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Review

COVID-19 and hepatitis B infection

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Abstract

The 2019 coronavirus disease (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has emerged as a major burden worldwide, resulting in serious public health challenges. Hepatitis B virus (HBV) infection is another widely spread virus that chronically affects about 257 million people. The management of patients with HBV infection has gained attention in the context of the COVID-19 pandemic. Patients with COVID-19 have varying levels of liver involvements, resulting from direct viral effects on the liver as well as hepatotoxic drugs. This was demonstrated by elevated levels of liver enzymes, particularly evident in those patients with severe SARS-CoV-2 infection. However, scarce information is available on the management of COVID-19 patients having an underlying chronic liver disease, including HBV infection. Studies have shown reactivation of HBV infection following treatment with tocilizumab and corticosteroids, emphasizing the need for caution when using these agents to treat COVID-19 patients with HBV infection. HBV screening and prophylaxis should be considered in patients with elevated transaminases levels and also in high prevalence populations. In patients with advanced liver disease, attention must be given to minimize the risk of liver decompensation. Nevertheless, further investigation is needed to enable an evidence-based approach to the care of these patients.

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Introduction

The 2019 coronavirus disease (COVID-19) has become a global pandemic with unimaginable implications. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a strain of the coronavirus, causes COVID-19, has spread globally and turns out to be a major cause of morbidity and mortality. The clinical manifestations of COVID-19 are not only respiratory. Multi-organ involvement, such as gastrointestinal, cardiovascular, and neurological systems, has also been reported [1]. The SARS-CoV-2 binding to the
angiotensin-converting enzyme-2 (ACE2) receptors, extensively present not only in the pulmonary alveolar epithelial cells, nasopharyngeal, and oral mucosa but also in the endothelium and vascular smooth muscle cells, brain, gastrointestinal tract, liver, and renal system, may account for this multisystem illness [2]. A considerable number of patients present gastrointestinal and hepatobiliary symptoms that commonly include diarrhea, vomiting, anorexia, abdominal pain, and up to 50% of patients can have abnormal liver function test and rarely acute liver failure [3–7]. Several theories might explain the hepatic involvement in SARS-CoV-2 include direct viral effect on the liver cells, abundance of ACE receptors in cholangiocytes, drug-induced liver injury, reactivation of HBV with the use of immunosuppressive medications [8–11].

The impact of COVID-19 on liver function in patients with chronic liver disease, namely hepatitis B virus (HBV) infection [defined as hepatitis B surface antigen (HBsAg) positive], is far from being understood. HBV remains a major public health burden. Per the World Health Organization (WHO), about 257 million individuals suffer from chronic hepatitis B (CHB) globally, and HBV is responsible for nearly 900,000 deaths each year, mostly as a result of complications of cirrhosis and hepatocellular carcinoma (HCC) [12,13]. It is still unclear whether HBV itself could make patients more vulnerable to COVID-19 or if COVID-19 leads to worse outcomes in patients with underlying HBV infection.

Some of the current drugs used to treat SARS-CoV-2, such as corticosteroids are potentially hepatotoxic [14], and it is also known that prolonged use of corticosteroids can increase the risk of HBV reactivation [15]. Therefore, management of these patients deserves close attention as the relation between HBV and COVID-19 is far from being understood.

The present review aims to discuss the available information on COVID-19 in patients with pre-existing CHB and their clinical management.

**COVID-19 and the liver**

A recent study reported that up to 50% of hospitalized COVID-19 patients could have hepatic manifestations that range from asymptomatic abnormalities in liver enzymes to rarely acute liver failure [7]. Another report from China found that 2-11% of COVID-19 patients suffered from underlying chronic liver disease, and 14-53% cases reported elevated alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels during the course of the disease [16]. The increase in ALT and AST is usually mild, although higher aminotransferase levels are associated with severe acute hepatitis [17–19]. Elevation of AST is usually greater than ALT, and it has been associated with COVID-19 severity [20,21]. AST and ALT are more commonly elevated than bilirubin or alkaline phosphatase [10]. It is unclear whether these liver abnormalities are signs for underlying liver diseases in critically-ill patients, direct viral damage, or result of severe inflammatory response, or a combination of the previous factors (Figure 1) [22]. Nevertheless, liver dysfunction appears to be mild and not clinically significant in majority of patients [23]. Potential risk factors for severe COVID-19 are age, comorbidities, advanced liver disease, and liver transplanted patients. These individuals need close monitoring [11].
Liver damage in COVID-19 patients might be directly caused by the SARS-CoV-2 infection of the liver cells. ACE2, the entry cell receptor for SARS-CoV-2, is expressed in both hepatocytes and cholangiocytes [24]. Cholangiocytes are involved in several functions of liver physiology related to immune response, and disturbance in their function leads to a cytopathic effect that can result in hepatobiliary damage [11]. The suggestion that ACE2 receptor expression is enriched in cholangiocytes might explain the dysregulation of liver function [10]. The fact that cholestatic function indicators, such as gamma-glutamyl transferase (GGT), are observed in COVID-19 patients supports this hypothesis [16,24,25].

Impairment in the functioning of innate immune response may also induce liver injury in COVID-19 [11]. The activation of inflammatory markers, such as C-reactive protein (CRP), white blood cells, and cytokines, may contribute to multi-organ injuries [16,20,26,27]. Hepatic inflammation could activate innate immune system and release of cytokines, resulting in hepatic injury [28]. Lymphopenia was correlated to hepatic damage, as well as CRP greater than 20 mg/L [11]. It has been reported that 63% to 70.3% of COVID-19 patients with severe diseases have lymphopenia, which is associated with fatal outcomes [29,30].

Another possibility for liver impairment in COVID-19 patients, especially during hospitalization, relates to drug hepatotoxicity. This might explain the large spectrum of abnormal liver tests across the different therapeutic modalities for the treatment of COVID-19 [11,31]. The systemic inflammatory response, such as cytokine storm and pneumonia-associated hypoxemia, and the drug-induced hepatic injury, which could be serious in patients with severe forms of COVID-19 requiring hospitalization [24,32]. Hepatotoxic drugs include antimicrobial, nonsteroidal anti-inflammatory drugs, herbal supplements, and other antiviral drugs, such as a combination of lopinavir and ritonavir, remdesivir or favipiravir plus other agents used in clinical trials (chloroquine and hydroxychloroquine, azithromycin, camostat, or tocilizumab). It was observed that liver damage could return to normal when the infection subsides or when these largetoxic agents are discontinued [31]. Also, patients with Child-Pugh B/C cirrhosis are at greater risk of drug toxicities [22].

Chronic liver diseases represent a major high burden globally. Preliminary results of an international registry observed greater mortality rates due to COVID-19 in patients having chronic liver disease and the severity of baseline liver disease associated with increased mortality [33]. However, the number of patients with HBV in this registry is relatively small.

**Pre-existing HBV infection and risk of COVID-19**

The majority of the reports on the prevalence of HBV infection in patients with COVID-19 comes from China. The prevalence of HBV in COVID-19 patients ranges from 0.8% to 12.2% across several studies. The largest cohort study enrolling 1099 hospitalized patients from Wuhan found that 2.1% had HBV infection [34]. A single-centre, retrospective study including 123 COVID-19 patients reported that 12.2% of them had HBV infection, and more patients experience a severe COVID-19 condition (46.7% vs. 24.1%) and higher mortality rate (13.3% versus 2.8%) [35]. Another report of 31 individuals with severe COVID-19 observed
a 6.5% (2/31) rate of co-infection by HBV and suggested delayed SARS-CoV-2 clearance in HBV co-infected patients (mean difference, 10.6 days; 95% CI, 6.2-15.1 days) [36]. These prevalence rates are surprisingly lower to those reported in the general Chinese population in two studies [7,37] and similar or even higher in another two Chinese studies. Very few data on HBV and COVID-19 are available in studies outside China. A large study, including 5700 hospitalized patients with COVID-19 in the United States, has shown that only 0.1% (8/5700) of patients were co-infected with HBV [18] (Table 1). In all the previous studies, there was not enough data to establish the stage of HBV infection and which percentage of individuals with CHB were naïve or were receiving antiviral therapy.

The effect of host immune status on SARS-CoV-2 infection is another interesting aspect, but still unclear. CHB results in a reduced virus-specific T-cell reactivity, a phenomenon known as “immune exhaustion.” This is manifested by an impaired ability of T-lymphocytes to produce adequate cytokines [41]. Recently, it has been suggested that the exhaustion of T-lymphocytes might affect their ability to respond to other viruses, namely SARS-CoV-2, reducing the degree of “cytokine storm” observed in COVID-19 patients and leading to less severe disease [37]. If this is merely a coincidence or a consequence of immune dysregulation deserves further investigation and might open additional venues on the prevention and treatment of COVID-19.

There is currently a paucity of data on the occurrence of SARS-CoV-2 infection at different stages of CHB natural history. It would be interesting and imperative to know how COVID-19 would impact the ‘immune tolerant’ or ‘immune active’ phases of CHB. Also, the significance of HBV genotype of these patients with relation to COVID-19 infection needs to be explored.

**Impact of COVID-19 in patients with pre-existing CHB**

Several reports suggest that pre-existing liver disease could be associated with a worse outcome in patients with COVID-19 due to altered immune function [33,42–45]. A study performed in the U.S. with 2780 patients with COVID-19, including 250 patients with chronic liver disease, showed that patients with chronic liver disease had higher rates of mortality than those without liver disease (12% versus 4%) [42]. The two most common pre-existing liver diseases were nonalcoholic fatty liver disease (NAFLD) 42% and alcoholic liver disease 8%; while CHB present in 4%, the mortality risk was independent of age, race, nicotine use, body mass index, hypertension, and diabetes [42].

The preliminary results of a large, multicenter, international registry of over 150 consecutive case reports of COVID-19 in patients with chronic liver disease found greater mortality rates from COVID-19 in patients with chronic liver disease and cirrhosis [33]. The most frequent pre-existing liver diseases were NAFLD (22.4%), alcoholic liver disease (19.7%), hepatitis B (11.8%), and hepatitis C (10.5%). They described that deaths were liver-related in 12% of patients. Hepatic decompensation occurred in 36.9% of patients and was strongly associated with a subsequent risk of death, not necessarily coupled with respiratory symptoms [33]. Similar results were observed in another retrospective study of 50 cirrhotic patients with confirmed COVID-19. The 30-day mortality rate was higher in cirrhotic COVID-19 patients...
than COVID-19 patients without cirrhosis, suggesting the association of COVID-19 with liver function worsening and increased mortality in cirrhotic patients [46]. It is not surprising that higher mortality in HBV cirrhotic patients may depend on the disease severity (having a high Model for End-Stage Liver Disease score).

Patients under immunosuppressive therapy are at risk for severe COVID-19 and its complications [47]. Although reports have shown high mortality rates in transplant recipients, registry reports lack comparisons with a non-transplant population [48–50]. Male patients; >65 years of age; and with comorbid conditions like hypertension, obesity, diabetes, and hyperlipidemia were considered risk factors for severe COVID-19.

Data on the outcome of COVID-19 patients with HCC is scarce. Most patients with HCC have underlying chronic liver disease and not only fall under the high-risk category for COVID-19 but are likely to have worse outcome especially from delay in surveillance, diagnostic and therapeutic interventions from countries lockdown, hospital overcapacity with COVID-19 patients and the fear from many patients to go to healthcare facilities from contracting COVID-19 [51]. Currently, several registries are looking at the impact of COVID-19 in the outcome of HCC (Liver Cancer Outcome in the COVID-19 Pandemic, CERO-19).

**Outcome of patients with hepatitis B and COVID-19**

Limited studies evaluated the impacts of COVID-19 on patients living with viral hepatitis, namely HBV [7,39,40,52]. These sparse reports have shown somewhat altered liver function in patients co-infected with HBV. This was demonstrated by elevated levels of ALT and AST, particularly evident in those admitted to intensive care units. The results of these studies are rather contradictory. Some studies have shown that there is no basis on the aggravation of hepatic injury in SARS-CoV-2/HBV co-infection or extended stay in hospital [36,39,40]. On the other hand, other studies reported that co-infection is associated with severity and poor prognosis of COVID-19 and that liver function should be frequently assessed in these patients [34,35,47,52] (Table 2).

Currently, there is scant evidence that HBV itself makes patients more vulnerable to COVID-19 or more likely to become severely ill, unless they already present end-stage liver disease.

**Impact of potential treatment for COVID-19 on CHB**

The treatment of COVID 19 with potential hepatotoxic and immunosuppression drugs might impose risks in terms of HBV reactivation and the severity of the HBV disease course (Figure 2). The RECOVERY trial showed that in patients hospitalized with COVID-19, administration of 6 mg dexamethasone given once daily for up to ten days decreased 28-day mortality in patients on invasive mechanical ventilation or oxygen, but not for those who did not have respiratory support [14]. Following this evidence, the use of dexamethasone has been endorsed by several treatment guidelines, including those convened by the U.S. National Institutes of Health [55].
Like all immunosuppressive regimens, corticosteroids may lead to a reactivation of previously acquired infections. Special concerns have been posed on HBV reactivation used in the context of COVID-19, and several lines of evidence suggest that occult HBV infection (defined as the presence of HBV DNA in serum or liver of HBsAg-negative patients) might be reactivated in patients undergoing corticosteroid therapy [15,56]. Therefore, attention must be paid to HBV reactivation following corticosteroid therapy, especially during the administration of high doses after considerable time and whenever other immunosuppressants are co-administrated [15,57,58]. This type of therapy requires HBV prophylaxis, and an HBV screening should be considered through determination of HBsAg, anti-HBc, and anti-HBs antibodies.

The risk of HBV reactivation when other immunosuppressive drugs are used, namely tocilizumab or baricitinib, is important to consider [59]. Reactivation of HBV following the use of tocilizumab and prednisone was described particularly when these drugs have been used in patients with rheumatoid arthritis. Therefore, HBV prophylaxis should also be considered in these cases [59–64].

The risk of HBV reactivation is of particular concern in countries, including Sub-Saharan Africa, where there is an extremely underdiagnosed and highly prevalent HBV infection. Careful attention towards these vulnerable populations must consider clear strategies to mitigate this risk during the growing pandemics. These will be necessary for low-income countries not only to tackle emerging pandemics, but also pre-existing ones [65].

Some drugs used empirically for severe COVID 19 such as interferon alfa and lopinavir-ritonavir have been associated with ALT elevations and even with hepatic decompensation. Caution is necessary when initiating COVID-19 related therapy in patients with advanced liver disease. Remdesivir, the only specific drug approved for severe COVID-19, has been associated with transaminase elevations in clinical trials, including in healthy volunteers and patients with COVID-19. It is not recommended in patients with ALT ≥5 times the upper limit of normal (ULN) at baseline and should be discontinued in patients who develop ALT ≥5 ULN during treatment with remdesivir. No clinical studies with remdesivir have been conducted in patients with hepatic impairment.

Drug-drug interactions between antivirals for Hepatitis B and COVID-19 medications should be evaluated [66]. Currently, the main concern is the coadministration of tenofovir disoproxil fumarate (TDF) or tenofovir alafenamide (TAF) and lopinavir–ritonavir. The last drug might increase the concentration of tenofovir by 32–51% with TDF and by 275–316% with TAF and therefore, an increased risk of renal impairment [54,67]. The recommendation is a close monitoring to renal function to adjust the dose of TDF or switch to entecavir. Withdrawal of oral antiviral medicines may induce virological and biochemical relapses in some CHB patients. Therefore, it is recommended not to stop nucleoside analogues in patients with COVID-19 [54,68,69].

In those patients with HBV, it is important to be aware of the risk for HBV reactivation related to medications, such as tocilizumab and corticosteroids, used in the context of COVID-19. Reactivation of
HBV following the use of tocilizumab and prednisone has been described, and thus prophylaxis against HBV reactivation should be a consideration [19,20]. In addition, chronic HBV therapy where indicated as per guidelines [21] can be initiated in those with newly diagnosed HBV and continued if receiving therapy, regardless of COVID-19. Last but not least, caution needs to be exercised in initiating COVID-19-related therapy in those with advanced liver disease; thus, established guidelines on such use need to be followed to minimize the risk for hepatic decompensation, although the risk/benefit of an intervention is likely to weigh in heavily in dealing with the highly lethal condition of COVID-19. In those patients with HBV, it is important to be aware of the risk for HBV reactivation related to medications, such as tocilizumab and corticosteroids, used in the context of COVID-19. Reactivation of HBV following the use of tocilizumab and prednisone has been described, and thus prophylaxis against HBV reactivation should be a consideration [19,20]. In addition, chronic HBV therapy where indicated as per guidelines [21] can be initiated in those with newly diagnosed HBV and continued if receiving therapy, regardless of COVID-19. Last but not least, caution needs to be exercised in initiating COVID-19-related therapy in those with advanced liver disease; thus, established guidelines on such use need to be followed to minimize the risk for hepatic decompensation, although the risk/benefit of an intervention is likely to weigh in heavily in dealing with the highly lethal condition of COVID-19. In those patients with HBV, it is important to be aware of the risk for HBV reactivation related to medications, such as tocilizumab and corticosteroids, used in the context of COVID-19. Reactivation of HBV following the use of tocilizumab and prednisone has been described, and thus prophylaxis against HBV reactivation should be a consideration [19,20]. In addition, chronic HBV therapy where indicated as per guidelines [21] can be initiated in those with newly diagnosed HBV and continued if receiving therapy, regardless of COVID-19. Last but not least, caution needs to be exercised in initiating COVID-19-related therapy in those with advanced liver disease; thus, established guidelines on such use need to be followed to minimize the risk for hepatic decompensation, although the risk/benefit of an intervention is likely to weigh in heavily in dealing with the highly lethal condition of COVID-19.

Management of patients with hepatitis B during the COVID-19 pandemic

The COVID-19 pandemic requires the utilization of healthcare resources, which may affect patient care, especially those who have chronic liver disease and require continuous clinical monitoring. The delay of care of patients other than COVID-19 patients during the current pandemic may contribute to CHB patients developing negative consequences from lack of continuity of antiviral therapy to delay HCC surveillance and consequently presenting with an advanced terminal stage. CHB patients are at risk of developing HCC and require close monitoring and surveillance. However, to protect vulnerable populations, the management of HCC as suffered an enormous disruption in all stages. Healthcare systems are facing limited resources, so surveillance of HCC has been deferred in many countries [70].

CHB therapy can be initiated in patients with newly diagnosed HBV or continued in CHB patients regardless of COVID-19 [63]. It is important to note that anti-HBV drug discontinuation can lead to HBV
flare up and more frequent monitoring, which may require frequent laboratory visits and interactions with laboratory staff, which is by itself increase the risk of COVID-19 transmission.

In COVID-19 HBsAg-positive patients, who are not on anti-HBV therapy, prophylaxis with TDF, TAF, and ETV is needed in the case of prolonged corticosteroid or immunosuppressant drugs usage, to decrease the risk of reactivation and the possibility of liver failure [72].

A study, including 77,590 HIV-positive patients receiving antiretroviral therapy, found lower rates of COVID-19 in HIV patients taking ART when compared to individuals in the general population. This incidence was particularly lower among HIV-patients whose antiretroviral combination included TDF/emtricitabine (FTC) [73]. The authors suggested that nucleoside/nucleotide drugs disrupt the ability of the virus to infect human cells and that the immune-modulatory properties of TDF might dampening the production of inflammatory cytokines implicated in severe COVID-19. The potential role of FTC in decreasing the risk of infection by SARS-CoV-2 and reducing the severity of the disease needs to be evaluated in further studies.

**Hepatitis B and potential COVID-19 vaccination**

There are currently over 2,600 clinical trials underway for COVID-19 therapies, demonstrating the strategic plethora in search of a pharmaceutical response to SARS-CoV-2 [74]. This is an emergent field evolving at a fast pace and producing large amounts of information. Nevertheless, the effect of this virus on CHB patients still deserves attention, and clinical trials are urgently needed in patients co-infected with both diseases. Besides, there are massive developments in making COVID-19 vaccines globally. Another important aspect in the near future is developing a strategy for COVID-19 vaccination in different types of patients. Data suggest that patients with advanced liver disease are believed to have poor immune system, and consequently, a vulnerable population who should receive priority for vaccination once vaccines become available. Previous experience with the use of influenza vaccine in patients with liver diseases has shown promising outcomes in terms of efficacy and safety [75,76]. Therefore, a vaccine against SARS-CoV-2 will have a major impact on the rates of transmission and help control the pandemic, particularly for populations at high risk of developing severe COVID-19.

**Summary and future perspectives**

Both COVID-19 and HBV are global viral diseases that deserve close attention. Several studies suggested that hepatitis B infection does not associate with a higher risk of infection by SARS-CoV-2. However, there is scarce and contradictory data on the impact of CHB on COVID-19 patients. It seems that in patients with advanced liver disease, the mortality of COVID-19 is higher than in those with chronic hepatitis but further data are needed. Drugs used for therapy of severe COVID-19 such as tocilizumab and corticosteroids are associated with a higher risk of HBV reactivation, highlighting the need for caution when using these agents in treating COVID-19. In these cases, prophylaxis against HBV reactivation should be considered. Further investigation is needed not only to assess the effect of SARS-CoV-2 on these patients but also to evaluate
the extent to which treatment for COVID-19 can reactivate viral hepatitis and aggravate liver injury. Finally, with future development of vaccines for COVID-19, patients with liver diseases should be considered a potential priority population for receiving the vaccine based on preliminary data of high mortality of COVID-19 in patients with liver disease as well as researchers should be ready to study the efficacy and safety of the vaccines in patients with liver disease in clinical trials as well as from real-world registry.

Disclosure statement
Authors declare no conflict of interests.

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**Figure 1**: Impact of SARS-CoV-2 infection on patients with hepatitis B

**Figure 2**: Impact of potential COVID-19 treatment on patients with hepatitis B
## Table 1 – Prevalence of Hepatitis B Virus infection in COVID-19 patients in different studies and clinical outcomes

<table>
<thead>
<tr>
<th>Authors</th>
<th>Country</th>
<th>COVID-19 cases</th>
<th>No. of HBsAg +ve (%)</th>
<th>Local HBV prevalence</th>
<th>Outcome of COVID-19 in non-HBV patients</th>
<th>Outcome of COVID-19 in HBV patients</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guan et al. [34]</td>
<td>China</td>
<td>1099</td>
<td>23 (2.1%)</td>
<td>7.2%</td>
<td>84.0% (904) non-severe cases; 15.7% (172) severe cases</td>
<td>95.7% (22) non-severe cases; 4.3% (1) severe case</td>
<td>No more severe liver disease</td>
</tr>
<tr>
<td>Chen X et al. [35]</td>
<td>China</td>
<td>123</td>
<td>15 (12.2%)</td>
<td>7.2%</td>
<td>24.1% (26) severe cases; 73.1% (79) non-severe cases; 2.8% (3) patients died</td>
<td>46.7% (7) severe cases; 40% (6) non-severe cases; 13.3% (2) patients died</td>
<td>HBV patients have more severe liver disease (46.7% vs 24) And higher mortality 13.3% vs. 2.8%</td>
</tr>
<tr>
<td>Chen J et al. [38]</td>
<td>China</td>
<td>249</td>
<td>2 (0.8%)</td>
<td>7.2%</td>
<td>86.3% (215) patients were discharged after 16 days of hospitalization. 0.8% (2) patients died</td>
<td>Not reported</td>
<td>Similar outcome</td>
</tr>
<tr>
<td>Li et al. [39]</td>
<td>China</td>
<td>342</td>
<td>7 (2.0%)</td>
<td>7.2%</td>
<td>Symptoms, laboratory tests, chest CT scan, hospitalization days, and ICU admission rate were similar to the HBV group</td>
<td>No patient developed severe liver-related complications during hospitalization</td>
<td>This was a case series of COVID-19 patients with HBV infection. All patients received antiviral treatment (lopinavir/ritonavir, interferon α-2b, arbidol, oseltamivir).</td>
</tr>
<tr>
<td>Chen L et al. [40]</td>
<td>China</td>
<td>326</td>
<td>20 (6.1%)</td>
<td>7.2%</td>
<td>No differences in the level of liver function parameters between the two groups</td>
<td>No significant differences in severity of liver disease, outcome or length of hospitalization</td>
<td></td>
</tr>
<tr>
<td>Richardson et al. [18]</td>
<td>USA</td>
<td>5700</td>
<td>8 (0.1%)</td>
<td>0.4%</td>
<td>9.7% (553) patients died</td>
<td>Not reported</td>
<td></td>
</tr>
<tr>
<td>Authors</td>
<td>No of COVID19 cases</td>
<td>Patients with HBV</td>
<td>Liver enzymes</td>
<td>Main conclusion</td>
<td></td>
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<tr>
<td>Li et al. [39]</td>
<td>342</td>
<td>7</td>
<td>Elevated ALT, AST and Tbil</td>
<td>No patient developed severe liver-related complications during hospitalization</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chen L et al. [40]</td>
<td>326</td>
<td>20</td>
<td>Elevated ALT, AST and lower prealbumin</td>
<td>No evidence that SARS-CoV-2/HBV co-infection could aggravate liver injury or extend duration of hospitalization.</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Guan et al. [34]</td>
<td>1099</td>
<td>23</td>
<td>With or without elevated ALT or AST</td>
<td>95.7% of co-infected patients represented non-severe cases, and only 4.3% of SARS-CoV-2/HBV patients were severe.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zha et al. [36]</td>
<td>31</td>
<td>2</td>
<td>Not reported</td>
<td>An existing HBV infection may delay SARS-CoV-2 clearance (further investigation is needed to corroborate this finding due to small sample size)</td>
<td></td>
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<tr>
<td>Chen X et al. [35]</td>
<td>123</td>
<td>15</td>
<td>Increased level of Tbil</td>
<td>Patients with HBV infection appeared to have a higher incidence of liver cirrhosis and increased mortality</td>
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<tr>
<td>Zou et al. [52]</td>
<td>105</td>
<td></td>
<td>Elevated ALT, AST, Tbil, GGT and ALP</td>
<td>Liver injury in patients with SARS-CoV-2 and chronic HBV co-infection is associated with severity and poor prognosis of disease. Liver function should be evaluated frequently.</td>
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<tr>
<td>Cai et al. [53]</td>
<td>298</td>
<td>5</td>
<td>Higher AST, ALT and GGT in severe disease</td>
<td>4 non-severe and 1 severe cases</td>
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ALT=alanine aminotransferase. AST=aspartate aminotransferase. Tbil – total serum bilirubin. ALP=alkaline phosphatase. GGT= gamma-glutamyl transferase. HBV=hepatitis B virus.
Hepatitis B virus/COVID-19 Coinfection

> 50% of patients with COVID-19 experience hepatic abnormalities

1 - Direct effect of SARS-CoV-2
2 - Immune-mediated liver injury
3 - Drug-induced liver injury
4 - Manifestations of underlying liver disease
Impact of COVID-19 treatment on patients with hepatitis B

Prolonged use of corticosteroid or immunosuppressant drugs → ↑ risk of HBV reactivation.

Corticosteroid hepatotoxicity

Coadministration of TDF or TAF and lopinavir-ritonavir
Remdesivir can increase ALT/AST

Consider screening for HBV in patients with COVID-19 and start HBV prophylaxis if indicated

Do not stop HBV therapy