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The Association of Liver Enzymes with Disease Severity in PCR positive COVID-19 Patients

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Abstract

Introduction: This study aimed to examine the relationship between liver enzymes and severity of COVID-19. Furthermore, patients with clinical diagnosis (PCR negative) and patients with definitive laboratory diagnosis (PCR positive) of COVID-19 were compared in terms of disease severity.
Method: This cross-sectional study enrolled 158 patients with COVID-19 admitted based on chest CT scan findings to the COVID-19 ward of Shahid Mohammadi Hospital, affiliated with Hormozgan University of Medical Sciences (Iran).Reverse-transcriptase polymerase chain reaction (RT-PCR) test was performed for all the patients, who were accordingly divided into groups of PCR negative COVID-19 with clinical diagnosis, and COVID-19 with definitive laboratory diagnosis.
Results: The results indicated a significant elevation of AST (Aspartate transaminase) and Alanine transaminase (ALT) in the PCR positive group compared to the PCR negative group ($p = 0.02$, $p = 0.04$, respectively). The results also showed a correlation between AST level and COVID-19 severity ($p < 0.01$, OR = 2.06). Moreover, a significant correlation was observed between ESR and the levels of AST and ALT ($r = 0.24$ for AST, $r = 0.47$ for ALT).
Conclusion: AST and ALT significantly increased in the PCR positive group compared to the PCR negative group, and AST was correlated with COVID-19 severity. Furthermore, a significant correlation was observed between ESR and the levels of AST and ALT. Therefore, COVID-19 involves liver both directly and through the inflammatory system.

Keywords: COVID-19; Severity; Liver Enzymes

Introduction

COVID-19 is a respiratory disease caused by the SARS-CoV-2 virus that has rapidly spread throughout the world since the end of 2019 and that has become a major health concern for healthcare systems [1,2]. SARS-CoV-2 infects the host cells via the ACE2 receptor that is expressed in many tissues, including the lung, the heart, and the digestive system [3]. ACE2 receptor is moderately expressed in the liver tissue, and reduced liver function is shown in the laboratory blood test results of some of these patients [4-6]. Different mechanisms such as the direct effect of the virus, systemic infection caused by the virus, and hypoxia can lead to liver damage in these patients; however, it is not yet clear which mechanism plays the most prominent role [7,8]. Despite the high prevalence of abnormal liver enzyme levels reported in patients with COVID-19, their relationship with the prognosis of the disease is still controversial [9,10]. In addition to the

patients' clinical presentation, respiratory complaints, and CT scan results, a large number of patients with COVID-19 show changes in hematological and biochemical tests [11,12]. Slight changes in these results at different ages and in patients with COVID-19 who suffer underlying diseases remain questionable.

This study was designed to examine the biochemical, hematological, and epidemiological changes in patients with COVID-19 and their relationship with COVID-19 prognosis. Furthermore, a comparison was made between patients with a clinical diagnosis and those with definitive laboratory diagnosis.

Methods

Study population: This study enrolled 158 patients with COVID-19 admitted based on chest CT scan findings to the COVID-19 ward of Shahid Mohammadi Hospital, affiliated with Hormozgan University of Medical Sciences (Iran) from March 1st to June 1st, 2020. CT positivity defined based on lesion distribution, lesion location, lesion density (ground glass opacity, consolidation, or mixed), thickness of interlobular and intralobular septa, enlarged lymph nodes within the mediastinum and pleural effusion [13]. Reverse-transcriptase polymerase chain reaction (RT-PCR) test was performed for all the patients, who were accordingly divided into groups of PCR negative COVID-19 with clinical diagnosis, and COVID-19 with definitive laboratory diagnosis.

Patients with a history of cirrhosis, viral hepatitis, fatty liver, NASH (nonalcoholic steatohepatitis), NAFLD (nonalcoholic fatty liver disease), drug induced hepatitis, autoimmune hepatitis, hepatocellular carcinoma, and a history of alcohol use were excluded. Subject evaluation: The following blood tests were run for all the patients: a complete blood count (CBC) (Sysmex kx21), liver enzyme erythrocyte sedimentation rate (ESR) via Westergreen method, BUN, and LDH (Mindry bs 800).

The glomerular filtration rate (GFR) was calculated via the following equation:

$$GFR = \frac{n(140 - Age) \times \text{body weight}}{Creatinin \times 72}$$

In this study, lymphocyte ≤ 1500 per mm3, Lactate Dehydrogenase (LDH) ≥ 500, U/L, ALT (SGPT) ≥ 40 U/L, and AST (SGOT) ≥ 40 U/L were regarded as abnormal. Severe disease was defined as respiratory rate≥30, systolic blood pressure<90 mmHg and decreased level of consciousness [14].

Statistical analysis: The data were analyzed in IBM-SPSS v. 22. The quantitative variables of the two groups were compared by a t-test. The qualitative variables of the two groups were compared by a chi-squared test. Furthermore, the relationship between two quantitative variables was examined by Pearson's correlation coefficient.

Results

A total of 158 patients with respiratory COVID-19 diagnosed based on clinical findings and chest CT scan were examined. The participants' mean age was 52 ± 17 years, 54% of whom were men, and 46% were women.

Based on the PCR test results, the patients were divided into PCR positive (n = 130) and PCR negative (n = 28) groups. The mean age of the patients was 50 ± 17 years in the PCR positive group, and 62 ± 16 years in the PCR negative group, showing a significant difference (Table 1).

Variables	PCR		P value
	Yes	No	
Age(Years)	50±17	62±16	0.001
ESR(mm/h)	39±22	34±19	0.2
LDH(U/L)	570±432	521±413	<0.01
AST(IU/L)	58±31	42±24	0.02
ALT(IU/L)	54±29	41±22	0.04
ALP(IU/L)	265±162	187±81	<0.01
Neutrophil (%)	73	67	0.03
Lymphocyte (%)	19	25	0.01
WBC(*106/L)	6000	9000	<0.01
BUN(mg/dl)	56±34	43±27	<0.001
Hb(g/dl)	11.3±2.1	12.1±2.7	0.3
Platelet(*106/L)	204000±83000	237000±104000	0.04

Table1: The relationship of age and laboratory variables with PCR.

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As for inflammatory factors examined in this study, the mean baseline ESR was 39 ± 22mm/hr in the PCR positive group, and 34 ± 19 in the PCR negative group, but the difference was not significant (P = 0.2) (Table-1). However, LDH level was significantly different between the two groups (P < 0.001) as it was 570 ± 432U/L in the PCR positive group, and 521 ± 413U/L in the PCR negative group.

Liver enzymes were checked at baseline, when ALT was 54 ± 29 IU/Lin the PCR positive group and 41 ± 22IU/L in the PCR negative group, showing a significant difference (p = 0.04).

The difference between the two groups was also significant for AST (p = 0.02) as it was 58 ± 31IU/L in the PCR positive and 42 ± 24IU/L in the PCR negative group.

The correlation between the blood level of inflammatory factors (ESR) and the level of liver enzymes was also investigated. A significant correlation was observed between ESR level and ALT level (p = 0.01), with a correlation coefficient of r = 0.47. Furthermore, a significant correlation was observed between the ESR level and AST level (p = 0.03), with a correlation coefficient of r = 0.24.

The level of the Alkaline Phosphatase (ALP) was 265 ± 162 IU/L in the PCR positive group and 187 ± 81 IU/L in the PCR negative group, showing a significant difference (p < 0.001).

A significant difference was observed between the two groups in terms of the WBC count (p < 0.01), which was $6*10^9$/L in the PCR positive and $9*10^9$/L in the PCR negative group.

The neutrophil percentage was 73% in the PCR positive, and 67% in the PCR negative group; this value was significantly higher in the PCR positive group (p = 0.03) (Table 1).Kidney damage was assessed using mean BUN, which was 56 ± 34mg/dl and 43 ± 27mg/dl in the PCR positive and negative groups, respectively, showing a significant difference (p < 0.001) (Table 1).The mean platelet count was 204000 ± 83000/µl and 237000 ± 104000/µl in the PCR positive and negative groups, in respective order, and was significantly lower in the PCR positive group (p = 0.04) (Table 1).In this study, the patients were divided into two groups based on disease severity.

Severe (ICU admitted): Patients who developed respiratory rate≥30, systolic blood pressure<90 mmHg or decreased level of consciousness (n = 23) [13].

Non-severe: Patients who did not developed respiratory rate≥30, systolic blood pressure<90 mmHg or decreased level of consciousness (n = 135) [13].

Baseline laboratory findings revealed that LDH was ≥ 500U/L in 65% and 35% of the patients in the severe and non-severe groups, respectively (p = 0.04) (Table 2). Moreover, 60% and 40% of the patients in the severe and non-severe groups had AST ≥ 40 IU/L, respectively (p < 0.001). The risk of admission to ICU for AST ≥40 IU/L was OR = 2.06 (0-5). Also, 53% and 46% of the patients in the severe and non-severe groups had ALT ≥ 40 IU/L, respectively (OR = 1, p < 0.001) (Table 2). Furthermore, thrombocytopenia (Platelet < 150000/µl) was respectively observed in 53% and 18% of the patients in the severe and non-severe groups (p = 0.001). The risk of ICU admission due to thrombocytopenia was OR = 4 (1-12) (Table 2).

Variables		Refer to Intensive Care Unit (ICU)		P value	OR (CI 95%)
		Yes	No		
Age(years)	≥65	15, 65%	103, 77%	<0.01	1(0-2)
	<65	8, 35%	32, 33%		
LDH(U/L)	≥500	15, 65%	46, 35%	0.04	3(1-9)
	<500	8, 35%	89, 65%		
ALT(IU/L)	≥40	12, 53%	61, 46%	<0.01	1(0-3)
	<40	11, 47%	74, 54%		
AST(IU/L)	≥40	14, 60%	58, 93%	<0.01	2.06(0-5)
	<40	9, 40%	77, 57%		
Platelet(*106/L)	<150000	12, 52%	25, 18%	0.001	4(1-12)
	≥150000	11, 47%	110, 82%		
Lymphocyte/mcl	≤1500	19, 83%	73, 55%	0.01	4(1-12)
	>1500	4, 17%	62, 45%		

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Diabetes Mellitus	Yes	15, 65%	23, 17%	0.04	2(0-6)
	No	8, 35%	112, 83%		
Hypertension	Yes	13, 57%	43, 32%	0.02	2(1-6)
	No	10, 43%	92, 68%		
GFR (ml/min/1.73 m^2)	≥60	16, 70%	17, 12%	<0.01	15(5-44)
	<60	7, 30%	118, 88%		
PCR	Positive	16, 70%	114, 84%	<0.01	1(0-2)
	Negative	7, 30%	21, 16%		

Table2: The relationship of age and laboratory variables with ICU admission.

In addition, lymphopenia was observed in 53% of the patients in the severe group while the non-severe group had lymphocyte count ≤ 1500. The risk of ICU admission due to lymphopenia was OR = 4 (1-12) (Table 2).

Assessing the correlation of kidney function with disease severity revealed that 70% and 12% of the patients in the severe and non-severe groups, respectively, had GFR ≤ 60 ml/min/1.73 m^2. The risk of ICU admission due to Glomerular Filtration Rate (GFR) ≤ 60 ml/min/1.73 m^2 was OR = 15 (5-44). A history of diabetes was reported in 65% of the severe group and 17% of the non-severe group (p = 0.04). The risk of ICU admission due to diabetes was OR = 2 (0-6).

Discussion

The comparison of the two groups of PCR positive and negative patients showed a significant difference in terms of age, AST, ALP, ALT, leukocytes, lymphocytes, neutrophils, platelets, and BUN. The results indicated the lower mean age in the PCR positive group (p = 0.001). Moreover, a significant correlation was found between ESR and the levels of AST and ALT (r = 0.24 for AST, r = 0.47 for ALT).

The results indicated a significant elevation of AST, ALT, and ALP in the PCR positive group compared to the PCR negative group. These results are supported by the results of Mardani [15]. AST elevation was also introduced in the meta-analysis by Kumar-M, et al. as one of the enzymes indicating liver damage in patients with COVID-19 [16]. In the meta-analysis by Wu, et al. ALT elevation was reported as the most prevalent liver enzyme change in admitted patients with COVID-19 [17]. Several meta-analyses have reported a significant correlation between COVID-19 and changes in liver biochemical markers [16-19]. Although its mechanism of action is not known yet, an increase in transaminases may be attributed to extrahepatic factors such as thyroid diseases, muscle diseases, and hemolysis [20]. Moreover, an increase in transaminases less than five times the upper limit of normal is prevalent in primary healthcare [20]. Still, the virus can directly cause liver damage, which has been confirmed with the presence of SARS-COV-1 particles in the liver tissue is some SARS cases, although virus titers were low and no virus inclusions were observed [21]. Another possible mechanism is cell damage caused in cholangiocytes that express the ACE2 receptor (through which the SARS-CoV-2 infects the host cells) on their surface [8,22]. This can also justify the less prevalent release of ALP, which is a specific marker for hepatocytes [8]. The other possible damage mechanisms include the effects of hypoxia and systemic inflammation caused by the virus on organs such as the liver, as well as the hepatotoxicity resulting from drugs [8,23,24].

Our results also showed a significant correlation between ESR and the levels of AST and ALT (r = 0.24 for AST, r = 0.47 for ALT). Tan, et al. also reported the significant correlation between the ESR level in the first stage of the disease and the disease severity and lung damage [24]. Overall, the ESR increase in patients with COVID-19 can be due to the increase in acute phase proteins as the disease exacerbates, which supports the hypothesis that systemic inflammation can lead to liver damage [23,25]. Cases of microvesicular steatosis and moderate lobular and portal activity can also support the drug hepatotoxicity mechanism [26]. In addition, acute hepatitis caused by COVID-19 highlights the importance of liver damage in this disease [27].

Although the liver damage mechanisms of SARS-CoV-2 are not fully known yet, we assume that a combination of the mentioned mechanisms is responsible for liver damage. Based on the reported cases, and the relationship between elevated liver enzymes in COVID-19 as well as elevated ESR, the role of systemic inflammation in liver damage in patients with severe COVID-19 may be more prominent than other mechanisms. Therefore, patients with increased liver enzymes require more care. Moreover, with regard to the prevalence of increased liver damage markers and the significant increase in liver enzymes among PCR positive cases, the increase in liver enzymes can be regarded as a criterion for diagnosing patients in the absence of the PCR test.

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Our results demonstrated a significant increase in the LDH level of PCR positive cases ($p < 0.01$). The results of Mardani, et al. also reported a significant increase in LDH in PCR positive patients [15]. Our results also indicated a significant elevation of neutrophils and a reduction of lymphocytes in the PCR positive group compared to the PCR negative group. Similarly, Mardani, et al. reported a significant increase in neutrophils and a reduction in lymphocytes in the PCR positive group [15]. Our results also showed a significant decrease in platelet count in the PCR positive group. The study by Zhang, et al. showed similar results in terms of reduced lymphocyte, increased neutrophil, and reduced platelets in the PCR positive patients, but the results were not statistically significant [28]. The small sample size in their study may explain this lack of significance.

In our study, BUN was significantly higher in the PCR positive patients than that in the PCR negative group ($p < 0.001$). The results by Yang, et al. also showed increased BUN in 13.7% of the patients with COVID-19 that, when taken together with other factors such as creatinine and GFR, could indicate kidney damage [29].

We also examined the severity of the disease and the type of diagnosis (with PCR or with clinical presentation); the results demonstrated a higher percentage of PCR positive patients in the non-severe group. However, the results showed that laboratory diagnosis and clinical diagnosis of COVID-19 do not differ in terms of disease severity ($p < 0.01$, OR = 1). Contrary to our results, Zhang, et al. reported a higher number of patients with severe COVID-19 in the PCR positive group ($p = 0.015$), but they did not report a significant correlation with disease severity [28]. Although PCR can definitively diagnose COVID-19, cases of false negative have also been reported, which highlights the importance of diagnosis based on clinical and radiological presentation [30,31]. Our results also indicated changes in other hematologic and laboratory factors which, along with clinical presentation, may help doctors in the absence of any para-clinical factors during the COVID-19 outbreak. We recommend more studies on these laboratory changes, though.

Our findings in terms of the patients' characteristics and a history of underlying diseases showed a significant correlation between disease severity and age > 65 years; these results indicate an equal risk for having severe or non-severe disease (OR = 1, $p < 0.01$). On the other hand, the results of the meta-analysis by Zheng, et al. evaluated the risk of COVID-19 progress in patients aged < 65 years to be six times higher (OR = 6.06) [32]. Nevertheless, the factor of age is always highlighted in research [33,34].

Our findings also demonstrated a significant correlation between underlying diseases (diabetes and hypertension) and the severity of COVID-19. The findings indicated a two-time higher risk of contracting COVID-19 in patients with diabetes (OR = 2, $p = 0.04$). Other studies report the importance of diabetes with a 9.8% prevalence among patients with COVID-19 with a two-fold increase in disease severity (OR = 2.16, $p < 0.01$) [35]. Hypertension led to a two-fold increase in the risk of COVID-19 (OR = 2, $p = 0.02$). The study by Zheng, et al. similarly showed a hypertension-related increase in patients with severe COVID-19 [32].

The fact that age and underlying diseases play a role in other infections [36-38] highlights the importance of paying attention to older patients and those with comorbidities. In terms of biomarkers, our results showed a correlation between AST and COVID-19 severity ($p < 0.01$, OR = 2.06). Mardani, et al. reported significantly higher AST levels in those with positive PCR results from among patients suspected of COVID-19 [15]. As for disease severity, Omrani-Nava, et al. reported a strong correlation between AST level and admission to ICU (OR = 97.08) [38]. This difference in results can be attributed to several factors, such as geographical differences, sample size differences, and the comparison of patients with a control group from the aggregated results of a cohort study. Kumar-M, et al. also found a significant relationship between patients with severe disease and AST compared to the non-severe group, which shows less difference with our results (RR = 2.30) [16]. Other studies also report a significant relationship between disease severity in patients with COVID-19 and increased AST [18,19].

However, in our study, changes in ALT in both groups of patients with severe and non-severe disease had the same ratio (OR = 1, $p < 0.01$). Several studies have reported a significant relationship between ALT and COVID-19 severity [18,19].

The relationship between the ALP level and COVID-19 severity was not significant in our study. Kumar-M, et al. reported a significant relationship between ALP level and severe COVID-19 compared to non-severe COVID-19 (RR = 1.99) [16]. Our small sample size can explain this difference in results and the lack of a significant finding.

These findings for liver enzymes can show an increase in liver damage in patients with severe COVID-19. In the absence of effective hepatoprotective treatments [8], these results highlight the importance of preventing exacerbation of the disease as well as provision of more care for patients with severe COVID-19.

Furthermore, GFR significantly led to 15-fold increase in patients with severe COVID-19 and GFR<60 (OR = 15, $p < 0.01$). Similarly, Wang, et al. reported the reduction in GFR

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is correlated with a higher disease severity and a reduction in the survival of patients with COVID-19 [39]. A significant increase in the level of BUN and creatinine in patients with COVID-19 suggests kidney damage [29,40,41]. Still, more studies are needed on the pathophysiology and relationship of kidney diseases with COVID-19.

Our results were not limited to hepatic and renal markers, but also showed the correlation of the significantly increased LDH to > 500 U/L with COVID-19 severity ($p = 0.04$, OR = 3). Other studies report similar results in terms of LDH [42-45]. In the study by Ji, et al., LDH > 500 U/L was significantly related with COVID-19 severity (hazard ratio = 9.8) [46].

The results of our hematological examinations demonstrated a significant correlation between platelet count < 150,000 and COVID-19 severity (OR = 4, $p = 0.001$), a result that is consistent with the results of the study by Yang, et al. [47] in which platelet count was significantly lower in the non-survivor group than that in the survivor group [47]. The results of a meta-analysis by Lippi, et al. demonstrated that a lower platelet count increases the risk of severe COVID-19 five folds (OR = 5.1) [48].

Our other tests showed a significant correlation between a higher COVID-19 severity in patients with a lower lymphocyte count ($p = 0.01$, OR = 4). Other studies confirm our results in terms of a reduction in lymphocyte count and COVID-19 severity [49-52]. These findings suggest that more attention should be paid to lymphocyte count in patients with COVID-19.

A limitation of the present study was its small sample size as it reduced the statistical power, and we could not reach a significant level in some tests. However, our results show that changes in liver enzymes and hematologic factors, along with other complaints and clinical examinations, can be used when we suspect COVID-19 in the absence of PCR. We also assume that liver damage in patients with COVID-19 is largely affected by inflammatory reactions of the immune system; still, more studies are warranted on the mechanism of liver and kidney damage in these patients and its management.

Conclusion

AST and ALT significantly increased in the PCR positive group compared to the PCR negative group. AST was correlated with COVID-19 severity. Our study also showed a significant correlation between ESR and the levels of AST and ALT. Therefore, COVID-19 involves liver both directly and through the inflammatory system, as noted in our study.

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