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# IMPACT OF COVID-19 ON PATIENTS WITH LIVER CIRRHOSIS OF VIRAL ETIOLOGY

*The coronavirus disease (COVID-19) pandemic has created a global public health emergency. Patients with cirrhosis were considered to be more susceptible to viral infection due to a dysregulated immune response. Patients with cirrhosis experience varying degrees of COVID-19-associated liver injury, which may be due to direct cytotoxicity of the virus, activation of the systemic immune system, drug-related liver injury, or reactivation of pre-existing liver disease. Clinical symptoms in patients with liver cirrhosis and COVID-19 were similar to those in the general population with COVID-19, with a lower proportion of patients presenting with gastrointestinal symptoms. Although respiratory failure is the leading cause of death in cirrhotic patients with COVID-19, a significant proportion do not have initial respiratory symptoms. Most data show that patients with cirrhosis have relatively higher rates of morbidity and mortality associated with COVID-19. Advanced liver cirrhosis has also been proposed as an independent factor influencing poor prognosis and the need to consider palliative care for COVID-19.*

***Key words****: COVID-19; SARS-CoV-2; Cirrhosis of the liver; liver damage; Forecast; Therapy*

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# ВЛИЯНИЕ COVID-19 НА ПАЦИЕНТОВ С ЦИРРОЗОМ ПЕЧЕНИ ВИРУСНОЙ ЭТИОЛОГИИ

*Пандемия коронавирусной инфекции (COVID-19) привела к глобальной чрезвычайной ситуации в области общественного здравоохранения. Пациенты с циррозом считались более восприимчивыми к вирусной инфекции из-за нарушения регуляции иммунного ответа. У пациентов с циррозом печени наблюдается различная степень поражения печени, связанного с COVID-19, что может быть связано с прямой цитотоксичностью вируса, активацией системной иммунной системы, повреждением печени, связанным с реактивацией ранее существовавшего заболевания печени. Хотя дыхательная недостаточность является основной причиной смертности пациентов с циррозом печени, больных COVID-19, у значительной части из них отсутствуют начальные респираторные симптомы. Большинство данных показывают, что у пациентов с циррозом печени относительно более высокий уровень заболеваемости и смертности, связанный с COVID-19. Поздняя стадия цирроза печени также была предложена как независимый фактор, влияющий на плохой прогноз и необходимость рассмотрения паллиативной помощи при COVID-19.*

***Ключевые слова:*** *COVID-19; SARS-CoV-2; Цирроз печени; Острое поражение печени; Прогноз; Терапия*

**Introduction.** COVID-19 is generally a self-limiting disease, but it can progress to acute respiratory distress syndrome (ARDS), septic shock, and death, especially in older adults or those with underlying medical conditions including cirrhosis, hypertension, diabetes, and cancer [1]. The estimated case fatality rate for COVID-19 ranges from 2% to 6% [2].

The clinical manifestations of COVID-19 patients may be non-specific, but most of them present with fever, cough accompanied by shortness of breath, fatigue, or sputum production [3]. Notably, approximately 14% to 53% of patients suffer from varying degrees of liver injury, although most of these injuries are mild and

transient, with a fair prognosis in patients without pre-existing liver disease. In contrast, COVID-19 in patients with pre-existing liver disease has been reported to result in higher rates of hospitalization and mortality [4,5]. Among these pre-existing liver diseases, cirrhosis is a chronic liver disorder that involves the collapse of liver structure and distortion of vascular architecture. Cirrhosis is associated with innate immune dysfunction and alteration of the gut-liver axis; patients with cirrhosis are particularly at increased risk of infections and associated complications . It remains unclear whether immunocompromised patients infected with COVID-19 are at higher risk of adverse outcomes. It is unclear whether patients with human immunodeficiency virus infection are at higher risk of mortality due to COVID-19 [6]. In addition to the studies involving the aforementioned immunocompromised patients, several studies have investigated the clinical and biochemical characteristics associated with the prognosis of COVID-19 in patients with liver cirrhosis, leading to some preliminary conclusions. This article summarized the current epidemiology, clinical characteristics, pathophysiology of liver injury, outcomes, and treatments of patients with liver cirrhosis and COVID-19.

According to WHO, as of the end of December 2020, there have been more than 79 million confirmed cases of COVID-19 in over 200 countries and 1.7 million deaths [5]. Previous studies have shown that 2–11% of patients with COVID-19 had pre-existing liver disease, and approximately 0.6% of patients with COVID-19 had underlying liver disease in a recent large-scale population-based study in the UK [6]. In contrast, the literature on the prevalence of liver cirrhosis in patients with COVID-19 is limited. Two large-scale studies from the US found that 0.3% (19/5700) and 1.8% (50/2780) of patients with COVID-19 had cirrhosis [7]. Similarly, two studies from Portugal and China found that 0.8% (6/756) and 2.4% (3/123) of COVID-19 patients had pre-existing liver cirrhosis, respectively [8]. Overall, a small proportion of COVID-19 patients have underlying liver cirrhosis. However, it has been suggested that individuals with cirrhosis are more susceptible to SARSCoV-2 infection due to an altered immune response. One study from the United States and

another from China reported the incidence of SARS-CoV-2 infection in hospitalized patients with cirrhosis to be 6.6% (37/556) and 16.8% (17/101), respectively [9]. Collectively, although they represent a small proportion of COVID-19 patients, patients with cirrhosis are more susceptible to viral infection than the general population.

**The purpose** of this review is the effect of covid-19 on patients with cirrhosis of the liver of viral etiology.

**Materials and methods.** The data showed that the clinical manifestations of patients with cirrhosis and COVID-19 were similar to those in the general population with COVID-19, with fever and cough remaining the most common symptoms, followed by dyspnea and sputum production [10]. Interestingly, although patients with and without cirrhosis developed respiratory and cardiovascular symptoms, patients with cirrhosis were less likely to develop gastrointestinal symptoms (e.g., diarrhea, nausea, vomiting). Possible explanations include a higher proportion of baseline gastrointestinal symptoms in patients with cirrhosis and their use of medications (e.g., lactulose), which may also lead to an underestimation of the proportion of patients with COVID-19-related gastrointestinal symptoms.

Laboratory test data are lacking; however, available data have shown that patients with cirrhosis and COVID-19 are significantly more likely to develop thrombocytopenia than the group of patients with cirrhosis but not COVID-19 [11]. Interestingly, the early (usually occurring within the first week of hospitalization) and rapid deterioration of liver biochemical parameters (e.g., aminotransferases), but not bile duct enzymes (e.g., alkaline phosphatase, γ-glutamyl transferase), in these patients with cirrhosis may indicate that COVID-19-associated liver injury is more often drug-induced or hypoxic in this patient group. However, further histological and experimental studies are needed to confirm this finding. Thus, although it is suggested that patients with cirrhosis and COVID-19 have elevated levels of biochemicals in both the liver and bile ducts (e.g. aminotransferase, bilirubin, alkaline phosphatase, γ-glutamyl transferase), regardless of the presence of respiratory

symptoms, the European Association for the Study of Liver Diseases (EASL) and the American Association for the Study of Liver Diseases (AASLD) recommend that all patients with cirrhosis with new or worsening Alzheimer's disease or development of ACLF undergo testing for SARS-CoV-2 during the COVID-19 pandemic [10,12].

**Results and discussion.** The proposed mechanisms underlying liver injury in COVID-19 patients include direct pathogenic viral cytotoxicity, systemic immune activation and cytokine storms, drug-induced liver injury, reactivation of pre-existing liver disease, and hypoxic hepatitis.

Compared with normal liver, cirrhotic liver is more vulnerable to direct viral injury due to widespread ACE2 expression; increased cytokine levels and immune response; similar degree of drug-induced liver injury; greater activation of pre-existing liver disease; and more severe hypoxic hepatitis. The arrow represents the magnitude of each effect on the liver.

It has been suggested that SARS-CoV-2 uses the same ACE2 receptor as SARS-CoV to enter host cells, resulting in inflammatory responses and cytopathic effects. ACE2 receptors are widely distributed in the human body and are highly expressed in type II alveolar cells in the lung, esophageal epithelial cells, absorptive enterocytes in the ileum and colon, myocardial cells, proximal tubular cells in the kidney, and urothelial cells in the bladder [13]. In normal human liver, ACE2 receptor expression is particularly high in bile duct epithelial cells (i.e., cholangiocytes) and vascular endothelium; only a small proportion of hepatocytes are ACE2 positive. Destruction of cholangiocytes due to the cytopathic effect of SARS-CoV-2 leads to bile duct injury and further liver damage. In contrast, ACE2 expression was detected in the majority of hepatocytes in cirrhotic nodes, as well as in cholangiocytes and vascular endothelial cells. Patients with liver cirrhosis also have increased circulating ACE activity and angiotensin II levels, which may facilitate viral entry into host cells, making them more vulnerable to direct virus-associated cytotoxicity, leading to more severe liver dysfunction and serious clinical consequences [13,15].

Patients with liver cirrhosis were found to have a higher likelihood of severe COVID-19 than the general healthy population, with proportions ranging from 18.6% to 35.3% [14]. Pre-existing liver cirrhosis was found to be a risk factor for severe COVID-19. In addition, patients with liver cirrhosis were also more likely to develop complications of COVID-19, including ARDS (28.6% to 52%), respiratory failure requiring mechanical ventilation (4% to 38%), shock (6% to 30%), renal failure requiring renal replacement therapy (1.5% to 19%), need for extracorporeal membrane oxygenation (9.5%), and need for intensive care unit (ICU) admission (3% to 43%) [15]. Notably, many more patients with COVID-19 developed an adverse outcome than those receiving the appropriate level of care (i.e., 52% of patients had ARDS, but only 4% of patients developed CF and were admitted to intensive care units). Thus, the true number of patients with cirrhosis requiring intensive care in these studies may have been underestimated[16].

Compared with the general population with COVID-19, patients with cirrhosis and COVID-19 had a higher mortality rate, ranging from 9% to 42.3%. Decompensated cirrhosis has been identified as an independent risk factor for mortality; patients with cirrhosis are also at higher risk of COVID-19-related hospitalization and mortality. Compared with other studies, a nationwide population-based study from Korea found no association of cirrhosis with mortality in patients with COVID-19. The authors also demonstrated a significantly lower risk of mortality and other complications in patients with cirrhosis and COVID-19. However, the inclusion of all patients with cirrhosis (including hospitalized and non-hospitalized patients) and the lack of data on the etiology and severity of cirrhosis in this study may limit the extrapolation of the results [8,11]. In contrast, the cirrhosis and COVID-19 group had more COVID-19-related complications (eg, respiratory failure, need for MV, shock), suggesting possible different causes of mortality in the two groups. Taken together, compared with the general COVID-19 population, patients with cirrhosis and COVID-19 have a higher risk of in-hospital mortality, but

there is still insufficient evidence to support the idea that COVID-19 increases the risk of ACLF or mortality in patients with cirrhosis [12,13].

**Conclusion.** In the context of the COVID-19 pandemic, although patients with liver cirrhosis constitute a small proportion of the general population, they are more vulnerable to viral infection, resulting in both hepatic and extrahepatic complications, which are further associated with a higher risk of mortality and more severe outcomes. Due to immune dysfunction, patients with liver cirrhosis show distinct features of COVID-19-related liver injury. More importantly, it is still unknown whether COVID-19 is a trigger for AD or ACLF in patients with liver cirrhosis. Since there is no pharmacological therapy proven to be effective in patients with cirrhosis and Covid-19, maintaining standard care for cirrhosis and preventing viral transmission are the cornerstones of treatment. As COVID-19 vaccines have become available, their safety and efficacy in patients with liver cirrhosis require further study.

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