REVIEW ARTICLE

Impact of COVID-19 on pre-existing liver disease

Impacto de COVID-19 en enfermedad hepatica pre-existente

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Abstract

Patients with chronic liver disease of any etiology who become infected with SARS-CoV-2 have been found to have a higher risk of mortality compared to those patients who do not have chronic liver disease. A literature review was conducted in the relationship between COVID 19 and preexistence of liver disease. The proportion of COVID-19 patients with abnormal liver function on admission ranged from 40 % to 75 % and the proportion with liver injury was close to 30%. Current studies show an important association between preexisting liver disease and COVID-19. The presence of cirrhosis is now an independent predictor of severity for COVID-19 and prolonged hospitalization in this group of patients. Patients with cirrhosis have a higher mortality rate, and this rate rises with increasing severity.

Keywords: *Pre-existing liver disease. COVID-19. COVID and cirrhosis.*

Resumen

Pacientes con enfermedad hepática crónica de cualquier etiología que se infectan con SARS-CoV-2 tienen un mayor riesgo de mortalidad en comparación con aquellos pacientes que no tienen enfermedad hepática crónica. Se llevó a cabo una revisión de la literatura en relación a lo publicado de COVID 19 y enfermedad hepática pre-existente. La proporción de pacientes con COVID-19 con función hepática anormal al ingreso osciló entre el 40 % y el 75 % y la proporción con daño hepático fue cercana al 30 %. Los estudios actuales muestran una asociación importante entre la enfermedad hepática preexistente y la COVID-19. La presencia de cirrosis es ahora un predictor independiente de gravedad para COVID-19 y hospitalización prolongada en este grupo de pacientes. Los pacientes con cirrosis tienen una mayor tasa de mortalidad y esta tasa se incrementa con el aumento de la gravedad de la enfermedad hepática.

Palabras clave: *Lesión hepática pre-existente. COVID 19. COVID y cirrosis.*

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Date of reception: 13-08-2023
Date of acceptance: 15-09-2023
DOI:10.24875/CIRU.23000409

Cir Cir. 2024;92(1):131-136
Contents available at PubMed
www.cirugiaycirujanos.com

Introduction

COVID-19, the disease caused by Coronavirus SARS-CoV-2, emerged in 2019 causing a worldwide public health problem. The infectiousness of COVID-19 impacted all age groups. Patients with different etiologies of chronic liver disease were some of the more affected. Although initial data reported that previous liver disease was not associated with severity, later studies showed an important association between pre-existing liver disease like hepatitis B, hepatitis C and metabolic associated fatty liver disease (MAFLD) and the severity of COVID-19 infection[1], even increasing risk of mortality compared with patients without liver disease[2]. Patients with alcohol-related liver disease, nonalcoholic fatty liver disease, cirrhosis and hepatocellular carcinoma are at higher risk of both severity and chance of death after infection[3]. Several theories might explain the hepatic involvement of COVID-19, including the direct viral effect on the liver cells, the abundance of ACE receptors in cholangiocytes and SARS-CoV-2 affinity to these receptors, drug-induced liver injury, and reactivation of Hepatitis B Virus (HBV) with the use of immunosuppressive medications[4]. Other factors relevant to liver injury are related to immune-mediated collateral damage, dysbiosis, hypoxia, and exacerbation of preexisting liver disease[3,4].

Epidemiology

Gastrointestinal and liver manifestations were reported in up to 40% of Mexican patients infected by SARS-CoV-2 since the beginning of the pandemic. Medical associations related to gastroenterology and hepatology issued guidelines for the identification, management and treatment of patients with COVID-19 hepatic manifestations, as well as for patients with pre-existing liver disease and liver transplant[5,6].

Overall, the prevalence of abnormal liver function tests (LFT) on admission in COVID-19 patients ranged from 40% to 75%, while liver injury approached 30%. Mexican patients showed mild aspartate transaminase (AST) and alanine transaminase (ALT) elevation, accompanied by a slight elevation in the total bilirubin, a mild decrease in albumin levels[5] and a cholestatic pattern (gamma glutamyl transferase (GGT) and alkaline phosphatase (ALP) increased) in up to 20% of the patients. Patients with abnormal LFT on admission presented higher mortality 18.7% compared to those with normal liver biochemistries 12.2% ($p < 0.0001$). After excluding patients with a history of chronic liver disease, abnormal LFT on admission were independently associated with death and severe COVID-19, both adjusted by age, gender, diabetes, pneumonia and body mass index > 30. Similar results were shown in a recent prospective multicenter international cohort among 829 hospitalized patients (203 from Mexico), in whom hypertransaminasemia was present in 267 patients (32.3%) and liver injury during hospitalization was associated with a higher hospital stay (> 10 days) and worse outcome[6].

MAFLD and COVID-19

Obesity is a known risk factor for respiratory infection and many other chronic diseases, including MAFLD. Nowadays, it has been considered an independent predictor for SARS-CoV-2 complications in adults. As expected, due to the high prevalence of overweight and obesity in our population, studies in Mexican COVID-19 patients have found a high prevalence of metabolic comorbidities, including hypertension, MAFLD and type 2 diabetes. In a retrospective study in 155 hospitalized Mexican patients, abnormal LFT was present in 96.8%, prevalence of steatosis was 42.6% and of significant liver fibrosis was 44.5%[7]. Liver fibrosis by FIB-4 was associated with risk of intensive care unit (ICU) admission (OR 1.74; $p = 0.023$) and mortality (OR 6.45, $p = 0.002$); but no independent associations were found. A more recent study[8] found in 432 hospitalized patients with COVID-19 that 40.6% fulfilled criteria for MAFLD. Although the authors did not find significant differences in the outcomes of hospitalized patients with MAFLD and those without MAFLD, a significant increase in the risk of mechanical ventilation requirement, acute kidney injury, and mortality in patients with MAFLD and advanced liver was found[9,10].

In the liver, the innate immune mechanisms play a central role in COVID-19 outcome and in the transition to hepatic inflammation, macrophages have a critical role. Some studies suggested receptors for SARS-CoV-2 are also present in liver cells. DPP4, the potential SARS-CoV-2 receptor, is multifunctional including its roles in glucose homeostasis, inflammation, and the immune system. Indented as a novel adipokine in adipose tissue (AT), DPP4 is strongly expressed on the apical surfaces of the polarized epithelium of various organs such as lung and liver, and increased DPP4 results in failures to resolve inflammation and chronic subclinical activation of the immune system[10,11].

The presence of inflammatory pathways, mainly cytokine storm, present either in obesity and in COVID-19 patients could increase liver inflammation or be a marker of metabolic risk factors further aggravating the clinical outcome. Thus, MAFLD should be considered as prognostic indicator during COVID-19[10]. A systematic review concluded that the risk of severe COVID-19 is 4-6 times higher in patients with MAFLD associated with obesity, fibrosis and age of > 60 year. Until now in our country, no studies have been published linking the prevalence of MAFLD and the severity of COVID-19[12]. Obese patients with no alcoholic steatohepatitis (NASH) show a higher expression of ACE2 and TMPRSS2, suggesting that the advanced stages of MAFLD could predispose individuals to SARS-CoV-2 entry factors. In patients with metabolic disorders, and in consequence adipocyte dysregulation, the involvement of the angiotensin 1-7 system and its underlying inflammatory environment, SARS-CoV-2 infection leads to a more severe outcome[13,14]. In several reports it had been observed that COVID-19 patients with fatty liver had a four-fold increased risk of severe COVID-19 compared with patients without fatty liver[15-17].

Liver injury is much worse in severe COVID-19 patients than in patients with mild symptoms. Singh et al. investigated the interaction of preexisting liver disease and COVID-19. Based on a large, diverse cohort of 2,780 COVID-19 patients in the United States, this study indicated that liver abnormalities were found in the vast majority of patients regardless of preexisting liver disease, but patients with liver disease were at higher risk for hospitalization and mortality[18,19]. It has been reported that among patients with preexisting liver disease, MAFLD was the most frequent (about 40%) and this patient had a higher risk of progression to severe COVID-19, higher abnormal liver tests at admission to discharge and longer viral shedding time[19].

Zheng et al. evaluated 214 patients with confirmed COVID-19 from three hospitals in Wenzhou, China, and 66 had MAFLD (45 with and 21 without obesity). The presence of obesity in MAFLD patients conferred a six fold higher risk of severe infection (unadjusted OR 5.77, 95% CI 1.19–27.91, p = 0.029) and the association with obesity and COVID-19 severity remained after adjustment for age, sex, smoking habits, diabetes, hypertension, and dyslipidemia (adjusted OR 6.32, 95% CI 1.16–34.54, p = 0.033)[20]. In nondiabetic patients with COVID-19, the presence of MAFLD was associated with an increased risk of severe infection and it was higher by increasing the number of metabolic factors[21]. A recent meta-analysis reported that a higher NLR (Neutrophil-to-Lymphocyte Ratio) is strongly associated with poorer hospital outcomes in patients with COVID-19. In the same cohort of 310 Asian patients, it has been recently demonstrated that patients with imaging- defined MAFLD and increased NLR values on admission have higher risk of severe illness from COVID-19 independently of age, sex, and metabolic comorbidities[22,23].

Vázquez-Medina et al. was to explore the implications of MAFLD and to study the interaction between advanced fibrosis (AF) and each of these diseases in the death and intubation of patients hospitalized with COVID-19. Study retrospective with 359 patients hospitalized with confirmed COVID-19 infection. The death rate was statistically significantly higher in the MAFLD group compared to the control group (55% vs. 38.3%, p = 0.02). The MAFLD (44.09% vs. 20%, p = 0.001) group had statistically significantly higher intubation rates than the control group[24].

Liver fibrosis, cirrhosis and COVID-19

Chronic liver disease can remain compensated for a long time even if the cause that generated it remains, however, if a second injury or damage is added to it, it is presumably that it will decompensate. In a prospective cohort study coordinated by the Latin American Association for the Study of the Liver (ALEH) in 1611 hospitalized patients with confirmed SARS-CoV-2 infection in 38 different hospitals in 11 Latin American countries, liver function tests were found to be abnormal at admission in 45.2% of the cohort. Overall, 8.5% had chronic liver disease and 3.4% had cirrhosis. Patients with abnormal liver tests at admission had a higher mortality of 18.7% compared to those with normal liver biochemistry of 12.2%. The authors concluded that the presence of abnormal liver tests at admission is independently associated with mortality and severe COVID-19 in hospitalized patients with COVID-19 infection and can be used as a surrogate marker of inflammation[1]. Patients with cirrhosis have a 20-30% risk of decompensation presenting as acute decompensation in chronic liver failure and high 30-day mortality.

Mantovani A et al. included 11 observational studies for a total of 2034 adult individuals (median age 49 years [IQR 45–54], 57.2% men). The overall prevalence of chronic liver disease at baseline was 3%.

Individuals with severe COVID-19 disease had relevant alterations of liver enzymes and coagulation profile, probably due to the innate immune response against the virus, and chronic liver disease was not shown to influence the severity of COVID-19[25]. Furthermore, in another retrospective study in hospitalized patients with COVID-19, the prevalence of hepatic steatosis and advanced liver fibrosis using noninvasive assessment prediction models was high; at least one liver function test abnormality was observed in 96.8% of COVID-19 patients[7]. The study of these patients and defining the role of cirrhosis in the evolution has been difficult since most patients present some of the associated comorbidities. A multicenter study done by Bajaj et al. in patients with cirrhosis + COVID-19 (n = 37) compared with age/gender-matched patients with COVID-19 alone (n = 108) and cirrhosis alone (n = 127). It was concluded that cirrhosis plus COVID-19 had similar mortality compared with patients with cirrhosis alone but higher than patients with COVID-19 alone[26]. On the other hand, a large study by Moon et al. in 103 patients with cirrhosis and 49 with non-cirrhotic chronic liver disease were enrolled, it showed a mortality of 12.2% of chronic liver disease without cirrhosis, 24% Child-Pugh class A, 43% Child-Pugh class B, and 63.0% Child-Pugh class C. The cause of death in patients with cirrhosis was reported as COVID-19 lung disease in 78.7%, cardiac-related in 4.3%, and liver-related in 12.2%[27]. In a study by Sarin et al[28]. the patterns of liver damage were studied, thus collecting data in 13 Asian countries on patients with known or newly diagnosed chronic liver disease with confirmed COVID-19, in 228 patients (185 with chronic liver disease without cirrhosis and 43 with cirrhosis) it was determined that 80% presented comorbidities, 61% associated with MAFLD and 60% of viral etiology. 43% of patients with chronic liver disease without cirrhosis presented with acute liver injury, and 20% of patients with cirrhosis also presented with acute-on-chronic liver failure. In decompensated cirrhotic patients, liver injury was progressive in 57% of patients, with a mortality of 43%. Increased bilirubin and the AST/ALT ratio predicted mortality among patients with cirrhosis, with a Child-Turcotte Pugh score of 9 or greater at presentation predicting high mortality. Patients with chronic liver disease, diabetes and associated obesity had a worse evolution, they are more vulnerable and need to be closely monitored.

Two international registries collected data from 745 patients with chronic liver disease (CLD) and SARS-CoV-2 (including 386 with and 359 without cirrhosis) and compared them with data from patients without CLD with SARS-CoV-2 from a UK hospital network. Mortality was 32% in patients with cirrhosis versus 8% in those without ($p < 0.001$). Mortality in patients with cirrhosis increased according to Child-Pugh class (A [19%], B [35%], C [51%]) and the main cause of death was respiratory failure (71%). Acute liver decompensation occurred in 46% of patients with cirrhosis, of whom 21% had no respiratory symptoms. Half of those with liver decompensation had acute-on-chronic liver failure. The authors concluded that as the largest such cohort to date, early-stage liver disease and alcohol-related liver disease were shown to be independent risk factors for death from COVID-19. These data have important implications for the risk stratification of CLD patients worldwide during the COVID-19 pandemic. This international registry study demonstrates that patients with cirrhosis are at increased risk of death from COVID-19. COVID-19 mortality was particularly high among patients with more advanced cirrhosis and those with alcohol-related liver disease[29].

Viral hepatitis and COVID-19

Some medications used to treat SARS-CoV-2 include cortisone and immunosuppressive medications such as tocilizumab, increases the risk of hepatitis B virus reactivation. Few studies have evaluated the evolution of patients with hepatitis B infection who are infected with COVID-19. It has been documented that these patients have alterations in liver function tests, such as elevation of aminotransferases (AST, ALT), particularly when admitted to an intensive care unit. The results of these studies are rather contradictory. Some studies have shown that there is no basis for the aggravation of hepatic injury in SARS-CoV-2/HBV coinfection or extended stay in hospital. On the other hand, other studies reported that coinfection is associated with the severity and poor prognosis of COVID-19 and that liver function should be frequently assessed in these patients[30]. The risk of drug hepatotoxicity in COVID-19 patients is high, steroid use has been linked to hepatitis B virus reactivation, especially in those patients who received high doses of steroids, but also with other immunosuppressants such as tocilizumab or baricitinib.

On the other hand, in patients who are being treated for hepatitis B with tenofovir disoproxil fumarate (TDF) or tenofovir alafenamide (TAF), care should be taken

with the interaction with COVID-19 drugs such as lopinavir-ritonavir, as they may increase the concentration of TDF or TAF. Treatment for hepatitis B in new patients can be started despite the COVID-19 pandemic, patients already receiving treatment for hepatitis B it is important not to stop medications as they could have a relapse of HBV[31].

In patients with COVID-19, a history of Hepatitis C Virus (HCV) and seropositive HCV infection leads to accentuated SARS-CoV-2 viral virulence and is a strong predictor of in-hospital mortality irrespective of baseline comorbidities, admission laboratory variables, or COVID-19-induced liver injury. The pathophysiology of the infection of HCV and SARS-CoV-2 may have similar pathways. SARS-CoV-2 uses the ACE-2 receptor as a main point of entry to the target cell[32]. One molecule that has been identified to potentiate SARS-CoV-2 viral entry is the transmembrane protease serine 2 (TMPRSS2), which is suggested to affect the S protein at the cell surface and induces SARS-CoV-2-cellular membrane fusion[33]. Importantly, TMPRSS2 is over-expressed in patients with HCV which may lead to the exaggerated SARS-CoV-2 infection in these patients. Studies have shown that in chronic HCV infection there is a correlation between the production of pro-inflammatory cytokines, such as INF-γ and TNF-α, and progressive liver injury, while the regulatory cytokines such as IL-4 and IL-10 may modulate the pro-inflammatory immune response induced by the virus[34]. The history of HCV in these patients seems to add a cumulative mortality risk to any clinical or laboratory profile. The mechanisms involved may be related to extrahepatic effects of HCV leading to enhanced ACE2/TMPRSS mechanisms of SARS-CoV-2 viral entry and may also be related to baseline cytokine-mediated pro-inflammation and endothelial dysfunction. The realization and understanding of these mechanisms may help in better characterization of the disease and investigating possible therapeutic options in this subgroup of patients, which is of significant importance as an initial step towards the selection of at-risk groups that can benefit the most from developing vaccines at an earlier stage of the disease.

Drug-induced liver injury (DILI) and COVID-19

DILI is a common cause of liver injury, identified by the elevation of liver enzymes associated with the initiation or suspension of a suspected drug. In the first and second wave of COVID-19 cases, DILI was described as an injury pattern predominantly hepatocellular, instead of a cholestatic pattern. Histologically, microvesicular steatosis, portal fibrosis, inflammatory infiltrate, and necrosis have been found. The mechanism of hepatic injury is multifactorial and includes the presence of the COVID-19 virus in the vascular endothelium affecting the porta-hepatic system, in addition to hypoxia-reperfusion and release of reactive oxygen species[35]. Several therapeutic strategies have been implemented since the beginning of the Pandemic, most of them have been identified as causing DILI with the following patterns of involvement described: tocilizumab (predominantly cholestasis), remdesivir (hepatocellular), chloroquine (hepatocellular), azithromycin (predominantly cholestasis), acetaminophen (hepatocellular, dose-dependent), lopinavir/ritonavir (hepatocellular, cholestasis or mixed). For the evaluation of the suspected causality of the drug, it is recommended to use the CIOMS/RUCAM scale to prevent risks associated with its use[36,37].

The evaluation of DILI in patients with COVID-19 is a challenge in clinical practice due to unclear factors and polypharmacy that interact in the clinical course of patients[38]. In an initial systematic review of 12 articles, it was reported that the combined incidence of DILI was 25.4% (95% CI, 14.2-41.4) and particularly the incidence of DILI in 208 patients treated with remdesivir was 15.2% (95% CI, 6.4-32), while the incidence was higher with lopinavir/ritonavir 37.2% (95% CI, 22.7-54.6) in a series of 775 patients with COVID-19. Concerning the biochemistry affectation of the liver, hyperbilirubinemia was the most frequent adverse effect of lopinavir/ritonavir, whereas DILI by remdesivir frequently elevated aminotransferases more. In some studies, DILI was attributed to more than one drug[39].

DILI should be considered among the important differentials of liver injury in COVID-19 patients. In Mexico, as in other parts of the world, the desperation for effective therapy at the beginning of the pandemic led to the indiscriminate and irrational use of drugs that could potentially trigger DILI. It is probable that many of the abnormal LFT in our Mexican patients were associated with the following drugs: hydroxychloroquine, ivermectin, dexamethasone, azithromycin, lopinavir/ritonavir, baricitinib, tocilizumab and remdesivir[40].

Funding

The authors declare no funding was received.

Conflicts of interest

The authors declare no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article. Furthermore, they have acknowledged and followed the recommendations as per the SAGER guidelines depending on the type and nature of the study.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

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