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ABOUT COVER

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Current management of liver diseases and the role of multidisciplinary approach

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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

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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.

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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 academics 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 bioactive 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 microvesicles 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 (FXR β /NR1H5) has been uncovered 8 years later. FXR β 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). FXR β 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, underlying 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 cytolytic. 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 seen 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 Mn²⁺ 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 involvement 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[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 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[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].

Hydroxymethylglutaryl-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.

Hydroxymethylglutaryl-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.

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