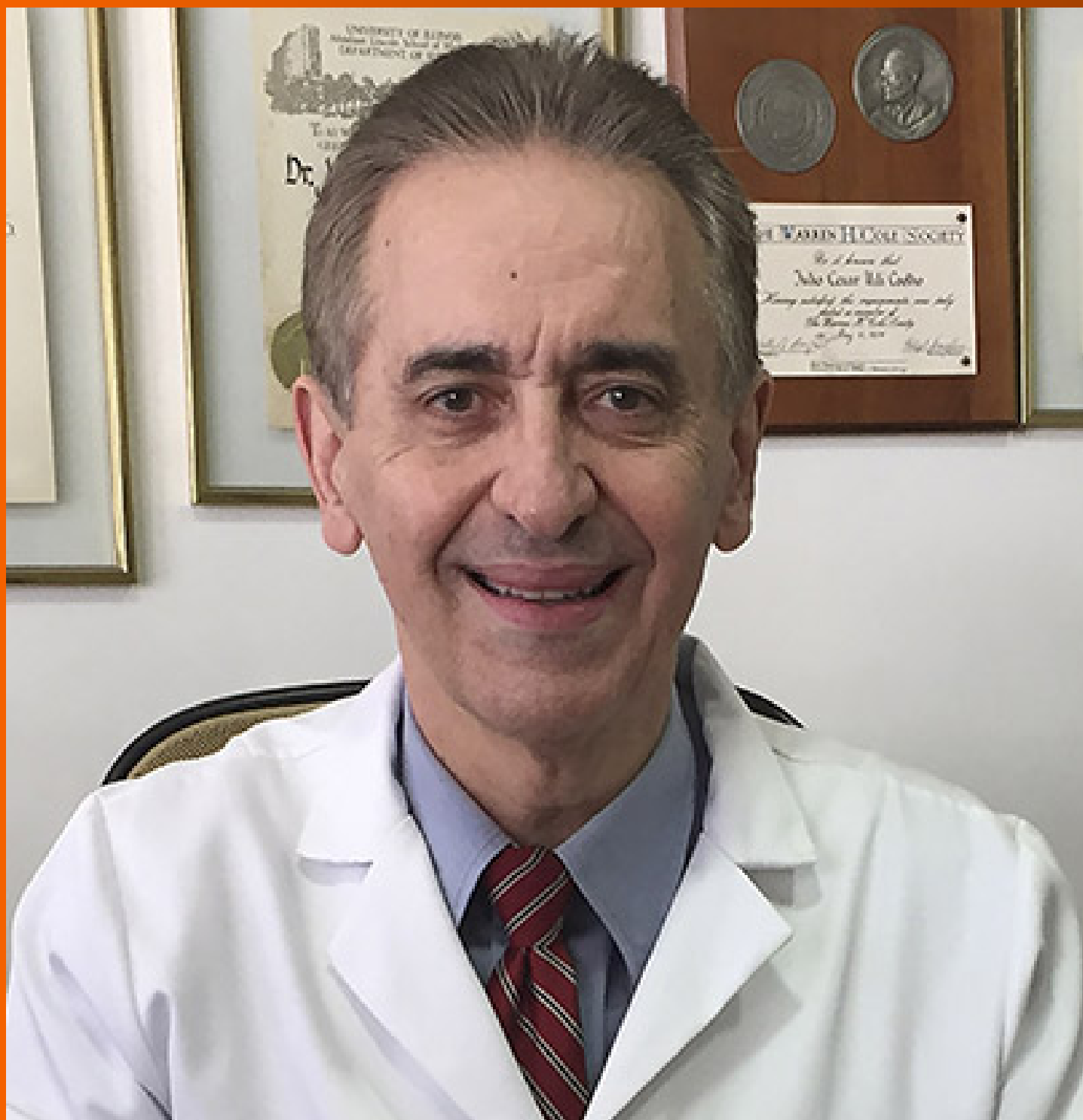


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The primary aim of *World Journal of Hepatology* (*WJH*, *World J Hepatol*) is to provide scholars and readers from various fields of hepatology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

*WJH* mainly publishes articles reporting research results and findings obtained in the field of hepatology and covering a wide range of topics including chronic cholestatic liver diseases, cirrhosis and its complications, clinical alcoholic liver disease, drug induced liver disease autoimmune, fatty liver disease, genetic and pediatric liver diseases, hepatocellular carcinoma, hepatic stellate cells and fibrosis, liver immunology, liver regeneration, hepatic surgery, liver transplantation, biliary tract pathophysiology, non-invasive markers of liver fibrosis, viral hepatitis.

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# Impact of COVID-19 pandemic on liver, liver diseases, and liver transplantation programs in intensive care units

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## Abstract

Emerging worldwide data have been suggesting that coronavirus disease 2019 (COVID-19) pandemic consequences are not limited to the respiratory and cardiovascular systems but encompass adverse gastrointestinal manifestations including acute liver injury as well. Severe cases of liver injury associated with higher fatality rates were observed in critically ill patients with COVID-19. Intensive care units (ICU) have been the center of disposition of severe cases of COVID-19. This review discusses the pathogenesis of acute liver injury in ICU patients with COVID-19, and analyzes its prevalence, consequences, possible drug-induced liver injury, and the impact of the pandemic on liver diseases and transplantation programs.

**Key Words:** COVID-19; Critical care; Drugs; Liver; Liver transplantation; Outcome; Severe liver injury

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**Core Tip:** In this manuscript, liver dysfunction is seen more in patients with more severe disease upon presentation. It is difficult to separate the independent effect of viral infection from various treatment modalities, including antibiotics and experimental antiviral drugs that are used in these patients.

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## INTRODUCTION

More than a year ago, the global pandemic started from its epicentre in Wuhan. In coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), the lung is the main organ targeted by the virus[1]. The organism exhibits a wide range of severity and a diverse disruption of extra-pulmonary systems, including gastrointestinal, renal, cardiac[2,3], hepatic[4], and even multi-organ damage[2,5]. Moderate or severe symptoms have been reported in almost 20% of all COVID-19 patients, while 5% progress into critical stages of the disease[6].

The rate of intensive care unit (ICU) admission due to COVID-19 is quite variable, ranging from 3% to 100% in literature[7]. The liver could be affected in COVID-19 through several mechanisms, including virus-related liver cell injury, disorganized immune response, drug-induced liver injury (DILI) and ischemic liver dysfunction in the settings of multisystem organ failure[8]. The reported rate of COVID-19-induced liver injury ranged from 14.8% in one study[9] and up to 74% in another[10]. In a case series of critically ill patients with COVID-19, liver injury was frequent but transient and non-severe[11]. Patients may not be equally affected by the pandemic, certain patient populations are potentially more vulnerable. Immunocompromised patients and patients with cirrhosis are probably more susceptible to worse outcomes after SARS-CoV-2 infection[5]. The data in literature on how chronic immunosuppression can influence COVID-19 outcomes is scarce[6]. This minireview will discuss the pathogenesis of acute liver injury in ICU patients with COVID-19, focusing on its prevalence, consequences, DILI, and its impact on existing liver diseases and liver transplantation programs.

## PATHOGENESIS OF LIVER INJURY IN COVID-19

Liver injury in COVID-19 can be related to the direct cytopathic effect of the virus, DILI, uncontrolled immune reaction, or sepsis[12]. SARS-CoV-2 ribonucleic acid has been detected in blood and stool samples of COVID-19 patients who presented with diarrhoea, indicating the liver's probable involvement in the disease pathogenesis[13, 14]. It has been suggested that there is a considerable expression of angiotensin-converting enzyme 2 (ACE2) receptors in cholangiocytes, where SARS-CoV-2 binding may adversely affect liver function. Moreover, COVID-19 may worsen the underlying chronic liver disease(s) (CLD), leading to hepatic decompensation or acute-on-chronic liver failure and increasing the risk of mortality, particularly in critically ill patients[12, 15-17]. However, in severe COVID-19, liver damage is more likely due to the inflammatory cytokine storm[12,18] rather than the direct cytopathic effects of the virus[12].

The progression of SARS-CoV-2 infection has been divided into four phases: Upper and lower respiratory tract infection, usually treated as outpatients, COVID-19 associated lung injury, usually treated as inpatients, systemic inflammatory response syndrome (SIRS), and systemic failure. Liver involvement is often observed in the latter phases but can also occur in the earlier ones. In SIRS, pro-thrombotic factors accumulate due to bone marrow and liver acute phase response causing thrombosis, whereas in the last phase, multi-organ vascular dysfunction and cytokine storm occur in view of the ongoing interaction between the lung and systemic inflammation[19].



Hypoxic hepatitis (HH), known as shock liver or ischemic hepatitis, is an acute liver injury resulting from liver hypoxia[20]. The extensive complex vascular supply together with high metabolic efficacy results in a liver vulnerable to circulatory disturbances. Critically ill patients with circulatory or respiratory manifestations which may influence liver perfusion are at higher risk of HH[3,21,22]. The mechanism by which SARS-CoV-2 infection leads to HH is not fully understood. Multiple theories have been postulated, including hypoxemia developed due to COVID-19 pneumonia [2] and systemic stress caused by SIRS[19]. Both may provide a route to a compensatory decrease in peripheral and splanchnic blood flow, resulting in decreased hepatic blood flow leading to hepatocellular hypoxia[23]. Reperfusion injury is mediated by the generation of reactive oxygen species when ischemic hepatocytes are re-exposed to oxygen, leading to cell injury *via* lipid peroxidation[24]. Waseem and Chen[21] defined the diagnostic criteria for HH as circulatory or respiratory failure with a dramatic but transient rise in serum aminotransferases activity when excluding other causes of liver cell necrosis, especially viral or drug-induced hepatitis[21]. A visual summary of liver injury in COVID-19 is presented in Figure 1.

## PREVALENCE AND CONSEQUENCES OF COVID-19-ASSOCIATED LIVER INJURY

The liver injury induced by COVID-19, including its pattern and severity, has not been uniformly defined or well characterized[25,26]. Some definitions reported in the literature, including DILI, are presented in Table 1. Secondary liver injury was the most common, being the first occurrence[3]. Liver injury has been reported as the elevation of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels[25,26]. Thus, the liver injury appears to be of a hepatocellular (56%) rather than cholestatic (24%) or mixed (19%) pattern[3,25-28], while jaundice is uncommon[3]. Alkaline phosphatase (ALP) and gamma-glutamyl transferase (GGT) as markers of bile duct injury have not increased significantly in the respective studies[3,25]. However, not all liver function tests (LFTs) have been strictly reported[29].

Liver injury in COVID-19, manifested as changes in LFTs, is usually mild and transient[26,30-33] and does not require treatment[30,32]. However, severe cases have been reported[26,30,32]. Mild, moderate, and severe injuries were reported in 45%-65%, 21%, and 6.4% of the cases, respectively[25-27]. In one study, mild elevation in LFTs levels was reported in 90% of patients admitted to hospital with marked elevation during hospital stay[34]. Elevation in AST levels is more common than ALT and other LFTs[29,30]. In one report, the acute liver injury occurred on day 17 after the onset of symptoms[28]. In patients with severe COVID-19, the elevation in the transaminases and bilirubin levels was at least double that in patients with mild and moderate disease[33]. Elevation in GGT levels was more noticeable in severe cases, while ALP levels usually remained normal in both mild and severe cases[35]. Variable and inconsistent degrees of LFTs abnormalities, ranging from 3.75% to more than 50% of all patients, have been described[5,25,33,36]. A meta-analysis found a pooled incidence of elevated liver enzymes by 23.1%[37]. Although some studies did not show a statistical difference in abnormal LFTs between patients with severe and non-severe disease[37,38] or between survivors and non-survivors[39], many other studies have consistently shown elevated LFTs to be more prevalent in fatal or severe disease[1,2,14,28,34,40-43] in up to 58%-78% of cases[40,44,45].

Patients with LFTs abnormalities had a more severe inflammation[25-27] and degree of organ dysfunction[27]. At least two meta-analyses have confirmed the association between liver injury and the severity of COVID-19[46,47]. Liver injury had prognostic implications in patients with COVID-19. Liver injury or abnormal LFTs were associated with increased risk of ICU admission[25,27,48,49], intubation[25,49], mechanical ventilation need[27], acute renal injury, vasopressor use[25,27], long hospital stays[27], mortality[25,27,28,37,48,49], and composite of ICU admission and mortality[27,50]. Tables 2 and 3 present selected liver injury-related markers and clinical outcomes of non-survivors[39,43,44,51-55], or patients with severe disease[1,2,9,28,34,40,42,56-63], including those admitted to ICU due to COVID-19[1,2,57].

## PRE-EXISTING LIVER DISEASE IN COVID-19-ASSOCIATED LIVER INJURY

Underlying CLD in patients with COVID-19 have been reported in several studies and

**Table 1** Reported definitions for liver injury in coronavirus disease 2019

Term	Definition(s)
Liver disorder	Serum ALT or AST > 2 × ULN, TB > 2 × ULN, ALP ≥ 2 ULN[75]
Liver injury or acute liver injury	ALT and/or AST above 3 × ULN, ALP, GGT, and/or TB above 2 × ULN[9,34] ALT and/or AST ≥ 2 × ULN, with TB ≥ 2 × ULN and/or INR ≥ 1.7[70] ALT levels above 3 × the ULN[28]
Mild liver injury	ALT above the ULN and below 2 × the ULN[25]
Moderate liver injury	ALT between 2-5 × the ULN[25]
Severe liver injury	ALT above 5 × the ULN[25] Any elevation of enzymes above 3 × the ULN and bilirubin above 2 × the ULN[5]
Liver test abnormalities	Elevation of the following serum liver enzymes: ALT > 40 U/L, AST > 40 U/L, GGT > 49 U/L, ALP > 135 U/L, and TB > 17.1 μmol/L[34]
De novo LFTs abnormality	The occurrence of abnormal LFTs in patients with normal LFTs at admission[27]
LFTs elevation	Increase in serum liver enzyme levels above the ULN[27,28]
Mild LFTs elevations	Elevation 1-2 times above the ULN[25,34]
Hepatocellular or hepatocyte type	The pattern of abnormal LFTs with predominantly elevated ALT and AST[27] Patients with raised ALT and/or AST more than 3 × the ULN[34] AST/ALT activity is higher than the ALP/GGT activity, with liver enzyme activities calculated by multiples of their ULN[34]
Cholestatic or cholangiocyte type	Pattern of abnormal LFTs with predominantly elevated ALP and GGT[27] Patients with raised ALP or GGT 2 × the ULN[34] ALP/GGT activity was higher than the AST/ALT activity, with the liver enzyme activities calculated by multiples of their ULN[34]
Mixed type	Mixed pattern when the extents of AST/ALT and ALP/GGT are similar[27] A combination of both ALT/AST elevated more than 3 × the ULN and ALP/GGT twice the ULN[34]
Drug-induced liver injury	Any elevation in liver enzymes or TB after the initiation of the drug in the absence of identified common causes of liver disease[5]

ALT: Alanine aminotransferase; ALP: Alkaline phosphatase; AST: Aspartate aminotransferase; GGT: Gamma-glutamyl transpeptidase; INR: International normalized ratio; LFTs: Liver function tests; TB: Total bilirubin; ULN: Upper limit of normal.

ranged from 2% to 11%[30,36,64], up to 19% in one study[65]. Pooled prevalence of pre-existing CLD in one meta-analysis was 3%[66], which was comparable to that of another meta-analysis (3.6%)[5]. The latter reported pooled prevalence of CLD of 3.9% and 4.7% among severely infected patients and the non-survivors, respectively[5]. Compared with patients without underlying liver diseases, the odds ratio (OR) of developing severe disease was 0.81 [95% confidence interval (CI): 0.31-2.09,  $P = 0.67$ ][67]. The presence of underlying liver disease was associated with increased the risk of mortality and hospitalization, before {[risk ratio (RR): 2.8, 95%CI: 1.9-4.0,  $P < 0.001$ ]; (RR: 1.7, 95%CI: 1.2-2.0,  $P < 0.001$ )} and after propensity matching [(RR: 3.0, 95%CI: 1.5-6.0,  $P = 0.001$ ); (RR: 1.3, 95%CI: 1.1-1.6,  $P = 0.006$ )], when compared to those without liver diseases, respectively[68].

The presence of CLD was also found to be an independent predictor for ICU admission (adjusted OR 1.77, 95%CI: 1.03-3.04,  $P = 0.04$ ) and mechanical ventilation need (adjusted OR 2.08, 95%CI: 1.20-3.60,  $P = 0.0092$ )[65]. The reported etiologies of the pre-existing liver diseases before COVID-19 included chronic viral hepatitis B and C, alcoholic and metabolic liver disease, cirrhosis of any cause, and others[5,26,31]. Liver cirrhosis is the end-stage of these liver-related diseases[31]. In one study ( $n = 363$ ), 19% of patients had a pre-existing liver disease with the predominance of non-alcoholic fatty liver disease (NAFLD) (79.7%). Compensated cirrhosis, decompensated cirrhosis, and viral hepatitis B and C accounted for 8.7%, 4.3%, 2.9%, and 8.7% of all patients, respectively[65]. In contrast, the reported rates in one meta-analysis of 107 studies ( $n = 20874$ ) were, CLD/cirrhosis in 61.1%, NAFLD in 19.5%, hepatitis B in 17.8%, and hepatitis C in 0.73% of patients[5].



Table 2 Reported data on survivors versus non-survivors in coronavirus disease 2019

Ref.	N (all) n (non-survivors)	Age (year)	Male	Pre-existing CLD	Type of liver disease	Elevated LFTs on admission (%)	LFTs levels on admission. ALT/AST/ALP/GGT (U/L)/TB (μmol)	Selected complications or clinical outcomes
Cao <i>et al</i> [51]. China	N = 102 (n = 17)	53 vs 72	47.1% vs 76.5%	2.4% vs 5.9%	-	ALT: NR vs 41.1%	ALT: NR vs 40	ALI: 24.7% vs 76.5%; ARDS: 5.9% vs 88.2%; Shock: 3.5% vs 41.1%; MV: 2.4% vs 70.6%
Chen <i>et al</i> [52]. China	N = 274 (n = 113)	51 vs 68	55% vs 73%	-	HBV surface antigen positivity	ALT: 19% vs 27%; AST: 16% vs 52%	ALT: 20 vs 28; AST: 25 vs 45; ALP: 64 vs 76; GGT: 28 vs 42; TB: 8.4 vs 12.6	ALI: 2% vs 9%; ARDS: 52% vs 100%; Shock: 0% vs 41%; MV: 82% vs 16%
Chen <i>et al</i> [53]. China	N = 55 (n = 19) <sup>1</sup>	72 vs 77	50% vs 84.2%	2.8% vs 5.3%	-	ALT: 19.4% vs 31.6%; AST: 50% vs 73.7%	ALT: 40 vs 44; AST: 55 vs 78	MV: 30.6% vs 68.4%
Du <i>et al</i> [54]. China	N = 85 <sup>2</sup>	65.8	72.9%	5.9%	-	ALT: 16.5%; AST: 32.9%; TB: 35.3%	ALT: 72.9; AST: 94.4; TB: 18.4	ALI: 35.3%; ARDS: 74.1%; Shock: 81.2%; MV: 93% <sup>3</sup>
Wu <i>et al</i> [42]. China	N = 84 (n = 44) <sup>4</sup>	50 vs 68.5	77.5% vs 65.9%	3.5% <sup>5</sup>	-	-	ALT: 35 vs 39; AST: 38.5 vs 37; TB: 11.6 vs 14.5	MV: 57.5% vs 97.8% <sup>3</sup> ; Others reported as association
Yang <i>et al</i> [55]. China	N = 92 <sup>2</sup>	69.8	53.3%	3.3%	-	-	ALT: 27; AST: 31; TB: 13.6	ALI: 16.5%; ARDS: 80.2%; MODS: 15.4%
Yang <i>et al</i> [39]. China	N = 52 (n = 32)	51.9 vs 64.6	70% vs 66%	-	-	-	TB: 13.1 vs 19.5	ALI: 30% vs 28%; ARDS: 45% vs 81%; MV: 35% vs 94%
Zhang <i>et al</i> [44]. China	N = 82 <sup>2</sup>	72.5	65.9%	2.4%	-	ALT: 30.6%; AST: 61.1%; TB: 30.6%	ALT: 26; AST: 72; TB: 13.6	Hepatic damage: 78%; Liver-associated death: 1.2%; MV: 40.2%
Zhou <i>et al</i> [43]. China	N = 191 (n = 54)	52 vs 69	59% vs 70%	-	-	ALT: 24% vs 48%	ALT: 27 vs 40	ARDS: 7% vs 93%; Shock: 0% vs 70%; MV: 2% vs 100% <sup>3</sup>

<sup>1</sup>Patients ≥ 65 years subgroup (55 of 203 patients).<sup>2</sup>Reported fatal cases only.<sup>3</sup>Invasive and non-invasive mechanical ventilation.<sup>4</sup>Subgroup of patients who developed acute respiratory distress syndrome (ARDS) after admission and those who progressed from ARDS to death (total patients = 201).<sup>5</sup>Reported for all patients.

ALT: Alanine aminotransferase; ALI: Acute liver injury; ALP: Alkaline phosphatase; ARDS: Acute respiratory distress syndrome; AST: Aspartate aminotransferase; CLD: Chronic liver disease; GGT: Gamma-glutamyl transpeptidase; HBV: Hepatitis B virus; LFTs: Liver function tests; MODS: Multiple organ dysfunction syndrome; MV: Mechanical ventilation; N and n: Number of patients; NR: Not reported; TB: Total bilirubin.

Hepatitis B virus co-infection may subject COVID-19 patients to an exacerbated liver injury[30] and a more severe disease[69]. Acute liver injury in COVID-19 patients with hepatitis was significantly higher than that in patients without chronic hepatitis (15.0% vs 7.0%,  $P < 0.001$ )[70]. Patients with NAFLD, renamed as metabolic-associated fatty liver disease[26,31], had a significantly higher likelihood of abnormal LFTs, longer viral shedding time, and higher rate of COVID-19 progression (OR: 6.4, 95%CI: 1.5-31.2), compared to those without NAFLD[71]. NAFLD was significantly associated with ICU admissions (adjusted OR: 2.30, 95%CI: 1.27-4.17,  $P = 0.03$ ) and mechanical ventilation need, (adjusted OR: 2.15, 95%CI: 1.18-3.91,  $P = 0.02$ ) but not with mortality [65]. Furthermore, NAFLD in younger patients (< 60 years) was associated with the prevalence of severe COVID-19 (adjusted OR: 2.67, 95%CI: 1.13-6.34,  $P = 0.03$ )[72]. COVID-19 patients with liver cirrhosis were found to be at increased risk of mortality compared with those without the disease (RR: 4.6, 95%CI: 2.6-8.3,  $P < 0.0001$ )[68,71]. Multivariate analysis showed that liver cirrhosis was an independent predictor for mortality (adjusted OR: 12.5, 95%CI: 2.16-72.5,  $P = 0.009$ ) but not for ICU admission or mechanical ventilation need[65].

**Table 3** Reported data on critically ill, intensive care units, or severe coronavirus disease 2019 patients

Ref.	N (all), n (severe disease). Patient population	Age (year)	Male	Pre-existing CLD	Type of pre-existing CLD	Elevated LFTs on admission (%)	LFTs levels on admission. ALT/AST/ALP/GGT (U/L)/TB (μmol)	Selected complications or clinical outcomes
Arentz <i>et al</i> [56]. United States	N = 21. Critically ill	70	52%	4.8%	Cirrhosis	-	ALT: 108; AST: 273; ALP: 80; TB: 0.6 mg/dL	ALI: 14.3%; Severe ARDS: 57.1%; MV: 71%; Death: 52.4%
Cai <i>et al</i> [34]. China	N = 318 (n = 85) <sup>1</sup> . Non-severe vs severe	47. All patients	47.5%. All patients	5%. All patients	ALD, NAFLD, HVB	ALT: 6.4% vs 21.1%; AST: 0.68% vs 18.8%; GGT: 5.1% vs 29.4%; TB: 1.2% vs 7%	-	MOF: 0% vs 11.7%
Cai <i>et al</i> [9]. China	N = 298 (n = 58). Non-severe vs severe	41 vs 62.5	44.1% vs 67.2%	8.3% vs 13.7%	NAFLD: 3.3% vs 10.3%; ALD: 3.3% vs 1.7%; HBV: 1.7% vs 1.7%	-	ALT: 20 vs 26.8; AST: 26 vs 36; ALP: 61 vs 58; GGT: 21 vs 35.2; TB: 10.9 vs 11.2	ALI: 9.6% vs 36.2%; Discharge: 93.3% vs 75.9%; Hospital-stay: 19 d vs 27 d; Death: 0% vs 5.2%
Du <i>et al</i> [57]. China	N = 109. Non-ICU vs ICU	72.7 vs 68.4	65.5% vs 70.6%	3.4% vs 0%	-	ALT: 13.8% vs 19.6%; AST: 49% vs 43.1%	ALT: 21.6 vs 27; AST: 32 vs 40	Invasive MV: 0% vs 64.7%; Hospital-stay: 12.5 d vs 15.9 d
Guan <i>et al</i> [40]. China	N = 1099 (n = 173). Non-severe vs severe	45 vs 52	58.2% vs 57.8%	2.4% vs 0.6%	HBV	ALT: 19.8% vs 28.1%; AST: 18.2% vs 39.4%; TB: 9.9% vs 13.3%	-	ARDS: 1.1% vs 15.6%; MV: 0% vs 38.7%; Discharge: 5.4% vs 2.9%; Hospital-stay: 11 d vs 13 d; Death: 0.1% vs 8.1%
Huang <i>et al</i> [2]. China	N = 41 (n = 13). Non-ICU vs ICU	49 vs 49	68% vs 85%	4% vs 0%	-	AST: 25% vs 62%	ALT: 27 vs 49; AST: 34 vs 44; TB: 10.8 vs 14	ARDS: 4% vs 85%; Shock: 0% vs 23%; Invasive MV: 0% vs 15%; Discharge: 75% vs 54%; Death: 4% vs 38%
Lei <i>et al</i> [28]. China	N = 5771 (n = 1186). Non-severe vs severe	55 vs 59	45.1% vs 55.3%	1.2% vs 2.1%	Viral hepatitis Cirrhosis	-	ALT: 23 vs 26; AST: 22 vs 31; ALP: 65 vs 63; TB: 10.3 vs 10.6	Reported as association not absolute values
Li <i>et al</i> [58]. China	N = 548 (n = 269). Non-severe vs severe	56 vs 65	45.2% vs 56.9%	1.1% vs 0.7%	HBV	ALT: 22.3% vs 24.1%; AST: 23.3% vs 43.4%; TB: 2.3% vs 6.4%	-	ALI: 15.8% vs 23%; ARDS: 9.7% vs 68%; MV: 4% vs 34.2% <sup>2</sup> ; Discharge: 72.9% vs 31.7%; Death: 1.1% vs 32.5%
Mo <i>et al</i> [59]. China	N = 155 (n = 85) <sup>3</sup> . General vs refractory	47 vs 61	44.3% vs 64.7%	2.9% vs 5.9%	-	-	ALT: 20 vs 28; AST: 32 vs 37	Critical case: 4.3% vs 40%; MV: 0% vs 41.2%; Others reported as association
Wan <i>et al</i> [60]. China	N = 135 (n = 40). Mild vs severe	44 vs 56	54.7% vs 52.5%	1% vs 2.5%	-	AST: 16% vs 37.5%	ALT: 21.7 vs 26.6; AST: 22.4 vs 33.6; TB: 8.6 vs 9.8	ARDS: 1.1% vs 50%; Shock: 0% vs 2.5%; Discharge: 10.5% vs 12.5%; Death: 0% vs 2.5%
Wang <i>et al</i> [1]. China	N = 138 (n = 36). Non-ICU vs ICU	51 vs 66	52% vs 61.1%	3.9% vs 0%	-	-	ALT: 23 vs 35; AST: 29 vs 52; TB: 9.3 vs 11.5	ARDS: 4.9% vs 61.1%; Shock: 1% vs 30.6%; Invasive MV: 0% vs 47.2%
Wu <i>et al</i> [42]. China	N = 201 (n = 84) <sup>4</sup> . Non-ARDS vs ARDS	48 vs 58.5	58.1% vs 71.4%	3.5% <sup>5</sup>	-	-	ALT: 27 vs 35; AST: 30 vs 38; TB: 10.5 vs 12.9	MV: 0% vs 78.6% <sup>2</sup> ; Others reported as association
Zhang <i>et al</i> [61]. China	N = 221 (n = 55). Non-severe vs severe	51 vs 62	44% vs 63.6%	1.8% vs 7.3%	-	-	ALT: 22 vs 32; AST: 27 vs 51; TB: 9.6 vs 11.4	ARDS: 0% vs 87.3%; Shock: 0% vs 27.3%; MV: 1.2% vs 74.6% <sup>2</sup> ; Discharge: 21.1% vs 12.7%; Death: 0% vs 21.8%
Zhang <i>et al</i> [62]. China	N = 140 (n = 58). Non-severe vs severe	51.1 vs 64	46.3% vs 56.9%	5% vs 6.9%	Fatty liver and abnormal liver function	-	-	-

Zheng <i>et al</i> [63]. China	N = 161 (n = 40 vs 57 30). Non-severe vs severe	50.4% vs 46.7%	3.1% vs 0%	-	ALT: 6.1% vs 16.7%; AST: 7.6% vs 40%; TB: 4.6% vs 10%	ALT: 19.3 vs 23.9; AST: 23.4 vs 31.6; TB: 10.7 vs 12.7	-
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<sup>1</sup>Total number of patients is 417 and 318 is the number for patients with liver injury (for which the comparison between severe and non-severe disease was done).

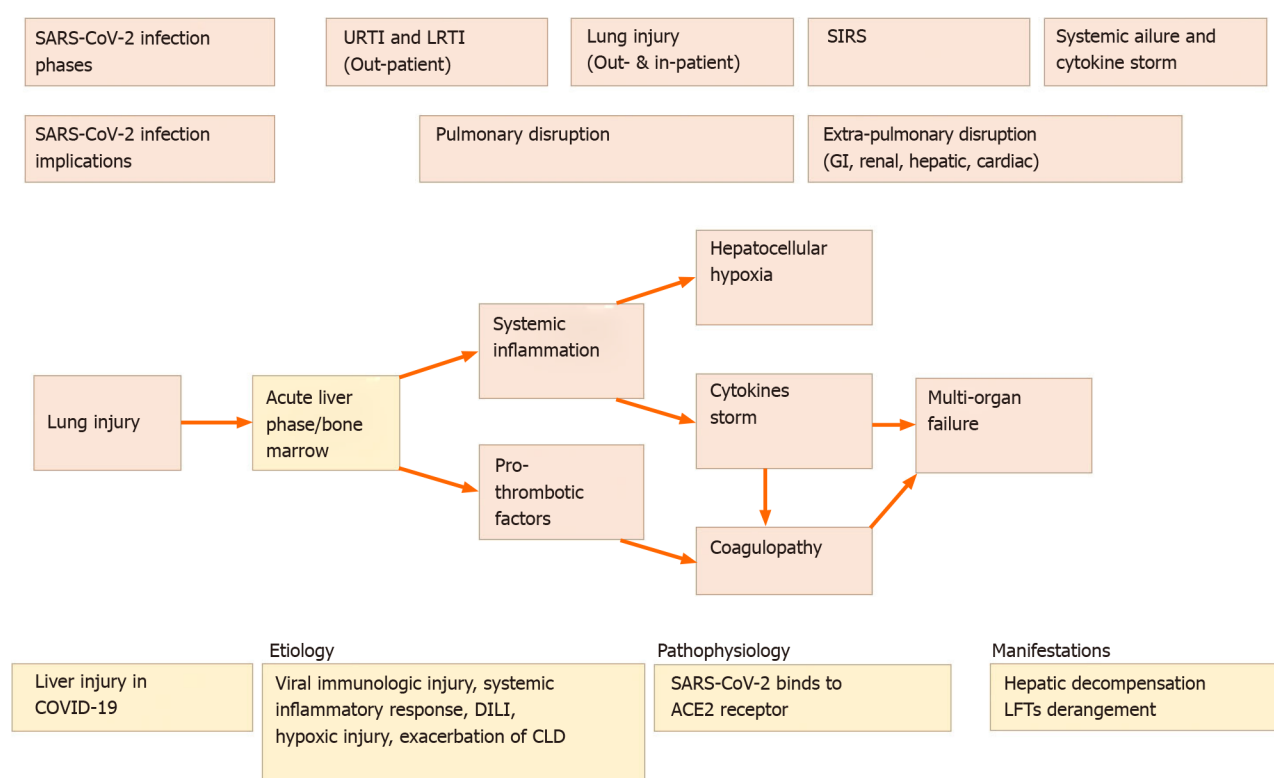
<sup>2</sup>Invasive and non-invasive mechanical ventilation.

<sup>3</sup>Reported patients with refractory and critical illness and  $\geq 10$  d of treatment in hospital.

<sup>4</sup>Subgroup of patients who developed acute respiratory distress syndrome (ARDS) after admission and those who progressed from ARDS to death.

<sup>5</sup>Reported for all patients.

ICU: Intensive care units; ALD: Alcoholic liver disease; ALT: Alanine aminotransferase; ALP: Alkaline phosphatase; ALI: Acute liver injury; ARDS: Acute respiratory distress syndrome; AST: Aspartate aminotransferase; CLD: Chronic liver disease; GGT: Gamma-glutamyl transpeptidase; HBV: Hepatitis B virus; LFTs: Liver function tests; MOF: Multiorgan failure; MV: Mechanical ventilation; N and n: Number of patients; NAFLD: Non-alcoholic fatty liver disease; TB: Total bilirubin.



**Figure 1 Pathogenesis of liver injury in coronavirus disease 2019.** ACE2: Angiotensin-converting enzyme 2; COVID-19: Coronavirus disease 2019; CLD: Chronic liver disease(s); DILI: Drug-induced liver injury; GI: Gastrointestinal; LRTI: Lower respiratory tract infection; LFTs: Liver function tests; SARS-CoV-2: Severe acute respiratory syndrome coronavirus-2; SIRS: Systemic inflammatory response syndrome; URTI: Upper respiratory tract infection.

## DILI IN PATIENTS WITH COVID-19

Numerous medications that are currently used to treat SARS-CoV-2 infection carry the risk of hepatotoxicity. Given that many medications are being used in combination, the interpretation of the commonly seen raised liver transaminases in patients with COVID-19 can be biased. While the efficacy of these medications towards improving COVID-19's morbidity and mortality is still to be proven, their safety should be monitored closely[73]. A retrospective study aimed to investigate adverse drug reactions (ADRs) in 217 COVID-19 patients using a hospital pharmacovigilance system in China found that 82 patients experienced 94 ADRs, with 13.8% of them were categorized as liver disorders. A multivariate analysis showed that the occurrence of ADRs has been associated with the length of stay (OR: 2.02, 95%CI: 1.03–3.96,  $P = 0.04$ ), number of drugs used in hospital (OR: 3.12, 95%CI: 1.60–6.27,  $P = 0.001$ ) and underlying diseases (OR: 2.07, 95%CI: 1.02–4.23,  $P = 0.045$ )[73]. In a prospective study using pharmacovigilance system in Spain, patients with COVID-19 had a higher incidence of hepatitis as a serious ADR than that in non-COVID-19 patients (45.1% vs 23.7%)[74]. In a meta-analysis of 10 studies, DILI in COVID-19 was reported in 25.4%

of the total patients[5]. Therapies that have been implicated in hepatotoxicity included remdesivir, lopinavir/ritonavir, oseltamivir, hydroxychloroquine, paracetamol[5], tocilizumab[74], in addition to antibiotics, non-steroidal anti-inflammatory drugs, herbal medications, and interferon[34]. In a retrospective, observational cohort study ( $n = 1827$ ), the use of lopinavir/ritonavir, hydroxychloroquine, remdesivir, and tocilizumab was associated with statistically significant abnormal ALT and AST levels (*i.e.*,  $> 5 \times$  upper limit of normal)[75].

Data on DILI's clinical significance have not been consistent. Sun *et al*[73] reported 18.1% of ADRs to be of serious severity, with 82.3% of them related to liver injury[73]. Ramirez *et al*[74] reported a mortality rate of 30.5% in COVID-19 patients with serious ADRs compared with 3.9% in non-COVID-19 patients with serious ADRs[74]. However, Kulkarni *et al*[5] concluded that remdesivir and lopinavir/ritonavir DILI was not life-threatening[5]. A systematic review and network meta-analysis of 110 studies reported no association between a regimen or an agent with non-cardiac severe adverse events[76]. In a multicenter and retrospective study ( $n = 565$ ) on hospitalized COVID-19 patients, *de novo* LFTs abnormality was noted with tocilizumab (82% *vs* 52%;  $P = 0.009$ ) and lopinavir/ritonavir (64% *vs* 48%;  $P = 0.045$ ). Moreover, there was a trend towards an increased composite endpoint of death or transfer to ICU associated with *de novo* LFTs abnormality with an incidence of 14% *vs* 5% ( $P = 0.069$ )[27]. Although published data regarding the incidence, severity and clinical significance of DILI have not been consistent, it warrants close monitoring of LFTs. Table 4 summarizes the reported DILI of selected therapies against COVID-19[5,27,34,74,75,77-95].

## DRUG-DRUG INTERACTIONS BETWEEN IMMUNOSUPPRESSIVE THERAPY AND COVID-19 AGENTS

Calcineurin inhibitors (CNIs), such as cyclosporine and FK506 (tacrolimus), antimetabolite drugs, such as mycophenolate mofetil (MMF), mycophenolic acid, and corticosteroids are commonly used for immunosuppression after liver transplantation (LTX) [96]. Some centres adopted dose modifications based on expert opinion with many uncertainties regarding the best approach for combination therapies and immunosuppressive agents against COVID-19. In two large academic centers in New York City including 90 patients with solid organ transplant, antimetabolite drugs doses were reduced or held in 88% of patients, steroids in 7%, and CNIs in 18%, with no reported acute rejection cases at 20-day follow-up[6]. In a prospective European study of 57 liver transplant patients with COVID-19, immunosuppression therapy doses were reduced in 39% of patients and discontinued in 7%. Reduction or continuation of therapy did not affect mortality, while the discontinuation effect was not assessed[97]. Drug interactions between COVID-19 medications and immunosuppression therapy were also considered. For instance, lopinavir-ritonavir combination interacts with CNIs and MMF, it is not recommended to be used with steroids[98] and has been reported to interact with mechanistic target of rapamycin (mTOR) as well[18]. Moreover, tocilizumab may decrease CNIs plasma concentration, unlike remdesivir which does not interact with the immunosuppressive drugs[98]. Hydroxychloroquine has been reported to interact with CNIs and mTOR[18]. Relevant recommendations included checking for drug interactions[18,98], dose reduction of steroids, CNIs and MMF[98,99], switching mTOR to CNIs[18], switching MMF and CNIs to steroids, and withdrawal of agents such as CNIs and MMF in severe COVID-19[99]. Monitoring of immunosuppressive drug levels should be warranted when possible[98,99]. The European Society of Clinical Microbiology and Infectious Diseases advised not to reduce the doses of immunosuppressive drugs in liver transplanted patients and raised the importance of considering vaccination with *Streptococcus pneumonia* and influenza vaccines[100].

## IMPACT OF COVID-19 ON LIVER TRANSPLANTATION PROGRAMS

### General measures

The unprecedented disturbance created by the COVID-19 pandemic has impacted different sectors of health care systems worldwide. For instance, elective services were cancelled or postponed while lifesaving transplant programs, including those for a liver transplant, have been continued. However, the non-lifesaving transplant services

**Table 4** Reported effects of selected coronavirus disease 2019 therapies on liver

Medication (class)	Pattern of liver injury	Evidence
Corticosteroids (Anti-inflammatory agent)	Acute liver injury[77]	Multicenter cohort study ( $n = 774$ ); COVID-19 with ARDS: Incidence of ALI versus control (18.3% <i>vs</i> 9.9%; $P = 0.001$ ) [77]  Meta-analysis; critically ill COVID-19 patients: No association with serious adverse effects[78]  RECOVERY trial: No reported serious ADRs or DILI[79]
Favipiravir (RdRp inhibitor)	Abnormal LFTs[80]  Elevation of transaminases levels[81]	RCT ( $n = 150$ ); mild-to-moderate COVID-19: Abnormal LFTs versus control 6.8% <i>vs</i> 2.7%[80]  RCT; moderate COVID-19: Elevated ALT and AST were reported[81]
Hydroxychloroquine (Antimalarial agent)	Liver toxicity is not common[82]. Elevation of transaminases levels[74,75,82-84]	Retrospective study ( $n = 153$ ): Elevation in AST (11%) and ALT (9%)[82]  RCT ( $n = 504$ ); mild-to-moderate COVID-19: Elevation in ALT or AST elevation 10.6% in HCQ plus azithromycin, 9% in HCQ, and 3.5% in control arm ( $P = 0.008$ )[83]  Systematic review: Elevations of LFTs was transient[84]  Recovery trial: No reported DILI[85]
Interferon	-	Data on safety in COVID-19 patients is scarce
Lopinavir/ritonavir (Protease inhibitor)	Rise in liver function parameters[5,27,34,74,86]  Hyperbilirubinemia[5,34]	RCT ( $n = 199$ ): Elevated AST versus control (2.1% <i>vs</i> 5.1%), elevated ALT (1.1% <i>vs</i> 1%), elevated TB (3.2% <i>vs</i> 3%)[86]  Meta-analysis: DILI in 37.2% of patients (as hyperbilirubinemia followed by elevation of transaminases)[5]
Remdesivir (RdRp inhibitor)	Not well established. Elevation of transaminases levels[5,75,87-89]. Elevation of TB levels[88]. Hypoalbuminemia[88]	Case series: Elevated aminotransferases in 23 % discontinuation in 4% of patients[87]  RCT ( $n = 237$ ) in severe COVID-19: Elevated TB versus placebo (10% <i>vs</i> 9%) and AST (5% <i>vs</i> 12%), hypoalbuminemia (13% <i>vs</i> 15%). Discontinuation in 1% of patients[88]  Open-label, phase 3 trial: Elevated ALT (5%-6%) and AST (7%-8%)[89]  Meta-analysis: Pooled incidence of DILI of 15.2%[5]  Meta-analysis: No difference as compared to placebo in liver enzymes elevation[90]
Tocilizumab (Humanized recombinant monoclonal antibody)	Elevation of transaminases levels[27,75,91-94]. Liver injury as early as 24 h with a 40-fold increase in transaminases that normalized in 10 d[91]	Case series; 7 severe COVID-19 patients: Up to 4.5 folds elevated baseline ALT and AST. Transaminases normalized in 3 wk[92]  Retrospective study ( $n = 1827$ ): AST $> 5 \times$ ULN in 69.1%, and ALT $> 5 \times$ ULN in 72.1% of patients[75]  Observational study ( $n = 104$ ): Minor increase of AST, ALT ( $P < 0.001$ ) and GGT ( $P = 0.003$ ; no safety concerns on follow up[93]  RCT ( $n = 243$ ): ALT elevation versus placebo (5% <i>vs</i> 4.9%), AST elevation in 3.7%[94]  RCT ( $n = 130$ ); moderate or severe COVID-19: No increase in hepatitis risk[95]

COVID-19: Coronavirus disease 2019; ADRs: Adverse drug reactions; ALI: Acute liver injury; ALT: Alanine aminotransferase; ALP: Alkaline phosphatase; AST: Aspartate aminotransferase; DILI: Drug-induced liver injury; GGT: Gamma-glutamyl transpeptidase; HCQ: Hydroxychloroquine; LFTs: Liver functions tests; RCT: Randomized controlled trial; RdRp: RNA-dependent RNA polymerase; TB: Total bilirubin; ULN: Upper limit of normal.

were frequently delayed, exposing patients to emergency situations[101]. LTX is the most common solid organ transplantation procedure after the kidney, with a global rate of 3.7 *per* million population[102]. The indication of LTX in the acute phases of liver diseases includes acute liver cell failure, metabolic liver diseases, advanced



complicated cirrhosis, and CLD associated with systemic complications[103]. Elective LTX indications include advanced cirrhosis associated with deteriorating synthetic function, renal function, and the related complications[104]. The general precautions before LTX currently comprise a COVID-19 testing for both donors and recipients awaiting transplant and consenting for the possible hazard of acquiring nosocomial COVID-19[100]. The standard method of COVID-19 testing is through a nasopharyngeal swab or intraoperative bronchoalveolar lavage. Viral load should be measured in positive cases. The transplant team should be adequately screened, and the risk of exposure identified[101]. Hollander and Carr[105] advised on the use of telemedicine, such as virtual clinics or *via* phone calls, to minimize both healthcare providers and patient's exposure to COVID-19[105]. The success of telemedicine in the Chinese territory during the peak of the pandemic could be transposed to future networking to use information and communication technology extensively during the care of patients with COVID-19[106].

### ***ICU care of liver transplant patients in the era of COVID-19***

Strict infection control measures are required in the post-operative care of LTX patients to prevent nosocomial infections that include COVID-19[107]. During the admission of LTX patients, they should be directed to separate rooms away from the general wards, and strict disinfection and isolation practices should be in place. Medical and surgical rounds should be minimized, and laboratory testing and radiological studies should be reduced to the least required[108]. Acquiring symptoms suggestive of COVID-19 in a LTX patient should prompt urgent evaluation with the relevant investigations[105]. Other challenges prompted by the COVID-19 pandemic include the increased demand for ICU beds, requiring health care practitioners to work in a dynamic way to maximize ICU bed utilization[109]. During the pandemic, the settings required for ICU should include separate units equipped with high-efficiency particulate air filters[110]. The goals of ICU disposition for LTX patients comprise neurological monitoring, hemodynamic monitoring and support, early weaning from the mechanical ventilator, preventing nosocomial infections and graft-related complications and enhancing early graft recovery[111]. Some institutes screen for COVID-19 in LTX recipients[112]. Simple and effective measures could be implemented to shorten the ICU stay for LTX patients through fast-track procedures, including operating room early extubation, reduction of ventilation time, and direct transfer from the recovery room to surgical wards[113,114]. Transplant services constantly demand resources, which have become extremely limited with the emergence of the COVID-19 pandemic due to staff shortage, saturation of the ICU, and drainage of supplies. Exceptional scarcity of donors and demand for organs also aggravate this problem[115,116].

### ***Transplantation outcome during COVID-19 pandemic***

Reports regarding the outcomes of LTX patients have been inconsistent. Although early reports have not found more severe or worse outcomes among immunosuppressed patients[117], subsequent data showed that solid organ transplant recipients diagnosed with COVID-19, including LTX, seemed to be at increased risk of severe disease, morbidity, and poor outcomes[6,118], such as high mortality with an in-hospital mortality rate of 29%[119]. Bossini *et al*[120] reported a higher rate of acute respiratory distress syndrome (ARDS) and death among patients who received solid organs[120], while others reported similar outcomes in COVID-19 patients with and without solid organ transplant[121]. In a multi-centre study of ICU patients after solid organ transplant, the rate of ARDS, duration of mechanical ventilation, vasopressors requirements, and death were similar between groups[122].

### ***Vaccination considerations***

It was reported that in liver transplant recipients, COVID-19 infection was not associated with increased mortality. However, these patients are subjected to severe disease, as evidenced by a higher rate of both ICU admission and mechanical ventilation use[123]. The European Association for the Study of the Liver (EASL) suggested a particular form of judging the vaccination decision based on patient's morbidities[124]. The immune response to COVID-19 vaccination could be lower in LTX patients when compared with healthy subjects. Poor response to vaccination is affected by age, renal function, and enhanced immune suppression[125].



## IMPLICATIONS AND FUTURE DIRECTIONS

The COVID-19 pandemic has been presented as an unprecedented global health care crisis, causing significant setbacks among various health care services including the management of CLD. Besur *et al*[35] reported that screening for CLD, its complications and regular follow up visits were deferred which affected slowing or reversing the progression of CLD and worsened the prognosis of patients with CLD. Late identification of CLD complications such as hepatocellular carcinoma (HCC) could also affect the clinical outcomes in these patients. Social distancing measures have put CLD patients at risk of malnutrition, reduced mental health capacity, and decompensation [35]. The evidence associating acute liver injury with poor patients' outcomes and increased severity of COVID-19 is growing, and more research is necessary to further explain the relation between liver biomarkers changes and patients' outcomes in COVID-19[126]. Various factors influence the course of COVID-19, and there is a need for international collaborative registries to clarify the full spectrum of the disease. The registries, Surveillance Epidemiology of Coronavirus (COVID-19) Under Research Exclusion (SECURE-Cirrhosis) and Coronavirus (COVID-19) in liver disease reporting registry (COVID-HEP) were established to report data on patients with liver disease. The last report published in August 2020 by SECURE-Cirrhosis and the EASL supported COVID-Hep, reported 158 deaths (31%) among patients who had cirrhosis and developed SARS-CoV-2 infections[127]. When this article was written, the latest update from both COVID-Hep and SECURE-Cirrhosis registries reported 1341 cases that included 645 cases with cirrhosis, 205 liver transplant recipients and 270 deaths as of February 12, 2021[128].

COVID-19 pandemic has disrupted various healthcare services worldwide, limiting the services offered to urgent and emergent cases. These changes in services, clinician behaviour and re-organization of hospital activities can indirectly affect morbidity and mortality[129]. delaying or halting diagnostic and therapeutic services for diseases with a high global burden such as cardiovascular diseases can contribute to long-term and indirect adverse health outcomes. For example, cardiac diagnostics procedures, stress tests[129], emergency department (ED) and hospital admissions, procedures and treatments were markedly declined during the pandemic year as compared with that of the previous years[130]. In 909 inpatient and outpatient centres from 108 countries, the rate of cardiac diagnostic procedures decreased by 42% and 64% as of March and April 2020, respectively, with the highest reduction of 78% observed for the stress tests, as compared with March 2019.[130]. A further 22% reduction was noted in low and low-middle income countries, which might be attributed to inaccessible personal protective equipment and telehealth services[130].

In United Kingdom, a cross-sectional study conducted in nine hospitals compared the hospitals' cardiovascular activity data between October 2019 and May 2020 with the respective weeks in 2018 and 2019. There was a marked decline in ED attendances, admissions and hospital procedures and treatments[129]. Patients with other chronic diseases which require close follow up have been negatively affected as well. A cross-sectional study of six referral centres in France showed that in 2020 significantly fewer patients with HCC were referred to the multidisciplinary tumour board ( $P = 0.034$ ) and fewer received the first diagnosis of HCC ( $P = 0.083$ ) compared with 2019[131]. Therapy optimization and frequency of follow-up visits were also affected by the global pandemic in response to social distancing and re-allocation of services towards fighting COVID-19. A delay in therapy modification for more than one month was noted in 21.5% *vs* 9.5% of patients during 2020 compared with 2019 ( $P < 0.001$ ), respectively[131]. In patients with hepatitis C virus who were following up for HCC, there was significant reduction in their scheduled visits, *i.e.*, by before 75%, 63.0%, and 49.1% in March to May 2020, respectively, compared with 97% before February 2020 [132]. Surgical interventions for HCC have significantly declined or stopped across many centers in the world due to increased risk of blood transfusion, ICU stay, prolonged hospitalization and developing COVID-19 after surgery[133]. In a national survey by the Italian Association for the Study of the Liver, HCC treatment was affected; where surgical treatment was reduced in 44% and suspended in 44% of the participating centres, while the loco-regional treatment was reduced in 34% and suspended in 8% of the centres[134].

## CONCLUSION

The pathogenesis and characteristics of COVID-19-related multifactorial liver injury

can be explained by multiple mechanisms. The knowledge about the full spectrum of SARS-CoV-2 infection is being accumulated, given the novelty of the disease and the constantly reported new data. Liver dysfunction is commonly seen in patients presenting with the severe form of COVID-19. Various therapeutic options used for COVID-19 can lead to DILI and contribute to the exacerbation of the existing liver injury. It is challenging to identify the causal factor in the settings of infection, sepsis, and/or hypoxia, especially when the liver enzymes abnormalities are non-specific. The underlying liver disease has not been linked with poor outcomes. Hospitalized patients or those with liver comorbidities should be monitored closely. Patients with COVID-19 and LTX must maintain strict infection control and monitor drug interactions while maintaining immunosuppressive therapy at regular doses. Future research would help explain liver injury associated with SARS-CoV-2 infection and design specific guidelines for the management of COVID-19 in these patients.

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