ISSN 1948-5182 (online)

World Journal of *Hepatology*

World J Hepatol 2022 November 27; 14(11): 1920-1984

Published by Baishideng Publishing Group Inc

World Journal of Hepatology

Contents

Monthly Volume 14 Number 11 November 27, 2022

World Journal of Hepatology

Monthly Volume 14 Number 11 November 27, 2022

Contents

ABOUT COVER

Editorial Board Member of *World Journal of Hepatology*, Cristiane A Villela-Nogueira, FAASLD, MD, PhD, Full Professor, Internal Medicine Department, Hepatology Division, School of Medicine, Federal University of Rio de Janeiro, Rio de Janeiro 21941-913, Brazil. crisvillelanog@gmail.com

AIMS AND SCOPE

The primary aim of *World Journal of Hepatology* (*WJH*, *World J Hepatol*) is to provide scholars and readers from various fields of hepatology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJH mainly publishes articles reporting research results and findings obtained in the field of hepatology and covering a wide range of topics including chronic cholestatic liver diseases, cirrhosis and its complications, clinical alcoholic liver disease, drug induced liver disease autoimmune, fatty liver disease, genetic and pediatric liver diseases, hepatocellular carcinoma, hepatic stellate cells and fibrosis, liver immunology, liver regeneration, hepatic surgery, liver transplantation, biliary tract pathophysiology, non-invasive markers of liver fibrosis, viral hepatitis.

INDEXING/ABSTRACTING

The *WJH* is now abstracted and indexed in PubMed, PubMed Central, Emerging Sources Citation Index (Web of Science), Scopus, Reference Citation Analysis, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Superstar Journals Database. The 2022 edition of Journal Citation Reports® cites the 2021 Journal Citation Indicator (JCI) for *WJH* as 0.52. The *WJH*'s CiteScore for 2021 is 3.6 and Scopus CiteScore rank 2021: Hepatology is 42/70.

RESPONSIBLE EDITORS FOR THIS ISSUE

NAME OF JOURNAL
World Journal of Hepatology

ISSN
ISSN 1948-5182 (online)

LAUNCH DATE
October 31, 2009

FREQUENCY
Monthly

EDITORS-IN-CHIEF
Nikolaos Pyrsopoulos, Ke-Qin Hu, Koo Jeong Kang

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/1948-5182/editorialboard.htm

PUBLICATION DATE
November 27, 2022

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS
https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH
https://www.wjgnet.com/bpg/gerinfo/240

PUBLICATION ETHICS
https://www.wjgnet.com/bpg/GerInfo/288

PUBLICATION MISCONDUCT
https://www.wjgnet.com/bpg/gerinfo/208

ARTICLE PROCESSING CHARGE
https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS
https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION
https://www.f6publishing.com

World Journal of Hepatology

Submit a Manuscript: https://www.f6publishing.com

World J Hepatol 2022 November 27; 14(11): 1920-1930

DOI: 10.4254/wjh.v14.i11.1920

ISSN 1948-5182 (online)

EDITORIAL

Current management of liver diseases and the role of multidisciplinary approach

Nouhoum Bouare

Specialty type: Gastroenterology and hepatology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): D
Grade E (Poor): E, E

P-Reviewer: Kamran M, Pakistan; Shi YJ, China; Thandassery RB, United States

Received: August 17, 2022
Peer-review started: August 17, 2022
First decision: September 26, 2022
Revised: October 10, 2022
Accepted: November 16, 2022
Article in press: November 16, 2022
Published online: November 27, 2022

Nouhoum Bouare, Department of Assurance Quality and Biosafety/Biosecurity, National Institute of Public Health, Bamako 1771, Mali

Corresponding author: Nouhoum Bouare, DSc, PhD, Research Scientist, Department of Assurance Quality and Biosafety/Biosecurity, National Institute of Public Health, Hippodrome, Bamako 1771, Mali. nouhoumsamakoro@yahoo.fr

Abstract

Liver is an organ having extremely diversified functions, ranging from metabolic and synthetic to detoxification of harmful chemicals. The multifunctionality of the liver in principle requires the multidisciplinary and pluralistic interventions for its management. Several studies have investigated liver function, dysfunction and clinic. This editorial work discusses new ideas, challenges and perspectives of current research regarding multidisciplinary and pluralistic management of liver diseases. In one hand the discussions have carried out on the involvement of extracellular vesicles, Na^+/H^+ exchangers, severe acute respiratory syndrome coronavirus 2 and Epstein–Barr virus infections, Drug-induced liver injury, sepsis, pregnancy, and food supplements in hepatic disorders. In the other hand this study has discussed hepatocellular carcinoma algorithms and new bio-chemical and imaging experiments pertaining to liver diseases. Relevant articles with an impact index value "> 0" from reference citation analysis, which is an open multidisciplinary citation analysis database based on artificial intelligence technology, have served for the study's argumentation. This work may be a useful tool for the clinical practice and research in managing and investigating liver disorders.

Key Words: Liver management; Liver function; Liver dysfunction; Liver clinic; Liver diagnosis; Multidisciplinary approach

Core Tip: This study uses an open multidisciplinary citation analysis database based on artificial intelligence technology to deal with multidisciplinary and pluralistic approaches of liver diseases management, providing a useful and practical tool for physician and scholars.

Citation: Bouare N. Current management of liver diseases and the role of multidisciplinary approach. *World J Hepatol* 2022; 14(11): 1920-1930
URL: https://www.wjgnet.com/1948-5182/full/v14/i11/1920.htm
DOI: https://dx.doi.org/10.4254/wjh.v14.i11.1920

INTRODUCTION

Liver is an organ having extremely diversified functions, ranging from metabolic and synthetic to detoxification of blood-harmful chemicals. The biliary-metabolic function is highly important in the digestive system. The liver helps in controlling sugar levels to provide the energy needed for biliary and pancreatic functions. The energy generated allows bile to transform food into essential nutrients that can be assimilated into the blood. This energy also allows the pancreas to produce certain digestive enzymes. Cholesterol is produced in both the liver and pancreas. Individuals with surgically sectioned pancreas (in portion or entirety) may have high cholesterol levels subsequent to hepatic hyperproduction of cholesterol in response to an increased fatty diet. Many people with liver disease have clinical symptoms as a result of conditions such as prediabetes, insulin resistance, and type 2 diabetes[1].

Infection is also a common characteristic of liver dysfunction, which can progress to chronicity. It can be caused by liver tropism viruses [including hepatitis B virus (HBV) and hepatitis C virus (HCV)]. Secondarily liver dysfunction can occur *via* other viruses, such as cytomegalovirus, Epstein–Barr virus (EBV), *Mycobacterium avium*-intracellular complex, or human immunodeficiency virus (HIV-1)[2].

In principle, the multifunctionality of liver requires multidisciplinary and pluralistic interventions for its preservation or management.

A multidisciplinary approach can be defined as a program that integrates different disciplines to exploit diverse perspectives to illustrate topics, themes, or problems. Such programs are benefited by diverse perspectives from different disciplines to study a subject[3]. This makes it possible to deepen knowledge of the subject under its multiple facets to provide efficient responses.

A pluralistic approach promotes mutual understanding and collaboration around a topic or problem, similar to a multidisciplinary approach. Such an approach is vital for interdisciplinary courses because it helps academies and students address multiple phenomena of concern through different disciplines[4]. A pluralistic intervention approach was suggested to mark an efficient response to the coronavirus disease 2019 (COVID-19) pandemic[5].

This editorial work reports new ideas, challenges, and future directions of current research in the field of the multidisciplinary and pluralistic management of liver diseases.

LIVER MANAGEMENT

Function and physiology

Exosomes (micronized vesicles) are known to play a role in the intercellular transportation of diverse bioreactive molecules. Abundant evidence was suggestive of exosomes involvement in the pathologies pertaining to liver such as: Chronic viral hepatitis, fibrosis and cirrhosis, Non-alcoholic fatty liver disease (NAFLD), alcoholic liver disease, and hepatocellular carcinoma (HCC). These microvesicules are present in almost all the bodily fluids. Hence exosomal miRNAs and proteins may be new potential biomarkers for liver disease[6,7]. Regarding liver disease treatment, exosomes can contribute in immune- and cell-based therapy. Exosomes may even serve in the transportation of medicines, nutrients and nucleic-acids[6,7].

Extracellular vesicles (EVs) are defined as particles wrapped in lipid bilayers, which are secreted by various replicable nuclei-free cells. EVs may be categorized according to their biogenesis process (exosomes, microvesicles, and apoptotic bodies) or length (small EVs < 200 nm and medium/large EVs ≥ 200 nm)[7-9]. EVs are drawing attention of scientists owing their remarkable roles in maintaining and regulating liver homeostasis. Abundant evidence shows EVs involvement in intrahepatic cells communications, and extrahepatic transportation between the liver and other organs *via* diverse pathological conditions. However, a comprehensive experiments answering the question "how EVs contribute to the pathogenesis and therapy processes in the liver?" is needed to develop innovative EV-based approaches for hepatic disease diagnosis and therapy[7]. We agree with the authors that even if there are technical limitations and knowledge lacking about EV cargoes, biogenesis, delivery, and utilization, these particles have the high potential to be the targets and tools in novel cell-free EV-based treatment for currently incurable hepatic diseases.

There are many nucleic receptors (NRs) in humans and mice[10]. NRs are categorized into 7 subfamilies in function of the structural homology. Metabolic NRs in majority belong to the NR1 subfamily (including farnesoid X receptor [FXRα/NR1H4] designed as FXR). FXR, a metabolic nuclear receptor, was prior described as a receptor that recognizes farnesol before to be cloned in 1995, while a

second form (FXRβ/NR1H5) has been uncovered 8 years later. FXRβ is an additional NR in mice, encoding a human and primate pseudogene. While the two FXRs share 50% amino acid identity, they differ regarding the ligand specificity. The release of co-repressors and recruitment of co-activators to trigger the transcriptional process occur, when a metabolic ligand is bound to the NRs or RXR (heterodimer partner). FXRβ is trans-activated by the lanosterol (cholesterol precursor), but its functional role is unknown. Bile acids are reported as natural ligands of FXR; to note they differ in their chemical characteristics (*i.e.*, affinity and trans-activation ability to bind FXR). The liver plays a central metabolic role by processing nutritional inputs and metabolic outputs. Food consumption triggers the secretion of bile acids, which are detectable by the bile acid receptor FXR in the liver and intestine. Hepatic and intestinal FXRs cooperate to regulate postprandial nutrient disposal into a network where metabolic nuclear receptors interact. FXR has been a fascinating target for diverse metabolic disorders and its agonist obeticholic acid has served as second-line therapy in primary biliary cholangitis. Panzitt *et al*[10] reviewed the FXR central- and integrator- role in response to feeding intake *via* the metabolic processing of chemicals such as carbohydrates, lipids, proteins and bile acids. The authors discussed FXR effects upon autophagic turnover, inflammation, amino acid and protein metabolism. They reported knowledge on how FXR signaling is affected by both its isoforms and posttranslational changes. Authors suggest that the changes in FXR signaling may be considered with regard to the pharmacological targeting of FXR in clinical experiments. Whereas FXR agonists may be promising targets for metabolic disorders therapy, distinct metabolic parameters may be worsening[10].

NHEs (Na^+/H^+ ions transporters) are present in diverse organisms in which they participate in regulation process at the cellular, tissue, and systemic levels[11]. Li *et al*[11] have described NHEs' physiopathology in the liver. Although NHEs participate in diverse inflammatory stimuli, there is still need to investigate their effect into the liver regarding selective targeted therapy. Numerous studies have shown the slight toxicity for NHEs' inhibitors, and many of them (including cariporide) were experienced in preclinical and clinical trials. Many studies have only analyzed the effects of single factors, without considering that various transporters may interact with NHEs in physiological and pathological conditions. The authors suggest a more comprehensive studies using methods to inhibit, regulate, and target the function of NHEs in liver disease[11].

Dysfunction and pathology

The need to assess abnormalities linked to COVID-19 in different organs and systems is becoming clear. Bobermin *et al*[12] reported the link between liver disorder and brain dysfunction likely due to factors such as ammonia, inflammatory mediators and cytokines. Considering the versatility of astrocyte functions, we hypothesize these cells can extremely contribute to this relationship because they receive and integrate peripheral signals stimulating central nervous system. To note liver damage may potentiate the risk of neurological dysfunction in patient with COVID-19, hence the need to monitor hepatic function after infection. Whereas transient encephalopathy is associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, COVID-19 may trigger late neurological dysfunctions such as cognitive deficits, neurodegenerative and psychiatric disorders[12]. Patients with COVID-19 may develop gastrointestinal symptoms accompanied by respiratory symptoms[13]. Recognizing and diagnosing gastrointestinal symptoms is difficult. Clinicians should be aware that gastrointestinal disorders may characterize COVID-19. These clinical manifestations may allow early COVID-19 diagnosis, isolation, and treatment. Owing the evidence of fecal-oral contagion of SARS-CoV-2, there is need to intensify infection control and standardize healthcare practices[13]. Choudhary *et al*[14] discussed the literature regarding COVID-19 outcomes in patients with cirrhosis and liver transplant recipients. They reported the link between COVID-19 and a high mortality in patients with cirrhosis. This COVID-19 burden is significantly higher in decompensated cirrhotic patients than in compensated ones and in cirrhotic patients than in non-cirrhotic patients with chronic liver disease. Liver transplantation has decreased owing to the fear of COVID-19, hence patients with decompensated cirrhosis are at risk of wait-list mortality. Older age and comorbidities were associated with COVID-19 mortality in liver transplant recipients[14].

Wu *et al*[15] reported that COVID-19 severity and mortality were associated with liver dysfunction. The death patients and those with severe COVID-19 had high serum aspartate transaminase level compared to the survivors and patients without severe COVID-19. They hypothesized that their findings may be useful for liver clinical management in patients with COVID-19. Nevertheless, the authors reported the study limitations. Informations such as types of liver damage, drug use, nutritional factors, and parameters assessing liver function were missing. In fact, risk stratification in the subgroup analysis of patients with liver damage was not possible. Only the available data were those related to the age and sex of study patients. Other cofactors such as body mass index, underling chronic diseases, instruments and experimental techniques, and sample size may have influenced the results. The authors suggest conducting large-scale prospective studies to verify these results[15]. Liver damage is frequent in patients with SARS-CoV-2 infection, especially in severe COVID-19 or underlying chronic liver disease[16]. Patients with COVID-19 had better evolution during their hospital stay despite persistent cytolysis. The exact origin of liver abnormalities was not determined in the study. Further investigations are required to assess the impact of SARS-CoV-2 on HBV infection. In patients with chronic HBV, the evolution was better with antiviral B resumption. The authors recommend careful monitoring of

biochemical parameters in patients with COVID-19[16].

As for the liver damage linked to viral infection, EBV, along with chronic viral hepatitis B and C, plays a significant role in the development of virus-mediated autoimmune liver diseases as well as damage to other organs (intestine, heart, kidneys, thyroid gland, *etc.*)[17]. The similarity of these nosologies is also evident in the nature of the disease course: The presence of a primary infection in a manifest or latent form with possible progression toward chronicity and periodic reactivation occurrence. The wide distribution of pathogens in the human population may favor mixed EBV, HBV, and HCV infections. However, this problem has not been adequately addressed in the scientific literature. This study suggests that EBV plays a role in the occurrence of liver and extrahepatic pathologies. The combination of this pathogen with HBV and HCV requires further in-depth studies [17].

Clinic, enzymology and immunology

Drug induced liver injury (DILI) should be suspected in patients with recent elevations in liver biochemistry parameters[18]. To date, there are no helpful biomarkers for clinical and laboratory diagnoses. Diagnosis is dependent on the temporal relationship with the recent consumption of drugs, herbals, and dietary supplements, along with a high liver marker level, excluding competing etiologies. Any implicated product should be discontinued, and the patient must follow *a fortiori* for jaundice occurrence. Liver transplantation may be required, because the risk of liver-related damage death (around 10%) is linked to the jaundice. DILI therapy is only symptomatic, such as itching, because no specific treatment is currently available. Patients with coagulopathy or jaundice usually require hospitalization. Given immunomodulatory therapy for cancer is inducing DILI, corticosteroids dose-based experiments are required, since ultrahigh doses recommended by oncological societies are not trivial [18]. Liver implication in COVID-19 infection may reach 16%-29% of patients, with a high proportion in adult and older patients[19]. The appearance of liver involvement during COVID-19 requires attention. Although evidence-based prospective experiments are lacking, the underlying mechanisms are complex (including cholangiopathy, cytokine storm, and DILI). The most probable mechanism may be DILI; hence taking into account the liver injury triggered by certain medicines is required, *a fortiori* in severe patients with underlying hepatic disorders. Liver toxicity and specific hepatic biochemical markers are linked to COVID-19 death and severity, therefore a well-designed management of patients with hepatic injury is required[19]. Aleem *et al*[20] reported a link between remdesivir and transient mild-to-moderate elevation of liver biochemistry parameters in hospitalized patients with COVID-19. The authors primarily recommend performing a baseline pretherapeutic biochemical test before conducting daily monitoring during the treatment; second, to exclude possible drugs adverse reaction (including hepatotoxicity and medicines interaction); and third, to discontinue remdesivir infusions in patients with *de novo* alanine transaminase or aspartate transaminase elevations 10 times above the upper normal limit[20].

D'Ardes *et al*[21] reported on the topic hepatic damage and coagulopathy. Liver damage triggered by microvascular thrombosis is hypothesized; this mechanism is supported by postmortem results. Another evidence demonstrated a correlation between coagulation and hepatic dysfunction in patients with COVID-19. Nevertheless the authors suggest further investigation to better identify the link between coagulation, liver damage and COVID-19[21].

Sepsis condition may trigger hepatic injury (including hypoxic hepatitis, cholestasis, DILI, and secondary sclerosing cholangitis)[22]. The death rate caused by sepsis is extremely higher in cirrhotic patients, which is suggestive for more probable infection, accurate diagnosis, and suitable antimicrobial therapy. Sepsis is currently defined as sepsis-3 using systemic inflammatory response syndrome criteria, and based on organ dysfunction symptoms. This organ defect may be evaluated by the sequential organ failure assessment (SOFA) and quick SOFA scores[22].

The role of hyperthyroidism and liver dysfunction has been reported[23]. Hepatic biochemical abnormalities in untreated thyrotoxicosis patients is closed between [15%-76%], which may be explained by the conditions such as: direct liver cell injury, heart failure comorbidity, underlying autoimmune disorders *a fortiori* in hyperthyroidism, preexisting hepatic disease, and drugs combining antithyroid medicine. While some patients may experience mild liver injury, around 1%-2% may develop fulminant hepatitis. A timely initiation of thionamides allows to normalize hepatic enzymes levels. Clinicians should suspect hyperthyroidism in patients with unexplained hepatic defect or unexplained Jaundice[23].

Rifampin used alone could not be responsible for liver toxicity reported in clinical assays; this damage may be due to the induction-mediated accumulation of drug's hepatotoxic metabolite in case of rifampin concomitant administration[24]. In fact, liver defect could be triggered by metabolite activation of some a number of medicines. The role of rifampin in metabolic activation regarding DILI needs to be considered when conducting rifampin drug-drug interaction experiments, *a fortiori* those with unknown metabolic profiles[24].

Birkness-Gartman *et al*[25] reported some a number of hepatic disorders in pregnancy condition. Although intrahepatic cholestasis is anodyne in pregnancy condition, it may be linked to fetal morbidity and death with elevated serum bile acids. Pre-eclampsia, eclampsia, and [hemolysis, elevated liver enzymes and low platelets syndrome (HELLP)] are more frequently linked to maternal and fetal

damages, which may necessitate expedient delivery. High hepatic enzymes levels may be see in condition such as hyperemesis gravidarum. Pregnant women are at high risk to develop severe hepatitis E, herpes virus infection, Budd-Chiari syndrome, and gall-stones. Preexisting chronic hepatic diseases may be worsening in pregnancy condition. In addition hepatocellular adenoma and carcinoma may be challenging for diagnosis and management in pregnancy. Fetal damages in fatty acid beta-oxidation such as long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency may have an involvement on both conditions acute fatty liver of pregnancy and HELLP[25].

Regarding complementary medicine, food supplements such as resveratrol, propolis, anthocyanin, and cinnamon are reported to have some effects on liver enzymes. Whereas there have been conflicting results regarding the effects of resveratrol on NAFLD, a systematic review reports that this supplementation has no NAFLD-related effect. However, the authors suggest further investigations pertaining to resveratrol supplementation effects on liver enzymes[26]. A study has shown the beneficial effect of propolis supplementation on biological parameters such as: alanine aminotransferase (ALT), aspartate aminotransferase (AST), fasting plasma glucose, hemoglobin A1c, insulin, C-reactive protein and tumor necrosis factor-α[27]. Sangsefidi *et al*[28] reported a significant association between the duration of anthocyanin supplementation experiment with the levels of ALT and AST. However, ALT-related results should be interpreted with caution due to study limitation. Further representative experiments are still needed. Cinnamon supplementation is suggested to have a beneficial effect on ALT and AST levels in type 2 diabetic patients. Further experiments *a fortiori* in patients with liver enzymes abnormality are needed to assess the clinical effects of cinnamon supplementation[29]. Grape products are reported to have no established effect on hepatic enzymes in adults. Further investigations are required due to the study's limitation[30].

Diagnosis

Many biomarkers or mixed tests are being experienced to estimate liver fibrosis threshold for cirrhosis diagnosis; some of them are commercialized. However, the gold standard test remains biopsy (an invasive and risky procedure). Benyair *et al*[31] investigated sH2a, a soluble form of asialoglycoprotein receptor in human. They detected for the first time sH2a in human serum. The levels of sH2a were constant in the healthy group and extremely decreased in the group of patients with liver cirrhosis. The authors suggest that sH2a may be a useful non-invasive biomarker, to estimate the functional mass of hepatocytes[31].

Hepatic steatosis [fatty liver disease (FLD)] is caused by lipid accumulation in hepatocytes. During the chronic stage, lobular inflammation occurs and the disease may progress to liver fibrosis, cirrhosis, and HCC. The early diagnosis of patients is recommended, because they respond better to the medication in this stage. Physical examination is often unremarkable in the early stages of FLD. Several techniques, such as laboratory tests, imaging, and biopsy, can be used to diagnose and monitor FLD and hepatic fibrosis. Ultrasound is an effective imaging method to diagnose and monitor patients with liver disorders. Ultrasonography combined with elastography presents a great interest regarding the follow-up of these patients. This combined imaging method that evaluates organ stiffness, has well demonstrated liver alterations (including hardening, fibrosis and cirrhosis)[32]. Except magnetic resonance (MR) elastography, the authors discussed the application of various ultrasound elastography techniques such as transient-, point shear wave-, and two-dimensional shear wave- elastography. Although liver fibrosis and NAFLD diagnosis is complex, the scientists are enthusiastically investigating this topic. Ultrasound elastography is improving in term of image quality, handling, quantification, and range of tissue characteristics. The authors suggested that it is a promising means for the replacement of invasive procedure in steatosis diagnosis[32].

Diagnosis parameters to estimate hepatic disease severity (including albumin-bilirubin index, Model for End Stage Liver Disease, and Child-Turcotte-Pugh score) have shown a good correlation with gadoxetic acid-enhanced MRI in hepatobiliary phase[33]. Bastati *et al*[33] have estimated the accuracy of the functional liver imaging score (FLIS) in predicting both hepatic decompensation and transplant-free survival in patients with CLD. FLIS, a derivative method from gadoxetic acid-enhanced MRI, may predict an initial hepatic decompensation among compensated advanced CLD patients. This is a less complex and noninvasive imaging method that has predicted transplant-free survival among advanced CLD patients. An MRI-based FLIS is a death predictor in compensated and decompensated advanced CLD as reported by Bastati and coworkers. However, authors reported limitations (including possible selection bias due to the study retrospective design. Nevertheless, they suggested that this bias is less probable, since gadoxetic acid–enhanced MRI was used as standard of care for patients with focal hepatic nodules or masses or CLD at their institution. Another potential bias was reported regarding the lack of histologic proof for CLD etiology in most patients.

Gadoxetic acid disodium (Gd3+) is a contrast agent that tends to dominate magnetic resonance imaging (MRI) as far as the clinical diagnosis of liver tumors is concerned. However, the need for safer alternatives arises because of the non-trivial side effects associated with Gd3+ ions[34]. Kim *et al*[34] carried out in-depth *in vivo* MRI studies and immunohistochemical experiments using three hepatic tumor (HCC, neuroendocrine carcinoma, and adenocarcinoma) models, and demonstrated that hollow manganese silicate nanoparticles (HMS), as a liver-specific MR contrast agent, exhibit high effectiveness in hepatic tumor characterization by exerting burst-release of Mn^{2+} ions switching to physiological acidic

conditions. HMS MRI time-sequential characteristics better reflect biological features such as vascularity, cellularity, mitochondrial activity, and hepatocellular specificity, thus are improving HMS bioimaging conspicuity, which allows a specific characterization of diverse hepatic tumors. HMS-enhanced MR has shown through a necrotic HCC model that the extent of tumor necrosis was correlated to residual mitochondrial activity. This multi-responsive spatio-biological distribution and function of HMS, as a result of a time-depending bioimaging, coupled with a slight systemic toxicity, supports the clinical potential in terms of accurate diagnosis and treatment response in diverse hepatic tumors[34].

Non-invasive determination of absolute indocyanine green (ICG) concentration and methods to calculate circulating blood volume have not been developed. To solve this problem, Savchenko *et al*[35] experimented with the use of combined methods (invasive and non-invasive) to assess the rate of removal of dyes on a single platform, which allows post-processing of data obtained by optical densitometry. This study aimed to develop an invasive method to estimate plasma elimination of ICG for diagnosing liver function. The authors used a program for collecting and displaying data, and an experimental technique to assess ICG concentrations in various solutions. The measurements from aqueous dye, albumin solution, and blood plasma correlated with the data from a commercial UV/visible spectrophotometer. This platform is cost-effective, easy of use, and allows a quick real-time determination of results. The authors suggest that this new system can evaluate liver function and predict its recovery with higher accuracy than existing methods[35]. Schwarz *et al*[36] conducted an extensive retrospective analysis among patients who were diagnosed for preoperative ICG clearance before hepatic resection in a university hospital setting. In patients with both poor ICG clearance and risk factors such as male sex, major liver resections should be a caution option and patients informed in consequence. While parenchymal sparing surgery and combinations with intraoperative ablations of small lesions are suggested, extensive resection is not recommended. The authors suggested ICG clearance testing is a helpful tool selecting patients at risk to develop postoperative hepatic dysfunction. Suggestive liver remnant anticipation in patients with poor ICG clearance needs to be further investigated[36]. However, the authors reported study's limitations due to its retrospective design, and the overlap of preoperative ICG clearance testing values which was noticed in both patients with presence and absence of hepatic abnormality. They suggest the use of multiple parameters and not a single ones to better estimate the risk for liver resection[36]. Jinghua Li *et al*[37]reported *via* a retrospective study the usefulness of ICG fluorescence imaging-guided technique for the safe application of laparoscopic right posterior hepatectomy.

Liver HCC management

Regarding BCLC recommendations patients with HCC (stage B) are not selected for hepatic resection, but they may benefit of palliative medication[38]. Furthermore, patients with Child–Pugh class B are not usually eligible for liver resection. However, the best survival benefit of resection has been demonstrated by many studies regarding patients selected in very early-, early-, and intermediate-BCLC stage. Moreover, this therapy provides better outcomes when multinodular liver and large tumors in patients with portal hypertension and Child–Pugh class B cirrhosis. Romano *et al*[38] explored this controversial topic and showed liver resection may improve the short- and long-term survival for patients with BCLC-B and Child–Pugh B HCC. However, the authors suggest further investigations to identify patients with intermediate-stage HCC most likely to benefit from hepatic resection[38].

In patients with BCLC-B/C stage disease, there is a need to identify the benefits of direct-acting antivirals (DAAs). Furthermore, the possibility of modifying the natural history of these patients should be prospectively investigated[39]. Due to the lack of studies experiencing DAA impact in these patients, Reig *et al*[39] proposed making decisions on a patient-by-patient approach. If liver dysfunction in patients with BCLC-B/C is only linked to HCV infection, DAA prioritization should be based on a patient-by-patient approach; thus each patient should be informed about potential advantages and risks of this therapy[39].

The BCLC model evolves to better improve patient's outcomes. The management of patients with HCC is accomplished in a multidisciplinary model through specialties such as hepatology, surgery, medical oncology, radiology, interventional radiology (IR) and radiation oncology[40-43]. The BCLC staging system is preferred because it considers tumor, patient, and liver characteristics and links them to specific therapies[40,41]. Reig *et al*[41] recently updated the BCLC algorithm providing new insights in the clinical management of HCC. Note that three main setups are clearly delineated for patients with this malignancy. Initial step stratifies patients in function of disease evolvement status, which is linked to first therapy option. A focus should be kept on the combination of the overall required patient's characteristics for choosing the option expected to fulfill the best survival condition. Robust scientific evidence supports the initial recommendations. The "clinical decision-making" section highlights the complexity of individualized management and need to personalize decisions regarding tumour burden, incorporating the concepts of treatment stage migration (TSM) and untreatable progression. We agree with the authors that any exhaustive algorithm should not be expected for each patient. Hence a multiparametric evaluation for each patient is required; this should be integrated into multidisciplinary tumour boards with the active collaboration of all partners involved in care. To be effective such boards should clearly establish initial approach from which individual decisions can be made[41]. This update

recognizes liver transplantation (LT) as one of the main study objectives[43]. Interventional radiologists (IRs) can play a central role in multi-directional treatment to promote liver transplantation.

This latest update is being improved. Lucatelli *et al*[43] contributed to clarify the role of IRs into BCLC 0/A/B stages. For instance: In BCLC 0, ablation is better; whether it is no feasible, resection may be prioritized and then transarterial chemo-embolization considering TSM concept. Transarterial radio-embolization (TARE) is recommended only for single HCC B 8 cm given the LEGACY trial findings[41]. Although we can see a limited role given to TARE, there is hope. Owing the negative phase III trials, no role for IRs in BCLC C patients. As expected, allocation and TSM arise the complexity of the algorithm, but bring it closer to daily practice[43,44]. However, we are still far from reaching level one evidence [43].

In the context of expanded therapy options pertaining to TSM, external beam radiotherapy (EBRT) that is missing in the 2022 updated guidelines, may be a useful option in algorithms for HCC[42]. The safety and efficacy of EBRT have been enough demonstrated regardless BCLC stage. Hallemeier *et al*[42] recognize important advances in BCLC 2022 update even if EBRT is missing. Based on the current available evidence, the authors suggest to incorporate EBRT into BCLC guidelines when "first treatment options" suitable or not feasible, or disease progression after first therapy. Owing the American Society for Radiation Oncology recommendations, they propose EBRT option for future BCLC updates as follow: (1) In BCLC 0/A HCC, EBRT may be an alternative non-surgical as definitive treatment or as a bridge to transplant; (2) in BCLC B/C, EBRT may be used with or without embolization or systemic treatment; and (3) in BCLC D HCC, EBRT may serve as palliative therapy for tumor-related pain. Authors acknowledge the usefulness of current and future trials for overall therapies in refining HCC therapy options, and suggest further EBRT experiments pertaining to HCC[42].

Elhence *et al*[44] recognize that this latest BCLC HCC update is improved regarding BCLC B group stratification, a possible novel immunotherapy for BCLC-C group and LT option when tumor burden is suitable for transplant regardless liver dysfunction. However, according to the authors, there is a lot to be done regarding the use of hepatic function in BCLC stage allocation and linking with the first therapy option. In fact, this new BCLC update recommends classifying a patient's liver function in two categories (preserved- and end-stage- liver function) for stage attribution and prognosis. A dichotomic classification may not achieve the goal of stage attribution as it is susceptible to misinterpretation. The authors recognize that the treatment decisions for patients with HCC are often complex and should consider multiple dimensions and not single variable. However, the use of such staging allocation systems is linked to the unambiguity, because they are only open to an interpretation[44].

Beside BCLC HCC therapy we describe other strategies for the management of liver diseases.

LT is recommended for patients with end-stage liver disease. However, the discordance between offer and demand for suitable organs implies extended criteria in the field of transplantation, a fortiori for steatotic liver grafts. To mitigate the risks linked to these criteria, a new platform such as ex situ oxygenated machine perfusion (MP) is being experienced for dynamic preservation, reconditioning, and viability tests to enhance organ use. MP at hyperthermic (> 38°C) condition (HyMPs) has received little attention. The liver plays an important role in the regulation of the core body temperature. Although hyperthermia significantly modifies vasculature and cellular and metabolic processes, it preserves liver structural integrity[45]. In a state of mild hyperthermia (38°C-40°C), induced vasodilation redirects blood flow out of the liver tissue, this leads to significant changes in the production of cellular proteins and metabolites. Heat shock protein responses amplify to protect cells from membrane protein dysfunction due to heat stress. This modified metabolism in the hepatic tissue increases glycogenolysis and reduces triglyceride stores *via* the lipolysis pathway. The mitochondrial respiration increases, indicating a hypermetabolic state. Consequently, the increase in CO_2 production may be considered as a real-time measure indicator of metabolism during MP. The authors suggest that HyMP may promote steatotic liver optimization. Initial evidence supports the high potential value of mild hyperthermia in conditioning steatotic livers before to conduct transplantation[45].

Margonis *et al*[46] reported a great interest in solid benign liver tumors regarding the advanced knowledge upon pathophysiology of these lesions. The authors conducted an evidence-based review by focusing on the diagnosis and management of these tumors. They suggest further investigations to better understand the underlying pathogenesis and natural history of benign liver tumors to provide clinicians with evidence-based guidelines for therapeutic optimization of patients with such lesions[46].

Hydroxymethyglutaryl-coenzyme A reductase inhibitors (statins) are a commonly prescribed class of medication for hyperlipidemia and coronary artery disease (CAD) treatment. This medicine has a proven benefit in reducing death rate for patients with CAD. These drugs have the potential for adverse effects, including myalgia, myopathy, and hepatotoxicity[47]. The authors summarized recent data on statin-associated liver toxicity and highlighted the low risk of DILI. Preclinical data support the potential hepatoprotective effects of statin therapy. They also reviewed preclinical data, suggesting the potential hepatoprotective effects of statin therapy[47].

CONCLUSION

Investigations regarding liver function have revealed the involvement of extracellular vesicles (exosomes), FXR and ions exchangers (Na^+/H^+) in liver physiology and hepatic disorders. Exosomal miRNAs and proteins may be novel potential markers for hepatic disease. The effects of selective targeted therapy of NHEs on the liver are inconclusive, and more comprehensive studies using methods to inhibit and regulate the function and target NHEs in liver-related damage are needed. Regarding liver dysfunction the relationship between COVID-19 and liver dysfunction has been extensively discussed. Although liver defects are commonly reported, especially in patients with severe COVID-19 or underlying chronic liver disease, the exact association with liver abnormalities is still unknown. Further studies are needed to investigate the impact of SARS-CoV-2 on HBV infection. The role of EBV should be considered in the occurrence of liver and extrahepatic pathologies. The combination of this pathogen with HBV and HCV requires further in-depth study. To date, there are no specific tools for the diagnosis and treatment of DILI. As for the increase in indirect DILI induced by immunomodulatory therapy of cancer, controlled trials comparing different doses of corticosteroids are required, since the higher doses recommended by oncological societies are not anodyne.

The rate of mortality due to sepsis is extremely elevated in cirrhotic patients, which suggests more probable infection, accurate diagnosis, and suitable antimicrobial therapy.

Unknown liver disorder or unexplained jaundice should attract clinician attention to suspect hyperthyroidism.

Pregnancy condition may worsen chronic hepatic diseases state, while hepatocellular adenoma and carcinoma may be challenging for diagnosis and management in pregnancy. Fatty acid beta-oxidation disorder, linked to long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency, may cause acute fatty liver and HELLP in the fetus.

New biochemical and imaging methods have also been described. Based on the necrotic HCC model, HMS or HMS-enhanced MR demonstrated that the size of tumor necrosis is correlated with mitochondrial activity. The time-dependent bioimaging improvement of HMS and weak systemic toxicity support the impactful clinical potential for better management of various hepatic tumors, in terms of accurate diagnosis and therapeutic response. Despite the progress made in ultrasound elastography, there is still need to improve in terms of image quality, ease of use, quantitation, and range of measurable tissue characteristics. This imaging technique is suggested as a promising method to completely replace liver biopsy for steatosis diagnosis.

The level of sH2a in human serum is considerably reduced in cases of hepatic cirrhosis. Consequently, sH2a may be a helpful non-invasive biomarker for functional mass evaluation of numerous liver cell types. A system for collecting and displaying data and assessing ICG concentration in various solutions has been developed, which allows a performant diagnosis of liver function and prediction of its recovery with high accuracy.

HCC management has been discussed regarding BCLC algorithms. BCLC HCC 2022 update incorporates novelties such as: (1) Staging stratification of patients in function of their evolutionary status, which is linked to the first treatment option (combination of all patient's characteristics required for choosing the option expected to provide the best survival); (2) the "clinical decision-making" section highlights individualized management and need to personalize decisions regarding tumour burden (incorporating the concepts of TSM and untreatable progression); (3) further stratification in BCLC-B group; (4) novel immunotherapy options for BCLC-C group; and (5) LT option when tumor burden is suitable for transplantation. Another new idea is the EBRT incorporation suggestion into BCLC guidelines. HyMP could be a promising therapeutic approach to optimize the use of steatotic livers. Evidence supports the usefulness of mild hyperthermia in conditioning steatotic livers. IRs can even play an important role in increasing the number of transplanted patients. There is a lot to be done regarding the use of liver function in BCLC stage allocation and linking with the first treatment option. Owing the negative phase III trials, the new BCLC update does not recognize any role to IRs in BCLC C patients. HCC management will evolve as new informations become available and novel therapeutic approaches will be experienced. Further RCTs of EBRT for HCC are needed.

Solid benign liver tumors need to be further investigated to better understand the underlying pathogenesis and natural history of the disease to optimize the treatment of patients with these lesions.

Hydroxymethyglutaryl-coenzyme A reductase inhibitors (statins), a pharmacological class of medicine with proven benefits, reduces CAD mortality. These drugs have been reported to have potential adverse effects, mainly myalgia, myopathy, and hepatotoxicity. Recent data on statin-associated liver toxicity highlights low clinical DILI risk attributable to this drug. Moreover, preclinical data suggests potential hepatoprotective effects of statin therapy.

HyMP could be a promising therapeutic approach to optimize the use of steatotic livers. Evidence supports the usefulness of mild hyperthermia in conditioning steatotic livers.

IRs can even play an important role in increasing the number of transplanted patients.

This work may be helpful for physicians and researchers in managing and further investigating liver defects. In addition to the study's perspectives, future experiments should be focused on either aspect of liver diseases management: decompensated cirrhosis, hepatocellular carcinoma, transplantation, COVID-19 and liver, or pathophysiology of liver damage to make more impact.

FOOTNOTES

Author contributions: The author discusses hot spots, problems and futures direction of current research in the field of multidisciplinary and pluralistic management of liver diseases.

Conflict-of-interest statement: All the author declares no conflict of interest.

Country/Territory of origin: Mali

ORCID number: Nouhoum Bouare 0000-0002-8362-6740.

S-Editor: Liu JH
L-Editor: A
P-Editor: Liu JH

REFERENCES

1 Liver Function In Digestive System | How It Works. REAL REAL REVIEWS. Available from: https://therealrealreviews.com/Liver-function-indigestive-system-how-it-works
2 **Spengler U**, Fischer HP, Caselmann WH. Liver Disease Associated with Viral Infections. *Zakim and Boyer's Hepatology* 2011 [DOI: 10.1016/B978-1-4377-0881-3.00034-6]
3 Glossary of Curriculum Terminology. Available from: https://inee.org/sites/default/files/resources/UNESCO_IBE_2013_IBE_glossary_of_curriculum_terminology.pdf
4 **Abolghasemi M**, Ghahramani M, Abbasian H. Pluralistic approach to research methods: A necessary step towards interdisciplinary courses. *TTEM* 2012; **7**: 100-102 Available from: https://www.researchgate.net/publication/287053713_Pluralistic_approach_to_research_methods_A_necessary_step_towards_interdisciplinary_courses
5 **Bouare N**, Minta DK, Dabo A, Gerard C. COVID-19: A pluralistic and integrated approach for efficient management of the pandemic. *World J Virol* 2022; **11**: 20-39 [PMID: 35117969 DOI: 10.5501/wjv.v11.i1.20]
6 **Cai S**, Cheng X, Pan X, Li J. Emerging role of exosomes in liver physiology and pathology. *Hepatol Res* 2017; **47**: 194-203 [PMID: 27539153 DOI: 10.1111/hepr.12794]
7 **Lee Y**, Kim JH. The emerging roles of extracellular vesicles as intercellular messengers in liver physiology and pathology. *Clin Mol Hepatol* 2022; **28**: 706-724 [PMID: 35232008 DOI: 10.3350/cmh.2021.0390]
8 **Théry C**, Witwer KW, Aikawa E, Alcaraz MJ, Anderson JD, Andriantsitohaina R, Antoniou A, Arab T, Archer F, Atkin-Smith GK, Ayre DC, Bach JM, Bachurski D, Baharvand H, Balaj L, Baldacchino S, Bauer NN, Baxter AA, Bebawy M, Beckham C, Bedina Zavec A, Benmoussa A, Berardi AC, Bergese P, Bielska E, Blenkiron C, Bobis-Wozowicz S, Boilard E, Boireau W, Bongiovanni A, Borràs FE, Bosch S, Boulanger CM, Breakefield X, Breglio AM, Brennan MÁ, Brigstock DR, Brisson A, Broekman ML, Bromberg JF, Bryl-Górecka P, Buch S, Buck AH, Burger D, Busatto S, Buschmann D, Bussolati B, Buzás EI, Byrd JB, Camussi G, Carter DR, Caruso S, Chamley LW, Chang YT, Chen C, Chen S, Cheng L, Chin AR, Clayton A, Clerici SP, Cocks A, Cocucci E, Coffey RJ, Cordeiro-da-Silva A, Couch Y, Coumans FA, Coyle B, Crescitelli R, Criado MF, D'Souza-Schorey C, Das S, Datta Chaudhuri A, de Candia P, De Santana EF, De Wever O, Del Portillo HA, Demaret T, Deville S, Devitt A, Dhondt B, Di Vizio D, Dieterich LC, Dolo V, Dominguez Rubio AP, Dominici M, Dourado MR, Driedonks TA, Duarte FV, Duncan HM, Eichenberger RM, Ekström K, El Andaloussi S, Elie-Caille C, Erdbrügger U, Falcón-Pérez JM, Fatima F, Fish JE, Flores-Bellver M, Försönits A, Frelet-Barrand A, Fricke F, Fuhrmann G, Gabrielsson S, Gámez-Valero A, Gardiner C, Gärtner K, Gaudin R, Gho YS, Giebel B, Gilbert C, Gimona M, Giusti I, Goberdhan DC, Görgens A, Gorski SM, Greening DW, Gross JC, Gualerzi A, Gupta GN, Gustafson D, Handberg A, Haraszti RA, Harrison P, Hegyesi H, Hendrix A, Hill AF, Hochberg FH, Hoffmann KF, Holder B, Holthofer H, Hosseinkhani B, Hu G, Huang Y, Huber V, Hunt S, Ibrahim AG, Ikezu T, Inal JM, Isin M, Ivanova A, Jackson HK, Jacobsen S, Jay SM, Jayachandran M, Jenster G, Jiang L, Johnson SM, Jones JC, Jong A, Jovanovic-Talisman T, Jung S, Kalluri R, Kano SI, Kaur S, Kawamura Y, Keller ET, Khamari D, Khomyakova E, Khvorova A, Kierulf P, Kim KP, Kislinger T, Klingeborn M, Klinke DJ 2nd, Kornek M, Kosanović MM, Kovács ÁF, Krämer-Albers EM, Krasemann S, Krause M, Kurochkin IV, Kusuma GD, Kuypers S, Laitinen S, Langevin SM, Languino LR, Lannigan J, Lässer C, Laurent LC, Lavieu G, Lázaro-Ibáñez E, Le Lay S, Lee MS, Lee YXF, Lemos DS, Lenassi M, Leszczynska A, Li IT, Liao K, Libregts SF, Ligeti E, Lim R, Lim SK, Linē A, Linnemannstöns K, Llorente A, Lombard CA, Lorenowicz MJ, Lörincz ÁM, Lötvall J, Lovett J, Lowry MC, Loyer X, Lu Q, Lukomska B, Lunavat TR, Maas SL, Malhi H, Marcilla A, Mariani J, Mariscal J, Martens-Uzunova ES, Martin-Jaular L, Martinez MC, Martins VR, Mathieu M, Mathivanan S, Maugeri M, McGinnis LK, McVey MJ, Meckes DG Jr, Meehan KL, Mertens I, Minciacchi VR, Möller A, Møller Jørgensen M, Morales-Kastresana A, Morhayim J, Mullier F, Muraca M, Musante L, Mussack V, Muth DC, Myburgh KH, Najrana T, Nawaz M, Nazarenko I, Nejsum P, Neri C, Neri T, Nieuwland R, Nimrichter L, Nolan JP, Nolte-'t Hoen EN, Noren Hooten N, O'Driscoll L, O'Grady T, O'Loghlen A, Ochiya T, Olivier M, Ortiz A, Ortiz LA, Osteikoetxea X, Østergaard O, Ostrowski M, Park J, Pegtel DM, Peinado H, Perut F, Pfaffl MW, Phinney DG, Pieters BC, Pink RC, Pisetsky DS, Pogge

von Strandmann E, Polakovicova I, Poon IK, Powell BH, Prada I, Pulliam L, Quesenberry P, Radeghieri A, Raffai RL, Raimondo S, Rak J, Ramirez MI, Raposo G, Rayyan MS, Regev-Rudzki N, Ricklefs FL, Robbins PD, Roberts DD, Rodrigues SC, Rohde E, Rome S, Rouschop KM, Rughetti A, Russell AE, Saá P, Sahoo S, Salas-Huenuleo E, Sánchez C, Saugstad JA, Saul MJ, Schiffelers RM, Schneider R, Schøyen TH, Scott A, Shahaj E, Sharma S, Shatnyeva O, Shekari F, Shelke GV, Shetty AK, Shiba K, Siljander PR, Silva AM, Skowronek A, Snyder OL 2nd, Soares RP, Sódar BW, Soekmadji C, Sotillo J, Stahl PD, Stoorvogel W, Stott SL, Strasser EF, Swift S, Tahara H, Tewari M, Timms K, Tiwari S, Tixeira R, Tkach M, Toh WS, Tomasini R, Torrecilhas AC, Tosar JP, Toxavidis V, Urbanelli L, Vader P, van Balkom BW, van der Grein SG, Van Deun J, van Herwijnen MJ, Van Keuren-Jensen K, van Niel G, van Royen ME, van Wijnen AJ, Vasconcelos MH, Vechetti IJ Jr, Veit TD, Vella LJ, Velot É, Verweij FJ, Vestad B, Viñas JL, Visnovitz T, Vukman KV, Wahlgren J, Watson DC, Wauben MH, Weaver A, Webber JP, Weber V, Wehman AM, Weiss DJ, Welsh JA, Wendt S, Wheelock AM, Wiener Z, Witte L, Wolfram J, Xagorari A, Xander P, Xu J, Yan X, Yáñez-Mó M, Yin H, Yuana Y, Zappulli V, Zarubova J, Žėkas V, Zhang JY, Zhao Z, Zheng L, Zheutlin AR, Zickler AM, Zimmermann P, Zivkovic AM, Zocco D, Zuba-Surma EK. Minimal information for studies of extracellular vesicles 2018 (MISEV2018): a position statement of the International Society for Extracellular Vesicles and update of the MISEV2014 guidelines. *J Extracell Vesicles* 2018; **7**: 1535750 [PMID: 30637094 DOI: 10.1080/20013078.2018.1535750]

9 **Xu R**, Greening DW, Zhu HJ, Takahashi N, Simpson RJ. Extracellular vesicle isolation and characterization: toward clinical application. *J Clin Invest* 2016; **126**: 1152-1162 [PMID: 27035807 DOI: 10.1172/JCI81129]

10 **Panzitt K**, Wagner M. FXR in liver physiology: Multiple faces to regulate liver metabolism. *Biochim Biophys Acta Mol Basis Dis* 2021; **1867**: 166133 [PMID: 33771667 DOI: 10.1016/j.bbadis.2021.166133]

11 **Li T**, Tuo B. Pathophysiology of hepatic Na^+/H^+ exchange (Review). *Exp Ther Med* 2020; **20**: 1220-1229 [PMID: 32742358 DOI: 10.3892/etm.2020.8888]

12 **Bobermin LD**, Quincozes-Santos A. COVID-19 and hyperammonemia: Potential interplay between liver and brain dysfunctions. *Brain Behav Immun Health* 2021; **14**: 100257 [PMID: 33870235 DOI: 10.1016/j.bbih.2021.100257]

13 **Cao TT**, Zhang GQ, Pellegrini E, Zhao Q, Li J, Luo LJ, Pan HQ. COVID-19 and its effects on the digestive system. *World J Gastroenterol* 2021; **27**: 3502-3515 [PMID: 34239265 DOI: 10.3748/wjg.v27.i24.3502]

14 **Choudhary NS**, Dhampalwar S, Saraf N, Soin AS. Outcomes of COVID-19 in Patients with Cirrhosis or Liver Transplantation. *J Clin Exp Hepatol* 2021; **11**: 713-719 [PMID: 33994708 DOI: 10.1016/j.jceh.2021.05.003]

15 **Wu ZH**, Yang DL. A meta-analysis of the impact of COVID-19 on liver dysfunction. *Eur J Med Res* 2020; **25**: 54 [PMID: 33148326 DOI: 10.1186/s40001-020-00454-x]

16 **M'bodj K**, Abid H, Adil N, Abkari ME, Aqodad N. What would be the impact of COVID-19 on liver function of a patient with chronic hepatitis B? *Pan Afr Med J* 2021; **38**: 225 [PMID: 34046130 DOI: 10.11604/pamj.2021.38.225.28123]

17 **Solomay TV**, Semenenko TA, Ivanova MY. [The role of Epstein-Barr viral infection and hepatitis B and C in liver pathology.]. *Vopr Virusol* 2019; **64**: 215-220 [PMID: 32167686 DOI: 10.36233/0507-4088-2019-64-5-215-220]

18 **Björnsson ES**. Clinical management of patients with drug-induced liver injury (DILI). *United European Gastroenterol J* 2021; **9**: 781-786 [PMID: 35084797 DOI: 10.1002/ueg2.12113]

19 **Du M**, Yang S, Liu M, Liu J. COVID-19 and liver dysfunction: Epidemiology, association and potential mechanisms. *Clin Res Hepatol Gastroenterol* 2022; **46**: 101793 [PMID: 34428501 DOI: 10.1016/j.clinre.2021.101793]

20 **Aleem A**, Mahadevaiah G, Shariff N, Kothadia JP. Hepatic manifestations of COVID-19 and effect of remdesivir on liver function in patients with COVID-19 illness. *Proc (Bayl Univ Med Cent)* 2021; **34**: 473-477 [PMID: 34219928 DOI: 10.1080/08998280.2021.1885289]

21 **D'Ardes D**, Boccatonda A, Cocco G, Fabiani S, Rossi I, Bucci M, Guagnano MT, Schiavone C, Cipollone F. Impaired coagulation, liver dysfunction and COVID-19: Discovering an intriguing relationship. *World J Gastroenterol* 2022; **28**: 1102-1112 [PMID: 35431501 DOI: 10.3748/wjg.v28.i11.1102]

22 **Kim TS**, Choi DH. Liver Dysfunction in Sepsis. *Korean J Gastroenterol* 2020; **75**: 182-187 [PMID: 32326684 DOI: 10.4166/kjg.2020.75.4.182]

23 **Yorke E**. Hyperthyroidism and Liver Dysfunction: A Review of a Common Comorbidity. *Clin Med Insights Endocrinol Diabetes* 2022; **15**: 11795514221074672 [PMID: 35153522 DOI: 10.1177/11795514221074672]

24 **Ibrahim SM**, Pithavala YK, Vourvahis M, Chen J. A literature review of liver function test elevations in rifampin drug-drug interaction studies. *Clin Transl Sci* 2022; **15**: 1561-1580 [PMID: 35470578 DOI: 10.1111/cts.13281]

25 **Birkness-Gartman JE**, Oshima K. Liver pathology in pregnancy. *Pathol Int* 2022; **72**: 1-13 [PMID: 34818440 DOI: 10.1111/pin.13186]

26 **Wei S**, Yu X. Efficacy of resveratrol supplementation on liver enzymes in patients with non-alcoholic fatty liver disease: A systematic review and meta-analysis. *Complement Ther Med* 2021; **57**: 102635 [PMID: 33271299 DOI: 10.1016/j.ctim.2020.102635]

27 **Hallajzadeh J**, Milajerdi A, Amirani E, Attari VE, Maghsoudi H, Mirhashemi SM. Effects of propolis supplementation on glycemic status, lipid profiles, inflammation and oxidative stress, liver enzymes, and body weight: a systematic review and meta-analysis of randomized controlled clinical trials. *J Diabetes Metab Disord* 2021; **20**: 831-843 [PMID: 34178866 DOI: 10.1007/s40200-020-00696-w]

28 **Sangsefidi ZS**, Mozaffari-Khosravi H, Sarkhosh-Khorasani S, Hosseinzadeh M. The effect of anthocyanins supplementation on liver enzymes: A systematic review and meta-analysis of randomized clinical trials. *Food Sci Nutr* 2021; **9**: 3954-3970 [PMID: 34262751 DOI: 10.1002/fsn3.2278]

29 **Mousavi SM**, Jayedi A, Bagheri A, Zargarzadeh N, Wong A, Persad E, Akhgarjand C, Koohdani F. What is the influence of cinnamon supplementation on liver enzymes? *Phytother Res* 2021; **35**: 5634-5646 [PMID: 34212447 DOI: 10.1002/ptr.7200]

30 **Ghaffar S**, Naqvi MA, Fayyaz A, Abid MK, Khayitov KN, Jalil AT, Alsaikhan F, Hammid AT, Al-Gazally ME, Mohammadparast V, Jannat B, Nouri M. What is the influence of grape products on liver enzymes? *Complement Ther Med* 2022; **69**: 102845 [PMID: 35671889 DOI: 10.1016/j.ctim.2022.102845]

31 **Benyair R**, Kondratyev M, Veselkin E, Tolchinsky S, Shenkman M, Lurie Y, Lederkremer GZ. Constant serum levels of secreted asialoglycoprotein receptor sH2a and decrease with cirrhosis. *World J Gastroenterol* 2011; **17**: 5305-5309 [PMID:

22219600 DOI: 10.3748/wjg.v17.i48.5305]
32 **da Silva LCM**, de Oliveira JT, Tochetto S, de Oliveira CPMS, Sigrist R, Chammas MC. Ultrasound elastography in patients with fatty liver disease. *Radiol Bras* 2020; **53**: 47-55 [PMID: 32313337 DOI: 10.1590/0100-3984.2019.0028]
33 **Bastati N**, Beer L, Mandorfer M, Poetter-Lang S, Tamandl D, Bican Y, Elmer MC, Einspieler H, Semmler G, Simbrunner B, Weber M, Hodge JC, Vernuccio F, Sirlin C, Reiberger T, Ba-Ssalamah A. Does the Functional Liver Imaging Score Derived from Gadoxetic Acid-enhanced MRI Predict Outcomes in Chronic Liver Disease? *Radiology* 2020; **294**: 98-107 [PMID: 31743083 DOI: 10.1148/radiol.2019190734]
34 **Kim JG**, Jang MS, Kumari N, Choi JK, Im GH, Kwon T, Lee JH, Lee WJ, Lee IS. Differential characterization of hepatic tumors in MR imaging by burst-released Mn^{2+}-ions from hollow manganese-silicate nanoparticles in the liver. *Biomaterials* 2020; **230**: 119600 [PMID: 31727420 DOI: 10.1016/j.biomaterials.2019.119600]
35 **Savchenko E**, Kolokolnikov I, Velichko E, Osovskikh V, Kiseleva L, Musakulova Z. Design of Liver Functional Reserve Estimation Technique Based on Optical Densitometry. *Diagnostics (Basel)* 2020; **10** [PMID: 32824396 DOI: 10.3390/diagnostics10080599]
36 **Schwarz C**, Plass I, Fitschek F, Punzengruber A, Mittlböck M, Kampf S, Asenbaum U, Starlinger P, Stremitzer S, Bodingbauer M, Kaczirek K. The value of indocyanine green clearance assessment to predict postoperative liver dysfunction in patients undergoing liver resection. *Sci Rep* 2019; **9**: 8421 [PMID: 31182746 DOI: 10.1038/s41598-019-44815-x.]
37 **Li J**, Li X, Zhang X, Wang H, Li K, He Y, Liu Z, Zhang Z, Yuan Y. Indocyanine green fluorescence imaging-guided laparoscopic right posterior hepatectomy. *Surg Endosc* 2022; **36**: 1293-1301 [PMID: 33683434 DOI: 10.1007/s00464-021-08404-2]
38 **Romano F**, Chiarelli M, Garancini M, Scotti M, Zago M, Cioffi G, De Simone M, Cioffi U. Rethinking the Barcelona clinic liver cancer guidelines: Intermediate stage and Child-Pugh B patients are suitable for surgery? *World J Gastroenterol* 2021; **27**: 2784-2794 [PMID: 34135554 DOI: 10.3748/wjg.v27.i21.2784]
39 **Reig M**, Cabibbo G. Antiviral therapy in the palliative setting of HCC (BCLC-B and -C). *J Hepatol* 2021; **74**: 1225-1233 [PMID: 33582128 DOI: 10.1016/j.jhep.2021.01.046]
40 **Burak KW**, Kneteman NM. An evidence-based multidisciplinary approach to the management of hepatocellular carcinoma (HCC): the Alberta HCC algorithm. *Can J Gastroenterol* 2010; **24**: 643-650 [PMID: 21157578 DOI: 10.1155/2010/410574]
41 **Reig M**, Forner A, Rimola J, Ferrer-Fàbrega J, Burrel M, Garcia-Criado Á, Kelley RK, Galle PR, Mazzaferro V, Salem R, Sangro B, Singal AG, Vogel A, Fuster J, Ayuso C, Bruix J. BCLC strategy for prognosis prediction and treatment recommendation: The 2022 update. *J Hepatol* 2022; **76**: 681-693 [PMID: 34801630 DOI: 10.1016/j.jhep.2021.11.018]
42 **Hallemeier CL**, Apisarnthanarax S, Dawson LA. BCLC 2022 update: Important advances, but missing external beam radiotherapy. *J Hepatol* 2022; **76**: 1237-1239 [PMID: 34990748 DOI: 10.1016/j.jhep.2021.12.029]
43 **Lucatelli P**, Guiu B. 2022 Update of BCLC Treatment Algorithm of HCC: What's New for Interventional Radiologists? *Cardiovasc Intervent Radiol* 2022; **45**: 275-276 [PMID: 35088139 DOI: 10.1007/s00270-021-03047-1]
44 **Elhence A**, Shalimar. Liver dysfunction in Barcelona Clinic Liver Cancer-2022 update: Clear as day or still in fog? *J Hepatol* 2022; **76**: 1236-1237 [PMID: 34954248 DOI: 10.1016/j.jhep.2021.12.016]
45 **Thorne AM**, Ubbink R, Brüggenwirth IMA, Nijsten MW, Porte RJ, de Meijer VE. Hyperthermia-induced changes in liver physiology and metabolism: a rationale for hyperthermic machine perfusion. *Am J Physiol Gastrointest Liver Physiol* 2020; **319**: G43-G50 [PMID: 32508156 DOI: 10.1152/ajpgi.00101.2020]
46 **Margonis GA**, Ejaz A, Spolverato G, Rastegar N, Anders R, Kamel IR, Pawlik TM. Benign solid tumors of the liver: management in the modern era. *J Gastrointest Surg* 2015; **19**: 1157-1168 [PMID: 25560181 DOI: 10.1007/s11605-014-2723-x]
47 **Meurer L**, Cohen SM. Drug-Induced Liver Injury from Statins. *Clin Liver Dis* 2020; **24**: 107-119 [PMID: 31753243 DOI: 10.1016/j.cld.2019.09.007]

World Journal of Hepatology

Submit a Manuscript: https://www.f6publishing.com

World J Hepatol 2022 November 27; 14(11): 1931-1939

DOI: 10.4254/wjh.v14.i11.1931

ISSN 1948-5182 (online)

MINIREVIEWS

Haemochromatosis revisited

Aline Morgan Alvarenga, Pierre Brissot, Paulo Caleb Junior Lima Santos

Specialty type: Genetics and heredity

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Barisani D, Italy; Liu Z, China

Received: May 3, 2022
Peer-review started: May 3, 2022
First decision: June 8, 2022
Revised: June 27, 2022
Accepted: November 2, 2022
Article in press: November 2, 2022
Published online: November 27, 2022

Aline Morgan Alvarenga, Paulo Caleb Junior Lima Santos, Department of Pharmacology - Escola Paulista de Medicina, Universidade Federal de São Paulo, São Paulo 04044-020, Brazil

Pierre Brissot, University of Rennes1, Rennes 35065, France

Corresponding author: Paulo Caleb Junior Lima Santos, PhD, Adjunct Professor, Department of Pharmacology - Escola Paulista de Medicina, Universidade Federal de São Paulo, 03 de Maio Street, 100. INFAR, 4° andar - Vila Clementino - São Paulo, SP, São Paulo 04044-020, Brazil. paulo.caleb@unifesp.br

Abstract

Haemochromatosis is a genetic disease caused by hepcidin deficiency, responsible for an increase in intestinal iron absorption. Haemochromatosis is associated with homozygosity for the *HFE* p.Cys282Tyr mutation. However, rare cases of haemochromatosis (non-*HFE* haemochromatosis) can also be caused by path-ogenic variants in other genes (such as *HJV, HAMP, TFR2* and *SLC40A1*). A working group of the International Society for the Study of Iron in Biology and Medicine (BIOIRON Society) has concluded that the classification based in different molecular subtypes is difficult to be adopted in clinical practice and has proposed a new classification approaching clinical questions and molecular complexity. The aim of the present review is to provide an update on classification, path-ophysiology and therapeutic recommendations.

Key Words: Haemochromatosis; Iron overload; *HFE*; Molecular diagnosis; Hepcidin

Core Tip: Haemochromatosis is a genetic disease caused by hepcidin deficiency, responsible for an increase in intestinal iron absorption. Haemochromatosis is associated with homozygosity for the *HFE* p.Cys282Tyr mutation. However, rare cases of haemochromatosis (non-*HFE* haemochromatosis) can also be caused by pathogenic variants in other genes (such as *HJV, HAMP, TFR2* and *SLC40A1*). A working group of the International Society for the Study of Iron in Biology and Medicine (BIOIRON Society) has concluded that classification based on different molecular subtypes is difficult to be adopted in clinical practice and has proposed a new classification approaching clinical questions and molecular complexity. The aim of the present review is to provide an update on classification, pathophysiology and therapeutic recommendations.

Citation: Alvarenga AM, Brissot P, Santos PCJL. Haemochromatosis revisited. *World J Hepatol* 2022; 14(11): 1931-1939
URL: https://www.wjgnet.com/1948-5182/full/v14/i11/1931.htm
DOI: https://dx.doi.org/10.4254/wjh.v14.i11.1931

INTRODUCTION

Haemochromatosis is characterized as systemic iron overload of genetic origin caused by hepcidin deficiency, including decreased production of this hormone or decreased activity of hepcidin-ferroportin binding[1] (Figure 1). Iron overload leads to damage such as liver cirrhosis, cardiomyopathy, diabetes, arthritis, hypogonadism and skin pigmentation. Therapeutic phlebotomy is effective and safe [2]. Iron chelation, mostly confined to iron overload related to chronic anaemia needing repeated transfusions, is an alternative (or adjuvant) treatment in haemochromatosis, especially when phlebotomies are medically contraindicated[3] or iron overload is so great that iron depletion is urgently needed.

Mostly, the disease is related to homozygosity for the gene *HFE* p.Cys282Tyr genetic alteration (which is the classical type 1 haemochromatosis). p.Cys282Tyr/p.His63Asp compound heterozygosity has been reported to be linked to haemochromatosis. Rarely, the cases of haemochromatosis can be caused by pathogenic variants in the other genes (called non-*HFE* haemochromatosis). Juvenile haemochromatosis corresponds classically to type 2, which can be subdivided into type 2A, related to mutations in the hemojuvelin gene, and type 2B, related to mutations in the hepcidin gene. Furthermore, mutations in the *TFR2* and *SLC40A1* genes can be associated to haemochromatosis (more details below)[4].

The clinical diagnosis of iron overload is of course the starting point before treating and monitoring the patient. Early diagnosis and treatment are essential for improving survival and for a better quality of life[5]. The present review focuses on new information on classification, pathophysiology, and therapeutic recommendations.

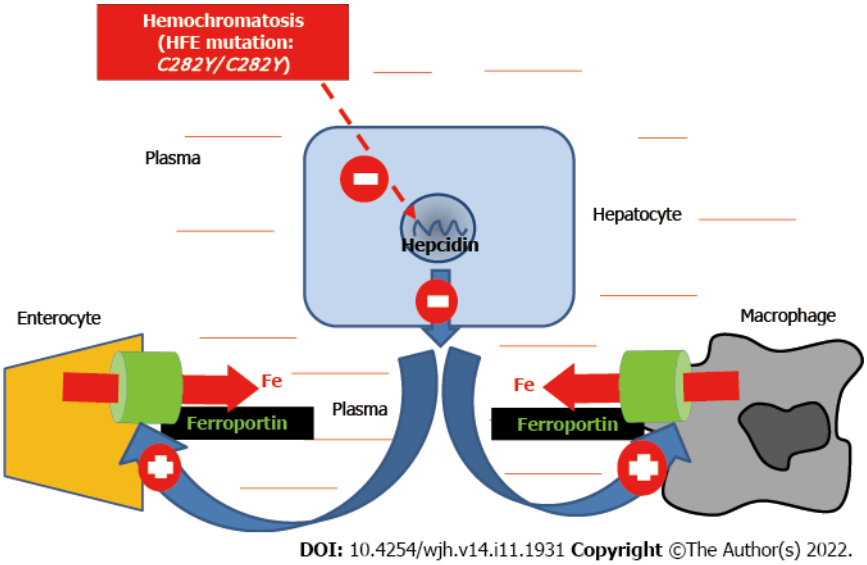
EPIDEMIOLOGY

The HEIRS study evaluated, among other aspects, the prevalence of the *HFE* p.Cys282Tyr and p.His63Asp genetic alterations in a sample with 100000 adults during a period of 5 years in the United States and Canada. Among the obtained results, 299 subjects were homozygous for p.Cys282Tyr, and the estimated prevalence of p.Cys282Tyr homozygous was of 0.44% in white non-Hispanic subjects, 0.11% in native and American indigenous, 0.027% in Hispanic, 0.014% in Black, 0.012% in Pacific Island descendants and 0.000039% in Asiatic[6] subjects.

A review that selected 27 studies, totalling 6302 samples of subjects of European countries, showed the average prevalence of 0.4% for p.Cys282Tyr homozygotes and 9.2% for p.Cys282Tyr heterozygotes [7]. A cohort study with 22 centres across England, Scotland, and Wales in UK Biobank, including 451243 participants of European descent, identified 2890 (0.6%) individuals with p.Cys282Tyr homozygous genotype. The authors diagnosed haemochromatosis in 21.7% (95% confidence interval 19.5%-24.1%, 281/1294) of men and 9.8% (8.4%-11.2%, 156/1596) of women. Since p.C282Y-associated iron overload is preventable and treatable provided intervention is early, their findings justify re-examination of options for expanded early case ascertainment and screening[8]. Another study in blood donors in Brazil found 2.1% for the *HFE* 282Tyr allelic frequencies[9].

SYSTEMIC IRON REGULATION

Plasma iron finds its source in enterocytes and macrophages. It circulates, bound to transferrin, its iron transporter that can link up to two atoms of ferric iron (Fe^{3+}). Transferrin-bound iron binds to transferrin receptor 1 on the plasma membrane of most cells, and forms a complex that is endocytosed. In the acidic environment of the endosome, ferric iron is reduced to ferrous iron (Fe^{2+}) through the activity of a ferrireductase (STEAP3). Ferrous iron is, then, released from the endosome to the cytosol *via* DMT1, and forms a labile iron pool. Iron leaves the cell through the activity of ferroportin, which is the only known protein to ensure cellular iron export into the plasma. Ferroportin export activity is regulated by the circulating hormone called hepcidin[10-13]. Hepcidin is a peptide essentially liberated by the hepatocytes[14-16]. The ferroportin-hepcidin binding at the level of the cell membrane induces the internalization, ubiquitination and degradation of intracellular ferroportin so that plasmatic levels of hepcidin strongly affect plasma iron concentration[17]. Low levels of hepcidin increase iron export from the enterocytes and macrophages, leading in turn to increased plasma iron concentration and transferrin



DOI: 10.4254/wjh.v14.i11.1931

Figure 1 Mechanism of iron overload in *HFE*-related hemochromatosis. The *C282Y/C282Y* mutations (homozygosity for *C282Y*) lead to decreased synthesis of the iron hormone hepcidin, which in turn causes an increased activity of the iron export protein ferroportin both at the digestive and splenic levels. The result is increased plasma iron leading to organ iron overload.

saturation (TS) (Figure 2).

The adequate content of body iron requires the maintenance of plasma iron concentration within normal limits (12-25 μM) and the regulation of TS. Normal TS is between 20% and 45%, allowing adequate iron delivery to the cells[18]. In mammals, plasma iron binds to transferrin that is synthetized by the hepatocytes and, once released in the plasma, receives two atoms of ferric iron by an active process involving ferroxidase enzymes. When TS increases, non-transferrin bound iron may appear in the plasma and can lead to cell toxicity. The body is not capable of increasing iron excretion, even in case of iron excess. This holds true for genetic iron overload related to increased intestinal iron absorption, as well as for secondary iron overload that can be caused by repeated blood transfusions in the setting especially of chronic haemolytic anaemias, and various other haematological situations[19-24].

DIAGNOSIS

The diagnostic approach to haemochromatosis has become a noninvasive one, meaning that liver biopsy is no more needed. Indeed, haemochromatosis can be diagnosed on the sole combination of clinical, laboratory and imaging data.

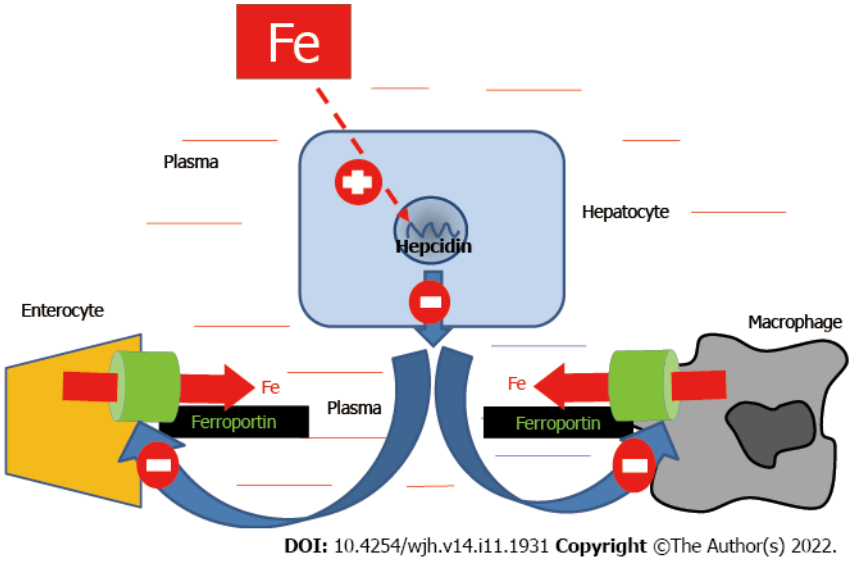
Clinical features

Haemochromatosis can be asymptomatic for many years, and the lack of symptoms usually persists until adulthood, > 30 years old (and often > 40 in men and > 50 in women) in *HFE*-related haemochromatosis. In non-*HFE* haemochromatosis, the symptoms can appear around 20-30 years old. In general, the symptoms are diverse, which explains the frequent and harmful diagnosis delay[25-27].

Among the most common symptoms are fatigue and joint pain[28]. The dermatological signs are mainly melanoderma (dark pigmentation of the skin), but can also include skin dryness and nails alterations (and paradoxically koilonychia, a classical symptom of iron deficiency anaemia). The main liver symptoms are hepatomegaly and slight transaminase increase, contrasting with well-preserved liver functioning. Haemochromatosis can cause diabetes, hypogonadism or hypopituitarism[29]. It is of utmost importance to have in mind that *HFE*-haemochromatosis is only present in Caucasian populations or descents, and that non-*HFE* haemochromatosis, although much rarer, can be observed in many ethnic groups.

Laboratory tests

The most common diagnostic biochemical tests consist of the following plasma parameters: iron, transferrin saturation (TS - determined from plasma transferrin concentration rather than from total iron binding capacity) and serum ferritin (SF). Increased TS is the earliest biochemical abnormality in haemochromatosis, reflecting increased iron absorption. It is > 45% (often > 60% in men and > 50% in women) and should be confirmed by a second assay. SF (> 300 μg/L in men and postmenopausal women, and > 200 μg/L in premenopausal women) can be raised in the inflammatory process, the



DOI: 10.4254/wjh.v14.i11.1931

Figure 2 Schematic representation of systemic iron regulation. Physiologically, increased plasma iron leads to an increased synthesis of the iron hormone hepcidin, causing in turn decreased activity of the iron export protein Ferroportin both at the digestive and splenic levels, which leads to compensatory decreased plasma iron. The reverse mechanism occurs in case of physiological iron deficiency. Please note that, in haemochromatosis, the body behaves as if it was chronically iron deficient.

metabolic syndrome (especially with diabetes), alcohol consumption and liver injury[30,31].

Genetic testing

Genetic testing is indicated whenever the patient has confirmed high levels of TS, provided other mechanisms than body iron excess have been ruled out (especially hypotransferrinemia due to hepatocellular failure, nephrotic syndrome or malnutrition). Haemochromatosis should not be seen as a simple monogenic disease, but as the complex result of the environment interaction, lifestyle and genetic factors that have not yet been fully identified. In case of *HFE* p.Cys282Tyr homozygosity, it is widely accepted that this genetic profile forms the necessary basis for the development of body iron excess[32]. Concerning the profile of compound heterozygosity p.Cys282Tyr and p.His63Asp, it can only predispose to mild iron overload and the physician should be careful when informing the patient, because alluding to haemochromatosis can cause unnecessary anxiety to the patient and its family[33,34].

When genetic testing for *HFE* provides a negative result, further genetic explorations, related to other genes involved in iron metabolism and hepcidin synthesis, can be conducted, requiring expert laboratories. Non-*HFE* haemochromatosis is less influenced by cofactors and characterized by a more severe and homogeneous clinical condition appearing at a younger age. Modern approaches, based on next generation sequencing (NGS), widely expand the possibilities of diagnosing these rare entities, but, at the same time, raise challenges for interpreting the results. NGS requires expert centres, either public or private, and its cost remains high but tend to decrease over time[35].

It should be kept in mind that, for most clinical practice worldwide, screening of *HJV*, *HAMP*, *TFR2* and *SLC40A1*, and even of *HFE*, through direct sequencing is not widely available. Treatment is usually not dependent on molecular diagnosis[36-39]. It is therefore important to remember that, in this setting of difficult access to genetic identification, patients with a clinical diagnosis of haemochromatosis should not wait for the result of a DNA test before starting treatment.

Imaging tests

Magnetic resonance imaging (MRI) can be useful to assess and quantify body iron overload, especially in the liver, without forgetting to evaluate also the iron status of the spleen (the contrast between major liver iron excess and absence of spleen iron overload being highly suggestive of hepcidin deficiency). Laboratory examinations together with MRI have now largely replaced liver biopsy[40,20-22].

THERAPEUTIC RECOMMENDATIONS

The standard treatment for haemochromatosis remains phlebotomy (or therapeutic bleeding). This treatment has been shown to be effective and safe and has contributed to the reduction of morbidity and mortality in patients with haemochromatosis[41]. With each phlebotomy of 500 mL blood, approximate 250 mg iron are extracted and subsequently mobilized in a compensatory process from the organs

where it had accumulated (especially the liver). Repeated phlebotomies result in the total removal of excess iron from the body. The therapeutic schedule must be individually adapted to each patient, and should take into account the patient's levels of ferritin (according to the local reference values), age, gender and comorbidities. Recent studies have observed a beneficial effect in early and sustained treatment of patients with excess iron, even when iron overload was mild and/or SF only mildly elevated [32,42].

Table 1 shows two treatment phases: initial or intensive (induction), and the maintenance phase. Haemochromatosis patients under venesection therapy should never stop watching their iron parameters since the natural trend of increased iron absorption persists opening the risk of progressive iron excess reconstitution. Oral iron chelation is the commonly recommended treatment for iron overload related to chronic anaemia requiring regular blood transfusions. However, iron chelators may also be used as an alternative, or adjuvant, form of treatment in rare cases of haemochromatosis in which phlebotomies are contraindicated, not feasible due to problems in venous access, or if efficacy may not be not sufficiently achieved with phlebotomies alone in case of massive iron excess[43].

In the future, hepcidin-based treatments could potentially become an adjunct treatment to phlebotomy in the intensive phase or a substitute in the maintenance phase. The interest of restoring hepicidin levels is, of course, based on the fact that hepcidin deficiency is the mechanism accounting for the development of iron overload in patients with haemochromatosis[44].

EVOLUTION OF HAEMOCHROMATOSIS NOMENCLATURE

A working group of the International Society for the Study of Iron in Biology and Medicine (BIOIRON Society) proposed a new classification for haemochromatosis. The recent advances of pathophysiology and molecular basis of iron metabolism have highlighted that haemochromatosis is caused by mutations in at least five genes, resulting in insufficient hepcidin production or, rarely, resistance to hepcidin action. All these different data have led to a disease classification based on different molecular subtypes, mainly reflecting successive gene discoveries. When analysing the name of the disease, we can see the relation of something circulating in the blood haemo-) being responsible for skin and organ damage and pigmentation (-chromatosis). The work of recognizing excess iron as the aetiology of organ toxicity took several decades, and was attributable to Joseph Sheldon in 1935, who was also the first to suggest the genetic origin of the metabolic defect. Over time, it became evident that the genetic basis of haemochromatosis was more heterogeneous than initially thought, and several variants in other iron-controlling genes were progressively associated with the disorder. Unlike in the past, fully expressed and potentially lethal haemochromatosis with the full-blown picture associating liver cirrhosis, diabetes, endocrine dysfunction, and heart failure is rarely seen in current clinical practice. The novel classification aims to be practical whenever a detailed molecular characterization of haemochromatosis is not available[45].

Previous classification of haemochromatosis

Table 2 shows the previous classification of haemochromatosis. Most cases of haemochromatosis are caused by homozygous *HFE* p.Cys282Tyr genotype (type 1 haemochromatosis). The *HFE* gene is located on chromosome 6p21, encodes the haemochromatosis protein (HFE) which plays, through a not yet fully elucidated mechanism, a role in hepcidin regulation. As previously mentioned, the main symptoms are arthropathy, skin hyperpigmentation, liver damage, diabetes, endocrine dysfunctions, cardiomyopathy and hypogonadism. Haemochromatosis can also be caused, but much more rarely, by changes in other genes than *HFE*. These rare cases of haemochromatosis can be due to pathogenic variants in other genes, corresponding to non-*HFE* haemochromatosis. There were four entities: juvenile haemochromatosis (JH) or type 2 haemochromatosis, subdivided into two forms: Type 2A JH, caused by mutations in the *HJV* gene on chromosome 1q21, and type 2B JH, caused by mutations in the *HAMP* gene on chromosome 19q13. Type 2A genetic changes are involved in hepcidin synthesis, and are related to the BMP co-receptor. It has an early onset, in subjects younger than 30 years, and corresponds to severe forms of haemochromatosis. Type 2B haemochromatosis is related to a genetic defect of the *HAMP* gene, which encodes hepcidin. The main signs and symptoms are hypogonadism and cardiomyopathy. Haemochromatosis types 3 and 4 are caused by mutations in the *TFR2* and *SLC40A1* genes on chromosomes 7q22 and 2q32. Type 4 haemochromatosis, due to *SLC40A1* mutations, is divided into 4A and 4B and has autosomal dominant inheritance. In type 4A, also named ferroportin disease, there is an alteration of ferroportin export activity leading to massive iron overload in the spleen, whereas TS is not elevated. Type 4B haemochromatosis is related to a gain of function process leading to ferroportin resistance to hepcidin and to clinical phenotype very close to that of type I haemochromatosis[46,47].

New classification of haemochromatosis proposed by an international expert working group

This working group proposed to de-emphasize the use of the molecular subtype criteria in favour of a classification better related to clinical issues. The group included both clinicians and basic scientists during a meeting in Heidelberg, Germany. The main ideas showing the need for changing the

Table 1 Review about therapeutic recommendations

Who to start treatment	Patient with homozygous genotype *HFE p.Cys282Tyr (C282Y/C282Y)* and with biochemical indication of iron overload, namely, fasting transferrin saturation increase (≥ 45%) together with serum ferritin increase (> 300 μg/L for men and postmenopausal women, and > 200 μg/L in premenopausal women).
Initial phase or intensive (of induction)	Phlebotomies of 400-500 mL (according to body weight) weekly or every 2 wk (depending on the amount of initial iron excess). Objective: to reach a serum ferritin value of 50 μg/L, in the absence of anaemia.
Maintaining phase	One phlebotomy every 1-4 mo, depending on iron parameters.Objective: to maintain ferritin levels around 50 μg/L (without anaemia; haemoglobin levels should not be < 11 g/dL). Plasma ferritin should be verified prior to each phlebotomy, and transferrin saturation approximately twice a year.
When to stop	Patients presenting iron overload should never stop checking their iron parameters, and their treatment must be planned according to their iron parameters, general health condition, and age.

Table 2 Previous classification of haemochromatosis

Haemochromatosis types	Gene	Location	Inheritance	Gene product function	Main clinical manifestations
1	*HFE*	6p21.3	AR	Involved in hepcidin synthesis *via* BMP6, interaction with TFR1.	Iron overload and known manifestation of classical haemochromatosis (*HFE* type). Arthropathy, skin hyperpigmentation, liver damage, diabetes, endocrine dysfunction, cardiomyopathy, hypogonadism.
2A	*HJV*	1p21	AR	Involved in hepcidin synthesis, BMP co-receptor.	Type 2: earlier onset, < 30 yr. Severe iron overload and juvenile form of haemochromatosis.
2B	*HAMP*	19q13	AR	Hepcidin, produced mainly in hepatocytes, downregulates iron efflux from enterocytes *via* ferroportin.	Hypogonadism and cardiomyopathy more prevalent. Severe iron overload and juvenile form of haemochromatosis.
3	*TFR2*	7q22	AR	Transferrin receptor 2, mediates cellular uptake of transferrin-bound iron and is involved in hepcidin synthesis.	Phenotypes can range from moderate to severe form of haemochromatosis.
4A	*SLC40A1*	2q32	AD	Ferroportin is an iron exporter in duodenal.	Lower tolerance to phlebotomies with risk of anaemia. The phenotype strongly differs from newly defined haemochromatosis (mild clinical symptoms, major spleen iron overload, major hyperferritinemia without transferrin saturation increase).
4B	*SLC40A1*		AD	Ferroportin acting a hepcidin receptor.	Very rare; in general, clinically similar to *HFE*-haemochromatosis.

TFR2: Transferrin receptor 2; *HFE*: Encodes *HFE* protein; *HJV*: Encodes hemojuvelin; *HAMP*: Encodes hepcidin; *TFR2*: Encodes transferrin receptor 2; *SLC40A1*: Encodes ferroportin; BMP6: Bone morphogenetic protein 6, AR: Autosomal recessive; AD: Autosomal dominant.

nomenclature were as follows: (1) Poor applicability in clinical practice; (2) Need for complex cooperation between geneticists, bioinformaticians and clinicians for resolving the most difficult cases, to determine the pathogenic nature or not of many variants; (3) Former type 4A haemochromatosis represents an iron overload syndrome strongly and clinically distinct from haemochromatosis (due to a different pathogenesis); (4) Former type 3 can correspond to JH; (5) Former type 3 haemochromatosis can be observed at an older age than JH[45]; and finally (6) Former type 4B, which corresponds to a hepcidin-refractory syndrome shares a similar phenotype to hepcidin-deficiency-related forms of haemochromatosis. Table 3 presents this new classification.

Rigorously speaking, the term haemochromatosis should now be reserved for a unique genetic clinicopathological condition characterized by increased TS, iron overload in the liver (but not in the spleen), prevalent involvement of periportal hepatocytes with iron spared Kupffer cells, and signs and/or symptoms associated with iron overload. Therefore, the term haemochromatosis should no longer be applied to all the previous subtypes. Finally, the panellists agreed that the definition of haemochromatosis should also include the absence of haematological signs of a primary/predominant red blood cell disorder, such as anaemia or reticulocytosis. In summary, as stated by the panellists, the novel classification proposed is based on a pathophysiological cornerstone (hepcidin deficiency) and a distinct clinical/biochemical phenotype. It recognizes the difficulties of a complete molecular characterization and has the potential of being easily shareable between practicing physicians and referral centres. Avoiding any ambiguity is essential for clear and effective communication that will facilitate proper diagnosis and treatment of haemochromatosis and was the main incentive for a real nom-

Table 3 New classification of haemochromatosis proposed by the working group

New classification	Molecular pattern	Note
HFE-related	*p.Cys282Tyr* homozygosity or compound heterozygosity of *p.Cys282Tyr* with other rare *HFE* pathogenic variants or *HFE*deletion.	Low penetrance; consider presence of host-related or environmental cofactors for iron overload. In subjects with other *HFE* genotypes (*p.Cys282Tyr/His63Asp* compound heterozygosity or p.His63Asp homozygosity) consider second-line genetic testing for rarer variants.
Non *HFE*-related	Rare pathogenic variants in non-*HFE* genes: - *HJV*-related; - *HAMP*-related; - *TFR2*-related; - *SLC40A1* (very rare gain-of-function variant)-related.	Potentially, variants in any hepcidin-regulatory gene may be causative (the effects of novel mutations should be confirmed through functional and epidemiological studies). Molecular subtypes characterization only at specialized canters, but diagnosis of non-*HFE* related haemochromatosis is sufficient to start phlebotomies at nonspecialized centres[1].
Digenic[2]	Double heterozygosity and/or double homozygosity/heterozygosity for variants in two different genes involved in iron metabolism (*HFE* and/or non-*HFE*).	More commonly, *p.Cys282Tyr* variants in *HFE* gene might coexist with variants in other genes; rarely, both variants involve non-*HFE* genes.
Molecularly undefined	Molecular characterization (still) not available after sequencing of known genes (provisional diagnosis).	Patients should be referred (or DNA should be sent) to specialized centers.

[1]Providing that iron overload is confirmed by magnetic resonance imaging (MRI). If MRI is not accessible, close monitoring of haemoglobin level is needed to avoid occurrence of anaemia.
[2]Caution is needed to interpret as digenic inheritance results from next generation sequencing outputs reporting several variants in gene panels. Whenever possible, strict criteria for defining pathogenic variants should be adopted, and corroborated by family segregation and/or functional studies.

enclature review[48].

CONCLUSION

It is strongly proposed to adopt, from now on, this new and more relevant classification of haemochromatosis that can be easily shared between practicing doctors and reference canters and will contribute to facilitate the diagnosis and therefore to improve the therapeutic management of haemochromatosis patients.

FOOTNOTES

Author contributions: Alvarenga AM, Brissot P, and Santos PC have contributed equally to this work.

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

Country/Territory of origin: Brazil

ORCID number: Paulo Caleb Junior Lima Santos 0000-0002-8297-0793.

S-Editor: Wu YXJ
L-Editor: Kerr C
P-Editor: Wu YXJ

REFERENCES

1 **Brissot P**, Pietrangelo A, Adams PC, de Graaff B, McLaren CE, Loréal O. Haemochromatosis. *Nat Rev Dis Primers* 2018; **4**: 18016 [PMID: 29620054 DOI: 10.1038/nrdp.2018.16]
2 **Santos PC**, Krieger JE, Pereira AC. Molecular diagnostic and pathogenesis of hereditary hemochromatosis. *Int J Mol Sci* 2012; **13**: 1497-1511 [PMID: 22408404 DOI: 10.3390/ijms13021497]

3 **Adams P**, Altes A, Brissot P, Butzeck B, Cabantchik I, Cançado R, Distante S, Evans P, Evans R, Ganz T, Girelli D, Hultcrantz R, McLaren G, Marris B, Milman N, Nemeth E, Nielsen P, Pineau B, Piperno A, Porto G, Prince D, Ryan J, Sanchez M, Santos P, Swinkels D, Teixeira E, Toska K, Vanclooster A, White D; Contributors and Hemochromatosis International Taskforce. Therapeutic recommendations in HFE hemochromatosis for p.Cys282Tyr (C282Y/C282Y) homozygous genotype. *Hepatol Int* 2018; **12**: 83-86 [PMID: 29589198 DOI: 10.1007/s12072-018-9855-0]

4 **Alvarenga AM**, da Silva NK, Fonseca PFS, Oliveira TGM, da Silva Monteiro JB, Cançado RD, Naoum FA, Dinardo CL, Brissot P, Santos PCJL. Novel mutations in the bone morphogenetic protein 6 gene in patients with iron overload and non-homozygous genotype for the HFE p.Cys282Tyr mutation. *Blood Cells Mol Dis* 2020; **84**: 102444 [PMID: 32464486 DOI: 10.1016/j.bcmd.2020.102444]

5 **Fonseca PFS**, Cançado RD, Naoum FA, Dinardo CL, Fonseca GHH, Gualandro SFM, Krieger JE, Pereira AC, Brissot P, Santos PCJL. Quality of life scores differs between genotypic groups of patients with suspected hereditary hemochromatosis. *BMC Med Genet* 2018; **19**: 3 [PMID: 29301508 DOI: 10.1186/s12881-017-0513-5]

6 **McLaren CE**, Barton JC, Adams PC, Harris EL, Acton RT, Press N, Reboussin DM, McLaren GD, Sholinsky P, Walker AP, Gordeuk VR, Leiendecker-Foster C, Dawkins FW, Eckfeldt JH, Mellen BG, Speechley M, Thomson E; Hemochromatosis and Iron Overload Study Research Investigators. Hemochromatosis and Iron Overload Screening (HEIRS) study design for an evaluation of 100,000 primary care-based adults. *Am J Med Sci* 2003; **325**: 53-62 [PMID: 12589228 DOI: 10.1097/00000441-200302000-00001]

7 **Hanson EH**, Imperatore G, Burke W. HFE gene and hereditary hemochromatosis: a HuGE review. Human Genome Epidemiology. *Am J Epidemiol* 2001; **154**: 193-206 [PMID: 11479183 DOI: 10.1093/aje/154.3.193]

8 **Pilling LC**, Tamosauskaite J, Jones G, Wood AR, Jones L, Kuo CL, Kuchel GA, Ferrucci L, Melzer D. Common conditions associated with hereditary haemochromatosis genetic variants: cohort study in UK Biobank. *BMJ* 2019; **364**: k5222 [PMID: 30651232 DOI: 10.1136/bmj.k5222]

9 **Santos PC**, Cançado RD, Terada CT, Rostelato S, Gonzales I, Hirata RD, Hirata MH, Chiattone CS, Guerra-Shinohara EM. HFE gene mutations and iron status of Brazilian blood donors. *Braz J Med Biol Res* 2010; **43**: 107-114 [PMID: 20027482 DOI: 10.1590/s0100-879x2009007500031]

10 **Babitt JL**, Huang FW, Xia Y, Sidis Y, Andrews NC, Lin HY. Modulation of bone morphogenetic protein signaling in vivo regulates systemic iron balance. *J Clin Invest* 2007; **117**: 1933-1939 [PMID: 17607365 DOI: 10.1172/jci31342]

11 **Casanovas G**, Mleczko-Sanecka K, Altamura S, Hentze MW, Muckenthaler MU. Bone morphogenetic protein (BMP)-responsive elements located in the proximal and distal hepcidin promoter are critical for its response to HJV/BMP/SMAD. *J Mol Med (Berl)* 2009; **87**: 471-480 [PMID: 19229506 DOI: 10.1007/s00109-009-0447-2]

12 **Meynard D**, Kautz L, Darnaud V, Canonne-Hergaux F, Coppin H, Roth MP. Lack of the bone morphogenetic protein BMP6 induces massive iron overload. *Nat Genet* 2009; **41**: 478-481 [PMID: 19252488 DOI: 10.1038/ng.320]

13 **Corradini E**, Rozier M, Meynard D, Odhiambo A, Lin HY, Feng Q, Migas MC, Britton RS, Babitt JL, Fleming RE. Iron regulation of hepcidin despite attenuated Smad1,5,8 signaling in mice without transferrin receptor 2 or Hfe. *Gastroenterology* 2011; **141**: 1907-1914 [PMID: 21745449 DOI: 10.1053/j.gastro.2011.06.077]

14 **Huang FW**, Pinkus JL, Pinkus GS, Fleming MD, Andrews NC. A mouse model of juvenile hemochromatosis. *J Clin Invest* 2005; **115**: 2187-2191 [PMID: 16075059 DOI: 10.1172/JCI25049]

15 **Truksa J**, Lee P, Beutler E. Two BMP responsive elements, STAT, and bZIP/HNF4/COUP motifs of the hepcidin promoter are critical for BMP, SMAD1, and HJV responsiveness. *Blood* 2009; **113**: 688-695 [PMID: 18997172 DOI: 10.1182/blood-2008-05-160184]

16 **Xiao X**, Dev S, Canali S, Bayer A, Xu Y, Agarwal A, Wang CY, Babitt JL. Endothelial Bone Morphogenetic Protein 2 (Bmp2) Knockout Exacerbates Hemochromatosis in Homeostatic Iron Regulator (Hfe) Knockout Mice but not Bmp6 Knockout Mice. *Hepatology* 2020; **72**: 642-655 [PMID: 31778583 DOI: 10.1002/hep.31048]

17 **Fonseca PF**, Cançado RD, Uellendahl Lopes MM, Correia E, Lescano MA, Santos PC. HAMP Gene Mutation Associated with Juvenile Hemochromatosis in Brazilian Patients. *Acta Haematol* 2016; **135**: 228-231 [PMID: 27007796 DOI: 10.1159/000444119]

18 **Lescano MA**, Tavares LC, Santos PCJL. Juvenile hemochromatosis: *HAMP* mutation and severe iron overload treated with phlebotomies and deferasirox. *World J Clin Cases* 2017; **5**: 381-383 [PMID: 29085829 DOI: 10.12998/wjcc.v5.i10.381]

19 **Papanikolaou G**, Tzilianos M, Christakis JI, Bogdanos D, Tsimirika K, MacFarlane J, Goldberg YP, Sakellaropoulos N, Ganz T, Nemeth E. Hepcidin in iron overload disorders. *Blood* 2005; **105**: 4103-4105 [PMID: 15671438 DOI: 10.1182/blood-2004-12-4844]

20 **Piperno A**. "Classification and diagnosis of iron overload. *Haematologica* 1998; **83**: 447-455 [DOI: 10.1017/cbo9780511666476.018]

21 **Andrews NC**. A genetic view of iron homeostasis. *Semin Hematol* 2002; **39**: 227-234 [PMID: 12382197 DOI: 10.1053/shem.2002.35632]

22 **Camaschella C**. Understanding iron homeostasis through genetic analysis of hemochromatosis and related disorders. *Blood* 2005; **106**: 3710-3717 [PMID: 16030190 DOI: 10.1182/blood-2005-05-1857]

23 **Fix OK**, Kowdley KV. "Hereditary hemochromatosis. *Minerva medica* 2008; **99**: 605-617 [DOI: 10.1016/B978-1-4377-0121-0.50252-X]

24 **Barton JC**, McDonnell SM, Adams PC, Brissot P, Powell LW, Edwards CQ, Cook JD, Kowdley KV. Management of hemochromatosis. Hemochromatosis Management Working Group. *Ann Intern Med* 1998; **129**: 932-939 [PMID: 9867745 DOI: 10.7326/0003-4819-129-11_Part_2-199812011-00003]

25 **Pietrangelo A**. Inherited metabolic disease of the liver. *Curr Opin Gastroenterol* 2009; **25**: 209-214 [PMID: 19342951 DOI: 10.1097/MOG.0b013e328329e13d]

26 **Brissot P**, Bardou-Jacquet E, Jouanolle AM, Loréal O. Iron disorders of genetic origin: a changing world. *Trends Mol Med* 2011; **17**: 707-713 [PMID: 21862411 DOI: 10.1016/j.molmed.2011.07.004]

27 **Pietrangelo A**. Hereditary hemochromatosis: pathogenesis, diagnosis, and treatment. *Gastroenterology* 2010; **139**: 393-408, 408.e1 [PMID: 20542038 DOI: 10.1053/j.gastro.2010.06.013]

28 **Powell**, Lawrie W. , Rebecca C. Seckington, and Yves Deugnier. "Haemochromatosis. *The Lancet* 2016; **388**: 706-716

[DOI: 10.1016/S0140-6736(15)01315-X]

29 **Doyard M**, Chappard D, Leroyer P, Roth MP, Loréal O, Guggenbuhl P. Decreased Bone Formation Explains Osteoporosis in a Genetic Mouse Model of Hemochromatosiss. *PloS One* 2016; **11**: e0148292 [PMID: 26829642 DOI: 10.1371/journal.pone.0148292]

30 **Aslan D**, Crain K, Beutler E. A new case of human atransferrinemia with a previously undescribed mutation in the transferrin gene. *Acta Haematol* 2007; **118**: 244-247 [PMID: 18097132 DOI: 10.1159/000112726]

31 **European Association for the Study of the Liver**. EASL clinical practice guidelines for HFE hemochromatosis. *J Hepatol* 2010; **53**: 3-22 [PMID: 20471131 DOI: 10.1016/j.jhep.2010.03.001]

32 **Bacon BR**, Adams PC, Kowdley KV, Powell LW, Tavill AS; American Association for the Study of Liver Diseases. Diagnosis and management of hemochromatosis: 2011 practice guideline by the American Association for the Study of Liver Diseases. *Hepatology* 2011; **54**: 328-343 [PMID: 21452290 DOI: 10.1002/hep.24330]

33 **Santos PC**, Dinardo CL, Cançado RD, Schettert IT, Krieger JE, Pereira AC. Non-HFE hemochromatosis. *Rev Bras Hematol Hemoter* 2012; **34**: 311-316 [PMID: 23049448 DOI: 10.5581/1516-8484.20120079]

34 **Gurrin LC**, Bertalli NA, Dalton GW, Osborne NJ, Constantine CC, McLaren CE, English DR, Gertig DM, Delatycki MB, Nicoll AJ, Southey MC, Hopper JL, Giles GG, Anderson GJ, Olynyk JK, Powell LW, Allen KJ; HealthIron Study Investigators. HFE C282Y/H63D compound heterozygotes are at low risk of hemochromatosis-related morbidity. *Hepatology* 2009; **50**: 94-101 [PMID: 19554541 DOI: 10.1002/hep.22972]

35 **Walsh A**, Dixon JL, Ramm GA, Hewett DG, Lincoln DJ, Anderson GJ, Subramaniam VN, Dodemaide J, Cavanaugh JA, Bassett ML, Powell LW. The clinical relevance of compound heterozygosity for the C282Y and H63D substitutions in hemochromatosis. *Clin Gastroenterol Hepatol* 2006; **4**: 1403-1410 [PMID: 16979952 DOI: 10.1016/j.cgh.2006.07.009]

36 **Sandhu K**, Flintoff K, Chatfield MD, Dixon JL, Ramm LE, Ramm GA, Powell LW, Subramaniam VN, Wallace DF. Phenotypic analysis of hemochromatosis subtypes reveals variations in severity of iron overload and clinical disease. *Blood* 2018; **132**: 101-110 [PMID: 29743178 DOI: 10.1182/blood-2018-02-830562]

37 **Brissot P**, de Bels F. Current approaches to the management of hemochromatosis. *Hematology Am Soc Hematol Educ Program* 2006; 36-41 [PMID: 17124037 DOI: 10.1182/asheducation-2006.1.36]

38 **Cancado RD**, Alvarenga AM, Santos PCJ. HFE hemochromatosis: an overview about therapeutic recommendations. *Hematol Transfus Cell Ther* 2022; **44**: 95-99 [PMID: 34824033 DOI: 10.1016/j.htct.2021.06.020]

39 **Wood JC**. Estimating tissue iron burden: current status and future prospects. *Br J Haematol* 2015; **170**: 15-28 [PMID: 25765344 DOI: 10.1111/bjh.13374]

40 **St Pierre TG**, Clark PR, Chua-anusorn W, Fleming AJ, Jeffrey GP, Olynyk JK, Pootrakul P, Robins E, Lindeman R. Noninvasive measurement and imaging of liver iron concentrations using proton magnetic resonance. *Blood* 2005; **105**: 855-861 [PMID: 15256427 DOI: 10.1182/blood-2004-01-0177]

41 **Gandon Y**. "Non-invasive assessment of hepatic iron stores by MRI. *The Lancet* 2004; **363**: 357-362 [DOI: 10.1016/S0140-6736(04)15436-6]

42 **Bardou-Jacquet E**, Morcet J, Manet G, Lainé F, Perrin M, Jouanolle AM, Guyader D, Moirand R, Viel JF, Deugnier Y. Decreased cardiovascular and extrahepatic cancer-related mortality in treated patients with mild HFE hemochromatosis. *J Hepatol* 2015; **62**: 682-689 [PMID: 25450707 DOI: 10.1016/j.jhep.2014.10.025]

43 **Cançado R**, Melo MR, de Moraes Bastos R, Santos PC, Guerra-Shinohara EM, Chiattone C, Ballas SK. Deferasirox in patients with iron overload secondary to hereditary hemochromatosis: results of a 1-yr Phase 2 study. *Eur J Haematol* 2015; **95**: 545-550 [PMID: 25684349 DOI: 10.1111/ejh.12530]

44 **Ong Sim Y**. "Reduction of body iron in HFE-related haemochromatosis and moderate iron overload (Mi-Iron): a multicentre, participant-blinded, randomised controlled trial." The Lancet Haematology 4.12 (2017): e607-e614 [DOI: 10.1016/S2352-3026(17)30214-4]

45 **Girelli D**, Busti F, Brissot P, Cabantchik I, Muckenthaler MU, Porto G. Hemochromatosis classification: update and recommendations by the BIOIRON Society. *Blood* 2022; **139**: 3018-3029 [PMID: 34601591 DOI: 10.1182/blood.2021011338]

46 **Liu J**, Sun B, Yin H, Liu S. Hepcidin: A Promising Therapeutic Target for Iron Disorders: A Systematic Review. *Medicine (Baltimore)* 2016; **95**: e3150 [PMID: 27057839 DOI: 10.1097/MD.0000000000003150]

47 **Santos PC**, Cançado RD, Pereira AC, Chiattone CS, Krieger JE, Guerra-Shinohara EM. HJV hemochromatosis, iron overload, and hypogonadism in a Brazilian man: treatment with phlebotomy and deferasirox. *Acta Haematol* 2010; **124**: 204-205 [PMID: 21071928 DOI: 10.1159/000321493]

48 **Brissot P**. "Hemochromatoses. *Revue Francophone des Laboratoires* 2021; **533**: 33-43 [DOI: 10.1016/S1773-035X(21)00169-6]

World Journal of Hepatology

Submit a Manuscript: https://www.f6publishing.com

World J Hepatol 2022 November 27; 14(11): 1940-1952

DOI: 10.4254/wjh.v14.i11.1940

ISSN 1948-5182 (online)

MINIREVIEWS

Current status of disparity in liver disease

Tomoki Sempokuya, Josh Warner, Muaataz Azawi, Akane Nogimura, Linda L Wong

Specialty type: Gastroenterology and hepatology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Bellini MI, Italy; Lee S, South Korea; Lee S, South Korea

Received: September 18, 2022
Peer-review started: September 18, 2022
First decision: November 5, 2022
Revised: November 9, 2022
Accepted: November 16, 2022
Article in press: November 16, 2022
Published online: November 27, 2022

Tomoki Sempokuya, Division of Gastroenterology and Hepatology, Department of Internal Medicine, University of Nebraska Medical Center, Omaha, NE 68198, United States

Josh Warner, Department of Internal Medicine, University of Nebraska Medical Center, Omaha, NE 68198, United States

Muaataz Azawi, Division of Gastroenterology and Hepatology, Sanford Center for Digestive Health, Sioux Falls 57105, SD, Uruguay

Akane Nogimura, Department of Public Health, Nagoya City University Graduate School of Medical Sciences, Nagoya 467-8601, Aichi, Japan

Akane Nogimura, Division of Psychiatry and Cognitive-Behavioral Medicine, Nagoya City University Graduate School of Medical Sciences, Nagoya 467-8601, Aichi, Japan

Linda L Wong, Department of Surgery, John A. Burns School of Medicine, University of Hawaii at Manoa, Honolulu, HI 96813, United States

Corresponding author: Tomoki Sempokuya, MD, Doctor, Division of Gastroenterology and Hepatology, Department of Internal Medicine, University of Nebraska Medical Center, 982000 Nebraska Medical Center, Omaha, NE 68198, United States. tsempoku@hawaii.edu

Abstract

Disparities have emerged as an important issue in many aspects of healthcare in developed countries and may be based on race, ethnicity, sex, geographical location, and socioeconomic status. For liver disease specifically, these potential disparities can affect access to care and outcome in viral hepatitis, chronic liver disease, and hepatocellular carcinoma. Shortages in hepatologists and medical providers versed in liver disease may amplify these disparities by compromising early detection of liver disease, surveillance for hepatocellular carcinoma, and prompt referral to subspecialists and transplant centers. In the United States, continued efforts have been made to address some of these disparities with better education of healthcare providers, use of telehealth to enhance access to specialists, reminders in electronic medical records, and modifying organ allocation systems for liver transplantation. This review will detail the current status of disparities in liver disease and describe current efforts to minimize these disparities.

Key Words: Disparity; Transplant; Race; Age; Gender; Hepatitis

Core Tip: The liver is a uniquely complex system, the function of which can be difficult for patients to conceptualize. Given the complexity associated with managing liver disease, patients of different backgrounds can face significant disparity in care, which populations are at increased risk, and what factors cause these differences are not well understood. This review aims to summarize the disparities that exist in patients with liver disease and to bring attention to interventions that have been successful in reducing disparity among vulnerable populations.

Citation: Sempokuya T, Warner J, Azawi M, Nogimura A, Wong LL. Current status of disparity in liver disease. *World J Hepatol* 2022; 14(11): 1940-1952
URL: https://www.wjgnet.com/1948-5182/full/v14/i11/1940.htm
DOI: https://dx.doi.org/10.4254/wjh.v14.i11.1940

INTRODUCTION

In 2017, an estimated 1.5 billion people worldwide had some type of chronic liver disease, and this increased by nearly 35% from the previous decade[1]. About 60% of this chronic liver disease was due to non-alcoholic fatty liver, while 38% was due to viral hepatitis and 2% due to alcohol-related liver disease. Both acute and chronic liver diseases are prevalent worldwide, but the specific etiology of liver disease has geographic variations based on underlying risk factors[2]. In general, viral hepatitis, especially hepatitis B virus (HBV) infections, is more common in Asian and African countries. Non-alcoholic fatty liver disease (NAFLD) is more common in North American and Latin American countries due to a high prevalence of obesity. In addition, underlying genetic factors, such as the Patatin-like phospholipase domain-containing protein 3 (PNPLA3) allele, may contribute to a different phenotype of liver disease[3].

However, the true prevalence of liver disease may be a function of the health care providers available to make these diagnoses. A study from the American Association for the Study of Liver Disease (AASLD)'s workforce study group reported a critical shortage of hepatology providers[4]. They identified about 8000 gastroenterologists, hepatologists, and advanced practice providers who had practices in which ≥ 50% of their time was spent in hepatology. Their modeling analysis predicted that by 2033, the United States would have 35% fewer hepatology providers than needed to care for the population. As the recognition and management of the liver disease can be complex and often require specialized care, patients with liver disease will be at risk of receiving suboptimal care based on accessibility to hepatologists. This review will discuss the studies to characterize the current status of disparities in liver disease and describe current efforts to minimize disparities.

VIRAL HEPATITIS

Hepatitis A, B, and C viruses (HAV, HBV, and HCV, respectively) are the most common causes of viral hepatitis. Hepatitis Delta is less common and tends to occur as a coinfection with HBV. Hepatitis E, though less common than the others, is similar to HAV as it is transmitted *via* the fecal-oral route. HBV is primarily transmitted vertically, especially in Asian countries, but like HCV, this can be transmitted with direct blood contact from transfusions, intravenous drug use, other needle stick injuries, tattoos, or sexual contact. The incidence of these viruses varies based on geographic and socioeconomic factors, but there are also disparities in access to the prevention and treatment of these viruses. Outcome may also differ by race as Asians had higher HBV mortality while non-Hispanic Whites had increased HCV mortality despite the decrease in all other ethnic groups[5].

Disparities in vaccination

Prevention of these viruses can be accomplished with vaccination, proper screening of the blood supply for transfusion, minimizing food contamination and public education. Only HAV and HBV can be prevented with appropriate vaccines. Access to immunizations may be limited by geographic and socioeconomic factors, and populations affected by this disease prevention disparity may be at an increased risk for HBV infection. A descriptive epidemiologic study in rural China showed that HBV vaccination was more likely among those in higher income quintiles, higher education levels, and non-farm occupations[6]. A cross-sectional study from South Korea evaluated HBV vaccination rates among the homeless population, finding only 39.8% completed their HBV vaccination series[7]. In the United States (U.S.), other factors decrease the probability of vaccination, including the vaccine costs, service fees, travel costs, the time required to receive a vaccine, and older age. Overall, income was the single greatest variable affecting HBV vaccination inequality, with a relative weight of > 52%[8]. Advanced

age, lower income, a lack of private insurance, and lower education levels have a marked negative influence on the completion of immunization[7]. Residing within an urban area was associated with a higher compliance rate with completing the vaccinations. Clearly, the availability of vaccinations alone is not enough to ensure universal protection by immunization.

Disparities in screening for viral hepatitis

Proper identification of patients with viral hepatitis may also depend on access to care. More than 80% of HBV in the U.S. were not diagnosed, and 40% of patients with HCV in the U.S. from 2015-2018 were unaware that they had this infection[9]. Currently, the Center for Disease Control (CDC) recommends a one-time HCV screening for all adults aged 18 or older and for all pregnant women during each pregnancy. A systematic review of 19 studies reported that screening for HCV in the general population was variable in terms of cost-effectiveness[10]. However, screening intravenous drug users, pregnant women, HIV-infected, and certain immigrant populations may be more consistently cost-effective. For HBV, the AASLD recommends screening of HBV for persons born in areas in which HBV is endemic, pregnant women, dialysis patients, or those with high-risk behavior, including intravenous drug use [11].

However, there are barriers to successful HBV screening in Asian and Pacific Islander (API) communities, including cultural beliefs of wellbeing, misinformation about HBV, and lack of access to culturally sensitive healthcare[8].

Disparities in treatment of viral hepatitis

While community campaigns can promote screening for viral hepatitis, screening can only be truly effective if there is an appropriate linkage to care. Of the estimated 700000 people with HBV in the U.S., only 15% are aware of their diagnosis, and only 4.5% are receiving treatment[12]. While HCV infection is not preventable with vaccination, it is curable with direct-acting antiviral (DAA) medications. However, the high cost of these medications may have further exacerbated disparities in HCV care. In a large cohort of 29544 patients with HCV in 4 different health care systems, older age and enrollment in commercial insurance correlated with increased rates of HCV treatment[13]. Patients not receiving treatment had more comorbidities, including HIV, mental health disorders, and non-HCC cancers. Additionally, the Hispanic race and those with Medicare, Medicaid, and indigent care/no insurance were significantly less likely to receive treatment. Even after access to DAAs improved (after 2014), the treatment of chronic HCV remained low at < 20%, and patients who were Hispanic and with publicly funded or no insurance were less likely to receive treatment[13]. Jung *et al*[14] found socioeconomic disparities in prescribing patterns for DAA medications among Medicare patients. Schaeffer *et al*[15], in exploring low HCV treatment rates among underserved African Americans in San Francisco found that most of those not receiving treatment were lost to follow-up before eligibility was determined.

Other potential disparities

Other factors that affect the diagnosis and progression of viral hepatitis that may potentially be perceived as disparities include gender, genetic factors, diet, environment/geography, and other patient comorbidities. Higher rates of specific circulating microRNAs, which may increase disease progression, were found in Black patients diagnosed with HCV-mediated HCC and cirrhosis[16]. This may be a contributing factor to the high prevalence of chronic HCV in this population. An ecologic study done in New York City demonstrated a geographic disparity in HCV-related mortality[17]. Neighborhoods with higher proportions of Hispanic and Black residents, poverty, non-English speaking households, and/or lower mean education level were positively associated with HCV mortality. Women with HCV also had a lower fibrosis score at younger ages, but this disparity does not persist after 50 years of age[18]. Rates of fibrosis progression were also highest among women with low socioeconomic status and among those with HIV coinfection. This population is also less likely to achieve sustained virologic response (SVR). However, racial disparities can be eliminated once SVR is achieved in terms of liver disease progression and overall survival[19].

Vulnerable populations

Vulnerable populations have been the focus of numerous efforts aiming to understand and address the disparities in the prevention, screening, and treatment of viral hepatitis. Incarcerated individuals are particularly susceptible to viral infections both chronically and acutely. Worldwide, the prevalence of HCV is 10%-30% in prisoners, with an overall prevalence of 17.7%[20]. In 2019, an HAV outbreak occurred at a county jail in Minnesota, U.S.[21]. In response, the county jail's health service promoted HAV vaccination among inmates, increasing vaccination from 0.6 to 7.1% within three days. Homeless individuals are another vulnerable population with limited access to appropriate healthcare. HCV screening in 6767 homeless individuals in Los Angeles, California, identified that 11.4% were HCV antibody positive. More than half of these patients were viremic, but 95% of the viremic patients were treated successfully with resources that were accessible within the local community[22]. A study in New South Wales, Australia, was done to identify the hurdles to treatment in the indigenous Aboriginal people, who have a high prevalence of HCV[23]. They interviewed 39 Aboriginal Australians in-depth

and identified several specific challenges, including a lack of information provided at diagnosis, the stigma associated with HCV, and concerns about treatment's side effects and efficacy. Several groups have created healthcare policies to improve HCV screening and treatment, such as the Cherokee Nation Health Services in 2012. Through their collaborative efforts with the Center for Disease Control, HCV testing and treatment were significantly increased among Cherokee individuals[24]. Similar strategies have since been implemented by the Indian Health Services, resulting in HCV screening rate increases from 7.9% to 32.5%[25]. With targeted efforts and programs, identification and treatment of viral hepatitis can be possible in these vulnerable populations.

NON-ALCOHOLIC FATTY LIVER DISEASE

Racial/ethnic disparities

The prevalence of NAFLD has continued to increase and now accounts for about 60% of all chronic liver disease, which surpasses all other etiologies. In fact, NASH is the leading cause of liver transplantation among Asians and Hispanics[26]. Much of the NAFLD is driven by the high prevalence of obesity and metabolic syndrome. Nearly 2 billion people in the world are currently overweight, and by 2040, one billion people are expected to be living with obesity[27]. There was a strong association between NAFLD prevalence and national economic status[28]. European countries had a higher NAFLD prevalence (28.04%) than the Middle East (12.95%) and East Asia (19.24%). A systemic review and meta-analysis published in 2019 showed that roughly 16.7% of U.S. populations and 50% of the high-risk population had NAFLD[29]. In the United States, both the NAFLD prevalence and the risk for developing non-alcoholic steatohepatitis was the highest among Hispanics, followed by Whites, and the lowest in Blacks[29]. Underlying genetic factors may affect the progression of fatty liver disease. Hepatic steatosis within Hispanic communities may be partially attributable to the high rates of obesity, metabolic syndrome, and PNPLA3 polymorphism but this disparity in hepatic steatosis may be more evident in Hispanic communities of Mexican descent[30]. Asians have more central fat deposition at a lower body mass index (BMI) and have a higher prevalence of NAFLD with BMI < 25 kg/m^2, compared to Western countries[31]. It is estimated that 8-19% of people with BMI < 25 kg/m^2 have NAFLD. Underlying genetic factors such as the PNPLA3 polymorphism may play a role in the development of lean NAFLD; 13%-19% of Asians have PNPLA3 rs738409 GG genotype, compared to 4% in White and 25% of Hispanics. It is also important to note that the high prevalence of HBV infections in Asian countries poses a risk for concurrent chronic HBV infection and NAFLD. Unfortunately, few studies have explored the problem of multiple contributing factors in the totality of a patient's liver condition.

Gender disparities

While the predisposing factors for NAFLD have not been entirely elucidated, variations in sex hormones, insulin resistance, and hyperlipidemia may contribute to gender differences apparent in NAFLD. The prevalence of NAFLD is higher in men but increases steadily with age in women, especially after menopause, such that 31% of women over 60 years have NAFLD. A lower prevalence was noted in postmenopausal women on hormone replacement therapy[32]. While this suggests that estrogen may play a protective role in NAFLD, a longer duration of estrogen has been shown to increase the likelihood of NALFD development[33]. Women may also be at risk of faster liver fibrosis progression than men[34]. Furthermore, lower total testosterone level has been associated with severe NAFLD in men[35,36]. Differences in hyperlipidemia may also contribute to prognosis with NAFLD, and eventual outcomes as women with NAFLD were more likely to have a less atherogenic lipid profile and more favorable cardiovascular risk profile compared to males[37]. NASH is currently the leading cause of liver transplantation among females[26].

Disparities in access to care /difficulties in diagnosis

The shortage of hepatology providers may outpace the epidemic of patients with chronic liver disease, especially NAFLD. While primary care providers may be managing diabetes, hyperlipidemia, and obesity, there are no definitive guidelines on clinical management of NAFLD, so much of NAFLD is likely undiagnosed. A U.S.-based study showed that only 5.1% of patients with NAFLD were aware of their diagnosis[38]. Currently, universal screening for NAFLD is not recommended, but certain high-risk populations may benefit from screening for NAFLD; including metabolic syndrome, age older than 50-year-old, type 2 diabetes for more than 10 years, or obesity with BMI > 35 kg/m^2[39]. Without definitive strategies for diagnosis and therapy, primary care providers may rely on their hepatology colleagues for assistance; however, referral patterns may vary by race, insurance, location, and availability of a tertiary referral center for liver disease. One study showed that only 17% of Blacks were referred to specialized care, compared to 92% of Hispanics and 97% of Whites[38]. Efforts are currently underway to develop more uniform guidelines to assist providers with NAFLD. Because patients with NAFLD have concurrent diabetes, cardiovascular disease and dyslipidemia, multidisciplinary care with various specialists is essential[40,41].

ALCOHOL-ASSOCIATED LIVER DISEASE

Three million deaths worldwide are due to harmful alcohol use, accounting for 5.3% of all deaths and 13.5% of deaths in people aged 20-39 years[42]. Alcohol intake and the sequelae of excessive consumption are complex problems that vary widely depending on socioeconomic, cultural, religious, geographic, and racial factors. Patterns of alcohol use can be related to a myriad of social problems, including racial discrimination, socioeconomic disadvantage, and interpersonal issues, and can be magnified by stressors and current events. The coronavirus disease 2019 (COVID-19) pandemic necessitated social distancing and isolation, which markedly increased the rate of excessive alcohol use (binge drinking)[43]. One modeling study predicted this increase would ultimately affect long-term mortality and morbidity[44]. Disparities in alcohol-associated liver disease may also be related to the differences in any of these factors, and alcohol frequently exacerbates those with underlying chronic liver disease from any other etiology.

Racial disparities

Underlying genetic factors and cultural differences contribute to the behavior related to alcohol consumption and thus rates of alcohol-associated liver disease. For moderate alcohol intake, Blacks had increased mortality secondary to liver disease, but not Whites[45]. This study suggested that Black individuals were more susceptible to alcohol-associated liver injury. This observation may be due to underlying comorbidities and genetic polymorphisms. During the COVID-19 pandemic, Black patients were more likely to be treated for alcoholic hepatitis, pancreatitis, and gastritis[43]. Providers' racial bias may also influence treatment decisions for alcoholic liver disease. A recent United Network for Organ Sharing (UNOS) based study suggested that Black patients with alcohol-associated liver disease had less access to liver transplantation, but socioeconomic factors may have confounded this conclusion[46]. A population-based study from the U.S. National Vital Statistics System from 2007 to 2016 demonstrated that non-Hispanic Whites had the highest mortality rates for alcoholic liver disease; however, increases were seen in all Asian subgroups, with the highest increase in Japanese[5].

Gender disparities

Gender disparity for alcohol-associated liver disease can be attributed to differences in alcohol metabolism and perhaps social and cultural biases in women with heavy alcohol consumption. Men and women metabolize alcohol differently, as women typically have a higher serum alcohol level per drink [46]. Such factors may impact whether an individual seeks treatment and the severity of liver disease at presentation. For the treatment of alcohol use disorder, appropriate care provided by a mental health provider is often necessary, but only 10% of patients utilize this service. Women were less likely to seek specialist treatment for alcohol use disorder and to receive relapse prevention medications[47]. In recent years, there has been a rapid increase in the prevalence and mortality of women with alcohol-associated liver disease, especially alcoholic hepatitis[48]. This trend was more evident in Asian and Native American women. However, women with alcohol-associated liver disease were less likely to pursue liver transplant evaluation[46]. Among liver transplant recipients due to alcohol-associated liver disease, women had higher model for end-stage liver disease (MELD) scores, higher rates of renal failure requiring dialysis, and higher rates of ventilator dependence before the transplant than men[49]. Men with alcohol-associated liver disease were more likely to be listed and receive liver transplantation than their female counterparts[50]. A history of other substance abuse was also more common in men, while women more often had an underlying psychiatric illness. Women were 9% less likely than men to experience long-term graft loss, though this gender disparity was isolated to patients with additional comorbidities.

Geographic disparities

Patterns of alcohol use may differ based on geography, and this may be related to restrictions on the purchase of alcohol, laws/prosecution of drivers under the influence of alcohol, and local advertising of alcoholic beverages. Many states have policies to regulate alcohol in the United States, though specific restrictions differ by state. Hadland *et al*[51] showed a strong correlation between state alcohol policies and the incidence and mortality of alcohol-associated cirrhosis. Mortality of alcohol-associated cirrhosis was highest among males in Western states and states with proportionally higher American Indians/Alaska Natives. A stricter alcohol policy was associated with lower mortality in females but not males. Among non-Indigenous descendants, more robust alcohol policy environments were linked to lower alcoholic cirrhosis mortality rates in both sexes.

AUTOIMMUNE LIVER DISEASE

Autoimmune liver disease includes autoimmune hepatitis (AIH), primary sclerosing cholangitis (PSC), and primary biliary cholangitis (PBC). While the etiology of autoimmune liver is largely unclear, it is likely less to be related to behavioral or preventable causes. Disparities in autoimmune liver disease

may be related to genetic factors, concurrent illnesses and socioeconomic issues that affect access to care. The current literature is predominantly based on White patients, and the data from racial minorities are limited[52]. Autoimmune liver disease often requires complex treatment provided by a hepatologist and often in coordination with a rheumatologist. Those with less access to specialists may experience inadequate or delayed care. In addition, racial minorities and recent immigrants may have issues with language barrier, which impacts health literacy and may result in resistance to treatment. Genetic polymorphism with the subtype of PNPLA3 in Hispanic patients with AIH predicted more severe liver disease and increased mortality after liver transplantation[53,54]. A single-center, retrospective case-control study evaluated the association between race/ethnicity and AIH[55]. After controlling age and sex, the odds of AIH were higher among Black, Latinos, or API compared to Whites. Though not quite statistically significant, Black patients trended to have higher ALT, IgG, INR, bilirubin, inflammation on biopsy, hospitalizations, and other concomitant autoimmune diseases. A small study suggested worse outcomes for Black and Asian patients with AIH[52]. A National inpatient sample-based study on PBC showed increased hospitalization rates in Hispanics and females[56]. Patients with PBC who were Black or had Medicaid have had significantly higher in-hospital mortality[57]. Black patients with PSC with inflammatory bowel disease reportedly had worse PSC-related survival outcomes and higher need for liver transplantation[52,58]. More studies are needed to clarify the impact of socioeconomic and racial disparities on each of these specific autoimmune liver diseases.

MALIGNANCY

HCC is the sixth most common malignancy and the second leading cause of cancer mortality worldwide. It frequently develops in patients with underlying liver diseases, such as those with cirrhosis, HCV, or HBV infections[59]. While appropriate surveillance can facilitate early detection HCC and improve survival, most cases are found at an advanced stage. There are significant differences in the incidence of HCC by race, but this may be likely be related to differences in the underlying chronic liver disease that predisposed a patient to HCC.

Gender disparities

HCC occurs two to four times higher in men compared to women[18,60]. Some of this is likely due to the differences in viral hepatitis between genders and behavioral risk factors which may have led to viral hepatitis. In addition, differences in comorbidities such as alcohol use, smoking, and obesity may contribute to hepatocarcinogenesis and outcome. In the United States, increased mortality rates for HCC from 2000 to 2015 were seen in less educated patients, particularly men[61]. In contrast, women had significantly lower mortality from HCC[62], possibly due to early detection and response to the first treatment[10]. Studies have also suggested that estrogen may have protective role in HCC development through reduction of interleukin-6 mediated hepatic inflammatory responses[60].

Racial disparities

While the etiology of liver disease is an essential factor affecting incidence and survival in HCC, previous U.S. studies have shown that age-adjusted HCC incidence was highest in APIs, followed by Hispanics, Blacks, and Whites[63,64]. Among Asian ethnic groups, the highest HCC incidence rates were observed among Vietnamese, Cambodians, and Laotians. Southeast Asians were twice as likely to have HCC as other Asians and an 8-fold risk compared to Whites. While Asian countries have a considerably higher burden of disease, there are subgroups within these countries that demonstrate differences in HCC. A study from China, showed differences in mortality between Mongols *vs* Non-Mongols, primarily attributed to the difference in underlying HBV infections[65]. For other races, Black patients had a lower survival overall from HCC than their White or Hispanic counterparts[66]. Black patients typically present with advanced stages of HCC at the time of diagnosis and are thus less likely to receive curative treatment[66,67]. Even after adjusting for stages, Blacks and Hispanics were less likely to receive curative treatment for HCC and lower healthcare utilization for HCC. Blacks had a higher risk of inpatient mortality[68]. On the other hand, Asians are more likely to have underlying HBV infection without underlying cirrhosis; therefore, they are more likely to undergo curative resection[66].

Socioeconomic status

The role of socioeconomic status has been evaluated for disparities in HCC outcomes. A Surveillance, Epidemiology and End Results (SEER) database study showed that patients who reside in the area with a higher cost of living index was associated with stage I disease, smaller tumor size, and increased likelihood of surgical intervention or loco-regional therapy[69]. Earlier detection of HCC in wealthier patients may infer more effective surveillance in this population. Similar findings were found in a study based on the Korean National Health Insurance sampling cohort[70]. This study of 7325 patients showed a decreased 5-year mortality for HCC among lower-income patients and middle-aged men. HCC outcomes also vary by hospital. Safety-net hospitals in the U.S. provide much of the care for

patients with lower household income, education levels, and racial minorities. HCC patients in these safety-net hospital were less likely to undergo liver resection or transplantation and had higher procedure-specific mortality[71]. Insurance and employment status may also affect specialist referral and outcome. In a study conducted in China, Wu *et al*[72] showed increased mortality from HCC in patients with a basic health insurance compared to those with an employment-based insurance. Unemployment may also be a factor in HCC development and care. A U.S. census and National Health Interview survey based study showed that there was that alcohol use disorder and viral hepatitis was nearly 40% higher among the unemployed, and HCC mortality was worse in the unemployed group [73].

Geographic disparities

Place of residence may also affect the incidence and survival in HCC. A U.S. based SEER database study based on 83638 patients showed that rural and suburban residents had higher HCC mortality and were less likely to receive treatment than urban residents[74]. Insurance status itself may not guarantee appropriate access to healthcare providers as patients are unable to pay for associated costs in travelling to tertiary referral centers. Lee *et al*[75] showed in the SEER database and CDC's cancer registries that there was a state-level racial and ethnic disparity in the incidence of HCC. This incidence trends had some correlation with obesity rates of the states. Geographic disparities were also identified in a study from Australia, where HCC incidence was highest amongst those residing in metropolitan cities and remote areas with high Indigenous populations[76].

Disparities in surveillance for HCC

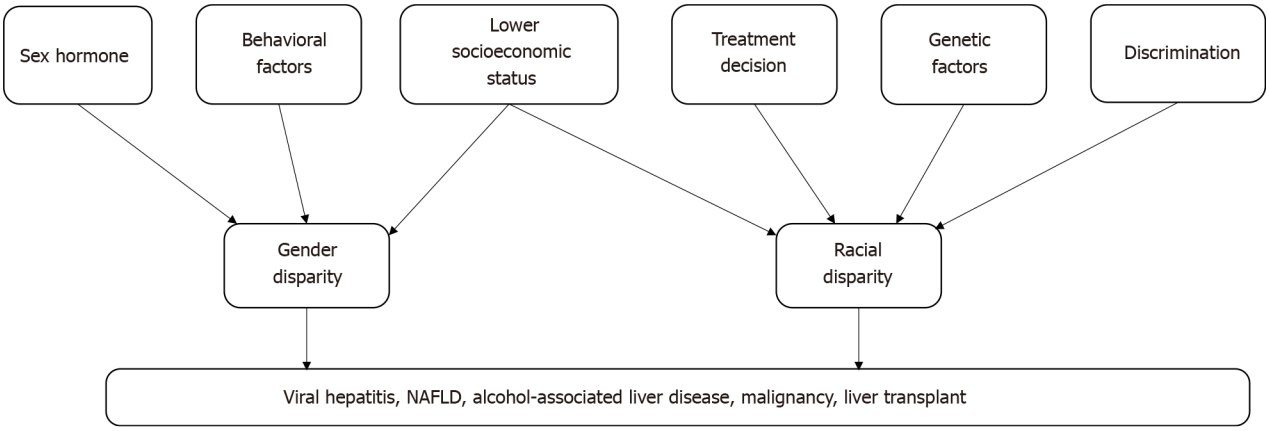
While primary care providers are very familiar with screening for common cancers like breast and colon, many are not aware of current surveillance guidelines for HCC. As such, access to hepatologist or gastroenterologist may improve the rate of appropriate HCC surveillance. Current AASLD guidelines for HCC surveillance recommend ultrasound every 6 mo with or without alpha feto-protein, in patients with cirrhosis, chronic HBV, and chronic HCV with greater than stage 3 fibrosis[59]. Therefore, an appropriate surveillance for HCC requires recognition of the underlying chronic liver disease, appropriate testing and then referral for contrast-enhanced imaging for suspicious lesions. Without recognition of the underlying chronic liver disease and indications, surveillance cannot occur. As mentioned previously, many patients in the U.S. have unrecognized viral hepatitis and will neither receive antiviral agents nor undergo surveillance[9,12,77]. Despite guidelines, only 17% of HCC are detected in early stages (BCLC 0 and A) in the U.S., while European countries was 10%-30%[78]. On the other hand, Japan implemented nationwide HCC surveillance in 1980's with free testing for hepatitis B surface antigen and HCV Ab in the clinics and meticulous surveillance. This eventually led to early-stage detection of HCC in 60%-65% of patients. Factors such as race, obesity, ascites, operator's experience may also affect the early detection rates of HCC[12,79,80]. Finally, there is likely a complex interplay between these factors, socioeconomics and access to care that all affect surveillance and early detection in HCC.

LIVER TRANSPLANTATION

Liver transplantation is considered the definitive treatment for end stage liver disease and early-stage HCC that is not amenable to resection. Because this is a risky operation, an expensive endeavor and a limited resource, it is not unexpected that disparities would be evident. Patients must be medically suitable with no active non-HCC malignancy, no ongoing infection, and adequate cardiovascular function. In addition, patients must be medically compliant, without active substance abuse and have financial stability/medical insurance coverage to ensure adequate access to immunosuppressive medications post-transplant. Unfortunately, the COVID-19 pandemic influenced liver transplant access among the minority population. A UNOS-based study showed minority had a more significant reduction in transplant (Minority: 15% *vs* White: 7% reduction) and listing for transplant (14% *vs* 12% reduction, respectively), despite a higher median MELD score (23 *vs* 20, respectively) during early COVID-19 period[81]. The reduction in transplants became more prominent for patients with public insurance than private insurance. Another study from Mexico showed an unequal reduction of liver transplantation for public (88% reduction) and private (35% reduction) hospitals during the COVID-19 pandemic[82].

Gender disparity

In the United States, the MELD-Na score is the current organ allocation method for liver transplantation. This score is predictive of mortality on the waiting list but can create disparities. Gender disparities can occur because differences in muscle mass in males *vs* females affects creatinine, which is a variable in MELD. The current allocation system does not account for these sex differences in creatinine and anthropometric measure. In fact, Locke *et al*[83] showed that women had higher waitlist mortality and less likelihood of receiving deceased donor liver transplantation. Another cohort study by



DOI: 10.4254/wjh.v14.i11.1940

Figure 1 Summary of liver disease disparity. NAFLD: Non-alcoholic fatty liver disease.

Cullaro *et al*[84] showed that women were 10% more likely to be removed from the waitlist for being too sick for liver transplantation. One study found that women removed from the list were older, had non-HCV liver disease, and had higher rates of hepatic encephalopathy. Another cohort study on liver transplantation for NASH showed that women were less likely to be White and listed with MELD exception points[85]. In multivariable analysis, women with NASH were 19% less likely to receive liver transplantation compared to men with NASH through the follow-up period even after adjusting for multiple other factors. Overall, women were less likely to have liver transplantation while more likely to die without transplant, be removed from the waiting list due to clinical deterioration or remain on the waiting list without liver transplantation. In order to decrease gender disparities in liver transplantation, Kim *et al*[86] attempted to address sexual disparity by creating an updated MELD 3.0, incorporating sex difference, which may provide a better mortality prediction. Efforts are currently underway to implement this in the U.S. Another study from Toronto, Canada, highlighted that there is a broader availability of living donor liver transplants (LDLT) to women, which may provide a protective factor to minimize the gender disparity[87].

Racial disparity

Racial disparities in transplant can be seen in wait list mortality, use of simultaneous liver-kidney transplant (SLK), LDLT and eventual outcomes. A study on the UNOS liver transplant registry showed lower waitlist mortality among Asian compared to White after correcting for the MELD score[88]. Black patients tended to have higher MELD scores at the time of listing for liver transplantation but similar rates of waitlist mortality after correcting for MELD scores. Patients with end stage liver disease often have comorbid renal dysfunction, and SLK is considered. However, Black and Hispanic patients with renal dysfunction who are listed for liver transplantation were more likely to undergo SLK than White [89]. LDLT was noticeably lower among Hispanic, Black, and Asian patients compared to White patients. Blacks in particular, were less likely to inquire about LDLT during the evaluation process[90].

Finally, there are disparities in outcome and survival after liver transplantation. Differences in outcome after transplant may be biologically driven and may also be related to medical compliance. Blacks and women with HBV had worse long-term outcomes post-transplant compared to other races [91]. Recurrence of HBV was significant for Blacks even ten years post liver transplant, affecting the survival rate. While there have been racial disparities to liver transplantation in the past, the U.S. continues to develop broader sharing policies and allocation schemes which have helped equalize access to liver transplantation for all populations[92]. Longer term coverage of immunosuppression by Medicare and other insurances will also help improve long-term outcomes after liver transplant.

CONCLUSION

Disparities in liver disease and treatment are frequent and may be related to gender, race, geography, socioeconomic status and specific behaviors that predispose to liver disease (Figure 1). The need for complex management of these diseases, limited resources of liver transplantation and the inadequate number of specialists to care for these patients is further magnifying these disparities. Future studies should focus on evaluation of a language barrier among immigrant in regard to disparity and interventions to address these disparities.

ACKNOWLEDGEMENTS

A literature review was provided by Danielle Westmark, MLIS, IPI PMC, and Cindy Schmidt, M.D., M.L.S., from the Leon S. McGoogan Health Sciences Library at the University of Nebraska Medical Center.

FOOTNOTES

Author contributions: Sempokuya T, Warner J, Azawi M, Nogimura A contributed to the literature review, manuscript drafting, and editing; Wong LL contributed to study supervision, manuscript drafting, and editing; all of the authors have approved the final version of the manuscript.

Conflict-of-interest statement: Wong LL is a speaker bureau for Eisai. All other authors do not have any conflicts of interest.

Country/Territory of origin: United States

ORCID number: Tomoki Sempokuya 0000-0002-7334-3528; Josh Warner 0000-0002-0208-0492; Muaataz Azawi 0000-0003-0700-9641; Akane Nogimura 0000-0001-5696-9900; Linda L Wong 0000-0003-3143-5384.

Corresponding Author's Membership in Professional Societies: American Association for the Study of Liver Diseases; American College of Gastroenterology; American Gastroenterological Association; American Society for Gastrointestinal Endoscopy.

S-Editor: Wang JL
L-Editor: A
P-Editor: Wang JL

REFERENCES

1 **GBD 2017 Disease and Injury Incidence and Prevalence Collaborators**. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet* 2018; **392**: 1789-1858 [PMID: 30496104 DOI: 10.1016/S0140-6736(18)32279-7]
2 **Moon AM**, Singal AG, Tapper EB. Contemporary Epidemiology of Chronic Liver Disease and Cirrhosis. *Clin Gastroenterol Hepatol* 2020; **18**: 2650-2666 [PMID: 31401364 DOI: 10.1016/j.cgh.2019.07.060]
3 **Sliz E**, Sebert S, Würtz P, Kangas AJ, Soininen P, Lehtimäki T, Kähönen M, Viikari J, Männikkö M, Ala-Korpela M, Raitakari OT, Kettunen J. NAFLD risk alleles in PNPLA3, TM6SF2, GCKR and LYPLAL1 show divergent metabolic effects. *Hum Mol Genet* 2018; **27**: 2214-2223 [PMID: 29648650 DOI: 10.1093/hmg/ddy124]
4 **Russo MW**, Fix OK, Koteish AA, Duggan K, Ditmyer M, Fuchs M, Chung RT, Reddy G. Modeling the Hepatology Workforce in the United States: A Predicted Critical Shortage. *Hepatology* 2020; **72**: 1444-1454 [PMID: 32898922 DOI: 10.1002/hep.31425]
5 **Li AA**, Kim D, Kim W, Dibba P, Wong K, Cholankeril G, Jacobson IM, Younossi ZM, Ahmed A. Disparities in mortality for chronic liver disease among Asian subpopulations in the United States from 2007 to 2016. *J Viral Hepat* 2018; **25**: 1608-1616 [PMID: 30112849 DOI: 10.1111/jvh.12981]
6 **Zhu D**, Guo N, Wang J, Nicholas S, Wang Z, Zhang G, Shi L, Wangen KR. Socioeconomic inequality in Hepatitis B vaccination of rural adults in China. *Hum Vaccin Immunother* 2018; **14**: 464-470 [PMID: 29072546 DOI: 10.1080/21645515.2017.1396401]
7 **Park B**, Choi KS, Lee HY, Jun JK, Park EC. Socioeconomic inequalities in completion of hepatitis B vaccine series among Korean women: results from a nationwide interview survey. *Vaccine* 2012; **30**: 5844-5848 [PMID: 22828587 DOI: 10.1016/j.vaccine.2012.07.022]
8 **Nguyen CT**, Lin SY. Hepatitis B Screening in Asian and Pacific Islanders: New Guidelines, Old Barriers. *J Immigr Minor Health* 2015; **17**: 1585-1587 [PMID: 25354568 DOI: 10.1007/s10903-014-0123-7]
9 **National Center for HIV VH, STD, and TB Prevention**. New estimates reveal declines in hepatitis C treatment in the U.S. between 2015 and 2020. [accessed 2022 Aug 21]. Available from: https://www.cdc.gov/nchhstp/newsroom/2021/2014-2020-hepatitis-c-treatment-estimates.html#:~:text=It's%20estimated%2040%20percent%20of,all%20people%20with%20risk%20factors
10 **Geue C**, Wu O, Xin Y, Heggie R, Hutchinson S, Martin NK, Fenwick E, Goldberg D; Consortium; ECDC. Cost-Effectiveness of HBV and HCV Screening Strategies--A Systematic Review of Existing Modelling Techniques. *PLoS One*

2015; **10**: e0145022 [PMID: 26689908 DOI: 10.1371/journal.pone.0145022]
11 **Koh C**, Zhao X, Samala N, Sakiani S, Liang TJ, Talwalkar JA. AASLD clinical practice guidelines: a critical review of scientific evidence and evolving recommendations. *Hepatology* 2013; **58**: 2142-2152 [PMID: 23775835 DOI: 10.1002/hep.26578]
12 **Nguyen MH**, Wong G, Gane E, Kao JH, Dusheiko G. Hepatitis B Virus: Advances in Prevention, Diagnosis, and Therapy. *Clin Microbiol Rev* 2020; **33** [PMID: 32102898 DOI: 10.1128/CMR.00046-19]
13 **Wong RJ**, Jain MK, Therapondos G, Shiffman ML, Kshirsagar O, Clark C, Thamer M. Race/ethnicity and insurance status disparities in access to direct acting antivirals for hepatitis C virus treatment. *Am J Gastroenterol* 2018; **113**: 1329-1338 [PMID: 29523864 DOI: 10.1038/s41395-018-0033-8]
14 **Jung J**, Du P, Feldman R, Kong L, Riley T 3rd. Racial/Ethnic and Socioeconomic Disparities in Use of Direct-Acting Antivirals Among Medicare Beneficiaries with Chronic Hepatitis C, 2014-2016. *J Manag Care Spec Pharm* 2019; **25**: 1236-1242 [PMID: 31663464 DOI: 10.18553/jmcp.2019.25.11.1236]
15 **Schaeffer S**, Khalili M. Reasons for HCV non-treatment in underserved African Americans: implications for treatment with new therapeutics. *Ann Hepatol* 2015; **14**: 234-242 [PMID: 25671833]
16 **Devhare PB**, Steele R, Di Bisceglie AM, Kaplan DE, Ray RB. Differential Expression of MicroRNAs in Hepatitis C Virus-Mediated Liver Disease Between African Americans and Caucasians: Implications for Racial Health Disparities. *Gene Expr* 2017; **17**: 89-98 [PMID: 27765085 DOI: 10.3727/105221616X693594]
17 **Ford MM**, Desai PS, Maduro G, Laraque F. Neighborhood Inequalities in Hepatitis C Mortality: Spatial and Temporal Patterns and Associated Factors. *J Urban Health* 2017; **94**: 746-755 [PMID: 28623451 DOI: 10.1007/s11524-017-0174-x]
18 **Corsi DJ**, Karges W, Thavorn K, Crawley AM, Cooper CL. Influence of female sex on hepatitis C virus infection progression and treatment outcomes. *Eur J Gastroenterol Hepatol* 2016; **28**: 405-411 [PMID: 26745470 DOI: 10.1097/MEG.0000000000000567]
19 **Le AK**, Zhao C, Hoang JK, Tran SA, Chang CY, Jin M, Nguyen NH, Yasukawa LA, Zhang JQ, Weber SC, Garcia G, Nguyen MH. Ethnic disparities in progression to advanced liver disease and overall survival in patients with chronic hepatitis C: impact of a sustained virological response. *Aliment Pharmacol Ther* 2017; **46**: 605-616 [PMID: 28766727 DOI: 10.1111/apt.14241]
20 **Salari N**, Darvishi N, Hemmati M, Shohaimi S, Ghyasi Y, Hossaini F, Bazrafshan MR, Akbari H, Mohammadi M. Global prevalence of hepatitis C in prisoners: a comprehensive systematic review and meta-analysis. *Arch Virol* 2022; **167**: 1025-1039 [PMID: 35165781 DOI: 10.1007/s00705-022-05382-1]
21 **Zellmer L**, Peters L, Silva RS. Hennepin County Adult Detention Center's Response to a 2019 Hepatitis A Outbreak in Minnesota. *Am J Public Health* 2021; **111**: 839-841 [PMID: 33734843 DOI: 10.2105/AJPH.2021.306159]
22 **Benitez TM**, Fernando SM, Amini C, Saab S. Geographically Focused Collocated Hepatitis C Screening and Treatment in Los Angeles's Skid Row. *Dig Dis Sci* 2020; **65**: 3023-3031 [PMID: 31974916 DOI: 10.1007/s10620-020-06073-0]
23 **Treloar C**, Jackson C, Gray R, Newland J, Wilson H, Saunders V, Johnson P, Brener L. Care and treatment of hepatitis C among Aboriginal people in New South Wales, Australia: implications for the implementation of new treatments. *Ethn Health* 2016; **21**: 39-57 [PMID: 25665723 DOI: 10.1080/13557858.2015.1004870]
24 **Mera J**, Vellozzi C, Hariri S, Carabin H, Drevets DA, Miller A, Reilley B, Essex W, Gahn D, Lyons L, Leston J, Ward JW. Identification and Clinical Management of Persons with Chronic Hepatitis C Virus Infection - Cherokee Nation, 2012-2015. *MMWR Morb Mortal Wkly Rep* 2016; **65**: 461-466 [PMID: 27172175 DOI: 10.15585/mmwr.mm6518a2]
25 **Reilley B**, Leston J, Hariri S, Neel L, Rudd M, Galope M, Ward J, Vellozzi C. Birth Cohort Testing for Hepatitis C Virus - Indian Health Service 2012-2015. *MMWR Morb Mortal Wkly Rep* 2016; **65**: 467-469 [PMID: 27171026 DOI: 10.15585/mmwr.mm6518a3]
26 **Noureddin M**, Vipani A, Bresee C, Todo T, Kim IK, Alkhouri N, Setiawan VW, Tran T, Ayoub WS, Lu SC, Klein AS, Sundaram V, Nissen NN. NASH Leading Cause of Liver Transplant in Women: Updated Analysis of Indications For Liver Transplant and Ethnic and Gender Variances. *Am J Gastroenterol* 2018; **113**: 1649-1659 [PMID: 29880964 DOI: 10.1038/s41395-018-0088-6]
27 **The World Obesity Federation**. World Obesity Atlas 2022. [accessed 2022 Aug 24]. Available from: https://www.worldobesity.org/resources/resource-library/world-obesity-atlas-2022
28 **Zhu JZ**, Dai YN, Wang YM, Zhou QY, Yu CH, Li YM. Prevalence of Nonalcoholic Fatty Liver Disease and Economy. *Dig Dis Sci* 2015; **60**: 3194-3202 [PMID: 26017679 DOI: 10.1007/s10620-015-3728-3]
29 **Rich NE**, Oji S, Mufti AR, Browning JD, Parikh ND, Odewole M, Mayo H, Singal AG. Racial and Ethnic Disparities in Nonalcoholic Fatty Liver Disease Prevalence, Severity, and Outcomes in the United States: A Systematic Review and Meta-analysis. *Clin Gastroenterol Hepatol* 2018; **16**: 198-210.e2 [PMID: 28970148 DOI: 10.1016/j.cgh.2017.09.041]
30 **Shaheen M**, Pan D, Schrode KM, Kermah D, Puri V, Zarrinpar A, Elisha D, Najjar SM, Friedman TC. Reassessment of the Hispanic Disparity: Hepatic Steatosis Is More Prevalent in Mexican Americans Than Other Hispanics. *Hepatol Commun* 2021; **5**: 2068-2079 [PMID: 34558824 DOI: 10.1002/hep4.1775]
31 **Fan JG**, Kim SU, Wong VW. New trends on obesity and NAFLD in Asia. *J Hepatol* 2017; **67**: 862-873 [PMID: 28642059 DOI: 10.1016/j.jhep.2017.06.003]
32 **Lonardo A**, Nascimbeni F, Ballestri S, Fairweather D, Win S, Than TA, Abdelmalek MF, Suzuki A. Sex Differences in Nonalcoholic Fatty Liver Disease: State of the Art and Identification of Research Gaps. *Hepatology* 2019; **70**: 1457-1469 [PMID: 30924946 DOI: 10.1002/hep.30626]
33 **Wang J**, Wu AH, Stanczyk FZ, Porcel J, Noureddin M, Terrault NA, Wilkens LR, Setiawan VW. Associations Between Reproductive and Hormone-Related Factors and Risk of Nonalcoholic Fatty Liver Disease in a Multiethnic Population. *Clin Gastroenterol Hepatol* 2021; **19**: 1258-1266.e1 [PMID: 32801014 DOI: 10.1016/j.cgh.2020.08.012]
34 **Chen XY**, Wang C, Huang YZ, Zhang LL. Nonalcoholic fatty liver disease shows significant sex dimorphism. *World J Clin Cases* 2022; **10**: 1457-1472 [PMID: 35211584 DOI: 10.12998/wjcc.v10.i5.1457]
35 **Mo MQ**, Huang ZC, Yang ZH, Liao YH, Xia N, Pan L. Relationship between total testosterone, sex hormone-binding globulin levels and the severity of non-alcoholic fatty liver disease in males: a meta-analysis. *Ther Adv Endocrinol Metab* 2022; **13**: 20420188221106879 [PMID: 35785018 DOI: 10.1177/20420188221106879]

36 **Phan H**, Richard A, Lazo M, Nelson WG, Denmeade SR, Groopman J, Kanarek N, Platz EA, Rohrmann S. The association of sex steroid hormone concentrations with non-alcoholic fatty liver disease and liver enzymes in US men. *Liver Int* 2021; **41**: 300-310 [PMID: 32860311 DOI: 10.1111/liv.14652]

37 **Du T**, Sun X, Yuan G, Zhou X, Lu H, Lin X, Yu X. Sex differences in the impact of nonalcoholic fatty liver disease on cardiovascular risk factors. *Nutr Metab Cardiovasc Dis* 2017; **27**: 63-69 [PMID: 27956025 DOI: 10.1016/j.numecd.2016.10.004]

38 **Le MH**, Yeo YH, Cheung R, Wong VW, Nguyen MH. Ethnic influence on nonalcoholic fatty liver disease prevalence and lack of disease awareness in the United States, 2011-2016. *J Intern Med* 2020; **287**: 711-722 [PMID: 32128904 DOI: 10.1111/joim.13035]

39 **Kanwal F**, Shubrook JH, Younossi Z, Natarajan Y, Bugianesi E, Rinella ME, Harrison SA, Mantzoros C, Pfotenhauer K, Klein S, Eckel RH, Kruger D, El-Serag H, Cusi K. Preparing for the NASH Epidemic: A Call to Action. *Gastroenterology* 2021; **161**: 1030-1042.e8 [PMID: 34416976 DOI: 10.1053/j.gastro.2021.04.074]

40 **Kumar S**, Wong R, Newberry C, Yeung M, Peña JM, Sharaiha RZ. Multidisciplinary Clinic Models: A Paradigm of Care for Management of NAFLD. *Hepatology* 2021; **74**: 3472-3478 [PMID: 34324727 DOI: 10.1002/hep.32081]

41 **Zoncapè M**, Liguori A, Tsochatzis EA. Multi-disciplinary clinic models for the management of non-alcoholic fatty liver disease. *Hepatobiliary Surg Nutr* 2022; **11**: 586-591 [PMID: 36016750 DOI: 10.21037/hbsn-22-58]

42 **World Health Organization**. Alcohol. May 9, 2022. [accessed 2022 Aug 30]. Available from: https://www.who.int/news-room/fact-sheets/detail/alcohol

43 **Damjanovska S**, Karb DB, Cohen SM. Increasing Prevalence and Racial Disparity of Alcohol-Related Gastrointestinal and Liver Disease During the COVID-19 Pandemic: A Population-Based National Study. *J Clin Gastroenterol* 2022 [PMID: 34999643 DOI: 10.1097/MCG.0000000000001665]

44 **Julien J**, Ayer T, Tapper EB, Barbosa C, Dowd WN, Chhatwal J. Effect of increased alcohol consumption during COVID-19 pandemic on alcohol-associated liver disease: A modeling study. *Hepatology* 2022; **75**: 1480-1490 [PMID: 34878683 DOI: 10.1002/hep.32272]

45 **Fan L**, Zhu X, Shingina A, Kabagambe EK, Shrubsole MJ, Dai Q. Racial Disparities in Associations of Alcohol Consumption With Liver Disease Mortality in a Predominantly Low-Income Population: A Report From the Southern Community Cohort Study. *Am J Gastroenterol* 2022; **117**: 1523-1529 [PMID: 35416798 DOI: 10.14309/ajg.0000000000001768]

46 **Kaplan A**, Wahid N, Fortune BE, Verna E, Halazun K, Samstein B, Brown RS Jr, Rosenblatt R. Black patients and women have reduced access to liver transplantation for alcohol-associated liver disease. *Liver Transpl* 2022 [PMID: 35848134 DOI: 10.1002/lt.26544]

47 **Mellinger JL**, Fernandez A, Shedden K, Winder GS, Fontana RJ, Volk ML, Blow FC, Lok ASF. Gender Disparities in Alcohol Use Disorder Treatment Among Privately Insured Patients with Alcohol-Associated Cirrhosis. *Alcohol Clin Exp Res* 2019; **43**: 334-341 [PMID: 30667521 DOI: 10.1111/acer.13944]

48 **Bertha M**, Shedden K, Mellinger J. Trends in the inpatient burden of alcohol-related liver disease among women hospitalized in the United States. *Liver Int* 2022; **42**: 1557-1561 [PMID: 35451173 DOI: 10.1111/liv.15277]

49 **Matsuoka L**, Izzy M, Feurer ID, Rega SA, Ziogas IA, Alexopoulos SP. Sex and Gender Disparities in Pretransplant Characteristics and Relationships with Postoperative Outcomes in Liver Transplant Recipients with Alcoholic Liver Disease. *Exp Clin Transplant* 2020; **18**: 701-706 [PMID: 32552631 DOI: 10.6002/ect.2020.0063]

50 **McElroy LM**, Likhitsup A, Scott Winder G, Saeed N, Hassan A, Sonnenday CJ, Fontana RJ, Mellinger J. Gender Disparities in Patients With Alcoholic Liver Disease Evaluated for Liver Transplantation. *Transplantation* 2020; **104**: 293-298 [PMID: 31283683 DOI: 10.1097/TP.0000000000002843]

51 **Hadland SE**, Xuan Z, Blanchette JG, Heeren TC, Swahn MH, Naimi TS. Alcohol Policies and Alcoholic Cirrhosis Mortality in the United States. *Prev Chronic Dis* 2015; **12**: E177 [PMID: 26469950 DOI: 10.5888/pcd12.150200]

52 **Lee BT**, Tana MM, Kahn JA, Dara L. We Are Not Immune: Racial and Ethnic Disparities in Autoimmune Liver Diseases. *Hepatology* 2021; **74**: 2876-2887 [PMID: 34056734 DOI: 10.1002/hep.31985]

53 **Wong RJ**, Gish R, Frederick T, Bzowej N, Frenette C. The impact of race/ethnicity on the clinical epidemiology of autoimmune hepatitis. *J Clin Gastroenterol* 2012; **46**: 155-161 [PMID: 21814143 DOI: 10.1097/MCG.0b013e318228b781]

54 **Mederacke YS**, Kirstein MM, Großhennig A, Marhenke S, Metzler F, Manns MP, Vogel A, Mederacke I. The PNPLA3 rs738409 GG genotype is associated with poorer prognosis in 239 patients with autoimmune hepatitis. *Aliment Pharmacol Ther* 2020; **51**: 1160-1168 [PMID: 32323349 DOI: 10.1111/apt.15722]

55 **Lee B**, Holt EW, Wong RJ, Sewell JL, Somsouk M, Khalili M, Maher JJ, Tana MM. Race/ethnicity is an independent risk factor for autoimmune hepatitis among the San Francisco underserved. *Autoimmunity* 2018; **51**: 258-264 [PMID: 29890851 DOI: 10.1080/08916934.2018.1482884]

56 **Adejumo AC**, Akhtar DH, Dennis BB, Cholankeril G, Alayo Q, Ogundipe OA, Kim D, Ahmed A. Gender and Racial Differences in Hospitalizations for Primary Biliary Cholangitis in the USA. *Dig Dis Sci* 2021; **66**: 1461-1476 [PMID: 32535779 DOI: 10.1007/s10620-020-06402-3]

57 **Galoosian A**, Hanlon C, Tana M, Cheung R, Wong RJ. Race/Ethnicity and Insurance-Specific Disparities in In-Hospital Mortality Among Adults with Primary Biliary Cholangitis: Analysis of 2007-2014 National Inpatient Sample. *Dig Dis Sci* 2020; **65**: 406-415 [PMID: 31489564 DOI: 10.1007/s10620-019-05809-x]

58 **Trivedi PJ**, Crothers H, Mytton J, Bosch S, Iqbal T, Ferguson J, Hirschfield GM. Effects of Primary Sclerosing Cholangitis on Risks of Cancer and Death in People With Inflammatory Bowel Disease, Based on Sex, Race, and Age. *Gastroenterology* 2020; **159**: 915-928 [PMID: 32445859 DOI: 10.1053/j.gastro.2020.05.049]

59 **Marrero JA**, Kulik LM, Sirlin CB, Zhu AX, Finn RS, Abecassis MM, Roberts LR, Heimbach JK. Diagnosis, Staging, and Management of Hepatocellular Carcinoma: 2018 Practice Guidance by the American Association for the Study of Liver Diseases. *Hepatology* 2018; **68**: 723-750 [PMID: 29624699 DOI: 10.1002/hep.29913]

60 **Wu EM**, Wong LL, Hernandez BY, Ji JF, Jia W, Kwee SA, Kalathil S. Gender differences in hepatocellular cancer: disparities in nonalcoholic fatty liver disease/steatohepatitis and liver transplantation. *Hepatoma Res* 2018; **4** [PMID: 30687780 DOI: 10.20517/2394-5079.2018.87]

61 **Ma J**, Siegel RL, Islami F, Jemal A. Temporal trends in liver cancer mortality by educational attainment in the United States, 2000-2015. *Cancer* 2019; **125**: 2089-2098 [PMID: 30957228 DOI: 10.1002/cncr.32023]

62 **Rich NE**, Murphy CC, Yopp AC, Tiro J, Marrero JA, Singal AG. Sex disparities in presentation and prognosis of 1110 patients with hepatocellular carcinoma. *Aliment Pharmacol Ther* 2020; **52**: 701-709 [PMID: 32598091 DOI: 10.1111/apt.15917]

63 **Yang B**, Liu JB, So SK, Han SS, Wang SS, Hertz A, Shariff-Marco S, Lin Gomez S, Rosenberg PS, Nguyen MH, Hsing AW. Disparities in hepatocellular carcinoma incidence by race/ethnicity and geographic area in California: Implications for prevention. *Cancer* 2018; **124**: 3551-3559 [PMID: 30113700 DOI: 10.1002/cncr.31598]

64 **Pham C**, Fong TL, Zhang J, Liu L. Striking Racial/Ethnic Disparities in Liver Cancer Incidence Rates and Temporal Trends in California, 1988-2012. *J Natl Cancer Inst* 2018; **110**: 1259-1269 [PMID: 29617913 DOI: 10.1093/jnci/djy051]

65 **He WQ**, Gao X, Gao L, Ma Y, Sun D, Sun J. Contrasting Trends of Primary Liver Cancer Mortality in Chinese Mongol and Non-Mongol. *Asian Pac J Cancer Prev* 2021; **22**: 2757-2763 [PMID: 34582643 DOI: 10.31557/APJCP.2021.22.9.2757]

66 **Wagle NS**, Park S, Washburn D, Ohsfeldt RL, Rich NE, Singal AG, Kum HC. Racial, Ethnic, and Socioeconomic Disparities in Curative Treatment Receipt and Survival in Hepatocellular Carcinoma. *Hepatol Commun* 2022; **6**: 1186-1197 [PMID: 34796703 DOI: 10.1002/hep4.1863]

67 **Ha J**, Yan M, Aguilar M, Tana M, Liu B, Frenette CT, Bhuket T, Wong RJ. Race/Ethnicity-specific Disparities in Hepatocellular Carcinoma Stage at Diagnosis and its Impact on Receipt of Curative Therapies. *J Clin Gastroenterol* 2016; **50**: 423-430 [PMID: 26583267 DOI: 10.1097/MCG.0000000000000448]

68 **Kangas-Dick A**, Gall V, Hilden P, Turner A, Greenbaum A, Sesti J, Paul S, Carpizo D, Kennedy T, Sadaria Grandhi M, Alexander HR, Wang S, Geffner S, August D, Langan RC. Disparities in utilization of services for racial and ethnic minorities with hepatocellular carcinoma associated with hepatitis C. *Surgery* 2020; **168**: 49-55 [PMID: 32414566 DOI: 10.1016/j.surg.2020.03.017]

69 **Sempokuya T**, Patel KP, Azawi M, Ma J, Wong LL. Increased morbidity and mortality of hepatocellular carcinoma patients in lower cost of living areas. *World J Clin Cases* 2021; **9**: 6734-6746 [PMID: 34447820 DOI: 10.12998/wjcc.v9.i23.6734]

70 **Kim DJ**, Yoo JW, Chang JW, Yamashita T, Park EC, Han KT, Kim SJ. Does low income effects 5-year mortality of hepatocellular carcinoma patients? *Int J Equity Health* 2021; **20**: 151 [PMID: 34465351 DOI: 10.1186/s12939-021-01498-z]

71 **Hoehn RS**, Hanseman DJ, Dhar VK, Go DE, Edwards MJ, Shah SA. Opportunities to Improve Care of Hepatocellular Carcinoma in Vulnerable Patient Populations. *J Am Coll Surg* 2017; **224**: 697-704 [PMID: 28069526 DOI: 10.1016/j.jamcollsurg.2016.12.023]

72 **Wu J**, Liu C, Wang F. Disparities in Hepatocellular Carcinoma Survival by Insurance Status: A Population-Based Study in China. *Front Public Health* 2021; **9**: 742355 [PMID: 34805067 DOI: 10.3389/fpubh.2021.742355]

73 **Singh GK**, Siahpush M, Altekruse SF. Time trends in liver cancer mortality, incidence, and risk factors by unemployment level and race/ethnicity, United States, 1969-2011. *J Community Health* 2013; **38**: 926-940 [PMID: 23689953 DOI: 10.1007/s10900-013-9703-z]

74 **Zhou K**, Pickering TA, Gainey CS, Cockburn M, Stern MC, Liu L, Unger JB, El-Khoueiry AB, Terrault NA. Presentation, Management, and Outcomes Across the Rural-Urban Continuum for Hepatocellular Carcinoma. *JNCI Cancer Spectr* 2021; **5** [PMID: 33442663 DOI: 10.1093/jncics/pkaa100]

75 **Lee YT**, Wang JJ, Luu M, Tseng HR, Rich NE, Lu SC, Nissen NN, Noureddin M, Singal AG, Yang JD. State-Level HCC Incidence and Association With Obesity and Physical Activity in the United States. *Hepatology* 2021; **74**: 1384-1394 [PMID: 33728665 DOI: 10.1002/hep.31811]

76 **Clark PJ**, Stuart KA, Leggett BA, Crawford DH, Boyd P, Fawcett J, Whiteman DC, Baade PD. Remoteness, race and social disadvantage: disparities in hepatocellular carcinoma incidence and survival in Queensland, Australia. *Liver Int* 2015; **35**: 2584-2594 [PMID: 25900432 DOI: 10.1111/liv.12853]

77 **Kim HS**, Rotundo L, Yang JD, Kim D, Kothari N, Feurdean M, Ruhl C, Unalp-Arida A. Racial/ethnic disparities in the prevalence and awareness of Hepatitis B virus infection and immunity in the United States. *J Viral Hepat* 2017; **24**: 1052-1066 [PMID: 28581638 DOI: 10.1111/jvh.12735]

78 **Kudo M**. Management of Hepatocellular Carcinoma in Japan as a World-Leading Model. *Liver Cancer* 2018; **7**: 134-147 [PMID: 29888204 DOI: 10.1159/000484619]

79 **Wong LL**, Reyes RJ, Kwee SA, Hernandez BY, Kalathil SC, Tsai NC. Pitfalls in surveillance for hepatocellular carcinoma: How successful is it in the real world? *Clin Mol Hepatol* 2017; **23**: 239-248 [PMID: 28706177 DOI: 10.3350/cmh.2017.0008]

80 **Wong LL**, Hernandez B, Kwee S, Albright CL, Okimoto G, Tsai N. Healthcare disparities in Asians and Pacific Islanders with hepatocellular cancer. *Am J Surg* 2012; **203**: 726-732 [PMID: 22227170 DOI: 10.1016/j.amjsurg.2011.06.055]

81 **MacConmara M**, Wang B, Patel MS, Hwang CS, DeGregorio L, Shah J, Hanish SI, Desai D, Lynch R, Tanriover B, Zeh H 3rd, Vagefi PA. Liver Transplantation in the Time of a Pandemic: A Widening of the Racial and Socioeconomic Health Care Gap During COVID-19. *Ann Surg* 2021; **274**: 427-433 [PMID: 34183513 DOI: 10.1097/SLA.0000000000004994]

82 **Servin-Rojas M**, Olivas-Martinez A, Ramirez Del Val F, Torres-Gomez A, Navarro-Vargas L, García-Juárez I. Transplant trends in Mexico during the COVID-19 pandemic: Disparities within healthcare sectors. *Am J Transplant* 2021; **21**: 4052-4060 [PMID: 34387936 DOI: 10.1111/ajt.16801]

83 **Locke JE**, Shelton BA, Olthoff KM, Pomfret EA, Forde KA, Sawinski D, Gray M, Ascher NL. Quantifying Sex-Based Disparities in Liver Allocation. *JAMA Surg* 2020; **155**: e201129 [PMID: 32432699 DOI: 10.1001/jamasurg.2020.1129]

84 **Cullaro G**, Sarkar M, Lai JC. Sex-based disparities in delisting for being "too sick" for liver transplantation. *Am J Transplant* 2018; **18**: 1214-1219 [PMID: 29194969 DOI: 10.1111/ajt.14608]

85 **Loy VM**, Joyce C, Bello S, VonRoenn N, Cotler SJ. Gender disparities in liver transplant candidates with nonalcoholic steatohepatitis. *Clin Transplant* 2018; **32**: e13297 [PMID: 29804305 DOI: 10.1111/ctr.13297]

86 **Kim WR**, Mannalithara A, Heimbach JK, Kamath PS, Asrani SK, Biggins SW, Wood NL, Gentry SE, Kwong AJ. MELD

3.0: The Model for End-Stage Liver Disease Updated for the Modern Era. *Gastroenterology* 2021; **161**: 1887-1895.e4 [PMID: 34481845 DOI: 10.1053/j.gastro.2021.08.050]

87 **Karnam RS**, Chen S, Xu W, Chen C, Elangainesan P, Ghanekar A, McGilvray I, Reichman T, Sayed B, Selzner M, Sapisochin G, Galvin Z, Hirschfield G, Asrani SK, Selzner N, Cattral M, Lilly L, Bhat M. Sex Disparity in Liver Transplant and Access to Living Donation. *JAMA Surg* 2021; **156**: 1010-1017 [PMID: 34406347 DOI: 10.1001/jamasurg.2021.3586]

88 **Robinson A**, Hirode G, Wong RJ. Ethnicity and Insurance-Specific Disparities in the Model for End-Stage Liver Disease Score at Time of Liver Transplant Waitlist Registration and its Impact on Mortality. *J Clin Exp Hepatol* 2021; **11**: 188-194 [PMID: 33746443 DOI: 10.1016/j.jceh.2020.07.011]

89 **Chang SH**, Wang M, Liu X, Alhamad T, Lentine KL, Schnitzler MA, Colditz GA, Park Y, Chapman WC. Racial/Ethnic Disparities in Access and Outcomes of Simultaneous Liver-Kidney Transplant Among Liver Transplant Candidates With Renal Dysfunction in the United States. *Transplantation* 2019; **103**: 1663-1674 [PMID: 30720678 DOI: 10.1097/TP.0000000000002574]

90 **Nobel YR**, Forde KA, Wood L, Cartiera K, Munoz-Abraham AS, Yoo PS, Abt PL, Goldberg DS. Racial and ethnic disparities in access to and utilization of living donor liver transplants. *Liver Transpl* 2015; **21**: 904-913 [PMID: 25865817 DOI: 10.1002/lt.24147]

91 **Campsen J**, Zimmerman M, Trotter J, Hong J, Freise C, Brown RS Jr, Cameron A, Ghobrial M, Kam I, Busuttil R, Saab S, Holt C, Emond JC, Stiles JB, Lukose T, Chang MS, Klintmalm G. Multicenter review of liver transplant for hepatitis B-related liver disease: disparities in gender and ethnicity. *Clin Transplant* 2013; **27**: 829-837 [PMID: 24033475 DOI: 10.1111/ctr.12224]

92 **Zhang Y**. The Impact of the Share 35 Policy on Racial and Ethnic Disparities in Access to Liver Transplantation for Patients with End Stage Liver Disease in the United States: An Analysis from UNOS Database. *Int J Equity Health* 2017; **16**: 55 [PMID: 28340592 DOI: 10.1186/s12939-017-0552-8]

World Journal of Hepatology

Submit a Manuscript: https://www.f6publishing.com

World J Hepatol 2022 November 27; 14(11): 1953-1963

DOI: 10.4254/wjh.v14.i11.1953

ISSN 1948-5182 (online)

ORIGINAL ARTICLE

Retrospective Study

Liver test abnormalities in asymptomatic and mild COVID-19 patients and their association with viral shedding time

Si-Yi Yu, Jia-Rong Xie, Jun-Jun Luo, Hong-Peng Lu, Lei Xu, Jun-Jie Wang, Xue-Qin Chen

Specialty type: Gastroenterology and hepatology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Mahmoud MZ, Saudi Arabia; Nasa P, United Arab Emirates

Received: October 1, 2022
Peer-review started: October 1, 2022
First decision: October 17, 2022
Revised: October 25, 2022
Accepted: November 21, 2022
Article in press: November 21, 2022
Published online: November 27, 2022

Si-Yi Yu, Jia-Rong Xie, Hong-Peng Lu, Lei Xu, Department of Gastroenterology, Ningbo First Hospital, Ningbo 315010, Zhejiang Province, China

Jun-Jun Luo, Department of Cardiology, Ningbo First Hospital, Ningbo 315010, Zhejiang Province, China

Jun-Jie Wang, Department of Information Technology, Ningbo First Hospital, Ningbo 315010, Zhejiang Province, China

Xue-Qin Chen, Department of Traditional Medicine, Ningbo First Hospital, Ningbo 315010, Zhejiang Province, China

Corresponding author: Xue-Qin Chen, Doctor, Professor, Department of Traditional Medicine, Ningbo First Hospital, No. 59 Liuting Street, Ningbo 315010, Zhejiang Province, China. cxq2316@163.com

Abstract

BACKGROUND

Asymptomatic infections and mild symptoms are common in patients infected with the Omicron variant, and data on liver test abnormalities are rare.

AIM

To evaluated the clinical characteristics of asymptomatic and mild coronavirus disease 2019 (COVID-19) patients with abnormal liver test results.

METHODS

This retrospective study included 661 laboratory-confirmed asymptomatic and mild COVID-19 patients who were treated in two makeshift hospitals in Ningbo from April 5, 2022 to April 29, 2022. Clinical information and viral shedding time were collected, and univariate and multivariate logistic regression models were performed in statistical analyses.

RESULTS

Of the 661 patients, 83 (12.6%) had liver test abnormalities, and 6 (0.9%) had liver injuries. Abnormal liver tests revealed a reliable correlation with a history of liver disease ($P < 0.001$) and a potential correlation with male sex and obesity ($P < 0.05$). Elevated alanine aminotransferase was reliably associated with obesity ($P < 0.05$) and a history of liver disease ($P < 0.001$). Elevated aspartate transaminase (AST)

was reliably correlated with a history of liver disease ($P < 0.001$), and potentially correlated with age over 30 years ($P < 0.05$). There was a reliable correlation between AST ≥ 2× the upper limit of normal and a longer viral shedding time, especially in mild cases.

CONCLUSION

Obesity and a history of liver disease are risk factors for liver test abnormalities. Being male and an older age are potential risk factors. Attention should be given to liver tests in asymptomatic and mild COVID-19 patients, which has crucial clinical significance for evaluating the viral shedding time.

Key Words: COVID-19; Liver test abnormalities; Asymptomatic carriers; Mild cases; Viral shedding time; Risk factors

Core Tip: This is the first clinical study focusing on liver test abnormalities in asymptomatic and mild coronavirus disease 2019 patients. Unlike studies concerning severe cases, we focused on the association between liver test results and viral shedding time in patients infected with the Omicron BA2.2 variant, with a relatively high proportion of asymptomatic carriers and mild cases. The viral shedding time for patients with elevated aspartate transaminase were significantly longer, especially in mild patients. This provides crucial evidence for identifying high-risk patients with a prolonged viral shedding time.

Citation: Yu SY, Xie JR, Luo JJ, Lu HP, Xu L, Wang JJ, Chen XQ. Liver test abnormalities in asymptomatic and mild COVID-19 patients and their association with viral shedding time. *World J Hepatol* 2022; 14(11): 1953-1963
URL: https://www.wjgnet.com/1948-5182/full/v14/i11/1953.htm
DOI: https://dx.doi.org/10.4254/wjh.v14.i11.1953

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a respiratory disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). This highly contagious disease poses a great threat to global public health. By September 2, 2022, the disease had resulted in 601189435 infections and 6475346 deaths [1]. In addition to respiratory symptoms and fever, 14%-69% of patients with COVID-19 have abnormal liver function tests, mainly manifested by elevations of hypoalbuminemia, gamma-glutamyl transferase, alanine aminotransferase (ALT) and aspartate aminotransferase (AST)[2,3]. Patients with severe diseases are more likely to develop elevated liver tests, suggesting an association between liver injury and the severity of disease[2,4]. Possible mechanisms of COVID-19-related liver injury include direct SARS-CoV-2-induced cytopathic injury to hepatocytes and cholangiocytes, immune dysregulation and hypoxic liver injury, and drug-induced liver injury[5].

The Omicron B.1.1.529 (BA.1) variant was first discovered in South Africa on November 9, 2021[6]. Omicron variants have rapidly replaced delta variants due to their strong interpersonal infectivity, which has caused a worldwide pandemic. Compared with patients infected with previous variants, those infected with the Omicron variants are younger, have fewer comorbidities, and develop lower severity and mortality, and asymptomatic infections and mild symptoms are more common[7-9]. However, no studies have systematically focused on liver abnormalities in asymptomatic carriers or mild cases. Previous studies have revealed that liver test abnormalities are associated with prolonged hospitalization time and viral shedding time in COVID-19 patients[10,11], indicating a prognostic indicator of poor outcome. At present, no studies have examined the association between liver abnormalities and viral shedding time in asymptomatic and mild COVID-19 patients.

The epidemic prevention policies of different countries are established based on their own political, economic and health conditions, which are in line with the national circumstances and none is superior to others. This study was carried out under the policy of Chinese government, aiming to determine the clinical characteristics of liver test abnormalities in asymptomatic and mild COVID-19 patients infected with the Omicron BA2.2 variant[12] and their association with the viral shedding time. Our research provides suggestions for health policymakers and medical practitioners.

MATERIALS AND METHODS

Participants

In this cross-sectional study, we recruited patients with COVID-19 who were treated in Ningbo Makeshift Hospital and Dapengshan Makeshift Hospital in Ningbo, Zhejiang from April 5, 2022 to April 29, 2022. All patients were transferred from Shanghai. The inclusion criteria were as follows: (1) Age over 14 years; (2) complete clinical information; and (3) asymptomatic carriers or mild cases of COVID-19. Asymptomatic carriers were those who had positive etiological tests of COVID-19 but with no clinical symptoms or imaging features of COVID-19. Mild cases were defined as confirmed cases with mild clinical symptoms and no pneumonia manifestation on imaging[13]. The exclusion criteria were as follows: (1) Ordinary cases whose pneumonia manifestation could be seen in imaging, or severe cases with respiratory distress[13]; and (2) patients who were transferred to designated hospitals for further diagnosis and treatment due to underlying diseases or other reasons. This study complied with the Declaration of Helsinki and was approved by the Ethics Committee of Ningbo First Hospital (No. 2022RS069).

Measures

The clinical information of patients, including age, sex, height, weight, symptoms, medical history (hypertension, diabetes, and liver diseases), and laboratory tests (complete blood count, liver tests, chest computed tomography (CT) scans, and nucleic acid tests for COVID-19), were retrospectively collected. Obesity was defined as a body mass index (BMI) ≥ 28 kg/m^2. Symptoms included fever, fatigue (weakness and muscle soreness), respiratory symptoms (sore throat, dry throat, cough, and chest stuffiness), and gastrointestinal symptoms (nausea, anorexia, and diarrhea). The patients' symptoms were collected from the electronic medical records, and were double-checked on the day of discharge. Liver diseases included chronic hepatitis B, alcoholic/nonalcoholic fatty liver disease (NAFLD) and other liver diseases. NAFLD was defined as hepatic steatosis detected by ultrasound or CT, excluding secondary causes and excessive alcohol consumption (> 30 g/d for males, and > 20 g/d for females). Hepatitis B was defined as positive serum hepatitis B surface antigen. Complete blood counts, liver and kidney tests, and chest CT scans were performed on the admission day, and nasal swabs for SARS-CoV-2 were tested every two days. All patients received Chinese medicine and symptomatic therapy (if necessary), but not antivirals or monoclonal antibodies.

Real-time reverse transcription PCR was used to detect SARS-CoV-2, and primers targeting the open reading frame 1ab (ORF1ab) and nucleocapsid protein N were used for amplification and detection. The corresponding sequences for ORF1ab were 5'-CCCTGTGGGTTTTACACTTAA-3'(F), 5'-ACGATTGT-GCATCAGCTGA-3' (R), and 5'-CY3-CCGTCTGCGGTATGTGGGAAAGGTTATGG-BHQ1-3' (probe), and those for N were 5'-GGGGAACTTCTCCTGCTAGAAT-3' (F), 5'-CAGACATTTTGCTCTCAAGCTG-30' (R), and 5'-FAM-TTGCTGCTGCTTGACAGATT-TAMRA-3' (probe). The methods were based on the criteria provided by the National Health Commission of the People's Republic of China[14].

Liver test abnormalities were defined as elevations of the following liver enzymes in serum: ALT > 50 U/L (male) or 40 U/L (female), AST > 40 U/L (male) or 35 U/L (female), and total bilirubin (TBIL) > 17.1 μmol/L. Liver injury was defined as ALT and/or AST more than 3× the upper limit of normal (ULN) and/or TBIL more than 2 × ULN[15].

Viral shedding was defined as the cycle threshold (Ct) values of both ORF1ab and N greater than 35. The viral shedding time was defined as the duration from the first positive nucleic acid test to the first negative result (two consecutive negatives). Patients were discharged with significantly recovered respiratory symptoms and two consecutive negative nucleic acid tests.

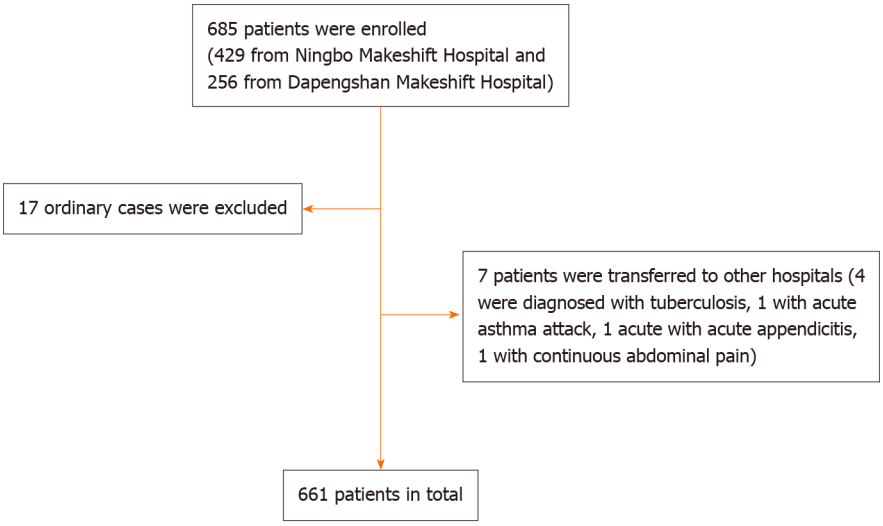
Statistical analysis

Data were analyzed by IBM SPSS (version 26.0). Continuous variables were described by the means ± standard deviation (SD) or medians and interquartile range (IQR), while categorical variables were described by the frequency and percentage. For continuous variable comparison, independent sample T tests or one-way analysis of variance were used for normally distributed data, and Mann–Whitney U tests or Kruskal–Wallis tests were used for nonnormally distributed data. For categorical variable comparison, chi-square tests or Fisher's exact tests were applied. Ordinal logistic regression analyses were used to identify risk factors associated with liver test abnormalities, and multiple linear regression analyses were used to identify factors associated with the viral shedding time. $P < 0.05$ (two-sided) was considered statistically significant. The results of statistical ayalyses can be re-verified if any party wishes to confirm the credibility.

RESULTS

Study design and participant criteria

The participant recruitment process is shown in Figure 1. In total, 429 patients in Ningbo Makeshift



DOI: 10.4254/wjh.v14.i11.1953

Figure 1 Inclusion flow chart.

Hospital and 256 patients in Dapengshan Makeshift Hospital were selected according to the inclusion criteria. Excluding 17 ordinary cases and 7 patients who were transferred to designated hospitals (4 cases of pulmonary tuberculosis diagnosed with CT scan, one case of acute asthma attack, one case of acute appendicitis, and one case of persistent abdominal pain), 661 participants were included in the final sample.

As shown in Table 1, the median age was 33 years (IQR 27-44 years), 331 (50.1%) were male, and the median BMI was 22.8 kg/m^2 (IQR 20.7-25.2). A total of 130 (19.7%) had underlying diseases, of whom 57 (8.6%) had liver diseases. 45 (6.8%) had NAFLD, 11 (1.7%) had hepatitis B, and 1 (0.2%) had both. A total of 425 (64.3%) patients developed a fever, and 619 (93.6%) patients had mild cases. Eighty-three (12.6%) patients had liver test abnormalities and 6 (0.9%) had liver injuries. The number of patients with elevations in ALT, AST and TBIL was 53 (8.0%), 61 (9.2%), and 4 (0.6%), respectively, with a majority of mild liver test abnormalities (Supplementary Table 1). Some patients reported medicines taken before admission, including traditional Chinese medicine (382, 57.8%), nonsteroidal anti-inflammatory drugs (NSAIDs) (89, 13.5%), and other medicines for cold (91, 13.8%).

Clinical features of COVID-19 patients with liver test abnormalities

As shown by a univariate logistic regression model, liver test abnormalities were significantly associated with male sex [odds ratio (OR) 1.699, 95% confidence interval (CI) 1.061-2.721, $P = 0.027$], obesity (OR 2.707, 95%CI 1.384-5.291, $P = 0.004$) and a history of liver disease (OR 2.707, 95%CI 1.384-5.291, $P = 0.004$) but not with age, disease type, clinical manifestations or medication history (Figure 2). The correlated factors in the univariate model were taken as key factors. A multivariate logistic regression model for key factors indicated that liver test abnormalities were only associated with a history of liver disease (OR 8.004, 95%CI 4.319-14.835, $P < 0.001$). A multivariate logistic regression model for all factors showed that liver test abnormalities were significantly associated with the age of 30-49 years (compared with age 14-30 years, OR 1.970, 95%CI 1.073-3.618, $P = 0.029$), male sex (OR 1.728, 95%CI 1.005-2.971, $P = 0.048$), and a history of liver disease (OR 8.265, 95%CI 4.315-15.831, $P < 0.001$). Based on the above models, liver test abnormalities had a reliable correlation with a history of liver disease, and a potential correlation with male sex and obesity.

As revealed by all three models in Supplementary Figure 1, elevated ALT had a firm correlation with obesity (univariate logistic regression: OR 3.82, 95%CI 1.84-7.94, $P < 0.001$; multivariate logistic regression for key factors: OR 2.57, 95%CI 1.15-5.70, $P = 0.021$; multivariate logistic regression for all factors: OR 3.31, 95%CI 1.37-7.98, $P = 0.009$) and a history of liver disease (univariate logistic regression: OR 9.54, 95%CI 5.01-18.16, $P < 0.001$; multivariate logistic regression for key factors: OR 8.30, 95%CI 4.21-16.36, $P < 0.001$; multivariate logistic regression for all factors: OR 9.05, 95%CI 4.31-19.01, $P < 0.001$). Therefore, ALT elevation was reliably correlated with obesity and a history of liver disease.

A univariate logistic regression model indicated that elevated AST was associated with a history of liver disease (OR 8.18, 95%CI 4.40-15.24, $P < 0.001$, Supplementary Figure 2). A multivariate logistic regression model on all factors showed that AST elevation was associated with older age (age of 30-49 years *vs* age of 14-29 years: OR 2.48, 95%CI 1.18-5.20, $P = 0.016$; age over 50 years vs. age of 14-29 years: OR 2.81, 95%CI 1.14-6.97, $P = 0.025$) and a history of liver disease (OR 7.84, 95%CI 3.89-15.78, $P < 0.001$) (Supplementary Figure 2). Therefore, the AST elevation had a reliable correlation with a history of liver disease, and a potential correlation with age over 30 years.

Table 1 Characteristics of 661 patients with coronavirus disease 2019 by liver tests

Characteristics	Liver tests			Total
	Normal	Abnormal	Injury	
Number (%)	578 (87.4)	77 (11.6)	6 (0.9)	661
Age, yr, median (IQR)	33 (27-44)	33 (29.5-40.5)	32.5 (30-48)	33 (27-44)
14-29	209 (36.1)	19 (24.7)	1 (16.7)	229 (34.6)
30-49	271 (46.9)	43 (55.8)	4 (66.7)	318 (48.1)
≥ 50	98 (17.0)	15 (19.5)	1 (16.7)	114 (17.2)
Males, *n* (%)	280 (48.4)	47 (61.0)	4 (66.7)	331 (50.1)
BMI, kg/m^2, median (IQR)	22.7 (20.4-25.0)	23.5 (21.2-26.5)	25.8 (23.0-28.8)	22.8 (20.7-25.2)
< 18.5	33 (5.7)	3 (3.9)	0 (0)	36 (5.4)
18.5-23.9	320 (55.4)	37 (48.1)	3 (50)	360 (54.5)
24-27.9	149 (25.8)	24 (31.2)	0 (0)	173 (26.2)
> 28	38 (6.6)	10 (13.0)	3 (50)	51 (7.7)
Comorbidities, *n* (%)				
Hypertension	36 (6.2)	3 (3.9)	1 (16.7)	40 (6.1)
Diabetes	22 (3.8)	2 (2.6)	2 (33.3)	26 (3.9)
Liver disease	30 (5.2)	24 (31.2)	3 (50)	57 (8.6)
Disease type, *n* (%)				
Asymptomatic cases	37 (6.4)	5 (6.4)	0 (0)	42 (6.4)
Mild cases	541 (93.6)	72 (93.5)	6 (100)	619 (93.6)
Symptoms, *n* (%)				
Fever	371 (64.2)	51 (66.2)	3 (50)	425 (64.3)
Fatigue	276 (47.8)	37 (48.1)	4 (33.3)	317 (48.0)
Respiratory symptoms	483 (83.6)	64 (83.1)	6 (100)	553 (83.7)
GI symptoms	170 (29.4)	26 (33.8)	1 (16.7)	197 (29.8)
Medication				
Chinese medicine	336 (58.1)	40 (51.9)	6 (100)	382 (57.8)
NSAIDs	77 (13.3)	11 (14.3)	1 (16.7)	89 (13.5)
Other medicines for cold	82 (14.2)	9 (11.7)	0 (0)	91 (13.8)

IQR: Interquartile range; BMI: Body mass index; GI: Gastrointestinal; NSAIDs: Nonsteroidal anti-inflammatory drugs.

In summary, obesity and a history of liver disease were risk factors for abnormal liver test results, and male sex and age over 30 years were potential risk factors. These findings are of great clinical significance for evaluating high-risk subjects with liver abnormalities among asymptomatic and mild COVID-19 patients.

Association between viral shedding time and liver test abnormalities

The association between the viral shedding time and abnormal liver test results was analyzed in 657 participants after excluding 4 subjects with missing data. As shown in Table 2, the viral shedding time of patients with AST ≥ 2 × ULN were significantly prolonged (< 2 × ULN *vs* ≥ 2 × ULN, viral shedding time: 10.51 ± 2.76 d *vs* 12.40 ± 3.57 d, P = 0.033). As suggested by three models in Figure 3, AST ≥ 2 × ULN had a reliable correlation with the viral shedding time (univariate linear regression: coefficient 1.893, 95%CI 0.158-3.628, P = 0.033; multivariate linear regression of key factors: coefficient 1.862, 95%CI 0.140-3.584, P = 0.034; multivariate linear regression for all factors: coefficient 2.778, 95%CI 0.615-4.942, P = 0.012). In contrast, there was no significant correlation between ALT elevation and the viral shedding time. In addition, mild cases or female sex were associated with a longer viral shedding time (Table 2, Figure 3).

Table 2 Comparison of viral shedding time by liver tests and other characteristics

Characteristics		Viral shedding time (day, mean ± SD)	*P* value
Age, yr	14-29	10.31 ± 2.60	0.129
	30-49	10.55 ± 2.78	
	≥ 50	10.96 ± 3.11	
Gender	Male	10.27 ± 2.77	0.015
	Female	10.80 ± 2.78	
BMI, kg/m^2	< 27.9	10.62 ± 2.67	0.487
	≥ 28	10.90 ± 3.11	
Comorbidities	Hypertension	10.51 ± 3.16	0.958
	Diabetes	11.04 ± 3.37	0.364
	Liver disease	10.41 ± 3.01	0.725
Disease type	Asymptomatic cases	9.26 ± 3.16	0.002
	Mild cases	10.62 ± 2.73	
ALT	< 2×ULN	10.54 ± 2.78	0.983
	≥ 2×ULN	10.56 ± 2.74	
AST	< 2×ULN	10.51 ± 2.76	0.033
	≥ 2×ULN	12.40 ± 3.57	

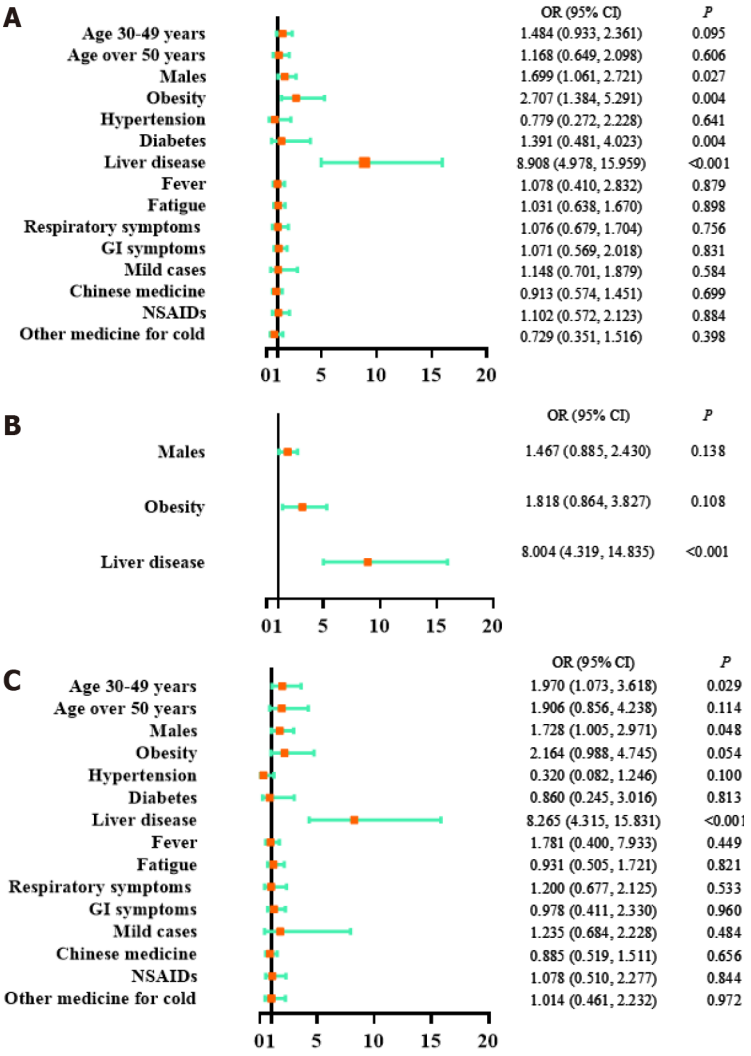
ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BMI: Body mass index; ULN: Upper limit of normal; SD: Standard deviation.

The correlations between the AST elevation or disease types and the viral shedding time were further analyzed. As shown in Supplementary Table 2, the viral shedding time of mild cases with AST ≥ 2 × ULN was significantly prolonged (AST ≥ 2 × ULN & mild cases *vs* AST < 2 × ULN & mild cases *vs* AST < 2 × ULN & asymptomatic carriers: 12.40 ± 3.57 d *vs* 10.59 ± 2.71 d *vs* 9.26 ± 3.16 d, $P = 0.001$). Therefore, it is suggested that great attention should be given to the liver test results of asymptomatic and mild COVID-19 patients, which has crucial clinical significance for predicting the viral shedding time.

DISCUSSION

To the best of our knowledge, this is the first clinical study focusing on liver test abnormalities in asymptomatic and mild COVID-19 patients. In the current epidemic of the Omicron BA2.2 variant, 12.6% of COVID-19 patients developed liver test abnormalities, and 0.9% developed liver injuries. The majority of the liver test abnormalities were mild. The ratio of abnormal liver tests in our study was lower than previous data of 14%-69%[2,3]. One possible reason for this was that our participants were all asymptomatic carriers or mild cases, among whom abnormal liver test results were uncommon. Previous studies revealed normal ALT and AST levels in asymptomatic patients, which were significantly lower than those with symptomatic infection[16]. In contrast, our study showed no differences in liver tests between asymptomatic carriers and mild cases. The probable reason was that all of the symptomatic patients in our study were mild cases, which weakened the difference between the two groups.

As shown in our study, the risk factors for liver test abnormalities in asymptomatic and mild COVID-19 patients included obesity and a history of liver disease, and the potential risk factors included male sex and age over 30 years. Previous studies suggested that preexisting chronic liver diseases, such as NAFLD, chronic hepatitis B, and alcoholic liver disease, were high-risk factors for liver injury in COVID-19[17-19]. Consistent with these findings, our study verified a strong correlation between abnormal liver test results and a history of liver disease. Virus-induced cytokine storms, impaired mitochondrial activity, or endoplasmic reticulum stress may aggravate the preexisting liver disease, which further leads to the progression of liver injury[20]. In addition, liver test abnormalities were more common in males, which was similar to a previous study[21]. The higher estrogen level in females may play a protective role[22]. In addition, elevated ALT was strongly associated with obesity. This may be due to a high ratio of NAFLD patients among obese individuals, and fatty liver diseases can result in elevated ALT levels[18]. There was a potential correlation between elevated AST and age over 30 years. Since AST is known to reflect the injury of organs, such as myocardium and skeletal muscle, these



DOI: 10.4254/wjh.v14.i11.1953

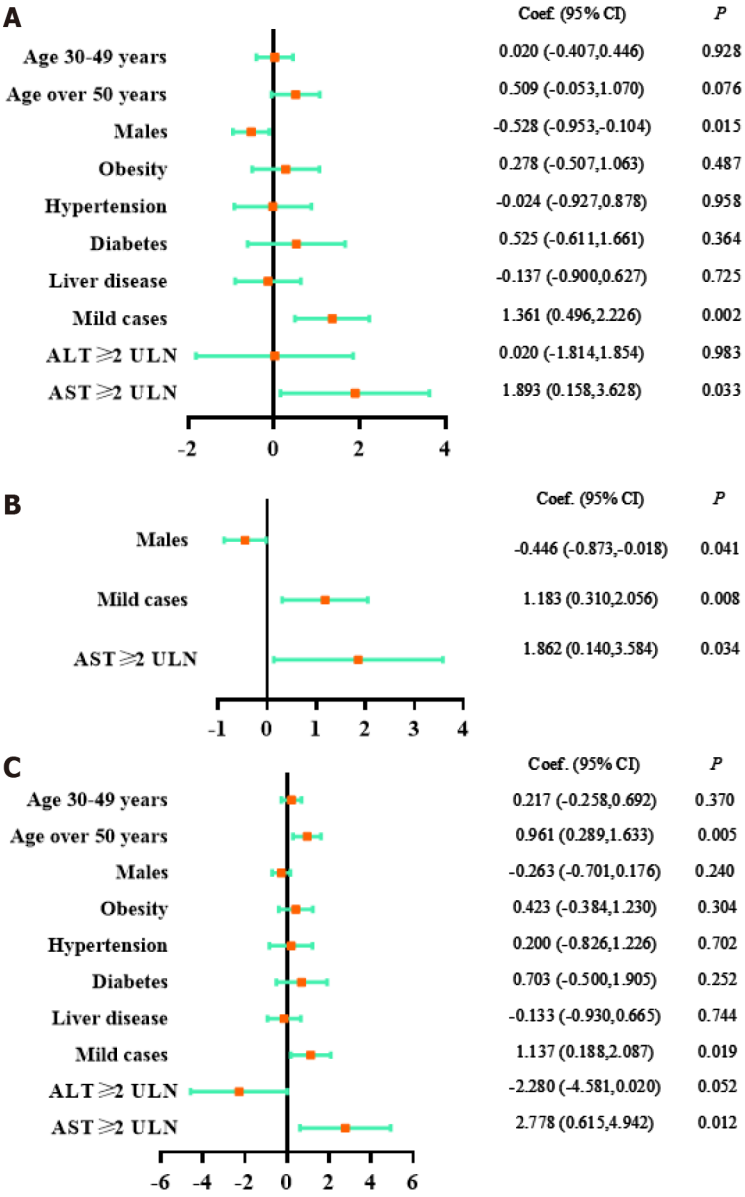
Figure 2 Logistic regression models on factors associated with liver tests. A: Univariate logistic regression model; B: Multivariate logistic regression model on key factors; C: Multivariate logistic regression model on all factors; age: *vs* age 14-29 years; GI: Gastrointestinal; NSAIDs: Nonsteroidal anti-inflammatory drugs; OR: Odds ratio; CI: Confidence interval.

organic injuries may occur more frequently in elderly patients with COVID-19.

Medications for COVID-19 treatment, such as antibiotics and antiviral medications (*e.g.*, lopinavir/ritonavir) have been reported to cause liver injury[10]. This study focused on the liver test features of COVID-19 patients in the early stage of the disease. These patients had rarely taken antibiotics or antiviral medications, while some had taken Chinese medicine, NSAIDs or other cold medicines for a short period. Importantly, no association was found between these medications and liver test abnormalities in COVID-19 patients.

As reported in hospitalized COVID-19 patients, abnormal liver test results at admission were associated with a prolonged hospitalization time and viral shedding time[10,11]. Early elevation of AST was closely related to mortality, suggesting that it might be a predictor of poor prognosis for COVID-19 [23]. Similarly, we also found a reliable association between the increase in AST and a prolonged viral shedding time in asymptomatic and mild COVID-19 patients. We speculate that the lower immunity of patients with elevated AST levels might affect the viral clearance. The viral shedding time was even longer in mild cases with elevated AST. Similar results have been previously revealed in which the viral shedding duration was longer in symptomatic patients than in asymptomatic patients[16,24]. Lymphocyte-mediated immune responses may play a vital role[15].

Our study has two advantages. First, unlike studies concerning severe cases[2,4,15,23], we focused on the association between liver test results and viral shedding time, especially in patients infected with the Omicron BA2.2 variant, with a relatively high proportion of asymptomatic carriers and mild cases. The viral shedding time for patients with elevated AST were significantly longer, especially in mild patients. This provides crucial evidence for identifying high-risk patients with a prolonged viral shedding time. Second, we analyzed the risk factors for liver test abnormalities. Male sex, older age, obesity, and a history of liver disease may increase the risk of liver abnormalities, which can be used to identify high-



DOI: 10.4254/wjh.v14.i11.1953

Figure 3 Linear regression models on factors associated with viral shedding time. A: Univariate logistic regression model; B: Multivariate logistic regression model on key factors; C: Multivariate logistic regression model on all factors; age: *vs* age 14-29 years; ULN: Upper limit of normal; Coef.: Coefficient; CI: Confidence interval.

risk patients with abnormal liver test results.

One limitation of our research is that we only measured the levels of ALT, AST, and TBIL, but failed to obtain other liver test results, such as γ-glutamyl transpeptidase and alkaline phosphatase, and we did not monitor the dynamic alterations of the liver tests. The absence of these indicators may have led to an incomplete assessment of liver abnormalities. Another limitation is that we only recruited participants from two makeshift hospitals in Ningbo, but not from multiple regions. This may have led to a limited sample size and underrepresentation of the sample.

CONCLUSION

We evaluated the liver test features of asymptomatic and mild COVID-19 patients during the epidemic of the Omicron BA2.2 variant. Patients with a history of liver disease or male patients were more likely to develop liver test abnormalities or liver injury. Those who were obese or had a history of liver disease tended to develop ALT elevation, and those who were aged over 30 years or had a history of liver disease tended to develop AST elevation. The increase in AST in the early stage was closely associated with a prolonged viral shedding time, especially in mild cases. Attention should be given to the liver test data of asymptomatic and mild COVID-19 patients, which has important clinical significance for

evaluating the viral shedding time.

ARTICLE HIGHLIGHTS

Research background

Data on liver test abnormalities in asymptomatic and mild coronavirus disease 2019 (COVID-19) patients are rare.

Research motivation

This study evaluated the clinical characteristics of asymptomatic and mild COVID-19 patients with abnormal liver test results.

Research objectives

We aimed to determine the liver test abnormalities in asymptomatic and mild COVID-19 patients and their association with the viral shedding time, providing suggestions for health policymakers and medical practitioners.

Research methods

Clinical information and viral shedding time were collected retrospectively from 661 laboratory-confirmed asymptomatic and mild COVID-19 patients. Univariate and multivariate logistic regression models were performed in statistical analyses.

Research results

Elevated alanine aminotransferase was associated with obesity and a history of liver disease. Elevated aspartate transaminase (AST) was correlated with a history of liver disease age over 30 years. There was a correlation between AST ≥ 2× the upper limit of normal and a longer vital shedding time.

Research conclusions

Obesity and a history of liver disease are risk factors for liver test abnormalities. Liver test abnormality in asymptomatic and mild COVID-19 patients has clinical correlation with the viral shedding time.

Research perspectives

Attention should be given to liver tests in asymptomatic and mild COVID-19 patients, which has crucial clinical significance for evaluating the viral shedding time.

FOOTNOTES

Author contributions: Yu SY designed the study and drafted the manuscript; Yu SY, Luo JJ, Lu HP and Wang JJ organized the data; Yu SY and Xie JR performed the statistical analyses; Chen XQ and Xu L supervised the study design and conduction.

Supported by the Ningbo Medical Science and Technology Program, No. 2019Y32; Ningbo 2025 Science and Technology Major Project, No. 2021Z018; and Ningbo Natural Science Foundation of China, No. 2021J263.

Institutional review board statement: This study was approved by the Ethics Committee of Ningbo First Hospital (No. 2022RS069).

Informed consent statement: The data of our study was collected retrospectively, and the informed consent was exempted by the Ethics Committee of Ningbo First Hospital.

Conflict-of-interest statement: All the authors declare that they have no conflict of interest.

Data sharing statement: No additional data are available.

Country/Territory of origin: China

ORCID number: Si-Yi Yu 0000-0002-8295-1066; Jia-Rong Xie 0000-0002-1262-3411; Xue-Qin Chen 0000-0002-1828-1985.

S-Editor: Liu JH
L-Editor: A
P-Editor: Liu JH

REFERENCES

1 **World Health Organization**. WHO Coronavirus (COVID-19) Dashboard. (accessed on 3 Sep 2022). Available online: https://covid19.who.int/
2 **Nasa P**, Alexander G. COVID-19 and the liver: What do we know so far? *World J Hepatol* 2021; **13**: 522-532 [PMID: 34131467 DOI: 10.4254/wjh.v13.i5.522]
3 **Bloom PP**, Meyerowitz EA, Reinus Z, Daidone M, Gustafson J, Kim AY, Schaefer E, Chung RT. Liver Biochemistries in Hospitalized Patients With COVID-19. *Hepatology* 2021; **73**: 890-900 [PMID: 32415860 DOI: 10.1002/hep.31326]
4 **Guan WJ**, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, Liu L, Shan H, Lei CL, Hui DSC, Du B, Li LJ, Zeng G, Yuen KY, Chen RC, Tang CL, Wang T, Chen PY, Xiang J, Li SY, Wang JL, Liang ZJ, Peng YX, Wei L, Liu Y, Hu YH, Peng P, Wang JM, Liu JY, Chen Z, Li G, Zheng ZJ, Qiu SQ, Luo J, Ye CJ, Zhu SY, Zhong NS; China Medical Treatment Expert Group for Covid-19. Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med* 2020; **382**: 1708-1720 [PMID: 32109013 DOI: 10.1056/NEJMoa2002032]
5 **Herta T**, Berg T. COVID-19 and the liver - Lessons learned. *Liver Int* 2021; **41** Suppl 1: 1-8 [PMID: 34155789 DOI: 10.1111/liv.14854]
6 **Tegally H**, Wilkinson E, Giovanetti M, Iranzadeh A, Fonseca V, Giandhari J, Doolabh D, Pillay S, San EJ, Msomi N, Mlisana K, von Gottberg A, Walaza S, Allam M, Ismail A, Mohale T, Glass AJ, Engelbrecht S, Van Zyl G, Preiser W, Petruccione F, Sigal A, Hardie D, Marais G, Hsiao NY, Korsman S, Davies MA, Tyers L, Mudau I, York D, Maslo C, Goedhals D, Abrahams S, Laguda-Akingba O, Alisoltani-Dehkordi A, Godzik A, Wibmer CK, Sewell BT, Lourenço J, Alcantara LCJ, Kosakovsky Pond SL, Weaver S, Martin D, Lessells RJ, Bhiman JN, Williamson C, de Oliveira T. Detection of a SARS-CoV-2 variant of concern in South Africa. *Nature* 2021; **592**: 438-443 [PMID: 33690265 DOI: 10.1038/s41586-021-03402-9]
7 **Maslo C**, Friedland R, Toubkin M, Laubscher A, Akaloo T, Kama B. Characteristics and Outcomes of Hospitalized Patients in South Africa During the COVID-19 Omicron Wave Compared With Previous Waves. *JAMA* 2022; **327**: 583-584 [PMID: 34967859 DOI: 10.1001/jama.2021.24868]
8 **Dyer O**. Covid-19: Omicron is causing more infections but fewer hospital admissions than delta, South African data show. *BMJ* 2021; **375**: n3104 [PMID: 34916213 DOI: 10.1136/bmj.n3104]
9 **Garrett N**, Tapley A, Andriesen J, Seocharan I, Fisher LH, Bunts L, Espy N, Wallis CL, Randhawa AK, Miner MD, Ketter N, Yacovone M, Goga A, Huang Y, Hural J, Kotze P, Bekker LG, Gray GE, Corey L; Ubuntu Study Team. High Asymptomatic Carriage With the Omicron Variant in South Africa. *Clin Infect Dis* 2022; **75**: e289-e292 [PMID: 35353885 DOI: 10.1093/cid/ciac237]
10 **Fan Z**, Chen L, Li J, Cheng X, Yang J, Tian C, Zhang Y, Huang S, Liu Z, Cheng J. Clinical Features of COVID-19-Related Liver Functional Abnormality. *Clin Gastroenterol Hepatol* 2020; **18**: 1561-1566 [PMID: 32283325 DOI: 10.1016/j.cgh.2020.04.002]
11 **Jiang S**, Wang R, Li L, Hong D, Ru R, Rao Y, Miao J, Chen N, Wu X, Ye Z, Hu Y, Xie M, Zuo M, Lu X, Qiu Y, Liang T. Liver Injury in Critically Ill and Non-critically Ill COVID-19 Patients: A Multicenter, Retrospective, Observational Study. *Front Med (Lausanne)* 2020; **7**: 347 [PMID: 32656222 DOI: 10.3389/fmed.2020.00347]
12 **Zhang X**, Zhang W, Chen S. Shanghai's life-saving efforts against the current omicron wave of the COVID-19 pandemic. *Lancet* 2022; **399**: 2011-2012 [PMID: 35533708 DOI: 10.1016/S0140-6736(22)00838-8]
13 **National Health Commission of the People's Republic of China**, National Administration of Traditional Chinese Medicine. Guidelines for the diagnosis and treatment of coronavirus disease 2019 (trial version eighth) (in Chinese), Chinese Medicine, 2022(4) [DOI: 10.21147/j.issn.1000-9604.2019.04.02]
14 **National Health Commission of the People's Republic of China**, Guidelines for the prevention and control of coronavirus disease 2019 (trial version eighth) (in Chinese), 2021. (accessed on 3 Sep 2022). Available from: http://www.gov.cn/xinwen/2021-05/14/content_5606469.htm
15 **Cai Q**, Huang D, Yu H, Zhu Z, Xia Z, Su Y, Li Z, Zhou G, Gou J, Qu J, Sun Y, Liu Y, He Q, Chen J, Liu L, Xu L. COVID-19: Abnormal liver function tests. *J Hepatol* 2020; **73**: 566-574 [PMID: 32298767 DOI: 10.1016/j.jhep.2020.04.006]
16 **Han H**, Xu Z, Cheng X, Zhong Y, Yuan L, Wang F, Li Y, Liu F, Jiang Y, Zhu C, Xia Y. Descriptive, Retrospective Study of the Clinical Characteristics of Asymptomatic COVID-19 Patients. *mSphere* 2020; **5** [PMID: 33028689 DOI: 10.1128/mSphere.00922-20]
17 **Sarin SK**, Choudhury A, Lau GK, Zheng MH, Ji D, Abd-Elsalam S, Hwang J, Qi X, Cua IH, Suh JI, Park JG, Putcharoen O, Kaewdech A, Piratvisuth T, Treeprasertsuk S, Park S, Wejnaruemarn S, Payawal DA, Baatarkhuu O, Ahn SH, Yeo CD, Alonzo UR, Chinbayar T, Loho IM, Yokosuka O, Jafri W, Tan S, Soo LI, Tanwandee T, Gani R, Anand L, Esmail ES, Khalaf M, Alam S, Lin CY, Chuang WL, Soin AS, Garg HK, Kalista K, Batsukh B, Purnomo HD, Dara VP, Rathi P, Al Mahtab M, Shukla A, Sharma MK, Omata M; APASL COVID Task Force, APASL COVID Liver Injury Spectrum Study (APCOLIS Study-NCT 04345640). Pre-existing liver disease is associated with poor outcome in patients with SARS CoV2 infection; The APCOLIS Study (APASL COVID-19 Liver Injury Spectrum Study). *Hepatol Int* 2020; **14**: 690-700 [PMID: 32623632 DOI: 10.1007/s12072-020-10072-8]
18 **Chen VL**, Hawa F, Berinstein JA, Reddy CA, Kassab I, Platt KD, Hsu CY, Steiner CA, Louissaint J, Gunaratnam NT,

Sharma P. Hepatic Steatosis Is Associated with Increased Disease Severity and Liver Injury in Coronavirus Disease-19. *Dig Dis Sci* 2021; **66**: 3192-3198 [PMID: 32980956 DOI: 10.1007/s10620-020-06618-3]

19 **Zhou YJ**, Zheng KI, Wang XB, Sun QF, Pan KH, Wang TY, Ma HL, Chen YP, George J, Zheng MH. Metabolic-associated fatty liver disease is associated with severity of COVID-19. *Liver Int* 2020; **40**: 2160-2163 [PMID: 32573883 DOI: 10.1111/liv.14575]

20 **Nardo AD**, Schneeweiss-Gleixner M, Bakail M, Dixon ED, Lax SF, Trauner M. Pathophysiological mechanisms of liver injury in COVID-19. *Liver Int* 2021; **41**: 20-32 [PMID: 33190346 DOI: 10.1111/liv.14730]

21 **Li J**, Zhang YH, Wang F, Liu B, Li H, Tang GD, Chang ZG, Liu AH, Fu CY, Gao J, Li J. Sex differences in clinical findings among patients with coronavirus disease 2019 (COVID-19) and severe condition. MedRxiv. 2020. (accessed on 3 Sep 2022). Available from: https://www.medrxiv.org/content/10.1101/2020.02.27.20027524v1

22 **Jacobsen H**, Klein SL. Sex Differences in Immunity to Viral Infections. *Front Immunol* 2021; **12**: 720952 [PMID: 34531867 DOI: 10.3389/fimmu.2021.720952]

23 **Ding ZY**, Li GX, Chen L, Shu C, Song J, Wang W, Wang YW, Chen Q, Jin GN, Liu TT, Liang JN, Zhu P, Zhu W, Li Y, Zhang BH, Feng H, Zhang WG, Yin ZY, Yu WK, Yang Y, Zhang HQ, Tang ZP, Wang H, Hu JB, Liu JH, Yin P, Chen XP, Zhang B; Tongji Multidisciplinary Team for Treating COVID-19 (TTTC). Association of liver abnormalities with in-hospital mortality in patients with COVID-19. *J Hepatol* 2021; **74**: 1295-1302 [PMID: 33347952 DOI: 10.1016/j.jhep.2020.12.012]

24 **Chen Y**, Li P, Ding Y, Liu M, Liu L, Yi B, Wu T, Dong H, Lao X, Ding K, Wang H, Zhang D, Tan X, Wang Z, Xu G, Cao G. Epidemiological feature, viral shedding, and antibody seroconversion among asymptomatic SARS-CoV-2 carriers and symptomatic/presymptomatic COVID-19 patients. *J Infect Public Health* 2021; **14**: 845-851 [PMID: 34118734 DOI: 10.1016/j.jiph.2021.05.003]

World Journal of Hepatology

Submit a Manuscript: https://www.f6publishing.com

World J Hepatol 2022 November 27; 14(11): 1964-1976

DOI: 10.4254/wjh.v14.i11.1964

ISSN 1948-5182 (online)

ORIGINAL ARTICLE

Observational Study

Elevated calprotectin levels are associated with mortality in patients with acute decompensation of liver cirrhosis

Camila Matiollo, Elayne Cristina de Morais Rateke, Emerita Quintina de Andrade Moura, Michelle Andrigueti, Fernanda Cristina de Augustinho, Tamara Liana Zocche, Telma Erotides Silva, Lenyta Oliveira Gomes, Mareni Rocha Farias, Janaina Luz Narciso-Schiavon, Leonardo Lucca Schiavon

Specialty type: Gastroenterology and hepatology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): A
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Liu LP, China; Metawea MI, Egypt

Received: October 2, 2022
Peer-review started: October 2, 2022
First decision: October 11, 2022
Revised: October 18, 2022
Accepted: November 2, 2022
Article in press: November 2, 2022
Published online: November 27, 2022

Camila Matiollo, Elayne Cristina de Morais Rateke, Emerita Quintina de Andrade Moura, Michelle Andrigueti, Clinical Analysis Laboratory Unit, University Hospital, Federal University of Santa Catarina, Florianopolis 88040-900, Brazil

Fernanda Cristina de Augustinho, Tamara Liana Zocche, Telma Erotides Silva, Division of Gastroenterology, University Hospital, Federal University of Santa Catarina, Florianópolis 88040-900, Brazil

Lenyta Oliveira Gomes, Mareni Rocha Farias, Department of Pharmaceutical Sciences Health Sciences Center, Federal University of Santa Catarina, Florianópolis 88040-370, Brazil

Janaina Luz Narciso-Schiavon, Leonardo Lucca Schiavon, Division of Gastroenterology, Department of Internal Medicine, Federal University of Santa Catarina, Florianopolis 88040-900, SC, Brazil

Corresponding author: Leonardo Lucca Schiavon, PhD, Associate Professor, Division of Gastroenterology, Department of Internal Medicine, Federal University of Santa Catarina, Florianopolis, Brazil. leo-jf@uol.com.br

Abstract

BACKGROUND

Acute decompensation (AD) of cirrhosis is related to systemic inflammation and elevated circulating cytokines. In this context, biomarkers of inflammation, such as calprotectin, may be of prognostic value.

AIM

To evaluate serum calprotectin levels in patients hospitalized for complications of cirrhosis.

METHODS

This is a prospective cohort study that included 200 subjects hospitalized for complications of cirrhosis, 20 outpatients with stable cirrhosis, and 20 healthy controls. Serum calprotectin was measured by enzyme-linked immunosorbant assay.

RESULTS

Calprotectin levels were higher among groups with cirrhosis when compared to healthy controls. Higher median calprotectin was related to Child-Pugh C, ascites, and hepatic encephalopathy. Higher calprotectin was related to acute-on-chronic liver failure (ACLF) and infection in the bivariate, but not in multivariate analysis. Calprotectin was not associated with survival among patients with ACLF; however, in patients with AD without ACLF, higher calprotectin was associated with a lower 30-d survival, even after adjustment for chronic liver failure-consortium (CLIF-C) AD score. A high-risk group (CLIF-C AD score ≥ 60 and calprotectin ≥ 580 ng/mL) was identified, which had a 30-d survival (27.3%) similar to that of patients with grade 3 ACLF (23.3%).

CONCLUSION

Serum calprotectin is associated with prognosis in patients with AD without ACLF and may be useful in clinical practice to early identify patients with a very low short-term survival.

Key Words: Inflammation; Liver cirrhosis; Acute-on-chronic liver failure

Core Tip: Acute decompensation (AD) of cirrhosis is associated with systemic inflammation and increased circulating cytokines. In this context, inflammatory markers, such as calprotectin, may be of prognostic value. This is a prospective cohort study that included 200 subjects hospitalized for complications of cirrhosis, 20 outpatients with stable cirrhosis, and 20 healthy controls. Serum calprotectin was associated with prognosis in patients with AD without acute-on-chronic liver failure and may be useful in clinical practice to early identify patients with a very low short-term survival.

Citation: Matiollo C, Rateke ECM, Moura EQA, Andrigueti M, Augustinho FC, Zocche TL, Silva TE, Gomes LO, Farias MR, Narciso-Schiavon JL, Schiavon LL. Elevated calprotectin levels are associated with mortality in patients with acute decompensation of liver cirrhosis. *World J Hepatol* 2022; 14(11): 1964-1976
URL: https://www.wjgnet.com/1948-5182/full/v14/i11/1964.htm
DOI: https://dx.doi.org/10.4254/wjh.v14.i11.1964

INTRODUCTION

Cirrhosis is characterized by fibrosis and nodule formation of the liver, secondary to different mechanisms of liver injury that lead to chronic necroinflammation[1]. The natural history of cirrhosis is usually marked by a long-lasting compensated phase, followed by a decompensated stage characterized by the occurrence of complications such as ascites, hepatic encephalopathy, and gastrointestinal bleeding related to portal hypertension[2]. Parallel to worsening liver function and progression of portal hypertension, there is a derangement in the immune system denominated as cirrhosis-associated immune dysfunction (CAID). CAID is a complication associated with a dynamic coexistence of both acquired immunodeficiency, which contributes to the high rate of infection in patients with decompensated cirrhosis, and systemic inflammation, which may exacerbate the clinical manifestations of cirrhosis, such as hemodynamic changes and kidney injury[3,4].

Systemic inflammation is a consequence of persistent and inadequate stimulation of immune system cells. Advanced cirrhosis, particularly decompensated disease, is associated with increasing disorders of gut homeostasis, including changes in microbiota, reduced motility, bacterial overgrowth, and increased intestinal permeability[5]. These factors intensify the systemic exposure to pathogen-associated molecular patterns (PAMPs) from intestinal microorganisms and their products, which provides chronic stimulation of pattern recognition receptors (PRRs), expressed on innate immune cells[3,4]. In addition, systemic inflammation can occur in patients with decompensated cirrhosis and acute-on-chronic liver failure (ACLF) even in the absence of bacterial infections due to the release of damaged liver damage-associated molecular patterns (DAMPs)[6]. Knowing the characteristics of the immune system of patients with cirrhosis is important for understanding and developing new diagnostic and therapeutic tools that reduce morbidity and mortality in these patients.

Calprotectin is a heterodimeric complex composed by S100A8 and S100A9 proteins, also called MRP8 and MRP14, or calgranulin A and B, respectively[7]. Calprotectin is found in neutrophils and monocytes, accounting for 60% of the cytosolic protein content of neutrophils[8]. Due to its high stability in biological fluids, calprotectin can be used in clinical practice as a marker of neutrophil activity in several chronic inflammatory diseases, infections, and cancer[7]. Fecal concentrations of calprotectin are well established in clinical practice to differentiate irritable bowel syndrome from inflammatory bowel disease and to monitor disease activity in Crohn's disease and ulcerative colitis[8]. Circulating calpro-

tectin levels, although less studied, were reported to be related to the presence of cirrhosis and severity of liver dysfunction[9,10]. However, these preliminary small studies focused on alcohol-induced liver disease and were mainly comprised by patients outside the context of acute decompensation (AD)[9, 10]. Hence, we aimed to evaluate circulating calprotectin in patients hospitalized for AD of cirrhosis, investigating its prognostic significance.

MATERIALS AND METHODS

Patients

This study is part of a project that aimed to follow a cohort of adult patients (≥ 18 years of age) admitted to the emergency room of a Brazilian tertiary hospital due to AD of liver cirrhosis. Details about the methodology were previously published[11] and are briefly presented below.

Consecutive subjects admitted to the emergency room for AD of cirrhosis between January 2015 and September 2018 were evaluated for inclusion. The exclusion criteria were: Hospitalization for elective procedures; hospitalization not related to complications of liver cirrhosis; hepatocellular carcinoma outside Milan criteria; severe extrahepatic disease; inflammatory bowel disease; inflammatory rheumatic disorders (such as psoriasis, rheumatoid arthritis, systemic lupus erythematosus, and ankylosing spondyloarthritis); extrahepatic malignancy; and use of immunosuppressive drugs.

The diagnosis of cirrhosis was established either histologically (when available) or by combination of clinical, imaging, and laboratory findings in patients with evidence of portal hypertension. AD was defined by acute development of hepatic encephalopathy, large ascites, gastrointestinal bleeding, bacterial infection, or any combination of these.

Twenty healthy individuals evaluated during routine laboratory tests and 20 patients with stable cirrhosis followed at our outpatient clinic served as control groups. Details about the inclusion and exclusion criteria for the control groups were previously published[12] and are available at Supplementary material and methods.

The study protocol complies with the ethical principles of the Declaration of Helsinki and was approved by the Ethics Committee on Human Research of the Federal University of Santa Catarina.

Methods

Patients were evaluated within 24 h of admission by one of the researchers involved in the study. They were followed during their hospital stay and 30-d mortality was evaluated by phone call in case of hospital discharge. In case of more than one hospital admission during the study period, only the most recent hospitalization was considered.

Active alcoholism was defined as an average overall consumption of 21 or more drinks per week for men and 14 or more drinks per week for women during the 4 wk before enrolment (one standard drink is equal to 12 g absolute alcohol)[13]. All patients admitted for AD of cirrhosis in our institution are actively screened for bacterial infections. A diagnostic paracentesis was performed in all patients with ascites at admission. Spontaneous bacterial peritonitis (SBP) was diagnosed when the neutrophil count in the ascitic fluid was ≥ 250 neutrophils/mm^3 in the absence of intra-abdominal source of infection, regardless of negative culture[14]. Hepatic encephalopathy was graded according to West-Haven criteria[15] and, if it was present, a precipitant event was actively investigated and lactulose was initiated and the dose adjusted as needed. All subjects with acute variceal bleeding received intravenous octreotide and an antibiotic (intravenous ceftriaxone) and underwent urgent therapeutic endoscopy after stabilization. Severity of liver disease was estimated using the Child-Pugh classification system[16] and model for end-stage liver disease (MELD)[17] calculated based on laboratory tests performed at admission. ACLF, chronic liver failure (CLIF)-sequential organ failure assessment (SOFA), and CLIF-consortium (CLIF-C) AD scores were defined as proposed by the European Association for the Study of the Liver-Chronic Liver Failure Consortium[18,19].

Serum calprotectin levels

Blood samples were obtained within 24 h following hospitalization (inpatients) and after medical evaluation (outpatients). Peripheral blood samples were centrifuged at 3000 *g* for 10 min at room temperature within 1 h following collection. Serum samples were then aliquoted and stored at -80 °C until analysis. Serum calprotectin levels were measured using a commercial quantitative sandwich enzyme-linked immunosorbant assay kit (FineTest, REF EH4140, Wuhan, China) according to the manufacturer's instructions. All measurements were performed in duplicates. Results were determined from a standard curve carried out from six human calprotectin standards, with a lower detection threshold of 15.625 ng/mL.

Statistical analysis

The normality of variable distribution was determined by the Kolmogorov-Smirnov test. The correlation between numerical variables was evaluated using Spearman's correlation coefficient. Continuous

variables were compared using the Student's *t*-test in case of a normal distribution or Mann-Whitney test in the remaining cases. Categorical variables were evaluated by the chi-square test or Fisher's exact test, as appropriate. Multiple logistic regression analysis was used to explore factors independently associated with ACLF and infection. Univariate and multivariate Cox regression analyses were performed to investigate the relationship between variables of interest and survival. The best cutoffs of calprotectin for predicting mortality were chosen based on the receiver operating characteristics (ROC) curves. Survival curves were calculated using the Kaplan-Meier method and survival differences between groups were compared using a log-rank test. All tests were performed using SPSS software, version 17.0 (SPSS, Chicago, IL, United States). A P value of less than 0.05 was considered statistically significant.

RESULTS

Sample characteristics and assessment of calprotectin levels according to study group

Two hundred and forty patients were involved in this research: 200 subjects admitted for AD, 20 individuals with stable cirrhosis, and 20 healthy controls. Age and gender were similar across the study groups. The main characteristics of the two groups with cirrhosis are depicted in Table 1. In hospitalized patients, the mean age was 57.29 ± 11.56 years and 71.5% were male. The most frequent etiology of cirrhosis was alcohol (53.0%), followed by hepatitis C (29.0%) and non-alcoholic steatohepatitis (12.6%). Hospitalized subjects were mainly categorized as Child-Pugh C (45.5%) and the mean MELD score was 17.6 ± 7.0.

Figure 1 shows the levels of calprotectin according to the study group. No significant difference in circulating calprotectin was noted when hospitalized patients were compared to the stable cirrhosis group (477.2 ng/mL *vs* 369.5 ng/mL, $P = 0.127$). However, healthy subjects showed significantly lower calprotectin levels as compared to subjects hospitalized for AD (98.88 ng/mL *vs* 477.2 ng/mL, $P < 0.001$) and outpatients with stable cirrhosis (98.88 ng/mL *vs* 369.5 ng/mL, $P < 0.001$).

Factors associated with calprotectin levels in hospitalized cirrhotic patients

No significant correlations were observed between calprotectin levels and numerical variables studied (Supplementary Table 1).

Male patients had higher serum calprotectin levels (530.5 *vs* 368.2 ng/mL, $P = 0.015$). When calprotectin concentrations were evaluated according to the presence of specific complications, significantly higher median values were observed among patients with ACLF (577.8 *vs* 453.3 ng/mL, $P = 0.047$), infection within the first 48 h (581.3 *vs* 446.5 ng/mL; $P = 0.012$), ascites (552.7 *vs* 385.9 ng/mL; $P = 0.004$), and hepatic encephalopathy (581.3 *vs* 428.1 ng/mL; $P = 0.026$) (Figure 2A-D). On the other hand, significantly lower median values were observed among patients with upper gastrointestinal bleeding (UGIB) (401.4 *vs* 532.4 ng/mL; $P = 0.036$) (Figure 2E). Median calprotectin levels were similar regardless of the diagnosis of acute alcoholic hepatitis (475.8 *vs* 478.6 ng/mL; $P = 0.964$) or alcoholic liver disease as a cause of cirrhosis (512.7 *vs* 450.6 ng/mL; $P = 0.118$). Patients with hepatitis C virus-related cirrhosis had higher serum calprotectin concentrations (716.5 *vs* 427.8 ng/mL, $P = 0.001$) (Figure 2F). No differences were observed regarding other causes of cirrhosis.

Serum calprotectin concentrations were higher in Child-Pugh C patients compared with Child-Pugh A (586.4 ng/mL *vs* 313.8 ng/mL, $P = 0.006$) and Child-Pugh B (586.4 ng/mL *vs* 406.7 ng/mL, $P = 0.002$). There was no difference in calprotectin concentrations between Child-Pugh A and B patients (313.8 ng/mL *vs* 406.7 ng/mL, $P = 0.163$).

Calprotectin levels according to the presence of ACLF or infection in patients admitted for complications of cirrhosis

Variables related to ACLF are exhibited in Supplementary Table 2. ACLF at admission was associated with higher calprotectin levels in the bivariate analysis (577.75 *vs* 453.05 ng/mL, $P = 0.047$). The logistic regression analysis was performed to evaluate variables independently associated with ACLF. The following covariates were included: Gender, ascites, leukocyte count, sodium, C-reactive protein (CRP), and calprotectin. Other covariates with statistical significance in the bivariate analysis, such as hepatic encephalopathy, creatinine, INR, Child-Pugh, and MELD, were not incorporated in this analysis because they are closely related to the CLIF-SOFA score and ACLF definition. In the logistic regression analysis, ACLF was independently related to male gender (odds ratio [OR] = 2.782, 95% confidence interval [CI]: 1.277-6.867, $P = 0.026$), ascites (OR = 2.793, 95%CI: 1.270-6.143, $P = 0.011$), and leukocyte count (OR = 1.087, 95%CI: 1.003-1.178, $P = 0.041$). Serum calprotectin concentrations were not associated to the presence of ACLF in the logistic regression analysis.

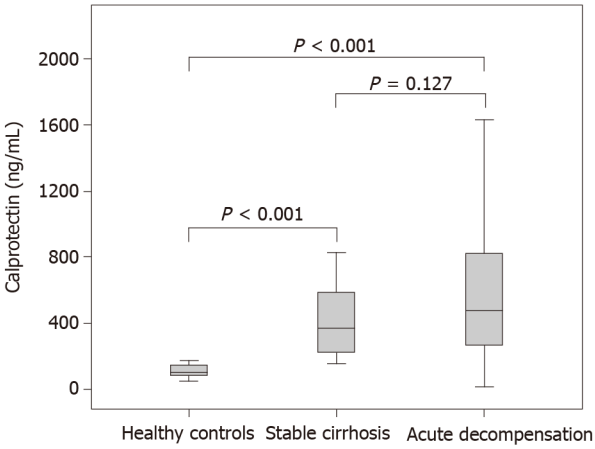
Factors associated with bacterial infection were also analyzed and are depicted in Supplementary Table 3. As previously mentioned, in the bivariate analysis, higher calprotectin was observed among patients with bacterial infection detected in the first 48 h of hospitalization (581.30 *vs* 446.50 ng/mL, $P = 0.012$). A multiple logistic regression analysis was performed including the following variables: Active alcoholism, UGIB, Child-Pugh C, MELD, CRP, and calprotectin. Other variables with

Table 1 Characteristics of included patients

Parameter	Stable cirrhosis (*n* = 20)	Acute decompensation (*n* = 200)	*P* value
Age (yr), mean ± SD	51.35 ± 12.68	57.29 ± 11.56	0.056
Male gender, *n* (%)	15 (75.0)	143 (71.5)	0.740
Etiology of cirrhosis[1], *n* (%)			
Alcohol	12 (60.0)	106 (53.0)	0.549
Hepatitis C	6 (30.0)	58 (29.0)	0.925
Hepatitis B	3 (15.0)	10 (5.0)	0.102
Cryptogenicautoimmune	2 (10.0)	8 (4.0)	0.229
Autoimmune	0 (0.0)	11 (5.5)	0.605
NASH	0 (0.0)	25 (12.6)	0.139
Other[2]	2 (10.0)	11 (5.5)	0.335
Active alcoholism, *n* (%)	0 (0.0)	34 (17.0)	0.049
Prior decompensation, *n* (%)	15 (75.0)	173 (86.5)	0.182
Laboratory data			
Leukocyte count (×10^9), median	4.96	6.54	0.008
Sodium (mEq/L), mean ± SD	138.05 ± 1.50	136.24 ± 5.21	< 0.001
Creatinine (mg/dL), median	0.8	1.11	< 0.001
INR, median	1.15	1.46	< 0.001
Albumin (g/dL), mean ± SD	3.54 ± 0.34	2.63 ± 0.68	< 0.001
CRP (mg/L), median	3.0	18.2	< 0.001
Total bilirubin (mg/dL), median	1.10	2.20	< 0.001
Calprotectin (ng/dL), median	396.5	477.2	0.127
Child-Pugh score, mean ± SD	6.40 ± 1.60	9.24 ± 1.92	< 0.001
Child-Pugh A, *n* (%)	13 (65.0)	12 (6.0)	< 0.001
Child-Pugh B, *n* (%)	6 (30.0)	97 (48.5)	0.114
Child-Pugh C, *n* (%)	1 (5.0)	91 (45.5)	< 0.001
MELD score, mean ± SD	9.4 ± 1.8	17.6 ± 7.0	< 0.001
Complication at evaluation, *n* (%)			
Ascites	2 (10.0)	125 (62.5)	< 0.001
Hepatic encephalopathy	3 (15.0)	99 (48.5)	< 0.001
Gastrointestinal bleeding	-	66 (33.0)	
Bacterial infection	-	70 (35.0)	
Alcoholic hepatitis	-	11 (5.5)	
CLIF-SOFA, median	-	7.00	
ACLF, *n* (%)	-	56 (28.0)	
ACLF grade, *n* (%)			
Grade 1	-	37 (18.5)	
Grade 2	-	11 (5.5)	
Grade 3	-	8 (4.0)	

[1]More than one etiologic factor could be present in specific cases.
[2]Other etiologic factors included primary biliary cirrhosis, sclerosing cholangitis.
NASH: Non-alcoholic steatohepatitis; SD: Standard deviation; INR: International normalized ratio; CRP: C-reactive protein; MELD: Model for end-stage

liver disease; CLIF-SOFA: Chronic liver failure - sequential organ failure assessment; ACFL: Acute-on-chronic liver failure.



DOI: 10.4254/wjh.v14.i11.1964

Figure 1 Box plot of serum calprotectin levels among healthy controls, stable cirrhostics, and hospitalized cirrhotics with acute decompensation. The line across the box indicates the median value; the box contains the 25% to 75% interquartile range; and the whiskers represent the highest and the lower values. There were no differences in calprotectin levels between patients with acute decompensation and stable cirrhosis patients (P = 0.127). Significantly lower calprotectin levels were observed among healthy controls compared to stable cirrhosis (P < 0.001) and patients with acute decompensation (P < 0.001).

statistical significance in the bivariate analysis were not included in the regression analysis because they have already been included. In this analysis, infection was independently associated with high CRP values (OR = 1.027, 95%CI: 1.015-1.040, P < 0.001) and inversely related to hospitalization for UGIB (OR = 0.157, 95%CI: 0.061–0.401, P < 0.001).

Circulating calprotectin and survival in hospitalized patients with cirrhosis

During the first 30 d, 39 patients died (20%). Four patients were excluded from the survival analysis due to loss of follow-up. Survival analysis was performed considering the whole group and separately accordingly to the presence or absence of ACLF at admission. Calprotectin was not associated with 30-d survival in univariate Cox regression analysis when all patients were included (hazard ratio [HR] = 1.012, 95%CI: 0.996-1.028, P = 0.134) and when evaluating only those with ACLF at admission (HR = 0.982, 95%CI: 0.932-1.034, P = 0.491). However, when considering only subjects without ACLF, calprotectin levels were associated with 30-d mortality (HR = 1.018, 95%CI: 1.002-1.034, P = 0.024). A complete survival analysis among patients without ACLF is presented in Table 2.

Due to the relatively low number of events observed in the subgroup without ACLF, we chose to include in a multivariate Cox regression analysis only calprotectin and CLIF-C AD score, the recommended prognostic model in this context[19]. In this analysis, both serum calprotectin (HR = 1.021, 95%CI: 1.003-1.040, P = 0.023) and CLIF-C AD score (HR = 1.178, 95%CI: 1.00-1.262, P < 0.001) were independently associated with 30-d survival.

The area under the ROC curve for calprotectin to predict 30-d mortality was 0.773 ± 0.058 in patients without ACLF. Figure 3A shows the Kaplan-Meier curve for calprotectin concentrations dichotomized at a cutoff of 580 ng/mL. The Kaplan-Meier survival probability was 96.5% in patients with calprotectin levels < 580 ng/mL and 72.7% for subjects with results ≥ 580 ng/mL (P < 0.001). At this cutoff point, calprotectin levels showed a sensitivity of 83.3%, specificity of 67.5%, positive predictive value of 27.3%, and negative predictive value of 96.5% for predicting 30-d mortality. The positive likelihood ratio was 2.563 and the negative likelihood ratio was 0.247.

The Kaplan-Meier survival probability was also calculated according CLIF-C AD score categorized at a cutoff of 60[19]. The Kaplan-Meier survival probability was 93.3% in individuals with a CLIF-C AD score < 60 and 54.5% in those with a value ≥ 60 (P < 0.001) (Figure 3B). At this cut-off point, CLIF-C AD score showed a sensitivity of 55.6%, specificity of 90.2%, positive predictive value of 45.5% and negative predictive value of 93.3% to predict 30-d mortality. The positive likelihood ratio was 5.694 and the negative likelihood ratio was 0.492.

A subsequent analysis associating both variables was performed. The Kaplan-Meier survival probability was 98.7% in subjects with a CLIF-C AD score < 60 and calprotectin concentration < 580 ng/mL, 84.1% in subjects with a CLIF-C AD score ≥ 60 and calprotectin concentration < 580 ng/mL, 81.4% in subjects with a CLIF-C AD score < 60 and calprotectin concentration ≥ 580 ng/mL, and 27.3% in subjects with a CLIF-C AD score ≥ 60 and calprotectin concentration ≥ 580 ng/mL (Figure 3C).

Table 2 Univariate Cox-regression analysis of factors associated with 30-d mortality among patients hospitalized for acute decompensation of cirrhosis without acute-on-chronic liver failure

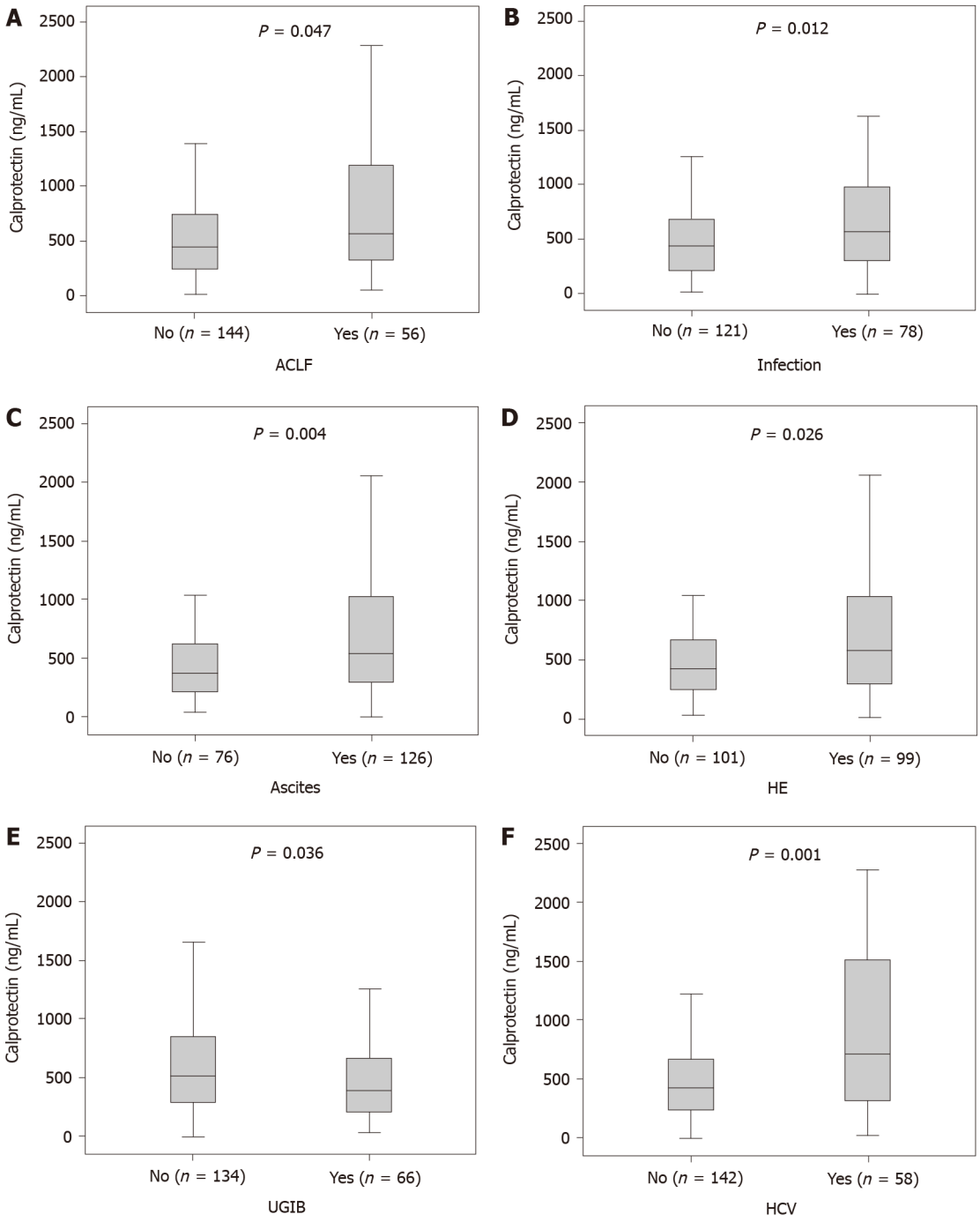
Parameter	Survivors (*n* = 123)	Non-survivors (*n* = 18)	Univariate analysis	
			HR (95%CI)	*P* value
Age (yr), mean ± SD	55.80 ± 11.67	60.67 ± 9.36	1.039 (0.994–1.085)	0.087
Male gender, *n* (%)	77 (62.6)	15 (83.3)	2.743 (0.794–9.754)	0.111
Active alcoholism, *n* (%)	21 (17.1)	2 (11.1)	0.610 (0.140–2.654)	0.510
PPI, *n* (%)	60 (49.6)	11 (64.7)	1.755 (0.649–4.745)	0.268
Beta-blockers, *n* (%)	55 (45.5)	7 (41.2)	0.853 (0.325–2.241)	0.747
Prior decompensation, *n* (%)	104 (84.6)	16 (88.9)	1.409 (0.324–6.129)	0.647
Complication at admission, *n* (%)				
Ascites	60 (48.8)	18 (100.0)	8.588 (2.644–27.898)	0.035
Hepatic encephalopathy	43 (35.0)	13 (72.2)	4.231 (1.508–11.869)	0.006
UGIB	47 (38.2)	5 (27.8)	0.660 (0.235–1.851)	0.429
Bacterial infection	43 (35.0)	11 (61.1)	2.678 (1.038–6.910)	0.042
Laboratory data				
Leukocyte count (x10^9), median	5.51	8.21	1.096 (1.012–1.186)	0.024
Sodium (mEq/L), mean ± SD	137.05 ± 4.45	136.17 ± 6.38	0.962 (0.872–1.060)	0.432
Creatinine (mg/dL), median	1.00	1.02	1.940 (0.525–7.167)	0.320
INR, median	1.39	1.78	2.931 (1.840–4.668)	< 0.001
Albumin (g/dL), mean ± SD	2.65 ± 0.53	2.29 ± 0.92	0.328 (0.140–0.770)	0.010
CRP (mg/L), median	13.15	30.05	1.014 (1.004–1.024)	0.004
Total bilirubin (mg/dL), median	2.00	3.90	1.259 (1.137–1.394)	< 0.001
Calprotectin (ng/mL), median	372.7	838.3	1.018 (1.002–1.034)	0.024
MELD score, mean ± SD	14.10 ± 3.98	20.52 ± 3.85	1.276 (1.168–1.393)	< 0.001
Child-Pugh C, *n* (%)	38 (30.9)	17 (94.4)	31.205 (4.151–234.60)	< 0.001
CLIF-SOFA, median	6.00	8.00	1.835 (1.419–2.373)	< 0.001
CLIF-C ADs, median	49.07	60.29	1.173 (1.097-1.254)	< 0.001

HR: Hazard ratio; CI: Confidence interval; PPI: Proton-pump inhibitor; UGIB: Upper gastrointestinal bleeding, INR: International normalized ratio; CRP: C-reactive protein; ACFL: Acute-on-chronic liver failure; MELD: Model for end-stage liver disease; CLIF-SOFA: Chronic liver failure - sequential organ failure assessment; CLIF-C ADs: Chronic liver failure consortium acute decompensation score.

Since the second and third groups had very similar survival rates, 84.1% and 81.4%, both were grouped. Thus, three groups were obtained according to the presence of factors CLIF-C AD score ≥ 60 or calprotectin ≥ 580 ng/mL. The Kaplan-Meier analysis showed a survival probability of 98.7% in patients without any of the factors (CLIF-C AD score < 60 and calprotectin < 580 ng/mL), 83.6% in the presence of one factor (CLIF-C AD score ≥ 60 or calprotectin ≥ 580 ng/mL), and 27.3% in the case of two factors (CLIF-C AD score ≥ 60 and calprotectin ≥ 580 ng/mL). The *P* value was 0.002 when the first and second groups were compared, and *P* < 0.001 for comparison between the first and third groups, and also for comparison between the second and third groups (Figure 3D). Based on this new classification, CLIF-C AD score ≥ 60 combined with calprotectin ≥ 580 ng/mL showed a sensitivity of 44.4%, specificity of 97.6%, positive predictive value of 72.7%, and negative predictive value of 92.6% to predict 30-d mortality. The positive likelihood ratio was 18.222 and the negative likelihood ratio was 0.569.

DISCUSSION

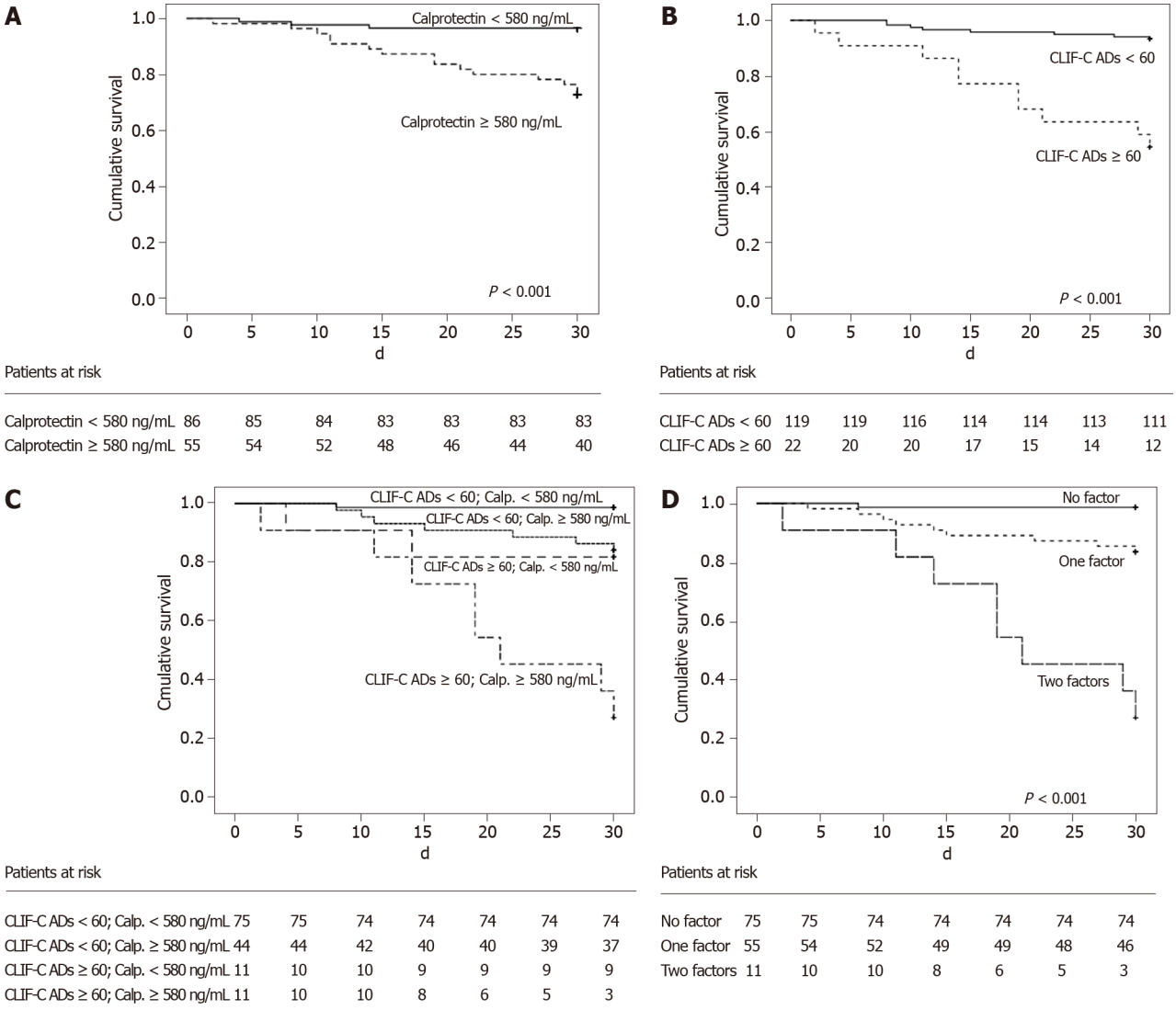
In the present study, no differences in serum calprotectin levels were observed when patients with stable cirrhosis were compared with individuals hospitalized for AD. However, healthy subjects had



DOI: 10.4254/wjh.v14.i11.1964

Figure 2 Box plot of serum calprotectin levels in patients with acute decompensation of cirrhosis according to the presence of specific complications. The line across the box indicates the median value; the box contains the 25% to 75% interquartile range; and the whiskers represent the highest and the lower values. A-D: Significantly higher calprotectin levels were observed among patients with (A) acute-on-chronic liver failure (P = 0.047), (B) infection (P = 0.012), (C) ascites (P = 0.004), and (D) hepatic encephalopathy (HE) (P = 0.026); E: Lower levels of calprotectin were observed among patients with upper gastrointestinal bleeding (UGIB) (P = 0.036); F: Higher levels in patients with hepatitis C virus infection (HCV) (P = 0.001).

lower calprotectin concentrations than both groups of patients with cirrhosis. Plasma calprotectin levels were previously studied in patients with alcohol-induced cirrhosis. In that study including 84 patients and 16 healthy controls, no differences in calprotectin levels were found between healthy controls and subjects with compensated or decompensated alcoholic cirrhosis[9]. Higher circulating calprotectin in patients with cirrhosis included in the present study probably reflects specific characteristics of our cohort, but also may be a consequence of the relatively small sample size of that preliminary study. Conversely, other studies have shown that faecal calprotectin concentrations are higher in patients with liver cirrhosis compared to healthy patients[20,21] and in acute decompensation when compared to stable cirrhosis[22].



DOI: 10.4254/wjh.v14.i11.1964

Figure 3 Cumulative 30-d survival of patients hospitalized with acute decompensation of cirrhosis without acute-on-chronic liver failure according to calprotectin levels categorized at 580 ng/mL and CLIF-C acute decompensation score at 60. A: The Kaplan-Meier survival probability was 96.5% in subjects with a calprotectin level < 580 ng/mL and 72.7% in those with a value ≥ 580 ng/mL ($P < 0.001$); B: The Kaplan-Meier survival probability was 93.3% in individuals with a CLIF-C acute decompensation (AD) score < 60 and 54.5% in those with a value ≥ 60 ($P < 0.001$); C: The Kaplan-Meier survival probability was 98.7% in subjects with a CLIF-C AD score < 60 and calprotectin concentration < 580 ng/mL, 84.1% in subjects with a CLIF-C AD score ≥ 60 and calprotectin concentration < 580 ng/mL, 81.4% in subjects with a CLIF-C AD score < 60 and calprotectin concentration ≥ 580 ng/mL, and 27.3% in subjects with a CLIF-C AD score ≥ 60 and calprotectin concentration ≥ 580 ng/mL; D: The Kaplan-Meier survival probability was 98.7% in subjects with none of the factors (CLIF-C AD score < 60 and calprotectin concentration < 580 ng/mL), 83.6% in subjects with one of the factors (CLIF-C AD score ≥ 60 and calprotectin < 580 ng/mL or CLIF-C AD score < 60 and calprotectin ≥ 580 ng/mL), and 27.3% in subjects with both factors (CLIF-C AD score ≥ 60 and calprotectin ≥ 580 ng/mL), in which $P = 0.002$ between the first and second groups, and $P < 0.001$ between the first and third, and between the second and third groups.

Significantly higher serum calprotectin levels were observed in patients with ascites, those with hepatic encephalopathy, and Child-Pugh C patients. Data on circulating calprotectin concentrations in cirrhosis are scarce. An early study by Homann and colleagues observed no relationships between plasma calprotectin and variables related to liver disease severity, such as albumin and total bilirubin [9]. On the other hand, another paper from the same group reported a weak positive correlation between calprotectin plasma levels and the Child-Pugh score, but without significant difference between Child-Pugh classes[10]. In the present study, higher calprotectin levels were associated with the presence of ACLF and bacterial infection in the bivariate exploration, but not in the logistic regression analysis. Although no previous studies addressed this biomarker and ACLF, higher plasma calprotectin was associated with bacterial infection in patients with alcohol-related cirrhosis in a small study[9]. In addition, ascitic fluid calprotectin has been recently reported to be increased in SBP and might represent a practical alternative to the traditional ascitic polymorphonuclear cell count[23]. Outside the context of liver cirrhosis, elevated circulating calprotectin was reported in other conditions characterized by a robust inflammatory response such as tuberculosis[24], sepsis[25,26], COVID-19[27], and several rheumatic diseases[28].

When we evaluated the group of patients hospitalized for complications of cirrhosis as a whole, serum calprotectin concentrations were not associated with prognosis. On the other hand, when we addressed only those with AD without ACLF, circulating calprotectin was related to 30-d mortality even after adjustment for CLIF-C AD score. In a previous study including patients with alcoholic cirrhosis, plasma calprotectin levels was related to a shorter survival, exhibiting higher prognostic value than other classical markers in these patients, such as albumin, bilirubin, and ascites[9]. Later, the same research group studied plasma and ascitic fluid calprotectin concentrations in patients with various etiologies of liver cirrhosis[10]. In both studies, plasma calprotectin was a significant marker of poor survival in alcohol-induced cirrhosis, but had no prognostic value in other etiologies[9,10]. It is noteworthy that this finding of a possible selective regulation of calprotectin in alcoholic liver disease was not confirmed in a longitudinal study of active drinkers, in which patients and controls had similar fecal calprotectin values[29]. These studies predated the establishment of the ACLF concept and, unlike our study, did not consider the categorization of patients in AD or ACLF. Patients with cirrhosis requiring hospitalization for AD episodes are known to have a widely variable prognosis, depending on whether or not they have ACLF[18]. ACLF impacts not only the natural history of cirrhosis, but also the progression of cirrhosis-associated immune dysfunction that migrates to a predominantly immunodeficient phenotype similar to that found in sepsis[30]. Thus, an influence of ACLF on circulating inflammatory markers is expected and further studies are still needed to explain the difference in the prognostic value of calprotectin in patients with AD and ACLF.

CLIF-C AD score was devised as a prognostic parameter in patients hospitalized for AD of cirrhosis without ACLF. In the original study, it was established that patients with a score ≥ 60 should be classified as having a high risk for 90-d mortality, with rates above 30%[19]. In the present study, patients were grouped into three categories according to the observed prognostic factors (CLIF-C AD score and calprotectin level). The Kaplan-Meier survival probability was 98.7% in subjects with none of the factors (CLIF-C AD score < 60 and serum calprotectin < 580 ng/mL), 83.6% in subjects with either factor (CLIF-C AD score ≥ 60 or serum calprotectin ≥ 580 ng/mL), and 27.3% in subjects with both factors (CLIF-C AD score ≥ 60 and serum calprotectin ≥ 580 ng/mL). A similar cutoff point of calprotectin (524 ng/mL) was previously suggested to assess survival in alcohol-induced cirrhosis[10]. Thus, the combination of the two factors may be useful in identifying patients with a very low 30-d mortality rate, allowing for better individualization of care and eventually establishing criteria for early hospital discharge, thus reducing complications of prolonged hospitalization[19]. On the other hand, a high-risk group (CLIF-C AD score ≥ 60 and serum calprotectin ≥ 580 ng/mL) was also identified, which have a 30-d survival (27.3%) similar to patients with grade 3 ACLF (23.3%)[18]. Those patients at the high category might be candidates for early interventions that could improve survival, including evaluation for liver transplantation.

CONCLUSION

In conclusion, serum calprotectin levels are increased in patients with cirrhosis and correlated with variables associated with the severity of liver disease. Higher circulating calprotectin is associated with a worse 30-d survival in those hospitalized for AD without ACLF, but not among ACLF patients. The combination of serum calprotectin and CLIF-C AD score is able to better stratify the prognosis and may be particularly useful in clinical practice to early identify patients with AD of cirrhosis and a very low short-term survival, even in the absence of ACLF at admission.

ARTICLE HIGHLIGHTS

Research background

Systemic inflammation is a hallmark of advanced cirrhosis. Calprotectin is a biomarker of neutrophil activity with high stability in biological fluids. Circulating levels of calprotectin may be an interesting biomarker of systemic inflammation in cirrhosis.

Research motivation

There is a need for inflammatory biomarkers for practical and objective use in cirrhosis. Serum calprotectin has gained relevance in recent years in several other diseases characterized by systemic inflammation.

Research objectives

To investigate factors associated with serum calprotectin levels in acute decompensation of cirrhosis, and to evaluate circulating calprotectin as a prognostic biomarker in patients with complications of cirrhosis.

Research methods

This is a prospective cohort study that included three study groups: 200 subjects hospitalized for complications of cirrhosis, 20 outpatients with stable cirrhosis, and 20 healthy controls. Serum calprotectin was collected at hospital admission in the group with acute decompensation. Hospitalized patients were followed for 30 d for survival analysis

Research results

Higher calprotectin was associated with variables related to more advanced liver disease, acute-on-chronic liver failure (ACLF), and infection. Calprotectin was not associated with survival among patients with ACLF. In patients with acute decompensation without ACLF, higher calprotectin was inversely associated with 30-d survival. The combination of calprotectin with the CLIF-C AD score offered a better prognostic discrimination than the variables alone.

Research conclusions

Serum calprotectin are increased in liver cirrhosis and correlated with variables associated with the severity of liver disease. Higher circulating calprotectin is associated with a worse 30-d survival in those hospitalized for complications of cirrhosis without ACLF. The combination of serum calprotectin and CLIF-C AD score is able to better stratify the prognosis than any of the factors alone.

Research perspectives

The routine incorporation of the calprotectin test is a reality. Serum calprotectin may allow early identification of patients with a very low short-term survival, even in the absence of ACLF at admission. Larger, multicentric future studies are recommended to validate these results.

FOOTNOTES

Author contributions: Schiavon LL and Narciso-Schiavon JL designed the research; Rateke ECM and Matiollo C contributed to sample handling and general laboratory analysis; De Augustinho FC, Zocche TL, Silva TE, Macalli C, and Narciso-Schiavon JL collected the clinical data; Moura EQA Andrigueti M, Gomes LO, and Farias MR contributed to specific laboratory analysis; Schiavon LL and Matiollo C analyzed the data and wrote the paper; Farias MR and Narciso-Schiavon JL reviewed the manuscript.

Supported by Conselho Nacional de Desenvolvimento Científico e Tecnológico.

Institutional review board statement: The study protocol complies with the ethical principles of the Declaration of Helsinki and was approved by the Ethics Committee on Human Research of the Federal University of Santa Catarina.

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

Conflict-of-interest statement: There is no conflict of interest regarding this manuscript.

Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author upon request at leo-jf@uol.com.br. Participants gave informed consent for data sharing.

STROBE statement: The authors have read the STROBE Statement—checklist of items, and the manuscript was prepared and revised according to the STROBE Statement—checklist of items.

Country/Territory of origin: Brazil

ORCID number: Camila Matiollo 0000-0001-6144-6776; Elayne Cristina de Morais Rateke 0000-0002-0459-7903; Emerita Quintina de Andrade Moura 0000-0003-4051-5335; Michelle Andrigueti 0000-0002-1479-3780; Fernanda Cristina de Augustinho 0000-0003-3190-7177; Tamara Liana Zocche 0000-0002-7948-0953; Telma Erotides Silva 0000-0002-9041-8915; Lenyta Oliveira Gomes 0000-0001-8971-5827; Mareni Rocha Farias 0000-0002-4319-9318; Janaina Luz Narciso-Schiavon 0000-0002-6228-4120; Leonardo Lucca Schiavon 0000-0003-4340-6820.

S-Editor: Liu JH

L-Editor: Wang TQ

P-Editor: Liu JH

REFERENCES

1 **Tsochatzis EA**, Bosch J, Burroughs AK. Liver cirrhosis. *Lancet* 2014; **383**: 1749-1761 [PMID: 24480518 DOI: 10.1016/S0140-6736(14)60121-5]

2 **D'Amico G**, Morabito A, D'Amico M, Pasta L, Malizia G, Rebora P, Valsecchi MG. New concepts on the clinical course and stratification of compensated and decompensated cirrhosis. *Hepatol Int* 2018; **12**: 34-43 [PMID: 28681347 DOI: 10.1007/s12072-017-9808-z]

3 **Albillos A**, Lario M, Álvarez-Mon M. Cirrhosis-associated immune dysfunction: distinctive features and clinical relevance. *J Hepatol* 2014; **61**: 1385-1396 [PMID: 25135860 DOI: 10.1016/j.jhep.2014.08.010]

4 **Irvine KM**, Ratnasekera I, Powell EE, Hume DA. Causes and Consequences of Innate Immune Dysfunction in Cirrhosis. *Front Immunol* 2019; **10**: 293 [PMID: 30873165 DOI: 10.3389/fimmu.2019.00293]

5 **Wiest R**, Lawson M, Geuking M. Pathological bacterial translocation in liver cirrhosis. *J Hepatol* 2014; **60**: 197-209 [PMID: 23993913 DOI: 10.1016/j.jhep.2013.07.044]

6 **Chen GY**, Nuñez G. Sterile inflammation: sensing and reacting to damage. *Nat Rev Immunol* 2010; **10**: 826-837 [PMID: 21088683 DOI: 10.1038/nri2873]

7 **Pruenster M**, Vogl T, Roth J, Sperandio M. S100A8/A9: From basic science to clinical application. *Pharmacol Ther* 2016; **167**: 120-131 [PMID: 27492899 DOI: 10.1016/j.pharmthera.2016.07.015]

8 **Menees SB**, Powell C, Kurlander J, Goel A, Chey WD. A meta-analysis of the utility of C-reactive protein, erythrocyte sedimentation rate, fecal calprotectin, and fecal lactoferrin to exclude inflammatory bowel disease in adults with IBS. *Am J Gastroenterol* 2015; **110**: 444-454 [PMID: 25732419 DOI: 10.1038/ajg.2015.6]

9 **Homann C**, Garred P, Graudal N, Hasselqvist P, Christiansen M, Fagerhol MK, Thomsen AC. Plasma calprotectin: a new prognostic marker of survival in alcohol-induced cirrhosis. *Hepatology* 1995; **21**: 979-985 [PMID: 7705809]

10 **Homann C**, Christensen E, Schlichting P, Philipsen EK, Graudal NA, Garred P. Ascites fluid and plasma calprotectin concentrations in liver disease. *Scand J Gastroenterol* 2003; **38**: 415-420 [PMID: 12739714 DOI: 10.1080/00365520310000870]

11 **Silva PE**, Fayad L, Lazzarotto C, Ronsoni MF, Bazzo ML, Colombo BS, Dantas-Correa EB, Narciso-Schiavon JL, Schiavon LL. Single-centre validation of the EASL-CLIF consortium definition of acute-on-chronic liver failure and CLIF-SOFA for prediction of mortality in cirrhosis. *Liver Int* 2015; **35**: 1516-1523 [PMID: 24840673 DOI: 10.1111/liv.12597]

12 **da Silva TE**, Costa-Silva M, Correa CG, Denardin G, Alencar MLA, Coelho MSPH, Muraro-Wildner L, Luiza-Bazzo M, González-Chica DA, Dantas-Correa EB, Narciso-Schiavon JL, Schiavon LL. Clinical Significance of Serum Adiponectin and Resistin Levels in Liver Cirrhosis. *Ann Hepatol* 2018; **17**: 286-299 [PMID: 29469045 DOI: 10.5604/01.3001.0010.8659]

13 **Addolorato G**, Leggio L, Ferrulli A, Cardone S, Vonghia L, Mirijello A, Abenavoli L, D'Angelo C, Caputo F, Zambon A, Haber PS, Gasbarrini G. Effectiveness and safety of baclofen for maintenance of alcohol abstinence in alcohol-dependent patients with liver cirrhosis: randomised, double-blind controlled study. *Lancet* 2007; **370**: 1915-1922 [PMID: 18068515 DOI: 10.1016/S0140-6736(07)61814-5]

14 **Runyon BA**; AASLD Practice Guidelines Committee. Management of adult patients with ascites due to cirrhosis: an update. *Hepatology* 2009; **49**: 2087-2107 [PMID: 19475696 DOI: 10.1002/hep.22853]

15 **Bajaj JS**. Review article: the modern management of hepatic encephalopathy. *Aliment Pharmacol Ther* 2010; **31**: 537-547 [PMID: 20002027 DOI: 10.1111/j.1365-2036.2009.04211.x]

16 **Pugh RN**, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. *Br J Surg* 1973; **60**: 646-649 [PMID: 4541913 DOI: 10.1002/bjs.1800600817]

17 **Wiesner R**, Edwards E, Freeman R, Harper A, Kim R, Kamath P, Kremers W, Lake J, Howard T, Merion RM, Wolfe RA, Krom R; United Network for Organ Sharing Liver Disease Severity Score Committee. Model for end-stage liver disease (MELD) and allocation of donor livers. *Gastroenterology* 2003; **124**: 91-96 [PMID: 12512033 DOI: 10.1053/gast.2003.50016]

18 **Moreau R**, Jalan R, Gines P, Pavesi M, Angeli P, Cordoba J, Durand F, Gustot T, Saliba F, Domenicali M, Gerbes A, Wendon J, Alessandria C, Laleman W, Zeuzem S, Trebicka J, Bernardi M, Arroyo V; CANONIC Study Investigators of the EASL–CLIF Consortium. Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. *Gastroenterology* 2013; **144**: 1426-1437, 1437.e1 [PMID: 23474284 DOI: 10.1053/j.gastro.2013.02.042]

19 **Jalan R**, Pavesi M, Saliba F, Amorós A, Fernandez J, Holland-Fischer P, Sawhney R, Mookerjee R, Caraceni P, Moreau R, Ginès P, Durand F, Angeli P, Alessandria C, Laleman W, Trebicka J, Samuel D, Zeuzem S, Gustot T, Gerbes AL, Wendon J, Bernardi M, Arroyo V; CANONIC Study Investigators; EASL-CLIF Consortium. The CLIF Consortium Acute Decompensation score (CLIF-C ADs) for prognosis of hospitalised cirrhotic patients without acute-on-chronic liver failure. *J Hepatol* 2015; **62**: 831-840 [PMID: 25463539 DOI: 10.1016/j.jhep.2014.11.012]

20 **Gundling F**, Schmidtler F, Hapfelmeier A, Schulte B, Schmidt T, Pehl C, Schepp W, Seidl H. Fecal calprotectin is a useful screening parameter for hepatic encephalopathy and spontaneous bacterial peritonitis in cirrhosis. *Liver Int* 2011; **31**: 1406-1415 [PMID: 22093455 DOI: 10.1111/j.1478-3231.2011.02577.x]

21 **Alempijević T**, Štulić M, Popovic D, Culafic D, Dragasevic S, Milosavljevic T. The role of fecal calprotectin in assessment of hepatic encephalopathy in patients with liver cirrhosis. *Acta Gastroenterol Belg* 2014; **77**: 302-305 [PMID: 25509200]

22 **Riva A**, Gray EH, Azarian S, Zamalloa A, McPhail MJW, Vincent RP, Williams R, Chokshi S, Patel VC, Edwards LA. Faecal cytokine profiling as a marker of intestinal inflammation in acutely decompensated cirrhosis. *JHEP Rep* 2020; **2**: 100151 [PMID: 32838247 DOI: 10.1016/j.jhepr.2020.100151]

23 **Hadjivasilis A**, Tzanis A, Ioakim KJ, Poupoutsi I, Agouridis AP, Kouis P. The diagnostic accuracy of ascitic calprotectin for the early diagnosis of spontaneous bacterial peritonitis: systematic review and meta-analysis. *Eur J Gastroenterol Hepatol* 2021; **33**: 312-318 [PMID: 32541235 DOI: 10.1097/MEG.0000000000001813]

24 **Gopal R**, Monin L, Torres D, Slight S, Mehra S, McKenna KC, Fallert Junecko BA, Reinhart TA, Kolls J, Báez-Saldaña R, Cruz-Lagunas A, Rodríguez-Reyna TS, Kumar NP, Tessier P, Roth J, Selman M, Becerril-Villanueva E, Baquera-Heredia J, Cumming B, Kasprowicz VO, Steyn AJ, Babu S, Kaushal D, Zúñiga J, Vogl T, Rangel-Moreno J, Khader SA. S100A8/A9 proteins mediate neutrophilic inflammation and lung pathology during tuberculosis. *Am J Respir Crit Care Med* 2013; **188**: 1137-1146 [PMID: 24047412 DOI: 10.1164/rccm.201304-0803OC]

25 **Huang L**, Li J, Han Y, Zhao S, Zheng Y, Sui F, Xin X, Ma W, Jiang Y, Yao Y, Li W. Serum Calprotectin Expression as a Diagnostic Marker for Sepsis in Postoperative Intensive Care Unit Patients. *J Interferon Cytokine Res* 2016; **36**: 607-616 [PMID: 27610929 DOI: 10.1089/jir.2016.0037]

26 **Gao S**, Yang Y, Fu Y, Guo W, Liu G. Diagnostic and prognostic value of myeloid-related protein complex 8/14 for sepsis. *Am J Emerg Med* 2015; **33**: 1278-1282 [PMID: 26206243 DOI: 10.1016/j.ajem.2015.06.025]

27 **Mahler M**, Meroni PL, Infantino M, Buhler KA, Fritzler MJ. Circulating Calprotectin as a Biomarker of COVID-19 Severity. *Expert Rev Clin Immunol* 2021; **17**: 431-443 [PMID: 33750254 DOI: 10.1080/1744666X.2021.1905526]

28 **Ometto F**, Friso L, Astorri D, Botsios C, Raffeiner B, Punzi L, Doria A. Calprotectin in rheumatic diseases. *Exp Biol Med (Maywood)* 2017; **242**: 859-873 [PMID: 27895095 DOI: 10.1177/1535370216681551]

29 **Montalto M**, Gallo A, Ferrulli A, Visca D, Campobasso E, Cardone S, D'Onofrio F, Santoro L, Covino M, Mirijello A, Leggio L, Gasbarrini G, Addolorato G. Fecal calprotectin concentrations in alcoholic patients: a longitudinal study. *Eur J Gastroenterol Hepatol* 2011; **23**: 76-80 [PMID: 21030869 DOI: 10.1097/MEG.0b013e32834101f9]

30 **Wasmuth HE**, Kunz D, Yagmur E, Timmer-Stranghöner A, Vidacek D, Siewert E, Bach J, Geier A, Purucker EA, Gressner AM, Matern S, Lammert F. Patients with acute on chronic liver failure display "sepsis-like" immune paralysis. *J Hepatol* 2005; **42**: 195-201 [PMID: 15664244 DOI: 10.1016/j.jhep.2004.10.019]

World Journal of Hepatology

Submit a Manuscript: https://www.f6publishing.com

World J Hepatol 2022 November 27; 14(11): 1977-1984

DOI: 10.4254/wjh.v14.i11.1977

ISSN 1948-5182 (online)

CASE REPORT

Multiple hepatic infarctions secondary to diabetic ketoacidosis: A case report

Vitoria Mikaelly da Silva Gomes, Gustavo de Sousa Arantes Ferreira, Luise Cristina Torres Rubim de Barros, Barbara Moreira Ribeiro Trindade dos Santos, Lorenna Paulinelli Bahia Vieira

Specialty type: Gastroenterology and hepatology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Feng X, China; Surani S, United States

Received: May 21, 2022
Peer-review started: May 21, 2022
First decision: July 25, 2022
Revised: August 8, 2022
Accepted: October 27, 2022
Article in press: October 27, 2022
Published online: November 27, 2022

Vitoria Mikaelly da Silva Gomes, Luise Cristina Torres Rubim de Barros, Barbara Moreira Ribeiro Trindade dos Santos, Lorenna Paulinelli Bahia Vieira, Department of General Surgery, Hospital das Clinicas da Universidade Federal de Minas Gerais, Belo Horizonte 30130100, Minas Gerais, Brazil

Gustavo de Sousa Arantes Ferreira, Liver Transplantation, Instituto de Cardiologia do Distrito Federal, Brasilia 70673900, Distrito Federal, Brazil

Gustavo de Sousa Arantes Ferreira, Lorenna Paulinelli Bahia Vieira, Department of General Surgery, Hospital Metropolitano Doutor Celio de Castro, Belo Horizonte 30620090, Minas Gerais, Brazil

Corresponding author: Gustavo de Sousa Arantes Ferreira, MD, MSc, Surgeon, Teacher, Liver Transplantation, Instituto de Cardiologia do Distrito Federal, Setor Sudoeste, S/N, Brasilia 70673900, Distrito Federal, Brazil. gustferr@ufmg.br

Abstract

BACKGROUND

Hepatic infarctions (HI) are ischemic events of the liver in which a disruption in the blood flow to the hepatocytes leads to focal ischemia and necrosis. Most HI are due to occlusive events in the liver's blood vessels, but non-occlusive HI may occur. They are associated with disruption of microvasculature, such as in diabetic ketoacidosis. While HI usually presents as peripheral lesions with clear borders, irregular nodular lesions may occur, indistinguishable from liver neoplasms and presenting a diagnostic challenge.

CASE SUMMARY

We report a case of multiple extensive HI in a patient with poorly controlled diabetes mellitus, who first presented to the emergency room with diabetic ketoacidosis. He then developed jaundice, thrombocytopenia, and a marked elevation of serum aminotransferases. An ultrasound of the liver showed the presence of multiple irregular lesions. Further investigation with a computerized tomography scan confirmed the presence of multiple hypoattenuating nodules with irregular borders and heterogeneous appearance. These lesions were considered highly suggestive of a primary neoplasm of the liver. While the patient was clinically stable, his bilirubin levels remained persistently elevated, and he underwent an ultrasound-guided percutaneous biopsy of the largest lesion.

Biopsy results revealed extensive ischemic necrosis of hepatocytes, with no signs of associated malignancy. Three months after the symptoms, the patient showed great improvement in all clinical and laboratory parameters and extensive regression of the lesions on imaging exams.

CONCLUSION
This case highlights that diabetic ketoacidosis can cause non-occlusive HI, possibly presenting as nodular lesions indistinguishable from neoplasms.

Key Words: Hepatic infarction; Non-occlusive infarcts; Diabetic ketoacidosis; Pseudotumor of the liver; Liver infarcts; Case report

Core Tip: Hepatic infarction (HI) is usually caused by occlusion of the blood vessels supplying the liver. Non-occlusive HI secondary to diabetic ketoacidosis is an exceedingly rare occurrence, with few cases described in the literature. We report a case of HI secondary to diabetic ketoacidosis, whose diagnosis was complicated by the atypical aspect of the infarction areas on the imaging exams. The appearance of multiple irregular and heterogenous nodules was suggestive of metastatic liver neoplasm, and correct diagnosis could only be obtained by biopsy. This case demonstrates a rare cause of HI, and highlights the diagnostic challenges posed by its atypical presentations.

Citation: Gomes VMDS, Ferreira GSA, Barros LCTR, Santos BMRTD, Vieira LPB. Multiple hepatic infarctions secondary to diabetic ketoacidosis: A case report. *World J Hepatol* 2022; 14(11): 1977-1984
URL: https://www.wjgnet.com/1948-5182/full/v14/i11/1977.htm
DOI: https://dx.doi.org/10.4254/wjh.v14.i11.1977

INTRODUCTION

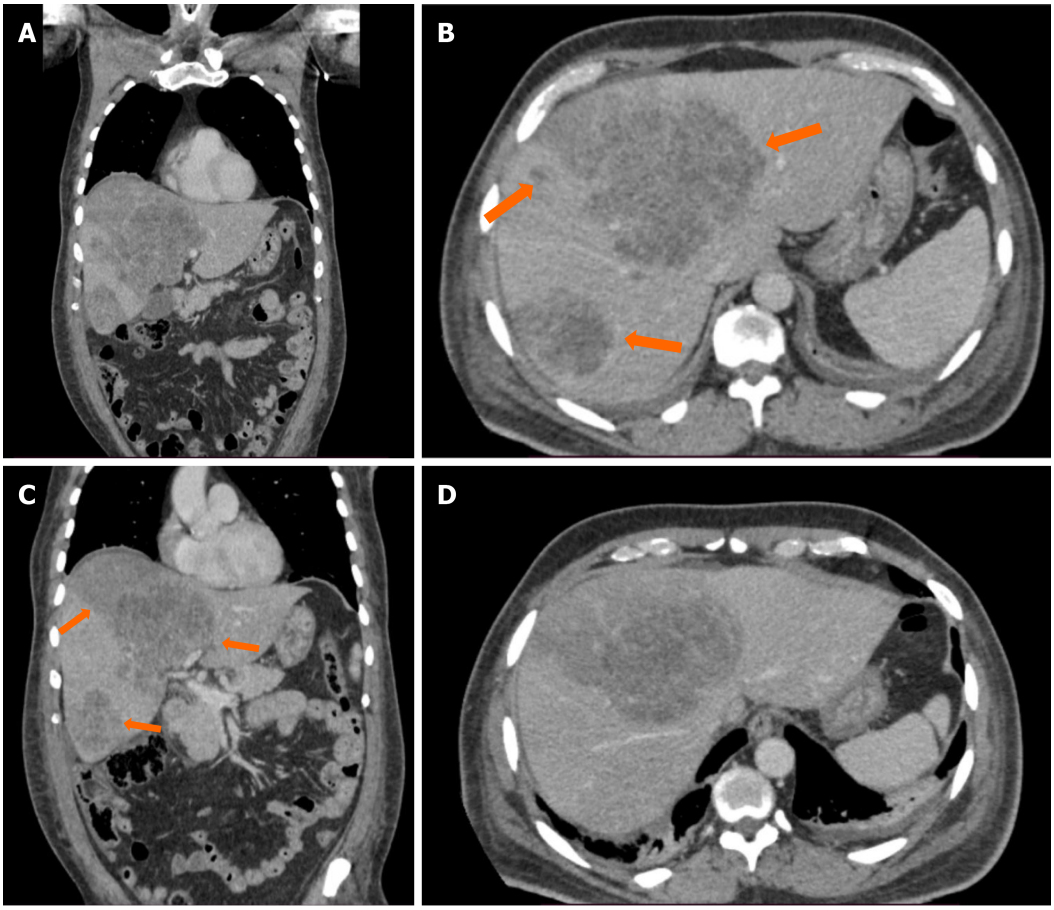
Hepatic infarctions (HI) are ischemic events of the liver in which a disruption in the blood flow to the hepatocytes leads to focal ischemia, necrosis, and, in severe cases, hepatocellular dysfunction[1]. Due to the dual blood supply that the liver receives from the hepatic artery and the portal vein, HI occurs less commonly than infarctions in other abdominal organs[2]. Most HI is a consequence of occlusive events in either blood vessels supplying the liver. Common causes are portal vein thrombosis, hepatic artery thrombosis, trauma, pancreatitis, surgery (liver transplantation in particular), or hilarious neoplasms[1,3-5]. However, non-occlusive HI may rarely occur[3,4,6]. These uncommon events are associated with disruption of the liver microvasculature and can be secondary to rheumatologic diseases (polyarteritis nodosa, scleroderma, systemic lupus erythematosus, Churg-Strauss syndrome), infection, polycythemia vera, hemodynamic shock, and severe preeclampsia, among other causes[6].

Diabetic ketoacidosis (DK) has been described as a potential cause of non-occlusive HI in a limited number of cases reported in the medical literature[3,6-8]. The pathophysiology of HI in patients with DK is not completely understood but is thought to be multifactorial. Elevated levels of catecholamines released in DK might induce vasoconstriction and liver ischemia[3]. Dehydration and hypotension often present in DK decrease blood flow to the liver, further contributing to ischemia[3]. The low levels of 2, 3-diphosphoglycerate in patients with DK may affect hepatocyte oxygenation, and widespread atherosclerosis, endothelial dysfunction, and hypercoagulability–that are commonly found in patients with diabetes–can also play a role in the occurrence of HI[3,6,7]. Abdominal pain, nausea, jaundice, and fever are the most common symptoms of HI[3,6]. Transaminase levels are elevated, and hyperbilirubinemia, leukocytosis, and disorders of hemostasis are also frequent findings in HI[3,6,8].

CASE PRESENTATION

Imaging examinations

An ultrasound of the liver with doppler evaluation of the hepatic vessels showed multiple heterogeneous nodular lesions in both lobes, with no signs of the hepatic artery or portal vein thrombosis. He then underwent a computerized abdominal tomography (CT) scan on the same date, which revealed the presence of multiple heterogenous lesions in both lobes of the liver, which were hypoattenuating with slight peripheral enhancement in the late phase of the study (Figure 1A and B). Of note, there was a clear wedge-shaped delineation between affected parenchyma and normal areas in the periphery of the



DOI: 10.4254/wjh.v14.i11.1977

Figure 1 Computed tomography scan of the liver. A: Coronal view of the portal phase, showing multiple nodular lesions in both lobes of the liver; B: Axial view of the portal phase, showing multiple nodular lesions in both lobes of the liver, with discrete peripheral enhancement; C: Coronal view of the portal phase, showing the marked and linear transition from the wedge-shaped area of infarction and adjacent liver parenchyma; D: Axial view of the portal phase, showing the marked and linear transition from the wedge-shaped area of infarction and adjacent liver parenchyma.

liver (Figure 1C and D). The largest lesions were located on liver segments IV and VI, measuring 127 mm and 95 mm, respectively. Based on the imaging exams, primary metastatic neoplasm of the liver (most likely cholangiocarcinoma) or multiple liver abscesses were considered the most likely diagnoses. However, given the lack of clinical and laboratory markers of infection and the sudden onset of symptoms associated with elevation of transaminases, HI was also considered a differential diagnosis. The patient was discharged from the intensive care unit (ICU) 6 d after admission. A control CT scan was obtained 10 days after admission, with no difference in the aspect of the liver lesions but an additional finding of subsegmental pulmonary thromboembolism in the right lung. Anticoagulation with therapeutical doses of enoxaparin was initiated while the patient remained asymptomatic. A magnetic resonance imaging (MRI) scan 16 d after admission showed the same irregular nodular lesions, with a slight peripheral enhancement of the lesions by the contrast medium (gadolinium). As the patient remained clinically well but with significant cholestasis, the decision was made to perform an ultrasound-guided liver biopsy to determine the lesions' definitive diagnosis, which was made 20 days after patient admission.

Chief complaints

A 57-year-old male patient was transferred to the ICU of a tertiary hospital due to a diagnosis of DK with hemodynamical instability. He had first presented to an emergency medical service complaining of diffuse abdominal pain.

Laboratory examinations

Blood and urine exams obtained at arrival at the emergency department (Table 1) showed marked ketonuria, hyperglycemia (470 mg/dL), acidosis (pH of 7.27 and bicarbonate of 15 mEq/L), the elevation of aminotransferases [aspartate aminotransferase (AST) of 2356 U/L and alanine aminotransferase (ALT) of 2438 U/L], and thrombocytopenia (9380 platelets/mcL). At admission to the ICU, there was a decrease in aminotransferase levels (AST of 1121 U/L and ALT of 1546 U/L) but an increase in bilirubin levels (total bilirubin of 1.59 mg/dL). A serological panel for viral hepatitis, dengue fever, and

Table 1 Laboratory data

Variable	Reference range	Admission on the emergency room	Admission on the ICU	One week after admission	Two weeks after admission	Three weeks after admission	Three months after admission
Hemoglobin (g/dL)	13-16.9	13.8	13.6	11.8	9.8	9.5	11.2
Leukocytes (leukocytes/mm^3)	4000-10200	4580	4353	14350	9615	8172	5414
Platelets (platelets/mm^3)	140000-400000	9380	15000	110000	262000	306000	290000
Glucose (mg/dL)	70-99	470	425				
AST (U/L)	5-40	2356	805		135	149	108
ALT (U/L)	7-56	2438	1489		56	56	58
Bilirubin: total /direct (mg/dL)	0-1.2/0-0.3	1.24/0.91	2.5/2.2	10.2/8.3	12.5/10.6	10.1/8.9	3.6/1.4
Alkaline phosphatase (U/L)	40-150	168	193			376	407
Gamma-glutamyl transferase (U/L)	7-45		178			770	1665
Creatinine (mg/dL)	0.7-1.3	1.6	1.3		1.1	0.9	1.2
Arterial blood pH	7.36-7.44	7.27	7.43	7.42			
Arterial blood bicarbonate (mEq/L)	22-28	15	16.7	18			
Lactate (mmol/L)	0.5-2.2		4.4	2			
Albumin (g/dL)	3.4-5.4		2.3	1.7			3.4
International normalized ratio	0.8-1.1		1.41	1.37			1.09
Carcinoembryonic antigen (ng/mL)	0-2.5			1			
Cancer antigen 19-9 (U/mL)	0-37			4			
Alpha-fetoprotein (ng/mL)	1.3-7.8			8			

ICU: Intensive care unit; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase.

yellow fever yielded negative results. While the patient remained hemodynamically stable, he developed jaundice as his bilirubin levels steadily increased, and he underwent an abdominal ultrasound 2 d after admission.

Physical examination

On arrival at the ICU, physical examination was unremarkable, except for light tenderness on deep palpation of the right upper quadrant during the abdominal exam. Vital signs were within the normal range of values, and the patient was afebrile.

Personal and family history

The patient suffered from hypertension and poorly controlled diabetes mellitus, with irregular use of metformin. He had a previous history of smoking tobacco but was abstinent for more than 20 years and ingested small amounts of alcohol once per week.

History of past illness

At the moment of his arrival in the emergency room, the patient was noticed to be tachycardic and hypotensive. He was placed in close monitoring and was diagnosed with monomorphic ventricular tachycardia, being subject to successful synchronized electrical cardioversion, improving his hemodynamical condition. Treatment with ceftriaxone was started and intravenous insulin, as he had significant hyperglycemia (470 mg/dL). After this procedure, he was transferred to the ICU of a tertiary hospital for stabilization and further investigation.

History of present illness

The patient complained of diffuse abdominal pain that had started 2 d prior and progressively worsened, associated with malaise, asthenia, nausea, and vomiting.

FINAL DIAGNOSIS

Histology of the liver biopsy showed extensive mononuclear infiltration of the liver, associated with intracellular cholestasis, and areas of ischemic necrosis, with no signs of associated malignancy (Figure 2). Tissue cultures obtained at the same moment showed no signs of bacterial growth. These results confirmed the diagnosis of non-occlusive HI, secondary to DK.

TREATMENT

The patient was discharged from the hospital 21 days after admission, with optimized control of diabetes and anticoagulation with oral rivaroxaban.

OUTCOME AND FOLLOW-UP

While the patient still had significant cholestasis at the moment of discharge, his jaundice began to improve 1 mo after the onset of the symptoms, and bilirubin levels returned to normal after another month. The patient remains asymptomatic and well during two months of outpatient follow-up, and an ultrasound scan obtained 3 mo after the onset of the symptoms revealed small, focal areas of heterogeneity on the right lobe of the liver, measuring no more than 4 cm, therefore showing significant regression of the lesions.

DISCUSSION

Non-occlusive HI secondary to DK is a rare occurrence, with a small number of cases reported in the literature (Table 2). Its correct diagnosis depends on a high index of clinical suspicion during the evaluation of diabetic patients presenting with abdominal pain and elevation of aminotransferases. While imaging exams can usually correctly determine the presence of HI, atypical presentations may pose a diagnostic challenge. Prolonged hypotension, as described in the case reported, can be a significant factor in the occurrence of HI[8]. CT scan is the most commonly used imaging exam in the diagnosis of HI. While findings of peripheral lesions with clearly limited borders are characteristic of HI, with triangular or wedge-shaped areas of low attenuation, irregular nodular lesions of central location may be present in extensive infarction, indistinguishable from liver neoplasms[3,9,10]. These central parenchyma pseudo nodular lesions are found in about 25% of HI[10]. Enhancement of HI by the contrast medium is generally patchy and heterogenous, with areas of more extensive necrosis remaining hypoattenuating in all phases, while areas that remain isoattenuating in the portal venous phase are suggestive of viable liver tissue[1,10]. A high attenuation, thin subcapsular rim may be present in some cases, which must be distinguished from liver abscesses[9]. Gas formation has been described in both sterile and infected infarcts, and the presence of gas is not an unequivocal marker of infected necrosis of the liver[1,10]. Bile lakes may be present as a late complication of large infarcts due to ischemic necrosis of bile duct epithelium, with jaundice persisting for several weeks[1].

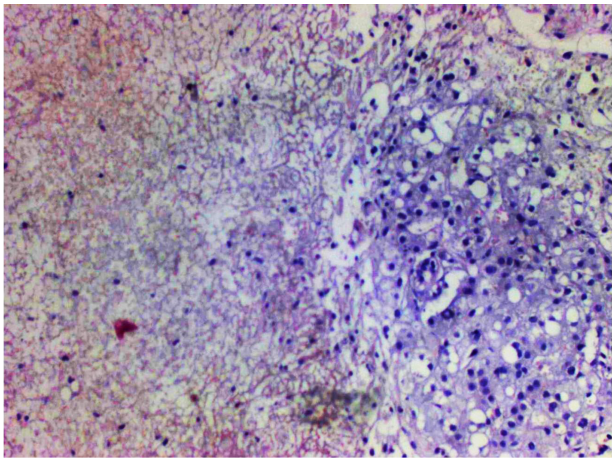
In some cases reported in the literature, diagnosis of hepatic infarction was only established postoperatively, with resection being performed due to the aspect of the lesion being highly suggestive of a liver neoplasm in the imaging exams[3,6]. MRI can be helpful in the diagnosis of HI, showing lesions of heterogeneous intensity, with the center of the lesion being more apparent than the rim, restricted diffusion, no significant enhancement, and little or no mass effect, which helps in differentiating HI from liver neoplasms[3,11,12]. Using a gadoxetate disodium contrast medium may further increase specificity in the differential diagnosis of HI[5].

In the case we reported, both CT and MRI were unable to differentiate the lesions from the liver's primary neoplasms or liver abscesses. Besides the clinical history of acute onset of symptoms with no signs of infection, there was also one finding in the imaging exams that were suggestive of HI: The wedge shape marked delimitation between the areas affected by the infarction and normal liver parenchyma, which was visible in the peripheral areas of the liver and coexisted with the nodular areas which were more centrally located. The use of percutaneous biopsy to confirm the diagnosis of HI is a novel aspect in this case report, as in previously reported cases, HI was diagnosed either by imaging exams or surgical exploration (Table 2). Since correct diagnosis could not be confirmed by imaging

Table 2 Cases of hepatic infarction secondary to diabetic ketoacidosis reported in the literature

Journal	Ref.	Year	Patient	Diagnosis	Outcome
Gastroenterology	Sundaram *et al*[6]	1978	36-year-old male	Laparotomy and biopsy	Recovery
World Journal of Gastroenterology	Deng *et al*[3]	2006	53-year-old male	Hepatectomy	Recovery
Brazilian Journal of Intensive Care	Paes *et al*[7]	2007	67-year-old female	Necropsy	Death
Practical Diabetes International	Chen *et al*[8]	2007	53-year-old female	CT	Death
International Journal of Clinical and Experimental Medicine	Xu *et al*[12]	2017	45-year-old female	Laparoscopic biopsy	Recovery
Open Journal of Case Reports	Tiwari *et al*[11]	2021	37-year-old male	MRI	Recovery

CT: Computed tomography; MRI: Magnetic resonance imaging.



DOI: 10.4254/wjh.v14.i11.1977

Figure 2 Liver biopsy. Histological analysis of the liver biopsy, showing extensive mononuclear infiltration of liver tissue, associated with intracellular cholestasis, and areas of ischemic necrosis. Hematoxylin and eosin staining, magnification 40 ×.

exams and considering a high clinical suspicion of HI, liver biopsy was seen as the next step in the investigation to avoid unnecessary surgical exploration with significant morbidity to the patient and also to avoid missing a diagnosis of liver neoplasm, which could coexist or even be the cause of a liver infarction. Histological analysis of HI is characterized by the presence of a centrilobular zone of parenchymal necrosis, in contrast to a peripheral zone with relative preservation of portal tracts, hepatic veins, and intralobular stroma[2,9].

Non-occlusive liver infarcts usually regress after a while as regeneration of the liver occurs. While the necrotic tissue present at the site of a HI is usually sterile, an infection may occur due to biliary tract or hematogenous dissemination of bacteria, with progression to a liver abscess that may require treatment with antibiotics and/or percutaneous drainage[6]. In the case we reported, the patient showed no signs of infection, and tissue cultures obtained at the moment of the liver biopsy showed no signs of bacterial growth. His persistently elevated bilirubin levels may be attributed to the formation of bile lakes in the central areas of necrosis and the significant disruption of the biliary drainage of the areas of liver parenchyma adjacent to the areas most affected by the HI. The benefits of anticoagulant therapy in the management of HI are uncertain, and unless the infarction is associated with vascular occlusion or a thrombotic etiology, the use of anticoagulants is not generally recommended[13]. In this case, the patient received anticoagulation due to concomitant pulmonary thromboembolism. This thromboembolic event raises the question of whether a hypercoagulable state may also play a role in the genesis of HI associated with DK, as microvascular thrombosis of the liver may aggravate the ischemic insult already present due to the other mechanisms of aggression in DK that were previously discussed.

CONCLUSION

DK is a rare cause of non-occlusive HI that must be remembered in diabetic patients with abdominal pain and elevated markers of hepatic injury. While in the imaging exams, HI usually presents itself as wedge-shaped areas of hypoattenuation on the periphery of the liver, atypical presentations with

irregular nodular areas of central location may occur, which are indistinguishable from liver neoplasms. Using ultrasound-guided percutaneous biopsy may provide the correct diagnosis in these cases, avoiding unnecessary surgical exploration.

ACKNOWLEDGEMENTS

The authors would like to acknowledge the important contribution of Dr. Neto RT and the CONLAB laboratory in the diagnostic investigation of the case reported and in the elaboration of this manuscript.

FOOTNOTES

Author contributions: Barros LCTR and Santos BMRT designed the report; Gomes VMS and Ferreira GSA collected the patient's clinical data, analyzed the data and wrote the paper; Barros LCTR, Santos BMRT and Vieira LPB reviewed the paper.

Informed consent statement: Consent was obtained from the patient, and the signed Informed Consent Form was provided to the publisher.

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

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

Country/Territory of origin: Brazil

ORCID number: Vitoria Mikaelly da Silva Gomes 0000-0003-3785-7115; Gustavo de Sousa Arantes Ferreira 0000-0002-2225-9190; Luise Cristina Torres Rubim de Barros 0000-0001-5499-8548; Barbara Moreira Ribeiro Trindade dos Santos 0000-0002-7792-5920; Lorenna Paulinelli Bahia Vieira 0000-0002-5727-6396.

S-Editor: Xing YX
L-Editor: A
P-Editor: Xing YX

REFERENCES

1 **Torabi M**, Hosseinzadeh K, Federle MP. CT of nonneoplastic hepatic vascular and perfusion disorders. *Radiographics* 2008; **28**: 1967-1982 [PMID: 19001652 DOI: 10.1148/rg.287085067]
2 **CARROLL R**. Infarction of the human liver. *J Clin Pathol* 1963; **16**: 133-136 [PMID: 14018909 DOI: 10.1136/jcp.16.2.133]
3 **Deng YG**, Zhao ZS, Wang M, Su SO, Yao XX. Diabetes mellitus with hepatic infarction: a case report with literature review. *World J Gastroenterol* 2006; **12**: 5091-5093 [PMID: 16937516 DOI: 10.3748/wjg.v12.i31.5091]
4 **Francque S**, Condat B, Asselah T, Vilgrain V, Durand F, Moreau R, Valla D. Multifactorial aetiology of hepatic infarction: a case report with literature review. *Eur J Gastroenterol Hepatol* 2004; **16**: 411-415 [PMID: 15028975 DOI: 10.1097/00042737-200404000-00008]
5 **Maruyama M**, Yamada A, Kuraishi Y, Shibata S, Fukuzawa S, Yamada S, Arakura N, Tanaka E, Kadoya M, Kawa S. Hepatic infarction complicated with acute pancreatitis precisely diagnosed with gadoxetate disodium-enhanced magnetic resonance imaging. *Intern Med* 2014; **53**: 2215-2221 [PMID: 25274233 DOI: 10.2169/internalmedicine.53.2395]
6 **Sundaram M**, Srivisal S, Lagos JA, Ho JE. Angiographic demonstration of non-occlusive hepatic infarction with scintigraphic and microscopic correlation. *Gastrointest Radiol* 1978; **3**: 39-42 [PMID: 97117 DOI: 10.1007/BF01887033]
7 **Paes T**, Gazoni FM, Pinheiro Junior Nde F, Guimarães HP, Lopes RD, Lanzoni VP, Vendrame LS, Lopes AC. [Liver ischemic necrosis and diabetes mellitus: case report]. *Rev Bras Ter Intensiva* 2007; **19**: 490-493 [PMID: 25310169 DOI: 10.1590/S0103-507X2007000400015]
8 **Chen M**, Croxson S. Triad: diabetic ketoacidosis, elevated liver enzymes and abdominal pain–think liver infarct! *Pract Diab Int* 2007; **24**: 302-303 [DOI: 10.1002/pdi.1128]
9 **Adler DD**, Glazer GM, Silver TM. Computed tomography of liver infarction. *AJR Am J Roentgenol* 1984; **142**: 315-318 [PMID: 6607598 DOI: 10.2214/ajr.142.2.315]
10 **Giovine S**, Pinto A, Crispano S, Lassandro F, Romano L. Retrospective study of 23 cases of hepatic infarction: CT findings

and pathological correlations. *Radiol Med* 2006; **111**: 11-21 [PMID: 16623301 DOI: 10.1007/s11547-006-0002-y]

11 **Tiwari HA**, Khan AS. Magnetic resonance imaging of non-occlusive hepatic infarction associated with diabetic ketoacidosis. *Open J Case Rep* 2021; **2**: 140

12 **Xu W**, Dong D, Tong L, Chi B, Gong F. A round-shaped hepatic infarction detected in a diabetes patient: MRI findings and literature review. *Int J Clin Exp Med* 2017; **10**: 12726-12729

13 **Klein SH**, Klein ED, Ackerman Z, Hiller N. Liver infarction: to treat or not to treat? *Intern Med J* 2018; **5**: 28-31 [DOI: 10.5430/crim.v5n2p28]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com