Kinetic patterns of liver enzyme elevation with COVID-19 in the USA

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COVID-19 is a global pandemic that started in Wuhan, China. COVID-19 related liver enzyme elevations have been described however the clinical presentation, enzyme kinetics, and associated laboratory abnormalities of these patients have not been well described. Five cases of COVID-19 associated liver enzyme elevations are reported here. We found that COVID-19 related liver enzyme elevations occurred in a hepatocellular pattern and persisted throughout the initial hospitalization in all patients. Abnormalities in lactate dehydrogenase and ferritin levels were seen in all five cases. In conclusion, abnormalities in aminotransferase, lactate dehydrogenase, and ferritin levels are commonly seen in COVID-19 related liver injury. Elevated aminotransferase levels often persist throughout the entire hospitalization. However, the clinical course of COVID-19 related liver injury appears benign. Eur J Gastroenterol Hepatol XXX: 00–00

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Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a novel coronavirus, is the responsible pathogen for the coronavirus disease 2019 (COVID-19) [1]. COVID-19 most commonly presents with a variety of upper and lower respiratory symptoms, fevers, digestive symptoms, laboratory findings suggestive of lymphopenia or thrombocytopenia, and abnormalities on chest CT imaging [2]. COVID-19 can range in severity from mild disease, which occurs in the majority of cases, to severe/critical disease resulting in respiratory failure, septic shock, and multi-organ failure [3].

Severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) are two other highly syndromes caused by pathogenic human coronaviruses. Previous studies have shown that SARS and MERS can both cause liver dysfunction and current observations show that SARS-CoV-2 can similarly cause liver injury [4]. Liver enzyme elevations in the setting of COVID-19 have been reported in cohort studies, occurring more often in patients with severe disease [5]. Patients display a hepatocellular pattern of injury with elevations in aspartate aminotransferase (AST) and alanine aminotransferase (ALT); these elevations are reported to occur in 16.1–53.0% and 21.3–32.0% of COVID-19 patients, respectively (Table 1) [2,6–8]. Abnormalities in other hepatic parameters such as total bilirubin, gamma-glutamyl transferase, prothrombin time, and albumin have also been noted (2, 5, 8, and 11) [2,5,7].

Despite previous reports from China, information is sparse regarding the clinical course of COVID-19 patients with liver dysfunction, especially in the USA. This is important because it is now known that there are two major strains (L and S) of SARS-CoV-2 that may have different clinical disease severity with the L strain being more prevalent early in the initial outbreak in China [9]. In this study, we report the clinical presentation, course, and liver enzyme kinetics of five patients with COVID-19 related liver injury seen in the USA.

Cases

Five patients diagnosed with COVID-19 with PCR testing (Roche cobas SARS-CoV-2 assay) obtained via nasopharyngeal swab were included in this case series. All patients were ruled out for common etiologies of hepatitis, such as viral and autoimmune. Clinical characteristics and laboratory data for all five patients are shown in Table 2.

Daily trends of AST and ALT are shown in Fig. 1a and b. Patient 1 was a 26-year-old male with a history of childhood asthma who presented with fevers, cough, sore throat, and mild dyspnea for approximately 1 week before the diagnosis of COVID-19 on admission. Patient 2 was a 62-year-old male with a history of cerebrovascular disease, non-insulin dependent diabetes mellitus, and metabolic syndrome who presented from his nursing facility with fevers and dyspnea for 1 week before the diagnosis of COVID-19 on admission. Patient 3 was a 46-year-old female who presented with fevers, cough, and diffuse abdominal pain for 4 days before diagnosis of COVID-19 on admission. Patient 4 was a 46-year-old female who presented with a newly diagnosed deep venous thrombosis, admitted for thrombolysis, thrombectomy, and inferior vena cava filter

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placement. Five days after admission, she was noted to have chest CT findings of ground-glass opacities despite a lack of respiratory symptoms, and a COVID-19 test was sent and resulted positive. Patient 5 was a 29-year-old pregnant female at 10 weeks of gestation who presented with fever, sore throat, and congestion for 2 days before the diagnosis of COVID-19 on admission. She was started on hydroxychloroquine therapy.

**Discussion**

Herein, we report the clinical presentation and the kinetics of liver enzymes elevations during the hospitalization of five COVID-19 patients with COVID-19 related liver injury. The pattern of liver injury in all patients was primarily hepatocellular with elevated AST and ALT levels that persisted throughout the entire hospital course except in cases of patient 2 and patient 3, where enzyme levels significantly decreased by the end of the hospitalization. Significant elevations in serum lactate dehydrogenase (LDH) and ferritin levels were seen in all patients. None of the patients developed any signs of acute liver failure.

There are several hypotheses regarding the mechanism of action of COVID-19 and liver test abnormalities [4,5]. The first hypothesis is that COVID-19 can trigger an immune-mediated liver injury in certain individuals who develop severe

| Table 1. Summary of available evidence on the prevalence of aspartate aminotransferase/alanine aminotransferase elevations in COVID-19 patients |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Country of origin | Number of COVID-19 patients | Type of patients | Underlying liver disease (%) | Patients with elevated liver tests |
| Arentz et al. [14] | USA | 21 | ICU | 4.8% | 14.3% elevation of AST or ALT >3x ULN |
| Chen et al. [7] | China | 99 | All | N/A | 28% elevated ALT |
| Huang et al. [6] | China | 41 | All | 2% | 22.2% elevated AST |
| Shi et al. [15] | China | 81 | All | 9% | 53% elevated AST |
| Xu et al. [8] | China | 62 | All | 11% | 16.1% elevated AST |
| Yang et al. [13] | China | 52 | ICU | N/A | 29% evidence of liver dysfunction |
| Zhang et al. [5] | China | 58 | All | N/A | 28.6% evidence of liver dysfunction |

ALT, alanine aminotransferase; AST, aspartate aminotransferase; HBV, hepatitis B virus; LDH, lactate dehydrogenase; N/A, not available; TB, total bilirubin.

| Table 2. Summary of available evidence on the prevalence of aspartate aminotransferase/alanine aminotransferase elevations in COVID-19 patients |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Patient 1 | Patient 2 | Patient 3 | Patient 4 | Patient 5 | Lab reference range |
| Age | 26 | 62 | 46 | 46 | 29 | - |
| Sex | Male | Male | Male | Female | Female | - |
| PMH | Childhood asthma | CVA; NIDDM; hypertension; hyperlipidemia | NIDDM; hypertension; Deep vein thrombosis | Pregnant (10 weeks) | - |
| COVID-19 directed treatments | None | Hydroxychloroquine | Azithromycin | None | Hydroxychloroquine | - |
| Peak AST (U/L) | 452 | 501 | 316 | 339 | 487 | 1–35 |
| Peak ALT (U/L) | 484 | 563 | 397 | 251 | 403 | 1–45 |
| Peak ALP (U/L) | 79 | 156 | 96 | 77 | 69 | 38–126 |
| Peak LDH (U/L) | 477 | 619 | 696 | 1178 | 439 | 100–220 |
| Albumin (g/dl) | 3.0 | 2.1 | 2.9 | 2.5 | 3.7 | 3.5–4.5 |
| Ferritin (ng/ml) | 2134 | 2017 | 2190 | 457 | 4332 | 30–400 |
| Total IgG (immunoglobulins) | 1819 | 1201 | 1279 | Not done | 1282 | 700–1600 |
| CRP | 38.7 | 275 | 14.5 | Not done | 39.2 | 0–5 |
| ANA | Negative | Negative | Negative | Not done | Negative | Negative |
| Hepatitis A/B/C serologies | Negative | Negative | Negative | Negative | Negative | Negative |
| Chest CT findings | Not done | Ultrasound – normal | Large unilateral pleural effusion and enlarged liver | Not done | Not done | - |
| Liver imaging | Ultrasound – echogenic and echotexture | Ultrasound – normal contour | Ultrasound – normal echotexture | Not done | Ultrasound – mildly enlarged, increased echogenicity | - |
| LOS | 11 days | 13 days | 5 days | 8 days | 4 days | - |
| Maximum oxygen requirements | 10 L/min NRB | 6 L/min NC | Room air | Room air | Room air | - |

ALP, alkaline phosphatase; ALT, alanine aminotransferase; ANA, antinuclear antibodies; AST, aspartate aminotransferase; COVID-19, coronavirus 2019; CRP, c-reactive protein; CVA, cerebrovascular accident; LDH, lactate dehydrogenase; LOS, length of stay; NC, nasal cannula; NIDDM, non-insulin dependent diabetes mellitus; NRB, non-rebreather; PMH, past medical history; TB, total bilirubin.
liver dysfunction related to an exaggerated cytokine storm, ultimately resulting in multi-organ failure and acute respiratory distress syndrome [10]. On histological examination, evidence of over-activation of T cells and increased Th17 and high cytotoxicity of CD8 T cells has been reported [11]. Another possible mechanism is via direct insult by SARS-CoV-2 akin to SARS-CoV. Finally, a third hypothesis is injury via an ischemic process related to hypoxia. Reports from China suggest a higher rate of AST compared to ALT elevation consistent with ischemic liver injury due to hepatic zone 3 coagulative necrosis. Our data did show significantly elevated LDH levels in all five patients [2].

It is currently unclear how long COVID-19 related liver dysfunction will persist or whether the presence of liver dysfunction affects survival. Yao et al. [12] reported 40 cases of COVID-19-related liver injury with recovery within 1 week after treatment for COVID. In a study of only critically ill COVID-19 patients from China, liver dysfunction was present in six of 20 (30%) survivors and nine of 32 (28%) non-survivors [13]. The findings from this study suggest that the presence of liver dysfunction does not affect survival. Additional long-term follow-up will be helpful to assess presence or absence of persistent liver injury.

In summary, we report a single-center experience in the USA of five cases of COVID-19 related liver injury. Injury in all cases occurred in a hepatocellular pattern with concomitant derangements in other tests such as LDH and ferritin noted. There are potentially multiple mechanisms for liver injury including immune-mediated hepatitis, viral insult, or ischemic injury related to COVID-19 pneumonia. Although isolated liver failure due to COVID-19 has not yet been reported, further studies are needed to elucidate the short- and long-term clinical impact of COVID-19 related liver dysfunction.

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Conflicts of interest

D.D.: Participates on the advisory board and received research grants from Gilead and Abbvie. For the remaining authors, there are no conflicts of interest.

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