**Name of Journal:** *World Journal of Virology*

**Manuscript NO:** 66296

**Manuscript Type:** MINIREVIEWS

**Impact of COVID-19 on liver disease: From the experimental to the clinic perspective**

Gato S *et al*. Impact of COVID-19 on liver disease

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**Author contributions:** Ampuero J conceived and designed the review; Muñoz-Hernandez R, and Sousa JM collected data from the literature; Gato S, and Lucena-Valera A drafted the manuscript; Ampuero J and Romero-Gómez MR critically revised the manuscript.

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**Received:** March 24, 2021

**Revised:** May 18, 2021

**Accepted:** August 13, 2021

**Published online:** November 25, 2021

**Abstract**

Coronavirus disease 2019 (COVID-19) has caused a global pandemic unprecedented in over a century. Although severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a predominantly respiratory infection, various degrees of liver function abnormalities have been reported. Pre-existing liver disease in patients with SARS-CoV-2 infection has not been comprehensively evaluated in most studies, but it can critically compromise survival and trigger hepatic decompensation. The collapse of the healthcare services has negatively impacted the diagnosis, monitoring, and treatment of liver diseases in non-COVID-19 patients. In this review, we aim to discuss the impact of COVID-19 on liver disease from the experimental to the clinic perspective.

**Key Words:** SARS-CoV-2; COVID 19; Liver disease; Transaminases

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**Citation:** Gato S, Lucena-Valera A, Muñoz-Hernandez R, Sousa JM, Romero-Gómez M, Ampuero J. Impact of COVID-19 on liver disease: From the experimental to the clinic perspective. *World J Virol* 2021; 10(6): 301-311

URL: https://www.wjgnet.com/2220-3249/full/v10/i6/301.htm

DOI: https://dx.doi.org/10.5501/wjv.v10.i6.301

**Core Tip:** The outbreak of coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has posed a critical threat to global public health. Beyond the respiratory symptoms, some patients with COVID-19 show liver damage. In this scenario, it has been suggested that there might be a specific relationship between SARS-CoV-2 infection and liver injury.

**INTRODUCTION**

Coronaviruses are enveloped single-stranded RNA viruses belonging to the Coronaviridae family and Orthocoronavirinae subfamily[1]. They cause zoonotic infections in humans, predominantly associated with the upper respiratory tract[2]. Two coronaviruses caused relatively recent epidemics: severe acute respiratory syndrome coronavirus (SARS-CoV) in 2003 and the Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012[3].

The outbreak of coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), first reported in China in December 2019, has posed a critical threat to global public health[4,5]. Therefore, COVID-19 has been declared an international public health emergency by the World Health Organization (WHO). As of 21st March 2021, more than 122 million confirmed cases and over 2.7 million deaths have been reported[6] (Figure 1).

In most cases, the infection is followed by a benign course with usual characteristics of viral pneumonia, such as fever, dry cough, and lymphopenia. A relatively low percentage of patients require hospitalization and intensive care for acute respiratory failure secondary to diffuse alveolar damage. There is also an important incidence of extrapulmonary manifestations, such as acute kidney injury, cardiovascular disease, neurological disorders, or hypercoagulation[7].

On the other hand, some patients with COVID-19 show different degrees of liver injury, showing mainly elevated serum transaminase and lactate dehydrogenase levels and hypoalbuminemia[8-10]. In this scenario, it has been suggested that there might be a specific relationship between SARS-CoV-2 infection and liver injury. Thus, this article reviews the impact of COVID-19 on liver disease from the experimental to the clinic perspective.

**MECHANISMS OF LIVER DAMAGE IN COVID-19**

***Direct cytopathic effect of SARS-CoV-2***

As with SARS-CoV, angiotensin-converting enzyme 2 (ACE2) appears to be the susceptible receptor for SARS-CoV-2 and is expressed in more than 80% of lung alveolar cells. *In vitro* studies from the SARS epidemic identified ACE2 as the host receptor for viral entry[11], but in this new coronavirus, a recent study showed a 10-20-fold higher receptor binding affinity[12].

The hepatic distribution of ACE2 is quirky; it is highly expressed in the endothelial layer of small blood vessels but not in the sinusoidal endothelium. Indeed, a study revealed that the ACE2 cell surface receptor was more highly expressed in cholangiocytes (59.7%) than hepatocytes (2.6%). Both the level of ACE2 expression in cholangiocytes and lung alveolar type 2 cells are similar, indicating that the liver could be a potential target for SARS-CoV-2[13].

SARS-CoV-2 exerts a cytopathic effect by directly binding to ACE2 positive cholangiocytes. They are involved in liver physiology functions, including regeneration and adaptive immune response mechanisms; thus, their disruption can cause hepatobiliary damage. This is supported by cholestatic markers, including gamma-glutamyl transferase, which can be found in some case reports of COVID-19[14-16]. Permissiveness to SARS-CoV-2 infection was observed in a human organoid model of liver ductal organoids. In this experiment, the viral infection damaged the barrier and bile acid transporting functions of cholangiocytes through the dysregulation of genes implicated in tight junction formation and bile acid transportation, supporting the susceptibility of cholangiocytes in SARS-CoV-2 infection[17]. On the other hand, a significant increase in mitotic cells and ballooned hepatocytes was observed in liver biopsies of patients with SARS-associated coronavirus infection, suggesting that it may induce apoptosis of liver cells[18]. Moreover, the virus was detected in liver tissue, although the viral load was relatively low.

A recent study demonstrated that SARS-CoV-specific protein 7a induces apoptosis *via* a caspase-dependent pathway in cell lines of different organs, including the liver, further confirming the supposition that SARS-CoV-2 directly affects the liver tissue[19]. Nevertheless, some authors have refuted this hypothesis since the disorder of liver function is usually mild, and there is no evidence that late-onset symptoms are associated with greater liver damage[20].

***Host inflammatory response to SARS-CoV-2***

As we have described previously, liver injury in patients with COVID-19 might be due to the viral infection in liver cells. However, it might also be due to other causes such as drug-induced liver injury and systemic inflammation induced by cytokine storm or pneumonia-associated hypoxia[15].

A well-established driver of liver injury is hepatic inflammation, involving the activation of innate immune cells and the release of cytokines[21] (Figure 2). A possible cause of liver injury in COVID-19 can be the dysregulation of the innate immune response. Noticeable activation of inflammatory markers, including abnormal levels of C-reactive protein (CRP), lymphocytes, neutrophils, and cytokines - particularly interleukin-6 (IL-6) - are found in patients with COVID-19[15,22-24]. In some of the available case series of COVID-19, a correlation between lymphopenia and liver injury was observed. Moreover, high levels of CRP and a low lymphocyte count were independent risk factors for liver injury. Notably, lymphopenia in COVID-19 studies was observed in 63% to 70.3% of patients, and those with lower lymphocyte counts were more susceptible to fatal outcomes[22]. These impairments have also been reported in some systemic viral infections, such as cytomegalovirus, herpes simplex virus, Epstein-Barr virus, parvovirus, and adenovirus, in which we can also observe the immune activation and inflammation caused by circulating cytokines[25]. Furthermore, some studies have reported higher serum pro-inflammatory cytokines and chemokine levels in patients with abnormal liver function than those with normal liver function[22]. Hence, these data point to a relationship between liver damage and the inflammatory response induced by SARS-CoV-2 infection.

***Drug-induced liver injury***

The liver is involved in the metabolism of many drugs, and some therapeutic agents used to treat SARS-CoV-2 show potential hepatotoxicity. For example, alanine transaminase (ALT) and aspartate aminotransferase (AST) elevations were reported in 4%-6% of patients treated with remdesivir[26], and tocilizumab can also cause mild elevations in liver transaminases[27]. However, it seems unlikely that the leading cause of liver injury is the treatment as alterations in liver transaminases are usually reported at the time of hospital admission.

**FREQUENCY OF LIVER IMPAIRMENT IN COVID-19**

The prevalence of elevated liver enzymes occurs between 15% and 53% of patients with COVID-19[28,29]. The difference in the prevalence may be related to the exclusion of patients with a previous liver disease[30]. The most common disorder includes elevated aminotransferases (AST and ALT) up to 1-2 times the upper limit of normal, while the elevation of total bilirubin (TB) and alkaline phosphatase is less common. A recent study of 2073 patients with SARS-CoV-2 infection documented liver abnormalities in 1282 (61.8%) of these patients. This study observed liver impairment more frequently in patients with severe COVID-19. Besides, they described cholestasis and mixed types of liver abnormalities as independent variables associated with death[31]. Another recent meta-analysis that included more than 5000 patients from 26 studies also demonstrated that liver function (AST, ALT, and TB) was related to intensive care unit (ICU) admission and non-fatal severe complications[32]. The findings of these studies make us consider incorporating the liver profile to the routine inflammatory markers at the time of hospital admission in patients with SARS-CoV-2 infection to improve their management and anticipate the prognosis.

**ROLE OF PRE-EXISTING CHRONIC LIVER DISEASE**

Several studies have analyzed the impact of chronic liver disease on SARS-CoV-2 infection. First, the prevalence of underlying liver disease in hospitalized patients for COVID-19 ranges between 0.6% to 1.4%[33]. A recent international registry of 745 patients with chronic liver disease (CLD) and SARS-CoV-2 has observed an increased risk of major adverse outcomes and death in cirrhotic patients according to the Child-Pugh class[34]. In this study, a significant increase in ICU requirement, renal replacement therapy and rates of death according to Child Pugh class [A (19%), B (35%), C (51%)] has been observed. These findings have been demonstrated by other studies, proving an increase in complications and mortality with cirrhosis and Child Pugh score of 9 or more[35]. The mortality rate was 32%-34% for cirrhotic patients compared with CLD without cirrhosis, who had a similar risk of mortality than patients without any liver disease[36,37]. Although lung disease remained the predominant cause of death, SARS-CoV-2 infection appeared to precipitate acute hepatic decompensation in patients with cirrhosis[35,38].

The preexisting liver disease most often associated with COVID-19 is metabolic-associated fatty liver disease (MAFLD)[39]. A multicenter retrospective study by Zheng *et al*[40] demonstrated that the severity of SARS-CoV-2 infection was greater in patients with MAFLD and obesity[40,41].

There is disparity in the data on chronic hepatitis infection prevalence in COVID-19, with percentages ranging from 0.1% to more than 10% in relation to the prevalence of hepatotropic viruses in the area[42,43]. In China, a country with an intermediate-to-high prevalence of chronic hepatitis B (HBV) infection, a surprisingly low prevalence of chronic HBV in COVID-19 patients has been observed. Anugwom *et al*[44] have reported an incidence of HBV of 1.36%, while the corresponding rates of HBV ranged from 7% to 11% in patients without SARS-CoV-2. This may be explained by "immune exhaustion", as HBV infection provides an inadequate immune response during SARS-CoV-2 infection. Furthermore, chronic hepatitis infection does not appear to lead to a worse prognosis in patients with COVID-19[45]. This fact could be explained by the potential *in vitro* antiviral effect of the drugs used for chronic infection with hepatotropic viruses (inhibitors of the NS5A protein or nucleotide analogs)[46-48]. However, this has not been demonstrated in patients under active *in vivo* treatment[49,50].

Finally, the role of SARS-CoV-2 on autoimmune liver diseases has not been adequately evaluated. However, some studies have not observed a higher incidence of SARS-CoV-2 infection and severe complications than in the general population[51,52]. To date, there is no evidence to support or recommend a decrease or change in the immunosuppressive therapy in these patients.

**SARS-CoV-2 INFECTION AND LIVER TRANSPLANT PATIENTS**

In liver transplant (LT) recipients, immunosuppression following LT may increase the likelihood of SARS-CoV-2 infection[53,54]. Once a transplant recipient is infected with SARS-CoV-2, the virus may remain to infect for a longer duration due to higher viral titers and a prolonged replication period[55]. On the other hand, immunosuppressive agents could ameliorate the systemic inflammation induced by the cytokine storm[56].

Some of the available case series in LT patients with COVID-19 show a higher hospitalization rate (40%-86.5%)[54,57-60], as well as an increase in ICU admission requirements and invasive ventilation[59,61] in these patients. Despite the fact that mortality in LT recipients by COVID-19 is approximately 20% (8%-30.6%)[54,57-60], several studies have not shown that COVID-19-related mortality could be greater in hospitalized LT patients than in the general population[59,61]. Risk factors associated with poor prognosis in LT patients with COVID-19 are older age[53,57,60,62], diabetes mellitus[57-60], chronic kidney disease[60], and liver injury (ALT > 2 times ULN)[58].

On the other hand, it has not been clearly established how the immunosuppressive treatment influences the prognosis of LT patients with COVID-19. For instance, a study showed that mycophenolate might increase the risk of severe COVID-19 in a dose-dependent manner[54], while tacrolimus use has had a positive independent effect on survival[60]. Therefore, it could be concluded that increased disease severity and mortality in LT patients with COVID-19 is caused by the higher prevalence associated with comorbidities than by the effect of immunosuppressive treatment. In fact, in LT recipients without COVID-19, international guidelines recommend against reducing immunosuppression. However, in patients diagnosed with COVID-19, a reduction of immunosuppression should be considered.

**IMPACT OF THE PANDEMIC IN THE HEPATOLOGY UNITS**

Since the beginning of the SARS-CoV-2 pandemic, the healthcare system has supported a substantial impact, and the hepatology units have suffered notable changes in the organization. The access to medical consultations has been limited due to the hospital overload and strict orders to stay at home, the resources and staff reallocation have caused a decrease in the care of non-COVID pathologies. After a year of pandemic, the epidemiology of COVID-19 has proven to be unpredictable, however, it is urgent to anticipate and plan to mitigate the consequences of the pandemic and achieve a dynamic balance of resources.

***Screening of hepatocellular carcinoma***

The prevalence of hepatocellular carcinoma (HCC) has increased globally in the last few years. Significant efforts have been made to decrease HCC-related mortality. For this reason, HCC screening using imaging tests at regular intervals has been implemented and standardized, and is strongly recommended by the international clinical guidelines[63,64].

A recent retrospective study comprising 127 hospitals showed a significant diminution of HCC control during the pandemic, showing screening rates below 50% compared to 2019[65]. Other studies have also found similar results with a decreased HCC surveillance by ultrasound and, more important than this, a decrease in diagnostic tests such as computed tomography or magnetic resonance imaging[66]. Thus, a significant increase in HCC-related mortality could be observed in the next months.

On the other hand, the COVID-19 pandemic has also impacted the management of HCC patients. A recent French multicenter study of 670 patients described a significant decrease in the rate of patients with HCC referred for specific treatment. The rate of patients with a treatment delay of more than one month was higher in 2020 compared to 2019 (21.5% *vs* 9.5%, *P* < 0.001)[67].

***Screening of hepatitis C virus***

There were 1.7 million incident cases and 400000 deaths attributable to hepatitis C virus (HCV) in 2015; thus, this viral hepatitis has been recognized as a major cause of death[68]. A breakthrough in HCV treatment occurred in 2013 with the introduction of direct-acting antivirals. For this reason, the WHO approved some ambitious aims to eliminate HCV by 2030, including the reduction of new HCV cases by 80% and HCV-related deaths by 65% for 2030.

The pandemic has caused a slowing or even the halt of HCV elimination programs. The impact of COVID-19 on viral hepatitis in a recent survey has shown that only 47 (36%) of 132 responders could access viral hepatitis testing, and 28 people on treatment for hepatitis were unable to access their medication at this time[69]. Although the real impact is far from being seen, different studies have been carried out to measure the future consequences. Blach *et al*[70] using a previously validated Markov model, compared a “no delay” *vs* “one-year delay” scenario in elimination programs and evaluated changes in HCV liver-related deaths and liver cancer. Over the next ten years, the authors estimated that a single-year delay scenario could result in over 72300 liver-related deaths and 44800 excess cases of HCC[71].

To avoid the delay in HCV elimination programs, integrated circuits for massive and combined HCV, HBV, and SARS-CoV-2 diagnosis have been proposed[72]. Giacomelli *et al*[73] have developed a screening program using rapid immunochromatographic testing (RICT) for SARS-CoV-2 antibodies and a rapid HCV test in a single visit in three Italian cities. The results demonstrated that 2.9% of the tests were positive for HCV antibodies, and 54% of them did not know their serological status.

***LT programs***

During the SARS-CoV-2 pandemic, there has been an initial worldwide decline in the number of LTs for several reasons. Firstly, there has been a drastic decrease in liver donors, as well as in the availability of ICU beds for both donors and recipients. Secondly, testing organ donors for the presence of the virus is recommended, and those that are positive should be ineligible for donation. Thirdly, the evaluation of potential candidates for LT has been temporarily limited due to the lower availability of hospital resources, as well as to prevent exposure to SARS-CoV-2 in patients with advanced CLD. Finally, at the beginning of the pandemic, there was a temporary decrease in LT recommendations for patients at greater risk of worsening and mortality due to transplant delay: patients with acute liver failure, high MELD score, and HCC at upper limits of the Milan criteria[74-76].

In the United States (US), the impact on LT between March and August 2020 was evaluated using historical trends between 2016 and 2020. Within the first ten weeks of the pandemic, a dramatic decrease in new listings for LT (11%-21%), deceased donor LT (9%-13%), and living donor LT (42%-49%) was found. Besides, there was a reduction of 59% in patients included in the waiting list for LT. Despite these initial data, the mortality risk of LT waitlist candidates was not significantly different before and after COVID-19[77]. On the other hand, a national survey conducted in the US between March 24th and 31st 2020 showed that 67.7% of LT centers had stopped performing live donor LT[78]. A similar evolution in LT was observed in Italy. Considering the period of the first outbreak (March 1st–March 31st), a decrease of around 35% in LT was recorded due to the decrease in the number of donations[79]. In France, there was a 28% decrease in the number of organ donations in 2020 (543 in 2020 *vs* 752 organ donations in 2019) and a 22% decrease in the number of liver transplantations (435 in 2020 *vs* 556 in 2019)[80], comparing two similar periods (January 1st-May 31st 2019 *vs*. January 1st-May 31st 2020). In Spain, during the first COVID-19 wave (between March 13th-April 23rd), the mean number of donors decreased from 7.2 to 1.2 per day, and the weekly mean number of LTs decreased from 23.6 to 5.7[81]. Throughout the year 2020, the number of donors and LTs reduced by 22.8% and 15.7% (1034 *vs* 1227), respectively, compared to 2019[82].

**CONCLUSION**

It is accepted that SARS-CoV-2 infection can cause liver damage, representing a relevant outcome that affects the prognosis of COVID-19. A direct pathogenic effect on the liver, systemic inflammation, and immune dysfunction appear to play a relevant role in this association. In this scenario, liver function tests such as AST, ALT, and bilirubin levels at admission have been related to a poor COVID-19-related prognosis, including more ICU admission requirements and deaths. Finally, we must pay attention to maintaining an adequate monitoring and follow-up of patients with liver diseases, focusing on the risk of cirrhosis decompensation and HCC screening.

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**Footnotes**

**Conflict-of-interest statement:** No conflicts of interest.

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

**Peer-review started:** March 24, 2021

**First decision:** May 5, 2021

**Article in press:** August 13, 2021

**Specialty type:** Gastroenterology and hepatology

**Country/Territory of origin:** Spain

**Peer-review report’s scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): B

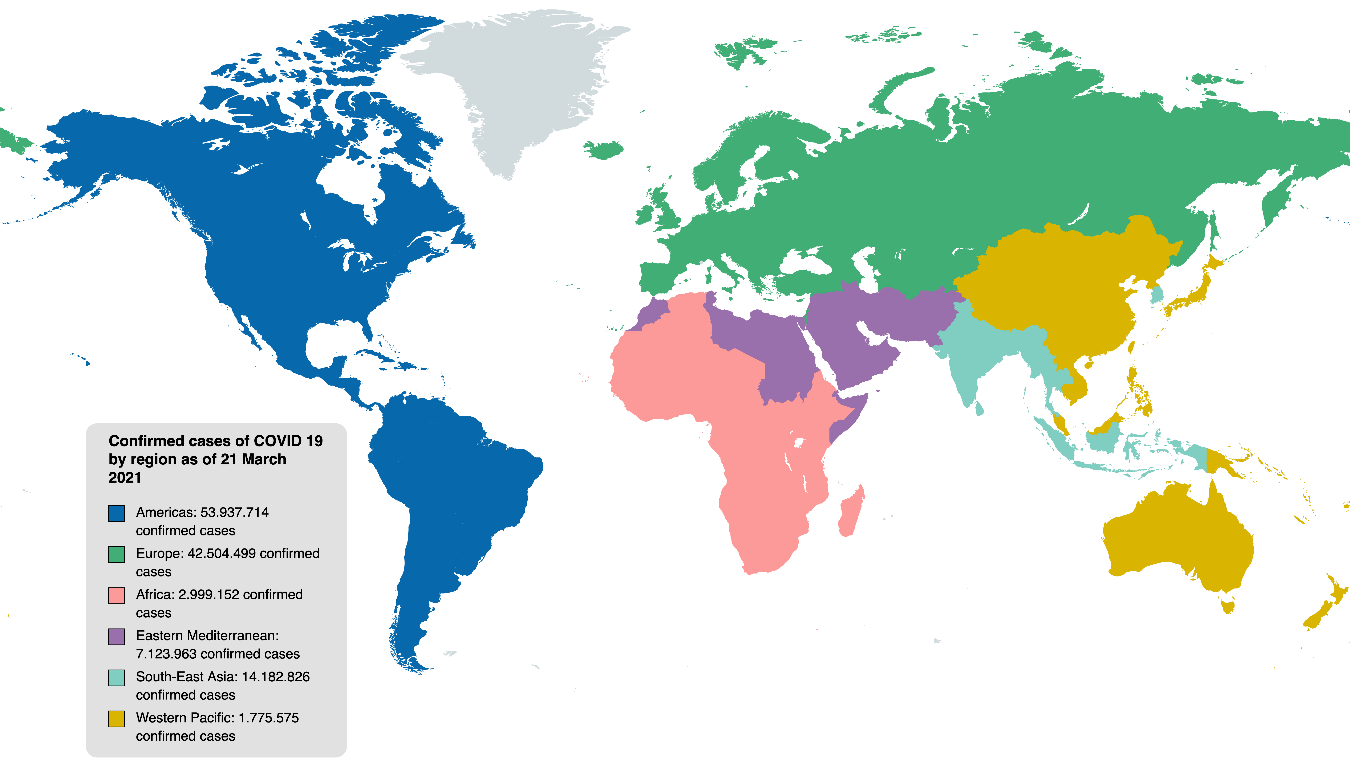
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Grade D (Fair): 0

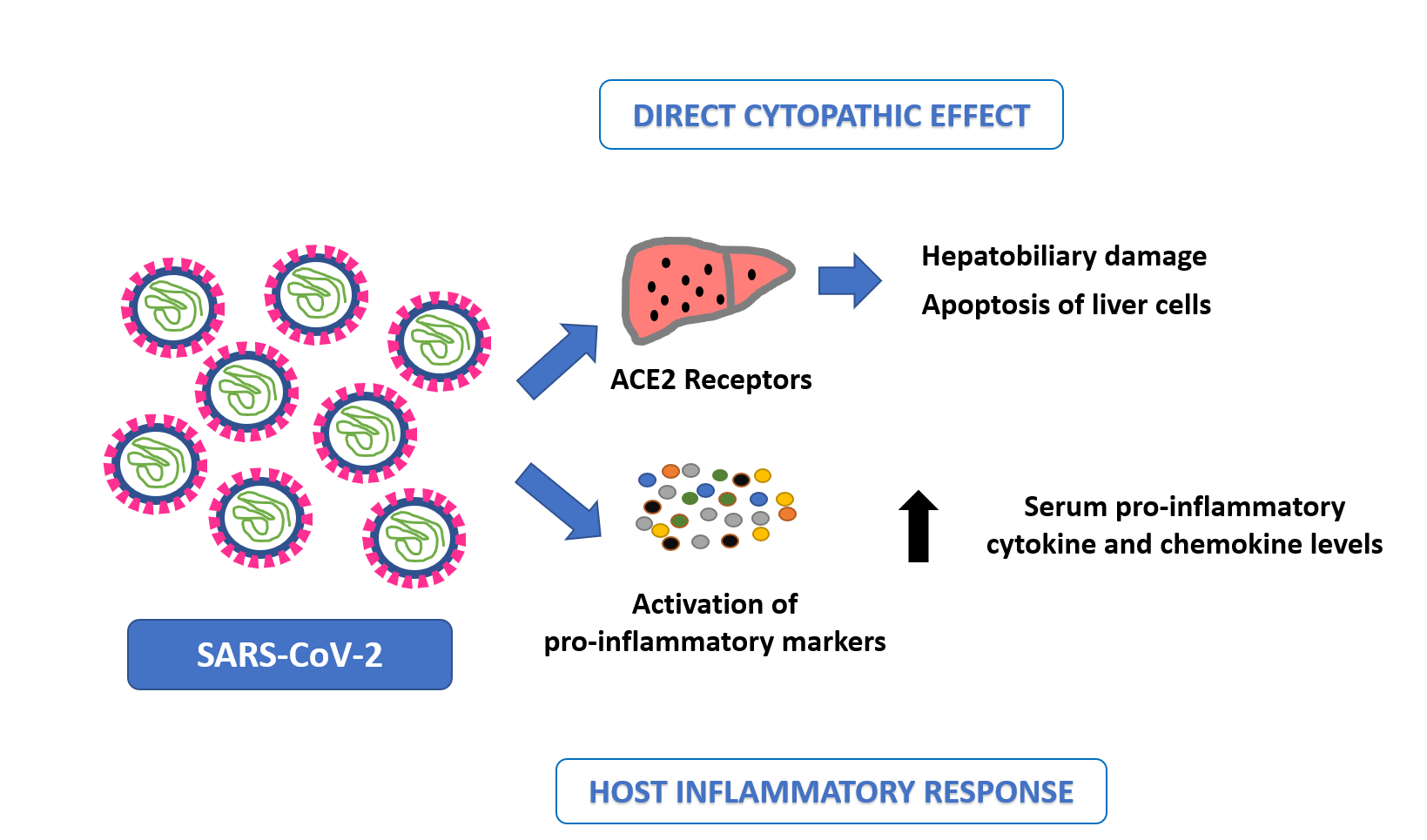
Grade E (Poor): 0

**P-Reviewer:** Fallatah H **S-Editor:** Wang JL **L-Editor:** Webster JR **P-Editor:** Xing YX

**Figure Legends**



**Figure 1 Coronavirus outbreak: World map of confirmed cases (updated March 21st, 2021).** COVID-19: Coronavirus disease 2019.

**Figure 2 Proposed mechanisms of liver injury related to severe acute respiratory syndrome coronavirus 2 infection.** SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.



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