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Angiotensin-converting enzyme 2 receptors, chronic liver diseases, common medications, and clinical outcomes in coronavirus disease 2019 patients

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Abstract

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus responsible for coronavirus disease 2019 (COVID-19), enters affected cells through the angiotensin-converting enzyme 2 (ACE2) receptor, which is highly expressed in type II alveolar cells, enterocytes, and cholangiocytes. SARS-CoV-2 infection causes fever, dry cough, and breathing difficulty, which can progress to respiratory distress due to interstitial pneumonia, and hepatobiliary injury due to COVID-19 is increasingly recognized. The hepatobiliary injury may be evident at presentation of the disease or develop during the disease progression. The development of more severe clinical outcomes in patients with chronic liver diseases (CLD) with or without cirrhosis infected with SARS-CoV-2 has not been elucidated. Moreover, there is limited data related to common medications that affect the disease severity of COVID-19 patients. Additionally, ACE2 receptor expression of hepatobiliary tissue related to the disease severity also have not been clarified. This review summarized the current situation regarding the clinical outcomes of COVID-19 patients with chronic liver diseases who were treated with common medications. Furthermore, the association between ACE2 receptor expression and disease severity in these patients is discussed.

Key Words: SARS-CoV-2; COVID-19; Hepatobiliary tissue; Angiotensin converting enzyme 2; Chronic liver disease; Common medications; Clinical outcome

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Core Tip: With more than 100 million confirmed cases worldwide, hepatobiliary injury has been reported in many coronavirus disease 2019 (COVID-19) patients. The

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association between COVID-19 and hepatobiliary injury refers to any hepatobiliary damage during disease progression and treatment in COVID-19 patients with or without chronic liver diseases or common medications. Angiotensin-converting enzyme 2 receptor may be a significant factor in hepatobiliary derangement due to its high expression in cholangiocytes, and it is also an entry point of severe acute respiratory syndrome coronaviruses 2. Moreover, drug-induced liver injury and cytokine storm may be an added risk in severe clinical outcomes. Close monitoring of liver function in COVID-19 patients is mandatory.

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INTRODUCTION

Knowledge of the fundamental physiology of angiotensin-converting enzyme 2 (ACE2) has cumulated more than 20 years since its discovery in 2000 and has greatly increased our understanding of the renin-angiotensin system (RAS)[1,2]. The RAS is an essential hormone system with critical roles in blood pressure regulation, vascular biology, nervous system, electrolyte homeostasis, tissue injury, and lipid homeostasis[3,4]. ACE is the key-driven enzyme in classical RAS. On the other hand, the protective RAS is regulated by ACE2 and counterbalances many of the classical deleterious effects of the RAS[5,6]. ACE2 has definite roles ranging from catalytic activities with numerous substrates, as the receptors for severe acute respiratory syndrome coronaviruses (SARS-CoV) and SARS-CoV-2, and as an amino acid transporter[7-10]. ACE2 regulates the RAS by converting angiotensin (Ang) I and II into Ang 1-9 and Ang 1-7, respectively. Clinical and animal studies demonstrated a physiological and pathophysiological aspect of ACE2 in cardiovascular disease (CVD), and activating ACE2 may evoke protective outcomes against hypertension and CVD[11-13].

Since the end of 2019, ACE2 has amassed interest as the cellular receptor of SARS-CoV-2, the causative virus of the coronavirus disease 2019 (COVID-19) pandemic that emerged from Wuhan, China. It has rapidly spread through China, crossed the global borders of 221 countries, and infected 101529722 people, with 2186606 deaths resulting in a 2.15% mortality rate[14]. The clinical manifestations of COVID-19 patients include cough, fever, sore throat, diarrhea, and loss of sense of taste or smell. More than 80% of infected patients have mild symptoms, 14% have severe symptoms, and 5% have a critical illness. Older patients and those with medical co-morbidities are at risk of a severe disease course[15]. Previous studies demonstrated liver damage in nearly 60% of patients suffering from SARS. They also found SARS-CoV virus particles in the hepatocytes of patients[16]. Moreover, SARS-CoV-2 is associated with hepatic dysfunction ranging from 14% to 53% with abnormal levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) without known liver disease[17-19]. Patients with severe or critical outcomes showed higher frequency and degree of liver dysfunction, while in milder patients, the liver injury was transient[20]. Liver injury in COVID-19 patients included psychological stress, systemic inflammation response, drug toxicity, the progression of pre-existing chronic liver diseases (CLD), and other factors[21]. Hence, three possible scenarios have been postulated. Firstly, patients with CLD and pre-existing co-morbidity diseases may be more prone to the severe clinical outcomes of COVID-19, including oxygen desaturation and hypoxemia due to severe pneumonia or the cytokine storm. Secondly, liver enzyme abnormalities are the consequence of drug toxicity. Thirdly, SARS-CoV-2 directly or indirectly causes liver injury[22-24]. Although ACE2 receptors are abundantly present in type 2 alveolar cells, they are also expressed in the gastrointestinal tract, vascular endothelium, hepatocytes, and cholangiocytes and may be the significant factors in disease severity. This review will clarify the relationship between CLD, common medications, and the expression of ACE2 with the clinical outcomes in COVID-19 patients.

ACE2 RECEPTOR

Physiology of ACE2 receptor

ACE2 receptor resembles the ACE receptor and plays a crucial role in the renin-angiotensin-aldosterone system (RAAS), including blood pressure control and electrolyte homeostasis. The liver produced angiotensinogen, which is cleaved by renin from the kidney, results in Ang I. After that, ACE catalyzes the conversion of Ang I to Ang II. Ang II is the significant active RAAS portion and exerts its effects *via* Ang II type 1 receptor. Furthermore, Ang II's main effects include vasoconstriction, renal sodium reabsorption, potassium excretion, aldosterone synthesis, blood pressure elevation, and induction of pro-inflammatory and pro-fibrotic pathways. ACE2 splits Ang II to Ang (1-7) and Ang I to Ang (1-9). Furthermore, Ang (1-9) is cleaved by ACE to Ang (1-7). Ang (1-7) exerts vasodilatation, anti-inflammatory, and anti-fibrotic effects through the Mas receptor to counterbalance Ang II's action. Notably, ACE2 functionally counteracts the physiological role of ACE and creates the tissue balance of ACE and ACE2, which determines the pro-inflammatory, pro-fibrotic, or anti-inflammatory and anti-fibrotic pathways[25,26] (Figure 1). The common drugs prescribed for RAAS blockade in several disease conditions can affect this balance. Moreover, many dietary factors (high sodium, high fat, and high fructose intake) can also shift the ACE/ACE2 balance towards pro-inflammatory and pro-fibrotic[27-29].

Expression of ACE2 receptor in hepatobiliary tissue

In 2004, Hamming *et al*[30] investigated the immuno-localization of ACE2 in 93 human specimens and found that ACE2 was present in endothelial cells from small arteries, large arteries, and veins in the studied tissues. Marked ACE2 immuno-staining was found in type I and typed II alveolar epithelial cells in normal lungs. ACE2 was abundantly demonstrated in enterocytes of all small intestine but not in the enterocytes of the large intestine. ACE2 was not found in lymphoid tissues and hepatocytes. Recently, Xu *et al*[31] investigated ACE2 expression in the oral cavity mucosa and various organs, including the intestine, kidney, stomach, bile duct, liver, lungs, thyroid, esophagus, bladder, breasts, uterus, and prostate. They found that ACE2 could be expressed in various organs. The mean expression of ACE2 in the liver, bile duct, and lungs was 6.86 ± 1.35 , 7.23 ± 1.16 , 5.83 ± 0.71 , respectively. This result demonstrated that the expression of ACE2 in the lungs and the liver was not different. Moreover, Zhao *et al*[32] identified ACE2 expression sparsely in cholangiocytes of human liver ductal organoids cells. Anti-ACE2 immuno-staining further confirmed the presence of ACE2 receptors on those cells. Furthermore, Li *et al*[33] explored the underlying liver injury mechanism by profiling ACE2 expression with CLD expression data. They found that the liver tissues with chronic diseases, such as cirrhosis, non-alcoholic steatohepatitis, simple steatosis, and dysplasia, could express higher levels of ACE2 than normal liver tissues.

The relationship between common medications and ACE2 expression

Sinha *et al*[34] performed *in vitro* and *in vivo* studies to identify the clinically approved drugs that could modify ACE2 expression. They found that ACE inhibitors (ACEIs) but not angiotensin II type-I receptor blockers (ARBs) tend to upregulate ACE2 expression, and anti-adrenergic drugs other than alpha/beta-blockers tend to down-regulate ACE2 expression. Moreover, calcium channel blockers (CCBs) do not significantly change ACE2 expression, consistent with the finding that they do not act on the RAAS. This evidence provides preliminary *in vitro* support for the use of CCBs as an alternative to ACEIs in COVID-19 patients with hypertension. They also studied the 13 approved anti-diabetic drugs related to ACE2 expression, and they could not demonstrate that the drugs significantly altered ACE2 expression. Surprisingly, they reported that intravenous dexamethasone injection could increase ACE2 expression. They also demonstrated the effect of vancomycin, which increased an ACE2 expression. Saheb SharifAskari *et al*[35] studied the effect of common medications on the expression of ACE2 receptors in human primary hepatocytes. They found that the top three drugs that increased ACE2 expression were penicillamine, ethambutol, and vitamin A. The top five drugs that decreased ACE2 expression were colchicine, acetaminophen, sulindac, diazepam, and nimesulide. The top five drugs that did not change ACE2 expression were ibuprofen, lornoxicam, mefenamic acid, meloxicam, and methyltestosterone.

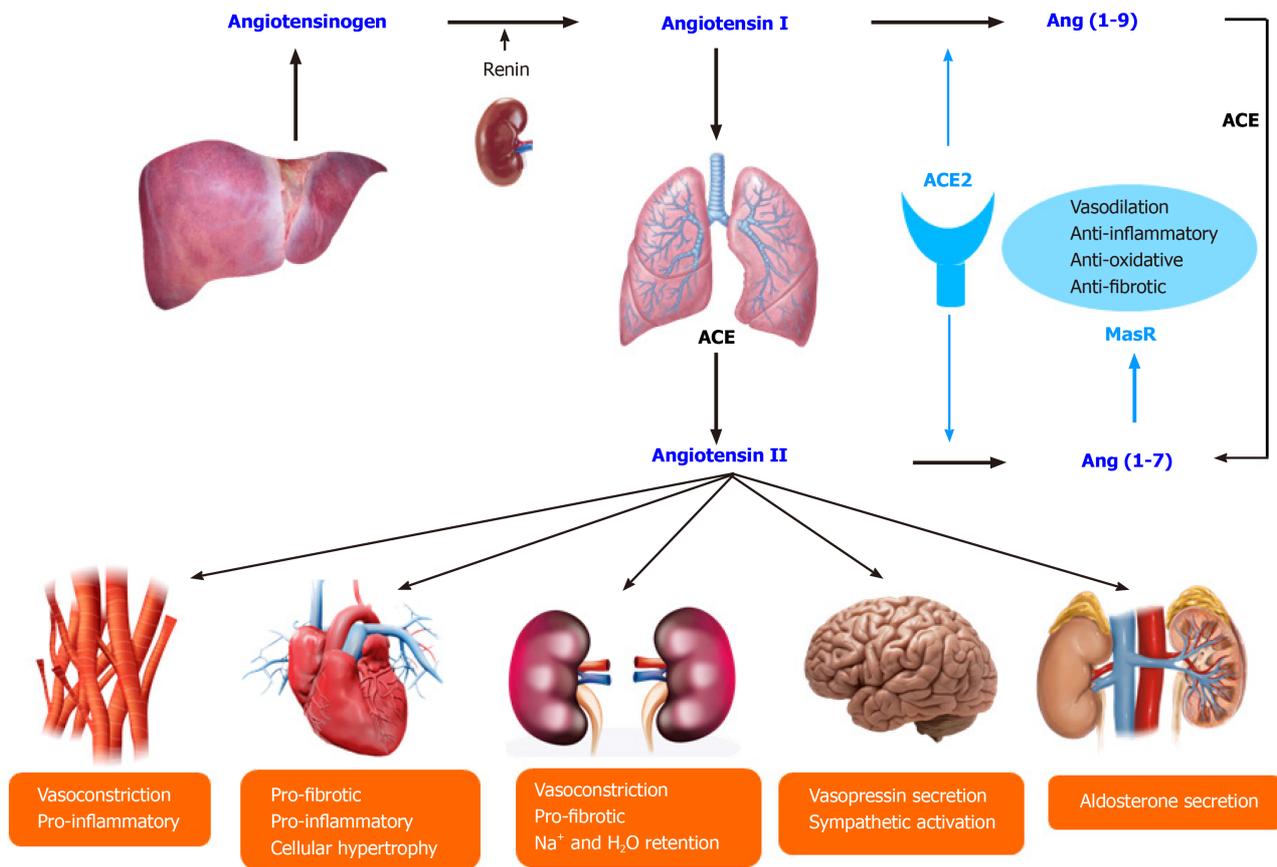


Figure 1 The renin-angiotensin-aldosterone system and the physiology of angiotensin-converting enzyme 2. ACE: Angiotensin-converting enzyme.

COVID-19 AND HEPATOBILIARY INJURY

Laboratory evidence of hepatobiliary injury

Previous studies have shown that nearly 60% of SARS patients developed a hepatobiliary injury and that SARS-CoV antigens were detected in liver tissues by reverse transcription-polymerase chain reaction[36,37]. Hepatobiliary injury in COVID-19 patients was also demonstrated by abnormal transaminase levels linked to the disease severity and the clinical outcome. Abnormal liver enzymes in COVID-19 patients were first reported by Chen *et al*[38]. They analyzed data of 99 COVID-19 patients from Wuhan and found that 43 cases (43.4%) had elevated ALT, AST, and lactic dehydrogenase. Most of them had a mild elevation of AST and ALT, and only one patient had very high ALT levels of 7590 U/L and AST levels of 1445 U/L. Recently, Kulkarni *et al*[39] conducted a systematic review with meta-analysis to evaluate the liver manifestations and clinical outcomes in 20874 COVID-19 patients. They found that the pooled incidence of elevated AST and ALT in COVID-19 was 23.1% (19.3%-27.3%) at initial presentation. Moreover, 24.4% (13.5%-40%) of the patients developed elevated AST and ALT during the illness. They also reported the prevalence of underlying CLD as 3.6% among the 15407 COVID-19 patients. The pooled incidence of drug-induced hepatobiliary injury was 25.4% (14.2%-41.4%). They found that the development of severe COVID-19 in CLD patients had an odds ratio (OR) of 0.81 [95% confidence interval (CI): 0.31-2.09] compared with non-CLD patients. Furthermore, COVID-19 patients with elevated AST and ALT had increased risk of mortality (OR = 3.46, 95%CI: 2.42-4.95, $P < 0.001$) and severe disease (OR = 2.87, 95%CI: 2.29-3.6, $P < 0.001$) when compared with the patients without elevated AST and ALT.

Recently, Del Zompo *et al*[40] conducted a systematic review with meta-analysis to elucidate the prevalence of hepatobiliary injury in 20724 COVID-19 patients with or without pre-existing CLD. They found that the pooled prevalence of abnormal liver function tests (LFTs) on admission was 46.9% [AST 26.5%, ALT 22.8%, gamma-glutamyl transferase (GGT) 22.5%, alkaline phosphatase (ALP) 5.7%, and total bilirubin (tBIL) 8.0%]. The elevation of ALT, AST, and tBIL were independent predictors of disease severity and in-hospital mortality. Wong *et al*[41] conducted

another systematic review with meta-analysis to evaluate the prevalence and degree of liver injury in 5961 severe and non-severe COVID-19. They found that the OR for elevated ALT was 2.5, AST was 3.4, hyperbilirubinemia was 1.7, and hypoalbuminemia was 7.1, which were higher in critical COVID-19. They concluded that hepatobiliary injury is more common in COVID-19 patients with severe clinical outcomes than in COVID-19 patients with non-severe clinical outcomes.

Mao *et al*[42] conducted another meta-analysis to evaluate the prevalence and prognosis of gastrointestinal symptoms and hepatobiliary injury in 6686 patients with COVID-19. They found that the pooled prevalence of liver co-morbidities was 3%, including chronic hepatitis and liver cirrhosis. The pooled prevalence of liver injury from 12 studies ($n = 1267$) was 19%. The prevalence of elevated ALT was 18%, AST was 21%, tBIL was 6%, and decreased albumin was 6%. They also reported a higher risk of abnormal LFT in patients with severe COVID-19 than those with the non-severe disease.

Kumar-M *et al*[43] conducted another meta-analysis to evaluate the overall prevalence, stratified prevalence based on severity, estimated risk ratio (RR), and estimated standardized mean difference (SMD) of liver function parameters in severe compared to non-severe COVID-19 patients with a total number of 28659 subjects. They found that the most frequent abnormalities were hypoalbuminemia (61.27%), elevated GGT = 27.94%, elevated ALT = 23.28%, and elevated AST = 23.41%. Furthermore, the relative risk (RR) of these abnormalities was higher in the patients with severe COVID-19 when compared to non-severe disease (hypoalbuminemia RR = 2.65; GGT RR = 2.31; AST RR = 2.30; and ALT RR = 1.76). The pooled prevalence and RR of CLD as a pre-existing co-morbidity were 2.64% and 1.69%, respectively. They concluded that the most frequent hepatobiliary injury was hypoalbuminemia followed by elevated GGT, elevated AST, and elevated ALT, which were more common in severe COVID-19 patients.

Youssef *et al*[44] conducted a meta-analysis of 3428 COVID-19 patients to elucidate the relationship between hepatobiliary injuries and the severity of COVID-19 disease. They found that the patients who had severe presentations of COVID-19 had hypoalbuminemia (SMD = 0.68), elevated AST (SMD = 0.36), elevated ALT (SMD = 0.44), and elevated tBIL (SMD = 0.40). They also reported that severe COVID-19 patients had a higher OR of developing acute hepatobiliary injury (OR = 1.93). They concluded that hepatobiliary injury was related to a critical outcome of COVID-19 patients. Close monitoring of the development of liver dysfunction is beneficial in early warning of unfavorable outcomes.

Wang *et al*[45] conducted a meta-analysis to evaluate the association of liver injury and gastrointestinal symptoms (GIS) with the progression of COVID-19 in 3024 patients. They found that 53% of patients had a hepatobiliary injury, and the degree of hepatobiliary damage was associated with disease severity. The prevalence of GIS was relatively low and was not associated with disease progression, with diarrhea of 9.1%, nausea/vomiting of 5.2%, and abdominal pain of 3.5%.

Wu *et al*[46] conducted a meta-analysis to explore the probable clinical severity and mortality of COVID-19 patients and their liver dysfunction in 3722 COVID-19 patients. They found a significant connection between hepatobiliary dysfunction and mortality in COVID-19 patients with a pooled OR of 1.98. There was a significant association between elevated AST and severity of COVID-19 with a pooled OR of 4.48 and a pooled weighted mean difference of 3.35. They also found a significant difference between elevated tBIL and severe COVID-19 (pooled OR = 1.91 and pooled weighted mean difference = 1.18). They concluded that the mortality and severity of COVID-19 patients are significantly associated with hepatobiliary dysfunction.

Samidoust *et al*[47] conducted a meta-analysis study to investigate the incidence of liver injury among 4191 COVID-19 patients. They found that the pooled prevalence of liver injury was 19.5%. They concluded that hepatobiliary system is the most frequently damaged outside of the respiratory system. Wu *et al*[48] conducted the meta-analysis to explore the incidence, risk factors, and prognosis of abnormal liver biochemical tests in 7228 COVID-19 patients. They found that the pooled prevalence of any abnormal liver biochemistry parameters on admission and during hospitalization was 27.2% and 36%, respectively. The most common prevalence was hypoalbuminemia followed by GGT, AST, ALT, tBIL, and ALP (39.8%, 35.8%, 21.8%, 20.4%, 8.8%, and 4.7%). Moreover, severe or critical patients had a significantly higher pooled incidence of abnormal liver biochemistry parameters on admission than mild or moderate patients. Non-survival patients also had a significantly higher incidence of abnormal liver biochemical indicators than survival patients (RR = 1.34). They concluded that abnormal liver biochemical tests are common and are closely related to the severity and prognosis of COVID-19 patients.

Mantovani *et al*[49] conducted the meta-analysis to assess the overall prevalence of CLD among 2034 COVID-19 patients. They found that the overall prevalence of CLD at baseline was 3%, and patients with severe COVID-19 disease had relevant increases of liver enzymes and coagulation profile due to the innate immune response against the SAR-CoV-2 virus. Sultan *et al*[50] conducted the meta-analysis to summarize international data on the gastrointestinal (GI) and liver manifestations of SAR-CoV-2 infection and treatment in 10890 COVID-19 patients. They found that elevated AST, elevated ALT, and elevated tBIL are observed in approximately 15%-20% of COVID-19 patients. These findings inform that the clinician should perform a careful evaluation of patients with new-onset GI symptoms for classic and atypical symptoms of COVID-19. All hospitalized COVID-19 patients may benefit from liver enzyme monitoring, particularly in drug treatment with known hepatotoxic potential.

Pathological finding of hepatobiliary injury

Xu *et al*[51] reported the first post-mortem findings of a patient who succumbed to severe COVID-19. They found that the liver histology showed moderate microvesicular steatosis and mild inflammatory infiltrates in the hepatic lobule and portal tract. They do not know whether these changes were from the direct viral injury or drug toxicity. Wichmann *et al*[52] conducted a prospective cohort study to perform the autopsies of 12 consecutive COVID-19 deaths, including post-mortem computed tomography and histopathologic and virologic analyses. The median patient age was 73 years (52 to 87 years), 75% of patients were male, and death occurred in the hospital ($n = 10$) or outpatient department ($n = 2$). They did not report the histopathology of the hepatobiliary system; however, they could demonstrate the detection of SARS-CoV-2 ribonucleic acid in the lungs of 12 patients (1.2×10^4 to 9×10^9 copies/mL) and the pharynx of nine patients. In five of these patients, viral ribonucleic acid was also detected in the heart, liver, and kidney. They concluded that SARS-CoV-2 might spread *via* the bloodstream and infect other organs, including the hepatobiliary system. Tian *et al*[53] performed post-mortem needle core biopsies of lung, liver, and heart in four patients who died of COVID-19 pneumonia. They found that the liver histopathology showed mild lobular infiltration by small lymphocytes, centrilobular sinusoidal dilatation, focal macrovesicular steatosis, and patchy hepatic necrosis in the periportal and centrilobular areas. Tabary *et al*[54] reviewed multiple organs, including lung, GI tract, liver, kidney, skin, heart, blood, spleen, lymph nodes, brain, blood vessels, and placenta, in COVID-19-related pathological alterations. The liver found hepatocyte degeneration with lobular focal necrosis, congestion of hepatic sinuses with microthrombus, fibrosis of portal tract, the proliferation of portal vein branches, mononuclear leukocyte, and neutrophil infiltration within the portal area and moderate microvascular steatosis. Yao *et al*[55] conducted another histopathology of the hepatobiliary system. They found that the liver exhibits mild sinusoidal dilation, with mildly increased small lymphocytes infiltration in sinusoidal spaces. Mild to moderate steatosis and multifocal hepatic necrosis have been reported. These findings confirmed that the hepatocellular injury in COVID-19 patients should be considered as a significant factor in disease severity.

CLD AND CLINICAL OUTCOME

The COVID-19 patients with pre-existing CLD usually face a relatively high risk of poor clinical outcomes. Li *et al*[33] established that patients with CVDs could express higher ACE2 expression than those without heart diseases. Furthermore, ACE2 was upregulated in patients with type 2 diabetes (T2D) compared to the individuals without T2D. For CLD such as cirrhosis, non-alcoholic steatohepatitis, and simple steatosis, ACE2 could express higher levels than normal liver tissues. The upregulation of ACE2 expression in patients with CLD may result in greater susceptibility to SARS-CoV-2 infection of hepatobiliary tissues. Sarin *et al*[56] conducted The APASL COVID-19 Liver Injury Spectrum Study (APCOLIS Study) to evaluate the liver injury patterns of SARS-CoV-2 in 185 CLD patients without cirrhosis compared with 43 CLD patients with cirrhosis. They found that pre-existing CLD, like metabolic associate fatty liver disease, obesity, and diabetes, was present in nearly 80% of the patients. Moreover, SARS-CoV-2 infection produces acute liver injury in 43% of CLD patients without cirrhosis. Nearly half of decompensated cirrhosis patients develop liver-related complications, which were more severe and had higher mortality. The liver injury pattern in CLD patients was mostly a hepatocellular injury. Notably, elevated serum ALP and elevated GGT were detected, indicating virus-related injury to hepatobiliary

tissue due to the overexpression of ACE2 on cholangiocytes. They also found acute, chronic liver failure (ACLF) or acute decompensation in 20% of the cirrhotic patients, which indicated that SARS-CoV-2, a non-hepatotropic virus, can directly precipitate a severe hepatic injury to cause liver failure in cirrhotic patients. They concluded that pre-existing CLD is an added risk in severe COVID-19 patients. Liver-related complications, overall complications, and clinical outcomes correlated with the existing hepatic reserve. Moreover, acute liver injury is more severe and more progressive with higher mortality in COVID-19 patients with decompensated cirrhosis.

Marjot *et al*[57] conducted an international registry study to evaluate the impact of COVID-19 on patients with pre-existing CLD. They recruited 745 patients with CLD who were infected with SARS-CoV-2 (386 with cirrhosis and 359 without cirrhosis) and compared them to non-CLD patients with SARS-CoV-2 infection. They found that the mortality rate was 32% in COVID-19 patients with cirrhosis compared to 8% in those without cirrhosis. Mortality in cirrhosis patients increased according to Child-Pugh Class [A (19%), B (35%), and C (51%)] and 71% of death was an acute respiratory distress syndrome. Compared to COVID-19 patients without CLD ($n = 620$), the propensity-score-matched analysis revealed a significant increase in mortality in those with Child-Pugh B cirrhosis (+ 20.0%) and Child-Pugh C cirrhosis (+ 38.1%). Acute hepatic decompensation developed in 46% of cirrhosis patients, of whom 21% had no respiratory symptoms. Half of those with hepatic decompensation had ACLF. They concluded that baseline liver disease and alcohol-related liver disease are independent risk factors for death from COVID-19. Another group of investigators from Korea conducted a multicenter study to evaluate the clinical outcomes in 1005 COVID-19 patients related to pre-existing CLD and the predictors of disease severity and mortality. They found that liver cirrhosis was more common in COVID-19 patients with severe pneumonia than in non-severe pneumonia (4.5% *vs* 0.9%). The overall survival rate significantly decreased in COVID-19 patients with liver cirrhosis than in those without liver cirrhosis. The presence of liver cirrhosis was found to be an independent predictor of severe clinical outcome. They suggested that more robust personal protection and more intensive treatment for COVID-19 with pre-existing CLD should be highly recommended[58].

Del Zompo *et al*[40] conducted the meta-analysis to elucidate the prevalence of hepatobiliary injury in COVID-19 patients with or without pre-existing CLD. They explored 36 studies, including 20724 patients with SARS-CoV-2 infection, and found that LFTs alterations were reported in up to 47% of unselected patients with COVID-19 and were associated with severe clinical outcomes or in-hospital mortality. COVID-19 was associated with a high risk of liver decompensation or mortality. Vánca *et al*[59] conducted the meta-analysis to evaluate the prognostic value of on-admission LFTs and pre-existing CLD on the clinical course of COVID-19. They evaluated 50 studies with 17205 COVID-19 patients. They reported that the decreased platelet count, elevated ALT, elevated AST, increased C-reactive protein, and the presence of acute or CLDs at the time of admission could predict severe clinical outcomes of COVID-19 patients. Significantly, the pre-existing CLD or acute liver injury combined with SARS-CoV-2 infection was an important factor in predicting mortality rate.

COMMON MEDICATIONS TREATMENT AND CLINICAL OUTCOME IN COVID-19 PATIENTS

Several publications reviewed the role of RAS inhibitors in COVID-19 patients and found that there is no definitive evidence indicating harmful effects of RAS inhibitors. Because ACE and ACE2 are different enzymes, ACEIs do not inhibit ACE2, making this class' harmful effect unlikely[60-62]. Other common anti-hypertensive drugs are ARBs, which have been shown to upregulate ACE2 in animal studies, but these findings do not translate into clinical observations related to COVID-19[63]. Drager *et al*[64] summarized that the available clinical evidence points to a neutral or even beneficial effect on clinical outcomes in COVID-19 patients who received ACEIs or ARBs. Luo *et al*[65] conducted a retrospective analysis to compare the outcome of metformin users and non-users in 283 hospitalized COVID-19 patients with diabetes (104 used metformin, and 179 did not use metformin). They found that in-hospital mortality was significantly lower in the metformin group [3/104 (2.9%) *vs* 22/179 (12.3%), $P = 0.01$]. They concluded that metformin might offer benefits in COVID-19 patients. However, they did not mention the relationship between metformin and hepatobiliary injury in their study. Treatment of common co-morbidities such as cardiovascular, hepatobiliary, and metabolic disorders often requires continuous use

of several medications, which may result in an additive increase in the expression of ACE2. Furthermore, the combined effect of chronic use of these medications could affect liver susceptibility in COVID-19 patients. Although the increased risk of developing severe clinical outcomes in COVID-19 patients should not be the direct effect of common medications, we should be vigilant about the possible effects of those medications.

CONCLUSION

Several factors have been associated with the alteration of ACE2 expression and COVID-19 severity and progression. Although ACE2 is widely expressed in various human tissues and most of its determinants have been well recognized, ACE2-expressing organs do not equally participate in COVID-19 pathophysiology, implicating that other factors are involved orchestrating cellular infection resulting in several organs injury. Abnormal LFTs are reported in up to half of the patients with COVID-19 infection. The disease severity, pre-existing CLD, and some common medications presented risks for hepatobiliary injury in COVID-19 patients. It has been demonstrated that SARS-CoV-2 may directly bind to ACE2 positive cholangiocytes and cause severe hepatic injury. However, pre-existing CLD and some common medications could also upregulate ACE2 expression in the hepatobiliary tissues and cause more severe clinical outcomes in COVID-19 patients. Furthermore, other contributing mechanisms such as drug-induced liver injury, activation of the immune system, and cytokine storm may be the other contributing factors in severe clinical outcomes.

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