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Original Research Article

Association of liver function tests with severity of disease in patients with COVID-19

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ABSTRACT

Background: We aimed to investigate the association of liver function tests with disease severity at admission and during hospitalization in patients with coronavirus disease 2019 (COVID-19).
Methods: Blood tests of patients who were hospitalized due to COVID-19 were retrospectively analyzed. Liver tests included serum aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transferase, total bilirubin, and albumin. Besides these, C-reactive protein and ferritin were also analyzed in the study. Levels of these tests at admission and peak levels during hospitalization were then recorded. Severe COVID-19 infection was defined as the reason for ICU admission. Both the associations of the levels of liver tests at admission and peak levels during hospitalization with severe disease were evaluated.
Results: The study included a total of 602 patients, and 127 (21.1%) of the patients were hospitalized in the ICU. In our study, only albumin level abnormality was significantly associated with severe disease in COVID-19 patients at admission. However, during hospitalization, a significant association was found between severe disease and abnormal AST, ALT, GGT, T.BIL, albumin, and ferritin levels. During hospitalization, it was also observed that the rates of severe disease cases increased as AST, ALT, GGT, and T.BIL levels increased.
Conclusions: Abnormal liver function tests may be a predictor for severe disease in patients with COVID-19. It is therefore important to monitor liver function tests in hospitalized patients.

Keywords: COVID-19, Liver function tests, Severity of disease

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). This disease first emerged in Wuhan, China in December 2019.[1] It then spread to other countries and continents, triggering a pandemic.[2] Even though COVID-19 is an infection that predominantly affects the respiratory system, it evolves into a systemic infection affecting the lungs, kidneys, liver, and almost every other organ. ACE II receptors act as cell surface receptors facilitating the entry of SARS-CoV-2. These receptors are differentially expressed in respiratory, gastrointestinal, and hepatobiliary cells.[3] Hepatic involvement in COVID-19 could be related to the direct cytopathic effect of the virus, an uncontrolled immune response, sepsis, or drug-induced liver injury. Given the higher expression of ACE2 receptors in cholangiocytes, this makes the liver a potential target for SARS-CoV-2.[2] There are studies in the literature evaluating liver function tests in COVID-19 patients, with varying results. Previously, the prevalence of abnormal liver tests in

COVID-19 patients was reported as 14.9% in some studies from China and 40-67.5% in some studies from the US.[4-7] Furthermore, although there are studies assessing the association between liver function tests and disease severity, very few studies have evaluated liver function tests separately both at admission and during hospitalization. In the present study, we intended to assess the liver function tests of patients hospitalized due to COVID-19, both at admission and during hospitalization, and to demonstrate the association of these tests with disease severity.

METHODS

The study group was composed of patients hospitalized in the Emergency Hospital built owing to the COVID-19 pandemic. Blood tests of patients hospitalized due to COVID-19 between June 20, 2020 and April 25, 2022 were retrospectively reviewed. Two liver test values were obtained: those obtained on admission and those obtained during ICU hospitalization. Laboratory results of a total of 1264 patients were evaluated. Liver tests included serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), total bilirubin (T.BIL), and albumin. Besides liver function tests, C-reactive protein (CRP) and ferritin as acute phase reactants were also analyzed in the study. Patients without any of these tests on admission and during hospitalization were excluded from the study. Accordingly, a total of 602 patients, 335 males, and 267 females, were included in the study. Alkaline phosphatase (ALP) was not included in the study because it was not measured in most of the patients. Abnormalities of the tests in the study were defined as follows: AST >35 U/l, ALT >35 U/l, GGT >36 U/l, TBIL >1.2 mg/dl, albumin <3.5 mg/dL, CRP >5 mg/l, ferritin >150 µg/l (for women) and >400 µg/l (for men). Abnormal AST and ALT levels were further categorized as 1-2 times, 2-5 times, 5-15 times, and >15 times the upper limit of normal (ULN) in accordance with the American College of Gastroenterology guideline. A similar application was done for GGT and TBIL. Severe COVID-19 was defined as the reason for intensive care unit (ICU) hospitalization. The association of liver function tests with severe disease was assessed according to both values at admission and peak values during hospitalization. Disease severity was also assessed according to gender and age groups.

Statistical analysis

Statistical analyses were made with the help of the SPSS version 25.0 computer program. The compatibility of the variables with normal distribution was analyzed by histogram plots and the Kolmogorov-Smirnov test. Mean, standard deviation, median, and min-max values were used to present descriptive analyses. Comparisons of categorical variables were made using the Chi-square test. Mann Whitney U test was utilized to evaluate nonparametric variables that did not show normal distribution between the two groups. Significant cut-off values that could predict intensive care unit hospitalization were analyzed by ROC Analysis, p values below 0.05 were considered statistically significant.

RESULTS

A total of 602 patients, 335 males, and 267 females, were included in the study. The patients' ages ranged between 18-98 years with a mean of 60.67±16.46 years. A total of 127 (21.1%) patients were seen to be hospitalized in the intensive care unit and were considered to have severe disease. The remaining 475 (78.9%) patients who were not hospitalized in intensive care were included in the non-severe disease group (Table 1).

Table 1: Distribution of patients according to age, gender, and disease severity.

Parameters		N	%
Gender	Male	335	55.65
	Female	267	44.35
Age (years)	<40	77	12.79
	41-60	215	35.71
	>60	310	51.50
Disease Severity	Non-severe	475	78.90
	Severe	127	21.10
Age		Mean±SD	Median (IQR)
		60.67±16.46	62 (18-98)

The relationship between disease severity and gender and age was analyzed and it was noted that the rates of severe disease increased significantly with increasing age (p<0.001). No significant association was found between gender and disease severity (Table 2).

Table 2: The association between disease severity and gender and age.

Parameters		Non-severe		Severe		P value
		N	%	N	%	
Gender	Male	270	80.60	65	19.40	0,254[1]
	Female	205	76.78	62	23.22	
Age (years)	<40	70	90.91	7	9.09	<0,001[2]
	41-60	186	86.51	29	13.49	
	>60	219	70.65	91	29.35	

[1]Ki-Kare Test [2]Linear-by-Linear Association

Data obtained from the liver function tests, ferritin, and CRP of COVID-19 patients at admission and peak levels during hospitalization are presented in (Tables 3-4). When the test results at the time of admission were assessed, only the abnormality in albumin level was associated with severe disease (Table 5). According to the test results during hospitalization, as AST, ALT, GGT, and TBIL levels increased, the rates of severe disease also increased. The rates of severe disease were

significantly higher in patients with low albumin and high ferritin levels (Table 6).

Table 3: Distribution of patients according to the results of tests at admission and during hospitalization.

Parameters		Admission		Hospitalization	
		N	%	N	%
AST	Normal	347	57.64	201	33.39
	1-2 x ULN	180	29.90	224	37.21
	2-5 x ULN	72	11.96	120	19.93
	5-15 x ULN	3	0.50	36	5.98
	>15 x ULN	-	-	21	3.49
ALT	Normal	414	68.77	191	31.73
	1-2 x ULN	128	21.26	176	29.24
	2-5 x ULN	51	8.47	169	28.07
	5-15 x ULN	9	1.50	55	9.14
	>15 x ULN	-	-	11	1.83
GGT	Normal	312	51.83	217	36.05
	1-2 x ULN	167	27.74	186	30.90
	2-5 x ULN	91	15.12	126	20.93
	5-15 x ULN	32	5.32	61	10.13
	>15 x ULN	-	-	12	1.99
T.BIL	Normal	587	97.51	554	92.18
	1-2 x ULN	12	1.99	34	5.66
	2-5 x ULN	3	0.50	11	1.83
	5-15 x ULN	-	-	2	0.33
Albumin	Abnormal	242	40.20	367	60.96
	Normal	360	59.80	235	39.04
CRP	Normal	30	4.98	22	3.65
	Abnormal	572	95.02	580	96.35
Ferritin	Normal	223	37.04	151	25.08
	Abnormal	379	62.96	451	74.92

The association between the severity of the disease and the levels of the test results was assessed. Accordingly, patients with severe disease had higher AST, CRP, and ferritin levels and lower albumin levels than those without severe disease at the time of admission (Table 7). During hospitalization, ALT, GGT, and TBIL levels were also significantly higher in patients with severe disease (Table 8). Significant cut-off values that could predict ICU admission were assessed and the sensitivity and specificity levels calculated for detected cut-off values are shown in Table 9. The ROC curve analysis of the tests is given in (Figure 1).

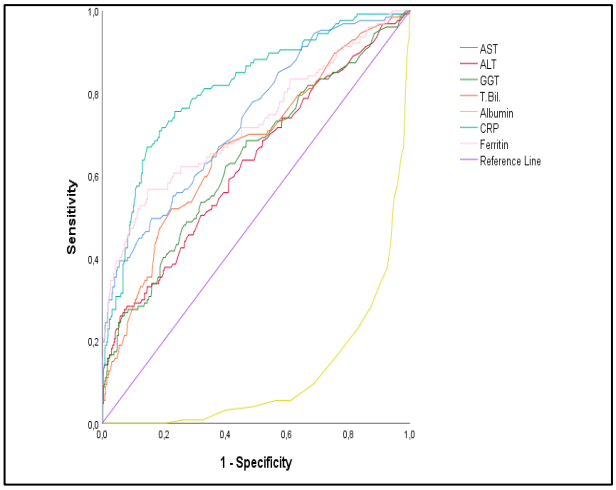

Figure 1: ROC curve analyses of tests.

DISCUSSION

Some previous studies have revealed that abnormal liver function tests are associated with COVID-19 infection. Abnormal liver function tests were reported in 4%-58% of Chinese cohorts and 39%-58% of US cohorts.[8,9] In our study, elevated AST and/or ALT were present in 289 patients (48%) at admission and 461 patients (76.5%) during hospitalization. Angiotensin-converting enzyme 2 was highly expressed not only in type II alveolar epithelial cells but also in bile duct cells. Many studies suggest that the angiotensin-converting enzyme 2 receptor is the cell entry receptor of SARS-CoV-2. All these outcomes suggest that SARS-CoV-2 may infect the bile duct cells and cause abnormal liver function in these patients.[10] Some studies have reported severe disease and higher mortality risk in COVID-19 patients with abnormal liver function tests.[11,12] Among previous studies evaluating liver function tests in COVID-19 patients, there are few studies evaluating the test results of the patients both at the time of admission and during hospitalization.

Table 4: Levels of test results at admission and during hospitalization.

Parameters	Admission		Hospitalization	
	Mean±SD	Median (Min-Max)	Mean±SD	Median (Min-Max)
AST	42.00±35.04	31 (8-525)	111.57±373.72	46 (10-7513)
ALT	35.88±36.91	24 (7-341)	100.9±234.08	54.5 (8-4100)
GGT	56.23±64.32	35 (7-462)	94.19±148.5	50 (8-1370)
T.BIL	0.55±0.38	0.5 (0.12-4.7)	0.76±0.84	0.6 (0.2-11.59)
Albumin	3.57±0.51	3.6 (1.5-5.2)	3.21±0.67	3.2 (1.5-4.8)
CRP	101.11±90.07	79.5 (1-884)	134.9±103.24	115 (1-637)
Ferritin	604.68±938.45	367.5 (5-16751)	1382.36±3191.31	522.5 (7-20000)

Table 5: The association between test abnormalities at admission and disease severity.

Admission		Non-severe		Severe		P value
		N	%	N	%	
AST	Normal	288	83.00	59	17.00	0.077[2]
	1-2xULN	127	70.56	53	29.44	
	2-5xULN	57	79.17	15	20.83	
	5-15x ULN	3	100.00	0	00	
ALT	Normal	319	77.05	95	22.95	0.063[2]
	1-2xULN	105	82.03	23	17.97	
	2-5xULN	42	82.35	9	17.65	
	5-15x ULN	9	100.00	0	00	
GGT	Normal	244	78.21	68	21.79	0.835[2]
	1-2xULN	137	82.04	30	17.96	
	2-5xULN	66	72.53	25	27.47	
	5-15x ULN	28	87.50	4	12.50	
T.BIL	Normal	463	78.88	124	21.12	0.918[2]
	1-2xULN	10	83.33	2	16.67	
	2-5xULN	2	66.67	1	33.33	
Albumin	Abnormal	161	66.53	81	33.47	<0.001[1]
	Normal	314	87.22	46	12.78	
CRP	Normal	27	90.00	3	10.00	0.126[1]
	Abnormal	448	78.32	124	21.68	
Ferritin	Normal	180	80.72	43	19.28	0.403[1]
	Abnormal	295	77.84	84	22.16	

[1]Ki-Kare Test [2]Linear-by-Linear Association

In a cohort study, a liver abnormality was documented in 46.2% of patients with COVID-19 at admission and 61.8% of patients during hospitalization. In this study, 73% of patients who died had liver abnormalities during admission, and the incidence of these liver abnormalities was higher in discharged patients (73.0% vs. 43.4%). Furthermore, the incidence of liver abnormalities during admission was also higher in patients who died (92.5% vs. 58.6%). Thus, liver test abnormalities were associated with poor prognosis. Patients with abnormal AST, ALP, GGT, TBIL, or D.BIL levels during admission had a higher mortality risk compared to patients with normal liver indices. Abnormal AST and direct bilirubin levels were most commonly detected in liver tests of deceased patients at admission and during hospitalization.[13] In another study by Hundt et al elevated AST and ALT levels were observed on admission in 66.9% and 41.6% of patients, respectively, and during hospitalization in 83.4% and 61.6% of patients, respectively.[14] In this study, a strong association was found between peak levels of liver function tests (AST, ALT, TBIL, ALP, albumin) at admission and ICU hospitalization. In our study, when the abnormal test results of COVID-19 patients at admission were assessed, we found a significant association only between abnormal albumin levels and severe disease. During hospitalization, a significant association was detected between abnormal AST, ALT, GGT, TBIL, albumin, and ferritin levels, and severe disease.

Table 6: The association between test abnormalities during hospitalization and disease severity.

Hospitalization		Non-severe		Severe		P value
		N	%	N	%	
AST	Normal	184	91.54	17	8.46	<0.001[2]
	1-2xULN	182	81.25	42	18.75	
	2-5xULN	93	77.50	27	22.50	
	5-15x ULN	15	41.67	21	58.33	
	>15xULN	1	4.76	20	95.24	
ALT	Normal	164	85.86	27	14.14	<0.001[2]
	1-2xULN	142	80.68	34	19.32	
	2-5xULN	137	81.07	32	18.93	
	5-15x ULN	32	58.18	23	41.82	
	>15xULN	0	00	11	100	
GGT	Normal	185	85.25	32	14.75	<0.001[2]
	1-2xULN	153	82.26	33	17.74	
	2-5xULN	98	77.78	28	22.22	
	5-15x ULN	37	60.66	24	39.34	
	>15xULN	2	16.67	10	83.33	
T.BIL	Normal	449	81.05	105	18.95	<0.001[2]
	1-2xULN	21	61.76	13	38.24	
	2-5xULN	4	36.36	7	63.64	
	5-15x ULN	0	00	2	100	
Albu-min	Abnormal	245	66.76	122	33.24	<0.001[1]
	Normal	230	97.87	5	2.13	
CRP	Normal	21	95.45	1	4.55	0.094[1]
	Abnormal	454	78.28	126	21.72	
Ferritin	Normal	135	89.40	16	10.60	<0.001[1]
	Abnormal	340	75.39	111	24.61	

[1]Ki-Kare Test [2]Linear-by-Linear Association

It was also observed that the rates of severe disease increased as AST, ALT, GGT, and TBIL levels increased during hospitalization. When evaluated according to the levels of the test results; those with severe disease had higher AST, CRP, Ferritin levels, and lower albumin levels than those without severe disease at the time of admission. During hospitalization, ALT, GGT, and TBIL levels were significantly higher in patients with severe disease. Kumar et al found a significant association between abnormal liver function tests and severe disease in patients hospitalized due to COVID-19.[3] They also reported that advanced age and male gender were also associated with abnormal liver function tests.[3] Chaibi et al reported that liver function test abnormalities were associated with a poorer prognosis in patients with COVID-19 infection and may be a crucial biomarker for early detection of severe infection.[15] They also found that liver test abnormalities were more common in male patients. In our study, no significant relationship was detected between gender and disease severity.

Table 7: Comparison of test results levels at admission according to disease severity.

Admission	Non-severe		Severe		P value*
	Mean±SD	Median (IQR)	Mean±SD	Median (IQR)	
AST	41.53±37.15	31 (23-51)	43.78±25.67	36 (26-55)	0.011
ALT	37.45±39.85	25 (17-43)	29.98±21.92	24 (17-36)	0.303
GGT	56.49±64.19	35 (22-61)	55.27±65.04	35 (20-66)	0.640
T.BIL	0.55±0.38	0.5 (0.32-0.68)	0.54±0.38	0.49 (0.32-0.66)	0.523
Albumin	3.64±0.49	3.6 (3.3-4)	3.29±0.49	3.3 (3-3.6)	<0.001
CRP	92.16±86.86	73 (28-128)	134.57±94.22	130 (52-200)	<0.001
Ferritin	561.99±956.64	355 (171-660)	764.33±851.74	412 (222-1112)	0.026

*Mann Whitney U Test

Table 8: Comparison of levels of test results during hospitalization according to disease severity.

Hospitalization	Non-severe		Severe		P value*
	Mean±SD	Median (IQR)	Mean±SD	Median (IQR)	
AST	56.36±50	42 (29-66)	318.06±776.1	77 (44-221)	<0.001
ALT	71.01±66.66	52 (27-89)	212.69±478.21	75 (38-193)	<0.001
GGT	72.74±88.43	45 (26-80)	174.42±259.89	69 (36-197)	<0.001
T.BIL	0.64±0.44	0.58 (0.4-0.75)	1.17±1.56	0.8 (0.5-1.1)	<0.001
Albumin	3.41±0.55	3.4 (3.1-3.8)	2.49±0.53	2.5 (2.1-2.9)	<0.001
CRP	109.24±84.08	94 (42-154)	230.88±111.71	223 (158-306)	<0.001
Ferritin	694.76±1020.45	475 (212-849)	3954.09±6017.66	1320 (402-3497)	<0.001

*Mann Whitney U Test

Table 9: Cut-off values of the tests that can be a predictor of intensive care unit hospitalization.

Parameters	AUC (%95 CI)	P value	Cut-off	Sensitivity (%)	Specificity (%)
AST	0.738 (0.688-0.788)	<0.001	>81.5	49.60	84.00
ALT	0.63 (0.573-0.687)	<0.001	>163.50	28.30	92.00
GGT	0.64 (0.583-0.697)	<0.001	>54.5	62.20	59.90
T.Bil.	0.671 (0.616-0.725)	<0.001	>0.795	52.00	77.40
Albumin	0.885 (0.854-0.915)	<0.001	<2.95	77.20	82.90
CRP	0.812 (0.769-0.856)	<0.001	>169.5	71.70	80.60
Ferritin	0.726 (0.67-0.781)	<0.001	>1156	56.70	85.00

However, there was a significant association between increasing age and severe disease. Most authors have reported an increased risk of ICU hospitalization and mortality.[16-19] However, a few studies did not find any increased risk of mortality in patients with abnormal liver function tests.[17,20]

In our study, only abnormal albumin levels were significantly associated with severe disease at admission, whereas during hospitalization, abnormalities in all tests except CRP were associated with severe disease. Therefore, we think that monitoring liver tests, especially during hospitalization, is important to predict the development of severe disease.

Limitations

Current study has several limitations. These include the exclusion of patients' medications and comorbidities. However, although it is thought that elevated liver tests in some patients may be related to the used drugs, the variety of used drugs increases, especially in patients with severe disease progression. Therefore, elevated liver test results can be useful in predicting severe disease, whether or not they are caused by medications.

CONCLUSION

In our study, there is an association between liver test abnormalities and severe disease in hospitalized COVID-19 patients. Therefore, monitoring liver tests in hospitalized COVID-19 patients can be useful for predicting progression of severe disease.

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