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## Opinions

# COVID-19 and the liver: What do we know after six months of the pandemic?

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## ARTICLE INFO

## Article history:

Received 31 August 2020

Accepted 2 September 2020

Available online 18 September 2020

## Keywords:

Liver disease

SARS

COVID-19 symptoms

COVID-19 comorbidities

## ABSTRACT

Despite liver injury in patients infected with severe acute respiratory syndrome (SARS) coronavirus (CoV)-2 (SARS-CoV-2) is associated with prolonged hospitalization, and liver dysfunction is mainly described in patients with severe viral disease. How liver abnormalities may affect virus infection is still unknown. Improved understanding of host genetics, lifestyle, underlying comorbidities and adequate follow-up of patients with liver damage are critical in the new scenario of the pandemic virus.

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Severe acute respiratory syndrome (SARS) coronavirus (CoV)-2 (SARS-CoV-2), the etiological agent that causes coronavirus disease 2019 (COVID-19), which was declared a pandemic by the World Health Organization (WHO) in March 2020, presents primarily as a lower respiratory tract infection, but the multisystemic nature of the disease is apparent in severe cases. Indeed, a broad spectrum of symptoms associated with COVID-19 have been identified, which range from asymptomatic disease to mild and moderate symptoms and severe symptoms associated with critical illness resulting in acute respiratory distress syndrome, respiratory failure or multiorgan dysfunction and/or death.

Currently, fever and cough remain the most prevalent symptoms in adults infected by SARS-CoV-2 [2]. Cardiovascular and hematological complications are frequent and have been associated with poor prognosis. Gastrointestinal symptoms are also frequently encountered. Furthermore, recent studies have reported that over one-third of infected patients develop a broad spectrum of neurological symptoms. The skin, kidneys, endocrine organs, eyes and liver are also affected by systemic COVID-19 disease [1].

Although data on COVID-19-related liver abnormalities in patients remain limited, liver injury in patients is associated with prolonged hospitalization [3]. In this context, the article by Wong et al. in *Annals of Hepatology* reporting a systemic meta-analysis to assess the prevalence and degree of liver disease in severe and non-

severe SARS-CoV-2 infected individuals reveals that liver injury is mostly associated with severe forms of COVID-19 rather than non-severe disease [4]. The mean levels of ALT, AST and bilirubin are higher in the severe COVID-19 group than in the nonsevere group. This is in agreement with the elevated ALT/AST levels reported in 16–53% of patients at the beginning of the pandemic [5]. In addition, the incidence of hyperbilirubinemia is 1.7-fold increased among COVID-19 patients who are critically ill, and indirect markers of liver injury, including hypoalbuminemia, have been found to be increased by seven-fold in patients with severe COVID-19 [4].

The extensive range of symptoms associated with COVID-19 may be related to the tropism of the virus for angiotensin-converting enzyme 2 (ACE2), expressed on different human cells [1]. In particular, liver damage in patients with SARS-CoV-2 infection might be directly caused by the viral infection of liver cells, since ACE2 is expressed in both liver cells and bile duct cells [6], and pathological studies in patients infected with SARS identified in 2003 reveal the presence of the virus in liver tissue. The liver enzyme abnormalities might also be explained by the effect of antibiotics and antiviral drugs administered to patients and the infection-associated cytokine storm [5]. Moreover, underlying pre-existing liver diseases could contribute to liver ALT/AST elevation. Therefore, the current treatments for COVID-19, including steroid use, can promote the reactivation of dormant chronic hepatitis B infection, which is a major cause of liver disease. Thus, all of these factors should be considered by physicians to appropriately handle infection.

Underlying comorbidities, including chronic diseases (diabetes, hypertension, obesity and cardiovascular disease), have been associated with adverse COVID-19 outcomes. According to the WHO,

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approximately 46% of global diseases and 59% of mortality are related to chronic diseases. In particular, chronic liver damage rates have been steadily increasing over the years throughout the world having adverse effects in population irrespective of age, race, sex and geographical region. Infectious processes mainly associated with viral diseases (hepatitis B, C and E virus infections) as well as diet and nutrition are important determinants of liver damage. In addition, the evidence supports that obesity-associated inflammation is a risk factor for nonalcoholic fatty liver disease (NAFLD) [7]. This is relevant because obesity is considered a 21st century pandemic with a prevalence of 1.9 billion worldwide [8]. Indeed, obesity and overweight represent unfavorable factors for SARS-CoV-2 infection. This is in agreement with the fact that obesity is associated with a chronic inflammatory state. Thus, when this condition is considered in light of the new scenario of the pandemic virus, it suggests that there may be an increase in complications and unfavorable results [9]. Therefore, the exact impact of obesity on SARS-CoV-2 infection in the setting of liver disease needs to be further investigated.

There are both intracountry and intercountry differences in the estimated prevalence of comorbidities related to COVID-19 outcomes, which presents issues with regard to generalizing the findings. The same problem applies for determining the impact of liver disease on COVID-19 progression. An example is the fact that despite the availability of effective interventions for the prevention and treatment of hepatitis B and C, they are still a major cause of liver injury burden worldwide, particularly in low-income countries, whereas as a result of obesity, the incidence of pandemic NAFLD is variable throughout the world. Additionally, host genetics involved in SARS-CoV-2 infection need to be evaluated in detail. Currently, genetic polymorphisms associated with virus entry and host immune response have been found to be related to the onset and progression of SARS. These findings might be extrapolated to SARS-CoV-2 because of the close genetic relatedness of these two viruses. However, the studies have been predominantly performed in Asian populations [10], and it is important to consider that genetic variations may have distinct effects on diverse populations because of environmental pressures. For instance, the differences in the burden of metabolic diseases as well as the adoption of unhealthy lifestyles promoting overweight and obesity may have an effect on viral infection outcomes [11]. Therefore, genetic variants that have not been associated with severe forms of SARS in Asia may have a significant effect in other populations. This also applies to liver disease in the context of infection. Thus, the study of host genetic related to liver abnormalities in distinct populations is required to establish its contribution to the liver dysfunction observed in severe COVID-19 patients.

An additional challenge imposed by the COVID-19 pandemic is the fact that the ambulatory clinical care of patients with chronic diseases has to change. To avoid transmission, follow-up by telemedicine has been recommended for the routine care of patients with chronic liver diseases. It is accepted that telemedicine improves the efficiency of healthcare delivery at reasonable cost opportunities for patients with chronic liver diseases by increasing their access to tertiary care. However, telemedicine may not be available in many countries, and strategies including phone calls ad/or virtual consultation for remote care must be used [12]. By taking into account that the severity of most COVID-19-associated

liver injuries is considered mild, suggesting that liver failure is uncommon among critical COVID-19 patients and the fact that liver dysfunction has been mainly described in patients with severe disease upon presentation. Optimal follow-up of patients with liver damage by telemedicine or virtual consultation are needed. This allows to physicians to be alert to the potential of clinical deterioration when COVID-19-associated liver injury is observed.

The COVID-19 pandemic reveals the need for effective mitigation measures for the most prevalent diseases worldwide. Such is the case for chronic metabolic disorders such as diabetes, obesity and hypertension. Diabetes and obesity can also impact liver function, resulting in complications and unfavorable scenarios in emergency situations such as the one we are currently experiencing. Close monitoring of patients with liver disease is necessary to understand the physiopathology associated with SARS-CoV-2 infection. This allows for the design of detailed guidelines for handling COVID-19 cases with the ultimate goal of containing the virus.

### Declaration of interest

There are no conflicts of interest to declare.

### References

- [1] Gavriatopoulou M, Korompoki E, Fotiou D, Ntanasis-Stathopoulos I, Psaltopoulou T, Kastritis E, et al. Organ-specific manifestations of COVID-19 infection. *Clin Exp Med* 2020;27:1–14, <http://dx.doi.org/10.1007/s10238-020-00648-x>.
- [2] Grant MC, Geoghegan L, Arbyn M, Mohammed Z, McGuinness L, Clarke EL, et al. The prevalence of symptoms in 24,410 adults infected by the novel coronavirus (SARS-CoV-2; COVID-19): a systemic review and meta-analysis of 148 studies from 9 countries. *PLoS One* 2020;15:e0234765, <http://dx.doi.org/10.1371/journal.pone.0234765>.
- [3] Zhang C, Shi L, Wang FS. Liver injury in COVID-19: management and challenges. *Lancet Gastroenterol Hepatol* 2020;5:428–30, [http://dx.doi.org/10.1016/S2468-1253\(20\)30057-1](http://dx.doi.org/10.1016/S2468-1253(20)30057-1).
- [4] Wong YJ, Tan M, Zheng Q, Li W, Kumar R, Fock KM, et al. A systemic review and meta-analysis of the COVID-19 associated liver injury. *Ann Hepatol* 2020, in press.
- [5] Ridruejo E, Soza A. The liver in times of COVID-19: what hepatologists should know. *Ann Hepatol* 2020;19:353–8, <http://dx.doi.org/10.1016/j.aohp.2020.05.001>.
- [6] Prins GH, Olinga P. Potential implications of COVID-10 in non-alcoholic fatty liver disease. *Liver Int* 2020;40:2568–2568, <http://dx.doi.org/10.1111/liv.14484>.
- [7] GBD 2017 Cirrhosis Collaborators. The global, regional, and national burden of cirrhosis by cause in 195 countries and territories, 1990–2017: a systemic analysis for the Global Burden of Disease Study 2017. *Lancet Gastroenterol Hepatol* 2020;5:245–66, [http://dx.doi.org/10.1016/S2468-1253\(19\)30349-8](http://dx.doi.org/10.1016/S2468-1253(19)30349-8).
- [8] WHO. Obesity and overweight. WHO. [update 2018 February; cited 2019 November 5]. Available from: <https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight>.
- [9] de Siqueira JVV, Garrido-Almeida L, Zica BO, Batista-Brum, Barceló A, de Siqueira Galil AG, et al. Impact of obesity on hospitalizations and mortality, due to COVID-19: a systemic review. *Obes Res Clin Pract* 2020;23, <http://dx.doi.org/10.1016/j.orcp.2020.07.005>. S1871–403X(20)30553–30556.
- [10] Ovsyannikova IG, Haralambieva IH, Crooke SN, Poland GA, Kennedy RB. The role of host genetics in the immune response to SARS-CoV-2 and COVID-19 susceptibility and severity. *Immunol Rev* 2020;296:205–19, <http://dx.doi.org/10.1111/imr.12897>.
- [11] Ramos-Lopez O, Martinez-Lopez E, Roman S, Fierro NA, Panduro A. Genetic, metabolic and environmental factors involved in the development of liver cirrhosis in Mexico. *World J Gastroenterol* 2015;21:11552–66, <http://dx.doi.org/10.3748/wjg.v21.i41.11552>.
- [12] Arrese M. Telemedicine, COVID-19 and liver disease: revamping remote care initiatives in hepatology. *Ann Hepatol* 2020;19:339–40, <http://dx.doi.org/10.1016/j.aohp.2020.05.002>.