Liver-spleen axis dysfunction in COVID-19

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Core Tip: The severe acute respiratory syndrome coronavirus 2 has rapidly spread worldwide, primarily causing interstitial pneumonia, although many other organs can be involved. Here, we will discuss the current knowledge regarding the liver and spleen involvement caused by this infection.

INTRODUCTION
In December 2019, a novel coronavirus-related pneumonia was detected in a Chinese group of patients[1]. The pathogen was later named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)[2], and on 30th January 2020 the World Health Organization publicly declared the outbreak of the new virus-related disease, the so-called coronavirus disease 19 (COVID-19)[3].

The most common clinical manifestations of SARS-CoV-2 infection include fever, dry cough, dyspnoea, fatigue, and myalgia[4,5], but the increasing information in published literature reported a wide spectrum of extrapulmonary symptoms and signs, especially arising from the gastrointestinal tract[6]. Hepatic involvement in COVID-19 patients has been largely documented in several observational studies, highlighting a significant prevalence of liver impairment in hospitalized individuals and a correlation with the severity of the disease[7,8]. COVID-19 implications for individuals with a pre-existent chronic liver disease (CLD) have also been evaluated, and a few studies have focused on the management and prognosis of post-transplant patients[9,10].

Little is known about the splenic involvement in COVID-19 patients. The spleen plays a fundamental role in the immune system modulation, regulating the T and B cell responses to the antigenic targets in the blood, and the tropism of the coronaviruses for the spleen has been documented[11]. Although splenic alterations in autopic specimens have already been shown, and these anatomical changes might contribute to the abnormal immune reaction occurring in COVID-19[12], data on prognosis of COVID-19 individuals with splenic function impairment have been poorly investigated so far.

In this review, we aim at elucidating the pathological role of SARS-CoV-2 in patients with hepatic and splenic involvement, ranging from specific biochemical alterations to any histopathological modifications. Secondly, our purpose is to evaluate the impact of COVID-19 in individuals with a pre-existent diagnosis of hepatic disease or defective spleen function or asplenia.

MATERIALS AND METHODS
From January to March 2021 we searched on MEDLINE (PubMed) by using the medical subject heading terms “liver”, “hepatic”, “spleen”, “splenectomy”, “hyposplenic” matched with “coronavirus”, “COVID-19”, “SARS-CoV-2” for all articles published since database inception. More than 3000 papers were found with this search strategy, most of which were not strictly related to the subject of this review. Hence, we selected human studies exploring relationships between COVID-19 and liver or spleen function, as well as the outcomes of COVID-19 patients with CLD or spleen hypofunction/asplenia. Given the high number of papers and senior authors (SC, MVL, ADS), after a careful review, we selected the most important or representative ones, summarising current evidence. We also searched for additional papers in the reference lists of review articles, and they were included if deemed appropriate.
LIVER IMPAIRMENT IN COVID-19

Pathogenesis
Since the most recent studies reporting clinical manifestation of COVID-19 were carried out, the alteration of liver function tests (LFTs) has been reported[4,13-15]. These abnormalities, which still have an unclear clinical significance, have been repeatedly reported in patients suffering from a more severe disease[4,16-18]. The exact cause of liver damage during SARS-CoV-2 infection is partly unknown and most likely multifactorial (Figure 1)[18]. One of the possible explanations has been found in the direct insult of SARS-CoV-2 to the liver through the binding of the virus to the angiotensin-converting enzyme 2 (ACE2) receptor, which represents the main cell entry receptor for the virus[19-21]. ACE2 receptors, which are key players in regulating arterial blood pressure, are expressed in almost any tissue of the human body, especially in the lungs, kidneys, gut, liver and brain. Their polymorphisms may lead to a cardiovascular disease and a stroke[22]. However, the ACE2 receptor is highly expressed by cholangiocytes rather than hepatocytes; therefore, the hepatic damage would be channelled through the bile duct dysfunction, which might alter the immune responses and liver regeneration[20]. Nonetheless, it should be noted that alkaline phosphatase (ALP) is not constantly raised in these patients[23].

In addition to the aforementioned mechanisms, the cytokine storm resulting from the excessive immune response triggered by the virus could be another factor leading to liver damage[23,24]. An excessive increase in pro-inflammatory cytokines has been found in a high percentage of critically-ill COVID-19 patients, alongside with a reduction in T cells and an increase in the neutrophilic count. The hypothesis that the lymphocytopenia and C-reactive protein (CRP) levels are independently correlated to the presence of liver damage has been proposed, suggesting a role of the cytokine storm in causing liver dysfunction[25]. This hypothesis has also been proved with regard to organs other than the liver, including heart and kidneys[26], supporting the idea that the cytokine storm may cause shock and tissue damage. Another contributing factor is the use of potentially hepatotoxic drugs, including antibiotics (e.g., macrolides), antiviral agents especially used during the first wave of the pandemic, corticosteroids, and paracetamol[23,24]. Lastly, liver damage can be caused by hypoxia, as a result of severe respiratory failure[23,24,27].

Clinical findings
Liver abnormalities are rather common in COVID-19 patients. The proportion of COVID-19 inpatients with an elevated alanine aminotransferase (ALT) has been found to be as high as 36%, and a higher proportion (46%) also had raised aspartate aminotransferase (AST)[18,28]. On the contrary, ALP or gamma-glutamyl transpeptidase (GGT) alterations were reported more rarely[18,29]. Although rather common, in most cases liver injury is mild and it usually manifests in more critically-ill patients[18,30,31]. A mild-to-moderate increase of ALT was reported in 43/87 patients (49.4%), and a higher mortality rate was observed among those with deranged LFT[23,24]. Richardson et al[7], who enrolled more than 5000 patients with liver involvement, showed that acute hepatic injury, although rare, was associated with higher mortality. Liver involvement was reported in 2700 patients (39%), and 1% of the whole cohort developed acute liver injury. Another study enrolling more than 2000 patients confirmed these findings, reporting acute liver injury in a quarter of the included patients and severe liver injury in only 6.4% of the patients. However, this small proportion had a more complex clinical course, including intensive care admission and intubation need in more than 60% of the cases, renal replacement therapy in a third, and mortality as high as 42%[31]. A low incidence of severe liver injury (9%) was also reported by a German study enrolling 44 patients of which 6 had deranged ALT. Also, the German cohort reported AST to be more commonly deranged than ALT[28].

Although generally mild, liver impairment has been found to be associated to a higher rate of intensive care unit admission[30,32], as well as to a longer hospital stay[33]. Ponziani et al[30] reported liver involvement in 161 out of 515 patients enrolled (31.3%) and no cases of severe acute liver injury. Moreover, although liver involvement led to a higher need for intensive care, no increase in mortality was recorded among those patients. However, conflicting data have been published on the role of liver impairment in increasing mortality in patients without pre-existing liver disease. Medetalibeyoglu et al[32] reported that AST/ALT ratio was a good predictor of mortality (area under the curve [AUC]: 0.713; $P = 0.0001$) in a cohort of 554 individuals enrolled in Turkey, and that AST and ALT levels were independently
associated with an increased need for intensive care and with mortality ($P = 0.001$). Table 1 reports the main studies focusing on liver abnormalities in COVID-19 patients.

**Histological features**

Limited data are available about histological liver findings in COVID-19 patients. Lagana *et al.*[34] reported the histological features of 40 patients who died of COVID-19-related complications and who had liver biochemical abnormalities. Two-thirds of the included patients presented macrovesicular steatosis, which was most commonly panlobular, while 2 patients (7%) showed active steatohepatitis. Half of the included patients had mild lobular necroinflammation and, therefore, active hepatitis, which was mild in 80% of the cases and moderate in the remaining 20%. Similarly, portal inflammation was reported in 20 patients, 3 of which had interface hepatitis. Lobular mild and focal cholestasis changes were observed in 15 (38%) cases. Although the ACE2 receptor is mainly expressed by cholangiocytes in the liver, ductopenia was not reported. Vascular alterations (*i.e.* phlebosclerosis, portal arteriolar muscular hyperplasia, focal fibrinoid necrosis, and sinusoidal thrombus) were less common (15%). Interestingly, no significant correlation was found between laboratory and histological findings. Wang *et al.*[35] demonstrated, in 2 deceased COVID-19 patients, that SARS-CoV-2 can infect the liver causing direct cytopathy. They also reported massive hepatic apoptosis as well as binuclear hepatocytes. However, due to the small sample size, further studies are needed to confirm these preliminary findings.

**COVID-19 IN PATIENTS WITH A PRE-EXISTING CLD**

Immune dysregulation is known to affect people with CLD or cirrhosis, leading to the concern that these patients are at higher risk of having a more severe form of COVID-19[36]. A limited number of studies have investigated the role of COVID-19 in patients with a pre-existing CLD and most of them only included a limited number of patients from a restricted geographical area. It is to be noted that all these studies reported a higher mortality rate among CLD patients[37-43]. Marjot *et al.*[43] conducted one of the largest studies of CLD cases (745 patients) from 29 different countries. They showed
ALT: Alanine aminotransferase; ARDS: Acute severe respiratory distress syndrome; AST: Aspartate aminotransferase; COVID-19: Coronavirus disease 2019; GGT, Gamma-glutamyl transpeptidase; ICU: Intensive care unit.

Table 1 Main studies reporting liver involvement in patients without pre-existing liver disease

| Ref.          | Country   | Patients | Liver involvement criteria                  | Patients with liver involvement, n (%) | Main findings                                                                 |
|---------------|-----------|----------|---------------------------------------------|---------------------------------------|------------------------------------------------------------------------------|
| Fan et al[33] | China     | 148      | ALT > 40 U/L or AST > 35 U/L                | 55 (37.2)                            | Abnormal liver function is common in COVID-19 inpatients, leading to a longer hospital stay |
| Goyal et al[17]| United States | 375    | ALT > 40 U/L                                | 120 (32)                             | Mechanically ventilated patients more likely to have liver involvement.     |
| Lenti et al[29]| Italy    | 100      | ALT > 40 U/L or AST > 50 U/L                | 58/93 (62.4)                         | Liver involvement correlate to higher mortality and ICU need in those who develop ARDS |
| Medetalibeyoglu et al[32]| Turkey | 554      | ALT or AST > 40 U/L                         | 153 (27.6)                           | Higher rate of moderate-to-severe pneumonia and ICU admission need in patients with liver involvement |
| Phipps et al[31] | United States | 2273    | ALT > 50 U/L                                | 537 (24)                             | Severe liver involvement was rare (6.4%) and led to worse outcomes (ICU admission, higher mortality) |
| Porziani et al[30]| Italy    | 515      | AST > 45 U/L or ALT > 45 U/L or GGT > 61   | 161 (31.3)                           | No cases of severe liver injury in this cohort. Liver involvement was generally mild and, although correlated to a higher need of ICU care, not associated to higher mortality |
| Richardson et al[77] | United States | 5700    | ALT > 60                                    | 2176 (39)                            | Acute liver injury occurred in 1% of the included patients and was associated with higher mortality |
| Schattenberg et al[28]| Germany   | 44       | ALT > 50 U/L                                | 6/38 (15.8)                          | Severe liver involvement was rare (9%), with AST more commonly deranged than ALT |

that CLD was associated with increased mortality according to the Child-Pugh class. They reported an increase in mortality, ranging from 19% in Child-Pugh-A patients to 51% in Child-Pugh-C patients. Although mortality has consistently reported to be increased in CLD patients, respiratory failure was found to be the main cause of death in these patients. Interestingly, alcohol-related liver disease was found to be independently associated to higher mortality. Liver decompensation was also reported to be common in cirrhotic patients (46%) with half of them having acute-on-chronic liver failure[44].

Among patients with CLD, liver transplant recipients were thought to represent a high risk category due to their frailty, comorbidities, and immunosuppressant therapy. Only few studies evaluated their clinical outcomes, showing conflicting results. Additionally, the majority of these studies are small case series in which patients did not always have the confirmation of SARS-CoV-2 infection[45-49]. Complying with preventive measures (i.e. frequent hand washing/sanitisation, use of surgical mask in public places and avoidance of public or crowded places) has been found effective to reduce the infection rate in this population[49]. A large multinational registry-based study[50], including 151 transplanted patients with laboratory-confirmed infection, showed that liver transplantation was not independently associated with higher mortality, hospitalisation rate or intensive care unit admission, whereas age and comorbidities were[47,50]. Tables 2 and 3 report the main studies focusing respectively on the outcome of COVID-19 in patients with CLD and in those with a transplanted liver.

**SPLEEN IMPAIRMENT IN COVID-19**

Spleen impairment in patients with COVID-19 has been poorly described. It is assumed that it may be driven by several mechanisms, including direct organ attack by the virus, cytokine-mediated immune pathogenesis, microvascular dysfunction, and lymphocyte apoptosis (Figure 2)[51].

Coronavirus detection in biopsies and autopsies has shown a tropism of this virus family for the spleen. The first available evidence is related to studies carried out on patients infected with SARS-CoV[11,52] and in experimental models of the Middle East respiratory syndrome[53]. In 2020, through immunohistochemistry techniques and the real-time reverse-transcript polymerase chain reaction assay, the SARS-CoV-2 nucleocapsid protein and the RNA were detected in the spleen tissue[54-56].
Table 2 Main studies reporting outcomes in patients with pre-existing chronic liver disease

| Ref.       | Country    | Patients | Patients with CLD, n (%) | Main findings                                                                 |
|------------|------------|----------|--------------------------|-------------------------------------------------------------------------------|
| Bajaj et al [40] | United States | 272      | 37 (13.6)                | Higher mortality in cirrhotic COVID-19 positive patients                       |
| Hashemi et al [41] | United States | 363      | 69 (19)                  | CLD patients had higher ICU admission and mechanical ventilation rate. CLD was a predictor of mortality |
| Iavarone et al [42] | Italy | 50       | 50 (100)                 | COVID-19 infection led to liver function deterioration. CLD patients had increased mortality |
| Marjot et al [43] | International | 1365    | 745 (54.6)               | CLD correlate to higher mortality rate according to the CPT class. ALD was an independent risk factor for mortality |
| Qi et al [39] | China      | 21       | 21 (100)                 | Respiratory failure was the cause of death in most patients                   |
| Singh et al [37] | United States | 250    | 60 (46.1)                | Pre-existing CLD patients had higher hospitalisation and mortality rates       |
| Sarin et al [38] | International | 228    | 228 (100)                | Decompensation of pre-existing CLD occurred in one fifth of cirrhotic patients |

CLD: Chronic liver disease; COVID-19: Coronavirus disease 2019.

Table 3 Main studies reporting outcomes in liver transplant patients

| Ref.       | Country    | Patients | Patients with LT | Main findings                                      |
|------------|------------|----------|------------------|---------------------------------------------------|
| Bhoori et al [45] | Italy | 151 (COVID-status unknown) | 151 (100) | 3 deaths recorded in long-term LT recipient on low immunosuppressant dose |
| Belli et al [47] | International | 103       | 103 (100)       | Mortality might correlate with age and longer time since LT                            |
| Donato et al [49] | Italy | 640 (8 COVID positive) | 640 (100) | Low prevalence of infection in LT patients who adhere to preventive measures |
| Lee et al [48] | United States | 38       | 38 (100)       | High mortality in LT patients regardless of time since transplant                      |
| Pereira et al [46] | United States | 90       | 14 (15)        | Solid organ transplant recipient had more severe outcomes                               |
| Webb et al [50] | International | 778     | 151 (19.4) | LT patients did not have a higher mortality, ICU admission or hospitalisation rate; age and comorbidities correlated with outcomes |

COVID: Coronavirus disease; ICU: Intensive care unit; LT: Liver transplant.

This tropism of coronaviruses for the spleen, as for other organs, seems to be mediated by the presence of the ACE2 receptor. In fact, a study published in 2004 already described ACE2 receptors in the red pulp sinus endothelium[57]. More recent studies have confirmed the expression of ACE2 receptor in the splenic tissue, although at lower levels compared to others (i.e. small intestine, testis, kidneys, heart, thyroid, and adipose tissue)[58,59]. These studies also highlighted no difference, according to sex and age, in ACE2 receptor expression. Further immunohistochemical studies detected this receptor in tissue-resident CD169+ macrophages[34].

Autopsy studies have revealed interesting anatomical changes in the spleen during SARS-CoV-2 infection[60-63], including a reduction in the splenic cellular composition, with a specific depletion of T and B lymphocyte pools. Some authors assumed that this lymphocytopenia was linked to SARS-CoV-2-induced apoptosis, via Fas/Fas-ligand signalling, as well as increased interleukin (IL)-6 secretion by macrophages[34]. Furthermore, other frequent histopathological features were the white pulp atrophy and the reduction or absence of lymphoid follicles, with increased red pulp to white pulp proportion. In addition, spleen autopsies frequently showed a congested and haemorrhagic appearance. Microscopic studies of splenic vessels revealed, in many cases, a splenic infarction due to arterial thrombosis and proliferation of fibrous tissue in the sinuses.
Table 4 Summary of the main studies reporting coronavirus disease 2019 (COVID-19) related spleen dysfunction

| Ref.          | Country    | Patients | Patients with spleen involvement, n (%) | Main findings                                                                 |
|---------------|------------|----------|----------------------------------------|-------------------------------------------------------------------------------|
| Feng et al[54]| China      | 6        | 6 (100)                                | ACE2 expression on tissue-resident CD169+ macrophages in spleen; viral NP antigen found in ACE2+ cells in spleen; direct damage of spleen tissue (lymph follicle depletion, splenic nodule atrophy, lymphocyte reduction, etc.) |
| Remmelink et al[55] | Belgium    | 17       | 11 (65)                                | SARS-CoV-2 RNA detected in spleen autopsy samples by RT-PCR assay            |
| Sekulic et al [56] | United States | 2       | 2 (100)                                | SARS-CoV-2 RNA detected at high level in spleen FFPE samples by RT-PCR assay |
| Han et al[58]  | China      | 7356     | NA                                     | Expression of ACE2 in spleen tissue (lower than in other tissues), without difference according to sex |
| Li et al[59]   | China      | 31       | NA                                     | Expression of ACE2 in spleen tissue (lower than in other tissues), without difference according to sex and age |
| Xu et al[60]   | China      | 10       | 10 (100)                               | Decrease in spleen cell composition with decrease in lymphocyte components, white pulp atrophied, lymphoid follicles decreased or absent, increase in red pulp to white pulp ratio |
| Menter et al[61] | Switzerland | 21      | 6 (29)                                 | Acute splenitis and/or septic neutrophilic leucocytosis of the red pulp, suggesting vascular dysfunction in patients with COVID-19 |
| Lax et al[62]  | Austria    | 11       | 10 (90)                                | White pulp atrophy due to lymphocyte depletion, areas of haemorrhage with acute or chronic congestion |
| Duarte-Neto et al[63] | Brazil     | 5        | 5 (100)                                | Lymphoid hypoplasia in 100%, red pulp haemorrhages in 60%, splenitis in 40%, extramedullary haematopoeisis in 50%, endothelial changes in 80%, vasculitis and arterial thrombus in 20% |
| Lenti et al[64] | Italy      | 63       | 55 (87.3)                              | IgM memory B cell depletion that correlates with increased mortality and superimposed infections |
| Kaneko et al[65] | United States | 11     | 11 (100)                               | Loss of spleen germinal centres due to depletion of Bcl-6+ germinal centre B cells and Bcl-6+ germinal centre T follicular helper cells, resulting in a dysregulated humoral immune response |

COVID-19: Coronavirus disease 2019; FFPE: Formalin-fixed paraffin-embedded; NA: Not available; NP: Nucleocapsid protein; RT-PCR: Real-time reverse-transcript polymerase chain reaction; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

The functional impact of these anatomical damages has been poorly investigated. A recent study[12] assessed the splenic immunological function through the detection of circulating IgM+ IgD+ CD27+ B lymphocytes, also known as IgM memory B cells, a unique B cell population in the marginal zone of the spleen which plays a major role in early inflammatory responses, including those caused by viral and bacterial infections [64]. A high prevalence of persistent IgM memory B cell depletion was demonstrated in patients with COVID-19, resulting in a higher mortality rate and an increased risk of developing superimposed bacterial infections. Other molecular studies have suggested that the loss of germinal centres may be due to the depletion of Bcl-6+ germinal centre B cells and Bcl-6+ germinal centre T follicular helper cells, resulting in a dysregulated immune response during the SARS-CoV-2 infection[65]. Although further studies are needed, it can be assumed that splenic involvement could be one of the causes of immune perturbations associated with severe COVID-19[66]. It still has to be ascertained whether the spleen immunological defect is reversible or not. Conversely, the haemocateretic function, assessed by counting pitted red cells (PRCs; red cells with membrane abnormalities [pits] visible under interference phase microscopy[67]) was preserved in patients with acute COVID-19, contrary to what happens in asplenia and spleen hypofunction[12]. The long average life span of circulating erythrocytes (approximately 120 d) might explain the lack of PRC increase in the acute phase of COVID-19.

COVID-19 IN ASPLENIC OR HYPOSPLENIC PATIENTS

It is well known that asplenic or hyposplenic patients are predisposed to a greater risk of developing serious infections or overwhelming post-splenectomy infections, due to the defect in mounting the immune response against encapsulated bacteria[67,68].
Starting from these premises, it would be interesting to know whether patients with asplenia or spleen dysfunction could be more susceptible to Sars-CoV-2, both in terms of severity and incidence of the disease. Indeed, apart from a document drafted by the British Society of Haematology, stating that asplenic and hyposplenic patients are not exposed to a major risk of COVID-19, data regarding this population are completely missing\[69\]. Moreover, it is unknown whether patients who might develop spleen hypofunction as a consequence of COVID-19 could be more exposed to infections sustained by encapsulated bacteria and less responsive to vaccine immune-prophylaxis.

According to a single-centre, longitudinal, prospective, study conducted in an academic, tertiary referral hospital from Northern Italy, asplenic/hyposplenic patients did not seem to have an increased risk of developing COVID-19. The study had the purpose of characterising the spleen function, through circulating IgM memory B cell and PRC detection, in patients with COVID-19, in relation to their clinical outcome. Overall, 66 COVID-19 patients (mean age: 74 ± 16.6 years; 29 females) were enrolled; three patients had been splenectomised for trauma, all of them having IgM memory B cell depletion, and one of them died. Most COVID-19 patients had marked IgM memory B cell depletion, and this was associated to a higher mortality rate and a higher risk of developing superimposed infections\[12\]. Another important study conducted to identify, quantify, and analyse factors associated with COVID-19-related death in one of the largest cohort studies on this topic conducted so far (primary care records of 17278392 adults were linked to 10926 COVID-19-related deaths), considered asplenia as a comorbidity of interest. The results showed that 0.2% of the study population were affected by asplenia, and that the proportion of COVID-19-related death was 0.14%. In addition, asplenic COVID-19 patients had a 1.62 higher risk of death than individuals with a normal spleen function\[70\].

Indeed, further studies are needed to clarify the impact of SARS-CoV-2 in patients without a spleen or with spleen dysfunction. Table 4 reports the main studies reporting COVID-19 related spleen dysfunction.

**CONCLUSION**

While the involvement of the respiratory system in SARS-CoV-2 infection is well established, the impact on the liver and spleen has not been explored much. Some studies have shown a direct tropism of the virus for these organs, and this may be one of the mechanisms underlying their damage, in association with the systemic inflammatory response. Regarding the liver, its involvement seems to be quite common, especially in more severe cases of infection, resulting in a worse prognosis for these
patients. The spleen involvement, on the other hand, has been poorly investigated. The splenic immune function appears to be defective in COVID-19 patients, resulting in a higher mortality rate and superimposed infections. Further studies may lead to a better diagnostic and therapeutic approach in SARS-CoV-2-infected patients, especially those with pre-existing liver and spleen diseases, who seem to be at higher risk of a worse outcome.

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