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Prevention, diagnostic evaluation, management and prognostic implications of liver disease in critically ill patients with COVID-19

Valsamaki A *et al.* Liver disease in COVID-19 critically ill patients

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Abstract

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2, broke out in December 2019 in Wuhan city of China, and spread rapidly worldwide. Therefore, by March 2020, the World Health Organization declared the disease a global pandemic. Apart from the respiratory system, various other organs of the human body are also seriously affected by the virus. Liver injury in patients with a severe form of COVID-19 is estimated to be 14.8%-53%. Elevated levels of total bilirubin, aspartate aminotransferase and alanine aminotransferase and low levels of serum albumin and prealbumin are the main laboratory findings. Patients with pre-existing chronic liver disease and cirrhosis are much more prone to develop severe liver injury. This literature review presented the recent scientific findings regarding the pathophysiological mechanisms responsible for liver injury in critically ill patients with COVID-19, the various interactions between drugs used to treat the disease and the function of the liver, and the specific tests providing the possibility of early diagnosis of

severe liver injury in these patients. Moreover, it highlighted the burden that COVID-19 put on health systems worldwide and its effect on transplant programs and the care provided to critically ill patients in general and particularly to those with chronic liver disease.

Key Words: Coronavirus disease 2019; Severe acute respiratory syndrome coronavirus 2; Liver disease; Intensive care unit; Liver unit; Prealbumin

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Core Tip: The liver follows the respiratory system with a lower but considerable frequency of affection by severe acute respiratory syndrome coronavirus 2. Coronavirus disease 2019 causes acute and acute-on-chronic liver injury. The pathophysiological mechanisms are complex and multiple. Certain biomarkers such as fibrosis-4 score and non-invasive point-of-care methods such as ultrasonography or transient elastography can be extremely helpful in the early diagnosis of liver injury and the assessment of its progression. Health systems, intensive care units, liver units and transplant programs were seriously affected by the pandemic. The clinician should recognize the symptoms and signs of liver injury early and take the appropriate measures to reverse it.

INTRODUCTION

In December 2019, an epidemic of pneumonia of unknown origin broke out in Wuhan city, in the Hubei province of China, causing global concern because of its ease of transmission and the significant rates of morbidity and mortality that accompanied it. To diagnose and control this highly infectious disease, patients were immediately isolated and their clinical and epidemiological data were studied thoroughly. The

immediate mobilization of the global scientific community rapidly identified the cause (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]) of coronavirus disease 2019 (COVID-19)^[1]. In the immediate aftermath, the disease spread very rapidly to all the regions of the world, forcing the World Health Organization to declare the COVID-19 outbreak as a “global pandemic” on March 11, 2020.

Over the next years, the pandemic greatly affected the health systems of all the countries of the world causing, until September 16, 2022, more than 611550000 cases and more than 6525000 deaths^[2,3]. SARS-CoV2 species have been associated with three primary modes of transmission, known as “contact” “droplet” and “airborne” transmission^[4].

Among the organs affected by COVID-19 is the liver, with several early scientific reports describing various degrees of liver dysfunction and injury^[5]. The liver is responsible for the regulation of levels of many chemical substances and biomarkers in the human blood, carrying out crucial functions including, but not limited to: the production and excretion of bile; the excretion of bilirubin, cholesterol, hormones, and drugs; the metabolism of fats, proteins, and carbohydrates; enzyme activation; the storage of glycogen, vitamins, and minerals; synthesis of plasma proteins, such as albumin and clotting factors; the conversion of ammonia to urea; blood detoxification and purification; and the metabolism of haemoglobin for the use of its iron content. Chronic liver diseases are prevalent all over the world, imposing a significant burden on healthcare systems. According to Mohammed *et al*^[6], patients with known chronic liver disease present a higher risk of complications from COVID-19 in comparison with the general population, with mortality rate as high as 12%. Mortality from secondary liver injury in the intensive care unit (ICU) is significantly higher, ranging between 27%-48% for critically ill patients with cholestasis and between 40%-60% for critically ill patients with hypoxic liver injury^[7].

This literature review presented the recent scientific findings regarding the pathophysiological mechanisms responsible for the induction of liver injury in critically ill patients with COVID-19; the various interactions between drugs used to treat the

disease and the function of the liver; the tests providing the possibility of early diagnosis of severe liver injury in these patients; and the effect of the pandemic on health systems, transplant programs, and critically ill patients with or without pre-existing chronic liver disease.

An advanced search strategy was made to identify studies published until August 2022, using the key words “COVID-19” “Liver” and “Intensive Care Unit” in the Pubmed electronic bibliographic database. Initially, 560 studies were identified. These studies were reviewed based on their title and abstract, thus excluding 301 studies. The full texts of the remaining 259 studies were assessed for eligibility based on their relevance to the subject of our review, particularly focusing on critical illness and liver disease. Most of these studies were excluded because they referred to patients with mild or moderate COVID-19.

A total of 97 studies were finally included and analyzed for this systematic review.

Overall, limited evidence exists regarding the liver disease, critical illness, and COVID-19.

EFFECT OF COVID-19 ON THE LIVER

SARS-CoV-2 just like its predecessors SARS-CoV (responsible for the SARS epidemic in 2003) and MERS-CoV (responsible for the Middle East respiratory syndrome epidemic in 2012) is a coronavirus and shares sequence homology and genome similarities with them^[5]. The main symptoms caused by SARS-CoV-2, affecting more severely men than women, include fever, upper and lower respiratory symptomatology (cough, rhinorrhea, sore throat, flu-like symptoms, and dyspnea), general muscle aches, anosmia, ageusia and increased likelihood of occurrence of vascular thrombosis.

Several reports regarding SARS-CoV and MERS-CoV referred that both of them caused liver injury in a significant number of patients. For example, Chau *et al*^[8] reported three cases of hepatitis directly associated with SARS disease, and revealed that various degrees of impairment of liver function had been reported in up to 60% of the patients suffering from SARS. Alsaad *et al*^[9], after 14 years, reported portal and

lobular hepatitis at post-mortem histopathological findings in a 33-year-old male patient who died from MERS-CoV infection.

In May 2020, the results of a multicenter observational cohort study from 208 hospitals in the United Kingdom (20133 patients) were published, to investigate the outcome of patients with severe disease who were admitted to these hospitals^[10]. Their median age was 73 years (range 0–104 years), and 60% of them were men. The mortality rate in the cohort was 26%, whereas 41% of the patients were discharged alive, and the rest, 34% of them, continued to be hospitalized at the end of the study. Liver disease was among the pathological conditions associated with increased in-hospital mortality, along with sex (male gender), age, obesity, chronic pulmonary, chronic kidney and chronic cardiac disease.

Regarding particularly liver injury caused in patients severely affected by COVID-19, there are published reports estimating the relevant rates at levels of 14.8%- 53%^[11].

The imaging findings in these patients include hepatomegaly, gall bladder thickness, and prominence of the common bile duct in the ultrasonography, along with pericholecystic fat stranding and hypodensity of the liver in the computed tomography (CT) images^[12].

According to Nardo *et al*^[13], the most likely pathophysiological mechanisms involved in causing liver injury after severe infection from SARS-CoV-2 are as follows:

(1) Moderate hepatic steatosis: there is growing evidence that SARS-CoV-2 modifies the function and the activity of the mitochondria, downregulating nuclear-encoded mitochondrial genes which are associated with cellular respiration^[14]. Another cause of steatosis seems to be the induction of endoplasmic reticulum stress by SARS-CoV-2, which in turn has been shown to cause lipogenesis in the hepatic cells^[15]. Finally, another proposed possible mechanism is directly associated with the characteristic “cytokine storm”/cytokine release syndrome (CRS) observed in the severe forms of COVID-19. Interleukin (IL)-6 produced by the cytokine storm most probably causes hyperactivation of the mammalian target of rapamycin, which can induce lipogenesis inside the hepatic cell^[16]. In conclusion, the above-mentioned process of excessive

lipogenesis seems to be detrimental to the function of the hepatic cell and the liver as a whole, and on the other hand it enhances the potential of the virus, providing it with the necessary nutrient material to achieve its replication and exocytosis^[13,17].

(2) Cholestasis and bile duct alterations: Apart from IL-6, during the cytokine storm, a large number of other inflammatory cytokines are released, including IL-1 and tumour necrosis factor-alpha. These cytokines cause hepatocellular cholestasis, closely resembling cholestasis observed in severe cases of sepsis^[18]. An additional pathophysiological lesion that has been observed in these patients comes from the so-called “triple hit” to the bile ducts, consisting of (a) hypoxia due to respiratory failure, (b) systemic inflammatory response syndrome resulting in inflammation and fibrosis of the bile ducts, and (c) direct infection of the cholangiocytes from the virus^[19].

(3) Hypoxic hepatitis (HH): Pathophysiologically, the causes of HH during the course of severe COVID-19 are multifactorial, including (a) acute respiratory failure, (b) severe sepsis, (c) heart failure, including right-sided heart failure, (d) acute respiratory distress syndrome (ARDS), (e) a hyper-coagulate state, deteriorating the congestion of the liver, and (f) the hemodynamic effects of positive-pressure ventilation^[20].

(4) The gut–liver axis: Symptomatology from the gastrointestinal tract is common in patients with severe COVID-19, with relevant rates ranging from 4.9% to 74%. The most common symptoms are nausea, vomiting, diarrhea, loss of appetite, and abdominal pain^[21]. It is speculated that the damage caused by SARS-CoV-2 to the epithelial barrier of the small intestine may lead to the transmission of the virus into the hepatocytes through the portal vein, aggravating thereby the lesions of the liver parenchyma. In addition, alterations in gut microbiota caused either by drugs for COVID-19 or by the virus itself may play a significant role through the gut–liver axis.

(5) Injury induced by treating medications: As SARS-CoV-2 is novel to the scientific community and no specific therapy for COVID-19 has been found, numerous different drugs have been used in several cases outside their officially approved indications. Typical examples are the antimalarial drug hydroxychloroquine; antibiotics (mainly from the family of macrolides); antiviral agents such as lopinavir, ritonavir, and

remdesivir; immunomodulating medications such as tocilizumab and dexamethasone; and even anti-inflammatory and antipyretics in high doses^[22]. Many of them presented already-known hepatotoxic side effects. For example, corticosteroids have been implicated as a cause of glycogenosis or steatosis^[23], whereas tocilizumab is reported to cause drug-induced liver injury (DILI) in critically ill patients with COVID-19^[24]. Specific reference should be made to paracetamol, the most commonly used analgesic and antipyretic medication in the elderly, prescribed in many cases in high doses and for a long time. According to Mian *et al*^[25], old age and frailty decrease the clearance of paracetamol at percentages of 29%-45.7%, varying between 0.20-0.38 L/h/kg in older patients in comparison with values between 0.28-0.7 L/h/kg in younger ones. Another important influence of ageing is on the volume of distribution of paracetamol, which decreases at older patients, because of its incomplete distribution into body fat, with a consequent rising of paracetamol's plasma concentration in the elderly.

Nowadays, in the United States of America, severe DILI presents the leading cause of acute liver failure (ALF), ahead of all the other causes, even viral hepatitis. More than 1000 pharmaceutical agents have been identified as causes of serious liver disease, a figure that will increase significantly in the near future, as pharmaceutical industry is constantly developing new drugs for use by general population and patients. There are two main types of adverse reactions induced by drugs^[26,27]:

Type A (intrinsic adverse reactions), are dose dependent, producing predictable toxicities.

Type B (idiosyncratic adverse reactions) are difficult to be explained by their pharmacologic response or their dose, are associated with patient, drug or environmental risk factors, making them difficult to be predicted.

In order to early predict the occurrence of a severe DILI and take the appropriate preventive measures, various methods have been proposed. Hy's Law is one of the most commonly used, named after Dr. Hyman Zimmerman. It is based on the observation that patients with elevated serum total bilirubin who have received a medication causing hepatocellular (not hepatobiliary) injury, with absence of other

possible causes that could explain these disorders, are at high risk for fatal or requiring transplantation DILI, with mortality ranging between 10%-50%^[28]. Another valuable tool is the LiverTox free online database, which allows the clinicians to be informed about the latest data of the hepatotoxicity of various pharmaceutical agents, while at the same time they are assisted in the diagnosis and treatment of DILI^[29].

Another important area of scientific research is the way by which liver dysfunction of any aetiology has the potential to affect the accumulation and the toxicity of various drugs. According to Bosilkovska *et al*^[30], the physiologic changes that accompany any hepatic impairment alter the disposition of most of the drugs. Portosystemic shunting decreases the initial metabolism, increasing the oral bioavailability of highly extracted drugs, whereas a coexisting disorder in the production of drug-binding proteins can change drug's distribution. In addition, both the amount and the function of enzymes which are produced by the liver and are responsible for the metabolism of drugs are affected by hepatic damage. The final result is the reduction of drug clearance, along with increased plasma drug concentration, which are both difficult to be predicted. Thus, the pharmacologic properties of most of the drugs are altered during severe liver disease.

In conclusion, the mechanism of liver injury during COVID-19 is twofold^[31]: either SARS-CoV-2 attacks directly the hepatic cells and the cholangiocytes, or it causes damage to the liver parenchyma by activating (and dysregulating) the patient's immune system, probably in a similar way to the severe lung injury caused by the cytokine storm process. In several cases, the damage is caused by a combination of the above two mechanisms. In other cases, the liver is affected by the medication used against COVID-19.

The histopathological features that have been described in critically ill patients with COVID-19 and concurrent hepatic involvement are various and, in most cases, nonspecific. Characteristic and specific for the disease is the detection of SARS-CoV-2 RNA in liver tissue blocks in up to 55% of patients with severe liver injury^[32]. Lagana *et al*^[32] in a series of 40 critically ill patients who died from complications of COVID-19

reported that the most common hepatic histopathological findings were (a) macrovesicular steatosis (75% of the patients), (b) lobular and portal necroinflammation (50% of the patients), and (c) vascular pathology (primarily sinusoidal microthrombi) in a significantly smaller number of patients (15%). Finally, in another post-mortem report, the commonest findings in 22 critically ill patients who died from the disease were liver parenchymal congestion along with sinusoidal congestion and congestion of the small hepatic veins, extravasation of red cells into the Disse's space, necrosis of a large number of hepatic cells and macro- and micro- vacuolar steatosis^[33]. Nevertheless, all the above-mentioned findings seemed to be because of the combination of the organism's systemic response to inflammation and its co-morbidities, rather than the direct action of SARS-CoV-2 on the liver^[34].

DIAGNOSTIC AND PROGNOSTIC TOOLS FOR LIVER INJURY IN PATIENTS WITH COVID-19

Studies on the evolution of liver injury from SARS-CoV-2 and on factors that can predict the outcome are relatively few. Various outcome measures have been studied, including the following^[35]:

(1) Liver function tests (LFTs): A broad spectrum of abnormal LFTs has been described in patients with COVID-19. Aminotransferases (aspartate aminotransferase [AST] and alanine aminotransferase [ALT]), alkaline phosphatase, gamma-glutamyl transpeptidase (GGT), and bilirubin have been the most extensively studied markers of liver function in patients with COVID-19. Various studies have demonstrated a correlation between liver injury and disease severity, albeit most of these data are not strictly limited to critically ill patients^[36-39]. In several studies including severe and non-severe patients with COVID-19 strong association was found between LFTs (particularly AST) abnormalities and disease severity and mortality^[40-44]. Lok *et al*^[45], reporting similar results, suggested that immune system dysregulation may be a plausible contributing factor to the former association.

The role of microRNAs, which are considered to alter the immune response, is notable. To the best of our knowledge, only one study has found an association between liver-derived miR-122 and patient mortality in a cohort including patients with severe COVID-19^[46]. Whereas the role of microRNAs in the inflammatory process is well documented, their specific role in COVID-19 is yet to be clarified.

Focusing on critically ill patients, a wide range of abnormal LFTs has been reported, whereas the vast majority of published data deliberate on aminotransferases. The prevalence of abnormal LFTs seems to be higher in ICU patients than in ward patients with COVID-19, according to a large meta-analysis including 31 studies from various countries^[47]. In a study including 166 patients requiring mechanical ventilation, AST and ALT elevation served as predictive factors for the requirement of invasive mechanical ventilation^[48]. Similar results were reported by Yip *et al*^[49]. An independent association was found between aminotransferases elevation and ICU admission, mechanical ventilation, and/or death. In addition, an association was found between aminotransferases elevation and lopinavir/ritonavir plus interferon beta and corticosteroids use, and the researchers suggested a cautious use of medications to minimize hepatotoxicity.

Nevertheless, Roman *et al*^[50], in a study including exclusively critically ill patients with laboratory-proven liver damage, failed to demonstrate a correlation between liver injury severity and mortality. Azad Allarakia *et al*^[51] examined plausible associations between routine laboratory tests and disease severity. No difference was found regarding LFTs between ICU and ward patients; however, confounding factors were not adjusted. Similarly, in a study conducted early during the pandemic era, no association was found between disease severity and LFTs^[52].

Regarding mortality, in a large cohort including 3812 patients with COVID-19, an association between elevated ALT, AST, GGT levels and ICU admission was reported, and AST elevation was associated with risk of death after adjusting for confounding factors such as age, obesity, and previous liver disease^[41]. Following the aforementioned study, in Salik *et al*'s study, which included exclusively critically ill

patients, liver dysfunction and liver injury were associated with higher 7- and 28-d mortality in comparison with patients with COVID-19 without liver biochemistry abnormalities^[53]. Interestingly, in Kasapoglu *et al*'s study, although ICU patients had higher values of AST and GGT, only GGT among LFTs was found to be predictive of mortality in ICU patients^[54].

In addition to the aforementioned biomarkers, interest has been drawn to the role of albumin and prealbumin as prognostic markers of COVID-19 outcome. Hypoalbuminaemia is common among critically ill patients with COVID-19. There are various mechanisms not directly related to hepatocellular damage that lead to hypoalbuminaemia in these patients, including malnutrition, extravasation due to capillary leakage and decreased rate of synthesis. Furthermore, measurements of serum albumin in hospitalized patients are often affected by exogenous albumin administration. Prealbumin is a precursor of albumin with shorter half-life, thus can be used to assess protein status during shorter time-frame. Low prealbumin levels were associated with disease severity and may be of prognostic value as they were identified as independent predictors of mortality in critically ill patients with COVID-19^[55,56].

(2) Various non-invasive fibrosis estimators included the fibrosis-4 (FIB-4) score, the FORNS index for liver fibrosis, ¹¹ the AST to platelet ratio index (APRI) score, the non-alcoholic fatty liver disease (NAFLD) fibrosis score (NFS), and the AST to ALT ratio.

Of the above-mentioned biomarkers and scores, the FIB-4 score attracted interest and applicability. It is a scoring system that uses four simple parameters, readily available in all inpatients: the age, the platelet count, and the values of AST and ALT: a score of < ⁴ 1.45 has a negative predictive value of more than 90% for advanced fibrosis of the liver, whereas a score of > 3.25 has a positive predictive value of 65%, with 97% specificity^[57].

Crisan *et al*^[58] published the results of a retrospective cohort study (370 consecutive patients with COVID-19, from whom 289 presented with abnormal liver biomarkers on admission), to evaluate the predictive value of the various liver tests and estimators. They concluded that elevated FIB-4 score (values > 3.25) and elevated AST were the only two tests that were independently associated with higher mortality in these

patients. FIB-4 score is a valuable tool that can help clinicians identify existing undiagnosed liver disease or the possibility of rapid deterioration of liver function during COVID-19, so that patients with abnormal values receive priority in their inpatient management^[58].

Findings in association with the value of the FIB-4 score were also verified in the systematic review and meta-analysis of Liu *et al*^[59], who concluded that along with the FIB-4 score, the APRI score, the NFS and the FORNS index could also serve as indicators for identifying patients at high risk of developing severe COVID-19 with worse outcome. More specifically, one unit elevation of the APRI score increases the risk of death by 178%, higher NFS (≥ -1.5) increases the risk of developing severe COVID-19 by ten-fold, and increase of the FORNS index by one point increases the risk of death by 41%.

CRITICALLY ILL PATIENTS WITH ACUTE LIVER DISEASE AND COVID-19

Acute liver injury (ALI) has been reported in approximately 19% of patients with COVID-19; however, the percentage increases dramatically, up to 89.2%, in ICU patients^[60,61]. The spectrum of ALI in critically ill patients with COVID-19 is wide, varying from simple elevations of LFTs to ALF, the need for advanced support, and even the need for transplantation^[62-64]. For patients with severe liver injury (approximately 6.4% of all patients with distorted liver biochemistry), a severe disease course is expected^[65]. The correlation of impaired liver function with sudden death in patients with COVID-19 is another outstanding association^[66]. Most studies reported a predominance of the hepatocellular pattern^[67]. However, other distributions of liver injury pattern have been reported as well^[62].

HH as a clinical presentation of COVID-19 is observed in approximately 5.88% of ICU patients with COVID-19 and has a significant effect on patient survival^[68]. The diagnosis is made when the following criteria are met: (a) a massive but transiently elevated ALT level (more than 20-fold the upper limit of normal), (b) the presence of respiratory, cardiac or circulatory failure, and (c) exclusion of other causes of liver

injury^[69]. The close monitoring of cardiac and respiratory function and early aetiologic management of hemodynamic instability/shock is crucial for patients' survival when HH is suspected^[68].

Secondary sclerosing cholangitis is another not rare and devastating form of liver disease in COVID-19, which is associated with considerable morbidity and mortality. Contributing pathophysiological mechanisms include bile duct ischemia and toxic bile formation^[70]. The underlying histopathological findings consist of ischemic damage to the perihilar bile ducts^[71]. Ursodeoxycholic acid (UDCA) has been reported to give promising results; however, for a proportion of these patients, transplantation is required^[72].

Rare but devastating clinical presentations include liver abscess with necrosis^[73] and vascular thrombotic events in abdominal vessels such as portal and mesenteric vein thrombosis^[74].

ALF is a life-threatening condition ⁹ characterized by hepatic encephalopathy and coagulopathy in patients without pre-existing liver disease^[75]. During the pandemic, an increased incidence of hepatitis of unknown aetiology in the pediatric population has been reported with subsequent liver failure and the need for liver transplantation (LT) for a proportion of these children. This raised great concern about the possible vulnerability of children to this extremely severe complication. Although adenovirus is the main aetiological agent suspected to be responsible, the association with COVID-19 and the role of other contributing factors remain to be clarified^[76]. In adults, there are reports on other viruses as causative factors of ALF, such as the infection from or the reactivation of herpes simplex virus-1 following the immunosuppression that patients with COVID-19 receive for treating the CRS^[77].

When assessing critically ill patients with COVID-19 and ALI, the diagnostic approach basically remains the same as for any patient who has ALI and is severely ill. However, some differences exist that must be pointed out.

Current guidelines recommend against unnecessary imaging (*e.g.*, ultrasound [unless performed at the bedside], CT—magnetic resonance [MR] imaging/MR

cholangiopancreatography)^[78]. The transport of these patients requires special knowledge, equipment, and experience and should be kept for patients where the examination results may change the patient's management.

Approaches that do not require patient transportation are preferred. An approach regarding the hemodynamic monitoring of these patients uses invasive cardiac monitors based on the thermodilution method. These methods are invasive, expensive, and present septic and other catheter-related complications. Moreover, they have limitations in critically ill patients with liver failure such as the presence of ascites (extravascular third space fluid) or hepatic hydrothorax (extravascular lung water), which confuse the measurements and the lack of validation of these techniques on such patients. Remote point-of-care ultrasonography (POCUS) by a hepatologist or an ICU physician, with real-time interpretation by a cardiologist through telemedicine, is a trend that has been adopted in the COVID-19 era^[79]. Information on the hemodynamic status and the cause of the hemodynamic compromise of these patients is safely and accurately collected. Basic diagnoses such as pulmonary embolism or myocardial infarction are made at the bedside. The evaluation of intravascular volume status helps to differentiate between prerenal acute kidney injury and hepatorenal syndrome or between **transfusion-related acute lung injury and transfusion-associated circulatory overload**. **In addition**, this powerful and non-invasive tool contributes to the prompt identification of liver-related pathologies, including portal vein or hepatic vein thrombosis, the presence of ascites, suspected pneumothorax, and hemothorax. This approach has provided several solutions for liver units and ICUs during the pandemic. Another non-invasive method that has been evaluated for the assessment of liver injury during COVID-19 is the vibration-controlled transient elastography/FibroScan. It may serve as a tool for identifying patients with elevated liver stiffness and thus at greater risk of developing ALI and progressing to severe COVID-19 with worse clinical outcomes, even when no history of pre-existing liver disease is present^[80,81].

No special recommendations or measures exist which could prevent liver injury from COVID-19. The prophylaxis of the liver can only be achieved through measures that

prevent infection from SARS-CoV-2. Thus, current guidelines suggest using personal protective equipment for healthcare personnel in the liver and other departments, cancelling all elective/nonurgent procedures, and vaccinating with the approved vaccines the vulnerable population with or without pre-existing liver disease^[78,82]. Another approach is the use of dietary supplements as prophylaxis for severe disease and liver involvement. Among the supplements used for the prevention of COVID-19, several pieces of evidence exist on the possible protective role of vitamins C and D in humans, whereas in animal models, xanthohumol has an anti-inflammatory action on liver injury^[83].

Accordingly, no separate protocols exist for the treatment of liver injury from COVID-19. The implementation of the general therapeutic protocols for the disease is applicable^[84], with special care for liver protection and early detection of liver injury in patients with COVID-19^[85]. In cases of patients with progressive ALF, when the applied standard supportive care (hemodynamic, nutritional, respiratory support, avoidance of all unnecessary hepatotoxic factors) does not lead to the resolution of ALF, LT can be the final solution^[75]. Removing hepatotoxic metabolites such as **conjugated or unconjugated bilirubin, bile acids, phenols, fatty acids, cytokines, ammonia, or amino acids** with the use of extracorporeal blood purification techniques presents an interesting alternative approach, particularly when LT is not a feasible option or even as a bridging therapy toward transplantation^[86,87]. These techniques eliminate not only hepatic metabolites but also inflammatory mediators responsible for the CRS, leading to the preservation of organ function and prevention of organ failure while advanced support is offered in patients with COVID-19^[86].

CRITICALLY ILL PATIENTS WITH CHRONIC LIVER DISEASE AND COVID-19

Acute-on-chronic liver failure has been reported in patients with pre-existing liver disease^[40]. Particularly in patients with cirrhosis, the associated state of immunosuppression in conjunction with COVID-19 can lead to acute decompensation, most frequently manifested as worsening ascites with spontaneous bacterial peritonitis,

and to hepatic failure in patients with impaired and limited reserves^[40,88]. Liver injury has been observed in 26.7% of patients with severe pneumonia^[88]. ⁵ Despite the lack of coagulation factors in decompensated liver disease, a hypercoagulable state may be present in COVID-19, and hepatic impairment may be associated with greater activation of the coagulation pathways^[75,89].

In critically ill patients with COVID-19, pre-existing liver disease and evidence of liver impairment, LFTs must be frequently monitored^[85]. Typically, no specific treatment is indicated, and emphasis should be placed on cause-directed therapy.

UDCA may be added as a treatment in patients with liver injury, because of its anti-inflammatory and immunomodulatory properties^[88]. In the ICU setting, treatment with vasopressors should be administered with caution in patients with cirrhosis and COVID-19, to avoid detrimental effects on cardiac output. Moreover, caution should be taken while administering immunosuppressive agents, such as tocilizumab and baricitinib, as they may cause the reactivation of chronic hepatitis B. In such cases, antiviral prophylaxis is indicated^[88].

In terms of prognosis, it has been hypothesized that patients with chronic liver disease may be particularly vulnerable to developing severe COVID-19^[90]. Higher mortality rates have been observed in patients with COVID-19, pre-existing chronic liver disease, and cirrhosis caused by chronic hepatitis B and C^[40]. Moreover, patients with NAFLD present higher risk for progression to severe COVID-19^[91]. Patients with cirrhosis having ARDS have a worse prognosis than patients without cirrhosis, and pre-existing liver fibrosis ¹ is independently associated with a significantly higher risk of death in patients with severe COVID-19 admitted to the ICU^[92].

An approach to liver disease in critically ill patients with COVID-19 is proposed by the authors (Figure 1).

EFFECT OF THE PANDEMIC ON HEALTH SYSTEMS, ICUS, LIVER UNITS AND TRANSPLANT PROGRAMS

During the pandemic, health systems and ICUs were overburdened by critically ill patients. Higher mortality risk was observed and was associated with ICU patient load^[4,93,94]. In line with this, patients with chronic liver disease had significantly high mortality during the pandemic, leading to suggestions regarding their primary and emergency care and their access to intensive care and high-dependency units^[95]. In addition, the effect of the pandemic was significant on the treatment of complications of chronic liver disease such as hepatocellular carcinoma (HCC); surveillance for HCC and treatment of early-stage HCC were modified. Another significant change was the extensive use of telemedicine, to minimize patients' and healthcare workers' exposure to COVID-19^[96].

Transplant programs and care provided to LT recipients were also greatly affected. Living donor LT was suspended in some centers worldwide^[96]. As a response to these issues, national protocols were specially prepared^[97], and transplantation centers implemented special strategies to increase their successful transplantation rates^[98]. Recommendations point out the need for restoration of LT programs; however, prioritization of ¹patients with poor short-term prognosis (with acute/acute-on-chronic liver failure, high Model for End-stage Liver Disease score, and HCC at the upper limits of the Milan criteria) may be necessary in some cases^[67].

In general, transplant recipients present higher rates of severe disease and higher mortality rates, than nontransplant patients; thus, their exposure to COVID-19 should remain minimal^[78]. Immunosuppression should be reduced only under special circumstances, *e.g.*, symptomatic COVID-19, and with caution^[78,99]. COVID-19 screening should be performed for both donors and recipients. Charts regarding LT organ offers are available, to optimize the management of the procedures associated with LT in the COVID-19 era^[78].

CONCLUSION

Apart from the upper and lower respiratory system, the liver is also greatly affected by COVID-19. The pathophysiological mechanisms include cholestasis, bile duct

alterations, hepatic steatosis, involvement of the gut-liver axis, HH, and hepatitis induced by the drugs which are used to treat the actual disease. The hepatocyte seems to be affected both directly, by SARS-CoV-2 itself, and also by the immune system's disruption and dysregulation. Not only patients with or without pre-existing liver disease individually but also health systems and transplant programs were greatly affected by the pandemic, and great effort has been made, which needs to be continued to minimize the consequences. Scientific research over the past two years has shown that certain biomarkers can be extremely useful in the early diagnosis of liver injury and the evaluation of its progression. Non-invasive assessment with transient elastography or POCUS is the trend for evaluating particularly patients in the ICU setting where biopsy is difficult to perform because of coagulation abnormalities and transport for CT or MR imaging is difficult and potentially dangerous. Although in most cases, liver involvement in COVID-19 is mild, the clinician should be able to early recognize the symptoms and signs of liver dysfunction and not focus exclusively on symptomatology from the respiratory system.

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