

## REVIEW

# COVID-19 and the Liver: Lessons Learnt from the EAST and the WEST, A Year Later

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**Abstract**

Globally, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2 virus) has been a major cause for significant morbidity and mortality. Since the start of the pandemic, several hepato-biliary manifestations in coronavirus disease 2019 (COVID-19) have been described and unique considerations raised. The review aims to summarize the pathogenesis and hepato-biliary manifestations in COVID-19 and discuss the similarities, contrasting features and disease-specific management across a range of hepato-biliary diseases from the EAST and the WEST. Published studies and regional society guidelines from the EAST and the WEST were comprehensively reviewed and summarized. A wide range of hepato-biliary manifestations, including the infrequent and chronic manifestation of cholangiopathy, has been observed in COVID-19. The pathogenesis of liver injury is multifactorial and with scant evidence for a direct SARS-CoV-2 infection of the liver. Patients with non-alcoholic fatty liver disease, cirrhosis, and liver cancer are potentially at increased risk for severe COVID-19, and there are unique considerations in chronic hepatitis B or C, hepatocellular carcinoma, and in those immunosuppressed such as autoimmune hepatitis or liver transplant recipients. With the surges in SARS-CoV-2 infection, liver transplant activity has variably been impacted. Preliminarily, SARS-CoV-2 vaccines appear to be safe in those with chronic liver disease and in transplant recipients, while emerging data suggest the need for a third dose in immunosuppressed patients. In conclusion, patients with chronic liver disease, particularly cirrhosis, and liver transplant recipients, are vulnerable to severe COVID-19. Over the past year, several unique considerations have been highlighted across a spectrum of hepato-biliary diseases. Vaccination is strongly recommended for those with chronic liver disease and liver transplant recipients.

**KEYWORDS**

cirrhosis, COVID-19, hepatitis, liver transplant, vaccination

## 1 | INTRODUCTION

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2 virus) has affected people from different parts of the World and has been a major cause for significant morbidity and mortality to date. Coronavirus disease 2019 (COVID-19), the disease caused by SARS-CoV-2, can present with various clinical features and while

pulmonary manifestation is the most common, hepatic abnormalities can be encountered in up to 50% of infected individuals.<sup>1,2</sup> The spectrum is variable and can range from asymptomatic abnormalities in hepatic biochemical tests to severe liver injury with some reports of acute-on-chronic liver failure in patients with underlying cirrhosis.<sup>3-5</sup> Hepatic dysfunction has been associated with poor outcome and which has been noted to be more frequent in critically ill

patients.<sup>6</sup> The cause for hepatic dysfunction is hypothesized to be based on one or more factors such as ischaemic liver injury, immune-mediated liver injury, drug-induced liver injury, pre-existing liver diseases or a direct cytopathic effect of the virus.<sup>1,7</sup> Further, it has been noted that up to 2%–11% of patients with COVID-19 had pre-existing liver disease<sup>2</sup> and that patients with underlying cirrhosis had higher mortality.<sup>1</sup> This review highlights several observations, and the lessons learnt since the pandemic started, on liver manifestations in COVID-19, from the EAST and the WEST, including prevalence, severity and pathogenesis. Further, we also summarize on the similarities and contrasting features in outcomes and disease-specific management in those on immunosuppressive therapy, post-transplantation state, hepatocellular carcinoma (HCC), patients with chronic liver disease, compensated/decompensated cirrhosis, viral hepatitis, non-alcoholic fatty liver disease (NAFLD) and autoimmune liver diseases and also provide emerging data on the safety and efficacy of vaccines in those with chronic liver disease, as well as the immunosuppressed. While COVID-19 patients are encountered by a wide range of providers, including primary care, emergency room, infectious disease, gastroenterology, hepatology, critical care and palliative care specialties, this review aims to provide information specifically for those who evaluate and provide care to those with a spectrum of liver-related clinical situations in the context of COVID-19.

## 2 | LIVER MANIFESTATION OF COVID-19 FROM THE EAST AND THE WEST

Since the outbreak of the novel coronavirus (SARS-CoV-2) in Wuhan, China in December 2019, it was labelled a pandemic by WHO in March 2020 and globally has led to disastrous public health consequences. Although most of the COVID-19 cases have been mild, fatality due to respiratory failure and severe pneumonia is not uncommon with an estimated 2.5% case fatality rate worldwide,<sup>8</sup> and with a WHO estimated 3.8 million deaths globally by June 2021.<sup>9</sup> Liver impairment has been described as an elevation of aspartate transaminase (AST) or alanine transaminase (ALT) in around 10%–58%, mild bilirubin elevation in 3%–23%, slight alkaline phosphatase (ALP) elevation in 1%–10% and gamma-glutamyl transferase (GGT) elevation in 13%–54% in patients with COVID-19.<sup>2,10–29</sup> Most of the hepatic biochemical test abnormalities have been noted to return to normal values within 2–3 weeks and without specific treatment.<sup>23</sup> The pattern of liver injury is mostly hepatocellular rather than cholestatic although one would have expected a predominance of a cholestatic injury due to an abundance in the biliary epithelium of ACE2 receptors, to which the SARS-CoV-2 has an affinity.<sup>30,31</sup> Patients with severe COVID-19 seem to have higher rate of liver impairment as noted by ALT or AST being more than three-fold the upper limit of normal (ULN) or total bilirubin of more than two-fold of the ULN.<sup>7</sup> AST is usually higher than ALT and has been associated with severe COVID-19 and mortality, which could possibly be the result of immune-mediated inflammation or non-hepatic injury.<sup>32,33</sup>

Interestingly, a report from Cai Q et al. found that COVID-19 patients with abnormal hepatic biochemical tests had higher risk of progressing to severe disease during hospitalization (odds ratio (OR) = 2.73 with hepatocellular pattern, and OR = 4.44 with mixed cholestasis-hepatocellular injury pattern).<sup>22</sup> However, some studies found no correlation between hepatic biochemical test abnormalities and severe clinical consequences or survival.<sup>23,24</sup> Low serum albumin at hospital admission has been a marker of COVID-19 severity.<sup>34–36</sup> Fan et al. reported that patients with abnormal hepatic biochemical tests were more likely to be male, associated with higher levels of procalcitonin and C-reactive protein, and longer mean hospital stay compared to patients with normal tests (15.09 ± 4.79 days vs. 12.76 ± 4.14 days) ( $p = 0.021$ ).<sup>18</sup> Further, a multicentre cohort (COVID-LIVER-CHESS) from China ( $n = 70$ ) found that a longer time from illness onset to admission resulted in greater risk of liver injury in patients with COVID-19, thus suggesting the need of early detection of SARS-CoV-2 infection.<sup>37</sup> In contrast, severe COVID-19 is uncommon in children, and usually not associated with abnormal liver biochemistries; thus, when evaluating COVID-19-infected children with AST or ALT elevation, it is suggested that there be a search for underlying liver diseases and other coexisting infections.<sup>38,39</sup> Data on liver manifestations and prevalence of hepatic biochemical test abnormalities in reports on COVID-19 from the EAST and the WEST are summarized in Table 1 and Table 2. Because of a high prevalence of LFT abnormalities, regular monitoring of liver biochemistries should be performed in all COVID-19 patients.<sup>39</sup> It is important to always consider other aetiologies unrelated to COVID-19 when assessing COVID-19 patients with elevated liver enzymes; other viral infections such as hepatitis A, B and C should also be evaluated.<sup>40</sup> Data on pre-existing liver diseases were reported in several studies and has been around 2%–11%.<sup>2</sup> Patients with cirrhosis are at increased risk of infections and associated complications due to cirrhosis-associated immune dysfunction.<sup>41,42</sup> Mortality due to COVID-19 appears higher in patients with more advanced liver disease and the highest in cirrhosis.<sup>32,42</sup>

## 3 | POSSIBLE PATHOGENESIS OF HEPATIC MANIFESTATIONS IN COVID-19

SARS-CoV-2 is a single, positive-stranded RNA virus that replicates using a virally encoded RNA dependent RNA polymerase.<sup>32</sup> The underlying mechanisms of liver injury in those with COVID-19 are believed to be multifactorial, some of which are based on histopathology from core samples at autopsy.<sup>7</sup> (Figure 1).

1. Direct viral injury: the proposed pathogenesis of SARS-CoV-2-related liver injury may be based on the expression of ACE2 entry receptors by both hepatocytes and cholangiocytes. However, the ACE2 expression in the cholangiocytes (59.7%) is much higher than the hepatocytes (2.6%).<sup>31</sup> Accordingly, liver injury due to COVID-19 may result from direct viral damage to bile duct epithelial cells which have been known to have

TABLE 1 Liver manifestations and prevalence of hepatic biochemical test abnormalities in COVID-19 patients from the EAST

Study	N	Country	Pre-existing liver diseases	AST↑	ALT↑	Albumin↓	Bilirubin↑	ALP↑	GGT↑
Chen N et al. <sup>10</sup>	99	China	N/A	35%	28%	98%	18%	N/A	N/A
Guan WJ et al. <sup>11</sup>	1,099	China	2.1%	22.2%	21.3%	N/A	10.5%	N/A	N/A
Huang C et al. <sup>12</sup>	41	China	2%	37% (AST elevation in ICU setting 62% compared with non-ICU 25%)					
Shi H et al. <sup>13</sup>	81	China	9%	53%	N/A	N/A	N/A	N/A	N/A
Xu XW et al. <sup>14</sup>	62	China	11%	16.1%	N/A	N/A	N/A	N/A	N/A
Yang X et al. <sup>15</sup>	52	China	N/A	29% hepatic dysfunction					
Cai Q et al. <sup>16</sup>	298	China	9.4%	8.4%	13.1%	N/A	8.1%	0.3%	17.1%
Cao B et al. <sup>17</sup>	199	China	N/A	20.5%	41%	N/A	N/A	N/A	N/A
Fan Z et al. <sup>18,19</sup>	148	China	6.1%	21.6%	18.2%	N/A	6.1%	4.1%	17.6%
Zhang C et al. <sup>2</sup>	56	China	3.6%	28.6% abnormal liver function testing					
Huang Y et al. <sup>20</sup>	36	China	N/A	58.1%	13.3%	80.6%	12.9%	N/A	N/A
Cao M et al. <sup>21</sup>	198	China	3%	17.4%	10.8%	40%	2.6%	N/A	N/A
Cai Q et al. <sup>22</sup>	417	China	5%	18.2%	12.9%	N/A	23.2%	4.8%	16.3%
Zhang Y et al. <sup>23</sup>	115	China	N/A	14.8%	9.6%	54.8%	6.9%	5.2%	13.0%
Tang C et al. (meta-analysis) <sup>29</sup>	20,662	China	4.2%	23.6%	19.0%	37.5%	9.5%	N/A	N/A
Lei F et al. <sup>33</sup>	5,771	China	1.4%	ALT, AST, ALP, total bilirubin levels were associated with mortality risk, and elevated AST was associated with the highest mortality risk					
Fu Y et al. <sup>107</sup>	482	China	19.9%	20.3%	19.9%	41.3%	4.8%	Abnormal AST or total bilirubin on admission was associated with mortality	
Wang Y et al. <sup>108</sup>	156	China	N/A	Elevated aminotransferase 41%, liver enzyme abnormalities in patients with COVID-19 were associated with disease severity					
Ji D et al. <sup>30</sup>	202	China	NAFLD 37.6% Hepatitis B 3.5%	16.8%	50%	N/A	8.4%	2.5%	22.8%
Huang R et al. <sup>109</sup>	280	China	NAFLD 30.7%	13.6-26.4% (NAFLD 16.3-26.7%)	20-46.8% (NAFLD 40.7-65.1%)	N/A	9.3-25.7% (NAFLD 15.1-26.7%)	2.5-3.6% (NAFLD 0-1.2%)	15-32.9% (NAFLD 23.3-40.7%)
Zhou YJ et al. <sup>110</sup>	327	China	NAFLD 28.4%	COVID-19 was worse in younger patients with NAFLD and increased the likelihood of severe illness by approximately 3-fold					
Yadav DK et al. (meta-analysis) <sup>111</sup>	2,115	China	4%	High prevalence of liver injury (27%), patients with liver injury had more severe disease (OR = 2.57, p = 0.01) and higher mortality (OR = 1.66, p = 0.03), the overall mortality in patients with COVID-19 with liver injury 23.5%					
Dhampalwar S et al. <sup>112</sup>	12	India	Living donor liver transplant recipients	- 11 patients with mild COVID-19, 1 patient with severe disease and died. - Severe disease associated with comorbidities - Suggest overall favourable outcome of COVID-19 infection among LT recipients					

(Continues)

TABLE 1 (Continued)

Study	N	Country	Pre-existing liver diseases	AST↑	ALT↑	Albumin↓	Bilirubin↑	ALP↑	GGT↑
Sarin SK et al. (APCOLIS study) <sup>113</sup>	228	13 Asian countries	185 CLD patients and 43 cirrhosis (NAFLD 55%, viral 30%)	Mortality in CLD patients with COVID-19 vs. cirrhosis with COVID-19 (2.7% vs. 16.4%, <i>p</i> = 0.002), 43% of CLD presented as acute liver injury and 20% of patients with cirrhosis presented with either ACLF (11.6%) or acute decompensation (9%)					

Abbreviations: ACLF, acute-on-chronic liver failure; ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; CLD, chronic liver disease; GGT, gamma-glutamyl transferase; LT, liver transplant; N/A, not available; N, number of patients; NAFLD, non-alcoholic fatty liver disease; OR, odds ratio; ULN, upper limit of normal.

- a significance in liver regeneration and immune response.<sup>43</sup> Further, liver histopathology in those with COVID-19 has noted foci of hepatic necrosis both in periportal area (zone 1) and adjacent area to terminal hepatic veins (zone 3) without significant inflammatory cellular infiltration in the surrounding area, a feature consistent with the pattern of acute liver injury from a virus.<sup>7</sup> Additionally, isolation of SARS-CoV-2 RNA from post-mortem liver tissue through RT-PCR has been reported in a patient.<sup>44</sup> Recent published data suggest that mitochondrial proteins may directly interact with the virus,<sup>45</sup> providing a potential explanation for the AST-dominant liver injury.<sup>46</sup>
2. Drug-induced liver injury: treatment regimens for COVID-19 including antibiotics and antiviral agents (eg azithromycin, protease inhibitors, monoclonal Interleukin (IL)-6 receptor antagonists) can variably cause liver injury. Remdesivir (a nucleoside analog inhibitor of viral RNA polymerase) recently approved by the US Food and Drug Administration (FDA) was associated with a 23% increase in hepatic biochemical tests.<sup>47</sup> Some drugs used in combination such as acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs) and Chinese herbal medicines may account for hepatotoxicity. Microvesicular steatosis has often been observed again raising the possibility of drug-induced liver injury.<sup>48</sup>
  3. Underlying liver diseases: patients with COVID-19 may have underlying chronic liver diseases (CLD) such as hepatitis B, hepatitis C or non-alcoholic fatty liver disease (NAFLD), and some with cirrhosis. Treatment of these underlying diseases, for example anti-viral agents for hepatitis B or C, may be interrupted while treating COVID-19 which can then lead to HBV and HCV viral activity and exacerbate hepatic inflammation.<sup>48</sup> Further, corticosteroid treatment for COVID-19 may also facilitate hepatitis B viral replication.<sup>7</sup> Recent data on pre-existing liver diseases with COVID-19 from two international registries (SECURE-Cirrhosis and COVID-Hep) (*n* = 1102) (August 2020) reported aetiology of underlying cirrhosis to be alcohol in 29%, non-alcoholic steatohepatitis (NASH) 20%, hepatitis C 11%, hepatitis B 7%, autoimmune hepatitis 7% and combination aetiology in 5%.<sup>49,50</sup>
  4. Hyper-inflammatory cytokine storm: around 20% of COVID-19 patients can become severely ill and be characterized with increasing levels of inflammatory cytokines such as IL-1, IL-6, tumour necrosis factor (TNF), leading to a cytokine storm. With the hepatocytes being susceptible to hypoxic liver injury from severe COVID-19, this immune overreaction can result in further damage to hepatocytes which then can lead to a markedly abnormal hepatic biochemical profile.<sup>7</sup> To support this hypothesis, studies have noted that COVID-19 patients in ICU setting with multi-organ failures have features of severe hepatic dysfunction.<sup>23</sup> Further, post-mortem hepatic histopathology, in some, has noted only microvesicular steatosis, accompanied by overactivation of T cells, suggesting the likelihood of immune-mediated rather than direct cytopathic damage.<sup>30</sup>
  5. Hypoxic-ischaemic liver injury: ischaemic hepatitis is a condition characterized by AST-predominant hepatitis. Cardiomyopathy is a common consequence of COVID-19 infection, occurring in 33%

TABLE 2 Liver manifestations and prevalence of hepatic biochemical test abnormalities in COVID-19 patients from the WEST

Study	N	Country	Pre-existing liver diseases	AST↑	ALT↑	Albumin↓	Bilirubin↑	ALP↑	GGT↑
Vespa E et al. <sup>24</sup>	292	Italy	2%	18.5%	26.7%	N/A	10.6%	9.6%	36.2%
Grasselli G et al. <sup>25</sup>	1591	Italy	3%	Older patients (age ≥ 64 years) had higher mortality than younger patients (age < 64 years) (36% vs. 15%; <i>p</i> < 0.001), ICU mortality was 26%					
Cholankeril G et al. <sup>26</sup>	116	USA	2.8%	40% hepatic dysfunction, severity was associated with AST levels at presentation ( <i>p</i> = 0.009)			3.1%	0	N/A
Arentz M et al. <sup>27</sup>	21	USA	4.8%	Acute hepatic injury (AST or ALT >3 ULN) 14.3%					
Richardson S et al. <sup>28</sup>	5700	USA	0.5%	58.4%	39.0%	Acute hepatic injury (AST or ALT >15 ULN) 2.1%			
Phipps MM et al. <sup>14</sup>	2273	USA	5%	56–74%	24–45%	45% mild, 21% moderate, 6.4% severe liver injury, peak ALT was significantly associated with death (OR = 1.14; <i>p</i> = 0.044)			
Hundt MA et al. <sup>115</sup>	1827	USA	N/A (Obesity 42.5%)	66.9%	41.6%	56.7%	4.3%	13.5%	N/A
Bloom PP et al. <sup>116</sup>	60	USA	7%	Abnormal liver biochemistry 69%, AST elevation was common and associated with disease severity					
Lavarone M et al. <sup>5</sup>	50	Italy	Cirrhosis	67%	58%	Overall 30-day mortality rate of 34%, COVID-19 was associated with liver function deterioration and mortality in cirrhosis			
Cliff AK et al. <sup>117</sup> (population-based cohort study)	11,865	UK	Cirrhosis	Increased hazard ratio for COVID-19-related mortality in patients with cirrhosis Male HR = 1.29 (95%CI 0.83–2.02) Female HR = 1.85 (95%CI 1.15–2.99)					
Bajaj JS et al. <sup>67</sup>	- Patients with cirrhosis + COVID-19 ( <i>n</i> = 37) - Patients with COVID-19 ( <i>n</i> = 108) - Patients with cirrhosis ( <i>n</i> = 127)	North America and Canada	Cirrhosis	Patients with cirrhosis+ COVID-19 had higher mortality compared with patients with COVID-19 (30% vs. 13%, <i>p</i> = 0.03) but not between patients with cirrhosis+ COVID-19 and those with cirrhosis alone (30% vs. 20%, <i>p</i> = 0.16)					
Rabiee A et al. <sup>118</sup>	119	USA	LT recipients	-Mortality 22.3% -Moderate liver injury (ALT 2-5x ULN) 22.2%, severe liver injury (ALT >5x ULN) 12.3%, incidence of acute liver injury was lower in LT recipients -Liver injury in LT recipients was associated with mortality ( <i>p</i> = 0.007; OR = 6.91) and ICU admission ( <i>p</i> = 0.007; OR = 7.93)					
Colmenero J et al. <sup>73</sup>	111	Spain	LT recipients	Mortality 18%, severe COVID-19 31.5%, LT patients had an increased risk of acquiring COVID-19 but their mortality rates are lower than the matched general population					
Kates OS et al. <sup>119</sup>	73	USA	LT recipients	Within solid organ transplant cohort ( <i>n</i> = 482), LT was not associated with increased 28-day mortality ( <i>p</i> = 0.36)					

(Continues)

TABLE 2 (Continued)

Study	N	Country	Pre-existing liver diseases	AST↑	ALT↑	Albumin↓	Bilirubin↑	ALP↑	GGT↑
Webb GJ et al. <sup>74</sup> (SECURE-cirrhosis and COVID-Hep)	151	International registry	LT recipients	-Overall mortality 18.5% -LT did not significantly increase the risk of death -Age, creatinine, and non-liver cancer were associated with death among LT recipients					
Belli LS et al. <sup>120</sup>	243	Europe	LT recipients	-Mortality 20.2%, respiratory failure was the major cause of death -Age, diabetes, and chronic kidney disease were associated with death -Tacrolimus use (HR = 0.55, 95%CI 0.31-0.99) had a positive independent effect on survival					
Verhelst X et al. <sup>121</sup>	110	Belgium	Autoimmune hepatitis	Low infection rate (1.2%), survived 100%, hospitalization 3.5%, support that immunosuppressive treatment should not be stopped					
Di Giorgio A et al. <sup>61</sup>	148	Italy	Autoimmune liver diseases (AILD)	Confirmed cases of COVID-19 3%, survived 99%, died 1%, patients with AILD were not more susceptible to COVID-19 than the general population, tapering or withdrawing immunosuppression was not required					
Butt AA et al. <sup>122</sup> (ERCHIVES database)	SARS-CoV-2 with HCV = 975, SARS-CoV-2 without HCV = 975	USA	HCV	-HCV infected persons with SARS-CoV-2 are more likely to be admitted to a hospital -Mortality was not different between those with/ without HCV infection					
Kim D, et al. <sup>123</sup>	867 CLD = 620 (71.5%) Cirrhosis = 227 (26.2%) ALD = 94 NAFLD = 456 HBV = 62 HCV = 190 HCC = 22	US multicentre	Chronic liver disease and cirrhosis	The overall all-cause mortality was 14%, independent risk factor for overall mortality was ALD (HR = 2.42, 95%CI 1.29-4.55), decompensated cirrhosis (HR = 2.91, 95%CI 1.70-5.00) and HCC (HR = 3.31, 95%CI 1.53-7.16)					
Marjot T et al. <sup>57</sup> (SECURE-cirrhosis and COVID-Hep)	745 ALD = 179 NAFLD = 322 HBV = 96 HCV = 92 HCC = 48	Multinational	Chronic liver disease and cirrhosis	Mortality in patients with cirrhosis 32% versus chronic liver disease 8%, mortality in Child-Pugh class A (19%), B (35%), C (51%) -ALD was an independent risk factor for death (OR = 1.79) -After adjusting for baseline characteristics, NAFLD, viral hepatitis, and HCC had no independent association with death					

Abbreviations: ALD, alcoholic liver disease; ALP, alkaline phosphatase; ALT, alanine phosphatase; AST, aspartate transaminase; CLD, chronic liver disease; GGT, gamma-glutamyl transferase; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HR, hazard ratio; LT, liver transplant; N/A, not available; N, number of patients; NAFLD, non-alcoholic fatty liver disease; OR, odds ratio; SARS-CoV-2, The severe acute respiratory syndrome coronavirus 2; ULN, upper limit of normal.

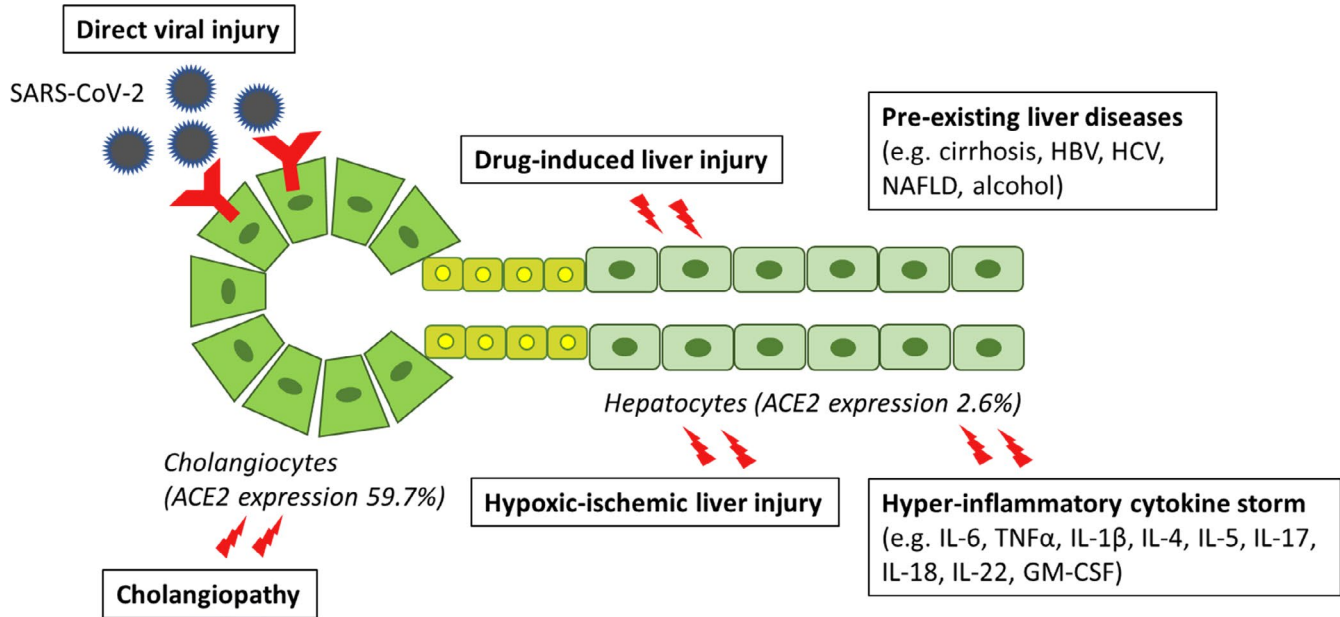


FIGURE 1 Proposed pathogenesis of hepatic manifestations in COVID-19

of individuals in one US series<sup>27</sup> which then can result in congestive hepatopathy and can be associated with elevations in aminotransferases and GGT levels.<sup>46,51</sup>

- Cholangiopathy: a novel entity of COVID-19 cholangiopathy has been described where features of bile duct strictures mimicking sclerosing cholangitis have been observed.<sup>52,53</sup> These patients had severe COVID-19 and had circulatory and ventilatory failure and required prolonged support. It is unclear at this stage if these represent changes of biliary tree ischemia or if they were a consequence of direct infection of SARS-CoV-2 of the liver and biliary tract.<sup>52,53</sup>

#### 4 | LIVER MANIFESTATIONS AND DISEASE-SPECIFIC MANAGEMENT FOR PATIENTS WITH CHRONIC LIVER DISEASE

Currently, there is no convincing evidence that patients with stable CLD without advanced fibrosis/cirrhosis due to hepatitis B/C, cholestatic liver disease such as primary biliary cholangitis (PBC) or primary sclerosing cholangitis (PSC) have increased susceptibility to severe COVID-19 infection, while contradictory data exist with regard to NAFLD, a condition associated with risk factors, such as obesity, diabetes mellitus and hypertension, for severe illness.<sup>2</sup> Pooled analysis data of CLD patients (6 studies from Wuhan, China) found no association between severe COVID-19 [OR = 0.96 (95%CI 0.36–2.52),  $p = 0.86$ ] and mortality [OR = 0.19 (95% CI 0.03–1.18),  $p = 0.31$ ]; however, there were relatively small number of patients with CLD included and thus larger scale studies are needed.<sup>54</sup> On the contrary, in a large cohort study of electronic health record data from over 17 million patients (>114,000 with CLD) in the United

Kingdom, CLD was a risk factor for in-hospital death from COVID-19 (HR = 1.61, 95%CI 1.33–1.95).<sup>55</sup> In another cohort of 2,780 US patients with COVID-19, CLD was associated with significantly higher mortality (RR = 2.8, 95%CI 1.9–4.0). The mortality risk was higher in patients with cirrhosis (RR = 4.6, 95%CI 2.6–8.3). Fatty liver disease and NASH were the most common aetiologies in the liver disease group, and the mortality risk was independent of risk factors such as body mass index, hypertension and diabetes.<sup>56</sup> Updated results from an International Registry (SECURE-Cirrhosis and COVID-Hep) on COVID-19-infected patients with CLD and cirrhosis (including 386 patients with cirrhosis, 359 with non-cirrhotic CLD from 21 countries across 4 continents) reported mortality rate in COVID-19-infected patients with cirrhosis to be around 32% which is far higher than in the general population. Mortality in CLD without cirrhosis is reported to be lower and at around 8%.<sup>57</sup>

##### 4.1 | Viral hepatitis

Chronic viral hepatitis does not appear to increase the risk for a severe course of COVID-19.<sup>11,54</sup> A small study from China ( $n = 23$ ) on clinical differences between HBV carriers and chronic hepatitis B/cirrhosis infected with COVID-19 showed no differences in terms of disease severity and length of hospital stay.<sup>58</sup> Currently, there is concern that COVID-19 care may lead to an acute shift in health-care resources to a point where there could be delays in diagnosis and initiating HCV therapy.<sup>39,40</sup> Thus, such an occurrence is likely to adversely impact the WHO's HCV elimination target of 2030; a 1-year delay in HCV diagnosis and treatment programs could cause excess HCV morbidity and mortality with an estimated additional 44,800 liver cancers and 72,300 deaths<sup>59</sup> and therefore attention should shift back to hepatitis programs as soon as appropriate.

## 4.2 | Autoimmune hepatitis (AIH)

There is no evidence that stable chronic liver disease due to autoimmune hepatitis, primary biliary cholangitis or primary sclerosing cholangitis has an increased susceptibility to SARS-CoV-2 infection.<sup>2,60</sup> Recent update from an international registry of COVID-19-infected chronic liver disease patients (SECURE-Cirrhosis and COVID-Hep) on August 2020 ( $n = 1102$ , cirrhosis = 508) reported AIH as an aetiology of cirrhosis in around 7%.<sup>49,50</sup> A phone-based survey in Northern Italy on health status of patients with autoimmune liver diseases during COVID-19 outbreak ( $n = 148$ ) found that such children and adults maintained good health status. COVID-19 was diagnosed in a similar percentage of patients as in the general population, and the outcome was favourable in most cases.<sup>61</sup> A case series of AIH patients with COVID-19-infection treated with immunosuppression in Italy ( $n = 10$ ) found that clinical outcome was comparable to that reported in a non-immunosuppressed population.<sup>62</sup>

## 4.3 | NAFLD

Emerging data suggest that NAFLD patients may be at higher risk for COVID-19.<sup>40</sup> Patients with NAFLD or NASH often have comorbidities such as diabetes mellitus, hypertension and obesity which can be associated with severe course of COVID-19 and longer viral shedding time.<sup>30,63</sup> A retrospective study from China in patients with COVID-19 ( $n = 202$ , NAFLD 37.6%) found that male sex (OR = 3.1; 95%CI 1.1–9.4), age > 60 years (OR = 4.8; 95%CI 1.5–16.2), higher body mass index (BMI) (OR = 1.3; 95%CI 1.0–1.8), underlying comorbidity (OR = 6.3; 95%CI 2.3–18.8) and NAFLD (OR = 6.4; 95%CI 1.5–31.2) were associated with COVID-19 progression.<sup>30</sup> Patients with NAFLD had a higher risk of disease progression (6.6% vs. 44.7%;  $p < 0.0001$ ), higher likelihood of liver dysfunction from admission to discharge (70% vs. 11.1%;  $p < 0.0001$ ) and longer viral shedding time ( $17.5 \pm 5.2$  days vs.  $12.1 \pm 4.4$  days;  $p < 0.0001$ ) compared to patients without NAFLD.<sup>30</sup> Within patients with NAFLD, non-invasive fibrosis scores [fibrosis-4 (FIB-4) index and NAFLD fibrosis score (NFS)] appeared to correlate with a higher likelihood of developing severe COVID-19, irrespective of metabolic comorbidities.<sup>64</sup> A large US multicentre observational study ( $n = 363$ , NAFLD 15.2%) demonstrated that NAFLD was independently associated with ICU admission (OR = 2.30, 95%CI 1.27–4.17) and mechanical ventilation (OR = 2.15, 95%CI 1.18–3.91), and presence of cirrhosis was an independent predictor of mortality (OR = 12.5, 95%CI 2.16–72.5).<sup>65</sup> It is unclear whether the risk is specific to NAFLD or to coexisting metabolic risk factors (e.g. diabetes, hypertension, cardiovascular diseases and obesity) which are known to be associated with COVID-19 severity.

## 4.4 | Cirrhosis

Patients with cirrhosis who develop COVID-19 have been observed to have higher mortality.<sup>5,57,66,67</sup> A multicentre-matched

cohort from North America compared mortality risk in those with cirrhosis and COVID-19 ( $n = 37$ ) vs. cirrhosis alone ( $n = 127$ ) vs. COVID-19 alone ( $n = 108$ ) and observed that patients with cirrhosis and COVID-19 had higher mortality compared to COVID-19 alone (30% vs. 13%,  $p = 0.03$ ), but comparable to cirrhosis alone (30% vs. 20%,  $p = 0.16$ ). Further, in those with acute-on-chronic liver failure (ACLF), the mortality rate was similar regardless of COVID-19 (55% vs. 36%,  $p = 0.25$ ).<sup>67</sup> This study also found that patients with cirrhosis hospitalized for COVID-19 were more likely to develop complications related to the viral infection rather than complications related to cirrhosis and were less likely to present with gastrointestinal symptoms compared to those with COVID-19 alone.<sup>67</sup> Another multicentre retrospective study from Italy in patients with cirrhosis and COVID-19 infection ( $n = 50$ ) noted an evolution to ACLF in around 28% and with a 30-day mortality rate of 34%.<sup>5</sup> The severity of lung and liver diseases (according to CLIF-C, CLIF-OF and MELD scores) independently predicted mortality, and in patients with cirrhosis, mortality was significantly higher in those with COVID-19 than those with cirrhosis-associated bacterial infections.<sup>5</sup> Concomitantly, a study from India in patients with CLD and cirrhosis infected with COVID-19 ( $n = 28$ ) reported poor outcomes in patients with cirrhosis, with worst survival rates in those with ACLF, and requirement of mechanical ventilation independently predicted mortality (hazard ratio = 13.68).<sup>66</sup> Ultimately, a large cohort from an international registry (SECURE-cirrhosis and COVID-Hep) ( $n = 745$  patients with CLD and SARS-CoV-2 including 386 with and 359 without cirrhosis) had demonstrated 32% mortality in patients with cirrhosis compared to 8% in those without cirrhosis ( $p < 0.001$ ). Mortality in patients with cirrhosis increased according to Child-Pugh class (A [19%], B [35%], C [51%]) and the main cause of death was from respiratory failure (71%). Acute hepatic decompensation occurred in 46% and half of those with hepatic decompensation had ACLF. Age, baseline liver disease stage (especially Child-Pugh class B and C) and alcohol-related liver disease were independent risk factors for death in those with COVID-19.<sup>57</sup>

## 4.5 | Liver transplant recipients and immunosuppressed patients

Immunosuppressed patients aged >60 years are more likely to acquire SARS-CoV-2 infection and may have prolonged viral clearance.<sup>11,68,69</sup> On the other hand, some data suggest that immunosuppressive agents may be protective through their effect on alleviating immune response, the main driver of COVID-19-related severe pulmonary injury.<sup>12,70</sup>

Recent data from the European liver transplant (LT) [COVID-LT ( $n = 57$ ) and SETH cohorts ( $n = 111$ )] reported crude incidence rate of COVID-19 to be around 0.5%–0.8%.<sup>71–73</sup> COVID-19 was associated with an overall and in-hospital fatality rate of 12% and 17%, respectively in LT recipients. A history of cancer was more frequent in patients with poorer outcome.<sup>72</sup> A large prospective



cohort of LT patients in Italy (SETH cohort) also reported the incidence of COVID-19 to be higher in LT patients, but mortality rates were lower than the matched general population; further, mycophenolate was found to be associated with a risk of developing severe COVID-19 in a dose-dependent manner.<sup>73</sup> Interestingly, a multicentre contemporaneous matched COVID-19 alone cohort study from two international registries (COVID-Hep and SECURE-Cirrhosis) including 151 LT recipients from 18 countries found that LT was not associated with increased mortality in patients infected with COVID-19<sup>74</sup> (mortality rate 18%),<sup>49,50</sup> whereas increased age and presence of comorbidities (eg creatinine levels and non-liver cancer) were associated with death among LT-recipients.<sup>74</sup> Such data are consistent with a national cohort from the UK (46,789 solid organ transplant (SOT) recipients, mortality 25.8% in SOT recipients with COVID-19) where increasing recipients' age was independently associated with mortality after diagnosis of COVID-19.<sup>75</sup> A report from US epicentre in SOT recipients ( $n = 90$ ) (KT 51%, LT 14%) hospitalized with COVID-19 also demonstrated comparable data of severe outcomes<sup>35,76</sup> in both early and long-term survivors<sup>76</sup> with overall mortality of 18%.<sup>35</sup> Data from the European Liver and Intestine Transplantation Association (ELITA)/ the European Liver Transplant Registry (ELTR) (149 LT centres, 103 COVID-19-infected LT recipients) found overall mortality in COVID-19-infected LT recipients of 16%, with higher mortality in patients aged  $\geq 60$  years and in male recipients<sup>77</sup> suggesting that LT candidates and recipients, especially elderly and those with comorbidities are at higher risk for severe COVID-19.<sup>78</sup>

#### 4.6 | Hepatocellular carcinoma (HCC)

Cancer patients are considered a high-risk group for developing severe COVID-19 disease due to additional comorbidities and immunosuppressed status especially those with recent chemotherapy or surgery ( $< 1$  month).<sup>79</sup> Mortality from COVID-19 in patients with cancer has been associated with age, sex and comorbidities, but not to the use of cytotoxic chemotherapy or other anticancer treatment.<sup>80</sup> Prevalence of COVID-19 infection in cancer patients has varied from 0.37% to 7.24%<sup>79,81-83</sup> and mortality rate in cancer patients with COVID-19 has been noted to be higher than non-cancer patients. Mehta et al. ( $n = 218$ ) demonstrated a higher mortality rate in patients with cancer and COVID-19 (28%) than in those without cancer (14%).<sup>84</sup> It is still an open-ended question whether HCC patients are also at increased risk of severe COVID-19. HCC is often associated with liver cirrhosis, suggesting that impaired immunity may increase the risk of developing severe COVID-19.<sup>85</sup> COVID-19 may exacerbate pre-existing liver disease and thus complicate cancer management.<sup>86</sup> Data on HCC patients with COVID-19 infection from currently available studies are limited. Zhang et al. reported COVID-19 infection in 28 cancer patients in China (7% with HCC) which were associated with poor outcomes especially if receiving antitumour treatment within

14 days, however, too small a number of HCC patients were in the study.<sup>82</sup> More robust experience was reported from a multicentre study from France in patients with HCC ( $n = 670$ , 293 exposed to SARS-CoV-2 and 377 unexposed)<sup>87</sup> in the COVID-19 era, where fewer patients with HCC presented to the multidisciplinary tumour board, especially with their first HCC diagnosis. Treatment strategy was modified in 13.1% of patients, and patients experienced significant treatment delay of longer than 1 month in 2020 compared with 2019 (21.5% vs. 9.5%,  $p < 0.001$ ). Around 7.1% of HCC patients had a diagnosis of active COVID-19 infection (52.4% hospitalized, 19.1% died).<sup>87</sup> Another experience from Italy (42 HCC patients) reported a delay in HCC treatment of  $\geq 2$  months in 26% of patients during COVID-19 era.<sup>88</sup>

Overall, if patients with chronic liver disease get infected with COVID-19 (especially if they have additional risk factors of developing severe COVID-19 such as hypertension, diabetes mellitus, obesity, cirrhosis, HCC or post-transplant status), early admission and early initiation of antiviral therapy if clinically indicated is recommended<sup>63</sup> (Figure 2). Global liver society recommendations<sup>32,42,60</sup> with some similarities and contrasting aspects in patients with chronic viral hepatitis, autoimmune liver diseases, NAFLD, cirrhosis, LT recipients and HCC are summarized in Table 3.

## 5 | IMPACT OF PANDEMIC COVID-19 ON PATIENTS ON THE WAITLIST FOR LIVER TRANSPLANTATION

In the early stages of COVID-19 pandemic, liver transplant communities faced multiple challenges, especially in a significant decrease in organ donation/retrieval and liver transplants. The overall reduction in deceased donor solid organ transplantations was 90.6% in France and 51.1% in the USA.<sup>89</sup> Netherlands also reported an immediate impact of COVID-19 on transplant activity with overall decrease of 67% (liver and lung transplant activity decreased  $\sim 50\%$ ) while there was an unexpected observation of an increase number of renal patients being removed from the waiting list due to clinical deterioration and mortality.<sup>90</sup> Another preliminary analysis on impact of COVID-19 outbreak on 22 Italian Liver Transplant Programs (I-BELT Study Group) found a reduction in overall LT activity, including living-related liver transplantation.<sup>91</sup> Notably, there was impact on healthcare resource capacity as COVID-19-infected cases intensity exceeded available healthcare capacity in many regions, thus relegating liver transplantation to a lower priority in order to adjust health resource utilization. For example, there had been a drastic decrease in liver donors and transplants in Lombardy, Italy because of the need for the increasing use of ICU beds to accommodate COVID-19-infected patients. However, 16 (out of 17) LT recipients were alive after an average of 30 days post-LT (2 cases of COVID-19 infection post-LT, only 1 died at post-LT day 30), and this study suggested no specific concerns in stopping LT program activity.<sup>92</sup>

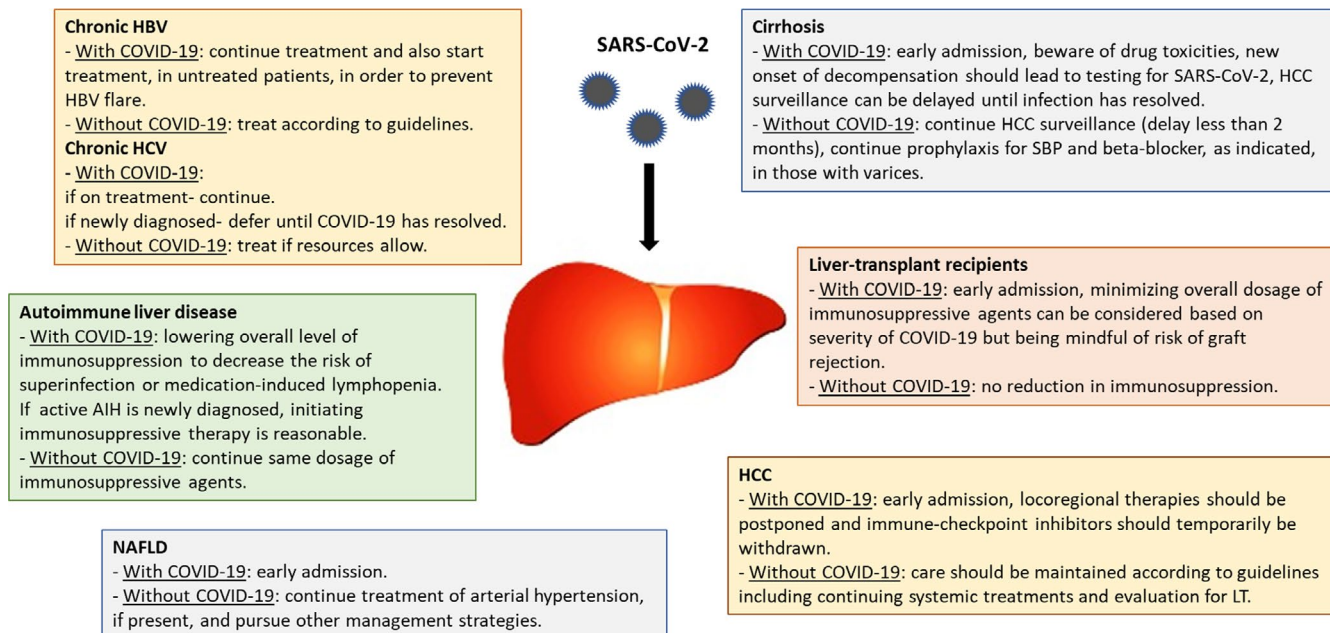


FIGURE 2 Management consideration of chronic liver disease and cirrhosis during COVID-19 era

While during the first wave of the pandemic, in the UK, there was a significant reduction in transplant activity,<sup>93</sup> restoration of near-normal donor activity was noted in June 2020. Of note, after the second wave due to the 'UK variant' mutated strain, in December 2020, a drop similar to the first wave, in the number of solid organ transplants was not noticed.<sup>94</sup> In contrast, the impact of the second wave in India was notably different and likely to have had a severe effect on transplantation services.<sup>94,95</sup> Thus, there has been a significant heterogeneity in transplant activity among the various regions of the World.<sup>96</sup>

## 6 | SARS-COV-2 VACCINATION IN CHRONIC LIVER DISEASE AND TRANSPLANT RECIPIENTS

Several types of SARS-CoV-2 vaccines have been developed in the EAST and the WEST such as mRNA vaccines from Pfizer-BioNTech (USA and Germany)<sup>97</sup> and Moderna (USA),<sup>98</sup> adenoviral-vectored vaccines from Oxford-AstraZeneca (UK) and inactivated vaccines from Sinopharm/Sinovac (China).<sup>99</sup> Vaccines, in general, are known to be less effective in patients with cirrhosis<sup>100</sup> and liver transplant recipients.<sup>101,102</sup> Current data from vaccine studies of both the BNT162b2 mRNA COVID-19 vaccine (Pfizer-BioNTech) (included 126 patients with liver diseases/18,860 patients receiving vaccination)<sup>97</sup> and the mRNA-1273 (Moderna) (included 100 patients with liver diseases/15,181 patients receiving vaccination)<sup>98</sup> demonstrated consistent efficacy among subgroup with coexisting conditions in general and comparable with overall population, while there were small numbers of chronic liver disease patients in the trials. To date, it is unclear whether SARS-CoV-2 vaccines are equally effective in those with chronic liver disease/ cirrhosis/ transplanted

population/ immunosuppressed patients compared to the general population, particularly against the rapidly emerging viral variants. Preliminary data support safety in the transplant recipients<sup>103</sup> while antibody response after one dose has been suboptimal at 17% in this cohort.<sup>104</sup> Response after the second dose of SARS-CoV-2 mRNA vaccine increased to 54%.<sup>105</sup> A retrospective study from France on three doses of the BNT162b2 mRNA COVID-19 vaccine (Pfizer-BioNTech) in solid organ transplant recipients ( $n = 101$ ) reported significant improvement in anti-SARS-CoV-2 antibody response (up to 68% at 4 weeks after the third dose)<sup>106</sup>; accordingly, the French National Authority for Health recommends the use of a third dose of vaccine in immunosuppressed patients.<sup>106</sup> While more data on safety and efficacy evolve, it would seem prudent to strongly recommend vaccination to our patients with chronic liver disease and transplant recipients.

## 7 | CONCLUSION

SARS-CoV-2 virus has infected vast majority of people around the World from around December 2019, and now in 2021, we continue to deal with it with surges of infection variably occurring around the Globe. While those with several comorbidities such as obesity and chronic kidney disease are at risk for severe COVID-19, those with chronic liver disease, particularly cirrhosis, and liver transplant recipients are also vulnerable to severe COVID-19. As observations continue to be made on presentation and outcomes in those with liver disease, vaccination strategies are being implemented aggressively. Data on safety and efficacy of vaccines in those with chronic liver disease and liver transplant recipients is emerging while there remain several unresolved issues that include, but not limited to, re-infection rates and outcomes (even after vaccination), management

TABLE 3 Guideline recommendations and unique considerations of liver manifestations in the EAST and the WEST

Liver diseases	AASLD recommendation <sup>32</sup>	EASL-ESCMID position paper <sup>42,63</sup>	APASL recommendation <sup>60</sup>
Chronic viral hepatitis (HBV and HCV)	<ul style="list-style-type: none"> <li>-Recommendation include continuation of treatment for hepatitis B or C if already on treatment</li> <li>-There is no contraindication to initiating treatment of hepatitis B and C, as clinically warranted, in patients without COVID-19</li> <li>-In patients with COVID-19, initiating hepatitis B treatment is usually not immediately warranted but not contraindicated, and should be considered when there is clinical suspicion of hepatitis B flare or when initiating immunosuppressive agents, corticosteroids, or IL-6 monoclonal antibody</li> <li>-Initiating treatment of hepatitis C in a patient with COVID-19 is not immediately warranted and can be delayed till after resolution of COVID-19</li> </ul>		
<b>Unique aspects in the EAST and the WEST</b>			
<b>EAST</b>			
-Multicentre study from China reported prevalence of HBV infection in COVID-19 patients ranging from 2.1-12.2% <sup>11,124,125</sup>			
<b>WEST</b>			
-In a large series ( $n = 5700$ ) from the Northeastern United States, prevalence of HBV and HCV infections in COVID-19 infected patients were reported to be 0.1% and <0.1%, respectively <sup>28</sup>			
Autoimmune liver diseases	<ul style="list-style-type: none"> <li>-In patients with AIH without COVID-19, continuing the same dosage of immunosuppressive agents is recommended, as reducing or stopping immunosuppressive agents may cause disease flare</li> <li>-If active AIH is diagnosed, initiating immunosuppressive therapy is recommended despite COVID-19 infection<sup>40</sup></li> <li>-In AIH patients with active COVID-19 and elevated liver biochemistries, do not presume disease flare without biopsy confirmation<sup>32</sup></li> <li>-In patients with AIH and active COVID-19, consider lowering the overall level of immunosuppression to decrease the risk of superinfection or medication-induced lymphopenia and which should be individualized adjustment based on severity of COVID-19<sup>32</sup></li> <li>-Vaccination for <i>Streptococcus pneumoniae</i> and influenza should be emphasized<sup>63</sup></li> </ul>		
<b>Unique aspects in the EAST and the WEST</b>			
<b>EAST</b>			
-(APASL recommendation) Patients with autoimmune liver disease and severe COVID-19, corticosteroid should not be discontinued and stress-doses may be required (does not elaborate on the type of corticosteroid) <sup>60</sup>			
<b>WEST</b>			
-(AASLD recommendation) In patients with AIH and active COVID-19, consider lowering the overall level of immunosuppression, particularly anti-metabolite dosages (eg azathioprine or mycophenolate) to decrease the risk of superinfection <sup>32</sup>			
-(EASL recommendation) Considering budesonide as a first-line agent to induce remission in patients without cirrhosis who have a flare of autoimmune hepatitis <sup>42</sup>			
-(EASL recommendation) In patients treated with corticosteroids who develop COVID-19, corticosteroid dosing should be sufficient to prevent adrenal insufficiency. Conversion to dexamethasone should only be considered in patients with COVID-19 who require hospitalization and respiratory support <sup>42</sup>			
NAFLD	<ul style="list-style-type: none"> <li>-Early admission should be considered for all patients with NAFLD who become infected with SARS-CoV-2<sup>42</sup></li> </ul>		
<b>Unique aspects in the EAST and the WEST</b>			
<b>EAST</b>			
-Patients with NAFLD have higher risk of progression to severe COVID-19 <sup>30,126</sup> especially in younger NAFLD patients <sup>110</sup>			
-COVID-19-infected patients with NAFLD are more likely to develop liver injury, but usually mild in nature <sup>30,109</sup>			
-Clinical outcomes were comparable between COVID-19-infected patients with NAFLD and without NAFLD <sup>109</sup>			
-Fibrosis scores appear to correlate with severity of COVID-19 <sup>64</sup>			
<b>WEST</b>			
-NAFLD represents a high risk for severe COVID-19 especially in male gender, <sup>127</sup> independent of metabolic syndrome. <sup>126,128</sup>			
-NAFLD associated with increased risk of hospitalization <sup>129</sup> and ICU admission <sup>65</sup> for COVID-19.			
-Presence of cirrhosis was an independent predictor of mortality <sup>65</sup>			
-Mortality was associated with inflammatory response but not with fibrosis staging <sup>127</sup>			
-Patients receiving ACEIs and ARBs should remain on them even in the setting of COVID-19 <sup>32</sup>			

(Continues)

TABLE 3 (Continued)

Liver diseases	AASLD recommendation <sup>32</sup>	EASL-ESCMID position paper <sup>42,63</sup>	APASL recommendation <sup>60</sup>
<b>Cirrhosis</b>	<ul style="list-style-type: none"> <li>-Patients with cirrhosis or liver cancer are potentially at increased risk for severe COVID-19, low threshold for SARS-CoV-2 testing if symptomatic</li> <li>-If COVID-19 is diagnosed, early admission is recommended</li> <li>-Every patient with acute decompensation or ACLF should be tested for SARS-CoV-2 infection</li> <li>-Continue HCC surveillance as close to schedule as circumstances allow, an arbitrary delay around 2 months is reasonable<sup>39</sup></li> <li>-If patients are infected with COVID-19, prevention of drug toxicities such as limited dosage of acetaminophen (&lt;2 g/day) is suggested</li> <li>-Due to cancellation of elective endoscopy, primary prophylaxis with beta-blocker in patients with clinically significant portal hypertension is justified<sup>40</sup></li> </ul>	<ul style="list-style-type: none"> <li>- Patients with cirrhosis should be considered at increased risk for severe COVID-19</li> <li>-All patients with new onset of hepatic decompensation or ACLF should be tested for SARS-CoV-2 even in the absence of respiratory symptoms</li> <li>-Early admission should be considered for all patients with cirrhosis infected with SARS-CoV-2</li> <li>-Prophylaxis on spontaneous bacterial peritonitis (SBP), gastrointestinal haemorrhage, and hepatic encephalopathy should be maintained in order to prevent admission due to portal hypertension-related complications</li> <li>-Do not administer NSAIDs in patients with cirrhosis and portal hypertension</li> <li>-All patients should receive vaccination for <i>Streptococcus pneumoniae</i> and influenza</li> </ul>	<ul style="list-style-type: none"> <li>-Consider delay screening for varices, non-invasive tool such as LSM, FIB-4 or platelet count may be used to identify patients with high risk of variceal bleeding (Baveno VI criteria)<sup>63</sup></li> </ul>
<p><b><u>Unique aspects in the EAST and the WEST</u></b></p> <p><b>EAST</b></p> <ul style="list-style-type: none"> <li>-A study from India in patients with cirrhosis infected with COVID-19 reported poor outcomes in patients with cirrhosis, with the worst survival rates in ACLF<sup>66</sup></li> </ul> <p><b>WEST</b></p> <ul style="list-style-type: none"> <li>-A multicentre North American study found that patients with cirrhosis+ COVID-19 had similar mortality compared with patients with cirrhosis alone, but higher than patients with COVID-19 alone<sup>67</sup></li> <li>-An international registry (SECURE-cirrhosis and COVID-Hep) demonstrated that patients with cirrhosis experienced high rates of hepatic decompensation and death following COVID-19 infection, and mortality increased with greater Child-Pugh class<sup>57</sup></li> <li>-A multicentre retrospective study from Italy found that mortality in patients with cirrhosis and COVID-19 was significantly higher than those with cirrhosis and bacterial infections<sup>5</sup></li> </ul>			
<b>Liver transplant recipients and immunosuppressive agents</b>	<p><b>Transplant recipients without COVID-19</b></p> <ul style="list-style-type: none"> <li>- No reduction in immunosuppression in asymptomatic post-liver transplant patients without known COVID-19 as reduction can precipitate acute rejection.</li> <li>- Emphasis on the importance of vaccination for <i>Streptococcus pneumoniae</i> and influenza.</li> </ul> <p><b>Transplant recipients with COVID-19</b></p> <ul style="list-style-type: none"> <li>-Early admission is recommended</li> <li>-In LT recipients with active COVID-19 and elevated liver biochemistries, do not presume acute cellular rejection without biopsy confirmation.</li> <li>-Minimizing dosage of immunosuppressive agents should be considered case-by-case under specialist consultation based on severity of COVID-19 and risk of graft rejection.</li> <li>-Lower the overall level of immunosuppression, especially anti-metabolite dosages (eg azathioprine or mycophenolate) to decrease the risk of superinfection</li> <li>-Close monitoring of calcineurin inhibitor levels, for features of acute kidney injury, and also for potential drug-drug interactions.</li> <li>-Anti-IL-6 therapeutics have not been shown to increase the risk of acute cellular rejection</li> </ul>	<p><b>Transplant recipients without COVID-19</b></p> <ul style="list-style-type: none"> <li>- Advise against reduction of immunosuppressive therapy to prevent SARS-CoV-2 infection.</li> <li>- All patients should receive vaccination for <i>Streptococcus pneumoniae</i> and influenza.</li> </ul> <p><b>Transplant recipients with COVID-19</b></p> <ul style="list-style-type: none"> <li>- Reduction should only be considered under special circumstances (eg medication-induced lymphopenia, or bacterial/fungal superinfection in case of severe COVID-19) after consultation with a specialist.</li> <li>- Drug levels of calcineurin inhibitors and mechanistic target of rapamycin inhibitors should be closely monitored when they are administered together with drugs such as hydroxychloroquine, protease inhibitors or alongside new trial drugs for COVID-19.</li> <li>- Early admission should be considered for all LT recipients who develop COVID-19.</li> </ul>	<p><b>Transplant recipients without COVID-19</b></p> <ul style="list-style-type: none"> <li>- Immunosuppressive doses should not be reduced in long-term LT patients in the absence of COVID-19 infection.</li> <li>- All LT recipients should receive vaccination against influenza and pneumococcal infection.</li> </ul> <p><b>Transplant recipients with COVID-19</b></p> <ul style="list-style-type: none"> <li>- Reduction of immunosuppression may be considered in patients diagnosed with moderate COVID-19 infection.</li> <li>- Immunosuppression should be reduced in patients with lymphopenia, fever, or worsening pneumonia.</li> </ul>

(Continues)

TABLE 3 (Continued)

Liver diseases	AASLD recommendation <sup>32</sup>	EASL-ESCMID position paper <sup>42,63</sup>	APASL recommendation <sup>60</sup>
	<b><i>Unique aspects in the EAST and the WEST</i></b>		
	<b>EAST</b>		
	-Immunosuppression and immunodeficiency were associated with increased risk of severe COVID-19 disease <sup>130</sup> However, case reports have suggested that temporary reduction of immunosuppressive agents during COVID-19 infection is justified <sup>131</sup>		
	-A multicentre study from India (LDLT = 31) reported on the perioperative safety and good outcomes in carefully timed LDLT (1 COVID-19 infected), even in COVID-19 hotspots <sup>132</sup>		
	<b>WEST</b>		
	-Some studies reported higher mortality rates in liver and other solid organ transplant recipients and at around 20–25% <sup>35,73–77,133,134</sup>		
	-Elderly, obesity, male sex, history of cancer and comorbidities were associated with severe COVID-19 in immunosuppressed patients and transplant recipients <sup>70,72,74,76,77,135</sup>		
	-Results from 2 International registries (COVID-Hep and SECURE-Cirrhosis) found that LT state, overall, was not associated with increased mortality, but increased age and presence of comorbidities were <sup>74</sup>		
	-Gastrointestinal symptoms were common in solid organ transplant recipients being infected with COVID-19 <sup>35,76</sup>		
	-Complete discontinuation of immunosuppression after COVID-19 diagnosis is not recommended; mycophenolate was associated with severe disease and should be temporary withdrawn or switched to other immunosuppressants <sup>71,73</sup>		
	-Reports from Italy (especially in paediatric LT recipients) showed low mortality rates in transplant recipients <5% <sup>70,136</sup>		
<b>HCC and other cancers</b>	<ul style="list-style-type: none"> <li>- Continue to do surveillance in those at risk for HCC (eg cirrhosis, chronic hepatitis B) as close to schedule as allow; an arbitrary delay of 2 months is reasonable</li> <li>- Avoid HCC surveillance in patients with COVID-19 until infection is resolved</li> <li>- Proceed with liver cancer treatments or surgical resection when able rather than delaying them because of the pandemic</li> </ul>	<ul style="list-style-type: none"> <li>- HCC surveillance should only be deferred based on available resources and the individual risk assessment. Patients with increased risk (e.g. patients with elevated AFP, advanced cirrhosis, chronic hepatitis B, HCV-related cirrhosis, NASH/ diabetes) should be prioritized</li> <li>- In patients with COVID-19, HCC surveillance can be deferred until after recovery</li> <li>- For HCC patients, care should be maintained according to guidelines including continuing systemic treatments and evaluation for LT</li> <li>- For HCC patients infected with COVID-19, early admission is recommended. Locoregional therapies should be postponed and immune-checkpoint inhibitors should temporarily be withdrawn</li> </ul>	<ul style="list-style-type: none"> <li>- During the pandemic, for newly diagnosed HCC patients, postponing of elective transplant, resection surgery, or radiotherapy may be considered</li> <li>- Ablative procedures, TACE, kinase inhibitors or immunotherapy may be initiated. Change of immunotherapy schedules to 4–6 weeks may be considered</li> <li>- Among uninfected HCC patients who are already on treatment, HCC treatment should proceed as deemed appropriate</li> <li>- If HCC patients get infected with COVID-19, withhold immunotherapy directed towards HCC</li> </ul>
	<b><i>Unique aspects in the EAST and the WEST</i></b>		
	<b>EAST</b>		
	-Risk factors for severe COVID-19 infection in patients with cancer include the last anticancer treatment within 14 days and advanced age ( $\geq 65$ years) <sup>81,82</sup>		
	-In contrast, some studies reported mortality from COVID-19 in patients with cancer found to be associated with age, sex, and comorbidities, <sup>80,137</sup> but not to the use of cytotoxic chemotherapy or other anticancer treatment <sup>80</sup>		
	<b>WEST</b>		
	-Increased age, male sex, smoking status, number of comorbidities, ECOG performance status of $\geq 2$ , and active cancer were independent factors associated with increased 30-day mortality <sup>138</sup>		
	-During COVID-19 era, fewer patients with HCC presented to the multidisciplinary tumour board, and patients with HCC experienced significant treatment delay longer than 1 month in 2020 compared with 2019 (21.5% vs. 9.5%, $p < 0.001$ ) <sup>87</sup>		

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ACLF, acute-on-chronic liver failure; AFP, alpha-fetoprotein; AIH, autoimmune hepatitis; ALT, alanine transaminase; ARB, angiotensin II receptor blocker; AST, aspartate transaminase; ECOG, Eastern Cooperative Oncology Group; FIB-4, fibrosis-4; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; LDLT, living-donor liver transplant; LFT, liver function test; LSM, liver stiffness measurement; LT, liver transplant; N, number of patients; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; NSAIDs, non-steroidal anti-inflammatory drugs; TACE, trans-arterial chemoembolization.

of immunosuppressive agents in post-LT patients during severe COVID-19 infection, and responses to different types of COVID-19 vaccines, particularly with the emergence of mutant strains, in those with chronic liver disease/ cirrhosis and immunosuppressed states such as post-LT.

#### CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

#### DATA ACQUISITION

Review of the literature.

## REFERENCES

1. Fix OK, Hameed B, Fontana RJ, et al. Clinical best practice advice for hepatology and liver transplant providers during the COVID-19 Pandemic: AASLD Expert Panel Consensus Statement. *Hepatology*. 2020;72(1):287-304.
2. Zhang C, Shi L, Wang F-S. Liver injury in COVID-19: management and challenges. *Lancet Gastroenterol Hepatol*. 2020;5(5):428-430.
3. Ji D, Zhang D, Yang T, et al. Effect of COVID-19 on patients with compensated chronic liver diseases. *Hepatology*. 2020;73(5):701-710.
4. Qiu H, Wander P, Bernstein D, Satapathy SK. Acute on chronic liver failure from novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). *Liver Int*. 2020;40(7):1590-1593.
5. Iavarone M, D'Ambrosio R, Soria A, et al. High rates of 30-day mortality in patients with cirrhosis and COVID-19. *J Hepatol*. 2020;73(5):1063-1071.
6. Jothimani D, Venugopal R, Abedin MF, Kaliamoorthy I, Rela M. COVID-19 and the liver. *J Hepatol*. 2020;73(5):1231-1240.
7. Li Y, Xiao S-Y. Hepatic involvement in COVID-19 patients: Pathology, pathogenesis, and clinical implications. *J Med Virol*. 2020;92(9):1491-1494.
8. Case fatality rate of the ongoing COVID-19 pandemic. Accessed November 14, 2020. <https://ourworldindata.org/mortality-risk-covid>
9. WHO Coronavirus Disease (COVID-19) Dashboard Accessed June 12, 2021. [https://covid19.who.int/?gclid=EAlaQobChMlQqr tIK2C7QIVGxwrCh3LcQm2EAAYASAAEgKaefD\\_BwE](https://covid19.who.int/?gclid=EAlaQobChMlQqr tIK2C7QIVGxwrCh3LcQm2EAAYASAAEgKaefD_BwE)
10. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *The Lancet*. 2020;395(10223):507-513.
11. Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med*. 2020;382(18):1708-1720.
12. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020;395(10223):497-506.
13. Shi H, Han X, Jiang N, et al. Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study. *Lancet Infect Dis*. 2020;20(4):425-434.
14. Xu X-W, Wu X-X, Jiang X-G, et al. Clinical findings in a group of patients infected with the 2019 novel coronavirus (SARS-Cov-2) outside of Wuhan, China: retrospective case series. *BMJ (Clin Res)*. 2020;368:m606.
15. Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Resp Med*. 2020;8(5):475-481.
16. Cai Q, Huang D, Ou P, et al. COVID-19 in a designated infectious diseases hospital outside Hubei Province, China. *Allergy*. 2020;75(7):1742-1752.
17. Cao B, Wang Y, Wen D, et al. A trial of lopinavir-ritonavir in adults hospitalized with severe Covid-19. *N Engl J Med*. 2020;382(19):1787-1799.
18. Fan Z, Chen L, Li J, et al. Clinical features of covid-19-related liver functional abnormality. *Clin Gastroenterol Hepatol*. 2020;18(7):1561-1566.
19. Fan Z, Chen L, Li J, et al. Clinical features of COVID-19 related liver damage. *medRxiv*. <https://doi.org/10.1101/2020.02.26.20026971>
20. Huang Y, Yang R, Xu Y, Gong P. Clinical characteristics of 36 non-survivors with COVID-19 in Wuhan, China. *medRxiv*. <https://doi.org/10.1101/2020.02.27.20029009>
21. Cao M, Zhang D, Wang Y, et al. Clinical features of patients infected with the 2019 novel coronavirus (COVID-19) in Shanghai, China. *medRxiv*. <https://doi.org/10.1101/2020.03.04.20030395>
22. Cai Q, Huang D, Yu H, et al. COVID-19: Abnormal liver function tests. *J Hepatol*. 2020;73(3):566-574.
23. Zhang Y, Zheng L, Liu L, Zhao M, Xiao J, Zhao Q. Liver impairment in COVID-19 patients: A retrospective analysis of 115 cases from a single centre in Wuhan city, China. *Liver Int*. 2020;40(9):2095-2103.
24. Vespa E, Pugliese N, Piovani D, et al. Liver tests abnormalities in COVID-19: trick or treat? *J Hepatol*. 2020;73(5):1275-1276.
25. Grasselli G, Zangrillo A, Zanella A, et al. Baseline characteristics and outcomes of 1591 patients infected With SARS-CoV-2 admitted to ICUs of the Lombardy Region, Italy. *JAMA*. 2020;323(16):1574-1581.
26. Cholankeril G, Podboy A, Aivaliotis VI, et al. High prevalence of concurrent gastrointestinal manifestations in patients with severe acute respiratory syndrome coronavirus 2: Early experience From California. *Gastroenterology*. 2020;159(2):775-777.
27. Arentz M, Yim E, Klaff L, et al. Characteristics and outcomes of 21 critically ill patients With COVID-19 in Washington State. *JAMA*. 2020;323(16):1612-1614.
28. Richardson S, Hirsch JS, Narasimhan M, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City Area. *JAMA*. 2020;323(20):2052-2059.
29. Tang C, Zhang K, Wang W, et al. Clinical characteristics of 20,662 patients with COVID-19 in mainland China: A systemic review and meta-analysis. *medRxiv*. <https://doi.org/10.1101/2020.04.18.20070565>
30. Ji D, Qin E, Xu J, et al. Non-alcoholic fatty liver diseases in patients with COVID-19: A retrospective study. *J Hepatol*. 2020;73(2):451-453.
31. Chai X, Hu L, Zhang Y, et al. Specific ACE2 expression in cholangiocytes may cause liver damage after 2019-nCoV infection. *bioRxiv*. <https://doi.org/10.1101/2020.02.03.931766>
32. Clinical best practice advice for hepatology and liver transplant providers during the covid-19 pandemic: AASLD expert panel consensus statement (Released: June 25, 2020). <https://www.aasld.org/sites/default/files/2020-06/AASLD-COVID19-ExpertPanelConsensusStatement-June252020-v2-FINAL.pdf>
33. Lei F, Liu YM, Zhou F, et al. Longitudinal association between markers of liver injury and mortality in COVID-19 in China. *Hepatology*. 2020;72(2):389-398.
34. Liu W, Tao ZW, Wang L, et al. Analysis of factors associated with disease outcomes in hospitalized patients with 2019 novel coronavirus disease. *Chin Med J*. 2020;133(9):1032-1038.
35. Pereira MR, Mohan S, Cohen DJ, et al. COVID-19 in solid organ transplant recipients: Initial report from the US epicenter. *Am J Transplant*. 2020;20(7):1800-1808.
36. Xu L, Liu J, Lu M, Yang D, Zheng X. Liver injury during highly pathogenic human coronavirus infections. *Liver Int*. 2020;40(5):998-1004.
37. Qi X, Liu C, Jiang Z, et al. Multicenter analysis of clinical characteristics and outcomes in patients with COVID-19 who develop liver injury. *J Hepatol*. 2020;73(2):455-458.
38. Lu X, Zhang L, Du H, et al. SARS-CoV-2 Infection in Children. *N Engl J Med*. 2020;382(17):1663-1665.
39. Clinical insights for hepatology and liver transplant providers during the COVID-19 pandemic (Released: April 7, 2020). <https://www.aasld.org/sites/default/files/2020-04/AASLD-COVID19-ClinicalInsights-4.07.2020-Final.pdf>
40. Major Updates to COVID-19 Clinical Insights Document (Released April 16, 2020). <https://www.aasld.org/sites/default/files/2020-04/COVID19-ClinicalInsightsUpdates-4162020.pdf>
41. Albillos A, Lario M, Álvarez-Mon M. Cirrhosis-associated immune dysfunction: distinctive features and clinical relevance. *J Hepatol*. 2014;61(6):1385-1396.
42. Boettler T, Marjot T, Newsome PN, et al. Impact of COVID-19 on the care of patients with liver disease: EASL-ESCMID position paper after 6 months of the pandemic. *JHEP Reports*. 2020;2(5):100169.
43. Banales JM, Huebert RC, Karlsen T, Strazzabosco M, LaRusso NF, Gores GJ. Cholangiocyte pathobiology. *Nat Rev Gastroenterol Hepatol*. 2019;16(5):269-281.
44. Tian S, Xiong Y, Liu H, et al. Pathological study of the 2019 novel coronavirus disease (COVID-19) through postmortem core biopsies. *Mod Pathol*. 2020;33(6):1007-1014. <https://doi.org/10.1038/s41379-020-0536-x>

45. Gordon DE, Jang GM, Bouhaddou M, et al. A SARS-CoV-2 protein interaction map reveals targets for drug repurposing. *Nature*. 2020;583(7816):459-468.
46. Schaefer EAK, Arvind A, Bloom PP, Chung RT. Interrelationship between coronavirus infection and liver disease. *Clin Liv Dis*. 2020;15(5):175-180.
47. Grein J, Ohmagari N, Shin D, et al. Compassionate use of remdesivir for patients with severe Covid-19. *N Engl J Med*. 2020;382(24):2327-2336.
48. Li J, Fan J-G. Characteristics and mechanism of liver injury in 2019 coronavirus disease. *J Clin Transl Hepatol*. 2020;8(1):13-17.
49. Surveillance Epidemiology of Coronavirus (COVID-19) Under Research Exclusion (SECURE)-CIRRHOSIS Registry, Updates and Data. Accessed May 7, 2021. <https://covidcirrhosis.web.unc.edu/updates-and-data/>
50. COVID-19 in Patients with Liver Disease or Transplantation (COVID-Hep) Registry. Accessed May 7, 2021. [https://www.covid-hep.net/img/update\\_20200825.pdf](https://www.covid-hep.net/img/update_20200825.pdf)
51. Weisberg IS, Jacobson IM. Cardiovascular diseases and the liver. *Clin Liver Dis*. 2011;15(1):1-20.
52. Faruqi S, Okoli FC, Olsen SK, et al. Cholangiopathy after severe COVID-19: clinical features and prognostic implications. *Am J Gastroenterol*. 2021;116(7):1414-1425.
53. Roth NC, Kim A, Vitkovski T, et al. Post-COVID-19 cholangiopathy: a novel entity. *Am J Gastroenterol*. 2021;116(5):1077-1082.
54. Lippi G, de Oliveira MHS, Henry BM. Chronic liver disease is not associated with severity or mortality in Coronavirus disease 2019 (COVID-19): a pooled analysis. *Eur J Gastro Hepatol*. 2021;33(1):114-115.
55. Williamson E, Walker AJ, Bhaskaran KJ, et al. OpenSAFELY: factors associated with COVID-19-related hospital death in the linked electronic health records of 17 million adult NHS patients. *medRxiv*. <https://doi.org/10.1101/2020.05.06.20092999>
56. Singh S, Khan A. Clinical characteristics and outcomes of coronavirus disease 2019 among patients with preexisting liver disease in the United States: A Multicenter Research Network Study. *Gastroenterology*. 2020;159(2):768-771.e763.
57. Marjot T, Moon AM, Cook JA, et al. Outcomes following SARS-CoV-2 infection in patients with chronic liver disease: An international registry study. *J Hepatol*. 2021;74(3):567-577.
58. Zhang B, Huang W, Zhang S. Clinical features and outcomes of Coronavirus Disease 2019 (COVID-19) patients with chronic hepatitis B virus infection. *Clin Gastroenterol Hepatol*. 2020;18(11):2633-2637.
59. Blach S, Kondili LA, Aghemo A, et al. Impact of COVID-19 on global HCV elimination efforts. *J Hepatol*. 2021;74(1):31-36.
60. Lau G, Sharma M. Clinical practice guidance for hepatology and liver transplant providers during the COVID-19 pandemic: APASL expert panel consensus recommendations. *Hep Intl*. 2020;1-14.
61. Di Giorgio A, Nicastro E, Speziani C, et al. Health status of patients with autoimmune liver disease during SARS-CoV-2 outbreak in northern Italy. *J Hepatol*. 2020;73(3):702-705.
62. Gerussi A, Rigamonti C, Elia C, et al. Coronavirus Disease 2019 in autoimmune hepatitis: a lesson from immunosuppressed patients. *Hepatol Commun*. 2020;4(9):1257-1262.
63. Boettler T, Newsome PN, Mondelli MU, et al. Care of patients with liver disease during the COVID-19 pandemic: EASL-ESCMID position paper. *JHEP Rep*. 2020;2(3):100113.
64. Targher G, Mantovani A, Byrne CD, et al. Risk of severe illness from COVID-19 in patients with metabolic dysfunction-associated fatty liver disease and increased fibrosis scores. *Gut*. 2020;69(8):1545-1547.
65. Hashemi N, Viveiros K, Redd WD, et al. Impact of chronic liver disease on outcomes of hospitalized patients with COVID-19: A multicentre United States experience. *Liver Int*. 2020;40(10):2515-2521.
66. Shalimar EA, Vaishnav M, et al. Poor outcomes in patients with cirrhosis and Corona Virus Disease-19. *Indian J Gastroenterol*. 2020;39(3):285-291.
67. Bajaj JS, Garcia-Tsao G, Biggins SW, et al. Comparison of mortality risk in patients with cirrhosis and COVID-19 compared with patients with cirrhosis alone and COVID-19 alone: multicentre matched cohort. *Gut*. 2021;70(3):531-536. <https://doi.org/10.1136/gutjnl-2020-322118>
68. Liu H, He X, Wang Y, et al. Management of COVID-19 in patients after liver transplantation: Beijing working party for liver transplantation. *Hep Intl*. 2020;14(4):432-436.
69. Qin J, Wang H, Qin X, et al. Perioperative presentation of COVID-19 disease in a liver transplant recipient. *Hepatology*. 2020;72(4):1491-1493.
70. D'Antiga L. Coronaviruses and immunosuppressed patients: The facts during the third epidemic. *Liver Transpl*. 2020;26(6):832-834.
71. Rodriguez-Peralvarez M, Salcedo M, Colmenero J, Pons JA. Modulating immunosuppression in liver transplant patients with COVID-19. *Gut*. 2021;70(7):1412-1414.
72. Becchetti C, Zambelli MF, Pasulo L, et al. COVID-19 in an international European liver transplant recipient cohort. *Gut*. 2020;69(10):1832-1840.
73. Colmenero J, Rodriguez-Peralvarez M, Salcedo M, et al. Epidemiological pattern, incidence, and outcomes of COVID-19 in liver transplant patients. *J Hepatol*. 2021;74(1):148-155.
74. Webb GJ, Marjot T, Cook JA, et al. Outcomes following SARS-CoV-2 infection in liver transplant recipients: an international registry study. *The Lancet Gastroenterology & Hepatology*. 2020;5(11):1008-1016.
75. Ravanan R, Callaghan CJ, Mumford L, et al. SARS-CoV-2 infection and early mortality of waitlisted and solid organ transplant recipients in England: A national cohort study. *Am J Transplant*. 2020;20(11):3008-3018.
76. Lee BT, Perumalswami PV, Im GY, et al. COVID-19 in liver transplant recipients: an initial experience From the US epicenter. *Gastroenterology*. 2020;159(3):1176-1178.e1172.
77. Belli LS, Duvoux C, Karam V, et al. COVID-19 in liver transplant recipients: preliminary data from the ELITA/ELTR registry. *Lancet Gastroenterol Hepatol*. 2020;5(8):724-725.
78. Polak WG, Fondevila C, Karam V, et al. Impact of COVID-19 on liver transplantation in Europe: alert from an early survey of European Liver and Intestine Transplantation Association and European Liver Transplant Registry. *Transpl Int*. 2020;33(10):1244-1252.
79. Liang W, Guan W, Chen R, et al. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. *Lancet Oncol*. 2020;21(3):335-337.
80. Lee LYW, Czazier J-B, Angelis V, et al. COVID-19 mortality in patients with cancer on chemotherapy or other anticancer treatments: a prospective cohort study. *The Lancet*. 2020;395(10241):1919-1926.
81. Yu J, Ouyang W, Chua MLK, Xie C. SARS-CoV-2 transmission in patients with cancer at a tertiary care hospital in Wuhan, China. *JAMA Oncol*. 2020;6(7):1108-1110.
82. Zhang L, Zhu F, Xie L, et al. Clinical characteristics of COVID-19-infected cancer patients: a retrospective case study in three hospitals within Wuhan, China. *Ann Oncol*. 2020;31(7):894-901.
83. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA*. 2020;323(11):1061-1069.
84. Mehta V, Goel S, Kabarriti R, et al. Case fatality rate of cancer patients with COVID-19 in a New York Hospital System. *Cancer Discov*. 2020;10(7):935-941.
85. Kudo M, Kurosaki M, Ikeda M, et al. Treatment of hepatocellular carcinoma during the COVID-19 outbreak: The Working Group report of JAMTT-HCC. *Hepatol Res*. 2020;50(9):1004-1014.
86. Chan SL, Kudo M. Impacts of COVID-19 on liver cancers: during and after the pandemic. *Liver Cancer*. 2020;9(5):491-502.

87. Amaddeo G, Brustia R, Allaire M, et al. Impact of COVID-19 on the management of hepatocellular carcinoma in a high-prevalence area. *JHEP Rep.* 2021;3(1):100199.
88. Iavarone M, Sangiovanni A, Carrafello G, Rossi G, Lampertico P. Management of hepatocellular carcinoma in the time of COVID-19. *Ann Oncol.* 2020;31(8):1084-1085.
89. Loupy A, Aubert O, Reese PP, Bastien O, Bayer F, Jacquelinet C. Organ procurement and transplantation during the COVID-19 pandemic. *The Lancet.* 2020;395(10237):e95-e96.
90. de Vries APJ, Alwayn IPJ, Hoek RAS, et al. Immediate impact of COVID-19 on transplant activity in the Netherlands. *Transpl Immunol.* 2020;61:101304.
91. Gruttadauria S. Preliminary analysis of the impact of the coronavirus disease 2019 outbreak on Italian liver transplant programs. *Liver Transpl.* 2020;26(7):941-944.
92. Maggi U, De Carlis L, Yiu D, et al. The impact of the COVID-19 outbreak on liver transplantation programs in Northern Italy. *Am J Transplant.* 2020;20(7):1840-1848.
93. Thorburn D, Taylor R, Whitney J, et al. Resuming liver transplantation amid the COVID-19 pandemic. *Lancet Gastroenterol Hepatol.* 2021;6(1):12-13.
94. Pathanki AM, Mirza DF. Liver transplantation during the times of COVID-19 - viruses, vaccines and beyond. *J Clin Exp Hepatol.* 2021;11(4):411-413. <https://doi.org/10.1016/j.jceh.2021.1004.1014>.
95. Pahari H, Shellagi N, Nath B. Deceased donor liver transplantation in India in the COVID-19 Era: current scenario and future perspectives. *Transpl Proc.* 2020;52(9):2684-2687.
96. De Carlis R, Vella I, Incarbone N, et al. Impact of the COVID-19 pandemic on liver donation and transplantation: A review of the literature. *World J Gastroenterol.* 2021;27(10):928-938.
97. Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 Vaccine. *N Engl J Med.* 2020;383(27):2603-2615.
98. Baden LR, El Sahly HM, Essink B, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. *N Engl J Med.* 2021;384(5):403-416.
99. Zhang Y, Zeng G, Pan H, et al. Safety, tolerability, and immunogenicity of an inactivated SARS-CoV-2 vaccine in healthy adults aged 18-59 years: a randomised, double-blind, placebo-controlled, phase 1/2 clinical trial. *Lancet Infect Dis.* 2021;21(2):181-192.
100. Aggeletopoulou I, Davoulou P, Konstantakis C, Thomopoulos K, Triantos C. Response to hepatitis B vaccination in patients with liver cirrhosis. *Rev Med Virol.* 2017;27(6):e1942.
101. Duchini A, Hendry RM, Nyberg LM, Viernes ME, Pockros PJ. Immune response to influenza vaccine in adult liver transplant recipients. *Liver Transpl.* 2001;7(4):311-313.
102. McCashland TM, Preheim LC, Gentry MJ. Pneumococcal vaccine response in cirrhosis and liver transplantation. *J Infect Dis.* 2000;181(2):757-760.
103. Ou MT, Boyarsky BJ, Motter JD, et al. Safety and reactogenicity of 2 doses of SARS-CoV-2 vaccination in solid organ transplant recipients. *Transplantation.* 2021. Ahead of Print.
104. Boyarsky BJ, Werbel WA, Avery RK, et al. Immunogenicity of a single dose of SARS-CoV-2 messenger RNA vaccine in solid organ transplant recipients. *JAMA.* 2021;325(17):1784-1786.
105. Boyarsky BJ, Werbel WA, Avery RK, et al. Antibody response to 2-Dose SARS-CoV-2 mRNA vaccine series in solid organ transplant recipients. *JAMA.* 2021;325(21):2204-2206.
106. Kamar N, Abravanel F, Marion O, Couat C, Izopet J, Del Bello A. Three doses of an mRNA Covid-19 vaccine in solid-organ transplant recipients. *N Engl J Med.* 2021.
107. Fu Y, Zhu R, Bai T, et al. Clinical features of patients infected with coronavirus disease 2019 with elevated liver biochemistries: A multicenter, retrospective study. *Hepatology.* 2021;73(4):1509-1520.
108. Wang Y, Liu S, Liu H, et al. SARS-CoV-2 infection of the liver directly contributes to hepatic impairment in patients with COVID-19. *J Hepatol.* 2020;73(4):807-816.
109. Huang R, Zhu L, Wang J, et al. Clinical features of COVID-19 patients with nonalcoholic fatty liver disease. *Hepatol Commun.* 2020;4(12):1758-1768. <https://doi.org/10.1002/hep4.1592>.
110. Zhou YJ, Zheng KI, Wang XB, et al. Younger patients with MAFLD are at increased risk of severe COVID-19 illness: A multicenter preliminary analysis. *J Hepatol.* 2020;73(3):719-721.
111. Yadav DK, Singh A, Zhang Q, et al. Involvement of liver in COVID-19: systematic review and meta-analysis. *Gut.* 2021;70(4):807-809.
112. Dhampalwar S, Saigal S, Choudhary N, et al. Outcomes of coronavirus disease 2019 in living donor liver transplant recipients. *Liver Transpl.* 2020;26(12):1665-1666.
113. Sarin SK, Choudhury A, Lau GK, et al. Pre-existing liver disease is associated with poor outcome in patients with SARS CoV2 infection; The APCOLIS Study (APASL COVID-19 Liver Injury Spectrum Study). *Hep Intl.* 2020;14(5):690-700.
114. Phipps MM, Barraza LH, LaSota ED, et al. Acute Liver Injury in COVID-19: prevalence and association with clinical outcomes in a large U.S. Cohort. *Hepatology.* 2020;72(3):807-817.
115. Hundt MA, Deng Y, Ciarleglio MM, Nathanson MH, Lim JK. Abnormal liver tests in COVID-19: A retrospective observational cohort study of 1,827 Patients in a major U.S. Hospital Network. *Hepatology.* 2020;72(4):1169-1176.
116. Bloom PP, Meyerowitz EA, Reinus Z, et al. Liver biochemistries in hospitalized patients With COVID-19. *Hepatology.* 2021;73(3):890-900.
117. Clift AK, Coupland CAC, Keogh RH, et al. Living risk prediction algorithm (QCOVID) for risk of hospital admission and mortality from coronavirus 19 in adults: national derivation and validation cohort study. *BMJ (Clin Res ed).* 2020;371:m3731.
118. Rabiee A, Sadowski B, Adeniji N, et al. Liver Injury in Liver transplant recipients with coronavirus disease 2019 (COVID-19): U.S. multicenter experience. *Hepatology.* 2020;72(6):1900-1911.
119. Kates OS, Haydel BM, Florman SS, et al. COVID-19 in solid organ transplant: a multi-center cohort study. *Clin Infect Dis.* 2020;ciaa1097. <https://doi.org/10.1093/cid/ciaa1097>.
120. Belli LS, Fondevila C, Cortesi PA, et al. Protective role of tacrolimus, deleterious role of age and comorbidities in liver transplant recipients with Covid-19: results from the ELITA/ELTR Multi-center European Study. *Gastroenterology.* 2021;160(4):1151-1163 e1153.
121. Verhelst X, Somers N, Geerts A, Degroote H, Van Vlierberghe H. Health status of patients with autoimmune hepatitis is not affected by the SARS-CoV-2 outbreak in Flanders, Belgium. *J Hepatol.* 2021;74(1):240-241.
122. Butt AA, Yan P, Chotani RA, Shaikh OS. Mortality is not increased in SARS-CoV-2 infected persons with hepatitis C virus infection. *Liver Intl.* 2021;41(8):1824-1831.
123. Kim D, Adeniji N, Latt N, et al. Predictors of outcomes of COVID-19 in patients with chronic liver disease: US Multi-center Study. *Clin Gastroenterol Hepatol.* 2021;19(7):1469-1479.
124. Chen X, Jiang Q, Ma Z, et al. Clinical characteristics of hospitalized patients with SARS-CoV-2 and hepatitis B virus Co-infection. *medRxiv.* 2020;35(6):842-845.
125. Zha L, Li S, Pan L, et al. Corticosteroid treatment of patients with coronavirus disease 2019 (COVID-19). *Med J Aust.* 2020;212(9):416-420.
126. Sachdeva S, Khandait H, Kopel J, Aloysius MM, Desai R, Goyal H. NAFLD and COVID-19: a pooled analysis. *SN Compr Clin Med.* 2020;1-4.
127. Forlano R, Mullish BH, Mukherjee SK, et al. In-hospital mortality is associated with inflammatory response in NAFLD patients admitted for COVID-19. *PLoS One.* 2020;15(10):e0240400.
128. Mahamid M, Nseir W, Khoury T, et al. Nonalcoholic fatty liver disease is associated with COVID-19 severity independently of metabolic syndrome: a retrospective case-control study. *Eur J Gastro Hepatol.* 2020. <https://doi.org/10.1097/MEG.0000000000001902>.



129. Bramante C, Tignanelli CJ, Dutta N, et al. Non-alcoholic fatty liver disease (NAFLD) and risk of hospitalization for Covid-19. *medRxiv*. <https://doi.org/10.1101/2020.09.01.20185850>.
130. Gao Y, Chen Y, Liu M, Shi S, Tian J. Impacts of immunosuppression and immunodeficiency on COVID-19: A systematic review and meta-analysis. *The Journal of Infection*. 2020;81(2):e93-e95.
131. Gao F, Zheng KI, Gu JY, George J, Zheng MH. COVID-19 and liver transplantation: Lessons learned from three reported cases. *Transpl Infect Dis*. 2020;22(4):e13335.
132. Varghese J, Malleeswaran S, Patcha RV, et al. A multicentric experience on living donor liver transplantation in COVID-19 hotspots in India. *Liver Transpl n/a(n/a)*.
133. Fernández-Ruiz M, Andrés A, Loinaz C, et al. COVID-19 in solid organ transplant recipients: A single-center case series from Spain. *Am J Transplant*. 2020;20(7):1849-1858.
134. Webb GJ, Moon AM, Barnes E, Barritt AS, Marjot T. Determining risk factors for mortality in liver transplant patients with COVID-19. *Lancet Gastroenterol Hepatol*. 2020;5(7):643-644.
135. Heimbach JK, Taner T. SARS-CoV-2 infection in liver transplant recipients: collaboration in the time of COVID-19. *Lancet Gastroenterol Hepatol*. 2020;5(11):958-960.
136. Bhoori S, Rossi RE, Citterio D, Mazzaferro V. COVID-19 in long-term liver transplant patients: preliminary experience from an Italian transplant centre in Lombardy. *Lancet Gastroenterol Hepatol*. 2020;5(6):532-533.
137. Deng G, Yin M, Chen X, Zeng F. Clinical determinants for fatality of 44,672 patients with COVID-19. *Crit Care*. 2020;24(1):179.
138. Kuderer NM, Choueiri TK, Shah DP, et al. Clinical impact of COVID-19 on patients with cancer (CCC19): a cohort study. *Lancet*. 2020;395(10241):1907-1918.

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