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Short Communication

Association of coagulopathy with liver dysfunction in patients with COVID 19

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Aim: Liver dysfunction is sometimes observed in patients with coronavirus disease 2019 (COVID 19), but most studies are from China, and the frequency in other countries is unclear. In addition, previous studies suggested several mechanisms of liver damage, but precise or additional mechanisms are not clearly elucidated. Therefore, we examined COVID 19 patients to explore the proportion of patients with liver dysfunction and also the factors associated with liver dysfunction.

Methods: We retrospectively examined 60 COVID 19 patients hospitalized at the Hospital affiliated with The Institute of Medical Science, The University of Tokyo (Tokyo, Japan). Patients who presented ≥40 U/L alanine aminotransferase (ALT) levels at least once during their hospitalization were defined as high ALT patients, and the others as normal ALT patients. The worst values of physical and laboratory findings during hospitalization for each patient were extracted for the analyses. Univariable and multivariable logistic regression models with bootstrap (for 1000 times) were carried out.

Results: Among 60 patients, there were 31 (52%) high ALT patients. The high ALT patients were obese, and had significantly higher levels of D dimer and fibrin/fibrinogen degradation products, as well as white blood cell count, and levels of C reactive protein, ferritin, and fibrinogen. Multivariable analysis showed D dimer and white blood cells as independent factors.

Conclusions: Considering that higher D dimer level and white blood cell count were independently associated with ALT elevation, liver dysfunction in COVID 19 patients might be induced by microvascular thrombosis in addition to systemic inflammation.

Key words: COVID 19, D dimer, liver dysfunction, thrombosis

INTRODUCTION

CORONAVIRUS DISEASE 2019 (COVID-19) was first identified in Wuhan, China, at the end of 2019, and subsequently spread worldwide. Recent studies of COVID-19 have shown the incidence of liver injury, indicated by abnormal levels of hepatic transaminases. A review article by Jothimani *et al.* showed that liver dysfunction was observed in 14–53% of patients with COVID-19,[1] but most of the studies are from China, and there are only a few available data from other countries, including Japan. In addition, several studies showed that liver dysfunction was more frequently observed in patients with severe COVID-19, and also that the patients with liver dysfunction might have a risk of developing severe disease.[2,3] The possible mechanisms of liver damage in COVID-19 are suggested as follows: direct injury by the virus itself, systemic inflammation, hepatic ischemia and hypoxia, pre-existing liver diseases, and adverse effects by antiviral drugs.[4] Several studies investigated the factors related to liver dysfunction of COVID-19 patients in China, but there are few reports from other Asian countries. Therefore, in the present study, we examined the COVID-19 patients hospitalized at the Hospital affiliated with The

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Institute of Medical Science, The University of Tokyo (IMSUT Hospital) Tokyo, Japan, and investigated the rate of patients with liver dysfunction, as well as the factors associated with liver dysfunction, to explore the relationship between liver dysfunction and disease progression.

METHODS

BETWEEN 6 MARCH and 28 May 2020, 61 patients were admitted to IMSUT Hospital, with diagnosis of COVID-19 by real-time PCR of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). One patient with acute leukemia continued hospitalization for chemotherapy; therefore, this patient was excluded from the analysis. Among 60 patients, 57 were Japanese, two were Korean, and one was American. The patients who had ≥40 U/L alanine aminotransferase (ALT) levels at least once during their hospitalization were regarded as high-ALT patients, and the others as normal-ALT patients. Physical and laboratory findings were recorded during the hospitalization, and the worst values for each patient were extracted for the analyses. Univariable and multivariable logistic regression models with bootstrap (for 1000 times) were carried out for assessing the factors associated with liver dysfunction, defined here as ALT ≥40 U/L. Variable selection was carried out by backward elimination using $P < 0.05$ as the cut-off. When variables were correlated with each other, only one variable was chosen based on clinical relevance. Aspartate aminotransferase was highly correlated with ALT and thus not included in the variable selection. A sensitivity analysis was carried out by excluding patients with radiologically confirmed fatty liver from the final multivariable model. In our hospital, laboratory data of D-dimer and fibrin/fibrinogen degradation products (FDP) were presented in a quantitative manner if the values were above the cut-off levels. The cut-off levels of D-dimer and FDP were 0.5 and 2.5, respectively. We analyzed data of D-dimer and FDP as dichotomous values using the upper normal range values at our laboratory (1.0 for D-dimer and 2.5 for FDP). Stata MP 16.1 (StataCorp, College Station, TX, USA) was used. The ethics approval for this study was granted by the ethics board of The Institute of Medical Science, The University of Tokyo (2020–5-0420).

RESULTS

WE EXPERIENCED 60 hospitalized patients. Most of the patients had mild severity of COVID-19, but some patients had moderate severity, requiring non-invasive oxygen administration. None of the patients were intubated, nor were they transferred to the intensive care unit, and they were finally discharged without symptoms. The mean age was 45.6 years (standard deviation 15.0), and 72% (43/60) were men. Among them, serum ALT levels reached ≥40 U/L (high-ALT) in 31 patients (52%) at least once during their hospitalization, and had never been ≥40 U/L (normal-ALT) in the other 29 patients (48%). The patients' backgrounds and laboratory data are shown in Table 1. In the univariable analysis, the high-ALT patients had significantly higher bodyweight compared with the normal-ALT patients. In addition, the high-ALT patients had significantly lower SpO_2 and higher white blood cell (WBC) count, C-reactive protein, ferritin, and fibrinogen, as well as liver-related laboratory tests, such as aspartate aminotransferase and alkaline phosphatase. Interestingly, the high-ALT patients had elevated D-dimer and FDP compared with the normal-ALT patients. Finally, multivariable analysis showed that the elevated D-dimer (adjusted odds ratio 6.01, 95% confidence interval 1.19–30.43, $P = 0.03$) and WBC count (adjusted odds ratio 1.06 per every 100/μL increase, 95% confidence interval1.01–1.12, $P = 0.03$) were independently associated with the elevation of ALT (Table 2).

The number of patients given antiviral drugs, such as favipiravir, lopinavir/ritonavir, hydroxychloroquine, and ciclesonide, was higher in the high-ALT patients (17/31, 55%) than the normal-ALT patients (10/29, 34%; Table 1). Nevertheless, 13 out of 17 patients in the high-ALT group presented ALT elevation before taking these drugs. In two patients, ALT elevation was apparently observed during or after the administration of antiviral drugs (lopinavir/ritonavir or hydroxychloroquine), and might be considered as adverse effects of these drugs. When these two patients were excluded from the analysis, the levels of D-dimer and FDP, as well as WBC, C-reactive protein, ferritin, and fibrinogen, were still significantly increased in the high-ALT patients (data not shown). The days of hospitalization were not different between the high-ALT and normal-ALT patients. The days from the onset of symptoms to the discharge in the high-ALT patients were longer than those in the normal-ALT patients, but when the patients who were discharged without the confirmation of serial negative PCR results (4 in the high-ALT and 9 in the normal-ALT) were excluded from the analysis, the days from the onset to the discharge were not statistically different (20.9±5.7 days in the high-ALT and 18.5±3.2 days in the normal-ALT).

As the bodyweight in the high-ALT patients was heavier than that in the normal-ALT patients, it is possible that potential fatty liver diseases might contribute to ALT elevation. As a sensitivity analysis, we carried out the same analysis as above by excluding those with radiologically

Table 1 Characteristics, laboratory data, and clinical management of patients with or without elevation of alanine aminotransferase

Characteristic	Normal-ALT (n = 29)	High-ALT (n = 31)
Age (years)	45.2 (16.6)	46.0 (13.6)
Sex		
Male	59% (17)	84% (26)
Female	41% (12)	16% (5)
Bodyweight (kg)	61.4 (10.9)	90.1 (33.9)
Height (cm)	166.9 (8.6)	172.7 (11.3)
BMI (kg/m2)	22.0 (3.2)	29.9 (9.6)
BT (°C)†	37.3 (0.9)	37.7 (0.9)
SpO2 (%)‡	96.8 (1.6)	95.5 (2.0)
AST (U/L)†	26.0 (10.2)	67.1 (37.7)
ALT (U/L)†	21.8 (8.5)	97.4 (59.1)
ALP (U/L)†	203.1 (61.5)	286.8 (179.8)
γGTP (U/L)†	39.0 (29.3)	138.8 (121.0)
LDH (U/L)†	247.8 (119.0)	345.5 (134.6)
Albumin (g/dL)‡	3.8 (0.5)	3.6 (0.6)
Total bilirubin (mg/dL)†	0.6 (0.2)	0.7 (0.3)
CRP (mg/dL)†	2.8 (3.8)	7.7 (8.4)
Ferritin† (log10 ng/mL)	2.5 (0.4)	2.9 (0.4)
PT-INR	1.06 (0.07)	1.07 (0.08)
Fibrinogen (mg/dL)	427.8 (111.7)	517.0 (150.7)
FDP elevated	37% (10)	74% (23)
Not elevated (<2.5 μg/mL)	63% (17)	26% (8)
D-dimer elevated	19% (5)	61% (19)
Not elevated (<1.0 μg/mL)	81% (22)	39% (12)
BUN (mg/dL)†	13.9 (4.3)	12.9 (3.3)
Creatinine (mg/dL)†	0.8 (0.3)	0.8 (0.2)
White blood cell (×100/μL)†	52.0 (15.3)	74.0 (26.1)
Lymphocyte count (/μL)‡	1295.8 (470.9)	1352.9 (706.8)
Platelet (×10000/μL)‡	21.2 (8.7)	25.7 (8.5)
Hemoglobin (g/dL)‡	13.4 (1.6)	14.0 (1.6)
Antivirals (F/LR/HC/S)§	8:1:2:0	7:2:8:2
Days of hospitalization	9.6 (3.9)	9.5 (5.2)
Days from onset to admission	8.2 (4.8)	10.9 (5.7)
Days from onset to discharge	17.8 (3.4)	20.3 (6.0)

Data are shown as the mean (standard deviation) or % (number).
†Maximum or ‡minimum value during hospitalization.
§F, favipiravir; LR, lopinavir/ritonavir; HC, hydroxychloroquine; S, ciclesonide. One patient took HC and S and two patients took F and HC.
γGTP, γ-glutamyl transpeptidase; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BT, body temperature; BUN, blood urea nitrogen; CRP, C-reactive protein; FDP, fibrin/fibrinogen degradation products; LDH, lactase dehydrogenase; SpO_2, percutaneous saturation of oxygen.

defined fatty liver. Chest computed tomography scan was carried out for the diagnosis of pneumonia on admission in all of the 60 patients, except one high-ALT patient; therefore, we used the images to detect the presence of fatty liver diseases. The cut-off value of liver-to-spleen ratio we used for the diagnosis of fatty liver was 0.9.[5] There were 10 and two patients with fatty liver in the high-ALT and normal-ALT patients, respectively. By comparing 20 high-ALT and 27 normal-ALT patients without radiologically confirmed fatty liver, we observed similar results with overall analysis (Table 3).

There were 19 patients who presented abnormal levels of both D-dimer (≥1.0) and ALT (≥40). Most of the patients presented the peak levels of ALT and D-dimer simultaneously during the hospitalization, mostly at admission. There was a patient with pulmonary embolism in the high-ALT patients. This patient had high levels of D-dimer and FDP at admission, but the level of ALT was within the normal range. After starting the administration of heparin, the levels of D-dimer and FDP were temporarily decreased, but again increased after 7 days. Concomitantly, the ALT level increased. Finally, this patient was discharged due to recovery from the symptoms, although the levels of D-dimer and ALT were slightly high. In the case of this patient, it is possible that adverse drug effects might have contributed to liver dysfunction, but considering that the levels of D-dimer and ALT increased together despite the administration of heparin, it is possible that liver dysfunction was induced, at least partially, by intrahepatic microvascular thrombosis after pulmonary embolism.

DISCUSSION

IN THE PRESENT study, we investigated 60 patients with COVID-19, and found 31 (52%) patients had liver dysfunction defined by the elevation of ALT. Meta-analysis by Sultan *et al.* showed that the prevalence of ALT elevation among COVID-19 patients was 15.0%.[6] In contrast, 31.6% of non-intensive care unit patients, which was similar to those in the present study regarding disease severity, had elevated levels of ALT.[7] The prevalence in our present cohort was higher than that of the aforementioned study. The exact reason for the difference remains to be elucidated, but differences in patients' backgrounds, including nationality, might be associated. There is one study from a Japanese institution showing the clinical characteristics of COVID-19 patients, including liver function tests.[8] In that study, 13% of patients with asymptomatic or mild COVID-19 on admission presented ALT elevation, but as the patients were from the *Diamond Princess*, many patients of nationalities other than Japanese were included (47% were from countries other than east Asia).

By comparing the clinical data between the high-ALT and normal-ALT patients with COVID-19, we found that the high-ALT patients had heavier bodyweight, higher

Table 2 Univariable and multivariable logistic regression on the factors associated with the elevation of alanine aminotransferase

		Univariable		Multivariable	
Characteristic	*n*	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Age (years)	60	1.00 (0.97–1.04)	0.86		
Sex					
Male	43	Reference			
Female	17	0.27 (0.07–1.02)	0.05		
Bodyweight (kg)	60	1.09 (1.02–1.15)	0.01		
Height (cm)	60	1.06 (0.97–1.16)	0.17		
BMI (kg/m^2)	60	1.31 (1.00–1.72)	0.05		
BT (°C)†	60	1.61 (0.72–3.60)	0.25		
SpO_2 (%)‡	60	0.68 (0.50–0.94)	0.02		
ALP (U/L)†	60	1.01 (1.00–1.01)	0.03		
γGTP (U/L)†	60	1.03 (0.99–1.07)	0.09		
LDH (U/L)†	60	1.01 (1.00–1.01)	0.07		
Albumin (g/dL)‡	60	0.41 (0.13–1.29)	0.13		
Total bilirubin (mg/dL)†	60	6.64 (0.86–51.12)	0.07		
CRP (mg/dL)†	60	1.17 (1.01–1.35)	0.04		
Ferritin† (log_{10} ng/mL)	59	16.49 (1.94–140.11)	0.01		
PT-INR	58	3.74 (0.001–10357)	0.74		
Fibrinogen (mg/dL)	58	1.01 (1.00–1.01)	0.02		
FDP elevated	33	4.89 (1.52–15.70)	0.008		
not elevated (<2.5 μg/mL)	25	Reference			
D-dimer elevated	24	6.97 (1.99–24.44)	0.002	6.01 (1.19–30.43)	0.03
not elevated (<1.0 μg/mL)	34	Reference		Reference	
BUN (mg/dL)†	60	0.93 (0.78–1.10)	0.38		
Creatinine (mg/dL)†	60	1.00 (0.07–14.95)	1.00		
White blood cell (×100/μL)†	60	1.07 (1.02–1.12)	0.004	1.06 (1.01–1.12)	0.03
Lymphocyte count (/μL)‡	60	1.00 (1.00–1.00)	0.74		
Platelet (×10000/μL) ‡	60	1.06 (0.99–1.15)	0.10		
Hemoglobin (g/dL)‡	60	1.24 (0.87–1.76)	0.23		

†Maximum or ‡minimum value during hospitalization.
γGTP, γ-glutamyl transpeptidase; ALP, alkaline phosphatase; BMI, body mass index; BT, body temperature; BUN, blood urea nitrogen; CRP, C-reactive protein; FDP, fibrin/fibrinogen degradation products; LDH, lactase dehydrogenase; PT-INR, prothrombin time international normalized ratio; SpO_2, percutaneous saturation of oxygen.

inflammation, and, interestingly, higher levels of FDP and D-dimer. It might be possible that patients with heavier bodyweight had potential fatty liver diseases, which might contribute to the elevation of ALT. However, we obtained similar results when the patients with apparent fatty liver diagnosed by CT scan image (liver-to-spleen ratio <0.9) were excluded from the analysis. Stronger systemic inflammation, described by high levels of WBC, C-reactive protein, and ferritin, was observed in the high-ALT patients, which also might contribute to liver damage by direct or indirect actions of cytokines and chemokines. Elevated levels of D-dimer and FDP observed in the high-ALT patients indicate hyperactivated coagulation/fibrinolysis system. Recently, the coagulopathy and the subsequent increased risk of thrombosis have been investigated in COVID-19 patients, and the association of organ damage by acute thrombosis, such as pulmonary embolism and stroke with progression to severe disease, has been shown.[9,10] In most of the high-ALT patients with high D-dimer level, the elevation of ALT and D-dimer was observed simultaneously, suggesting that the liver injury might be induced, at least partially, by intrahepatic circulatory disorders triggered by potential intrahepatic microvascular thrombosis. On this point, the present data might be coincident with the finding of a previous study showing the histopathological changes of the hepatocytes with slight vesicular steatosis and watery degeneration, and a few inflammatory cells, suggesting ischemic or hypoxic damage.[2] In contrast, several studies showed that COVID-19 patients with liver dysfunction had higher risks

Table 3 Univariable and multivariable logistic regression on the factors associated with the elevation of alanine aminotransferase, excluding those with radiologically confirmed fatty liver

		Univariable		Multivariable	
Characteristic	*n*	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Age (years)	47	1.02 (0.97–1.07)	0.45		
Sex					
Male	32	Reference			
Female	15	0.22 (0.05–0.94)	0.04		
Bodyweight (kg)	47	1.11 (1.00–1.22)	0.05		
Height (cm)	47	1.11 (1.00–1.23)	0.05		
BMI (kg/m^2)	47	1.35 (0.98–1.86)	0.07		
BT (°C)†	47	1.82 (0.83–4.01)	0.14		
SpO2 (%)‡	47	0.68 (0.48–0.96)	0.03		
ALP (U/L)†	47	1.01 (1.00–1.01)	0.007		
γGTP (U/L)†	47	1.03 (0.99–1.07)	0.20		
LDH (U/L)†	47	1.01 (1.00–1.01)	0.09		
Albumin (g/dL)‡	47	0.19 (0.03–1.02)	0.05		
Total bilirubin (mg/dL)†	47	3.30 (0.25–43.7)	0.37		
CRP (mg/dL)†	47	1.21 (0.99–1.48)	0.07		
Ferritin† (log_{10} ng/mL)	46	19.5 (0.83–463.0)	0.07		
PT-INR	44	20.2 (0.002–217742)	0.53		
Fibrinogen (mg/dL)	45	1.01 (1.00–1.01)	0.04		
FDP elevated	27	8.5 (1.96–36.8)	0.004		
not elevated (<2.5 μg/mL)	18	Reference			
D-dimer elevated	20	12.0 (2.53–56.9)	0.002	13.0 ($5.28x10^{-10}$-$3.19x10^{11}$)	0.83
not elevated (<1.0 μg/mL)	25	Reference		Reference	
BUN (mg/dL)†	47	0.94 (0.78–1.14)	0.52		
Creatinine (mg/dL)†	47	1.31 (0.09–19.8)	0.85		
White blood cell (×100/μL)†	47	1.07 (1.02–1.13)	0.008	1.06 (0.65–1.73)	0.81
Lymphocyte count (/μL)‡	47	1.00 (1.00–1.00)	0.75		
Platelet (×10000/μL)‡	47	1.05 (0.97–1.14)	0.23		
Hemoglobin (g/dL)‡	47	1.05 (0.67–1.65)	0.82		

†Maximum or ‡minimum value during hospitalization.
γGTP, γ-glutamyl transpeptidase; ALP, alkaline phosphatase; BMI, body mass index; BT, body temperature; BUN, blood urea nitrogen; CRP, C-reactive protein; FDP, fibrin/fibrinogen degradation products; LDH, lactase dehydrogenase; PT-INR, prothrombin time international normalized ratio; SpO_2, percutaneous saturation of oxygen.

of severe diseases, and that severe patients had a significantly higher incidence of liver dysfunction.[2,3] In fact, complicated pulmonary embolism was observed in one high-ALT patient in the present study. In view of these findings and our present data, it is possible that patients with liver dysfunction have potential coagulopathy, which induces thrombosis of other organs, leading to the progression to severe disease. While preparing this manuscript, Sonzogni *et al.* reported post-mortem wedge liver biopsies from 48 patients who died from severe COVID-19.[11] They showed marked derangement of the intrahepatic blood vessel network with variable degrees of partial/complete luminal thrombosis, suggesting that liver damage might be induced by vascular thrombosis.

The present study had several limitations. First, this was a single-center study, and the number of patients was small. Second, the description of the patients' backgrounds, including past history of liver dysfunction, alcohol drinking, and the history of infection with hepatitis viruses, is insufficient.

In conclusion, we found that higher D-dimer level and WBC count were independently associated with the elevation of ALT by multivariable analysis, suggesting the potential coagulopathy might be associated with liver damage through microvascular thrombosis in addition to systemic inflammation. We speculate that some of the COVID-19 patients with liver dysfunction might have a potential systemic coagulopathy, which could be associated with developing severe disease.

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