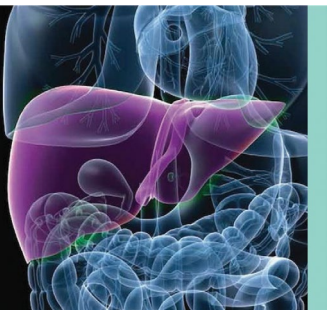

Interrelationship Between Coronavirus Infection and Liver Disease

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The novel coronavirus severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) is currently estimated to have infected more than 3 million individuals worldwide and causes the clinical syndrome of coronavirus disease 2019 (COVID-19). Although the primary clinical manifestation is pulmonary disease, increasing data support the involvement of multiple organ systems, including the gastrointestinal (GI) tract and liver, with more than 60% of patients presenting with GI symptoms (anorexia, diarrhea, nausea, and vomiting) and a significant proportion presenting with elevated liver biochemistries.[1-4]

The SARS-CoV-2 virus is an enveloped, single-stranded virus, and the angiotensin-converting enzyme 2 (ACE2) receptor is thought to be a major receptor for the viral spike protein and critical for infectivity.[5,6] The ACE2 protein is found at high levels in the colon, biliary system, and liver,[7] and RNA shedding in the GI tract is well described.[8] These data suggest that the SARS-CoV-2 may have tropism for the GI tract and liver, and that these may be sites of active viral replication and either direct or indirect tissue injury (Fig. 1).

Liver injury in the setting of COVID-19–related illness poses a unique challenge to the clinician. First, there is often uncertainty whether there is preexisting undiagnosed liver disease. Second, many of the medications used to treat moderate and severe disease have their own profiles of liver toxicity. Finally, in the subset of patients who experience critical illness, multiple factors may influence the trajectory of liver injury. We summarize what is known about liver injury in COVID-19 and provide diagnostic clues to contributing factors to the liver biochemical profile.

EPIDEMIOLOGY AND CLINICAL ASSOCIATIONS OF LIVER INJURY IN COVID-19

Several published studies have characterized the frequency and severity of liver biochemistry abnormalities on presentation, and a few have determined whether these abnormalities are associated with increased disease-related morbidity or death, as summarized in

Abbreviations: ACE2, angiotensin-converting enzyme 2; ALT, alanine aminotransferase; AST, aspartate aminotransferase; COVID-19, coronavirus disease 2019; FDA, US Food and Drug Administration; GGT, gamma-glutamyl transferase; GI, gastrointestinal; OR, odds ratio; PT, prothrombin time; SARS, severe acute respiratory syndrome.

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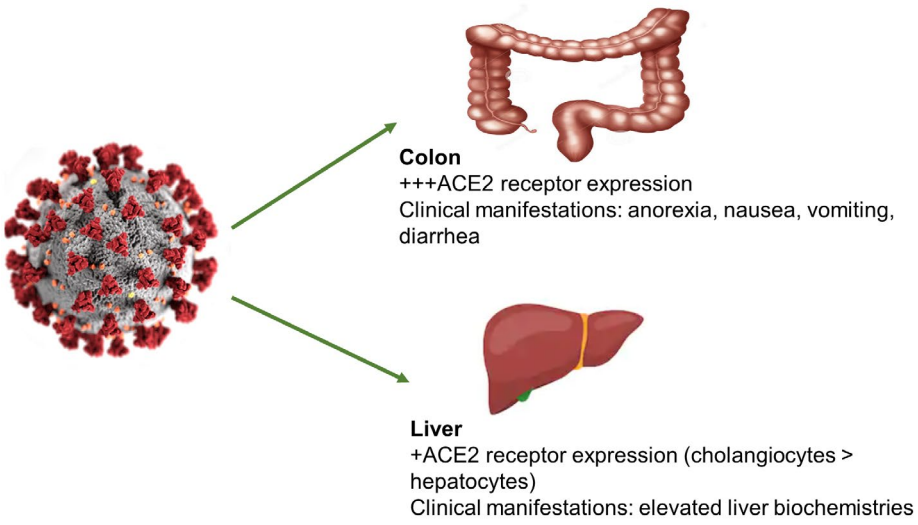

FIG 1 SARS-CoV-2 and the GI tract and liver.

TABLE 1. FREQUENCY OF LIVER BIOCHEMISTRY ABNORMALITIES ON ADMISSION AND ASSOCIATION WITH OUTCOMES

Laboratory Test	% Patients With Abnormal Value*	Association With Severe Disease†	Association With Death	Comments
AST	16%-58%[9,10,12,16-19]	Yes[13,14,16,18]	Yes[21]	In 1 review of 12 published and unpublished reports, AST was the most frequently elevated biochemistry, and more frequently abnormal in severe disease[22]
ALT	13%-39%[9,10,12,17,23]	Yes[13,16,18] No[20]	Yes[21,23]	Risk for in-hospital death is associated with ALT > 40 (OR: 2.87 [1.48-5.57]; $P = 0.0018$) and PT ≥ 16[23]
Alkaline phosphatase	5%[12]	Yes[13]		
TBili	11%-23%[10,12,17]	Yes[16] No[13,18]		
Albumin	38%-98%[17,18]	Yes[16,18,20,24]	Yes[23]	Murray lung injury score is highly correlated with albumin ($r = -0.959$, $P < 0.001$)[24]
GGT	16%[12]	Yes[13]		Increase in GGT in one study was observed despite normal alkaline phosphatase level[12]
PT	5%-6%[17,23]	Yes[16] No[18]	Yes[23]	Elevated PT on admission significantly associated with risk for death (OR: 4.62 [1.29-16.50]; $P = 0.019$)[23]

*Above normal limits, as designated by study authors.
†Abnormal laboratory value at any point in disease course. Severe disease is a composite definition composed of author designation of "severe disease," disease progression, lung injury, and intensive care unit level care. Abbreviation: TBili, Total Bilirubin

Table 1.[9,10,12-14,16-24] The largest published study to date encompassed 5700 hospitalized patients in New York and examined admission serologies: aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were both frequently elevated (58.4% and 39.0% of subjects, respectively), and a separate large cohort found elevations to be more common in severe disease.[9] Two studies suggest that a higher proportion (44%-81%) of patients with underlying liver disease had abnormal liver biochemistries on admission.[11,12] Elevations have been generally modest on admission, but available data suggest they become more frequently (93% in one series) and more severely deranged during the course of hospitalization.[12-14] Furthermore, liver impairment at admission has not been consistently associated with length of hospital stay,[11,15] but has been found to correlate with time from illness onset to admission and with adverse outcomes.[14,15] Liver biochemistries do not appear to be associated with GI manifestations in COVID-19.[2]

PATTERNS OF LIVER INJURY

Aminotransferase elevation is the most common abnormality in patients presenting with COVID-19 (Table 1).

Published reports suggest that AST is more frequently elevated than ALT.[9,10,13,22] Elevated alkaline phosphatase is rare, and an increase in bilirubin has less commonly been observed. However, interestingly, one report found elevated gamma-glutamyl transferase (GGT) levels in nearly 50% of subjects.[12] The trajectory of liver biochemistry changes during hospitalization for COVID-19 infection is marked by elevation in aminotransferases, with rare severe liver injury, and liver test abnormalities are more frequent in patients with more severe COVID-19.[12,14]

This pattern of liver injury is unlike that commonly observed in other forms of viral hepatitis, such as hepatitis B and C, but at least one report describes a similar pattern during influenza A/H1N1 influenza infection.[25,26] In the prior severe acute respiratory syndrome (SARS) outbreak of 2003, a similar pattern of liver injury was observed.[27] The pattern of abnormal liver biochemistries characterized by an AST level greater than ALT, with accompanying GGT elevation, is also commonly encountered in both alcoholic liver disease and ischemic or congestive liver injury.[28] Thus, the liver injury observed in COVID-19 may reflect a direct viral effect, but other potential contributors must be considered, both at the time of initial presentation and during disease progression and management.

POTENTIAL CAUSES OF LIVER INJURY IN COVID-19

Hepatic injury from SARS-CoV2 infection is observed from the time of initial contact with the medical system, suggesting that the primary insult is unrelated to medical management but rather due to either direct effect of the virus or a consequence of the systemic disease. However, the trajectory of liver injury is likely influenced by multiple additional factors (Fig. 2).

There may be a direct viral cytopathic effect, given the known presence of the ACE2 receptor in the liver.[5,29] In SARS infection, viral RNA was detected in liver tissue.[30,31] Further, recently published data suggest that mitochondrial proteins may directly interact with the virus,[32] providing a potential mechanistic explanation for the AST-dominant injury profile. Alternatively, the robust inflammatory response seen in COVID-19 may play a central role. The immune response to SARS-CoV-2 is characterized by very high levels of IL-6,[33] which has been implicated in both the inflammatory and the repair responses in liver disease.[34]

Cardiomyopathy is a well-described consequence of COVID-19, occurring in 33% of individuals in one US series.[35] Thus, it is possible that cardiac dysfunction and

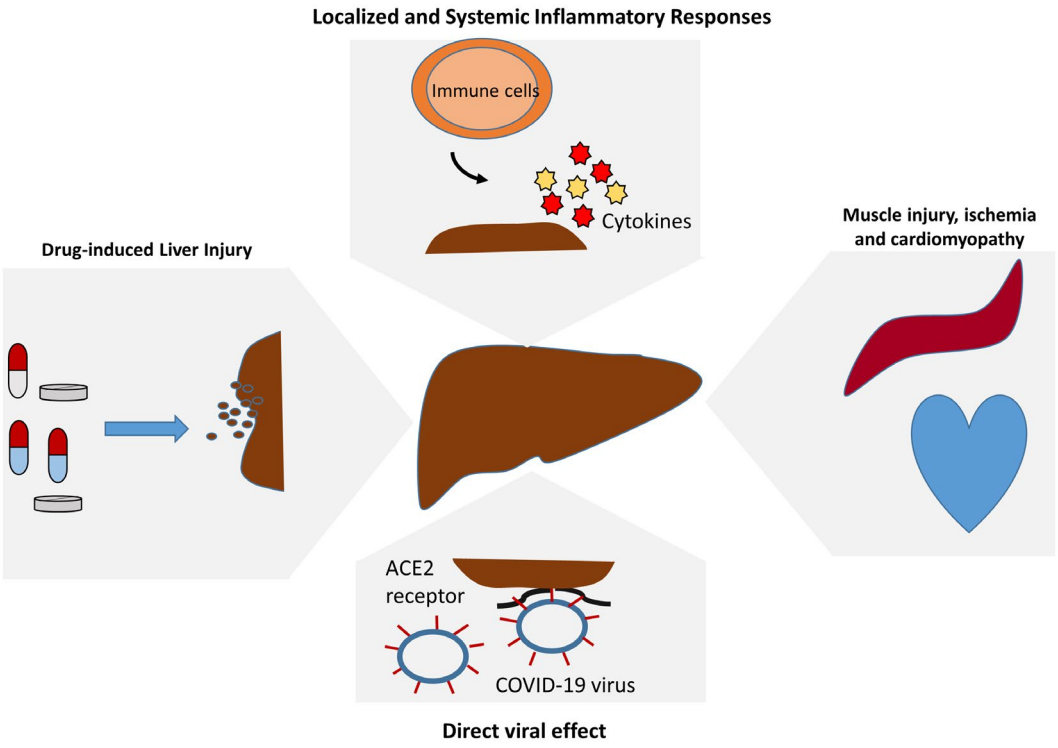

FIG 2 Potential mechanisms of liver injury and abnormal biochemistries.

TABLE 2. DRUGS COMMONLY USED IN COVID-19 AND HEPATOTOXICITY PROFILE

Drug	Liver Toxicity Score	Pattern of Injury	Time Frame of Injury	Comments
Acetaminophen	A	Hepatocellular	Protracted therapy (>4 g daily): 3-7 days Single overdose: 24-72 hours	Injury due to overdose is often associated with jaundice, confusion, renal insufficiency, and hepatic failure, at 48-96 hours
Azithromycin	A	Cholestatic > hepatocellular	Cholestatic: 1-3 weeks Hepatocellular: 1-3 days	Associated with fatigue, jaundice, abdominal pain, and pruritus
Statins	A/B	Hepatocellular > cholestatic	6 months to several years	
Hydroxychloroquine	C	Very rare	NR*	Case report level data
Lopinavir/ritonavir	D	Hepatocellular/cholestatic/mixed	1-8 weeks	May exacerbate underlying chronic viral hepatitis
Remdesivir	NA**	Hepatocellular	5-25 days	ALT elevation observed in the majority of healthy patients; FDA recommends hepatic function testing prior to initiating, and then daily while on therapy; stop drug if ALT > 5 times the upper limit of normal[41]

*Not reported.
**Not applicable.
Data are adapted from LiverTox (livertox.nih.gov).[43]

hepatic congestion contribute to hepatic injury in severe COVID-19 infection. Congestive hepatopathy may occur as a consequence of an acute cardiomyopathy, and it is commonly associated with elevations in aminotransferases and GGT.[36,37] Severe ischemic hepatitis is a condition characterized by severe AST-predominant hepatitis[38] and may be observed in critically ill patients with COVID-19. The infrequently observed alkaline phosphatase elevation occurs late in COVID-19 disease progression and could reflect the cholestasis of sepsis, critical illness,[39] or medication effect.

An increasing number of drugs are being investigated and empirically used in hospitalized patients with COVID-19. Many of these medications have a distinct risk, time course, and pattern of liver injury, as summarized in Table 2.[41] Remdesivir (a nucleoside analog inhibitor of viral RNA polymerase, recently approved for use under a US Food and Drug Administration [FDA] Emergency Use Authorization) is experiencing growing use in COVID-19 trials and was associated with a 23% increase in liver enzymes in one small published report.[40]

CONCLUSIONS

There is a high prevalence of abnormal liver biochemistries on presentation in patients with COVID-19. In light of the risk for additional injury due to the complications and management of moderate-to-severe disease, it is important to monitor hepatic enzymes during the course of disease.[42] If biochemistries worsen during disease progression, consideration must be given to possible contributors, including cardiac dysfunction, cytokine storm, ischemia, sepsis, and medication effect.

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