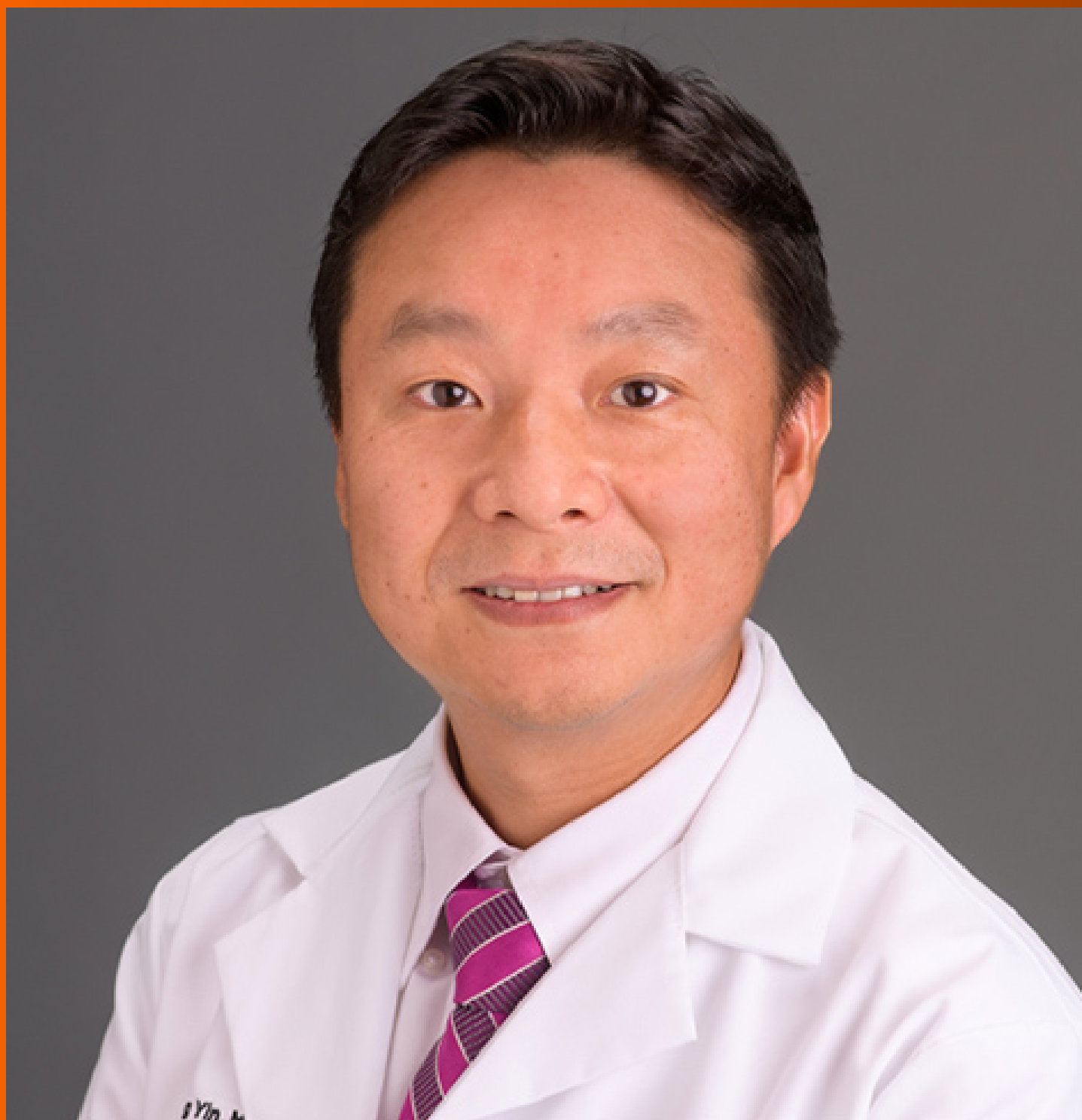


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Patterns of liver profile disturbance in patients with COVID-19

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Abstract

Fever and cough are the most common clinical symptoms of coronavirus disease 2019 (COVID-19), but complications (such as pneumonia, respiratory distress syndrome, and multiorgan failure) can occur in people with additional comorbidities. COVID-19 may be a new cause of liver disease, as liver profile disturbance is one of the most common findings among patients. The molecular mechanism underlying this phenomenon, however, is still unknown. In this paper, we review the most current research on the patterns of change in liver profile among patients with COVID-19, the possible explanation for these findings, and the relation to pre-existing liver disease in these patients.

Key Words: Liver functions; COVID-19; Liver profile; Alanine transaminase; aspartate transaminase; Bilirubin

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Core tip: Disturbance in the liver profile caused by coronavirus disease 2019 is not a rare event. However, this disturbance is usually mild and has a hepatocellular rather than a cholestatic pattern. It can affect a large number of patients, especially those with a more serious disease course.

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) is caused by the recently discovered severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). This virus was initially reported in Wuhan, China (December 2019) and then spread rapidly worldwide to affect 220 countries and territories, causing serious harm to global public health[1,2]. By July 9, 2021, COVID-19 affected 186 358 041 people worldwide, with 4 026 907 deaths[2]. SARS-CoV-2 mainly infects the respiratory system, while multiorgan involvement by COVID-19 has been reported since the emergence of the disease[3]. Disease progression is widely influenced by the presence of chronic medical illnesses and extra-pulmonary organ damages[3,4]. In severe cases, patients can develop pneumonia, acute respiratory distress syndrome, severe sepsis and shock, multiorgan failure, and consequently death[3].

Deteriorated liver function tests have been reported as a frequent manifestation of SARS-CoV-2 infection, although their clinical significance is still under investigation[3]. COVID-19-associated liver injury is defined as any liver damage occurring during disease progression and treatment of COVID-19 in patients with or without pre-existing liver disease[4,5]. The reported patterns of liver injury include hepatocellular, cholestatic and mixed patterns[6]. In this review, we discuss the patterns and mechanisms of liver injury in patients with COVID-19 with and without an underlying chronic liver disease.

MECHANISMS OF LIVER INJURY

Emerging data on abnormal liver enzymes seen in SARS-CoV-2-infected patients raise several questions. For example, are these abnormalities due to direct viral damage, drug-induced liver injury, unknown pre-existing liver disease, or an indirect consequence of viral damage to other systems (cardiopulmonary, hemostasis)? To answer this, liver samples from infected patients were examined, and moderate microvascular steatosis with mild lobular and portal activity was reported[7].

Regarding direct cytotoxicity, as SARS-CoV-2 binds to target cells through angiotensin-converting enzyme receptor-2 (ACE2), ACE2 receptors are found abundantly in the cholangiocytes (59.7%) as compared with the hepatocytes (2.6%). Thus, the liver is a potential target for direct viral infection[8].

Several drugs have been trialed on SARS-CoV-2 patients, such as hydroxychloroquine and azithromycin. Unfortunately, ambiguous results have been obtained, but a possible exacerbation of liver injury was identified[9]. This ambiguity leads to many questions regarding the management of SARS-CoV-2 and pre-existing liver disease[9]. Many of those infected with SARS-CoV-2 regularly use paracetamol as it is the recommended antipyretic medication. An unintentional overdose of paracetamol contributing to raised alanine transaminase (ALT) cannot be ruled out in patients with nonremitting pyrexia, as paracetamol is a well-recognized cause of fulminant hepatic failure. This also needs to be taken into consideration when evaluating liver injury in these patients[10].

A study by Fan *et al*[7] has raised the issue of drug-induced liver injury as a possible cause of liver injury seen in COVID-19 patients. They reported that patients who received lopinavir or ritonavir after admission showed a higher incidence of liver injury and required a more extended hospital stay. It is also possible that these patients were given antivirals because they had a more severe presentation, which might have affected their liver. Cai *et al*[6] also reported that lopinavir/ritonavir administration was associated with increased odds of liver injury. Although evidence suggests that lopinavir and ritonavir have no clinical effect on SARS-CoV-2, future application of antiviral drugs should also take into account their effects on the liver[11].

One of the supposed mechanisms of liver injury is immune-mediated damage due to the severe inflammatory response following COVID-19 infection[12]. Inflammatory biomarkers including C-reactive protein, serum ferritin, lactate dehydrogenase (LDH), D-dimer, interleukin (IL)-6 and IL-2 were significantly elevated in patients with severe COVID-19[13]. SARS-CoV-2 has been shown to lead to a hypercoagulable state, thereby increasing the risk of thromboembolism[14]. Microvascular thromboses can cause end-stage organ damage and may potentially affect the liver and alter its perfusion. Moreover, high levels of alkaline phosphatase (ALP) have been noted in COVID-19 patients suffering from thrombotic events. In other cases, ALP levels have been average or mildly raised[15]. Other mechanisms include mitochondrial dysfunction and hepatic steatosis induced by COVID-19[15].

Few studies have investigated the alteration of microbes in patients with SARS-CoV-2 infection. Dysbiosis is marked by a decrease in beneficial strains and an increase in opportunistic or pathogenic bacterial strains associated with the pathogenesis of inflammatory bowel disease and liver disease progression[16]. Thus, abnormal liver function tests are presumably multifactorial with potential contributions from immune-mediated inflammatory response, drug-induced liver injury, liver congestion, and extra-hepatic release of transaminases, likewise direct viral invasion of the hepatocytes.

HISTOPATHOLOGICAL FINDINGS IN LIVER TISSUE OF COVID-19 PATIENTS

The histopathological findings reported in patients with COVID-19 suggest that SARS-CoV-2 can spread widely in the epithelium lining the respiratory tract, digestive tract, distal convoluted tubules of the kidney, sweat glands of the skin, and epithelium of the testis, including spermatogonia and Sertoli cells [17].

Focal necrosis and degeneration of the hepatocytes and biliary plugging of the small bile ducts have been observed in the liver of patients with COVID-19. Other pathological changes described include the accumulation of glycogen in hepatocytes, together with atypical lymphocytic infiltration in the portal tract, liver cirrhosis, and regeneration with macrovesicular steatosis. Sinusoidal dilatation in zone 3, mild lymphocytic infiltration, and patchy hepatic necrosis have also been observed in the portal triad and centrilobular areas [17]. In addition to the direct viral effect of SARS-CoV-2 infection, the use of hepatotoxic drugs, pre-existing chronic liver disease, and COVID-19-related hyperinflammatory conditions can lead to hepatic injury, particularly when the patient is in a hypoxic state [18,19].

PATTERNS OF LIVER PROFILE DISTURBANCES IN PATIENTS WITH COVID-19

Disturbances in liver profile occur in 16%–78% of patients infected with SARS-CoV-2 [20–22]. The prevalence of liver injury is influenced by varied definitions of the upper limit of normal between the studies, geographical variability in the prevalence and type of pre-existing liver diseases, in addition to COVID-19 disease severity and intensive care unit (ICU) admission.

In a large cohort from China, including 1099 patients from 552 hospitals, Guan *et al* [3] observed elevated levels of aspartate transaminase (AST) in 112 (18.2%) patients with the nonsevere disease and 56 (39.4%) patients with severe disease. The proportion of patients with abnormal ALT in severe cases (28.1%) was higher than in mild cases (19.8%). Similarly, Huang *et al* [4] reported that the proportion of liver injury in ICU patients (61.5%) was higher than that in non-ICU patients (25.0%).

Most studies have reported mild disturbances of liver function [< 2 times upper limit of normal (ULN)] that correlated with COVID-19 severity, although liver failure was unusual [23]. Elevations > 5 times ULN have also been reported [24]. The predominant pattern of disturbances in liver profile in COVID-19 patients is higher AST elevation than ALT elevation [25–28]. These abnormalities can be associated with slightly elevated total bilirubin levels in up to 35% of cases [29].

In the literature, there is variation in how the liver injury is categorized. Elevations > 3 times ULN are usually referred to as severe liver injury, while a study from the United States defined severe liver injury as elevation > 5 times ULN [24]. Cai *et al* [6] classified patients with raised ALT and/or AST > 3 times ULN as having the hepatocyte type; patients with raised ALP or -glutamyl transferase (GGT) twice ULN as having the cholangiocyte type; and patients with a combination of both ALT/AST elevated > 3 times ULN and ALP/GGT twice ULN were classified as mixed type. The hepatocellular pattern of liver injury is the predominant pattern, and a minority of patients show a cholestatic pattern with elevated bilirubin and/or elevated ALP, even in the severe liver injury category [24,29]. Cai *et al* [6] reported that patients with the hepatocyte or mixed types at admission or during hospitalization had significantly higher odds of progressing to severe disease than patients with normal liver functions.

Synthetic liver function is also affected in patients with COVID-19, particularly in severe cases [24,27]. A meta-analysis by Wu *et al* [28] found that low serum albumin and high GGT were the most frequent abnormalities on admission and that ALT elevation occurred most frequently during hospitalization, which they speculate may have been due to the inclusion of patients with pre-existing liver disease.

As the liver plays a significant role in the production of albumin, acute-phase reactants, and coagulation factors, COVID-19-related liver injury may impact the multisystem manifestations of COVID-19, such as acute respiratory distress syndrome, coagulopathy, and multiorgan failure. A moderate loss of hepatic function could alter safety profile and therapeutic efficacy of antiviral drugs that are metabolized in the liver [29]. Hyperbilirubinemia and liver stiffness measured by transient elastography are associated with a more severe outcome [30,31].

LIVER PROFILE IN PATIENTS WITH DIFFERENT LIVER DISEASE CATEGORIES

Patients with chronic viral hepatitis, cirrhosis, fatty liver, or other liver diseases may already have persistent liver damage when infected with COVID-19. The proportion of patients with underlying CLD was rarely provided across the studies, and only limited data have been reported. Currently, no studies have studied the histological changes in patients with COVID-19 and underlying chronic liver disease. However, early before the COVID-19 outbreak revealed a greater than 30-fold increase in ACE-2 expression in the liver of patients with hepatitis C virus-related liver cirrhosis compared with healthy individuals. Moreover, liver mRNA expression of ACE-2 and TMPRSS-2 was up-regulated in patients with obesity and non-alcoholic steatohepatitis but not with steatosis alone [32].

PATIENTS WITH LIVER CIRRHOSIS AND COVID-19

Patients with cirrhosis and liver tumors may be more vulnerable to SARS-CoV-2 infection because of an immunodeficient status[33]. A large study including 2780 patients with COVID-19 reported that patients with chronic liver disease (CLD) were at approximately threefold greater significant risk for mortality than patients without CLD; this risk was markedly higher in patients with hepatic cirrhosis (about fivefold)[34]. Moreover, a recent study reported higher mortality among cirrhotic patients with COVID-19 than in patients with COVID-19 without cirrhosis[35]. In another study by Sarin *et al*[36], including 185 noncirrhotic patients with CLD and 43 cirrhotic patients, higher rates of severe liver injury and mortality were shown following COVID-19 disease, especially in patients with more decompensated liver disease (Child–Pugh score ≥ 9). Furthermore, some patients with cirrhosis may develop either acute-on-chronic liver failure (ACLF) or acute decompensation[37].

Patients with CLD, particularly those with autoimmune hepatitis or liver-transplant recipients receiving immunosuppressive drugs, are at greater risk of acquiring infection due to their altered function of the immune system[38,39]. However, the interaction between pre-existing CLD and COVID-19 has not been adequately investigated. Nonetheless, it is known that patients with cirrhosis are prone to develop a decompensated liver disease or ACLF if they acquire bacterial, fungal or viral diseases[40]. Liver-related complications in patients with COVID-19, *e.g.*, hepatic encephalopathy, hematemesis, and liver cell failure, have not been investigated in cohort studies with large numbers of patients[41]. Finally, given the expression of ACE2 receptor in cholangiocytes, cholestasis could be aggravated in patients with primary biliary cholangitis or primary sclerosing cholangitis after infection with SARS-CoV-2. Nevertheless, to the best of our knowledge, no data about exacerbations in these patients are available[41].

Patients with liver cirrhosis may develop ACLF because of overwhelming inflammatory responses [42]. Such patients have a significantly higher risk of secondary bacterial infection and a more severe course of influenza, including the development of organ failure, secondary infections, and death[43]. In a study of 111 decompensated cirrhotics in Wuhan, none of these patients had clinical symptoms suggestive of SARS-CoV-2 infection when a precautionary approach was implemented, namely, protective measures for outpatients, hospital staff training, new processes for diagnosis and treatment, and emergency plans[44]. In contrast, a comparator group of 101 decompensated cirrhotics at five other hospitals where preventative measures had not been implemented reported an incidence of COVID-19 cases of 16.8%. There are limited data about SARS-CoV-2 infection in liver cirrhosis, but it is expected to be a risk factor for a severe COVID-19 course. Thus, protective measures to prevent infection with SARS-CoV-2 and precautions for cirrhotic complications are of utmost importance[45].

PATIENTS WITH LIVER TRANSPLANTATION AND COVID-19

Patient management after liver transplantation is complicated. Excessive doses of immunosuppressive drugs leads to severe infections, while inadequate immunosuppression predisposes to rejection and graft loss[46].

Data on COVID-19 infection in patients with liver transplantation are still lacking. Qin *et al*[47] described a patient who acquired COVID-19 infection during the perioperative period of liver transplantation. Tacrolimus and glucocorticoids were maintained and gradually titrated to lower doses, and the patient recovered safely[47]. There are possible risks associated with transplantation in SARS-CoV-2-positive recipients, as the virus may be transmitted to the donor[48]. COVID-19 has a negative effect on the postoperative transplant course, especially in older and obese patients with comorbidities [49]. Colmenero *et al*[50] reported a higher risk for acquiring COVID-19 infection in liver transplant patients in a prospective Spanish cohort of liver transplant patients but with lower mortality rates compared with the general population. They found that mycophenolate treatment was an independent risk factor for severe COVID-19 (almost fourfold increased risk).

Immunosuppressive drugs impact immune responses, increasing the risk for severe infections caused by common viral agents (*e.g.*, influenza virus)[51]. In coronavirus infection, the host response plays an essential role in the disease process. Dysregulated innate immune responses to infection can cause tissue damage. Surprisingly, when an infection of an immunocompromised host occurs, it may be protected by a weaker immune response against the infectious agent. This is supported by experience thus far in coronavirus outbreaks[52]. Transplant patients were expected to have poor outcomes; however, at the end of an outbreak, no reported COVID-19 cases in transplant patients were recorded[53].

The Hospital Papa Giovanni XXIII in Bergamo hosts one of Europe's largest centers for pediatric liver transplantation and is located in the "red zone" for the Italian outbreak of COVID-19. Among 200 transplanted patients, including 10 hospitalized patients and three with positive PCR for SARS-CoV-2, none of them developed pulmonary manifestations[15]. In a systematic review by Kulkarni *et al*[54] that included 1522 liver transplant recipients with COVID-19 infection, of whom 23% developed severe COVID-19, mortality rate was 17.4% with no difference in mortality compared to nontransplanted patients (39 704 patients). Graft dysfunction occurred in 2.3% of the cases. Nearly 60% of patients

needed modification of their immunosuppression. Kulkarni *et al*[54] concluded that there are no significant differences in the risk of adverse outcome among transplanted and nontransplanted patients [54]. There is still a need for further studies to share experiences with patients under immunosuppression.

A prospective study from a Bulgarian center of liver transplantation reported the outcome of three recipients with COVID-19. One patient had mild, one moderate, and one severe COVID-19 disease. Only the patient with severe disease had underlying chronic diseases (hypertension, diabetes mellitus and obesity). The patients with mild and moderate disease received tacrolimus and mycophenolate mofetil, while the patient with severe COVID-19 received tacrolimus only. A dose reduction of tacrolimus was undertaken following serum level evaluation without changing the dose of the mycophenolate mofetil for those on dual therapy. The case fatality rate was 33.3% as the patient with the severe disease died from respiratory failure[55]. Thus, elective liver transplantation was postponed at transplant centers in areas with high COVID-19 prevalence and limited resources to reduce the risk of infection and save resources[56]. For liver transplant recipients with COVID-19, adjustments to immunosuppression are individualized based on COVID-19 severity, the used treatment regimen, time post-transplant, and the risk of allograft rejection[56].

PATIENTS WITH VIRAL HEPATITIS AND COVID-19

Kumar *et al*[57] showed that SARS patients with chronic hepatitis B virus (HBV) and chronic hepatitis C virus (HCV) infection were at high risk of developing severe hepatitis. This may be attributable to the delayed clearance from the body of HBV in patients with COVID-19[3]. In addition, in the study by Guan *et al*[3], 23 (2.1%) of 1099 confirmed COVID-19 cases were found to have HBV infection. The authors reported that patients with severe illness were more likely to have HBV than those without severe illness (2.4% *vs* 0.6%). In another study in Shanghai, China, eight of 148 positive patients for SARS-CoV-2 had chronic HCV or HBV infection, but there was no significant difference in the proportion with CLD between the abnormal liver function and normal liver function groups[7]. However, other studies have shown that chronic HBV infection is not associated with a worse prognosis than that in patients without HBV infection[58,59].

Guan *et al*[3] investigated 1099 patients with PCR-confirmed COVID-19; of whom 2.1% had chronic hepatitis B (CHB). Only one of their patients developed severe COVID-19, thus they suggested that CHB does not affect the outcome of COVID-19. In contrast, a recent study by Wang *et al*[60] included 109 patients with CHB and 327 patients without HBV infection, and reported that patients with CHB were more likely to develop severe COVID-19 disease (27.5% *vs* 5.2%, respectively) with higher mortality. They have reported that factors affecting COVID-19 severity in patients with CHB include elevated total bilirubin, ALP, AST, ALT, LDH and D-dimer and decreased serum albumin and albumin to globulin ratio[60]. Studies are still lacking about isolated chronic hepatitis C and COVID-19 disease.

NONALCOHOLIC FATTY LIVER DISEASE AND COVID-19

Patients with nonalcoholic fatty liver disease (NAFLD) or nonalcoholic steatohepatitis usually have other comorbidities *e.g.*, diabetes, hypertension, and obesity, which carries higher risk of severe COVID-19[61]. Cai *et al*[61] investigated 14 patients with NAFLD and infected with SARS-CoV-2; six of whom developed severe disease and more deteriorated outcomes. NAFLD is associated with more severe COVID-19 disease (approximately fourfold increased risk) and a prolonged period of viral shedding [62]. Moreover, a multicenter study reported a higher risk of ICU admission and mechanical ventilation, but not overall mortality, among patients with CLD principally due to NAFLD[63]. Obesity, arterial hypertension, diabetes, and cardiovascular diseases are common in patients with NAFLD and they are considered independent risk factors for severe COVID-19 disease[64].

LIVER PROFILE CHANGES IN ASYMPTOMATIC COVID-19 PATIENTS

To our knowledge, no data are available on liver enzyme abnormalities in asymptomatic patients with COVID-19 infection. Bongiovanni and Zago reported a case of COVID-19 infection presenting as acute hepatitis in the absence of respiratory symptoms. The abnormalities in liver biochemistry quickly normalized without specific therapy[65]. Abnormalities in hepatobiliary and inflammatory markers along with theories of hepatic injury in COVID-19 are listed in Table 1.

Table 1 Abnormalities in hepatobiliary and inflammatory markers along with theories of hepatic injury in coronavirus disease 2019

Ref.	Country	Study type	No. of patients with coronavirus disease	Pre-existing liver disease	Hepatobiliary function markers	Inflammatory markers	Possible theories of hepatic injury
Chen <i>et al</i> [66]	China	Retrospective case series	99	No histories of hepatic diseases	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
Cai <i>et al</i> [61]	China	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	Overall disease exacerbation: Inflammatory factor storm
Yang <i>et al</i> [67]	China	Retrospective case series	52	No histories of hepatic diseases reported	29% had liver dysfunction (no specifics given)	ESR (max., 50 mm/h) increased in 60.9% LYM (min, 0.91_109/L) reduced in 38.3%	None described
Shi <i>et al</i> [68]	China	Retrospective case series	81	Hepatitis or liver cirrhosis in 9% of cases	AST (> 40 U/L) increased in 53% of patients, lower in asymptomatic patients	LYM (<1.0_109/L) increased in 67%	None described

ALT: Alanine transaminase; AST: Aspartate transaminase; TIBIL: Total bilirubin; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; IL-6: Interleukin 6; LDH: Lactate dehydrogenase; ALB: Albumin; LYM: Lymphocyte.

CONCLUSION

COVID-19-related liver injury is usually mild and of a hepatocellular pattern. It may affect a significant proportion of patients, especially those with a more severe disease course.

FOOTNOTES

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