

Alteration of Liver Biomarkers in Patients with SARS-CoV-2 (COVID-19)

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Introduction: Coronavirus disease 2019 (COVID-19) emerged in China and spread worldwide. In this study, we assessed the characteristics of markers of the liver in patients with COVID-19 to provide new insights in improving clinical treatment.

Patients and Methods: We recruited 279 patients who confirmed COVID-19 and the data of liver biomarkers and complete blood count of patients were defined as the day onset when the patients admitted to the hospital.

Results: The average of LDH value was 621.29 U/L in all patients with COVID-19, and CPK was 286.90 U/L. The average AST was 44.03 U/L in all patients, and ALT was 31.14 U/L. The AST/ALT ratio was 1.64 in all patients. The measurement of CRP was increased by 79.93% in all patients. Average ALT and AST values of patients with elevated ALT were significantly increased in comparison to patients with normal ALT (P -value = 0.001), while AST/ALT ratio was significantly decreased compared to patients with normal ALT (P -value = 0.014). In addition, the average LDH of patients with elevated ALT was significantly increased compared to patients with normal ALT (P -value = 0.014).

Conclusion: Hepatic injury and abnormal liver enzymes related to COVID-19 infection is an acute non-specific inflammation alteration.

Keywords: SARS-CoV-2, COVID-19, hepatic injury, liver enzymes, aminotransferases

Introduction

Since December 2019, coronavirus disease 2019 (COVID-19) was first reported in China and has led to a major concern of health problems worldwide.¹ COVID-19 is caused by a novel coronavirus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).^{2,3} SARS-CoV-2 is classified as a single-stranded and positive-sense RNA virus, which belongs to the genus *Betacoronavirus*.⁴ This virus is closely related to two bat-derived SARS-like coronaviruses (88–99% similarity) including bat-SL-CoVZXL21 and bat-SL-CovZC45, while it is more distant from Middle East respiratory syndrome coronavirus (MERS-CoV, approximately 50% similarity) and SARS-CoV (approximately 79% similarity).⁴ The outstanding symptoms of COVID-19 are acute atypical pneumonia and pulmonary damage, which can progress to multiple organ failure leading to death in patients with underlying co-morbidities.^{2,3,5} However, ordinary symptoms of respiratory system infection were found in non-severe cases.^{2,3,5} The most common underlying diseases are cardiovascular disease and hypertension among adult patients followed by diabetes mellitus.^{5,6} Adults older than 18 years of age are the most common patients infected with SARS-CoV-19⁵ and there are some cases of children aged between 2 and 15 years.⁷ In some cases, liver

dysfunction followed by COVID-19 has also been observed, which could indicate a possibility for hepatic injury caused by COVID-19. The liver is constantly exposed to viruses, antigens, bacteria, and their products with inflammatory potential, which leads to hepatic injury. Several factors such as excessive alcohol consumption, exposure to toxins, viral infections and bile duct obstruction could cause hepatic injury.⁸ Viral agents such as hepatitis B virus (HBV), hepatitis C virus (HCV) and hepatitis E virus (HEV) are common causes of varying degrees of hepatic injury.^{9–11} Furthermore, some reports demonstrated that SARS-infected patients and MERS-infected patients had an increased value of liver enzyme and various degrees of hepatic injury.^{12,13} Li et al¹⁴ reported that C-reactive protein (CRP) index in patients with elevated alanine aminotransferase (ALT) level was significantly higher. They suggested that cytokine storm syndrome may cause COVID-19-related hepatic injury.¹⁴ However, the mechanism and reason for COVID-19-related hepatic injury is still unclear. At this time, COVID-19-related hepatic injury remains controversial and there is no more research regarding this issue. It is required to find the relationship between COVID-19 and its related hepatic injury, which could solve and decrease the practical clinical problems, and improve clinical treatment. Therefore, in this study, we assessed the characteristics of markers of liver function in patients with COVID-19 to provide new insights to better follow these patients.

Methods and Materials

Patient Selection

In this retrospective study, we recruited 279 patients with confirmed COVID-19 from 23 February to 19 March 2020 at Imam-Reza teaching and treatment hospital, Tabriz, Iran. This hospital was isolated and all wards of the hospital admitted patients with COVID-19 infection. All the patients were hospitalized and COVID-19 infection had been confirmed with real-time PCR and chest CT scan. All patients had no history of liver diseases and chronic hepatitis viral infection and their liver disease was due to COVID-19 disease. Samples of throat and nasopharyngeal swabs were collected from patients suspicious for COVID-19 for RT-PCR diagnosis. Pneumonia was diagnosed based on the Infectious Diseases Society of America/American Thoracic Society (IDSA/ATS) guidelines.¹⁵ Briefly, patients with pneumonia were diagnosed as having pneumonia who had at least one of the clinical symptoms of fever, cough, pleuritic chest pain, and

dyspnea, as well as a finding of coarse crackles or elevated inflammatory biomarkers or auscultation and a new inflammation on chest CT. Pulmonary radiology showed that the lesions of COVID-19 in all patients progressed more than 50% within 24–48 hours. Treatment was done based on a combination of azithromycin and hydroxychloroquine and supportive therapy.

Baseline Data Collection

All laboratory reports were retrospectively extracted from the hospital information system (HIS). The data of liver function biomarkers and complete blood count (CBC) was defined as the day of onset when the patients were admitted to the hospital. The liver function tests included ALT, AST, lactate dehydrogenase (LDH).

Statistical Analysis

Microsoft Excel version 2016 was used for statistical analysis. All quantitative analyses were represented by the mean and standard deviation (STDEV). *t*-Student, Mann–Whitney *U*, and Chi-square tests were used to compare the differences between COVID-19 patients with elevated ALT group and normal ALT group. In addition, Spearman correlation coefficients were used to describe the strength and direction analysis of the linear relationship between ALT, AST, CPK and LDH variables. Significance was set as a *P*-value < 0.05.

Results

The average age of all patients with COVID-19 was almost 59 years old and 164 (58.78%) patients were male and 115 (41.22%) were female. The average LDH value was 621.29 U/L in all patients with COVID-19, and creatine phosphokinase (CPK) was 286.90 U/L. The average AST was 44.03 U/L in all patients and ALT was 31.14 U/L. The AST/ALT ratio was 1.64 in all patients. The measurement of CRP was increased by 79.93% in all patients. Patients' red blood cell values, platelet values and their indexes were normal. Furthermore, patients' white blood cell values were normal. The results are shown in Table 1.

In total, for 279 patients, laboratory results showed that 41 (14.70%) patients had an elevated ALT value, while only 9.75% (4 of 41) of those with elevated ALT had a normal AST value. Seven patients (17.07%) with elevated ALT were recruited from the intensive care unit (ICU), while 22 patients (9.24%) with normal ALT were recruited from the ICU. There were more male patients

Table 1 Characteristics of Patients with COVID-19 and Characteristics of the ALT Elevated Group in Comparison to the Normal Group of Patients with COVID-19

Indicators	Normal Range	Value	Patients with Normal ALT (n=238)	Patients with Elevated ALT (More Than 47) (n=41)	P-value
Age (years)	–				0.054
Min		18	18	25	
Max		94	94	88	
Mean ± STDEV		58.99 ± 16.96	59.79 ± 17.06	54.29 ± 15.76	
Sex	–				0.017
Male, n (%)		164 (58.78)	133 (55.88)	31 (75.61)	
Female, n (%)		115 (41.22)	105 (44.12)	10 (24.39)	
LDH (U/L)	140–280				0.014
Min		189	240	189	
Max		3738	2016	3738	
Mean ± STDEV		621.29 ± 352.86	578.37 ± 252.02	866.18 ± 642.20	
CPK (U/L)	Male: 39–308 Female: 26–192				0.150
Min		20	20	29	
Max		8124	2240	8124	
Mean ± STDEV		286.90 ± 724.06	213.46 ± 259.34	720.20 ± 1757.48	
AST (U/L)	0–31				<0.001
Min		8	8	18	
Max		368	131	368	
Mean ± STDEV		44.03 ± 43.36	33.47 ± 16.78	105.10 ± 82.93	
ALT (U/L)	0–47				<0.001
Min		6	6	48	
Max		384	47	384	
Mean ± STDEV		31.14 ± 3790	21.13 ± 9.73	89.27 ± 73.22	
AST/ALT ratio	<1				<0.001
Min		0.37	0.43	0.37	
Max		4.29	4.29	4.12	
Mean ± STDEV		1.64 ± 0.72	1.71 ± 0.69	1.25 ± 0.79	
CRP	–				0.922
Negative		56 (20.07)	48 (20.17)	8 (19.51)	
1+		83 (29.75)	67 (28.15)	16 (39.02)	
2+		62 (22.22)	50 (21.01)	12 (29.27)	
3+		55 (19.71)	52 (21.85)	3 (7.32)	
4+		23 (8.24)	21 (8.82)	2 (4.88)	
WBC (10³/μL)	Male: 4–11				0.188
Min		0.70	1.10	0.7	
Max		21.50	21.50	19.5	
Mean ± STDEV		7.38 ± 3.96	7.25 ± 3.86	8.13 ± 4.47	
RBC (10⁶/μL)	Male: 4.7–6.1 Female: 4.2–5.4				0.457
Min		2.47	2.77	2.47	
Max		6.29	6.20	6.29	
Mean ± STDEV		4.53 ± 0.65	4.54 ± 0.60	4.46 ± 0.90	
HB (g/dl)	Male: 13.5–17.5 Female: 12–15.5				0.956
Min		6.30	8.10	6.3	
Max		18.30	18.30	17.1	
Mean ± STDEV		13.25 ± 2.11	13.23 ± 1.95	13.37 ± 2.91	

(Continued)

Table I (Continued).

Indicators	Normal Range	Value	Patients with Normal ALT (n=238)	Patients with Elevated ALT (More Than 47) (n=41)	P-value
HCT (%) Min Max Mean \pm STDEV	Male: 45–52 Female: 37–48	21.30 56.10 39.99 \pm 5.57	23.80 56.10 40.03 \pm 5.20	21.3 50.9 39.74 \pm 7.45	0.617
MCV (fl/cell) Min Max Mean \pm STDEV	80–96	66 105 88.58 \pm 5.71	66 56.10 40.03 \pm 5.20	76 104 89.51 \pm 5.31	0.256
MCH (pg/cell) Min Max Mean \pm STDEV	27–33	20 44 29.33 \pm 2.60	20 35 29.21 \pm 2.49	21 44 30.00 \pm 3.12	0.163
MCHC (g/dl) Min Max Mean \pm STDEV	31–37	27 48 33.10 \pm 1.91	27 37 33.04 \pm 1.63	27 48 33.44 \pm 3.09	0.446
Platelet ($10^4/\mu\text{L}$) Min Max Mean \pm STDEV	15–450	17 694 176.01 \pm 83.70	17 694 178.79 \pm 86.58	32 329 159.88 \pm 62.99	0.121
Neutrophil (%) Min Max Mean \pm STDEV	45–74	0 95.40 74.85 \pm 12.82	0 95.40 74.04 \pm 13.15	53.9 95.2 79.79 \pm 9.38	0.003
Lymphocyte (%) Min Max Mean \pm STDEV	16–45	2.80 55 19.18 \pm 10.21	3.10 55 19.86 \pm 10.28	2.8 44.1 15.18 \pm 8.91	0.009
Diff result mixed (%) Min Max Mean \pm STDEV	–	0.80 26.60 5.49 \pm 3.49	0.80 26.60 5.48 \pm 3.61	1.7 11.4 5.55 \pm 2.86	0.913
RDW (%) Min Max Mean \pm STDEV	11.5–14.5	11.40 47.80 16.37 \pm 6.74	11.40 47.80 16.55 \pm 6.82	11.9 36.5 15.32 \pm 6.24	0.325
PDW (%) Min Max Mean \pm STDEV	10–17.9	9.10 21.20 10.15 \pm 0.99	9.10 21.20 13.31 \pm 2.24	10.4 19.3 13.38 \pm 2.46	0.869
MPV (fl) Min Max Mean \pm STDEV	9.4–12.3	8 13.10 10.15 \pm 0.99	8 13.10 10.13 \pm 0.99	8.8 12.5 10.26 \pm 0.99	0.523

(Continued)

Table 1 (Continued).

Indicators	Normal Range	Value	Patients with Normal ALT (n=238)	Patients with Elevated ALT (More Than 47) (n=41)	P-value
P-LCR (fl)	7.5–10.5				0.572
Min		11.20	11.20	18.4	
Max		46.70	46.70	45.2	
Mean ± STDEV		27.13 ± 7.37	27 ± 7.34	27.83 ± 7.61	

Abbreviations: ALT, alanine aminotransferase; AST, aspartate transaminase; CPK, creatine phosphokinase; CRP, C-reactive protein; HB, hemoglobin; HCT, hematocrit; LDH, lactate dehydrogenase; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; MPV, mean platelet volume; PDW, platelet distribution width; P-LCR, platelet-large cell ratio; RBC, red blood cell; RDW, red cell distribution width; WBC, white blood cell.

with elevated ALT in comparison to normal patients (P -value = 0.017). Furthermore, the average age of patients with elevated ALT was almost lower than patients with normal ALT (P -value = 0.054). The average ALT and AST values of patients with elevated ALT were significantly increased in comparison with patients with normal ALT (approximately 89 U/L and 105 U/L vs 21 U/L and 33 U/L, respectively; P -value < 0.001), while the AST/ALT ratio was significantly decreased in comparison to patients with normal ALT (1.25 vs 1.71, P -value= 0.014). Also, the average LDH of patients with elevated ALT was significantly increased compared to patients with normal ALT (approximately 866 U/L vs 578 U/L, P -value = 0.014; [Figure 1](#)). In addition, the ALT values were positively correlated with the AST values in patients with elevated ALT (P < 0.001). Also, there was a positive correlation in values of AST with CPK and LDH (P < 0.05) and CPK values with AST and LDH values (P < 0.05) in patients with elevated ALT ([Figure 2](#)), while all values were positively correlated with each other in patients with normal ALT (P < 0.05). Furthermore, we classified the patients by degree of ALT evaluation (1X ALT, 1.5X ALT, 2X ALT, 3X ALT and more than 3X ALT) and found that AST values were significantly different between groups (P < 0.001) and increased AST values were significantly increased in 3X ALT and more than 3X ALT groups (P = 0.033 and P < 0.001, respectively).

The blood differential cells' results showed that the average neutrophil percentage of patients with elevated ALT was significantly increased in comparison to patients with normal ALT (P -value = 0.003), while the average lymphocyte percentage was significantly decreased compared to patients with normal ALT (P -value = 0.009).

Discussion

COVID-19 infection mainly causes pulmonary symptoms, but this infection may simultaneously lead to other organ

injuries such as cardiac muscle, kidneys, and liver.^{7,16,17}

As shown in this study, an increase in factors of hepatic injury has occurred in COVID-19 patients. Liver enzymes including ALT and AST are useful biomarkers of hepatic dysfunction in patients.^{18–20} Most liver diseases initially cause mild symptoms, but they must be detected early. Liver dysfunction can be crucially important in some diseases. The hepatic injury could be determined by tests that are associated with liver function (e.g. albumin), liver cellular integrity (e.g. ALT and AST), and some are associated with conditions linked to the biliary tract (e.g. alkaline phosphatase (ALP) and gamma-glutamyl transferase (GGT)).^{18–20} The liver is constantly exposed to viruses, antigens, bacteria, and their products with inflammatory potential, which leads to hepatic dysfunction. Multitudinous factors such as excessive alcohol consumption, exposure to toxins, viral infections and bile duct obstruction prevention could cause hepatic injury.⁸ Viral agents such as HBV, HCV and HEV are common causes of varying degrees of hepatic insufficiency.^{9–11} Furthermore, some reports demonstrated that SARS-infected patients and MERS-infected patients had an increased value of liver enzyme and various degrees of hepatic injury.^{12,13} In our study, we found that 41 of 239 COVID-19 patients had higher values of liver enzymes (e.g. ALT and AST). Similarly to our study, in recent studies, researchers revealed that transaminases (e.g. ALT and AST) were increased in patients with COVID-19.^{14,16} Chen et al¹⁶ demonstrated that 43 of 99 COVID-19 patients had various liver enzyme abnormalities (i.e. ALT and AST) and one patient had severe increase hepatic enzyme (ALT 7590 U/L, AST 1445 U/L) leading to hepatic dysfunction. Moreover, our results showed that the LDH value was increased in COVID-19 patients, as well as being significantly increased in patients with elevated ALT in comparison to patients with normal ALT. These results are consistent with other studies^{7,14,21,22} and this phenomenon

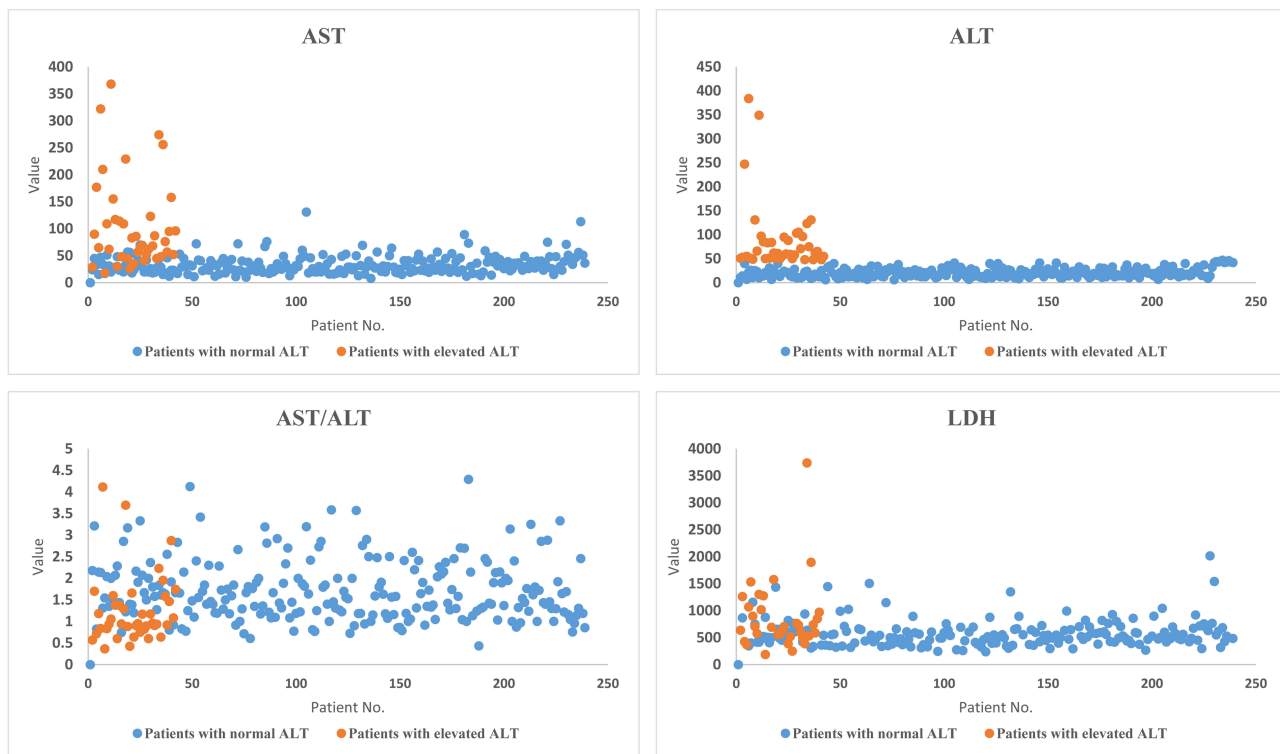


Figure 1 Distribution of ALT, AST, AST/ALT ratio, and LDH values among the elevated ALT and normal ALT patients with COVID-19. Each point in the diagrams show the values of the individual patients. Orange points belong to the elevated ALT patients and blue points to the normal ALT patients. The values of ALT, AST, AST/ALT ratio, and LDH of the elevated ALT patients were increased in comparison to the normal ALT patients (P -value < 0.05).

may be due to the cell apoptosis induced by COVID-19 infection or to the use of antiviral compounds. Some studies suggested that the increased levels of LDH are an indicator for evaluating anti-influenza activity of antiviral compounds.^{23,24} Also, Mori et al²³ suggested that influenza virus-infected cells are responsible for the LDH leakage due to releasing virus particles from host cells because antiviral drugs such as ribavirin, carbodine, and 3-deazaguanine pyrazofurine inhibited the LDH leakage. Uchide et al²⁵ also suggested that the apoptosis cell degeneration induced by influenza virus infection is associated with increasing LDH value. In addition, LDH is one of the diagnostic markers of lung diseases and liver diseases. Therefore, a significant increase in LDH values in patients with elevated ALT may be due to the simultaneous involvement of lungs and liver.

CRP, as an inflammatory response to factors released by macrophages and adipocytes, is produced in the liver.²⁶ In the present study, an increase of CRP was found in almost 80% of COVID-19 patients. Similarly to patients with other coronaviruses such as avian flu H7N9 and H1N1 influenza strains,^{27,28} CRP is increased in COVID-19 patients, and researchers reported that increased CRP is an observed

clinical characteristic of most patients with COVID-19 infection.^{16,29,30} Additionally, we found that there were no differences in CRP values between the elevated ALT group and the normal ALT group. In addition, CRP values were not significantly associated with ALT and AST. This indication was consistent with Guan et al³¹ and Li et al¹⁴ who found the abnormal rate of ALT and AST among COVID-19 patients. While, inconsistent with our results, Li et al¹⁴ found that the CRP values were closely associated with hepatic injury in COVID-19 patients, and CRP was significantly higher in the elevated ALT group and the increase of CRP was associated with ALT level. These differences may be the result of a large number of samples or of using a lower-sensitivity diagnostic CRP kit in our study. Furthermore, Zhao et al³² suggested that ACE2 is the putative receptor of SARS-CoV2. Additionally, Chai et al¹⁷ demonstrated that specific ACE2 expressed in the liver as well as in the lungs may cause hepatic injury in COVID-19 patients. Some other studies suggested that the systemic inflammatory response to the drug used in the treatment of COVID-19 infection and pneumonia-associated hypoxia may be caused by a hepatic injury in COVID-19 patients.^{30,33,34} According to the studies of Xu et al³³ and Zhang et al,³⁰ distinguishing between the

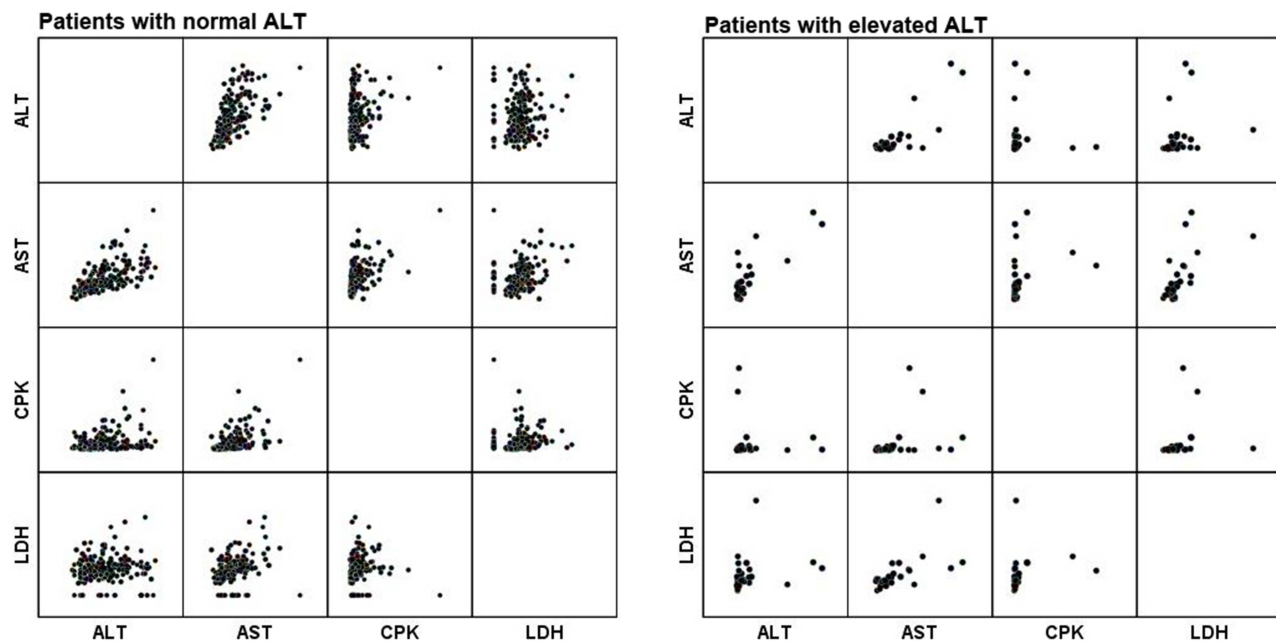


Figure 2 Correlation of the ALT, AST, CPK and LDH values with each other in patients with normal ALT and elevated ALT. The positive correlation was shown between the ALT and AST values in patients with elevated ALT, while the positive correlation between all values was shown with each other in patients with normal ALT.

pathological report of hepatic dysfunctions caused by a drug used in the treatment or caused by COVID-19 infection is difficult because some of the patients had a regime of lopinavir/ritonavir and interferon α -2b.

There were some limitations in this study, including some of the patients who died due to COVID-19 infection, owing to overloading of patients with COVID-19, assessment of other risk factors and conditions that may be changed in following up was not possible. Therefore, we focused on risk factors that are presented in the early identification of hepatic injuries. We expect these results could help medical settings to manage hepatic injury caused by COVID-19 infection.

Conclusion

These results suggested that hepatic injury and abnormal values of liver enzymes related to COVID-19 infection is an acute non-specific inflammation alteration. In addition, elevation of liver enzymes may be related to general immune activation and cytokine storming.

Abbreviations

CBC, complete blood count; COVID-19, coronavirus disease 2019; CPK, creatine phosphokinase; CRP, C-reactive protein; HBV, hepatitis B virus; HCV, hepatitis C virus; HEV, hepatitis E virus; HIS, hospital information system; LDH, lactate dehydrogenase; SARS-CoV-2, severe acute

respiratory syndrome coronavirus 2; STDEV, standard deviation.

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Disclosure

The authors report no conflicts of interest in this work.

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