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EDITORIAL

From metabolic dysfunction-associated fatty liver disease to metabolic dysfunction-associated steatotic liver disease: Controversy and consensus

Li Chen

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Abstract

The newly released nomenclature of metabolic dysfunction-associated steatotic liver disease (MASLD) in the 2023 European Association for the Study of the Liver Congress has raised great clinical concerns. This marks the second instance of significant renaming of non-alcoholic fatty liver disease since the introduction of metabolic dysfunction-associated fatty liver disease (MAFLD) in 2020. The nomenclature and definitions of MASLD and MAFLD exhibit significant disparities as well as substantial consensus. The disparities regarding the framework of nomenclature, the definitions, the clinical management, and the impact on the clinical outcomes between MASLD and MAFLD were comprehensively compared in this editorial. Additionally, the consensus reached by the MASLD and MAFLD definitions also emphasizes positive diagnosis rather than negative diagnosis within the framework of establishing a diagnostic approach. Furthermore, they acknowledged the pivotal role of metabolic dysfunction in the pathogenesis of MAFLD or MASLD and the positive role of increasing the awareness of the disease in public. Fortunately, the non-invasive tests remains effective in the MASLD and MAFLD era. Elucidating these disparities would contribute to a more comprehensive comprehension of the nature of steatotic liver disease and enhance clinical practice. Thus, more efforts are required to reach more consensus about these important topics.

Key Words: Non-alcoholic fatty liver disease; Metabolic dysfunction-associated fatty liver disease; Metabolic dysfunction-associated steatotic liver disease; Nomenclature; Metabolic risk factors

Core Tip: The nomenclature for non-alcoholic fatty liver disease has undergone name changes twice in a span of three years. However, there exist significant disparities and some consensus between the transition from metabolic dysfunction-associated fatty liver disease to metabolic dysfunction-associated steatotic liver disease. Clarifying these discrepancies would greatly benefit clinical practice and trials.

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INTRODUCTION

With the escalating prevalence of obesity and type 2 diabetes mellitus (T2DM) in the general population, fatty liver disease has become a predominant etiology of chronic liver disease worldwide[1,2]. Non-alcoholic fatty liver disease (NAFLD), first named by Jurgen Ludwig in 1986, was defined as hepatic steatosis affecting at least 5% of hepatocytes without any other causes of liver injury[3]. NAFLD encompasses a histological spectrum of disorders ranging from non-alcoholic fatty liver (NAFL) to non-alcoholic steatohepatitis (NASH) and can progress to liver cirrhosis or hepatocellular carcinoma[4]. Due to its exclusionary diagnostic criteria, the term NAFLD has encountered significant challenges in both diagnosis and treatment, particularly when patients with NAFLD present with concurrent alcohol consumption or viral hepatitis. In 2020, a novel nomenclature of "metabolic dysfunction-associated fatty liver disease (MAFLD)" was proposed by a panel of international experts from 22 countries to address these concerns.

The MAFLD framework emphasizes the importance of metabolic dysfunction, as demonstrated by the revised definitions of overweight/obesity, T2DM, or the presence of at least two metabolic risk abnormalities, regardless of the underlying etiologies and comorbidities such as alcohol consumption and viral hepatitis[5]. However, the revised definition of MAFLD, which encompasses alcoholism and acknowledges the coexistence of multiple etiologies, raises concerns regarding its impact on the natural history and therapeutic development of the condition, as well as the potential stigmatization associated with the term "fatty". Recently, three large pan-national liver associations, including the American Association for the Study of Liver Disease, European Association for the Study of the Liver, and Latin American Association for the Study of the Liver, proposed a novel nomenclature for steatotic liver disease (SLD) and metabolic dysfunction-associated SLD (MASLD) through a modified Delphi process. In this novel nomenclature, the umbrella term, SLD, is classified into two distinct subcategories based on the presence and absence of a cardiometabolic risk factor (CMRF). Furthermore, the subcategory of CMRF is further classified into MASLD and MetALD depending on the alcohol consumption. MASLD is defined as the presence of hepatic steatosis in conjunction with at least one CMRF and no other discernible cause[6]. Within a span of merely 3 years, two distinct nomenclatures were successively proposed. The magnitude of the controversy surrounding these nomenclatures remains substantial, with societies yet to reach a consensus. Therefore, elucidating the disparities and similarities between MASLD and MAFLD is imperative.

THE CONTROVERSY BETWEEN MASLD AND MAFLD

The disparity in the framework of nomenclature between MASLD and MAFLD

MASLD is a branched term under the overarching term of SLD, which encompasses a broad spectrum of causes contributing to hepatic steatosis. The term MASLD, which excludes alcoholic consumption and other concomitant etiologies, is parallel with MetALD, alcoholic liver disease (ALD), other specific etiology SLD, and cryptogenic SLD. From this perspective, MASLD can be regarded as a negative diagnosis. MASLD focuses on the intricate relationship between hepatic fat deposition and metabolic dysfunction while excluding the effects of alcohol. While MAFLD is a positive diagnosis regardless of alcohol consumption or other concomitant liver diseases. MAFLD is a single overarching term encompassing the primary and secondary fatty liver disease as long as it meets the criteria of metabolic dysfunction. Nevertheless, the MAFLD leads to more heterogeneity in the disease spectrum compared to MASLD. Given the global popularity of alcohol consumption, the coexistence of NAFLD and alcohol consumption poses challenges for diagnosing NAFLD; this issue can be readily resolved by adopting the term MAFLD. However, alcohol consumption interacts with components of the metabolic syndrome to exert synergistic or supra-additive effects on the development and progression of liver disease, further complicating the natural history of MAFLD[7]. The introduction of the term MetALD provides a framework to study the natural history of such a distinct subcategory that has both alcohol consumption and metabolic dysfunction.

The disparity in the definitions of MASLD and MAFLD

Regarding the identification of steatosis, the MASLD criteria recommend confirmation through either imaging or histological methods. While the MAFLD criteria confirm steatosis by histological methods, or non-invasive tests (NITs) based on imaging approach or blood biomarkers. Moreover, the MAFLD criteria enumerate the NITs including

ultrasound, vibration-controlled transient elastography, computed tomography or magnetic resonance imaging (MRI), MRI–derived proton density fat fraction, and fatty liver index. From this perspective, the MAFLD criteria provide more options for the identification of steatosis.

One of the most prominent distinctions between MASLD and MAFLD is the identification of metabolic risk factors, which intend to identify patients likely to have insulin resistance as the main cause of hepatic steatosis. According to the MAFLD criteria, two out of seven metabolic risk factors must be met for patients without T2DM or obesity as outlined below: waist circumference ≥ 102/88 cm in Caucasian men and women or ≥ 90/80 cm in Asian men and women; blood pressure ≥ 130/85 mmHg; plasma triglycerides ≥ 1.70 mmol/L; plasma high density lipoprotein-cholesterol < 1.0 mmol/L for men and < 50 mg/dL < 1.3 mmol/L for women; prediabetes (fasting glucose levels 5.6 to 6.9 mmol/L, or 2-h postload glucose levels 7.8–11.0 mmol or HbA1c 5.7% to 6.4%); homeostasis model assessment-insulin resistance (HOMA-IR) score ≥ 2.5; and plasma high-sensitivity C-reactive protein (hs-CRP) level > 2 mg/L. The MASLD criteria necessitate the fulfillment of at least one out of the five cardiometabolic risk factors, which are similar to those outlined in the MAFLD criteria, except HOMA-IR and hs-CRP levels. As HOMA-IR and hs-CRP levels are not universally measured in all clinical settings, the MASLD criteria are more accessible and intuitive than the MAFLD criteria. A recent study has demonstrated that the MASLD criteria outperforms the MAFLD criteria in identifying fatty liver disease among lean patients, despite the absence of hs-CRP data[6]. However, which criterion is superior in identifying metabolic dysfunction and insulin resistance remains unclear.

The difference in the management of steatohepatitis

The MAFLD definition abandons the dichotomous stratification into steatohepatitis and non-steatohepatitis, which was established during the NAFLD era. The dichotomous classification of steatohepatitis and non-steatohepatitis may fail to capture the complete spectrum of disease response to alterations in underlying metabolic dysfunctions or pharmacological interventions[5]. The MAFLD definition places greater emphasis on the degree of activity and stage of fibrosis, rather than being entangled in the presence or absence of steatohepatitis. These changes inevitably exerted a significant impact on clinical trials, particularly in terms of endpoint selection, as the current objective of drug development is to achieve the resolution of NASH without any deterioration in liver fibrosis[8]. However, the definition of MASLD emphasizes that the presence of steatohepatitis carries prognostic implications and should remain an important distinction. Consequently, retaining the term "steatohepatitis" is imperative in both clinical practice and trial endpoints. Moreover, the MASLD definition suggests replacing the term NASH with metabolic dysfunction-associated steatohepatitis (MASH), which may reduce the confusion in clinical practice and trials[6]. The MASLD definition also permitted the integration of MASH with additional assessment of fibrosis severity.

The difference in the impact on clinical outcomes

The divergent framework of nomenclature and definition between MASLD and MAFLD implies the likelihood of disparate impact on clinical outcomes. Due to the heterogeneous nature of MAFLD, MAFLD has a more detrimental impact on clinical outcomes compared to MASLD. Based on the Third National Health and Nutrition Examination Survey (NHANES III), studies have demonstrated that MAFLD is associated with an elevated risk of all-cause and cardiovascular mortality, whereas NAFLD alone does not increase the risk of all-cause mortality[9]. MAFLD criteria identified a significant group of individuals with more comorbidities and worse prognosis compared with those with NAFLD only [10]. However, another study demonstrated no observed differences in cumulative all-cause and cause-specific mortality between MAFLD and NAFLD after adjusting for alcohol-associated liver disease[11].

A recent NHANES III study demonstrated that both the MAFLD-only and MASLD/MAFLD overlap subgroups exhibited significantly higher all-cause mortality, as opposed to the MASLD-only subgroup. With regard to cause-specific mortality, MAFLD was significantly associated with an increased risk for cardiovascular disease -related and diabetes-related mortalities, whereas MASLD was independently related to a higher risk of diabetes-related mortality[12]. Another study based on NHANES III also failed to demonstrate the association between MASLD and all-cause mortality after adjustment for demographic and other factors such as body mass index and hepatitis B and C viral infections. On the contrary, MetALD and ALD were significantly associated with all-cause mortality[13].

The difference in stigmatization of nomenclature

The renaming is partly motivated by the stigmatization associated with terms such as "fatty" and "nonalcoholic." During the Delphi process, the terms "nonalcoholic" and "fatty" were deemed to be stigmatizing by 61% and 66% of panelists, respectively[6]. However, the vote percentage does not surpass the priori threshold of ≥ 67%, thus failing to achieve a consensus. Perceptions of stigma differ widely across different languages and cultures. In certain Indian languages, the term "fatty" is associated with robust health and would be considered a compliment. There is no justification for stigmatizing "non-alcoholic" fatty liver disease, as it is not "alcoholic"[14]. Depending on the regions and cultural contexts, the transition from "fatty" to "steatosis" may be either ambiguous or unattainable. Additionally, the term "steatosis" can be overly medicalized, which may confuse the patients[15]. Interestingly, a recent survey in Mexico revealed that 69.5% of participants expressed that incorporating the term "alcohol" in the disease nomenclature carries a stigmatizing connotation and advocated for its exclusion. In contrast, 85.6% of participants indicated that they do not perceive the inclusion of "fatty" as stigmatizing and preferred retaining it to enhance effective communication regarding the disease[16]. Some experts argued that the change from NAFLD to MASLD and destigmatization is driven by political correctness rather than scientific rationale[14]. To date, the Asian Pacific Association for the Study of the Liver still advocates MAFLD and does not endorse MASLD, highlighting the ongoing controversy among various associations.

THE CONSENSUS BETWEEN MASLD AND MAFLD

The consensus on positive diagnosis and metabolic dysfunction

Both MASLD and MAFLD definitions adapt positive criteria and abandon the exclusive criterion of "non-alcoholic." Once hepatic steatosis is identified, either by histopathology or by imaging method, the diagnosis of steatotic liver disease or fatty liver disease is established. Both MASLD and MAFLD acknowledge metabolic dysfunction as the primary driver of disease progression. Moreover, metabolic dysfunction independently contributes to cardiometabolic outcomes. The complex interplay of metabolic, inflammatory, and vascular mechanisms exacerbates systemic atherogenesis; thereby, promoting the development and progression of cardiovascular diseases[17].

The consensus on increasing the awareness of the disease

The previous term NAFLD, which has been in use for four decades, is an exclusive criterion that implies no association with alcoholic consumption and overlooks the role of metabolic dysfunction in its pathogenesis. The term MASLD or MAFLD conveys an intuitive message to patients regarding the etiology, facilitating their comprehension of pathophysiology and treatment. The wide spread of novel nomenclature will enhance public awareness about metabolic dysfunction as an etiology for liver disease.

The consensus on the effectiveness of NITs

The changes in nomenclature raise a concern regarding the continued effectiveness of the NITs established in previous decades, which were based on extensive epidemiological data. The worries about the potential negative impact of changes in diagnostic criteria for biomarkers is warranted. Fortunately, the extensively validated NITs still can be applied under novel criteria. A recent liver biopsy-based study demonstrated that the Index of NASH (ION) exhibited superior discriminatory ability for detecting the presence of MASLD, while the aspartate aminotransferase to platelet ratio index and fibrosis-4 score effectively differentiated severe fibrosis stages[18].

UNRESOLVED QUESTIONS

The novel MASLD nomenclature also raises new questions. Firstly, in some patients, the hepatic steatosis vanishes while progressing to cirrhosis. The absence of steatosis prompts the question of whether such patients should be diagnosed with cryptogenic SLD or MASLD-cirrhosis[19]. Secondly, should the patients who drink more than 350/420 g/wk and fulfill one out of five CMRFs be diagnosed with MetALD, or should they be diagnosed with ALD? Conversely, should the patients who intake alcohol below 350/420 g weekly and without CMRFs be diagnosed as ALD, or should they be diagnosed with MetALD? Thirdly, patients with coexisting fatty liver and hepatitis B should be diagnosed as MASLD or other specific etiology SLD?

CONCLUSION

The term NAFLD has been proposed for nearly four decades; however, with time, it no longer adequately encompasses the pathophysiology of fatty liver disease, necessitating a change in its nomenclature. Indeed, the modification of a well-established or entrenched term poses great challenges. Within more than just 3 years, two distinct nomenclatures, namely MAFLD and MASLD, have been proposed sequentially. The novel nomenclatures not only modify the framework and operational definitions but also provide fresh insights into the pathophysiology and treatment strategies. More importantly, the renaming has significantly enhanced public awareness. Nevertheless, the substantial disparities between MAFLD and MASLD imply controversies among various professional associations, thereby may confuse physicians and patients. More research and debates are needed to reach a consensus in the future.

FOOTNOTES

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REVIEW

Multifunctional roles of inflammation and its causative factors in primary liver cancer: A literature review

Hong-Jin Chen, Ting-Xiong Huang, Yu-Xi Jiang, Xiong Chen, Ai-Fang Wang

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Abstract

Primary liver cancer is a severe and complex disease, leading to 800000 global deaths annually. Emerging evidence suggests that inflammation is one of the critical factors in the development of hepatocellular carcinoma (HCC). Patients with viral hepatitis, alcoholic hepatitis, and steatohepatitis symptoms are at higher risk of developing HCC. However, not all inflammatory factors have a pathogenic function in HCC development. The current study describes the process and mechanism of hepatitis development and its progression to HCC, particularly focusing on viral hepatitis, alcoholic hepatitis, and steatohepatitis. Furthermore, the roles of some essential inflammatory cytokines in HCC progression are described in addition to a summary of future research directions.

Key Words: Inflammation; Primary liver cancer; Hepatocellular carcinoma; Nonalcoholic fatty liver disease; Hepatitis virus

Core Tip: Primary liver cancer is the second most common tumor in the world, and the number of deaths due to this disease is increasing every year. A large number of studies have shown that inflammation has a certain regulatory effect in the occurrence and exacerbation of liver cancer. However, the function of inflammation in liver cancer remains to be studied. This review introduces the classification of hepatitis, the correlation between various inflammatory factors and hepatocellular carcinoma (HCC), and some of the anti-inflammatory drugs used in the treatment of HCC.

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INTRODUCTION

Liver cancer is categorized into primary and secondary liver cancer. Primary liver cancer involves hepatocellular carcinoma (HCC), intrahepatic cholangiocarcinoma, and other rare cancer types. In contrast, secondary liver cancer is due to cancer cell metastasis from different body parts to the liver *via* the bloodstream[1]. Notably, HCC accounts for 95% of primary liver cancer cases and is one of the leading types and fatal liver cancer forms. HCC development is closely associated with hepatitis C virus (HCV), hepatitis B virus (HBV), and nonalcoholic fatty liver disease (NAFLD)[2]. Alcoholic fatty liver may cause alcoholic steatohepatitis (ASH), leading to progressive fibrosis and cirrhosis, and can develop into HCC[3]. All these processes leading to HCC involve a series of reactions from inflammation to cirrhosis, resulting in HCC. Therefore, inflammation is clinically significant as the initiating factor in HCC.

Inflammation is a defensive response of the human body against stimulation and is divided into acute and chronic inflammation. Acute or short-term hepatic inflammation is a nonfibrotic condition caused by lipopolysaccharide, hepatitis virus, and other factors, and disappears within hours or days. Chronic or long-term inflammation, driven by chronic oxidative stress, is one of the critical processes in HCC development and progression[4]. More studies are investigating the presence of inflammation in the occurrence and development of liver cancer, but its exact role remains unclear. Immune cells in the tumor microenvironment either suppress or promote tumorigenesis, participating in adaptive and innate immunity and defense mechanisms to eliminate foreign agents. Persistent chronic inflammation accelerates the growth and proliferation of tumor cells[5]. Bioactive molecules released from immune cells in the tumor microenvironment stimulate carcinogenesis programming and enhance tumor development[6]. Several inflammatory cytokines, including interleukin (IL)-22, a member of the IL-10 family[7], play a positive role in liver regeneration and the anti-inflammatory response. Other cytokines, including IL-1β and IL-17A, serve as tumor-promoting cytokines, inducing liver disease progression and hepatocarcinogenesis[8,9]. This review summarizes the recent evidence on HCC mechanisms caused by various hepatitis viruses and discusses the role of inflammatory signaling pathways in HCC progression and development (Figure 1).

DIFFERENT CAUSATIVE FACTORS IN INFLAMMATION AND HCC

Role of viral hepatitis in HCC

Viral hepatitis caused by infection with hepatitis viruses A, B, C, D, and E is a global epidemic leading to acute or chronic hepatitis, and even acute severe hepatitis related to a high mortality rate. Due to differences in the structure and features of viruses, they selectively infect the liver using various routes[10]. Approximately 80% of HCC cases are related to HBV or HCV infections, leading to cirrhosis and progressing to HCC.

Hepatitis B virus: Hepatitis B virus (HBV) can integrate its double-stranded DNA (dsDNA) into host cells to develop pregenomic RNA (pgRNA). Then, pgRNA is encapsulated into icosahedral capsids formed by the hepatitis B virus core antigen protein, meditated by polymerase action. Within the capsid, gpRNA is reverse-transcribed into single-stranded DNA (ssDNA), after which the DNA is enveloped to become infectious virions. HBV contains the gene fragments HBV X protein and HBV C protein in its genome. These gene fragments are critical regulatory proteins with crucial roles in HBV-induced HCC pathogenesis. They directly activate or inhibit the expression of hepatocyte growth-related genes, including CTbp2, HMBGA1, and CA10, affecting its transformation to HCC[11-13]. In addition to the direct effects on the host genome to attenuate stability and enhance gene mutations and chromosomal rearrangements with oncogenic or proto-oncogene expression, HBV accelerates HCC progression through multiple mechanisms. For instance, HBV promotes HCC by inducing inflammation and oxidative stress, and altering the immune cell interaction for immune evasion. Bing-Qing Zheng reported that HBsAg (surface antigen) suppressed STAT3 expression and activation in natural killer (NK) cells of chronic hepatitis B (CHB) patients by reducing the IL-21 stimulation response[14]. HBV also activates the phosphatase and tensin homolog (PTEN)/β-actin/c-Myc pathway to promote programmed cell death protein 1 expression, inhibiting T-cell activity and indirectly enhancing the immune evasion of HBV in CHB infection[15]. Furthermore, chronic HBV infection leads to CHB-induced inflammatory damage in hepatic cells due to the persistent activation of inflammatory cells and chemokines[16], causing chronic severe hepatitis or liver cancer. Overall, CHB linked

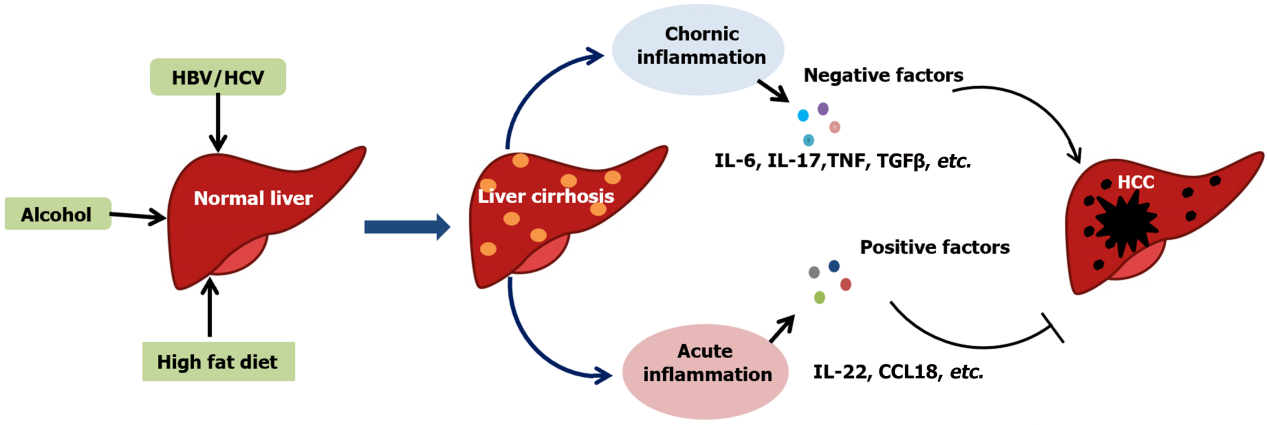

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Figure 1 The relationship between inflammation and hepatocellular carcinoma. HCC: Hepatocellular carcinoma; HBV: Hepatitis B virus; HCV: Hepatitis C virus; IL: Interleukin; TNF: Tumor necrosis factor; TGF: Transforming growth factor.

with HBV infection has a weak direct stimulatory role in HCC progression. However, the infection depends more on regulating various immune-related active molecules within the hepatocyte microenvironment.

Hepatitis C virus: HCV belongs to the Flaviviridae family and is an enveloped ssRNA virus. Unlike HBV infection, HCV infection mainly presents as asymptomatic chronic hepatitis, of which 20%-30% of patients progress to liver cirrhosis, and 7% suffer liver cancer[10]. As the released immune cells form a complex HCV-induced HCC tumor microenvironment, Guo-He Song performed single-cell RNA sequencing on immune cells from nontumor and HCV-associated HCC liver tissues[17]. This discovery highlighted novel macrophage and T-cell subsets, of which M2 macrophages significantly expressing CCL18 were enriched in advanced HCC patients. CCL2, CCL20, CXCL8, or CXCL10 were highly induced by the synergistic activity of HCV core protein and chemokines such as interferon (IFN)-γ and IL-1β in fibroblasts or liver sinusoidal endothelial cells (LSECs). These chemokines result in HCV-induced hepatic injury of the LSECs by recruiting leukocytes and activating hepatic stellate cells (HSCs), enabling the development and progression of fibrosis and cirrhosis [18]. CCL2 and CXCL10 are upregulated in macrophages, promoted by the HCV core protein, by interacting with the gC1qR and nuclear factor-kappaB (NF-κB) signaling pathways[19]. Tumor necrosis factor (TNF)-α, IL-1β, IL-6, IL-10, IL-18, and transforming growth factor (TGF)-β are the most relevant inflammatory cytokines associated with HBV/HCV-induced HCC *via* multiple pathways[20]. The IL-6 GC and TGF-β1 TT genotypes promoted HCC development in the HCV-infected population by altering the transcription and stability of the protein structures. These could be potential markers for the early diagnosis of HCC[21].

Role of alcoholic hepatitis in HCC

Excessive alcohol consumption can cause alcoholic liver disease (ALD), such as steatosis, ASH, fibrosis, cirrhosis, and HCC. In the liver, alcohol is metabolized using three major oxidative pathways. First, alcohol is oxidized to acetaldehyde by alcohol dehydrogenase, with NAD^+ as the cofactor[22], cytochrome P450 2E1 (CYP2E1) in the microsomal ethanol oxidizing system[23], and the heme-containing enzyme catalase[24]. Subsequently, acetaldehyde is oxidized to acetate by aldehyde dehydrogenase (ALDH). Acetaldehyde damages DNA and impairs the antioxidant defense system, decreasing antioxidant and detoxification enzymes. Adducts from acetaldehyde can disturb cellular function, promoting alcohol-induced liver injury. CYP2E1 induced by chronic alcohol intake enhances alcohol metabolism to acetaldehyde, leading to liver injury and producing reactive oxygen species (ROS)[25]. These ROS attack the hepatocyte mitochondria and reduce ALDH activity. Additionally, mutagenic etheno-DNA adducts, stimulated by CYP2E1, are essential in genetic damage and liver carcinogenesis[26]. Long-term alcohol use causes excessive CYP2E1 along with oxidative stress, producing ROS [27]. Such exposure results in structural damage, mitochondrial dysfunction, mitochondrial stress in hepatocytes, and apoptotic signal upregulation.

Long-term alcohol consumption and liver dysfunction induce alcoholic hepatitis (AH), which is linked with severe ASH and high mortality rates in the short term[28]. Excessive consumption of alcohol causes damage to the microtubule structure and dysfunction of liver cells in patients with AH, which affects the efficiency of nutrient transport. Protein adducts formed by acetaldehyde can block DNA repair and hepatocyte mitochondria, contributing to the dysfunction of oxygen utilization, collagen synthesis, and extracellular matrix accumulation, resulting in liver fibrosis, cirrhosis, and carcinogenesis[29].

Interestingly, innate immunity activation leads to carcinogenesis in two ways: it leads to alcohol-induced liver injury and results in hepatoprotection, regeneration, and anti-inflammatory reactions to decrease alcohol-induced liver damage [30]. Alcohol consumption elevates lipopolysaccharides and activates the MyD88-independent TRIF/IRF-3 pathway using Toll-like receptor 4 (TLR4), causing oxidative stress, TNF-α release, and liver damage[31]. However, TLR4 and complement factors also promote Kupffer cells to secrete protective cytokines such as IL-6 and anti-inflammatory cytokines such as IL-10. Inflammatory cytokines such as TNF-α, IL-1, and IL-6 are enhanced in the serum of ALD patients [32]. IL-10 plays a positive hepatoprotective role *via* the STAT3 signaling pathway[33]. In contrast, IL-6 and p-STAT3 are

highly expressed in HCC patients[34]. TNF-α acts as a pro-tumorigenic cytokine and activates NF-κB and c-Jun N-terminal kinase (JNK) signaling pathways in liver carcinogenesis[35]. NK cells can develop IFN-γ to attenuate liver cell regeneration and kill hepatocytes[36]. However, the function of NK and NK T cells in hepatocytes remains unexplored. IL-1β plays an essential role in the progression of inflammation, alcohol-induced liver steatosis, and liver injury[37]. IL-22 has beneficial effects on hepatic inflammation and regeneration, while F-652, an IL-22 agonist, is a promising AH treatment candidate[38]. IL-17A functions as a tumor-promoting cytokine regulating inflammatory responses and cholesterol synthesis in developing hepatic steatosis, fibrosis, and HCC in an experimental alcohol-induced mouse model [9]. Some of the inflammatory factors have various roles in different stages. If their expression can be upregulated or downregulated during a specific period, these factors could exert their unique therapeutic effects on AH to HHC.

Role of NAFLD in HCC

NAFLD is a global disease characterized by excessive fat accumulation in the liver and is not associated with excessive alcohol use. NAFLD progression occurs through several stages, such as simple steatosis, steatohepatitis, fibrosis, and cirrhosis, leading to HCC. NAFLD encompasses a group of liver diseases from non-alcoholic fatty liver (NAFL) to non-alcoholic steatohepatitis (NASH)[39]. NAFL is a simple steatosis of liver cells without inflammation[40]. Furthermore, NAFL development is accompanied by an inflammatory response, causing NASH and liver cancer with cirrhosis[41]. NASH is characterized by the long-term accumulation of triglycerides or clearance disorders in liver cells, progressing to HCC[42]. The presence of steatosis, inflammation, and hepatocyte damage typically characterizes NASH. These are associated with a higher incidence of cirrhosis and liver cancer with NASH mortality than in NAFL[43-45]. TLR9-MyD88 signaling stimulates Kupffer cells to synthesize IL-1β, which contributes to hepatocyte damage and activates HSCs, promoting NASH development[46]. IL-33 is released during chronic hepatocellular stress to activate ILC-2 in the liver and produce IL-13, facilitating HSC activation and the onset of hepatic fibrosis[47]. Notably, the IL-33/ST2 axis has dual roles in diet-induced NASH, wherein an IL-33 supplement ameliorates hepatic steatosis but exacerbates hepatic fibrosis [48]. TNF-α promotes liver fibrosis while cooperating with TIMP-1 produced by HSCs[49]. In a recent study, IL-17A was tested at a high concentration in early-stage fibrosis with increased expression of profibrotic markers in the tissue slice culture, which revealed a significant role of IL-17A in promoting liver fibrosis in human liver tissue[50]. IL-22 treatment ameliorated CXCL1/high-fat diet-induced NASH and methionine choline-deficient diet-induced NASH *via* multiple targets, suppressing liver inflammation[51].

Others

Primary biliary cholangitis (PBC) is a chronic cholestatic liver disease with chronic and persistent bile stasis in the liver while causing cirrhosis and liver failure[52]. Some case reports show that cirrhosis is an HCC risk factor in PBC patients [53,54]. Diabetes is categorized into type 1 (T1DM) and type 2 (T2DM) diabetes. Diabetes liver fibrosis (DHF) is a chronic complication that progresses to liver disease. The main reason for DHF is to activate quiescent HSCs *via* high glucose stimulation[55]. T2DM possesses an elevated risk of advanced fibrosis in NAFL patients[56]. Clinical analysis revealed that 1 out of 20 T1DM patients and 1 out of 5 T2DM patients have elevated liver hardness (an indicator to evaluate liver fibrosis), suggesting severe or advanced liver fibrosis. Obese or T2DM patients have an increased risk of developing NASH, which can progress to cirrhosis and HCC if unchecked.

KEY INFLAMMATORY FACTORS AND HCC

Interleukin family

The IL family, with more than 40 members, was first investigated in 1976. According to the structural homology of cytokines, the IL family has seven subfamilies, including IL-1, IL-2, IL-6/IL-12, IL-10, IL-17, and chemokine α subfamilies.

IL-1 subfamily: The IL-1 subfamily includes IL-1α, IL-1β, IL-18, and IL-37[57]. Inhibition of IL-1 signaling using its agonist weakens hepatic inflammation and promotes liver regeneration, helping recovery from liver injury in AH[58,59]. In NAFLD, mice lacking IL-1α and IL-1β had inhibition of hypercholesterolemia steatosis to steatohepatitis and liver fibrosis[60]. Lack of IL-1α in Kupffer cells of mice with hypercholesterolemia weakens liver inflammation and inflammatory cytokine expression[61]. IL-1α release at different locations affects the development direction of HCC differently. Urinary excretion of IL-1α suggests an HCC-promoting effect, wherein the antitumor immune response is inhibited through myeloid-derived suppressor cells recruitment into the tumor microenvironment. Simultaneously, systemic IL-1α administration directly activates T cells to inhibit HCC development[62]. IL-1β secretion by macrophages was reduced in HBV and hepatitis D virus (HDV) infection, while IL-1β inhibited HBV and HDV replication[63]. IL-1β exerts antiviral effects by inhibiting ERK2 activation by elevating IFN-α, which inhibits HCV replication[64]. IL-1 receptor antagonists improve inflammasome-dependent ASH in mice[37]. Mice lacking the IL-1β activation gene can inhibit the development of obesity-induced NAFLD[65]. IL-1β receptor antagonists can inhibit liver fibrosis in mice, while IL-1β, a component of the NLRP3 inflammasome, can reduce liver fibrosis in NASH mice[66]. IL-1β is highly involved in hepatic lipogenesis by enhancing triglyceride accumulation and induces pathogenic liver steatosis in obesity-induced NAFLD[67]. M1 macrophages induce programmed cell death ligand 1 (PD-L1) expression in hepatoma cells *via* IL-1β signaling. This key checkpoint molecule mediates HCC immune escape[68]. IL-1β-mediated homologous box C10 overexpression enhances HCC metastasis by upregulating 3-phosphoinositol-dependent protein kinase 1 (PDPK1) and vasodilator-stimulated phosphoprotein (VASP) expressions[69].

IL-6/IL-12 subfamily: This subfamily consists of IL-6, IL-12, IL-23, IL-27, and IL-35A[70]. A case-control experimental study unraveled the potential susceptibility of IL-6 gene polymorphisms against HBV infection[71]. IL-6 regulates microRNA-125b expression in HCV infection using the STAT3 pathway, causing HCV infection onset and possibly progressing to HCC[72]. In AH, IL-6 promotes microRNA-223-rich exosome production, mitigating NAFLD-associated fibrosis[73]. Additionally, caffeine improves NAFLD with a tandem between muscle production of IL-6 and liver STAT3 activation[74]. The activation of IL-6/STAT3 signaling enhances LCSC production by hepatoma cells and resists sorafenib in hepatoma cells. This is an essential factor in inducing the occurrence, development, and metastasis of liver cancer[75]. Inhibiting IL-6/STAT3 signaling can lead to HCC cell apoptosis[76].

IL-10 subfamily: This subfamily consists of IL-10, IL-19, IL-20, IL-22, IL-24, and IL-26[77]. In a clinical study, polymorphisms in IL-19 increased susceptibility to HBV infection in children[78]. IL-19 inhibits the progression from NAFLD to NASH *in vitro*, while its deficiency in mice leads to pro-inflammatory cytokine expression in the liver[79]. IL-22 positively affects liver inflammation and impaired hepatic regeneration in AH patients and reduces ethanol-induced liver steatohepatitis in mice[38,80]. IL-22 exerts hepatoprotective effects in NAFLD-related liver fibrosis and injury[51,81,82]. However, the role of IL-22 in viral hepatitis is controversial, wherein some studies have reported its positive effects [83], while others indicated that it promotes liver fibrosis and HCC[84,85]. IL-22 exerts pro-tumorigenic effects on hepatocytes in HCC, while IL-22 BP ameliorates liver carcinogenesis[86]. IL-22 overexpression promotes HCC progression, while metformin treatment suppresses IL-22-induced liver cell proliferation, migration, and invasion by reacting with the Hippo signaling pathway[87].

IL-17 subfamily: The IL-17 subfamily comprises IL-17A, IL-17B, IL-17C, IL-17D, IL-17E, and IL-17F[88]. IL-17 expression and the methylation status of its gene promoter can enhance CHB progression[89]. Polymorphisms in the IL-17 gene are related to HCV infection in humans[90,91]. In NAFLD, IL-17 promotes M1 macrophage polarization and exacerbates the hepatic inflammatory response, accelerating NAFLD progression in mice[92]. High-fat diets lead to IL-17A expression, accelerate NAFLD progression by inhibiting fatty acid β oxidation, and promote triglyceride accumulation[93]. This prevents fibrosis in steatohepatitis in mice by inhibiting IL-17-mediated inflammation[94]. In an experimental model of alcohol-induced HCC, IL-17 promotes HCC by regulating the inflammatory response of macrophages and cholesterol synthesis in fatty hepatocytes[9]. IL-17 can also promote non-ASH and HCC[95]. In particular, IL-17A can enhance HCC invasion *via* the AKT pathway and restrict the autophagy of HCC cells by inhibiting Bcl2 degradation[96,97]. IL-17 can improve HepG2 cell proliferation *in vitro* and *in vivo* by activating the IL-2/STAT6 pathway[98].

Chemokine α subfamily: Endoplasmic reticulum stress induces IL-8 transcription and inhibits interferon reactivity in human hepatocytes to increase HBV proliferation[99]. Interferon induces IL-8 to inhibit the production of HBV surface antigen using human hepatocytes[100]. Blocking the recruitment effect of IL-8 on neutrophils can reverse ASH in mice [101,102]. In NAFLD, liver TLR2 expression is positively associated with circulating IL-8 levels. TLR2-mediated pathways are critical for NAFLD/NASH progression, and NASH progression is slower in TLR2 knockout mouse models than in wild-type mouse models[103]. HBV-induced IL-8 inhibits antitumor immunity and elevates HCC metastasis[104]. IL-8 promotes the upregulated signaling of integrin-β3 and HCC cell invasion by activating the PI3K/Akt pathway[105]. Thus, inhibiting IL-8 expression can suppress HCC growth[106,107].

TNF

TNF is a cytokine and an adipokine that plays significant roles in various cellular events, including cell proliferation, cell differentiation, and cell death. As a pro-inflammatory cytokine, TNF is actively involved in inflammation-related carcinogenesis. Gene variation in TNF is associated with increased susceptibility to HBV and HCV infection[108,109]. One study evaluated the inhibition of TNF/NF-κB signaling and macrophage M1-type polarization, suggesting a promising approach for attenuating NAFLD progression to NASH[110]. Anti-TNFR1 treatment significantly reduces liver injury and fibrosis without affecting protective TNFR2 signaling in high-fat diet-induced NAFLD[111]. Anti-TNF-α compromises HCC progression and prolongs survival time in mice by decreasing tumor cell viability[112]. TNF-α induces mesenchymal stem cells mobilization to the injured liver site to participate in the inflammatory microenvironment formation and promotes liver cancer development[113]. TNF-α-mediated extracellular Ca^{2+} influx in HCC accelerates cell apoptosis, suggesting the function of TNF-α as a tumor-killing (pro-apoptotic) cytokine[114]. In addition, TNF-α polymorphism is associated with an elevated risk of HCC[115-117]. The role of TNF-α in the development and progression of HCC requires further exploration.

CXC motif chemokine family

Hepatic stellate cell–induced CXCL1 enhances the malignant development of HCC through the MIR4435-2HG/miR-506-3p/TGFβ axis, which could be a potential target in HCC therapy[118]. Inhibiting the CXCL1-CXCR2 loop improves doxorubicin efficacy in HCC, reducing macrophage recruitment in the tumor microenvironment and restricting tumor progression[119]. CXCL2 is a tumor suppressor, and its high expression significantly enhances the overall survival rate in HCC. Exogenous expression of CXCL2 inhibits cell proliferation in HCC by causing cell cycle arrest and apoptosis[120]. CXCL3 expression is upregulated in HCC and is highly associated with poor prognosis. This promotes CD133 + CSC proliferation through Erk1/2 phosphorylation[121]. CXCL5 knockdown inhibits cell proliferation and invasion through the miR-577/NF-κB axis, while CXCL5 overexpression is a potential indicator of poor prognosis in HCC patients[122]. Circ-HOMER1 causes cell growth and HCC aggressiveness by suppressing the miR-1322 function on CXCL6[123]. The expression level of CXCL6 in HCC tissues is significantly lower than in the adjacent normal tissues[124]. Tumor-associated macrophages caused by the CXCL8/miR-17 cluster enhance tumor cell growth and metastasis in HCC[125].

CXCL10 accelerates epithelial-mesothelial transition of HCC cells through MMP-2 activation[126]. CXCL10 remodels the intrahepatic tumor microenvironment of fibrosis-related HCC, while CXCL10 depletion promotes the invasion and infiltration of immune cells in the invasive tumor margin, resulting in an antitumorigenic microenvironment[127]. CXCL11/CXCR3 can positively regulate the stemness of α2δ1+ HCC tumor-initiating cells by improving self-renewal and tumorigenic properties *via* the ERK1/2 pathway[128]. SOX4-induced CXCL12 in HCC leads to tumor-distant metastasis by regulating CXCR4 in endothelial cells and reticular fibers while shaping the tumor microenvironment and neovascularization[129]. Compared with CHB patients or healthy control subjects, serum CXCL13 is significantly higher in HCC patients, and a positive result is associated with tumor size and metastasis[130]. In a clinical study, CXCL14 mRNA expression and serum CXCL14 levels were decreased in HBV-related HCC tissues. This indicates an advanced disease stage with severe hepatitis and impaired liver function[131]. CXCL14 represses cell proliferation in HCC and expedites apoptosis by inhibiting the Akt/mTOR signaling pathway[132]. Exogenous administration of CXCL14 prohibits angiogenesis in HCC and decelerates cell proliferation, invasion, and migration[133]. Allograft inflammatory factor 1 (AIF1)-induced M2 polarization macrophages secrete CXCL16, facilitating microvascular invasion and tumor progression [134]. Upregulated expression of CXCL17 in HCC promotes tumor cell proliferation and inhibits autophagy by controlling the LKB1-AMPK pathway[135]. MiR-325-3p overexpression attenuates angiogenesis, cell proliferation, migration, and invasion in HCC by restricting the CXCL17/CXCR8 axis[136]. Thus, CXCL2, CXCL6, and CXCL14 are negatively associated with HCC development and progression, while CXCL1, CXCL3, CXCL5, CXCL8, CXCL10, CXCL11, CXCL12, CXCL13, and CXCL17 play an inverse role.

TGF-β

TGF-β is a multifunctional regulator of various processes, including angiogenesis, immunity, and cancer[137,138]. TGF-β exists as three isoforms: TGF-β1, TGF-β2, and TGF-β3. All these can interrupt different stages of HCV propagation *via* the TGF-β/SMAD signaling pathway[139]. ECM1-mediated TGF-β activation promotes liver fibrosis by initiating HSCs[140]. TGF-β1 promotes HBV/HCV-induced fibrogenesis in hepatocytes and HSCs by interacting with the OCT4/Nanog pathway[141]. TGF-β inhibition significantly suppresses high-fat diet-induced inflammation and hepatic fibrosis, ameliorating obesity-related NAFLD and NASH[142,143]. Breviscapine and corosolic acid, TGF-β inhibitors, can alleviate NASH *via* multiple pathways by decreasing hepatic lipid accumulation, inflammation, and fibrogenesis[144,145]. In HCC, high TGF-β1 expression predicted shorter survival and poor disease prognosis in HCC patients[146]. In clinical studies, treating advanced HCC patients with the TGF-βR1/ALK5 inhibitor galunisertib can reduce AFP (alpha fetoprotein) and TGF-β1 in the body and prolong survival time[147,148]. In addition, galunisertib can improve sorafenib effectiveness in HCC patients[149]. In summary, TGF-β promotes the occurrence and development of HCC *via* inflammation-mediated cancer development (Table 1).

CURRENT CLINICAL THERAPIES

There is a significant correlation between inflammation and tumors, and regulating inflammation to treat the tumor could be an effective approach. The efficacy of nonsteroidal anti-inflammatory drugs (NSAIDs) in treating tumors is evident. They can exert their anticancer effect regardless of whether administered alone or combined[150]. The therapeutic effect of NSAIDs on HCC has been demonstrated, and aspirin can decrease the risk of death from liver cancer induced by chronic liver disease[151]. Celecoxib also promotes the apoptosis of HCC cells by inhibiting Akt expression[152]. In addition, inhibiting certain inflammatory factors can inhibit HCC development. Inhibition of the NLRP3 inflammasome can hinder the growth of HCC cells and promote autophagy[153,154]. 17β-Estradiol (E2) can induce NLRP3 inflammasome activation, trigger pyroptosis, and inhibit HCC progression[155]. Furthermore, IL-6 inhibition can cause HCC cell senescence[156]. The IL-6/STAT3 pathway can enable the metastasis and proliferation of HCC. Thus, inhibiting this pathway can enhance malignant HCC progression[157,158]. Trilobolide-6-O-isobutyrate inhibited IL-6/STAT3 pathway activation to decrease HCC progression[159]. Ursodeoxycholic acid inhibited IL-8 induced ERK phosphorylation, suppressing IL-8 induced angiogenesis[160]. Neurotensin controls IL-8 expression and interferes with EMT (epithelial-mesenchymal transition)-mediated HCC invasion and migration[161]. Dicer collaborates with lenvatinib to downregulate the expression of IL-8 and inhibit HCC growth[106]. In an alcoholic hepatitis mouse model, IL-22 can improve non-ASH through multiple targets while inhibiting inflammation and anti-fibrosis. Moreover, metformin inhibits IL-22 expression, attenuating HCC cell proliferation, migration, and invasion, and promotes apoptosis[87]. Targeting IL-22 has performed well in early HCC clinical experiments, with a good safety and efficacy profile[38,162].

Notably, anti-inflammatory drugs are combined to treat HCC with beneficial therapeutic effects. Pre-clinical studies have indicated that aspirin, a nonsteroidal anti-inflammatory drug, can elevate the sensitivity to various anti-cancer drugs. These include sorafenib and doxorubicin while overcoming sorafenib resistance *in vitro* and *in vivo*[163]. Additionally, aspirin limits NF-κB activation of SLC7A11 transcription by B inhibits the growth of HCC, leading to ferroptosis[164]. However, aspirin is negatively related to the early reported incidence rate of HCC in the general population, which should be considered in the future, particularly in gastrointestinal ulcer patients[165,166]. Another cohort study discovered that using NSAIDs could decrease the risk of early HCC recurrence two years after radical hepatectomy, irrespective of the patient's age, hepatectomy range, viral hepatitis status, basic diabetes, and cirrhosis[167]. Curcumin, a traditional Chinese medicine extract, has excellent anti-inflammatory effects. Curcumin overcame lenvatinib resistance, a first-line treatment drug for unresectable advanced liver cancer, by inhibiting epidermal growth factor receptor[168]. Combining steroid anti-inflammatory drugs dexamethasone and N-acetylcysteine can be employed for post-thrombotic syndrome and post-conventional transcatheter arterial chemoembolization, which is the standard

Table 1 The key inflammatory factors in liver diseases

Disease	Promotion genes	Inhibition genes
Virus hepatitis	IL-6[71]; IL-8[101,102]; IL-17[90,91]; IL-22[84,85]; TNF[108,109]; TGF-β[139];	IL-1β[63,64]; IL-22[83]
Alcoholic hepatitis	IL-1β[37]; IL-8[101,102]	IL-6[73]; IL-22[38,80]
NAFLD	IL-1α[60,61]; IL-1β[60,67-69]; IL-8[103]; IL-17[92-94]; TNF[110-112]; TGF-β[144,145]	IL-19[79]; IL-22[51,81,82]
HCC	IL-1β[68,69]; IL-6[75,76]; IL-8[105-107]; IL-17[96-98]; IL-22[86,87]; CXCL1[118,119]; CXCL3[121]; CXCL5[122]; CXCL8[125]; CXCL10[126,127]; CXCL11[128]; CXCL12[129]; CXCL13[130]; CXCL16[134]; CXCL17[135]; CXCR3 [128]; CXCR4[129]; TGF-β[146-148]	CXCL2[120]; CXCL6[123, 124]; CXCL14[131,132]

IL: Interleukin; TNF: Tumor necrosis factor; TGF: Transforming growth factor; HCC: Hepatocellular carcinoma; NAFLD: Nonalcoholic fatty liver disease.

treatment for mid-term HCC. Only two out of 50 participants experienced mild allergic dermatitis[169,170]. Currently, only a few anti-inflammatory drugs have undergone clinical trials. More effective anti-inflammatory drugs can be applied in clinical trials of HCC by continuously enhancing fundamental experiments.

CONCLUSION

Emerging studies demonstrated that inflammation, particularly chronic inflammation, is crucial in liver deterioration. Moreover, uncontrolled inflammation is a critical factor in liver cancer development. However, at this stage, some acute inflammatory factors have the opposite effect on HCC, indicating that the role of inflammation in HCC requires more exploration regarding new regulatory factors. These factors have great development prospects for the mechanism underlying malignant HCC progression and future clinical treatment.

FOOTNOTES

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REVIEW

Cell-type specific role of autophagy in the liver and its implications in non-alcoholic fatty liver disease

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Abstract

Autophagy, a cellular degradative process, has emerged as a key regulator of cellular energy production and stress mitigation. Dysregulated autophagy is a common phenomenon observed in several human diseases, and its restoration offers curative advantage. Non-alcoholic fatty liver disease (NAFLD), more recently renamed metabolic dysfunction-associated steatotic liver disease, is a major metabolic liver disease affecting almost 30% of the world population. Unfortunately, NAFLD has no pharmacological therapies available to date. Autophagy regulates several hepatic processes including lipid metabolism, inflammation, cellular integrity and cellular plasticity in both parenchymal (hepatocytes) and non-parenchymal cells (Kupffer cells, hepatic stellate cells and sinusoidal endothelial cells) with a profound impact on NAFLD progression. Understanding cell type-specific autophagy in the liver is essential in order to develop targeted treatments for liver diseases such as NAFLD. Modulating autophagy in specific cell types can have varying effects on liver function and pathology, making it a promising area of research for liver-related disorders. This review aims to summarize our present understanding of cell-type specific effects of autophagy and their implications in developing autophagy centric therapies for NAFLD.

Key Words: Autophagy; Non-alcoholic fatty liver disease; Hepatocytes; Macrophages; Hepatic stellate cells

Core Tip: This review presents a succinct overview of the cell-specific distinct effects of autophagy modulation on hepatic pathophysiology and its implication on the progression of non-alcoholic fatty liver disease (NAFLD). The effects of autophagy alteration on hepatocyte lipid metabolism, macrophage polarization and hepatic stellate cell plasticity are reviewed and discussed with reference to NAFLD pathobiology.

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INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is a hepatic manifestation of metabolic syndrome and a risk factor for diabetes, cardiovascular ailments, and hepatocellular cancers[1-3]. It is classically defined as hepatic steatosis which has developed in individuals with no or moderate alcohol consumption. The initial clinical presentation of NAFLD involves benign steatosis that may progress to a more severe form of the disease termed non-alcoholic steatohepatitis (NASH)[4]. NASH is characterized by increased hepatocyte damage, hepatocyte ballooning, inflammation, and fibrosis[5]. Several factors including high calorie diets, sedentary lifestyle, gut-microbiome, and genetic predisposition, constitute a multiple-hit basis of the progression of benign steatosis to NASH in certain individuals[6,7]. NASH is one of the leading causes of liver transplants worldwide[5]. Presently, there are no approved drug therapies for NAFLD and NASH. As physical activity is a key determinant of metabolic control, lifestyle modifications remain the only available treatment so far[8]. Furthermore, the prevalence of NAFLD, which is currently > 30%, has increased significantly in the last ten years with a nearly 50% increase occurring between 1990-2006 to 2016-2019[2]. At the molecular level, the development of NAFLD involves pathological changes in several hepatic cells including hepatocytes, macrophages, hepatic stellate cells (HSCs), endothelial cells and cholangiocytes[9]. Intracellular changes in the cellular metabolism, mitochondrial energetics, organellar homeostasis, redox hormesis and epigenetic changes in cellular plasticity govern the tissue damage and inflammatory milieu observed during NAFLD progression[10-13].

Autophagy is a cellular quality control process which is activated in response to energy crisis and cellular stress[14-16]. Historically, the liver has been recognized as an organ with high autophagy activity and hepatocytes and Kupffer cells were the first cell types where the metabolic role of autophagy and lysosomes were discovered[17,18]. Autophagy serves as a key regulator of hepatocyte, lipid, and carbohydrate metabolism in the liver[19]. Similarly, autophagy in liver macrophages and HSCs differentially regulates their plasticity from a quiescent to activated phenotype[20]. In this review, we will describe the distinct roles of cell-type specific autophagy in hepatic physiology and its deregulation in NAFLD.

AUTOPHAGY MECHANISMS

The term autophagy means “self-digestion” and plays a pivotal role in maintaining cellular homeostasis by recycling damaged or unnecessary cellular components. Autophagy ensures cell survival and contributes to various physiological and pathological processes. To date, three types of autophagy have been described: macroautophagy, micro-autophagy, and chaperone-mediated autophagy (CMA)[21]. Autophagy involves subcellular membrane trafficking to sequester a portion of cytoplasmic constituents and organelles by a membrane-sac (termed the phagophore) to form a double-membrane structure termed the autophagosome. The autophagosome is then transported to the lysosome for bulk protein degradation (proteolysis) of the sequestered intracellular materials by the lysosomal hydrolases. The breakdown products are utilized as an internally derived source of energy. Autophagy may be adaptive or constitutive. Constitutive autophagy is a mechanism of ‘cellular housekeeping’ that involves the removal of damaged or senescent organelles and helps to preserve basal energy balance. However, adaptive autophagy is characterized by recycling of intracellular constituents (proteins, lipids, glycogens, and organelles) to fulfill energy requirements in the event of nutrient deficiency. CMA is a selective cellular process where specific proteins are targeted for degradation by lysosomes with the help of chaperone proteins.

Macro-autophagy (hereafter referred to as autophagy) is a highly orchestrated process that can be divided into several key stages: Initiation, elongation, maturation, and degradation. The coordinated activity of several regulatory components tightly regulates the process of autophagy from initiation to termination. Autophagy genes, often referred to as autophagy-related genes (*Atgs*), are a group of genes responsible for regulating and executing the autophagic process within cells[22]. More than 30 autophagy-related (*ATG*) proteins have been identified and characterized thus far. The autophagic process is initiated by a serine-threonine protein kinase, Unc-51 Like autophagy activating kinase 1 (ULK1)[23]. The mammalian target of rapamycin (mTOR) is a central regulator of cell growth and metabolism and is known to inhibit autophagy when active. In nutrient-rich conditions, mTOR is activated, preventing autophagy initiation by phosphorylating the autophagy-initiating complex, ULK1/2. This phosphorylation inhibits ULK1/2 and prevents autophagosome formation. In contrast, AMP kinase (AMPK) is a sensor of cellular energy status. When energy levels are

low (*e.g.*, during nutrient deprivation or stress), AMPK is activated. Activated AMPK phosphorylates ULK1/2, relieving the inhibition imposed by mTOR and promoting autophagy initiation. Additionally, AMPK activation further stimulates autophagy by inhibiting mTOR directly and by activating transcription factors such as transcription factor EB (TFEB), which control the expression of *Atgs* and various lysosomal genes. When activated, TFEB promotes autophagy by enhancing the production of autophagy-related proteins and lysosome biogenesis[24].

The initiation phase is primarily governed by the mTOR and AMPK pathways. The ULK1/2 complex plays a central role in autophagy initiation and is comprised of ULK1, *ATG13*, *ATG101* and *FIP200*[25]. When mTOR is inhibited or AMPK is activated in response to nutrient deprivation or stress, ULK1 is activated by phosphorylation, and in turn, phosphorylates *ATG13* and *FIP200* to initiate the process of autophagosome formation[26]. Once initiated, autophagy proceeds through the elongation and maturation stages. Key proteins like autophagy-related protein 5 (*ATG5*) and *ATG12* form complexes that contribute to the elongation (expansion) of the isolation membrane, which eventually seals to form the autophagosome, a double-membraned vesicle that engulfs cellular cargo[27]. *ATG5* is part of a complex with *ATG12* and *ATG16L1*, which is crucial for elongation of the phagophore and closure of the autophagosome. *ATG8* or lipid-conjugated microtubule-associated protein 1A/1B-light chain 3 (LC3-phosphatidylethanolamine), which is lipidated and incorporated into the autophagosomal membranes, plays a central role in the biogenesis and elongation of autophagosomes[28].

The autophagy receptor or adaptor proteins facilitate the tethering of target proteins and organelles destined for degradation on to the autophagosome. Sequestosome1, also known as p62/SQSTM1 is a cargo receptor that recognizes ubiquitinated cargo, such as damaged organelles or proteins, and targets them for selective autophagic degradation. P62 contains LC3-interacting regions to interact with LC3 on the autophagosome membrane. Once the double-membrane vesicle is formed, it travels along the microtubules to the lysosome, where the outer membrane of the autophagosome fuses with lysosomes *via* the interaction of a synaptosome complex containing STX17, SNAP29, RAB7, and VAMP8 with LAMP1 on the lysosome[28]. Inside the autolysosomes, the lysosomal enzymes enable the degradation of the cargo.

AUTOPHAGY IN NAFLD

NAFLD is characterized by the accumulation of excess fat (triglycerides) in the liver, independent from excessive alcohol consumption. Demonstration that autophagy plays a significant role in the pathogenesis of NAFLD comes from several lines of evidence described below:

ATG gene knockout mouse models

Studies performed in liver-specific autophagy gene (*ATG5* and *ATG7)* knockouts revealed a lipolytic role of autophagy, and mice deficient in either of these genes showed increased hepatic steatosis[29]. The loss of autophagy genes also increased hepatocyte susceptibility to gut endotoxin-induced injury[30]. Autophagy is also known to regulate hepatic inflammation. In this regard, hepatic macrophages also known as Kupffer cells derived from *ATG5*$^{-/-}$ mice fed with a high-fat diet (HFD), developed a pro-inflammatory phenotype resulting from macrophage polarization[31].

Studies involving pharmacological/non-pharmacological autophagy inducers in animal models of NAFLD

Preclinical experiments performed with a classical autophagy inducer, such as, rapamycin resulted in the reduction of hepatic steatosis and injury in animals fed a HFD[32]. Similarly, the administration of autophagy inducing hormones such as thyroid hormone, ghrelin, glucagon like peptide-1 and vitamin D also increased autophagy in mouse liver and reduced steatosis in animals fed high calorie diets[33-38]. In addition, several natural compounds including caffeine, epigallocatechin gallate, and resveratrol, together with several herbal extracts derived from traditional Chinese and Indian medicines, have exhibited potent pro-autophagy activity which is associated with their anti-NAFLD effect in animals[39-49]. Besides pharmacological agents, lifestyle modifications including intermittent fasting[50,51] and exercise [52-54] also induce hepatic autophagy as a means to delay and/or reduce NAFLD/NASH progression.

Analysis of liver autophagy in human NAFLD

Assessment of autophagy in the liver biopsies of patients with progressive degree of severity showed impaired autophagy characterized by reduced expression of lysosomal cathepsins, accumulation of p62 and decreased autophagy flux[55,56]. Furthermore, the impairment of autophagy strongly correlated with markers of hepatic injury and inflammation[55,56]. More recently, whole exome sequencing data has revealed pathogenic mutations in human autophagy-related genes which increases susceptibility to NAFLD development[57,58]. Notably, the defects in autophagy observed in human NAFLD are similar to that observed in murine models of NAFLD, in which an early increase in autophagic flux is followed by a late block in autophagic flux and a concomitant increase in endoplasmic reticulum (ER)-stress[56,59].

AUTOPHAGY IN HEPATOCYTES

Hepatocytes are cells of parenchymal origin, and are the metabolic hub of the liver. These are the primary functional cells of the liver and play a central role in metabolic processes, detoxification, and protein secretion. Not surprisingly, autophagy has been widely studied in these cells under physiological and pathological conditions including NAFLD. Hepatocytes rely on autophagy to remove damaged organelles, manage energy balance, and regulate lipid metabolism.

The biological effects of autophagy on hepatocytes and its modulation under NAFLD are described below.

Role of autophagy in hepatocyte lipid and carbohydrate metabolism

Hepatocytes store excess neutral lipids in the form of lipid droplets (LDs) which are composed of triacylglycerol (TAG). These TAG stores can be degraded by lipases to release free fatty acids (FFAs) as fuel for ATP production. The lipolysis of TAGs mediated by an autophagy-lysosomal pathway was termed "lipophagy" in hepatocytes undergoing starvation[29]. The sequence of events involved in lipophagy consists of the engulfment of LDs by the autophagosomes, followed by their fusion with lysosomes where lipolysis of TAG takes place. The FFAs released from the lysosomes can then be utilized for mitochondrial fat oxidation[29]. The key lipase involved in this process is known as lysosomal lipase[29]. Defects in hepatocyte lipophagy are suspected to be a major cause of early NAFLD development in humans[60-62]. In addition to lipophagy, CMA also plays a key role in the lipolysis of TAGs within hepatocytes[63]. In this regard, both LD-associated proteins perilipin 2 and perilipin 3 have been identified as CMA substrates and their degradation *via* CMA precedes lipolysis by lipophagy[63]. Additionally, lipid degradation by microautophagy termed "macrolipophagy" has been reported to occur in mouse hepatocytes supplemented with oleate, followed by nutrient starvation[64]. Lipophagy has been shown to be activated by MTORC1 inhibition[65], fibroblast growth factor-21[36], as well as by the activation of nuclear receptors including thyroid hormone receptors, peroxisome proliferator-activated receptor alpha and TFEB exhibiting anti-steatosis effects[47,66-69]. More recently, the induction of lipophagy was shown to enhance lysosomal mediated lipid exocytosis, thereby ameliorating NASH in animal models[70].

Surprisingly, autophagy and autophagy genes have also been implicated in the assembly of TAGs in hepatocytes. Reports have shown that the loss of autophagy genes such as *MAP1LC3*[71], *ATG7*[72] and *FIP200*[30] leads to decreased LD accumulation in hepatocytes (Figure 1). This opposing effect by autophagy, as described above suggests paradoxical dual roles of autophagy in LD assembly *vs* degradation which may be due to the differential effects of *ATG* genes and nutrient status in cells[73].

Besides its role in lipid metabolism, autophagy also plays a significant role in hepatocyte carbohydrate metabolism by regulating glycogen breakdown[74]. The lysosomal α-acid glucosidase can hydrolyze glycogen and release free glucose [75]. Excessive glycogen deposition in hepatocytes commonly coexists with hepatic injury in both patients with NAFLD [76] and those with glycogen storage disease type Ia (GSD Ia)[77]. GSD Ia is the most common glycogen storage disease. It is caused by the loss-of-function mutation of glucose-6-phosphatase, the enzyme converting glucose-6-phosphate to free glucose. Besides glycogen, GSD Ia is also characterized by excess lipid accumulation in the liver, and is now considered a fatty liver-like disease. Recently, the induction of autophagy was shown to attenuate the development of hepatic steatosis and reduce glycogen content in an animal model of GSD Ia[78]. These results, therefore, suggest an intricate interplay between hepatocyte autophagy and glycogenolysis.

Autophagy and hepatocyte lipotoxicity

Lee *et al*[79] used the term "Lipotoxicity" for the first time to describe the harmful effects of lipid species such as saturated FFAs (SFAs) and cholesterol in non-adipose organs. At the molecular level, NAFLD/NASH induced lipotoxicity in hepatocytes is characterized by increased oxidative stress, mitochondrial dysfunction, impaired unfolded protein response (UPR), pro-inflammatory cytokine production, and cell death[80,81]. Intriguingly, basal autophagy inhibition is also observed in response to SFAs such as palmitic acids[82]. Chronic SFAs administration impairs autophagosomal-lysosomal fusion, causes disruption of hepatocyte autophagy through suppression of the immune surveillance protein DDX58/Rig-1 (DExD/H box helicase) and stimulates the STING-MTORC1 pathway contributing to the autophagy inhibition reported in advanced NAFLD[65,82,83]. Therefore, restoration autophagic flux has emerged as an important strategy to counter lipotoxicity in hepatocytes[84].

In addition to being involved in macromolecular breakdown of lipids, proteins and carbohydrates, autophagy is also involved in selective removal of damaged organelles. The autophagic removal of mitochondria, known as "mitophagy" is a process of mitochondrial pruning that prevents the accumulation of damaged mitochondria resulting from increased oxidative stress[85]. Defective mitophagy has been shown to be associated with impaired mitochondrial β-oxidation and increased oxidative stress and lipoapoptosis in both animal models as well as in human NAFLD[86,87]. In hepatocytes, the accumulation of damaged mitochondria resulting from lipotoxicity, may lead to mitochondrial mediated apoptosis as well as activation of the inflammasome complex[88]. Therefore, the induction of mitophagy ensures both sustained mitochondrial energetics as well as cell survival (Figure 1). Several mechanisms have been proposed to regulate mitophagy in NAFLD[35,88-96]. Acyl coenzyme A: lysocardiolipin acyltransferase-1 expression was shown to be elevated in HFD fed mice, and its silencing restored mitophagy in isolated hepatocytes with observable improvement in mitochondrial architecture and reduced hepatic steatosis in mice[97]. Furthermore, the plant flavanol quercetin alleviates HFD-induced hepatic steatosis by activating AMPK-dependent mitophagy[98]. Furthermore, sirtuin 3 overexpression stimulates mitophagy and protects hepatic cells against palmitic acid-induced oxidative stress[99]. Mitophagy is also induced by thyroid hormone[100] through increased reactive oxygen species (ROS) production from mitochondria, the release of intracellular calcium, and activation of calcium/calmodulin-dependent protein kinase kinase and AMPK to both maintain mitochondrial fat oxidation as well as prevent further cell damage by ROS.

Autophagy also protects hepatocytes against lipotoxicity-induced oxidative stress by degrading Kelch like ECH associated protein 1 (KEAP1), which results in nuclear factor, erythroid 2 Like 2 (NRF2/NFE2L2) nuclear translocation and transcription of antioxidant genes[101]. Autophagy gene ULK1 was shown to enhance the interaction of autophagy adapter protein p62/SQSTM1 with KEAP1 which results in the autophagy-mediated degradation of KEAP1 and NRF2 mediated protection from lipotoxicity (Figure 1)[102].

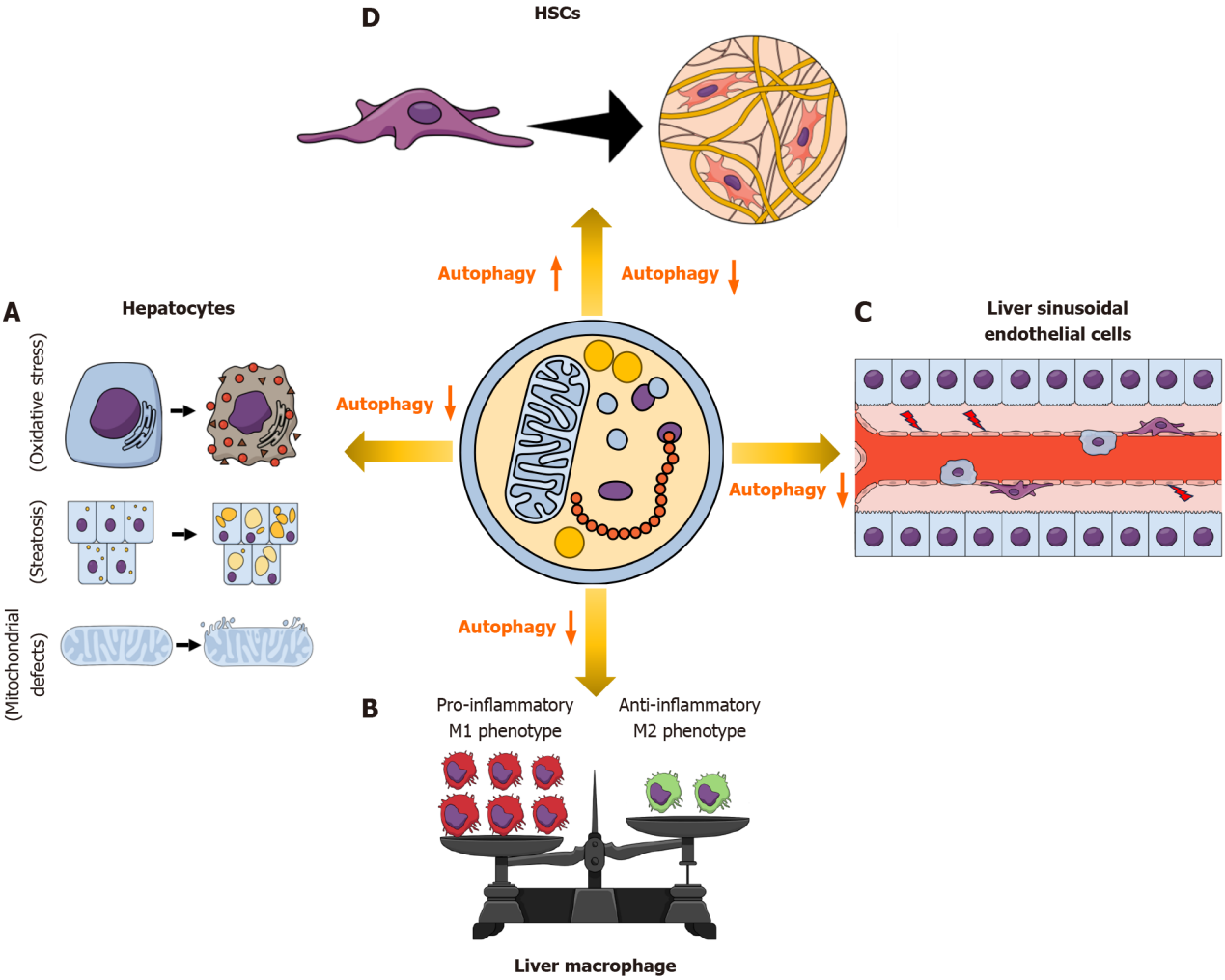

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Figure 1 Cell-specific effects of autophagy modulation on liver pathology in non-alcoholic fatty liver disease. A: Hepatocytes: Loss of autophagy results in accumulation of oxidative protein and lipid adducts, triacylglycerols and defective mitochondria; B: Macrophage/Kupffer cells: Inhibition of macrophage autophagy results in increased generation of pro-inflammatory M1 polarized macrophages, which increases inflammation during non-alcoholic fatty liver disease (NAFLD)/non-alcoholic steatohepatitis progression; C: Liver sinusoidal endothelial cells (LSECs): Loss of autophagy in LSECs results in cellular stress and loss of cellular integrity, resulting in increased NAFLD progression; D: Hepatic stellate cells (HSCs): The effect of autophagy on HSCs is conflicting, with some studies demonstrating its anti-fibrotic action while others support its pro-fibrotic action by regulating the transformation of quiescent HSCs into collagen-secreting myofibroblasts. HSCs: Hepatic stellate cells.

SFA-induced ER-stress and impaired UPR response also are key features associated with NAFLD progression in humans[56,103]. SFAs, cause ER stress by increasing saturated diacyl glycerolipid and saturated phospholipid accumulation in the ER, which causes persistent inositol-requiring enzyme-1α, and protein kinase RNA-like ER kinase activation in hepatocytes[104,105]. Eventually SFA-induced hepatocyte lipoapoptosis occurs owing to continuous UPR activation, which results in Jun N-terminal kinase and C/EBP Homologous Protein-mediated overexpression of proapoptotic proteins such as p53 upregulated modulator of apoptosis[106]. Autophagy serves as a key degradative mechanism for misfolded proteins in hepatocytes thus alleviating ER-stress caused by SFAs[107]. In this regard, HFD feeding was associated with increased hepatic ER stress and insulin resistance in autophagy defective animals[108]. Surprisingly, rescue experiments with *ATG7* gene overexpression dramatically relieved lipid-induced ER-stress in the mouse liver, as well as hepatic insulin sensitivity[108]. Besides degrading specific misfolded proteins, autophagy can also degrade parts of damaged ER by a process known as "ER-Phagy". Although the mechanistic basis of this process is still not very clear in hepatocytes, its role in NAFLD pathogenesis was highlighted by RNA sequencing data revealing numerous ER-phagy receptors such as ATL3, SEC62, and RTN3 which were differentially regulated in patients with NAFLD/NASH[107]. These data point towards ER-phagy playing an essential role during NASH and underscores its importance as a possible novel strategy for NASH treatment.

SFA exposure in hepatocytes triggers the NLRP3-inflammasone signaling, leading to the activation of interleukin (IL)-1 β which causes hepatocyte cell death[109-112]. The inhibition of inflammasome activation and hepatocyte pyroptosis is another way of cellular protection conferred by autophagy in hepatocytes[35].

AUTOPHAGY IN LIVER MACROPHAGES

The liver is a vital organ with diverse functions, including metabolism, detoxification, and immune regulation. Within the liver's intricate cellular landscape, Kupffer cells, the resident macrophages, are critical players in immune surveillance and tissue homeostasis. Autophagy, a conserved intracellular process, has emerged as a key regulator of Kupffer cell functions and liver physiology. Autophagy in Kupffer cells, plays a pivotal role in maintaining hepatic homeostasis, regulating inflammation, by eliminating misfolded or aggregated proteins, removing damaged organelles and invading pathogens[113].

Macrophages are highly heterogeneous immune cells, which can polarize to diverse phenotypes in response to the surrounding microenvironment[114]. During inflammation or injury, macrophage polarization determines the fate of an organ[114]. When an organ or a tissue is inflicted with an infection or injury, macrophages are first polarized to their pro-inflammatory M1 phenotype to facilitate the removal of antigens and necrotic cells by releasing pro-inflammatory cytokines. Furthermore, the M1 macrophages polarize with the M2 macrophages at the stage of repair, to secrete anti-inflammatory cytokines and suppress inflammation, which promotes tissue repair and remodeling. Autophagy regulates macrophage polarization in NAFLD[31,115,116]. Macrophage autophagy reduces chronic inflammation and lowers the progression of organ fibrosis by inhibiting M1 macrophage polarization[117] (Figure 1). Impaired macrophage autophagy increased immune response and chronic hepatic inflammation and injury in obese mice[31]. Ubiquitin-specific protease 19-induced macrophage autophagy promoted anti-inflammatory M2-like macrophage polarization[116]. Chronic liver injury results in organ scarring, termed liver fibrosis. Tissue-resident macrophages are the crucial regulators of organ fibrosis[118]. Inflammation plays a vital role and may be a cause of fibrosis[119]. As macrophage autophagy inhibits macrophage polarization to pro-inflammatory M1 type, it may be a potential target for organ fibrosis. Macrophage activation and polarization are increasingly being recognized to play an essential role in liver inflammation and fibrosis [120]. Autophagy inhibited the release of inflammatory cytokines, particularly IL-1, from hepatic macrophages and reduced HSC activation to protect against liver fibrosis in mice[121]. Also, the suppression of Atg5 showed increased liver inflammation and fibrosis *via* the enhanced mitochondrial ROS/NF-κB/IL-1α/β pathway in autophagy-deficient liver macrophages[122]. Macrophage autophagy was reported to downregulate hepatic inflammation by inhibiting inflammasome-dependent IL-1β production[123]. Spermine, a polyamine, reduced liver injury by inhibiting the pro-inflammatory response of liver-resident macrophages by inducing autophagy[124]. LC3-associated phagocytosis (LAP) inhibited inflammation and liver fibrosis by pharmacological as well as genetic interventions. Inhibition of LAP aggravated the pro-inflammatory and pro-fibrotic phenotype in the liver[125]. Autophagy is also involved in immune regulation in liver macrophages. It promotes antigen presentation and major histocompatibility complex-II expression, facilitating efficient antigen recognition by T cells. Conversely, defective autophagy can lead to exaggerated inflammatory responses[126]. Dysregulation of autophagy in Kupffer cells can have wide-ranging implications for liver diseases, making it an attractive target for future therapeutic interventions. Further research into the precise mechanisms and therapeutic potential of autophagy modulation in liver macrophages is warranted to advance our understanding of liver pathophysiology and develop novel treatment strategies.

AUTOPHAGY IN HSCs

Among several cell types that contribute to liver function and pathology, HSCs have emerged as key players in the development of liver fibrosis, a common endpoint in chronic liver diseases. Autophagy, a cellular process of self-digestion and recycling, has gained increasing attention due to its role in HSC biology and its implications in liver disease progression. Autophagy in HSCs is intricately involved in maintaining metabolic homeostasis. It ensures an efficient turnover of cellular components, provides energy during stress or activation, and helps regulate key signaling pathways. Dysregulation of autophagy in HSCs can disrupt these metabolic processes and contribute to liver fibrosis and disease progression.

Upon liver injury or inflammation, HSCs undergo activation, transforming into proliferative, fibrogenic myofibroblasts that contribute to fibrous scar formation[127]. The role of autophagy in HSC activation remains paradoxical and context specific. Studies performed in HSCs *in vitro* and *in vivo* showed the profibrotic effect of autophagy induction during transforming growth factor beta induced HSC activation[128] (Figure 1). Specifically, autophagy is proposed to induce the activation of HSCs through lipophagy, a selective type of autophagy that degrades LDs[129]. On the other hand, autophagy also plays a critical role in maintaining HSC quiescence and limiting their activation. Inhibition of autophagy in activated HSCs has been associated with increased fibrogenesis, while induction of autophagy can suppress their activation and collagen production[130] (Figure 1). Indeed, HSC autophagy attenuated liver fibrosis by inhibiting the release of extracellular vesicles[131]. Autophagy in HSCs was recently shown to induce the release of miR-29a. Inhibition of autophagy reduced miR-29a secretion and repressed fibrogenic gene expression in a mouse model of liver fibrosis and in patients with chronic hepatitis C infection[132]. These findings underscore the therapeutic potential of targeting autophagy in HSCs to mitigate liver fibrosis and, consequently, liver disease progression. Autophagy in HSCs has significant implications for liver disease. Understanding these mechanisms holds promise for developing targeted therapies to modulate HSC metabolism and mitigate liver fibrosis. The role of autophagy in maintaining HSC quiescence and limiting fibrogenesis makes it a promising target for therapeutic intervention. Pharmacological agents that regulate autophagy in HSCs are being investigated for their potential to halt or reverse liver fibrosis and alleviate the burden of liver diseases worldwide. Furthermore, strategies to enhance the specificity of these interventions to HSCs also hold promise for minimizing their off-target effects.

Autophagy in liver sinusoidal endothelial cells (LSECs)

LSECs form the first barrier of defense in the liver owing to their unique position, lining the sinusoidal lumen. Endothelial dysfunction is known to play a key role in liver injury[133]. Autophagy maintains cellular integrity, phenotype and homeostasis and can be found in various cell types, including liver endothelial cells[134]. Decreased autophagy has been observed in liver endothelial cells of patients with NASH as compared to patients with simple steatosis or those with normal liver[135]. The selective disruption of *ATG5* or *ATG7* in endothelial cells impairs the normal endothelial phenotype and favors liver injury, inflammation and fibrosis in mice exposed to prolonged HFD feeding or carbon tetrachloride[133,135] (Figure 1).

CONCLUSION

Autophagy in the liver plays key role in hepatic metabolism, immunomodulation, and cellular plasticity with profound effects on NAFLD progression. Future research should focus on better understanding the role of autophagy in inter-cellular crosstalk among various cell types of the liver and its targeting as a future therapy for NAFLD/NASH in humans. Investigating hepatocyte-specific autophagy mechanisms and their response to various stressors, such as nutrient imbalances, oxidative stress, and toxic insults, is crucial to explore the therapeutic potential of autophagy modulation in NAFLD/NASH. Understanding how autophagy affects inflammation and antigen presentation in Kupffer cells could provide insights into liver-related immune disorders and manipulating autophagy in these cells may have implications for treating conditions like liver fibrosis. Additionally, exploring how autophagy contributes to LSEC integrity, angiogenesis, and regulation of blood flow may provide a better understanding of its role in liver health and disease. Furthermore, the deduction of molecular mechanisms by which autophagy influences HSC activation and collagen production can provide insights into therapeutic strategies for liver fibrosis.

Given the dynamic sequence of involvement of different cell types and the pleiotropic effect of autophagy during NAFLD progression, an optimal therapeutic time-window for targeting autophagy should be identified. Finally, identifying biomarkers of autophagy flux in humans would be useful clinically to monitor disease progression and response to treatment. Clinical trials of autophagy modulating drugs for NAFLD/NASH treatment could provide significant therapeutic advances, particularly since there are no pharmacological treatments for this disease.

FOOTNOTES

Co-corresponding authors: Rohit A Sinha and Amit Goel.

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MINIREVIEWS

Any role for transarterial radioembolization in unresectable intrahepatic cholangiocarcinoma in the era of advanced systemic therapies?

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Abstract

Intrahepatic cholangiocarcinoma (iCCA) is recognized as the second most frequently diagnosed liver malignancy, following closely after hepatocellular carcinoma. Its incidence has seen a global upsurge in the past several years. Unfortunately, due to the lack of well-defined risk factors and limited diagnostic tools, iCCA is often diagnosed at an advanced stage, resulting in a poor prognosis. While surgery is the only potentially curative option, it is rarely feasible. Currently, there are ongoing investigations into various treatment approaches for unresectable iCCA, including conventional chemotherapies, targeted therapies, immunotherapies, and locoregional treatments. This study aims to explore the role of transarterial radioembolization (TARE) in the treatment of unresectable iCCA and provide a comprehensive review. The findings suggest that TARE is a safe and effective treatment option for unresectable iCCA, with a median overall survival (OS) of 14.9 months in the study cohort. Studies on TARE for unresectable iCCA, both as a first-line treatment (as a neo-adjuvant down-staging

strategy) and as adjuvant therapy, have reported varying median response rates (ranging from 34% to 86%) and median OS (12-16 mo). These differences can be attributed to the heterogeneity of the patient population and the limited number of participants in the studies. Most studies have identified tumor burden, portal vein involvement, and the patient's performance status as key prognostic factors. Furthermore, a phase 2 trial evaluated the combination of TARE and chemotherapy (cisplatin-gemcitabine) as a first-line therapy for locally advanced unresectable iCCA. The results showed promising outcomes, including a median OS of 22 mo and a 22% achievement in down-staging the tumor. In conclusion, TARE represents a viable treatment option for unresectable iCCA, and its combination with systemic chemotherapy has shown promising results. However, it is important to consider treatment-independent factors that can influence prognosis. Further research is necessary to identify optimal treatment combinations and predictive factors for a favorable response in iCCA patients.

Key Words: Intrahepatic cholangiocarcinoma; Transarterial radioembolization; Locoregional treatment; Overall Survival; Response rates; Neo-adjuvant therapy; Combined Therapies; Prognostic factors

Core Tip: Intrahepatic cholangiocarcinoma (iCCA), the second most common type of liver cancer, is frequently diagnosed at an advanced stage due to limited diagnostic tools and undefined risk factors. Surgery, the potential cure, is often infeasible. Ongoing investigations into unresectable iCCA treatment include chemotherapy, targeted therapy, immunotherapy, and locoregional treatments. Transarterial radioembolization (TARE) demonstrates safety and effectiveness, with a median response rates (34%-86%) and OS (12-16 mo) varying due to patient heterogeneity. Key prognostic factors include tumor burden, portal vein involvement, and patient performance status. The median overall survival reported after TARE is of 22 mo with 22% of tumor down-staging. TARE is a viable unresectable iCCA treatment, especially when combined with systemic chemotherapy. Nonetheless, further research is needed to optimize treatment combinations and identify predictive factors for favorable responses in iCCA patients.

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INTRODUCTION

Epidemiology, clinical characteristics and treatment of cholangiocarcinoma

Cholangiocarcinoma (CCA) is a diverse group of bile duct tumors, divided into three subtypes: intrahepatic (iCCA), perihilar (pCCA), and distal (dCCA)[1]. With increasing rates, CCA is the second most common liver cancer globally[2]. CCA rates are stable in regions with reduced alcohol-related live disease, but increasing in Europe and America due to higher alcohol intake, viral hepatitis infections, an increase in obesity rates, and the prevalence of non-alcoholic fatty liver disease (NAFLD)[1,3]. The prevalence and incidence of CCA result from a complex interplay of evolving risk factors, including chronic biliary tract inflammation and biliary stasis[1]. Risk factors include primary sclerosing cholangitis, congenital choledochal cysts, liver fluke infections, hepatolithiasis, cirrhosis, hepatitis B and C, NAFLD, obesity, asbestos exposure, diabetes, smoking, and alcohol. Some cases have no identifiable risk factors, making early diagnosis challenging[4]. Late-stage diagnosis leads to poor outcomes, and surgery is the primary curative option, aiming for R0 resection and preserving future liver remnant function. Hepatobiliary resection is preferred for iCCA and pCCA[5], while treatment approaches for dCCA are similar to pancreatic head cancer[4]. Neoadjuvant therapy is not typically recommended, but promising results have been seen in using neoadjuvant treatment as a bridge to liver transplantation [1,6]. The role of chemoradiation therapy as adjuvant treatment is uncertain, with potential benefits for pCCA and dCCA patients with R1 surgical margins. Ongoing trials explore combined cytoriductive therapy (cisplatin and gemcitabine) in an adjuvant setting[1]. Liver transplantation is considered for unresectable pCCA and iCCA cases without extrahepatic disease. Palliative treatments are the option for those ineligible for transplant[1]. Immunotherapies in CCA have limited data, and their role is under investigation, either alone or in combination with other treatments[6].

Local-regional therapies are an option for iCCA patients to manage tumor growth and complications. Limited evidence supports their use in pCCA and dCCA[7]. Common loco-regional treatments include external beam radiotherapy, trans-arterial chemoembolization (TACE), image-guided thermal ablation, trans-arterial radioembolization (TARE), and hepatic chemosynthesis. TARE has gained attention, though with limited evidence[1,6,7].

TARE techniques

TARE is a minimally invasive technique to treat liver cancer, used for both hepatocellular carcinoma (HCC) and CCA. TARE involves the delivery of small beads, called microspheres, which are coated with a radioactive material, to the tumor through the blood vessels.

The liver receives blood from two sources: The hepatic artery and the portal vein; moreover, the hepatic parenchyma has a sinusoidal cytoarchitecture. Both these aspects promote the use of intra-arterially delivered treatments, such as TACE and TARE[8]. TARE is a technique that allows the delivery of a radioactive drug directly to the tumor, minimizing systemic irradiation and preserving the health of the liver. This is achieved by introducing microspheres into the tumor's blood vessels through a catheter inserted into the femoral artery and guided to the liver using imaging techniques like angiography. These microspheres lodge in the small blood vessels that supply the tumor, leading to a reduction in blood flow to the cancer cells and ultimately causing their death. Different types of microspheres, such as Lipiodol, glass, resin, or polymer, have been used, along with various radioisotopes like Phosphorus-32 (^{32}P), Yttrium-90 (^{90}Y), Iodine-131 (^{131}I), Holmium-166 (^{166}Ho), Lutetium-177 (^{177}Lu), and Rhenium-186/188 ($^{186/188}$Re), all of which are beta emitters[8,9]. Current TARE agents use β-particle-emitting radioisotopes, although some pioneering studies are now investigating the development and use of α-particle-emitting radioisotopes[10]. Targeted alpha therapy is a highly effective treatment due to the densely ionizing track and the short path length (40-90 μm) of the emitted α-particles, resulting in a high linear energy transfer (50-30 keV/μm). Actinium-225 is one of the α-particle emitting radionuclides currently being explored for clinical applications. A recent study utilizing a mouse model demonstrated that survival rates significantly improved when using [225Ac]Ac-DOTA-TDA-Lipiodol® in comparison to control groups[10].

^{90}Y-loaded microspheres are commonly used in TARE and have proven to be a crucial tool in the treatment of primary and secondary liver tumors, with a positive safety profile[11].

^{90}Y, a radionuclide that emits beta particles, has a physical half-life duration of 64.2 hours. It does not emit gamma photons but produces secondary "bremsstrahlung" photons. Although it has a low positron emission of 32 decays per million, the maximum and mean energies of its beta particles are 2.28 MeV and 0.94 MeV, respectively, and in soft tissue, it has maximum and mean penetration depths of 11 mm and 4 mm, respectively[12]. ^{90}Y can be loaded onto either glass or ion-exchange resin microspheres, enabling the delivery of high radiation doses to tumors while sparing normal hepatic parenchyma[13,14].

Observations indicate that radioembolization is well-tolerated by patients with a good performance status, consistent with current literature[14,15].

Prior to TARE, angiography of the aorta, superior mesenteric artery, and celiac trunk is performed to assess the hepatic vascular architecture, liver contact with surrounding structures, portal vein patency, and the presence of arterio-portal shunting[16]. Non-target vessels with microspheres injection can lead to adverse events, and although coil embolization of non-target vessels was previously routine, it is no longer recommended as a standard procedure[17]. One common arterio-portal shunt is between the liver and the lung, which is accurately visualized using ^{99m}-Technetium labeled macroaggregated albumin (^{99m}Tc-MAA). It acts as a surrogate marker for ^{90}Y microspheres and is injected into the left and right hepatic arteries. After injection, any arteriovenous connections around the tumor are sharpened[17]. After ^{99m}Tc-MAA injection, to assess and quantify pulmonary shunts, known as Lung Shunt Fraction, hepatic planar scintigraphy and single-photon emission computed tomography/computed tomography (SPECT/CT) scans are subsequently conducted [18], as significant pulmonary shunts can cause late radiation lung toxicity. ^{99m}Tc-MAA SPECT/CT imaging also aids in identifying possible gastrointestinal shunts, which, if not correctable through catheter embolization, can be an absolute contraindication for treatment[19,20]. Furthermore, ^{99m}Tc-MAA SPECT/CT acquisition helps define the treatment field and calculate the required activity of ^{90}Y microspheres. When planning whole liver or selective, non-ablative or ablative TARE, it is advised to adopt a personalized method that utilizes dosimetry, grounded either in partition models or voxel-based models[21].

After microspheres injection a ^{90}Y PET/CT scan is performed to assess treatment success by visualizing tumor targeting, quantifying absorbed dose post-treatment, and predicting complications such as radioembolization-induced liver disease[22,23].

TARE is considered a safe and effective treatment option with minimal side effects, and it can be repeated as necessary. It is a valuable alternative for patients who are not suitable for surgery, and it can also be combined with other treatments such as systemic chemotherapy, immunotherapy, or other local therapies to improve outcomes in iCCA.

MATERIAL AND METHODS

A comprehensive literature search was conducted using PubMed, Embase (from 2008 to 2021), and the Cochrane Library to identify relevant studies. In order to maximize the inclusion of pertinent articles, personal knowledge of the relevant literature was utilized, the reference lists of retrieved papers were reviewed, and a manual search was performed in key journals. The search strategy employed a combination of medical subject headings (MeSH) terms and free language words to capture a wide range of relevant publications.

TARE AS A THERAPEUTIC STRATEGY IN ICCA

Locoregional treatments, including radiofrequency ablation, hepatic artery infusion, TACE, drug-eluting bead TACE, and

TARE, have been extensively studied for unresectable cholangiocarcinoma iCCA[24,25]. These treatments have shown increased median overall survival (OS) compared to traditional systemic chemotherapy, with acceptable toxicity profiles [24].

In general patients eligible for locoregional treatments should meet specific criteria, including: (1) Eastern Cooperation Oncology Group (ECOG) performance status ≤ 2; (2) Adequate laboratory tests (A neutrophil count exceeding 1.5 × 10^9/L, A platelet count over 50 × 10^9/L); (3) Adequate kidney function (creatinine level below 2.0 mg/dL); (4) Proper liver functionality (bilirubin level under 2.0 mg/dL); and (5) The ability to undergo hepatic angiography[7].

Locoregional treatments are not recommended in cases of pregnancy, breastfeeding, an expected lifespan of under three months, or in instances of clinical liver failure. TARE is typically recommended for scenarios with minimal or no spread of the tumor beyond the liver, although interpretations of this condition vary[12]. It's important to note that in patients with iCCA, lymph node metastases haven't demonstrated a detrimental effect on OS and thus shouldn't be viewed as a disqualifying factor for TARE. Nevertheless, the presence of solid organ metastases necessitates individualized treatment decisions[12,25].

TARE as an option for locoregional treatment was first described in a study by Ibrahim *et al*[26], which included 24 patients with histologically diagnosed iCCA. The median OS was 14 months, with two patients achieving downstage with resectable disease and/or liver transplantation. At follow-up imaging, the tumor response indicated partial shrinkage in 27% of cases, stable disease in 68%, and only 5% showed disease progression. In total, an objective tumor response, defined as any reduction in size, was noted in 86% of the patients[26].

Moreover, for inoperable patients treated with TARE, a systematic review by Boehm *et al*[24] reported a cumulative median OS of 13.9 months (95%CI: 9.5-18.3) and a radiologic response according to RECIST criteria of 27.4% (95%CI: 17.4%-37.5%) for complete or partial response and 54.8% (95%CI: 45.2%-56.7%) for stable disease. Another retrospective study by Gangi *et al*[15] of a cohort of patients with unresectable iCCA who underwent TARE as first- or second-line treatment showed a median OS of 12.0 months (95%CI: 8.0-15.2), with a radiologic partial response in 6.2% of patients, stable disease in 64.2%, and progressive disease in 29.6% of patients at 3 mo.

Two other studies showed encouraging results for inoperable ICCA: Pellegrinelli *et al*[27] showed a median OS of 16 mo at three months, while Robinson *et al*[14], analyzing data from the Registry for Radiation-Emitting SIR-Spheres in non-resectable Liver Tumors, reported a median OS of 14.0 mo (95%CI: 12.1-22.3) and a median progression-free survival of 5.8 months (95%CI: 4.6-7.2) for the entire cohort of patients treated with TARE. Notably, this last study demonstrated an objective radiologic response, assessed by RECIST criteria, in 34% of patients (8% complete response, 26% partial response), while 67% of patients achieved disease control[14].

TARE has been explored in combination with systemic chemotherapy to further enhance treatment success.

A recent phase-2 trial evaluated the combination of systemic chemotherapy using cisplatin and gemcitabine with TARE for unresectable iCCA[28]. The study reported a median OS of 22 mo (95%CI: 14-52 mo), with a one-year OS rate of 75% (95%CI: 62%-89%) and a two-year OS rate of 45% (95%CI: 30%-61%). The objective response, based on RECIST criteria at three months, was 39% (90%CI: 26%-53%). Additionally, the disease control rate at three months was 98% (95%CI: 89%-99%). Additionally, 22% of patients (9 patients) were able to undergo downstaging for potential surgical intervention. Although these results are promising, they still need to be confirmed through a phase-3 trial. Unfortunately, a similar trial combining cisplatin plus gemcitabine chemotherapy and TARE was prematurely halted due to insufficient patient recruitment[6]. A recent study shared findings on the combined use of TARE and CT-guided high-dose-rate interstitial brachytherapy (CT-HDRBT)[29]. A further possible approach involves an ablative method where a radioactive source, specifically Iridium 192, is inserted directly into neoplastic lesions *via* catheters under the guidance of CT imaging[30,31]. This technique overcomes size limitations and restrictions due to tumor location[32]. Among patients with CCA treated with either TARE or CT-HDRBT, the median OS was 29 mo, overall, the available evidence suggests that TARE could play a role in treating unresectable iCCA, both as a standalone therapy and when combined with systemic chemotherapy (Table 1).

Discrepancies in OS among the available studies are due to significant differences in study designs, sample size, and association with other treatment options. Therefore further studies are required to establish TARE effectiveness in randomized trial and to better investigate its potential in combination with other approaches[6].

However, the treatment of advanced-stage iCCA remains a complex task that often requires the combination of different therapeutic strategies to develop the optimal treatment approach for patients. In this context, TARE may play a role, also as observed in in real life experience[9], as a combination treatment to further increase treatment success and improve patient care (Figure 1).

Patient selection is a critical aspect of TARE for iCCA. It involves assessing the extent of the disease, extrahepatic tumor spread, liver function, and overall health. Lobar or segmental perfusion involves the selective delivery of radioactive microspheres to specific regions of the liver, making precise patient selection even more crucial. High-quality imaging, such as angiography and CT or magnetic resonance imaging (MRI) scans, is essential to identify the arterial supply to the tumor and determine the optimal catheter placement for microsphere delivery. Advanced software tools are used for treatment planning to calculate the required dose and ensure minimal radiation to healthy liver tissue.

Moreover, the optimal radiation dose and the selection of embolic agents represent important issues.

Concerning the radiation dosage, with the use of resin microspheres, the activity level of ^{90}Y to be administered is determined based on the assumption that a mean absorbed dose of 40 Gy or less to the non-tumoral liver is safe. Additionally, for iCCA, a minimum mean target-absorbed dose to the tumor of 100-120 Gy is recommended[21]. The cut-offs for calculating ^{90}Y activity change when glass microspheres are used. In this case, the mean absorbed dose for the nontumorous liver, which is considered safe, is less than 75 Gy, and the minimum mean absorbed target dose for the tumor, which is recommended to significantly increase OS, is higher than 260 Gy[12,33]. A systematic review of dosimetry after iCCA treatment shows that the mean delivered tumor dose is approximately 200 to 250 Gy for glass-

Table 1 Characteristics of the included studies evaluating transarterial radioembolization in intrahepatic cholangiocarcinoma

Ref.	Study design	N patients	Inclusion criteria	Technique	Median OS (mo)	R-response (%)
Ibrahim *et al* [26], 2008	Report	24	Histological diagnosis; Unresectable disease; ECOG ≤ 2; Neutrophil > 1.5 × 10^9/L; Platelet > 50 × 10^9/L; Creatinine < 2.0 mg/dL; Bilirubin < 2.0 mg/dL; Able to undergo angiography	^{90}Yttrium (^{90}Y); Radioembolization	14	86
Boehm *et al* [24], 2015	Systematic Review and Metanalysis	127	Unresectable disease; TARE treatment	^{90}Yttrium (^{90}Y); Radioembolization	13.9	27.4 (partial or complete; 54 (stable disease)
Gangi *et al* [15], 2018	Single Center; Retrospective study	85	Histological diagnosis; Unresectable disease; ECOG ≤ 2; Platelet > 50 × 10^9/L; Creatinine ≤ 2.0 mg/dL; Bilirubin ≤ 2.0 mg/dL; INR ≤ 1.5	^{90}Yttrium (^{90}Y); Radioembolization	12	6.2 (partial response); 64 (stable disease)
Pellegrinelli *et al*[27], 2021	Single center; Retrospective study	6	Unresectable disease; ECOG ≤ 2; Platelet > 50 × 10^9/L; Bilirubin < 2.0 mg/dL; Prothrombin time > 50%; Able to undergo angiography	^{90}Yttrium (^{90}Y); Radioembolization	16	NA
Robinson *et al* [14], 2022	Registry data	95	NA		14	34
Edeline *et al* [28], 2020	Phase 2; Clinical Trial	41	Unresectable disease; Never received CT; Never received intra-arterial treatment	^{90}Yttrium (^{90}Y); Radioembolization + Cisplatin and Gemcitabine	22	39
Fleckenstein *et al*[29], 2022	Single center; Retrospective study	9	Unresectable disease; At least one TARE treatment; At least one CT-HDRBT treatment	^{90}Yttrium (^{90}Y); Radioembolization + CT-HDRBT	29	NA

NA: Not available; CT: Computed tomography; CT-HDRBT: CT-guided high-dose-rate interstitial brachytherapy; R-response: Radiologic response; ECOG: Eastern Cooperation Oncology Group; OS: Overall survival; TARE: Transarterial radioembolization; INR: International normalized ratio.

based treatments and 80 to 130 Gy for resin-based treatments[34]. A recent study using glass microspheres further increased the dose for treatment of iCCA, suggesting that segmental transarterial radioembolization at > 400 Gy is an ablative approach that is feasible in terms of safety and efficacy[35].

A more subtle point, but one of potential clinical importance, is the selection of embolic agents and their infusion methods tailored to TARE in the context of iCCA. The glass microspheres, which are insoluble and infused with Y^{90}, measure between 20-30 μmol/L in diameter and possess an activity of 2500 Bq per sphere at calibration time. These microspheres are designated for use in cases of inoperable HCC and HCC with complications due to portal vein thrombosis. They have received approval from the United States Food and Drug Administration under a humanitarian exemption, which is based on their established safety and potential clinical benefits. A total count of 1.2 million microspheres generates an activity of 3 GBq (as stated in the TheraSphere® Yttrium-90 microspheres package insert, Kanata CMN. http://www.therasphere.com/physicians-package-insert/TS_PackageInsert_USA_v12.pdf). Resin microspheres are made of biocompatible resin and have a diameter ranging from 20-60 μmol/L, with an activity of 50 Bq per sphere. They contain a lower concentration of Y90 per sphere compared to glass microspheres, necessitating a larger number of spheres to administer a specific dose. This results in a higher embolic effect for the same dose delivery. To achieve 3 GBq of activity, between 40-80 million resin microspheres (each with 50 Bq) are required, in contrast to the 1.2 million needed for glass microspheres, as detailed in the SIRS-Spheres® Yttrium-90 microspheres package insert from Singapore Science Park SSM. http://www.sirtex.com/media/29845/ssl-us-10.pdf). Consequently, glass microspheres have the least embolic effect for the same prescribed activity because they are injected in much smaller numbers. The increased quantity of resin microspheres, despite the same prescribed activity level, could potentially lead to a more even distribution of the dose, resulting in a heightened biological effect, which includes both toxicity and efficacy. For resin ^{90}Y-microspheres, given the higher embolic load, no blind infusions should be performed. The microspheres are delivered slowly at a rate of no more than 5 mL/min, as rapid delivery may cause reflux. During the procedure, the radiologist must repeatedly check the position of the catheter to ensure its position and continued forward flow. In the case of glass ^{90}Y-microspheres, due to the small number of microspheres used, it's not necessary to completely saturate the entire vascular bed or to use continuous fluoroscopic guidance during infusion. Typically, a full infusion can be completed in about 5 minutes through a slow, manual injection while the patient breathes normally[12].

Another recent option is the use of microspheres containing holmium-166 (^{166}Ho), which are now available in Europe as an alternative to ^{90}Y microspheres[12,36]. ^{166}Ho offers advantages with its shorter half-life (26.8 h), high-energy beta and gamma radiation, and MRI-friendly properties[37]. Treatment planning uses the same microspheres as radioembolization, eliminating the need for ^{99m}Tc MAA. Clinical evidence supports the efficacy and safety of 166Ho in unresectable cancer[37]. Based on the latest usage guidelines, it's permissible for the average dose absorbed by the treated volume to surpass 60 Gy, provided that the average dose absorbed by the entire liver remains below 60 Gy. This approach aims to strike a balance between effective treatment and the safety of the liver[38].

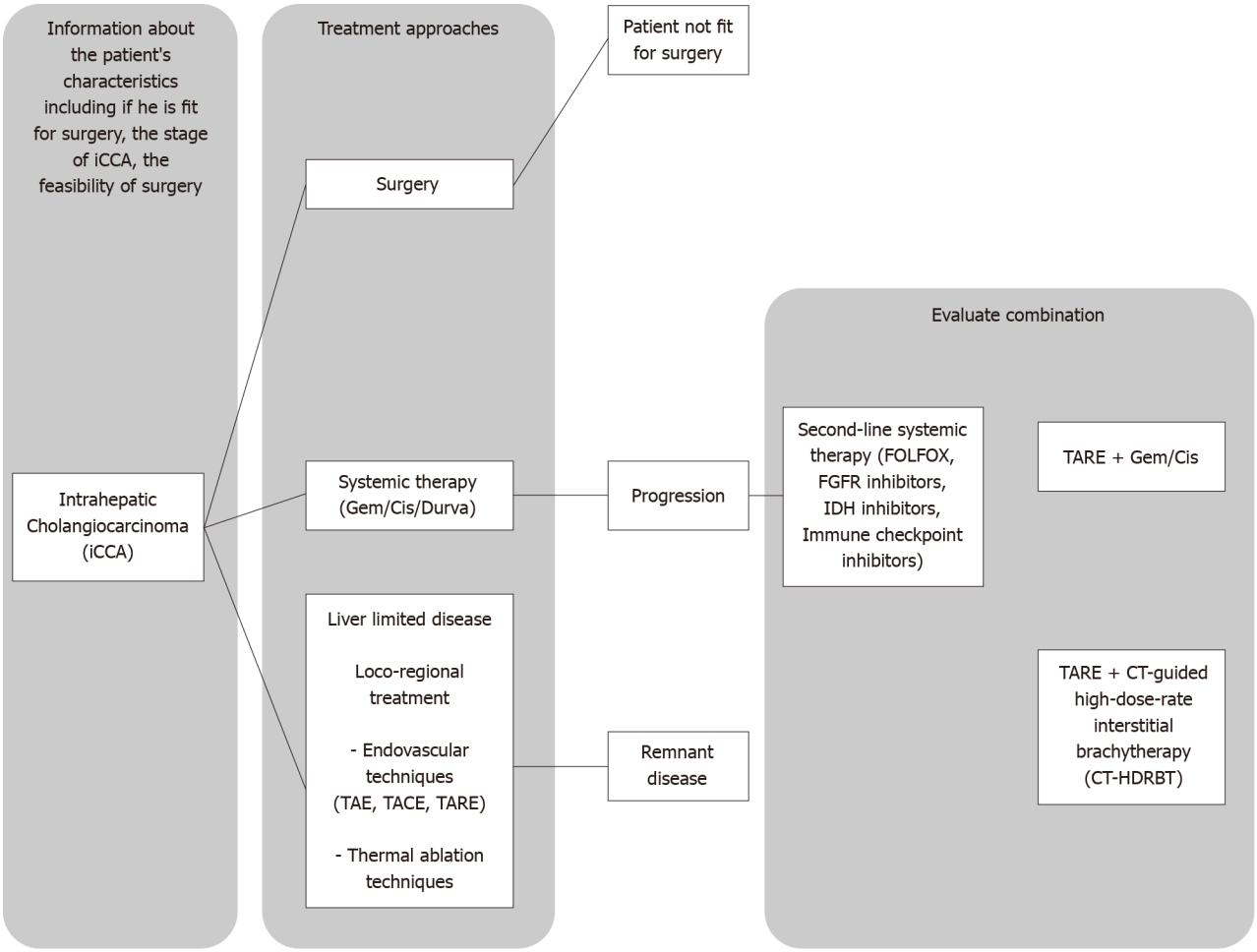

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Figure 1 Simplified algorithm for therapies in managing advanced-stage intrahepatic cholangiocarcinoma. iCCA: Intrahepatic cholangiocarcinoma; TAE: Trans-arterial embolization; TACE: Trans-arterial chemoembolization; TARE: Transarterial radioembolization; FGFR: Fibroblast Growth Factor Receptor FOLFOX: FOL: Folinic acid (leucovorin), F: Fluorouracil (5-FU), OX: Oxaliplatin; IDH: Isocitrate Dehydrogenase; CT: Computed tomography; CT-HDRBT: CT-guided high-dose-rate interstitial brachytherapy.

TOXICITIES

TARE for iCCA has demonstrated a favorable safety profile overall (Table 2). Ibrahim *et al*[26] reported a low incidence of severe adverse events (grade 3 or 4) in their study, with 17% of patients experiencing grade 3 albumin toxicities and 4% experiencing grade 3 bilirubin toxicities. Mild to moderate (grade 1 or 2) clinical toxicities were more common and included fatigue (75% of patients), transient abdominal pain (38%), vomiting (13%), anorexia (8%), and nausea (4%). Moderate to severe clinical toxicities were infrequent, with one patient (4%) developing a gastroduodenal ulcer, three patients (14%) developing ascites, and two patients (9%) developing pleural effusion. Two patients died within 30 d after the procedure. A subsequent review and meta-analysis by Boehm *et al*[24] found that TARE was associated with minor treatment-related complications such as minor pain, fatigue, nausea/vomiting, and fever, while major complications were rare, occurring in less than 1 event per patient. Liver-related complications varied widely, including increases in liver enzyme levels, the development of hepatic abscesses, and cases of liver failure. Overall, grade 3 or 4 toxicities were low following TARE.

Pellegrinelli *et al*[27] reported a low incidence of complications and side effects in their study of TARE. Out of 70 patients, 12 developed grade 1 side effects such as nausea, abdominal pain, fever, and vascular-like pseudoaneurysm. Only two patients encountered severe (grade 3) side effects: one suffered from radiation-induced cholecystitis due to unintended accumulation of ^{90}Y microsphere, while the other developed angiocholitis. No hepatic dysfunction or deaths related to TARE were observed[27]. Similarly, other studies, including those by Robinson *et al*[14] and Gangi *et al*[15] reported no mortality associated with TARE. Biochemical toxicities were generally mild to moderate, with 3%-10% of patients experiencing grade 3 biochemical toxicities. Constitutional toxicities were mostly grade 1 or 2, such as abdominal pain, fatigue, nausea, and vomiting, with rare occurrences of grade 3 or 4 constitutional toxicities. The toxicities observed in the study by Fleckenstein *et al*[29] were also mild to moderate, with few adverse events reported. When TARE was combined with systemic chemotherapy in a study by Fleckenstein *et al*[29], the toxic effects observed were primarily due to chemotherapy, with prevalent hematologic toxic effects of grade 3 or higher. The authors suggested a possible association between TARE and chemotherapy in the development of these hematologic toxic effects. However, in patients

Table 2 Transarterial radioembolization induced toxicities

Paper	Mild to moderate (grade 1-2)		Severe (grade 3-4)	
	Biochemical (%)	Constitutional (%)	Biochemical (%)	Constitutional (%)
Ibrahim *et al*[26], 2008	-	Fatigue (75); Abdominal pain (38); vomiting (13); anorexia (8)	Albumin (17); Bilirubin (4)	Gastroduodenal Ulcer (4); Ascites (14); Pleural effusion (9)
Gangi *et al*[15], 2018	(53)	Fatigue (42.3); Abdominal Pain (18.8); Weight loss (7.1); Ascites (5.9)	Bilirubin and Alkaline phosphatase elevation (9)	Liver abscess (2)
Pellegrinelli *et al*[27], 2021	-	-	-	Cholecystitis and angiocholitis (2.85)
Robinson *et al*[14], 2022	-	-	Bilirubin (10.5), Albumin (2.6), AST increase (7.8), ALT increase (5.2)	Abdominal pain, Cholecystitis (4.1)

AST: Aspartate transaminase; ALT: Alanine transaminase.

with cirrhosis, the number of hepatic toxicities was high. Liver toxic effects such as ascites, altered liver function tests, cholangitis, and acute cholecystitis were more common in cirrhotic patients. Among cirrhotic patients treated with TARE without chemotherapy, liver failure occurred in 75% of cases (9 out of 12 patients), including non-reversible cases, compared to 17% in patients without cirrhosis (all reversible cases). It was concluded that the combination of chemotherapy and TARE should be avoided in patients with cirrhosis, while liver toxicities in patients without cirrhosis were manageable, and no irreversible liver toxic effects were observed[28].

The researchers determined that combining chemotherapy with TARE is not advisable for patients who have cirrhosis. On the contrary, liver toxicities was passable in patients without cirrhosis, and no irreversible liver toxic effect was seen.

PROGNOSTIC FACTORS

Several studies have investigated both tumor-independent and tumor-dependent factors that may influence the prognosis of patients undergoing TARE for iCCA. The initial study by Ibrahim *et al*[26] showed that ECOG performance status had an impact on OS, with grade 0 having a significantly higher median OS compared to grade 1 or 2. On the other hand, tumor-dependent factors such as previous systemic chemotherapy, portal vein invasion, and infiltrative tumor morphology were associated with a poorer prognosis. These factors indicate a more advanced or aggressive disease, suggesting that TARE may be a viable treatment option for unresectable iCCA without portal vein involvement and/or infiltrative behavior.

Similarly, Gangi *et al*[15] found a correlation between ECOG performance status score and median OS. Patients treated with TARE who had ECOG performance status scores of 0 and 1 had a median OS of 18.5 mo, while those with a score of 2 had a median OS of 5.5 mo (P = 0.0012). Additionally, patients with symptoms or signs of liver failure, indicated by low serum albumin levels, low international normalized ratio, and elevated aspartate aminotransferase, had lower OS. Poorly differentiated tumor histology was also associated with lower OS, as previously described by Ibrahim *et al*[26]. The relationship between metastatic disease and prognosis remains more controversial[14,15].

In contrast, Edeline *et al*[28] did not find any correlation between ECOG performance status and median OS in their study. Similarly, Pellegrinelli *et al*[27] did not identify any tumor-independent factors that correlated with patients' median OS.

CONCLUSION

To summarize, the available literature suggests that TARE may have a role in the treatment of iCCA, either as a standalone treatment or in combination with systemic chemotherapy. However, further randomized trials and investigations of combination therapies are necessary to establish its efficacy and confirm its safety. TARE for iCCA is generally considered to have a favorable safety profile, with low rates of severe adverse events. However, caution should be exercised when combining TARE with systemic chemotherapy, particularly in patients with underlying cirrhosis, as they may be at a higher risk of liver toxic effects. Concomitant use of chemotherapy and TARE should be avoided in these patients. It is important to note that advancements in systemic therapies have resulted in improved prognosis for iCCA patients. Therefore, the role of TARE should be assessed within the context of these newer treatment options. Further randomized studies are needed to determine the optimal patient population, treatment regimen, and long-term outcomes associated with TARE in iCCA.

FOOTNOTES

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ORIGINAL ARTICLE

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Study of liver cirrhosis over twenty consecutive years in adults in Southern China

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Abstract

BACKGROUND

Liver cirrhosis (LC) is a prevalent and severe disease in China. The burden of LC is changing with widespread vaccination of hepatitis B virus (HBV) and antiviral therapy. However, the recent transition in etiologies and clinical features of LC cases requiring hospitalization is unclear.

AIM

To identify the transition in etiologies and clinical characteristics of hospitalized LC patients in Southern China.

METHODS

In this retrospective, cross-sectional study we included LC inpatients admitted between January 2001 and December 2020. Medical data indicating etiological diagnosis and LC complications, and demographic, laboratory, and imaging data were collected from our hospital-based dataset. The etiologies of LC were mainly determined according to the discharge diagnosis, and upper gastrointestinal bleeding, ascites, hepatic encephalopathy, spontaneous bacterial peritonitis, hepatocellular carcinoma (HCC), portal vein thrombosis, hepatorenal syndrome, and acute-on-chronic liver failure (ACLF) were considered LC-related complications in our study. Changing trends in the etiologies and clinical characteristics were investigated using logistic regression, and temporal trends in proportions of separated years were investigated using the Cochran-Armitage test. In-hospital prognosis and risk factors associated with in-hospital mortality were also invest-

igated.

RESULTS

A total of 33143 patients were included in the study [mean (SD) age, 51.7 (11.9) years], and 82.2% were males. The mean age of the study population increased from 51.0 years in 2001-2010 to 52.0 years in 2011-2020 ($P < 0.001$), and the proportion of female patients increased from 16.7% in 2001-2010 to 18.2% in 2011-2020 ($P = 0.003$). LC patients in the decompensated stage at diagnosis decreased from 68.1% in 2001-2010 to 64.6% in 2011-2020 ($P < 0.001$), and the median score of model for end-stage liver disease also decreased from 14.0 to 11.0 ($P < 0.001$). HBV remained the major etiology of LC (75.0%) and the dominant cause of viral hepatitis-LC (94.5%) during the study period. However, the proportion of HBV-LC decreased from 82.4% in 2001-2005 to 74.2% in 2016-2020, and the proportion of viral hepatitis-LC decreased from 85.2% in 2001-2005 to 78.1% in 2016-2020 (both P for trend < 0.001). Meanwhile, the proportions of LC caused by alcoholic liver disease, autoimmune hepatitis and mixed etiology increased by 2.5%, 0.8% and 4.5%, respectively (all P for trend < 0.001). In-hospital mortality was stable at 1.0% in 2011-2020, whereas HCC and ACLF manifested the highest increases in prevalence among all LC complications (35.8% to 41.0% and 5.7% to 12.4%, respectively) and were associated with 6-fold and 4-fold increased risks of mortality (odds ratios: 6.03 and 4.22, respectively).

CONCLUSION

LC inpatients have experienced changes in age distribution and etiologies of cirrhosis over the last 20 years in Southern China. HCC and ACLF are associated with the highest risk of in-hospital mortality among LC complications.

Key Words: Liver cirrhosis; Epidemiology; Etiology; Upper gastrointestinal bleeding; Hepatocellular carcinoma; In-hospital mortality

Core Tip: The etiologies and clinical characteristics of liver cirrhosis (LC) in hospitalized patients changed during the 2001-2020 period in Southern China. The mean age and female proportion have increased but the disease severity at LC diagnosis has alleviated over time. The proportion of hepatitis B virus-LC has decreased, while proportions of LC caused by alcoholic liver disease, autoimmune hepatitis and mixed etiology have increased gradually. Among all complications of LC, hepatocellular carcinoma and acute-on-chronic liver failure manifest the highest increase in prevalence and are associated with the highest risk of in-hospital mortality.

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INTRODUCTION

Liver cirrhosis (LC) is the end stage of progressive liver fibrosis and causes more than 1.3 million deaths worldwide annually, whereas the underlying etiologies, including hepatitis B virus (HBV) infection, hepatitis C virus (HCV) infection, and alcohol intake, negatively impact 1.5 billion people[1-3]. China accounts for a large proportion of the regional burden of LC, with an estimated 7 million cirrhotic patients, and the annual incident cases are approximately 220000[4,5].

Because of widespread HBV vaccination and the development of potent antiviral treatment for HBV and HCV, the LC mortality rate has greatly decreased from 20.0 per 100000 person-years in the 1980s to 15.8 per 100000 person-years in the 2010s globally[2]. However, there have been 10%-20% increases in LC incidence from 2000 to 2015 in North America, Europe, and East Asia[4,5]. Meanwhile, hospital-based studies from North America and Japan found that the proportion of viral hepatitis LC decreased, whereas non-viral etiologies, including LC caused by alcoholic liver disease (ALD), metabolic dysfunction-associated steatotic liver disease (MASLD) and autoimmune hepatitis (AIH), increased over the years[6,7]. Previous studies in China also reported similar changing trends[8,9], but the recent transition in etiologies of LC patients is unclear. Continuous work investigating the trend of newly diagnosed LC is urgent and critical to facilitate clinical practice and evidence-based policy-making. Furthermore, most previous studies defined 'cirrhosis' as LC and chronic liver diseases together, whereas data addressing clinically diagnosed LC cases, especially cases requiring hospitalization with detailed clinical features, were scant[1,2]. In this context, we conducted this study to investigate changing trends in etiologies, clinical features and in-hospital prognosis of LC inpatients. Moreover, we compared the recent data to our previous study to explore the etiological evolution of LC over 20 years[8].

MATERIALS AND METHODS

Study design

We performed this retrospective cross-sectional study based on data extracted from the electronic dataset of medical records of our hospital, which is a university-affiliated, tertiary medical center and specialized liver center in Southern China. The diagnosis of LC was based on the discharging diagnosis code established according to the International Classification of Diseases, tenth revision. Hospitalization records with a diagnostic code of cirrhosis (K70, K71, K74) or discharge diagnosis of LC admitted from Jan 2011 to Dec 2020 were extracted. In clinical practice, LC diagnosis is established according to clinical manifestations of impaired liver function and/or portal hypertension in combination with typical biochemical and radiological findings or liver biopsies[7,10]. Patients were included if they were aged 18 years or older at the time of diagnosis. To ensure that these were incident cases, we only collected the first admission record during the study period, and patients with a diagnosis of cirrhosis within the prior 5 years before the first admission were excluded. Moreover, we excluded patients who had no definite etiologies at diagnosis and did not undergo necessary laboratory tests to confirm etiologies. The patient selection flowchart is shown in Figure 1. This study was approved by the institutional review board of our hospital and conducted in accordance with the Declaration of Helsinki as revised in 2013. Informed consent was waived because we used deidentified retrospective data. This article follows the Strengthening the Reporting of Observational Studies in Epidemiology reporting guidelines[11].

Classification of etiologies and LC-related complications

The etiologies of LC were mainly determined according to the discharge diagnosis in the medical record. If the etiology was not confirmed in the discharge diagnosis, further screening of the collected data was performed to confirm the etiology according to the criteria elaborated in our previous work[8]. Generally, viral hepatitis was diagnosed according to universally accepted serological criteria, including positivity of HBs antigen for HBV infection and positivity of HCV antibodies or HCV RNA for HCV infection. The diagnosis of ALD was based on established criteria[8,12]. Considering other non-viral etiologies, several classifications require attention as follows: (1) LC caused by primary biliary cholangitis, primary sclerosing cholangitis or biliary cirrhosis secondary to biliary tract obstruction was classified as cholestatic LC; (2) LC caused by Wilson's disease, hemochromatosis, MASLD, glycogen storage disease, or amyloidosis was classified as genetic or metabolic LC; and (3) LC caused by more than one etiology was classified as LC of mixed etiology, except for HBV-HCV overlap LC, which was classified as HBV + HCV LC[7,8].

Upper gastrointestinal bleeding (UGIB), variceal bleeding, ascites, hepatic encephalopathy (HE), spontaneous bacterial peritonitis (SBP), hepatocellular carcinoma (HCC), portal vein thrombosis (PVT), hepatorenal syndrome (HRS), and acute-on-chronic liver failure (ACLF) were considered LC-related complications in our study. UGIB and variceal bleeding were diagnosed according to discharge diagnosis, or symptoms of hematemesis or melena, in combination with esophageal varices/gastric varices in the diagnosis or procedure code for band ligation, injective sclerotherapy or tissue glue injection[10]. Ascites was diagnosed according to discharge diagnosis, procedure code for paracentesis, or corresponding imaging findings. HE, HCC and PVT were diagnosed according to discharge diagnosis or corresponding imaging findings. ACLF was diagnosed according to discharge diagnosis, or acute aggravation of bilirubinemia and coagulation dysfunction on the basis of chronic liver disease per Chinese guideline[13]. SBP and HRS were diagnosed based on discharge diagnosis[6]. Liver decompensation was defined as the presence of any one of ascites, variceal bleeding, HE, or jaundice[14].

Data collection

Demographic, clinical and laboratory data at the index admission were extracted along with imaging reports of abdominal ultrasound, computerized tomography or magnetic resonance. Moreover, variables associated with etiologies and complications were also collected. Outcome variables, including deaths and liver transplantation (LT) during hospitalization and intensive care unit (ICU) admission, were only collected during the 2011-2020 period. Data from adult patients in our previous study[8] were collected to delineate the evolution of etiologies, clinical features, and complications of LC from 2001 to 2020 (Figure 1).

Statistical analysis

Categorical variables were described using counts and percentages, and comparisons were performed with the chi-square test or Fisher's exact test when appropriate. Quantitative variables were described using means ± SD or medians and interquartile range (IQR), and Student's *t* test or Mann-Whitney U test were performed as applicable. The trend of etiological proportion every 5 years was investigated using ordered logistic regression, and temporal trends in proportions of separated years were assessed using the Cochran-Armitage test. Moving average analysis and univariable linear regressions were performed to investigate trends in the mean ages of the study population, and the coefficient of determination (R square) was used to measure the strength of the correlation between mean ages and diagnosis years. Logistic regressions were used to explore risk factors for in-hospital mortality. Two-tailed *P* values of < 0.05 were considered statistically significant. All data were analyzed using R statistics version 4.2.0 (R Core Team, Vienna, Austria).

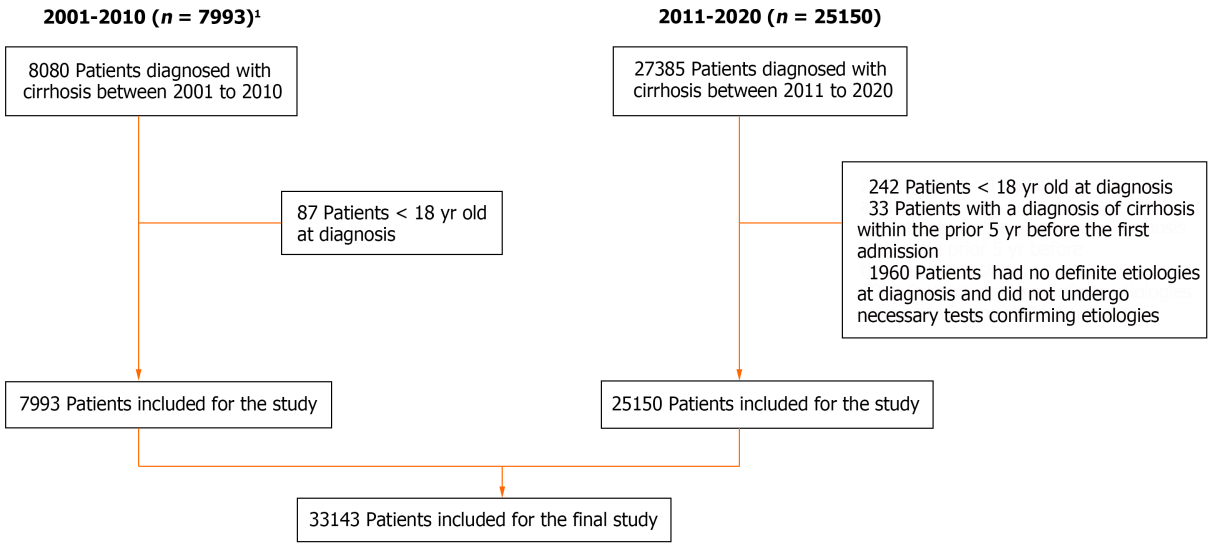

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Figure 1 Flowchart of the study population selection. A total of 33143 patients were finally included in the study out of 35465 patients diagnosed with liver cirrhosis from 2001 to 2020. [1]Detailed patient selection was elaborated in our previous study[8].

RESULTS

Overall characteristics of the study population

A total of 33143 patients were included in the study from Jan 2001 to Dec 2020 (7993 patients in 2001-2010 and 25150 patients in 2011-2020). Baseline characteristics are shown in Table 1. The mean age at diagnosis was 51.7 years, and 82.2% of patients were men. The median (IQR) model for end-stage liver disease (MELD) score was 12 (8.0, 18.0), and 31.7% of patients had MELD scores of 15 or above. As many as 65.5% of patients were in the decompensated stage, and the most prevalent complications were ascites (50.3%), HCC (36.7%) and UGIB (14.3%). During the 2011-2020 period, 6.8% of patients were referred from the emergency room, and 54.0% of patients were reimbursed by medical insurance for hospitalization (Supplementary Table 1).

Transition in baseline characteristics

The mean age of LC inpatients increased from 51.0 years in 2001-2010 to 52.0 years in 2011-2020 ($P < 0.001$) (Table 1). Three-year moving average analysis showed that the increasing trend was continuous, and the value increased linearly from 50.6 years in 2001-2003 to 52.6 years in 2018-2020 ($R^2 = 0.764$, Figure 2). The proportion of female patients increased from 16.7% in 2001-2010 to 18.2% in 2011-2020 ($P = 0.003$). During the 2001-2020 period, the proportion of patients in the decompensated stage decreased from 68.1% to 64.6% ($P < 0.001$), and the median MELD score also decreased from 14.0 to 11.0 ($P < 0.001$) (Table 1). Meanwhile, HCC and UGIB increased by nearly 10% and over 2%, respectively (both $P < 0.001$). During the 2011-2020 period, the proportion of patients with ACLF and patients referred from the emergency department increased dramatically from 5.7% to 12.4% and 5.1% to 8.1%, respectively (both $P < 0.001$) (Supplementary Table 1).

Etiology distribution and transition in etiology percentages over 20 years

The top three causes of LC were viral hepatitis (79.3%), ALD (7.1%) and mixed etiology (7.6%) in the entire population, and this pattern of constitution did not change over the 20 years (Table 2). HBV cirrhosis accounted for 75.0% of the entire population, and 94.5% of the patients had viral hepatitis. HCV and HBV + HCV etiologies accounted for 3.6% and 0.8%, respectively. The etiology distribution is presented in Table 2.

To determine the transition in etiology over the 20-year study period, we divided the study population into four groups, which were defined as 2001 to 2005, 2006 to 2010, 2011 to 2015 and 2016 to 2020. As shown in Table 2, proportions of the top three etiologies changed dramatically over the years. Viral hepatitis decreased from 85.2% to 78.1%, and ALD and mixed etiology increased by 2.5% and 4.5%, respectively (all P for trend < 0.001). Meanwhile, AIH and cholestatic etiology steadily increased from 0.4% to 1.2% (P for trend < 0.001) and 1.0% to 1.8% (P for trend = 0.018), respectively. As the major cause of viral hepatitis LC, HBV cirrhosis also decreased from 82.4% to 74.2% during the period (P for trend < 0.001). When comparing the proportions of separated years, the Cochran-Armitage test for P trend (CAP) found no statistical significance (CAP values > 0.05) (Table 2). Temporal trends of the major etiologies are illustrated in Figure 3. When comparing the proportion of different age groups (≤ 40 years as the young-age group, 41-65 years as the middle-age group, and > 65 years as the old-age group) in different etiologies, the proportion of young-aged patients gradually decreased from 21.2% in 2001 to 15.7% in 2020, whereas the proportion of middle-aged patients and old-aged patients increased from 65.6% to 69.6% and 13.3% to 14.7%, respectively (Figure 4A). Similar patterns of trends were also observed when restricting the population to HBV LC (Figure 4B). CAP found no statistical significance when comparing the proportions of separated years (CAP values > 0.05).

Table 1 Transition in characteristics of the study population over 20 years

Characteristic	Total population, *n* = 33143	2001-2010, *n* = 7993	2011-2020, *n* = 25150	*P* value
Age (yr, mean ± SD)	51.7 (11.9)	51.0 (12.3)	52.0 (11.8)	< 0.001
Gender (male, %)	27237 (82.2)	6658 (83.3)	20579 (81.8)	0.003
Laboratory test (mean ± SD)				
Albumin (g/L)	34.1 (6.3)	33.4 (6.4)	34.2 (6.2)	< 0.001
Bilirubin (umol/L)	87.7 (139.4)	98.3 (148.9)	85.4 (137.1)	< 0.001
Prothrombin INR	1.45 (0.65)	1.53 (0.65)	1.44 (0.65)	< 0.001
MELD score (Median, IQR)	12.0 (8.0,18.0)	14.0 (10.0, 19.0)	11.0 (8.0,18.0)	< 0.001
Decompensation[1] (*n*,%)	21701 (65.5)	5443 (68.1)	16258 (64.6)	< 0.001
Complications				
UGIB	4729 (14.3)	998 (12.5)	3731 (14.8)	< 0.001
Ascites	16656 (50.3)	4444 (55.6)	12212 (48.6)	< 0.001
HE	1901 (5.7)	535 (6.7)	1366 (5.4)	0.007
HCC	12159 (36.7)	2392 (29.9)	9767 (38.8)	< 0.001
PVT	2449 (7.4)	403 (5.0)	2046 (8.1)	< 0.001
HRS	713 (2.2)	291 (3.6)	422 (1.7)	< 0.001

[1]Presence of any one of ascites, variceal bleeding, hepatic encephalopathy, or jaundice (total bilirubin > 51.3 umol/L). INR: International normalized ratio; MELD: Model for end-stage liver disease; IQR: Interquartile range; UGIB: Upper gastrointestinal bleeding; HE: Hepatic encephalopathy; HCC: Hepatocellular carcinoma; PVT: Portal vein thrombosis; HRS: Hepatic renal syndrome.

Table 2 Transition in etiological proportions over 20 years, *n* (%)

Etiology	2001-2005, *n* = 2870	2006-2010, *n* = 5123	2011-2015, *n* = 10538	2016-2020, *n* = 14612	*P* value[1]	*P* value[2]
Viral hepatitis	2444 (85.2)	4046 (79.0)	8385 (79.6)	11418 (78.1)	< 0.001	0.780
HBV	2366 (82.4)	3852 (75.2)	7788 (73.9)	10835 (74.2)	< 0.001	0.747
HCV	66 (2.3)	159 (3.1)	484 (4.6)	474 (3.2)	0.951	0.912
HBV + HCV	12 (0.4)	35 (0.7)	113 (1.1)	109 (0.7)	0.685	0.932
Alcohol	155 (5.4)	304 (5.9)	753 (7.1)	1155 (7.9)	< 0.001	0.869
Autoimmune hepatitis	12 (0.4)	41 (0.8)	87 (0.8)	170 (1.2)	< 0.001	0.875
Cholestatic	29 (1.0)	92 (1.8)	154 (1.5)	266 (1.8)	0.005	0.925
Genetic or Metabolic	21 (0.7)	62 (1.2)	105 (1.0)	191 (1.3)	0.019	0.923
Mixed etiology	102 (3.6)	374 (7.3)	864 (8.2)	1188 (8.1)	< 0.001	0.771
Cryptogenic	74 (2.6)	153 (3.0)	70 (0.7)	36 (0.2)	< 0.001	0.746

[1]Determined using ordered logistic regression model by comparing proportions of the separated four 5-yr groups.
[2]Determined using Cochran-Armitage test by comparing proportions of separated years from 2001 to 2020. HBV: Hepatitis B virus; HCV: Hepatitis C virus.

In-hospital prognosis and risk factors for in-hospital mortality over the 2011-2020 period

A total of 264 (1.0%) patients died during the index hospitalization. Over 80% of deaths were caused by liver-related diseases, including 107 cases (40.5%) of liver failure, 63 cases (23.9%) of HCC, and 27 cases (10.2%) of UGIB. The in-hospital mortality was stable at approximately 1% during the 2011-2020 period (P = 0.372). Meanwhile, 242 patients (1.0%) received LT, and the rate of LT increased by 3.0% during the last ten years (P < 0.001). A total of 1010 patients (4.0%) were admitted to the ICU, and the ICU admission rate increased from 2.7% to 5.0% during the last ten years (P < 0.001) (Supplementary Table 2). In multivariable regression, as shown in Table 3, transferring from the emergency department resulted in a nearly 3-fold increased risk of in-hospital mortality (adjusted OR: 2.97, 95%CI: 2.01-4.38). MELD scores of 15 or above and older age also increased the risk of mortality (OR: 3.55, 95%CI: 2.24-5.64, and OR: 1.90, 95%CI:

Table 3 Risk factors of in-hospital mortality from 2011 to 2020

Characteristics, *n* = 25150	Unadjusted		Adjusted[1]	
	OR	*P* value	OR (95%CI)	*P* value
Age[2]	1.49	0.011	1.90 (1.28-2.80)	0.001
Gender	1.25	0.230	0.93 (0.58-1.49)	0.761
Etiology				
Viral hepatitis	1.10	0.583	--	--
Alcohol	0.89	0.721	--	--
Other etiologies	Reference	--	--	--
Referring site				
Emergency	6.11 (4.67-7.99)	< 0.001	2.97 (2.01-4.38)	< 0.001
Clinic	Reference	--	Reference	--
Insurance status[3]	1.09 (0.84-1.41)	0.558		
MELD[4]	6.85 (5.15-9.09)	< 0.001	3.55 (2.24-5.64)	< 0.001
Liver transplantation	1.22 (0.57-2.63)	0.764	--	--
Residence				
Rural area	3.40 (0.84-13.73)	0.070	3.33 (0.81-13.73)	0.096
Urban area	Reference	--	Reference	--
Complications				
Ascites	2.70 (2.06-3.53)	< 0.001	1.74 (1.18-2.56)	0.005
UGIB	2.13 (1.62-2.81)	< 0.001	2.35 (1.59-3.46)	< 0.001
HE	10.63 (8.22-13.74)	< 0.001	3.27 (2.20-4.84)	< 0.001
HCC	1.42 (1.15-1.81)	0.005	6.03 (4.07-8.94)	< 0.001
SBP	4.06 (3.15-5.23)	< 0.001	1.34 (0.92-1.96)	0.123
ACLF	8.60 (6.73-11.00)	< 0.001	4.22 (2.70-6.59)	< 0.001

[1]Adjusted by all variables with *P* value < 0.10 and age, gender in univariate logistic analysis. Multivariate logistic analysis is performed.
[2]≥ 65 years *vs* < 65 yr.
[3]Medical insurance vs self-paying.
[4]Model for end-stage liver disease (MELD) score ≥ 15 points *vs* MELD score < 15 points. OR: Odds ratio; MELD: Model for end-stage liver disease; UGIB: Upper gastrointestinal bleeding; HE: Hepatic encephalopathy; HCC: Hepatocellular carcinoma; SBP: Spontaneous bacterial peritonitis; ACLF: Acute-on-chronic liver failure.

1.28-2.80, respectively). LC complications associated with increased mortality were ascites (OR: 1.74, 95%CI: 1.18-2.56), UGIB (OR: 2.35, 95%CI: 1.59-3.46), HCC (OR: 6.03, 95%CI: 4.07-8.94), ACLF (OR: 4.22, 95%CI: 2.70-6.59), and HE (OR: 3.27, 95%CI: 2.20-4.84). Meanwhile, male gender, LC etiology, medical insurance, LT, and residential areas of patients were not associated with in-hospital mortality (Table 3).

DISCUSSION

This large sample cross-sectional study showed the transition in etiologies and characteristics of newly diagnosed LC in our medical center during the past two decades. We found that HBV remained the most prevalent cause of LC throughout the study period, but the percentage decreased gradually, especially in people younger than 40 years old. Meanwhile, LC cases caused by ALD and AIH are increasing over time. Regarding clinical characteristics, LC patients are aging and less likely to be decompensated at diagnosis. Moreover, we found that the in-hospital mortality rate was relatively low, and emergency referral, a higher MELD score and LC complications were associated with in-hospital mortality. Since a considerable proportion (52%) of patients are from regions of Southern China other than Guangdong Province, our single-center-based findings may suggest the changing trend of LC etiologies and clinical features in entire Southern China[8].

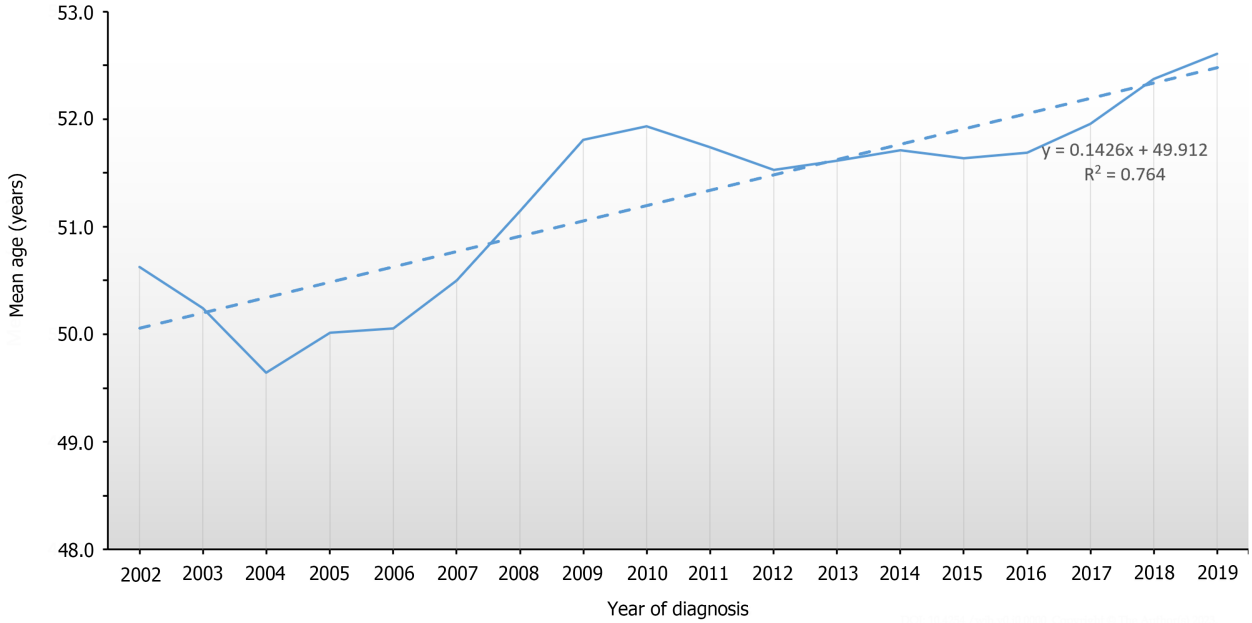

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Figure 2 Trend in the mean age of the study population in 2001-2020. The three-year moving averages in ages were calculated and shown. The mean age of cirrhotic patients increased continuously over the 20-year study period, with a high coefficient of determination in linear regression (R^2 = 0.764). The three-year moving averages were plotted on the central year, as the year of diagnosis in the horizontal axis (*e.g.* 2002 represented 2001-2003, and 2019 represented 2018-2020).

Etiologies

The viral hepatitis-predominant pattern in etiology in our study is consistent with a global report (42% HBV infection and 21% HCV infection in LC) and some recent studies from other East Asian regions[15,16]. Meanwhile, the > 70% HBV contribution indicated that China is still a highly endemic area of HBV infection. However, the continuous decreases in the proportion of patients with HBV cirrhosis measured every 5-year period in our study reflected an overall descending trend of HBV contribution to LC, which was in line with recent studies from other regions of China[9,17]. The descending proportion should be attributed to the widespread HBV vaccination and the subsequent declining prevalence of HBV in China[4]. Contrast to our results, there was a slight increase of 5.5% in HBV-related LC incidence in China (7.7/100000 in 2000 *vs*. 8.1/100000 in 2015) according to Global Burden of Disease 2015 study data[5]. However, the same study reported a 38% and 8.8% increase in the incidence of alcoholic-related LC and non-viral non-alcoholic LC, respectively, which would actually result in a relative decrease in the proportion of HBV-related LC when added up. Furthermore, HBV-related LC data in the above study included cases of HBV overlapping with other etiologies, whereas our study defined HBV-LC as mono HBV infection. Considering the difference in etiology definition, our study is supposed to be more accurate to reflect the trend of HBV LC. Given the low prevalence of HBV carriers of only 1.0% among children born after 1999 in China, newly diagnosed cases of HBV LC are expected to decline continuously in the future[18].

Our data showed a continuous increase in the alcoholic LC proportion during the last two decades, while the percentage increased from 5.7% in the 2000s to 7.6% in the 2010s. Alcohol-use disorder is one of the main causes of liver disease-related mortality and accounts for approximately 50% of LC cases worldwide[19]. In China, ALD has become the second leading cause of end-stage liver disease and possesses the highest percentage change in age-standardized incidence among all LC etiologies[5,20]. Significant increases in admissions and the proportion of alcoholic cirrhosis have recently been reported in LC inpatients, and our data are consistent with the data from Northern China[9,17]. Regarding the increasing trend in alcohol consumption over the last three decades in China[21], alcoholic LC cases are expected to continue rising in the future. Our data support the allocation of more resources to reduce the burden of alcohol use disorder.

Clinical characteristics

It is interesting to note that our data showed an increasing trend in the age of LC patients; in addition, a slight but significant increase in the female proportion was also observed (1.5% increase, P = 0.003). Our findings are consistent with a recent nationwide survey from Japan showing a mean age nearly 2 years older when comparing patients from 2015-2017 to patients from 2008-2010 (68.2 years *vs*. 66.4 years)[7]. Moreover, a hospital-based study from Southwest China reported a nonsignificant increase in the mean age of LC patients from 52.3 years in 2003 to 52.7 years in 2013[22]. Plausible explanations are as follows: first, decreased HBV incidence in young adults and improved survival of LC patients, which resulted in an increased proportion of older patients and more patients admitted at an older age[6]; second, increased incidence of non-viral LC cases, especially alcoholic and autoimmune liver diseases, who were older at diagnosis compared to HBV LC (Supplementary Table 3). Population-based studies in North America have shown decreasing mortality rates of LC, whether for in-hospital mortality or for 1-year mortality, and the benefits may largely be

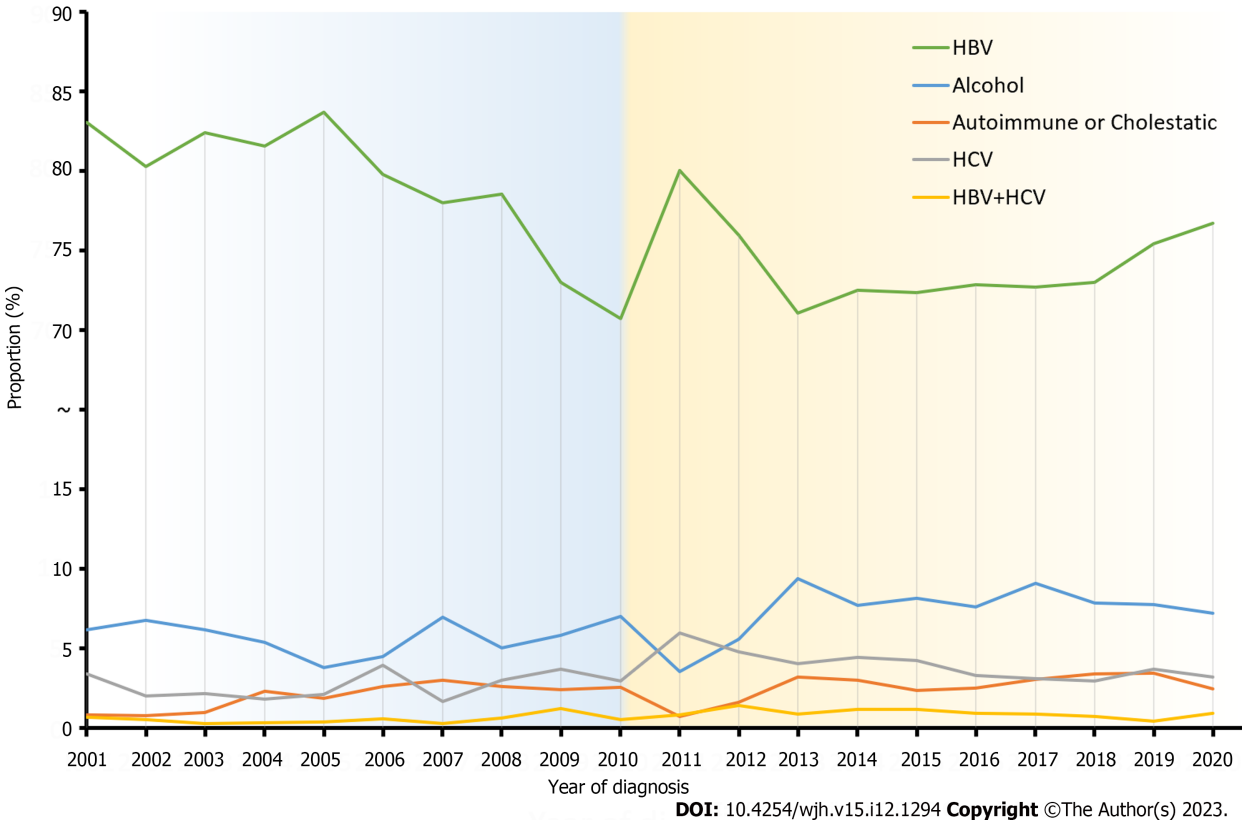

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Figure 3 Temporal trends of viral hepatitis and other major etiologies in 2001-2020. The proportion of hepatitis B virus-liver cirrhosis (HBV-LC) decreased dramatically during the 2001-2010 period but fluctuated and decreased slightly during the 2011-2020 period. Meanwhile, proportions of alcoholic-LC and autoimmune or cholestatic-LC have increased during the 20-year period. Hepatitis C virus (HCV)-LC and (HBV + HCV)-LC have not shown explicit trends. The Cochran-Armitage test for *P* trend found no statistical significance ($P > 0.05$) when comparing proportions in separated years ($P > 0.05$). HBV: Hepatitis B virus; HCV: Hepatitis C virus.

due to improved care[23]. For hospitalized patients with cirrhosis, timely endoscopic treatment and paracentesis and available LT and intensive care have been linked to improved survival[10,24,25]. On the other hand, the increased female proportion can be explained by the decreased proportion of viral hepatitis LC, which has more male patients, and the increased proportion of non-viral LC, especially for AIH LC, which affects more female patients. Moreover, improved health resources to women may also contribute to the increasing female proportion (Supplementary Table 1).

Another notable finding is that the decreasing trend in the HBV proportion is most prominent in patients ≤ 40 years, while the proportions of both young LC patients and young HBV-LC patients are decreasing significantly (Figure 4). Our data are likely to be the outcome of a low prevalence of HBV infection in young adults in China and are also in line with observations from North America[6]. Importantly, the transition has implications for the future because viral hepatitis, especially CHB, is highly associated with liver decompensation and liver cancer[26,27]. Reducing new diagnoses in young people may greatly reduce the burden of end-stage liver disease and liver cancer in the future.

In-hospital mortality and risk factors

Apart from illustrating the transition of etiologies and clinical features of LC, we also investigated in-hospital outcomes and associated risk factors. The overall in-hospital mortality was 1.0% in our study, which is similar to that in nationwide and regional studies in China[25,28]. In contrast to a decline of 17.6% in the mortality rate of cirrhosis and chronic liver disease in China from 1990 to 2016, we did not observe a descending trend in in-hospital mortality in our study[20]. However, considering the dramatic increase in liver decompensation, LC complications, and ICU admissions in our study population, which indicates an increase in disease severity over time, the observed stable in-hospital mortality is reasonable. In-hospital mortality is considered a hard endpoint of inpatient prognosis and varies across countries. In the 2010s, the reported mortality rates were 5.4% to 7.6% in the United States, 9.1% in Korea, and 11.6% in Spain[23,29-31]. The discrepancy between data from other hospitals and ours may be due to differences in patient selection and criteria for patient admission. Moreover, well-equipped service of intensive care and increased LTs may also contribute to improving patient prognosis[10,23]. Our results are of clinical significance to report satisfactory inpatient care in Southern China.

Reported risk factors for in-hospital mortality included older age, HE, HCC, gastrointestinal bleeding, and sepsis from previous studies[29,31], and our data supported the observation by finding that all major LC complications are associated with poor outcomes. In addition, we emphasized that HCC and ACLF were associated with the highest risk of in-hospital mortality (OR 6.0 and 4.6, respectively) and increased faster than other complications (Supplementary Table 1). Our data are consistent with the increasing trend of HCC and ACLF in China[1,32]. With the rising burden of HCC and ACLF, more attention should focus on early diagnosis and timely treatment of the two severe complications[33,34].

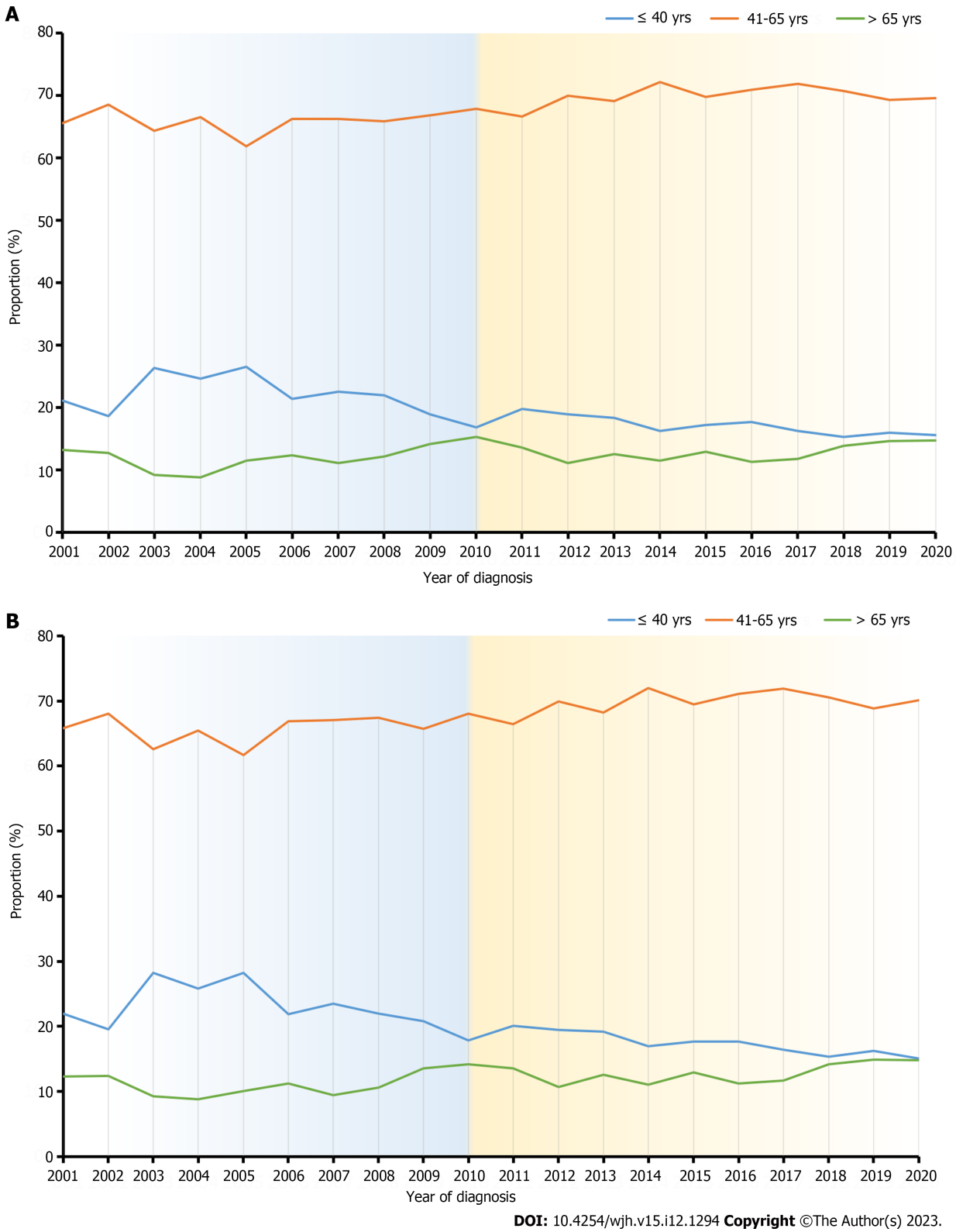

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Figure 4 Temporal trends in different age groups of the study population. A: In the whole population, the proportion of patients ≤ 40 years was decreasing (21.2% in 2001 to 15.7% in 2020), and those aged 41-65 years and > 65 years were increasing (65.6% in 2001 to 69.6% in 2020, and 13.3% in 2001 to 14.7% in 2020, respectively) during the 20-year study period; B: In patients with hepatitis B virus-liver cirrhosis, the proportion ≤ 40 years decreased (22.0% in 2001 to 15.1% in 2020), and those aged 41-65 years and > 65 years increased (65.8% in 2001 to 70.1% in 2020, and 12.3% in 2001 to 14.8% in 2020, respectively) during the 20-year study period.

Strengths and limitations

In this study, we revealed the evolution of etiologies and clinical characteristics of hospitalized LC patients over the last 20 years in a large-sample dataset. Meanwhile, we filled the knowledge gap to reveal in-hospital mortality and associated risk factors, which were scarcely reported in China previously. However, there are several limitations to this study. First, as a retrospective study, although we searched cases using both diagnosis codes and literal discharge diagnosis, there are still possibilities of missing cases of LC due to the lack of LC-indicative diagnosis in the original database. Moreover, the retrospective design in HBV endemic region may also result in the underestimation of MASLD, and therefore this study cannot reveal the trend of MASLD-derived LC. Second, different from manual data extraction in the 2001-2010 dataset, data extraction in 2011-2020 is automatic from a single admission note, whereas there are no subsequent data to supplement the diagnosis when the primary etiology cannot be confirmed. The consequent case exclusion due to uncertain etiologies may explain the turbulence in temporal trends in the 2011-2020 period, especially the variance in the proportion of HBV LC between 2010 and 2011. Third, the cross-sectional study did not include follow-up data after patient discharge, so the actual mortality rate over time is unclear. Future studies focusing on trend of prognosis of LC are highly needed. Fourth, the epidemiological indications based on our single-center study are limited, and care should be taken when applying our findings to other countries or regions.

CONCLUSION

In conclusion, our study showed a decreased ratio of viral hepatitis LC, especially HBV LC, and an increased ratio of alcoholic and AIH LC in real-world inpatients over the past two decades. In-hospital mortality has been low over the last 10 years, and HCC and ACLF are the strongest risk factors for mortality. Further multicenter studies are needed to reveal the actual incidence of LC in China, and more attention should be given to the rising burden of HCC and ACLF in LC patients.

ARTICLE HIGHLIGHTS

Research background

Liver cirrhosis (LC) is the end stage of chronic liver disease and is associated with significant morbidity, mortality and healthcare utilization. China accounts for a large proportion of the regional burden of LC. Thanks to widespread hepatitis B virus (HBV) vaccination and the potent antiviral treatment for HBV and hepatitis C virus, the LC mortality has greatly decreased.

Research motivation

In the context of changing burden of LC, the recent transition in etiologies and clinical features of LC is unclear in China.

Research objectives

Our main objective was to identify the transition in etiologies and clinical characteristics of hospitalized LC patients in Southern China. Furthermore, in-hospital prognosis and associated risk factors were also investigated.

Research methods

We included LC inpatients admitted from 2001 to 2020 in this retrospective, cross-sectional study. The etiologies of LC were mainly determined according to the discharge diagnosis, and upper gastrointestinal bleeding, ascites, hepatic encephalopathy, spontaneous bacterial peritonitis, hepatocellular carcinoma (HCC), portal vein thrombosis, hepatorenal syndrome, and acute-on-chronic liver failure (ACLF) were considered LC-related complications. Changing trends in the etiologies and clinical characteristics were investigated using logistic regression, and temporal trends in proportions of separated years were investigated using the Cochran-Armitage test.

Research results

The study included a total of 33143 patients and the mean age increased from 51.0 years in 2001-2010 to 52.0 years in 2011-2020 ($P < 0.001$). In the meantime, proportion of decompensated LC and the score of model for end-stage liver disease decreased. During the study period, HBV remained the major etiology of LC (75.0%), but the proportion of HBV-LC decreased from 82.4% in 2001-2005 to 74.2% in 2016-2020 (P for trend < 0.001). Meanwhile, the proportions of LC caused by alcoholic liver disease and autoimmune hepatitis both increased slightly (both P for trend < 0.001). In-hospital mortality was low, and HCC and ACLF were associated with 6-fold and 4-fold increased risks of mortality.

Research conclusions

Our study showed a decreased ratio of HBV LC, and an increased ratio of alcoholic and autoimmune hepatitis LC in real-world inpatients over the past two decades. HCC and ACLF were identified as the strongest risk factors for in-hospital mortality.

Research perspectives

Our large sample cross-sectional study showed the transition in etiologies and characteristics of newly diagnosed LC in our medical center over the past twenty years and the findings may reflect the changing trend of LC in entire Southern China. Future multicenter studies are needed to reveal the changing incidence of LC in China, and more attention should be given to the rising burden of HCC and ACLF in LC patients.

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FOOTNOTES

Co-first authors: Xing Wang and Jin-Ni Luo.

Author contributions: Wang X, Luo JN, Wu XY and Wu B planned and designed the study; Wang X, Luo JN, Wu XY and Zhang QX collected the data; Wang X and Luo JN performed the data analysis; Wang X and Luo JN drafted the manuscript; Wu B critically revised the manuscript; all authors have approved the submitted manuscript. Wang X and Luo JN contributed equally to this work as co-first authors. Wang X and Luo JN are designated as co-first authors due to their equal and substantial contributions to the study conception, design, data acquisition, and data analysis, as well as manuscript preparation and editing, each playing pivotal roles in ensuring the integrity and quality of the research.

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Institutional review board statement: This study was reviewed and approved by the Ethics Committee of the Third Affiliated Hospital of Sun Yat-sen University and carried out in compliance with the Declaration of Helsinki.

Informed consent statement: As the study used anonymous and pre-existing data, the requirement for the informed consent from patients was waived.

Conflict-of-interest statement: The authors declare no conflict of interest.

Data sharing statement: All data relevant to the study have been included in the article or uploaded as Supplementary Table 1. The dataset for this study is available from the corresponding author on reasonable request and fulfilment of regulatory requirements.

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Retrospective Study

Peri-operative score for elderly patients with resectable hepatocellular carcinoma

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Abstract

BACKGROUND

Liver resection is the mainstay for a curative treatment for patients with resectable hepatocellular carcinoma (HCC), also in elderly population. Despite this, the evaluation of patient condition, liver function and extent of disease remains a demanding process with the aim to reduce postoperative morbidity and mortality.

AIM

To identify new perioperative risk factors that could be associated with higher 90- and 180-d mortality in elderly patients eligible for liver resection for HCC considering traditional perioperative risk scores and to develop a risk score.

METHODS

A multicentric, retrospective study was performed by reviewing the medical records of patients aged 70 years or older who electively underwent liver resection for HCC; several independent variables correlated with death from all causes at 90 and 180 d were studied. The coefficients of Cox regression proportional-hazards model for six-month mortality were rounded to the nearest integer to assign risk factors' weights and derive the scoring algorithm.

RESULTS

Multivariate analysis found variables (American Society of Anesthesiology score, high rate of comorbidities, Mayo end stage liver disease score and size of biggest lesion) that had independent correlations with increased 90- and 180-d mortality. A clinical risk score was developed with survival profiles.

CONCLUSION

This score can aid in stratifying this population in order to assess who can benefit from surgical treatment in terms of postoperative mortality.

Key Words: Hepatocellular carcinoma; Score; Laparoscopy; Surgical resection; Elderly patients; Multivariate analysis

Core Tip: To support the decision-making process in elderly patient with resectable hepatocellular carcinoma (HCC) and understand who can benefit from surgical treatment in terms of postoperative mortality, we analyzed data from 11 hepato-biliary centers during a 10-years period. A multivariate analysis was performed to find variables (American Society of Anesthesiology score, high rate of comorbidities, Mayo end stage liver disease score and size of biggest lesion) that had independent correlations with increased 90- and 180-d mortality. The evaluation of elderly patients who underwent liver resection for HCC need to be supported by any form of possible analysis of risk.

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INTRODUCTION

The life expectancy of the population has increased in recent years, and this led to an increased rate of malignant disease in elderly population[1,2]. Hepatocellular carcinoma (HCC) became even more frequent in elderly population[3,4].

According to current guidelines liver resection, ablation and liver transplant are still the mainstay treatments for HCC.

Liver resection presented better overall and disease-free survival than other curative treatments[5]. Despite this, liver resection presented a significant risk postoperative morbidity and mortality.

The approach of liver disease in elderly population needed of an accurate stratification of patients at risk, with the involvement of multidisciplinary preoperative assessment.

The aim of our study was to analyze a population of elderly patients who underwent liver resection for HCC, to investigate the possible presence of risk predictors of postoperative mortality at 90 and 180 d.

MATERIALS AND METHODS

Study Design

A multicentric, retrospective cohort study was carried out by reviewing the medical records of patients aged > 70 years or over undergoing liver resection for HCC from January 2009 to January 2019. We evaluated all preoperative independent variables linked with patients (demographics data), with lesion (number and size, calculated on the preoperative imaging) and preoperative clinical assessment in eligible patients. The primary endpoint was to define 90 d and 180 d mortality rate. The second one was to explore the association among variables and post operative mortality rate.

Statistical Analysis

All analyses were conducted using STATA software, version 16 (Stata-Corp LP, College Station, Tex). Data are reported as means (standard deviations) for continuous variables or numbers (percentages) of patients for categorical variables. Six-month follow-up was chosen to analyze at least 20 fatal events after the surgery. Associations between baseline pre-operative variables with six-month mortality were evaluated using a univariate Cox proportional-hazards model. A score point system was derived from the multivariable Cox proportional-hazards model including univariate predictors with $P < 0.05$. For a dichotomous risk factor, the estimated regression coefficient was rounded to the nearest integer. For a non-dichotomous risk factor, continuous or discrete, the estimated regression coefficient was multiplied by observed values, rounded to the nearest integer and rescaled to assign zero points to the lowest risk-category. Hazard ratios (HRs) with their 95%CI were reported. The discriminative ability of the models was assessed using the Harrell's concordance index (C-index). Patients were stratified into three groups of risk by the estimated six-month mortality probability (low-risk < 5%, mid-risk 5%-10%, and high-risk > 10%). The cumulative mortality was displayed using Kaplan-Meier estimates with comparison between curves based on the Log-Rank statistic. The score was internally validated by resampling 1000 bootstrap replications. The bias was calculated as the difference between estimation and the mean of the bootstrap sample. Theoretical profiles were constructed by combining variables of the final model as well as a risk score for death in the period. The cut off of 6 mo as final follow up has been chosen to obtain an appropriate number of events, but its significance was validated at 3 mo. A P value < 0.05 was considered statistically significant.

RESULTS

A total of 429 patients, who underwent liver resection for HCC were included (Table 1). The majority of patients were male (n = 319, 74.3%, and 110 females, 25.7%), aged ≥ 70 years (mean of 75.3 ± 4.1 years); 20 deaths (4.7%) occurred up to 180 d after surgery, as shown in Table 1.

Two hundred fifty-seven patients, 60% presented an American Society of Anesthesiology (ASA) score III-IV, and the median range of Mayo end stage liver disease (MELD) score was 7 (7.4 ± 2.1). Roughly one third of patients was affected by more of 2 comorbidities (n = 142, 33.1%). Most patients presented a single, unilobar lesion (n = 421, 98%). Most of patients underwent to a minor hepatectomy, while only 54 patients (13.1%) underwent to a major hepatectomy, according to Brisbane classification.

The overall survival curve calculated by the Kaplan–Meier estimator is shown in Figure 1. The ASA score, MELD score, the presence of Comorbidities > 2 and the size of the biggest lesion presented in the univariate analysis an HR greater than 1, as shown in Table 1. They are used as predictor factors in the multivariate analysis (Table 2). Table 3 showed a score system which provides a balanced weight for each variable. Combining the four variables we obtained different profiles of patients with a different preoperative risk, based on personal score, groupable in a low-risk (< 5% at 6 mo), mid-risk (5%-10% at 6 mo) and high-risk class (> 10% at 6 mo) (Table 4 and Figure 2).

Figure 2 showed the curves of six-month mortality probability, according to the different profile created on various score. The rate of mortality probability significantly increased from patients with score 2 to patients with score 6: Patients with a score ≥ 2 presented a 5.7% of mortality, patients with a score ≥ 3 presented a 7%, patients with a score ≥ 4 showed a 9.3% of mortality, patients with a score ≥ 5 showed a 13.6%, patients with a score ≥ 6 presented 22.9% of mortality.

We performed an Internal validation using a bootstrapping technique with 1000 resamples, the derived score point system had good discrimination as 0.803 of the Harrell C-Index (bootstrap 95%CI 0.741-0.875). The bias of the estimated risk assigned to 1 point of the score, as the difference between coefficient estimation in the derivation model (0.875) and the mean of the bootstrap sample (0.888), it was negligible (-0.013).

Table 1 Characteristics of samples used to study the variables and deaths 180 d after surgery, *n* (%)

	All		Alive at 180 d		Death at 180 d		HR	*P* value
	N	*n* = 429	*N*	*n* = 409	*N*	*n* = 20		
Age, yr	429	75.3 ± 4.1	409	75.3 ± 4.1	20	76.9 ± 4.9	1.52 (0.94-2.47)	0.086
Male	429	319 (74.4)	409	306 (74.8)	20	13 (65.0)	0.61 (0.24-1.54)	0.296
BMI	429	26.9 ± 3.5	409	26.9 ± 3.6	20	26.9 ± 0.9	0.97 (0.52-1.82)	0.921
ASA score	429	2.60 ± 0.50	409	2.59 ± 0.50	20	2.90 ± 0.31	4.49 (1.47-13.74)	0.008
Comorbidity > 2	429	142 (33.1)	409	129 (31.5)	20	13 (65.0)	3.92 (1.56-9.82)	0.004
HBV	429	80 (18.6)	409	80 (19.6)	20	0 (0.0)	-	-
HCV	429	217 (50.6)	409	210 (51.3)	20	7 (35.0)	0.51 (0.2-1.28)	0.151
ALD	429	60 (14.0)	409	56 (13.7)	20	4 (20.0)	1.58 (0.53-4.72)	0.415
Others	429	72 (16.8)	409	63 (15.4)	20	9 (45.0)	4.3 (1.78-10.37)	0.001
F4 cirrhosis	429	178 (41.5)	409	173 (42.3)	20	5 (25.0)	0.46 (0.17-1.27)	0.134
CHILD A	429	370 (86.2)	409	353 (86.3)	20	17 (85.0)	0.92 (0.27-3.13)	0.891
MELD score	429	7.4 ± 2.1	409	7.4 ± 2.0	20	8.9 ± 2.7	1.25 (1.09-1.44)	0.001
Albumin	382	3.80 ± 0.60	367	3.80 ± 0.60	15	3.71 ± 0.77	0.75 (0.33-1.73)	0.504
Bilirubin	424	1.05 ± 0.64	404	1.05 ± 0.64	20	0.99 ± 0.54	0.81 (0.37-1.76)	0.587
Creatinin	425	1.03 ± 0.36	405	1.02 ± 0.36	20	1.17 ± 0.42	2.55 (0.9-7.2)	0.077
INR	422	1.20 ± 0.23	402	1.20 ± 0.23	20	1.17 ± 0.28	0.51 (0.07-3.8)	0.508
AST	424	68 ± 61	405	69 ± 61	19	48 ± 41	0.92 (0.85-1)	0.045
ALT	201	51 ± 80	182	52 ± 82	19	41 ± 48	0.98 (0.91-1.05)	0.540
GGT	192	145 ± 218	174	145 ± 218	18	146 ± 228	1 (0.98-1.02)	0.958
Platelets	425	191 ± 92	406	191 ± 92	19	177 ± 85	0.98 (0.93-1.04)	0.509
Number of lesions	429	1.09 ± 0.30	409	1.09 ± 0.31	20	1.05 ± 0.22	0.54 (0.08-3.77)	0.531
Size of biggest lesion (mm)	429	33 ± 10	409	32 ± 10	20	37 ± 13	1.26 (1.01-1.58)	0.043
Bilobar lesion	429	8 (1.9)	409	8 (2.0)	20	0 (0.0)	-	-
Preop treatment	429	53 (12.4)	409	50 (12.2)	20	3 (15.0)	1.24 (0.36-4.23)	0.732
Major HTC	429	56 (13.1)	409	55 (13.4)	20	1 (5.0)	0.34 (0.05-2.56)	0.297

BMI: Body mass index; ASA: American Society of Anesthesiology; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; GGT: Gamma-glutamyl transferase; Major HTC: Hepatectomy; ALD: Alcoholic liver disease; HBV: Hepatitis B virus; HCV: Hepatitis C virus; MELD: Mayo end liver disease score; INR: International normalized ratio; HR: Hazard ratio.

Table 2 Multivariate analysis

	Beta	HR	*P* value
ASA score	1.189	3.28 (1.04-10.34)	0.042
Comorbidity 2	1.071	2.92 (1.14-7.45)	0.025
MELD	0.202	1.22 (1.06-1.41)	0.005
Size of largest lesion	0.046	1.05 (1.01-1.09)	0.034
C-index = 0.807	-	-	-

ASA: American Society of Anesthesiology; MELD: Mayo end liver disease; HR: Hazard ratio.

Table 3 Score point system

	Values	Points
ASA score	1	0
	2	0
	3	2
	4	3
Comorbidity > 2	Yes	1
MELD	< 8	0
	8-12	1
	> 12	2
Size of largest lesion (mm)	≤ 10	0
	10-32	1
	> 32	2
	Max score	8

ASA: American Society of Anesthesiology; MELD: Mayo end liver disease.

Table 4 Stratification of mortality risk on preoperative score

Score	Number and prevalence, *n* (%)	Three-month mortality, %	Six-month mortality, %
≥ 2 *vs* ≤ 1	366 (85.3) *vs* 63 (14.7)	3.3 *vs* 0.0	5.7 *vs* 0.0
≥ 3 *vs* ≤ 2	296 (69.0) *vs* 133 (31.0)	4.1 *vs* 0.0	7.0 *vs* 0.0
≥ 4 *vs* ≤ 3	213 (49.7) *vs* 216 (50.3)	5.3 *vs* 0.5	9.3 *vs* 0.5
≥ 5 *vs* ≤ 4	102 (23.8) *vs* 327 (76.2)	5.0 *vs* 2.2	13.6 *vs* 2.2
≥ 6 *vs* ≤ 5	28 (6.5) *vs* 401 (93.5)	11.3 *vs* 2.3	22.9 *vs* 3.6

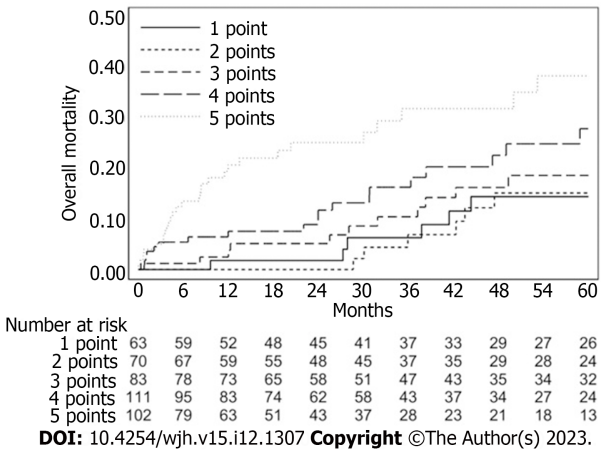

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Figure 1 Overall mortality.

DISCUSSION

The present study observed a population of elderly patients (≥ 70 years) who underwent liver resection for HCC, and it showed that a simple preoperative score, resulting from the evaluation of presence and degree of ASA score, MELD score, the presence of more than 2 comorbidities and the size of the biggest lesion, can predict 90 d and 180 d mortality rate.

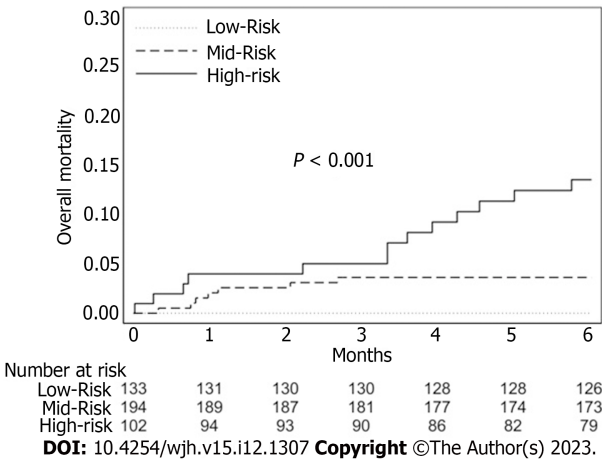

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Figure 2 Profile risk of six-month mortality probability.

The process of 'aging society' resulted in an increasing rate of surgical oncological elderly patients and it made necessary to provide an accurate preoperative assessment to optimize the choice of the best possible treatment. Liver resection represented the treatment of choice for resectable HCC, even in elderly population[6-9]. Age itself should not be a contraindication to liver resection in treatment of HCC, but this population needed a more accurate selection and preoperative evaluation of benefits and drawback.

The assessment of liver function needed to be linked with the identification of modifiable and not modifiable risk factors to improve surgical outcomes. There were several predictive of 30 d mortality after liver resection for HCC[10-13]. MELD score was often considered a significant parameter, as well in our study where this score was ranged in 3 degrees with a different impact on final sum. Conversely Lee *et al*[14] in a nationwide cohort study recognized the Platelet-Albumin-Bilirubin score had an higher sensitivity and specificity than MELD or Albumin-Bilirubin score[15].

With the aim to better explore the concept of 'frailty' in this population also the ASA score gained more relevance. In our results an ASA score of 1-2 or 3-4 can weight in a different significantly way on the final score and so have impact on the post operative mortality probability. Not only the evaluation of the degree of pathological physical state, but also the presence of more of 2 comorbidities resulted significant as risk predictor in our score. The limit was represented by not knowing the type of comorbidity which made impossible to optimize the stratification. Preoperative evaluation of the physiological age could be more useful in predicting risk of postoperative morbidity and mortality than chronological age [16,17], but several external validation of comprehensive score are needed.

As previously reported the size of largest tumor was a useful factor to predict prognostic outcomes after liver resection for HCC[13,18,19]. Also our results showed in univariate and multivariate analysis how an increasing size could be a risk factor on postoperative mortality. In the setting of liver disease almost completely represented by a single nodule of HCC, a size > 32 mm could impact on postoperative mortality risk as a MELD score > 12. The idea of the importance of morphological tumor data was yet explored by Mazzaferro[18] with 'Metroticket paradigm' before, and 'Up to7 criteria' after, more useful in the context of liver transplantation, but it had represented the substrate for comprehensive measures as reported by Tokumitsu *et al*[12] with its NxS score which provide a cut off value of tumor burden to predict the prognosis following hepatectomies for HCC[12]. Despite this, prognosis of HCC was more complex than other solid tumors because it depended not only from tumor burden but also from liver function reserve.

ASA score, MELD score, the presence of more than 2 comorbidities and the size of the lesion were all non-modifiable factor. Our work underlined how the process of decision making could be delicate in elderly patients with HCC. The association of evaluation of liver (functional and oncological) disease and the physiological age of patients needed to be assessed before surgery[19-20] to better stratifying patients at risk and to implement preoperative and postoperative programs of rehabilitation which could bridge the gap of physiopathological state[21].

However, this study had some limitations. First of all, because of its retrospective nature, there was a possibility of an unavoidable selection bias. Secondly, the surgical procedures included were laparoscopic and open approach without considering their different impact on the postoperative outcomes. In addition, our aim was to evaluate 90 and 180 d mortality but another key point was represented by postoperative complications and their correlations with preoperative and intraoperative data. This could be the focus for future works.

CONCLUSION

In conclusion, our score resulted from granular evaluation of possible risk factors for the postoperative mortality at 90 d and 180 d in elderly patients resected for HCC.

It would be a simple and useful tool to provide a better cognition of patients who could benefit of liver resection and to improve 180 d mortality.

ARTICLE HIGHLIGHTS

Research background

Liver resection represented one of the mainstay treatment for hepatocellular carcinoma (HCC). The approach of liver disease in elderly population needed of an accurate stratification of patients at risk, with the involvement of multidisciplinary preoperative assessment.

Research motivation

Liver resection is burdened by a variable rate of postoperative morbidity and mortality. Elderly patients represented more often the major rate of patients who underwent liver resection for HCC. This aspect makes mandatory an accurate preoperative assessment and a specific evaluation of potential postoperative risk.

Research objectives

The aim of our study was to analyze a population of elderly patients who underwent liver resection for HCC, to investigate the possible presence of risk predictors of postoperative mortality at 90 and 180 d.

Research methods

Associations between baseline pre-operative variables with six-month mortality were evaluated using a unit-variate Cox proportional-hazards model. A score point system was derived from the multi-variable Cox proportional-hazards model.

Research results

The American Society of Anesthesiology (ASA) score, Mayo end stage liver disease score, the presence of comorbidities > 2 and the size of the biggest lesion are included in the stratification of the score. Combining the four variables we obtained different profiles of patients with a different preoperative risk at 6 mo: Low-risk < 5%, mid-risk 5%-10% and high-risk class > 10%.

Research conclusions

This score can aid in stratifying this population in order to assess who can benefit from surgical treatment in terms of postoperative mortality.

Research perspectives

Randomized controlled studies are needed to better explore these results.

FOOTNOTES

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Institutional review board statement: This study does not require approval from the hospital ethics committee.

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.

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ORIGINAL ARTICLE

Observational Study

Serum omentin-1 is correlated with the severity of liver disease in patients with chronic hepatitis C

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Abstract

BACKGROUND

Patients with chronic hepatitis C virus (HCV) infection have increased serum omentin-1. Omentin-1 is an anti-inflammatory adipokine, and higher levels may be a direct effect of HCV infection. Successful elimination of HCV by direct acting antivirals almost normalized circulating levels of various molecules with a role in inflammation.

AIM

To evaluate the effect of HCV infection on serum omentin-1, serum omentin-1 levels of HCV patients were measured before therapy and at 12 wk after therapy end. Associations of serum omentin-1 with parameters of inflammation and liver function were explored at both time points. Serum omentin-1 levels of patients with and without liver cirrhosis, which was defined by ultrasound or the fibrosis-4 (FIB-4) score, were compared.

METHODS

Serum omentin-1 levels were measured by enzyme-linked immunosorbent assay in 84 chronic HCV patients before therapy and at 12 wk after therapy end where sustained virological response 12 (SVR12) was achieved in all patients. Serum omentin-1 of 14 non-infected controls was measured in parallel.

RESULTS

In patients with chronic HCV, serum omentin-1 levels were not related to viral load or viral genotype. HCV patients with liver steatosis and HCV patients with

diabetes had serum omentin-1 levels comparable to patients not suffering from these conditions. Serum omentin-1 levels at SVR12 were similar in comparison to pretreatment levels. In addition, serum levels did not differ between HCV-infected patients and non-infected controls. Serum omentin-1 levels did not correlate with leukocyte count or C-reactive protein. Positive correlations of serum omentin-1 with bilirubin and the model for end-stage liver disease score (MELD) were detected before therapy and at SVR12 in the whole cohort. Bilirubin and the MELD score also positively correlated with serum omentin-1 levels in the subgroup of patients with ultrasound diagnosed liver cirrhosis before therapy. At SVR12, serum omentin-1 levels of patients with liver cirrhosis negatively correlated with albumin. Before therapy start, patients with high FIB-4 scores had increased serum omentin-1 in comparison to patients with a low score. Serum omentin-1 levels of patients with liver cirrhosis defined by ultrasound were increased at baseline and at SVR12.

CONCLUSION

Present study showed that liver cirrhosis, but not HCV infection per se, is related to elevated serum omentin-1 levels.

Key Words: Direct acting antivirals; Hepatitis C; Liver cirrhosis; Adipokine

Core Tip: Omentin-1 is an adipokine well described for its anti-inflammatory and insulin-sensitizing functions. Aim of this study was to identify the effect of hepatitis C virus (HCV) infection and liver cirrhosis on serum omentin-1 levels. This study showed that circulating omentin-1 levels of HCV infected patients and non-infected healthy controls were similar. Accordingly, serum omentin-1 levels did not change upon effective elimination of the virus by direct acting antiviral therapy. Serum omentin-1 was not associated with diabetes or C-reactive protein in the HCV cohort. Patients with liver cirrhosis had increased serum omentin-1 levels before treatment and at sustained virological response 12 in comparison to HCV patients without liver cirrhosis. This analysis shows that increased serum omentin-1 levels of chronic HCV patients with liver cirrhosis persist after viral elimination. Serum omentin-1 has no role in the favourable metabolic outcomes of HCV eradication.

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INTRODUCTION

Chronic infection with hepatitis C virus (HCV) causes systemic and hepatic inflammation, which drive the development and progression of liver fibrosis[1,2]. Highly effective elimination of HCV by direct acting antivirals (DAAs) rapidly improves inflammation and circulating levels of various cytokines and chemokines decline[3-5]. Interestingly, levels of pro- as well as anti-inflammatory cytokines were reduced shortly after start of DAA therapy[3-6]. Regression of liver fibrosis after HCV cure is possible, and complete reversal is expected to take several years[7]. Non-invasive tests for scoring of liver fibrosis are sonographic shear-wave elastography and transient elastography, and improvement of these measures at sustained virological response 12 (SVR12) or SVR24 is correlated with the resolution of liver inflammation[4,8]. The fibrosis-4 (FIB-4) score is calculated from age, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) as well as platelet number, and was found accurate to assess advanced liver fibrosis in patients with HCV[9]. ALT and AST levels rapidly decline after start of DAA therapy, and lower FIB-4 scores at SVR12 are attributable to reduced hepatic inflammation[4,10].

Omentin-1 was first described as intelectin-1, a protein expressed in the intestine, which recognizes complex carbohydrates of bacterial cell walls. Later on, omentin-1 was shown to be highly expressed by stromal vascular cells of visceral adipose tissues. Omentin-1 protects from oxidative stress and exerts anti-inflammatory effects in macrophages, endothelial cells and adipocytes[11]. Omentin-1 serum levels are decreased in obesity and negatively correlate with fasting insulin levels[12]. There is convincing evidence that low serum omentin-1 levels in obesity contribute to impaired insulin signalling and insulin resistance[12-14].

Insulin resistance in chronic HCV infection is common, but the underlying mechanisms are not fully understood. HCV-infected patients with elevated aminotransferase levels also had increased serum omentin-1. In this cohort, HCV patients with type 2 diabetes had lower serum omentin-1, which was negatively correlated with the homeostasis model assessment of insulin resistance (HOMA-IR) index and fasting insulin levels[15]. Serum omentin-1 concentrations of HCV patients with liver cirrhosis stratified by a HOMA-IR index below and above 2.5 were, however, similar[16]. Insulin resistance is associated with liver steatosis, which was not related to altered serum omentin-1 levels. Moreover, there was

no correlation of serum omentin-1 levels with liver inflammation grades[16,17].

However, patients with alcoholic liver cirrhosis and patients with HCV-related liver cirrhosis had increased serum omentin-1 levels in comparison to healthy controls[17,18]. No significant differences in omentin-1 serum levels were found regarding the severity of liver cirrhosis assessed by the model of end stage liver disease (MELD) score or Child-Pugh score[18,19]. Accordingly, another study could not observe associations of serum omentin-1 levels with histologically scored fibrosis stages in patients with HCV[17]. In contrast, it was also reported that HCV patients with advanced liver fibrosis, which was histologically scored, had higher serum omentin-1 levels in comparison to those patients with a lower score[16].

Current studies suggest that serum omentin-1 is increased in chronic HCV, but whether this is caused by viral infection or related to liver disease severity has not been clarified to date. Aim of this study was to examine the effect of efficient virus elimination by DAA therapy on serum omentin-1 levels and to describe associations of serum omentin-1 levels with measures of liver disease severity.

MATERIALS AND METHODS

Study cohort

This prospective study included patients with chronic HCV from September 1, 2014 to February 27, 2017, and was conducted at the Department of Internal Medicine I at the University Hospital Regensburg. Patients with an indication for therapy with DAAs (drug combinations used were sofosbuvir/daclatasvir, sofosbuvir/ledipasvir, sofosbuvir/velpatasvir, glecaprevir/pibrentasvir, or elbasvir/grazoprevir) according to recent guidelines participated in the study [20]. The patients were older than 18 years, and had not been treated for HCV before. Patients with decompensated liver cirrhosis, hepatitis B virus or human immunodeficiency virus co-infection were excluded. The 14 controls were patients not infected with HCV, and without any severe diseases such as liver cirrhosis. This group included eight females and six males. Age was 63 (38-87) years and body mass index (BMI) was 26.9 (17.8-43.4) kg/m^2, and both measures were similar to the patient cohort ($P > 0.05$ for all).

The study protocol was approved by the ethical committee of the University Hospital of Regensburg (14-101-0049, date of approval May 22, 2014) and was performed according to the updated guidelines of good clinical practice and updated Declaration of Helsinki. Informed consent was obtained from all patients. Laboratory measures were provided by the Institute of Clinical Chemistry and Laboratory Medicine, University Hospital Regensburg.

Ultrasound examination and calculation of fibrosis-4 score

Cirrhosis diagnosis by ultrasound relied on nodular liver surface, small liver size, and coarse liver parenchyma[21]. The FIB-4 score is an accepted non-invasive fibrosis score[22]. Cut-off values for the FIB4-score were: fibrosis > 3.25, no fibrosis: < 1.3 for patients < 65 years, and < 2 for patients older than 65 years[23].

Omentin-1 enzyme-linked immunosorbent assay

Serum aliquots were stored at -80 °C and thawed immediately before being used. Serum was used undiluted for omentin-1 measurement with the Human Intelectin-1/Omentin DuoSet enzyme-linked immunosorbent assay (R&D Systems; Catalog #: DY4254-05; Wiesbaden-Nordenstadt, Germany).

Measurement of IL-6 and IL-10

Levels of the cytokines interleukin (IL)-6 and IL-10 were quantified using Multiplex Luminex® Assays (Merck, KGaA, Germany) as described before[4].

Statistical analysis

Data are shown as boxplots, which represent the minimum value, the maximum value, the median, the first quartile and the third quartile. Small circles and asterisks above the boxes are outliers. Data in tables are given as median value, and the minimum value and the maximum value are listed in brackets. The non-parametric Mann-Whitney U test and Kruskal-Wallis test were used for comparison of two or more independent groups, respectively (SPSS Statistics 26.0 program). Students' *t*-test (Ms Excel) was used for analysis of paired data and Spearman correlation for correlation analysis (SPSS Statistics 26.0 program). A value of $P < 0.05$ was regarded significant.

RESULTS

Association of serum omentin-1 levels with age, body mass index, gender, liver steatosis and diabetes in patients with chronic HCV infection

Eighty-four patients with chronic HCV infection (Table 1) and 14 non-infected controls were included in the study. Serum omentin-1 levels of controls and HCV patients were similar (Figure 1A). In the HCV cohort, serum omentin-1 levels of females and males were comparable (Figure 1B). Associations of serum omentin-1 with the BMI (r = -0.082, P = 0.486) or age (r = 0.092, P = 0.408) were not identified. The 15 diabetic HCV patients had similar omentin-1 serum levels in comparison to the non-diabetic HCV patients (Figure 1C). Ten of the patients with diabetes had liver cirrhosis, as was

Table 1 Gender distribution, age, body mass index, model for end stage liver disease score, and laboratory parameters of the 84 patients before therapy start

Parameter	Before therapy	Patients at SVR12
Gender (F/M)	37/47	36/42
BMI kg/m^2	26.5 (18.4-40.4)	26.8 (18.4-40.4)
Age yr	56 (24-82)	57 (24-82)
MELD score	7 (6-19)	7 (6-19)
ALT U/L	70 (22-247)	26 (6-135)[c]
AST U/L	64 (14-1230)	23 (10-1390), *n* = 76[c]
Bilirubin mg/dL	1.0 (1.0-4.3)	1.0 (1.0-2.8)
Albumin g/L	37.3 (19.0–45.5), *n* = 83	39.1 (26.1-47.7)[c]
INR	1.1 (1.0-2.3)	1.1 (1.0-2.8)
Creatinine mg/dL	1.0 (1.0-1.3)	1.0 (1.0-1.4)
GFR ml/min	98 (47-161)	94 (52–129)
Leukocyte number/L	6.1 (2.2-12.3)	6.2 (1.9-38.6), *n* = 77
CRP mg/L	2.9 (2.9-29.9)	2.9 (2.9-20.4)
PCT ng/mL	0.08 (0.01–11.02), *n* = 83	0.04 (0.01-0.15)[c]
Platelet number/nL	157 (38-364)	171 (38-312), *n* = 77
HDL mg/dL	52 (19-103), *n* = 78	51 (23-100), *n* = 71
LDL mg/dL	91 (31-204), *n* = 78	117 (38-243), *n* = 70[c]

[c]*P* < 0.001.

Data of the 78 patients where serum was available at SVR12 are also listed. In the case that laboratory values were not obtained of all patients, the number (*n*) of patients of whom these measures were known is given. ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BMI: Body mass index; CRP: C-reactive protein; GFR: Glomerular filtration rate; HDL: High density lipoprotein, INR: International normalized ratio; LDL: Low-density lipoprotein; MELD: Model for end stage liver disease; PCT: Procalcitonin.

diagnosed by ultrasound imaging. In the cirrhosis group diabetic and non-diabetic patients had comparable serum omentin-1 levels (P = 1.00). Thirty-eight patients of the HCV cohort had liver steatosis but serum omentin-1 did not differ from patients without liver steatosis (Figure 1D).

Associations of serum omentin-1 with viral load and genotype in patients with HCV

Serum omentin-1 was not related to viral load (r = -0.100, P = 0.364). HCV genotypes were 1a (22 patients), 1b (39 patients) and 3a (15 patients), and rare genotypes (8 patients) were assigned to one group. Serum omentin-1 levels did not vary between HCV genotypes (Figure 1E).

Correlations of serum omentin-1 levels with measures of inflammation and liver function before and after DAA treatment

In the whole cohort, serum omentin-1 levels positively correlated with the MELD score (r = 0.428, P < 0.001), bilirubin (r = 0.435, P < 0.001), international normalized ratio (INR) (r = 0.380, P < 0.001) and procalcitonin (r = 0.365, P = 0.001), and negatively with platelet number (r = -0.303, P = 0.005), albumin (r = -0.297, P = 0.006) and low density lipoprotein (LDL) (r = -0.426, P < 0.001). Partial correlation of serum omentin-1 with LDL controlled for the MELD score was not significant (P = 0.075). Serum omentin-1 levels did not correlate with creatinine (r = 0.176, P = 0.107) or glomerular filtration rate (r = -0.042, P = 0.705).

DAA therapy cleared HCV effectively and viral load was significantly reduced at four weeks after therapy start and at SVR12 (P < 0.001 in comparison to pre-treatment levels)[24]. At SVR12, ALT, AST, ferritin and procalcitonin were declined, and albumin and LDL were increased in contrast to levels before therapy (Table 1). Serum omentin-1 levels did not change during therapy (Figure 2).

Associations between serum omentin-1 and most of the clinical markers of liver disease severity persisted at SVR12. Serum omentin-1 levels correlated with the MELD score (r = 0.314, P = 0.005), bilirubin (r = 0.435, P < 0.001), albumin (r = -0.255, P = 0.025), INR (r = 0.293, P = 0.009) and LDL (r = -0.265, P = 0.027). Partial correlation of omentin-1 and LDL corrected for the MELD score was not significant (P = 0.625).

Serum omentin-1 did not correlate with creatinine (r = 0.047, P = 0.685) or glomerular filtration rate (r = -0.112, P = 0.334).

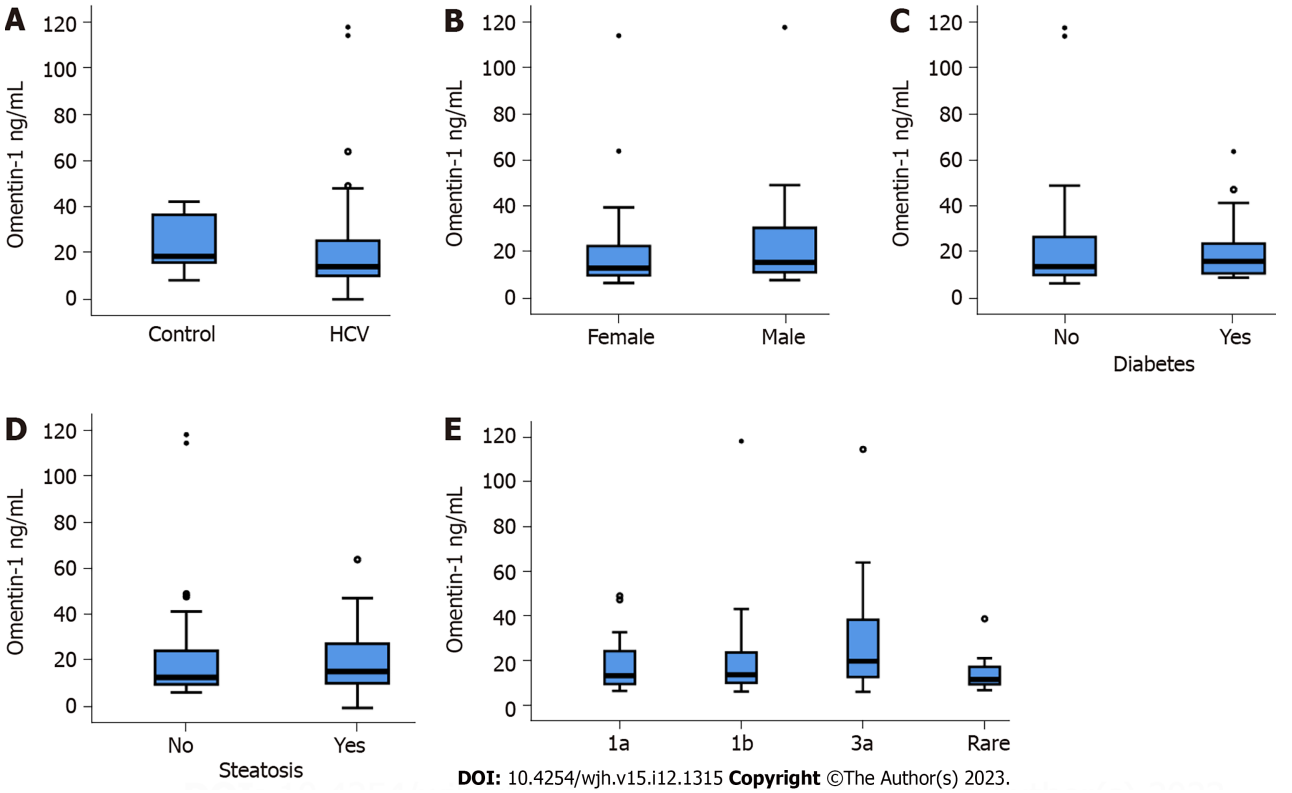

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Figure 1 Serum omentin-1 levels of controls and patients with chronic hepatitis C virus. A: Serum omentin-1 Levels of 14 controls and 84 patients with chronic hepatitis C virus (HCV); B: Serum omentin-1 levels of 37 female and 47 male HCV patients; C: Serum omentin-1 levels of 15 patients with and 69 patients without diabetes; D: Serum omentin-1 levels of 38 patients with and 46 patients without steatosis; E: Serum omentin-1 levels of patients categorized for HCV genotype (Rare group signifies 8 patients with genotypes other than 1a, 1b, and 3a). The small circles or asterisks above the boxes mark outliers.

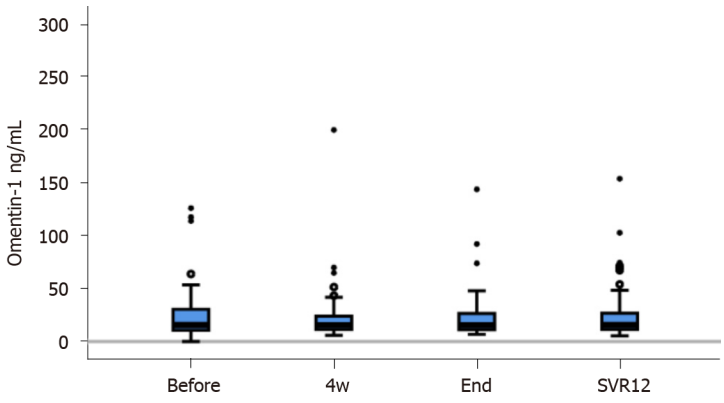

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Figure 2 Serum omentin-1 levels during direct acting antiviral therapy. Omentin-1 serum levels before therapy start (Before), at 4 wk after therapy start (4w), at therapy end (End) and at sustained virological response 12 (SVR12). Small circles or asterisks above the boxes mark outliers.

Serum omentin-1 did not correlate with leukocyte count (r = -0.205, P = 0.061), C-reactive protein (r = 0.117, P = 0.290), IL-6 (0.022, P = 0.113) or IL-10 (r = -0.138, P = 0.218) levels before DAA therapy. At SVR12 no significant associations between serum omentin-1 with leukocyte count (r = -0.093, P = 0.423), C-reactive protein (r = -0.098, P = 0.394), IL-6 (r = 0.067, P = 0.578) or IL-10 (r = 0.225, P = 0.058) were found.

Serum omentin-1 in relation to non-invasive measures of liver fibrosis

Before therapy, the 31 patients with liver cirrhosis diagnosed by ultrasound examination had higher omentin-1 (Figure 3A). The FIB-4 index for non-invasive scoring of liver fibrosis indicated higher omentin-1 serum levels of patients with advanced liver fibrosis in comparison to patients with low and intermediate scores (Figure 3B). Positive correlations with the MELD score (r = 0.375, P = 0.031) and bilirubin (r = 0.481, P < 0.005), and a negative correlation with LDL (r = -0.626, P < 0.001) were observed in the sub-cohort of the 31 patients with ultrasound diagnosed liver cirrhosis before therapy.

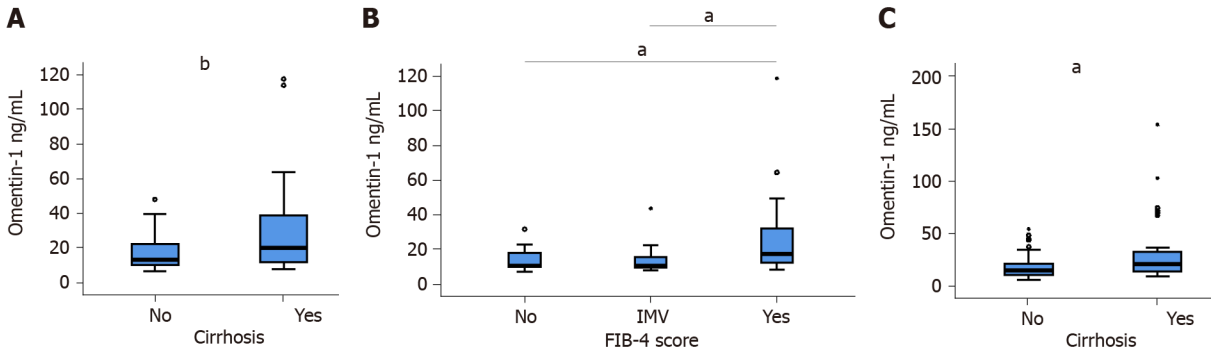

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Figure 3 Serum omentin-1 in relation to liver fibrosis. A: Serum omentin-1 levels of hepatitis C virus (HCV) patients with liver cirrhosis and non-cirrhotic patients, which was diagnosed by ultrasound before therapy; B: Serum omentin-1 levels of HCV patients categorized according to the fibrosis-4 score (26 patients no fibrosis = No; 18 patients had intermediate values = IMV, 40 patients had fibrosis = Yes) before therapy; C: Serum omentin-1 levels of HCV patients without and with liver cirrhosis, which was diagnosed by ultrasound, at sustained virological response 12 (SVR12). Small circles and stars above the boxes mark outliers. [a]*P* < 0.05, [b]*P* < 0.01.

AT SVR12, in the subgroup of patients with ultrasound diagnosed liver cirrhosis, a negative correlation of albumin and serum omentin-1 was detected (r = -0.436, P = 0.018). Serum omentin-1 levels of patients with cirrhosis were higher in contrast to HCV patients without cirrhosis at SVR12 (Figure 3C).

DISCUSSION

Here, we have shown that serum omentin-1 is increased in HCV patients with advanced liver fibrosis. HCV infection per se did not affect serum omentin-1 levels, which were not related to viral titer or genotype, did not decline upon efficient elimination of HCV and were similar among HCV patients and non-infected controls.

In our previous study we have measured serum omentin-1 levels of patients with liver cirrhosis[18], and the 37 patients with alcoholic liver cirrhosis and the 3 patients with HCV related cirrhosis had similar levels (P = 0.693). Though the number of patients with HCV caused cirrhosis was small, this finding is in accordance with the assumption that HCV infection has no effect on serum omentin-1 levels.

Omentin-1 is best described for its role as an insulin-sensitizer[11,12]. Serum omentin-1 was, however, similar between diabetic and non-diabetic HCV patients in accordance with previous studies. It has been shown before that patients with liver cirrhosis and diabetes had similar omentin-1 levels in comparison to non-diabetic cirrhosis patients[19]. In addition, chronic HCV patients with a high HOMA-IR index had omentin-1 levels comparable to patients with a low index[16]. In apparently healthy cohorts, serum omentin-1 correlated negatively with the HOMA-IR index[14,25], and this association seems to be lost in chronic HCV.

HCV infection can promote diabetes and liver steatosis[26]. Metabolic dysfunction–associated fatty liver disease (MAFLD) is relatively common in the general population, and accordingly, is abundant in patients with HCV[27]. MAFLD is associated with insulin resistance, and reduced levels of circulating omentin-1[11,28]. In the HCV cohort, serum omentin-1 levels of patients with hepatic steatosis did not change. The diagnosis of MAFLD in patients with HCV infection is, however, challenging[27] and virus-induced fatty liver was not discriminated from metabolic liver steatosis in our study. Therefore, we can only conclude that liver steatosis either caused by HCV and/or by metabolic dysfunction is not related to changed serum omentin-1 levels.

HCV is classified into eight genotypes and more than 80 subtypes[29]. Most prevalent in Europe is HCV genotype 1 and the subtypes 1a and 1b[30], and 61 of our patients were infected by 1a or 1b. The second most prevalent genotype in our study cohort was 3a. HCV genotypes differ in their clinical features, and insulin resistance and liver steatosis are more common in genotype 1 and 3 infection[31]. Serum omentin-1 levels of patients infected with genotype 1a, 1b or 3a were, however, similar.

In accordance with previous data[16], serum omentin-1 levels were not associated with viral load. Highly efficient elimination of HCV by DAA treatment had no effect on the circulating levels of omentin-1. This indicates that hepatic and systemic inflammation caused by HCV infection[4] do not change serum omentin-1 levels. In line with this suggestion the current analysis showed that serum omentin-1 levels of HCV patients and controls were similar.

HCV patients with advanced liver fibrosis had increased serum omentin-1 levels when liver fibrosis was assessed by the non-invasive FIB-4 score or diagnosed by ultrasound. Higher concentrations of omentin-1 have been described in HCV patients with liver cirrhosis in comparison to healthy controls[17,18]. Current findings suggest that severe liver disease and not viral infection is the cause of increased serum omentin-1 levels.

Serum omentin-1 levels did, however not increase with higher Child-Pugh scores and did not correlate with the MELD score in patients with mostly alcoholic liver cirrhosis[18]. In our HCV patients with liver cirrhosis, serum omentin-1 levels did not correlate with the MELD score at SVR12. At this time, there was an association between serum omentin-1 and albumin, a biomarker for impaired hepatic function. Small cirrhosis cohorts and relatively weak associations between

serum omentin-1 levels and laboratory measures of liver disease may prevent the observation of significant associations. Future research has to identify the causes for higher serum omentin-1 levels in patients with advanced liver fibrosis.

LDL of patients with liver cirrhosis is reduced[32-34], and negative correlation of serum omentin-1 levels with LDL is in this context. Negative associations of serum omentin-1 and LDL have been reported in healthy controls[35] and this finding is in line with the beneficial metabolic effects of this adipokine[11]. In HCV infection and at SVR12 the protective effects of omentin-1 against dyslipidemia could not be observed.

Increased serum omentin-1 levels of patients with advanced liver disease may originate from visceral adipose tissues with high omentin-1 expression[11]. It has been also suggested that impaired hepatic clearance of serum omentin-1 by the damaged liver contributes to higher serum levels[18]. Serum omentin-1 levels of patients with chronic HCV were not correlated with the hepatic mRNA expression of omentin-1[17], indicating that omentin-1 synthesis in the liver plays a minor role for systemic omentin-1 levels. Further study is needed to clarify the origin of higher serum omentin-1 in patients with liver cirrhosis.

Patients with end-stage renal disease had elevated serum omentin-1[36] indicating renal excretion of omentin-1. In the current analysis, which included patients with normal and slightly reduced glomerular filtration rates, associations between serum omentin-1 levels and markers for kidney function such as creatinine or glomerular filtration rates were not observed [37] This shows that minor renal dysfunction has no role for higher serum omentin-1 levels in HCV patients with liver cirrhosis.

Induction of omentin-1 levels of patients with liver cirrhosis is in agreement with studies on serum adiponectin levels, an anti-inflammatory adipokine functioning as an insulin sensitizer, whose circulating levels also decline in obesity[38, 39]. Serum adiponectin levels of patients with HCV, hepatitis B virus and MAFLD related liver cirrhosis were increased [40]. In these patient cohorts, circulating levels of adiponectin were not associated with BMI or markers of insulin sensitivity[41]. These findings suggest that adiponectin does not exert its protective roles in liver cirrhosis as seems to be the case for omentin-1.

A limitation of this study is that Child-Pugh scores were not included. Early guidelines commenting on treatment in patients with decompensated liver cirrhosis, who have Child-Pugh B or C, did not recommend the use of DAAs for these patients[42]. Our cohort was recruited shortly after these drugs were approved, and patients with decompensated cirrhosis were excluded. The Child-Pugh score of our cohort was not determined but from the clinical data of our patients we assume that most of them had Child-Pugh score A.

CONCLUSION

In summary, the current analysis showed that higher serum omentin-1 levels in chronic HCV infection is not a marker of metabolic health but rather indicates advanced liver fibrosis.

ARTICLE HIGHLIGHTS

Research background

Hepatitis C virus (HCV) infection can cause severe liver damage. Chronic HCV infection can be cured with direct acting antiviral therapy, which also decreases insulin resistance. Omentin-1 is regarded a beneficial adipokine and improves insulin resistance. Serum omentin-1 levels are increased in HCV infection. The effect of viral cure on serum omentin-1 levels has not been analysed as far as we know. Moreover, data regarding associations of omentin-1 with liver injury are discordant.

Research motivation

From a pathophysiological standpoint, it can be important to evaluate associations of serum omentin-1 levels with HCV infection and liver disease severity.

Research objectives

The objective of this study was to assess the effect of HCV clearance on serum omentin-1 levels, and to evaluate associations of serum omentin-1 levels with clinical markers of inflammation, liver steatosis, diabetes and liver dysfunction.

Research methods

This observational study included 84 patients with chronic HCV, and collected serum before therapy, at 4 wk after therapy start, at therapy end and at sustained viological response 12 (SVR12). Serum omentin-1 was measured by enzyme-linked immunosorbent assay. Serum omentin-1 levels of 14 controls were also determined.

Research results

The study found evidence of increased serum omentin-1 levels in patients with liver cirrhosis. HCV elimination did not change serum omentin-1 levels, suggesting that viral infection has no effect on serum omentin-1.

Research conclusions

Effective elimination of HCV is associated with favourable metabolic outcomes. This study indicates that omentin-1 has no role herein. Serum omentin-1 of HCV patients with liver cirrhosis is increased at baseline and SVR12, and may have a role in liver cirrhosis pathogenesis.

Research perspectives

Evaluation whether increased serum omentin-1 is just a marker of impaired liver function or contributes to liver damage.

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FOOTNOTES

Author contributions: Peschel G, Weigand K and Buechler C were the guarantors and designed the study; Peschel G, Weigand K and Grimm J participated in the acquisition of the serum samples; Buechler C participated in the analysis, and interpretation of the data, and drafted the initial manuscript; Peschel G, Weigand K, Grimm J, Müller M and Buechler C revised the article critically for important intellectual content.

Institutional review board statement: The study protocol was approved by the ethical committee of the University Hospital of Regensburg (14-101-0049, date of approval: May 22, 2014).

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ORIGINAL ARTICLE

Prospective Study

High incidence of periodontitis in patients with ascitic decompensated cirrhosis

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Abstract

BACKGROUND

Periodontitis has been associated with various liver diseases. However, the relevance of periodontitis in the progression of decompensated cirrhosis remains inconclusive. In particular, it is unclear whether the common periodontitis pathogens, *Porphyromonas gingivalis* (*P. gingivalis*) and *Actinobacillus actinomycetemcomitans* (*A. actinomycetemcomitans*), can be detected not only in the oral mucosa but also in ascites and stool.

AIM

To investigate the significance of periodontitis, *P. gingivalis*, and *A. actinomycetemcomitans* in cirrhosis patients with ascitic decompensation.

METHODS

This prospective study was conducted at the University Hospital Hamburg-

Eppendorf, a tertiary center in Northern Germany. A cohort of 27 patients with ascitic decompensated liver cirrhosis underwent dental examinations to assess the association between periodontitis and various clinical parameters of cirrhosis, as well as patient outcomes. PCR was used to test gingival samples, ascites, and stool for the presence of *P. gingivalis* and *A. actinomycetemcomitans*. Gingival samples were collected by probing the deepest gum pocket of a sextant and wiping them on a cotton swab.

RESULTS

Periodontitis was diagnosed in 22 out of 27 (82%) ascite patients, which is significantly more common than in a control cohort of 100 unselected patients (59%, $P = 0.04$). *P. gingivalis* was detected in the gingiva of six patients, and one of them also had *P. gingivalis* in their stool. However, *P. gingivalis* was not found in the ascites of any patient. Five out of six patients with *P. gingivalis* had periodontitis (83%). *A. actinomycetemcomitans* was not detected in any sample. Patients without periodontitis had a significantly higher mortality rate compared to those with periodontitis, and survival (Kaplan-Meier analysis) was longer in patients with periodontitis ($P = 0.02$). Transplant-free survival was also more common in patients with periodontitis compared to those without (63% *vs* 0%, $P = 0.02$).

CONCLUSION

Decompensated cirrhotic patients frequently suffer from periodontitis. However, there was no evidence of the translocation of *P. gingivalis* or *A. actinomycetemcomitans* into ascites. The survival of cirrhotic patients with periodontitis was not reduced.

Key Words: Cirrhosis; Ascites; Decompensation; Periodontitis; Survival; Gingiva

Core Tip: In this prospective cohort study, we aimed to assess the prevalence of periodontitis and the potential dissemination of classical periodontitis pathogens into ascites among 27 cirrhotic patients experiencing ascitic decompensation. We also compared this group with 100 unselected patients from a dental practice. Our findings revealed that decompensated cirrhotic patients often experience periodontitis. However, we did not observe any evidence of the translocation of *Porphyromonas gingivalis* or *Actinobacillus actinomycetemcomitans* into ascites. Furthermore, the presence of periodontitis did not appear to have a detrimental effect on the survival of cirrhotic patients.

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INTRODUCTION

Cirrhosis, the final stage of chronic liver disease, is a very serious condition associated with a significantly reduced life expectancy[1]. One of its most threatening complications is spontaneous bacterial peritonitis (SBP)[1,2]. It is assumed that bacteria from the intestinal flora migrate into the abdominal cavity and multiply in the ascites. In contrast, secondary bacterial peritonitis in patients with portal hypertension is caused by an abdominal source of infection, such as an abscess or perforation. Secondary bacterial peritonitis is much less common than SBP, accounting for approximately 15% of all peritonitis cases. It carries a 20% risk of mortality[3].

SBP is defined as the presence of more than 250 polymorphonuclear cells, specifically neutrophil granulocytes, per mm^3 in ascites[4]. Gram-negative bacteria, commonly found in the intestine, are the primary pathogens associated with SBP. The extent to which colonization of the oral flora contributes to the occurrence of SBP and whether bacteria from the oral cavity can enter the ascites through the intestinal tract and migration remain unclear.

Periodontitis, an inflammation of the gingiva, has garnered increasing interest over the past two decades. The presence of periodontitis has been linked to systemic inflammation. Animal experiments in mice have demonstrated a connection between periodontitis and the development of liver fibrosis[5].

Porphyromonas gingivalis (*P. gingivalis*), one of the most significant periodontal pathogens, is believed to enter the bloodstream through the oral mucosa, potentially leading to the release of various cytokines. Apart from direct translocation of *P. gingivalis* into the bloodstream through damaged gingiva with reduced barrier function, this bacterium can also easily move from the oral cavity to the intestine. It can be envisioned that the disruption of the intestinal microbiota composition by orally derived *P. gingivalis* may contribute to the gut-liver axis and the pathogenesis of SBP[6,7]. However, this aspect has not been thoroughly investigated.

The relevance of periodontitis has been studied in various patient cohorts with liver disease, including those with cirrhosis. A 1995 Vienna study involving 97 cirrhotic patients, including 64 with alcoholic cirrhosis and 33 with non-alcoholic cirrhosis, revealed that alcohol-dependent cirrhosis, but not cirrhosis in general, was associated with reduced oral hygiene ($P < 0.01$), decreased dental care ($P < 0.001$), the presence of periodontitis, and the need for dental treatment ($P < 0.001$)[8]. A study conducted in the United States prospectively examined whether periodontitis treatment influenced the oral-gut-hepatic axis in cirrhosis patients[9]. In this study, the impact of periodontal therapy was assessed in 26 cirrhotic patients receiving treatment compared to 24 cirrhotic patients without periodontitis therapy. Over an observational period of 30 d, the treated cirrhosis group exhibited improvements in dysbiosis in stool and saliva, as well as reductions in endotoxin and lipopolysaccharide-binding protein levels.

Additionally, both periodontitis and cirrhosis have the potential to trigger an inflammatory response and generate inflammatory mediators, which may enable them to mutually influence each other. In several patient cohorts, individuals with cirrhosis have been observed to exhibit poorer periodontal clinical parameters compared to those without cirrhosis [6].

Some studies have suggested a potential connection between periodontitis and liver diseases, including cirrhosis. It is theorized that the inflammatory responses associated with periodontitis may contribute to the development of liver diseases like cirrhosis. Chronic inflammation in the body can result in liver cell damage and expedite the progression of liver diseases.

However, it is crucial to emphasize that further research is required to fully comprehend and clarify the relationship between periodontitis and liver diseases such as cirrhosis.

These observations naturally raise the question of whether *P. gingivalis* also contributes to the development of SBP and whether this pathogen can be detected in ascites.

To investigate whether *P. gingivalis* and *Actinobacillus actinomycetemcomitans* (*A. actinomycetemcomitans*), bacteria typically associated with periodontitis, can be detected in ascites, we conducted a prospective study examining oral mucosal samples, ascites specimens and stool specimens for the presence of *P. gingivalis*. Mucosal samples were collected by penetrating the deepest gum pocket of a sextant and swabbing the area, followed by PCR testing. Additionally, we explored whether dental factors such as the detection of these bacteria, the presence of periodontitis, the number of teeth, and other variables were associated with the outcomes of patients with end-stage liver cirrhosis.

MATERIALS AND METHODS

Patients

In this prospective study, we invited all adult cirrhosis patients who required paracentesis at the University Hospital Hamburg-Eppendorf in Hamburg, Germany, between March 2021 and July 2021 to participate. This cohort comprises both inpatients and outpatients experiencing ascitic decompensation. Twenty-seven patients agreed to participate, provided written informed consent, and were subsequently enrolled in this study. Among these participants, 27 were afflicted with ascitic decompensation attributable to liver cirrhosis. The diagnosis of cirrhosis had previously been established based on clinical criteria in conjunction with liver elastography results and biopsies.

To assess patient follow-up, we conducted a review of medical records in January 2023. It is important to note that there were no interventions by the investigators between the time of study inclusion and this evaluation. Given that all patients were well-documented cases of end-stage liver cirrhosis under the care of our university hospital, we had access to comprehensive records maintained by the treating physicians.

An intraoral examination, encompassing a full mouth assessment, including the assessment of bleeding on probing, was conducted by a proficient dental medicine student (Ashouri MM under the supervision of the head of the Department of Periodontics, Preventive and Restorative Dentistry (author Beikler T). This comprehensive intraoral examination encompassed the evaluation of dental status, including the number of teeth, mucosal health, and oral hygiene, as measured by the sulcus bleeding index. The grading of periodontal disease was carried out in accordance with the guidelines and recommendations established by the European Federation of Periodontology/Oral Reconstruction and Rehabilitation[10].

All patients underwent a standardized interview and completed a questionnaire, which inquired about various parameters, including the frequency of their dental visits and their smoking habits.

To assess the prevalence of periodontitis in a control group unaffected by cirrhosis, we included 100 unselected patients from a typical dental practice as our control cohort. These patients were retrospectively studied and anonymized to protect their privacy. The control group comprised individuals who had undergone standardized periodontitis screening at a regular dental practice in Hamburg. Basic demographic information, such as age, sex, and periodontal status, was retrospectively analyzed for these anonymized patients in accordance with our local regulations and ethical guidelines. It is worth noting that this control cohort has been previously referenced in a prior publication[11].

Examinations

P. gingivalis was identified using species-specific PCR as previously described[12]. A probe was inserted into the deepest gum pocket of a sextant and then wiped onto a cotton swab, which was subsequently tested by PCR. Laboratory data and baseline patient characteristics, including alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin levels, age, clinical attachment loss – the most critical parameter for assessing periodontal tissue loss due to periodontal disease – the number of teeth, smoking status, and the patients' interest in dental medicine, were all recorded.

Statistical analysis

Continuous variables with a non-normal distribution were presented as the median and interquartile range. The distribution of these parameters among different groups was compared using the Mann-Whitney U-test. Categorical variables were expressed as numbers (%) and compared using Fisher's exact test. A significance level of $P < 0.05$ was used to determine statistical significance. Statistical analyses were conducted using SPSS, version 21.0 (IBM Corp., Armonk, NY, United States).

Ethical statement

This prospective study underwent review and received approval from the Ethics Committee of the Medical Council of Hamburg (PV-4081 and MC-368/18). The study adhered to the guidelines set forth in the Declaration of Helsinki. The retrospective analysis of the control cohort was conducted with complete anonymization, eliminating the need for further clarification or formal ethics committee approval in accordance with local laws and regulations.

RESULTS

In 22 out of 27 (82%) ascites patients, periodontitis was diagnosed. Characteristics of patients with periodontitis, in comparison with those without it, are presented in Table 1.

The age of the total cohort ranged from 37 to 76 years, with a median age of 57 years. Out of the total cohort, 15 individuals (56%) were male. Among the patients, nine (33%) had diabetes, and four (15%) were taking anticoagulants. Furthermore, 16 patients (59%) were diagnosed with alcoholic cirrhosis, five with non-alcoholic steatohepatitis (NASH) cirrhosis (19%), three (11%) had re-cirrhosis following liver transplantation, and one patient each (4%) had primary biliary cholangitis, hepatitis B virus (HBV), or hepatitis C Virus infections. Additionally, six patients had a Transjugular Intrahepatic portosystemic Shunt, and two patients had hepatocellular carcinoma (two with alcoholic liver cirrhosis, one with HBV, one with NASH). Notably, one of the patients with re-cirrhosis after transplantation had NASH as the underlying disease, another had primary sclerosing cholangitis, and one had alcoholic cirrhosis.

In order to assess the incidence of periodontitis in the cirrhosis cohort compared to the baseline incidence in the general population, we analyzed a retrospective cohort comprising 100 patients from a dental practice in Hamburg. This particular cohort has been previously described. Out of these subjects, 47 were male (47%), and their ages ranged from 17 to 89 years, with a median age of 51 years. Among these patients, 59 (59%) had periodontitis, a significantly lower rate than observed in the cirrhosis cohort, where the incidence was 82% ($P = 0.04$).

A notable finding was that a greater number of patients without periodontitis experienced mortality compared to those with periodontitis. Survival analysis using Kaplan-Meier methods indicated that patients with periodontitis had a longer survival duration compared to those without ($P = 0.02$, Figure 1). Additionally, transplant-free survival was more common among patients with periodontitis as opposed to those without (Table 1).

Among the patients, two had a complete set of teeth with no missing teeth (0/32), one patient had one missing tooth, two patients had three missing teeth, one patient had five missing teeth, six patients had six missing teeth, while one patient each had seven, eight, 13, 14, or 16 missing teeth. Additionally, three patients had ten missing teeth, two patients had 12 missing teeth, four patients had partial prostheses, and five patients were completely toothless and had total prostheses. Importantly, no association was found between the number of teeth and survival.

AST, ALT, bilirubin, and model for end-stage liver disease (MELD) scores showed no significant differences between patients with and without periodontitis (Table 1). Nonetheless, it is worth noting that there was a tendency towards a higher MELD score in patients without periodontitis, as depicted in Figure 2.

DISCUSSION

This study revealed a remarkably elevated incidence of periodontitis among cirrhotic patients (82%) when compared to healthy controls (59%, $P = 0.04$). This underscores the significance of regular dental check-ups for individuals with cirrhosis. Hepatologists should inquire explicitly about the dental care habits of their cirrhotic patients during medical history assessments and, if necessary, advocate for regular dental visits.

The identification of a substantial prevalence of periodontitis aligns with findings from a Danish study involving 262 cirrhotic patients. In this particular investigation, 46% ($n = 66$) exhibited severe periodontitis, 39% ($n = 55$) demonstrated moderate periodontitis, and only 15% ($n = 22$) displayed no or mild periodontitis[13]. Consequently, it is unequivocal that cirrhotic patients constitute a high-risk group for the development of periodontitis.

However, a far more critical question arises: whether periodontitis is correlated with reduced survival or transplant-free survival. In this regard, our study revealed that 63% of patients with periodontitis (12/22) survived without requiring transplantation, compared to 0% (0/5) of patients without periodontitis (Table 1, $P = 0.02$). Additionally, overall survival was superior among patients with periodontitis when compared to those without (Table 1, $P < 0.05$, Figure 1). Furthermore, there was a tendency toward higher MELD-score values in the five patients without periodontitis in contrast to the 22 patients with periodontitis (Figure 2). Hence, our preliminary study does not indicate worsened graft-free survival or a trend toward more severe liver damage (MELD score) in patients with periodontitis; in fact, it suggests slightly better outcomes. These findings diverge from a previously published study from Denmark[14]. In that study involving 184 cirrhotic patients, 44% had severe periodontitis, and unlike our study, there was a poorer survival

Table 1 Comparison of patients with and withour periodontitis

		Total cohort (*n* = 27)		*P* value
		Periodontitis (*n* = 22, 81.50%)	No periodontitis (*n* = 5, 28.50%)	
Male		12 (55%)	3 (60%)	1
Age, mean in years (range)		56 (37-76)	59 (56-68)	0.61
Smoker		17 (77%)	2 (40%)	0.13
Diabetes		8 (36%)	1 (20%)	0.62
Good oral hygiene		0 (0%)	3 (60%)	**< 0.01**
Outcome	Alive without transplantation	14 (63%)	0 (0%)	**0.02**
	Transplantation	5 (23%)	2 (40%)	0.61
	Deceased	3 (14%)	3 (60%)	**<0.05**
Motivated for oral hygiene (exact question was: "are you interested in oral hygiene")		12 (55%)	5 (100)%	0.11
MELD score, mean (range)		20 (15-25)	15 (7-22)	0.055
AST U/ml, mean (range)		75 (52-114)	109 (9-652)	0.83
ALT U/ml, mean (range)		66 (28-175)	50 (9-340)	0.15
Bilirubin mg/dL, mean (range)		6.0 (1.4-10.9)	3.3 (0.4-8.3)	0.17

P values determined by Mann-Whitney-test (age, aspartate aminotransferase, alanine aminotransferas, bilirubin, model for end-stage liver disease) and Chi-Square test (all other variables). AST: Aspartate aminotransferase; ALT: Alanine aminotransferas; MELD: Model for end-stage liver disease.

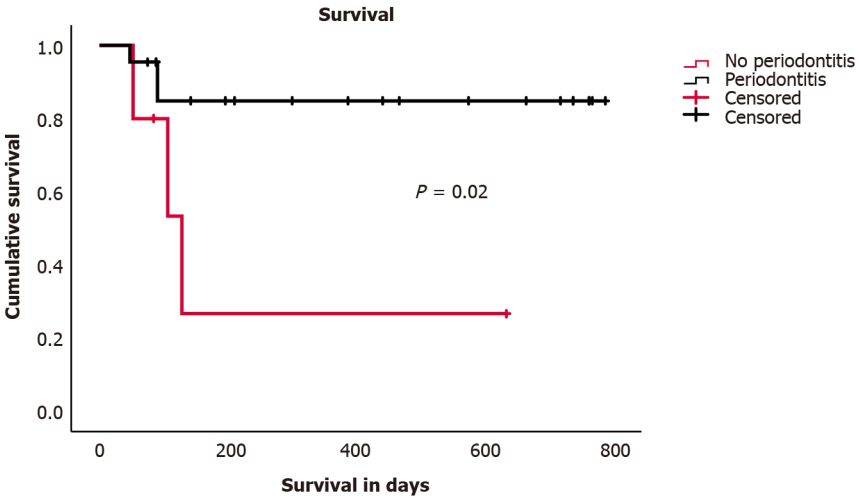

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Figure 1 Survival of patients with and without periodontitis (Kaplan-Meier analysis).

associated with the presence of severe periodontitis. The reasons behind this discrepancy and the tendency in our study toward better survival and lower MELD scores in cirrhotic patients with periodontitis remain unclear. However, it is crucial not to overinterpret this aspect, given the small sample size of five patients without periodontitis in our pilot study. Larger cohorts are needed to validate these findings, as less than 20% of the cirrhotic patients in our study did not have periodontitis.

A prior study established a link between the severity of NASH and the presence of periodontitis[11], a finding of particular relevance here. From a pathophysiological perspective, it is conceivable that the gingival entry point in periodontitis patients serves as a gateway for bacteria to enter the bloodstream, triggering cytokine release and inflammation. The intriguing aspect is that this inflammation did not appear to negatively impact the survival of our end-stage cirrhosis patients with ascites. Instead, our study revealed that patients without periodontitis had a less favorable survival outcome, which necessitates further investigation through large-scale studies.

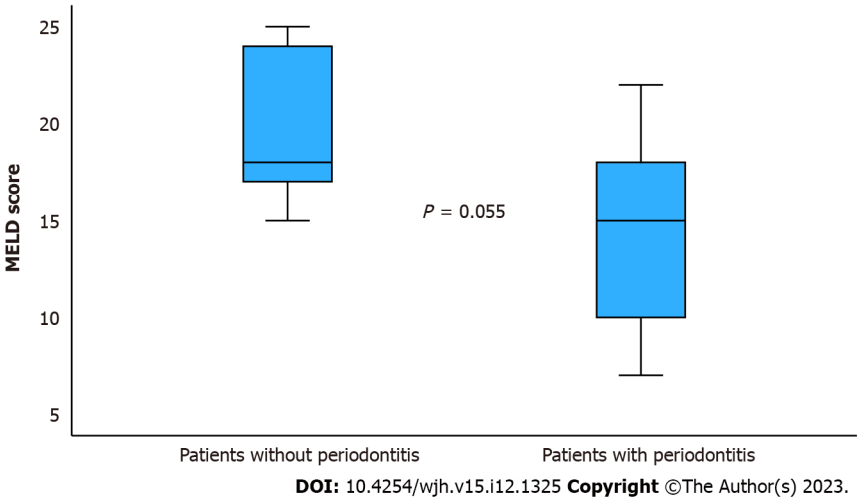

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Figure 2 Model for end-stage liver disease score in patients (Mann-Whitney test, *P* = 0.055: Not significant). MELD: Model for end-stage liver disease.

Our pilot study holds considerable validity, being based on a well-defined and thoroughly characterized cohort of 27 patients. Nevertheless, larger cohorts are imperative for further exploration of this question. The limitations of our study encompass not only the relatively small patient sample but also the single-center study design and the varied nature of the inquiries we pursued. We simultaneously investigated the prevalence of periodontitis in decompensated cirrhosis patients, the potential translocation of *P. gingivalis* and *A. actinomyctemcomitans* into ascites, and the association between periodontitis and survival in these patients. We successfully addressed two of these three questions, specifically the frequency of periodontitis in decompensated cirrhotic patients and the potential bacterial translocation into ascites. However, to elucidate the third question concerning the impact of periodontitis on survival, larger cohorts are indispensable. Additionally, future studies should also prospectively examine whether gingival status and bacterial colonization change over time.

It is especially pertinent in this context to consider whether periodontal therapy can potentially enhance the survival prospects of end-stage liver cirrhosis patients. A recent review article unequivocally demonstrated that periodontal therapy could exert a beneficial influence on the progression of NASH[15]. It is worth exploring to what extent this therapeutic approach might also be applicable to cirrhotic patients. Additionally, a recent study conducted in the United States, involving 442 cirrhosis patients, revealed a significant association between poor oral health and 3-month hospitalizations, irrespective of portal hypertensive complications, minimal hepatic encephalopathy, or frailty[16].

Nonetheless, the primary objective of our study was to investigate whether classical periodontitis pathogens, namely *P. gingivalis* and *A. actinomyctemcomitans*, could be detected in decompensated cirrhotic patients through translocation into the ascites. However, we did not observe such translocation in our study.

CONCLUSION

Based on our small pilot study, it appears that these two bacteria may not play significant roles in the development of ascites or potentially in the occurrence of SBP. This particular question had not been explored previously. While our study did not confirm the hypothesis that these microorganisms could enter ascites from the gingival reservoir in decompensated cirrhotic patients, this finding remains noteworthy because it provides conclusive clarification on the matter.

ARTICLE HIGHLIGHTS

Research background

This pilot study examines the prevalence of periodontitis in cirrhotic patients experiencing ascite decompensation.

Research motivation

Previous studies have not investigated whether bacteria from the oral mucosa associated with periodontitis can be translocated into the ascites of cirrhotic patients.

Research objectives

To investigate the significance of periodontitis in cirrhotic patients with ascites.

Research methods

This is a prospective cohort study. The oral hygiene and dental status of 27 patients with cirrhosis and ascites decompensation were documented. The prevalence of periodontitis in these patients was compared to that of 100 unselected patients from a standard dental practice. Samples from ascites and gingiva were tested for *Porphyromonas gingivalis* (*P. gingivalis*) and *Actinobacillus actinomycetemcomitans* (*A. actinomycetemcomitans*) using PCR.

Research results

Periodontitis was diagnosed in 22 out of 27 patients (82%) with ascites. This rate is significantly higher than in the control group of 100 unselected patients, where the rate was 59% (P = 0.04). *P. gingivalis* was identified in the gingiva of six patients and concurrently in the stool of one patient. However, *P. gingivalis* was not found in the ascites of any patient. Of the patients who tested positive for *P. gingivalis*, 83% (five out of six) suffered from periodontitis. *A. actinomycetemcomitans* was not detected in any of the samples. Significantly, a greater number of patients without periodontitis passed away compared to those with periodontitis, and the survival rate (as determined by the Kaplan-Meier analysis) was longer for patients with periodontitis (P = 0.02). Transplant-free survival was observed more often in patients with periodontitis than those without (63% *vs* 0%, P = 0.02).

Research conclusions

Periodontitis is common in cirrhotic patients with ascites.

Research perspectives

Hepatologists should recommend regular dental visits for cirrhotic patients. Future studies should assess whether this recommendation improves dental health and reduces the incidence of periodontitis.

FOOTNOTES

Author contributions: Pischke S and Ashouri MM contributed equally to this work; Pischke S, Ahouri MM, Peters U, Shiprov A, Schulze Zur Wiesch J, Sterneck M, Fischer F, Hüberner P, Mader M, Fischer L, Fründt T, Aarabi G and Beikler T designed this study and wrote the manuscript.

Institutional review board statement: This prospective study was reviewed and approved by the Ethics Committee of the Medical Council of Hamburg (PV-4081 and MC-368/18). The study was performed according to the recommendations of the Declaration of Helsinki. The retrospective analysis of the control cohort was completely anonymized and therefore did not require any clarification or formal ethics committee approval according to local laws and regulations.

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CASE REPORT

Drug induced autoimmune hepatitis: An unfortunate case of herbal toxicity from Skullcap supplement: A case report

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Abstract

BACKGROUND

The surge in traditional herbal dietary supplement (HDS) popularity has led to increased drug-induced liver injuries (DILI). Despite lacking evidence of efficacy and being prohibited from making medical claims, their acceptance has risen over sevenfold in the last two decades, with roughly 25% of United States (US) adults using these supplements monthly. An estimated 23000 emergency room visits annually in the US are linked to HDS side effects. NIH-funded research suggests HDS contribute to 7-20% of DILI cases, with similar trends in Europe—Spain reporting 2% and Iceland up to 16%. Patients with acute liver failure from HDS undergo liver transplantation more frequently than those from prescription medicines. Here we describe a case of drug-induced autoimmune hepatitis due to Skullcap supplements, this association appears to be the first documented instance in literature.

CASE SUMMARY

A middle-aged Caucasian woman, previously healthy, presented with sudden jaundice. Four months earlier, her liver enzymes were normal. She mentioned recent use of Skullcap mushroom supplements. Tests for chronic liver disease were negative. The first liver biopsy indicated severe resolving drug-induced liver injury. Despite treatment, she was readmitted due to worsening jaundice. Follow-up tests raised concerns about autoimmune hepatitis. A subsequent biopsy confirmed this diagnosis. The patient responded as expected to stopping the medication with improvement in liver enzymes.

CONCLUSION

This scenario highlights an uncommon instance of DILI caused by Skullcap supplements. It's crucial for hepatologists to recognize this connection due to the increasing prevalence of herbal supplements.

Key Words: Drug induced liver injury; drug induced autoimmune hepatitis; herbal

supplement; Skullcap; Case report

Core Tip: This case report highlights a rare presentation of drug induced liver injury from Skullcap supplement usage. While Chinese Skullcap (Scutellaria baicalensis) has been associated with a mixed hepatocellular and cholestatic picture of drug-induced liver injuries, the association of North American Skullcap is not as robust. Here we present a case of drug induced autoimmune hepatitis from North American Skullcap supplement use. Hepatologists must be aware of this association of rare histopathological presentation.

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INTRODUCTION

The rise in popularity of traditional herbal dietary supplements (HDS) has caused an increase in incidence of drug induced liver injury (DILI). Herbs and botanicals along with their extracts and metabolites fall under the umbrella term "dietary supplements" in the United States[1]. Even though these agents generally lack proof of efficacy and that their manufacturers are not permitted to make medical claims, their acceptance in the society has increased over 7-fold in the last two decades[2]. Approximately, 50% of the adult population in the United States admits to having used a "dietary supplement" in the last month[3]. It is estimated that there are 23000 emergency room visits in the United States each year are secondary to the side effects of HDS[4]. The true incidence of liver injury secondary in the United States to HDS is difficult to estimate. The NIH funded Drug Induced Liver Injury Network estimates that approximately 7%-20% all cases of DILI are secondary to HDS[5]. Which is akin to the data from Europe, with Spain reporting 2% of all DILI cases as secondary to HDS and Iceland reporting the rate as high as 16%[6,7]. In addition, patients presenting with acute liver failure secondary to HDS have been found to undergo liver transplantation more frequently than those with DILI from prescription medicines, (56.1 *vs* 31.9%, $P < 0.005$)[8]. As such, awareness about the side effects of these medications and a comprehensive understanding of their outcomes is paramount. Here we describe a case of drug induced autoimmune hepatitis (DIAIH) resulting from Skullcap supplements. To our understanding, this is the first such association described in literature

CASE PRESENTATION

Chief complaints

New onset Jaundice.

History of present illness

A 62-year-old Caucasian female, with Sjogren's disease presented with generalized fatigue, arthralgias, pruritus and new onset jaundice. She denied any prior history of liver disease, alcohol intake, intravenous or intranasal drug use, blood transfusions or needlestick injuries. She did however endorse taking Skullcap supplements over for 1-2 months due to long standing history of anxiety and insomnia.

History of past illness

Sjogren's syndrome; Anxiety; Insomnia.

Personal and family history

Nonsmoker, No alcohol or illicit Drug use. No gastrointestinal (GI) related malignancy or Liver disease in the family.

Physical examination

General: Age appropriate female in no distress. HEENT: Atraumatic, normocephalic; scleral icterus present, moist mucous membranes. Cyclic vomiting syndrome: S1,S2+ RRR. Lungs: Symmetric chest rise seen. Abdomen: Soft, non-distended, non-tender, baroreceptor sensitivity present, no palpable hepatomegaly appreciated. Extremities: No edema or clubbing. Skin: Jaundiced. Neuro: Alert, Awake, oriented × 3. No gross neurological deficits appreciated.

Laboratory examinations

The initial laboratory results on presentation that were pertinent: International normalized ratio (INR) 2.4, Alkaline Phosphatase (Alk Phos) 164 IU/L, aspartate transaminase (AST) 1091 IU/L, alanine transaminase (ALT) 980 IU/L, total bilirubin (T bili) 9.5 mg/dL. The R factor on initial calculation was 20.5, indicative of a primary hepatocellular injury pattern. Immunoglobulin G was elevated at 2573 mg/dL. Testing for Viral Hepatitis including - Hepatitis A, B, and C, cytomegalovirus, Epstein-Barr virus, and herpes simplex virus were all negative including serology and quantitative testing. ANA was positive given her history of Sjogren's disease. Her baseline AST, ALT, Alk phos and bilirubin were within normal range 4 months before presentation.

Imaging examinations

Magnetic resonance cholangiopancreatography done at admission did not show any signs obstruction or primary hepatic pathology.

Case Summary

Given her prior history of autoimmune disease and new onset hypergammaglobulinemia in the context of suspected DILI, a liver biopsy was pursued. Her initial liver biopsy revealed resolving centrilobular necrosis with predominant eosinophilic inflammation. Over the next 72 h, the liver enzymes showed a strong downward trend. As such, the patient was discharged with outpatient follow-up. However, the patient was re-admitted a month later with worsening jaundice, acute kidney injury, and new onset ascites concerning for subacute liver failure. Her LFTs were Alk Phos 619 IU/L, AST 1222 IU/L, ALT 540 IU/L, and T bili 6.6 mg/dL. Infectious workup was unremarkable. In the next few days, the transaminases showed a downtrend. However, the T bili continued to rise, reaching its peak at 11.8 gm/dl. Paracentesis showed a serum ascites albumin gradient of 1.4 which was consistent with portal hypertension. A repeat liver biopsy was pursued which revealed extensive plasma cells consistent with new onset autoimmune hepatitis resulting from previous DILI (Figure 1). Unfortunately, the patient's course was complicated by the development of spontaneous bacterial peritonitis, GI bleed and acute tubular necrosis necessitating dialysis. As such, she was never challenged with steroids. Due to her worsening status, she was listed for a simultaneous liver kidney transplantation. However, the patient finally did improve following a long and protracted course with resolution of jaundice but remained on hemodialysis.

FINAL DIAGNOSIS

DILI causing autoimmune Hepatitis.

TREATMENT

Cessation of culprit drug.

OUTCOME AND FOLLOW-UP

Resolution of Jaundice.

DISCUSSION

The last three decades have heralded an increased use of herbal medicinal products with up to 25% of the adult American population admitting to their use at some point[9]. These products are not regulated by the Food and Drug Administration and their side effect profile remains largely unknown. Skullcap is a plant native to North America (*Scutellaria lateriflora*), which has been used for centuries to treat anxiety, digestive disorders, and menstrual disorders. Skullcap extracts contain large quantities of flavonoids like scutellarin and baicalin which account for its sedative and antispasmodic activities[10]. However, Skullcap has been associated with a mixed hepatocellular and cholestatic pattern of liver injury. Additionally, majority of cases of DILI from Skullcap are attributed to Chinese Skullcap (*Scutellaria baicalensis)*, while the association of North American Skullcap with DILI is not as robust[11]. In our case, as is evident form the biopsy and the corresponding serology, the patient did have DIAIH.

Castiella *et al*[12] have postulated a-5-fold classification for drug induced autoimmune liver disease. Type 1, autoimmune hepatitis (AIH) with DILI: Reactivation of pre-existing AIH after the introduction of a new drug. Type 2, Drug induced Autoimmune Hepatitis (DIAIH): New onset AIH resulting from DILI. This results from an immune mediated reaction in a genetically primed individual, resulting in the necessitation of immunosuppressive treatment. Type 3, Immune Mediated DILI (IMDILI): acute or chronic liver injury that resolves upon cessation of the drug. DILI is often accompanied by a myriad of other features including fever, eosinophilia, lymphadenopathy, and rash. Individuals usually respond well to treatment and achieve sustained remission without relapse. Type 4, mixed autoimmune type: Mixed features of DI-AIH and IM-DILI. Individuals exhibit a full response to treatment, but assessing relapse is hindered

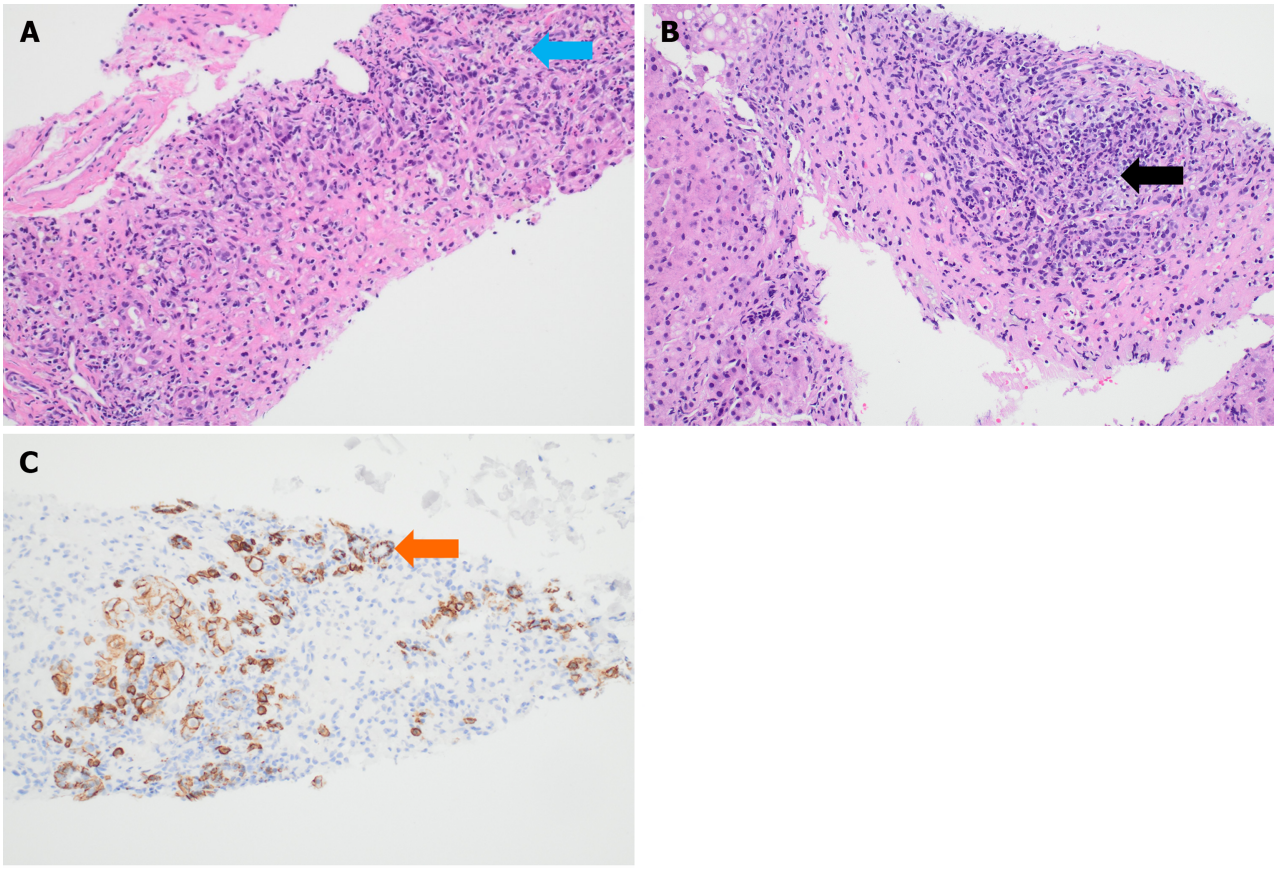

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Figure 1 Histopathology. A: Initial biopsy showing confluent centrilobular necrosis with interspersed eosinophils (blue arrow); B: Resolving centrilobular necrosis with plasma cells (black arrow); C: Immunohistochemical staining of plasma cells with CD 138 (orange arrow).

for non-hepatological reasons. Lastly, type 5 encompasses individuals with DILI and positive autoimmune antibodies. The significance of these antibodies remains uncertain.

CONCLUSION

This case outlines a rare presentation of DILI from Skullcap supplements. Hepatologists must be aware of this association as the popularity of herbal supplements continues to rise.

FOOTNOTES

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CASE REPORT

Hepatic pseudotumor associated with *Strongyloides* infection: A case report

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Abstract

BACKGROUND

Strongyloides sterocoralis is a parasitic infection caused by a roundworm that is transmitted through soil contaminated with larvae. It can infrequently cause hepatic abscesses in immunocompromised patients and is rarely reported to form hepatic lesions in immunocompetent hosts.

CASE SUMMARY

We present a case study of a 45-year-old female who presented with right upper quadrant abdominal pain and constitutional symptoms for several weeks. Cross-sectional imaging identified several malignant-appearing liver masses. Further investigation, including serological testing and histopathologic examination, revealed the presence of serum *Strongyloides* antibodies and hepatic granulomas with extensive necrosis. Following treatment with ivermectin for 2 wk, there was complete resolution of the liver lesions and associated symptoms.

CONCLUSION

This case highlights the importance of considering parasitic infections, such as *Strongyloides*, in the differential diagnosis of hepatic masses. Early recognition and appropriate treatment can lead to a favorable outcome and prevent unnecessary invasive procedures. Increased awareness among clinicians is crucial to ensure the timely diagnosis and management of such cases.

Key Words: Hepatic tumor; Liver mass; *Strongyloides sterocoralis*; Parasitology; Case report

Core Tip: Hepatic pseudotumor is a clinical entity that can mimic malignant tumors of the liver. We report a rare case of hepatic pseudotumor caused by *Strongyloides sterocoralis*. Combined with a review of cases indexed in PubMed, we summarize the infectious causes of hepatic pseudotumor. Recognition of hepatic mass-forming parasitic infections may expedite prompt medical management.

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INTRODUCTION

Inflammatory pseudotumors are mass-like lesions that have been described in various solid organs that mimic the appearance of a neoplasm[1]. Inflammatory pseudotumors represent a heterogeneous group of lesions of both infectious and inflammatory etiology, characterized histologically by the presence of fibroblasts or myofibroblasts and inflammatory cells and the lack of neoplastic cells. When occurring in the liver, hepatic pseudotumor often presents as a solitary, well-defined mass[1]. Due to its radiographic similarity to malignant liver tumors, potential misdiagnosis and unnecessary invasive interventions can occur. Given the variety of clinical presentations, including the absence of symptoms, the incidence of hepatic pseudotumor is not well characterized. It may account for 1% of all resected hepatic tumors[2], highlighting the importance of accurate diagnosis to prevent unneeded surgical resection. The pathogenesis of hepatic pseudotumor is poorly characterized but may be secondary to an exaggerated inflammatory response within the liver[1,3], as they often arise in the setting of infection, autoimmune disease, or recent trauma or surgery[1,3].

Strongyloidiasis is a parasitic infection known to infect the liver and biliary tree[3]. It is caused by the nematode *Strongyloides sterocoralis*, which is endemic in regions of West Africa, the Caribbean, and Southeast Asia – where the prevalence may be as high as 40%[4]. The parasitic larvae penetrate the skin and most commonly distribute to the gastrointestinal and pulmonary systems[5]. Less commonly, disseminated strongyloidiasis occurs when additional organs, including the liver, are involved[5,6]. Disseminated strongyloidiasis with hepatic infection has been primarily described in immunocompromised patients[7] but has rarely been observed in immunocompetent hosts[8].

Herein, we present a rare case of strongyloidiasis with hepatic involvement in an immunocompetent patient leading to the formation of a pseudotumor. By review of this case and the published literature, we summarize the incidence, diagnosis and treatment of *Strongyloides* pseudotumor.

CASE PRESENTATION

Chief complaints

A 45-year-old female was referred from the emergency room to hepatopancreatobiliary clinic for evaluation of liver lesions. She described several weeks of weight loss, decreased appetite, early satiety, fatigue, and right upper quadrant abdominal pain.

History of present illness

The patient was initially evaluated in the emergency room, where she reported a 15 lb weight loss secondary to abdominal pain and anorexia. The patient denied any change in bowel habits, sick contacts, or recent travel. The patient reported that her partner had immigrated from West Africa and that she had traveled there with him approximately 5 years earlier. She had also lived for several years in South Carolina, where *Strongyloides* may be endemic.

History of past illness

The patient had a history of hepatic steatosis, uterine fibroids, and morbid obesity. Upper and lower endoscopy had been performed 3 years earlier and were both found to be within normal limits.

Personal and family history

The patient denied any family history of malignancy.

Physical examination

The vital signs were as follows: Body temperature, 36.5°C; blood pressure, 136/76 mmHg; heart rate, 82 beats per min; and respiratory rate, 12 breaths per min. Abdominal exam was notable for tenderness in the right upper quadrant. There was no hepatosplenomegaly. There were no skin lesions present.

Laboratory examinations

Laboratory examination was notable for marked eosinophilia [0.9 × 10^3/mL (range 0.0-0.40)] and an elevated sedimentation rate (Westergren; 94 mm/h). Tumor markers were normal (alpha-fetoprotein < 1.8 ng/mL; carbohydrate antigen 19-9 16 U/mL; carcinoembryonic antigen 2.1 ng/mL). Liver function tests were normal, and hepatitis serologies were consistent with previous hepatitis B immunization. Human immunodeficiency virus (HIV) antibody (Ab)/p24 antigen screen, rapid plasma reagin, coccidioides Ab panel, cryptococcus antigen, and quantiFERON-TB Gold Plus were negative. Autoimmune markers were negative (anti-myeloperoxidase Ab < 0.2 units; anti-proteinase 3 Ab < 0.2 units; cytoplasmic antineutrophil cytoplasmic Ab (ANCA) < 1:2 titer; perinuclear ANCA (p-ANCA) < 1:20 titer; atypical p-ANCA < 1:20 titer; angiotensin converting enzyme, serum 42 U/L; anti-cyclic citrullinated peptide Ab, immunoglobulin G (IgG)/IgA 2 U; rheumatoid factor < 10.0 IU/mL; antinuclear Ab direct-negative).

Imaging examinations

An abdominal ultrasound performed in the emergency room noted a focal hypoechoic area within the right hepatic lobe centrally measuring 2.5 cm × 1.6 cm × 1.3 cm. Subsequently, a gadolium-enhanced magnetic resonance image demonstrated a non-cirrhotic liver with a peripherally T2 hyperintense and centrally T2 hypointense 3.7 cm × 3.2 cm × 3.7 cm lesion (Figure 1). Signal characteristics raised suspicion for a malignancy, but the rapid interval growth (from ultrasound-estimated size) suggested possible infection. A computerized tomography scan through the abdomen (Figure 2) demonstrated a low-density mass within the right hepatic lobe measuring up to 4.5 cm × 4.9 cm in the largest dimensions. There was peripheral enhancement with centripetal filling atypical for a hemangioma.

FINAL DIAGNOSIS

The final diagnosis was hepatic pseudotumor caused by *S. sterocoralis*.

TREATMENT

The treatment provided to the patient was ivermectin 24 mg by mouth daily for 2 wk.

OUTCOME AND FOLLOW-UP

Liver lesions and systemic symptoms both resolved shortly after treatment (Figure 3).

DISCUSSION

Inflammatory pseudotumor can be idiopathic, infectious, or inflammatory in nature; yet, there are several clinical features of hepatic pseudotumors that suggest an infectious etiology. We present a case of infectious hepatic pseudotumor caused by *S. sterocoralis*. The systemic symptoms of anorexia and malaise, coupled with marked eosinophilia, positive *Strongyloides* serum antibodies, and the presence of granulomas with necrosis on pathologic evaluation, along with clinical improvement with antihelminth therapy, support this rare diagnosis and highlight the importance of considering such infectious etiologies in the management of hepatic masses.

To date, the medical literature includes only two published reports of *Strongyloides* hepatic pseudotumor[7,8], which were diagnosed in patients with immunocompromise secondary to HIV or steroid use, respectively. While expected to be rare in the United States, the true prevalence of *Strongyloides* is not known. In the southeastern United States, particularly Appalachia, *Strongyloides* seroprevalence may approach 2%, and may be as high as 10% in South Carolina[9] - where the patient had previously resided. More commonly, *Strongyloides* is endemic to the soil of tropical and subtropical countries, where the nematode larvae migrate through the skin into human hosts and mature to the adult stage[10-12]. *Strongyloides* can perpetually reinfect a patient as the rhabditiform larvae develop into infective filariform larvae and pass into the feces. Strongyloidiasis may remain asymptomatic for many years in immunocompetent patients[10], whereas hyperinfection syndrome and disseminated strongyloidiasis are more common among immunosuppressed hosts[11,12]. In healthy individuals, nematodes have been shown to stay in the body for over 50 years without causing symptoms. It is plausible that this particular case represents a delayed presentation of a clinical exposure years prior with a long period of asymptomatic infection.

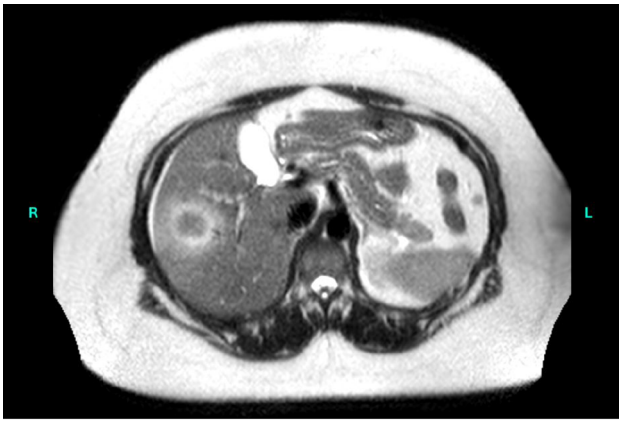

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Figure 1 Representative magnetic resonance imaging of hepatic pseudotumor. Gadolium-enhanced magnetic resonance imaging demonstrated a peripherally T2 hyperintense and centrally T2 hypointense lesion.

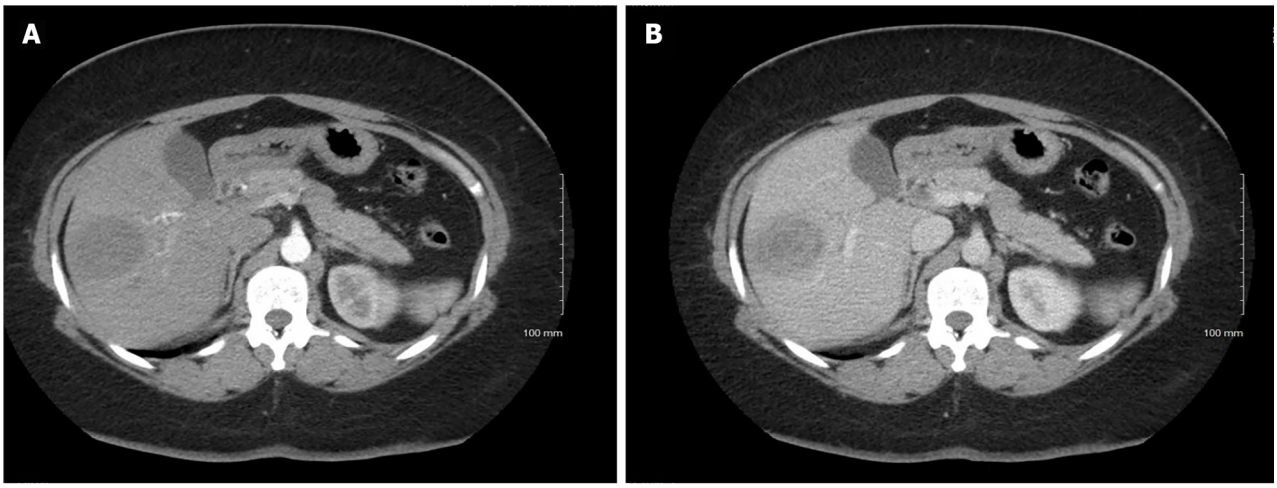

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Figure 2 Representative computerized tomography imaging of hepatic pseudotumor. A-B: Computerized tomography scan through the abdomen with arterial (A) and venous (B) phases demonstrated a low-density mass within the right hepatic lobe measuring up to 4.5 cm × 4.9 cm in largest dimensions. There was peripheral enhancement with centripetal filling; however, the enhancement was contiguous without significant nodularity and thus atypical for a hemangioma.

Other etiologies of infectious hepatic pseudotumor include *Mycobacterium tuberculosis*, *Brucella*, *Bartonella*, *syphilis*, *Candida,* and *Actinomyces*. *Tuberculosis* can cause a localized hepatic lesion, either as a tuberculoma with confluent granulomas and few organisms in immune competent individuals, or a tuberculous abscess, which is often suppurative and contains numerous organisms in immunocompromised hosts[13]. A *Brucelloma* is typically seen in the context of reactivation of remote infection, usually originating from animals or animal products from high-risk regions, typically surrounding the Mediterranean[14].The clinical presentation of hepatic *Brucelloma* overlaps with many of the symptoms of brucellosis, typically chronic, undulating fevers, malaise, and anorexia. There may be right upper quadrant pain. Diagnosis of hepatic *Brucelloma* is validated by serological positivity and positive cultures on blood or tissue samples. Hepatic cat scratch disease, caused by *B. henselae*, may present with abdominal lymphadenopathy and skin papules. It can form irregular stellate hepatic abscesses, histologically characterized by palisading histiocytes, lymphocytes, and a rim of fibrosis[13]. Hepatic syphilis can occur in both immunocompetent and immunocompromised patients[15-17]. Immunohistochemical stain for *Treponema pallidum* highlights the organisms in these pseudotumors; additionally, there is often periductal edema and neutrophilic pericholangitis in portal tracts outside the mass lesion. Hepatic *candidiasis* is most often observed in immunocompromised patients[18] and on histologic examination, may show granulomas or abscesses containing pseudohyphae and/or yeast forms[13]. Lastly, *Actinomycosis* can cause hepatic fibrotic masses containing characteristic sulfur granules and colonies of filamentous organisms[19,20]. In summary, patient history and exposures are important considerations when considering these infectious causes of hepatic pseudotumor in order to guide further testing for diagnostic confirmation.

While most hepatic pseudotumors are presumed to be a response to infection, the causative agent is not always identified. Additionally, there are several malignancies and inflammatory diseases that must be considered. Beyond primary (*i.e.* cholangiocarcinoma and hepatocellular carcinoma) and metastatic liver tumors, there are several neoplasms that particularly resemble hepatic pseudotumor. These include inflammatory myofibroblastic tumor (IMT), follicular

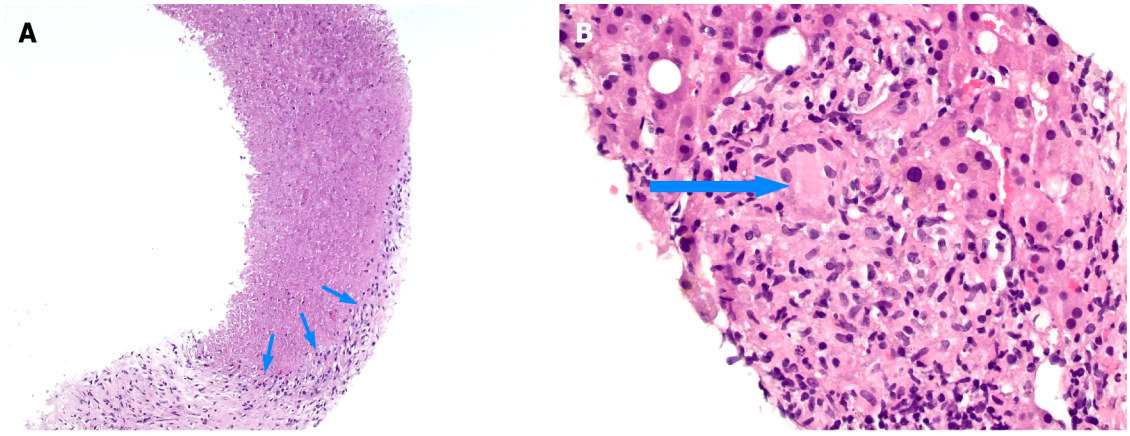

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Figure 3 Histologic examination of the liver lesion. A: The biopsy shows loose fibrous tissue (bottom) with large areas of necrosis rimmed by histiocytes (arrows), hematoxylin and eosin stain (100 ×); B: The adjacent viable hepatic parenchyma contains few non-necrotic granulomas. The arrow denotes a multinucleated giant cell within the granuloma, hematoxylin and eosin stain (400 ×).

dendritic cell tumor, and less commonly, Hodgkin lymphoma. When in question, further testing on tissue samples can help distinguish these diagnoses (IMT with *ALK* or *ROS1* expression; follicular dendritic cell tumor with *in situ* hybridization for Epstein-Barr virus; Hodgkin lymphoma with immunohistochemical analysis). Non-infectious inflammatory hepatic pseudotumor can be observed in IgG4-related disease. While most commonly manifested as a form of sclerosing cholangitis and thus a mimic of cholangiocarcinoma, IgG4-related hepatic pseudotumors can form adjacent to involved ducts[21,22]. Histologically, IgG4-related hepatic pseudotumors are characterized by numerous IgG4-positive plasma cells on immunohistochemical staining.

Several limitations warrant emphasis. For this case, the *Strongyloides* IgG Ab titer was not available, and was only reported by the laboratory as a binary (*i.e.* positive/negative); thus, we cannot comment on the degree of elevation that may be observed with this subset of hepatic disease. Second, for completeness of the presentation of the history and evaluation of this case, we hoped to include a representative image of the *Strongyloides* larvae from the stool examination, but this could not be provided by the commercial laboratory involved.

CONCLUSION

Hepatic masses are a heterogenous pathology of malignant, inflammatory and infectious etiologies. This rare case study of hepatic pseudotumor caused by strongyloidiasis infection highlights the broad diversity of diagnoses that need be considered, even in geographic regions and patient cohorts not typical of opportunistic infections. Moreover, the clinical presentation – namely, eosinophilia, positive serum antibodies and necrotic granulomas – review the typical features of *Strongyloides*-induced pseudotumor. Further research is warranted to elucidate the underlying biology of hepatic pseudotumor formation and improve diagnostic accuracy. Recognizing the pivotal role of infections in the differential diagnosis of hepatic pseudotumor is paramount for safeguarding patients from undergoing unnecessary invasive procedures. This approach not only facilitates accurate diagnosis and timely initiation of appropriate treatments but also prevents unwarranted interventions, underscoring the significance of a comprehensive consideration of infections in the diagnostic algorithm of hepatic pseudotumor cases.

FOOTNOTES

Author contributions: Grandhi MS, Alexander HR, and Ecker BL contributed to the conceptualization and supervision of the research; Gialanella JP, Alexander RH, Korpela K, and Ecker BL contributed to data collection and data analysis; Gialanella JP and Ecker BL contributed to the manuscript writing; All authors have read and approved the final manuscript.

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