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Original Article

Liver Function Abnormalities in COVID-19 Patients and their Association with Age and Sex: a Cross-Sectional Study

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Abstract

In December 2019, the onset of an unidentified disease known as pneumonia for an unknown reason occurred in Wuhan city, China. Liver dysfunction has occurred in COVID-19-infected patients. The current study investigated liver function abnormalities in COVID-19 infected patients and their relationship with age and sex. A cross-section study was designed and conducted at Al-Hakeem hospital in Al-Najaf city in Iraq. This study comprised 167 patients with SARS-CoV-2 confirmation using real-time polymerase chain reaction. Liver function test results were compared among different age groups and the two genders. The analysis of categorical variables was achieved via the Chi-square test. The differences in the continuous variables between both sexes were detected via Mann–Whitney U test. A statistically significant p-value was determined to be less than 0.05. IBM SPSS software (version 26) was utilized for data analysis. Among 167 patients with COVID-19 infection, 82 (49.1 %) had abnormal liver test and 85 (50.9%) were normal (*P*=0.816). No significant differences were noted in liver test abnormalities among the various age groups (*P*=0.784). The percentages of liver function abnormalities in males and females were (68.3 %) and (37.5 %) respectively. Significant differences were detected between males and females (*P*=0.001). The distribution of AST and ALT between males and females was shown to be significantly different (*P*=0.012) and (*P*=0.009), respectively. The ALP (U/L) and total bilirubin (mg/dL) median values between males and females were shown to be statistically insignificant. In our study, we estimated that the risk of liver function abnormalities was not significantly different among all age groups and infected males had a higher incidence of liver dysfunction with significant differences in serum AST and ALT levels between both sexes.

Keywords: COVID-19, Liver function abnormalities, Age, Sex

1. Introduction

In December 2019, the onset of an unidentified disease known as pneumonia for an unknown reason occurred in Wuhan city, China (1, 2). The agent that may lead to this disease is then discovered to be a new strain of coronavirus. The causative virus and the diseases are SARS-CoV-2 and COVID-19, respectively (3, 4). About 270 countries have been affected by the disease, with approximately 24,555, 400 infected cases and 802,760 deaths worldwide. SARS-CoV-2 is transmitted through respiratory droplets, which can be quickly and directly spread by coughing, sneezing, or indirectly in contact with infected surfaces (5). Fever, cough, dyspnea, myalgia, malaise, headache, nausea, vomiting, and diarrhea are the most repeated signs and symptoms of COVID-19

(6). Liver dysfunction has occurred in COVID-19-infected patients (7).

COVID-19 has been divided into three categories depending on clinical severity: mild infection includes uncomplicated infection of the upper respiratory tract with minor signs and symptoms such as fever, wet or dry cough, pharyngitis, congestion of the nose, malaise, and headache, with normal levels of SpO2 (90–94%) on room condition and breathing rate 24–30 (breaths/minute); moderate infection includes pneumonia without signs and symptoms of serious illness; Severe infection include pneumonia with respiratory distress signs and breathing rate >30 (breaths/minute) or SpO2 90% on room condition (6).

ACE-2 has been verified as the target receptor for SARS-CoV-2 in studies using single-cell RNA sequencing (8). Hepatocytes and bile duct cells containing ACE-2 receptors may be infected with SARS-CoV-2 leading to liver dysfunction (9). From a series of liver biopsies, pathological alterations such as mild lobular, portal activity, and micro-vascular steatosis were found, demonstrating that direct hepatocellular damage was induced via SARS-CoV-2, or drug-induced liver injury might be the source of the liver damage (10). Blood clots were detected in the kidneys, brain, and liver, indicating activation of the clotting cascade via endothelial damage and continuously elevated inflammatory markers, suggesting that systemic thromboembolism may play a role in COVID-19 patients' liver function abnormalities (11).

Considering the elevated prevalence, pathogenicity, and infectivity of liver damage in these patients, a thorough investigation of liver function is urgently needed. The current study investigated liver function abnormalities in COVID-19 infected patients and their relationship with age and sex.

2. Materials and Methods

A cross-section study was designed and conducted at Al-Hakeem hospital in Al-Najaf city in Iraq. This study comprised 167 patients admitted and treated from December 1 to December 28, 2020, with SARS-CoV-2 confirmation utilizing real-time polymerase chain reaction. This study's inclusion criteria include patients with a positive real-time polymerase chain reaction for SARS-CoV-2. Exclusion criteria include preexisting liver disease patients, hepatitis B and C, alcoholism, and patients using hepatotoxic medicines. Standard methods were used to perform a full clinical history and assessment, laboratory tests such as complete blood counts, and so on. The rise of the following hepatic enzymes in serum was defined as a liver test abnormality: AST (>38 U/L), ALT (>41 U/L), ALP (>135 U/L), and total bilirubin (>1.1 mg/dL).

2.1. Statistical analysis

All variables were estimated to be not normally distributed using Kolmogorov–Smirnov test. Categorical data were represented using frequencies and percentages. Medians and (interquartile ranges) [IQRs] were utilized to express continuous variables. The analysis of categorical variables was achieved via the Chi-square test. The continuous variables differences between both sexes were detected via Mann–Whitney U test. A statistically significant *P*-value was determined to be less than 0.05. IBM SPSS software (version 26) was utilized for data analysis.

3. Results

Among 167 patients with COVID-19 infection, 82 (49.1%) were abnormal- and 85 (50.9%) were normal liver test (P=0.816). Most participants aged ≥ 60 years, and the percentages of the abnormal liver test increased with increased age; (33.3%) for age (20-39) years to (51.9%) for age ≥ 60 years; however, no significant differences in liver test abnormalities were found among the various age groups (P=0.784). The percentages of liver function abnormalities in males and females were (68.3%) and (37.5%) respectively. Significant differences were detected between males and females (P=0.001) (Table 1).

According to the AST levels analysis, 59 of 82 (71.9%) subjects had elevated AST levels. Median AST in males was 42.0 (53.3-28.8) U/L, and in females was 52.0 (66.0-42.5) U/L. The distribution of AST between males and females was significantly different (*P*=0.012) (Table 2).

According to the ALT levels analysis, 62 of 82 (75.6%) subjects had elevated ALT levels. Median ALT in males was 56.0 (66.0-44.8) U/L, in females was 45.0 (58.5-26.00) U/L. ALT distribution between males and females was significantly different (*P*=0.009) (Table 2).

According to the ALP levels analysis, 22 of 82 (26.8%) subjects had elevated ALP levels. Median ALP in males was 79.00 (89.3-66.8) U/L, and in females was 81.0 (114.8-66.0) U/L. The median values of ALP between males and females were shown to be statistically insignificant (Table 2).

According to the total bilirubin levels analysis, 31 of 82 (37.8%) subjects had elevated total bilirubin levels. The median value of total bilirubin in males was 0.90 (1.00-0.80) mg/DL, and in females was 1.00 (1.02-0.77) mg/dL. The median values of total bilirubin between males and females were shown to be statistically insignificant (Table 2).

Table 1. Liver function characteristics of patients on admission

		Liver function		
	Total	**Normal**	**Abnormal**	***P*-value**
	167	85 (50.9%)	82 (49.1%)	0.816
		Age (years)		
20-39	15 (8.9%)	10 (66.7%)	5 (33.3%)	
40-59	71 (42.5%)	36 (50.7%)	35 (49.3%)	0.784
≥60	81 (48.5%)	39 (48.1%)	42 (51.9%)	
		Sex		
Male	63 (37%)	20 (31.7%)	43 (68.3%)	0.001
Female	104 (63%)	65 (62.5%)	39 (37.5%)	

Frequencies and percentages were used to represent the data. The Chi-square test was used for calculating *P*-value *P*<0.05 was indicated by bold data values

Table 2. Comparison of median hepatic enzymes values between male and female

	Median (IQRs)			
Sex	**AST (U/L)**	**ALT (U/L)**	**ALP (U/L)**	**T BIL (mg/dL)**
Male	42.0 (53.3-28.8)	56.0 (66.0-44.8)	79.00 (89.3-66.8)	0.90 (1.00-0.80)
Female	52.0 (66.0-42.5)	45.0 (58.5-26.00)	81.0 (114.8-66.0)	1.00 (1.02-0.77)
P-value	0.012	0.009	0.680	0.405

Medians (IQRs) were used to represent the data. *P*-values calculation was achieved via Mann–Whitney U test. *P*<0.05 was indicated by bold data. AST- Aspartate transaminase ALT- Alanine transaminase, ALP- alkaline phosphatase and T BIL- total bilirubin

4. Discussion

In this study, even though there were no significant differences, it may seem that older age is linked to a larger risk of liver damage or abnormal function. This result was in agreement with the results of another study (12). However, more research is required to support this finding. In the future, we hope to see additional studies on liver damage associated with COVID-19 in different age groups. Liver dysfunction percentages increased more likely in males (68.3%) than in females (37.5%) with (P= 0.001), which was consistent with other studies that showed that males have a higher incidence of liver dysfunction than females (13, 14). However, the present study revealed that females had a significant elevation in serum AST levels (P=0.012) with significantly lower serum ALT levels (P=0.009) compared with males.

On the other hand, no significant differences were noted in ALP and total bilirubin levels between both sexes (P>0.05). Few data exist that had reported differences in liver enzyme levels between males and females in patients with COVID-19. Kumar A (15) believed that the most severe cases of COVID-19 patients were females and suggested that AST levels are a good indicator of disease severity since they elevated as the disease progressed. Also, Hao S-R (16) concluded that male patients were at higher risk of ALT level elevation. These results were consistent with our results.

Hepatocytes contain a higher level of AST than ALT, but the latter is more highly concentrated in the cytoplasm than the former. Therefore, in the case of hepatitis due to viral infection, damaging the cytoplasmic membrane leads to infiltration of the cytoplasm and raises the level of plasma ALT than AST. However, in the case of mitochondrial and cytoplasmic membrane damage, plasma AST level is highly elevated compared with ALT, so one can conclude that plasma level of AST or ALT may indicate the type of liver cell damage (17).

It is indistinct whether SARS-CoV-2 directly affects liver function or not (12). According to certain studies, the target receptor for SARS-CoV-2 is the human ACE2 in alveolar epithelial cells (18, 19). As a result, SARS-CoV-2 infection is thought to affect the lungs primarily. Previous research suggested that the ACE2 receptor is exhibited via bile duct epithelial cells at a 20-times higher level than hepatocytes, demonstrating that bile duct epithelial cells may also damage by SARS-CoV-2 infection (9, 20). Significant elevations in serum ALP or total bilirubin (which might indicate bile duct damage) have only been observed within a few COVID-19 individuals (21). COVID-19 patients' liver histopathologic features showed no significant damage to hepatocytes or bile duct cells (19).

As a result, it is acceptable to believe that liver dysfunction associated with COVID-19 seems to be more likely the result of secondary liver injury than hepatotoxic treatment or the presence of systemic inflammation, hypoxia induced by respiratory distress syndrome, or multiple organ failure.

Our study estimated that: (1) The risk of liver function abnormalities was not significantly different among all age groups. (2) Infected males had a higher incidence of liver dysfunction than females. (3) Significant raising in serum level of AST in females relative to males was noted. (4) Significant raising in serum level of ALT in males relative to females was noted. (5) Serum levels of ALP and total bilirubin were not significantly different between both sexes.

Abbreviations

COVID-19, Coronavirus disease-19; ACE, angiotensin-converting enzyme; SpO2, oxygen partial pressure; SARS-CoV-2, Severe acute respiratory syndrome-coronavirus-2; ALP, Alkaline phosphatase; ALT, Alanine transaminase; AST, Aspartate transaminase; IQRs, interquartile ranges.

Authors' Contribution

Study concept and design: H. K. A.
Acquisition of data: H. A. M. A.
Analysis and interpretation of data: K. A. A.
Drafting of the manuscript: M. K. A.

Critical revision of the manuscript for important intellectual content: H. A. M. A.
Statistical analysis: H. A. M. A.
Administrative, technical, and material support: H. A. M. A.

Ethics

The approval of the study followed the University of Babylon's ethical committee. All participants provided informed consent.

Conflict of Interest

The authors declare that they have no conflict of interest.

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