EDITORIAL

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COVID-19 in Individuals with Chronic Liver Diseases

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INTRODUCTION

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused a pandemic leading to significant morbidity and mortality worldwide [1]. High risk groups for severe COVID-19, such as patients with solid organ transplantations, patients with cancer and obese and older individuals, have been identified since the beginning of the pandemic [2]. Patients with chronic liver diseases (CLD) were initially considered as high-risk individuals, mainly due to the fact that the virus itself affects the liver, and high serum transaminases levels seemingly predict poor outcome [3]. Moreover, alcoholic liver disease (ALD) was associated with poor outcomes since the beginning of the pandemic [4], further strengthening the connection between severe COVID-19 and CLD.

However, as more and more studies reached publication, we now understand that each chronic liver disease comes with a different COVID-19-related burden, determined mainly from type of liver disease, co-morbidities and liver fibrosis. Interestingly enough, in most CLD, controversies exist, while in autoimmune liver diseases, namely autoimmune hepatitis (AIH), primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC) data are scarce.

COVID-19 AND CHRONIC LIVER DISEASE

Alcohol-related Liver Disease (ALD)

Alcohol overconsumption is a well-known cause of immune system impairment, affecting the frequency, survival, and function of most immune cells, both systemically and in the lung [5, 6]. Given these facts, it is only natural that patients with ALD have been regarded as being at increased risk for severe COVID-19, since the beginning of the pandemic.

In fact, alcohol overconsumption was one of the first factors associated with an increased risk for severe COVID-19, in a study by Marjot et al. [4], a finding validated in a later study by Malet et al. [7], comprising 3,623 patients with ALD. In this study, the presence of ALD, alongside decompensated cirrhosis and HCC, was associated with a high risk for all-cause mortality [7]. Surprisingly enough, these patients were less likely to receive mechanical ventilation, raising the question of therapeutic effort limitation in individuals with alcohol overconsumption. Overall, ALD has risen as a commanding factor regarding worse COVID-19-related clinical outcome in patients with CLD, especially in those with significant fibrosis.

Metabolic-associated Steatotic Liver Disease (MASLD)

Metabolic-associated steatotic liver disease (MASLD) is often accompanied by over-expression of ACE2 receptors on hepatocytes and cholangiocytes, especially among obese individuals [8, 9]. This finding, led to the hypothesis of greater susceptibility of patients with MASLD to SARS-CoV-2 infection, a hypothesis supported by the fact that comorbidities linked to MASLD, such as type 2 diabetes mellitus (T2DM), constitute independent risk factors for severe COVID-19 [10].

In general, results regarding severe COVID-19 in MASLD patients, are largely conflicting, with many studies showing that these patients are at greater risk for severe disease with outcomes such as hospitalization, intubation, higher complication rate and worse COVID-19 clinical course, especially when the level of fibrosis increases, while others fail to reach this consumption. As an example, in a study by Wang et al. [11], the presence of MASLD acted as an aggravating factor even in young and non-obese patients, while Huang et al. [12], reported that despite the increase in transaminases among patients with MASLD, mortality rates were not higher than general population. Younossi et al. [13], indicated that MASLD

patients had higher odds of elevated liver function tests (LFTs) and liver injury during SARS-CoV-2 infection, but intensive care unit (ICU) admissions and mechanical ventilation were not significantly increased. Genetic analyses also did not reveal a causal relationship between MASLD and COVID-19 severity [14], highlighting the need for larger, well-designed studies.

Viral Hepatitis

Data regarding the effect of both chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infections are rather contradictory. Regarding chronic HBV infection (CHB), in the largest, so far, study, by Choe et al. [15], comprising 675 patients with CHB retrospectively compared with 18,485 non-CHB COVID-19 patients, no statistically significant differences regarding odds for mortality, intensive care admission and organ failure were found. Likewise, in two studies by Yip et al. [16], and Kang et al. [17], no higher risk for severe COVID-19 was found among HBV-infected individuals. Interestingly, in the only study including a high number of HBe-antigen positive patients, those presenting with abnormal liver function were found to have a higher risk for ICU admission and death [18]. In all studies, no HBV exacerbation was noted irrespective of the presence of anti-HBV treatment.

Regarding HCV infection, in a study by Cerbu et al. [19], conducted among patients with chronic HCV infection, but without cirrhosis, patients with active viral replication were found to be at a greater risk for severe disease, extended hospitalization in ICU as well as need for mechanical ventilation, compared to subjects under antiviral treatment or having achieved sustained virological response (SVR). In the contrary, another study, including 975 chronic HCV patients with COVID-19 and 975 matched, non-HCV-infected persons, indicated that despite a higher hospitalization rate among HCV patients; no difference was noted in ICU admission and overall mortality levels [20]. In both studies, in accordance with rest of available data, advanced liver fibrosis was associated with higher risk for severe COVID-19.

Autoimmune Liver Diseases

The term "autoimmune liver diseases" encompasses autoimmune hepatitis (AIH), primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC). Due to the rarity of the diseases, only a handful of studies exist assessing the severity of COVID-19 in these patients. In the first case series regarding 10 patients with AIH and COVID-19 from Italy back in April 2020, of whom 5 had computed tomography-confirmed COVID-19 pneumonia, disease course was similar to that of the non-immunosuppressed patients [21]. Of note, the dosage of immunosuppressive medication was reduced in 7 patients.

The main question regarding patients with autoimmune liver diseases, especially AIH, seems to be the burden of immunosuppressive treatment. In two large studies, from Marjot et al. [22] and Efe et al. [23], comparing patients with AIH with patients with other CLD and healthy individuals, no differences between the groups in terms of hospitalization, ICU admission and death were found, while the use of immunosuppressive therapy was not associated with worse outcomes, leaving only age and the presence of cirrhosis as significant risk factors. On the other hand, in another study by Efe et al. [24], including 254 patients with AIH, the use of immunosuppressive treatment, primarily cortisone and thiopurines and secondarily mycophenolate mofetil and tacrolimus, was associated with more severe COVID-19 [24], a finding in line with previous studies in patients with autoimmune rheumatic diseases [25, 26]

Regarding PBC patients with COVID-19, only one study exists, with a total of 85 PBC patients, showing a higher incidence of hospitalization and mortality, especially in those with a higher alkaline phosphatase (ALP); however 20% of the patients in this study had a BMI >30 kg/m^2, 17% T2DM and 33% arterial hypertension; on the contrary no such data exist regarding the control group, so the increased risk for severe COVID-19 in PBC patients should be treated with caution [27]. Lastly, no data regarding PSC patients exist.

Liver Cirrhosis

Patients with liver cirrhosis are characterized by immune dysfunction, leading amongst others in defective vaccine-response [28-30] and a high susceptibility in viral and bacterial infections. This, in conjunction with the fact that, most drugs used against SARS-CoV-2 are hepatotoxic and are therefore contra-indicated in severe liver insufficiency, has made liver cirrhosis to be presumed as a significant risk factor for severe COVID-19.

In fact, both the need for mechanical ventilation as well as overall death of liver cirrhosis patients have been found to be increased, with a mortality rate of up to 45%. In the two larger studies, comprising 3,207 and 8,941 patients with liver cirrhosis respectively, the presence of cirrhosis, especially with decompensation, alongside advanced age, alcohol abuse and comorbidities, like T2DM, hypertension and chronic obstructive pulmonary disease, were associated with increased mortality rates [31, 32]. Overall, advanced age, disease severity, as assessed by model for end stage liver disease (MELD) and Child-Turcotte-Pugh (CTP) scores and presence of decompensation seem to be the main factors leading to worse clinical outcomes, while in some studies low platelet count, high serum bilirubin levels and AST/ALT ratio also rose as aggravating factors.

Hepatocellular Carcinoma

As already mentioned, patients with cancer have been considered as high-risk individuals for severe COVID-19 since the beginning of the pandemic. This seems to hold truth also for patients with hepatocellular carcinoma (HCC), even though only a handful of studies have addressed the severity of COVID-19 in HCC patients. In the largest one of them, comprising 218 patients with HCC and 32 with intrahepatic cholangiocarcinoma, 18.4% of HCC died within 30 days after SARS-CoV-2 infection, while in 42.3% of them, HCC treatment had to be delayed or stop due to the infection, with the most important risk factor for COVID-19 related death [33]. On the contrary, Marjot et al. [4], in a large study, including 745 liver-diseased patients with 48 of them suffering from HCC, showed no higher prevalence of COVID-related death in these patients [4]. In this study, the presence of cirrhosis, especially when

decompensated, and ALD were the most important risk factors for COVID-19 related death. Overall, HCC seems to play a significant role in severe COVID-19; this seems to be even more important in decompensated cirrhosis, advanced age and most probably concomitant ALD, even though large studies are still lacking.

Liver Transplantation

Patients with liver transplantation (LT) were found to be prone to severe COVID-19 since the beginning of the pandemic. Immunosuppression and vaccine hyporesponsiveness were regarded the main reasons for these findings, with LT recipients showing ineffective T-cell responses and consequently decreased protection from SARS-CoV-2 infection in a variety of studies [34, 35].

Interestingly enough, many subsequent studies showed that LT per se was not correlated with either severe COVID-19 or higher mortality; instead "traditional" risk factors like advanced age, renal and cardiovascular co-morbidities were the key factors determining patients' clinical course [36, 37]. These findings were later confirmed in large meta-analyses; in the largest one of them, comprising 1,481 LT recipients from 17 studies, there was no difference in mortality among LT recipients hospitalized for COVID-19 when compared to non-transplant patients with similar comorbidities [38].

CONCLUSIONS

Patients with CLD are thought to be at high risk for severe COVID-19 infection. This hypothesis, deriving mainly from the hepatotropism of SARS-CoV-2 as well as the severe hepatotoxicity of antiviral drugs used, seems to hold truth for patients with cirrhosis, especially those decompensated, and patients with alcoholic liver disease. Patients with MASLD seem to be a high-risk group mainly due to their comorbidities, while those with HBV infection seem to carry the same risk as with the general population. The risk in those with HCV infection seems to increase alongside liver fibrosis. Lastly, data regarding patients with autoimmune liver diseases are scarce, so more studies regarding this population are mandatory before an assumption can be made.

Conflicts of interest: None to declare.

Authors' contribution: Both authors were responsible for conception of the study, data acquisition, drafting, revising and approving the manuscript.

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