ORIGINAL ARTICLE

Clinical features and mechanism of liver injury in patients with mild or moderate coronavirus disease 2019

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Abstract

Background and Aim: We aimed to identify clinical features that suggest that coronavirus disease 2019 (COVID-19) should be a differential diagnosis in patients presenting with a chief complaint of fever and abnormal liver function.

Methods: We retrospectively studied the presence or absence of abnormal liver function in 216 patients diagnosed with mild–moderate severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection between February and September 2020.

Results: Abnormal liver function was observed in 51 patients with mild–moderate COVID-19. The median peak aspartate aminotransferase (AST), alanine aminotransferase (ALT), and lactate dehydrogenase (LDH) levels were 57.5, 75.5, and 332.5 U/L, respectively. The median number of days from symptom onset to peak AST, ALT, and LDH were 8.5, 9, and 8.5, respectively. The median peak LDH/AST ratio was 9.0. Low lymphocyte-to-white blood cell ratio and elevated LDH were found to be independent contributing factors for intensive care unit (ICU) admission on a multivariate analysis.

Conclusions: AST-predominant AST/ALT/LDH elevation peaking 8–9 days after symptom onset and not accompanied by elevated alkaline phosphatase or gamma-glutamyl transferase may be a useful clinical feature for differentiating COVID-19 from other diseases. Since the median LDH/AST ratio was 9.0, it seems that the abnormal liver function caused by SARS-CoV-2 is an indirect damage to liver cells due to elevated cytokine levels caused by liver-infiltrating lymphocytes. SARS-CoV-2 infection should be considered in patients presenting with a chief complaint of fever and liver injury; those with a high lymphocyte-to-white blood cell ratio or and a high LDH/AST ratio may be admitted to the ICU.

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the pathogen that causes coronavirus disease 2019 (COVID-19), primarily leads to respiratory infections. The condition is highly infectious after symptoms appear, resulting in community spread1. The SARS-CoV-2 infection may also cause liver injury in 14–53% of patients.[1–10] Previous studies have suggested an association between abnormal liver function and COVID-19 severity,[6,10,11] while other studies have reported that elevated liver enzymes are more likely the result of cytokine storms accompanying multiple organ failure rather than due to injury to

the liver parenchyma.[11] Thus, in patients with severe COVID-19 who require mechanical ventilation or extracorporeal membrane oxygenation, elevated liver enzymes may be due to changes caused by SARS-CoV-2 infection as well as cytokine storms or hemodynamics.

Direct liver injury due to viral infection, indirect liver injury due to hypercytokinemia, infection of the hepatobiliary system, autoimmune disorders, and malignant tumors are commonly included in the differential diagnosis of fever with abnormal liver function. However, during the SARS-CoV-2 pandemic, it is essential to consider COVID-19 as well.

Therefore, we studied the frequency of abnormal liver function and its patterns among patients with mild–moderate COVID-19 to investigate whether the clinical features of SARS-Cov-2 cause liver injury. Our goal was to identify clinical features that suggest that COVID-19 should be included as a differential diagnosis in patients presenting with a chief complaint of fever and abnormal liver function.

Methods

We retrospectively reviewed the data of 216 patients diagnosed with mild–moderate SARS-CoV-2 infection upon presentation to Showa University Fujigaoka Hospital ($n = 107$), Showa University Koto Toyosu Hospital ($n = 80$), International Goodwill Hospital ($n = 12$), Showa University Hospital ($n = 11$), and Kikuna Memorial Hospital ($n = 6$) between February and September 2020. This study was approved by the Showa University Fujigaoka Hospital Institutional Review Board (registration no. F2020C40) and the director of each participating hospital and was conducted in accordance with the Declaration of Helsinki.

Data sources. We obtained and collected data from inpatient and outpatient medical charts. A definitive diagnosis of COVID-19 was defined as a positive result of a nucleic acid amplification test (real-time quantitative polymerase chain reaction or loop-mediated isothermal amplification) using a nasopharyngeal swab specimen.

SARS-CoV-2 infection severity was determined based on the Diagnosis and Treatment Guidelines for the Novel Coronavirus Infection, Third Edition.[12] Patients with mild, moderate I, or moderate II infection at presentation were included, while patients with severe infection were excluded. Mild infection was defined as patients with saturation of percutaneous oxygen (SpO_2) ≥96% and no respiratory symptoms or cough but no dyspnea. Moderate I patients had $93\% < SpO_2 < 96\%$ and dyspnea or evidence of pneumonia. Moderate II patients had SpO_2 ≤93% and required supplemental oxygen. Severe infection was defined as patients who were admitted to the intensive care unit (ICU) or required artificial ventilation (Appendix S1, Supporting information).

Outcome parameters. We examined age, sex, body mass index (BMI), presence of chronic liver disease, severity, medications used, and outcome as background factors; body temperature and SpO_2 as vital signs; and white blood cell (WBC) count, lymphocyte ratio, hemoglobin, platelets (Plt), prothrombin time, albumin (Alb), total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), C-reactive protein (CRP), procalcitonin, ferritin, and HbA1c levels. For patients with infection that became severe, we used data until severity increased.

Statistical analyses. Categorical parameters were compared using the chi-square test, continuous parameters with a normal distribution were compared using Student's *t*-test, and continuous parameters with a non-normal distribution were compared using Mann–Whitney *U*-test. Logistic regression analysis was used for multivariate analysis. $P < 0.05$ was considered statistically significant. SPSS (IBM, New York, NY, USA) for Windows was used for the analyses.

Results

The mean patient age was 49 years, the mean patient BMI was 23.3 kg/m^2, and 56.9% of the patients were male. Overall, 148 (68.5%) patients had mild infection, 47 (21.8%) had moderate I infection, and 21 (9.7%) had moderate II infection. Seven patients (3.2%) had an increase in severity and were admitted to the ICU. Five participants (2.3%) had comorbid chronic liver diseases. Patients were treated with favipiravir ($n = 34$, 15.7%) and ciclesonide ($n = 30$, 13.9%; combined with favipiravir in 27 patients), while the most commonly administered antibiotics were azithromycin ($n = 40$, 18.5%) and ceftriaxone ($n = 34$, 15.7%), with both antibiotics used concurrently in 26 patients. Favipiravir was combined with azithromycin in 23 patients and ceftriaxone in 21 patients (Table 1).

Abnormal liver function. Abnormal liver function was defined as AST >40 U/L or ALT >44 U/L. Six patients with comorbid chronic liver disease or acute cholangitis were excluded from the liver function analysis. Abnormal liver function was observed in 51 of the remaining 210 patients (24.2%). Next, 73 patients with mild infection were excluded because their condition did not require blood tests. Abnormal liver function was found in 37.2% of patients who had blood tests (Fig. 1). AST was elevated in 22.9% of patients, ALT in 17.1%, LDH in 26.7%, ALP in 2.4%, and GGT in 9.0% (Fig. 2). The median peak AST was 57.5 U/L (range: 41–178 U/L) and the median

Table 1 Patient characteristics ($n = 216$)

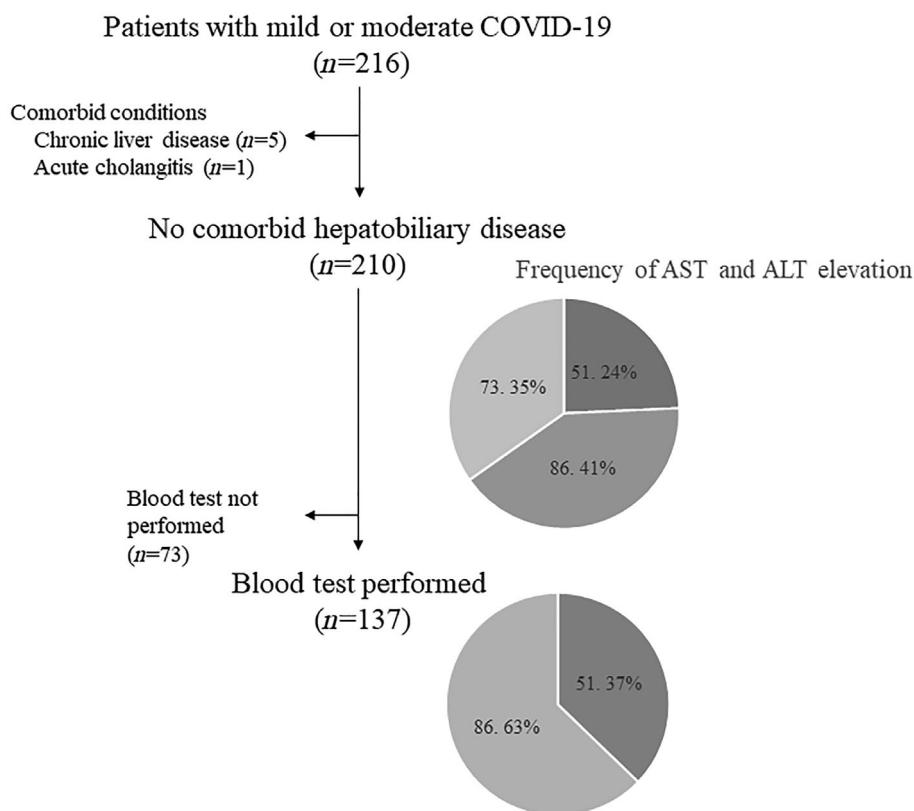|	
Age (years)	
Mean (SD)	49.0 (21.0)
Sex, *n* (%)	
Male	123 (56.9)
Female	93 (43.1)
BMI	
Mean (SD)	23.3 (4.5)
Severity, *n* (%)	
Mild	148 (68.5)
Moderate I	47 (21.8)
Moderate II	21 (9.7)
Chronic liver disease, *n* (%)	5 (2.3)
Hepatitis C	3 (1.4)
Primary biliary cholangitis	1 (0.5)
Unknown	1 (0.5)
Outcomes, *n* (%)	
Intensive care unit admission	7 (3.2)
Medication, *n* (%)	
Favipiravir	34 (15.7)
Ciclesonide	30 (13.9)
Remdesivir	5 (2.3)
Dexamethasone	7 (3.2)
Azithromycin	40 (18.5)
Clarithromycin	3 (1.4)
Ceftriaxone	34 (15.7)
Other Antibiotics	16 (7.4)
Acetaminophen	16 (7.4)

*$p < 0.05$.

Figure 1 Frequency of AST and ALT elevation in mild–moderate COVID-19 patients. ALT, alanine aminotransferase; AST, aspartate aminotransferase; COVID-19, coronavirus disease 2019. ■, Elevated AST and ALT group; ■, normal AST and ALT group; ■, missing; ■, AST and ALT elevated group; ■, AST and ALT non-elevated group.

number of days from symptom onset to peak AST was 8.5 (range: 1–32). The median peak ALT was 75.5 U/L (range: 47–166 U/L) and the median number of days from symptom onset to peak ALT was 9 (range: 1–32). The median peak LDH was 332.5 U/L (range: 249–673 U/L), and the median number of days from symptom onset to peak LDH was 8.5 (range: 2–39). The median peak LDH/AST ratio was 9.0 (range: 3.6–24.3) and the median number of days from symptom onset to peak LDH/AST ratio was 11 (range: 1–25) (Fig. 3).

The 137 patients who had blood tests were divided into an elevated AST and ALT group ($n = 51$) and a normal AST and ALT group ($n = 86$). The elevated AST and ALT group was significantly older ($P < 0.001$) and had significantly more males ($P = 0.021$) and more severe infections at presentation ($P < 0.001$). The elevated AST and ALT group also had more patients to whom favipiravir, ciclesonide, azithromycin, or ceftriaxone were administered (Table 2).

The patients were also divided into two groups by age based on ROC analysis: age ≥43 years, and <43 years. Univariate analysis demonstrated that higher AST and ALT levels were associated with patients aged 43 years (odds ratio [OR]: 8.78; 95% confidence interval [CI]: 3.18–24.24; $P < 0.0001$), male sex (OR: 2.43; 95% CI: 1.14–5.18; $P = 0.022$), patients with moderate infection at presentation (OR: 6.39; 95% CI: 2.94–13.89;

$P < 0.0001$), and those who received favipiravir (OR: 3.62; 95% CI: 1.60–8.18; $P = 0.002$), ciclesonide (OR: 5.08; 95% CI: 2.08–12.42; $P < 0.0001$), azithromycin (OR: 5.40; 95% CI: 2.41–12.99; $P < 0.0001$), or ceftriaxone (OR: 5.17; 95% CI: 2.23–12.00; $P < 0.0001$). Multivariate analysis identified age 43 years (OR: 6.18; 95% CI: 2.01–19.05; $P = 0.0015$), male sex (OR: 2.52; 95% CI: 1.04–6.11; $P = 0.0409$), and having a moderate condition at presentation (OR: 2.90; 95% CI: 1.12–7.51; $P = 0.0280$) as independently associated with AST and ALT elevation (Table 3).

ALP and GGT were measured in 129 patients and were found to be elevated in 19 patients. Univariate analysis identified male sex (OR: 3.977; 95% CI: 1.095–14.438; $P = 0.036$), high BMI (OR: 1.294; 95% CI: 1.098–1.526; $P = 0.002$), and ciclesonide use (OR: 3.273; 95% CI: 1.167–9.182; $P = 0.024$) as associated with elevated ALP and/or GGT, while high BMI (OR: 1.286; 95% CI: 1.059–1.560; $P = 0.011$) was found to be independently associated with elevated ALP and/or GGT levels on the multivariate analysis (Table 3).

Comparison by outcome. We divided the patients into two groups based on whether they required ICU admission: the non-ICU admission group ($n = 203$), in which COVID-19 improved without becoming more severe, and an ICU admission group ($n = 7$), in which COVID-19 became more severe and the
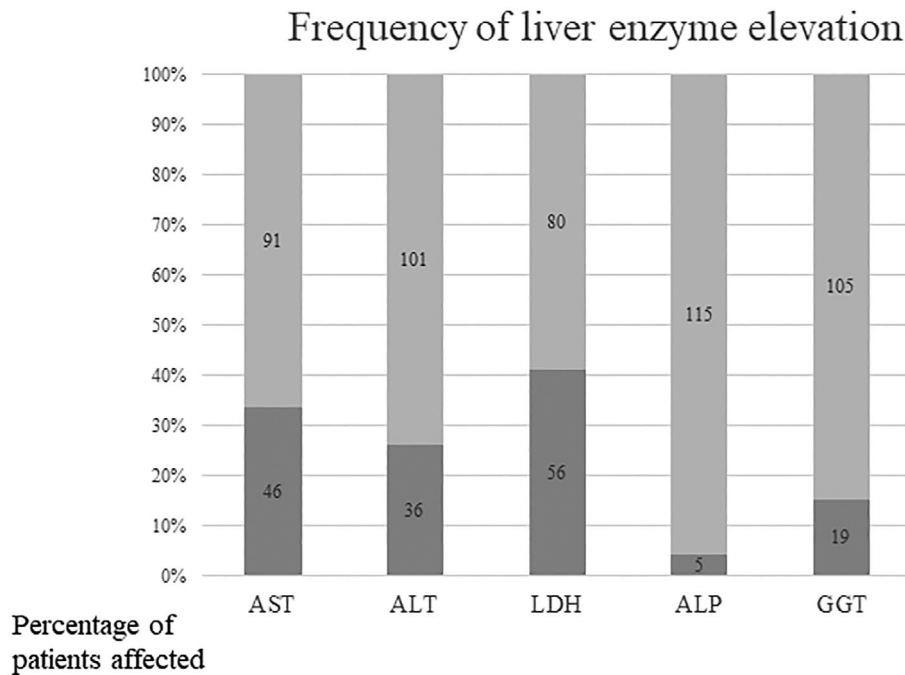
Frequency of liver enzyme elevation

Figure 2 Frequency of liver enzyme elevation. ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; LDH, lactate dehydrogenase; ULN, upper limit of normal. ▪, <ULN; ▪, ≥ULN.

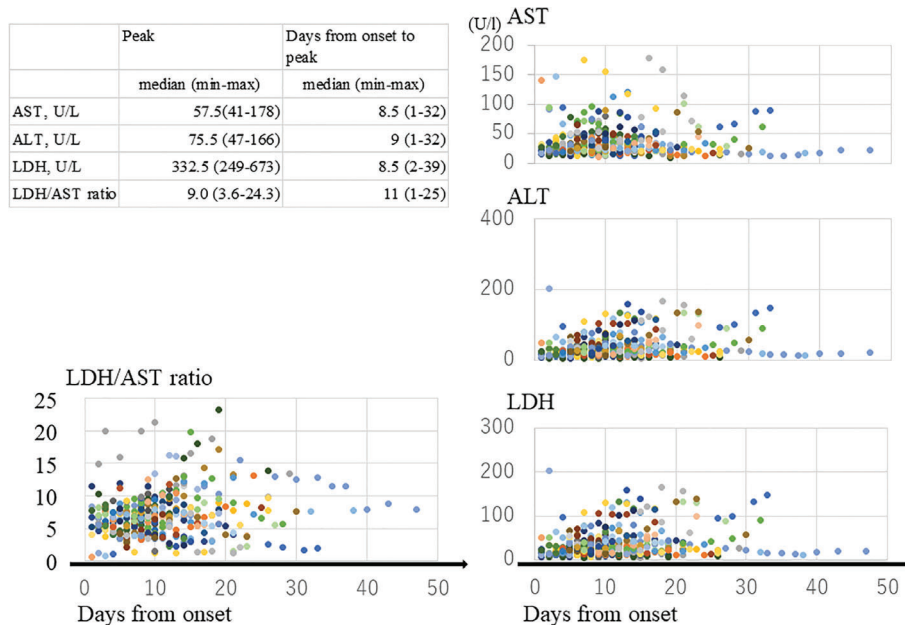|	Peak	Days from onset to peak
	median (min-max)	median (min-max)
AST, U/L	57.5(41-178)	8.5 (1-32)
ALT, U/L	75.5 (47-166)	9 (1-32)
LDH, U/L	332.5 (249-673)	8.5 (2-39)
LDH/AST ratio	9.0 (3.6-24.3)	11 (1-25)

Figure 3 AST, ALT, LDH, and LDH/AST ratio time series. ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDH, lactate dehydrogenase.

patient was admitted to the ICU. Patients in the ICU admission group were significantly older ($P = 0.015$) and had more severe infection at presentation ($P < 0.001$) than patients in the non-ICU admission group. This group also had significantly higher WBC count ($P = 0.007$), CRP ($P < 0.001$), AST ($P = 0.004$), ALT ($P = 0.047$), and LDH ($P = 0.004$), and significantly lower lymphocyte-to-WBC ratio ($P < 0.001$) and Alb ($P = 0.008$) (Table 4).

Table 2 Comparison of the elevated AST and ALT group and the normal AST and ALT group

	Normal AST and ALT group n = 86	Elevated AST and ALT group n = 51	P value
Age (years)			
Mean (SD)	46.8 (20.5)	61.6 (16.0)	<0.001*
Sex, n (%)			
Male	47 (54.7)	38 (74.5)	0.021*
Female	39 (45.3)	13 (25.5)	
BMI			0.086
Mean (SD)	22.4 (3.9)	24.2 (4.8)	
Severity at presentation, n (%)			<0.001*
Mild	59 (68.6)	13 (25.5)	
Moderate I	20 (23.3)	25 (49.0)	
Moderate II	7 (8.1)	13 (25.5)	
ICU admission, n (%)	2 (2.3)	5 (9.8)	0.055
Temperature (°C)	38 (36.4–40.0)	38.2 (34.9–40.6)	0.241
Medication, n (%)			
Favipiravir	13 (15.1)	20 (39.2)	0.001*
Ciclesonide	9 (10.5)	19 (37.3)	0.000*
Remdesivir	2 (2.3)	2 (3.9)	0.592
Dexamethasone	3 (3.5)	4 (7.8)	0.263
Azithromycin	13 (15.1)	25 (49.0)	<0.001*
Clarithromycin	2 (2.3)	1 (2.0)	0.888
Ceftriaxone	11 (12.8)	22 (43.1)	<0.001*
Acetaminophen	5 (5.8)	3 (5.9)	0.987

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; COVID-19, coronavirus disease 2019; ICU, intensive care unit.
*p < 0.05.

Table 3 Factors associated with abnormal liver function of COVID-19

	Univariable OR	(95% CI)	P value	Multivariable OR	(95% CI)	P value
Factors associated with AST and ALT elevation of COVID-19						
Age ≥43 years	8.78	3.18–24.24	<0.0001	6.18	2.01–19.05	0.0015
Male	2.43	1.14–5.18	0.022	2.52	1.04–6.11	0.0409
Moderate disease on the first visit	6.39	2.94–13.89	<0.0001	2.90	1.12–7.51	0.0280
Favipiravir	3.62	1.60–8.18	0.002	—	—	—
Ciclesonide	5.08	2.08–12.42	<0.0001	—	—	—
Azithromycin	5.40	2.41–12.99	<0.0001	—	—	—
Ceftriaxone	5.17	2.23–12.00	<0.0001	—	—	—
Factors associated with ALP and/or GGT elevation of COVID-19						
Male	3.977	1.095–14.438	0.036	—	—	—
BMI[†]	1.294	1.098–1.526	0.002	1.286	1.059–1.560	0.011
Cidesonide	3.273	1.167–9.182	0.024	—	—	0.011

[†]Per 1 unit increase.
95% CI, 95% confidence interval; ALP, alkaline phosphatase; BMI, body mass index; COVID-19, coronavirus disease 2019; GGT, gamma-glutamyl transferase; OR, Odds ratio.

Univariate analysis revealed that age (OR: 1.054; 95% CI: 1.011–1.099; $P = 0.013$), severity at presentation (OR: 7.750; 95% CI: 2.43–4.87; $P = 0.001$), ciclesonide use (OR: 5.110; 95% CI: 1.081–24.12; $P = 0.040$), azithromycin use (OR: 6.400; 95% CI: 1.37–29.87; $P = 0.018$), ceftriaxone use (OR: 15.623; 95% CI: 2.89–84.47; $P = 0.001$), low lymphocyte-to-WBC ratio (OR: 0.743; 95% CI: 0.595–0.929; $P = 0.009$), elevated AST (OR: 1.018; 95% CI: 1.001–1.036; $P = 0.042$), elevated LDH (OR: 1.011; 95% CI: 1.005–1.017; $P = 0.001$), and low Alb (OR: 0.208; 95% CI: 0.065–0.661; $P = 0.008$) were associated with an increase in infection severity, represented by the requirement of ICU admission. Multivariate analysis identified a low lymphocyte-to-WBC ratio (OR: 0.746; 95% CI: 0.597–0.932; $P = 0.010$) and elevated LDH (OR: 1.010; 95% CI: 1.004–1.016; $P = 0.002$) as independently associated with increased infection severity requiring ICU admission (Table 4).

Table 4 Comparison of the ICU admission group and nonadmission group

	Non-ICU admission group $n = 203$	ICU admission group $n = 7$	P value
Age (years)			
Mean (SD)	47.8 (20.8)	70.1 (17.6)	0.015[*]
Sex, n (%)			0.115
Male	113 (55.7)	6 (85.7)	
Female	90 (44.3)	1 (14.3)	
BMI			
Mean (SD)	23.2 (4.4)	25 (3.4)	0.309
Severity at presentation, n (%)			<0.001[*]
Mild	142 (70.0)	1 (14.3)	
Moderate I	45 (22.2)	1 (14.3)	
Moderate II	16 (7.9)	5 (71.4)	
Temperature (°C)	37.8 (36.0–40.2)	38.7 (34.9–40.6)	0.055
Medication, n (%)			
Favipiravir	31 (15.3)	2 (28.6)	0.342
Ciclesonide	26 (12.8)	3 (42.9)	0.023[*]
Remdesivir	4 (2.0)	0 (0.0)	0.708
Dexamethasone	7 (3.4)	0 (0.0)	0.617
Azithromycin	35 (17.2)	4 (57.1)	0.008[*]
Clarithromycin	3 (1.5)	0 (0.0)	0.746
Ceftriaxone	28 (13.8)	5 (71.4)	0.000[*]
Acetaminophen	15 (7.4)	0 (0.0)	0.455
Laboratory findings, median (minimum–maximum)			
White blood cell count, µL	5455 (2070–21020)	9370 (5180–13200)	0.007[*]
Lymphocyte-to-white blood cell ratio	22 (2.0–53.0)	6.8 (3.9–12.8)	0.000[*]
Platelet count, 10^4/µL	17.7 (2.6–50.8)	15.8 (11.9–24.6)	0.261
Aspartate aminotransferase, U/L	29 (11–178)	61 (30–94)	0.004[*]
Alanine aminotransferase, U/L	26 (7–166)	50 (30–91)	0.047[*]
Lactate dehydrogenase, U/L	208 (72–673)	463 (111–562)	0.004[*]
Gamma-glutamyl transferase, U/L	31 (8–312)	37 (31–294)	0.15
Albumin, g/dL	3.9 (1.7–5.1)	2.9 (1.6–3.8)	0.008[*]
C-reactive protein, mg/dL	2.46 (0.05–29.5)	14.3 (11.1–16.8)	0.000[*]
Ferritin, ng/mL	369 (11–2333)	675 (220–1279)	0.264
Hemoglobin A1c, %	6.1 (4.9–7.9)	7.3 (7.3–7.3)	0.223

	Univariable OR	(95% CI)	P value	Multivariable OR	(95% CI)	P value
Age[*]	1.054	1.011–1.099	0.013	—	—	—
Severity at presentation	7.750	2.43–24.87	0.001	—		—
Ciclesonide	5.110	1.081–24.12	0.040	—	—	—
Azithromycin	6.400	1.37–29.87	0.018	—		—
Ceftriaxone	15.623	2.89–84.47	0.001	—		—
Lymphocyte-to-white blood cell ratio	0.743	0.595–0.929	0.009	0.746	0.597–0.932	0.010
Aspartate aminotransferase, U/L[*]	1.018	1.001–1.036	0.042	—	—	—
Lactate dehydrogenase, U/L[*]	1.011	1.005–1.017	0.001	1.010	1.004–1.016	0.002
Albumin, g/dL[*]	0.208	0.065–0.661	0.008	—	—	—

[*]Per 1 unit increase.
95% CI, 95% confidence interval; BMI, body mass index; COVID-19, coronavirus disease 2019; ICU, intensive care unit; OR, odds ratio.

Discussion

The rate of abnormal liver function in COVID-19 patients has been reported as 14–53%.[1–10] Previous studies have found that abnormal liver function is more likely in patients with severe COVID-19. In their study of 1099 patients, Guan et al.[2] found that 18.2% of patients with non-severe COVID-19 and 39.4% of patients with severe COVID-19 had AST >40 U/L and 19.8% of patients with non-severe COVID-19 and 28.1% of patients with severe COVID-19 had ALT >40 U/L. A study of 41 patients by Huang et al.[3] reported AST levels >40 U/L in 8 of 13 (62%) ICU patients and 7 of 28 (25%) non-ICU patients.

We examined patients with mild–moderate COVID-19, in whom the effects of cytokine storms or hemodynamics were considered minimal. Age ≥43 years (OR: 6.18; 95% CI: 2.01–19.05;

$P = 0.0015$), male sex (OR: 2.52; 95% CI: 1.04–6.11; $P = 0.0409$), and moderate severity at initial examination (OR: 2.90; 95% CI: 1.21–7.51; $P = 0.0280$) were found to be independently associated with liver injury.

While obese patients may have elevated ALP or GGT, the liver injury observed in patients with mild–moderate COVID-19 is characterized by elevation of AST and ALT (AST elevation > ALT elevation) with a single peak occurring on day 8 or 9. This elevation is accompanied by elevated LDH, but not by elevated ALP or GGT. Furthermore, we did not observe any severe liver injuries in patients with AST and ALT ≥3 times the normal upper limit.

When a patient presents with abnormal liver function and fever, it is essential to rule out liver abscess, cholecystitis, cholangitis with obstructive jaundice, and other hepatobiliary infections via an abdominal ultrasound or computed tomography. Once these conditions have been ruled out, viral infections that result in hepatitis should be considered. We compared the clinical features of droplet/fecal–oral transmission of hepatitis viruses, herpesviruses, and measles morbillivirus (Appendix S2).

Hepatitis occurs in 75–90% of adults infected with the hepatitis A virus.[19] After an incubation period of 2–6 weeks, patients develop fever, general malaise, loss of appetite, and jaundice. Compared to other forms of acute viral hepatitis, symptoms of fever, headache, muscle ache, and stomachache are particularly severe. Hepatitis A infection is more likely to result in elevated ALP, GGT, and CRP than other viral liver infections, suggesting cholestasis. Although elevated CRP is also found in patients with COVID-19, elevated ALP and GGT are not typically found. Therefore, ALP and GGT levels can be used to differentiate COVID-19 and hepatitis A.

Patients with hepatitis E infections develop fever, general malaise, lack of appetite, and jaundice after an incubation period of 3–8 weeks. Hepatitis E is difficult to differentiate from hepatitis A using clinical symptoms.[20] Similar to hepatitis A, it may be possible to differentiate hepatitis E from COVID-19 using ALP and GGT levels.

The Epstein–Barr virus (EBV) causes mononucleosis in half of the infected patients aged ≥15 years and is accompanied by sore throat, headache, and swollen lymph nodes in addition to fever, general malaise, and lack of appetite. Liver injury is seen in 85–100% of patients and jaundice in 10% of patients with EBV.[15] Patients infected with EBV have an elevated WBC count and increased atypical lymphocytes. AST and ALT elevation most often peak approximately 2 weeks after symptom onset at 300–500 U/L. Furthermore, patients have significant LDH elevation caused by hepatocytes and lymphocytes. ALP and GGT levels are mildly elevated. The characteristics of SARS-CoV-2 infection, including AST and ALT elevation to only three times the upper limit of normal, normal ALP and GGT, and peak AST and ALT 8–9 days after symptom onset, can be used to differentiate it from EBV infection.

Primary infection with cytomegalovirus (CMV) in adults is rare and leads to fever, general malaise, and lack of appetite. Compared with EBV, CMV is less likely to be accompanied by sore throat and swollen lymph nodes.[18] Similar to EBV, an elevated WBC count and atypical lymphocytes are commonly seen in patients with CMV, as are elevated AST, ALT, and LDH; however, the extent of the elevation is lower than that seen in patients with EBV infection. Patients with CMV can be differentiated from patients with COVID-19 by their elevated ALP and GGT levels.

Liver injury is observed in 51–80% of adult patients with a primary measles morbillivirus infection.[13–16] The fever in these patients is most often bimodal. Patients have oral mucosal lesions prior to the development of red spots over the entire body. The WBC count is usually normal or low, and atypical lymphocytes can be observed in most cases. AST and ALT are often elevated to 100–300 U/L, and LDH is also elevated, similar to the liver enzyme profile of patients with EBV or CMV. ALT and LDH peak approximately 6–8 days and 4–5 days after the rash appears, respectively. Elevated ALP and GGT are rarely seen.[17] It may be difficult to differentiate measles morbillivirus from COVID-19 using blood test findings, but the two can be distinguished based on the clinical course, including bimodal fever, oral mucosal lesions, and full body rash.

During the SARS-CoV-2 pandemic, COVID-19 must be considered when treating patients with fever and abnormal liver function. The diagnosis can be made via an understanding of the patterns of abnormal liver function in COVID-19 and thorough interviews and physical examinations. In addition, we do not have to immediately discontinue the drug because it may not be a drug-induced liver injury if it is considered to be the natural course of SARS-CoV-2 infection.

The relationship between abnormal liver function and prognosis in patients with COVID-19 is unclear. A study of 52 patients by Yang et al.[6] reported no significant difference in the rate of complications with liver injury between survivors (30%) and non-survivors (28%). In contrast, Yip et al.[10] reported that elevated AST and ALT are independent predictors of severe cases of COVID-19. Zhou et al.[11] found that patients with elevated ALT, low Plt, and low Alb at admission had a higher mortality rate, suggesting that liver enzyme elevation may be the result of cytokine storms accompanying multiple organ failure rather than damage to the liver parenchyma.

Although only seven (3.2%) patients in this study required ICU admission, they had a significantly higher WBC count, CRP, AST, ALT, and LDH, and a significantly lower lymphocyte ratio and Alb level than non-ICU patients. Multivariate analysis identified low lymphocyte ratio and elevated LDH as independently associated with an increase in severity of COVID-19, suggesting that these factors may be useful in predicting deterioration in patients presenting with mild–moderate COVID-19.

LDH elevation is reported in 41–76% of patients with COVID-19,[1,2,11] and is more frequent in severe cases.[2,3,12] A study of 1099 patients reported that 37.2% of patients with non-severe COVID-19 had LDH >250 U/L compared with 58.1% of patients with severe COVID-19. The same study reported LDH elevation in 70.5% of patients who were admitted to the ICU and required mechanical ventilation.

LDH is present in most cells, and serum LDH increases in response to cell damage in many organs. Isozymes and LDH/AST ratio can be used to identify the organ causing elevation. For example, the normal LDH/AST ratio in the liver is 1 and the normal LDH/AST ratio in WBCs is 15. LDH elevation due to viral infection is thought to result from indirect liver injury caused by cytokines from liver-infiltrating lymphocytes when the LDH/AST ratio is 10–20. LDH elevation due to acute

viral hepatitis is thought to result from direct injury to hepatic cells caused by cytotoxic T lymphocytes when the LDH/AST ratio is <5.[21] According to previous studies,[16,18] the LDH/AST ratio is approximately 5–10 in patients with herpesvirus and measles morbillivirus infections. Therefore, abnormal liver function in patients with SARS-CoV-2 is likely a result of indirect damage following the activation of liver-infiltrating lymphocytes, as the LDH/AST ratio in this study was 9.0 (range: 3.6–24.0).

In this study, abnormal liver function was observed at a high frequency in patients with mild–moderate SARS-CoV-2 infection. During the SARS-CoV-2 pandemic, it is essential to include COVID-19 as a differential diagnosis when treating patients presenting with fever and liver injury with AST-predominant AST and ALT elevation peaking 8–9 days after symptom onset, LDH elevation, and no ALP or GGT elevation. Liver injury due to SARS-CoV-2 is thought to be indirect damage to the liver caused by elevated cytokine levels in the liver resulting from the activation of liver-infiltrating lymphocytes. This study has limitations. As the data of several patients lacked a medical history, it is possible that not all patients with existing liver disease were excluded. Furthermore, the rate of liver injury in patients with mild COVID-19 is unclear, as blood tests were not performed for most of these patients.

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Supporting information

Additional supporting information may be found in the online version of this article at the publisher's website:

Appendix S1. COVID-19 severity classification.

Appendix S2. Clinical features of viruses that cause liver function abnormalities.