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Abnormal Liver Function Tests in Patients With COVID-19: Relevance and Potential Pathogenesis

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The current pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has led to over 6 million cases and over 370,000 deaths as of June 1, 2020.[1] Although most patients infected with SARS-CoV-2 develop only mild symptoms, a minority of patients require hospitalization and intensive care.[2] Based on the available clinical data, abnormal liver function tests (LFTs) are frequently observed in patients with coronavirus disease 2019 (COVID-19), of which the underlying pathogenesis is incompletely understood. We reviewed the available information on the prevalence, nature, relevance, and the potential pathogenesis of altered LFTs in patients with COVID-19.

Epidemiology of Abnormal LFTs in Patients With COVID-19

Liver function tests include measures of hepatocyte injury (aspartate transferase [AST] and alanine transferase [ALT]), bile duct injury or cholestasis (alkaline phosphatase [ALP] and gamma-glutamyltransferase [GGT]), markers of hepatic clearance/biliary secretion capacity (bilirubin), as well as measures of synthetic capacity (prothrombin time and albumin). LFTs are not necessarily liver-specific. It has been suggested that elevated aminotransferases in COVID-19 could also originate from myositis rather than liver injury.[3] In a large descriptive study, the muscle damage marker creatinine kinase was elevated in 14% of patients with COVID-19.[4] Hypoalbuminemia was reported in 55% of hospitalized patients with COVID-19[5] and was associated with disease severity.[6] Hypoalbuminemia was an independent predictor of mortality.[7] Lower levels of pre-albumin in patients with severe COVID-19 were reported, suggesting decreased hepatic synthesis.[5] In the context of inflammation, hypoalbuminemia may also reflect albumin extravasation as a consequence of increased capillary permeability.[8] Additional factors that could explain the observed hypoalbuminemia in severe COVID-19 are increased catabolism and malnutrition.

The prevalence of ALT elevations among patients with COVID-19 ranged between 4% and 33% in Chinese cohorts (weighted average: 19%), but was as high as 39% in a large cohort from the New York City area[5,9-21] (Fig. 1). ALT elevations were generally mild, defined as less than 5 times the upper

Abbreviations: ACE2, angiotensin-converting enzyme 2; ALT, alanine transferase; AST, aspartate transferase; COVID-19, coronavirus disease 2019; CSS, cytokine storm syndrome; DIC, disseminated intravascular coagulation; GGT, gamma-glutamyltransferase; LFT, liver function test; MOF, multi-organ failure; NAFLD, nonalcoholic fatty liver disease; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TMPRSS2, transmembrane serine protease 2.

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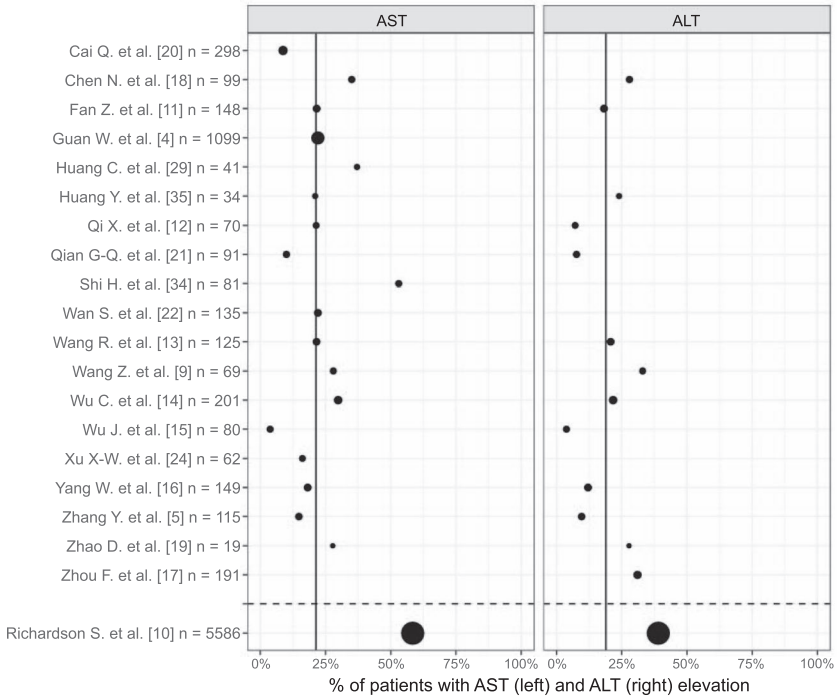

FIG. 1. Percentage of hospitalized COVID-19 patients with AST or ALT elevations on admission. The studies summarized included patients with all levels of disease severity. The size of the dots reflects the relative number of patients included in each study. The upper panels represent Chinese cohorts, whereas the lower panel represents a US cohort. The weighted averages are represented by the vertical black lines and refer to the Chinese cohorts.

reference limit.[9,10,14-19,21-34] The prevalence of AST elevations ranged between 4% and 53% in Chinese cohorts (weighted average: 21%) and was 58% in the US cohort[4,5,9-16,18,19,21,22,24,25,29,34,35] (Fig. 1). AST elevations were similarly less than 5 times the upper reference limit.[9,10,14-16,18,19,21-31,34,36] AST and ALT elevations had also been reported in patients with SARS caused by SARS-CoV.[37] Several case reports have described severe LFT abnormalities[18,38,39] or acute-on-chronic[40,41] liver failure in patients with COVID-19. Zhang et al.[33] reported that 1 of 82 deceased patients with COVID-19 had a hepatic cause of death, although it was not clear whether this patient had pre-existing liver disease.

Elevated ALP was reported in 2%-5% of patients,[5,11,25,42] and elevated GGT was reported in 13%-54% of patients (weighted average: 23%).[5,11,19,42] The prevalence of total bilirubin elevations ranged between 1% and 18% of patients with COVID-19 on admission.[4,5,15,16,18,25,35,43] It should be realized,

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however, that pre-existing liver disease was not comprehensively described in any of these studies.

Stratification of patients with COVID-19 according to disease severity, including the extent of respiratory distress and the need for intensive care unit (ICU) admission, indicated that plasma ALT and AST were elevated more frequently and to a greater extent in patients with severe COVID-19 compared to those with mild disease.[4,5,9,14,22,23,29,31,43-47] This was also the case for patients with SARS during the 2002-2004 SARS outbreak.[37]

The prognostic value of abnormal LFTs in COVID-19 is unclear. Some studies found that abnormal LFTs, particularly elevated AST and (peak) ALT, are associated with increased disease severity and mortality,[17,20,46,47] whereas other studies did not find an association with mortality,[48] disease progression,[5] ICU admission,[27,48] or length of hospital stay.[11]

Potential Pathogenesis of Abnormal Liver Function Tests in Patients With COVID-19

HEPATIC INFECTION WITH SARS-CoV-2

SARS-CoV-2 uses the angiotensin-converting enzyme 2 (ACE2) as docking and entry receptor on host cells.[49] Transmembrane serine protease 2 (TMPRSS2) is also involved in its cellular entry.[50]

Theoretically, direct virus-induced cytopathic effects could play a role in LFT abnormalities in COVID-19.[51] To determine whether SARS-CoV-2 is able to infect the liver, ACE2 expression has been studied in liver cells. Single-cell RNA-sequencing approaches indicated that ACE2 mRNA is expressed in a subpopulation of cholangiocytes, not or minimally in hepatocytes, and not in any other liver cell type.[52-55] In line with this, at the protein level, ACE2 was visualized by immunohistochemistry in a subset of cholangiocytes, but not in hepatocytes.[56,57] TMPRSS2 mRNA expression was found in a subset of hepatocytes and cholangiocytes.[58] Zhao et al. infected human liver ductal organoids with SARS-CoV-2 and showed increased expression of viral mRNA at 24 hours after infection.[59] In these organoids, 3% of cells co-expressed ACE2 and biliary markers, and of these, 68% co-expressed TMPRSS2. ACE2 expression in endothelial cells is debated.[56,57]

ACE2 is highly expressed on the brush border of small intestinal enterocytes.[56,57] Accordingly, SARS-CoV-2 infection was observed in human small intestine organoids,[60] and SARS-CoV-2 nucleocapsid was detected in the cytoplasm of intestinal biopsies of a patient with COVID-19.[61] Patients with COVID-19 with gastrointestinal symptoms were not more likely to have abnormal LFTs.[62] In a minority (<15%) of patients with COVID-19, viral RNA was detected in blood by PCR in low amounts.[29,63,64] Assuming brisk viral replication in the intestine, it appears plausible that viruses could enter the portal circulation to reach the liver. Hepatic Kupffer cells would attempt to clear the virus and initiate an inflammatory response. It is also possible that inflammatory mediators from the intestine could enter the portal system and sinusoids.

Evidence for direct hepatic infection was provided by showing SARS-CoV-2 particles without membrane-bound vesicles in the cytoplasm of hepatocytes of 2 patients with COVID-19 with LFT abnormalities.[45] However, no confirmatory PCR testing for viral nucleic acids was performed, leaving the possibility that these "spiked" inclusions could be of different origin.[65]

ROLE OF THE HOST INFLAMMATORY RESPONSE TO SARS-CoV-2 INFECTION

Following SARS-CoV-2 infection, the host immune response can be rapid and controlled, resulting in disease resolution with no or mild symptoms, or delayed and dysregulated, resulting in host-damaging complications. COVID-19 complications include acute respiratory distress syndrome, a coagulopathy reminiscent of disseminated intravascular coagulation (DIC) and thrombotic microangiopathy, multi-organ failure (MOF), and ultimately death.[66] An excessive release of early-response inflammatory factors, especially IL-6, IL-10, IL-2 and interferon gamma, correlates with disease severity[67] and may reflect cytokine storm syndrome (CSS). CSS is an excessive or uncontrolled release of pro-inflammatory cytokines that is associated with MOF.[68] The cascade of events leading to MOF includes an early phase of endothelial damage

and extravasation of inflammatory cells and release of mediators, and a later phase that includes amplification of inflammation and cell damage, which could affect various organs including the liver (bystander effect).[68] Additionally, CSS may result in DIC.[69] DIC is observed in critical and nonsurvivor patients with COVID-19, as evidenced by raised D-dimer levels and prolonged prothrombin time,[70] as well as autopsy findings of pulmonary embolism and thrombotic microangiopathy in multiple organs.[71]

Endothelitis was observed in the liver of patients with COVID-19,[72] and fibrin microthrombi were found in liver sinusoids.[73] The largest series of liver biopsies taken at autopsy (48 cases) reported massive dilation of portal vein branches, luminal thrombosis, portal tract fibrosis, and microthrombi in the sinusoids.[74] The altered LFTs observed in critical patients with COVID-19 could therefore be related to CSS leading to shock and coagulopathy, which affect liver perfusion and result in cell death. Indeed, several studies reported that patients with severe COVID-19 had higher plasma aminotransferases on admission compared to those with mild disease, concomitantly with higher inflammatory markers.[4,5,9,11,14,22,23,29,31,44,46,75]

In patients with mild COVID-19, abnormal LFTs on admission may not be related to general inflammation. Zhao et al.[19] compared patients with mild COVID-19 pneumonia to patients with non-COVID-19 pneumonia and comparable disease severity. There were no differences in C-reactive protein and IL-6 between the two groups. While none of the patients with non-COVID-19 pneumonia had elevations in AST, ALT, or GGT on admission, elevations were observed in 28%, 28%, and 44% of patients with COVID-19, respectively, suggesting that patients with mild COVID-19 may have LFT abnormalities independently of the inflammatory status. One explanation for these findings is that the specific inflammation caused by SARS-CoV-2 is more likely to cause LFT abnormalities compared with general inflammation elicited by other pathogens. Whether LFT abnormalities are present in patients with asymptomatic or paucisymptomatic COVID-19 who do not require hospitalization is unknown.

DRUG-INDUCED LIVER INJURY

Alterations in LFTs in patients with COVID-19 have been reported at hospital admission, implying that patients may develop these before starting drug treatment. However, a comprehensive description of pre-existing conditions and prior medication use is lacking.

Many medications used for the symptoms or the management of patients with COVID-19, such as acetaminophen, antivirals, antibiotics, corticosteroids and immune-modulators, are potentially hepatotoxic.

Fan et al.[11] retrospectively studied the relationship between medication use and LFTs in 148 patients with COVID-19. Among patients with no LFT abnormalities on admission, 48% developed them about a week after admission. Whereas 58% of those who developed LFT abnormalities after admission had received lopinavir-ritonavir, only 31% of those with normal LFTs had received it. However, due to the retrospective nature of this study, lack of treatment randomization should be taken into account. Cai et al. reported 7 times higher odds of LFT alterations after the use of lopinavir-ritonavir.[20] In contrast, in a clinical trial including 199 patients with severe COVID-19, the AST, ALT, and total bilirubin elevations were not more frequent in the lopinavir-ritonavir group compared with those given standard care. Patients with severe liver disease were excluded from the trial.

Remdesivir was recently reported to be superior to placebo in shortening the time to recovery of hospitalized patients with COVID-19.[76] In a trial comparing remdesivir treatment for either 5 or 10 days, severe but not immediately life-threatening ALT/AST elevations were reported in 4%-6% of patients, and life-threatening AST/ALT elevations in 2%-3% of patients, necessitating treatment discontinuation.[77]

Acetaminophen is frequently used for COVID-19 symptom relief and can cause alterations in aminotransferases even at therapeutic doses.[78] However, no studies have assessed its role in COVID-19 management specifically.

Preliminary data did not associate hydroxychloroquine treatment with significant LFT abnormalities.[79,80]

PRE-EXISTING LIVER DISEASES AND COVID-19

Abnormal LFTs at admission could result from pre-existing (chronic) liver diseases. Reported prevalence rates of pre-existing liver disease in patients with COVID-19 vary from 1%-11%.[42,47,81,82] As

most studies reporting LFTs are retrospective, the aforementioned numbers are subject to underreporting, but it appears unlikely that pre-existing liver disease accounts for all observed abnormalities in LFTs.

Whether the presence of pre-existing liver disease could affect the course of COVID-19 and *vice versa* is largely unclear. Plasma inflammatory markers were not more elevated in patients with chronic liver diseases,[44,47] and no association was found between pre-existing liver disease and COVID-19 severity or mortality.[83] However, chronic liver disease comprises a spectrum of conditions that may differentially affect outcomes. Patients with advanced liver disease are generally at an increased risk of infection due to cirrhosis-associated immune dysfunction.[84] Another patient category that raises concerns is liver transplant recipients and patients with auto-immune liver disease receiving immunosuppressant drugs. However, based on currently available data, there is no reason to believe that these patients are at a higher risk of infection or more severe complications compared with the general population.[85,86] One study reported high mortality in liver transplant recipients, but these patients also displayed comorbidities.[87] It is speculated that immunosuppression could even be beneficial, as it might reduce the risk of developing a hyper-inflammatory state and CSS. Conversely, however, it may increase virus-induced injury and the risk for bacterial or fungal superinfection.

METABOLIC DYSFUNCTION–ASSOCIATED FATTY LIVER DISEASE AND COVID-19 SEVERITY

Several studies have identified obesity as a significant risk factor for the severity of COVID-19 disease, independent of associated co-morbidities such as age, type 2 diabetes mellitus, and hypertension.[51,88-93] Nonalcoholic fatty liver disease (NAFLD), also known as nonalcoholic associated fatty liver disease, is highly associated with obesity but also observed in lean individuals.[94] In the initial studies characterizing patients with COVID-19, NAFLD was rarely reported, but as a common (and possibly asymptomatic) hepatic condition, it may account for some of the LFT alterations observed on admission. Moreover, it could explain the differences in ALT/AST prevalence observed between the large US cohort and the Chinese cohorts (Fig. 1). NAFLD prevalence is higher in the United States (24%) than in China (15%).[95] NAFLD is closely related to obesity and other lifestyle-related metabolic disorders (e.g., type 2 diabetes). In the U.S. COVID-19 cohort, 42% of patients were obese and 34% had diabetes.[10] In contrast, in the largest Chinese cohort, obesity was not reported, but diabetes prevalence was 15%.[4]

Patients with NAFLD displayed more rapid disease progression and longer viral shedding time compared to patients without NAFLD.[96] Increased risk for severe disease was observed if NAFLD was present alongside obesity,[97] in patients without diabetes,[98] in younger patients,[99] and in patients with increased hepatic fibrosis scores.[100] Although it is unclear how obesity and NAFLD could increase COVID-19 severity, similar pathways relating to alterations in the immune response, macrophage activation and (low-grade) inflammation, often present in both conditions, are thought to play a key role.[100-103] NAFLD increases hepatotoxicity of certain drugs, including acetaminophen, which could also aggravate LFT alterations in the course of COVID-19.[104,105]

OTHER CAUSES OF LFT ELEVATIONS IN CRITICALLY ILL PATIENTS

In critical patients with COVID-19, hepatic injury may be caused by changes in hemodynamics and oxygen delivery. Hypoxic hepatitis can cause sharp increases in aminotransferases in the setting of respiratory failure, shock, or cardiac failure.[106] During acute cardiac failure, which may occur in critical patients with COVID-19,[107] the systemic arterial pressure suddenly drops, leading to a reduction in hepatic arterial perfusion and hepatocellular hypoxia. The pathogenesis comprises not only hepatic ischemia, but also hepatic venous congestion due to elevated central venous pressure, which may predispose hepatocytes to even more significant hypoxic injury.[108] Similar hemodynamic alterations in the liver may occur in mechanically ventilated patients in response to high positive end-respiratory pressure (PEEP).[109,110] Whether these hemodynamic alterations can alter LFTs is unclear.[110] Importantly, the use of high PEEP is usually unnecessary for the respiratory management of patients with COVID-19, as lung compliance is relatively high.[111]

Conclusions

Mildly abnormal plasma LFTs, especially AST and ALT, are frequently observed in patients with COVID-19 on admission and are associated with severe disease and increased inflammatory markers. In general, abnormal LFTs in patients with COVID-19 do not lead to significant liver function impairment or failure, and liver-directed treatment is unnecessary.

The pathogenetic mechanisms for abnormal LFTs in COVID-19 are not fully understood: They are likely multifactorial and, while direct SARS-CoV-2 infection in hepatocytes and/or cholangiocytes appears unlikely, microthrombotic endothelialitis, immune dysregulation, drug-induced liver injury, and hepatic ischemia related to hypoxia and MOF could all play a role.

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