stomach	206	10.23	10.86	286	11.34	11.24	447	6.17	6.87	1.15 (0.84-1.46)	0.62 (-0.23-1.48)
Liver	151	7.02	7.96	144	5.15	5.66	129	2.57	1.98	0.73 (0.56-0.91)	0.37 (0.28-0.45)

ASR: Age-standardized rate; CI: Confidence interval; IRR: Incidence rate ratio.

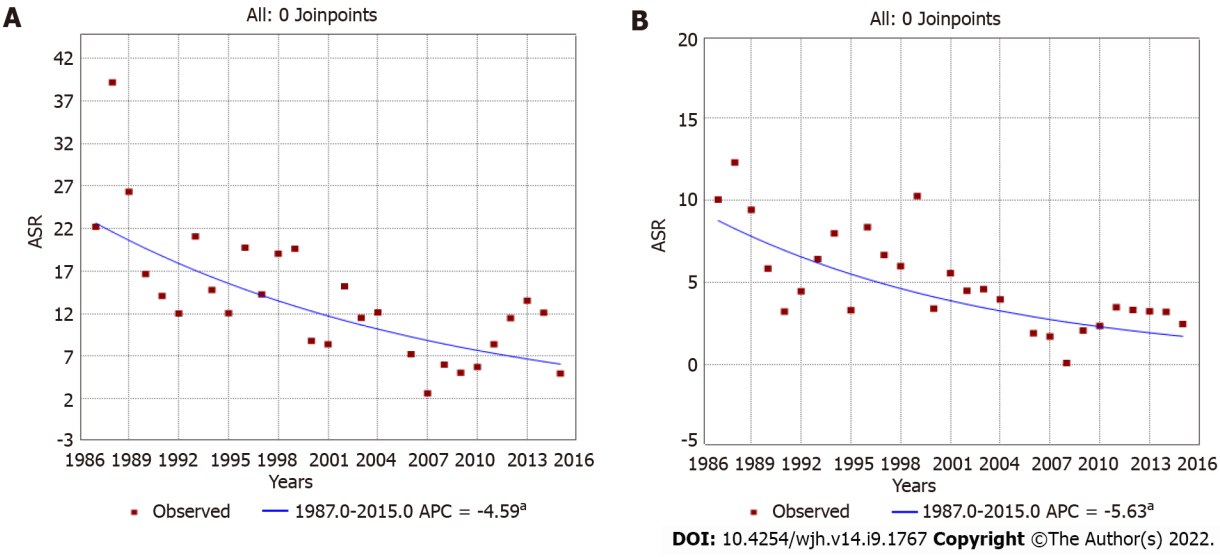

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Figure 2 Liver cancer incidence (age-standardized rate) trends over 28 years of cancer registration data in Bamako, Mali. [a]Indicates that the Annual Percent Change is significantly different from zero at the alpha = 0.05 level. Final Selected Model: 0 Joinpoints. A: Male; B: Female. ASR: Age-standardized rates.

DISCUSSION

In this study, we have analyzed data from the population-based cancer registry covering the district of Bamako over 28 years of registration (1987-2015) to assess trends in the incidence of liver cancer, one of the most common forms of cancer in the West African population. We have compared incidence rates over three defined periods, 1987-1996, 1997-2006, and 2007-2015. Over these periods, liver cancer showed a remarkable and progressive decrease in the ASR in both genders and in all age groups, with a significant annual percentage change of -4.59 among males and of -5.63 among females. Such a large reduction in incidence rate was not observed for other common cancers in the adult population of the district of Bamako. Notably, over the entire registration period, incidence rates for breast and prostate cancers significantly increased, a trend also observed in other West African countries[27,28] as well as globally in low-resource countries[29].

Factors such as westernized diet, urbanization, increasing awareness, and improved registration and diagnosis have been implicated, although their precise specific contributions are yet to be fully

established. In Mali, the fact that only liver cancer showed a strong and systematic decrease in incidence rate suggests that the decrease is not a bias caused by changes or discontinuity in cancer diagnosis or registration practices. A review of clinical practices indicated that clinical diagnosis and main symptoms for liver cancer have remained stable over the entire study period (28 years). Of note, the proportion of patients who received confirmation based on biopsy/cytology analysis substantially increased from 5.7% in 1987-1996 to 55.6% in 2007-2015. However, there is no evidence that the absence of biopsy/cytology analysis has been used as a criteria to exclude patients from registration. In this respect, it should be noted that registration for other cancers (stomach, prostate, bladder, cervix, and breast) did not show such an important decrease despite increased usage of biopsy/cytology analysis in diagnosis. Therefore, we suggest that increased usage of microscopy as a diagnostic tool cannot be considered as the main explanation for the observed decrease in liver cancer incidence.

Trends in liver cancer incidence rates show contrasting patterns across the world. In an analysis of the data collected between 1978 and 2012 from 42 countries worldwide (registry data from CI5 volumes V-XI, CIplus and NORDOCAN database), Petrick *et al*[4] found that incidence rates significantly increased in India, across the Americas, in Oceania, and in most European countries. On the other hand, incidence rates remained the highest in Eastern and Southeastern Asian countries, though the rates in those countries have been decreasing in recent years.

In the area of Qidong city, Eastern China, a dramatic reduction of liver cancer incidence has been seen in young adults over a period of 28 years (1980-2008)[30]. Qidong city is known as an area of very high liver cancer incidence associated with endemic HBV and high dietary exposure to aflatoxin. Overall, a 45% reduction in liver cancer incidence and mortality rates occurred among the Qidonese. Compared with 1980-1983, the age-specific liver cancer incidence rates in 2005-2008 significantly decreased 14-fold for ages 20-24, 9-fold for ages 25-29, 4-fold for ages 30-34, 1.5-fold for ages 35-39, 1.2-fold for ages 40-44, and 1.4-fold for ages 45-49 but increased at older ages[30]. Etiological interventions aimed at reducing risk factors for HBV have been developed in this area of China since the early 1980s, namely universal neonatal HBV vaccination (from 1980) and expanded access to commercial rice (controlled for low aflatoxin levels) instead of contaminated maize as the staple food (beginning in 1988).

Retrospective studies on the distribution of aflatoxin-albumin adducts in randomly selected subsets of serum collected during screening surveys between 1982 and 2009 revealed that median levels declined from 19.3 pg/mg albumin in 1989 to 3.6 pg/mg in 1995, 2.3 in 1999, 1.4 pg/mg in 2003, and undetectable (< 0.5 pg/mg) in 2009[31]. These results suggest that the dramatic decrease in incidence in this population is most likely due to reduction in aflatoxin exposure, whereas neonatal HBV vaccination may only have a limited impact since the vast majority of the subjects developing liver cancer during the period under consideration (1983-2008) were born before the start of universal HBV vaccination programs[30,31].

Available data on population-based cancer registries in Africa that have assessed liver cancer trends over a comparable period of time show a very different pattern to the one observed in Bamako, Mali. In the Gambia, a study on liver cancer trends from 1988 to 2006 has shown a small decrease among males during the period 1988-2006 (from 38.36 for the period 1988-1997 to 32.84 per 10^5 p-years in the period 1998-2006), while it clearly increased among females (from 11.71 for the period 1988-1997 to 14.9 p-years in the period 1998-2006) [annual percentage change: +3.01 (95%CI: 0.3-5.8)][20]. In the district of Kampala, Uganda, registration was initiated in 1960 but was interrupted between 1980 and 1991 due to the political context. The comparison between the periods before 1980 and after 1991 showed stability in the rate of liver cancer among males and an increase of more than 50% among females[19]. A reduction in the rate of liver cancer has been documented in a group of gold miners originating from Mozambique and working in South Africa. In this group, liver cancer incidence decreased from 80.4 per 10^5 p-years in 1964-1971 to 40.8 in 1972-1979 and 29.9 per 10^5 p-years in 1981[32,33]. However, in this later cohort, data were not population-based. To our knowledge, our observation of a dramatic decrease in the incidence of liver cancer in Bamako, Mali is not matched in any other African context.

Our observations based on the cancer registry of the Bamako district require cautious interpretation because of multiple possible bias that may affect cancer registration in low-resource contexts. A recent review of trends in the global epidemiology of liver cancer has highlighted the lack of data of sufficient quality in most parts of sub-Saharan Africa[4]. As underlined in our study, increased usage of biopsy/cytology confirmation has taken place over the study period and may have led to under-registration of cases for which this confirmation was not available. With all due caution, however, we consider that our observations on liver cancer in the Bamako district deserve to be documented in the literature. Of note, stomach cancer, which shares demographic and clinical signs that overlap with liver cancer (age-related incidence rates, signs and symptoms, and sex distribution) showed only small changes in incidence in the Bamako district during the study period[27]. Patients with stomach cancer are often diagnosed in the same medical services as those with liver cancer, and it could be expected that biases may equally affect the registration of both cancers.

In Qidong city, the liver cancer decrease was mainly due to a reduction in aflatoxin exposure[31]. In Mali, there is only limited information available on temporal variations in the prevalence of the main documented risk factors for HCC, namely chronic infection by HBV and exposure to dietary aflatoxins. A study of HBV chronic carriers in Bamako indicated that the incidence rate of chronic carriers was 18.8%[16]. There is no evidence that this rate has recently decreased. Universal infant HBV vaccination

was introduced in Mali in 2002 and is unlikely to have a significant effect on the circulation of HBV and on population rates of chronic carriers in the target age groups for liver cancer before at least one decade.

The presence of aflatoxin in peanuts (groundnuts) and their derived products at several points of the food supply chain from cultivation to marketing have been documented in several small surveys carried out in different parts of the peanut production area (Southern Mali)[34-36]. A survey conducted in public markets of Kita, Kolokani, and Kayes collected peanuts and peanut pastes over 7 mo between 2010 and 2011 from 30 different small retailers in each location. In these samples, contamination with aflatoxin was found to be above the permissible range (> 20 μg/kg) and ranged between 105 and 530.2 μg/kg. The level of aflatoxin was higher in peanut pastes and increased with the length of storage at the level of the small retailers, indicating that post-harvest contamination increased during storage[36].

Despite the continuous presence of aflatoxin as a food contaminant, it is possible that actual levels of individual exposure in the Bamako district have decreased over the past years. Several reasons could potentially explain the decrease in the incidence of liver cancer in the population of Bamako. First, changes in lifestyle and diversification of diet may have led to a decrease of the proportion of locally produced aflatoxin-contaminated products in the daily food intake. Indeed, a study exploring the association between the food variety score, dietary diversity score and nutritional status of children, and socioeconomic status level of the household has shown that children from the urban area in Mali have more dietary diversity than children from rural areas[37]. This study also reported that the food variety and dietary diversity in urban households with the lowest socioeconomic status were higher than the one found among rural households with the highest socioeconomic status[37].

Second, the systematic implementation of effective measures for reducing aflatoxin levels in crops in villages across the peanut production area has led to a measurable reduction in aflatoxin levels documented in several local surveys[35,36]. These measures include pre- and post-harvest management options such as selection of host plant resistance, soil amendments, timely harvesting and postharvest drying methods, use of antagonistic biocontrol agents, and awareness campaigns, as well as training courses to disseminate technology to the end-users[35].

A study conducted in Bamako in chronic HBV carriers suggested that overall these carriers were exposed to aflatoxin to a lesser extent than HBV carriers from rural Gambia[16]. In this study, the mutant R249S of the *TP53* gene, a mutation specific to aflatoxin exposure, was used as a surrogate to measure levels of exposure to aflatoxin. In Bamako, HBV carriers had an average plasma concentration of R249S of 311 copies/mL, while in rural areas of the Gambia the concentration varied between 480 to 5690 copies/mL. These data corroborate the idea that aflatoxin levels have reduced in the staple diet of people living in Bamako. Whether a decrease in exposure to aflatoxin is the cause of the decrease in incidence of liver cancer is a tantalizing hypothesis that may have a profound impact for promoting further efforts to reduce population exposure.

Further assessment of a possible effect of decreased aflatoxin intake will require detailed studies on biomarkers of exposure as well as comparison between the urban area of Bamako and rural areas of Mali and other West African countries where contaminated peanuts may still represent a major part of the diet. The data presented here warrant further studies to uncover the sociocultural and biological changes that have occurred over the study period and might explain the decrease in liver cancer reported in this article.

CONCLUSION

In conclusion, this study reported a dramatic decrease in the registration of primary liver cancer over 28 years in an urban population of West Africa. This decrease cannot be accounted for by universal childhood HBV vaccination, which was only introduced recently (2002). There is evidence that reduction of exposure to aflatoxin has occurred over the study period, caused by changing lifestyle and dietary patterns in this population. This suggests that controlled reduction of aflatoxin may achieve rapid and important protective effects against liver cancer in West Africa. However, our observations require cautious interpretation because of possible bias that might affect liver cancer registration in this low-resource context.

ARTICLE HIGHLIGHTS

Research background

There is evidence that trends in the incidence of liver cancer in different parts of the world are undergoing contrasting changes.

Research motivation

There is very little data on liver cancer incidence trends in sub-Saharan Africa.

Research objectives

Using the cancer registry of the Bamako district, Mali, we have studied incidence trends of liver cancer over 28 years (from 1987 to 2015) by sex.

Research methods

Age-standardized rates were estimated using a direct standardization method by considering the world population. The incidence rate ratio and corresponding 95% confidence intervals were estimated using the early period as reference (1987-1996). The average annual percent change of the trends was evaluated from Joinpoint regression models.

Research results

Overall, the age-standardized incidence of liver cancer varied substantially across the three periods of the study. There was a significant decrease of liver cancer incidence over the study period in males and females.

Research conclusions

This study showed a decrease in the registration of primary liver cancer in an urban population of West Africa between 1987 and 2015. Lifestyle changes and diversification of diet may have led to a decrease in exposure to aflatoxin-contaminated products.

Research perspectives

Future studies are warranted to explore the potential reasons for this decrease in order to better understand the specific etiological factors of liver cancer in West Africa.

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FOOTNOTES

Author contributions: Amadou A, Sighoko D, Hainaut P, and Gormally E designed the study, analyzed the data, and wrote the manuscript; Coulibaly B, Traoré C, Kamaté B, Mallé BS, Kemayou Yoghoum FN, Biyogo Bi Eyang S, and Bayo S contributed to the collection of the data; de Seze M, Bourgeois D, and Curado MP analyzed the data; and all authors have read and approved the manuscript.

Institutional review board statement: On behalf of the ministry of health, the regional cancer registry for Bamako district was used to support cancer surveillance activities. It is an official authoritative source of information on cancer incidence and survival in Mali. Relevant policies, regulations, and laws are strictly implemented to guide the handling of information in cancer registries. These procedures protect the confidentiality and privacy of both cancer patients and healthcare professionals. After declassifying the patient information, with no identifiers for cancer patients, the regional cancer registry provides access to the data for researchers in the form of databases.

Informed consent statement: The informed consent was waived.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Data sharing statement: Data from the cancer registry of Bamako, Mali are available on demand from the cancer registry.

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ORIGINAL ARTICLE

Retrospective Study

Modified preoperative score to predict disease-free survival for hepatocellular carcinoma patients with surgical resections

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Abstract

BACKGROUND

No prognostic models specific to hepatocellular carcinoma patients receiving surgical resection have been considered strong and convincing enough for survival prediction thus far, and there are no models including only preoperative predictors. We derived a nomogram to predict disease-free survival in a previous study.

AIM

To simplify our score and compare research outcomes among other scoring systems.

METHODS

We retrospectively reviewed data from 1106 patients with hepatocellular carcinoma who underwent liver resection at the Linkou Chang Gung Memorial Hospital between April 2003 and December 2012. Multivariate analyses were conducted to identify the significant survival predictors. Homogeneity, Harrell's C-index, and Akaike information criterion were compared between our score, AJCC 8th edition, Tokyo score, and Taipei Integrated Scoring System (TTV-CTP-AFP model).

RESULTS

Among the 1106 patients, 731 (66.1%) had tumor recurrence at a median follow-up of 83.9 mo. Five risk factors were identified: platelet count, albumin level,

indocyanine green retention rate, multiplicity, and radiologic total tumor volume. Patients were divided into three risk groups, and the 5-year survival rates were 61.7%, 39%, and 25.7%, respectively. The C-index was 0.617, which was higher than the Tokyo score (0.613) and the Taipei Integrated Scoring System (0.562) and equal to the value of the AJCC 8th edition (0.617).

CONCLUSION
The modified score provides an easier method to predict survival. Appropriate treatment can be planned preoperatively by dividing patients into risk groups.

Key Words: Hepatocellular carcinoma; Preoperative; Prediction; Tumor recurrence

Core Tip: This retrospective study recruited over 1000 patients and developed a simple preoperative score to evaluate the recurrence risk of hepatocellular carcinoma after surgical resection. Despite the lack of pathological features, predictive power was satisfactory. Appropriate treatment can be planned preoperatively by dividing patients into risk groups.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is a complex malignant tumor associated with various clinical risk factors. HCC arises from a cirrhotic or non-cirrhotic liver with different degrees of viral or metabolic etiological exposure[1] and develops in molecular and intratumoral heterogeneities[2,3]. These reasons cause difficulty in developing staging systems for outcome prediction worldwide[4]. Although well-known conventional staging systems, such as Okuda *et al*[5], the AJCC 8th edition (TNM)[6], BCLC[7], JIS[8], and CLIP[9], are derived from large samples containing patients in early and advanced stages, they all have limitations. So far, no prognostic models specific to HCC patients receiving surgical resection have been considered strong and convincing enough for survival prediction, and there are no models including only preoperative predictors.

During the past few decades, researchers have attempted to enhance the predictive power of models in five major ways. First, markers other than alpha fetoprotein (AFP) were identified that contribute to prognosis prediction, including AFP-L3, glypican-3, cyclase-associated protein 2, and so forth[10]. Second, tumor size and numbers were replaced with total tumor volume (TTV), which is more representative of tumor burden presentation[11,12]. Third, models were developed for specific groups of patients to increase prediction accuracy, such as hepatitis B virus/hepatitis C virus-related[13,14], AFP-positive/negative[15], specific Child-Pugh classification, within/beyond the Milan criteria[13], and so on. Fourth, a more precise statistical method, such as a nomogram[16-18], has been prioritized. Finally, new risk factors have been sought; however, they proved difficult to identify.

Based on the above enhancement goals, we derived a preoperative nomogram to predict disease-free survival (DFS) using a multivariate Cox regression model[19]. Prognostic factors included viral hepatitis, platelet count, albumin, indocyanine green (ICG) retention rate, tumor multiplicity, and radiologic TTV. We chose AFP as the only tumor marker for survival prediction analysis because it is widely used and highly accessible compared to other enzymes, cytokines, or genetic biomarkers. However, an AFP cut-off value of 200 did not result in a satisfactory survival prediction. Finally, the patients were grouped into three categories: Low, intermediate, and high risk of recurrence. The high-risk group had a poor median DFS of 12.4 mo and with a 5-year DFS rate of only 21.1%. Despite the large number of subjects and very long-term follow-up in the former study, the lack of comparison with other staging systems limited its credibility. Thus, the aims of the present study were to collect data from a larger sample, simplify the score, and compare the research outcomes with those derived from other scoring systems.

MATERIALS AND METHODS

Study population and clinical characteristics

Patients with HCC who underwent surgical resection at the Linkou Chang Gung Memorial Hospital between April 2003 and December 2012 were recruited retrospectively. The diagnosis of HCC was pathologically confirmed. Laboratory data before primary liver resection (LR) were obtained from medical records. Preoperative computed tomography (CT)/magnetic resonance imaging images were obtained for TTV calculation using the following formula: Length × (width)^2 × 0.52, a modified method for ellipsoid volume measurement[20,21]. A total of 1106 subjects who had met the eligibility criteria were selected after excluding patients with double malignancy, missing data, a positive pathological margin, or 30-d mortality like our previous study (Figure 1). The median follow-up was 83.9 mo. This study was approved by the local ethics committee of the Chang Gung Memorial Hospital.

Treatment and follow-up

LR was completed histologically when there was no evidence of distant metastasis. After surgery, the patients were followed up regularly by monitoring liver function tests, AFP levels, and liver ultrasonography every 3 mo. Dynamic CT of the liver was performed if necessary. Tumor recurrence was defined using clinical, radiological, and/or pathological criteria similar to the initial HCC diagnosis. DFS was calculated based on the period between the date of surgery and tumor recurrence.

Statistical analysis

Descriptive statistics for clinicopathological variables are presented. Statistical significance was defined as a P value < 0.05. The optimal cutoff values of TTV were determined using the maximally selected rank statistics in *R*. The Kaplan-Meier method and log-rank test were used for DFS analysis. Significant variables associated with DFS in the univariate analysis were included in the multivariate Cox proportional hazards model. Scores were assigned to each prognostic predictor according to the results. The performances of the different scoring systems were compared using the likelihood ratio χ^2 score for homogeneity, linear trend χ^2 score, Harrell's concordance index for discriminatory ability, and Akaike information criterion for prognostic stratification. All analyses were conducted using the SPSS software (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, version 20.0. Armonk, NY, United States) and R version 4.0.5 [R Core Team (2021)]. R: Language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. https://www.R-project.org/).

RESULTS

Patient clinicopathologic characteristics

Demographic characteristics are shown in Table 1. The majority of the patients were men (78%) with viral hepatitis (83%). A higher percentage of patients were over the age of 55 (61%) and only 0.01% were Child-Pugh C. A majority of patients had a lower international normalized ratio (91%), total bilirubin (91%), ICG clearance (68%), and higher albumin (92%) levels. Seventy-one percent of the patients had an AFP level < 200 ng/mL. Regarding tumor burden, more patients had solitary tumors (77%) and a radiologic TTV ≤ 32.0 cm^3 (58%). Pathologically, fewer patients had liver cirrhosis (47%), tumor rupture (3%), Edmondson-Steiner grade III/IV (38%), or microvascular invasion (29%). A higher percentage of tumor capsules (83%) and pathological TTV ≤ 32.8 cm^3 (59%) were noted. Seven hundred thirty-one (66.1%) patients had tumor recurrence at a median follow-up of 83.9 mo.

Risk factors identified in the preoperative prognostic model

After pooling data from the two databases, platelet count (P = 0.003), total bilirubin (P = 0.032), albumin (P = 0.001), ICG clearance rate (P < 0.0001), multiplicity of tumor (P < 0.0001), and radiologic TTV (P < 0.0001) were significantly associated with DFS in univariate analysis. Viral hepatitis, which was found to have predictive potential in a previous study, did not show prognostic significance in the univariate analysis (P = 0.111). Five predictors remained significant in multivariate analysis, including platelet count [P = 0.001, hazard ratio (HR) = 1.498, 95% confidence interval (CI): 1.192-1.882], albumin (P = 0.005, HR = 1.462, 95%CI: 1.121-1.907), ICG clearance rate (P = 0.001, HR = 1.289, 95%CI: 1.104-1.507), multiplicity of tumor (P < 0.0001, HR = 1.694, 95%CI: 1.422-2.019), and radiologic TTV (P < 0.0001, HR = 1.743, 95%CI: 1.501-2.024) (Table 2). With these factors, the score was calculated by assigning 2 points for platelet count, multiplicity, and TTV and 1 point each for albumin and ICG according to the calculation of the regression coefficient formula (Table 3). The percentages of patients with risk scores from 0 to 7 were 28.3%, 13.0%, 28.4%, 15.3%, 9.3%, 4.3%, 1.3%, and 0.1%, respectively. Patients with 0, 1-2, and 3-7 points were categorized into low-, intermediate-, and high-risk groups, according to the ascending possibility of the 16th, 50th, and 84th percentiles.

Table 1 Clinicopathological characteristics and univariate analysis of 1106 patients

	n (%)	*P* value
Preoperative variables		
Age (yr)		0.202
≤ 55	436 (39)	
> 55	670 (61)	
Sex		0.098
Male	863 (78)	
Female	243 (22)	
Viral hepatitis		0.111
No viral hepatitis	185 (17)	
Hepatitis B or C or B + C	921 (83)	
Child Class		0.964
A/B	1099 (99)	
C	7 (1)	
Platelet count (10^3/μL)		0.003
< 100	124 (11)	
≥ 100	982 (89)	
Total bilirubin (mg/dL)		0.032
≤ 1.3	1010 (91)	
> 1.3	96 (9)	
PT-INR		0.053
≤ 1.2	1004 (91)	
> 1.2	102 (9)	
Albumin (g/dL)		0.001
< 3.5	86 (8)	
≥ 3.5	1020 (92)	
AFP (ng/mL)		0.116
< 200	785 (71)	
≥ 200	321 (29)	
ICG (%)		< 0.0001
≤ 10	748 (68)	
> 10	358 (32)	
Multiplicity		< 0.0001
Solitary	852 (77)	
Multiple	254 (23)	
Radiologic TTV (cm^3)		< 0.0001
mean ± SD	113.06 ± 237.13	
≤ 32.0	645 (58)	
> 32.0	461 (42)	
Postoperative variables		
Resection margin (cm)		0.082
≤ 1.0	817 (74)	

> 1.0	249 (23)	
Liver cirrhosis		0.001
No	585 (53)	
Yes	521 (47)	
Tumor rupture		0.004
No	1076 (97)	
Yes	30 (3)	
Edmondson-Steiner grade		< 0.0001
I/II	682 (62)	
III/IV	424 (38)	
Capsule		0.789
No	192 (17)	
Yes	914 (83)	
Microvascular invasion		< 0.0001
No	786 (71)	
Yes	320 (29)	
Pathologic TTV (cm^3)		< 0.0001
mean ± SD	131.59 ± 293.81	
≤ 32.8	652 (59)	
> 32.8	454 (41)	

PT-INR: International normalized ratio of prothrombin time; AFP: Alpha fetoprotein; ICG: Indocyanine green; TTV: Total tumor volume; SD: Standard deviation.

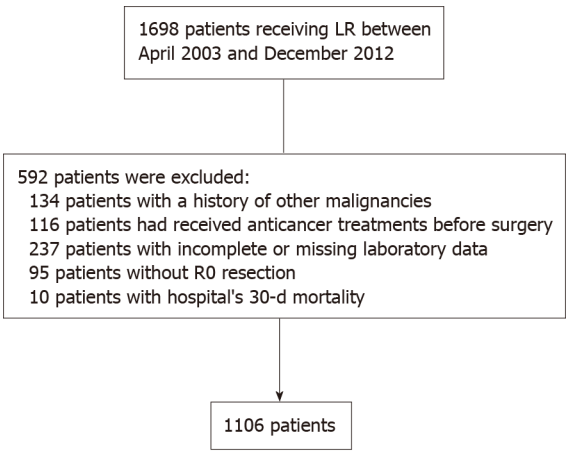

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Figure 1 Flow chart of the study population selected. LR: Liver resection.

Radiological errors between CT and pathology

When radiological error of multiplicity was examined using a cross table, only 1 subject out of 1106 patients with solitary tumor was misdiagnosed with multiplicity on CT. In contrast, 51 subjects with multiple tumors were misdiagnosed with solitary tumors on CT. The diagnostic sensitivity, specificity, positive predictive value, and negative predictive value of CT were 79.9%, 99.9%, 99.5%, and 94.5%, respectively. The overall accuracy was 95.3%. As for optimal radiological TTV cutoff value (32.0 cm^3), the diagnostic sensitivity, specificity, positive predictive value, and negative predictive value of the CT scan were 89.7%, 92.1%, 88.9%, and 92.7%, respectively, achieving accuracy of 91.1%.

Table 2 Univariate and multivariate analysis of prognostic factors

	UV *P* value	HR	95%CI	MV *P* value
Platelet count (10^3/μL)	0.003		1.192-1.882	0.001
< 100		1.498		
≥ 100		1		
Total bilirubin (mg/dL)	0.032			-
≤ 1.3				
> 1.3				
Albumin (g/dL)	0.001		1.121-1.907	0.005
< 3.5		1.462		
≥ 3.5		1		
ICG (%)	< 0.0001		1.104-1.507	0.001
≤ 10		1		
> 10		1.289		
Multiplicity	< 0.0001		1.422-2.019	< 0.0001
Solitary		1		
Multiple		1.694		
Radiologic TTV (cm^3)	< 0.0001		1.501-2.024	< 0.0001
≤ 32.0		1		
> 32.0		1.743		

UV: Univariate; HR: Hazard ratio; CI: Confidence interval; MV: Multivariate; ICG: Indocyanine green; TTV: Total tumor volume.

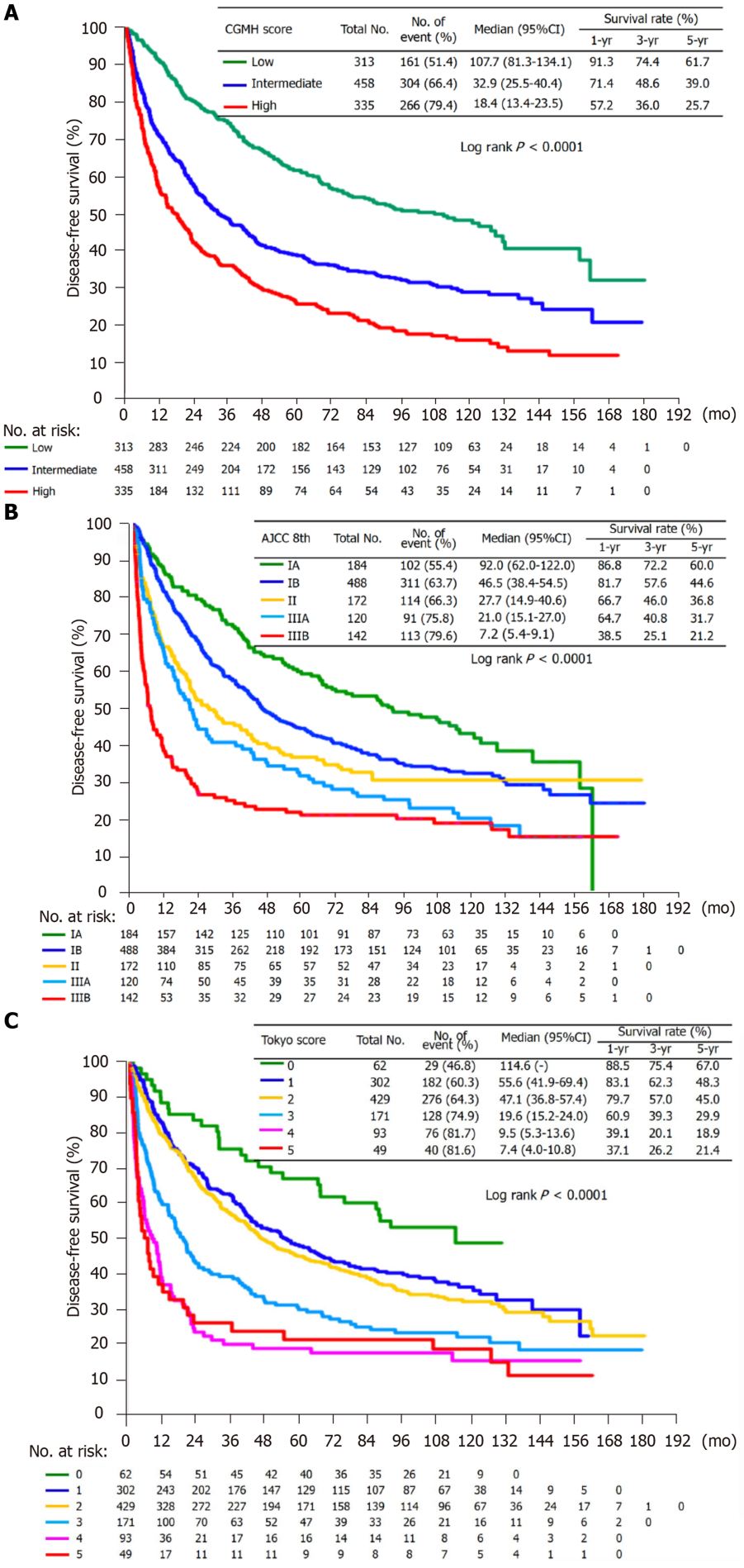
Table 3 Point values for risk groups according to the Cox regression model

Predictor variables	Regression coefficients (β)	Categories	Reference value (W)	B ($W-W_{REF}$)	Points = β ($W-W_{REF}$)/constant B
Platelet count (10^3/μL)	0.4039	< 100000	1	0.4039	2
		≥ 100000	0 (W_{REF})	0	0
Albumin (g/dL)	0.3805	< 3.5	1	0.3805	1
		≥ 3.5	0 (W_{REF})	0	0
ICG (%)	0.2544	≤ 10	0 (W_{REF})	0	0
		> 10	1	0.2544[1]	1
Multiplicity	0.5274	Solitary	0 (W_{REF})	0	0
		Multiple	1	0.5274	2
Radiologic TTV (cm^3)	0.5558	≤ 32.0	0 (W_{REF})	0	0
		> 32.0	1	0.5558	2

[1]Base constant (constant B).
ICG: Indocyanine green; TTV: Total tumor volume.

Performance comparison of four prognostic models

The performance of our score was further compared with those of the AJCC 8th edition (TNM), Tokyo score, and Taipei Integrated Scoring System (TTV-CTP-AFP model). Figure 2 displays the survival curve of each group and the postoperative 1-, 3-, and 5-year DFS rates of the different scoring systems. There were statistically significant differences in long-term survival between the three groups. The 5-year DFS rates of our score from low-to high-risk groups were 61.7%, 39.0%, and 25.7%, respectively; AJCC 8th edition from stage IA to IIIB were 60.0%, 44.6%, 36.8%, 31.7%, and 21.2%, respectively; six groups of the


A
CGMH score | Total No. | No. of event (%) | Median (95%CI) | Survival rate (%) 1-yr 3-yr 5-yr
Low 313 161 (51.4) 107.7 (81.3-134.1) 91.3 74.4 61.7
Intermediate 458 304 (66.4) 32.9 (25.5-40.4) 71.4 48.6 39.0
High 335 266 (79.4) 18.4 (13.4-23.5) 57.2 36.0 25.7
Log rank P < 0.0001
Disease-free survival (%)
No. at risk:
Low 313 283 246 224 200 182 164 153 127 109 63 24 18 14 4 1 0
Intermediate 458 311 249 204 172 156 143 129 102 76 54 31 17 10 4 0
High 335 184 132 111 89 74 64 54 43 35 24 14 11 7 1 0
B
AJCC 8th | Total No. | No. of event (%) | Median (95%CI) | Survival rate (%) 1-yr 3-yr 5-yr
IA 184 102 (55.4) 92.0 (62.0-122.0) 86.8 72.2 60.0
IB 488 311 (63.7) 46.5 (38.4-54.5) 81.7 57.6 44.6
II 172 114 (66.3) 27.7 (14.9-40.6) 66.7 46.0 36.8
IIIA 120 91 (75.8) 21.0 (15.1-27.0) 64.7 40.8 31.7
IIIB 142 113 (79.6) 7.2 (5.4-9.1) 38.5 25.1 21.2
Log rank P < 0.0001
Disease-free survival (%)
No. at risk:
IA 184 157 142 125 110 101 91 87 73 63 35 15 10 6 0
IB 488 384 315 262 218 192 173 151 124 101 65 35 23 16 7 1 0
II 172 110 85 75 65 57 52 47 34 23 17 4 3 2 1 0
IIIA 120 74 50 45 39 35 31 28 22 18 12 6 4 2 0
IIIB 142 53 35 32 29 27 24 23 19 15 12 9 6 5 1 0
C
Tokyo score | Total No. | No. of event (%) | Median (95%CI) | Survival rate (%) 1-yr 3-yr 5-yr
0 62 29 (46.8) 114.6 (-) 88.5 75.4 67.0
1 302 182 (60.3) 55.6 (41.9-69.4) 83.1 62.3 48.3
2 429 276 (64.3) 47.1 (36.8-57.4) 79.7 57.0 45.0
3 171 128 (74.9) 19.6 (15.2-24.0) 60.9 39.3 29.9
4 93 76 (81.7) 9.5 (5.3-13.6) 39.1 20.1 18.9
5 49 40 (81.6) 7.4 (4.0-10.8) 37.1 26.2 21.4
Log rank P < 0.0001
Disease-free survival (%)
No. at risk:
0 62 54 51 45 42 40 36 35 26 21 9 0
1 302 243 202 176 147 129 115 107 87 67 38 14 9 5 0
2 429 328 272 227 194 171 158 139 114 96 67 36 24 17 7 1 0
3 171 100 70 63 52 47 39 33 26 21 16 11 9 6 2 0
4 93 36 21 17 16 16 14 14 11 8 6 4 3 2 0
5 49 17 11 11 11 9 9 8 8 7 5 4 1 1 0
0 12 24 36 48 60 72 84 96 108 120 132 144 156 168 180 192 (mo)

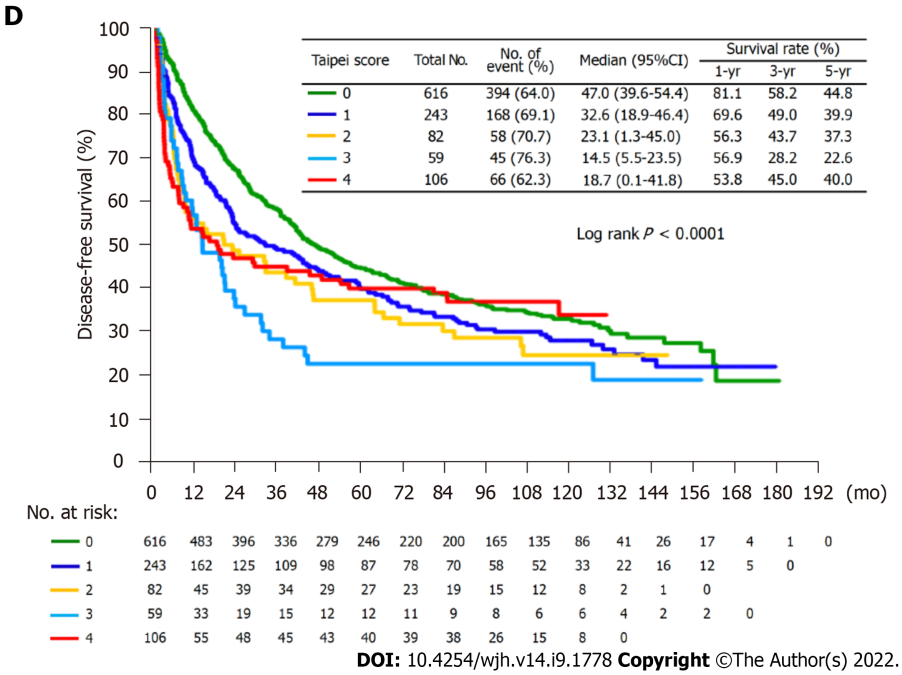


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Figure 2 Disease-free survival curves of four scoring systems. A: CGMH score; B: AJCC 8th edition; C: Tokyo score; D: Taipei score. CI: Confidence interval.

Tokyo system were 76.0%, 48.3%, 45.0%, 29.9%, 18.9%, and 21.4%, respectively; and the five Taipei groups were 44.8%, 39.9%, 37.3%, 22.6%, and 40.0%, respectively. Table 4 illustrates the HR of the risk groups among the four scoring systems. The three groups of our score and the five groups of AJCC 8th edition appeared to have growing risks according to HR. However, the highest risk groups in the Tokyo and Taipei scores with lower HR (4.10 *vs* 4.14 in Tokyo; 1.26 *vs* 1.79 in Taipei) lost discrimination ability for risk stratification. Our score exhibited the highest likelihood ratio (χ^2), linear trend (χ^2), and lowest Akaike information criterion value, indicating the best homogeneity, discriminatory ability, and prognostic prediction ability (Table 5). We also had an acceptable C-index value (0.617) equal to the AJCC 8th edition and superior to the Tokyo (0.613) and Taipei (0.562) scores.

DISCUSSION

Preoperative characteristic differences between two databases

In the nomogram of the preoperative prediction model that we modeled after the former database, TTV had the highest points of 100, and viral hepatitis was assigned 61 points. Viral hepatitis ranked fifth among only six risk factors above the ICG clearance level (39 points). Although the proportion of patients with or without viral hepatitis was similar between the two databases, this factor did not show a predictive potential in this study. In contrast, ICG remained significant and had the lowest regression coefficient, similar to our previous results. Notably, viral hepatitis remains the main cause of HCC in the Western Pacific Region, even with widespread hepatitis B virus vaccination. However, the prevalence of viral hepatitis is relatively low in western countries. For example, only 3192 cases of acute hepatitis B and 4136 cases of acute hepatitis C were reported in the United States in 2019 (there are an estimated 257 million people living with hepatitis B virus and 71 million with hepatitis C virus globally)[22]. In other words, without the factor of viral hepatitis, this score may be more applicable to western populations for DFS prediction.

Additionally, a significantly lower percentage of multiplicity was observed in the current database. The annual number of cases of living-donor liver transplantation for HCC at our hospital has increased from 5 to approximately 30 over the past two decades. While the proportion of patients undergoing liver transplantation continues to rise, fewer patients with multiple tumors according to Milan criteria choose to receive LR. As for other preoperative variables, no patients had Child-Pugh class C in the newly collected data. More patients had better platelet counts, bilirubin, international normalized ratio, albumin, and ICG clearance levels. Another popular predictor, neutrophil-to-lymphocyte ratio, was not included in the regression analysis in a previous study because of the large amount of missing data. The complete neutrophil-to-lymphocyte ratio compiled from the new database was not statistically significant in the univariate analysis (cutoff value: 2.5, $P = 0.962$).

Table 4 Discrimination measures and hazard ratios evaluated among four scoring systems

Scoring system	CGMH			AJCC 8th edition			Tokyo			Taipei		
	Estimate	SE		Estimate	SE		Estimate	SE		Estimate	SE	
Measures of discrimination												
Harrell's C_H	0.617	0.01		0.617	0.01		0.613	0.011		0.562	0.01	
Gonen and Heller's C_{GH}	0.599	0.009		0.586	0.009		0.587	0.01		539	0.009	
Royston & Sauerbrei's D	0.672	0.066		0.577	0.065		0.589	0.066		0.292	0.067	
Prognostic scoring system	HR	95%CI of HR	*P* value	HR	95%CI of HR	*P* value	HR	95%CI of HR	*P* value	HR	95%CI of HR	*P* value
CGMH: Low[1]	1			1			1			1		
Intermediate, high	1.81	1.50-2.19	< 0.0001	1.35	1.08-1.69	0.009	1.55	1.04-2.29	0.03	1.21	1.01-1.45	0.039
AJCC 8th edition:	2.74	2.25-3.34	< 0.0001	1.69	1.29-2.21	< 0.001	1.7	1.16-2.49	0.007	1.43	1.08-1.88	0.012
IA[1], IB, II, IIIA, IIIB				2.08	1.57-2.76	< 0.0001	2.64	1.76-3.96	< 0.0001	1.79	1.31-2.44	< 0.001
Tokyo: 0[1], 1, 2, 3, 4, 5				3.15	2.41-4.12	< 0.0001	4.14	2.70-6.36	< 0.0001	1.26	0.97-1.64	0.079
Taipei: 0[1], 1, 2, 3, 4							4.1	2.54-6.63	< 0.0001			

[1]Reference category.
The CGMH risk groups were categorized according to the ascending possibility of the 16th, 50th, and 84th percentiles.
CI: Confidence interval; HR: Hazard ratio; SE: Standard error.

Table 5 Performance of prognostic scoring systems

Prognostic scoring system	Homogeneity	Discriminatory ability	Akaike information criterion
	Likelihood ratio χ^2	Linear trend χ^2	
CGMH	106.05	106.48	9305.48
AJCC 8th	81.53	94.16	9336.01
Tokyo	93.02	109.45	9324.52
Taipei	18.76	20.41	9396.77

Our score and the AJCC 8th edition were equally matched in predictive power but simpler

TTV and multiplicity ranked first and second, respectively, in the predictive power of our score. Because of our concern about possible radiology errors between CT scans and pathology, the probability was calculated. As indicated by our results, there was only a slight chance (0.49%) that multiple tumors would be mistaken for solitary tumors on CT. Approximately 18% of the patients were found to have multiple lesions when HCC was newly diagnosed. Eighty percent had identical pathological findings, but some daughter nodules that were difficult to detect on preoperative imaging caused diagnostic errors. Fifty-one subjects were missed out of 254 cases, with multiplicity confirmed by pathology. However, sensitivity (79.9%), specificity (99.9%), and overall accuracy (95.3%) remained highly satisfactory. Likewise, the CT scan performed remarkably well in distinguishing TTV. A possible reason for this finding is that the accuracy of CT scans was more limited in advanced HCC with a cirrhosis background. Patients who underwent LR in our hospital were mostly Child A, BCLC 0, or A without severe liver cirrhosis, leading to a more precise and accurate detection rate.

When comparing our score with the AJCC 8th edition, the low-risk group had a very close median DFS compared to the stage IA group, both exceeding 90%. The intermediate group had a similar median DFS of less than 40%, similar to the stage II group. The high-risk group had a median DFS of less than 20%, which was between the stage IIIA and IIIB groups. In fact, for those who had recurrence in different groups, 28.2%, 52.5%, and 64.7% of patients had recurrence beyond the Milan criteria from the low-to high-risk groups, respectively. In this regard, patients with recurrence beyond the Milan criteria at variable stages of AJCC 8th edition with the following percentages were correlated with our risk groups: IA, 25.5%; IB, 41.8%; II, 61.4%; IIIA, 53.8%; and IIIB, 83.2%. Thus, the high-risk group of our score not only had an extremely high rate of recurrence of up to 79.4% but also had more advanced recurrence with limited treatment strategies. Simply put, even with a less delicate grouping, patients

demanding adjuvant therapy and close monitoring could be accurately and conveniently selected from our score.

A better choice than the Tokyo or Taipei score for differentiating patient risk

The Tokyo scoring system, published by Shindoh *et al*[23] in 2020, uses three risk factors (tumor size > 2 cm, multiple lesions, and microvascular invasion) after pathological diagnosis. The score has the major advantage of simplicity over the classic prognostic staging systems, such as the TNM[6], Okuda *et al*[5], CLIP[9], JIS[8], CUPI[24], and GRETCH[25,26] but still requires pathological features. The Taipei Integrated System, developed by Yang-Ming University in 2010, was a true preoperative score derived from the Taiwanese population[27]. Although the Tokyo score had a C-index nearly comparable to our score, it was found to have an inferior discrimination ability and ambiguous hazard ratios in high-risk groups in this study, similar to the Taipei score.

The advantage of preoperative staging system in the near future

The age of multidisciplinary treatment is emerging, including targeted therapy, immunotherapy, and even cell therapy. Before reaching a consensus regarding adjuvant HCC therapy following resection, more evidence is needed. For instance, the STORM trial in 2016 noted that adjuvant sorafenib had no significant recurrence-free survival benefit[28], whereas a meta-analysis by Huang *et al*[29] published in 2021 demonstrated that adjuvant sorafenib could not only prolong overall and recurrence-free survival but also reduce the recurrence rate. The effectiveness of adjuvant therapy, let alone the use of neoadjuvant therapy, remains controversial. Currently, neoadjuvant therapy has only been applied for disease downstaging to achieve potentially curative resection or tumor progression limitations to protect patients from exceeding transplant criteria[30]. Adjuvant therapy may be introduced as a neoadjuvant treatment to provide survival benefits or prevent recurrence. The preoperative staging system will play a vital role in risk stratification.

CONCLUSION

The modified preoperative score provides an easier way to predict disease-free survival for HCC patients with surgical resections. Despite the lack of pathological features, predictive power was satisfactory. Appropriate preoperative treatment can be planned by simply dividing patients into three risk groups.

ARTICLE HIGHLIGHTS

Research background

No preoperative prognostic models specific to hepatocellular carcinoma patients receiving surgical resection have been considered strong and convincing enough for survival prediction.

Research motivation

We previously derived a nomogram but aimed to simplify the score and compare it with other scoring systems.

Research objectives

To develop a simple preoperative score with satisfactory predictive power compared to postoperative scoring systems.

Research methods

Significant risk factors were identified using a multivariate Cox proportional hazards model. The homogeneity, Harrell's C-index, and Akaike information criterion of the different scoring systems were compared.

Research results

Five risk factors were identified, and patients were divided into three risk groups. The C-index of our preoperative score was 0.617, which is equal to the value of the AJCC 8th edition.

Research conclusions

A modified score was established for survival prediction, and patients were divided into risk groups for preoperative treatment planning.

Research perspectives

Specific treatment or monitoring plan modifications for each risk group should be studied and potential correlation with survival benefit should be investigated.

FOOTNOTES

Author contributions: Lai Y designed and performed the research and wrote the paper; Hung HC and Lee JC contributed to the analysis; Wang YC, Cheng CH, Wu TH, Lee CF, Wu TJ, Chou HS, and Chan KM provided clinical advice; Kao CY contributed to the final manuscript; Lee WC supervised the report.

Institutional review board statement: This study was approved by the local ethics committee of Chang Gung Memorial Hospital, No. 104-3900B.

Informed consent statement: Because of retrospective study, signed informed consent form is not needed. However, Chang-Gung Memorial Hospital has given permission to conduct this study.

Conflict-of-interest statement: The authors declare that there are no conflict of interests.

Data sharing statement: The data that support the findings of this study are available from the corresponding author, Lee WC, upon reasonable request.

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ORIGINAL ARTICLE

Retrospective Study

Liver magnetic resonance imaging for evaluation of response to treatment after stereotactic body radiation therapy of hepatocellular carcinoma

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Abstract

BACKGROUND

Although stereotactic body radiation therapy (SBRT) is increasingly used, its application has not yet been regulated by the main international guidelines, leaving the decision to multidisciplinary teams.

AIM

To assess magnetic resonance imaging (MRI) features of hepatocellular carcinoma (HCC) treated with SBRT, highlighting the efficacy of the treatment and the main aspects of the lesion before and after the procedure.

METHODS

As part of a retrospective study, 49 patients who underwent SBRT for HCC between January 2013 and November 2019 were recruited. Each patient under-

went a pre-treatment MRI examination with a hepatospecific contrast agent and a similar follow-up examination within 6 mo of therapy. In addition, 22 patients underwent a second follow-up examination after the first 6 mo. The following characteristics were analysed: Features analysed compared to pre-treatment MRI examination, presence or absence of infield and outfield progression, ring-like enhancement, signal hyperintensity in T2-weighted sequences in the perilesional parenchyma, capsular retraction, and "band" signal hypointensity in T1-weighted gradient echo fat saturated sequences obtained during hepatobiliary excretion.

RESULTS

Signal hyperintensity in the T2-weighted sequences showed a statistically significant reduction in the number of lesions at the post-SBRT first control ($P = 0.0006$). Signal hyperintensity in diffusion-weighted imaging-weighted sequences was decreased at MRI first control ($P < 0.0001$). A statistically significant increase of apparent diffusion coefficient values from a median of 1.01 to 1.38 at the first post-control was found ($P < 0.0001$). Capsular retraction was increased at the late evaluation ($P = 0.006$). Band-like signal hypointensity in the hepatobiliary phase was present in 94% at the late control ($P = 0.006$). The study of the risk of outfield progression *vs* infield progression revealed a hazard ratio of 9.

CONCLUSION

The efficacy of SBRT should be evaluated not in the first 6 mo, but at least 9 mo post-SBRT, when infield progression persists at very low rates while the risk of outfield progression increases significantly.

Key Words: Hepatocellular carcinoma; Stereotactic body radiation therapy; Magnetic resonance imaging; Histopatology; Outcome; Radiology

Core Tip: As part of a retrospective study, 49 patients who underwent stereotactic body radiation therapy (SBRT) for hepatocellular carcinoma between January 2013 and November 2019 were recruited. Each patient underwent a pre-treatment magnetic resonance imaging examination with a hepatospecific contrast agent and a similar follow-up examination within 6 mo of therapy. In addition, 22 patients underwent a second follow-up examination after the first 6 mo. The study results show that the efficacy of SBRT should be evaluated not in the first 6 mo, but at least 9 mo post-SBRT, when infield progression persists at very low rates while the risk of outfield progression increases significantly.

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INTRODUCTION

Although stereotactic body radiation therapy (SBRT) is increasingly used, its application has not yet been regulated by the main international guidelines, leaving the decision to multidisciplinary teams. Lack of diffusion and standardization of treatment indications makes the radiological definition of outcome particularly complex and not completely concordant with the main therapy evaluation systems (modified Response Evaluation Criteria in Solid Tumors [mRECIST] and European Association for the Study of the Liver [EASL]). By analysing the magnetic resonance imaging (MRI) semeiological characteristics of the hepatocellular carcinoma (HCC) lesions treated by SBRT and the remaining liver parenchyma, it would be possible to evaluate further evolution over time and changes in the diagnostic process following therapy[1].

In addition, search of possible correlations between MRI findings and clinical, laboratory, and radiotherapy data could help to prevent radio-induced liver damage and to implement customized treatment planning. This has made it possible to use this treatment in different stages of HCC, both in patients with early-stage unifocal disease and in patients not eligible for other loco-regional therapies and for palliative purposes[2,3].

From a technical point of view, the number of target lesions as well as their location within the liver are potential limitations in treatment planning and dose distribution. A minimum distance of at least 5 mm of the target HCCs from adjacent hollow viscera is recommended, otherwise the dose has to be reduced to match tolerance of neighboring organs.

Semeiotic characteristics of SBRT-treated lesions differ from the imaging of other locoregional therapies: Whereas the latter results in immediate devascularization of tumor, radiotherapy leads to histological changes in the lesion and surrounding parenchyma that are gradual over time. Reflecting evolution of histological changes, an acute, subacute, or chronic stage can also be distinguished[4-10].

The main aim of the study was to analyse MRI features of HCC lesions treated by SBRT and the remaining liver parenchyma, to monitor how these properties evolve over time and how these aspects may modify subsequent diagnostic course of therapy.

MATERIALS AND METHODS

Patient population

A retrospective observational study was conducted in 49 patients (mean age 64.44 years, range 48.71-84.51), 22 females and 27 males, undergoing radiotherapy between January 2013 and November 2019.

In 29 (59%) patients, SBRT was chosen as the first treatment option, and in 20 (41%) patients, it was in combination with previous locoregional treatments on the same lesion. Six (12%) of these patients subsequently underwent liver transplantation (bridge therapy).

Sixty-one lesions were treated; among those, 42 were newly diagnosed HCCs and 19 were focal lesions that had already undergone previous treatment and were therefore attributable to persistent or recurrent disease.

In the period between January 2013 and June 2020, each patient underwent an MRI examination with a hepatospecific contrast agent prior to treatment, and a similar follow-up examination within 6 mo of therapy (mean time 4 mo). In addition, 22 patients (a total of 36 lesions) underwent a second follow-up after the first 6 mo (mean time 9 mo).

Imaging protocol

All MRI examinations were performed with 1.5 T equipment (Philips Achieva), with a hepatospecific contrast agent (Primovist 0.25 mmol/mL, Bayer Schering Pharma, Berlin, Germany) infused at a dose of 0.1 mL/kg with a flow rate of 2 mL/sec.

Imaging analysis before treatment

The acquired images were re-evaluated using the PACS system (Synapse PACS, Tokyo, Japan) by a radiologist with 15 years of experience in abdominal MRI.

For each lesion, the following characteristics were analysed and catalogued: Newly diagnosed HCC or previously treated HCC (persistence or recurrence of disease); Liver segment; Centroparenchymal or subcapsular location (distance from glissonian surface ≤ 10 mm); Diameter of hypervascularised tissue in the arterial phase; Diameter of the lesion in basal (T1-weighted in-phase and out-of-phase) sequences; Diameter in hepatobiliary excretory phase sequences; Average lesion diameter; Presence or absence of signal hyperintensity in the T2-weighted sequences, in relation to the surrounding parenchyma; Presence or absence of signal enhancement on diffusion-weighted imaging (DWI); and apparent diffusion coefficient (ADC) value (obtained by manually positioned region of interest [ROI]).

Radiotherapeutic data analysis

All lesions that did not show an increase in size or contrast-enhancement intensity in the arterial phase were considered free of progressing disease, and therefore treatment was assessed as effective. Tumor staging was performed according to the BCLC system. Pre-treatment Child-Pugh score, pretreatment ALBI, occurrence of RILD, Child-Pugh score variation after treatment, ALBI change after treatment, total liver volume, and planning target volume (PTV) were also assessed.

Imaging analysis after treatment

The following features were analysed in the post-treatment MRI examinations: Features analysed on pre-treatment MRI examination; Presence or absence of infield progression: Signs of disease progression within the treated field (increase in size and/or increase in intensity of arterial contrast-enhancement); Presence or absence of outfield progression: Signs of disease progression outside the radio-treated field according to mRECIST criteria; Presence or absence of ring-like enhancement (altered vascularity of the parenchyma adjacent to the treated lesion); Presence or absence of signal hyperintensity in T2-weighted sequences in the perilesional parenchyma; Presence or absence of capsular retraction; Presence or absence of "band" signal hypointensity in T1-weighted gradient echo fat saturated sequences obtained in the perilesional parenchyma; T1-weighted sequences obtained during hepatobiliary excretion of irradiated parenchyma; Calculation of the volume of "band" area in T1-weighted gradient echo fat

saturated sequences acquired during hepatobiliary excretion by manual segmentation using polygonal ROIs, using the OsiriX DICOM Viewer software. A retrospective analysis was performed comparing pre-treatment MRI characteristics with subsequent follow-ups.

RESULTS

Almost 55.7% of the treated lesions had a subcapsular location; the distribution in the different hepatic segments was as follows: 3 in S1, 4 in S2, 2 in S3, 8 in S4, 10 in S5, 5 in S6, 9 in S7, and 20 in S8 (Figures 1-5).

The average diameter of the lesions was 17 mm (SD 13-24mm), a value that was significantly reduced both at the first control (10 mm, SD 11-20mm) and at the second follow-up (10 mm, SD 7-15mm) (Table 1).

Five (8.2%) out of 61 lesions were hypovascular HCC. The remaining lesions showed typical post-contrast features with a mean diameter of 17 mm (range 12-24 mm), with a statistically significant reduction at follow-up (Figure 6).

Both the diameter during the hepatobiliary phase and in basal T1 weighted sequences underwent a size reduction at both controls (Figure 7).

On pre-treatment MRI, signal hyperintensity in the T2-weighted sequences was found in 62% of lesions, but it was only 30% at the post-SBRT first control, with a statistically significant reduction in the number of lesions ($P = 0.0006$).

Signal hyperintensity in DWI-weighted sequences was found in 68% of lesions and in only 18% at MRI first control ($P < 0.0001$). For both T2 and DWI variations, no statistically significant changes were found between first and second MRI controls (Figure 8).

These variations were associated with a statistically significant increase of ADC values, which increased from a median of 1.01 at the pre-treatment examination to 1.38 at the first post-control ($P < 0.0001$).

In most of the lesions, the typical characteristics of the action of SBRT were identified. In particular, at the first MRI examination, 82% of the lesions showed ring-like enhancement and 84% perilesional hyperintensity in T2-weighted sequences. These percentages tended to decrease at the second MRI examination (69% and 75%, respectively) (Figure 9).

Capsular retraction was evident in 33% of cases at the first control, a features that significantly increased to 64% at the late evaluation ($P = 0.006$).

Band-like signal hypointensity in the hepatobiliary phase was present at the first control in 95% of cases and in 94% at the late control ($P = 0.006$). The mean volume of the area of hypointensity calculated by manual segmentation was 85.47 cm^3 (range 15.21-248.16) (Figure 10).

Considering the mRECIST criteria for evaluation of response to therapy, at the first examination signs of infield progression were observed in 5% of cases (3 lesions), while it was 18% for outfield progression signs (Figure 11).

At the second MRI check-up, only one (3%) case of infield progression and 19 (28%) cases of outfield progression were observed (Figure 12).

The study of the risk of outfield progression *vs* infield progression revealed a hazard ratio of 9.

The risk increased as time progressed, with a sharp increase in the cumulative outfield progression hazard of around 9 after the end of therapy, as shown by the Kaplan-Meier-curve study (Figure 13).

The time free from progression through the Kaplan-Meier curve showed a plateau of onset of infield progression around 9 mo, an interval in which outfield progression tended to increase.

A direct relationship was also found between the area of band hypointensity during hepatobiliary excretion calculated by segmentation and PTV.

The two volumes were linked by a parabolic correlation: Up to certain volumes of PTV, the area of hypointensity also increased in a directly proportional manner. For particularly high PTV values (greater than 300 cm^3), the hepatic reaction area remained at significantly lower values.

No further statistically significant correlations were found between the available clinical data, the radiotherapy data obtained, and the radiological findings.

DISCUSSION

In the acute stage (1-3 mo post-SBRT), typical peripheral hyperarterization can be seen, which persists or subsides in the subsequent post-contrast phases, referred to as ring-like enhancement. These changes imply the phenomena of venous congestion and reactive hyperemia in the treated area[10].

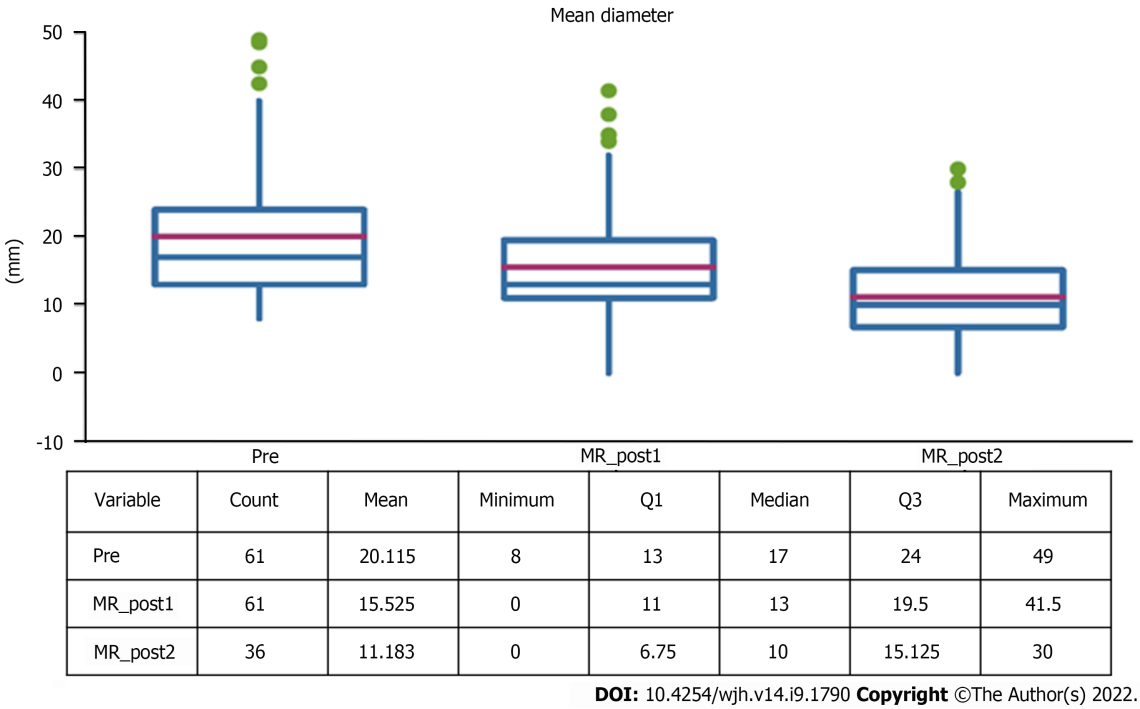
In the subacute stage (3-6 mo post-SBRT), the parenchyma involved shows relative hypoattenuation in basal and portal acquisitions, with progressive enhancement in the late phase, related to the occlusion of the centrolobular veins and reduced intravenous contrast clearance[6].

In the chronic stage (more than 6 mo after treatment), imaging will reveal changes caused by radio-induced fibrosis[6,11].

Table 1 Magnetic resonance imaging characteristics at pre- and post- stereotactic body radiation therapy follow-ups

	End of SBRT	1° MRI FU	(Pre *vs* 1°FU)	2° MRI FU	(1° *vs* 2°FU)
T (mo)	0	4.1 (3.1- 6.7)	< 0.0001	9.3 (6.2-12.3)	
Arterious D	17 (12-24)	0 (0-16)	< 0.0001	0 (0-0)	< 0.005
T1-weighted D	17 (12-23)	13 (11-21)	< 0.0001	11 (8-17)	< 0.005
HBP D	17 (13-24)	13 (10-19)	< 0.0001	10 (7-16)	< 0.005
Average D	17 (13-24)	13 (11-20)		10 (7-15)	< 0.009
ADC	1.0	1.4	< 0.0006	1.4	0.19
T2-weighted hyperintensity	38 (62%)	18 (30%)	< 0.0001	9 (25%)	0.81
DWI	41 (68%)	11 (18%)		3 (9%)	0.34
Ring enhancement		50 (82%)		25 (69%)	0.24
Perilesional T2 hyp		51 (84%)		27 (75%)	0.44
HBP band-like		58 (95%)		34 (94%)	0.74
Capsular retraction		20 (33%)		23 (64%)	0.006
Infield progression		3 (5%)		1 (3%)	
Outfield progression		11 (18%)		10 (28%)	

SBRT: Stereotactic body radiation therapy; FU: Follow-up; MRI: Magnetic resonance imaging; T: Time; D: Diameter; HBP: Hepatobiliary phase; ADC: Apparent diffusion coefficient; DWI: Diffusion-weighted imaging.



Variable	Count	Mean	Minimum	Q1	Median	Q3	Maximum
Pre	61	20.115	8	13	17	24	49
MR_post1	61	15.525	0	11	13	19.5	41.5
MR_post2	36	11.183	0	6.75	10	15.125	30

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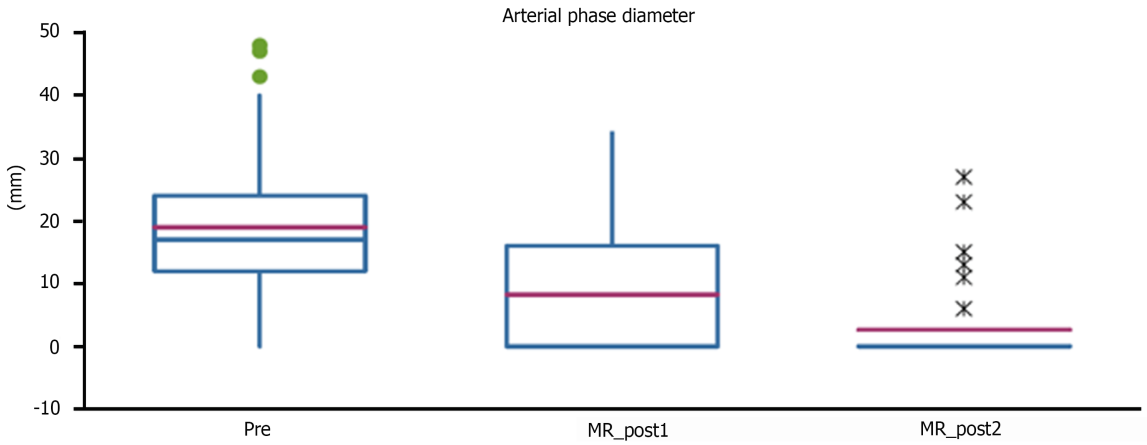
Figure 1 Change in lesion diameter. MR: Magnetic resonance.

The study showed the effectiveness of the treatment in controlling local disease, in particular, as already described in the literature, the reduction in the diameters of the lesion assessed (arterial, hepatobiliary, and basal sequences) also becomed increasingly marked at the controls following the first[5,6].

This phenomenon is attributable to microscopic phenomena due to venocclusion that leads to fibrosis and collapse of the liver lobules at a late stage, and a reduced nutrient supply to the lesion and a progressive volumetric reduction of the whole radio-treated parenchyma[12,13].

In addition to the analysis of the classical criteria for locoregional treatment, the study focused on the analysis of signal intensities in the T2- and DWI-weighted sequences. Both sequences provide



Variable	Count	Mean	Minimum	Q1	Median	Q3	Maximum
Pre	61	19	0	12	17	24	48
MR_post1	61	8.2459	0	0	0	16	34
MR_post2	36	2.6389	0	0	0	0	27

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Figure 2 Tissue diameter with wash-in at pre-stereotactic body radiation therapy and follow-ups. MR: Magnetic resonance.

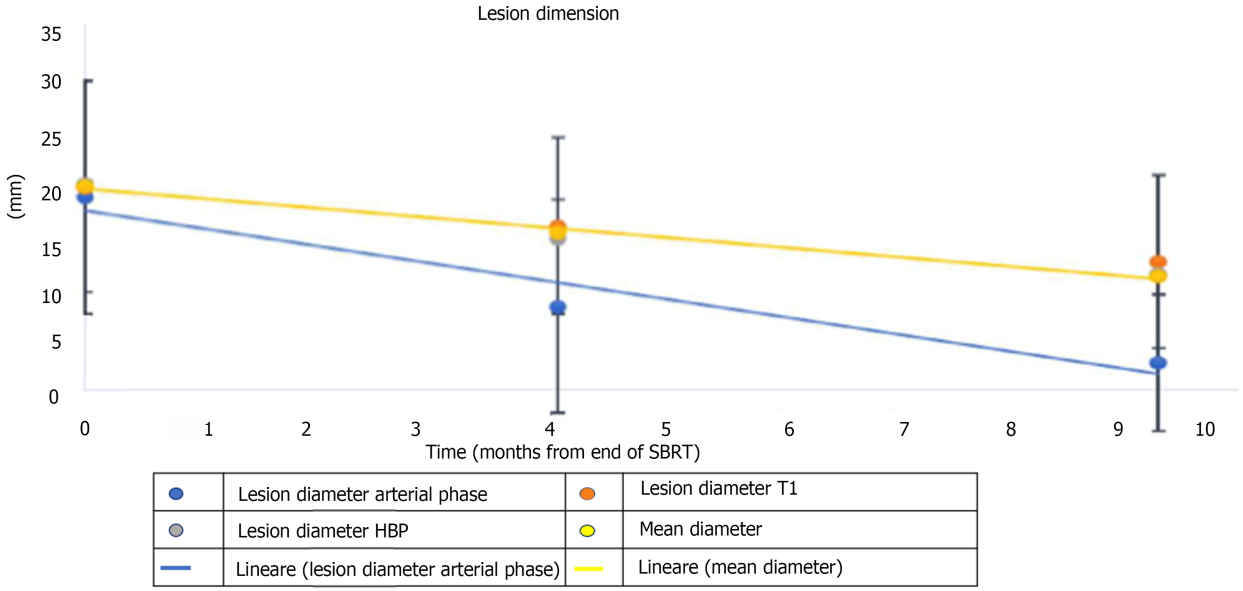

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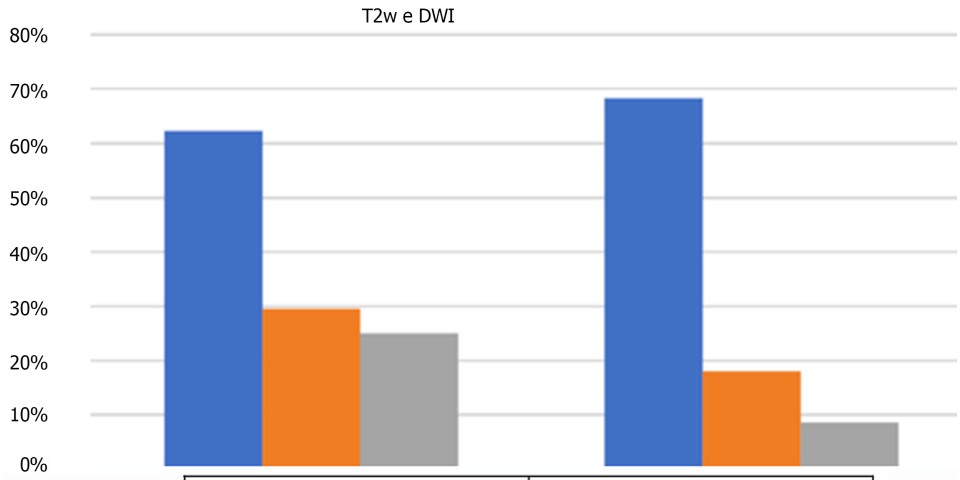
Figure 3 Variation in lesion diameters over time in basal, arterial, and hepatobiliary excretion phases.

information about the nature of the tissue and the cellularity of the lesion and are therefore useful "sentinel" parameters of treatment outcome.

Signal hyperintensity both in the long TR and DWI sequences tended to decrease at the first control, remaining stable at subsequent controls, showing isointensisty to the surrounding liver parenchyma[6,10].

There is a statistically significant increase in the ADC values measured before and after SBRT, probably due to a reduction in the cellularity of the lesions due to necrosis.

As already described by Oldrini *et al*[10], persistence of arterial enhancement after stereotactic radiotherapy is common. In particular, arterial enhancement persisted in our population, but its diameter tended to decrease over time, probably due to progressive and slow necrosis and intralesional gigantocellular reaction. If this hypervascularisation, especially in a short-distance follow-up, was to be assessed in the same way as other locoregional therapies according to mRECIST criteria, it would be considered as a persistence of viable tissue and evaluated as ineffective[9,10]. This is in contradiction



	T2w	DWI
Pre	62%	68%
MR_post1	30%	18%
MR_post2	25%	9%

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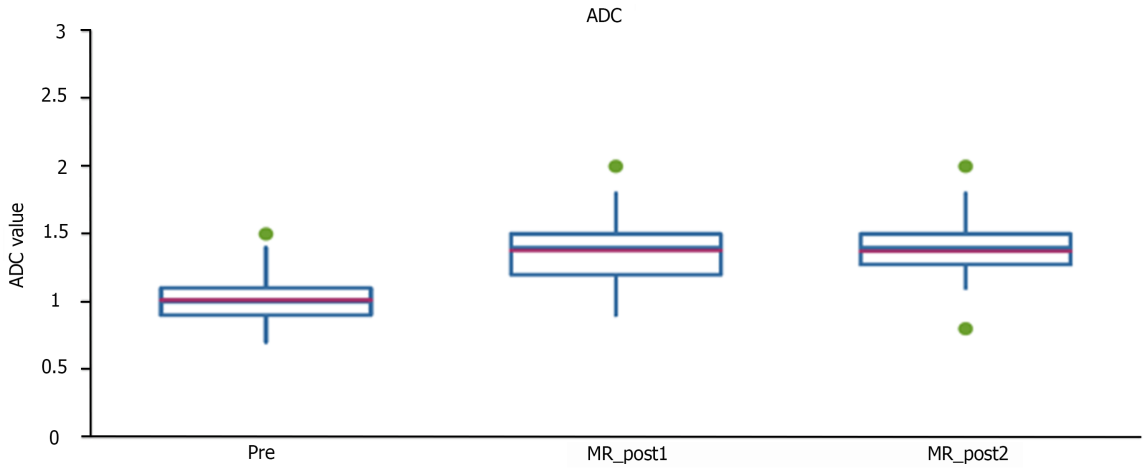
Figure 4 Frequency of signal hyperintensity in T2-weighted and diffusion-weighted imaging sequences. MR: Magnetic resonance; DWI: Diffusion-weighted imaging.



Variable	Count	Mean	Minimum	Q1	Median	Q3	Maximum	*P*
Pre	61	1.01	0.7	0.9	1	1.1	1.5	
MR_post1	61	1.38	0.9	1.2	1.4	1.5	2	< 0.0001
MR_post2	36	1.37	0.8	1.275	1.4	1.5	2	

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Figure 5 Apparent diffusion coefficient value at pre-stereotactic body radiation therapy and follow-ups. MR: Magnetic resonance; ADC: Apparent diffusion coefficient.

with what was reported in the literature, attesting to a percentage of complete response to SBRT that tends to progressively increase up to 90% at 12-24 mo after treatment, a figure confirmed by our study in which infield progression at the second control was 3%.

For a correct interpretation of post-procedural imaging, it is essential to recognize features in the peri-injury parenchyma and how they change over time: Peripheral hypervascularisation, signal hyperintensity in long TR sequences, and band hypointensity in the hepatobiliary excretion phase.

In the context of computed tomography (CT), the imaging characteristics of focal hepatic reaction have been well described. In the immediate post-treatment, hyperdensity occurs in early vascular phase

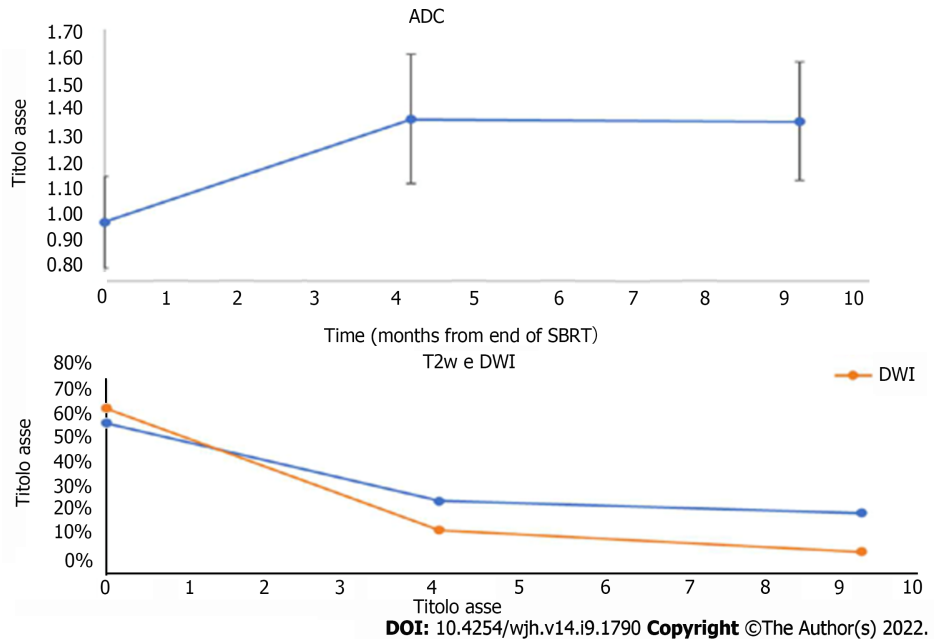

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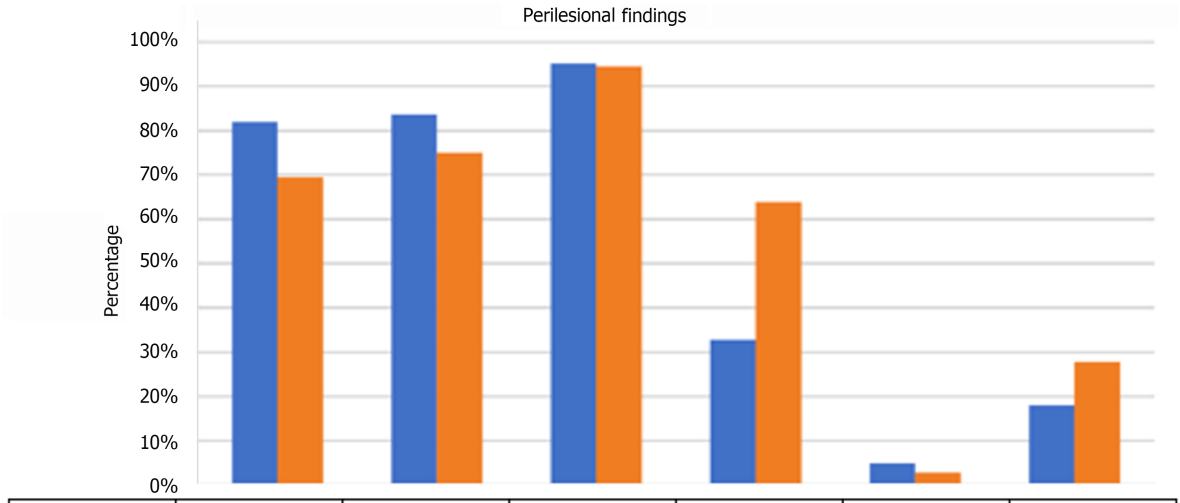
Figure 6 Comparison of changes in T2-weighted and diffusion-weighted imaging findings and apparent diffusion coefficient values over time. ADC: Apparent diffusion coefficient; DWI: Diffusion-weighted imaging; T2W: T2-weighted; SBRT: Stereotactic body radiation therapy.



	Ring-like enhancement	Perilesional T2-hyperintinsity	HBP band-like focal reaction	Capsular retraction	INFIELD progression	OUTFIELD progression
MR_post1	82%	84%	95%	33%	5%	18%
MR_post2	69%	75%	94%	64%	3%	28%

DOI: 10.4254/wjh.v14.i9.1790

Figure 7 Frequency of perilesional parenchyma findings. MR: Magnetic resonance; HBP: Hepatobiliary phase.

as a consequence of sinusoidal congestion and reduced venous drainage, which gradually subsides in the portal and late phases. This may make it difficult to distinguish any persistence of hypervascularised lesional tissue in the arterial phase.

Over time, as fibrosis sets in, there will be contrastographic impregnation of the closely packed parenchyma closely contiguous to the lesion, included in the field of irradiation in the late stages[14].

The above contrastographic features, defined as "ring-like" enhancement, were similarly present in the MRI survey of our population.

Associated with this aspect is the signal hyperintensity of the treated areas in the acquisitions with T2-weighted and fat saturated T2-weighted sequences, which is also an indicator of radio-induced venoocclusive damage, which in the earliest phases is due to oedema and hyperemia, and with time to fibrosis[15].

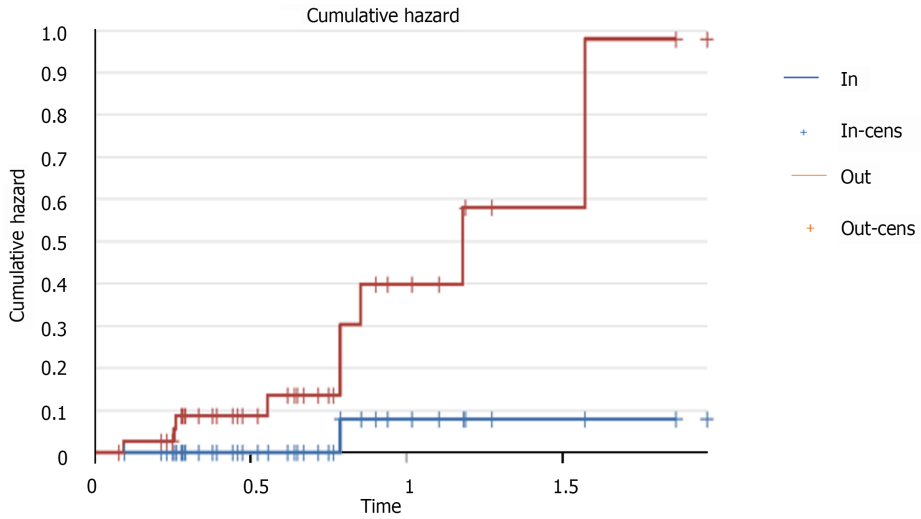


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Figure 8 Risk of presenting infield and outfield progression over time.

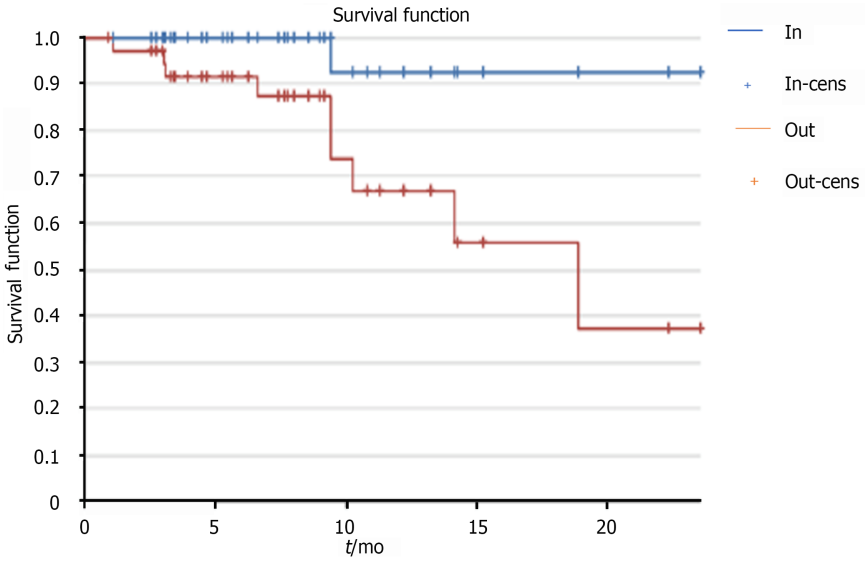

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Figure 9 Infield and outfield progression and impact on survival.

This latter factor is particularly evident in the phenomenon of capsular retraction, present in 64% of cases at the late follow-up.

All these described elements confirm the data available in the literature on the capability of multiparametric MRI in the evaluation of locoregional hepatic therapy both in terms of post-procedural control and follow-up.

The use of liver specific contrast agents, based on the functional alteration of the hepatocytes, allows precise delineation of the irradiated field, which will appear hypointense during excretion, with a typical "band" configuration[7,8,16]. This alteration further highlights how radiotherapy-induced structural changes in the liver through veno-venous disease can have a negative impact on the liver's immune system.

We have also found a direct correlation between the focal hepatic reaction volume calculated by segmentation and the PTV programmed by radiotherapy of the parabolic type.

The fact that beyond a certain PTV there is not an equal increase in the volume of focal hepatic reaction area could be explained by two factors, one of which is closely linked to the MRI method, which does not allow adequate quantification of the parenchyma. The other explanation could be due to the fibrotic response of the liver: Greater fibrosis in absolute terms results in a greater reduction in liver volume, thus negatively affecting the quantification of the area of hypointensity. According to some authors, this association could be exploited from a clinical-radiotherapeutic point of view both to assess the accuracy of centering and possibly modify it by reducing radio-induced damage, and to quantify "*in*

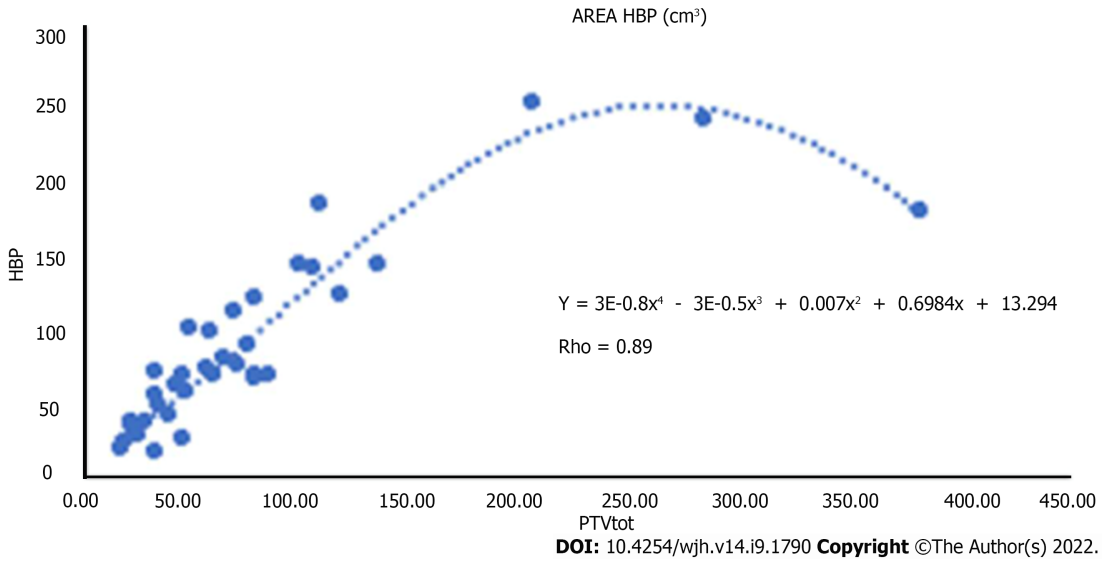

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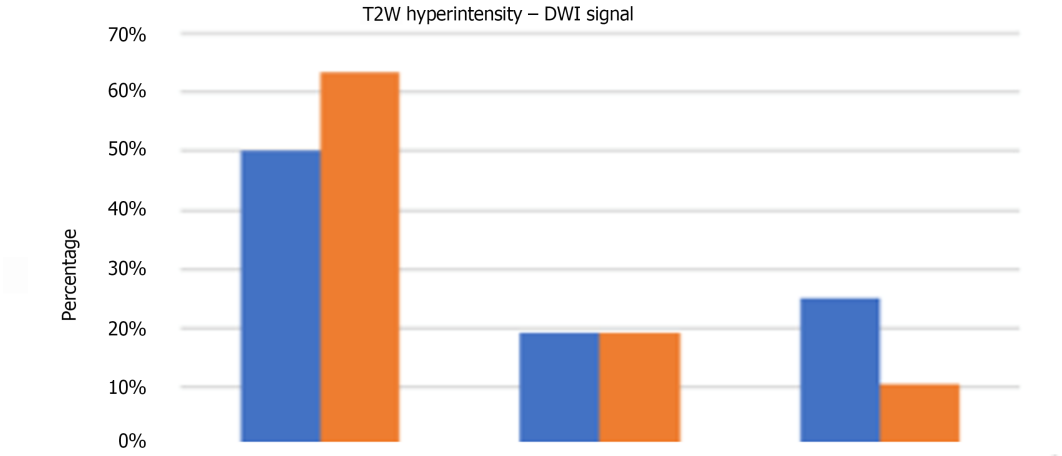
Figure 10 Relationship between hepatobiliary phase hypointensity area and planning target volume. HBP: Hepatobiliary phase.



	Pre	1st POST	2nd POST
T2W hyperintensity	50%	19%	25%
DWI intensity	63%	19%	11%

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Figure 11 T2-weighted hyperintensity and diffusion-weighted imaging signal percentage at pre-stereotactic body radiation therapy and follow-ups. T2W: T2-weighted; DWI: Diffusion-weighted imaging.

vivo" radiation-induced liver damage and use it as a quantitative biomarker of hepatotoxicity[17-20] .

Nevertheless, the integration of liver function parameters and MRI-quantifiable liver damage might in the future allow further customised dose delivery or provide additional information to the radiologist in the post-therapeutic evaluation, so as to identify possible biomarkers predictive of liver damage.

However, this finding, which can be obtained from the earliest post-treatment controls, underlines the technical accuracy of the procedure.

In our population, no correlation was found between the occurrence of toxicity, the change in blood values, and the radiological findings described.

The stability of these characteristics of good response to treatment and frequency of infield progression is concomitant with the rise of the frequency curve of outfield progression, which from the 9th month onwards is 9 times more frequent than local progression. This finding could lay a basis for different follow-up timing in patients treated by SBRT.

It is in fact known that histological changes cause long-term radiological effects, therefore delaying the first follow-up in selected patients beyond the usual 6 mo (all too often not respected) would allow radiologist to express more confidence in the treatment region and at the same time have a greater

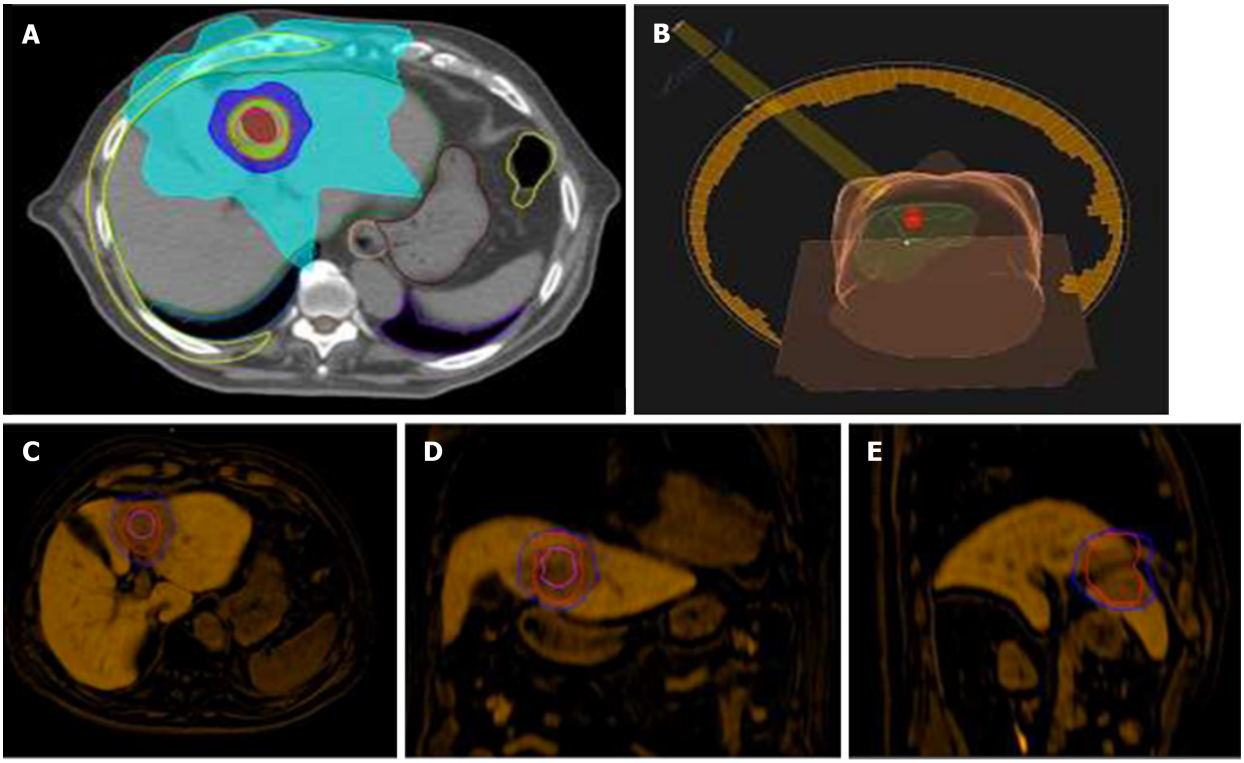

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Figure 12 Stereotactic body radiation therapy planning for hepatocellular carcinoma. A: Radiotherapy treatment planning with visualization of clinical target volume (pink line), planning target volume (red line), and areas of decreasing isodose; B: 3D rendering of the radiation beam and its incidence on the patient once positioned on the couch; C-E: Fusion Imaging of pre-stereotactic body radiation therapy planning (clinical target volume, pink line; planning target volume, red line; Isodose, 50% blue line) with magnetic resonance imaging images of the hepatobiliary excretion phase obtained 6 mo after the end of treatment. Band-like hypodensity during hepatobiliary excretion, an expression of functional resentment of the radio-treated parenchyma, is superimposed on the planning target volume area.

chance of detecting new liver lesions, thus allowing a better correct staging.

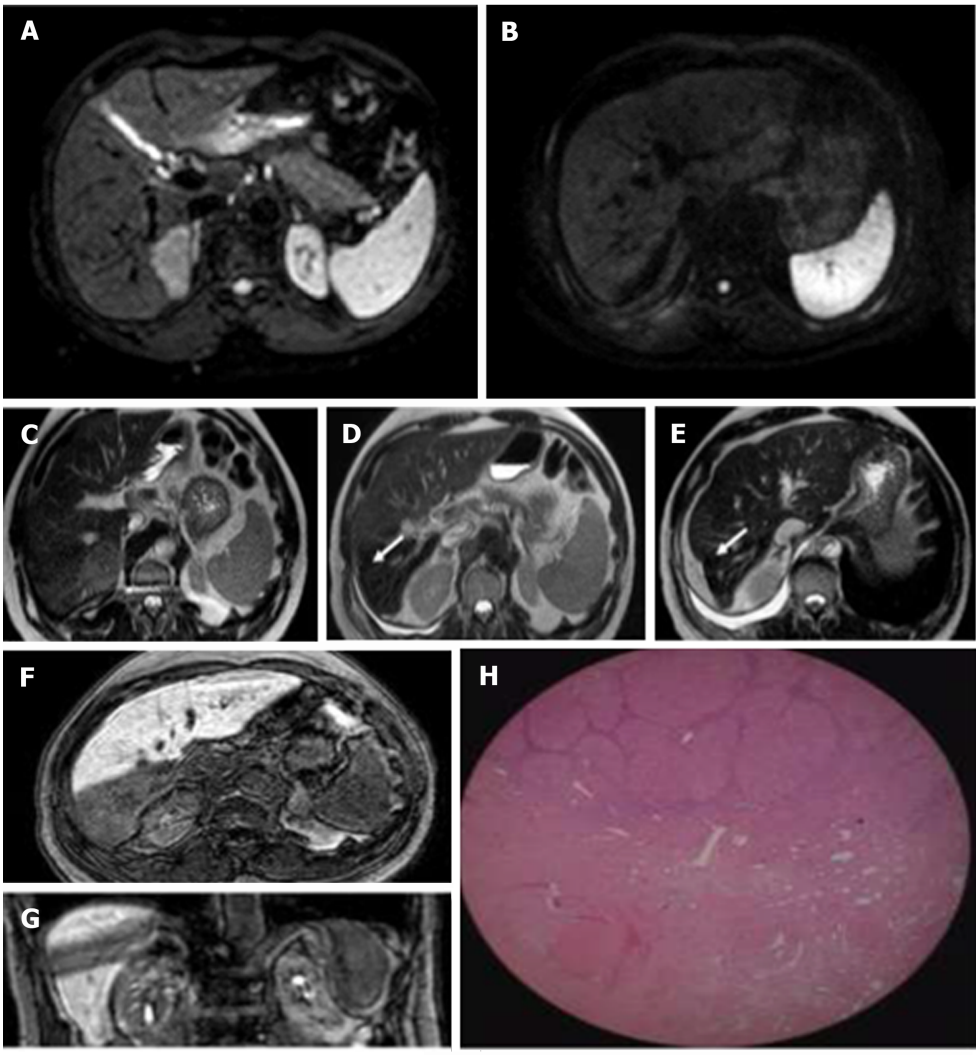
This study showed the effectiveness of treatment in controlling local disease; indeed, while infield progression decreased from 5% to 3% of the population at subsequent controls, outfield progression tended to increase (from 18% to 28%). However, although it is increasingly used in clinical practice today, the assessment of its effects by MRI is still lacking.

Limitations of this work are undoubtedly its retrospective nature. This leads both to a lack of systematic planning of the diagnostic procedure of the patients, which sometimes results in an incorrect and non-standardised timing, and to a low population size, since many patients, especially in the follow-ups after the first one, undergo CT scans. Moreover, given the highly differentiated indications, patients undergoing SBRT are a particularly heterogeneous population including individuals with very different lesion sizes and stages. It is therefore clear that this does not allow an indication of the impact of the treatment on survival.

In addition, as a treatment is particularly effective in controlling local disease, it is not possible to create two comparative subpopulations in order to identify any prognostic or predictive indicators of response to treatment.

CONCLUSION

In conclusion, our study emphasized the role of liver MRI after SBRT for HCC: A multiparametric approach using a liver specific contrast agent provides more information about lesion and liver parenchyma changes compared to conventional CT studies. The direct correlation between the area of hypointensity in the hepatobiliary phase and the PTV is indicative of the accuracy of the radiotherapy treatment and useful to define the infield and outfield progression of the disease.



DOI: 10.4254/wjh.v14.i9.1790 **Copyright** ©The Author(s) 2022.

Figure 13 Hepatocellular carcinoma in a 75-year-old man treated with stereotactic body radiation therapy. A and B: Diffusion-weighted imaging signal of a lesion located in segment VII, before and after treatment. In the pre-therapy evaluation, the nodule presented a marked narrowing of the diffusion of water molecules, a feature no longer present at post-stereotactic body radiation therapy (SBRT) examination; C: Hepatocellular carcinoma nodule located in segment VII characterized by intermediate signal on T2-weighted imaging; D and E: Initial capsular retraction (white arrow) was already evident at the first post-SBRT magnetic resonance examination and particularly evident at the 9 mo follow-up; F and G: SBRT outcomes characterised by an area of "band" hypodensity in the hepatic excretion phase in the axial and coronal sequences, corresponding to shaded hyperintensity in the T2-weighted sequences with the same distribution and morphology; H: These findings are an expression of treatment-induced fibrosis as demonstrated by the histological finding, where postradiotherapy fibrotic tissue can be identified after liver transplantation.

ARTICLE HIGHLIGHTS

Research background

Although stereotactic body radiation therapy (SBRT) is increasingly used, its application has not yet been regulated by the main international guidelines, leaving the decision to multidisciplinary teams.

Research motivation

Literature is lacking in works assessing the role of liver magnetic resonance imaging (MRI) in the evaluation of hepatocellular carcinoma (HCC) treated by SBRT.

Research objectives

To analyse MRI features of HCC lesions treated by SBRT and monitor how these properties evolve over time and how these aspects may modify subsequent diagnostic course of therapy.

Research methods

A retrospective observational study was conducted in 49 patients (mean age 64.44 years, range 48.71-84.51), 22 females and 27 males, undergoing radiotherapy between January 2013 and November 2019.

Research results

The most significant results came from the evaluation of infield and outfield progression. The risk increased as time progressed, with a sharp increase in the cumulative outfield progression hazard of around 9 after the end of therapy, as shown by the Kaplan-Meier curve study.

Research conclusions

A multiparametric approach using a liver specific contrast agent provides more information about lesion and liver parenchyma changes compared to conventional computed tomography studies. The direct correlation between the area of hypointensity in the hepatobiliary phase and the PTV is useful to define the infield and outfield progression of the disease.

Research perspectives

Future studies should enlarge the sample of patients and perform further follow-ups for the patients who have already undergone the first two checks.

FOOTNOTES

Author contributions: All authors equally contributed to this paper with conception and design of the study, literature review and analysis, manuscript drafting, critical revision, and editing, and approval of the final version.

Institutional review board statement: This retrospective observational study was previously approved by the Intercompany Ethics Committee of the City of Health and Science of Turin.

Informed consent statement: Patients were not required to give informed consent to the study because the analysis used anonymous clinical data that were obtained after each patient agreed to treatment by written consent.

Conflict-of-interest statement: All the authors are aware of the content of the manuscript and have no conflict of interest to disclose.

Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author at riccardoin@hotmail.it. Consent was not obtained but the presented data are anonymized and risk of identification is low.

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ORIGINAL ARTICLE

Retrospective Study

Hereditary hemochromatosis: Temporal trends, sociodemographic characteristics, and independent risk factor of hepatocellular cancer – nationwide population-based study

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Abstract

BACKGROUND

Hereditary hemochromatosis (HH) has an increased risk of hepatocellular cancer (HCC) both due to genetic risks and iron overload as iron overload can be carcinogenic; HH impacts the increasing risk of HCC, not only through the development of cirrhosis but concerning hepatic iron deposition, which has been studied further recently.

AIM

To evaluate HH yearly trends, patient demographics, symptoms, comorbidities, and hospital outcomes. The secondary aim sheds light on the risk of iron overload for developing HCC in HH patients, independent of liver cirrhosis complications. The study investigated HH (without cirrhosis) as an independent risk factor for HCC.

METHODS

We analyzed data from National Inpatient Sample (NIS) Database, the largest national inpatient data collection in the United States, and selected HH and HCC cohorts. HH was first defined in 2011 International Classification of Disease - 9th edition (ICD-9) as a separate diagnosis; the HH cohort is extracted from January 2011 to December 2019 using 275.01 (ICD-9) and E83.110 (ICD-10) diagnosis codes of HH. Patients were excluded from the HH cohort if they had a primary or secondary diagnostic code of cirrhosis (alcoholic, non-alcoholic, and biliary), viral

hepatitis, alcoholic liver disease, non-alcoholic fatty liver disease (NAFLD), and non-alcoholic steatohepatitis (NASH). We removed these patients from the HH cohort to rule out bias or ICD-10 diagnostic errors. The HCC cohort is selected from January 2011 to December 2019 using the ICD-9 and ICD-10 codes of HCC. We selected a non-HCC cohort with the 1:1 fixed ratio nearest neighbor (greedy) propensity score method using the patients' age, gender, and race. We performed multivariate analysis for the risk factors of HCC in the HCC and non-HCC matched cohort. We further analyzed HH without cirrhosis (removing HH patients with a diagnosis of cirrhosis) as an independent risk factor of HCC after adjusting all known risk factors of HCC in the multivariate model.

RESULTS

During the 2011-2019 period, a total of 18031 hospitalizations with a primary or secondary diagnosis of HH (excluding liver diseases) were recorded in the NIS database. We analyzed different patients' characteristics, and we found increments in inpatient population trend with a Ptrend < 0.001 and total hospital cost of care trend from $42957 in 2011 to $66152 in 2019 with a Ptrend < 0.001 despite no change in Length of Stay over the last decade. The multivariate analyses showed that HH without cirrhosis (aOR, 28.8; 95%CI, 10.4–80.1; $P < 0.0001$), biliary cirrhosis (aOR, 19.3; 95%CI, 13.4–27.6; $P < 0.0001$), non-alcoholic cirrhosis (aOR, 17.4; 95%CI, 16.5–18.4; $P < 0.0001$), alcoholic cirrhosis (aOR, 16.9; 95%CI, 15.9–17.9; $P < 0.0001$), hepatitis B (aOR, 12.1; 95%CI, 10.85–13.60; $P < 0.0001$), hepatitis C (aOR, 8.58; 95%CI, 8.20–8.98; $P < 0.0001$), Wilson disease (aOR, 4.27; 95%CI, 1.18–15.41; $P < 0.0001$), NAFLD or NASH (aOR, 2.96; 95%CI, 2.73–3.20; $P < 0.0001$), alpha1-antitrypsin deficiency (aOR, 2.10; 95%CI, 1.21–3.64; $P < 0.0001$), diabetes mellitus without chronic complications (aOR, 1.17; 95%CI, 1.13–1.21; P < 0.0001), and blood transfusion (aOR, 1.80; 95%CI, 1.69–1.92; $P < 0.0001$) are independent risk factor for liver cancer.

CONCLUSION

Our study showed an increasing trend of in-hospital admissions of HH patients in the last decade. These trends were likely related to advances in diagnostic approach, which can lead to increased hospital utilization and cost increments. Still, the length of stay remained the same, likely due to a big part of management being done in outpatient settings. Another vital part of our study is the significant result that HH without cirrhosis is an independent risk factor for HCC with adjusting all known risk factors. More prospective and retrospective large studies are needed to re-evaluate the HH independent risk in developing HCC.

Key Words: Hereditary hemochromatosis; Hepatocellular carcinoma, cirrhosis; Hepatitis; Diabetes mellitus; Nonalcoholic fatty liver disease; Nonalcoholic steatohepatitis; Wilson disease; Alpha1-antitrypsin deficiency; Blood transfusion; Epidemiology; Demographics; Big data; Hospitalization

Core Tip: Our study is a National Inpatient Sample -based study in which we aim to analyze hereditary hemochromatosis (HH) patients' characteristics, temporal trends, and sociodemographic characteristics over the last decade, in addition to studying this disease as an independent risk factor for developing hepatocellular cancer (HCC) without the stage of liver cirrhosis. Our large and diverse sample of about 18000 HH hospitalizations showed an increasing trend of inpatient admissions and costs with a similar length of hospital stay over the last decade. It also showed HH as an independent risk factor for HCC with an aOR close to 29 on multivariate analysis. We believe this will open the door for further retrospective and prospective studies to address disease trends and the understudied and independent relationship between HH and HCC in a large patient cohort.

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INTRODUCTION

Hereditary hemochromatosis (HH) is a genetic disorder of iron metabolism that increases alimentary iron absorption. It is a common inherited iron metabolism disorder characterized by increasing iron deposition in body organs[1]. Organs mainly involved in this disease include the liver, skin, pancreas, heart, joints, pituitary gland, and testes resulting in these organ dysfunctions[2]. As hepatocytes store the most considerable portion of the excess iron, the liver is the most affected organ leading to liver fibrosis, cirrhosis, and hepatocellular carcinoma (HCC)[3].

HCC is the most common type of primary liver cancer and is one of the leading causes of cancer-related death worldwide. It mainly affects patients suffering from chronic liver diseases such as viral, alcoholic, metabolic, or autoimmune hepatitis and cirrhosis[4]. Per one study, HCC incidence rates have been rising in the past three decades, and by the year 2025, more than a million individuals are expected to be affected annually[5].

HH has an increased risk of HCC both due to genetic risks and iron overload as iron overload can be carcinogenic; HH impacts the increasing risk of HCC, not only through the development of cirrhosis but concerning hepatic iron deposition, which has been studied further recently. The role of iron in carcinogenesis is presumed mainly through reactive oxygen species generation, which is studied in many disorders such as asbestos fibers exposure and endometriosis[6-8]. Interestingly, some studies have shown that excess body iron may be complicated by developing HCC independently of any underlying liver disease due to the carcinogenic effects of iron, which can promote direct malignant transformation in hepatocytes[9-11].

According to the Centers for Disease Control and Prevention, the prevalence of HH is one case in three hundred in the United States[12]. Given the rarity of the disease, in the past, only a few studies have been done to evaluate HH patients, their comorbidities, and the disease's effect on developing HCC.

MATERIALS AND METHODS

Data source

We analyzed data from NIS Database, the largest national inpatient data collection in the United States. The NIS is a part of the healthcare and cost utilization project (HCUP), developed through a federal-state industry partnership and maintained by the agency of healthcare research quality (AHRQ). The NIS is a weighted dataset containing over 7 million admissions per year, representing a 20% stratified sample of all discharges[13]. The NIS includes discharge weights to produce national or regional estimates. The discharge weights were calculated for NIS data by first stratifying the NIS hospitals on the same variables used for creating samples. These variables were census division, urban/rural location, *etc*. The discharge weights are applied to the unweighted data; the result estimates the number of discharges for the entire community hospitals in the US. The dataset comprises patients' demographic, clinical and economic data. All medical procedures and diagnoses are coded using the International Classification of Disease - 9th edition (ICD-9) until 2015 Q3 and upgraded to ICD-10 in September 2015 with redesigned sampling techniques and weights[14-16]. For analyzing trends for multiple years, we followed HCUP guidelines and used trend weight (Trendwt) for years before 2012 and discharge weights (discwt) with 2012 onward[17]. As the dataset is publicly available and lacks patients' identification, Institutional Review Board (IRB) approval or informed consent was not required under the Health Insurance Portability and Accountability Act[18].

Variables and outcomes

We worked on two separate data populations in this study, HH and HCC cohorts. HH was first defined in 2011 ICD-9 as a separate diagnosis in the NIS dataset; the HH cohort is extracted from January 2011 to December 2019 using 275.01 (ICD-9) and E83.110 (ICD-10) diagnosis codes of HH. Patients were excluded from the HH cohort if they had a primary or secondary diagnostic code of cirrhosis (alcoholic, non-alcoholic, and biliary), viral hepatitis, alcoholic liver disease, non-alcoholic fatty liver disease (NAFLD), and non-alcoholic steatohepatitis (NASH). We removed these patients from the HH cohort to rule out bias or ICD-10 diagnostic errors. The HCC cohort is also extracted from January 2011 to December 2019 using ICD-9 and ICD-10 codes. The primary outcomes of the HH cohort included HH yearly trends, demographics, symptoms, comorbidities, and hospital outcomes. The secondary outcomes on the HCC cohort investigated HH without cirrhosis as an independent risk factor for HCC after accounting for all known other risk factors of HCC.

Statistical analysis

We performed data and statistical analyses using R Studio 1.4 and SAS statistical software (SAS Institute Inc., Cary, NC, United States). Categorical variables are presented using the frequency distribution, and continuous variables such as age and total charges were presented using the mean ± standard deviation (SD). We performed weighted analysis to improve national estimates and followed year-specific AHRQ

recommendations[13]. Group comparisons were performed using the student's t-test for continuous variables and the χ^2 test for categorical variables. We divided age into five categories for group-level comparison (< 18; 18-44; 45-64; 65-84; and ≥ 85 years of age). The age group categories were selected from HCUPnet, an online tool for identifying, tracking, and analyzing healthcare statistics[19]. We computed established risk factors for HCC in HCC patients and compared them against matched non-HCC patients. We selected a non-HCC cohort with the 1:1 fixed ratio nearest neighbor (greedy) propensity score method using the patients' age, gender, and race. We performed hypothesis testing using a two-tailed *P* value with the significance level set at 0.05. Due to the limited number of HH patients, we did not remove patients with missing data on race, primary payer, median household income, discharge status, and hospital variables. The missing data was labeled as "other."

Model design

We performed a univariate analysis of risk factors for HCC from logistic regression models. We selected all significant variables in the univariate analysis in the first step. Next, we analyzed the variables for multicollinearity by creating a correlation matrix using Pearson correlation coefficients and removing highly correlated regressors. Then, the model is selected from the remaining regressors with lasso selection (shrinkage and regularization), choosing the external 10-fold cross-validation criteria. Finally, the multivariate analysis is performed on the selected model using multi-level mixed effect models with SAS's GLIMMIX procedure with hospital identifier as a random effect.

RESULTS

Patient characteristics

During the 2011-2019 period, a total of 18031 hospitalizations with a primary or secondary diagnosis of HH (excluding liver diseases) were recorded in the NIS database. Baseline demographic and hospital characteristics, comorbidities, clinical symptoms, substance use, and family history of HH patients are shown in Table 1 and Supplementary Table 1. HH patients in the United States were mostly male (62%), with a mean age of 62 years (SD ± 15); the majority were aged between 65–84 years old (44%; 95%CI; 42.2–45.7), predominantly white race (88%; 95%CI; 86.6–89.2) with Medicare insurance (52%; 95%CI; 49.9–53.6) and have highest estimated median household income in quartile 4 (29%; 95%CI; 27.2–30.5). In terms of hospital characteristics, the majority of HH patients were admitted to large (55%; 95%CI; 53.9–56.3) urban teaching (70%; 95%CI; 68.9–70.8) hospitals in the south region (30%; 95%CI; 29.4–31.6). The most common comorbidities included Hypertension (44%;95%CI; 42.0–45.5), lipid metabolism disorders (38%; 95%CI; 35.9–39.3), arrhythmias (24%; 95%CI; 22.1–25.1), coronary artery disease (19%; 95%CI; 17.2–20.2), thyroid disorders (18%;95%CI; 16.9–19.6), heart failure (16%; 95%CI; 14.5–17.1), obesity (16%; 95%CI; 15.1–17.9), and depression (15%; 95%CI; 13.5–16.1). Musculoskeletal pain (5.6; 95%CI; 4.79–6.42) was the most common clinical symptom, followed by malaise and fatigue (3.1%; 95%CI; 2.49–3.68), arthropathy (2.1%; 95%CI; 1.65–2.61), disorientation (2.1%; 95%CI; 1.61–2.54), weight loss (1.2%; 95%CI; 0.81–1.641), and hypogonadism (1.1%; 95%CI; 0.66–1.49).

Trends in Hospital admission, length of stay, and hospitalization cost for HH patients

Figure 1 shows the annual trends in hospital admissions for HH patients from 2011 to 2019. An increasing inpatient population trend) was observed in NIS from 861 patients in 2011 to 3535 patients in the weighted sample with Ptrend < 0.001. There has been no change in Length of Stay (LOS) over the last decade (Figure 2). Although LOS stays the same, an increasing trend is noted for the total hospital cost of care from $42957 in 2011 to $66152 in 2019 with Ptrend < 0.001 (Figure 3).

HCC risk factors' analysis

In our study, the incidence of liver cancer in HH patients is 1.2% (95%CI; 0.78–1.53), unrelated to cirrhosis, viral hepatitis, alcoholic liver disease, NAFLD, and NASH. We performed multivariate analysis for the risk factors of HCC in the HCC and non-HCC matched cohort. We analyzed HH without cirrhosis (removing HH patients with a diagnosis of cirrhosis) as an independent risk factor of HCC after adjusting all known risk factors of HCC in the multivariate model. Table 2 compared HCC risk factors in the HCC population (cases) *vs* age-, sex-, race- matched non-HCC (controls) cohort. HH with cirrhosis is 0.12% for cases *vs* 0.01% for controls with a *P* value of < 0.0001, and HH without cirrhosis is 0.05% for cases *vs* 0.005% for controls with a *P* value of < 0.0001.

We investigated multicollinearity among known risk factors for HCC by generating a correlation matrix. Supplementary Table 2 shows the correlation matrix using Pearson's correlation coefficients between variables. Multicollinearity occurs when independent variables in a regression model are correlated. However, this correlation is problematic as the regression model investigates associations, and multicollinearity among the predictor variables can obscure the computations[20]. Therefore, we excluded HH with Cirrhosis (correlation of 0.65 with HH without Cirrhosis), alcoholic liver disease (correlation of 0.97 with alcoholic cirrhosis), and alcohol (correlation of 0.69 with alcoholic cirrhosis)

Table 1 Patient characteristics, comorbidities in hereditary hemochromatosis (excluding liver diseases) patients

Variables	Weighted, *n*	Weighted, % (95%CI)
Total, *n*	18031	
Sex		
Female	6903	38.27 (36.59–39.9)
Male	11123	61.69 (59.9–63.4)
Age (y), mean (SD)	62.19 ± 34.36	
Age groups (yr)		
< 18	158	0.88 (0.54–1.20)
18-44	2046	11.37 (10.2–12.5)
45-64	7007	38.90 (37.15–40.6)
65-84	7933	43.93 (42.2–45.7)
85+	887	4.91 (4.15–5.69)
Race/Ethnicity		
White	15850	87.87 (86.6–89.2)
Black	315	1.76 (1.30–2.19)
Hispanic	545	3.01 (2.42–3.62)
Asian or Pacific Islander	105	0.58 (0.33–0.83)
Native American	30	0.17 (0.03–0.30)
Other	1186	6.60 (5.52–7.63)
Comorbidities		
Coronary artery disease	3357	18.61 (17.24–20.0)
Cardiomyopathy	900	4.99 (4.19–5.79)
Arrythmias	4250	23.57 (22.1–25.1)
Heart failure	2848	15.79 (14.5–17.1)
Liver cancer	209	1.16 (0.78–1.53)
HIV	35	0.19 (0.05–0.34)
Alpha1-antitrypsin deficiency	55	0.31 (0.11–0.49)
Disorders of porphyrin metabolism	105	0.58 (0.30–0.86)
Hepatomegaly	123	0.68 (0.38–0.98)
Splenomegaly	169	0.93 (0.56–1.32)
Hypertension	7892	43.76 (42.0–45.5)
Diabetes mellitus with chronic complications	2323	12.88 (11.7–14.1)
Diabetes mellitus without chronic complications	2485	13.78 (12.6–15.0)
Lipid metabolism disorders	6781	37.60 (35.9–39.3)
Thyroid disorders	3285	18.21 (16.9–15.6)
Pancreatitis	484	2.69 (2.13–3.23)
Pituitary disorders	259	1.43 (0.99–1.87)
Obesity	2971	16.48 (15.1–17.9)
Depression	2673	14.82 (13.5–16.1)
Symptoms		
Musculoskeletal pain	1011	5.61 (4.79–6.42)
Malaise and fatigue	557	3.09 (2.49–3.68)

Arthropathy	384	2.13 (1.65–2.61)
Weight Loss	219	1.22 (0.81–1.61)
Loss of appetite	87	0.49 (0.26–0.70)
Hypogonadism	193	1.07 (0.66–1.49)
Erectile dysfunction	140	0.78 (0.45–1.10)
jaundice	184	1.02 (0.67–1.38)
Disorientation	374	2.07 (1.61–2.54)
Family history		
Family history of diseases of the circulatory system	1109	6.15 (5.26–7.04)
Family history of diabetes mellitus	500	2.77 (2.17–3.37)
Family history of malignant neoplasms	814	4.51 (3.77–5.25)
Substance use		
Smoking	7577	42.02 (40.2–43.8)
Alcohol	1536	8.52 (7.49–9.54)
Cannabis use	219	1.22 (0.83–1.60)
Opioids	315	1.74 (1.29–2.20)

HIV: Human immunodeficiency virus.

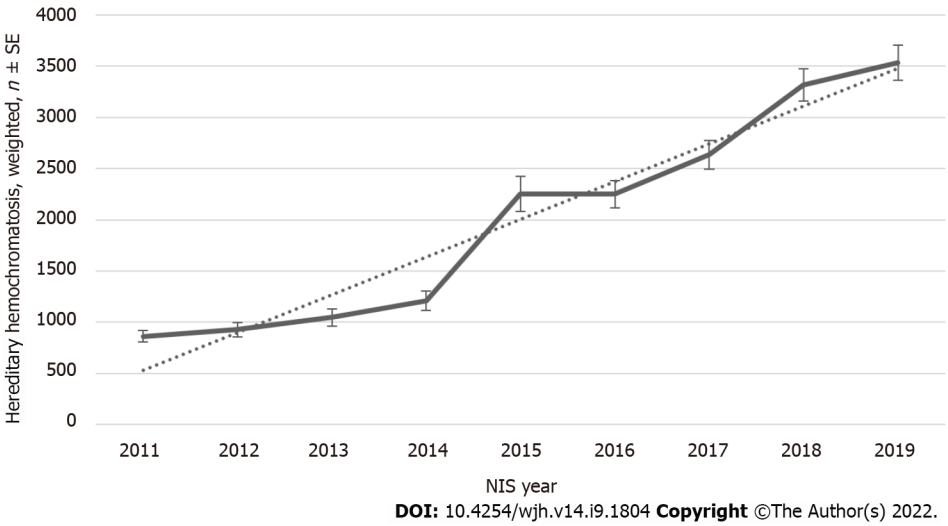

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Figure 1 Hereditary hemochromatosis patients admitted national inpatient sample 2011-2019. NIS: National inpatient sample.

from the prediction model.

Table 3 showed the univariate and multivariate analyses of HCC risk factors in weighted case-control cohort. We included known risk factors in the prediction model to ensure the completeness of the model. The multivariate analyses showed that HH without cirrhosis (aOR, 28.8; 95%CI, 10.4–80.1; $P < 0.0001$), biliary cirrhosis (aOR, 19.3; 95%CI, 13.4–27.6; $P < 0.0001$), non-alcoholic cirrhosis (aOR, 17.4; 95%CI, 16.5–18.4; $P < 0.0001$) alcoholic cirrhosis (aOR, 16.9; 95%CI, 15.9–17.9; $P < 0.0001$), hepatitis B (aOR, 12.1; 95%CI, 10.85–13.60; $P < 0.0001$), hepatitis C (aOR, 8.58; 95%CI, 8.20–8.98; $P < 0.0001$), Wilson disease (aOR, 4.27; 95%CI, 1.18–15.41; $P < 0.0001$), NAFLD or NASH (aOR, 2.96; 95%CI, 2.73–3.20; $P < 0.0001$), alpha1-antitrypsin deficiency (aOR, 2.10; 95%CI, 1.21–3.64; $P < 0.0001$), diabetes mellitus without chronic complications (aOR, 1.17; 95%CI, 1.13–1.21; $P < 0.0001$), and blood transfusion (aOR, 1.80; 95%CI, 1.69–1.92; $P < 0.0001$) are independent risk factors for liver cancer.

Table 2 Comparison of hepatocellular carcinoma risk factors in hepatocellular carcinoma *vs* age-, sex-, and race matched non-hepatocellular carcinoma patients, Weighted NIS 2011 to 2019

Variables	HCC = No, *n*, %Weighted, N = 542280, %	HCC = Yes, *n*, %Weighted, N = 548773, %	*P* value[1]
Hereditary hemochromatosis (without cirrhosis)	25 (0.005)	273 (0.05)	< 0.0001
Hereditary hemochromatosis (with cirrhosis)	55 (0.01)	651 (0.12)	< 0.0001
Alcoholic cirrhosis	8577 (1.58)	102871 (18.73)	< 0.0001
Non-alcoholic cirrhosis	9578 (1.75)	204717 (37.24)	< 0.0001
Biliary cirrhosis	193 (0.04)	2363 (0.43)	< 0.0001
Alcoholic liver disease	11551 (2.12)	105799 (19.27)	< 0.0001
NASH/NAFLD	6756 (1.24%)	46648 (8.52)	< 0.0001
Hepatitis B	2105 (0.39)	33358 (6.07)	< 0.0001
Hepatitis C	16857 (3.10)	210661 (38.40)	< 0.0001
Other viral hepatitis	4498 (0.83)	13317 (2.42)	< 0.0001
HIV	4679 (0.86)	7793 (1.42)	< 0.0001
HIV - Hepatitis B	246 (0.05)	1649 (0.30)	< 0.0001
HIV - Hepatitis C	1082 (0.20)	4834 (0.88)	< 0.0001
Obesity	76894 (14.12)	47330 (8.58)	< 0.0001
Diabetes mellitus with chronic complications	80055 (14.61)	69848 (12.64)	< 0.0001
Diabetes mellitus without chronic complications	110966 (20.51)	126860 (23.17)	< 0.0001
Hypertension	244715 (45.14)	216621 (39.45)	< 0.0001
Blood transfusion	14644 (2.65)	33381 (6.03)	< 0.0001
Alpha1-antitrypsin deficiency	163 (0.03)	641 (0.12)	< 0.0001
Disorders of porphyrin metabolism	68 (0.01)	353 (0.06)	< 0.0001
Glycogen storage diseases	50 (0.01)	105 (0.02)	0.0482
Wilson disease	33 (0.01)	143 (0.03)	0.0002
Smoking	193145 (35.40)	218897 (39.76)	< 0.0001
Alcohol	44983 (8.26)	119704 (21.79)	< 0.0001
Cannabis	8334 (1.52)	8775 (1.60)	0.1650
opioids	11534 (2.11)	16261 (2.95)	< 0.0001

[1]Pearson Chi-Square 2-tailed test for association of two categorical variables. HIV: Human immunodeficiency virus; HCC: Hepatocellular carcinoma; NIS: National inpatient sample; NASH: Non-alcoholic steatohepatitis NAFLD: Non-alcoholic fatty liver disease.

DISCUSSION

Current literature lacks enough studies that have assessed admitted HH patients' characteristics, which makes our case-control study unique, especially with its large sample size. Whether or not hepatic iron overload in HH patients is an independent risk factor for HCC without cirrhosis remains an understudied topic yet of important significance. Our study evaluates HH yearly trends, patient demographics, symptoms, comorbidities, and hospital outcomes. It sheds light on the risk of iron overload for developing HCC in HH patients, independent of liver cirrhosis complications. The study investigated HH without cirrhosis as an independent risk factor for HCC. Our study performed HCC risk factor analysis and found that HH without cirrhosis is about 29 times more likely to develop HCC. Thus, HH without cirrhosis is an independent risk factor for HCC. Previous studies showed that it could be from iron deposition and its carcinogenic effects or the HFE gene causing mutation[10,21].

A study published in March 2001 used the National Hospital Discharge Survey and census data to evaluate hemochromatosis hospitalization rates for adult patients admitted between 1979-1997. Total

Table 3 Univariate and multivariate analyses of clinical risk factors associated with liver cancer

Variables	Univariate analysis		Multivariate analysis	
	Unadjusted odds ratio[1] (95%CI)	*P* value	Adjusted odds ratio[2] (95%CI)	*P* value
Hereditary hemochromatosis (without cirrhosis)	10.887 (4.376-27.087)	< 0.0001	28.838 (10.387-80.068)	< 0.0001
Alcoholic cirrhosis	14.398 (13.701-15.131)	< 0.0001	16.881 (15.949-17.868)	< 0.0001
Non-alcoholic cirrhosis	33.241 (31.732-34.822)	< 0.0001	17.446 (16.507-18.439)	< 0.0001
Biliary cirrhosis	12.278 (8.858-17.019)	< 0.0001	19.245 (13.439-27.557)	< 0.0001
NASH/NAFLD	7.393 (6.982-7.828)	< 0.0001	2.955 (2.732-3.196)	< 0.0001
Hepatitis B	16.711 (15.149-18.434)	< 0.0001	12.145 (10.848-13.597)	< 0.0001
Hepatitis C	19.488 (18.798-20.203)	< 0.0001	8.576 (8.195-8.975)	< 0.0001
Other viral hepatitis	2.978 (2.762-3.211)	< 0.0001	1.357 (1.216-1.514)	< 0.0001
HIV	1.666 (1.537-1.807)	< 0.0001	0.649 (0.571-0.737)	< 0.0001
Obesity	0.571 (0.556-0.587)	< 0.0001	0.614 (0.590-0.640)	< 0.0001
Diabetes mellitus with chronic complications	0.845 (0.825-0.866)	< 0.0001	0.855 (0.824-0.887)	< 0.0001
Diabetes mellitus without chronic complications	1.168 (1.145-1.192)	< 0.0001	1.168 (1.132-1.205)	< 0.0001
Hypertension	0.792 (0.779-0.806)	< 0.0001	0.850 (0.828-0.872)	< 0.0001
Blood transfusion	2.356 (2.255-2.463)	< 0.0001	1.801 (1.689-1.919)	< 0.0001
Alpha1-antitrypsin deficiency	3.912 (2.669-5.735)	< 0.0001	2.100 (1.210-3.643)	0.0087
Disorders of porphyrin metabolism	5.145 (2.902-9.120)	< 0.0001	2.428 (1.163-5.066)	0.0187
Wilson disease	4.099 (1.800-9.332)	0.0008	4.269 (1.182-15.414)	0.0279
Smoking	1.204 (1.184-1.225)	< 0.0001	0.874 (0.851-0.897)	< 0.0001
opioids	1.412 (1.338-1.490)	< 0.0001	0.687 (0.631-0.749)	< 0.0001

[1]Univariate analysis is performed with logistic regression.
[2]Multivariate analysis is performed with multi-level mixed effect models. HIV: Human immunodeficiency virus; NASH: Non-alcoholic steatohepatitis NAFLD: Non-alcoholic fatty liver disease.

records were 79580, and the study concluded that the average age of studied patients was 62 years; 92% were white, and 62% were males. There was an increase in hospitalization from 1979 to 1997, mostly in males > 60 years. However, authors reported that sample sizes for each year were outside the range of reliability; this caused limitations in calculating the confidence intervals for the upward trend significance assessment, which was over 60% for HH-related hospitalizations increased rate (from 5.4 per 100000 US residents during 1979–1982 to 8.0 during 1993–1997). In this study, the most frequent co-diagnoses in HH-related hospitalizations were in order; heart, liver, joints, and diabetes diseases[22]. Patient demographics of our study showed a similar picture with 88% white patients and 62% male with a mean age of 62 years. Our study demonstrates a significant increase in the trend of hospital admissions of HH from 2011 to 2019, *i.e.*, 861 patients in 2011 to 3535 patients in 2019 in the weighted sample. Another study published in 2019 in New Jersey has evaluated the healthcare utilization and economic burdens of hemochromatosis in the United States by comparing costs 12 mo following the first hemochromatosis diagnosis. It showed an increase in the total health care costs ($20023 *vs* $16905; $P < 0.0001$) per patient, health care costs were 2%, 8%, 23%, and 43% higher for inpatient admissions, emergency visits, outpatient visits, and pharmaceutical prescriptions respectively compared with one year before diagnosis. Hemochromatosis patients plotted about $2732 more in total unadjusted costs and $1370 for inpatient services than controls. The annual health care costs among type 2 diabetes, hypertension, arthritis, and Chronic Kidney Disease patients with hemochromatosis were $6968, $7424, $2967, and $43847, respectively, higher than all these comorbidities without hemochromatosis; all these results were statistically significant[23]. When compared, our study supports these findings as inpatient hospital charges significantly increased over a decade (2011-2019) from $42957 to $66152. However, LOS remained unchanged throughout the study period.

Animal model studies have attested to the idea of hepatocarcinogenic effects of iron. Increased dietary iron in a rats model study is an example that showed a direct role of hepatic iron accumulation for HCC pathogenesis, and the study showed that preneoplastic nodules and HCC developed in the

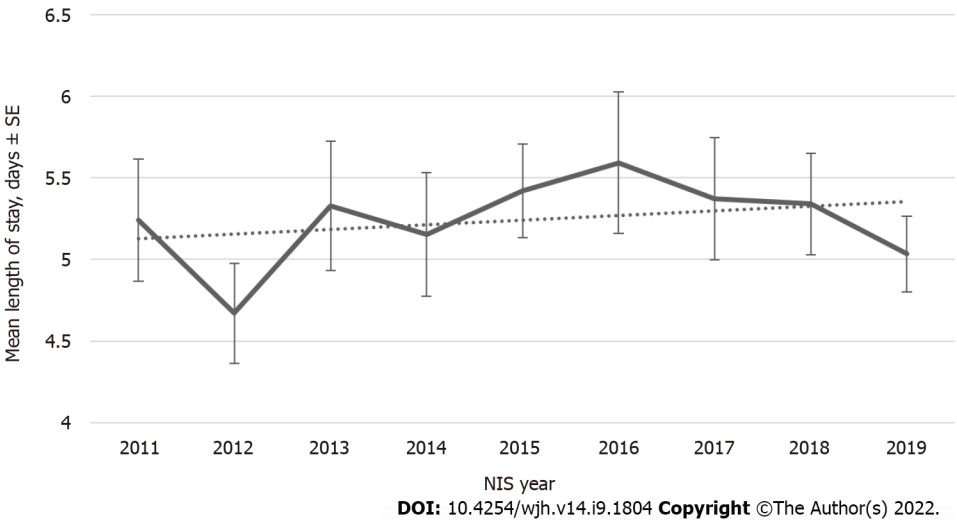

Figure 2 Mean length of stay of hereditary hemochromatosis national inpatient sample 2011-2019. NIS: National inpatient sample.

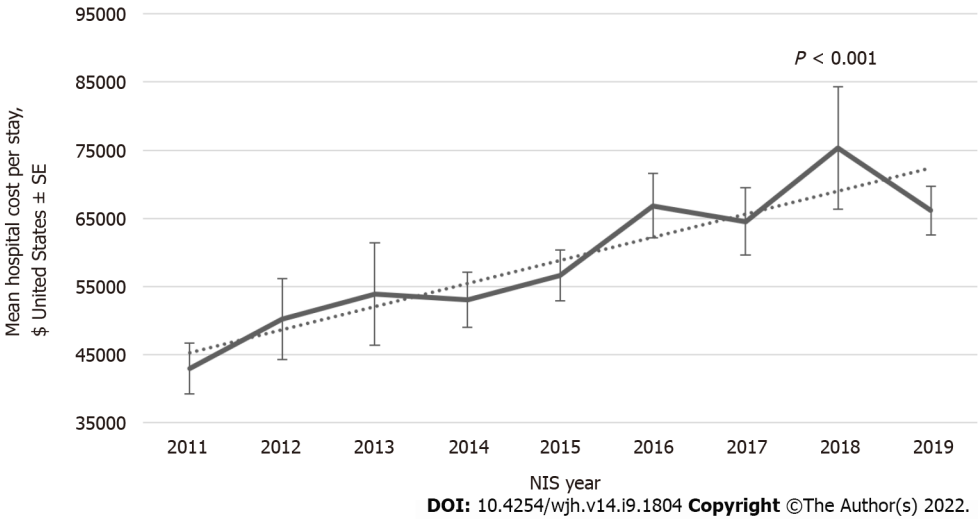

Figure 3 Mean hospital cost per stay of hereditary hemochromatosis patients national inpatient sample 2011-2019. NIS: National inpatient sample.

absence of cirrhosis or fibrosis[24]. Another study was performed on sixty Wistar albino rats that were fed an iron supplemented diet, confirmed an etiological association between heavy dietary iron intake and HCC also in the absence of fibrosis or cirrhosis by histologically examining some rats' livers which showed grade 4 iron overload comparable to advanced HH patients[25].

One study observed that drinking groundwater with a high iron content was associated with an increased incidence of HCC in southwestern coastal areas of Taiwan[26]. Iron concentrations in drinking water usually are less than 0.3 mg/L, whereas groundwater in these regions had significantly higher content with reported concentrations of 1.04 ± 0.20 mg/L[27]. The high rate of HCC among the residents of those regions has raised the possibility that iron has direct carcinogen effects on the hepatocytes based on these two studies.

As per a study done in 2004, HCC in non-cirrhotic patients was just mentioned in case reports[28], with only 10 cases in the English literature until 2007[29-31]. However, before that, a prospective study performed in 2001 had compared 230 patients with HH with the same number of matched patients of histologically proven non–iron-related chronic liver disease to assess the cancer development rate in both groups showed that HCC developed only in the cirrhotic patients[32].

In 2019, a comprehensive review study reported that 20% of HCC cases developed in a non-cirrhotic liver owing to multiple risk factors, these patients' presentations are usually in advanced stages due to lack of surveillance imaging in non-cirrhotic patients, in addition to a higher hepatic reserve in this patients' population[33].

Interestingly, a study that assessed livers in HCC without cirrhosis found a high percentage of an 83-90% range of mild iron overload detectable histologically and biochemically[11]. Other studies have also studied mutations in the HFE gene and reported mutations in the HFE gene in cases of iron overload and increased frequency of C282Y heterozygotes in HCC livers without cirrhosis[10,21]. So, based on these results, a study in Germany concluded that 15%-20% of HCC cases occur in non-cirrhotic livers, and the conclusion included that likely the level of hepatocellular toxicity necessary to reach cirrhosis level is not achieved. However, the carcinogenic effect is strong enough to induce HCC, possibly due to the influence of additional carcinogens like iron and gene mutations mentioned above and other disorders that are more associated with HCC risks without cirrhosis, including alpha-1-antitrypsin deficiency and NAFLD[34].

Currently, the American College of Gastroenterology guidelines from 2019 suggest against the routine surveillance of HCC in HH patients until they have more than stage 3 fibrosis[35].

LIMITATIONS AND STRENGTHS

Our study is unique as no such extensive study highlights sociodemographic and HH trends over the last decade. In addition, this study includes a large and diverse cohort of patients from all over the United States compared to local or regional studies done in the past. There are several limitations to our research. First, the NIS administrative database could be prone to selection bias and lacks disease process-specific variables and coding errors without formal validation. NIS entry is equivalent to one hospitalization. If a patient is admitted more than once, one patient may contribute multiple entries. Second, we lacked some of the patients' information like iron levels and other lab values. We also did not have information like fibrosis staging, hemochromatosis duration, serum ferritin level, or hepatic iron (siderosis grade). Third, although our study showed an increasing trend of hemochromatosis over the decade, it includes only inpatient admissions; outpatient encounters are not included in this study. In addition, this study's hemochromatosis treatment was not assessed, nor does the database have HFE gene mutation. Lastly, HH was identified by ICD-10 and ICD-9 diagnosis codes, and there was no ICD-9 code for HH before 2010, which may have affected the incidence of HH.

CONCLUSION

Our study showed an increasing trend of in-hospital admissions of HH patients and care costs in the last decade. These trends were likely related to advances in the diagnostic approach, which can increase hospital utilization and costs. Still, the LOS remained the same, which we think can be related to the that most management strategies can be done in outpatient settings. Another vital part of our study showed HH without cirrhosis as an independent risk factor for HCC. More retrospective studies are needed to re-evaluate HH risk in developing HCC.

ARTICLE HIGHLIGHTS

Research background

Hereditary hemochromatosis (HH) is an inherited genetic iron metabolism disorder characterized by high iron deposition in body organs due to elevated alimentary iron absorption. Because the liver is one of the most affected organs, HH is a risk factor for hepatocellular carcinoma (HCC) due to genetics and iron carcinogenic effects. HH as an independent risk factor of HCC and trends of admitted HH patients' characteristics and admission demographics are understudied research topics.

Research motivation

Current large cohort studies on temporal trends, length of stay (LOS), costs, and sociodemographic characteristics of admitted HH patients, in addition to HH being an independent risk factor of HCC, are limited.

Research objectives

We aim to evaluate patient characteristics, admission trends, LOS, and costs for admitted HH in the United States over the last decade. We also consider HH an independent risk factor for developing HCC without cirrhosis.

Research methods

We used the national inpatient sample database for our study. We identified a sample of 18031 hospital admissions of primary or secondary HH. We selected HH and HCC cohorts. HH was first defined in

2011 as ICD-9 as a separate diagnosis. The HH cohort was extracted from January 2011 to December 2019 using 275.01 (ICD-9) and E83.110 (ICD-10) diagnosis codes. We excluded patients with cirrhosis of different etiologies. The HCC cohort was selected from January 2011 to December 2019 using ICD-9 and ICD-10 codes for HCC. A non-HCC cohort was selected with the 1:1 fixed ratio nearest neighbor propensity score using patients' age, gender, and race. Multivariate analysis was performed for the risk factors of HCC in the HCC and non-HCC matched cohorts. We further analyzed HH without cirrhosis as an independent risk factor of HCC after adjusting all known risk factors of HCC in the multivariate model.

Research results

Most admitted HH patients were white males with a mean age of 62 years. Increments in HH inpatient population trend with a Ptrend < 0.001 and total hospital cost of care trend from $42957 in 2011 to $66152 in 2019 with a Ptrend < 0.001 were found despite no change in LOS over the last decade. The incidence of liver cancer in HH patients is 1.2% (95%CI: 0.78-1.53). HH without cirrhosis had 28.8 higher odds of developing HCC.

Research conclusions

There were increments in the trend of HH admissions and costs over the last decade with no changes in LOS. HH without cirrhosis is an independent risk factor for HCC.

Research perspectives

These trends could be related to advances in diagnostic approaches, which increase hospital admissions and costs. Still, outpatient-based management could be a related factor to the unchanged LOS.

FOOTNOTES

Author contributions: Haider M was responsible for study design and interpretations of results; Haider M and Al Sbihi A were responsible for literature review and manuscript preparation; Haider S was responsible for data collection; Chaudhary A and Edhi A were responsible for the overall supervision and final approval.

Institutional review board statement: Data from this study used de-identified data from the National Inpatient Sample Database (NIS) 2011-2019. A publicly available all-payer inpatient care database in the United States. Institutional Review Board Approval Form or Document is not required.

Informed consent statement: Data from this study used de-identified data from the National Inpatient Sample Database. A publicly available all-payer inpatient care database in the United States. Informed patient consent is not required.

Conflict-of-interest statement: All authors declare no conflict of interests for this article.

Data sharing statement: Data that support the findings of this study are publicly available at https://www.hcup-us.ahrq.gov/db/nation/nis/nisdbdocumentation.jsp.

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ORIGINAL ARTICLE

Observational Study

A retrospective study on use of palliative care for patients with alcohol related end stage liver disease in United States

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Abstract

BACKGROUND

Palliative care (PC) has been shown to be beneficial in end stage liver disease (ESLD), yet the hospitalization data for PC utilization is unknown.

AIM

To identify the trend of PC utilization for the special population of alcohol-associated ESLD patients, factors affecting its use and ascertain its impact on healthcare utilization.

METHODS

We analyzed around 78 million discharges from the 2007-2014 national inpatient sample and 2010-2014 national readmission database including adult patients admitted for decompensated alcohol-associated cirrhosis. We identified patients with PC consultation as a secondary diagnosis. Odds ratios (OR) and means were adjusted for confounders using multivariate regression analysis models.

RESULTS

Out of the total 1421849 hospitalizations for decompensated liver cirrhosis, 62782 (4.4%) hospitalizations had a PC consult, which increased from 0.8% (1258) of all alcohol-associated ESLD hospitalizations in 2007 to 6.6% in 2014 ($P < 0.01$). Patient and hospital characteristics associated with increased odds of PC utilization were advanced age, lower income, Medicaid coverage, teaching institution, urban location, length of stay > 3 d, prolonged ventilation, and administration of total parenteral nutrition (all $P < 0.01$). Palliative encounters in alcohol-associated ESLD and acute-on-chronic liver failure (ACLF) score were associated with increased odds of discharge to a rehabilitation facility, but significantly lower odds of 30-d readmissions (aOR: 0.35, 95%CI: 0.31-0.41), lower total hospitalization charges and lower mean hospitalization days (all $P < 0.01$).

CONCLUSION

Inpatient PC is sparingly used for patients with decompensated alcohol related liver disease, however it has increased over the past decade. PC consultation is associated with lower 30-d readmission rates on multivariate analysis, and lower hospitalization cost and length of stay in patients with ACLF score ≥ 2.

Key Words: Alcohol-associated cirrhosis; Palliative care; End stage liver disease; National inpatient sample; National readmission database

Core Tip: Alcohol related end stage liver disease (ESLD) carries a poor prognosis and is associated with significant loss of quality of life and symptom burden. We found that inpatient palliative care is sparingly used for patients with decompensated alcohol related liver disease, however it has increased over the past decade. Palliative care referral is associated with decreased hospitalization cost and length of stay in acute-on-chronic liver failure Positive alcohol-associated ESLD patients, as well as decreased rehospitalization rates in all alcohol associated ESLD patients.

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INTRODUCTION

Cirrhosis represents advanced chronic progressive liver disease, which eventually may lead to end stage liver disease (ESLD)[1]. ESLD is defined as the manifestations of decompensated liver cirrhosis or liver failure such as variceal hemorrhage, ascites, spontaneous bacterial peritonitis, hepatocellular carcinoma (HCC), hepatorenal syndrome, or hepatopulmonary syndrome[2]. While treatments are available to prevent further fibrosis and liver damage, once the disease reaches the stage of cirrhosis, the only existing cure is liver transplantation.

Alcoholic liver disease (ALD) presents a significant burden to our healthcare system, and contributes to 48% of cirrhosis related deaths in the United States. ALD comprises a broad spectrum of disease, ranging from early ALD to alcohol-associated steatohepatitis and advanced ALD, requiring liver transplantation. While in recent years, the number of patients with ALD receiving a liver transplant has increased, it is still a miniscule percentage of the patients with ALD[3]. A study from the United Nation for Organ Sharing Database found that the number of transplants for ALD was stable between 2002 and 2012, but rose by approximately 177 transplants per year between 2013 and 2015[4]. Meanwhile, the prevalence of alcohol-associated cirrhosis is increasing in the United States. In a privately insured population, the alcohol-associated cirrhosis prevalence rate increased by 43% over the course of a 7-year period from 2009 to 2015[5].

Patients with ESLD often experience symptoms such as abdominal pain secondary to ascites, fatigue, anorexia, depression and confusion[6]. As a result of the physical and psychological effects of ESLD, quality of life is often severely impacted. In fact, patients with ESLD have been shown to have a quality of life similar to patients with end stage heart or lung disease, as well as a symptom burden similar to patients with colorectal cancer[7,8]. Palliative care (PC) has shown to be effective in improving quality of life, decreasing economic burden of disease as well as improving survival in oncology, however its

use in advanced liver disease has been limited. A study by Barnes *et al*[9] showed an early palliative care referral of only 19% in 74 admitted patients. Only 17% of patients taken off the transplant list were actually referred to palliative care, and death occurred within 70 h of referral in half of these patients [10].

Palliative care is of special importance in patients with alcohol-associated liver disease as the life expectancy of patients with alcohol-associated cirrhosis is very low, 5-year and 10-year survival rates are 23 percent and 7 percent, respectively[11]. These rates are significantly worse than survival rates for patients whose cirrhosis was not caused by alcohol. These factors make early intervention by palliative care greatly beneficial to patients with alcohol-associated cirrhosis.

Due to the combination of disadvantageous positions for alcohol-dependent patients to secure a liver transplantation, poorer prognosis in this cohort, and the negative association of alcohol-associated liver disease patients to have a palliative care referral we aimed to study the implications of palliative care consult for this population[9]. In this study, we evaluate the use of palliative care for patients with decompensated alcohol-associated liver disease while they are admitted to the hospital for inpatient care in the United States.

MATERIALS AND METHODS

Data acquisition

We performed a retrospective, multicenter, observational study using data from two national databases, nationwide inpatient sample (NIS) from 2007 to 2014, and national readmission database (NRD) from 2010 to 2014. We utilized NIS until 2014 because the International Classification of Diseases (ICD) codes utilized by NIS have differed from the year 2015 to incorporate ICD-10 codes. We used different time periods for the two databases as NRD came into existence from the year 2010, unlike NIS which began from 1997. Both of these databases are a part of the healthcare cost and utilization project maintained by the agency for healthcare research and quality. The NIS is an administrative database consisting (until 2012) of all hospitalizations drawn from a sample of 20% of United States hospitals, and then weighted to be nationally representative of all United States hospitalizations[12]. NRD represents about half of all United States Hospitalizations, and provides a national estimate of readmission rates[13].

We performed separate analysis on both of the databases owing to their unique characteristics. The data cannot be merged from the two databases as the identifying information in both is encoded as different numbers. The NIS database provides information regarding the index hospital admission and includes patient demographic data, primary and secondary diagnosis, procedures, hospital characteristics, and inpatient and discharge mortality rates. Each record includes one primary and up to 24 discharge diagnoses, procedure codes, demographic data, hospitalized inpatient mortality indicator, payer status, total hospitalization charges and length of stay[10]. The NRD in addition to the information provided by NIS, also assigns a unique, unidentified patient association number to each patient, and tracks all patients at each hospital in each state throughout the calendar year.

Cohort selection

We used International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes to identify primary and secondary diagnosis codes of interest. To identify patients with end stage alcohol-associated liver disease, an entry was required to have the following diagnosis: (1) Diagnosis code for alcohol-associated cirrhosis (571.2) along with a diagnosis code for a decompensating event [defined by ICD-9-CM code of bleeding esophageal varices (456.0, 456.21), ascites (789.5, 789.59), and hepatic encephalopathy (572.2)]; and (2) Diagnosis code for other cirrhosis (571.5) with an alcohol disorder/comorbidity (571.1, 291x, 303x, 305x, 790.3, 980x, E860), and an event of decompensation (as defined above). This combination of ICD-9-CM codes for cirrhosis and complications has a positive predictive value of 78%, a negative predictive value of 91% for cirrhosis, with a c-statistic of 0.71[14].

We excluded patients who were less than 18 years old at the time of admission or who were transferred from another health facility. In keeping with the North American Consortium for the Study of End-Stage Liver Disease (NACSELD) exclusion criteria, we omitted patients with a history of prior liver transplant, human immunodeficiency virus or actively pregnant. Palliative care consultation was identified using the ICD codes (ICD 9: V66.7, ICD 10: Z51.5). Other factors such as cirrhosis complications, in-hospital death, medical complications, intensive care unit care, length of hospitalization and costs were examined as dependent variables. Independent variables included were age, sex, race, payer source (commercial or health maintenance organization, Medicare, Medicaid, self-pay, or other), comorbidity, nature of admission (emergent/urgent, or other), hospital bed-size, hospital location (rural or urban), geographic region and hospital teaching status. Figure 1 depicts the flow of the study cohort. The diagnostic codes associated with these diagnoses are shown in supporting Table 1.

Variables and statistical analysis

Data were analyzed using Stata 15.0 (StataCorp, College Station, TX). Pearson χ^2 test was used to compare proportions between the patients with PC and without PC. Associations between variables

Table 1 Baseline characteristics of cohort

Variable	Overall	Patients with palliative consult	Patients without palliative consult	*P* value
Number of patients	973246	47423	925823	
Patient characteristics				
Female	276401 (28.4%)	14037 (29.6%)	262933 (28.4%)	< 0.001
Age in yr	54.7 ± 004	57.2 ± 0.1	54.5 ± 0.04	< 0.001
Age divided into categories				
18-35	36010 (3.7%)	1327 (2.8%)	33329 (3.6%)	< 0.001
36-45	108030 (11.1%)	3604 (7.4%)	103692 (11.2%)	< 0.001
46-65	625797 (64.3%)	28975 (61.1%)	595304 (64.3%)	< 0.001
> 66	204381 (21%)	13136 (27.7%)	191645 (20.7%)	< 0.001
Race				
White	660834 (67.2%)	33433 (70.5%)	614746 (66.4%)	< 0.001
Black	96351 (9.9%)	4647 (9.8%)	95359 (10.3%)	< 0.001
Hispanic	160585 (16.5%)	6544 (13.8%)	161093 (17.4%)	< 0.001
Other	60341 (6.2%)	2940 (6.2%)	57401 (6.2%)	0.532
Charleston comorbidity index				
0 or 1	118736 (12.2%)	2371 (5%)	116653 (12.6%)	< 0.001
2	46715 (4.1%)	948 (2%)	38884 (4.2%)	< 0.001
3 or more	854509 (87.8%)	45051 (95%)	809169 (87.4%)	< 0.001
Median income in patient zip code				
$1–$38999	297813 (30.6%)	13894 (29.3%)	283301 (30.6%)	0.003
$39000–$47999	255963 (26.3%)	12946 (27.3%)	245343 (26.5%)	0.004
$48000–$62999	231632 (23.8%)	11144 (23.5%)	220345 (23.8%)	0.133
> $63000	187836 (19.3%)	9389 (19.8%)	178683 (19.3%)	< 0.001
Insurance provider				
Medicare	341609 (35.1%)	17878 (37.7%)	328667 (35.5%)	< 0.001
Medicaid	260829 (26.8%)	12045 (25.4%)	249046 (26.9%)	< 0.001
Private	255963 (26.3%)	12282 (25.9%)	243491 (26.3%)	< 0.001
Uninsured	114843 (11.8%)	5216 (11%)	109247 (11.8%)	< 0.001
Hospital characteristics				
Teaching hospital	514847 (52.9%)	28690 (60.5%)	486982 (52.6%)	< 0.001
Urban hospital	891493 (91.6%)	44387 (93.6%)	847128 (91.5%)	< 0.001
Hospital region				
Northeast	177130 (18.2%)	6828 (14.4%)	170351 (18.4%)	< 0.001
Midwest	199515 (20.5%)	9911 (20.9%)	189793 (20.5%)	0.832
South	345502 (35.5%)	16692 (35.2%)	328667 (35.5%)	0.104
West	251097 (25.8%)	13989 (29.5%)	237010 (25.6%)	< 0.001
Hospital size				
Small	122628 (12.6%)	4931 (10.4%)	118505 (12.8%)	< 0.001
Medium	258883 (26.6%)	12756 (26.9%)	246268 (26.6%)	0.002
Large	590760 (60.7%)	29734 (62.7%)	561048 (60.6%)	< 0.001

Hospital complications				
Variceal bleed	114843 (11.8%)	4789 (10.1%)	110428 (11.9%)	< 0.001
HRS	22619 (7.2%)	14942 (23.8%)	75917 (8.2%)	< 0.001
Hepatic encephalopathy	321171 (33%)	24375 (51.4%)	322186 (34.8%)	< 0.001
Ascites	605359 (62.2%)	34191 (72.1%)	565677 (61.1%)	< 0.001
SBP	23357 (2.4%)	1659 (3.5%)	21293 (2.3%)	< 0.001
Hepatocellular carcinoma	60341 (6.2%)	5927 (12.5%)	49994 (5.4%)	< 0.001
NACSELD-ACLF score				
0	495382 (50.9%)	11191 (23.6%)	482353 (52.1%)	< 0.001
1	389298 (40%)	22810 (48.1%)	366625 (39.6%)	< 0.001
2	64234 (6.6%)	8536 (18%)	56475 (6.1%)	< 0.001
3	22384 (2.3%)	4505 (9.5%)	18516 (2%)	< 0.001
4	973 (0.1%)	426(0.9%)	925 (0.1%)	< 0.001
ACLF ≥ 2	89538 (9.2%)	13420 (28.3%)	76843 (8.3%)	< 0.001
Mean ACLF score	0.64	1.21	0.61	< 0.001

HRS: Hepatorenal syndrome; SBP: Spontaneous bacterial peritonitis; NACSELD-ACLF: North American Consortium for the Study of End-Stage Liver Disease's definition of acute-on-chronic liver failure; ACLF: Acute-on-chronic liver failure.

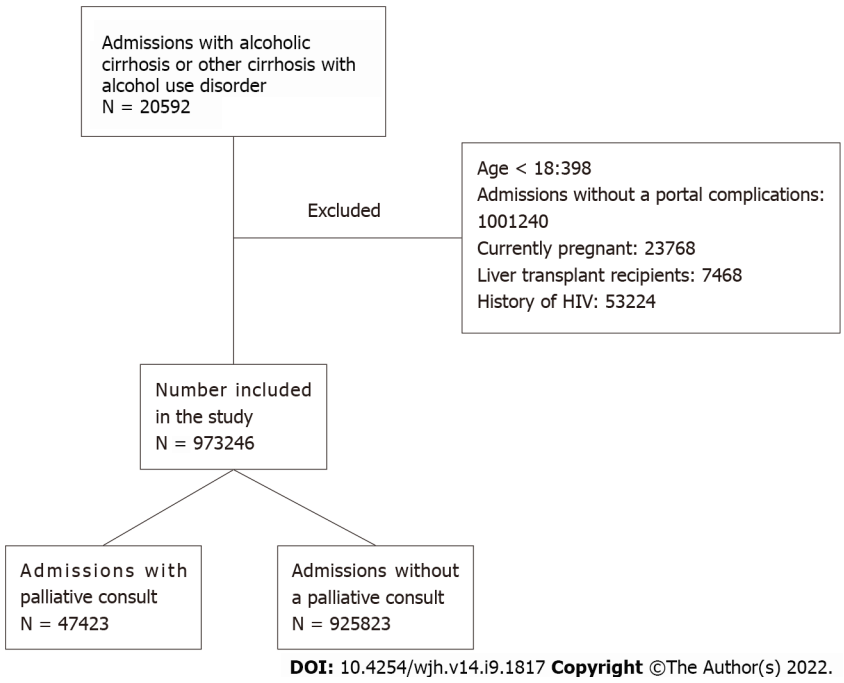

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Figure 1 Inclusion figure. HIV: Human immunodeficiency virus.

were analyzed using cross-tabulations and multivariate logistic regression modeling. Data were weighted and modified hospital and discharge weights to correct for changes in sampling over time were applied. Variance estimation was performed using procedures for survey data analysis with replacement. Strata with one sampling unit were centered at the population mean. Multivariable regression analysis models were used to adjust the results for potential confounders. Multivariable regression models were built by including all confounders that were significantly associated with the outcome of univariable analysis with a cutoff *P*-value of 0.05. The model controlled for age, sex, race, median household income of residents in the patient's zip code, insurance, charlson comorbidity index, hospital bedsize, academic status of hospital, hospital location, length of stay, acute-on-chronic liver failure (ACLF) score, history of hepatocellular carcinoma, acute infections, transjugular intrahepatic portosystemic shunt (TIPS) and total parenteral nutrition (TPN). Logistic regression was used for binary

outcomes and linear regression was used for continuous outcomes.

Outcomes variables

Our primary outcome of interest was the proportion of decompensated liver cirrhosis patients who received a PC consult during their hospitalization and their trend over the study period. Secondary outcomes were: (1) All-cause in-hospital mortality; (2) Healthcare total hospital charge; (3) Duration of hospitalization [Length of stay (LOS) in days], which were all encoded in the data set as unique variables; and (4) Major in hospital procedures and portal hypertensive complications, and these were compared between the two groups. We further categorized patients according to the number of organ failures based upon the NACSELD-ACLF, a bedside tool to predict short-term mortality in ESLD patients. This score has been previously validated using the NIS. A positive ACLF score is deemed as ≥ 2. We also included other complications of cirrhosis such as portal hypertension, hepatorenal syndrome and spontaneous bacterial peritonitis. We also identified procedures commonly performed in ESLD hospitalizations such as total parenteral nutrition, TIPS and prolonged mechanical ventilation.

RESULTS

There was a total of 2059524 hospitalizations for alcohol-associated cirrhosis recorded, out of which 973246 met our inclusion criteria of presenting with a portal complication. The majority of the patients were male (73.1%), white (67%), had a mean Charlson comorbidity index < 3 (83.6%) and belonged to the age group 46-65 years (68%). The mean age was 54.7 years. A palliative care encounter was recorded in only 4.8% of cases (n = 47423). On trending the utilization of palliative care, it was observed to have increased from 0.8% (956) of all ESLD hospitalizations in 2007 to 6.6% (9430) in 2014. Figure 2 depicts the trend of hospitalizations in both groups.

Factors affecting palliative care encounter

A palliative care encounter was more likely in female patients (29.6% *vs* 28.4% P < 0.01), patients older than 65 years (27.7% *vs* 20.7%, P < 0.01), whites (70.5% *vs* 66.4%, P < 0.01), Charlson comorbidity score ≥ 3 (95% *vs* 87.4%, P < 0.01) and medicare patients (37.7% *vs* 35.5%, P < 0.01), but was less likely for hispanic patients (13.8% *vs* 17.4%, P < 0.01), patients belonging to the lowest quarter of mean income (29.3% *vs* 30.6%, P = 0.003) and patients with medicaid (25.4% *vs* 26.9%, P < 0.001) or no insurance at all (11% *vs* 11.8%, P < 0.01). With regards to hospital characteristics, a significantly higher proportion of patients receiving palliative care were treated at teaching hospitals (60.5% *vs* 52.6%, P < 0.01), in urban locations (93.6% *vs* 91.5%, P < 0.01), large hospitals (62.7% *vs* 60.6%, P < 0.01) and in western states (29.5% *vs* 25.6%, P < 0.001), whereas patients in northeastern states (14.4% *vs* 18.4%, P < 0.01) were less likely to receive an inpatient palliative care consult.

On analyzing complications related with cirrhosis, patients receiving palliative care as inpatients had a significantly higher proportion of hepatic encephalopathy (51% *vs* 34 %, P < 0.001), ascites (72% *vs* 61%, P < 0.001), hepatorenal syndrome (23% *vs* 8%, P < 0.001), spontaneous bacterial peritonitis (3.5% *vs* 2.3%, P < 0.001) and HCC (12% *vs* 5%, P < 0.001), whereas patients with variceal bleeding (10% *vs* 12%, P < 0.001) were less likely to receive a palliative care. Palliative care consults were more common in all patients with North American Consortium for the Study of End-Stage Liver Disease's definition of acute-on-chronic liver failure (NACSELD-ACLF) score ≥ 1, with the proportion increasing by each grade (Grade 1: 48.1% *vs* 39.6%; Grade 2: 18% *vs* 6.1%; Grade 3: 9.5% *vs* 2%; Grade 4: 0.9% *vs* 0.1%, all P < 0.001).

In the palliative care cohort, more people received total parenteral nutrition, or TPN (2.9% *vs* 1.4%, P < 0.001) however, a lower number were liver transplant recipients (0.6% *vs* 1.8%, P < 0.001). There was no difference in receiving a transjugular intrahepatic systemic shunt, or TIPS (1.2% *vs* 1.3%, P = 0.359) between the two groups.

Multivariate logistic regression analysis of predictor variables for palliative consultation associated with alcohol related ESLD is shown in Table 2. After controlling for all other variables, hepatorenal syndrome (aOR: 3.4, 95%CI: 3.04-3.81, P < 0.001), ascites (aOR: 1.13, 95%CI: 1.03-1.24, P = 0.007), spontaneous bacterial peritonitis (SBP) (aOR: 3.32, 95%CI: 2.65-3.86, P < 0.001) and HCC (aOR: 1.78, 95%CI: 1.58-2.00, P < 0.001) were associated with higher odds of palliative care encounter than alcohol related ESLD patients. Patients with ACLF scores ≥ 2 were associated with higher odds of palliative care consult (aOR: 1.02 95%CI: 1.00-1.04, P < 0.001). Patient and hospital characteristics associated with increased palliative care utilization on multivariate regression were advanced age (aOR: 1.02, 95%CI: 1.00-1.04, P < 0.001), female sex (aOR: 1.07, 95%CI: 1.00-1.14, P < 0.001), uninsured (aOR: 1.52, 95%CI: 1.36-1.7, P < 0.001), teaching institution (aOR: 1.4, 95%CI: 1.28-1.53, P < 0.001), hospital bedsize > 400 beds (aOR: 1.25, 95%CI: 1.1-1.41, P < 0.001), and length of stay > 5 d (aOR: 1.18, 95%CI: 1.10-1.26, P < 0.001). Major infections during the hospitalization, as described above, had higher odds of palliative care use (aOR: 1.58, 95%CI: 1.48-1.69, P < 0.001). Other patient characteristics with increased odds of palliative consult included mechanical ventilation (OR: 3.32 95%CI: 3.1-3.54, P < 0.01), and administration of TPN (OR: 2.02, 95%CI: 1.8-2.27, P < 0.01).

Table 2 Multivariate regression for palliative consult

Variable	Adjusted odds ratio	95%CI	*P* value
Age	1.02	1.00-1.04	< 0.001
Median income in patient zip code			
$1-$38999	Reference		
$39000-$47999	1.07	0.98-1.16	0.117
$48000-$62999	0.99	0.9-1.08	0.983
> $63000	0.95	0.85-1.02	0.141
Female sex	1.07	1.00-1.14	0.023
Race			
Caucasian	Reference		
African Americans	0.81	0.72-0.9	< 0.001
Hispanic	0.71	0.64-0.78	< 0.001
Others	0.89	0.78-1.00	0.069
Charleson comorbidity index	1.1	1.08-1.12	< 0.001
Insurance status			
Medicare	Reference		
Medicaid	1.34	1.19-1.51	< 0.001
Private insurance	1.18	1.08-1.29	< 0.001
Uninsured	1.52	1.36-1.7	< 0.001
Teaching hospital	1.4	1.28-1.53	< 0.001
Bed size			
< 250 beds	Reference		
251-400 beds	1.24	1.09-1.42	0.001
> 400 Beds	1.25	1.1-1.41	< 0.001
Urban location	0.96	0.83-1.19	0.625
Length of stay by groups			
< 3 d	Reference		
3-5 d	0.92	0.84-1.00	0.065
> 5 d	1.18	1.10-1.26	< 0.001
Rehab transfer	4.07	3.29-5.04	< 0.001
ACLF Score			
1	2.53	2.35-2.71	< 0.001
2	6.05	5.5-6.66	< 0.001
3	9.86	8.75-11.1	< 0.001
4	10.61	7.32-15.42	< 0.001
ACLF ≥ 2	3.47	3.21-3.74	< 0.001
Hepatocellular carcinoma	1.78	1.58-2.00	< 0.001
Infection	1.58	1.48-1.69	< 0.001
Mechanical ventilation	3.32	3.1-3.54	< 0.001
Total parenteral nutrition	2.02	1.8-2.27	< 0.001
Hepatorenal syndrome	3.4	3.04-3.81	< 0.001
Ascites	1.13	1.03-1.24	< 0.001

Spontaneous bacterial peritonitis	3.34	2.65-3.86	< 0.001
Age	1.02	1.00-1.04	< 0.001
Female sex	1.07	1.00-1.14	0.023
Race			
Caucasian	Reference		
African Americans	0.81	0.72-0.9	< 0.001
Hispanic	0.71	0.64-0.78	< 0.001
Others	0.89	0.78-1.00	0.069
Charleson comorbidity index	1.1	1.08-1.12	< 0.001
Insurance status			
Medicare	Reference		
Medicaid	1.34	1.19-1.51	< 0.001
Private insurance	1.18	1.08-1.29	< 0.001
Uninsured	1.52	1.36-1.7	< 0.001
Teaching hospital	1.4	1.28-1.53	< 0.001
Bed size			
< 250 beds	Reference		
251-400 beds	1.24	1.09-1.42	0.001
> 400 Beds	1.25	1.1-1.41	< 0.001
Urban location	0.96	0.83-1.19	0.625
Length of stay by groups			
< 3 d	Reference		
3-5 d	0.92	0.84-1.00	0.065
> 5 d	1.18	1.10-1.26	< 0.001
Rehab transfer	4.07	3.29-5.04	< 0.001
ACLF ≥ 2	3.47	3.21-3.74	< 0.001

ACLF: Acute-on-chronic liver failure.

Effect of palliative care use on hospital outcomes

On multivariate analysis, total hospitalization charges (regression coefficient: $1813, 95%CI: -1106 to 4734, P = 0.224) and length of stay (regression coefficient: 0.342, 95%CI: -1.031 to 1.71, P = 0.625) were unchanged in patients with PC. Looking at patients who were NACSELD ACLF positive (ACLF ≥ 2), we saw that palliative care was associated with significantly reduced total hospitalization charges (regression coefficient: -$8405, 95%CI: -16721 to -90, P = 0.048) and length of stay (regression coefficient: -2.34 d, 95%CI: -2.88 to -1.81 d, P < 0.001).

Effect of palliative care consult on readmission rates

Utilizing the NRD 2010-2014, a total of 356215 patients with alcohol related ESLD met the inclusion criteria, out of which 164940 patients were readmitted, leading to a 30-d readmission rate of 46.3%. Table 3 shows the factors associated with readmission rates. On univariate analysis, we found palliative care, age, charlson comorbidity index, hospital location, teaching status, ACLF score and infection had a statistically significant association with readmission rates. We used these factors to analyze the association of PC with 30-d readmission rate with cox multivariate regression model. PC consult was associated with significantly lower odds of 30-d readmissions (aOR: 0.35, 95%CI: 0.31-0.41, P < 0.001). Other factors found to be associated were age (aOR: 0.99, 95%CI: 0.99-0.99, P < 0.001), charlson comorbidity index (aOR: 1.06, 95%CI: 1.05-1.06, P < 0.001), positive ACLF (aOR: 0.86, 95%CI: 0.81-0.91, P < 0.001), infection (aOR: 1.09, 95%CI: 1.07-1.13, P < 0.001) and hospital located in rural area (aOR: 0.86, 95%CI: 0.81-0.91, P < 0.001).

Table 3 Results of regression analysis looking at the factors associated with 30-d readmission rate

Variable	Unadjusted odds ratio	95%CI	*P* value	Adjusted odds ratio	95%CI	*P* value
Palliative care	0.36	0.31-0.41	< 0.001	0.35	0.31-0.41	< 0.001
Patient characteristics						
Age	0.99	0.99-0.99	< 0.001	0.99	0.99-0.99	< 0.001
Median income in patient zip code						
$1-$38999	Reference					
$39000-$47999	0.97	0.94-1.01	0.236			
$48000-$62999	1	0.97-1.04	0.655			
> $63000	1.02	0.99-1.06	0.133			
Female sex	1.01	0.99-1.04	0.188			
Race						
Caucasian	Reference					
African-Americans	0.77	0.52-1.12	0.175			
Hispanic	0.93	0.65-1.34	0.721			
Others	0.76	0.47-1.24	0.282			
Mean charlson comorbidity index	1.04	1.03-1.04	< 0.001	1.06	1.05-1.06	< 0.001
Insurance status						
Medicare	Reference					
Medicaid	1.14	1.11-1.18	< 0.001			
Private insurance	0.89	0.86-0.93	< 0.001			
Uninsured	0.75	0.71-0.78	< 0.001			
ACLF ≥ 2	0.89	0.84-0.95	0.001	0.86	0.81-0.91	< 0.001
Infection	1.07	1.04-1.10	< 0.001	1.09	1.07-1.13	< 0.001
Hospital characteristics						
Teaching hospital	1.05	1.02-1.05	< 0.001	1.02	0.99-1.05	0.208
Bed size						
< 250 beds	Reference					
251-400 beds	1	0.95-1.06	0.723			
> 400 Beds	1.02	0.97-1.07	0.37			
Rural location	0.85	0.83-0.88	< 0.001	0.86	0.81-0.91	< 0.001

ACLF: Acute-on-chronic liver failure.

DISCUSSION

In this large, nationally representative analysis of patients with alcohol-assocaited ESLD, only a small proportion of patients (4.4%) received palliative care. The rate is lower as compared to PC consultations for advanced cancers which was recorded at 9.9% using NIS[15]. While still low, there has been an encouraging increase in the utilization of palliative care from less than 1% in 2007 to almost 7 % of all inpatient encounters in 2014. This is comparable to an increase in PC consults in inpatients with all-cause ESLD, reported by Rush *et al*[16] over a similar time period, and can be attributed to the increased recognition of the role PC plays in improving quality of life and reducing disease burden.

We identified geographical, socioeconomic as well as racial disparities in PC referrals. This may be due to an incomplete understanding of the concept of palliative care amongst some patient populations, such as the hispanic population. In addition, access to healthcare services was also a significant factor as PC referrals were more common in large and urban hospitals. This follows the trend oncologists have reported amongst minorities and low-income groups[17].

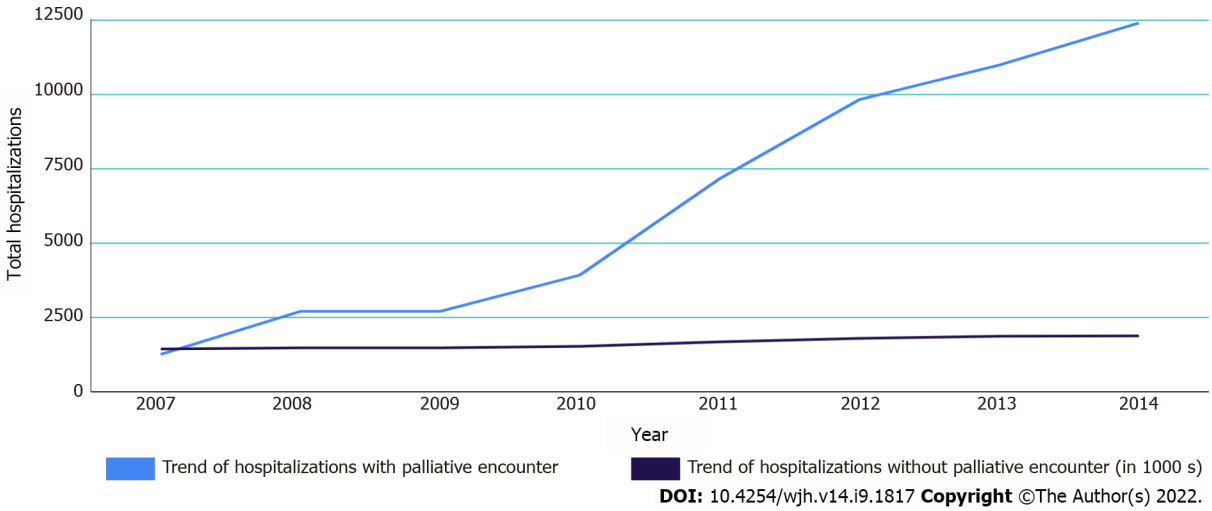

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Figure 2 Trend of palliative consults in hospitalized alcohol-associated end stage liver disease patients.

As expected, sicker patients were more likely to receive palliative consults. Patients with ≥ 4 ACLF score had ten times higher odds of a palliative consult as compared to patients with a score of zero. The ACLF score has been shown to have better predictive value. Patients who presented with variceal bleeding as a symptom of decompensated alcohol related ESLD were less likely to receive PC consults, this could be because of effective endoscopic interventions available compared to the more insidious and perhaps more advanced illness indicated by ascites and hepatorenal syndrome. Similarly, patients with HCC were more likely to receive PC consults, the oncological nature of their disease perhaps facilitating recognition of the need for palliative care. Hudson *et al*[18] have introduced a model to identify patients at high risk of impending death in patients with decompensated cirrhosis, which included patients with presence of 3 or more factors on admission to the emergency department, a history of 2 or more admissions in the prior 6 mo, ongoing alcohol use in the context of known alcohol-related liver disease, unsuitability for liver transplant, and World Health Organization Performance status 3 or 4 predicted 1-year mortality with a sensitivity of 72%.

Increased PC use seen in patients with prolonged ventilation and TPN suggest a delayed referral to PC, occurring after significant progression of disease. The timing of palliative care is important, and early PC has been shown to improve quality of life and prolong survival in other patient populations [19] and may help avoid aggressive and futile treatments[20]. Previous data has shown that alcohol-associated ESLD patients are more likely to have a delayed PC referral, with young age and recent alcohol use found to be predictors of late hospice referrals[21]. We saw that inpatients with positive ACLF score, length of stay and total hospitalization charges were significantly reduced with the use of PC services. This is likely as patients with positive ACLF score have a 6-mo mortality rate of 90%, thus meeting the criteria for hospice care as per medicare rules and are likely to have PC involved[22,23]. On analyzing the national readmission database, we found that PC was associated with a significantly reduced odds of 30-d readmission in alcohol associated ESLD patients, with an adjusted odds ratio of 0.35 on multivariate analysis, accounting for several factors found to be associated with readmission rates such as age and ACLF score. We found that the rate of readmissions in our cohort of alcohol-associated ESLD patients with C use was lower than that of all ESLD patients which has been studied before[24,25]. Also, utilization of PC was lower than all-ESLD patients, where it was 5.3% *vs* 4.4% for our cohort of patients.

Our study has several limitations. First, inherent to the nature of our retrospective discharge database, our analysis is limited by the errors in coding as well as missing data. Additionally, we were unable to identify interventions performed to alleviate decompensating events, and whether successful interventions reduced the referral to PC. The period over which our data has been collected has also witnessed changes in the management of alcohol related ESLD, with a significant increase in ALD liver transplantation. While survival in alcohol-associated cirrhosis remains low, increased transplantation potentially reduces the number of alcohol related ESLD patients. Our study does not account for this increase in liver transplantation.

Despite these limitations, the study has many advantages. To date, this is the largest study that measures the utilization of palliative care and its impact on the care of patients with alcohol associated liver disease. We utilized the largest and most inclusive readmission database in the United States. These data are collected from all hospitals in 22 states, so these data are reasonably generalizable, and we hope they will increase the validity of our study. We provided the first national estimate of 30-d readmission risk specifically for alcohol-associated ESLD which are known to have poorer access to healthcare in general and liver transplantation in particular. Also, we were able to grade patients using

ACLF scoring to better ascertain the referral rate for palliative care depending on the clinical condition of these patients.

The increase in adoption of PC for alcohol related ESLD suggests an increasing recognition of the role PC plays in mitigating symptom burden and improving quality of life in these patients. Early palliative care referrals[26], and easier access to high quality palliative care should be an integral part of managing patients with alcohol related ESLD, and special attention needs to be paid to ensure inclusion of ethnic minorities and patients of low socioeconomic status.

CONCLUSION

Inpatient palliative care is sparingly used for patients with decompensated alcohol related liver disease, however it has increased over the past decade. Palliative care referral is associated with decreased hospitalization cost and length of stay in ACLF positive alcohol-associated ESLD patients, as well as decreased rehospitalization rates in all alcohol-associated ESLD patients.

ARTICLE HIGHLIGHTS

Research background

Use of palliative care (PC) consultation has been steadily increasing, especially in the field of cirrhosis.

Research motivation

Alcohol-associated end stage liver disease (ESLD) patients are at a disadvantage for being referred to palliative care as they are younger and are more likely to belong to lower socioeconomic strata. The use of palliative care is especially important for this subgroup as the only definite treatment is liver transplant which is often not an option for these patients.

Research objectives

To assess the trend of PC use in patients hospitalized with alcohol associated ESLD as the primary diagnosis, study the baseline characteristics of these patients, evaluate the factors associated with increased PC use, study the impact of PC use on hospitalization outcomes and 30-d readmission rates.

Research methods

We used the national inpatient sample from 2007 to 2014, and the national readmission database from 2010 to 2014. We identified the patients admitted with alcoholic cirrhosis and at least one cirrhosis decompensation event. We identified patients with PC consultation as a secondary diagnosis. Baseline characteristics between the groups were compared with linear regression, and multivariate regression analysis model was used to assess the impact that PC use has on the hospitalization outcomes.

Research results

PC use has increased over 8 times during the study period and was used in 6.6% of alcohol-associated ESLD hospitalizations in 2014. PC use was more common in patients with ascites, hepatic encephalopathy and hepatocelluluar carcinoma. Other factors associated with increased PC use were females, whites, uninsured patients, teaching hospitals and patients with a higher North American Consortium for the Study of End-Stage Liver Disease's definition of acute-on-chronic liver failure score. The length of stay and total hospitalization costs were lower in patients with acute-on-chronic liver failure score ≥ 2 and receiving PC, but not significantly different in the overall cohort. PC use was associated with significantly lower 30-d readmission rates, with odds ratios of 0.35.

Research conclusions

PC use has been increasing over the years, however is still underutilized especially in select population and in rural areas. We show that PC use is associated with decreased length of stay in patients with more complications, and also leads to decreased 30-d readmission rates.

Research perspectives

This study calls for further research to assess the point during the disease course in which patients with alcohol-associated ESLD would benefit from PC use. Further research should also be conducted to assess for the reasons for decreased PC use in select disadvantaged population.

FOOTNOTES

Author contributions: Hans B and Gupta K contributed equally to this manuscript and should be considered co-first authors; Chang C and Kapuria D have equal contribution and are joint senior authors; Hans B and Gupta K devised the statistical analysis plan, wrote the statistical code and contributed in writing the manuscript; Kapuria D conceived the study idea and contributed in writing the manuscript; Khan A ran the statistical tests; Sohail SH performed a background literature search; Chang C was our faculty mentor who revised and edited the final manuscript; all authors provided critical feedback and helped shape the research analysis and manuscript.

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CASE REPORT

Primary hepatic leiomyosarcoma: A case report and literature review

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Abstract

BACKGROUND

Primary hepatic leiomyosarcoma (PHL) is a rare tumor with a very low incidence of about 0.2%.

CASE SUMMARY

A 48-year-old diabetic, hypertensive, and morbidly obese female patient presented with a history of abdominal pain and weight loss for 2 mo. She had no history of fever, jaundice, or other liver disease(s). Clinical examination revealed a palpable mass in the epigastrium. Imaging evaluation with a contrast-enhanced computed tomography (CT) scan of the abdomen and pelvis revealed an ill-defined enhancing hyper vascular hepatic mass of 9.9 cm × 7.8 cm occupying the left hepatic lobe with evidence of central necrosis, compression effect on the left hepatic vein, and partial wash-out on delayed images. On further workup, the maximum standardized uptake value on positron emission computed tomography scan was 6.4, which was suggestive of malignancy. The remaining part of the liver was normal without any evidence of cirrhosis. Ultrasound-guided biopsy of the mass showed smooth muscle neoplasm suggestive of leiomyos-arcoma. After optimization for co-morbidities, an extended left hepatectomy was planned in a multidisciplinary team meeting. On intraoperative ultrasound, the left hepatic lobe was entirely replaced by a large tumor extending to the caudate lobe with a compression effect on the middle and left hepatic veins. Final histopathology showed nodular and whorled white tumor comprised of spind-led/fascicular cells with moderate to severe pleomorphism and focal necrosis. The mitotic index was greater than 20 mitoses per 10 high-power fields. The resection margins were free of tumor. Immunohistochemistry (IHC) depicted a desmin-positive/caldesmon-negative/discovered on gastrointestinal stromal tumor 1-negative/cluster of differentiation 117-negative profile, confirming the definitive diagnosis as PHL.

CONCLUSION

This case report highlights the rare malignant mesenchymal hepatic tumor. To confirm PHL diagnosis, one requires peculiar histopathological findings with ancillary IHC confirmation. Management options include adequate/complete surgical resection followed by chemotherapy and/or radiotherapy.

Key Words: Leiomyosarcoma; Immunohistochemistry; Hepatectomy; Surgical resection; Case Report

Core Tip: Primary hepatic leiomyosarcoma is an extremely rare tumor among all primary hepatic malignancies, with approximately 70 cases worldwide, including our case. The rare nature of the disease has precluded its underlying pathogenesis. Clinical manifestations are usually nonspecific, and tumors are generally asymptomatic until they significantly increase in size. They have a relatively poor prognosis and aggressive metastatic potential. The preferred type of treatment is surgical excision, which is sometimes combined with adjuvant chemotherapy and radiotherapy; however, little is known about their effectiveness because of the disease rarity. In-depth studies are needed to shed light on this uncommon clinical entity.

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INTRODUCTION

Primary hepatic leiomyosarcoma (PHL) is a rare mesenchymal hepatic tumor whose clinical manifestations are often nonspecific and remain asymptomatic until there is a significant increase in tumor size causing a mass effect. This manuscript presents a case report of a 48-year-old woman with PHL.

CASE PRESENTATION

Chief complaints

A 48-year-old woman presented to the outpatient clinic with complaints of abdominal pain associated with weight loss.

History of present illness

The patient's symptoms started 2 mo prior with recurrent episodes of abdominal pain without any specific aggravating or relieving factor(s).

History of past illness

She had no documented history of fever, jaundice, liver disease(s), blood transfusion, tattooing, or alcohol abuse.

Personal and family history

Her co-morbidities included diabetes, hypertension, and obesity. She had no family history of carcinoma.

Physical examination

On examination, there was a palpable mass in the epigastrium. The rest of the clinical examination was unremarkable, without any signs of disease elsewhere in the body.

Laboratory examinations

Complete blood count, serum biochemical profile, coagulation profile, and carbohydrate antigen 19-9 were normal. Viral serology was nonreactive.

Imaging examinations

An initial imaging evaluation with a contrast-enhanced computed tomography (CT) scan of the abdomen and pelvis showed an ill-defined heterogeneous contrast-enhancing and hyper vascular mass

in the left lobe of the liver with extension up to the middle hepatic vein and compression effect on the left hepatic vein. The approximate measurement of the mass was 9.9 cm × 7.8 cm with central necrosis in the mass and partial wash-out on delayed images. The tumor encased the left portal vein branch at its point of bifurcation; however, the main portal vein and its right branch were not involved. No signs of hepatic cirrhosis were identified on imaging studies (Figure 1).

Positron emission tomography-CT (PET-CT) scan showed a maximum standardized uptake value (SUV) of the left hepatic mass of 6.4. The remaining liver had a standard baseline hepatic SUV (hepatic parenchymal baseline reference activity was up to 2.96 SUV).

No significant abnormality was seen above or below the diaphragm. In addition, the lungs, gastrointestinal (GI) tract, adrenal glands, kidneys, ovaries, and uterus did not show any evidence of primary disease or metastasis. No metastasis was found elsewhere in the body.

Ultrasound-guided biopsy was done, which showed cores of liver tissue with a proliferation of tumor cells having spindled-shaped nuclei with features of pleomorphism, up to 10 mitosis/10 high-power fields (HPFs), and necrosis. These findings suggested a spindle cell neoplasm raising a differential diagnosis of GI stromal tumor (GIST) and leiomyosarcoma. A panel of Immunohistochemical stains were applied that depicted a desmin-positive/caldesmon-negative/discovered on GIST1-negative (DOG1-)/cluster of differentiation 117-negative (CD117-) profile, thereby supporting the definitive diagnosis of PHL.

MULTIDISCIPLINARY EXPERT CONSULTATION

The case was discussed for management discussion in GI and hepatobiliary multidisciplinary team (MDT) meetings. According to MDT recommendations, surgical resection of the liver mass was planned, as there was no clinical and radiological evidence of metastatic disease or unknown primary disease elsewhere in the body.

FINAL DIAGNOSIS

The definitive preoperative diagnosis of the presented case was PHL in the absence of clinical and radiological evidence of metastatic disease or unknown primary disease elsewhere in the body.

TREATMENT

A formal extended left hepatectomy was performed. Staging laparoscopy was negative for metastasis, followed by a traditional laparotomy using a Mercedes Benz incision. The total operating time was 540 min with a blood loss of 300 milliliters.

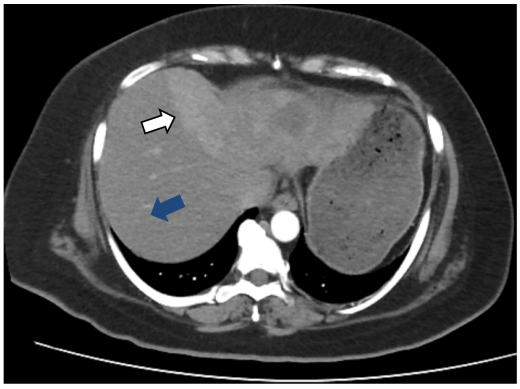
Intraoperatively, the left lobe of the liver was involved by a large tumor extending inferiorly to the caudate lobe (left side only) and superiorly up to the middle hepatic vein (MHV). MHV and its branches were sacrificed. An en bloc resection was achieved with an intact capsule (Figure 2). Resection margins were confirmed to be free of the tumor with the help of intraoperative ultrasound. Enlarged hilar nodes (hepatic artery lymph node) and periportal lymph node were also removed separately. No distant metastasis or aortocaval nodes were found per operatively.

Final diagnosis and histopathology

Grossly, the left hepatectomy specimen measured 18 cm × 12.5 cm × 9.5 cm. Serial slicing of the specimen revealed a tumor (10.5 cm × 7.5 cm) with a nodular and whorled white appearance. The hepatic capsule was intact without any evident perforation. The microscopic evaluation revealed a cellular tumor with a fascicular array of tumor cells having spindle-shaped nuclei with a moderate-to-severe degree of cellular pleomorphism and more than 20 mitoses per 10 HPFs. Necrosis was focally seen. Lympho vascular invasion was not identified (Figures 3 and 4). All three regional lymph nodes (hepatic artery, periportal, and gallbladder neck) were negative for metastasis.

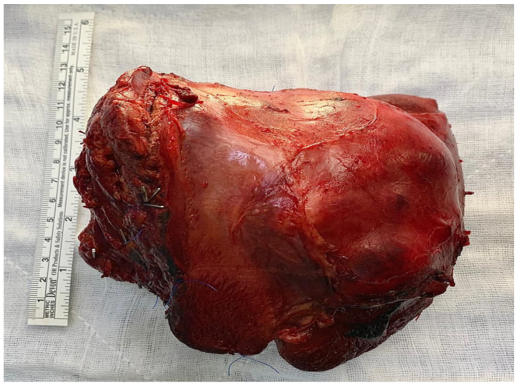
Immunohistochemical stain

Desmin (clone DE-R11, Ventana; Roche Diagnostics, Indianapolis, IN, USA), a marker of smooth muscle differentiation, was positive in tumor cells; and caldesmon (clone E-89; Cell Marque Co., Rocklin, CA, USA) was negative in tumor cells. In addition, CD117 (clone EP-10; Leica, Wetzlar, Germany) and DOG1 (clone SP31; Cell Marque) were also negative in tumor cells, ruling out the possibility of the closest differential diagnosis of GIST (Figure 5).



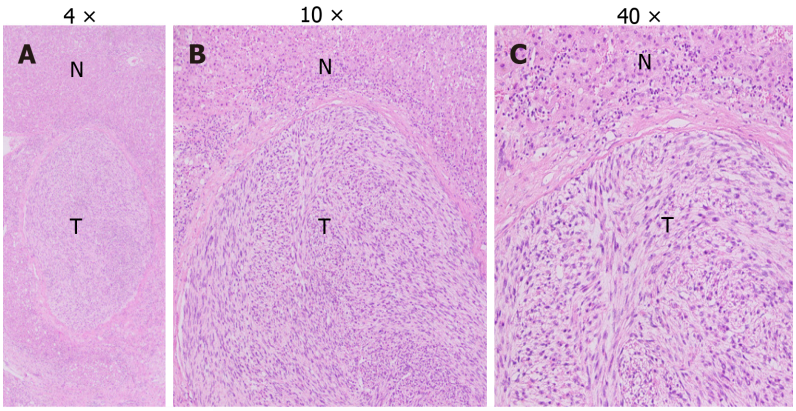
DOI: 10.4254/wjh.v14.i9.1830

Figure 1 Contrast enhanced tomography scan image demonstrating a large enhancing heterogeneous mass in the left lobe of the liver (white arrow), surrounding normal the liver tissue (blue arrow).



DOI: 10.4254/wjh.v14.i9.1830

Figure 2 Resected specimen.



DOI: 10.4254/wjh.v14.i9.1830

Figure 3 Leiomoyosarcoma, subsequent resection specimen. A: Original magnification: 4 ×, scale bar: 100 μm; B: The above figures show liver parenchyma with a central nodule/tumor fascicular array of cells having spindle-shaped nuclei, moderate degree nuclear atypia (original magnification: 10 ×; scale bar: 100 μm); C: Mitoses marked as T, and normal liver hepatocytes marked as N (original magnification: 40 ×; scale bar: 100 μm).

OUTCOME AND FOLLOW-UP

The postoperative recovery of the patient was uneventful. She was discharged on the 6th postoperative day. The patient remained asymptomatic until the follow-up visit after 6 mo. No short- or long-term postoperative complications were reported. CT and PET-CT scans were performed during this follow-up visit, which showed no evidence of recurrence and metastases. The patient was later presented in the MDT of Sarcoma, where it was decided to keep the patient under bi-annual surveillance, and no

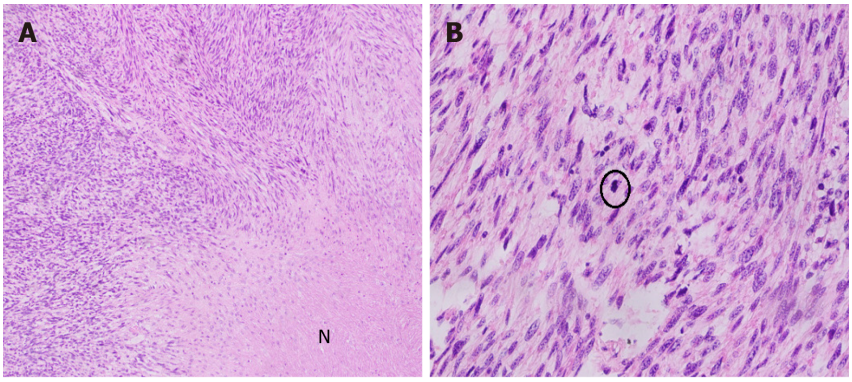


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Figure 4 Hematoxylin and eosin stain of leiomoyosarcoma. A: Hematoxylin and eosin stain of leiomoyosarcoma, resected specimen, a section of the liver shows fascicular array of cells with spindle-shaped nuclei (Original magnification: 100 ×; scale bar: 100 μm); B: A moderate degree nuclear atypia, and mitoses (encircled) along with areas of necrosis marked as N (original magnification: 400 ×; scale bar: 100 μm).

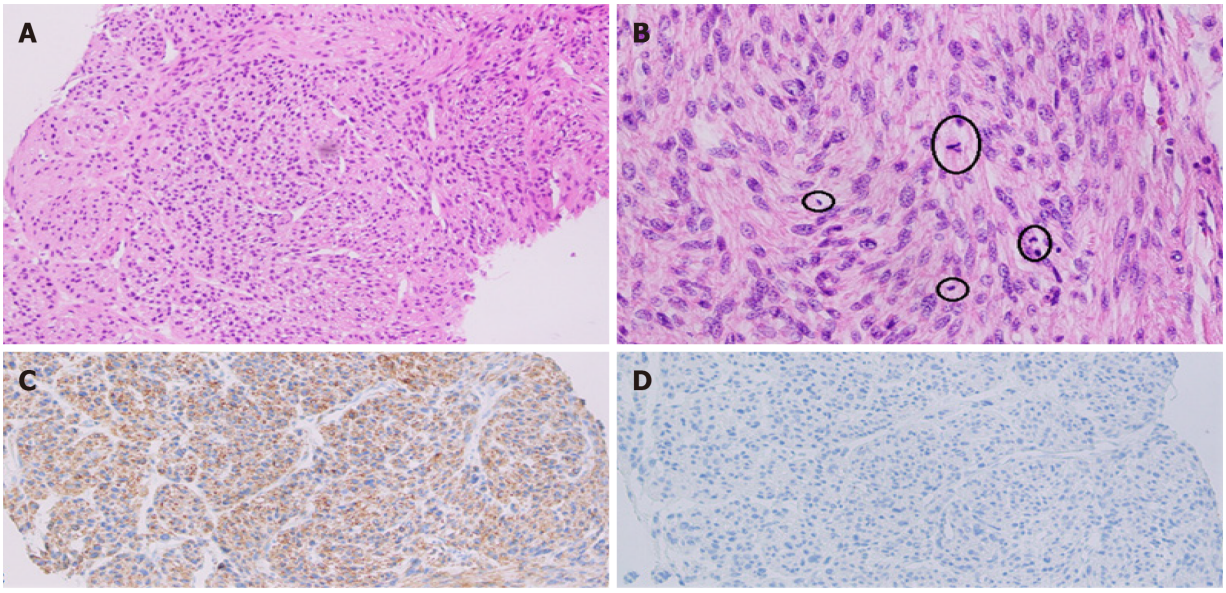

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Figure 5 Fascicular array of cells with spindle-shaped nuclei. A: Moderate degree nuclear atypia (original magnification: 100 ×; scale bar: 100 μm); B: Mitoses (encircled) (original magnification: 100 ×; scale bar: 100 μm); C: Immunostaining of desmin highlighting spindle-shaped cells (original magnification: 100 ×; scale bar: 100 μm); D: Caldesmon-negative (original magnification: 100 ×; scale bar: 100 μm).

adjuvant treatment was recommended.

DISCUSSION

Sarcomas from the liver are rare, constituting only 1%-2% of all primary hepatic malignant tumors[1,2]. Leiomyosarcoma accounts for 8%-10% of all hepatic sarcomas, whereas other hepatic sarcomas including angiosarcoma, fibrosarcoma, liposarcoma, embryonal sarcoma, malignant fibrous histiocytoma, carcinosarcoma, and epithelioid hemangioendothelioma collectively comprise nearly 70%-80% of hepatic sarcomas[3]. Hepatic leiomyosarcomas are generally metastatic, arising from the GI tract, uterus, retroperitoneum, or lungs, requiring careful staging[2]. To the best of our knowledge, only about 70 cases, including case series, have been published internationally, including our patient (Tables 1 and 2)[1].

Leiomyosarcoma potentially originates from the smooth muscle cells in the round ligament, intrahepatic blood vessels, and bile ducts. Tumors arising from intrahepatic veins have a worse prognosis because they tend to progress to Budd-Chiari syndrome. The differentiation between benign leiomyoma and low-grade leiomyosarcoma is based on mitotic figures per HPF, although variation occurs according to the site of origin[3,4].

Table 1 Management outcomes of published case reports of primary hepatic leiomyosarcoma

Ref.	Patient age in yr	Sex	Risk factor/s	Management	Follow-up/ outcome
Jeong *et al*[12], 2008	49	F		Wedge resection	Died at 18 mo
Cioffi *et al*[2], 1996	62	M			Died at 20 mo
O'Leary *et al*[27], 1982	69	M			Alive at 24 mo
Baur *et al*[28], 1993	69	F		Surgery	Recurrence after 10 yr
Sato *et al*[29], 2000	62	F			Diagnosis at autopsy
Iordanidis *et al*[30] , 2002	25	M		Surgery	Death at three mo
Lee *et al*[31], 2002	64	F		Right lobectomy + wedge resection of the left lobe	No evidence of disease at 24 mo
Shivathirthan *et al* [32], 2011	78	M		Chemotherapy, radiation	Death at 10 mo
Muranushi *et al* [33], 2019	62	M	Gastric gist post resection	Left hepatectomy+ resection of 3 other lesions	No evidence of disease
Watanabe *et al*[34], 1991	62	M		Lobectomy	No evidence of disease at 5 mo
Esposito *et al*[35], 2020	78	M		Left hepatectomy	No evidence of disease at 18 mo
Yoshikawa *et al* [36], 1977	58	F		Wedge resection	Death, 11th postoperative day
Bloustein[37], 1978	12	F		Trisegmentectomy, chemotherapy	No evidence of disease at 6 yr
Maki *et al*[6], 1987	86	F		Surgery	No evidence of disease at 5 mo
Holloway *et al*[15], 1996	63	M		Conservative	
Soyer *et al*[19], 1996	67	F		Surgery	
Tsuji *et al*[10], 2000	68	M	Hepatitis c		Diagnosis at autopsy
Fujita *et al*[9], 2002	33	F	Prior renal transplant	Right posterior segmentectomy	No evidence of disease at 24 mo
Giuliante *et al*[11], 2009	26	M	Hodgkin's lymphoma	Right lobectomy + wedge resection of segment id	Death at 25 mo
Liang *et al*[21], 2009	44	F		Liver transplant	Death at 34 mo
Shivathirthan *et al* [32], 2011	67	M		Extended left hepatectomy + partial resection of segment 6	No evidence of disease at 9 mo
Tsai *et al*[5], 2013	Five mo	M		Chemotherapy + partial hepatectomy (segment vi) + adjuvant chemotherapy	No evidence of disease at 48 mo
Feretis *et al*[24], 2019	68	F	Hepatitis b	Left hepatectomy+ cholecystectomy, chemotherapy, target therapy, redo surgery for recurrence	Recurrence at 18 mo 2nd recurrence at 21 mo died at 37 mo
Zhu *et al*[25], 2019	63	M		Unresectable tumor TACE (2011)	No evidence of disease at 82 mo
Vella *et al*[1], 2020	77	F		Right hepatectomy	No evidence of disease at 8 mo

F: Female; M: Male; TACE: Transcatheter arterial chemoembolization.

There is no apparent sex predilection with an approximate male-to-female ratio of 1:1 in the literature review of cases reported to date including our patient. Age at the time of presentation is variably reported with a range of 5 mo to 86 years (mean age of 51.3 years)[5,6].

No specific pathological causes of PHL have been identified to date, although the literature review shows an association with multiple etiological factors, including immunosuppression due to acquired immunodeficiency syndrome. Epstein-Barr virus infection is reported in two cases and a previous history of immunosuppression postrenal transplant in 1 case. The other reported associations include hepatitis C virus infection, exposure to thorotrast, and previously treated Hodgkin's lymphoma[7-11].

Table 2 Management outcomes of published case series of primary hepatic leiomyosarcoma

Ref.	Patient age in yr	Sex	Treatment	Follow up
Almogy *et al*[22], 2004	58	F	Surgery + chemotherapy	Death at 4 mo
	63	F	Surgery + chemotherapy	Death at 12 mo
Watanabe *et al*[34], 2008	63	F		Diagnosis at autopsy
	49	F		Diagnosis at autopsy
Matthaei *et al*[14], 2009	19	F	Liver transplant	Death at 73 mo
	64	F	Surgery	No evidence of disease 181 mo
	53	F	Surgery	Death at 21 mo
	55	M	Surgery	No evidence of disease at 133 mo
	51	M	Liver transplant	No evidence of disease at 144 mo
	59	M	Surgery	Death at 45 mo
	63	F	Surgery	No evidence of disease at 133 mo
Shamseddine *et al*[23], 2010	25	F	Right lobectomy	Death at 22 mo
	39	M	Extended right lobectomy	Death at 19 d
	30	M	Right lobectomy + chemotherapy	No evidence of disease at 12 mo
Esposito *et al*[35] ,2020	78	M	Left hepatectomy	No evidence of disease at 18 mo
	53	M	Right extended hepatectomy	Lung metastasis at seven mo death at 14 mo

F: Female; M: Male.

PHL usually pursues an indolent course being asymptomatic initially until they enlarge in size causing non-specific symptoms such as abdominal pain or discomfort, a palpable mass, fever, jaundice, anorexia, nausea or vomiting, and weight loss. The literature review revealed a single patient presenting as an emergency due to acute intraabdominal hemorrhage following tumor rupture. There is usually a single mass, although there are cases with multiple masses. Tumor size varies significantly ranging from 0.6 cm to 30 cm in the largest dimension (mean and median diameters of 10.3 cm and 9.1 cm, respectively). In our case, the tumor size was 10 cm in its largest dimension. The distribution of PHL within the liver segments and lobes also differs, with 2/3rd cases involving the right lobe and 1/3rd cases involving the left lobe. The case presented here involved the left lobe of the liver[6,11-16].

Histological examination usually shows intersecting bundles of spindle-shaped cells with hyperchromatic nuclei and mitotic figures. Immunohistochemistry shows positive results with smooth muscle actin, desmin, and vimentin, whereas cytokeratins, neuron-specific enolase, S-100 protein, α-fetoprotein, CD34, CD117, and DOG1 were not expressed.

Ultrasonography usually shows hypoechoic or heterogeneous echogenic mass. CT findings generally describe a hypodense and sometimes heterogeneous mass with inhomogeneous and often peripheral enhancement after intravenous contrast administration, which may show regions of cystic degeneration, demonstrated in our case[17]. Ferrozzi *et al*[18] reported that hemorrhagic necrosis, along with cystic degeneration and necrosis, are likely to be secondary to tumor growth. Magnetic resonance imaging characteristically displays homogeneous or heterogeneous hypointense T1-weighted images and hyperintense T2-weighted images[19]. PET-CT scan SUV max can be correlated with the tumor size, tumor-node-metastasis staging, and histology subtype[20]. In our case, the SUV max of the primary tumor was 6.4, with a baseline hepatic parenchymal SUV of 2.96.

Therapeutic options vary depending upon the tumor size and/or stage on initial presentation. Hepatic resection (wedge resection, segmentectomy, lobectomy, or extended hepatectomy with the intention of R0 resection) remains the only potentially curative surgical option for non-metastatic including our case. However, 4 patients with tumors confined within the liver had liver transplantation [14,21].

Some authors have also reported that adjuvant chemotherapy consisted of various drugs, including doxorubicin and ifosfamide, which help to attain prolonged survival after complete resection. In addition, three cases have been treated with radiotherapy as part of a combined adjuvant treatment along with chemotherapy[5,22-24].

Transarterial chemoembolization and transarterial infusion of epirubicin and carboplatin were also reported in individual cases as treatment modalities for PHL[25].

The median survival is 37.5 mo with a 5-year survival rate of about 40%; two large case series reported 67% disease-specific survival at 5 years after R0 resection. Matthaei *et al*[14] in a case series, reported more than 10 years of survival after hepatectomy. Chi *et al* reported a median overall survival of 19 mo with 1-, 2-, and 5-year survival rates of 61.2%, 41.1%, and 14.5% respectively[26].

Age is another crucial predictive factor for prognosis, with patients below 50 years achieving better survival. Currently, no effective therapeutic options have been reported for unresectable PHL. Fujita *et al*[9] reported a patient with metastatic leiomyosarcoma surviving 3 mo after diagnosis, who received only palliative and conservative therapy.

CONCLUSION

In conclusion, PHL is a rare malignant disease with often delayed presentation, relatively poor prognosis, and aggressive metastatic potential. The most preferred management options include surgical excision combined with chemotherapy and radiotherapy. However, very little is known about the efficacy of available therapeutic options because of the rarity of the disease. Therefore, in-depth studies are required to assess its causative, prognostic, and predictive parameters.

FOOTNOTES

Author contributions: Ahmed H and Bari H were the patient's surgeons, reviewed the literature, and contributed to manuscript drafting; Sheikh UN and Basheer MI performed the histopathological analyses and interpretation; All authors issued final approval for the version submitted.

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

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LETTER TO THE EDITOR

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Isabel Legaz, Manuel Muro

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Abstract

The authors of this study note that in liver transplantation (LT), the survival rates of hepatitis C virus (HCV)-positive donors and HCV-negative receivers are compa-rable to those of HCV-negative donors and recipients. Direct-acting antiviral (DAA) therapies have nearly 100% effectiveness in treating HCV. Between 2006 and 2016, the percentages of HCV-positive patients on the waiting list and HCV-positive LT recipients fell by 8.2 percent and 7.6 percent, respectively. Records from April 1, 2014, in which the donor and receiver were both at least 18 years old and had a positive HCV status, were the only ones eligible for the study. The analysis for this study was restricted to the first transplant recorded for each patient using a data element that documented the number of prior transplants for each recipient, although some recipients appeared multiple times in the data set. HCV-positive recipients or people with fulminant hepatic failure were the main beneficiaries of primary biliary cirrhosis among HCV-positive donors. However, there is still a reticence to use HCV-positive donor organs in HCV recipients due to clinical and ethical considerations. Similar survival rates between HCV-positive donors and recipients and HCV-negative donors and receivers illustrate the efficacy of these DAA regimens.

Key Words: Hepatitis C virus; Liver transplant; Graft survival; United network for organ sharing; Direct-acting antiviral

Core Tip: The scarcity of viable organs, which is quite limited, the waiting lists that reflect chronicity and the increase in time to transplantation, and the rate of physical deterioration resulting in death while waiting for a helpful organ for transplantation, promote the search for new ways, strategies, and protocols to increase the group of donors acceptable for transplantation, such as donors in asystole, donors with tumor processes, or donors with previous infection. The application of antivirals against the hepatitis C virus (HCV), with unprecedented success in the elimination of the pathogen, has led to the use of HCV-positive donors as optimal donors for HCV-negative recipients, with survival similar to that of both HCV-negative donors and recipients, which supports the use of these HCV-positive donors without restrictions.

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TO THE EDITOR

We have read with great attention and particular interest the review by Dhaliwal A *et al*[1] entitled "Impact of the use of positive organs for hepatitis C in liver transplantation: Analysis of the database of the United Network for Organ Sharing". The study noted that the survival rates of hepatitis C virus (HCV)-positive donors and -negative recipients following liver transplantation (LT) are comparable to those of HCV-negative donors and recipients. On the other hand, direct-acting antiviral (DAA) therapies have a nearly 100% effectiveness rate in the treatment of HCV infection[2-4].

The proportions of HCV-positive waiting list patients and HCV-positive LT recipients decreased by 8.2% and 7.6%, respectively, between 2006 and 2016[5]. HCV recurrence post-LT was the most frequent reason for graft failure prior to the availability of DAA treatment and significantly decreased recipient survival in patients with HCV positivity compared to HCV-negative patients[6,7]. This HCV recurrence significantly impacted the allocation of HCV-positive donors, severely underutilizing these organs, especially in HCV-negative recipients. Due to the strong potency and low risk of side effects of this new generation of DAAs, there is an increasing propensity to use organs from HCV-positive donors, especially those with high virus loads[8,9]. The United Network for Organ Sharing (UNOS) database was utilized in this study to compare the survival rates of HCV-negative donors and recipients with those of HCV-positive donors and recipients[10].

The authors of this intriguing study used information from the UNOS registry, which includes information on every transplant in the country. Records from April 1, 2014, in which the donor and receiver were both at least 18 years old and had a positive HCV status, were the only ones eligible for the study. Although some recipients appeared many times in the data set, the analysis for this study was limited to the first transplant recorded for each patient using a data element that tracked the number of prior transplants for each recipient. The primary outcome was overall survival time as of the most recent patient follow-up on September 7, 2018, with death being indicated by the composite indicator of death and censoring for those who did not die throughout the trial period. The authors used log-rank tests and group survival estimates at various time points of monitoring after transplantation to compare overall survival between groups. The investigation comprised a total of 24512 transplants, with 253 people who received transplants from positive donors to negative recipients. The duration of cold ischemia was comparable across all groups. Following cirrhosis caused by HCV, cirrhosis caused by non-alcoholic steatohepatitis, and hepatoma as the most frequent primary diagnoses were alcoholic cirrhosis/acute alcoholic hepatitis. Looking at survival rates at 1-year, 2-year, and 3-year intervals revealed that the particular group with a positive donor and negative recipient had lower survival rates than the other three groups (negative donor and positive recipient; positive donor and negative recipient; positive donor and positive recipient) which were all close together.

HCV-positive recipients or people with fulminant hepatic failure were the main beneficiaries of primary biliary cirrhosis among HCV-positive donors. However, due to clinical and ethical considerations, there is still reticence to use organs from HCV-positive donors in HCV-positive recipients. In a study of 99 recipients of liver grafts from HCV-positive donors, Lai *et al*[11] found that HCV-positive donor graft recipients had significantly higher unadjusted rates of advanced fibrosis at 1 and 3 years than HCV-positive donor graft recipients. According to Khapra *et al*'s study of 29 HCV-positive donor liver graft recipients, they exhibited significantly greater fibrosis and a faster rate of development[12].

However, studies of single-center experiences and large public databases, such as UNOS and the Scientific Registry of Transplant Receivers, have shown that recipients of livers from HCV-positive and HCV-negative donors had the same results since the introduction of DAAs[13-15].

It should be mentioned that there is currently no recognized procedure. The people who participated in this research were in preventive therapy. The information was obtained from a large population-

based study based on a well-known UNOS database that included many Americans. The authors concluded that the survival rates of HCV-positive donors and recipients and HCV-negative donors and receivers are identical. More studies should be carried out in the future in more national and international transplant registries to confirm these points.

FOOTNOTES

Author contributions: Muro M and Legaz I designed the research, performed the research, and wrote and revised the letter.

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