78086_Auto_Edited.docx

WORD COUNT 4597
TIME SUBMITTED 26-OCT-2022 10:10AM
PAPER ID 91940901

Name of Journal: *World Journal of Hepatology*
Manuscript NO: 78086
Manuscript Type: EDITORIAL

Current management of liver diseases and the role of multidisciplinary approach: a narrative review

Nouhoum Bouare

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. This work aimed to discuss new ideas, challenges and perspectives of current research regarding multidisciplinary and pluralistic management of liver diseases. We conducted a careful search from reference citation analysis search engine, based on artificial intelligence technology, to build an obvious bibliographic database. In one hand, this study has discussed the involvement of exosomes, remdesivir, and SARS-CoV-2 infection in hepatic damages. In the other hand, HCC algorithms and new biochemical and imaging experiments have been discussed along with COVID-19 and liver dysfunction. This work may be a useful tool for the clinical practice and research in managing and investigating liver disorders.

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 HBV and HCV). Secondarily liver dysfunction can occur *via* other viruses, such as cytomegalovirus (CMV), 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.

Bibliographic search

To build the study bibliography, we used the reference citation analysis (RCA) search engine, which is an open multidisciplinary citation analysis database based on artificial

intelligence technology. The search terms (search names or keywords) were as follows: “liver,” followed by the words “function,” “physiology,” “dysfunction,” “pathology,” “clinic,” “enzymes,” “immunology,” or “diagnosis.” The search was refined according to publication dates ranging between the periods 1985–2021 (the largest period), 2016–2021 (more or less recent date), 2021–2022 (more recent date), and 2022 (the current year). Preference has been given to sub-terms “review,” “minireview,” or “editorial” according to search results. To build a more homogeneous database, citation references were rearranged between topics of interest according to article title relevance (i.e., the identity or similarity of title keywords with the topic in question). We selected all articles with an impact index value "> 0" to further refine the search (Table 1). The data collection and analysis was initiated on June 02, 2022, and completed on July 11, 2022.

Liver management

Several studies have investigated liver function, dysfunction and clinic. Herein we have discussed the involvement of exosomes, remdesivir, SARS-CoV-2 and EBV infections, Na+/H+ exchangers (NHEs), and Drug-induced liver injury (DILI) in hepatic disorders. Beside we have discussed HCC algorithms and new biomedical and imaging methods pertaining to liver diseases.

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, NAFLD, ALD, and 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]. Regarding liver disease treatment, exosomes can contribute in immune- and cell-based therapy. Exosomes may even serve in the transportation of medicines and nucleic-acids [6].

Aleem *et al*. [7] 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 [7]. Liver damage is frequent in patients with SARS-CoV-2 infection, especially in severe COVID-19 or underlying chronic liver disease [8]. 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 [8].

Dysfunction and pathology

The need to assess abnormalities linked to COVID-19 in different organs and systems is becoming clear. Bobermin *et al.* [9] 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 SARS-CoV-2 infection, COVID-19 may trigger late neurological dysfunctions such as cognitive deficits, neurodegenerative and psychiatric disorders [9]. Patients with COVID-19 may develop gastrointestinal symptoms accompanied by respiratory symptoms [10]. 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 [10]. Choudhary *et al.* [11] 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 [11]. Wu *et al.* [12] 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 [12].

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.*) [13]. 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 [13].

NHEs (ion transporters) are present in diverse organisms in which they participate in regulation process at the cellular, tissue, and systemic levels [14]. Li *et al.* [14] 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 [14].

Clinic, enzymology and immunology

DILI should be suspected in patients with recent elevations in liver biochemistry parameters [15]. 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 [15].

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.* [16] 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 [16].

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) [17]. 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 [17].

Gadoxetic acid disodium (Gd3+), a new contrast agent, tends to dominate magnetic resonance imaging (MRI) as much 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 [18]. Kim *et al.* [18] 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 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 [18].

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.* [19] 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 [19].

Liver HCC management

Regarding BCLC recommendations patients with HCC (stage B) are not selected for hepatic resection, but they may benefit of palliative medication [20]. 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. Romanno *et al*. [20] 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 [20].

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 [21]. Due to the lack of studies experiencing DAA impact in these patients, Reig *et al.* [21] 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 [21].

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 [22-25]. The BCLC staging system is preferred because it considers tumor, patient, and liver characteristics and links them to specific therapies [22, 23]. Reig *et al.* [23] 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 multi-parametric 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 [23]. This update recognizes liver transplantation (LT) as one of the main study objectives [25]. Interventional radiologists (IRs) can play a central role in multi-directional treatment (MDT) to promote liver transplantation.

This latest update is being improved. Pierleone Lucatelli and Boris Guiu [25] 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 (TACE) considering TSM concept. Transarterial radio-embolization (TARE) is recommended only for single HCC B 8 cm given the LEGACY trial findings. [23]. 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 [25, 26]. However, we are still far from reaching level one evidence [25].

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 [24]. The safety and efficacy of EBRT have been enough demonstrated regardless BCLC stage. Hallemeier *et al.* [24] 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 (ASTRO) 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; 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 [24].

Elhence A and Shalimar [26] 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 [26]. 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 [26].

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 [27]. In a state of mild hyperthermia (38-40 ° 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 (HSP) 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 CO2

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 [27].

Margonis *et al.* [28] 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 [28].

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 [29]. 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 [29].

Study summary

New ideas

Exosome function (role in intercellular transportation, adaptive immune response, and mesenchymal stem cell-based therapy) and the potential for exosomal miRNA or proteins can be explored in liver therapeutic methods or biomarker options.

With respect to SARS-CoV-2 transmission, there has been an increase in fecal-oral contagion. Hence, there is an urgent need to update and intensify infection control to avoid fecal-oral transmission and standardize healthcare practices.

Based on the necrotic HCC model, HMS or HMS-enhanced MR demonstrated that the size of tumor necrosis was 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.

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.

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.

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; 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.

Challenges

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.

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.

To date, there are no specific tools for the diagnosis and treatment of DILI.

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.

Perspectives

HCC management will evolve as new informations become available and novel therapeutic approaches will be experienced. Further RCTs of EBRT for HCC are needed.

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.

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.

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.

CONCLUSION

Investigations regarding liver function have revealed the involvement of exosomes, remdesivir, hyperthermia, and SARS-CoV-2 infection in hepatic disorders. The

relationship between COVID-19 and liver dysfunction has been extensively discussed. New biochemical and imaging methods have also been described. HCC management has been discussed regarding BCLC algorithms. This work may be helpful for physicians and researchers in managing and further investigating liver defects. The study would be more comprehensive if the literature search was extended to other database engines to explore research methods and findings. This study is limited by possible additional literature that could appear outside the search period and date. In fine this study would be more impactful if it was restricted to either aspect of liver diseases management: decompensated cirrhosis, hepatocellular carcinoma, transplantation, COVID-19 and liver or pathophysiology of liver damage.

78086_Auto_Edited.docx

ORIGINALITY REPORT

6%
SIMILARITY INDEX

PRIMARY SOURCES

1	Anshuman Elhence, Shalimar. "Liver dysfunction in Barcelona Clinic Liver Cancer-2022 update: Clear as day or still in fog?", Journal of Hepatology, 2022 Crossref	72 words — 2%
2	Christopher Leigh Hallemeier, Smith Apisarnthanarax, Laura Ann Dawson. "BCLC 2022 update: Important advances, but missing external beam radiotherapy", Journal of Hepatology, 2022 Crossref	45 words — 1%
3	scholarworks.bwise.kr Internet	43 words — 1%
4	Pierleone Lucatelli, Boris Guiu. "2022 Update of BCLC Treatment Algorithm of HCC: What's New for Interventional Radiologists?", CardioVascular and Interventional Radiology, 2022 Crossref	24 words — 1%
5	www.researchgate.net Internet	22 words — < 1%
6	Georgios Antonios Margonis, Aslam Ejaz, Gaya Spolverato, Neda Rastegar, Robert Anders, Ihab R. Kamel, Timothy M. Pawlik. "Benign Solid Tumors of the Liver: Management in the Modern Era", Journal of Gastrointestinal Surgery, 2015 Crossref	20 words — < 1%

7	Maria Reig, Giuseppe Cabibbo. "Antiviral therapy in the palliative setting of HCC (BCLC-B and -C)", Journal of Hepatology, 2021 Crossref	19 words — < 1%
8	www.ncbi.nlm.nih.gov Internet	17 words — < 1%
9	Luiza de Campos Moreira da Silva, Julia Teixeira de Oliveira, Sandra Tochetto, Claudia Pinto Marques Souza de Oliveira et al. "Ultrasound elastography in patients with fatty liver disease", Radiologia Brasileira, 2020 Crossref	14 words — < 1%
10	Benyair, Ron. "Constant serum levels of secreted asialoglycoprotein receptor sH2a and decrease with cirrhosis", World Journal of Gastroenterology, 2011. Crossref	13 words — < 1%

EXCLUDE QUOTES	ON	EXCLUDE SOURCES	OFF
EXCLUDE BIBLIOGRAPHY	ON	EXCLUDE MATCHES	< 12 WORDS