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Editorial Board Member of *World Journal of Clinical Cases*, Wei Wang, MD, PhD, Associate Professor, Key Laboratory on Technology for Parasitic Disease Prevention and Control, Jiangsu Institute of Parasitic Diseases, Wuxi 214064, Jiangsu Province, China. wangwei@jipd.com

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OPINION REVIEW

COVID-19 combined with liver injury: Current challenges and management

Man-Ling Deng, Yong-Jun Chen, Mei-Ling Yang, Yi-Wen Liu, Hui Chen, Xiao-Qing Tang, Xue-Feng Yang

ORCID number: Man-Ling Deng 0000-0001-7499-0826; Yong-Jun Chen 0000-0002-2076-6295; Mei-Ling Yang 0000-0001-8782-8959; Yi-Wen Liu 0000-0001-9427-1482; Hui Chen 0000-0001-8122-2438; Xiao-Qing Tang 0000-0001-9151-3730; Xue-Feng Yang 0000-0002-3470-0350.

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Man-Ling Deng, Yi-Wen Liu, Hui Chen, Xue-Feng Yang, Department of Gastroenterology, The Affiliated Nanhua Hospital, Hengyang Medical College, University of South China, Hengyang 421002, Hunan Province, China

Yong-Jun Chen, Department of Neurology, The Affiliated Nanhua Hospital, Hengyang Medical College, University of South China, Hengyang 421002, Hunan Province, China

Mei-Ling Yang, Department of Oncology, The Affiliated Nanhua Hospital, Hengyang Medical College, University of South China, Hengyang 421002, Hunan Province, China

Xiao-Qing Tang, Institute of Clinical Medicine, The First Affiliated Hospital, Hengyang Medical College, University of South China, Hengyang 421001, Hunan Province, China

Corresponding author: Xue-Feng Yang, MD, Full Professor, Department of Gastroenterology, The Affiliated Nanhua Hospital, Hengyang Medical College, University of South China, No. 336 Dongfeng Road, Zhuhui District, Hengyang 421002, Hunan Province, China. yxf9988@126.com

Abstract

Coronavirus disease 2019 (COVID-19) combined with liver injury has become a very prominent clinical problem. Due to the lack of a clear definition of liver injury in patients with COVID-19, the different selection of evaluation parameters and statistical time points, there are the conflicting conclusions about the incidence rate in different studies. The mechanism of COVID-19 combined with liver injury is complicated, including the direct injury of liver cells caused by severe acute respiratory syndrome coronavirus 2 replication and liver injury caused by cytokines, ischemia and hypoxia, and drugs. In addition, underlying diseases, especially chronic liver disease, can aggravate COVID-19 liver injury. In the treatment of COVID-19 combined with liver injury, the primary and basic treatment is to treat the etiology and pathogenesis, followed by support, liver protection, and symptomatic treatment according to the clinical classification and severity of liver injury. This article evaluates the incidence, pathogenesis and prevention and treatment of COVID-19 combined with liver injury, and aims to provide countermeasures for the prevention and treatment of COVID-19 combined with liver injury.

Key Words: SARS-CoV-2; COVID-19; Liver function; Liver injury; Pathogenesis; Treatment

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Core Tip: The prevention and treatment of coronavirus disease 2019 (COVID-19) combined with liver injury face many challenges. First, the definition of COVID-19 combined with liver injury is not clear, the selected parameters and the time of statistics are inconsistent, and the conclusions about the incidence rate are consistent. Second, the etiology and mechanism of COVID-19 combined liver injury are not clear and need to be studied in depth. Third, there is a lack of effective treatment methods. This article provides and additional view of the incidence of COVID-19-associated liver injury and explores the contemporary management modalities.

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has spread globally, resulting in an ongoing pandemic[1]. As of February 15, 2021, the World Health Organization (WHO) has reported a total of 108579352 confirmed cases of COVID-19 in 184 countries by world region, with a cumulative total of 2396408 deaths[2]. The main target organ of SARS-CoV-2 infection is not only the lung but also many extrapulmonary tissues[3]. Among them, COVID-19 combined with liver injury has become a very prominent clinical problem and has garnered great attention[4]. The author of this article once reported that about one-fifth of the 48 COVID-19 patients have abnormal liver function[5]. At present, the prevention and treatment of COVID-19 combined with liver injury face many challenges, and several key problems need to be solved. For example, the diagnosis of COVID-19 combined with liver injury. Due to the inconsistent diagnostic criteria, a series of problems have arisen in the diagnosis and treatment of COVID-19 combined with liver damage. If the diagnostic criteria are too low, it may lead to overtreatment in clinical practice[6]. Another problem is the study of pathogenesis. It is necessary to determine whether SARS-CoV-2 can directly invade the liver, especially when angiotensin-converting enzyme 2 (ACE2) appears to be negligibly expressed on liver cells[4]. In addition, the mechanisms underlying liver dysfunction in COVID-19 patients are not fully understood; it may be multifactorial and related to hyperinflammation, dysregulated immune responses, abnormal coagulation, and drugs[4].

This article provides an additional view of the incidence, pathogenesis, prevention, and treatment of COVID-19-associated liver injury and explores the contemporary management modalities.

INCIDENCE OF COVID-19 COMBINED WITH LIVER INJURY

At present, the evaluation parameters for studying the incidence of COVID-19 liver injury are different. The liver function parameters generally include alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin (TB)[5-14]. Some also include alkaline phosphatase (ALP), γ-glutamyl transpeptidase (γ-GT), and so on[5]. Liver injury in COVID-19 patients lacks a clear definition[6]. Some researchers define liver damage as liver enzyme levels above the upper limit of normal (ULN)[5,7] and albumin below the lower limit of normal[5]; other researchers define it as liver enzyme levels 2 or 3 times or even 5 times higher than the ULN[8,9]. China's "New Coronavirus Pneumonia with Liver Injury Prevention, Diagnosis and Treatment Program" defined as COVID-19 combined with liver injury in the following situations, COVID-19 patients with or without underlying liver disease, the upper limit of serum ALT or AST higher than normal is called COVID-19 with abnormal liver function; ALT or AST ≥ 3 times the ULN or TB ≥ 2 times is called COVID-19 with liver

injury[10]. American College of Gastroenterology and British Society of Gastroenterology clinical guidelines define liver injury as an increase in ALT or AST by at least 3 × ULN, or an increase in alkaline phosphatase, TB, or direct bilirubin by at least 2 × ULN[11,12]. Due to the different parameters and criteria for evaluating liver function in patients with COVID-19, the incidence of liver injury varies widely across studies, from 4.8% to a striking 78%[13]. The difference in the incidence of liver injury in different studies is also related to the statistical time point. For example, Ding *et al*[14] calculated that the abnormal liver function rate of COVID-19 patients at hospitalization admission was 46.2% (958/2073), and the incidence of liver injury was 5.1% (105/2073); Statistics during hospitalization (during disease progression) showed that the abnormal liver function rate was 61.8% (1282/2073), and the incidence of liver injury was 14.3% (297/2073).

In short, due to the unclear definition of liver injury, the different selection of evaluation parameters, the inconsistent statistical time points (*i.e.* on admission or during disease progression), the incidence of COVID-19 combined with liver injury is extremely inconsistent in different research reports. Therefore, some academics suggest that researchers pay close attention to the terminology and its definition to avoid ambiguity in future analyses and overtreatment in clinical practice[6].

ETIOLOGY AND PATHOGENESIS OF COVID-19 COMBINED WITH LIVER INJURY

The mechanism of COVID-19 combined with liver injury is complex including direct injury, immune injury, ischemia and hypoxia, and drug injury. In addition, underlying diseases, especially chronic liver disease, can aggravate COVID-19 liver injury.

SARS-CoV-2 replication directly causes liver injury

An increasing amount of evidence has shown that SARS-CoV-2 can directly cause liver damage in COVID-19 patients. Tian *et al*[15] used reverse transcription polymerase chain reaction to detect the expression of SARS-CoV-2 nucleic acid in the liver of four cases of COVID-19, and the result was positive in one case. Wang *et al*[1] found a large number of liver cells apoptosis in the liver tissues of two cases patients with COVID-19 during the autopsy and SARS-CoV-2 virus particles in the liver cells through transmission electron microscopy.

SARS-CoV-2 mainly replicates in type II alveolar epithelial cells, which can cause tissue cell injury and destruction. The main manifestation of cell destruction is apoptosis[16]. Wang *et al*[1] also observed a large number of hepatocyte apoptosis and some binuclear hepatocytes in the autopsy of two COVID-19 patients. The hepatocellular lesion caused by SARS-CoV-2 infection is a typical viral infection. Therefore, Wang *et al*[1] believe that SARS-CoV-2 can directly cause liver injury.

The new coronavirus, like SARS virus, can use ACE2 as a receptor for cell entry[17-19]. There are differences in the expression of ACE2 in different tissues and even different cells in the same tissue[20,21]. Han *et al*[20] combined the Genotype-Tissue Expression and The Cancer Genome Atlas databases and found that ACE2 is most highly expressed in the small intestine, and the expression level is lower in the spleen, brain, muscle, pituitary, and skin tissues. It is also expressed in other tissues such as the kidney, heart, liver, and other tissues[20]. Chai *et al*[21] used the single-cell RNA sequencing method to determine that the expression of ACE2 in hepatic bile duct cells was significantly higher than that of hepatocytes (59.7% *vs* 2.6% of cells), and the average expression level of ACE2 mRNA in bile duct cells was 20 times higher than that of hepatocytes. Thus, it is speculated that the SARS-CoV-2 virus enters the bile duct cells through ACE2 to cause liver injury. However, based on current research, ACE2-expressing organs do not equally participate in COVID-19 pathophysiology, indicating that other mechanisms are involved in orchestrating cellular infection resulting in tissue injury[22]. However, clinical data show that some patients with COVID-19 do not have a significant increase in the serum indicators of bile duct cells such as ALP and γ-GT but do have increased ALT and AST levels, reflecting liver cell injury[23]. These data suggest that the specific causes of liver cell injury caused by SARS-CoV-2 virus still need a lot of research to clarify its mechanism. Other receptors (*e.g.*, dipeptidyl-peptidase 4, transmembrane serine protease 2) may also mediate the entry of SARS-CoV-2 virus into liver cells to cause liver injury[19,24]. It may even be caused by other mechanisms such as systemic inflammatory response, ischemia, and hypoxia[10].

Immune-mediated liver injury

As aforementioned, the main target organ of new coronary pneumonia is the lung, and immune dysfunction is one of the leading causes of lung injury. At present, the most discussed immune injury is the "cytokine storm", which is infection of the organism by microorganisms. Subsequent immune system-related reactions can further cause multiple organ injuries and acute respiratory distress syndrome to induce liver hypoxia and damage liver cells. Both of these reasons can lead to abnormal liver function indicators in the laboratory[25]. Studies have pointed out that in critically ill patients, the abnormal ratio and degree of cytoinflammatory factors are significantly higher than those in moderate to severe patients[26,27], accompanied by an increase in the proportion of neutrophils and lymphopenia[28]. Nevertheless, in critically ill patients, the probability and degree of liver injury are significantly higher than those of mild to moderate patients. In a large cohort of 5771 people, it was found that elevated ALT and AST were accompanied by lymphopenia and increased neutrophil count[28]. A retrospective study by Huang *et al*[29] found that the increase of cytoinflammatory factors, namely interleukin (IL)-1, IL-6, IL-8, and IL2R is negatively correlated with the reduction of albumin, and the liver is the main organ for albumin synthesis. This also further illustrates that the "cytokine storm" may be one of the potential causes of liver injury (Figure 1). In a recent study in the United States, it was noted that the systemic inflammatory response was excessive in patients with acute liver failure, which was manifested by significantly increased levels of inflammatory markers and cytokines, and the elevated levels of inflammatory markers were linearly related to the number of organ failures. The authors believed that it may be the inflammatory response in patients with new coronary pneumonia that triggers the occurrence of acute liver failure in patients with potential chronic liver disease[30].

Drug-induced liver injury

Drug-induced liver injuries in patients with COVID-19 is a factor that cannot be ignored[31]. According to the "New Coronavirus Infection Pneumonia Diagnosis and Treatment Program"[32], antiviral is one of the main treatment measures, and multiple antiviral drugs such as remdesivir, arbidol, darunavir, and lopinavir are recommended. Liver injury side effects can occur in these drugs[33]. In Fan *et al*[7]'s case-control study, the proportion of liver dysfunction who received ribinavir or lobinavir antiviral treatment was significantly higher than that of those who did not receive these two antiviral treatments, which confirmed that ribinavir or lobinavir navir antiviral drugs can cause liver injury. It is generally believed that the pathogenesis of liver injury from antiviral drugs is related to mitochondrial toxicity, hypersensitivity, and inducing autoimmune hepatitis[34]. Chloroquine (CQ) is an antimalarial that has been used for 70 years; it and its derivative, hydroxychloroquine (HCQ), have attracted wide attention for treating COVID-19[35]. To date, it remains uncertain whether CQ and HCQ are beneficial antiviral drugs for combating COVID-19[35]. There are many reports on the cardiac toxicity of CQ and HCQ, but few reports on liver injury[35,36]. Traditional Chinese medicine (TCM) plays an essential role in treating the new coronary pneumonia, but it can also cause liver injuries[37]. According to the different chemical structures of the risk ingredients in TCM, they are divided into alkaloids, glycosides, toxic proteins, terpenoids and lactones, anthraquinones, and heavy metals[37]. Mechanisms of the hepatotoxic ingredients in TCM-induced hepatotoxicity include cytochrome P450 (CYP450) induction, mitochondrial dysfunction, oxidative damage, apoptosis, and idiosyncratic reaction[37].

Impact of underlying diseases on patients' liver function

Generally, chronic diseases such as hypertension, diabetes, cardiovascular disease, chronic lung disease, chronic liver disease, and chronic kidney disease are one of the reasons for the severity of coronary pneumonia[38]. Ji *et al*[39] also concluded that patients with chronic obstructive pulmonary disease progress faster than patients without chronic obstructive pulmonary disease. Clinical studies have shown that the abnormal rate and average value of serum ALT and AST levels of SARS-CoV-2-infected patients with hepatitis B virus (HBV) are higher than those in SARS-CoV-2 patients without HBV infection, which indicates that HBV is one of the risk factors for liver injury in COVID-19 patients[40]. Compared with COVID-19 without HBV infection group, patients with dual infection had a higher proportion of severe/critically ill disease, higher levels of ALT, AST and activated partial thromboplastin[41]. Of course, there are clinical reports that the abnormalities of liver function are not uncommon on COVID-19 patients with chronic HBV infection in a case series[42]. These contradictory results need to be further screened by big data.

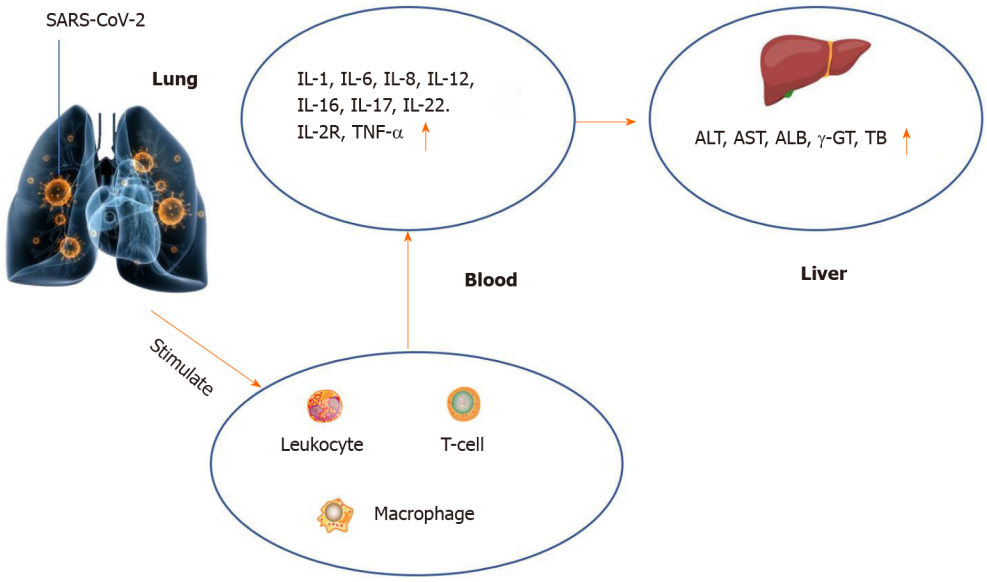

Figure 1 Cytokine-mediated liver injury sketch map. ALB: Alkaline phosphatase; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; γ-GT: γ-Glutamyl transpeptidase; IL: Interleukin; IL-2R: Interleukin-2 receptor; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; TB: Total bilirubin; TNF: Tumor necrosis factor.

Liver ischemia and hypoxia

The common symptoms of COVID-19 patients are fever and cough, with one-third of patients complaining of shortness of breath[43]. The author of this article reported that 9 out of 48 COVID-19 patients experienced dyspnea, accounting for about 18.8% of all patients[5]. Approximately one-third of patients may progress to acute respiratory distress syndrome requiring intensive care[43]. The results reported above suggest that after SARS-CoV-2 infection, ischemia and hypoxia in tissues and organs of COVID-19 patients is a common pathophysiological phenomenon[44]. Consequences of progressive hypoxia may include potentiation of viral proliferation, cytokine release, inflammation, intravascular coagulation, and pulmonary hypoxic vasoconstriction, which are also pathophysiologic characteristics of COVID-19 disease progression[43]. Liver ischemia and hypoxia, severe cases can cause hypoxic hepatitis[45].

PREVENTION AND TREATMENT OF COVID-19 COMBINED WITH LIVER INJURY

COVID-19 combined with liver injury has become a very prominent clinical problem. Timely detection and treatment are particularly important for the prevention and treatment of COVID-19 combined with liver injury.

Strengthen dynamic monitoring of liver function in COVID-19 patients

Since SARS-CoV-2 infection affects the whole body, which is necessary to monitor the body tissues and organs of all COVID-19 patients, including liver function. Routine examination items include liver function, various hepatitis virus markers, inflammatory factors (such as IL-6, C-reactive protein, procalcitonin), and bleeding coagulation function. If COVID-19 combined with liver injury is considered to be caused by basic diseases, blood glucose, blood lipids and other organ function indicators, which are such as B-type natriuretic peptides, N-terminal fragment brain natriuretic peptides or high-sensitivity troponin T must be monitored. Due to hypoxia progression may also be insidious in that patients may not be short of breath despite relatively low blood oxygen levels[43]. Therefore, whether patients with COVID-19 have breathing difficulties, blood oxygen saturation should be routinely monitored.

Timely stop or reduce the use of suspected liver injury drugs

When the liver function of COVID-19 patients is normal before hospitalization admission, and abnormalities gradually appear during the treatment process, the drug-induced liver injury should be considered[10]. The diagnosis of drug-induced

liver injury is exclusive. It needs to be combined with a medical history and related examinations to rule out other liver diseases, then causality assessment is used to determine the degree of correlation between liver injury and suspected drugs. For patients with suspected drug-induced liver injury, consideration should be given to discontinuing or reducing the use of suspicious drugs. For more details, please refer to the 2015 version of the "Guidelines for the diagnosis and treatment of drug-induced liver injury" for treatment[46].

Timely treatment of underlying diseases

If patients with chronic hepatitis B receive long-term antiviral therapy, the drug should not be stopped; those who need hormone therapy should also receive high-efficiency and low-resistance anti-hepatitis B drugs (*e.g.*, entecavir, tenofovir dipivoxil or propofol tenofovir) inhibit HBV replication from preventing HBV replication reactivation or hepatitis B attack[10]. For patients with hypertension, blood pressure needs to be closely monitored and maintained at a stable level[47]. For patients with coronary heart disease, it is recommended to actively control heart rate, stabilize hemodynamics, and protect the heart and other related treatments[47]. When COVID-19 patients have diabetes at the same time, for mild COVID-19 patients, if the patient's blood sugar is stable, the original hypoglycemic regimen can be used to control blood glucose. For critically severe COVID-19 patients, insulin pump is recommended to lower blood sugar, and the blood glucose range. It is recommended that fasting blood glucose be 7.8-10.0 mmol/L, and blood glucose should be controlled at 7.8-13.9 mmol/L 2 h after meal[47,48].

Rationally use of hepatoprotective drugs

There is currently no evidence that hepatoprotective drugs can improve the prognosis of patients, and patients with mild liver biochemical abnormalities generally do not need to use hepatoprotective drugs[10]. For patients with acute liver injury, the changes in liver function should be closely monitored, and 1-2 kinds of liver protection drugs with less side effects should be selected as appropriate[10]. Specific liver protection drugs include anti-oxidant hepatoprotective drugs and detoxification liver protection drugs such as reduced glutathione, glycyrrhizic acid liver protection drugs such as diammonium glycyrrhizinate capsules, magnesium magnesium isoglycyrrhizinate injection, liver cell membrane protection liver protection drugs such as polyene phosphatidyl choline, anti-oxidant hepatoprotective drugs such as silibinin and bicyclol, and cholinergic hepatoprotective drugs such as ursodeoxycholic acid and S-adenosylmethionine[49]. For patients with acute liver failure, actively carry out etiological treatment and symptomatic and supportive treatment. For details, please refer to China's "Guidelines for Diagnosis and Treatment of Liver Failure (2018 Edition)"[50].

Give effective oxygen therapy in time

COVID-19 patients have different degrees of hypoxemia, and many of them need to be given effective oxygen therapy in time[32]. Hypoxic hepatitis mostly occurs in severe or critical patients. At this time, liver injury is mostly caused by multiple organ dysfunction, ischemia and hypoxia. For patients with hypoxia, hypoxemia can be corrected by oxygen inhalation, mechanical ventilation, and airway management or extracorporeal membrane oxygenation; For patients with circulatory failure, vasoactive drugs can be used on the basis of fluid resuscitation to improve tissue perfusion. Used to improve oxygenation, reduce myocardial oxygen consumption, correct internal environment, remove inflammatory factors, and promote liver function recovery[10,32,44,45].

Choose appropriate antiviral drugs or methods

Antiviral therapy is a basic treatment. If the liver injuries associated with COVID-19 is not caused by antiviral drugs, antiviral treatment should be given as soon as possible to inhibit virus replication and accelerate virus clearance.

The eighth edition of the diagnosis and treatment plan recommends that the following drugs can continue to be tried and further evaluated in clinical applications[32]: α-interferon, ribavirin, CQ phosphate, and arbidol.

The current consensus is that antiviral drugs with potential antiviral effects should be used within 10 d after the onset of disease, because the virus is in the replication stage at this stage[51], and the combination use of two antiviral drugs is advocated[52].

Due to the unclear efficacy, some antiviral drugs are not recommended or cannot be used alone[53,54]. The eighth edition of the diagnosis and treatment plan does not

recommend the use of lopinavir/ritonavir and ribavirin alone, nor the use of HCQ or the combined use of azithromycin[32].

The efficacy of some drugs needs to be screened. Remdesivir is a drug officially approved by the United States Food and Drug Administration for the treatment of hospitalized patients with COVID-19, but the clinical efficacy results are conflicting[55,56].

When using antiviral drugs, pay attention to drug adverse reactions, con-traindications, and interactions with other drugs. It is not recommended to use more than 3 antiviral drugs at the same time[10].

If there are intolerable side effects such as liver injury, the relevant drugs should be stopped, and the convalescent plasma antiviral can be used when conditions permit. According to the currently available treatment data, plasma therapy for recovered patients is very effective for patients who still have viruses in their bodies[57,58]. In view of limited source of plasma sources in recovery patients from COVID-19, the development and use of therapeutic monoclonal antibodies against the new coronavirus is of great significant[59,60].

Choose appropriate anti-cytokine storm drugs or methods

Currently, treatments for cytokine storm caused by new coronavirus infection include: the IL-6 and receptor antagonists, blood purification, glucocorticoids, *etc*. Studies by Shruti Gupta and others found that among critically ill patients with new coronavirus pneumonia, patients treated with IL-6 receptor antagonist-cilizumab had a lower risk of in-hospital death during the first 2 d of admission to the intensive care unit. Patients treated with cilizumab early[61]. Stutuzumab is a drug that directly targets IL-6, which can directly bind to IL-6 to neutralize the biological effects caused by IL-6[62]. The efficacy of these two drugs on the cytokine storm caused by SARS-CoV-2 still needs further clinical trials to verify[63]. Since both cilizumab and stutuzumab can cause liver damage[63], it is recommended to avoid severe and critical COVID-19 patients with liver damage as much as possible. Glucocorticoids can be used to treat cytokine storm within a short period of time (generally recommended 3-5 d, no more than 10 d). For patients with drug-induced liver injury without contraindications, especially patients with severe liver injury, the early use of hormones is effective and safe[64]. On September 2, 2020, WHO also published a guidance document on the role of corticosteroids in the treatment of COVID-19[65]. In addition, blood purification can also be used for the early and mid-term treatment of cytokine storm in severe and critical COVID-19 patients with liver injury[10,32].

CONCLUSION

The prevention and treatment of COVID-19 combined with liver injury faces many challenges. First, the definition of COVID-19 combined with liver injury is not clear, the selected parameters and the statistics time are inconsistent, and the final conclusions on the incidence rate are consistent. Second, the etiology and mechanism of COVID-19 combined liver injury are not clear and need to be studied in depth. Third, there is a lack of effective treatment methods. The development and use of therapeutic monoclonal antibodies against the new coronavirus is of great significance.

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