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COVID-19 and severity of liver diseases: Possible crosstalk and clinical implications

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ABSTRACT

COVID-19-infected individuals and those who recovered from the infection have been demonstrated to have elevated liver enzymes or abnormal liver biochemistries, particularly with preexisting liver diseases, liver metabolic disorders, viral hepatitis, and other hepatic comorbidities. However, possible crosstalk and intricate interplay between COVID-19 and liver disease severity are still elusive, and the available data are murky and confined. Similarly, the syndemic of other blood-borne infectious diseases, chemical-induced liver injuries, and chronic hepatic diseases continued to take lives while showing signs of worsening due to the COVID-19 crisis. Moreover, the pandemic is not over yet and is transitioning to becoming an epidemic in recent years; hence, monitoring liver function tests (LFTs) and assessing hepatic consequences of COVID-19 in patients with or without liver illnesses would be of paramount interest. This pragmatic review explores the correlations between COVID-19 and liver disease severity based on abnormal liver biochemistries and other possible mechanisms in individuals of all ages from the emergence of the COVID-19 pandemic to the post-pandemic period. The review also alludes to clinical perspectives of such interactions to curb overlapping hepatic diseases in people who recovered from the infection or living with long COVID-19.

1. Introduction

According to estimates, 1 to 11 % of SARS-CoV-2 infected patients may have chronic hepatic diseases, which signifies the importance of investigating possible crosstalk between COVID-19 and underlying liver diseases for clinical management [1,2]. SARS-CoV-2 specific hepatotropism, virus-induced direct or indirect hepatic damage, and host immune system suppression by several mechanisms play an integral role in COVID-19 outcomes in patients with pre-existing acute and chronic liver diseases [3]. However, pathological mechanisms and clinical impact of direct SARS-CoV-2 infection on hepatic cells remain elusive [4]. The pandemic also profoundly impacted the global viral hepatitis response not only by pausing hepatitis community outreach, screening campaigns, and linkage to care programs but also by lack of personal protective equipment (PPE), overwhelmed healthcare systems, and looming austerity budgets threatening to roll back even the limited progress achieved in the field of hepatitis cure [4]. The data collected from real-world SARS-CoV-2 infected people and clinical experiences unveil that the virus influences the course of pre-existing hepatic disease progression. Similarly, the data collected from SECURE-Cirrhosis Registry and the COVID-HEP registry reveals the profound impact of underlying hepatic illnesses on COVID-19 outcomes [5]. In addition to that, increased alcohol consumption was noticed during the pandemic peak waves in a mistaken belief to protect against COVID-19 that not only increased the risks for alcoholic hepatitis but also many morbidities reported from acute methanol poisoning [6]. Furthermore, restricted social distance measures, as well as psychosocial stressors, also increased alcohol intake, which subsequently escalated alcohol use disorder (AUD) throughout the world [7]. AUD is always associated with comorbid clinical manifestations like diabetes mellitus (DM) and chronic kidney

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diseases (CKD) and, unfortunately, increases the risks for other complications in COVID-19-infected individuals [8]. The strict lockdown in many parts of the world also limited COVID-19 affectees' in-person participation in substance use disorder (SUD) support programs as well as confined routine screening campaigns and health service visits to assess how liver diseases are escalating COVID-19 outcomes and increased risks for infection [5].

On the other hand, adverse events associated with some therapies for treating alcoholic hepatitis and certain AUD also amalgamate the risks for severe disease outcomes in COVID-19 affectees [8]. For example, the effects of corticosteroids as an immunosuppressant have been demonstrated to aggravate some hepatic clinical manifestations in COVID-19, and hence caution is advised adequately regarding glucocorticoid administration in COVID-19 [9]. Furthermore, non-steroid anti-inflammatory drugs (NSAIDs) were prohibited by health authorities having more severe impacts on pre-existing hepatic diseases in COVID-19 [6]. Even though the alarmingly higher use of acetaminophen (paracetamol) as a pain killer resulted in chemical-associated hepatotoxicity, especially in individuals with alcohol use [10]. Interestingly, no standard guideline was followed to manage alcoholic hepatitis during the pandemic; hence, fears and barriers were raised about liver transplantation for AUD patients affected with COVID-19, which ultimately increased the risks for linkage to care and treatment relapse [11].

This review primarily focuses on the intricate interplay between COVID-19 and the severity of underlying liver diseases with their possible mechanisms evident from the real-world clinical data and the patient cohort registry (e.g., SECURE-Cirrhosis, and COVID-HEP). We also highlight how during the pandemic peak waves, the postponement of clinical visits to assess liver disease progression, deferment of treatment for preexisting liver diseases and viral hepatitis, and delays in liver transplantation procedures are now overburdening the healthcare systems and mounting the underlying disease outcomes. Briefly, we also overview the consensus guidelines and recommendations on the principles of care and management for patients with liver disease and infected with COVID-19 or with long COVID-19.

2. COVID-19 and hepatic system interaction

The devastating impact of the COVID-19 pandemic on human health is still significant as by the time to write this manuscript, the SARS-CoV-2 associated COVID-19 respiratory illness has infected around 682 million people and caused 6.8 million deaths worldwide (https://coronavirus.jhu.edu/map.html). Almost three years ago, initially starting as a small cluster of pneumonia cases in Wuhan, China, waves of the infection caused by SARS-CoV-2 variants swept the globe and have devastated healthcare facilities across nations [12]. As the virus variants rapidly evolved across the nations, the clinical manifestations of COVID-19 (i.e., dyspnea, cough, high-grade fever, and interstitial pneumonia) progressively involved severe comorbidities by damaging multiple body organs (e.g., lungs, liver, heart, and kidney) in infected individuals [13]. The host tropism of SARS-CoV-2 in multiple body organs also leads to the propagation of mild COVID-19 into severe infection form and directly or indirectly damages the host body functions or organs [4]. For example, the severity of COVID-19 has been associated with crucial changes in liver biochemistry and correlates preexisting hepatic illnesses with severe COVID-19 outcomes in infected patients [13]. Almost 15–65 % of SARS-CoV-2 affected individuals have been identified with liver diseases/problems[4]. Due to the worldwide spread of the pandemic and the implementation of social distance measures to reduce infection transmission, other risk factors like unhealthy eating patterns, alcohol consumption, and limited hepatology healthcare services might also escalate the trend of hepatic disease severity and complications[4]. In particular, acute and chronic hepatic abnormalities, increased protein levels in the blood, and other liver complications have been noted in COVID-19 patients. A pathological condition, non-alcoholic fatty liver disease-(NAFLD), has been noticed with significant immune response changes with the severity of COVID-19 [14]. The global prevalence of NAFLD is 25.2–29.8 %, with the clinical presentation of chronic inflammation, micro-vascular endothelial dysfunctioning, and abnormal immune responses [14]. Some studies demonstrate crosstalk between these clinical features of NAFLD with the severity and progression of SARS-CoV-2 infection [15]. The mechanistic perspective of COVID-19 is potentially linked with a burst of pro-inflammatory cytokines that might be involved in one of the pathways that leads to early and late liver biochemistry abnormalities [16]. Visible physiological abnormalities like aggressive systemic inflammation, dysregulated immune system responses leading to hepatic cirrhosis, and intestinal dysbiosis seems to be possible pathogenesis of liver ailments with the progression of COVID-19 [4].

Meanwhile, the possibility of overexpression of angiotensin-converting enzyme (ACE), the primary entry receptor for SARS-CoV-2 into multiple organs, has also been depicted with inadequate evidence of precisely diagnosed viral hepatotropism [4]. In the case of a healthy individual, ACE-2 receptors are found on the epithelial cells of the bile duct, parenchymal cells of the liver, and type 2 alveolar cells in the lungs [17]. Furthermore, the expression of ACE-2 receptors in cholangiocytes and hepatocytes is 60 % and 3 % of the overall liver cells, respectively [18]. The overexpression of ACE-2 receptors, systemic inflammation, and possible iatrogenic drug/treatment toxicities seems to be the fundamental mechanisms initiating hepatic damage in COVID-19 patients [17] (Fig. 1). Liver aminotransferase (e.g., Alanine aminotransferase (ALT) and Aspartate aminotransferase (AST)) levels are the leading indicators of liver health. Multiple published reports and case series explore abnormal liver biochemistries in patients infected with COVID-19 and their proposed clinical perspective in the progression or worsening of preexisting hepatic illnesses (e.g., NAFLD, non-alcoholic steatohepatitis (NASH), hepatic cirrhosis, hepatocellular carcinoma) and liver transplantation [13,19,20]. A case series of 43 COVID-19-infected patients reported abnormal liver functional profiles, including high levels of liver ALT & AST with acute liver dysfunctioning [13]. Total hyper-bilirubinemia and hypo-albuminemia were also observed in these cases. The mechanistic understanding of COVID-19-induced liver injury is still ascertained; however, it is attributed that SARS-CoV-2 binds to hepatocytes (mainly ACE2 of Cholangiocytes (endothelium hepatocytes)) where it mediates liver injury via ACE2/DPP_4 Dipeptidyl peptidase-4/CD26 interaction or the activation of immune response pathways (i.e., certain interleukins (i.e., 1L-1, IL-2, IL-6, IL-8, IL-10, 1L-17) and interferon-γ increase with the COVID-19)) or cause deep vein thrombosis [21,22].

Another study explored that 90 % of patients infected with SARS-CoV-2 also suffered from lymphopenia, 66 % with increased liver enzymes, and 25 % with diarrhea [22]. The findings of an experimental study alluded that human hepatoma cell lines (Huh 7.5) support the growth of the virus *in vitro*. Similarly, the critical roles of accessory cell surface receptors (e.g., high-density lipoprotein (HDL), scavenger receptor B type 1 (SR-B1) along with the activation of hepatocyte ACE2 receptors (cholangiocytes have the greatest ACE2 receptor concentration followed by hepatocytes)) for the entry of the virus into hepatocytes are also evident by some recent studies [4]. In contrast, variability at the gene expression level and upregulation of ACE2 receptors has been observed in the case of different pathophysiological states of liver diseases (e.g., ↑ACE2 expression in parenchymal cells during liver cirrhosis). Histopathological examination of liver biopsy specimens of COVID-19 patients indicated a wide range of microscopic pathological manifestations, including abnormal inflammatory fat droplets, abnormalities of mitochondria (i.e., mitochondrial dysfunction and apoptosis), and vascular blockade (i.e., microvascular thrombosis) [4]. However, large data are still elusive and murky as to evident direct correlations between COVID-19 severity in hepatic comorbidities and direct hepatocyte infection. The involvement of ACE2 receptors is of major significance regarding the replication, pathogenesis, and transmission of SARS-CoV-2 into different body organs, particularly in the

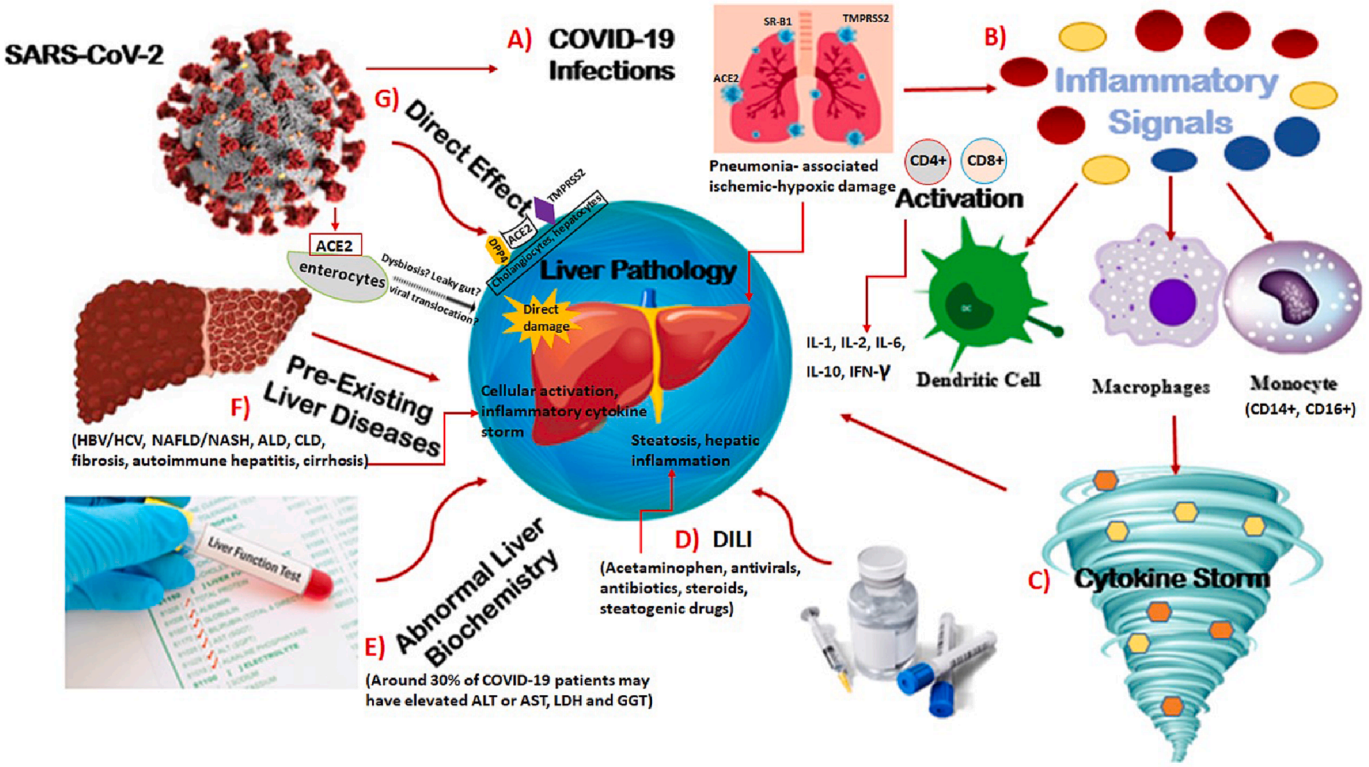

Fig. 1. SARS-CoV-2 entry into hepatocytes and probable mechanisms of liver injury: A) The first interaction between the SARS-CoV-2 and the angiotensin-converting enzyme 2 (ACE2) receptors takes place at the airway epithelial cells and alveoli of the lung tissue (ACE2 receptors are also expressed in the gastrointestinal tract, hepatocytes, cholangiocytes, and vascular endothelium) [4]. The robust viral replication and subsequent COVID-19 accumulate a variety of pro-inflammatory cytokines and chemokines in the lung tissue which further leads to the alveolar epithelial cells damage with reactive inflammatory cell proliferation and virus shedding [13]. B) Persistence viral replication and continuous shedding activate pathogenic T-helper cells (Th17 cells), which induce the production of granulocyte–macrophage colony-stimulating factor (GM-CSF), interleukin 6 (IL-6), and other proinflammatory factors ("cytokine storm"). The inflammatory monocytes (CD14+, CD16 +) respond to GM-CSF, producing a large amount of IL-6 and other proinflammatory factors (i.e., IL-1-β, Il-2, TNF-α, IFN-γ, IL-10) [100]. C) The inflammatory "cytokine storm" is responsible for immune damage in the lung and other organs like the liver. The virus diffuses from the damaged alveoli of the lung tissue into the capillaries and spreads through blood circulation. The virus invades the intestinal tract from blood circulation by damaging the intestinal mucosal epithelium and vascular barrier and enters the hepatocyte through the hepatic portal vein. It is hypothesized that SARS-CoV-2 invades the liver through the digestive tract or blood circulation. As no clear pathways have been identified and fully explained yet for the viral entry into hepatocytes, the suggested routes of SARS-CoV-2 entry into liver cells may be via receptors interaction like 1) ACE2/DDP_4 into hepatocytes 2) exaggerated immune responses during the COVID-19 course, and 3) thrombosis in the blood vessels by leading to ischemia/hypoxia and activation of reactive oxygen species (ROS). The further clinical manifestations of this interaction may increase liver ALT, AST, and bilirubin; however, a decrease in albumin with pathological alteration in the hepatocytes was reported in many studies. The additional mechanisms of intestine damage might include abnormal membrane permeability, viral persistence in enterocytes, dysbiosis, viral translocation, leaky gut, and the production of toxins traveling to the hepatocytes via the hepatic portal vein. The virus may reach bile through the intercellular vesicle pathway and infects hepatocytes. Liver mitochondrial dysfunction can propagate oxidant stress and the production of reactive oxygen species (ROS). In vitro, cell models also demonstrate the role of accessory receptors (e.g., high-density lipoprotein (HDL) receptor, scavenger receptor B type 1 (SR-B1) alongside ACE2 for cell entry. Furthermore, both biliary and hepatocyte organoid models also decipher the expression of necessary viral entry receptors (e.g., TMPRSS2) and recapitulate viral infection. Albeit controversy exists about the distribution and gene expression of ACE2 receptors on liver cell types, it is believed that cholangiocytes express the greatest receptor concentration followed by hepatocytes. The virus may reach and infect the intestine through the bile and then cause a secondary intestine infection [49]. D) Drug-induced liver injury (DILI) may involve the direct hepatotoxic effects of the drugs or may include the underlying effects of steatogenic drugs (see text). Several studies report that the extent of liver inflammation has been correlated with antiviral and anti-inflammatory therapies administered for the management of COVID-19 during the pandemic[63]. E) While disrupting various other functions of hepatic cells, COVID-19 may also dysregulate liver biochemistry in infected individuals. The so far published data estimate that up to 30 % of SARS-CoV-2 infected patients demonstrate elevated ALT or AST, LDH, and GGT levels in their liver function panel[49]. F) Pre-existing liver diseases (e.g., ALD, CLD, NAFLD/NASH, hepatic fibrosis, cirrhosis, hepatocellular carcinoma, chronic hepatitis B and C-induced hepatic decompensation, and ascites) may exacerbate COVID-19 outcomes in SARS-CoV-2 affectees and vice versa [175]. G) Many studies allude direct impact of SARS-CoV-2 on hepatocytes as virus-induced direct hepatic damage by several mechanisms (e.g., hepatic congestion, ischemic-hypoxic damage); however, pathological mechanisms and clinical impact of direct SARS-CoV-2 infection on hepatic cells remain elusive[56]. ACE2; angiotensin-converting enzyme 2, SARS-CoV-2; severe acute respiratory syndrome coronavirus 2, COVID-19; coronavirus infectious disease 19, GM-CSF; granulocyte–macrophage colony-stimulating factor, IL-6; interleukin-6, CD; cluster of differentiation, TNF- α; tumor necrosis factor-alpha; IFN- γ; interferon-gamma, DDP_4; Dipeptidyl peptidase-4, ALT; alanine aminotransferase, AST; aspartate aminotransferase, ROS; reactive oxygen species, HDL; high-density lipoprotein, SR-B1; scavenger receptor B type 1 (SR-B1), TMPRSS2; Transmembrane serine protease 2, LDH; lactate dehydrogenase, GGT; gamma-glutamyl transferase, ALD; acute liver disease, CLD; chronic liver disease, NAFLD; non-alcoholic fatty liver disease, NASH; non-alcoholic steatohepatitis.

liver [13]. The development of novel immunotherapeutics may inhibit the binding of the spike (S) protein to ACE2 receptors via *trans*-membrane protease serine 2 (TMPRSS2). Hence, this therapeutic approach may block the virus entry and spread in the hepatocytes, thus protecting the liver from injury [23].

3. Immune system dysregulation in COVID-19

To study SARS-CoV-2 hepatotropism and hepatotropic effects of the virus, both experimental and clinical models are prerequisites. Because the mechanisms of how SARS-CoV-2 directly approaches target liver

cells and direct hepatocyte infection remain inconclusive. One study demonstrates that the viruses reach the hepatocytes by portal circulation and activate the immune responses by activating kupffer cells and initiating up-regulation of host immune system pathways [24]. The up-regulation of pro-inflammatory cytokines due to the involvement of kupffer cells and hypoxia has been reported as the primary cause of liver injuries in patients suffering from COVID-19 as these factors activate the "inflammatory cytokine storm" when pathogenic T cells are activated [25]. A study involving 40 confirmed COVID-19 patients demonstrated that 13 were diagnosed with lymphopenia (i.e., ↓Lymphocyte count) and increased neutrophil count. Similarly, the highest levels of various cytokines (e.g., IL-2, IL4, IL6, IL8, IL10, IL17), TNF-α, IFN- γ, and ferritin were noticed in the peripheral blood, which might play a significant role in liver injury [25]. In addition to that, specific inflammatory markers like GM-CSF (granulocyte–macrophage colony-stimulating factor), macrophages protein 1-alpha, IFN-gamma inducible protein 10, monocyte chemo-attractant protein ten are also elevated due to hyper-activation of the immune responses leading to inflammation in the liver [25]. In addition, the disrupted coagulation profile (i.e., prothrombin time), elevated plasma levels of troponin and N terminal proB type natriuretic peptide (NT- pro-B NP), and D-dimers can also be observed [25]. Some studies also found elevated inflammatory biomarkers, cardiac & muscle injury indicators, LFTs (liver function tests), and RFTs (renal functional tests) along with abnormal coagulation profiles in COVID-19 patients with liver injuries [13].

4. The trajectory of liver function panel is pretty mind-boggling in COVID-19 patients

Multiple published studies have characterized the involvement of liver biochemistry abnormalities in the presentation of COVID-19 severity and frequency, and a few correlates abnormal liver function tests (LFTs) with increased hepatic ailments or mortalities [2,26–31] (Table 1). Aminotransferase (AST & ALT) elevation is the most common liver biochemistry abnormality observed in COVID-19 patients, and multiple studies report that AST levels are more frequently elevated than ALT [18,32–36]. Alkaline phosphatase levels rarely fluctuate, and elevations in bilirubin levels have less commonly been observed. Elevations in GGT levels have been documented less; however, one study reported in nearly 50 % of COVID-19-infected subjects [37]. More precisely, the trajectory of liver biochemistry projects elevation in liver AST & ALTs with rare severe hepatic injuries for COVID-19 during hospitalization, and LFT abnormalities have been reported more frequently in patients with more severe COVID-19 [29,37].

The underlying causes of abnormal liver biochemistries in COVID-19 affectees may be due to immune-mediated inflammatory responses, drug-induced liver injury (DILI), hepatic ischemia, extrahepatic release of aminotransferases, and possible direct cytopathic effects of the viral infection on hepatocytes [38,39]. Furthermore, in some cases, liver biopsy specimens were also characterized by non-specific findings, including steatosis, mild lobular or portal inflammation, and vascular pathology [40]. Elevations of serum AST levels among COVID-19 hospitalized patients positively correlate with ALT but have not been associated with markers of muscle breakdown metabolites (e.g., creatine kinase) or systemic inflammation (e.g., C-reactive protein (CRP) and ferritin)) [4,29]. It might infer that elevated hepatic enzymes in COVID-19-infected individuals could result from direct haptic injury, although SARS-COV-2-associated rhabdomyolysis is rarely reported [41]. Similarly, the elevation of AST often exceeds ALT during the viral infection course, which could be attributed to an atypical classic hepatocellular pattern of hepatic injury outside the COVID-19 contexts and may be due to ALD, DILI (e.g., lamotrigine, acetaminophen), ischemic hepatitis and cirrhosis [29]. The ample understanding of an AST elevation during COVID-19 progression remains incompletely defined; however, it could involve COVID-19-related mitochondrial dysfunction[40]. Microthrombotic disease may also result from virus-induced liver steatosis and altered hepatic perfusion [42]. A study examining biopsy and autopsy specimens reveals 29 % of the prevalence of hepatic vascular thrombosis among COVID-19 patients [43]. Multiple studies report venous and arterial thromboses as well-categorized clinical features of COVID-19 involving elevations in hepatic biochemistries [4]. Notably, no comprehensive studies have been documented to map the pattern of LFTs studies throughout the COVID-19 pandemic. Systemic hypoxia could also be a contributing factor, and AST elevations might be linked to other viral pneumonia (e.g., influenza A infection due to the H1N1 influenza virus). Influenza A infection may enhance AST levels in COVID-19 while diminishing peripheral oxygen saturations [44].

5. The prognostic significance of the elevated liver function profile is still debatable in COVID-19 patients

The prognostic significance of elevated LFTs in COVID-19-infected individuals is currently debated. Some clinical studies highly associate LFTs with severe infection outcomes, including shock, ICUs admissions, and mechanical ventilation [27,45–49]. On the other hand, some reports claim bias on these findings and demonstrate no apparent associations or likelihood between elevated liver enzymes, infection severity, and mortality [46,50,51]. However, some allude that abnormal LFTs, in particular, AST and ALT levels five times greater than the upper limit of normal, may be highly associated with an increased risk of death [51–54]. In this scenario, the prognostic significance of abnormal liver biochemistries could be attributed to robust host response and off-label aggressive therapies among those with severe COVID-19 illnesses [55] (Table 1).

The first report with elevated ALT, AST, and LDH enzyme levels was reported in early 2020 in 43 % of the 99 COVID-19 cases from Wuhan, China [31]. After that, this aspect of hepatic involvement in COVID-19 severity was much discussed and explored worldwide. Several clinical findings and autopsy studies demonstrate already elevated levels of the AST and ALT enzymes before the onset of COVID-19. However, an isolated elevation of these enzymes alone could be the indirect expression of systemic inflammation while suggesting that hepatic dysfunction during COVID-19 might be an expression of worse disease evolution [4,56]. The first clinical data from Wuhan, China, during the COVID-19 outbreak, favors this aspect, where 2–11 % of individuals had hepatic comorbidities, 14–53 % had abnormal serum aminotransferases levels during infection, and the rate of hepatic dysfunction was more in patients with the most severe clinical picture of the infection [57–59]. In another study of 417 COVID-19-infected Chinese patients, 76.3 % had abnormal liver function tests (ALT, AST, total bilirubin, GGT), and 21.5 % were noticed with hepatic injuries during the first and second weeks of their hospital admittance [60]. The patients with abnormal LFTs also had higher risks of progressing to severe hepatic morbidities. Hence, during hospitalization, the clinicians were concerned and carefully monitored the detrimental effects of certain COVID-19 medications on liver injury [60]. Acute hepatic injury was demonstrated in 15.4 % of 187 confirmed COVID-19 patients in Wuhan, China, along with characteristic GIT symptoms without clinically evident respiratory illnesses [61,62]. Furthermore, abnormal LFT levels were not found to be involved in the emergence of any specific symptom during COVID-19.

The observations from COVID-19 patients admitted to ICUs or standard care units demonstrated that one-third of infected individuals had elevated serum levels of ALT, AST, LDH, creatine kinase or myoglobin, abnormal PT, and high GGT during infection progression [54]. An extensive multicenter retrospective analysis of Chinese adults infected with SARS-CoV-2 explored a dynamic pattern of hepatic injury involving the first elevation of AST, followed by ALT in critically ill patients, and mild fluctuations of total bilirubin levels regardless of infection severity [54]. However, abnormal AST levels were strongly associated with the mortality risk in this patient cohort. Some studies also reported hyperbilirubinemia in 11 % to 18 % of cases [26,31]. However, a clear and severe cholestatic pattern was not seen during the

Table 1
Summary of selected studies deciphering abnormal liver biochemistries and their association with severe COVID-19 outcomes and death.

Laboratory test	COVID-19 studies	Study design	Study region and patient demographics and clinical characteristics	Abnormal liver biochemistry findings (% of patients)	Association with severe disease progression	Association with mortality
AST	Richardson et al. (May 2020) [2]	Case series	USA; $n = 5700$; COVID-19 plus hypertension ($n = 3026$); SARS-CoV-2 plus obesity (($n = 1737$); SARS-CoV-2 plus diabetes (($n = 1808$)	**16 %-58 %** Richardson et al. (May 2020), Guan et al. (Apr 2020), Cai et al. (Apr 2020), Huang et al. (Feb 2020), Chen et al. (May 2020), Chen et al. (Feb 2020), Xu et al. (Feb 2020)	Yes Cai et al. (Jul 2020), Bloom et al. (Mar 2021), Huang et al. (Feb 2020), Chen et al. (May 2020)	Yes Deng et al. (Jun 2020)
	Guan et al. (Apr 2020) [59]	Retrospective analysis	China; $n = 1099$; COVID-19 plus coexisting illness (hypertension and COPD) in 23.7 % of participants			
	Cai et al. (Apr 2020) [27]	Cross-sectional study	China; $n = 417$; COVID-19 plus diabetes (($n = 12$) hypertension ($n = 25$) and liver disease ($n = 4$)			
	Cai et al. (Jul 2020) [28]	Retrospective analysis	China; $n = 298$; COVID-19 plus diabetes (6.4 %), hypertension (12.8 %), cardiovascular disease (3.7 %), liver disease (2.7 %), or malignancies (1.3 %)			
	Bloom et al. (Mar 2021) [29]	Retrospective cohort analysis	USA; $n = 60$; COVID-19 plus CLD ($n = 4$), cirrhosis ($n = 1$) obese ($n = 48$), diabetes ($n = 14$), coronary artery disease ($n = 11$) and abnormal liver biochemistry on admission ($n = 41$)			
	Huang et al. (Feb 2020) [30]	Retrospective cohort analysis	China; $n = 41$; COVID-19 plus diabetes (($n = 8$), hypertension ($n = 6$), and cardiovascular disease ($n = 6$)			
	Chen et al. (May 2020) [31]	Retrospective, single-center study	China; $n = 99$; COVID-19 plus cardiovascular and cerebrovacular illness ($n = 40$), endocrine system disease ($n = 13$) and malignant tumor (($n = 1$)			
	Xu et al. (Feb 2020) [33]	Retrospective case series	China; $n = 62$; COVID-19 plus liver disease ($n = 7$), Hypertension ($n = 5$), and diabetes ($n = 1$)			
	Deng et al. (Jun 2020) [35]	Retrospective cohort analysis	China; $n = 225$; COVID-19 plus hypertension ($n = 40$), diabetes ($n = 17$), and heart disease ($n = 13$)			
ALT	Richardson et al. (May 2020) [2]	Case series	USA; $n = 5700$; COVID-19 plus hypertension ($n = 3026$); SARS-CoV-2 plus obesity ($n = 1737$); SARS-CoV-2 plus diabetes ($n = 1808$)	**13 %-39 %** Richardson et al. (May 2020), Guan et al. (Apr 2020), Cai et al. (Apr 2020), Chen et al. (May 2020), Zhou et al. (Mar 2020)	Yes Cai et al. (Jul 2020), Huang et al. (Feb 2020), Chen et al. (May 2020) No Liu et al. (Mar 2020)	Yes Deng et al. (Jun 2020), Zhou et al. (Mar 2020)
	Guan et al. (Apr 2020) [59]	Retrospective analysis	China; $n = 1099$; COVID-19 plus coexisting illness (hypertension and COPD) in 23.7 % of participants			
	Cai et al. (Apr 2020) [27]	Cross-sectional study	China; $n = 417$; COVID-19 plus diabetes (($n = 12$) hypertension ($n = 25$) and liver disease ($n = 4$))			
	Cai et al. (Jul 2020) [28]	Retrospective analysis	China; $n = 298$; COVID-19 plus diabetes (6.4 %), hypertension (12.8 %), cardiovascular disease (3.7 %), liver disease (2.7 %), or malignancies (1.3 %).			
	Huang et al. (Feb 2020) [30]	Retrospective cohort analysis	China; $n = 41$; COVID-19 plus diabetes ($n = 8$), hypertension ($n = 6$), and cardiovascular disease ($n = 6$)			
	Chen et al. (Feb 2020) [32]	Retrospective observational study	China; $n = 21$; COVID-19 plus hypertension ($n = 2$)			
	Chen et al. (May 2020) [31]	Retrospective, single-center study	China; $n = 99$; COVID-19 plus cardiovascular and cerebrovacular illness ($n = 40$), endocrine system disease ($n = 13$) and malignant tumor (($n = 1$)			
	Deng et al. (Jun 2020) [35]	Retrospective cohort analysis	China; $n = 225$; COVID-19 plus hypertension ($n = 40$), diabetes ($n = 17$), and heart disease ($n = 13$)			

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Table 1 (*continued*)

Laboratory test	COVID-19 studies	Study design	Study region and patient demographics and clinical characteristics	Abnormal liver biochemistry findings (% of patients)	Association with severe disease progression	Association with mortality
	Zhou et al. (Mar 2020) [36]	Retrospective multicenter cohort study	China; $n = 191$; COVID-19 plus hypertension ($n = 58$), diabetes ($n = 36$), and coronary heart disease ($n = 15$)			
Alkaline phosphatase	Cai et al. (Apr 2020) [27]	Cross-sectional study	China; $n = 417$; COVID-19 plus diabetes (($n = 12$) hypertension ($n = 25$) and liver disease ($n = 4$)	**5** % Cai et al. (Apr 2020)	Yes Cai et al. (Jul 2020)	–
	Cai et al. (Jul 2020) [28]	Retrospective analysis	China; $n = 298$; COVID-19 plus diabetes (6.4 %), hypertension (12.8 %), cardiovascular disease (3.7 %), liver disease (2.7 %), or malignancies (1.3 %)			
Total Bilirubin (Tbili)	Guan et al. (Apr 2020) [59]	Retrospective analysis	China; $n = 1099$; COVID-19 plus coexisting illness (hypertension and COPD) in 23.7 % of participants	**11** %−**23** %	Yes Huang et al. (Feb 2020)	–
	Cai et al. (Apr 2020) [27]	Cross-sectional study	China; $n = 417$; COVID-19 plus diabetes (($n = 12$) hypertension ($n = 25$) and liver disease ($n = 4$)	Guan et al.(Apr 2020), Cai et al. (Jul 2020), Chen et al. (Feb 2020)	No Cai et al. (Apr 2020), Chen et al. (May 2020)	
	Cai et al. (Jul 2020) [28]	Retrospective analysis	China; $n = 298$; COVID-19 plus diabetes (6.4 %), hypertension (12.8 %), cardiovascular disease (3.7 %), liver disease (2.7 %), or malignancies (1.3 %).			
	Huang et al. (Feb 2020) [30]	Retrospective cohort analysis	China; $n = 41$; COVID-19 plus diabetes ($n = 8$), hypertension ($n = 6$), and cardiovascular disease ($n = 6$)			
	Chen et al. (Feb 2020) [32]	Retrospective observational study	China; $n = 21$; COVID-19 plus hypertension ($n = 2$)			
	Chen et al. (May 2020) [31]	Retrospective, single-center study	China; $n = 99$; COVID-19 plus cardiovascular and cerebrovacular illness ($n = 40$), endocrine system disease ($n = 13$) and malignant tumor (($n = 1$)			
Albumin	Huang et al. (Feb 2020) [30]	Retrospective cohort analysis	China; $n = 41$; COVID-19 plus diabetes ($n = 8$), hypertension ($n = 6$), and cardiovascular disease ($n = 6$)	**38** %−**98** % Chen et al. (Feb 2020), Chen et al. (May 2020)	Yes Huang et al. (Feb 2020), Chen et al. (May 2020), Liu et al. (May 2020), Liu et al. (Mar 2020)	Yes Zhou et al. (Mar 2020)
	Chen et al. (Feb 2020) [32]	Retrospective observational study	China; $n = 21$; COVID-19 plus hypertension ($n = 2$)			
	Chen et al. (May 2020) [31]	Retrospective, single-center study	China; $n = 99$; COVID-19 plus cardiovascular and cerebrovacular illness ($n = 40$), endocrine system disease ($n = 13$) and malignant tumor (($n = 1$)			
	Liu et al. (May 2020)[34]	Retrospective observational study	China; $n = 78$; COVID-19 plus hypertension ($n = 8$), diabetes ($n = 5$), COPD ($n = 2$) and cancer ($n = 4$)			
	Zhou et al. (Mar 2020) [132]	Retrospective multicenter cohort study	China; $n = 191$; COVID-19 plus hypertension ($n = 58$), diabetes ($n = 36$), and coronary heart disease ($n = 15$)			
	Liu et al. (Mar 2020)[134]	Case series	China; $n = 12$; COVID-19 plus hypertension ($n = 3$), chronic heart disease ($n = 4$)			
Gamma Glutamyl Transferase (GGT)	Cai et al. (Apr 2020)[27]	Cross-sectional study	China; $n = 417$; COVID-19 plus diabetes (($n = 12$) hypertension ($n = 25$) and liver disease ($n = 4$)	**16** % Cai et al. (Apr 2020)	Yes Cai et al. (Jul 2020)	–
	Cai et al. (Jul 2020)[28]	Retrospective analysis	China; $n = 298$; COVID-19 plus diabetes (6.4 %), hypertension (12.8 %), cardiovascular disease (3.7 %), liver disease (2.7 %), or malignancies (1.3 %)			
Prothrombin time (PT)	Huang et al. (Feb 2020) [30]	Retrospective cohort analysis	China; $n = 41$; COVID-19 plus diabetes ($n = 8$), hypertension ($n = 6$), and cardiovascular disease ($n = 6$)	**5** % − **6** % Chen et al. (Feb 2020), Zhou et al. (Mar 2020)	Yes Huang et al. (Feb 2020) No Chen et al. (May 2020)	Yes Zhou et al. (Mar 2020)
	Chen et al. (Feb 2020) [32]	Retrospective observational study	China; $n = 21$; COVID-19 plus hypertension ($n = 2$)			
	Chen et al. (May 2020) [31]	Retrospective, single-center study	China; $n = 99$; COVID-19 plus cardiovascular and cerebrovacular illness ($n = 40$), endocrine system disease ($n = 13$) and malignant tumor ($n = 1$)			
	Zhou et al. (Mar 2020) [132]	Retrospective multicenter cohort study	China; $n = 191$; COVID-19 plus hypertension ($n = 58$), diabetes ($n = 36$), and coronary heart disease ($n = 15$)			

AST; aspartate aminotransferase, COVID-19; coronavirus infectious disease-19, SARS-COV-2, severe acute respiratory syndrome coronavirus-2, ALT; alanine aminotransferase, COPD; chronic obstructive pulmonary disease, CLD; chronic liver disease, GGT; gamma-glutamyl transferase, PT; prothrombin time.

infection. Another study from Guangzhou, China, reported elevated AST and ALT levels (6 % to 22 % and 21 % to 28 % respectively) in COVID-19-infected patients [63].

Interestingly, the studies from Wuhan, China, reported a proportion higher AST levels in 24 % to 37 % of patients as compared to the clinical studies from other regions of China (e.g., From Zhejiang, China, a proportion of 16 % AST abnormalities were reported) [64]. However, genetic and gender differences might be attributed to this scenario because a case series involving six patients documented higher AST levels in males than females (i.e., an average of 66 % *vs*. 35 %, respectively) [63]. Furthermore, these case reports indicated the highest probability of developing hepatic dysfunction in elderly patients. In addition, the elevation of AST and ALT levels was mild, and no intrahepatic cholestasis or liver failure was noticed [63,64]. On the other hand, liver biochemistry abnormalities during COVID-19 might be transient, and elevation of aminotransferase levels could be due to increased enzyme activities of the skeletal and heart muscles. Furthermore, these elevations may not alter hepatic-related morbidity and mortality in COVID-19-infected patients [13].

A further study investigating 5700 hospital-admitted patients in New York, USA, reported admission serologies with frequently elevated AST and ALT levels (58.4 % and 39.0 % of participants, respectively) [2]. Another cohort reported AST and ALT levels elevations in patients with severe COVID-19 [2]. Two studies demonstrated that a higher proportion of patients (44 % and 81 %, respectively) with underlying hepatic diseases had abnormal liver function profiles on hospital admission [27,64]. The AST and ALT elevations were generally modest on admission; however, they were observed more frequently and deranged in one case series (i.e., 93 %) during hospitalization [27–29]. On admission, hepatic impairment is not considered an associated factor for length of stay in the hospital, according to some studies [19,64]; however, it was recorded as a predisposing factor to adverse outcomes with COVID-19 progression in admitted patients [29,37]. Interestingly, no studies correlate abnormal LFTs with gastrointestinal discomfort in COVID-19 affectees [65].

In contrast, the pattern of hepatic injury observed in COVID-19 patients with other viral infections (e.g., HBV, HCV) was found entirely different except in one study that demonstrated a similar pattern of liver damage like SARS-CoV-2 due to influenza (A/H1N1) infection [44,66]. Moreover, the SARS-COV outbreak in 2003 also demonstrated a similar pattern of liver damage [67]. Acute liver diseases (ALDs) and ischemic or congestive hepatic injuries may express a similar pattern of abnormal liver biochemistries (e.g., elevated AST than ALT, with accompanying GGT) [68]. Hence, hepatic injuries in severe COVID-19-affected individuals may involve various potential contributors, including a direct viral infection and other indirect factors like underlying systemic diseases or hepatic biochemistry abnormalities, which must be considered at the initial presentation of the patient to the hospital during infection progression and their clinical management. As mentioned earlier, the direct viral cytopathic effect may also propagate mild COVID-19 to severe infection because of the known presence of ACE2 receptors in hepatocytes as viral RNA was detected in hepatic tissues after confirmed SARS-COV-2 infection [69,70]. Recent studies also explain that mitochondrial proteins may directly interact with the virus; hence it could potentially be a reason for the AST-dominant hepatic injury profile[40]. Similarly, the rapid activation of inflammatory responses also plays a central role in hepatic injury, where immune responses to the virus are associated with high levels of IL-6 production [71]. The rapid elevation of IL-6 levels during COVID-19 is potentially implicated in both the inflammatory and the repair responses in hepatic diseases [72].

6. Clinical implications of COVID-19 for pre-existing liver diseases

Pre-existing liver diseases, including chronic HBV infection, comorbid HBV/HCV infection (increases the risk of enhanced viral RNA replication), NAFLD (due to comorbid diabetes and cardiovascular disorders, and drug-susceptible NAFLD), hepatic cirrhosis, liver transplant, and immunosuppressants, and patients with HCC also represent a potential risk to exacerbate mild viral infection to severe COVID-19 complications [4]. It is because of this fact that underlying liver diseases represent a significant burden in China, as primarily HBV infection, NAFLD, and ALD affect approximately 300 million people in the country, and most of the preliminary studies deciphering pre-existing liver disease impact on COVID-19 severity were reported from China [13,73]. A similar trajectory of hepatic disorders associated with underlying metabolic disorders is frequent in resource-replete Western industrialized nations [74–76]. The literature has also documented possible crosstalk between SARS-CoV-2 infection and metabolic disorders to propagate hepatic steatosis. Similarly, NAFLD is considered the most common hepatic illness in European nations and documented a rising trend with a median of 20 % worldwide [77]. In the US, NAFLD prevalence ranges from 10 % to 46 % in different States among the different fractions of the population according to genetics, lifestyles, and healthcare services access [4] **(**Table 2**)**. A study by Ji et al. demonstrated that COVID-19 and pre-existing NAFLD in 202 patients developed hepatic injuries on hospital admission and during hospitalization (50 % and 75 % cases, respectively) [20]. NAFLD, higher body mass index, old age, and underlying hepatic morbidities were marked as contributing factors to COVID-19 progression [13,78]. Furthermore, the study inferred that patients with NAFLD were more susceptible to COVID-19 and SARS-CoV-2-associated hepatic complications [20]. Such patient populations may contribute to higher risks of developing steatohepatitis as NAFLD progresses in the long run. In addition, a pre-existing NAFLD could be more aggravated by inflammatory cytokines released upon COVID-19 infection [20,79]. Surprisingly, ACE2 expression was reported to be remarkably increased in hepatic injury both in humans and rats, which could be in response to increased hepatocellular hypoxia, another contributing factor to developing NAFLD by some other studies [4,79].

6.1. *Pre-existing NAFLD may exacerbate the COVID-19 course*

The studies document that pre-existing NAFLD in COVID-19 patients could be a potential risk of a severe course of viral infection because of NAFLD-associated metabolic comorbidities or abnormalities (e.g., diabetes mellitus, hypertension, and obesity) [78]. A study from New York involving more than 5000 patients demonstrated hypertension, obesity, and diabetes as the most common illnesses in COVID-19-affected patients [2]. Furthermore, obesity was noticed as the highest risk factor for requiring mechanical ventilation. The patient pool comprised more than 23 % of Hispanics more prone to NASH; contrary to previous reports, African Americans have a higher mortality rate due to COVID-19 and are even less likely to have NASH [2,5]. In an early investigation of 324 COVID-19-infected individuals from China, 70 patients (21.6 %) were diagnosed with fatty liver on computer tomography (CT) scan, which represented a higher percentage of the severe COVID-19 cases than the general prevalence of NAFLD in the population [19]. In another study reported from two COVID-19-designated hospitals in China, NAFLD was assessed in COVID-19-infected patients using hepatic steatosis index (HSI) or abdominal ultrasound examination [20]. The patients were evaluated as having stable and progressive COVID-19, and interestingly NAFLD was found to be highly associated with COVID-19 progression (i.e., worsening respiratory distress or lung CT scan during hospitalization) with an odds ratio of 6.4 (95 % CI: 1.5–31.2). Albeit higher BMI was also linked to COVID-19 progression, other comorbidities (e.g., diabetes, hypertension, and metabolic disorders) were not evaluated as individual contributing factors to increasing COVID-19 severity [20]. Furthermore, NAFLD may also increase the risk of COVID-19 progression, liver biochemistry abnormalities, an infection course during patient admission, and prolonged duration of SARS-CoV-2 shedding (17 *vs.* 12 days) as compared to individuals without NAFLD [20]. From a pathogenic

Table 2
Summary of selected studies depicting COVID-19 outcomes in patients with liver diseases, viral hepatitis, and liver transplantation.

COVID-19 studies	Study design	Study region	Demographic and clinical characteristics of patients	Association with mortality	Disease severity and mortality risks
Marjot et al. (Oct 2020) [148]	Large international Registry study	29 countries	COVID-19 plus cirrhosis (n = 386); COVID-19 plus CLD without cirrhosis (n = 359); COVID-19 plus non-CLD (n = 620); COVID-19 plus CLD (n = 745); COVID-19 plus ALD; COVID-19 plus HCC (n = 48); COVID-19 plus HBV (n = 96); COVID-19 plus HCV (n = 92)	Yes	Overall mortality based on Child-pugh class A (CP-A) score; 19 %, CP-B; 35 %, CP-C; 51 %. Increased risk of death cirrhosis *vs* CLD without cirrhosis: CP-A (OR 1.9, 95 % CI 1.03–3.5), CP-B (OR 4.1, 95 % CI 2.4–7.77), CP-C (OR 9.32, 95 % CI 4.80–18); ALD independent risk factor for mortality in COVID-19 plus ALD (OR 1.79, 95 % CI 1.03–3.13); COVID-19 plus HCC→ no independent association with mortality; COVID-19 plus HBV & HCV→ no independent association with mortality
Lee et al. (Oct 2020) [175]	Multicenter study	South Korea	COVID-19 plus with liver-related comorbidities (4.7 %); COVID-19 plus liver cirrhosis (1.4 %); COVID-19 plus cirrhosis with severe pneumonia (4.5 %); COVID-19 plus cirrhosis with non-severe pneumonia (0.9 %)	Yes	Overall less survival rate in COVID-19 plus liver cirrhosis as compared to COVID-19 without liver cirrhosis (log-rank test, $P = 0.003$); Disease severity risk in patients with COVID-19 plus liver cirrhosis (OR, 4.52; 95 % CI, 1.20–17.02; $P = 0.026$) and death (hazard ratio, 2.86; 95 % CI, 1.04–9.30; $P = 0.042$)
Vázquez-Medina et al. (Aug 2022) [176]	Retrospective study	Mexico	COVID-19 plus metabolic disorders (NAFLD, MAFLD & AF; $n = 359$)	Yes	Mortality rate COVID-19 plus NAFLD than COVID-19 without NAFLD (55 % *vs.* 38.3 %, $P = 0.02$); Disease severity risk in COVID-19 plus MAFLD (44.09 % *vs.* 20 %, $P = 0.001$) and COVID-19 plus NAFLD (40.51 % *vs.* 20 %, $P = 0.01$) than the control group. A significant association between COVID-19 plus NAFLD, advanced fibrosis, and death ($P = 0.01$). A significant interaction between COVID-19 plus MAFLD, advanced fibrosis, and death ($P = 0.006$) and intubation ($P = 0.049$).
Shao et al. (Feb 2021) [177]	Retrospective study	China	COVID-19 plus CLDs, metabolic disorders, and viral hepatitis (n = 1520); COVID-19 plus CLD (n = 127; 8.35 %); COVID-19 plus HBV (n = 64); COVID-19 plus CHC (n = 20), COVID-19 plus FLD (n = 37), COVID-19 plus cirrhosis (n = 6)	Yes	Overall higher rates of mortality (21.74 %; $P<0.001$) associated with CLDs and ICU admission (26.71 %; $P<0.001$); Increased risks for COVID-19 severity with FLD and cirrhosis; COVID-19-related mortality significant with hypertension between the groups (27.56 % with CLD *vs.* 37.19 % without CLD; $P = 0.034$)
Singh et al. (Oct 2022) [178]	Multicenter research network study	USA	COVID-19 infected patients (n = 2780); COVID-19 plus preexisting liver disease (n = 250; 9 %); COVID-19 plus cirrhosis (n = 50; 1.8 %); COVID-19 plus NAFLD (42 %)	Yes	Overall higher risk of mortality in the COVID-19 plus LD group (RR 2.8; 95 % CI,1.9–4.0; $P < .001$); COVID-19 plus cirrhosis had an even higher relative risk of mortality (RR, 4.6; 95 % CI, 2.6–8.3; $P < .001$); Higher risk of hospitalization for COVID-19 plus LD group
Moon et al. (Sep 2020) [179]	Two international registry	21 countries	COVID-19 plus cirrhosis (n = 103); COVID-19 plus CLD (n = 49); COVID-19 plus NAFLD (22.4 %); COVID-19 plus ALD (19.7 %); COVID-19 plus HBV (11.8 %); COVID-19 plus HCV (10.5 %)	Yes	Higher mortality in COVID-19 plus cirrhosis (39.8 %) and increased disease severity (27.8 %); Mortality in COVID-19 plus CLD but without cirrhosis (12.2 %); CP-A (23.9 %), CP-B (43.3 %) and CP-C (63 %); mortality in COVID-19 plus hepatic decompensation (63.2 %) compared to 26.2 % without it.
Ji et al. (Aug 2020) [20]	Retrospective study	China	COVID-19 plus NAFLD (n = 202); COVID-19 plus hepatic injury (n = 101; 50 %; n = 152; 75.2 %) on admission and during hospitalization respectively	Yes	Higher risk of disease progression in COVID-19 plus NAFLD (6.6 %; n = 5 *vs.* 44.7 %; n = 34/76; $p <0.0001$)
Ge et al. (Aug 2020) [180]	National COVID cohort study	USA	COVID-19 plus cirrhosis (n = 8941; 4 %); COVID-19 plus cirrhosis and NAFLD (n = 3492; 39 %); COVID-19 plus cirrhosis and HCV (n = 1707; 19 %); COVID-19 plus cirrhosis and AALD (n = 2518; 28 %); COVID-19 plus cirrhosis and HBV (n = 399; 4 %); COVID-19 plus cirrhosis and AIH (n = 303; 3 %); COVID-19 plus cirrhosis and decompensated cirrhosis (n = 5993; 67 %)	No	30-day death rates increased progressively from 3.9 % in COVID-19-negative plus cirrhotic to 8.9 % in COVID-19-positive plus cirrhotic patients (Univariate analysis: HR 2.37; 95 % CI, 2.18–2.58; $P < .01$: multivariate analysis: aHR 2.38; 95 % CI 2.18–2.59; $P < .01$); 90- day death rates increased progressively from 3.9 % in COVID-19-negative plus cirrhotic to 8.9 % in COVID-19-positive plus cirrhotic patients; For decompensated, COVID-19-positive plus cirrhosis had 2.20 aHR of death within 30 days (aHR 2.20; 95 % CI, 2.01-2.42; $P < .01$) compared to COVID-19 negative plus cirrhotic patients.
Bhoori et al. (Apr 2020) [181]	Prospective analysis	Italy	COVID-19 plus long-term (>10 years) liver transplant recipient ((n = 111); COVID-19 plus short-term (<2 years) liver transplant recipient (n = 40); Full immune suppression in COVID-19 plus long-term (>10 years) liver transplant recipient (n = 11;10 %); Full immune suppression in COVID-19 plus short-term (<2 years) liver transplant recipient (n = 28; 70 %) receiving ciclosporin concentration more than	Yes	COVID-19-related deaths in COVID-19 plus long-term (>10 years) liver transplant recipient (n = 3; 3 %); uneventful progression of COVID-19 in COVID-19 plus short-term (<2 years) liver transplant recipient (n = 3; 7.5 %)

(*continued on next page*)

Table 2 (*continued*)

COVID-19 studies	Study design	Study region	Demographic and clinical characteristics of patients	Association with mortality	Disease severity and mortality risks
			150 ng/mL or tacrolimus concentration more than 5 ng/mL		
Pereira et al. (Apr 2020) [91]	Multicenter study	USA	COVID-19 plus solid organ transplant recipients (n = 90); kidney recipient (n = 46); lung recipient (n = 17); liver recipient (n = 13); heart transplant (n = 9); dual-organ transplants (n = 5)	Yes	Overall mortalities due to COVID-19 (n = 16 (18 %); 24 % hospitalized; 52 % ICU); Severe COVID-19 outcomes in transplant recipients
Molnar et al. (SEP 2020) [182]	Multicenter cohort study	USA	COVID-19 plus SOT and non-SOT patients (n = 386); COVID-19 plus SOT patients (n = 98); COVID-19 plus non-SOT patients (n = 288)	Yes	Propensity score for death within 28 days of ICU admission in COVID-19 plus SOT and non-SOT patients (40 % and 43 %, respectively; RR 0.92; 95 % CI: 0.70-1.22); higher risk of acute kidney injury in SOT *vs* non-SOT patients (37 % *vs* 27 %; RR 1.34;95 % CI: 0.97-1.85)
Polak et al. (Oct 2020) [183]	European liver transplant registry	28 European countries	COVID-19 plus LT candidate (n = 57); COVID-19 plus LT recipients (n = 272)	Yes	Crude rate of mortality among COVID-19 plus LT candidate (n = 10; 18 %) and COVID-19 plus LT recipients (n = 36; 15 %)
Marjot et al. (Jan 2021) [149]	International registry study	35 countries	COVID-19 plus AIH (n = 70); 86 % immunosuppression; COVID-19 plus non-AIH CLD (n = 862); COVID-19 plus non-CLD (n = 769)	No	Immunosuppression→not an independent risk factor for mortality in COVID-19 plus AIH patients; equal mortality rates in COVID plus AIH *vs.* COVID-19 plus non-AIH with CLD; higher disease severity risks (hospitalization) in COVID-19 plus AIH compared to COVID-19 with non-CLD.

COVID-19; coronavirus infectious disease 19, CLD; chronic liver disease, ALD; alcohol-related liver disease, HBV; hepatitis B virus, HCV; hepatitis C virus, HCC; hepatocellular carcinoma, CP-A; Child-Pugh score -A, CP-B; Child-Pugh score -B, CP-C; Child-Pugh score -C, OR; odd ratio, CI; confidence interval, NAFLD; non-alcoholic fatty liver disease, MAFLD; metabolic associated fatty liver disease, AF; advanced fibrosis, CHC; chronic hepatitis C, FLD; fatty liver disease, ICU: intensive care unit, LD; liver disease; AALD; alcohol-associated liver disease, AIH; autoimmune hepatitis, HR; hazard ratio, aHR; adjusted hazard ratio, SOT; solid organ transplantation, LT; liver transplant.

etiology, the inflammatory pathways and their cytokine mediators common to NAFLD and COVID-19 might increase the risk of hepatic inflammation in pre-existing NAFLD subjects and further exacerbate hepatic injuries if these patients are reinfected with COVID-19. Multiple studies reported from China validate this hypothesis, where NAFLD was highly associated with high risks of COVID-19 progression and longer SARS-CoV-2 shedding time than individuals without NAFLD [20,27,29,30,60]. Notably, some studies consider non-cirrhotic patients with NAFLD or NASH as cardio-metabolic subjects having very high risks of COVID-19 complications [13,35,36]. Metabolic-associated fatty liver disease (MAFLD) based on obesity also increased 6-fold risk of severe COVID-19 in 214 patients, as reported in a study from China [80]. The risk even persisted after adjusting the demographic characteristics of the patients and metabolic comorbidities (e.g., DM, hypertension, and dyslipidemia). From a mechanistic point of view, increased ACE2 expression on hepatocytes and impaired innate immune system responses in NAFLD could be the potential mechanisms for severe COVID-19 outcomes; however, they are still elusive [4,79]. Hence the management of patients with NAFLD and comorbidities (e.g., diabetes, obesity, and hypertension) need much attention to prevent high risks for COVID-19 progression and severe outcomes.

6.2. *COVID-19 may worse hepatic cirrhosis to hepatic decompensation*

SARS-COV-2 infection potentially increases the risk of hepatic decompensation and hepatocellular carcinoma (HCC) in patients with hepatic cirrhosis [5]. The studies demonstrate that hepatic cirrhotic patients with COVID-19 have higher incidences of propagating hepatic decompensation and risk of mortality [29]. The COVID-19 pandemic has also interrupted the clinical management of hepatic cirrhosis in patients with or without COVID-19. Global efforts to evaluate the severity of hepatic cirrhosis, mortality, and new incidences with complications of cirrhosis in COVID-19 patients are underway, albeit the data are limited [5]. The small data set collected from combined COVID-HEP and SECURE-Cirrhosis registries indicates significantly higher morbidities (6 %) than overall mortality reported by the CDC for such patient populations [5]. Alcoholic use disorders were reported as the most responsible factor for mortalities, followed by NASH and hepatitis B virus infection [2]. The state of decompensation was noticed in 38 % of patients during their cirrhotic state progress toward hepatic decompensation (e.g., worsening ascites, encephalopathy, or acute renal injury) [5]. Furthermore, it was revealed that COVID-19-affected individuals were at higher risk for hepatic decompensation because of highly significant cytokine activation, cytokine-induced hepatocyte apoptosis, and necrosis-diminished liver reserve [81]. The findings also explore the undermining of the severity of the disease in patients with hepatic cirrhosis [5]. Therefore, patients with hepatic decompensation should be tested on a priority basis for SARS-COV-2 infection as a potential cause.

Besides the potential impact of the virus to cause complications in impaired hepatic patients, the pandemic also significantly disrupted cirrhotic surveillance and hepatic care flow during peak times in 2020 [82]. The healthcare systems were overburdened, and routine community healthcare services in almost every country were stopped or shifted to diagnose and treat COVID-19. Screening for esophageal varices was considered nonurgent and postponed except for highest-risk patients with variceal bleeding where endoscopy or follow-up band ligation allowed. Similarly, AASLD guidance also deferred HCC surveillance for two months after discussing the risk–benefit ratio while doing so for the patient [9]. Ultimately, this delay in linkage to care potentially increased the risks for variceal bleeding and later-stage HCC occurrence in COVID-19 hepatic impaired patients. Similarly, deferring or delaying elective procedures, including liver transplantation and locoregional therapy for HCC in many countries, results in progressions of hepatic diseases and overall mortality [82]. Alternative diagnostic and management strategies were emphasized, including serum-based markers, outpatient interventions (e.g., albumin infusions), integrated telehealth, and nonselective beta-blockers [83].

6.3. *Clinical implications of COVID-19 in liver transplant recipients*

A positional paper from EASL-ESCMID based on the clinical assessment of Chinese patients documented that chronic viral hepatitis infections (HBV and HCV) would not correlate to the risks of severe COVID-19 outcomes [78]. However, individuals with a pre-existing advanced hepatic illness and individuals waiting for liver transplants

(LT) coinfected with HBV/or HCV may face an increased risk or severe COVID-19 outcomes after transplantation [9,78]. However, It seems complicated to assess and associate infection severity and outcomes in LT patients infected with COVID-19 due to patient demographics and patterns of comorbidity [4]. Furthermore, geographical and chronological variations in assessment procedures, variable thresholds for diagnoses, and extent of individual exposure also put hurdles to evaluating the susceptibility of LT recipients to COVID-19. Interestingly, this fraction of the population is of paramount interest because most of them are frequently exposed to healthcare facilities, may contain concurrent comorbidities, and a majority have an absolute requirement for chronic immunosuppression before LT [4,84,85].

In this context, data from two studies conducted in Spain and the UK reveals that COVID-19 diagnoses are easier among LT recipients than the general infected populations. However, this frequent diagnosis is more attributable to close patient monitoring and a lower threshold for viral testing in the LT settings [86,87]. Therefore, further data from the rest of the world will clarify our understanding in this area, provided that a careful association exists with contemporary epidemiology. It is vital because not all LT recipients diagnosed with SARS-CoV-2 developed severe COVID-19, as 6 % were described as asymptomatic in the Spanish case series ($n = 111$), and 14 % had neither respiratory nor GI symptoms in a multinational case series ($n = 151$) [86,88]. Similarly, a German study pointed out no previous symptoms consistent with SARS-CoV-2 infection in 5 of 8 LT recipients with detectable IgG response who were previously exposed to SARS-CoV-2 [89]. However, in LT recipients who developed symptoms of COVID-19, their clinical manifestations of the respiratory system were more similar to those generally infected with SARS-CoV-2 infection [90,91]. Fever, cough, and dyspnea were noticed following the first week of the SARS-CoV-2 infection. One significant difference was the higher frequency of GI symptoms among LT recipients, where diarrhea was reported as much more significant in two early patient cohorts (31 % and 42 %, respectively) [90,91]. A propensity-matched analysis also confirmed the same proportion of GI symptoms in LT than those without[88]. On the other hand, hospitalized LT recipients with severe COVID-19 outcomes also showed marked elevations in their ferritin, D-dimer, and IL-6 levels on laboratory assays alongside lymphopenia. Chest radiology also showed well-recognized diffused parenchymal opacities without pleural effusion [90].

6.4. Liver transplantation outcomes in COVID-19 affectees are pretty complicated

The assessment of liver transplantation outcomes in COVID-19-affected individuals does not seem easy because the patient demographic characteristics and pattern of comorbidity are quite complicated within this patient population. Certain other factors may also contribute to complicating this assessment. For example, LT recipients are predominantly male and more likely to have renal impairment, DM-type II, and obesity than the general population [92–95]. The median age of LT recipients is also increasing by 56 years in the USA and the UK[96]. All these baseline patient characteristics are well reported to be associated with an increased risk of severe outcomes following SARS-CoV-2 infection and equally apply to LT recipients. For instance, LT recipient age and burden of comorbidity index (e.g., Charlson comorbidity Index) significantly correlated with mortality or severe infection course within LT recipients cohort studies [86,87]. Similarly, although minor LT recipients have significant hepatic dysfunction, if present, this could be an additional risk factor for severe COVID-19 outcomes in LT recipients [4,97]. While considering LT a risk for severe COVID-19, adjustment for concurrent comorbidity is needed. The available clinical data with concurrent comorbidity adjustments suggest no increased risks of severe COVID-19 outcomes for LT recipients compared to non-LT recipients. It seems true when comparing the two national LT and non-LT patient cohorts in Spain [86]. However, the derived data from registry work are open to reporting biases, even though the fatality rates from cohort studies are broadly consistent at around 20 % from the first wave of the COVID-19 pandemic [90,98]. The clinical record of patients from the UK also confirmed an increased mortality risk from COVID-19 in CLD patients, but no statistically significant difference in death rates was noticed in non-renal solid organ recipients [99]. Furthermore, considering the adjustment of concurrent morbidity (e.g., the Charlson Comorbidity Index) and its relative importance, pooled data from two large cohorts of COVID-19-infected LT recipients did not report any death for patients with a Charlson Comorbidity Index of 0 (the index is attributed for patient age greater than 50 years and not for LT itself) [88].

Some clinical studies also interpret that LT and associated immunosuppression and other plausible understandings do not pose an increased risk of poor outcomes in COVID-19 progression. For example, Firstly, adaptive immune responses are primarily limited by LT-associated immunosuppression rather than innate immune responses, which are paramount in determining SARS-CoV-2 infection outcomes [100]. The only innate immune response strongly linked to poor outcomes in SARS-CoV-2 infection upon LT-associated immunosuppression is the “specific deficits in the type I interferon innate response” [101,102]. Second, corticosteroid therapy (e.g., high-dose dexamethasone) induced immunosuppression may reduce mortality in severe SARS-CoV-2 infection [103]. Third, as reported and clinically proven for other viral strains (e.g., SARS-CoV- or MERS), LT and associated immunosuppression did not appear as the highest risk factor for severe infection outcomes [104]. Conversely, hepatic comorbidities confer the highest risk of severe infection in SARS-CoV-2 infected patients, as described in this review.

6.5. The impact of immunosuppressants and immunomodulatory therapies is still elusive in COVID-19 affectees

Unfortunately, the impact of immuno-modulatory/immunosuppressant therapies on SARS-CoV-2 infection and the implications of COVID-19 on immunosuppressed patients with CLD are not entirely elucidated. However, the available data only represent insights from solid organ transplant (SOT) patients and patients who were immune-suppressed for other clinical procedures. For example, a preliminary report of SOT recipients hospitalized with SARS-CoV-2 infection showed remarkably higher rates of infection severity, mechanical ventilation, and death, albeit the degree of patient illness was mild [91]. Conversely, the viral infection in SOT recipients did not show an increase in severe illness or hospitalization in one study from Italy [104]. Similarly, using immuno-modulating agents for other concomitant disorders (e.g., rheumatological disorders) did not increase the risk for severe SARS-CoV-2 infection [105]. Therefore, the use of immuno-modulating agents in COVID-19 affectees is emphasized by the AASLD and EASL guidelines, and a reduction in drug doses is not imperative even in the absence of viral infection and specific subsets of illnesses like lymphopenia, bacterial or fungal superinfection [9,106]. However, the dosage of immunosuppressive therapy (e.g., azathioprine, mycophenolate, and calcineurin inhibitor) may be reduced in severe lymphopenia or worsening pulmonary status [107].

7. Viral infections and hepatic comorbidities may alter liver function profile in COVID-19 affectees

Individuals with concomitant infections (e.g., HIV, HBV, and HCV) either alone or in coinfections (i.e., HIV/HCV, HIV/HBV, HBV/HCV) and the impact of the COVID-19 pandemic on the progression of these infections and associated hepatic comorbidities is still elusive [108]. Vulnerable and high-risk populations (e.g., patients who inject drugs, men who have sex with men, incarcerated people, and sex workers) to acquire these viral infections and their continuous observation of COVID-19 is also challenging and demand guidance on issues relevant to the pandemic impact on the progression of viral hepatitis infection

[108]. Both HBV and HCV infection have worldwide prevalence, and unfortunately, HBV is common in China, where the first cases of COVID-19 were reported [108]. Although, the preliminary data reported from China demonstrated a 3 % prevalence rate of underlying CLD in COVID-19-infected patients. However, it did not precisely clue the prevalence of HBV or HCV infections [83]. Concerns still exist about the impact of the COVID-19 pandemic on the course of HBV and HCV infections and associated liver comorbidities. COVID-19 surveillance data from the USA reported infrequent SARS-CoV-2 detection in individuals with HBV or HCV infections. A *meta*-data analysis from the Northeastern USA demonstrated a 0.1 % and <0.1 % prevalence of HBV and HCV infections in COVID-19 patients [2].

In contrast, a large pool of hospitalized patients from Wuhan, China, represented all 2.1 % of HBV infections, including 2.4 % of nonsevere and 0.6 % of severe cases in SARS-COV-2 infected patients [26]. Similarly, a single-center retrospective study from China reported a significantly high proportion of HBV infection (12.2 %; 15/123), a higher percentage of comorbid HBV (relative to HBV-negative patients having higher total bilirubin levels), and a higher mortality rate in COVID-19 patients (13.3 % *vs*. 2.8 %) [26]. In addition, one study reported a background HBV prevalence rate of 6.5 % (n = 2/31) in patients infected with COVID-19 while using corticosteroids as treatment [109].

Interestingly sparse clinical reports involving case series reveal a cross-talk between COVID-19 and HIV infection [110–113]. A study from Barcelona, Spain, demonstrates that approximately 1 % of HIV-infected hospitalized individuals were found COVID-19 positive [110]. Most of them were younger than 50 years, homosexual (men who have sex with men), and their clinical spectrum of infection was similar to HIV negative/COVID-19 positive. Similarly, sporadic reports indicate COVID-19 prevalence in HCV/HIV coinfected patients, and challenging to determine whether HIV mono-infection or HCV/HIV coinfection patients need adjustments to antiretroviral therapy (ART) based on potential drug-drug interactions [114]. Similarly, the neutralizing antibody responses against SARS-CoV-2 may be impaired or delayed in such patient populations. Hence, the frequency of COVID-19 prevalence and its impact on patients who inject drugs (PWIDs) has not been widely established. This patient population is highly vulnerable to the consequences of COVID-19 to several comorbid conditions in PWIDs (e.g., viral hepatitis, heart disease, and renal disease) [115].

Possible precautions are recommended for HBV or HCV therapies in patients with or without SARS-CoV-2 infection and COVID-19 manifestations of abnormalities in hepatic biochemical tests [9]. For example, The AASLD recommends the initiation of HCV therapy in newly identified cases of HCV in patients without a SARS-CoV-2 infection provided that adequate resources are available and those have not been deployed for COVID-19 activities (e.g., Pharmacy services, personal approval for DAA therapy, blood testing services, follow-up facilities through telemedicine or face-to-face) [9,108]. In those with COVID-19 and a recently diagnosed HCV infection, HCV therapy can be deferred until SARS-CoV-2 has cleared; however, already initiated regimens can be continued while monitoring for DDIs [65]. For HBV patients with COVID-19, the risk of HBV reactivation must be considered with medications like tocilizumab and corticosteroids [116]. HBV reactivation after administering tocilizumab and prednisone has been documented; hence prophylaxis against HBV reactivation should be considered [117].

On the contrary, chronic HBV treatment, as per guidelines, can be initiated or continued in newly diagnosed HBV cases regardless of their COVID-19 status [108]. However, caution should always be exercised while initiating COVID-19 therapy in patients with advanced hepatic diseases. Similarly, existing guidelines must be updated and followed to minimize the risk of hepatic decompensation. However, the risk-to-benefit ratio must be weighed out in dealing with the highly lethal condition of COVID-19 [108].

8. COVID-19 outcomes may be worsened in autoimmune hepatitis

COVID-19 outcomes could worsen in patients with autoimmune hepatitis or taking immunosuppressant medications [9,106]. Hence, such patients should be prioritized for SARS-COV-2 screening according to the recent AASLD guidelines. A more aggressive screening approach is required for COVID-19 patients with autoimmune hepatitis or previous liver transplantation according to these guidelines. Furthermore, the liver function profile should not only be considered for a suspected flare or acute cellular rejection but also undergo liver biopsy confirmation [9]. In addition to that, unnecessary drug withdrawal or reduction in drug dosage for a flare of autoimmune hepatic disease would increase the doses of corticosteroids along with the increased magnitude of exposure and risks of SARS-CoV-2 infection [9]. Hence the guidelines recommend tapering off immunosuppressive therapy in COVID-19 patients with hepatic disease but not stopping or discontinuing it except under particular circumstances (e.g., superadded bacterial infection or worsening respiratory failure) [78]. Surprisingly, some studies project the risk of graft rejection while reducing immunosuppression therapy [118,119]. Lastly, disturbances in the liver function profile in LT recipients can be an indirect consequence of SARS-CoV-2, as seen in other situations due to cytokine storm [100]. Hence, hepatic injury entirely based on elevated serum transaminase levels may happen in LT recipients and may associate with mortality; however, it seems less frequent than in comparison patient cohorts in some studies [88,98]. In addition, clinical data are scarce on SARS-CoV-2 infection in those with LT, and numerous issues need to address even though the weight of comorbidity determines SARS-CoV-2 outcomes more than LT status per se in such patient populations [88,98]. Furthermore, as earlier mentioned in this review, an immunosuppressant LT recipient imposes less severe infection outcomes from SARS-CoV-2 than those with an advanced CLD. It might be because international guidelines even supported the continuation of LT programs during the first and second waves of the pandemic.

9. Cardiomyopathies could be a consequence of SARS-CoV-2 infection

A US-based case series demonstrated cardiomyopathies, a well-described consequence of COVID-19 while occurring in 33 % of SARS-CoV-2 affected patients [120]. Therefore, cardiac dysfunction and hepatic congestion could contribute to hepatic injury in severe COVID-19. A bitter consequence of cardiomyopathy could be congestive hepatopathy in COVID-19-affected individuals, commonly associated with elevated aminotransferases and higher GGT levels [121,122]. In addition, severe ischemic hepatitis may be observed in critically ill COVID-19 patients with severe AST-predominant hepatitis [123]. The elevations in alkaline phosphatase levels are infrequently observed in the late stage of COVID-19 progression and could be a clinical spectrum for cholestasis of sepsis, critical illness, or medication effect [124].

10. Use of anti-inflammatory agents and antivirals against SARS-CoV-2 may cause severe hepatic outcomes

Hospitals empirically used many drugs to treat COVID-19 patients under the US FDA emergency use authorization (EUA). Most of these remedies have been reported with a definite risk and pattern of hepatic injury (e.g., acetaminophen, statins, hydroxychloroquine, and remdesivir) [4,13]. Remdesivir, a nucleoside analog inhibitor developed against Ebola virus infection, was effective against SARS-CoV-2 replication *in vitro* [13]. One small report alluded 23 % increase in liver enzymes with the growing use of remdesivir in COVID-19 clinical trials [125]. AASLD and the Asian Pacific Association for the Study of the Liver (APASL) recommend close monitoring of LFTs in CLD patients treated with remdesivir [107].

Furthermore, CLD patients with decompensated cirrhosis and individuals found with five times higher than the upper limit of normal ALT levels should not be treated with remdesivir [107]. The presence of microvascular steatosis and hepatic inflammation could be the underlying causes of liver damage following the administration of off-label drugs to treat the viral infection, as well as the use of antibiotics (macrolides, quinolones) to combat bacterial superinfections and the use of antipyretics or steroids as pain relievers [3,64,126]. Drug-metabolizing enzyme system (e.g., cytochrome *p*-450) in the liver could evolve hepatic toxicities as reported for certain drugs (e.g., azithromycin, lopinavir/ritonavir, hydroxychloroquine, and acetaminophen) [127–130]. Increased odds of hepatic injury were documented with lopinavir/ritonavir administration in one study conducted on 417 laboratory-confirmed COVID-19 patients in Shenzhen, China [27]. These findings were in line with the results of a retrospective study which showed frequent abnormal liver biochemistry with the administration of lopinavir/ritonavir in 148 patients after admission to Shangai hospital, China [64]. Hydroxychloroquine sulfate showed good efficacy and safety *in vitro* and against COVID-19 patients for short periods; however, a few cases of fulminant hepatic failure have been reported with its administration [131,132]. Acute hepatic injury may evolve after macrolide antibiotic administration (e.g., azithromycin) in COVID-19 patients with an average duration of treatment of 4 days and with the clinically evident presentation following about two weeks after drug cessation [133]. COVID-19-infected individuals may suffer from concomitant diseases (DM type I or II or hypertension) and receive antihypertensive therapies, including ACE inhibitors or Angiotensin II type I receptor blockers. The administration of these therapies may overexpress ACE2 expression [13]. Whether this receptor overexpression would facilitate, propagate, or worse, the consequence of COVID-19 is still murky and elusive [134,135].

Similarly, acetaminophen as an antipyretic may mediate hepatic damage, at least in part [135]. COVID-19-infected Individuals having metabolic abnormalities and NAFLD are more prone to drug-induced liver injury (DILI) [13]. The increased expression of cytokine MCP-1 acts as a modulator for DILI and further hits for steatohepatitis in COVID-19 [30,136]. Similarly, COVID-19-infected individuals with NAFLD/NASH may also be more susceptible to DILI or hepatic ischemia with the administration of steatogenic drugs (amiodarone, sodium valproate, tamoxifen, and methotrexate) [3].

11. Impact of COVID-19 vaccines on patients with CLDs

Since the emergence of the COVID-19 pandemic in 2019, the development of protective vaccines progressed at an unprecedented rate where both mRNA (Pfizer/BioNTech BNT162b2, Moderna mRNA-1273) and adenovirus vector-based vaccines (ChAdOx1-nCoV-19, d Gam-COVID-Vac (Sputnik V)) showed clinical promise both in terms of excellent efficacy and marked safety profiles in preventing symptomatic COVID-19 (62–95 %) [137–140]. Many participants were considered during the phase-III clinical trials of these vaccines; however, the ratio of participants with liver diseases was limited and only represented the data of<0.5 % of those enrolled (i.e., 100,000). Currently, most vaccines have been approved for emergency use authorization (EUA) and are in the late stage of getting licensing for regular prophylaxis use. Patients with specific disease states, including CLD, must be considered for vaccine clinical efficacies and safety [141]. Hepatic cirrhosis impairs adaptive immune responses, propagates systemic inflammation, and increases the risks of infection-related morbidity and mortality [142,143]. Hepatic cirrhotic patients exhibit impaired immune responses to existing licensed vaccines for pneumonia and HBV [144,145]. However, the data to justify this notion of poor response against SARS-CoV-2 vaccination is lacking. Hence, it is tough to determine which COVID-19 vaccine type would be more suitable for cirrhotic patients or whether alteration in standard vaccine dose frequencies or timing would be fruitful. The immunogenicity of COVID-19 vaccines in immunosuppressed and LT recipients remains to be determined as multiple reports demonstrate attenuated responses to vaccinations in different disease states [146]. As both mRNA and adenovirus-based vector vaccine platforms contain no live or attenuated virus, no safety concern exists for immunization of hepatic disease cohorts. Although some historical reports on vaccination raise concerns about the development of alloimmunity and graft rejection in SOT recipients; however, no shred of clinical evidence has emerged yet about COVID-19 vaccines in LT [4,146].

Similarly, the highest mortality rates due to COVID-19 in patients with decompensated cirrhosis have been documented; hence these patient cohorts must be highly prioritized for COVID-19 vaccines. As mentioned earlier, LT recipients have comparable mortality due to COVID-19 compared to matched general COVID-19-affected populations, even though higher rates of intensive care admission have been documented for such patient cohorts[88]. Interestingly, ICU admission to LT recipients has been proven comparatively more protective throughout the COVID-19 pandemic due to enhanced social distance measures. Therefore, like decompensated cirrhosis, LT recipients are also a vulnerable population to disseminate SARS-CoV-2; hence should also be prioritized for COVID-19 vaccines regardless to outweigh the potential risks. AASLD guidelines on COVID-19 vaccination (published in January 2021) reflect these principles to prioritize liver disease patients for vaccination [9]. Another challenge to encounter in patients with CLD would be the monitoring for post-vaccination infection, as these vaccines have almost been disseminated globally [4]. It is possible through data mining from international registry platforms (e.g., COVID-Hep, supported by EASL, and SECURE-Liver (supported by AASLD and formerly known as SECURE-Cirrhosis) [71]. This real-world clinical data will facilitate the exploration of mechanistic perspectives of innate and adaptive immune responses after COVID-19 vaccination in pre-existing hepatic diseases and LT subpopulations. Ironically, hepatologists, physicians, and healthcare providers (HCPs) would require a concrete coordinated response to sort out heterogeneity between vaccine candidates, laboratory immune assays, and hepatic disease phenotype in liver disease populations [4].

12. Impact of COVID-19 on liver disease care and research

The devastating impact of the COVID-19 pandemic not only jolts the world's leading economies but also overburdened the healthcare systems during and after the pandemic. During the early waves of the pandemic, measures of social distancing, infection prevention, and postponing other non-urgent medical procedures were essential for a national healthcare system to control and manage SARS-CoV-2 infection rightfully. However, collateral downstream effects of such policies significantly influenced the regular path of care cascade of patients with CLDs, including those with decompensated cirrhosis, HCC, and LT awaited. Consequently, increased hepatic decompensation, the onset of hepatic comorbidities complications, and transplant waiting list dropout were noticed [4,82]. Herein we briefly overview how COVID-19 disrupted clinical research in hepatology and the care cascade of other hepatic illnesses during and post-pandemic.

12.1. Hepatic cirrhosis assessment and management

Unfortunately, cirrhosis screening and linkage to care strategies were markedly affected in the European epicenter countries of the COVID-19 pandemic in 2020. In cirrhotic patients, it is a prerequisite to timely diagnose the underlying hepatic illnesses, screen for HCC and varcies, and treatment of cirrhosis complications [147]. It is vital because severe COVID-19 outcomes are of paramount interest in patients with cirrhosis. Recognizing cirrhotic patients infected with SARS-CoV-2 will encourage a low threshold for COVID-19 testing and help consider early hospital admission for those with a positive COVID-19 diagnosis [4]. Acute hepatic decompensation is demonstrated to be very common, as noticed in

47 % of patients with cirrhosis and COVID-19 affectees, and may clinically manifest as worsening ascites and encephalopathy [148]. It is worth mentioning here that hepatic decompensation may be the first and only clinical sign of SARS-CoV-2 infection in cirrhotic patients, as 24 % of affectees reflect no concurrent pulmonary symptoms [148]. Hence, it should be identified and managed along traditional treatment lines. The collected data advocates that patients with autoimmune hepatitis have similar mortality rates due to COVID-19 compared to the matched general population [149], and immunosuppression therapy cannot be considered an independent risk factor for death in such patient populations [149]. These findings suggest that deferring immunosuppressive therapies or reducing their doses would not be an appropriate choice for the clinicians in these patient populations during the SARS-CoV-2 infection course.

Despite sufficient evidence, the fate of decompensated cirrhotic patients also affected by COVID-19 at baseline is bleak because 80 % mortality was documented in those requiring ICU support [148]; however, this ratio was decreased over time as better care procedures were introduced during peak pandemic era. Most deaths in COVID-19 cirrhotic patients were reported due to respiratory failure; however, the etiological mechanisms of such mortalities remain unclear. However, pulmonary venothromboembolic disease (considered a hallmark of critical COVID-19) is presumed to contribute to giving an additional hypercoagulable state in cirrhotic patients. Although hospitalized COVID-19 patients are universally recommended for thromboprophylaxis; however, wide variations exist in clinical practice and between international guidelines to treat such patient populations [150,151]. Therefore there is an eager need to emerge unified risk stratification models and treatment algorithms for venothromboembolic diseases. Furthermore, as coagulopathy may clinically associate with cirrhosis and COVID-19, the coexistence of both illnesses may yield a cumulative risk of thrombotic complications in such patient populations [78].

On the contrary, it would be interesting to elucidate that either enhanced venothromboembolic prophylaxis may benefit such patients population as studied before the emergence of the COVID-19 pandemic demonstrated the benefit of anticoagulation in reducing hepatic portal pressures without an excess bleeding risk [152]. This hypothesis is greatly favored by the findings of a multicenter study in Northern Italy which demonstrated that the use of thromboprophylaxis in 40 COVID-19-affected cirrhotic patients showed no major hemorrhagic complications. Unfortunately, not all but many active and previously published clinical trials excluded advanced cirrhotic patients during the investigation of optimal thromboprophylaxis following hospital admission with COVID-19 [153,154].

Despite the remarkable clinical efficacies of anti-COVID-19 vaccines, developing oral antivirals against SARS-CoV-2 continues. However, surprisingly cirrhotic patients are marginally considered in clinical trials of these targeted antiviral therapies. An international registry study involving 29 countries and 130 different institutions deciphered that cirrhotic patients were less likely to receive antiviral treatment than the matched general population worldwide (33 % versus 52 %; $P < 0.001$) [148]. It emphasizes that clinical trials of COVID-19 agents should be carefully evaluated for drug hepatotoxicities to prevent patients with cirrhosis. As this patient population is already at high risk of death, unnecessary treatment modifications or deferring the treatment may escalate prescribing concerns and mortality rates. For example, a delayed antiviral treatment choice in individuals with chronic HBV or HCV infection and relapse of alcohol drinking problems can lead to viral infection progression and hepatic decompensation [155]. Similarly, postponing regular diagnostic or therapeutic paracentesis for tense ascites may convert the medical condition into one requiring an emergency hospital visit, and the chances of acute variceal hemorrhage are enhanced in patients without timely endoscopic surveillance.

12.2. HCC surveillance

The AASLD and EASL recommendations favor the continuation of HCC surveillance in vulnerable populations (e.g., advanced hepatic cirrhosis and chronic HBV and HCV infections) during the pandemic but also point out accessibility issues on imaging and radiology resources [9,78]. Therefore, AASLD suggests two months reasonable delay while discussing the risks-to-benefits ratio of HCC surveillance and management with the patient [9]. However, if HCC surveillance is postponed indefinitely, the proportion of patients eligible for curative treatments of HCC will inevitably increase [156]. In addition, the cascade of care for HCC requires timely feedback from clinicians, radiologists, and allied healthcare workers. Hence, a centralized and multidisciplinary care unit via telemedicine could be an appropriate way out for HCC surveillance and management during the COVID-19 pandemic. Interestingly, a multicenter study from France during the peak period of the COVID-19 pandemic in 2021 demonstrated a significant decrease in the ratio of new HCC diagnoses and double the rate of HCC treatment delay compared to the same period in 2020 [157]. However, the HCC treatment modality, including liver resection (hepatectomy), remained unchanged between the two periods [4].

Worldwide, the LT programs were affected in several ways by the COVID-19 pandemic [158,159]. All major guidelines (i.e., AASLD, EASL, and WHO) prohibit organ transplantation from deceased donors infected with COVID-19 [160]. In addition, live donor transplantation had been postponed or reduced to prevent the exposure and transmission risks of SARS-CoV-2, and LT was reserved only for urgent or super-urgent cases as hospital resources or ICU availability for specific periods [160,161]. Data from two organizations in the USA and UK (American United Network for Organ Sharing-Organ Procurement Transplant Network and the UK National Health Service Blood and Transplant service) also demonstrated that living liver donors were most affected by SARS-CoV-2 infection. However, this infectivity ratio demonstrated an inverse correlation between transplant activity and national virus infection rates [4]. Therefore, the organ procurement policies and protocols must have some flexibility to resume some transplant service provisions during the pandemic era, where liver donors can move quickly to liver recipient centers or local organ retrieval and liver transplant surgical teams can travel easily from liver recipient centers to liver donor hospitals [4].

12.3. Clinical research in hepatology and hepatic illnesses

Unfortunately, clinical research in hepatology always remained scarce for funding and logistic support compared to other viral infections (e.g., HIV). Furthermore, the ongoing COVID-19 pandemic also hindered the resumption of clinical trials due to uncertain dissemination of SARS-CoV-2 infection in patient cohorts and difficulties adhering to the study protocols [162]. Patient follow-ups for disease assessment and linkage to care are also hampered by following the quarantine measures and participant illness. Consequently, many research institutes and funding agencies stopped new clinical trials for viral diagnosis platforms and significant drug development. As the COVID-19 pandemic is ending or in a transition to becoming endemic, the resumption of patient visits for viral hepatic disease assessment, finding the missing millions with hepatitis in remote and out-reach territories using decentralized and point-of-care (POC) rapid diagnostic platforms and postal transportation of antiviral medications to the patient may accelerate the efforts to eliminate viral hepatitis by 2030 [163]. As the world economies have been seriously jolted because of COVID-19, research funds for hepatitis research will also be in deficit for the next few years [164]. Similarly, the pandemic has profoundly impacted the non-COVID basic and translational research all over the world, and the reinvigoration of the existing healthcare, research, and diagnostic setups used to combat SARS-CoV-2 would also take time to be utilized for other infections/diseases. National lockdown and social distancing policies kept closed

research institutions across the globe with significant setbacks in hepatology research, as well as laboratory closures, loss of experimental animal models, and spoilage of cell lines also disrupted novel hepatitis diagnosis and treatment development [165]. The delaying or rescheduling of regional seminars and international consortiums also slowed the exchange of valuable ideas and information about hepatitis research among scientific communities. After returning to normalcy from the COVID-19 pandemic, research funding and healthcare policies must be implemented in a manner to rejuvenate basic and applied research endeavors both in the prospect of achieving viral hepatitis elimination as well as the search for curative therapy for other hepatic diseases.

12.4. Viral hepatitis diagnosis and the cascade of care in the COVID-19 era

The overall healthcare burden of viral hepatitis is still significant worldwide despite the availability of vaccines and oral antivirals as curative treatments. In 2017, the WHO set an ambitious goal to eliminate viral hepatitis as a significant public health threat by 2030. Since then, healthcare providers, health policymakers, and patients have been integrated into the national hepatitis plan of various countries to scale up viral hepatitis screening, diagnosis, assessment, and treatment by implementing micro- and macro-elimination strategies [163]. Albeit the resources reserved for viral hepatitis screening, diagnosis, and disease assessment were transformed toward SARS-CoV-2 identification and community healthcare services were arbitrarily deferred or shifted to manage COVID-19 patients, some countries adopted the measures like telemedicine and automatic drug refill to ensure the continuation of curative antiviral therapies for hepatitis B and C infections [56]. Even though the pandemic significantly impacted new hepatitis incidence identification and delay in treatment initiation, particularly in vulnerable populations. A modeling study collecting data from 110 countries estimated that 1-year delay in the progress of viral hepatitis elimination programs/plans could increase hepatitis-induced HCC comorbidities by 44,800 and 72,300 hepatitis-related mortalities, respectively [166]. Despite this alarming number and the diversion of existing health resources and community healthcare services to coup COVID-19 pandemic, some positive changes in the care cascade of hepatitis paved the way to resume sustainable diagnosis, assessment, and management of hepatitis during the pandemic peak time. Widespread practical adaptations in the decentralization of viral hepatitis testing approaches through postal-spot testing, and the resumption of services like telehealth, telemedicine, and home-delivery medication proved beneficial to reduce the incidences of new viral hepatitis cases and a decrease in overall hepatitis-associated morbidities. The lesson learned from COVID-19 management could be implemented and transformed for viral hepatitis diagnosis and management with mass testing strategies, contact tracing, and vaccination delivery. Now, political will, a national hepatitis plan, and healthcare systems with these familiar approaches could be utilized to combat viral hepatitis at a population level [167]. Furthermore, this progress can also be amalgamated with newly evolved concepts of healthcare delivery (e.g., as we have seen the implementation of telehealth, telemedicine, postal and self-test approaches during the COVID-19 pandemic), viral hepatitis monitoring in remote areas, and broad interaction of primary care providers (PCPs) at home. All these approaches may generate promising and excellent outcomes both in terms of viral hepatitis diagnosis and treatment as well as will also deliver good hepatology care for the spectrum of other hepatic diseases and their severity [168].

13. Psychological and socioeconomic impact of COVID-19 on liver health

The psychological and socioeconomic behaviors of humans have understandably been modified by COVID-19 and beyond recognition to some extent. However, the more profound impact of these behavioral changes negatively influenced human liver health regarding their eating/drinking habits and patient coordination with healthcare providers and services [4]. Alcohol consumption was alarmingly increased, in particular during periods of social isolation. A study from the UK reported that during the first national 'lockdown' in the country, an additional 160 million British Pounds were spent stockpiling alcohol compared to the same period of the previous year [4]. Similarly, an escalation in alcohol purchasing was also noticed, even from the very poorest fraction of the country's population [4]. The same trend in alcohol consumption was noticed in the USA [8]. Consequently, an increase in regular alcohol consumption was translated into harmful drinking habits, particularly for liver health, during the first wave of COVID-19, where overall escalation was reported in up to 48 % of respondents [4,169]. Surprisingly, 17 % of the alcohol-abstinent individuals with a previous ALD were also found to relapse to drinking under lockdown [170].

On the contrary, the smoking trend was mainly in decline because of decreased light smokers under lockdown conditions [169]. A single-centered observational study from the UK unveiled more than double the number of critically ill inpatients with ALD (but without COVID-19) and referrals for ALD in June 2020 compared with the same period in June 2019 [171]. Increased alcohol consumption and its possible crosstalk between ALD and COVID-19 mortality are evident in many reported studies [4]. Hence, alcohol advice to the general public must be integral to the healthcare services and caregivers' protocols during the COVID-19 pandemic.

Some published reports also emphasize unhealthy lifestyles as a predisposing factor for NAFLD in COVID-19. A study from Italy demonstrated an average 1.5 kg body weight gain during the country's quarantine periods, reduced exercise, increased food intake, anxiety, and depression [172]. Another survey-based study from the US also explored similar findings where one-third of 4000 diabetes patients reported a suboptimal healthy diet and half did less exercise during the pandemic, respectively [4]. Despite these findings, It is noteworthy that until May 2021, no studies were recorded that could directly link and evaluate the incidences of NAFLD in the pandemic era. The patients' linkage to care while coordinating with caregivers has also been modified. National Data from the US Veterans Health Administration (VHA) expressed a one-third decrease in hospitalization of cirrhotic patients following the emergence of the pandemic than to the previous year. However, the magnitude of the liver disease severity was recorded as significantly higher in hospitalized patients [173,174]. Hence, potential exposure to SARS-CoV-2 in hospital-admitted cirrhotic patients may lead to delayed clinical presentations of liver disease severity with more advanced complications of cirrhosis.

14. Oral antivirals for COVID-19 and their use for patients with liver diseases

The COVID-19 pandemic is not over yet, and existing anti-COVID-19 vaccines have been reported with adverse events and reinfections in many patients worldwide. Similarly, vaccine efficacy and safety are still debatable in millions of immunocompromised individuals infected with novel SARS-CoV-2 variants [184]. The FDA-approved sole antiviral therapy "remdesvir" showed clinical promise in severely affected and hospitalized COVID-19 patients; however, several clincial trials have not fully demonstrated its beneficial effects on SARS-CoV-2[184]. Similarly, the regimen is expensive and can only be administered intravenously in a clinic or hospital setting. Many oral antivirals are in the pipeline to be evaluated against SARS-CoV-2 because adverse events associated with these regimens are proven mild in intensity and less frequent in preclinical trials than existing COVID-19 vaccines[184–186]. Herein, we briefly overview the oral arsenal of COVID-19 therapies because it is a crucial time to expand the treatment paradigms as SARS-CoV-2 variants are continuously emerging worldwide.

14.1. Molnupiravir

The US FDA issued an EUA for oral antiviral "molnupiravir" on 23 December 2021 for the treatment of mild to moderate COVID-19 in adults with positive SARS-CoV-2 RNA test and who are at high risk for progression to severe COVID-19, including hospitalization or death, and for whom alternative treatment options are not accessible or clinically appropriate [186]. It is an orally absorbed prodrug of ribonucleoside analog (N-hydroxycitidine (NHC)), which showed *in vitro* therapeutic activity against SARS-CoV-1 and −2. While incorporating incorrect base pairing with adenine in replicating viral genome, NHC causes lethal mutations and inhibits SARS-CoV-2 genome replication [186,187]. The drug is highly effective in limiting nasopharyngeal SARS-CoV-2 viral load. The regimen's efficacy depends on the lack of proofreading ability of viral RdRp, and its safety relies on effective proofreading by host DNA polymerases [186]. Overall, the regimen has relatively lower efficacy than other emergency authorized oral antiviral (i.e., nirmatrelvir-ritonavir co-packaged combination) and has not yet been therapeutically evaluated in transplant recipients. The regimen was found safe in doses of 400 to 1600 mg twice daily with no greater adverse events than placebo and no apparent dose–response related toxicity in preregistration early phase trials [186]. The clinical trials of molnupiravir in patients with five days of onset of COVID-19 symptoms demonstrated a 30 %–50 % reduction in subsequent clinical worsening of the infection symptoms (i.e., hospitalization was not required), and infection did not result in death [186,187]. A randomized, double-blind, placebo-controlled clinical trial (i.e., MOVe-OUT) involving adult patients over 18 years of age and older with a prespecified chronic medical condition or at increased risk of COVID-19 for other reasons without receiving a COVID-19 vaccine jab supported molnupiravir EUA in December 2021 [186]. The treatment endpoint was to determine the percentage of hospitalized patients or death due to any cause during 29 days of follow-up. 6.8 % of patients were hospitalized or died within this time frame in the treatment group (i.e., n = 709) compared to 9.7 % of the patients who received a placebo (n = 699). Only one death was reported with molnupiravir during the follow-up period compared to 9 participants who received a placebo [186]. The regimen's side effects are not serious (e.g., diarrhea, nausea, and dizziness) and are quite manageable. However, the regimen's safety and clinical effectiveness continue to be evaluated [186]. The regimen is not authorized to administer for the pre-exposure or post-exposure prevention of COVID-19 or the start of treatment in patients hospitalized due to COVID-19 because molnupiravir efficacy is not studied yet in individuals who started treatment after hospitalization due to SARS-CoV-2 infection [186]. Similarly, the drug is not a substitute for approved and authorized COVID-19 vaccines in individuals who are eligible for vaccination, and booster doses are recommended. The regimen is available in 200 mg capsules, with a recommended dose being four capsules twice daily for five days (i.e., 800 mg per day and 40 capsules in total) [186]. Longer treatment and therapy are not recommended for patients with COVID-19 signs and symptoms for more than five days. Currently, the clinical efficacy and safety of molnupiravir are under investigation for children, post-exposure COVID-19 prophylaxis, and patients not at high risk for complications [187]. However, the overall clinical efficacy and safety data of molnupiravir are limited and not fully defined. Hepatotoxicity or hepatic adverse effects associated with molnupiravir are not clearly understood, and long-term regimen administration without serious adverse effects remains to be assessed [187]. However, elevated serum aminotransferase levels were noticed in clinical trials, although they were uncommon, mild, and less frequent than placebo. Furthermore, episodes of clinically apparent liver injuries were not reported in pre-licensure studies where more than 900 patients were given 800 mg of molnupiravir twice daily for five days [187]. Serum elevation of aminotransferases is clinically evident and more commonly experienced in symptomatic COVID-19 patients (approximately 70 % of SARS-CoV-2 infected patients exhibit increased AST & ALT) [187]. Similarly, the elevation is more frequent in patients with known risk factors for SARS-CoV-2 infection severity (e.g., male sex, older age, higher BMI, and co-morbid conditions (e.g., diabetes and hypertension)). Therefore, it is too early to comment on molnupiravir-induced hepatoxicity (drug-induced liver injury (DILI)), increase in liver function profile, or hepatic impairment in COVID-19-treated patients as clinical data on its use are limited [187]. A short duration of therapy and lack of major hepatic metabolism could be plausible justifications for the lack of severe adverse events and hepatic injury from molnupiravir [187]. Similarly, the drug is orally absorbed and is a prodrug rapidly metabolized to NHC with little hepatic biotransformation. Furthermore, It is clinically evident that the prodrug and NHC are not substrates, inhibitors, or inducers of hepatic CYP450 enzymes, human P-gp, or assessed transport proteins; hence no drug-drug interactions have been documented yet with molnupiravir. However, the regimen is potentially teratogenic and is contraindicated in COVID-19 patients with abnormal liver function profiles [186,187].

14.2. Nirmatrelvir-ritonavir

The US FDA issued an EUA for Pfizer's Paxlovid® (nirmatrelvir-ritonavir co-packaged combination) on 22nd December 2021 for the treatment of mild-to-moderate COVID-19 in adults and children over age 12 and older weighing around 40 kg (~88 lb) with positive SARS-CoV-2 RNA test, and who are at high risk for progression to severe SARS-CoV-2 infection, including hospitalization or death [185]. However, the regimen is available by prescription only, and treatment should be started as soon as possible after positive SARS-CoV-2 RNA test and within five days of symptoms onset. The regimen was approved at a crucial time in the COVID-19 pandemic because novel SARS-CoV-2 variants are still emerging worldwide, and there is an eager demand to make oral antiviral treatment more accessible to SARS-CoV-2 patients who are at high risk for mild-to-moderate COVID-19 to severe infection [185]. However, the regimen is not authorized to be administered to patients for the pre-exposure or post-exposure prevention of SARS-CoV-2 infection or in those requiring hospitalization due to severe or critical COVID-19 or having COVID-19 signs or symptoms for more than five days [185]. The regimen is also not a substitute for anti-COVID-19 vaccines in patients for whom vaccines and a booster jab are recommended. The regimen is available as 150 mg of nirmatrelvir tablets in a fixed-dose combination (FDC) with 100 mg of ritonavir as a co-packaged formulation [185]. The recommended dose of Paxlovid® is the administration of three tablets taken together (two tablets of nirmatrelvir and one tablet of ritonavir) orally twice daily and for five days, a total of 30 tablets. However, the regimen is not recommended for long-term treatment of COVID-19 [185].

Paxlovid® co-packaged combination comprises 2nd generation SARS-CoV-2 protease inhibitor (PI; nirmatrelvir) and a pharmaceutical enhancer (ritonavir), which is actually an HIV-1 PI and CYP3A inhibitor [188]. Nirmatrelvir is a peptidomimetic PI of SARS-CoV-2:M^{pro} and exhibited *in vitro* antiviral activity against several coronaviruses, including SARS-CoV-1 and −2 [188]. Ritonavir maintains a higher plasma level and prolonged half-life of the active antiviral metabolite of nirmatrelvir by inhibiting the CYP3A4 enzyme [188]. It also inhibits CYP2D6 but induces CYP3A, CYP1A2, CYP2C9, CYP2C19, CYP2B6, and other hepatic enzymes (e.g., glucuronosyl transferase). Hence, the coadministration of potent CYP-inducer drugs along with Paxlovid® may decrease nirmatrelvir-ritonavir plasma levels and ultimately results in loss of virologic response rates and possible development of the antiviral-drug resistance [188]. Similarly, the concomitant administration of potent CYP3A4 inhibitors along with Paxlovid® may result in severe or life-threatening reactions and are contraindicated. Furthermore, the treatment cannot be initiated immediately with Paxlovid® after discontinuing those medications because their effects persist even after discontinuation [185,188].

The data supporting an EUA for Paxlovid® are from the EPIC-clinical

trial (NCT04960202; a randomized, double-blind, placebo-controlled) studying the regimen for the treatment of non-hospitalized symptomatic adults with a confirmed diagnosis of SARS-CoV-2 infection [185,188]. A total of 2246 adult patients (i.e., age ≥ 18 years and older with a prespecified risk for progression to severe COVID-19 and 60 years or above regardless of prespecified chronic medical conditions) were enrolled and randomized to receive either nirmatrelvir-ritonavir (n = 1039) or placebo (n = 1046) [185]. No study participants received a COVID-19 vaccine and had not been previously infected with SARS-CoV-2 infection. The primary outcome of the clinical trial was the relative risk reduction of hospitalization or all-cause death at day 28 for the study drug compared to the placebo [188]. Paxlovid® significantly reduced the proportion of COVID-19-related hospitalization or death (i.e., any cause of death) by 88 % (95 % CI: 75 %, 8 of 1039 [0.8 %] *vs.* 66 of 1046 [6.3 %]) compared to the placebo among patients treated within five days of infection symptoms onset and among those who did not receive any monoclonal antibody treatment for COVID-19 [185]. 0.8 % (i.e., 0/1039) of patients were hospitalized or died in the nirmatrelvir-ritonavir group compared to 6 % (12/1046) of the participants in the placebo group during 28 days of follow-up [185]. The safety and clinical efficacy of Paxlovid® for children, in patients with known SARS-CoV-2 exposure, and post-exposure prophylaxis are continued to be evaluated; however, the total clinical experience data are limited, and its safety is not fully defined [188]. For this reason, the use of Paxlovid® in undiagnosed or uncontrolled HIV-1 infection may lead to anti-HIV-1 drug resistance. Similarly, ritonavir may cause hepatic damage, so Paxlovid® administration should be avoided in patients with preexisting liver diseases, liver enzyme abnormalities, or hepatic inflammation [188]. The regimen is not recommended, nor is dosing provided for patients with severe kidney or hepatic impairment (Child-Pugh Class C) [185]. Preregistration clinical data of Paxlovid® deciphered elevated serum aminotransferase levels in the drug study group; however, they were uncommon, mild, and no more frequent than with placebo. No reported episodes of clinically apparent liver injury were documented among more than 1000 patients treated with Paxlovid® in prelicensure studies [188]. Like molnupiravir, the short duration of therapy (only five days) could be a probable reason for the lack of adverse events and hepatic injury from Paxlovid®. However, safety and clinical efficacy for long-term administration of Paxlovid® remain to be seen [188].

In conclusion, oral antivirals seem safer than the COVID-19 vaccine in general based on the availability of their prelicensure clinical data; however, no clinical studies have been conducted to compare their efficacies in large-scale populations[184]. Furthermore, oral drugs are less expensive, have the advantage of being produced on large scales, do not require refrigeration for storage and shipping, and do not need to be administered in hospitals than COVID-19 vaccines and other specific monoclonal antibodies [184].

15. Anti-HCV agents against COVID-19

Even amid the expanding use of COVID-19 vaccines, efforts have paved the way to repurpose approved drugs as treatment for SARS-CoV-2 infections in 2021 and are still to be continued [189]. Many studies are underway worldwide to test whether approved drugs, including statins, antivirals, and rheumatoid arthritis medicines, might help with SARS-CoV-2 infection [189,190]. Finding a new use for an existing drug is always fascinating in medicine; however, conducting clinical trials and showing that a "repurposing drug" works right if most people are getting better without that treatment is challenging. Similarly, developing new drugs takes a long time because their pharmacokinetics must be analyzed, and safety and efficacy tested in large trials [192]. In addition, the molecular virology of SARS-CoV-2 complicates efforts to prove medicines are effective because more extensive clinical studies are needed to spot the difference between COVID-19 vaccines and oral antivirals [192]. In this scenario, using approved, safe, and effective existing drugs to treat this novel coronavirus is the fastest and most cost-effective way. Efforts are underway to expand the arsenal of COVID-19 therapies by developing oral drugs for situations where other FDA-authorized treatments are not accessible or clinically appropriate, and oral therapies will be a fruitful treatment option for some high-risk COVID-19 populations for hospitalization or death [185]. One study conducted between July 2020 and October 2021 in Egypt demonstrated that an anti-hepatitis C virus (HCV) drug combination (sofosbuvir/ledipasvir; Harvoni®) and an anti-protozoal drug (nitazoxanide; Alinia®) appeared to clear SARS-CoV-2 [189]. SARS-CoV-2 shares similarities with HCV in the way it replicates. Molecular docking studies by computational analysis find drug ligands that bind to viral proteins, and both sofosbuvir/ledipasvir and nitazoxanide were found to block essential proteins of SARS-CoV-2 in this study [189]. Ledipasvir/sofosbuvir was approved in 2014 by the US FDA to treat HCV patients, and nitazoxanide is currently used to treat protozoal infections but has shown broad-spectrum antiviral properties. Therefore, it was investigated as a treatment for Middle East respiratory syndrome (MERS), influenza, and hepatitis C [192].

Moreover, both drugs are relatively inexpensive in Egypt as sofosbuvir/ledipasvir costs about US$40, and nitazoxanide costs about US$ 10 for 14 days of treatment [192]. The study demonstrated that the sofosbuvir/ledipasvir combination effectively eliminated SARS-CoV-2. If the drug is started early at the onset of COVID-19 signs and symptoms, the virus transmission can be prevented without complication, and mortality can also be avoided [189]. In the preliminary trial, 190 patients with mild to moderate COVID-19 were randomly divided into three groups. All patients in the three groups received standard care treatment (SCT) [189,192]. One group also received sofosbuvir/ledipasvir, and another group also received nitazoxanide. The trial end outcome was to determine quantitative viral clearance by qRT-PCR at intervals of 5, 8, 11, and 14 days [189].

Sofosbuvir/ledipasvir appeared to take effect within five days, with viral clearance in most patients within two weeks, while nitazoxanide had a weaker effect but still appeared to achieve a treatment benefit. 36.9 % of patients showed early viral clearance in the sofosbuvir/ledipasvir group on day 5, while 83.1 % achieved viral clearance by day 14 [189]. The difference between sofosbuvir/ledipasvir and the other two groups were statistically significant at all time points ($P < 0.001$); however, for nitazoxanide, it was statistically significant on day 14 ($P < 0.01$) with the group that only received SCT. 39.7 % of patients in the nitazoxanide group achieved viral clearance by day 14 compared to 19.4 % of the SCT group [189]. Albeit the patient demographics were significantly different in age and sex in all groups, the treatments were the only significant factors in the different rates of viral clearance in Cox Regression (i.e., for sofosbuvir/ledipasvir, HR was 17.88, 95 % CI: 6.66–47.98, and for nitazoxanide, the HR was 2.59, 95 % CI: 1.11–6.07). The investigators did not report severe adverse events or mortality in all patient groups [189]. The researchers are determined to investigate these drugs in larger clinical trials and with severely ill COVID-19 patients. It is crucial because most mild to moderate SARS-CoV-2 illnesses recover independently. Therefore, an effective antiviral would be especially useful in seriously ill patients with high viral loads [192]. However, until more extensive clinical trials are not done, these experimental/repurposing drugs should not recommend/prescribe to treat COVID-19. Furthermore, the treatment endpoints for such trials should include hospitalization and death since patients can remain severely ill with COVID-19 even after negative RT-PCR or test positive and have no symptoms [192].

Another study based on molecular docking methods also demonstrated that anti-HCV direct-acting antivirals (DAAs) could be effective therapeutic regimens for COVID-19 [190]. Molecular docking analysis revealed higher binding affinities for some anti-HCV DAAs (e.g., simeprevir, ledipasvir, and pibrentasvir) against SARS-CoV-2 protease than ivermectin (used as an antiparasitic, except tapeworms). Interestingly, all three DAAs possess different mechanisms of action to inhibit HCV replication and are administered in combination with other DAAs to

treat HCV. For example, Simeprevir is an NS3/4A protease inhibitor (PI) of HCV proteins, while ledipasvir and pibrentasvir inhibit an NS5A non-structural protein from preventing HCV replication. The study also demonstrated that other anti-HCV DAAs (e.g., glecaprevir, paritaprevir, and elbasvir) showed higher binding affinities according to Contini's top five hits, which typically uses to optimize the pharmacokinetic properties of drug molecules. For instance, glecaprevir and paritaprevir are HCV NS3/4A PIs, while elbasvir inhibits NS5A [190]. In addition, other anti-HCV PIs (e.g., grazoprevir, dasabuvir, and sofosbuvir) were also docked against COVID-19 protease in the study, but their ligand–protein interaction score was lower with COVID-19 protease than angiotensin II human acetate [190]. The study also depicted that using anti-HCV DAAs in combination as antivirals for COVID-19 based on their docking score could generate synergistic drug effects without potential drug-drug interactions. However, future research and further investigations by *in vitro*, in vivo, or preclinical trials are eagerly required to validate their safety and efficacy [190].

15.1. Potential pitfalls of repurposing drugs against COVID-19

Although a continual release of findings from studies of repurposed drugs against COVID-19 is ongoing daily, it serves as a hotline for new research on COVID-19 that has not yet undergone peer review [191]. As a result, physicians and patients face a deluge of treatment information and should try to adhere to guidelines and sound advice while avoiding the temptation of quick fixes, often fueled by misinformation. Similarly, we do not ascertain whether these medicines work for COVID-19 patients because the data on the large-scale administration of these drugs are scarce [191]. In addition, the race to find treatments for COVID-19 led to initial missteps as the heterogeneous outcomes of the infection were challenging, leading to unpowered studies and false conclusions from either observational trials or case series for these repurposed drugs [191]. It usually takes 18 months or longer to get a significant study of a drug organized and running, a timeline compressed during the COVID-19 pandemic. That made it challenging to interpret the effects of approved/repurposed drugs on COVID-19, and some studies were too small to truly gauge the value of approved drugs in this infection [191]. For example, even with the improvements in the quality of studies, questions remain about many drugs for which their supporters have had high hopes, particularly ivermectin. The National Institute of Health (NIH) treatment guidelines for COVID-19 demonstrate insufficient data for or against using ivermectin to treat SARS-CoV-2 infection [191]. The guidelines suggest that the findings from adequately powered, well-designed, and well-conducted clinical trials are needed to provide more specific evidence-based guidance on the role of ivermectin in the treatment of COVID-19. Moreover, the guideline from the Infectious Diseases Society of America (IDSA) for the treatment of COVID-19 opposes ivermectin use for treating hospitalized patients and those being seen outside of hospitals unless the drug is given in the context of a clinical trial. Hence guidelines maintained by IDSA and NIH are critical for clinicians trying to keep up during the pandemic [191]. Most healthcare systems have internal documents about COVID-19 protocols for repurposing drugs, which align with guidelines and should follow transparent, evidence-based treatment protocol practices. However, the current adamant support of ivermectin in some circles stems from heavy reliance on observational studies that are prone to bias and confounding. In this regard, the widespread use of ivermectin may complicate efforts to answer how well it works honestly. The drug is widely used in Latin America, so recruiting patients for clinical trials might be challenging. Unfortunately, people are not looking at data rigorously, as during the pandemic peaks in Brazil, fuelling sickness and death in the country spread an overwhelming amount of disinformation in communities [191]. At that time, hydroxychloroquine (an anti-malarial medication) and ivermectin were touted by politicians as the panacea to the COVID-19 pandemic and prescribed by clinicians as both COVID-19 prophylaxis and treatment. The pace of research on COVID-19 has accelerated beyond what could have been imagined before the pandemic, along with faster dissemination of even the earliest findings [192]. These factors contribute to the "infodemic of misinformation" about which approved/repurposing drugs might work against COVID-19 [191]. It seems true for hydroxychloroquine, where observational studies suggested a benefit but failed to be proved in a large randomized clinical trial [192].

Similarly, researchers had eyed colchicine as a potential COVID-19 treatment due to its effect on an inflammatory pathway also linked to more severe cases of COVID-19 [191]. However, in a randomized trial involving over 11,000 patients from three countries and over 2000 deaths, allocations to colchicine were not associated with reductions in mortality, duration of hospitalization, or the risk of being ventilated or dying for those not on ventilation at baseline [191]. Sometimes media outlets and various sources could amplify the findings and messages from clinical studies; nevertheless, clinicians should look to guidelines as a tool to manage COVID-19 patients during a time of rapid information flow. It does not seem easy to go back and look at each treatment and critically appraise them; however, clinicians need to stick with what is effective for patients infected with SARS-CoV-2 [191,192].

16. Conclusions

Hepatic overexpression of ACE2, abnormal liver biochemistries, underlying hepatic injury/disease, cholangiopathy, cytokine storm, and DILI could be the predisposing factors to worse COVID-19 outcomes in subjects with healthy liver as well as in patients with pre-existing liver diseases. Abnormal liver biochemistries have been documented more in clinical presentations of COVID-19 patients and should not be ignored for additional hepatic injury during the course of infection in patients with pre-existing advanced hepatic illnesses (cirrhosis, HCC, LT recipients). Possible crosstalk between COVID-19 and hepatic disease severity is evident from the preliminary observations of data collected from international registry platforms, patient cohort studies, and case series in areas with the rising tide of ALDs, AUD, and CLDs. Hepatic cirrhosis seems clinically more relevant in patients with high risks of severe COVID-19 outcomes and death. Specific questions remain unanswered regarding the clinical implications of COVID-19 on LT donors and recipients. Which aspects of the immune responses are helpful to immunosuppression in LT recipients as well as the risk of hepatic decompensation or graft rejection associated with COVID-19, is unknown. These patient populations should be considered in clinical trials of ongoing investigational antiviral drugs and therapeutic strategies for COVID-19 to weigh out their management. International guidelines for hepatology care must reshuffle patient workflow and clinical procedures recommendations to protect healthcare providers and patients from COVID-19 in the emergency, ICU, and in-patient hospital departments. Improving the cascade of care, particularly for those infected with COVID-19 and having liver cirrhosis, AUD, CLDs, or liver transplantation, will be crucial to improving current treatment guidelines and patient management of liver diseases and SARS-CoV-2 infection. SARS-CoV-2 RNA point of care (RNA-POC) testing will be essential to identify asymptomatic COVID-19 in out-reach communities, and anti-COVID-19 vaccine jabs will prevent further transmission of the virus in vulnerable populations (injection drug users, incarcerated persons, sex workers, HCV, HBV or HIV co-infected populations and illegal immigrants). Hepatology care can be better and more effectively delivered by telehealth and mobile application to distant communities not capable of serving by transplant and hepatology centers. Healthcare providers may schedule appropriate telehealth visits to outreach and high-risk populations to mitigate the effects of AUD, ALD treatment disruption, and social isolation. Intense and influential clinical research in hepatology will also amalgamate the efforts to manage hepatic comorbidities in the future spread of any viral pandemic. We lack oral antivirals for COVID-19 and some regimens that can be used in outpatient. While the treatments for COVID-19 have improved since the pandemic began, and vaccines have slowed down the transmission of the SARS-CoV-2

worldwide, highly efficacious, well-tolerable, and safe oral drugs are eagerly in demand to expand the arsenal of COVID-19 therapies.

CRediT authorship contribution statement

Mohammad T. Imam: Investigation, Resources. **Ziyad S. Almalki:** Investigation, Resources. **Abdullah R. Alzahrani:** Data curation. **Saeed S. Al-Ghamdi:** Data curation, Writing – review & editing. **Alaa H. Falemban:** Methodology, Project administration, Validation. **Ibrahim M. Alanazi:** Formal analysis, Software. **Naiyer Shahzad:** . **Munira Muhammad Alrooqi:** Visualization. **Qaiser Jabeen:** Formal analysis, Writing – review & editing. **Imran Shahid:** Conceptualization, Project administration, Supervision, Writing – original draft.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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