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Clinical features and potential mechanism of coronavirus disease 2019-associated liver injury

Mei-Wen Han, Ming Wang, Meng-Ying Xu, Wei-Peng Qi, Peng Wang, Dong Xi

Abstract

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2, has posed a serious threat to global public health security. With the increase in the number of confirmed cases globally, the World Health Organization has declared the outbreak of COVID-19 an international public health emergency. Despite atypical pneumonia as the primary symptom, liver dysfunction has also been observed in many clinical cases and is associated with the mortality risk in patients with COVID-19, like severe acute respiratory syndrome and Middle East respiratory syndrome. Here we will provide a schematic overview of the clinical characteristics and the possible mechanisms of liver injury caused by severe acute respiratory syndrome coronavirus 2 infection, which may provide help for optimizing the management of liver injury and reducing mortality in COVID-19 patients.

Key Words: COVID-19; Novel coronavirus; SARS-CoV-2; Liver injury

Core Tip: With the number of confirmed cases increasing worldwide, abnormal liver function has been observed in many patients with coronavirus disease 2019 (COVID-19). COVID-19-associated liver injury refers to any hepatic damage that occurs during disease progression and treatment in COVID-19 patients with or without underlying liver diseases. Underlying mechanisms may be viral infection in liver cells, systemic inflammation induced by cytokine storm, drug induced liver injury or pneumonia-associated hypoxia. A close monitor of liver function is recommended in COVID-19 patients, especially in critical individuals.
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INTRODUCTION

Since the 21st century, the outbreak of coronaviruses has brought great harm to human society; the most serious of which are the severe acute respiratory syndrome (SARS) in 2003, the Middle East respiratory syndrome (MERS) in 2012 and the novel coronavirus disease in 2019 (COVID-19). The ongoing outbreak of COVID-19 has become a pandemic. As of December 9, 2020, the total number of diagnosed cases globally exceeded 67530912 with a total of more than 1545140 infection-related deaths, carrying a mortality of approximately 2%.[1] Up to now, no specific antiviral therapies have been identified. Thus, an early monitor of critical complications is vital in preventing disease progression and improving survival.

With the number of confirmed cases increasing worldwide, abnormal liver function has been observed in many patients with COVID-19, making this organ one of the most frequently damaged outside of the respiratory system (summarized in Table 1). COVID-19-associated liver injury refers to any hepatic damage that occurs during disease progression and treatment in COVID-19 patients with or without underlying liver diseases[2]. However, due to the different design and sample size, the incidence and clinical manifestations of liver injury in these studies are not the same. The mechanism of hepatic damage caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is still unclear.

SARS-CoV, Middle East respiratory syndrome coronavirus (MERS-CoV) and SARS-CoV-2 are the causative agents of SARS, MERS and COVID-19, respectively, and they all belong to the highly pathogenic human beta coronaviruses[3]. Genomics analyses have found that SARS-CoV-2 shares 79.5% genome sequence similarity to SARS-CoV and 50% genome sequence homology to MERS-CoV[4]. SARS-CoV-2 uses the same cell entry receptor-angiotensin converting enzyme II (ACE2) as SARS-CoV[5]. These common points hint that SARS-CoV-2 may partly mimic SARS-CoV and MERS-CoV infection.

In this review, we summarized the characteristics and mechanism of liver injury caused by SARS-CoV-2 infection to provide a reference for further study.

Liver injury in SARS and MERS

Liver injury is not uncommon in patients infected with SARS-CoV and MERS-CoV according to previous studies[4]. In patients with SARS, liver injury mainly manifests as elevated alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) in the early phase of the disease and is associated with the severity of the illness[5-9]. The pathogenesis of hepatic damage caused by SARS-CoV appears to be multifactorial, including a direct injury to the target cells by the virus and an indirect injury mediated by subsequent immune system dysfunction. As the functional receptor for SARS-CoV, ACE2 is abundantly expressed on endothelial cells of the liver, implying that SARS-CoV may directly bind to ACE2 positive cells to dysregulate liver function[10-13]. Liver biopsies in SARS patients demonstrated localization of virus in liver and hepatocyte apoptosis, which further confirmed the direct injury by SARS-CoV[14]. In an analysis of 145 cases of SARS, serum interleukin (IL)-1β, IL-6 and IL-10 were higher in patients with elevated serum levels of ALT than those in ALT normal group, indicating that liver damage was part of the manifestation of system inflammation reactive syndrome induced by SARS-CoV infection[15]. In addition, some studies have also found that hypoxemia and medication are closely related to abnormal liver function[16-19].

Elevated liver enzymes and bilirubin levels, as well as decreased albumin levels were highlighted during the hospital course of MERS-CoV infection in a series of case reports[20-23]. Different from SARS-CoV, MERS-CoV uses dipeptide base peptidase 4 as a cellular receptor to infect cells[21]. In humans, dipeptide base peptidase 4 is expressed constitutively on epithelial cells of liver[22], suggesting a direct hepatic damage caused by MERS-CoV. MERS also involves a mechanism of the upregulation of proinflammatory cytokines, such as interferon-γ, tumor necrosis factor-α, IL-15 and IL-17[23]. However, studies on the relationship between cytokine storm and liver injury are scarce so far.
Table 1 Main characteristics related to liver injury in patients with coronavirus disease 2019 based on a series of case reports

<table>
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<th>Ref.</th>
<th>Sample size</th>
<th>Liver injury</th>
<th>Elevated ALT</th>
<th>Elevated AST</th>
<th>Elevated TBIL</th>
<th>Elevated ALP</th>
<th>Elevated GGT</th>
<th>Factors related to liver injury</th>
</tr>
</thead>
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<tr>
<td>[25]</td>
<td>1099</td>
<td>NA</td>
<td>21.3%: Severe</td>
<td>22.2%: Severe</td>
<td>10.5%: Severe</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>[25]</td>
<td>548</td>
<td>NA</td>
<td>23.1%: Severe</td>
<td>33.1%: Severe</td>
<td>4.4%: Severe</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>[27]</td>
<td>417</td>
<td>21.5%</td>
<td>42.1%: Severe</td>
<td>47.2%: Severe</td>
<td>64.2%: Severe</td>
<td>10.9%: Severe</td>
<td>48.5%: Severe</td>
<td>Older, male, higher BMI, Underlying liver diseases (NAFLD, alcoholic liver disease and chronic hepatitis B), drugs (lopinavir/ritonavir)</td>
</tr>
<tr>
<td>[29]</td>
<td>324</td>
<td>15.7%</td>
<td>10.5%</td>
<td>6.5%</td>
<td>1.2%</td>
<td>0.9%</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>[29]</td>
<td>298</td>
<td>14.8%</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>[24]</td>
<td>274</td>
<td>NA</td>
<td>22.0%: Deceased</td>
<td>31.0%: Deceased</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>[13]</td>
<td>148</td>
<td>37.2%</td>
<td>18.2%</td>
<td>21.6%</td>
<td>6.1%</td>
<td>4.1%</td>
<td>17.6%</td>
<td>Male, higher levels of procalcitonin and CRP, PCT, LDH, received lopinavir/ritonavir</td>
</tr>
<tr>
<td>[13]</td>
<td>85</td>
<td>38.8%</td>
<td>61.2%</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>[13]</td>
<td>79</td>
<td>36.7%</td>
<td>31.6%</td>
<td>35.4%</td>
<td>5.1%</td>
<td>NA</td>
<td>NA</td>
<td>Male, white blood cell counts, neutrophils, CRP, the extent of pulmonary lesions on CT</td>
</tr>
<tr>
<td>[14]</td>
<td>40</td>
<td>55%</td>
<td>52.5%</td>
<td>40%</td>
<td>25%</td>
<td>NA</td>
<td>NA</td>
<td>Many types of drugs, large amounts of hormones, underlying diseases, lymphocyte count, critical illness</td>
</tr>
<tr>
<td>[19]</td>
<td>82</td>
<td>78%</td>
<td>30.6%</td>
<td>61.1%</td>
<td>30.6%</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>


Clinical characteristics of liver injury in patients with COVID-19

Since Chen et al.[24] reported that 43 cases of 99 patients (43.4%) in Wuhan Jinyintan Hospital had different degrees of abnormal liver function, the abnormality of liver function test in patients with COVID-19 has aroused widespread concern among clinicians. As shown in Table 1, the incidence of liver injury ranged from 14.8% to 55.0% in recent case studies reporting clinical features of patients with COVID-19.[25-34] In death cases of COVID-19, the rate reached as high as 78.0%.[30] Liver injury presented in 30 out of 113 deceased patients from our previous report.[31] Abnormal liver function mainly manifests as slightly elevated ALT/AST and bilirubin levels, which usually occurs around the second week of the disease course.[32-34] Rarely, severe acute hepatitis associated with COVID-19 has been reported.[34]

Contradictory to other hepatitis-induced liver injury, AST-dominant aminotransferase elevation is common in COVID-19, which may provide a clue about the underlying pathophysiology of the impact of COVID-19 on liver. A retrospective study including 60 patients revealed that median AST was higher than ALT at admission (46 U/L vs 30 U/L) and during the hospital course.[35] In a multicenter retrospective cohort-derived data set of 5771 individuals, the elevation of serum AST level was earlier, more frequent and significant than the increase of ALT in severe patients, and AST levels had the highest correlation with mortality when compared with other indicators reflecting liver injury including elevated ALT, alkaline phosphatase (ALP) and total bilirubin (TBIL) levels in patients with COVID-19.[36] Likewise, an elevated baseline AST level has been shown to correlate with intensive care unit (ICU) admission, intubation and death in another study.[37]
To our knowledge, three possible reasons may account for this phenomenon. First, given that AST is also distributed in myocardium and skeletal muscle, the American Association for the Study of Liver Diseases has recommended consideration of myocarditis or cardiac injury as contributors to the AST elevation[4]. Second, recent data identified ribosomal proteins as important host-dependency factors for SARS-CoV-2[4]. Therefore, the virus may directly cause hepatic mitochondrial injury and subsequent AST elevation. Third, AST-predominant aminotransferase elevations have been reported in alcohol-related liver disease, ischemia and cirrhosis. It is possible that hypoxia as well as metabolic changes such as hepatic steatosis may account for AST elevation in COVID-19 patients[42,43].

It is worth noting that liver dysfunction is closely related to the severity of the disease. On the one hand, severe patients have a higher proportion of liver injury: Guan et al[44] extracted a cohort regarding 1099 patients with laboratory-confirmed COVID-19 from 552 hospitals in mainland China. The results showed more patients with severe disease had elevated AST and ALT than those with non-severe disease. Like the result, Wang et al[45] showed that more patients admitted to the ICU had elevated AST levels. Huang et al[46] showed that patients admitted to the ICU had significantly higher ALT levels. On the other hand, patients with abnormal liver tests had higher risks of progressing to a severe disease course: Bloom et al[47] showed that admission AST, peak AST and peak ALT were higher in intubated patients. Of 417 patients with COVID-19, patients with abnormal liver tests of hepatocellular, cholestatic or mixed type at admission had higher odds of progressing to severe pneumonia[48]. Among 146 confirmed SARS-CoV-2-infected patients, the emerging abnormal liver function after admission caused a prolonged length of stay[49]. In a large United States COVID-19 cohort of 3381 patients, 2273 patients who tested positive for SARS-CoV-2 had higher initial and peak ALT than those who tested negative[50]. Compared with mild [upper limit of normal (ULN) < ALT < two times ULN], moderate (two times ULN < ALT < five times ULN) and severe (ALT > five times ULN) liver injury, patients with severe liver injury (ALT > five times ULN) had a more severe clinical course, including higher rates of ICU admission (69%), intubation (65%), renal replacement therapy (33%) and mortality (42%).

Other hepatic manifestations in COVID-19 patients were hypoprothrombinemia and changes in coagulation[47,48]. A large cohort study including 2623 patients reported marked hypoalbuminemia in the critically ill and death groups than non-critically ill patients (38.2%, 71.2% and 82.4% on admission and 45.9%, 77.7% and 95.6% during hospitalization, respectively)[51]. Meanwhile, the patients in this study displayed dramatically prolonged activated partial thromboplastin time in critically ill patients reflected coagulopathy.

Further analysis shows that risk factors associated with hepatic damage include older males, a longer time from illness onset to admission, a history of drinking, higher serum levels of C-reactive protein (CRP), white blood cell counts, neutrophils and medication (lopinavir/ritonavir, hormones)[27-30,34]. Disease severity (severe/critical), CRP, lymphocyte count and the extent of pulmonary lesions on computed tomography are independent risk factors for liver injury[45-48].

Accumulating data reveals that patients with pre-existing liver diseases are more susceptible to SARS-CoV-2 infection and have poorer prognosis. In our study, viral hepatitis (hepatitis B and hepatitis C) was much more frequent among patients with liver injury than those without[50]. Another study revealed that COVID-19 patients with non-alcoholic fatty liver disease had a significantly higher likelihood of abnormal liver function from admission to discharge when compared to those with non-alcoholic fatty liver disease subjects[52]. Qiu et al[53] first reported a case of acute-on-chronic liver failure due to SARS-COV-2 infection in a patient with decompensated alcoholic cirrhosis. In a multicenter retrospective study, fifty cirrhotic patients with SARS-CoV-2 infection were studied to evaluate the impact of COVID-19 on the clinical outcome[54]. The results showed 30-d mortality rate was higher in cirrhotic patients with COVID-19 than in cirrhotic patients with bacterial infection and in COVID-19 patients without cirrhosis, indicating that COVID-19 was associated with liver function deterioration and elevated mortality in cirrhotic patients. In addition, a study of 2780 COVID-19-positive patients found that those with cirrhosis were at a particularly increased risk for mortality by analyzing a large United States database (risk ratio, 4.6; 95% confidence interval, 2.6-8.3)[55].

Whether the COVID-19 patients with more severe liver injury were positive for hepatotrophis viruses is still controversial. In a retrospective study, the authors analyzed liver function parameters including ALT, AST and TBIL in COVID-19 patients with or without HBV infection and found no significant differences between the two groups[56]. Another study reached a similar conclusion and further proved the
Mechanisms of liver injury in patients with COVID-19

Underlying mechanisms involved in liver injury in patients with COVID-19 are complex and interactive, which might include viral infection in liver cells, systemic inflammation induced by cytokine storm, drug induced liver injury or pneumonia-associated hypoxia\(^8\) (Figure 1).

Virus-induced cytopathic effects

It is well known that SARS-CoV-2 predominantly enters alveolar epithelial cells through the human ACE2 receptor, thus making the lung the main target organ of SARS-CoV-2 infection\(^6\). However, previous studies have found that ACE2 receptor is also specifically expressed in bile duct epithelial cells but is rarely expressed in hepatocytes\(^6\) and absent of Kupffer cells and hepatic stellate cells\(^6\). A further study employing single-cell ribonucleic acid-seq suggested that TROP2 cholangiocytes could be a main target for SARS-CoV-2 infection, leading to impaired liver regeneration and liver function\(^6\). In a mouse model of acute liver injury, ACE2 was upregulated in liver tissue due to compensatory proliferation of hepatocytes derived from bile duct epithelial cells\(^6\). During this compensatory process, some newborn hepatocytes still expressed ACE2 receptor and were susceptible to SARS-CoV-2. Recently, Wang et al\(^64\) investigated the patterns of liver impairment by electron microscopy and pathological studies in two COVID-19 cases. In this study, typical coronavirus particles were identified in the cytoplasm of hepatocytes. Histologically, massive hepatic apoptosis and binuclear hepatocytes were observed. Our previous clinical report showed that the bile duct injury related ALP and gamma-glutamyl transpeptidase was elevated in deceased patients\(^64\). These findings suggest that the liver injury in COVID-19 patients may be due to hepatocyte damage as well as cholangiocyte dysfunction.

Other studies reported conflicting results. For example, Qian et al\(^59\) showed that ALP, gamma-glutamyl transpeptidase and TBIL elevations were rare among 324 cases with SARS-CoV-2 pneumonia. Zhang et al\(^55\) reported that after SARS-CoV-2 infection, the overall ALP level is even lower than that with community-acquired pneumonia patients, implying that the duct epithelium injury by SARS-CoV-2 itself is very slight. Thus, SARS-CoV-2 infection may not be the major reason related to liver injury. Given the conflicting results above, the role of virus-induced cytopathic effects in COVID-19-related liver injury warrants further investigation.

Inflammatory cytokine storm

Cell entry of SARS-CoV-2 depends on binding of the viral spike (S) proteins to cellular ACE2 receptor and on spike protein priming by host cell proteases\(^5\). While the virus enters the cells via fusion with the host membrane, its antigen will be recognized by the antigen presentation cells and then presented to cytotoxic and regulatory T lymphocytes, which initiate an antiviral immune response that includes inflammatory cytokine production and a weak interferon response\(^5\). In young individuals with an intact immune system, the virus is cleared away during the initial phase, so they show only mild symptoms\(^6\). However, in the elderly and individuals with underlying chronic diseases, the insufficient viral clearance due to altered immune response will lead to a cytokine storm, which may trigger a violent attack to the body and cause multiple organ failure including the liver\(^4^5\). Inflammatory cytokine storm is an overactive inflammatory response caused by virus infection, which leads to persistent activation of lymphocytes and macrophages that secrete huge amounts of inflammatory cytokines\(^4^5\). For example, SARS-CoV-2 can rapidly activate pathogenic Th1 cells to secrete proinflammatory cytokines, such as granulocyte-macrophage colony-stimulating factor and IL-6\(^4^5\). Granulocyte-macrophage colony-stimulating
Figure 1 Potential mechanisms of liver injury in patients with coronavirus disease 2019. 1: Severe acute respiratory syndrome coronavirus-2 may directly bind to angiotensin converting enzyme II positive cholangiocytes to dysregulate liver function; 2: Inflammatory cytokine storm leads to persistent activation of lymphocytes and macrophages that secrete huge amount of inflammatory cytokine, thus contributing to lung as well as liver damage; 3: Drugs including antipyretics, antiviral medications (lopinavir/ritonavir), antibiotics (macrolides, quinolones) and steroids may have potential hepatotoxicity and lead to abnormal liver function; 4: Hepatic ischemia and hypoxia-reperfusion dysfunction induced by complications such as respiratory failure may cause liver damage, especially in critically ill patients.

factor further activates CD14+CD16+ inflammatory monocytes to produce large quantities of IL-6, tumor necrosis factor-α and other cytokines. Among these cytokines, IL-6 can bind to sIL-6R to activate STAT3 in nonimmune cells and can bind to membrane-bound IL-6 receptor to lead to pleiotropic effects on acquired and innate immune cells[73]. Meanwhile, sIL-2R may regulate cytotoxic T cells negatively and contribute to lymphopenia through IL-2 signaling inhibition[74].

Accumulating evidence revealed a broad spectrum of proinflammatory cytokines and chemokines dramatically increased in patients with liver dysfunction compared to those with normal liver function[10,32]. Consistent with these results, our data showed the levels of inflammatory markers including high sensitivity CRP, neutrophil-to-lymphocyte ratio, white blood cells, neutrophils, serum ferritin, lactate dehydrogenase, procalcitonin, erythrocyte sedimentation rate and proinflammatory cytokines including IL-2R, IL-6, tumor necrosis factor-α in the liver injury group were significantly higher compared with the group without liver injury[51]. In an analysis of 85 patients with COVID-19, lymphopenia and CRP may even serve as the risk factors related to hepatic injury[32]. Moreover, the postmortem liver biopsy in one patient confirmed that liver injury in COVID-19 is likely immune mediated[43]. These findings indicated that immune-mediated inflammatory response following SARS-CoV-2 infection may cause or contribute to liver damage. In the future, more research is needed to understand the concrete mechanisms involved in cytokine accumulation in COVID-19 and subsequent liver injury.

Drug-induced liver injury

Fever was one of the most common symptoms on admission and during hospitalization in patients with COVID-19[25]. Therefore, antipyretic therapy is very ordinary in infected patients. Acetaminophen, a common ingredient in antipyretic drugs, is proven to cause significant liver damage or induce liver failure according to a dose-dependent mechanism[75]. Recently, a 27-year-old healthy African American female with a positive SARS-CoV-2 test and acute liver failure secondary to acetaminophen overdose was reported[76]. She had a remote history of focal segmental glomerular sclerosis. To manage her pain, she ingested > 50 tablets of acetaminophen over the 3-4 d preceding presentation. Initial blood work revealed the acetaminophen level was 42 µg/mL (upper limit of normal 30 µg/mL) and elevated aminotransferases with alanine transaminase of 2791 U/L and aspartate transaminase of 3202 U/L. Two days after admission, her hepatic synthetic function worsened significantly, and aminotransferases peaked to an AST 9741 U/L and ALT 11322 U/L. Thus, although paracetamol is a safe and effective first line agent in almost all patients regardless of
Liver injury is a common complication in COVID-19 patients and may result from virus-induced cytopathic effects, immune mediated inflammation, drug toxicity and pneumonia-associated hypoxia. Like SARS and MERS, abnormal liver function mainly manifested as transient elevation of serum aminotransferases. Moreover, patients with abnormal liver tests had higher risks of progressing to severe disease. From a clinical perspective, in addition to actively dealing with the primary disease caused by SARS-CoV-2 infection, a close monitor of liver function is recommended in COVID-19 patients, especially in severe/critical individuals.

CONCLUSION

Liver injury is a common complication in COVID-19 patients and may result from virus-induced cytopathic effects, immune mediated inflammation, drug toxicity and pneumonia-associated hypoxia. Like SARS and MERS, abnormal liver function mainly manifested as transient elevation of serum aminotransferases. Moreover, patients with abnormal liver tests had higher risks of progressing to severe disease. From a clinical perspective, in addition to actively dealing with the primary disease caused by SARS-CoV-2 infection, a close monitor of liver function is recommended in COVID-19 patients, especially in severe/critical individuals.
Table 2 Management of coronavirus disease 2019 patients with liver disease

<table>
<thead>
<tr>
<th>Management of COVID-19 patients with liver disease</th>
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</thead>
<tbody>
<tr>
<td><strong>Out-patient care</strong></td>
</tr>
<tr>
<td>Use telemedicine or visits by phone wherever possible. Consider seeing in person only patients with urgent issues and clinically significant liver disease (e.g., jaundice, elevated ALT or AST &gt; 500 U/L, or recent onset of hepatic decompensation) [40,41,42,43]. Seeing at the fever clinic [40]</td>
</tr>
<tr>
<td><strong>Hospital treatment</strong></td>
</tr>
<tr>
<td>Separate management from non-COVID-19 patients [40,41,42,43]. Monitor liver biochemistries regularly, particularly in patients treated with remdesivir or tocilizumab [40]. Avoid ultrasound or other advanced imaging unless it is likely to change management, for example, clinical suspicion for biliary obstruction or venous thrombosis [40]. Hospitalize COVID-19 patients with advanced liver disease as soon as possible [41]</td>
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<tr>
<td><strong>Patients with hepatitis B, hepatitis C</strong></td>
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<tr>
<td>Document discussion with patient regarding CLD diagnosis and management [40]. Delay starting DAA therapy until after their recovery from COVID-19 disease if there is no suspicion of advanced liver disease [41]. Continue treatment and provide 90-d supplies for HBV oral antiviral drugs or a full course of DAA medications to complete HCV treatment [3].</td>
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<tr>
<td><strong>Patients with autoimmune liver disease</strong></td>
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<tr>
<td>Continue immunosuppressive therapy in stable patients with AIH [40]. Lower the doses of azathioprine or mycophenolate mofetil when patients develop lymphopenia [40]. Avoid liver biopsy and start empiric therapy in new patients presenting with features of AIH [40]. Avoid high doses of prednisone in AIH patients on corticosteroids [40].</td>
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<tr>
<td><strong>Patients with HCC</strong></td>
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<tr>
<td>Continue HCC surveillance schedule for high-risk subjects [40]. Document discussion of risks and benefits of delaying surveillance with patient [40]. Proceed with HCC treatments as appropriate [40]. Postpone elective transplant and resection surgery, withhold immunotherapy [40].</td>
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<tr>
<td><strong>Pretransplant and post-transplant patients</strong></td>
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<tr>
<td>Have low threshold for admitting patients on transplant waiting list diagnosed with COVID-19 [40,41,42]. Consider reduction of immunosuppressive therapy as appropriate for posttransplant patients with moderate COVID-19 [40,41,42]. Avoid reductions in immunosuppressive therapy in patients with mild COVID-19 disease [40,41,42].</td>
</tr>
</tbody>
</table>


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recommendations.

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GM-CSF+ T cells and inflammatory CD14+CD16+ monocytes in severe pulmonary syndrome


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