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Hepatocellular Damage and Severity of COVID-19 Infection in Iraqi Patients: A Biochemical Study

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Abstract

Background: Infection with COVID-19 can cause hepatic damages. Here, we aimed to examine the effect of COVID-19 infection on the serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumin, and procalcitonin (PCT) concentrations as markers to evaluate the liver function.

Methods: In this study, 56 patients infected with COVID- 19 and 28 healthy controls was recruited in Private Nursing Home Hospital of the Medical City, Baghdad. Patients were subdivided according to disease severity into severe and non-severe groups.

Results: The results showed that the mean±SD value of serum AST activity and serum PCT concentrations were elevated significantly in severe group in comparison to healthy control, ($p< 0.01$, $p< 0.001$) respectively. Also, the mean ±SD value of serum ALT activity was higher in severe group compared to the healthy subjects and non-severe ones, significantly ($p< 0.0001$, $p< 0.003$) respectively. While the mean value of serum albumin concentration of severe patients and non-severe group were significantly decreased compared to healthy subjects. The receiver operating characteristic curve (ROC) revealed that ROC value of albumin (0.992) differentiates between non-severe infected patients and healthy subjects, while the ROC value of serum ALT activity (0.735) differentiates between severe COVID-19 patients and non- severe ones.

Conclusions: Changes of liver function parameters in COVID-19 patients were mild to moderate and measurement of serum ALT activity is the best biomarker in differentiation between non-severe patients and severe ones and albumin concentration is excellent in discrimination between patients and controls.

Keywords: Serum aminotransferase enzymes, Albumin, Procalcitonin.

Introduction

Coronaviruses (CoVs) infect both humans and animals. They are in humans mainly causing many respiratory and intestinal infections, ranging from mild to lethal. Coronaviruses are enveloped positive-sensory, single-strand RNA viruses with a range between 26 and 32 kilobases, the largest RNA genomes known to date, about 30,000 nucleotides are present in the SARS-CoV-2 genome. It has ability to rapidly mutate and only recombine. It is understood that coronaviruses cause respiratory diseases, acute respiratory illnesses, including flu, syncytial respiratory diseases (1). In 2019 outbreak of coronavirus (COVID-19), which began in December 2019, spread sharply in China (2), where the patients are epidemiologically linked of a seafood , wet

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animals whole sale market in Wuhan, Hubei Province (3). It has a spherical body and covers with protein spikes. Those spikes aid the virus in binding to well cells and infecting them (4). SARS-CoV-2 structural proteins include glycoprotein (M) membrane, envelope protein (E), nuclear capsule protein (N) and spike protein (S). Linking with M protein aids in the establishment of N proteins and favor viral installation by settling the N protein-RNA complex at the interior virion. M-glycoprotein is the most considerable building protein for coronaviruses as the M protein cooperates with the S protein, it covers the two-layer membrane, permitting a small NH2 terminal region out of the virus and the long COOH terminal inside the virion, it might affect host cell binding and virus entrance, The glycosylated S virus protein can help prevent immune protection (5), COVID-19 takes about 79.5 percent of sequence symmetry that of SARS-CoV, according to full-length genome sequencing, and therefore the sequence of protein showed that it belongs to SARS-related coronaviruses class (6). The same receptor for angiotensin converting enzyme 2 (ACE2), COVID-19 and SARS-CoV are both entered the host cell. Thus, the SARS-CoV-2 virus was then renamed (7).

The liver is an important organ in the human body and may be more concerned about its sensitivity to viral particles. There is no clear evidence for the susceptibility of liver cells to SARS-CoV-2. Furthermore, the degree to which liver disorders are significant risk factors for COVID-19 severity and mortality is still unknown (8). The liver is the primary metabolism and detoxification organ of the human body, and even moderate loss of liver function could change the protection and therapeutic properties of liver-metabolized antiviral drugs. The presence of SARS-CoV-2 viral RNA has been established lately in the liver by qRT-PCR in the liver in spite that the exact replication cell site is yet unknown (9).

Albumin is a protein produced by the liver that has tremendous physiological roles such as supplying oncotic pressure, connecting and transferring substances, and preserving acid-base equilibrium, within other actions (10). Through the crucial disease, inflammatory mediators reduce the synthesis of albumin so that to prefer different acute phase reactants synthesis. Moreover, those mediators raise the permeability of vessels permitting albumin to get-away to outside, that might as well progress to reduced serum albumin levels (11).

Procalcitonin is the precursor of the calcitonin hormone. Different cell types outside of the thyroid gland develop PCT as a reply to pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) or bacterial endotoxins, increases in PCT level occur with severe inflammation, especially serious sepsis and systemic infection. The PCT is closely associated with systemic inflammation severity and declining levels are related to infection resolution (12).

The present research was designed to examine the role of serum aminotransferases enzymes (ALT & AST) activities, albumin and procalcitonin concentration to study the severity of coronavirus COVID-19 infection and correlations between the values of these laboratory parameters outcomes and CT- scan values.

Materials and Methods

The current retrospective observational study was performed at the Biochemistry Department, Medicine College, University of Baghdad, and at Private Nursing Home Hospital, Medical City, Baghdad, during the period from 19-10 - 2020 to end of 30-1- 2021. It included 56 patients affected by coronavirus Covid 19 who were diagnosed previously using CT- scan and RT-PCR and 28 healthy persons presented as controls. Inclusion criteria involved patients on admission and before starting any treatment regarding the coronavirus COVID-19 and those of more than 18 years old. While exclusion criteria involved patients who have had critical coronavirus, influenza-cold viral infection, autoimmune diseases, chronic liver diseases, chronic kidney diseases, chronic pulmonary diseases, and any acute or chronic illness other than coronavirus COVID-19. The

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range of the age for patients was between (30-80 years). Patients were sub-divided according to their infected Covid 19-disease severity into Group 1 (G1), which involved 28 severe patients, and Group 2 (G2) that included 28 non-severe patients. The subgrouping of these patients was achieved by consultant physician based on fact that severe patients have oxygen rate less than 93%, dyspnea, fever, cough, myalgia, headache, pharyngalgia, diarrhea, chest tightness and shortness of breath fear of cold (8). This study was carried out after approvals were acquired from the Biochemistry Department scientific committee, Medicine College, University of Baghdad, Medical City, Ministry of Health and vocal consent from each patient or her/ or his relative.

Three mL of blood sample were collected from the peripheral vein of each patient and control and moved out into gel plain tube that allows clotting for 15 minutes and then centrifuged for 10 minutes at 3000 g to obtain serum sample.

The separated serum was divided into two parts, one for direct measurements of albumin, aminotransferase enzymes (AST & ALT) on the same day of blood collection, and the second part was stored in aliquots at –20 °C until the time of measurements of procalcitonin.

Statistical analysis

Data of serum studied parameters was described and tabulated using mean ± standard deviation (SD) when the distribution is normal. Analysis of variance (ANOVA) was used to resolve the differences among the groups and Post hoc Tukey test was used to analyze specific different groups pairwise. Data with non- normal distribution including that of procalcitonin were presented and tabulated as median and Inter Quartile Range, (1st Q-3rd Q) values. In order to determine which groups are different from others when Kruskal–Wallis test was significant, post-hoc testing was conducted with the Dunn Test for pair-wise comparison. Pearson correlation was performed to test significant correlation among different variables. ROC analysis was applied for evaluating the power of study markers to discriminate between non-severe, severe, healthy controls best criterion values were selected, and their diagnostic criteria were presented. Alpha level for statistical significance was set to $p < 0.05$.

Results

The present study shows that there was a non-significant difference among the age of subjects in healthy, non-sever and sever COVID-19 groups (Table 1).

Table 1. The age and gender of healthy controls, non-severe COVID-19 patients, and severe COVID-19 patients.

Parameter	Healthy controls (n=28)	Non- severe COVID-19 (n=28)	Severe COVID-19 (n=28)
Age (Year) ^{NS}	56.21± 10.27	55.39± 9.85	59.50± 8.06

ANOVA and t-test revealed NS, non-significant difference among groups.

Also, the mean value of serum AST activities of severe patients (40.50± 20.89 U/L) was significantly greater than that of healthy subjects (29.04± 7.50, $p < 0.01$). However, there was no significant differences in mean value of AST between non-severe patients (34.36± 12.61 U/L) and healthy subjects and between non severe and severe patients. The mean value of serum ALT activities of severe group (56.89± 27.13 U/L) was significantly increased compared to that of healthy (30.14± 9.68 U/L, $p < 0.0001$) and non-severe patients' group (37.71± 14.88 U/L, $p < 0.003$), without significant variation between healthy and non-severe groups. The mean values of serum albumin concentration of severe patients (2.70± 0.31 g/dl, $p < 0.0001$) and non-severe group (2.99±0.34 g/dl, $P < 0.0001$) were significantly decreased compared to that of healthy subjects (4.76± 0.82 g/dl), without significant distinction between severe and non-severe patients. The result also showed that the

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median (1st Q-3rd Q) value of serum PCT concentrations of severe patients 164.70 pg/ml (80.01- 298.58) was significantly higher than in healthy subjects 74.7 pg/ml (38.16- 112.53, p< 0.001), without significant differences between severe and non-severe groups 143.68 pg/ml (52.79- 207.22) as well as between non-severe group and healthy controls (p=0.05), (Table 2).

Table 2. Mean (±SD) values of AST, ALT, albumin and Median (1st Q3rd Q) values of procalcitonin in healthy controls, non-severe COVID-19 patients, and severe COVID-19.

Parameter	Healthy (n=28)	Non-severe COVID-19 patients (n=28)	Severe COVID-19 patients (n=28)
AST (U/L)	29.04± 7.50	34.36± 12.61●●	40.50± 20.89●
ALT (U/L)	30.14± 9.68°	37.71± 14.88	56.89± 27.13*
Albumin (g/dl)	4.76± 0.82°	2.99± 0.34	2.70± 0.31■
Procalcitonin (pg/ml)	74.7 (38.16-112.53)	143.68 (52.79207.22)●●	164.70 (80.01-298.58)♦

T-test revealed ● significant increase in AST in severe than in controls (p< 0.015), ♦significant increase in procalcitonin in severe than in healthy (p<0.001), ANOVA test revealed * significant increase in ALT in severe than in healthy (p<0.0001) and non-severe (p<0.003), ■ significant decrease in albumin in severe than in healthy and non-severe (p<0.0001), ,●● non-significant difference in AST and procalcitonin between non-severe and each of control and severe, ° non-significant difference in ALT, and albumin between non- sever and control.

The results of the present study found several significant correlations in non-severe COVID-19 patients' group (Table 3). While there was a non –significant correlations between the studied parameters in the severe group of patients (Table 4).

Table 3. Correlation matrix showing correlation coefficients (Pearson) and p-values (Pearson) in non-severe patients.

Parameter		Albumin	CT%
Age	r	-0.46	0.38
	p	0.01	0.045
AST	r	-0.55	-0.08
	p	0.00	0.67
ALT	r	-0.33	-0.08
	p	0.09	0.69
Albumin	r		-0.34
	p		0.08
PCT	r	-0.25	0.61
	p	0.19	0.00

Table 4. Correlation matrix showing correlation coefficients (Pearson) and p-values (Pearson) in severe patients' group.

Parameter		Albumin	PCT	CT%
Age	r	0.01	0.18	0.32
	p	0.97	0.36	0.10
AST	r	-0.29	- 0.04	-0.10
	p	0.14	0.86	0.62
ALT	r	-0.11	-0.20	-0.29
	p	0.59	0.31	0.14
Albumin	r		-0.23	-0.31
	p		0.24	0.11
PCT	r	-0.23		0.03
	p	0.24		0.89

Table 5 shows receiver operating characteristic curve (ROC) and area under curve (AUC) of the studied parameters in diagnosis and differentiation of non-severe COVID -19 patients from healthy subjects. It shows that albumin was the best parameter in differentiation between the non- severe and healthy controls.

Table 5. Criterion values and coordinates of the ROC curve non- severe versus healthy.

Marker	Cut	AU	P-	Sensiti	Specific
Albumin(	≤ 3.4	0.9	<0.00	85.71	96.43
ALT	>34	0.6	0.061	34	53.57
AST (U/L)	>38	0.6	0.159	39.29	92.86
PCT	>119	0.6	0.037	53.57	78.57

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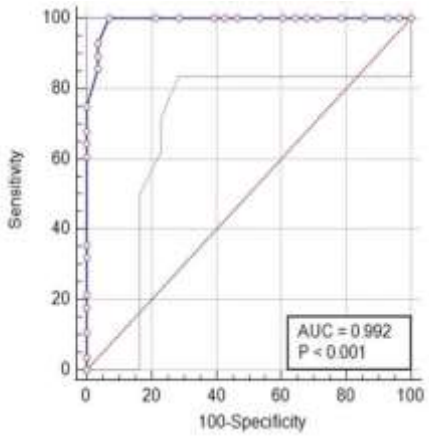

Fig. 1. ROC analysis for Albumin as discriminating between non-severe COVID-19 and healthy controls. Albumin had ROC and AUC value (0.992) in differentiation of non-severe COVID -19 patients from healthy subjects at cutoff value (≤3.40 g/dl) with sensitivity and specificity (SE=85.71& SP=96.43).

Table 6 shows ROC and AUC of the studied parameters in diagnosis and differentiation of severe and non- severe COVID -19 patients. It shows that none of the studied parameters was functional in differentiation between the two groups.

Table 6. Criterion values and coordinates of the ROC curve for different markers differentiating between severe and non-severe cases.

Marker	Cut off	AUC	P-value	Sensitivity	Specificity
Albumin(g/dl)	≤2.8	0.696	0.0055	71.43	64.29
ALT (U/L)	>46	0.735	0.0007	60.71	82.14
AST (U/L)	>45	0.589	0.253	39.29	85.7
PCT pg/ml	>52.79	0.601	0.1872	96.43	28.57

Discussion

The current study found that the mean (±SD) value of serum ALT activities of severe patients was significantly greater than that of healthy subjects, while the mean value of serum ALT activities of severe was higher significantly than that of healthy and non-severe patients. In addition, the mean values of serum albumin of severe and non-severe patients were significantly lower than that of healthy controls (Table 1). Fan et al. (2021) found that medium activities of AST and ALT in non-severe and severe patients were oscillated within the normal reference extent and exhibited an upward tendency (10, 13). Albumin levels in the severe group fluctuated within the normal range, but lower than in the non-severe group. Xie et al. (2020) detect an addition of ALT or AST nearly in one third of their non-critical patients (14). Increased liver function tests, such as AST and ALT were included in the growing mortality rate of COVID-19 (15). Present research discovers that patients with extended time from starting till admittance are more possibly to extend hepatic deterioration (16) and pathological proof also displayed moderate microvascular steatosis and modest liver lobular inflammation in patients with COVID -19 (17) suggesting that COVID-19 infection can progress to liver damage in several patients (14).

Hypoalbuminemia and increased AST levels were predominately monitored in crucial patients and the correlation of AST and albumin levels with disease intensity was also observed (15). Albumin serum levels in both critical and severe groups were found to be less than 4.0 g /dl (13). During hospitalization, usually patients with COVID -19 had fever and receive antipyretic drugs containing paracetamol which had a serious damage on the liver. Additionally, inspire that there is no specific antiviral treatment for COVID-19, most patients yet take unparticular antiviral drugs like ritonavir and lopinavir, that may cause hepatotoxicity and encourage liver

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damage. It has been observed that severe cases had serious symptoms of oxygen deficiency and chest tightness (13). Recent studies have noted that lipid aggregation, glycogen consuming, oxygen deficiency and ATP consumption in hepatocytes can immediately progress to hepatocyte decease (18), along with increasing of reactive oxygen species (ROS) and its peroxides that are represented as the second messengers, activate redox-sensitive transcription factors, moreover, stimulate the release of different pro-inflammatory factors and then cause liver injury (19). Remarkably, pooled analyses significantly demonstrated higher levels of ALT and AST in severe group patients of COVID-19 in comparison to non-severe group (20). Hence, three major assumptions have been proposed including damaging virus directly, systemic inflammation, and drug-induced damage. In a recent cohort study performed in China, scientists had observed an abnormal level of serum aminotransferase levels in severe group of COVID-19 patients in comparison to non-severe group (21). Although, the ratio of patients with transaminase abnormalities were high, they were mild which suggested that liver cell necrosis is rarely took place. Yet, there was a greater decrease of protein synthesis, especially albumin was stimulated by COVID-19 infection. The explained mechanism is that the rapid increase of inflammatory cytokines produces a prevention of protein synthesis in hepatocytes (22). In spite that the virus receptor, angiotensin-converting enzyme 2 (ACE2), can be observed in specific types of liver cells (23), the liver injury from viruses would change the enzymes first and then alter lipoproteins, coagulation functions and albumin only if the viral infection prevailed in the liver. Furthermore, the decrease in albumin related well with the upsurge of cytokines, encouraging the idea that liver damage is directly secondary to cytokine storm (21). The outcomes of the present research also observed that the mean value of PCT level was increased significantly in severe group compared to healthy control. Recent studies stated that increased PCT is correlated directly with the intensity of COVID-19 (19). A meta-analysis also observed that elevated PCT values are connected to a ~5- times higher risk of severe COVID-19 (24). The latter study also demonstrated that the serum PCT levels were about eight times higher in critical patients than in moderate patients and about four times higher in severe patients than in moderate patients. Serum PCT levels showed to be dependent on the disease severity and might be correlated with bacterial co-infection, as it was near the rate of increased PCT levels in patients with medium disease severity (25). Asghar et al. (2020) confirmed the use of PCT as a considerable biomarker of COVID-19, and the prognosis of the severity of the disease by PCT might be because of the greater co-infection rates by bacteria with an increased prevalence of pneumonia associated with a ventilator (23, 26). In addition, several new investigations have noticed a considerable correlation between the increased levels of PCT and the severity of the disease (27). Normally, the C-cells of the parathyroid gland produce the PCT. Yet, the increase of serum PCT level during infection appeared to be from neuroendocrine cells in the intestine and lungs. The presence of the proinflammatory cytokines, such as interleukin-6 and tumor necrosis factor-alpha appear to mediate the release of PCT (28). A present study concluded that patients infected with viral infection had much lower level of PCT compared to bacterial infection (29). Infected patients with COVID-19 with an increased level of serum PCT were correlated with a 5-times higher risk of severe disease progression (24).

The present study had concluded that liver involvement is common in COVID-19 infection and observed more currently in the severe COVID-19 group. The speculated explanations for the hepatic damage, in addition to the direct cytotoxicity effect of the virus, other mechanisms include cytokine upsurge, bacterial infection, and hypoxia and ischemia injury. More studies are needed to explain the pathogenesis of the liver injury in COVID-19 infection.

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Ethical Information and conflict of interest

The entire work had permitted by the Ethical Committees of local authorities. All participants provided an inscribed informed consent, and the research had conducted in line with the ethical morals identified in the 1975 treaty of Helsinki. The authors declare no potential conflicts of interest related to the present research.

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