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EDITORIAL

MAFLD in COVID-19 patients: an insidious enemy

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ABSTRACT

The pandemic Sars-CoV-2 infection represents a dramatic health challenge worldwide. Pneumonia is considered the major damage caused by the virus. However, recent data have highlighted the impact of the Sars-CoV-2 related disease namely COVID-19 on the liver. Hepatic abnormalities significantly increase during COVID-19 and a more severe infection occurs in patients with pre-existing liver diseases, among which the most frequent is metabolic-associated fatty liver disease (MAFLD). It has been described that MAFLD patients had a higher risk of progression to severe COVID-19, higher abnormal liver tests and longer viral shedding time. The presence of fibrosis in MAFLD patients is another risk factor for severity of COVID-19. Due to the overgrowing prevalence of MAFLD, it could be speculated that a large proportion of the population might be at risk of severe COVID-19 and the identification of these patients possibly by using liver enzymes as risk predictors may be crucial for an early diagnosis and for the management of the infection.

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Sars-CoV-2; infection; COVID-19; MAFLD; progressive liver disease

1. Introduction

In December 2019 a high rate of pneumonia cases of unknown origin was firstly described in Wuhan, Hubei Province, China, and a novel enveloped RNA betacoronavirus, named 2019-nCoV, was identified as the pathogen agent [1]. Within few months, Severe Acute Respiratory Syndrome Coronavirus-2 (Sars-CoV-2) infection and the related CoronaVirus Disease 19 (COVID-19) disease spread out from China throughout the world. It has been declared pandemic in early March 2020 by the World Health Organization (WHO) thus representing a global health challenge for all the affected countries.

The clinical features of COVID-19 are superimposable to those of Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS) as the epidemic viruses which cause them share more than 50% of genomic sequence with SARS-CoV-2.

COVID-19 is typically characterized by symptoms of viral pneumonia such as fever, fatigue, dry cough, anosmia, headache, which they can develop into respiratory failure. Nausea, vomiting, and diarrhea may also occur but less frequently. Symptoms may remain mild in most patients whereas older subjects (over 65 years), patients with hypertension, diabetes, morbid obesity, and cardiovascular disease have been identified as the most at risk for a more severe course of the disease [2].

The virus binds to and is internalized into the cells through the functional Angiotensin-converting enzyme 2 (ACE2) receptor whose ubiquitous distribution favors a systemic response to infection with the possible involvement of the heart, brain, liver, pancreas, and kidneys, causes changes in the immune system and may lead to multiorgan dysfunction.

2. Patients with COVID-19 have comorbidities related to the metabolic syndrome

The Metabolic Syndrome (MS), a cluster of conditions such as insulin resistance, obesity, diabetes mellitus (DM), hypertension, and hyperlipidemia [3], is emerging as a significant risk factor for worse outcomes in patients with COVID-19 [4]. A study conducted in US which evaluated 1482 patients hospitalized with Sars-CoV-2 infection in fourteen states revealed that 12% of the total patients had comorbidities and the most common were hypertension (49.7%), obesity (48.3%), DM (28.3%), and cardiovascular diseases (CVD) (27.8%) [5].

Obesity represents a risk factor for viral infections. Indeed, the chronic inflammation which characterize obese patients, compromises the immune response [6]. Data from two studies which enrolled 3615 and 4103 patients respectively who were positive for COVID-19 from New York City (NYC) revealed that subjects with severe obesity (BMI>35 Kg/m^2) had a higher risk to be hospitalized and developed a more severe infection [7,8]. Due to the pandemic prevalence of obesity worldwide, it represents a serious problem in COVID-19 patients and may impact on their mortality.

DM represents the second most common comorbidity in COVID-19 patients and may increase the death rate in infected patients. In a meta-analysis which included 40,000 COVID-19 patients from Wuhan, China, 8% of the total were diabetic [9]. Health data from 17.4 million adults in the UK were analyzed for risk factors associated with death from COVID-19 and it was found that after adjustment for other co-variates, uncontrolled DM was an independent risk for death (OR, 2.36, 95% CI 2.18–-2.56) [4]. The high incidence of diabetes in these patients may

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be ascribable to the presence of obesity or to dysregulation of ACE2 receptor. The latter is also expressed in endocrine pancreas and the high incidence of Sars-CoV-2 infection in diabetic patients may be linked to its high expression, as observed in rodent models of DM [10]. Drugs used for the treatment of diabetes as ACE inhibitors may further increase ACE2 expression. Moreover, a delay in the activation of Th1 cell-mediated immunity and a hyperinflammatory response are frequently observed in people with diabetes [11]. Finally, microvascular endothelial dysfunction is a frequent manifestation in patients with MS and hypo-fibrinolysis, elevated PAI-1 and complement levels, and increased platelet aggregation favors microthrombi formation [12]. These findings suggest that dysregulated immune response and microvascular dysfunction in DM may contribute to the poor outcomes in COVID-19.

Hypertension as well as CVD may worsen the prognosis of patients with COVID-19. Data from the Chinese Center for Disease Control and Prevention assessed a 2.3% mortality rate in a group of 44,672 infected subjects. However, this number was much higher among patients with hypertension and CVD, reaching 6% and 10.5%, respectively [13]. As for diabetes, ACE inhibitors and other drugs used to treat hypertension lead to higher expression of ACE2 receptor. The renin-angiotensin-aldosterone system (RAAS) which is associated with hypertension favors a pro-inflammatory and procoagulant state that may predispose to COVID-19 related multiorgan failure. However, the mechanisms underlying the association between Sars-CoV-2 infection with hypertension as well as diabetes need to be further investigated.

3. COVID-19 and the liver

As previously described for SARS and MERS, also Sars-CoV -2-related infection can affect liver function. To date, data regarding liver involvement in patients with COVID-19 are scant and the preexistence of chronic liver diseases is emerging as a risk factor for illness severity. According to the Centers for Disease Control and Prevention (CDC) patients with liver disease are more susceptible to Sars-CoV-2 and have a more severe infection [14]. Large-scale hospital-based studies have highlighted that 14–53% of COVID-19 patients have higher levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) paralleled by slightly increased bilirubin levels [15] and the increase in liver enzymes was more frequent in patients with a more serious infection. An impairment of liver functions in COVID-19 patients is also supported by low albumin levels which have been related to severe prognosis. A large study, which extracted data regarding 1099 patients with COVID-19 from mainland China, revealed that 21.3% and 22.2% had ALT and AST elevation respectively and the highest levels of transaminases have been found in critical cases. In a cross-sectional study among 417 patients recruited from the Third People's Hospital of Shenzhen, China, it has been described that 76.3% had abnormal liver tests and 21.5% had liver injury during hospitalization. Patients with abnormal liver enzymes were older, male and had higher body mass index (BMI). Moreover, they tended to have preexisting liver diseases as nonalcoholic or more recently re-defined metabolic associated fatty liver disease (MAFLD) [16], alcoholic liver disease (ALD) and viral hepatitis B and cirrhosis. In the latter, the risk of respiratory failure can also be determined by the underlying hepatopulmonary syndrome, porto-pulmonary hypertension, or hepatic hydrothorax [17,18]. As concerns the patterns of liver tests, 20.75% were hepatocyte type, 29.25% were cholestatic type, 43.4% were mixed type. The hepatocellular pattern was associated with more severe pneumonia compared to the cholestatic one.

Xu et al. firstly analyzed the postmortem hepatic biopsy specimens from a 50-years-old man deceased to COVID-19 and they found moderate microvesicular steatosis with mild, mixed lobular and portal activity to focal necrosis. Moreover, they observed hepatomegaly, hepatocytes degeneration, infiltration of neutrophil, lymphocytes, and monocytes in the portal area and microthrombosis.

It has been recently described that patients with alcohol use disorder (AUD) and ALD may be at higher risk to develop COVID-19. The increased susceptibility in these patients is due to the disruption of immune systems by alcohol and to the preexistence of medical conditions such as obesity and chronic kidney disease [19]. A case report demonstrated acute liver failure secondary to Sars-CoV-2 infection in a 56-years-old woman with decompensated cirrhosis.

A retrospective multicenter study (COVID-Cirrhosis-CHESS, ClinicalTrials. gov NCT04329559) included consecutive adult patients with laboratory-confirmed Sars-CoV-2 infection and preexisting cirrhosis from 16 hospitals in China. Most patients had compensated cirrhosis whose pathogenesis was mainly related to HBV infection. The cause of death in most patients with preexisting cirrhosis was respiratory failure rather than progression of liver disease whereas lower lymphocyte and higher direct bilirubin level might represent poor prognostic indicators in these patients [20]. Patients with decompensated cirrhosis and those after transplantation represent vulnerable patients with an increased risk of COVID-19 infection or more severe illness. It should take advantage of the experience gained during COVID-19 crisis to be ready for the management and surveillance of patients with advanced liver disease and to preserve the quality of care reserved to those patients [21].

4. Mechanisms of liver injury during Sars-CoV-2 infection

It is not known whether the elevation of liver enzymes is due to a preexisting liver disease in patients with a more severe Sars-Cov-2 infection, if it reflects liver damage caused directly by the virus or drug treatments or finally if they are the consequence of a sustained inflammatory response ('Cytokine storm') [22]. Indeed, in many subjects with COVID-19 infection, an uncontrolled immune response is observed with a high release of cytokines which leads to hyperinflammation and multi-organ damage. Circulating levels of interleukin-2 (IL-2), IL-6, IL-7, IL-10, tumor necrosis factor-alpha (TNF-α), Th17 and CD8 T cells, C reactive protein (CRP), ferritin, were significantly higher in patients with severe COVID-19 [22]. A sustained inflammatory response can cause cytopenia, coagulopathy, tissue damage/hepatitis (elevated lactate dehydrogenase (LDH), ALT, and AST levels) and activation of

macrophages/hepatocytes. The liver is enriched with innate immune cells such as macrophages, natural killer, natural killer T, and γδ T cells and it plays an important role in the immune system. Moreover, metabolic disorders among which obesity and MAFLD have been associated with increased hepatic production of proinflammatory cytokines as TNF-α and IL-6.

It has been hypothesized that in MAFLD patients the polarization of hepatic macrophages could switch from inflammation-promoting M1 to inflammation-suppressing M2 thus favoring COVID-19 progression [23], which in turn could increase MAFLD susceptibility to NASH in the long-term. The presence of fibrosis in the context of MAFLD might exacerbate the virus-induced 'Cytokine storm' and consequently the severity of infection possibly through the hepatic release of inflammatory cytokines [24].

It has been proposed that the presence of MAFLD with increased neutrophil-to-lymphocyte ratio (NLR), previously associated with poorer outcomes in COVID-19 patients, exacerbates the virus-induced inflammatory 'storm' possibly through the hepatic release of pro-inflammatory cytokines thus contributing to more severe infection [25]. Lipid accumulation and oxygen reduction in hepatocytes during shock and hypoxic conditions COVID-19 related may lead to hepatocytes death. The subsequent increase in reactive oxygen species and the peroxidation products can act as second messenger by activating redox-sensitive transcription factor, further increasing the release of inflammatory cytokines and inducing liver damage [26]. It could be speculated that the preexistence of fat accumulation and liver damage may amplify these processes.

Sars-Cov and Sars-Cov-2 share the same receptor, ACE2, to enter the cells. Preliminary data indicate that the ACE2 receptor is expressed in hepatic cells and, in particular, in cholangiocytes and endothelial ones suggesting that Sars-CoV-2 can directly target the liver thus altering its functionality. Recently, a single-cell transcriptomic experiment revealed that ACE2 presents the highest expression levels in cholangiocytes, followed by hepatocytes [27] and it is involved in a fine-tuning regulation of reactive cholangiocytes and in the activation of hepatic stellate cells (HSCs) thus participating to hepatic fibrotic processes [28]. Nonetheless, it could be speculated that the upregulation of ACE2 may be attributable to hepatocytes proliferation in response to acute liver injury induced by Sar-Cov-2 infection. Moreover, it has been reported that Sars-CoV-2 may also depend on co-receptors or other auxiliary membrane proteins as protease to facilitate its infection. A single cell RNA sequencing of 13 human tissues revealed that candidate co-receptors sharing the expression pattern of ACE2 are all peptidase including Alanyl Aminopeptidase (ANPEP), Dipeptidyl peptidase-4 (DPP4) and Glutamyl Aminopeptidase (ENPEP) [29]. However, MAFLD does not seem to affect the hepatic expression of genes involved in SARS-CoV-2 infection such as ACE2, cathepsin L protein (CSTL), Transmembrane Protease Serine 2 (TMPRSS2) and Phosphatidylinositol 3-phosphate 5-kinase (PIKFYVE) as highlighted by transcriptomic data [30] (Figure 1). In addition, the expression pattern of Sars-CoV-2 host-receptors in cell clusters associated with immune pathways, as inflammatory macrophages, natural killer cells, plasma cells, mature B cells, and cells of the liver endothelial microenvironment suggests a Sars-CoV-2 – immune-mediated liver damage (Figure 1).

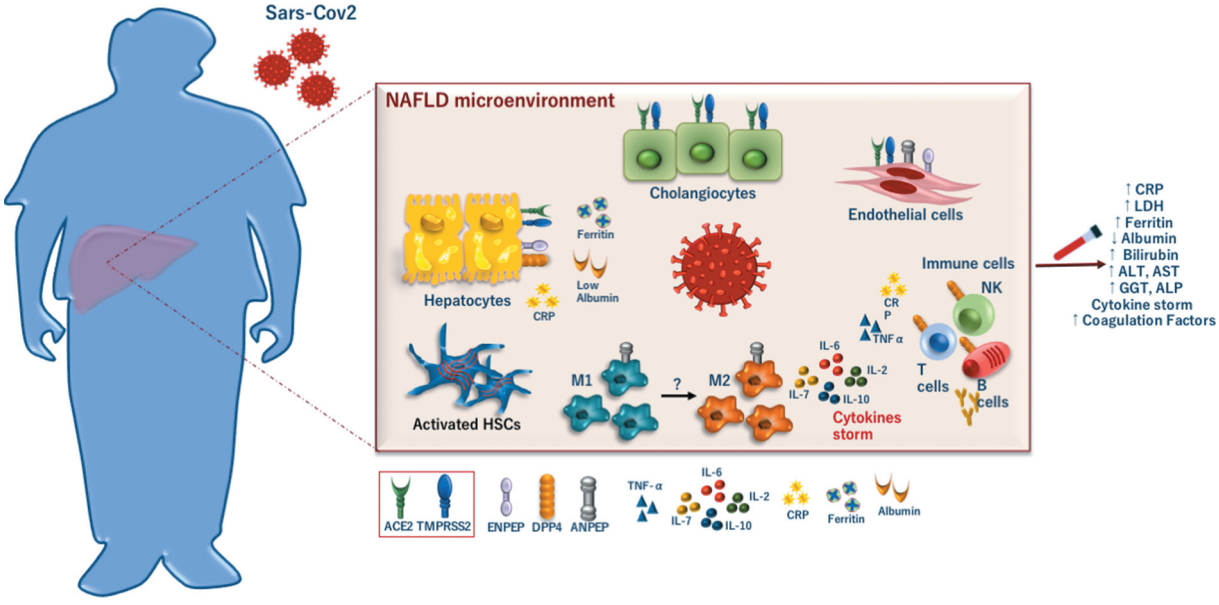

Figure 1. Distribution of the best known Sars-Cov-2 receptors on hepatic cells and metabolic alterations induced by the virus in MAFLD microenvironment.

Several studies demonstrated that a high proportion of COVID-19 patients displayed enhanced circulating ALT, AST, LDH, bilirubin levels, Gamma-glutamyl transferase (GGT), Alkaline Phosphatase (ALP), CRP, and ferritin levels. IN COVID-19 patients also occur an uncontrolled release of cytokines and chemokines commonly related to the 'cytokine storm'. Preexisting liver diseases, such as nonalcoholic fatty liver disease (MAFLD) may impact on COVID-19 severity illness. At hepatic level, Sars-Cov-2 may enter the cells using Angiotensin-converting enzyme 2 receptor (ACE2), mainly expressed by cholangiocytes, endothelial cells and then by the fatty-laden hepatocytes of MAFLD patients. Even more, Sars-Cov-2 infection depends on the priming by proteases among which TMPRSS2 and on several other co-receptors such as ANPEP, DPP4, and ENPEP. Kupffer cells might contribute to the production of inflammatory cytokines during Sars-Cov-2 infection. In MAFLD patients, the polarization of hepatic macrophages could switch from inflammation-promoting M1 to inflammation-suppressing M2, thus favoring COVID-19 progression. All these events may create a microenvironment that predispose to HSCs activation and to hepatic fibrosis perpetuation in MAFLD patients.

Microvesicular steatosis associated with mild inflammation may be caused by drugs used for the treatment of the infection (Drug-Induced Liver Injury-DILI). Paracetamol which is adopted by many people to contain fever has been related to liver injury. In addition, antiviral agent for COVID-19 such as lopinavir/ritonavir, remdesivir, chloroquine, tocilizumab, umifenovir may be hepatotoxic in some patients [15] or could reactivate hepatitis B virus infection causing further liver damage.

5. MAFLD and COVID-19: still much to be explored

MAFLD is the most common chronic disease in the world with a prevalence of 30% [31] and it is considered the hepatic manifestation of the MS. Although hepatic steatosis may remain a clinically benign condition, a fraction of subjects (approximately 25%) may progress to more severe forms including nonalcoholic steatohepatitis (NASH) characterized by inflammation and hepatocyte degeneration. NASH can progress to fibrosis, cirrhosis, and hepatocellular carcinoma (HCC). The relation between MAFLD and COVID-19 has not deeply investigated due to the lack of knowledge of liver disease history in patients with COVID-19. It has been reported that among patients with preexisting liver disease, MAFLD was the most frequent (about 40%) [17] and MAFLD patients had a higher risk of progression to severe COVID-19, higher abnormal liver tests at admission to discharge and longer viral shedding time [23]. Zheng et al. evaluated 214 patients with confirmed COVID-19 from three hospitals in Wenzhou, China, and 66 had a MAFLD (45 with and 21 without obesity). The presence of obesity in MAFLD patients conferred a sixfold 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) [32]. Increased levels of IL-6 have been observed in patients with MAFLD and especially in obese ones thus contributing to aggravate COVID-19 infection [33]. 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 [34].

In COVID-19 patients younger than 60-years, there was a two-fold higher prevalence of severe infection in patients with MAFLD compared to those without [35]. Hashemi and colleagues performed a retrospective cohort study of 363 patients positive for COVID-19 of whom 19% had chronic liver disease (CLD), including 15.2% with MAFLD. After adjustment for age, gender, obesity, cardiac diseases, hypertension, hyperlipidemia, diabetes, and pulmonary disorders, CLD and MAFLD were independently associated with Intensity Care Unit (ICU) admission (OR 1.77, 95% CI 1.03–3.04 and OR 2.30, 95% CI 1.27–4.17) and mechanical ventilation (OR 2.08, 95% CI 1.20–3.60 and OR 2.15, 95% CI 1.18–3.91) [36]. Currently, the evaluation of MAFLD under the context of COVID-19 is mainly based on imaging techniques and non-invasive markers [15]. Roca-Fernandez et al. evaluated the presence of fatty liver in symptomatic confirmed COVID-19 subjects who belong to the UK Biobank population and found an association between preexisting liver disease and obesity with severe COVID-19 [37]. Targher et al. have recently evaluated the impact of noninvasive fibrosis scores in 310 Asian patients with COVID-19, of whom 94 with MAFLD. The prognosis of MAFLD is strongly affected by the severity of fibrosis and it might impact on the outcome of COVID-19 infection. They found that patients with MAFLD with increased FIB-4 or nonalcoholic Fatty Liver Disease Fibrosis (NFS) scores are at high likelihood of having severe COVID-19 illness, independently of metabolic comorbidities. They suggested that the presence of MAFLD with significant/advanced fibrosis might exacerbate the virus-induced 'Cytokine storm', possibly through the hepatic release of proinflammatory cytokines, thereby contributing to severe COVID-19 [38,39]. A recent meta-analysis reported that a higher NLR 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 [25].

6. Concluding remarks

Patients with abnormal liver tests were at increased risk of more severe SARS-CoV-2 infection. The underlying mechanism of liver injury during COVID-19 may include a sustained inflammatory response, drug toxicity, and the preexistence of liver disease as MAFLD. Patients with MAFLD had higher risk of severe COVID-19, since they are more likely to have abnormal transaminases, higher viral shedding time, and more liver injury during hospitalization compared to non-MAFLD patients. The presence of fibrosis in MAFLD patients is another risk factor for severity of COVID-19. The observations that MAFLD patients have almost double the risk of the general population to progress to severe COVID-19 together with the epidemic proportion of MAFLD underline the importance to identify and monitor patients with preexisting liver disease, especially those with metabolic disorder, during and after COVID-19 crisis. It's also necessary to outline steps taking advantage of the experience gained during pandemic COVID-19 in order to preserve the quality of care and surveillance provided to patients with advance liver disease.

7. Expert opinion

Patients with abnormal liver tests were at increased risk of more severe SARS-CoV-2 infection. The underlying mechanism of liver injury during COVID-19 may include a sustained inflammatory response, drug toxicity and the pre-existence of liver disease as MAFLD. The observations that MAFLD patients havealmost double the risk of the general population to progressto severe COVID-19 together with the epidemic proportion of MAFLD underline the importance to identify and monitor patients with pre-existing liver disease, especially those with metabolic disorder, during and after COVID-19 crisis.

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Declaration of interest

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