Liver injury in COVID-19: The current evidence

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Abstract
Patients with novel coronavirus disease 2019 (COVID-19) experience various degrees of liver function abnormalities. Liver injury requires extensive work-up and continuous surveillance and can be multifactorial and heterogeneous in nature. In the context of COVID-19, clinicians will have to determine whether liver injury is related to an underlying liver disease, drugs used for the treatment of COVID-19, direct effect of the virus, or a complicated disease course. Recent studies proposed several theories on potential mechanisms of liver injury in these patients. This review summarizes current evidence related to hepatobiliary complications in COVID-19, provides an overview of the available case series and critically elucidates the proposed mechanisms and provides recommendations for clinicians.

Keywords
SARS-CoV2, COVID-19, liver injury, liver function test, cholangiocytes, lymphopenia, cytokine storm

Received: 30 March 2020; accepted: 8 April 2020

Key points
- Altered liver function tests are reported in up to half of the patients with COVID-19 infection.
- Disease severity, pre-existing liver disease and older age present a risk for liver injury.
- Drug-induced liver injury is an important consideration in patients with COVID-19.
- Hepatotoxic antiviral medications require careful monitoring of adverse effects.
- SARS-CoV-2 may directly bind to ACE2 positive cholangiocytes and can cause hepatic injury.
- Activation of the immune system and ‘cytokine storm’ may contribute to an immune-mediated process of hepatic injury in COVID-19.
- The control of cytokine dysregulation at an early stage could be beneficial to curb the disease progression.

Introduction
In the current pandemic coronavirus disease (COVID-19), almost every country in the world has now registered COVID-19 cases, and the confirmed cases have exceeded one million to date. While initial clinical studies, especially from China, the USA and Italy, have highlighted the dominant clinical symptoms including fever, cough, fatigue and shortness of breath, the later research unveiled shreds of evidence on the extrapulmonary manifestations of the disease. These reports highlighted that beyond severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a complicated

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course of the disease or even viral infection itself can lead to involvement of other organs and multi-organ failure. The liver is the primary organ for detoxification and metabolism, and maintaining an optimal function is imperative to engage all available therapeutic modalities in the treatment of COVID-19. Abnormal liver function requires clinical evaluation, continuous surveillance and, potentially, specific therapy. To support clinical decision making and optimize the outcome in the treatment of COVID-19, it will be crucial to clearly understand the possible mechanisms involved in liver injury. The current review summarizes the pathophysiology and potentially specific role of COVID-19 in liver disease based on the available data and case series published, ahead of print and non-peer-reviewed preprints as of 2 April. The search strategy is detailed in the Supplementary Material online.

Pathophysiological basis of liver injury in patients with COVID-19

Emerging data from small clinical case studies have proposed that liver injury in COVID-19 is frequently seen, but the extent and underlying mechanisms remain undetermined. Figure 1 summarizes the pathophysiological findings, which are discussed below.

Direct viral effect on the liver

The liver exerts a crucial function in host defense against microbes and is involved in most systemic infections as it receives both the portal and systemic circulation. Certain viruses exert a direct cytopathic effect on hepatocytes and cholangiocytes although, in most cases, the pathogenesis seems multifactorial. Yang et al. reported that SARS-CoV could cause direct cytopathic liver injury rather than inducing cellular stress from low oxygen supplies or cytokines as seen in sepsis. Autopsy studies in patients revealed that SARS-CoV was detectable in 41% of the liver tissue, with a maximum viral load of $1.6 \times 10^6$ copies/g of tissue. The pathological findings of liver biopsy specimens from SARS patients showed hepatocellular necrosis, mitoses, cellular infiltration and fatty degeneration. In a recent autopsy analysis of liver tissue from a patient with COVID-19, moderate microvesicular steatosis and mild inflammation in the lobular and portal area was observed. However, this pattern of histological injury is not specific for one etiology but can also be observed during sepsis or drug-induced liver injury (DILI).

The role of cholangiocytes in COVID-19

Similar to SARS-CoV, SARS-CoV-2 uses the angiotensin-2 converting enzyme (ACE2) receptor protein to attack the host system. The cell entry receptor, ACE2, is widely expressed across the human body, including the lungs (type II alveolar cells), gastrointestinal tract (esophageal epithelial cells and absorptive enterocytes of ileum and colon), hepatobiliary system (hepatocytes and cholangiocytes), cardiovascular system (myocardial cells), the renal system (proximal tubule cells and urothelial bladder cells) and the pancreas. Recent studies have observed that ACE2 expression in the cell clusters of cholangiocytes was significantly higher than that in the hepatocytes population (59.7% vs. 2.6%). The authors conclude that SARS-CoV-2 may directly bind to ACE2 positive cholangiocytes, but not hepatocytes, to exert a cytopathic effect. Cholangiocytes are involved in many aspects of liver physiology, including regeneration and adaptive immune response mechanisms, and the disruption of cholangiocyte function can cause hepatobiliary damage. This is supported by cholestatic markers, including gamma-glutamyl transferase (GGT), that can be found in some, but not all, case series of COVID-19.

Dysregulation of the innate immune system in COVID-19

Dysregulation of the innate immune response can be one aspect of liver injury in COVID-19. Patients with COVID-19 exhibit marked activation of inflammatory markers, including abnormal levels of C-reactive protein (CRP), lymphocytes, neutrophils and cytokines, in particular interleukin-6 (IL-6). These mechanisms may contribute to pulmonary and extrapulmonary injuries and the control of cytokine dysregulation at an early stage could be beneficial to curb the disease progression. Hepatic inflammation involving activation of innate immune cells and the release of cytokines is a well-established driver of liver injury from various causes. In some of the available case series of COVID-19, a correlation between lymphopenia and liver injury was observed and CRP $\geq 20$ mg/L and a lymphocyte count $< 1.1 \times 10^9$/L were independent risk factors for liver injury. Notably, lymphopenia in COVID-19 studies was reportedly observed in 63%
to 70.3% of patients and those with lower lymphocyte counts more susceptible to fatal outcomes.\textsuperscript{11}

### Clinical evidence

**Elevated liver function tests (LFTs) in COVID-19**

More than 20 publications to date reported abnormal levels of aminotransferases in patients with COVID-19.\textsuperscript{7–9,11–13,17–19,21,23–27,29–33,35,36} A recent systematic review and meta-analysis on LFT abnormalities provided a pooled elevation of aspartate aminotransferase (AST) in 33.3% and alanine aminotransferase (ALT) in 24.1% of cases.\textsuperscript{39} Various investigators across different studies reported a correlation between the severity of COVID-19 and the degree of liver dysfunction.\textsuperscript{8,11,25} In one retrospective study, one patient experienced severe hepatitis with ALT of

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**Figure 1.** Clinical characteristics and pathophysiology of liver injury from COVID-19. ACE2: angiotensin-2 converting enzyme

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Table 1. Abnormalities in hepatobiliary function and inflammatory markers along with the proposed theories of hepatic injury in COVID-19.

| Ref. no. | Author (et al.) | Publication type | Publication date | Study type | No. of patients with COVID-19 | Pre-existing liver diseases | Hepatobiliary function markers | Inflammatory markers (and other relevant blood tests) | Proposed possible theories of hepatic injury |
|----------|-----------------|------------------|------------------|------------|-------------------------------|-----------------------------|-----------------------------|----------------------------------------|---------------------------------------------|
| 12       | Huang C         | Published        | 24 Jan 2020      | Prospective case series | 41               | Chronic liver disease in one patient | AST (max., 48.0 U/L) increased in 37%, more in the ICU group | 73% had LDH >245 U/L (max., 408 U/L) 37% had LYM >1.0 x 10^9/L (max., 1.1 x 10^9/L) CRP, ESR, IL-6, and LDH elevated in 86%, 85%, 52%, and 76% of patients ALB and LYM reduced in 98% and 35% cases, respectively | Overall disease exacerbation: Cytokine storm |
| 17       | Chen N          | Published        | 30 Jan 2020      | Retrospective case series | 99              | No histories of hepatic diseases reported | ALT, AST, and TIBIL increased in 28%, 35%, and 18% of patients | CRP, ESR, IL-6, and LDH elevated in 86%, 85%, 52%, and 76% of patients ALB and LYM reduced in 98% and 35% cases, respectively | Overall disease exacerbation: Damage to T lymphocytes |
| 22       | Wang D          | Published        | 7 Feb 2020       | Retrospective case series | 138             | Chronic liver disease in 2.9% of patients | No significant liver abnormalities | LYM (Median: 0.8 x 10^9/L) reduced in 70.3% cases, and LDH (Median: 201 U/L) increased in 39.9% of patients | Overall disease exacerbation: Damage to T lymphocytes |
| 26       | Cai Q           | Preprint         | 19 Feb 2020      | Retrospective case series | 298             | 2.7% had liver disease (details unspecified) Severe cases were associated with underlying diseases | 14.8% experienced liver injury (ALT (max., 59.5 U/L) and AST (max., 65 U/L): 8.7 %, respectively) | CRP (max., 47.13 mg/dL) increased in 70% cases IL-6 (max., 28.72 ng/L) increased in 76% of patients ESR (max., 50 mm/h) increased in 60.9% LYM (min, 0.91 x 10^9/L) reduced in 38.3% | Overall disease exacerbation: Inflammatory factor storm |
| 21       | Xu XW           | Published        | 19 Feb 2020      | Retrospective case series | 62              | 11% had underlying liver disease (details unspecified) About half of them experienced symptoms for more than 10 days after illness onset | AST (max., 32 U/L) increased in 16% of patients | LYM reduced in 85% cases | Overall disease exacerbation: Inflammatory factor storm |
| 18       | Yang X          | Ahead of Print   | 24 Feb 2020      | Retrospective case series | 52              | No histories of hepatic diseases reported | AST (>40 U/L) increased in 53% of patients, lower in asymptomatic patients | LYM (≥1.0 x 10^9/L) increased in 67%. CRP (Mean: 6.9 mg/L) was lower in asymptomatic patients | Overall disease exacerbation: Cytokine storm |
| 23       | Shi H           | Published        | 24 Feb 2020      | Retrospective case series | 81              | Hepatitis or liver cirrhosis in 9% of cases | AST (>40 U/L) increased in 35% of patients, lower in asymptomatic patients | LYM (≥1.0 x 10^9/L) increased in 67%. CRP (Mean: 6.9 mg/L) was lower in asymptomatic patients LYM (Mean: 0.67 x 10^9/L) reduced and CRP (Mean: 37.92 mg/L) increased in severe cases | Overall disease exacerbation: Cytokine storm |
| 27       | Cao W           | Preprint         | 25 Feb 2020      | Retrospective case series | 128             | None described | ALT (Mean: 43.87 IU/L) and AST (Mean: 44.13 IU/L) increased in severe cases | None described | None described |
| 19       | Zhang B         | Preprint         | 27 Feb 2020      | Retrospective case series with the data of non-survivors | 82              | Liver disease in 2.4% cases | ALT (>40 U/L), AST (>40 U/L), and TIBIL (>20.5 mmol/L) increased in 30.6%, 61.1%, and 30.6% cases | LYM (<1.0 x 10^9/L), ALB (<40 g/L) and CD8+ cells (<220 x 10^9/L) reduced in 89.2%, 77.8%, and 98.3% cases, respectively LDH (>250 U/L) and CRP (>10 U/L) elevated in 93.2% and 30% of patients, respectively | Overall disease exacerbation: Viral invasion of organs Inflammatory factor elicitation Perturbation of immune system |
| Ref. no. | Author (et al.) | Publication type | Publication date | Study type | No. of patients with COVID-19 | Pre-existing liver diseases | Hepatobiliary function markers | Inflammatory markers (and other relevant blood tests) | Proposed possible theories of hepatic injury |
|---------|----------------|-----------------|-----------------|------------|-----------------------------|-----------------------------|-------------------------------|-----------------------------------------|-----------------------------------------------|
| 25      | Guan WJ        | Ahead of print  | 28 Feb 2020     | Retrospective case series | 1099         | Hepatitis B in 2.1% of patients | Increase of AST (>40 U/L) in 22.2%, ALT (>40 U/L) in 21.3%, and TBIL (>17.1 μmol/L) in 10.9% | Elevation of CRP (>10 mg/L) and LDH (>250 U/L) in 60.7% and 41.0%, respectively | None described |
| 7       | Fan Z          | Preprint        | 28 Feb 2020     | Retrospective case series | 148          | None described               | 50.7% of patients had liver function abnormalities at admission 21.6%, 18.2%, 17.6%, 6.1%, and 4.1% patients had elevated AST, ALT, GGT, TBIL, and ALP, respectively. | 35.1% showed LDH elevation CD4+ and CD8+ T cells decreased and CRP increased in abnormal liver function group | Drug-induced inflammatory factor storm Viral infection of the liver |
| 8       | Zhang C        | Published       | 4 Mar 2020      | Review with a description of unpublished case series | 56           | None described               | 28.6% of cases had abnormal liver functions One fatal case with evaluated liver injury (ref. no. 3) | None described Direct viral infection of liver cells Drug-induced immune dysfunction | None described |
| 24      | Huang Y        | Preprint        | 5 Mar 2020      | Retrospective case series with the data of non-survivors | 36           | No histories of hepatic diseases reported | ALT, AST and TBIL increased in 13.3%, 58.1%, and 12.9% of patients, respectively | LYM and ALB decreased in 70.6% and 80.6% cases, respectively. LDH and IL-6 increased in all patients. CRP increased in 96.97% of cases | None described |
| 11      | Li L           | Preprint        | 10 Mar 2020     | Retrospective case series | 85           | Hepatitis B, alcoholic liver disease, and fatty liver disease (n=2 in each category) | 24.7% had ALT elevation at admission | CRP ≥20 mg/L and LYM count <1.1 × 10^9/L were independent risk factors for hepatic injury. ALB (Mean: 33.4 g/L) in ALT elevated group was significantly lower | Inflammatory cytokine storm Deterioration of the disease with a dynamic process |
| 13      | Cui Y          | Ahead of print  | 17 Mar 2020     | Case report of an infant | 1            | A healthy infant with no medical history | ALT (94 IU/L), AST (100 IU/L) and TBIL (33.7 μmol/L) elevated | CD8+ T cells (2208 cells/μL) and LYM count (5.22 × 10^9/L) elevated Overall disease exacerbation: An initial increase in T helper 2 cell response, followed by suppression of inflammatory responses | None described |
| 9       | Xu L           | Ahead of print  | 14 Mar 2020     | Review with a comment of unpublished data | Not described | Not described               | GGT increased in severe cases (values not reported) | Not described Direct virus-induced cytotoxic effects Overshooting of inflammatory responses Viral hepatitis Drug-induced virally induced cytotoxic T cells Induction of a dysregulated innate immune response | None described |
| 28      | Bangash MN     | Ahead of Print  | 20 Mar 2020     | Review | – | – | – | – | Induction of a dysregulated innate immune response |
| 29      | Qin J          | Ahead of print  | 27 Mar 2020     | Case report | 1 | Hepatitis B HCC | ALT (80 U/L) and AST (132 U/L) declined post-liver transplantation but elevated gradually | LYM reduced to 0.64 × 10^9/L | None described |

(continued)
| Ref. no. | Author (et al.) | Publication type | Publication date | Study type | No. of patients with COVID-19 | Pre-existing liver diseases | Hepatobiliary function markers | Inflammatory markers (and other relevant blood tests) | Proposed possible theories of hepatic injury |
|---------|-----------------|-----------------|-----------------|------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------------------------|
| 30      | Xie H           | Ahead of print  | 2 Apr 2020      | Retrospective case series | 79            | Patients with previous liver diseases were excluded | 31.6%, 35.4% and 5.1% of patients had elevated ALT, AST and TBIL, respectively. Median (range) values were 36.5 (17.5–71.5) U/L, 34.5 (25.3–53.3) U/L and 12.7 (8.1–15.4) mmol/L, respectively. | CRP (max., 79.6 μmol/L) and ESR (max., 58 mm/h) increased, while LYM reduced (min., 0.9 × 10⁹/L) | Overall disease exacerbation: Disease severity |
| 31      | Zhang Y         | Ahead of print  | 2 Apr 2020      | Retrospective case series | 115           | Two patients had chronic Hepatitis B (excluded) | ALT and AST increased in 95.7% and 14.78% patients, respectively. TBIL elevation was rarely observed. | 54.78% had reduced ALB, significantly lower in severe cases. 57.39% had increased CRP, higher in severe cases (80.75 ± 69.18). | Dysfunction of immune system |
| 32      | Ding Q          | Ahead of print  | 20 Mar 2020     | Prospective case series | Five patients who had both COVID-19 and influenza infection | Two patients had Hepatitis B | ALT and AST increased in 40% (each) of cases, respectively. Acute liver injury occurred in 60% of patients | CRP increased in 80%, while LYM reduced in 80% of cases. | None described |
| 33      | Zhao D          | Ahead of print  | 12 Mar 2020     | Prospective case series | 19            | Hepatitis B in one patient | Liver function damage is more frequent in COVID-19 than other pneumonia patients. 27.78% (each) cases had elevated ALT and AST, respectively, while GGT increased in 44.4% | LDH increased in 31.58% of cases | Overall disease exacerbation: Dysregulation of immune system |
| 34      | Feng G          | Published      | 30 Mar 2020     | Review article | –             | – | – | – | Hypoxia-reperfusion dysfunction |
| 35      | Chen H          | Published      | 12 Feb 2020     | Retrospective case series | 9             | None described | 33% each had increased ALT and AST, respectively. One had ALT reaching 2093 U/L and AST reaching 1263 U/L. Elevated levels of ALT (max., 107 U/L) and AST (max., 95 U/L) were observed | 56% patients had LYM (< 10 × 10⁶ cells/L) reduction 75% of cases had elevated CRP (> 10 mg/L). Elevated CRP (max., 18.6 mg/L), LDH (max., 377 U/L) and ESR (max., 93 s) were reported | None described |
| 36      | Pan F           | Ahead of print  | 13 Feb 2020     | Retrospective case series | 21           | None described | – | – | None described |

ALB: albumin; ALP, Alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; GGT: gamma-glutamyl transferase; HCC: hepatocellular carcinoma; ICU: intensive care unit; IL-6: interleukin-6; LDH: lactate dehydrogenase; LYM: lymphocytes; max.: maximum; min.: minimum; TBIL: total bilirubin
In a report from Shanghai, 50.7% of patients presented with elevated LFTs at the time of hospitalization. Interestingly, these were more likely to have a moderate-to-high-grade fever when compared with the patients with normal LFT (44% vs. 27.4%; p = 0.035). On the other hand, mild and moderate cases experienced only discrete abnormal LFT values. These reports support the concept that the disease severity and an older age predispose to more severe liver injury from COVID-19. Based on these case series, patients with severe COVID-19 and pre-existing liver conditions should undergo surveillance and individually tailored therapeutic approaches for potential liver injury.

A recent randomized controlled trial of lopinavir and ritonavir in severe COVID-19 reported that elevated levels of AST, ALT and total bilirubin occurred as adverse effects in a few patients. Another case series from Wuhan reported that 55.4% of patients experienced liver injuries after treatment with lopinavir and ritonavir. Fan et al. published a retrospective study on COVID-19 and observed that the utilization rate of this drug combination was significantly higher in patients with abnormal LFTs compared with patients without LFT elevations (56.1% vs. 25%, p = 0.009). In this study, 47.3% of the discharged patients showed elevated LFTs at baseline, and 23.7% developed abnormalities during hospitalization, suggesting emerging liver injury from drugs or during the course of the infection. Importantly, LFT elevation during the hospital stay was associated with prolonged length of hospitalization.

Chloroquine, an old drug with a potential of repurposing for new treatment indications, has recently been tried in patients infected with SARS-CoV-2. After a profound success in inhibiting viral replication in vitro, concurrent clinical trials (>20) on chloroquine conducted at 10 hospitals across China have demonstrated superior efficacy in viral control. The pharmacodynamic activity of this drug in COVID-19 may involve the arresting of cytokine storms or the activation of CD8+ cells or by preventing endocytosis-mediated uptake of the virus. Importantly, hepatotoxicity related to chloroquine or hydroxychloroquine has rarely been reported.

In severe cases of COVID-19 with cytokine release, tocilizumab, an IL-6 antagonist, which is humanized IgG1 monoclonal antibody to the IL-6 receptor, has been used as a potential therapy for SARS-CoV-2. In previous clinical trials for other indications tocilizumab was reported to cause mild elevations of LFTs which were usually transient and commonly resolved within 2–6 weeks from exposure.

Remdesivir is an experimental antiviral nucleotide analog with broad activity against coronaviruses that is currently being trialed for SARS-CoV-2 infection. Safety data from ongoing studies will guide on its use in patients, but so far no reports of liver toxicity have emerged.

Patients with pre-existing liver disease

Scare data has been published for COVID-19 infection in patients with pre-existing liver disease. Experience from previous episodes of coronavirus infection can guide on the extent of hepatic involvement and on the management of patients with pre-existing liver disease. In SARS, the highest mortality rates were observed in the elderly and adults with underlying liver disease. Therefore, it has to be expected that the patients with COVID-19 are also more vulnerable to hepatic injury. In a case series from the Zhejiang province, a prevalence of 11% of underlying liver
disease was reported. About half of them experienced symptoms for more than 10 days after the illness onset. In another study from Wuhan, 9% of patients had the underlying liver disease of cirrhosis or hepatitis. Li et al., who investigated risk factors involved with hepatic injury, stated that two patients had presented with alcoholic liver disease at baseline. One of them had a moderate elevation of ALT (120 U/L) within a week of hospitalization, while the other showed no such abnormalities. In the initial cohort described from China, 2.7% exhibited hepatitis B virus infection with no mention of worsening outcomes. Therefore, the association of the pre-existing liver conditions with disease prognosis and outcomes in COVID-19 will have to be evaluated by comprehensive data registries which recently started enrolling patients (e.g. COVID-Hep Registry and SECURE-Cirrhosis Registry).

Liver transplant recipients

Management of post liver transplant recipients during the COVID-19 pandemic presents a special challenge for clinicians because of the limited data available and the crucial need to continue immunosuppressive drugs in these patients, which puts them at risk for more severe courses of COVID-19 infection and possible prolonged viral shedding. Case reports from China did not reveal an increased mortality in organ transplant recipients. Qin et al. reported the first case of SARS-CoV-2 infection in a patient with hepatocellular carcinoma who underwent liver transplantation. Lowering immunosuppression to the most acceptable level appears reasonable in infected liver transplant patients, in particular, in the setting of lymphopenia or clinical worsening of infection.

In addition clinicians have to be aware of drug–drug interactions in the transplant setting. In particular immunosuppressive drugs and ritonavir-boosted antiviral therapies exhibit relevant interactions through CYP34A which lead to increased levels of calcineurin and mTOR inhibitors. Accordingly, chloroquine-based regimes or remdesivir (compassionate use program only) appear to be safe, while boosted protease inhibitors should be avoided (see Table 2). Additionally, preventive strategies in those vulnerable patients include early and prolonged screening with polymerase chain reaction-based testing for patients with early symptoms, a contact history or infection. Personal

| Combination | Immunosuppressants | COVID-19 therapy | Potential risk of interactions | Recommendations |
|-------------|--------------------|-----------------|-------------------------------|-----------------|
| Calcineurin inhibitor (tacrolimus or ciclosporin) | Atazanavir or lopinavir/ritonavir or chloroquine or hydrocholoquine | Potentially increased exposure of immunosuppressant | Dose adjustment or close monitoring |
| Sirolimus | Atazanavir or lopinavir/ritonavir | Potentially increased exposure of immunosuppressant | Avoid coadministration |
| Sirolimus | Chloroquine or hydrocholoquine | Potentially increased exposure of immunosuppressant | Dose adjustment or close monitoring |
| Tacrolimus or ciclosporin or sirolimus | Tocilizumab | Potentially decreased exposure of immunosuppressant | Interaction of weak intensity; additional action/monitoring or dose adjustment unlikely required |
| Mycophenolate | Lopinavir/ritonavir | Potentially increased or decreased exposure of mycophenolate | Dose adjustment or close monitoring |
| Basiliximab | Tocilizumab | Enhanced immunosuppressive effect | Avoid coadministration |
| Azathioprine | Ribavarin | Myelotoxicity due to accumulation of 6-methylthioinosine monophosphate | Dose adjustment or close monitoring |
| Azathioprine | Tocilizumab or interferon-β | Additive hematological toxicity | Caution required; close monitoring of hematological parameters |

Modified from Liverpool Drug interactions Group (5 April 2020; https://www.hep-druginteractions.org/).
protective equipment in high risk settings can help to protect this vulnerable patient group.

**Summary and clinical recommendations**

Liver function abnormalities – predominantly AST elevation – in COVID-19 appear to be frequent but not severe in most cases. Direct viral hepatotoxicity, DILI, ‘bystander effects’ during a systemic viral infection and potentially sepsis, or exacerbation of an underlying liver disease have to be considered. Ex vivo studies offer that SARS-CoV-2 can selectively target the liver, in particular cholangiocytes through ACE2, and thus hepatobiliary injury appears plausible. Irrespective of the mechanisms involved in the hepatic injury of patients with COVID-19, activation of the immune-mediated pathway seems to be critical. Special high risk populations require close monitoring. These include the elderly population, patients with end-stage liver disease and liver transplant recipients. Symptomatic treatment with acetaminophen and avoidance of non-steroidal anti-inflammatory drugs in cirrhosis is recommended. Cautious use of antiviral agents in patients with decompensated liver disease and drug–drug interactions in post liver transplant patients has to be considered. As emphasized by a recent position paper of the European Study of Liver Disease, elective procedures and routine tests should be postponed according to the risk–benefit at the given time. On the other hand, emergency medical care needs to be done with appropriate measures to prevent infection.46

**Declaration of conflicting interests**

SA has nothing to declare. JMS has acted independently of this study as a consultant to Boehringer Ingelheim, Galmed, Genfit, Gilead Sciences, Intercept Pharmaceuticals, Novartis, Roche, Siemens Healthineers, and has received research funding from Gilead Sciences.

**Funding**

The authors received no financial support for the research, authorship, and/or publication of this article.

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