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Hepatic consequences of COVID-19 infection. Lapping or biting?

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**Abstract**

The outbreak of coronavirus disease 2019 (COVID-19) starting last December in China placed emphasis on liver involvement during infection. This review discusses the underlying mechanisms linking COVID-19 to liver dysfunction, according to recent available information, while waiting further studies. The manifestations of liver damage are usually mild (moderately elevated serum aspartate aminotransferase activities), and generally asymptomatic. Few patients can still develop severe liver problems, and therapeutic options can be limited. Liver dysfunction may affect about one-third of the patients, with prevalence greater in men than women, and in elderly. Mechanisms of damage are complex and include direct cholangiocyte damage and other coexisting conditions such as the use of antiviral drugs, systemic inflammatory response, respiratory distress syndrome-induced hypoxia, sepsis, and multiple organ dysfunction. During new COVID-19 infections, liver injury may be observed. If liver involvement appears during COVID-19 infection, however, attention is required. This is particularly true if patients are older or have a pre-existing history of liver diseases. During COVID-19 infection, the onset of liver damage impairs the prognosis, and hospital stay is longer.

1. Introduction

A novel coronavirus was reported to World Health Organization on Dec 30, 2019, as the cause of a cluster of pneumonia cases in China, city of Wuhan, Hubei Province. The first name of 2019-nCoV(human) was adopted on Jan 7, 2020, lately changed to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). COVID-19 infection became an outbreak throughout China on Feb 11, 2020 and subsequently was identified as a global pandemic on March 11, 2020, spreading to more than 120 countries, as a major threat to public health [1–3]. The COVID-19 pandemic suddenly represented an enormous burden of care [4], and raised issues related to medical ethics [5], since specific therapies and/or vaccines are missing, to date. COVID-19 may manifest in different ways. Many subjects may remain asymptomatic [6], but the exact number is still unknown. Specific settings might facilitate the spread of infection e.g., in skilled nursing facility where more than half of residents with positive test results were asymptomatic at the time of testing and most likely contributed to transmission [7,8]. The proposed 3-stage classification system of potential increasing severity for COVID-19 infection encompasses stage I (early infection), stage II (pulmonary phase), and stage III (hyperinflammation phase) [9]. Although the most frequent and critical clinical presentation is secondary to the involvement of the lung (fever, cough), the infection by SARS-CoV-2 virus may lead to a systemic and multi-organ disease [10], also involving the gastrointestinal tract (nausea/vomiting, or diarrhea) [11,12]. The liver appears to be the second organ involved, after the lung [13–15].

The present paper explores the available evidences on liver involvement in patients with COVID-19 infection, to provide a comprehensive understanding of the phenomenon, and to anticipate effective follow-up.

2. Symptoms

During COVID-19 infection, patients can be asymptomatic or present clinical symptoms ranging from fever, dry cough, headache to dyspnea and fatigue, to acute respiratory distress syndrome (ARDS), shock, and cardiac failure [9,16]. A nasopharyngeal swab is the collection method used to obtain a specimen for testing. Because the likelihood of the SARS-CoV-2 being present in the nasopharynx increases over time, repeated testing is often used [17]. Multi-organ...
involvement secondary to COVID-19 infection occurs in a subgroup of patients [10]. COVID-19 infection can be associated with myocardial injury [18–20], heart failure [18], vascular inflammation, myocarditis, cardiac arrhythmias [19], and hypoxic encephalopathy [21]. The progression and prognosis of COVID-19 infection is worse in the presence of diabetes mellitus [22,23]. The case-fatality rate increases with age (from 8% to 15% in the age range 70–79 years, and ≥80 years, respectively) and with associated diseases, i.e., 11%, 7%, 6%, 6%, and 6% in patients with cardiovascular disease, diabetes mellitus, chronic respiratory disease, hypertension, and cancer, respectively [24].

During COVID-19 infection, gastrointestinal manifestations may appear, as reported from China [11,12] and among U.S. patient population [25]. The appearance of gastrointestinal symptoms could even represent the chief complaints [10,26]. The overall prevalence of GI symptoms was 18% (diarrhea 13%, nausea, vomiting 10%, and abdominal pain 8%) in Hong Kong [27], and 11.4% in another study in Zhejiang province [26]. Gastrointestinal involvement could be the consequence of COVID-19. Angiotensin-Converting Enzyme 2 (ACE2) receptors at the enterocyte level (i.e. glandular cells of gastric, duodenal and distal enterocytes), resulting in malabsorption, unbalanced intestinal secretion and activated enteric nervous system, therefore diarrhea) [28,29]. In human small intestinal organoids, SARS-CoV-2 rapidly infects the enterocytes and strongly induces a generic viral response program, pointing to a marked viral replication in the intestinal epithelium [30].

Notably, continuous viral RNA shedding occurs into feces up to 11 days negativity of respiratory samples [31]. It is difficult to establish if the virus is viable using nucleic acid detection [31,32]. Further research is required by using fresh stool samples at later time points in patients with extended duration of faecal sample positivity to the possibility of fecal-oral route transmission [31]. A study reported that the virus can be detected but not cultivated from stool (despite high RNA concentration), consistent with the lack of transmission [33]. In a case-control study from USA (enrolling 278 COVID-19 positive patients and 238 COVID-19 negative patients), the presence of gastrointestinal symptoms was predictive of COVID-19 positivity, and symptoms were associated with slower and less severe disease course [34].

3. General mechanisms of damage

Most important pathogenic mechanisms act at local and systemic levels, and play a critical role in the evolution of the disease. Steps include: (i) Inoculation and multiplication in the human body, when the virus binds to ACE2 receptors [35–37] to enter the target cell [38]. Receptors are well expressed in epithelia of the lung, gastrointestinal tract, and vascular endothelium, also in the liver [39]. This early period of COVID-19 infection can evolve to the second stage of viral pneumonia.; (ii) Extra-pulmonary systemic hyperinflammation syndrome occurs in the minority of infected patients, and is characterized by the so-called “cytokine storm”. At this moment, several cytokine levels increase, namely interleukin (IL)-2, IL-6, IL-7, IL-10, and tumor necrosis factor (TNF). Additional inflammatory biomarkers include granulocyte-colony stimulating factor, interferon (IFN)-γ inducible protein 10, monocyte chemotactrant protein 1, macrophage inflammatory protein 1-α, lymphopoenia (in CD4+ and CD8+ T cells), decreased IFNγ expression in CD4+ T cells [40–42], and monocyte chemotactrant protein-1 (MCP-1) [42]. Increased serum levels of D-dimer, troponin and N-terminal pro B-type natriuretic peptide (NT-proBNP) can also occur, together with altered coagulation function [43–45]. An extensive meta-analysis included 21 studies describing 3,377 patients, and 33 laboratory parameters, with respect to severe and non-severe COVID-19 infection and (in another 3 studies totaling 393 patients) survivors and non-survivors of the disease. Patients with severe and fatal disease had significantly increased white blood cell count, and decreased lymphocyte and platelet counts compared to non-severe disease and survivors. Biomarkers of inflammation, muscle and cardiac injury, as well as liver and kidney function and coagulation measures also increased in patients with both severe and fatal COVID-19. Severe disease was characterized by elevated levels of interleukins 6 (IL-6) and 10 (IL-10) and serum ferritin [46].

4. Liver involvement

ACE2 receptors in the liver are expressed mainly in cholangiocytes (60% of cells), minimally expressed in hepatocytes (3% of cells), and absent in Kupffer cells [36,39,47]. The presence of these receptors, together with the local effects of systemic inflammation and possible iatrogenic toxicity seem to be the main mechanisms involved in the onset of liver damage in COVID-19 patients.

Involvement of the liver with elevated serum alanine aminotransferase (AST), aspartate aminotransferase (ALT), and lactate dehydrogenase (LDH) activities has been firstly reported this year in 43% of the 99 COVID-19 cases from Wuhan [48]. This aspect deserves further attention.

Although the level of serum transaminases could be already elevated before the onset of COVID-19, results from clinical reports and autopsy studies [26,49,50] suggest that liver dysfunction can be an expression of a worse disease evolution, and that an isolated elevation of transaminases alone is likely to be the indirect expression of a systemic inflammation.

Previous data from COVID-19 outbreak in China found that 2-11% of patients had liver comorbidities, 14-53% of patients presented with abnormal serum aminotransferases levels during the disease, and that the rates of liver dysfunction were more present in subjects with the most severe clinical presentation [26,49]. In another large series of 417 Chinese COVID-19 patients, abnormal liver tests (AST, ALT, total bilirubin, GGT) were present in 76.3% of patients and 21.5% of subjects showed liver injury during hospitalization, in particular during the first two weeks after admittance. In addition, patients with abnormal liver tests had higher risks of progressing to severe disease. One point was therefore that clinicians should carefully monitor the detrimental effects on liver injury mainly related to certain medications during hospital admission [51]. Acute liver injury had a prevalence of 15.4% in 187 patients with confirmed COVID-19 in Wuhan [52]. Whereas gastrointestinal symptoms may occur without clinically evident respiratory involvement [53], abnormal liver function tests during COVID-19 have not been linked with any specific symptoms.

4.1 Liver test abnormalities

Mild liver involvement occurs in more than one-third of infected patients who can show elevated serum ALT or AST, elevated LDH, creatinine kinase or myoglobin, abnormal prothrombin time and high gamma-glutamyl transferase (GGT) during COVID-19 progression, as observed at intensive care units (ICU) or normal care units (NCU) during hospitalization [10,49,54–59].

A large retrospective, multicenter study in Chinese adults with COVID-19 pneumonia described a dynamic pattern of liver injury indicators, with a first elevation of AST, followed by ALT in severe patients, and mild fluctuations of total bilirubin levels irrespective of disease severity. In this series of patients, AST levels were strongly associated with the mortality risk [60].

Hyperbilirubinemia was observed in 11% to 18% of cases [48,49]. A clear and severe cholestatic pattern is absent during COVID-19 infection. In a comprehensive review examining 14 eligible studies [61], elevated AST and ALT activities were reported in Guangzhou Medical University, China, in 6% to 22% and 21% to 28% of patients, respectively. In studies from Wuhan, AST levels were increased in 24% to 37% of patients, a proportion higher than in other Chinese regions (Zhejiang), reporting a proportion of 16%. A gender difference might exist in this respect [62], since the prevalence of AST increase is higher in men than women, as documented by six case series (i.e., average 66%...
vs. 35%, respectively). Case reports and case series also suggest that the probability of developing liver dysfunction increases with older age [61]. Notably, the elevation of aminotransferases was mild, with no report about intrahepatic cholestasis or liver failure. It is a possible that abnormal liver function tests during COVID-19 infection are transient. Abnormalities often coexist with increased enzyme activities from muscle and heart. Changes may not affect liver-related morbidity and mortality.

4.2. Mechanisms of liver damage directly or indirectly related to COVID-19 infection in the normal liver

The main target of COVID-19 is the lung via ACE2 receptors [63,64]. However, SARS-CoV2 RNA has been detected in feces [27,31,32], with a longer presence in faecal samples, as compared with respiratory samples [31]. The presence of the virus in gut lumen could lead to translocation into the liver via portal blood. The presence of the virus in gut lumen could involve either as a direct target of the SARS-CoV-2 (e.g. hepatocyte apoptosis [65] or caspase-dependent pathways [66]) and secondary to the complex pathways of systemic alterations promoted by the viral infection, mainly including inflammation and cytokine release (including IL-1, IL-6, IL-10 [67]), immune response, altered coagulation, hepatic ischemia and hypoxia, and sepsis-related abnormalities.

Addisonal elements possibly concurring to liver damage are drug-related injury and the progression of underlying liver diseases.

It is still under debate if these alterations can really be an expression of a clinically relevant liver injury requiring particular attention in the management of the disease [13, 68]. In one study, patients developing abnormal liver tests had higher risks of progressing to severe disease [51], and the finding is associated with longer hospital stay [62]. In addition, the more severe form of COVID-19 infection is a predisposing condition to a more evident liver damage [10, 49, 69], and therefore also patients admitted to ICU [59].

Table 1 depicts the most distinctive post-mortem histopathological changes of the liver from patients with COVID-19. Remarkably, liver failure and bile duct injuries were not reported in these studies. Liver damage is more likely to occur in patients with more severe disease [9], in whom concomitant alterations of liver function tests are more likely [10, 42]. Aggravating factors include ischemic/hypoxic liver injury [70], and immunologic, inflammatory and toxic mechanisms promoted by systemic sepsis [71]. Viral inclusions seem to be absent in the liver [57], but this possibility deserves further investigations, because of potential viral RNA translocation from intestine though portal blood.

| Reference       | Findings                                |
|-----------------|-----------------------------------------|
| Xu et al., 2020 | Microvesicular steatosis                |
| Liu et al., 2020| Mild lobular and portal activity         |
| Liu et al., 2020| Hepatomegaly                            |
| Liu et al., 2020| Hepatocyte degeneration                  |
| Liu et al., 2020| Lobular focal necrosis                   |
| Tian et al., 2020| Neutrophil infiltration                 |
| Tian et al., 2020| Infiltration of lymphocytes and monocytes(pancreas) |
| Tian et al., 2020| Congestion of hepatic sinuses with microthrombosis. |
| Ji et al., 2020  | Mild sinusoidal dilatation               |
| Ji et al., 2020  | Mild lobular lymphocytic infiltration    |
| Ji et al., 2020  | Patchy hepatic necrosis in the periportal and centrlobular areas |
| Ji et al., 2020  | Microvesicular steatosis                 |
| Ji et al., 2020  | Overactivation of T cells                |

Another possibility is the direct damage from COVID-19. Cholangiocytes express ACE2 receptors (more that 20-fold than in hepatocytes). Although cell damage can also occur at the level of bile ducts [72, 73], specific abnormalities of bile duct chemistry [49], major histological abnormalities [57], and liver failure [14] are rare. A major involvement of cholangiocytes during COVID-19 would parallel increased levels of serum alkaline phosphatase, but this is an uncommon finding. Likely, COVID-19 promotes liver damage mainly through ACE2 receptors expressed in endothelial cells [39]. These cells actively participate to liver ischemia-reperfusion damage and promote oxidant stress via reactive oxygen species (ROS) and nitric oxide (NO) derivatives [74].

COVID-19 infection can progress to the inflammatory cytokine storm [75], which involve both the innate (Toll-like receptors, TLRs) and the cellular adaptive immunity (killer T lymphocytes) [76, 77]. The deleterious sequence, resembling pictures evolving during sepsis, includes COVID-19 infection, activation of intrahepatic CD4+ and CD8+ T-cells, Kupffer cells, activation of B cells and release of antiviral antibodies [13, 78]. These pathways evolve towards apoptosis and necrosis of infected cells with release of damage-associated molecular patterns and inflammatory signals which can interact with TLRs [76, 77]. Further complications include bacterial infections, more pro-inflammatory signaling pathways, macrophage activation and more inflammatory responses. The involvement of the innate immune system, becoming defective during COVID-19 infection, is further supported by depressed platelet counts, activation of coagulative and fibrinolytic pathways, increased neutrophil counts and neutrophil to lymphocyte ratios, as well as hyperferritininemia [10]. Elderly patients go worse, in this respect [79]. This sudden and immense immune hyperactivation may result in multiple organ failure lungs but also to the liver, heart, and kidneys [75]. Serum levels of the monocyte chemoattractant protein-1 (MCP-1), in particular, are increased in COVID-19 patients [42]. This chemokine has a critical role in the pathogenesis of liver disease [80], and is able to exacerbate steatohepatitis [12].

A further mechanism of liver damage includes the pneumonia-associated hypoxic damage in the liver, as the consequence of respiratory distress syndrome, hyperinflammatory response, and multiple organ failure [61]. The prevalence of this condition should be lower than above-mentioned conditions [13]. Hepatocyte cell death will result from the ongoing status of hepatic ischemia and hypoxia-reperfusion dysfunction, leading to hyperaccumulation of lipids, production of reactive oxygen species and increased oxidant stress and further pro-inflammatory molecules [81]. In this context, mitochondrial damage may also play a role [82, 83].

4.3. The impact of a pre-existing liver disease

In general, an underlying liver disease represents a potential risk factor for COVID-19 evolution to severe infection [84]. Conditions might include the ongoing liver damage due to chronic hepatitis B, combined HBV/HCV hepatitis (with risk of enhanced replication of hepatitis virus [85]), nonalcoholic fatty liver disease (NAFLD)(because of associated comorbidities of diabetes and cardiovascular disorder, and increased susceptibility to drugs) [86] liver cirrhosis [87], patients undergo liver transplant and who are on immunosuppressants [71], patients with hepatocellular carcinoma and immune-deficient status [31]. Preventive measures are highly recommended in these patients [88]. The aspect related to an underlying liver disease, represents a major burden in China, where liver diseases, primarily viral hepatitis (predominantly hepatitis B virus, HBV), NAFLD and alcoholic liver disease affect approximately 300 million people [87]. Similar aspects, e.g. liver disorder connected with underlying metabolic abnormalities, are frequent in Western industrialized countries. In particular, the issue of COVID-19 infection and underlying metabolic abnormalities should also consider liver steatosis. NAFLD refers to the development of abnormal hepatic steatosis in the absence of other causes for secondary
hepatic fat accumulation. NAFLD is the most common liver disorder in Western industrialized countries, (prevalence ranging from 10 to 46% in the United States [89-91]) and a median of 20% worldwide with a documented rising trend with time [92]. This trend in North America and Europe is the consequence of the rising prevalence of major risk factors for NAFLD, including obesity, sedentary lifestyles, type 2 diabetes mellitus, dyslipidaemia, and metabolic syndrome [92-95]. However, lean non-alcoholic steatohepatitis (NASH) can develop as well [94] and is frequent in Asia [96]. Overall, factors contributing to NAFLD include the environment, the gut microbiome, disrupted glycolipid metabolic pathways, metabolic inflammation primarily mediated by innate immune signalling, comorbidities and genetic risk factors [97, 98].

In the study by Ji et al., 202 patients with COVID-19 infection and NAFLD (assessed by steatosis index and/or abdominal ultrasonography), developed liver injury in 50% and 75% of cases on admission and during hospitalization, respectively [99]. NAFLD [86], higher BMI [86], and age [79], as well as underlying liver disease [86] were associated with COVID-19 progression. Thus, patients suffering from NAFLD could be vulnerable to COVID-19 infection and viral-related complications. These patients might display an increased risk of NAFLD progression to steatohepatitis in the long-term [100]. Notably, ACE2 expression is significantly increased in liver injury in both humans and rats, likely in response to increasing hepatocellular hypoxia [101].

Furthermore, as described above, a previous NAFLD could be exacerbated by chemokines released during SARS-CoV-2 infection [12, 80].

In addition, the presence of NAFLD can put patients at increased risk of a severe course of COVID-19, due to the frequent coexistence of metabolic comorbidities such as diabetes, hypertension, and obesity [86]. Non-cirrhotic patients with NAFLD/NASH can be considered as cardio-metabolic subjects and, therefore, at very high risk of COVID-19 complications. From a pathogenic point of view, the presence of inflammatory pathways (in particular those involving cytokines) common to NAFLD [102-104] and COVID-19 [40-42, 46] might increase the risk of liver inflammation in subjects with NAFLD and further aggravate the outcome if these patients are infected with the SARS-CoV-2. In a Chinese retrospective study, the presence of NAFLD was linked with a high risk of COVID-19 progression, and with longer viral shedding time, as compared to patients without NAFLD [99].

According to the EASL-ESC MID position paper [86], based on the experience on Chinese patients [49], chronic viral hepatitis would not increase the risk of a severe course of COVID-19. However, in patients with advanced liver disease and after liver transplantation there is increased risk of infection and/or a severe course of COVID-19 [86, 105].

Patients with autoimmune hepatitis or on immunosuppressive medications can be at increased risk for severe COVID-19 outcomes [105, 106]. According to the recent AASLD guidelines, this group of patients should be prioritized for testing until further will become available. Furthermore, in COVID-19 patients with autoimmune hepatitis or previous liver transplantation, a more aggressive approach is required, i.e., a suspect flare or acute cellular rejection should not be based on liver biochemistry alone but should undergo liver biopsy confirmation [105]. In addition, a flare of autoimmune liver disease due to unnecessary drug reduction or withdrawal would lead to increased doses of steroids. This possibility, in turn, will expose patients to increased risks of SARS-CoV-2 infection [106]. The immunosuppressive therapy in COVID-19 patients with liver disease should be minimized but not stopped [105].

During COVID-19 pandemic and afterwards (“Phase 2”), measures of social distancing aimed at the primary prevention of the infection, see the key involvement of the national health system. Such measures can influence the regular path of care of patients with chronic liver diseases, particularly those with decompenated cirrhosis, hepatocellular carcinoma and waiting for liver transplantation [105].

Approach could lead to increased decompensation, morbidity, onset of complications or transplant waiting list dropout. In this context, the preventive care provided to these patients must be intensified and tools imply, whenever possible, telehealth programs and reorganization of care delivery [107].

4.4. The liver damage caused by agents used for treatment of the infection

During COVID19 infection, liver damage could originate following the use of drugs, as suggested by the presence of microvesicular steatosis, and liver inflammation [57]. Agents include potentially hepatotoxic antiviral drugs employed off-label to treat the infection, as well as the use of antibiotics (quinolones, macrolides) in preventing/treating bacterial superinfections, antipyretics, or steroids [62, 108].

Liver toxicity might involve the drug-cytochrome P-450 interaction, as reported for azithromycin [109, 110], lopinavir/ritonavir [62, 111], hydroxy-chloquine [112, 113], and acetaminophen [114, 115].

A study was conducted from clinical records and laboratory results from 417 laboratory-confirmed COVID-19 patients admitted to the hospital in Shenzhen, China, treatment with lopinavir/ritonavir lead to increased odds of liver injury [51]. This observation is in line with results from a retrospective study in 148 patients in Shangai Hospital, showing that abnormal liver function tests was more frequent among those receiving lopinavir/ritonavir after hospital admission [62]. Remdesivir, a nucleoside analog produg developed by Gilead Sciences (USA), is effective against COVID-19 replication in vitro [116] and in infected patients [117]. This drug produced similar effects on liver enzymes [118]. Hydroxy Chloroquine sulphate is also effective in vitro [116] and, in COVID-19 patients for short periods, appears to safe. Rare case of fulmint hepatic failure have been described with Hydroxy Chloroquine [119, 120]. Acute liver injury is also possible after azithromycin treatment, with a clinically evident presentation following about two weeks after drug cessation, and after an average duration of treatment of 4 days [121]. Several patients with concomitant diseases (i.e. diabetes type 1 or 2, or hypertensive), undergo antihypertensive therapies with ACE inhibitors and angiotensin II type 1 receptor blockers. In this context, a possibility is the onset of ACE2 overexpression. Whether this condition will facilitate COVID-19 infection and penetration, deserves further attention [122, 123]. There is no evidence, however, that ACE inhibitors will worsen the consequence of infection [123]. Many patients with fewer use antipyretic agents, namely acetaminophen [124]. This drug might mediate, at least in part, the liver damage [57].

Patients with underlying metabolic abnormalities and NAFLD might be more exposed to drug-induced liver damage (DILI) [99, 108]. As mentioned earlier, the cytokine MCP-1 is often increased in COVID-19 patients [42] and act as a further hit for steatohepatitis [125]. In addition, patients with NAFLD/nonalcoholic steatohepatitis (NASH) COVID-19 infection, might be more susceptible to DILI, as well as to therapy with steatogenic drugs (amiodarone, sodium valproate, tamoxifen and methotrexate), and/or ischemic damage to the liver [108].

According to the recent AASLD guidelines, regular monitoring of liver function should be considered in all hospitalized COVID-19 patients, in particular in those treated with remdesivir or tocilizumab, irrespective of baseline value of liver biochemistry [105].

Thus, mainly due to possible interplay between mechanisms of liver damage promoted by SARS-CoV-2 infection and potential drug-induced hepatic side-effects, liver function tests should be carefully monitored independently from the presence of a pre-existing liver disease. This is particularly true when using biological agents against targeting the inflammatory/immunological responses.

5. Conclusion

Preliminary observations accumulated from China, following the COVID-19 outbreak in Wuhan, show that liver involvement during
COVID-19 infection may affect about one-third of the patients, with prevalence greater in men than women, and elderly. Although the manifestations of liver damage are usually mild (elevated serum aminotransferases), mechanisms are complex, and include underlying liver injury, direct cholangiopathy, use of antiviral drugs, hyperinflammatory status, and underlying hypoxia (Figure 1). Thus, the appearance of liver involvement during COVID-19 infection requires attention. This is particularly true since typical patients are older, with a pre-existing history of liver diseases, and essentially because the prognosis of lung infection is worse, and hospital stay is longer. Furthermore, the impact of COVID-19 on subjects with pre-existing liver diseases should be clarified. Position papers from scientific societies on the management of such patients are appearing, in this respect [86].

**Declaration of Competing Interest**

The authors have no financial or other interest in the product or distributor of the product. Furthermore, they have no other kinds of associations, such as consultancies, stock ownership, or other equity interests or patent-licensing arrangements.

**Author Contribution**

Each author contributed substantially to the work with access to all materials and data. PP and ADC wrote the initial draft. MK and AM provided systematic literature review. FL and PP reviewed the final version of the paper. The corresponding author had final responsibility for the decision to submit for publication.
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