ISSN 2220-3249 (online)

World Journal of *Virology*

World J Virol 2023 January 25; 12(1): 1-67

Published by Baishideng Publishing Group Inc

World Journal of Virology

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INDEXING/ABSTRACTING

The *WJV* is now abstracted and indexed in PubMed, PubMed Central, Reference Citation Analysis, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Superstar Journals Database.

RESPONSIBLE EDITORS FOR THIS ISSUE

NAME OF JOURNAL
World Journal of Virology

ISSN
ISSN 2220-3249 (online)

LAUNCH DATE
February 12, 2012

FREQUENCY
Bimonthly

EDITORS-IN-CHIEF
En-Qiang Chen, Mahmoud El-Bendary

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https://www.wjgnet.com/2220-3249/editorialboard.htm

PUBLICATION DATE
January 25, 2023

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World J Virol 2023 January 25; 12(1): 44-52

DOI: 10.5501/wjv.v12.i1.44

ISSN 2220-3249 (online)

MINIREVIEWS

Commentary on COVID-19-induced liver injury in various age and risk groups

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Specialty type: Gastroenterology and hepatology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): D
Grade E (Poor): 0

P-Reviewer: Gulyaev SA, Russia; Nooripour R, Iran

Received: September 25, 2022
Peer-review started: September 25, 2022
First decision: November 5, 2022
Revised: November 15, 2022
Accepted: December 21, 2022
Article in press: December 21, 2022
Published online: January 25, 2023

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Abstract

Towards the end of 2019, a new type of coronavirus, severe acute respiratory syndrome, emerged in the city of Wuhan in China's Hubei Province. The first occurrence was described as a case of pneumonia. Coronavirus disease 2019 (COVID-19) can progress primarily with symptoms varying from a mild upper respiratory tract infection to severe pneumonia, acute respiratory distress syndrome, and death. Determining the mechanisms of action of this virus, which can affect all systems including gastrointestinal, is vital for predicting the progression of the disease and managing its treatment. It is important to demonstrate the mechanisms of action of COVID-19 in patients without a previously known chronic or systemic disease. Although there is still no specific treatment for the virus, various algorithms have been created. As a result of the applied algorithms, the response to the treatment was satisfactory in some patients, while unexpected side effects occurred in some patients. It helps to clarify whether the unwanted effects that occur are due to the effect of the disease or the side effects of the drugs used in the treatment. There is currently increasing interest in COVID-19 interaction with liver tissue. Therefore, we would like to discuss the details of liver injury/dysfunction in the current literature.

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

Core Tip: Coronavirus disease 2019 (COVID-19) can progress primarily with symptoms ranging from a mild upper respiratory tract infection to severe pneumonia, hepatic injury, and even death. There is currently increasing interest in COVID-19 interaction with liver tissue. We would like to discuss the details of liver injury/dysfunction in COVID-19 in the current literature.

Citation: Özdemir Ö, Arsoy HEM. Commentary on COVID-19-induced liver injury in various age and risk groups. *World J Virol* 2023; 12(1): 44-52
URL: https://www.wjgnet.com/2220-3249/full/v12/i1/44.htm
DOI: https://dx.doi.org/10.5501/wjv.v12.i1.44

INTRODUCTION

Hepatotropic viruses replicate in their main target liver, which can be involved in these viruses' infections. The host is mostly afflicted as a consequence of the immune response to viruses like hepatitis A, hepatitis B, hepatitis C, and hepatitis E viruses which can be a known reason for hepatitis and liver damage[1]. In non-hepatotropic viral infections like severe acute respiratory syndrome (SARS), Epstein-Barr virus infection, *etc.*, it is known that the liver is mainly affected as a result of immune infiltrates and reactions that occur as a result of the virus-induced immune system response. The result of this effect can range from mildly irregular liver biochemistry to fulminant hepatic failure. The liver is also affected by infections such as adenovirus, cytomegalovirus, and other opportunistic viruses in people with immunocompromised and other immune system disorders[2].

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is identified to result in severe acute respiratory syndrome through its host cell receptor, angiotensin-converting enzyme 2 (ACE-2). As a part of multi-organ involvement, cardiac, kidney, and liver injury can be seen[3]. The fact that coronavirus disease 2019 (COVID-19) is more important than diseases caused by many other viruses and needs to be investigated is its high mortality. In a meta-analysis of 3772 patients acquired from 326 studies examining SARS-CoV-2 and liver damage, it was demonstrated that there is a link between liver dysfunction and fatality[4]. Interestingly, besides the respiratory system, a significant proportion of SARS and COVID-19 patients showed signs of liver damage of varying degrees, the mechanism and effect of which have yet to be determined (Table 1).

PREVALENCE OF LIVER INJURY IN COVID-19

The prevalence of liver damage in COVID-19 patients differed from 16% to 29%. A meta-analysis showed that the rate of liver dysfunction among COVID-19 cases was 27.4%[5,6]. Fu *et al*[7] collected data from 355 patients in China and demonstrated that 39.6% of COVID-19 cases were afflicted with cholestasis, 51.9% with hypoproteinemia, and 39.0% with hepatocellular injury at presentation.

SUPPOSED MECHANISMS OF LIVER INJURY

The etiology of acute liver injury in COVID-19 patients remains unclear but is likely to be multifactorial (Table 1). It is supposed that it may be due to the direct invasion of hepatocytes by viruses, immune-mediated damage, the toxicity of drugs utilized in the treatment, hypoxia, ischemia, endothelial dysfunction, microthrombi formation, systemic inflammatory response syndrome, sepsis, or exacerbation of underlying liver disease[8].

ACE-2 receptors can be demonstrated in hepatic cholangiocytes and hepatocytes. These receptors make the gastrointestinal system a target for SARS-CoV-2 infection, which can vigorously infect and reproduce. The strong affinity of the SARS-CoV-2, particularly to cholangiocytes, results from a high binding rate to the ACE-2 receptor, which suggests that it is related to impaired hepatic function[9,10]. In a study, cell type-specific expression of ACE-2 was investigated in healthy liver tissues. The researchers showed that the virus can bind directly to ACE-2-positive cholangiocytes, but not hepatocytes. This finding suggests that liver abnormalities of SARS and COVID-19 patients are due to cholangiocyte dysfunction, not hepatocyte damage. What is confusing at this point is that in many studies conducted in China, elevation in aspartate aminotransferase (AST) instead of γ-glutamyl transpeptidase (GGT) and alkaline phosphatase (ALP) indicates cholangiocyte and bile duct damage [11]. But it should be in mind that this occurs only infrequently on hepatocytes, nevertheless it may be upregulated on hepatocytes during periods of physiologic stress[12]. Myalgia or myositis are also common symptoms in COVID-19 patients. Therefore, it may be necessary to examine the elevations in lactate dehydrogenase and creatinine kinase in COVID-19. The AST elevations observed in this circumstance can be ascribed to some degree to muscle injury[13].

In addition, it is known that patients with COVID-19 have severe hypoxia, and this hypoxemia significantly affects all organs, including the liver. As a part of SARS-CoV-2 infection in severe acute respiratory syndrome, capability to trigger severe hypoxia that was recalcitrant to the management of high inspired fractions of oxygen and high mean airway pressures was observed. Hypoxic hepatic damage is noticeable by alanine aminotransferase (ALT)/AST elevations owing to oxygen imbalance.

Table 1 Events in the liver from a broad perspective of severe acute respiratory syndrome coronavirus 2 infection

Effect	Mechanism	Result	Outcomes and morphological changes
SARS-CoV-2 virus	Genomic translations and replication	More viruses in circulation	Inflammation features. Usually, the biliary intrahepatic tree and bile duct did not show any significant histological alteration. Actin smooth muscle antibodies existed in pericytes which were in portal vein walls and adventitial areas
Viral proteins of SARS-CoV-2	SIRS -> stimulate cytokine storm	Increased TNF-α, IL-6, IL-1β, IL-2, IL-8, CCL2, CCL3, CCL5, CXCL10 levels. Decreased ($CD4^+$) T cell and NK cell counts	Increase in the number of portal vein branches associated with lumen massive dilatation and focal periportal abnormal vessels. Portal vein endotheliitis (fragmented smooth muscle layer). Scattered portal and lobular lymphocytes. Extremely activated Kupffer cells with large cytoplasm containing necrotic debris
Hypoxia	Hypoxic ischemic injury of all organs and also liver	Decreased SpO2 levels, mitochondrial dysfunction, and hypoxic hepatocytes express higher ACE-2 levels	Partial or complete luminal thrombosis of the portal and sinusoidal vessels, focal portal vein parietal fibrosis, enlarged and fibrotic vessels. A diffuse network of sinusoids decorated by CD34 suggests a disturbed circulation of blood within the liver
Drugs (antivirals, immune stimulants)	Liver damage	Increase in ALT, AST, LDH, CRP, D-dimer, ferritin, and bilirubin levels and a decrease in albumin levels	Portal fibrosis, lobular and mild portal inflammation
Drugs and viral proteins	The cytopathic effect, oxidative imbalance	Apoptosis and steatosis	Small and/or large droplets of steatosis in hepatocytes

ACE-2: Angiotensin-converting enzyme 2; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; LDH: Lactate dehydrogenase; CRP: C-reactive protein; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; SIRS: Systemic inflammatory response syndrome; TNF-α: Tumour necrosis factor-alpha; IL: Interleukin.

This shows that severe hypoxia may be one of the pathophysiological elements of hepatic injury in COVID-19[13,14].

Therapeutic agents, *e.g.*, hydroxychloroquine, immune modulators (tocilizumab, steroids, and anakinra), anti-retroviral drugs (remdesivir, favipiravir, and lopinavir), antibiotics (azithromycin and ceftriaxone), and antipyretics (paracetamol and ibuprofen), which are utilized in the management of COVID-19, also have hepatotoxic effects. Patients are recommended to have regular follow-ups who have management with single and/or combined use of these potential hepatotoxic drugs for possible hepatic injury[8,13].

The existence of viral particles in the feces of infected cases indicates that the gastrointestinal system is affected by SARS-CoV-2. This is another reflection that demonstrates the possible direct impact of SARS-CoV-2 on liver tissue, provided the close association between the bowel and the liver. The exact mechanisms of this suggested direct injury route are yet to be explained[15]. Even the gut microbiome is important at this point since ACE-2 is also expressed in the luminal intestinal epithelium. With the attachment of SARS-CoV-2 to the ACE-2 receptor, intestinal permeability and inflammation increase. All these events increase the risk of bacterial translocation, which leads to dysregulation of the gut microbiome and, *via* this pathway, to Gram-negative sepsis, through portal circulation[16]. This translocation is also partially responsible for liver damage in COVID-19 patients[17].

PATHOGENESIS

SARS-CoV-2 is a new positive-strand RNA virus from the beta coronavirus family and has a glycolipid envelope. The virus connects to the host's ACE-2 receptor to start an infection. The viral access and reproduction process begins. ACE-2 is existing in cardiomyocytes and most endothelial cells except for those lining the liver sinusoids, lungs, bile ducts, bowels, and kidneys[18]. The spike protein (S protein) is located on the SARS-CoV-2 surface that will attach to ACE-2. After binding to the cell membrane, the virus is detained when the viral envelope fuses with the host membrane. Moreover, the type 2 transmembrane serine protease, which is present in host target cells (predominantly alveolar epithelial type II cells), stimulates viral uptake. The viral genome accesses the cytoplasm and is converted to produce new virions. After the virus enters the cell by fusion with the host membrane, an antiviral immune response begins with the viral nucleocapsid proteins remaining on the cell surface. These viral nucleocapsid proteins are recognized by antigen-presenting cells. Viral antigens are passed to cytotoxic ($CD8^+$) and regulatory ($CD4^+$) T lymphocytes by major histocompatibility complexes, also known as human leukocyte antigens[19].

Viral-specific $CD8^+$ T cells stimulated as a response to viruses affecting organs other than the liver are thought to be involved in the manifestation of T cell-mediated hepatitis lacking viral antigens in the

liver. Even with the extrahepatic influence of viruses, liver damage can be seen when no virus is detected in the liver. Because most strains of these viruses infect only the epithelial cells of the airway and therefore viral antigens should not be existing in the liver. This phenomenon was detected by the effect of the influenza virus and defined as collateral damage[20].

Previous studies on viral infections other than SARS-CoV-2 are therefore important and show that the liver is involved in diseases not only by antigen-specific T-cell response activation but also by some clinical hepatic inflammation syndromes that are not easily explained. It is expected that lymphocytes are caught in the liver sinusoids and cause occlusion, reducing blood flow, and infiltrates consisting of inactivated lymphocytes are expected to increase liver damage. All of these and more may cause more liver damage with the effect of autoimmunity. Exacerbated inflammation in response to SARS-CoV-2 is also a cause of immune damage. The immense discharge of cytokines by the immune system in reaction to the viral infection can cause a cytokine storm and symptoms of sepsis that are the reasons for fatality in 28% of mortal COVID-19 patients[21].

OTHER ETIOPATHOGENETIC FACTORS IN LIVER DAMAGE INDUCED BY SARS-COV-2

Preexisting liver diseases

The relationship between chronic or dormant liver diseases and COVID-19 has been investigated in many studies. In the frequency of COVID-19, a higher number has not been determined in patients with previous liver disease, unlike the general population. Two to five percent of COVID-19 cases had known liver disease before contracting COVID-19. However, there is an opinion that there may be an increase in severe COVID-19 and death in chronic liver patients[5]. As liver damage increases, patients begin to worsen in their clinical condition and prognosis. Established hepatic diseases may have adversarial effects on COVID-19 prognosis, including severity, fatality, and need for mechanical ventilation[22].

Liver transplantation

After the liver transplantation in approximately 700 children with chronic liver disease, only three had SARS-CoV-2 infection and no lung or other system disease such as pneumonia was observed in these patients[23]. Also, in a different study that included data on 151 Liver transplant adults, six recipients fell ill with COVID-19, while three long-term liver transplant recipients died. Data from liver transplant recipients continue to be organized in the form of case reports[24]. It should be kept in mind that patients with liver transplantation receive immunosuppressive treatments and these treatments may initiate cytokine storms or increase viral spread with an asymptomatic course in mild COVID-19 infections[25].

Cholestatic liver disease

Considering the cells and organs where ACE-2 receptors are located, it is expected to be affected in cholestatic liver disease. The fatality rate was higher in patients with cholestasis[22].

Cirrhosis

The incidence of COVID-19 varies widely in patients with cirrhosis. In a study that analyses cirrhosis patients in China, it was reported that 5 of 16 cirrhosis patients died[26]. The reason can be cirrhosis-associated immune dysfunction. They are more likely to have poor outcomes from ARDS.

Other liver diseases

All liver diseases have interactions with COVID-19 resulting from their specific disorder[26]. Chronic low-grade inflammation known to be associated with metabolic dysfunction-associated fatty liver disease may worsen COVID-19 outcomes[22,27,28].

EFFECTS OF VARIOUS AGE AND RISK GROUPS ON LIVER INJURY

When the literature is examined, the striking point is that SARS-CoV-2 does not occur with the same clinical features in patients. Since the severity of the disease is also related to the liver, liver involvement is not the same in every patient. Liver injury varies in patients having previously known blood disease, susceptibility to thrombosis for portal/hepatic thrombosis or immunosuppression, *etc.*[29]. Risk factors such as age, gender, previous diseases, chronic or acute health status, various medications, coronary artery diseases, metabolic diseases, serologies for other viruses related to hepatitis, and other etiologies affect the severity of the disease[3,8].

Elevated liver enzymes were more frequent in males with severe COVID-19 than in females[30]. Also, male gender, older age, and lymphopenia were three important independent risk elements forecasting hepatic dysfunction among COVID-19 cases[7]. Additionally, a clinical study showed that pulmonary failure was related to poor prognostic indicators of hepatic failure[31].

When the pediatric group is examined, only scarcely data is in the pediatric literature. We believe that the reason for this may be a milder course or asymptomatic transmission of SARS-CoV-2 infection in children[32]. In the data of a study that examined SARS-CoV-2 infection by dividing it into two groups, the data of children who had COVID-19, the first group, and that of multi-system inflammatory syndrome in children and adolescents (MIS-C), the second group, were shared. Elevated ALT was found in 36% of the 291 patients, with 31% having COVID-19, and 51% having MIS-C. High levels of ALT in COVID-19 were accompanied by obesity, immune-compromised status, and chronic hepatic disease. Children with elevated ALT and MIS-C were more often boys. Children with MIS-C had a 2.3-fold augmented risk of high ALT compared to COVID-19. No relationship was detected between elevated ALT and fatality[29].

EFFECTS OF DRUGS ON COVID-19-INDUCED LIVER INJURY

With the onset of the pandemic, various guidelines have been published for the treatment algorithm for COVID-19. Some drugs have been removed from the list due to their side effects and benefits. Currently, no specific drug for the SARS-CoV-2 virus has been discovered, and studies on this subject are continuing. The effects of the commonly used medications on the liver are examined.

Remdesivir

Remdesivir is a nucleotide analog prodrug with antiviral activity against SARS-CoV-2. Recently, the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) endorsed remdesivir for the management of cases admitted with severe COVID-19. The most common adverse drug reaction reported in hospitalized patients treated with remdesivir with a diagnosis of severe COVID-19 was elevations in liver enzymes. There is limited data on the number of patients exposed to remdesivir in clinical studies reporting severe hepatotoxicity or drug-induced liver injury[33].

Adverse effects reported in at least 5% of all patients in remdesivir trials were decreased glomerular filtration rate, a decline in hemoglobin level, decreased lymphocyte count, pyrexia, increase in blood glucose and creatinine level, transaminase elevations, *etc.*, whose rates were generally similar between remdesivir and placebo[34]. In general, when the adverse events in the remdesivir group and the placebo group were compared, adversarial events were detected in 102 (66%) of 155 remdesivir users and 50 (64%) of 78 placebo users. However, 18 (12%) patients in the remdesivir group and 4 (5%) patients in the placebo group had to be discontinued early due to side effects (including gastrointestinal symptoms, aminotransferase or bilirubin elevations, and worsening cardiopulmonary status), which is more frequent with remdesivir than with placebo. However, when we examined the liver enzymes in cases where treatment was required to be terminated, it was observed that there was an indication in only three (2%) patients in the remdesivir group due to the increase in aspartate aminotransferase[35]. In a more comprehensive study describing the drug-induced liver injury and liver disorders caused by remdesivir, the data were different. Among 387 events with remdesivir listed in VigiBase, 130 hepatic adverse events (34%) were described; they were the most frequent adverse drug reactions. One hundred and fourteen cases had elevated liver transaminases. A more pronounced correlation of the incidence of hepatic failure has been reported with the use of remdesivir compared with hydroxychloroquine, lopinavir/ritonavir, or tocilizumab (odds ratio, 1.94; 95% confidence interval, 1.54-2.45)[36].

Baricitinib and JAK (Janus kinase) inhibitors

Tofacitinib and baricitinib are immunomodulators that are thought to have potent antiviral effects through interference with viral entry. There is not enough data on the side effects on the liver in clinical trials[37].

IL-6 pathway inhibitors (e.g., tocilizumab)

Serious adverse events in the trials were not greater with IL-6 pathway inhibitors than with comparators. It has been discussed in some studies that these inhibitors may be associated with an increased risk of secondary infections[38]. Tocilizumab and baricitinib which are used widely in COVID-19 may also cause HBV reactivation[37].

Glucocorticosteroids

Glucocorticosteroids may result in hepatic steatosis (fatty liver) that can infrequently cause systemic fat embolism or cirrhosis as an adverse effect[39].

Non-steroidal anti-inflammatory drugs

The use of paracetamol was considered relatively safe after the especially beginning of the COVID-19 epidemic and the effect of ibuprofen on ACE receptors was revealed. Therefore, patients suffering from COVID-19 frequently consumed paracetamol for its antipyretic and analgesic effects[40]. It is known that the effects of paracetamol are generally dose-dependent. However, hepatotoxicity risk can be seen

at levels much lower than the expected dose, even at therapeutic doses. At this point, genetic characteristics and metabolic differences may be due to immune-mediated mechanisms[41].

Non-steroidal anti-inflammatory drugs (NSAIDs) impede cyclooxygenase (COX)-1 and COX-2. Significant and well-known common side effects are on the gastrointestinal and renal systems. There are cases of liver toxicity reported and frequently encountered in the literature[42]. Currently, there is no strong evidence about the safety of the use of NSAIDs in COVID-19 patients[43].

HISTOLOGICAL FINDINGS OF LIVER INJURY INDUCED BY SARS-COV-2

Hepatic histology in cases with COVID-19 is nonspecific, comprising moderate microvesicular steatosis with mild, mixed lobular and portal activity and focal necrosis. In a series of 48 autopsies, pathologic hepatic outcomes consisted of focal portal and lobular lymphocytic infiltrates and changes indicative of hepatic vascular participation[44]. In another study conducted with the liver samples of 40 patients who died due to COVID-19, hepatic involvement was observed in all of the patients. Macrovesicular steatosis was the most frequent (30 cases, 75%), followed by mild lobular necroinflammation and portal inflammation (20 patients each, 50%). Vascular pathology, including sinusoidal microthrombi, was rare and observed in six (15%) cases. PCR using hepatic tissue samples was positive in 11 of 20 cases tested, but quantifying viral load in the liver is lacking[45].

DIFFERENT LABORATORY FINDINGS INDICATIVE OF LIVER INJURY INDUCED BY SARS-COV-2

An increase in liver transaminases has been detected in approximately two-thirds of patients with severe COVID-19. The analysis demonstrated that the more severe the coronavirus infection, the greater the levels of ALT, AST, total bilirubin, ALP, and GGT, and the lesser the level of albumin[46]. Mean levels of AST and ALT over 400 U/L have been reported[47]. Low albumin has been associated with severe COVID-19. Nevertheless, it is uncertain if hypoalbuminemia is a risk element for severe COVID-19 or if hypoalbuminemia is a consequence of severe COVID-19[7,48]. Although they are rare, cases progressing from liver damage to ischemia have been reported[49]. Liver functional indexes of two-thirds of COVID-19 cases stay abnormal 14 d after discharge[7].

BRIEF SUMMARY OF OUR OPINION

COVID-19 is still a multisystemic disease with many unknowns. It is known today that it affects the liver, albeit indirectly, as it has on all systems. Due to its mortal course, the disease has been tried to be treated with rapidly created emergency treatments and algorithms. However, the effectiveness of these treatments, which are performed without knowing the effects of SARS-CoV-2 on the organs, is controversial. It is an already known fact that more studies are needed on the virus and the pathogenesis of COVID-19. However, the side effects of drugs should also be analyzed in detail. The treatment and algorithms of liver failure, especially seen in the severe patient group, are confusing. Things to do in liver involvement due to virus and liver effects that can be seen due to drug side effects may be completely different. While it is necessary to ensure that the liver recovers from the cytopathic effects of the virus with the least damage and continues to fight the disease, it should also be noted that liver failure can be triggered by the drugs applied for this. In these two different situations, different procedures need to be implemented. At this point, we think that histopathological data can be used as we have mentioned in detail in our article. We would like to draw attention to the fact that most of the histopathology data were made postmortem in the studies. We can suggest that liver biopsy should be performed in patients with appropriate clinical status before the treatment procedures are discontinued or changed, and histopathological and immunological examinations should be on the agenda. Although liver biopsy is an invasive and costly procedure, we think that the data obtained may be useful in explaining the liver pathologies of the patients, as well as in providing an idea about the side effects of drugs and in the follow-up of the patients.

CONCLUSION

Liver diseases in COVID-19 have been studied in different groups, from mild to severe and chronic. In light of these studies, our general opinion is that SARS-CoV-2 infection will be more fatal in the case of liver disease. We think that both the direct injury to the liver and other etiological factors including the drugs used have an effect. Exploring liver injury related to COVID-19 has an important role in the

estimation of fatality and might be used for the creation of prognostic tools to recognize cases with possible worse consequences.

FOOTNOTES

Author contributions: Özdemir Ö and HE Melek Arsoy wrote the mini-review.

Conflict-of-interest statement: All the authors declare that they have no conflict of interest to disclose.

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S-Editor: Liu JH
L-Editor: Wang TQ
P-Editor: Liu JH

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