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

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

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

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†This paper is dedicated to the memory of an exceptional doctor, Tilemachos Zafeiridis (1974-2021), one year after his premature death, to remind us of how much we miss him

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Abstract

Coronavirus disease 2019 (COVID-19), caused by ~~Severe~~ severe ~~Acute~~ acute ~~Respiratory~~ respiratory ~~Syndrome~~ syndrome ~~Coronavirus~~ coronavirus 2 (SARS-CoV-2), broke out in December 2019 in ~~the city of~~ Wuhan city ~~in~~ of China, and ~~spread rapidly~~ spread rapidly ~~around the~~ worldwide.~~,~~ ~~so~~ Therefore, by March 2020, the World Health Organization (WHO) declared the disease a global pandemic. Apart from the respiratory system, ~~a number of~~ 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 ~~at the level of~~ to be 14.8%~~--~~53%. Elevated levels of total bilirubin, aspartate aminotransferase ~~(AST)~~, and alanine aminotransferase ~~(ALT)~~ and low levels of serum albumin are the main laboratory findings. Patients with ~~pre-~~pre-existing chronic liver disease and cirrhosis are much more prone to develop a severe liver injury.

This literature review ~~will present~~ presented the recent scientific findings regarding the pathophysiological mechanisms ~~which are~~ responsible for ~~the induction of~~ causing 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 ~~which give the~~ providing the possibility of early diagnosis of severe liver injury in ~~this category of~~ these patients. Moreover, ~~It~~ it ~~will also highlight~~ highlighted the burden that COVID-19 ~~induced~~ put ~~to~~ on health systems ~~around the~~ worldwide and its ~~impact~~ effect on transplant programs and on the care provided to critically ill patients in general and ~~especially~~ particularly to those with chronic liver disease.

~~Key word~~**Keywords:** COVID-19; SARS-CoV-2; Liver Disease; Intensive Care Unit; Liver Unit

Core Tip: ~~Liver~~ The liver follows the respiratory system ~~with~~ in being affected by SARS-CoV-2, wherein the effect is lower but considerable ~~frequency of affection from SARS-CoV-2~~. COVID-19 causes acute and acute-on-chronic liver injury. The pathophysiological mechanisms are complex and multiple. Certain biomarkers ~~like~~ such as ~~Fibrosis~~fibrosis-4 ~~(FIB-4)~~ score and ~~non-~~non-invasive point-of-care methods ~~like~~ such as ultrasonography or transient elastography can be ~~very~~ extremely ~~useful~~ helpful ~~for~~ in the early diagnosis of liver injury and the assessment of its progression. Health systems, ~~Intensive~~ intensive ~~Care~~ care ~~Units~~units, ~~Liver~~ liver ~~Units~~ units, and transplant programs were seriously affected by the pandemic. The clinician should ~~be able to early~~ recognize the symptoms and signs of liver dysfunction early and not focus exclusively on those of the respiratory system.

INTRODUCTION

In December 2019, an epidemic of pneumonia of unknown origin broke out in ~~the city of~~ Wuhan city, in the Hubei province of China, causing global concern because of ~~its ease of~~ easy transmission and the significant rates of morbidity and mortality that accompanied it. ~~In order to~~ 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 ~~resulted in the rapid identification of~~ identified the cause rapidly (~~[s~~Severe ~~Acute~~ acute ~~Respiratory~~ respiratory ~~Syndrome~~ syndrome ~~Coronavirus~~coronovirus-2 [~~(~~SARS-CoV-2~~)~~]) of ~~this disease [Coronavirus~~ coronavirus disease 2019 (COVID-19)~~]~~ [1].

In the immediate aftermath, ~~the spread of~~ the disease ~~to~~ spread very rapidly to all the regions of the world ~~was very rapid~~, forcing the World Health Organization (WHO) to declare the COVID-19 outbreak as a "global pandemic" on ~~the 11th of~~ March 11, 2020. ~~It is characteristic that~~ In just ~~in~~ a period of two weeks before ~~that specific date~~ March 11, 2020, the number of ~~the~~ cases outside China increased by 13 times, and~~, while~~ the number of countries in which the disease was identified increased by more than three times [2]. ~~.~~Over the next ~~years~~ years, the pandemic greatly affected the health systems of all the countries of the world, causing, until ~~the 16th of~~ September 16, 2022, more than 611~~.~~,550~~.~~,000 cases and more than 6~~.~~,525~~.~~,000 deaths [3].

Among the organs affected by COVID-19 is the liver, with ~~many~~ several early scientific reports describing various degrees of liver dysfunction and injury [4]. This literature review ~~will present~~ presented the recent scientific findings regarding the pathophysiological mechanisms ~~which are~~ responsible for ~~the induction of~~ causing 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~~liver~~;~~ the tests ~~which give the~~ providing the possibility of early diagnosis of severe liver injury in these ~~patients~~ patients; and the ~~impact~~ effect of the pandemic on health systems,

transplant ~~programs~~ programs, and critically ill patients with or without ~~pre-existing~~ preexisting chronic liver disease.

An advanced search strategy was ~~carried out~~ made to identify ~~papers~~ studies published ~~till~~ until August 2022, ~~combining~~ using the ~~key word~~keywords "COVID-19,"~~,~~ and "Liver," and "Intensive Care Unit" in the ~~Pubmed~~ PubMed electronic bibliographic database. Initially, 560 ~~articles~~ studies were identified. ~~Those~~ These ~~articles~~ studies were reviewed on the basis of their title and ~~abstract~~abstract,~~;~~ thus~~,~~ excluding 301 ~~articles~~studies. The full texts of the ~~rest~~ remaining 259 ~~articles'~~ studies ~~full texts~~ were assessed for eligibility on the basis of their relevance to the subject of our review, ~~especially~~ particularly focusing on critical illness and liver disease. Most of these studies were excluded because they referred to ~~COVID-19~~ patients with mild or moderate COVID-19~~disease severity~~.

A total of 87 ~~manuscripts~~ studies were finally included and analyzed for this systematic review.

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

~~IMPACT~~ EFFECT OF COVID-19 ON LIVER

SARS-CoV-2, just like its predecessors SARS-CoV (responsible for ~~the severe acute respiratory syndrome~~ 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 [4]. The main symptoms caused by SARS-CoV-2, ~~which affects~~ affecting more severely in men ~~more severely~~ than women, include fever, upper and lower respiratory symptomatology (cough, rhinorrhea, sore throat, flu-like symptoms, and ~~dyspnoea~~dyspnea), general muscle aches, ~~anosmia~~ anosmia, and 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. [5] reported three cases of hepatitis directly associated with SARS disease~~,~~ ~~while~~ and ~~mentioning~~ revealed that various degrees of impairment of ~~the~~ liver function ~~have~~

had been reported ~~to~~ in up to 60% of the patients suffering from SARS. ~~Fourteen years later,~~ Alsaad et al. [6], after 14 years, reported ~~findings of~~ portal and lobular hepatitis at ~~post-mortem~~ postmortem 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 (~~in total~~ 20~~.~~,133 patients) were published~~, in order~~ to investigate the outcome of patients with severe diseases ~~which~~ who were admitted to these hospitals [7]. Their median age was 73 years (~~range~~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 and chronic kidney ~~disease~~ diseases, 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 the level of 14.8%–53% [8].

The imaging findings in these patients include hepatomegaly, gall bladder ~~thickness~~ thickness, and prominence of the common bile duct in the ~~ultrasound~~ultrasonography, along with pericholecystic fat stranding and hypodensity of the liver in the computed tomography (CT) images [9].

According to Nardo et al. [10], the most likely pathophysiological mechanisms involved in ~~the production of~~ causing liver injury after severe infection ~~from~~ with 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 ~~(NEM)~~ genes which are ~~related to~~ associated with ~~the~~ cellular respiration [11]. Another cause of ~~the~~ steatosis seems to be the induction ~~by SARS-CoV-2~~ of ~~endoplasmatic~~endoplasmic reticulum stress by SARS-CoV-2, which in turn has been shown to cause lipogenesis in the hepatic cells [12]. Finally, another proposed possible mechanism is directly

related to associated with the characteristic "cytokine storm"/Cytokine cytokine Release release Syndrome syndrome (CRS) observed in the severe forms of COVID-19.: Interleukin (IL)-6 produced by the cytokine storm most probably causes hypeactivationhyperactivation of the mammalian target of rapamycin (mTOR), which has the ability to can induce lipogenesis inside the hepatic cell [13]. In conclusion, it seems that the above-mentioned process of excessive lipogenesis is seems to beon the one hand detrimental to the function of the hepatic cell and the liver as a whole;, and on the other hand however, it enhances the potential of the virus, providing it with the necessary nutrient material in order to achieve its replication and exocytosis [10,14].

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 Tumourtumor Necrosis necrosis Factor factor(TNF)-alpha. These cytokines cause hepatocellular cholestasis, which closely resembles resembling closely cholestasis observed in severe cases of sepsis [15]. 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 hypoxia due to respiratory failure, (b) Systemic systemic Inflammatory inflammatory Response response Syndrome syndrome(SIRS) resulting in inflammation and fibrosis of the bile ducts ducts, and (c) Direct direct infection of the cholangiocytes from the virus [16].
3) Hypoxic hepatitis (HH): Pathophysiologically, the causes of HH during the course of severe COVID-19 are multifactorial, including: (a) Acute acute respiratory failure, (b) Severe severe sepsis, (c) Heart heart failure, including right-sided heart failure, (d) Acute acute Respiratory respiratory Distress distress Syndrome syndrome(ARDS), (e) A a hyper-coagulablete state, deteriorating the congestion of the liver, and (f) The the haemodynamichemodynamic effects of positive-pressure ventilation [17].
4) The gut–liver axis: Symptomatology from the gastrointestinal tract is common in patients with severe COVID-19, with relevant rates ranging from

~~from~~ 4.9% to 74%. The most common are nausea, vomiting, ~~diarrhoea~~diarrhea, loss of ~~appetite~~ appetite, and abdominal pain [18]. 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~~ alterations in gut microbiota caused either by drugs for COVID-19 or by the virus itself may ~~also~~ play a significant role through the gut~~–~~–liver axis.

5) Injury induced by ~~the~~ treating medications: ~~Since~~ As SARS-CoV-2 is novel to the scientific community and no specific therapy for COVID-19 has been found, ~~a number of~~ numerous different drugs have been used in ~~many~~ several cases outside their officially approved indications. Typical examples are the antimalarial ~~drug~~ drugs hydroxychloroquine~~,~~ antibiotics (mainly from the family of ~~macrolids~~macrolides)~~,~~ antiviral agents such as lopinavir, ~~ritonavir~~ ritonavir, and remdesivir~~,~~ ~~immonumodulating~~immunomodulating medications such as tocilizumab and ~~dexamethazone~~dexamethasone; and even anti-inflammatory and antipyretics in high doses [19]. Many of them presented already known hepatotoxic side effects. For example, corticosteroids have been implicated as a cause of glycogenosis or steatosis [20], whereas tocilizumab is reported to cause drug-induced liver injury ~~(DILI)~~ in critically ill patients with COVID-19 [21].

In conclusion, the mechanism of liver injury during COVID-19 is twofold [22]: either SARS-CoV-2 attacks directly the hepatic cells and the ~~cholangiocytes~~cholangiocytes~~,~~ or it causes damage to the liver parenchyma by activating (and in fact dysregulating) the patient's immune system, probably in a similar way to the severe lung injury caused by the cytokine storm process. In ~~many~~ several cases, the damage is caused by a combination of the above two mechanisms.

The histopathological features that have been described in critically ill patients with COVID-19 and concurrent hepatic involvement are various and, in most cases, ~~non-specific~~nonspecific. Characteristic and specific for the disease is the detection of SARS-CoV-2 RNA in liver tissue ~~blocks~~blocks~~,~~ in up to 55% of patients with severe

liver injury [23]. Lagana et al. [23], 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 macrovesicular steatosis (75% of the patients), (b) Lobular lobular and portal necroinflammation (50% of the patients), and (c) Vascular vascular pathology (primarily sinusoidal microthrombi), in a significantly smaller number of patients (15%). Finally, in another post-mortem postmortem 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 the red cells into the Disse's space, necrosis of a large number of hepatic cells, and macro- and microvesicular steatosis [24]. Nevertheless, it seems that all the above-mentioned findings seemed to be are due to 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 [25].

PROGNOSTIC TOOLS ~~OF~~ 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 final outcome are relatively few. Various outcome measures have been studied, including the following [26]:

- Liver Function function Tests tests (LFTs): A broad spectrum of abnormal LFTs has been described in patients with COVID-19 patients. Aminotransferases ([aspartate aminotransferase [(AST]) and alanine aminotransferase [(ALT)]), alkaline phosphatase (ALP), Gammagamma-Glutamyl glutamyl Transpeptidase 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 [27–30]. In several studies, including severe and non-severe nonsevere patients with COVID-19, a strong association was found between LFTs (especially particularly AST) abnormalities, and disease severity and mortality [31–35]. Lok et al. [36], reporting similar results, suggest suggested that

immune system dysregulation may be a plausible ~~contribution~~ contributing factor to the former association.

In addition to the aforementioned biomarkers, interest has been drawn to the role of prealbumin as a prognostic factor of COVID-19 outcomes. ~~It has been shown that l~~Low prealbumin levels, as a marker of abnormal liver function, are ~~correlated~~ associated with disease severity and may be of prognostic value regarding mortality in critically ill patients [37,38].

~~Of note is t~~The role of microRNAs is notable, ~~that~~ which are considered to alter immune responses. To ~~our~~ the best of our knowledge, only one study has found an association between ~~the liver~~ liver-derived miR-122 and patient mortality in a cohort, including patients with severe COVID-19 [39]. Whereas the role of microRNAs in the inflammatory process is well ~~documented~~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, ~~whilst~~ whereas the vast majority of published data deliberate on aminotransferases. The prevalence of abnormal LFTs seems to be higher in ICU patients ~~in comparison with~~ than in ward patients with COVID-19, according to a large meta-analysis ~~that included~~ including 31 studies from various countries [40]. In a study~~,~~ including 166 patients requiring mechanical ventilation, AST and ALT elevation served as predictive factors for the requirement of invasive mechanical ventilation [41]. Similar results were reported by Yip TC et al. [42]. An independent association was found between aminotransferases elevation and ICU admission, mechanical ~~ventilation~~ ventilation, and/or death. In ~~Additionally~~addition, an association was found between aminotransferases elevation and ~~lopinavit~~lopinavir/~~litonavir~~ritonavir plus interferon b and corticosteroids use, and the researchers ~~suggest~~ suggested cautious use of medications ~~in order~~ to minimize hepatotoxicity.

Nevertheless, Roman et al., in a study~~,~~ including exclusively ~~critcally~~critically ill patients with ~~laboratory~~ laboratory-proven liver damage, failed to

demonstrate a correlation between liver injury severity and mortality [43]. Azad Allarakia et al. examined plausible associations between routine laboratory tests and disease severity. No difference was found regarding LFTs between ICU and ward ~~patients~~patients~~;~~ however~~, no adjustment for~~ confounding factors ~~was~~ were not ~~performed~~ adjusted [44]. Similarly, in a study conducted early during the pandemic era, no association was found between disease severity and LFTs [45].

Regarding mortality, in a large cohort, including 3812 ~~COVID-19~~ patients with COVID-19, an association between elevated ALT, AST, ~~GGT~~ and 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~~ obesity, and previous liver disease [32]. In accordance with the aforementioned study, ~~in the study of~~ in Salik et al.'s study, which included exclusively critically ill patients, liver dysfunction and liver injury were associated with higher 7-~~day~~ and 28-day mortality ~~in comparison with~~ than patients with COVID-19 without liver biochemistry abnormalities [46]. Interestingly, in ~~the study of~~ 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 [47].

- Various ~~non – invasive~~ non-invasive fibrosis estimators~~,~~ includ~~ed~~ing the fibrosis-4 (~~Fibrosis-4 (~~FIB-4)~~)~~ score, the FORNS index for liver fibrosis, the AST to platelet ratio index (APRI) score, the ~~Non~~non-~~-a~~Alcoholic ~~Fatty~~ fatty ~~Liver~~ liver disease (NAFLD) fibrosis (NFS) ~~score~~ score, and the AST to ALT ratio.

  Of the above-mentioned biomarkers and scores, ~~it is~~ the FIB-4 score ~~that~~ attracted interest and applicability. It is a scoring system ~~which~~ 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 <~~–~~1.45 has a negative predictive value of ~~over~~ 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 [48].

Crisan et al. published the results of a retrospective cohort study (370 consecutive patients with COVID-19, from whom 289 presented with abnormal liver biomarkers on admission)~~,~~ ~~in order~~ to evaluate the predictive value of the various liver tests and estimators [49]. They concluded that elevated FIB-4 score (values >~~-~~3.25) and elevated AST were the only two tests ~~which~~ that were independently associated with higher mortality in these patients. A ~~It is evident that t~~The FIB-4 score is a valuable tool ~~which~~ that can help ~~the~~ clinicians identify existing undiagnosed liver disease or the possibility of rapid deterioration of liver function during ~~the course of~~ COVID-19~~,~~ so ~~as~~ that patients with abnormal values receive priority in their inpatient management [49].

Findings in ~~relation to~~ association with the value of the FIB-4 score were also verified in the systematic review and meta-analysis of Liu et al. [50], who concluded that along with the FIB-4, ~~the~~ APRI ~~score~~, and ~~the~~ NFS score~~s, and~~ the FORNS index could also serve as indicators for identifying patients at high risk ~~for~~ of developing severe COVID-19 with the worse final outcome.

CRITICALLY ILL PATIENTS WITH ACUTE LIVER DISEASE AND COVID-19

Acute liver injury (ALI) has been reported in ~~about~~ approximately 19% of patients with COVID-19~~,~~; ~~but~~ however, the percentage ~~rises~~ increases dramatically, up to 89.2%, in ICU patients [51,52]. The spectrum of ALI in critically ill patients with COVID-19 is wide, varying from simple elevations of LFTs to acute liver failure (ALF), the need for advanced ~~support~~ support, and even the need for transplantation [~~,~~53–55]. For patients with severe liver injury (~~about~~ approximately 6.4% of all patients with distorted liver biochemistry), a severe disease course is expected [56]. The ~~Correlation~~ correlation of impaired liver function with sudden death in ~~COVID-19~~ patients with COVID-19 is another outstanding association [57]. Most studies reported a predominance of the hepatocellular pattern [58]. However, other distributions of liver injury patterns have been reported as well [53].

HH as a clinical presentation of COVID-19 is observed in ~~about~~ approximately 5.88% of ICU patients with COVID-19 ~~patients~~ and has a significant ~~impact~~ effect on patients' survival [59]. The diagnosis is made when the following criteria are met: (a) ~~A~~ a massive but transient elevated ALT level (~~[~~more than 20-fold the upper limit of normal ~~(ULN)]~~), (b) ~~The~~ the presence of respiratory, cardiac, or circulatory failure, and (c) ~~Exclusion~~ exclusion of other causes of liver injury [60]. The ~~Close~~ close monitoring of cardiac and respiratory function and early ~~a~~etiologic management of ~~haemodynamic~~hemodynamic instability/shock is crucial for patients' survival when HH is suspected [59].

Secondary sclerosing ~~chlolangitis~~cholangitis ~~(SSC)~~ is another not rare and devastating form of liver disease in COVID-19, which is ~~related~~ associated with considerable morbidity and mortality. Contributing pathophysiological mechanisms include bile duct ~~ischaemia~~ischemia and toxic bile formation [61]. The underlying histopathological findings consist of ~~ischaemic~~ischemic damage to the perihilar bile ducts [62]. Ursodeoxycholic acid (UDCA) has been reported to give promising ~~results~~ results; ~~but~~ however, for a proportion of these ~~patients~~ patients, transplantation is required [63].

Rare but devastating clinical presentations ~~include~~include: liver abscess with necrosis [64]~~,~~ and vascular thrombotic events in abdominal vessels ~~like~~ such as portal and mesenteric vein thrombosis [65].

ALF is a life-threatening condition~~,~~ characterized by hepatic encephalopathy~~,~~ and coagulopathy in patients without the ~~pre-existing~~ preexisting liver disease [66]. During the ~~pandemic~~ pandemic, ~~elevated~~ an increased incidence of hepatitis of unknown ~~aetiology~~etiology in the pediatric population was 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 the children to this extremely severe complication. Although ~~Adenovirus~~ adenovirus is the main ~~aetiological~~etiological agent suspected to be responsible, the association with COVID-19 and the role of other contributing factors remain to be clarified [67]. In ~~adults~~ adults, there are reports ~~of~~ on other viruses as causative agents of ALF,

such as the infection from or the reactivation of ~~Herpes~~ herpes ~~Simplex~~ simplex ~~Virus~~virus-1 (HSV-1) following the immunosuppression that ~~COVID-19~~ patients with COVID-19 receive for treating the CRS [68].

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

Current guidelines recommend against unnecessary imaging ~~[~~(e.g., ultrasound ~~[(~~unless performed at the bedside~~])~~, ~~CT~~ computed tomography-~~-~~magnetic resonance ~~[(~~MR~~])~~ imaging/MR cholangiopancreatography)~~]~~ [69]. The ~~Transport~~ transport of these patients requires special knowledge, ~~equipment~~ equipment, and experience and should be kept for ~~cases~~ patients where the ~~result of the~~ examination results may change the patient's management.

Approaches that do not require patient~~'s~~ transportation are preferred~~. Such an~~ -An approach regarding the ~~haemodynamic~~hemodynamic monitoring of these patients uses invasive cardiac monitors based on the thermodilution method. These methods are invasive, ~~expensive~~ 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 the ~~of~~ validation of these techniques on such patients. Remote ~~Point~~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 [70]. Information ~~regarding~~ on the ~~haemodynamic~~hemodynamic status and the cause of the ~~haemodynamic~~hemodynamic compromise of these patients ~~is~~ are safely and accurately ~~gathered~~collected. Basic diagnoses ~~like~~ such as pulmonary embolism or myocardial ~~infraction~~ infarction are made at the bedside. The ~~Evaluation~~ evaluation of intravascular volume status helps to differentiate between ~~pre-renal~~ prerenal acute kidney injury ~~(AKI)~~ and hepatorenal syndrome or between transfusion-~~related~~ associated acute lung injury ~~(TRALI)~~ and transfusion-associated circulatory

overload ~~(TACO)~~. In addition, ~~This~~ this powerful tool ~~also~~ contributes to the prompt identification of liver-related pathologies, including portal vein or hepatic vein thrombosis, the presence of ascites, suspected ~~pneumothorax~~ pneumothorax, and hemothorax. This approach has provided ~~many~~ several solutions for ~~Liver~~ liver ~~Units~~ units and ICUs during the pandemic.

Another ~~non-invasive~~ non-invasive method that has been evaluated for the assessment of liver injury during COVID-19 is ~~the Vibration~~vibration-~~Controlled~~ controlled ~~Transient~~ transient ~~Elastography~~ elastography (FibroScan). ~~Its application~~ It may serve as a tool for identifying patients with elevated liver stiffness and thus at greater risk ~~for~~ of developing ALI and ~~for~~ progressing to severe COVID-19 illness with worse clinical outcomes, even when no history of ~~pre-existing~~preexisting liver disease is present [71,72].

~~There are n~~No special recommendations or measures exist ~~whose implementation~~ which could prevent liver injury from COVID-19. The ~~Prophylaxis~~ prophylaxis of the liver can only be achieved through measures that ~~avert~~ prevent infection from SARS-CoV-2. Thus, current guidelines suggest using ~~use of~~ personal protective equipment ~~(PPE)~~ for healthcare personnel ~~at~~ in the liver and other departments, ~~cancel of~~ cance~~l~~lling all elective/nonurgent procedures, and ~~vaccination~~ vaccinating with the approved vaccines for a vulnerable population with or without ~~pre-existing~~ preexisting liver disease [69,73]. Another approach is the use of dietary supplements as prophylaxis ~~from~~ for severe disease and liver involvement. ~~Amongst~~ Among the supplements used for the prevention of COVID-19, several pieces of evidence exist~~s~~ on the possible protective role of vitamins C and D ~~have gathered more evidence about their possible protective role~~ in humans, whereas in animal models, xanthohumol ~~was found to have~~ has an anti-inflammatory action on liver injury [74]~~.~~.

~~Accordingly~~However, ~~there are~~ no separate protocols exist for the treatment of liver injury from COVID-19. The ~~Implementation~~ implementation of the general therapeutic protocols for the disease is applicable [75], with special care for liver protection and early detection of liver injury ~~at~~ in patients with COVID-19 ~~patients~~ [76]. In cases of progressive ALF not responding to ~~the~~ standard supportive ~~care~~ care, LT can be the final solution [66]. Removing hepatotoxic metabolites ~~like~~

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, ~~especially~~ particularly when LT is not a feasible option or even as a bridging therapy ~~towards~~toward transplantation [77,78]. 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 ~~at~~ in ~~COVID-19~~ patients with COVID-19 [77].

CRITICALLY ILL PATIENTS WITH CHRONIC LIVER DISEASE AND COVID-19

A~~Cases of a~~cute-on-chronic liver failure ~~have~~ has been reported~~,~~ in patients with ~~pre-existing~~ preexisting liver disease [31]. 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~~ peritonitis, and to hepatic failure in patients with impaired and limited reserves [31,79]. Liver injury has been ~~seen~~ observed in 26.7% of patients with severe pneumonia [79]. Despite the lack of coagulation factors in decompensated liver disease, a hypercoagulable state may be present in COVID-19, and hepatic impairment may be ~~related to~~ associated with ~~a~~ greater activation of the coagulation pathways [66,80].

In critically ill ~~COVID-19~~ patients with COVID-19 with ~~pre-existing~~ preexisting liver disease and evidence of liver impairment, LFTs must be frequently monitored [76]. ~~Usually~~Typically, no specific treatment is ~~indicated~~indicated, and emphasis should be placed on cause-directed therapy.

UDCA may be added as a treatment in patients with liver injury~~,~~ ~~due to~~ because of its anti-inflammatory and immunomodulatory properties [79]. In the ICU setting, treatment with vasopressors should be administered with caution in patients with cirrhosis and COVID-19~~, in order~~ to avoid detrimental effects on cardiac output.

Moreover, ~~Caution~~ caution should be ~~also given~~ taken ~~in the~~ while administeringration ~~of~~ immunosuppressive agents, such as tocilizumab and baricitinib, as ~~this~~ they may cause the reactivation of chronic hepatitis B. In such ~~case~~ cases, antiviral prophylaxis is indicated [79].

In terms of prognosis, it has been hypothesized that patients with chronic liver disease may be particularly vulnerable to developing severe COVID-19 infection [81]. Higher mortality rates have been observed in ~~COVID-19~~ patients with COVID-19 with ~~pre-existing~~ preexisting chronic liver disease and cirrhosis caused by chronic hepatitis B and C ~~have been observed~~ [31]. Moreover, ~~Patients~~ patients with NAFLD were ~~also found to be~~ at greater risk for progression to severe COVID-19 [82]. ~~Cirrhotic p~~Patients with cirrhosis having ARDS have a worse prognosis than patients without ~~cirrhosis~~ cirrhosis, and ~~pre-existing~~ preexisting liver fibrosis is independently associated with a significantly higher risk of death in patients with severe COVID-19 admitted to the ICU [83].

~~IMPACT~~ EFFECT OF THE PANDEMIC ON HEALTH SYSTEMS, ICUs, LIVER UNITS, AND TRANSPLANT PROGRAMS

During the ~~pandemic~~ pandemic, health systems and ICUs were ~~overwhelmed~~ overburdened by critically ill patients. Higher mortality risk was observed and was associated with ~~intensive care unit~~ ICU patient load [84,85]. In line with this ~~observation~~ , 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 [86]. In addition, ~~The~~ the effect of the pandemic was ~~also~~ significant on the treatment of complications of chronic liver disease ~~like~~ such as ~~Hepatocellular~~ hepatocellular ~~Carcinoma~~ carcinoma (HCC~~):~~); surveillance for HCC and treatment of early-stage HCC were modified. Another significant change was the extensive use of telemedicine~~, in order~~ to minimize patients' and healthcare workers' exposure to COVID-19 [87].

Transplant programs and care provided to LT recipients were also greatly affected. Living donor LT was suspended in some centers ~~around the~~ worldwide [87]. As a response to these issues, national protocols were specially prepared [88], and transplantation centers implemented special strategies to increase their successful transplantation rates [89]. Recommendations ~~stress~~ point out the need for restoration of LT ~~programs~~programs;~~,~~ ~~however~~ however, prioritization of patients with poor short-term prognosis ~~[~~(with acute/acute-on-chronic liver failure, high Model for End-~~stage~~ Stage Liver Disease ~~(MELD)~~ score, and HCC at the upper limits of the Milan criteria~~]~~) may be necessary in some cases [58].

In general, transplant recipients present higher rates of severe disease and higher mortality rates~~,~~ ~~compared to~~ than nontransplant patients; thus, ~~care should be taken so that~~ their exposure to COVID-19 ~~remains~~ should remain minimal [69]. Immunosuppression should be reduced only under special circumstances, ~~e.g.~~ e.g., symptomatic COVID-19, and with caution [69,90]. COVID-19 screening should be performed ~~to~~ for both donors and recipients. Charts regarding LT organ offers are available~~,~~ to optimize the management of the procedures ~~related to~~ associated with LT in the COVID-19 era [69].

CONCLUSION

Apart from the upper and ~~the~~ lower respiratory ~~systems~~systems, the liver is also greatly affected by COVID-19. The pathophysiological mechanisms by which liver injury is caused are complex and numerous, including 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 directly by both ~~directly, by~~ SARS-CoV-2 ~~itself, but also by~~ and the ~~the immune system's~~ disruption and dysregulation of the immune system.

Not only patients with or without ~~pre-existing~~ preexisting liver disease individually but also health systems and transplant programs were greatly affected by the ~~pandemic~~pandemic, and great effort ~~was~~ has been made, ~~and~~ which needs to be continued to minimize the consequences.

Scientific research over the ~~last~~ past two years has shown that certain biomarkers can be ~~very~~ extremely useful in the early diagnosis of liver injury and the evaluation of its progression. ~~Non – invasive~~ Non-invasive assessment with POCUS or transient elastography is the trend for evaluating ~~especially~~ particularly patients in the ICU setting where biopsy is difficult to perform ~~due to~~because of coagulation abnormalities and transport for CT or MR imaging ~~are~~ is difficult and ~~with dangers~~ dangerous for ~~the~~ patients' health.

Although, in most ~~cases~~ cases, liver involvement in COVID-19 is mild, the clinician should be able to early recognize the symptoms and signs of liver ~~dysfunction~~ dysfunction and not focus exclusively on symptomatology from the respiratory system.

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