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Hypertransaminasemia: Incidence and its Clinical Correlations in Patients with COVID-19 Infection

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Abstract

Background: coronavirus-19 disease recently emerged as a global pandemic affecting the respiratory system. However, during the course of the illness, the disease can directly or indirectly involve other body organs including the liver.

Objectives: This study aimed to determine the incidence of hepatic involvement and its clinical significance in COVID-19 patients.

Patients and Methods: This cross-sectional single-center study was conducted on 112 patients who have an infection with Covid 19 (proved by polymerase chain reaction). Depending on infection severity, patients were categorized into three groups (according to the guidelines of the Chinese National Health Committee): mild, moderate, and severe cases. Blood samples were collected from each patient and liver function tests were conducted. Abnormal hepatic enzyme was considered when any enzyme (alanine transaminase, aspartate transaminase, and alkaline phosphatase) was more than the upper normal laboratory value. Categorical variables were presented as numbers and percentages and analyzed with a Chi-square test. A $P \leq 0.05$ was considered statistically significant.

Results: Sixty-six patients (58.93%) had normal liver enzymes, while the other 46 (41.07%) had abnormal liver enzymes. The mean age of patients with elevated liver enzymes was 45.17±11.93 years which was significantly higher than that of normal liver enzymes patients (38.92±13.47 years). In severe cases, 45.65% of patients had elevated liver enzyme compared with 43.48% in moderate group and 10.87 % in mild group.

Conclusions: Acute liver injury as indicated by hypertransaminasemia is a frequent finding in COVID-19 patients. Elderly patients with moderate to severe COVID-19 are more prone to hepatic involvement.

Keywords: COVID-19 infection, hypertrasaminasemia, incidence, liver injury, hepatic enzymes

Introduction:

Coronavirus-19 infection (COVID-19) was first detected in December 2019 in Wuhan, China. As of January 2022, 380 million people globally were diagnosed with COVID-19 and more than 5 million of them died from the disease complications. (1).

COVID-19 is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (1). Although the vast majority of patients with this infection are either asymptomatic or have mild to moderate illness, about 20% of symptomatic patients develop severe disease with respiratory distress (2, 3).

Despite the fact that the main clinical manifestations of this infection have been related to lung injury, which is the main cause of death, laboratory tests have also shown abnormalities of other organ involvement, such as cardiac and liver involvement (4, 5). Liver function tests (LFT) abnormalities are seen in 14-53% of COVID-19 infection patients,

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unit (ICU) patients as compared to patients with mild to moderate infection (6, 7).

these findings are more common in intensive care

Various researches reported a relationship between COVID-19 infection severity and the degree of hepatic injury. A study from Shanghai showed that about 50% of patients have elevated hepatic enzymes at hospitalization time, and they have a moderate-to-high grade fever when compared with the patients with normal LFT (44% vs. 27.4%; p< 0.035) (8,9).

There are several proposed mechanisms by which COVID-19 can affect the liver. It was reported that SARS-CoV could cause direct hepatocyte injury rather than inducing cellular stress from hypoxemia or cytokines seen in sepsis (11, 12). Autopsy studies from infected patients reported that SARS-CoV was detectable in 41% of the liver tissue. The histopathological findings of biopsy from the liver in the infected patients showed hepatocyte injury, cellular mitoses, inflammatory cell infiltration, and fatty degeneration (13, 14).

Antibody-dependent enhancement of infection (ADE) may occur in patients with COVID-19 infection. ADE is defined as the interaction of

antibody against the virus with the Fc receptor and/or complement receptor to increase the ability of the virus to enter granulocytes, monocytes, and macrophages (15,16).

A previous study had shown that the levels of inflammation induced cytokines like interleukin (IL) and tumor necrosis factor (TNF) in patients with COVID infection are significantly higher in patients with elevated than with normal liver enzymes, which might indicate that systemic inflammatory response and cytokine storms were risk factors for hepatic injury in COVID 19 patients (17)

It has also been observed that the IL-2-receptor (IL-2R) and IL-6 in the serum of COVID-19 patients are significantly elevated and correlate with infection severity (2).

In addition, lung damage-related hypoxia can enhance hepatocyte ischemia and therefore, increase the toxic metabolites, which further induce liver injury, so the ischemia and hypoxia may be two important factors for hepatic injury in patients with severe COVID-19 infection. (18- 20).

Patients and Methods:

We studied 112 patients with confirmed COVID-19 from the 1st of April to the 1st of August 2021 at Baghdad Teaching Hospital. All patients were hospitalized and treated in an isolated ward and COVID-19 infection was diagnosed with real-time PCR and CT scan of the chest. All patients had reported no history of hepatic diseases. Patients with covid-19 pneumonia were diagnosed as having cough, and or dyspnea, as well as a finding of groundglass infiltrates on chest CT. Patients taking drugs that may affect liver function and those with co-morbid conditions such as DM, metabolic syndrome, and/ or alcohol consumption were excluded from the study.

Patients Categorization: The studied patients were categorized into three groups according to the guidelines of the Chinese National Health Committee (21): mild cases with normal chest imaging, moderate cases, with radiological findings of ground glass infiltrates and severe COVID-19 refers to cases meeting any of the following criteria: hypoxemia (SpO_2 <94% on room air), a respiratory rate >30 breaths/min or pulmonary infiltrates >50%.

Data collection: A liver function test and complete blood count (CBC) were done at the time of admission to the hospital. The liver function tests included TSB, ALT, AST, and alkaline phosphatase. Demographic and clinical data of patients were also collected.

Data Analysis: Our data were analyzed with Statistical Package for Social Sciences (SPSS) using simple descriptive statistics. Continuous variables were expressed as mean± standard deviation (SD), while binomial variables were expressed as frequency and percentages. Independent student t-test was used to compare serum levels of ALT, AST, and TB. Categorical variables were presented as numbers and percentages and analyzed with a Chi-square test. A P≤ 0.05 was considered statistically significant.

Results

The average age of the patients was 41.49 years, of whom 65 patients (58%) were males. Average serum AST, ALT, and ALP were 38.71 U/L, 44.95 U/L, and 138.31 U/L, respectively. (Table 1). Thirty-seven patients (33.04%) were found to have severe infection, 58 patients (51.79%) had moderate infection, and 17 patients (15.17%) with mild infection. In total, out of 120 patients, 46 (41.07%) had elevated liver enzymes (AST and/or ALT).

The association of elevated liver enzymes with the clinical characteristics

The mean age of patients with elevated liver enzymes was 45.17±11.93 years which was higher than the mean age of patients with normal liver enzymes (38.92±13.47 years) (P value is 0.013). The distribution of gender was comparable between the two groups with a no significant difference (p-value: 0.612).

In severe cases, 45.65% of patients had elevated liver enzyme compared with 24.24% in the moderate group and 33.04% in the mild group (P value is significant 0.05).

Although the AST/ALT ratio was higher in patients with elevated than normal liver enzymes (1.28±0.64 vs. 1.12±0.35), the difference was not significant (P value: 0.094).

Table 1: Demographic and Clinical characteristics of the patients

Variables	Values
Age, years	
Mean±SD	41.49±13.17
Range	16-85
Gender	
Male	65(58.04%)
Female	47(41.96%)
AST (U/L)	
Mean±SD	38.71±16.0
Range	10-214
ALT (U/L)	
Mean±SD	44.95±24.49
Range	10-260
ALP (U/L)	
Mean±SD	138.31±39.98
Range	22-400
TSB, mg/dL	
Mean±SD	0.63±0.27
Range	0-4.0
Severity	
Mild	17(15.17%)
Moderate	58(51.79%)
Severe	37(33.04%)

ALT: alanine aminotransferase, AST: aspartate aminotransferase, ALP: alkaline phosphatase, TSB: total serum bilirubin

Table 2: Association of elevated liver enzyme with the clinical characteristics of the patients

variables	Value	Patients with normal liver enzymes (n=66)	Patients with elevated liver enzymes (n=46)	p-value
Age, years				
Min	16	16	26	0.013
Max	85	72	85	
Mean±SD	41.49±13.17	38.92±13.47	45.17±11.93	
Gender				
Male	65(58.04%)	37(56.06%)	28(60.87%)	0.612
Female	47(41.96%)	29(34.94%)	18(39.13%)	
AST/ALT ratio				
Min	0.23	0.62	0.23	
Max	3.21	3.15	3.21	0.094
Mean±SD	1.19±0.5	1.12±0.35	1.28±0.64	
Severity				
Mild	17(15.17%)	12(18.18%)	5(10.87%)	0.04
Moderate	58(51.79%)	38(57.58%)	20(43.48%)	
Severe	37(33.04%)	16(24.24%)	21(45.65%)	

ALT: alanine aminotransferase, AST: aspartate aminotransferase, ALP: alkaline phosphatase,

Discussion

In our study, we reported that 46 (41) out of 112 patients with COVID-19 infection had elevated liver enzymes. A retrospective investigation of 148 patients with confirmed COVID-19 was undertaken by Fan et al, which showed that increased transaminases were found in 37.2% of patients which was very close to our results. Cai et al. also reported that 41% of patients had abnormal liver enzymes due to liver injury on presentation to the hospital; however, throughout their stay in the hospital, 76.3% of patients experienced abnormal liver tests. (30). In the US, Singh et al. underwent multi-center research to verify the clinical characteristics of COVID-19 patients; he elevated ALT elevations in about 50% of the patients (22). In addition, Xie et al. conducted a retrospective study of 79 COVID-19 patients in China, Thirty-one (31.6%) patients had increased ALT levels, while 35.4% of patients had increased AST levels, and 5.1% had elevated bilirubin, the hospital stay was longer for the patients with elevated transaminases than patients with normal liver function test, (15.4 versus 11.4 days) (23).

A much lower rate of elevated liver enzyme was reported by some studies. A report from China by Zhang et al. who carried out a case-control study of 234 patients consisting of 115 patients with COVI-19 and 119 patients admitted with community-acquired pneumonia (CAP), on admission, elevated ALT was seen in 9.57% of patients while 6.14% in CAP patients (24).

The variation in the prevalence of abnormal liver function in different studies can be attributed to several factors, the most important of which are the age of the patients, the presence of comorbidities, the rate of mild to severe cases, the male-female ratio, and the treatment received.

In the present study, the mean age of patients with elevated transaminases was significantly higher than those with normal liver enzymes (45.17±11.93 years versus 38.92±13.47, p-value is significant). This is discordant with an Iranian study on 279 patients in which the authors reported that patients with elevated liver enzymes had younger ages (54.29 ± 15.76 years) than those with normal liver enzymes (59.79 ± 17.06 years) (25).

The most interesting finding in the present study was higher frequency of patients who have severe and moderate than patient those have mild COVID infection (45.65% versus 43.48% versus 10.87%, p value is 0.04). These results were partially in line with many previous studies. In China also, Zhang et al. found that The mean ALT level in severe COVID-19 patients was higher than in mild disease (37.87 ± 32.17 U/L , 21.22 ± 12.67 U/L, respectively), and mean total bilirubin level was higher in severe COVID-19 disease than in mild disease (14.12 ± 6.37 μmol/L vs 10.27 ± 4.26 μmol/L, p< 0.001) (24). In another study, Omrani-Nava et al. compared the liver enzymes in 97 Iranian patients with COVID-19 with 186 healthy subjects; there was a significant association between the disease severity and AST / ALT ratio. The risk of admission to intensive care units was strongly associated with increased levels of AST as well as total bilirubin level (26).

Conclusion

Acute liver injury as indicated by hypertansaminasemia is a frequent finding in the Covid19 patients. Elderly patients with moderate to severe COVID-19 infection are more prone to hepatic involvement.

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Author contributions:

Both authors contributed to designing this research, acquisition and analysis of data, drafting and revising it critically and approval of the final version for publication.

Authors' declaration:

Conflicts of Interest: The authors declare no conflict of interest.

We confirm that all the Figures and Tables in the manuscript belong to the current study. Besides, the Figures and images, which do not belong to the current study, have been given permission for re-publication attached to the manuscript. Authors sign on ethical consideration's approval-Ethical Clearance: The project was approved by the local ethical committee in Baghdad teaching hospital

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ارتفاع انزيمات الكبد: نسبة الحدوث والعوامل السريرية في مرضى الكوفيد 19

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الخلاصة

خلفية الدراسة: ظهر مرض الفيروس التاجي (COVID-19) مؤخرًا باعتباره جائحة عالمية يستهدف اساسا الجهاز التنفسي. ومع ذلك ، وخلال مسار المرض ، يمكن أن تشمل الاصابة بشكل مباشر أو غير مباشر مختلف أعضاء الجسم ومنها الكبد.
الأهداف: هدفت هذه الدراسة إلى تقييم درجة حدوث وتأثير الاصابة بفايروس كوفيد -19 على الكبد
طرائق العمل: تضمنت هذه الدراسة المقطعية 112 مريضا يشتبه بإصابتهم بمتلازمة الجهاز التنفسي الحادة الشديدة. تم تصنيف المرضى إلى ثلاث مجموعات وفقًا لإرشادات لجنة الصحة الوطنية الصينية: الحالات الخفيفة والمتوسطة والشديدة. جمعت عينات الدم من كل مريض واجريت اختبارات وظائف الكبد. عرفت وظيفة الكبد غير الطبيعية على أنها ارتفاع في أي إنزيم (ألانين ترانس أمينار ،أسبارتات ترانساميناز وفوسفاتيز القلوي) أكثر من الحد الأعلى للقيمة المرجعية.
النتائج: أظهر 33.04٪ من المرضى اصابة شديدة، 51.79٪ اصابة متوسطة و 15.17٪ اصابة خفيفة.كانت الإقامة في الريف أكثر تكرارا بين المجموعة الشديدة (81.08٪) من المجموعة المتوسطة (18.97٪) أو المجموعة الخفيفة (23.53٪) مع وجود فرق معنوي. وأظهر ستة وستون مريضا (58.93٪) مستويات طبيعية من انزيمات الكبدي ، بينما أظهر 46 مريضا (41.07٪) انزيمات كبد مرتفعة. بلغ متوسط عمر المرضى الذين يعانون من ارتفاع إنزيمات الكبد 45.17 ± 11.93 سنة وهو أعلى معنويا من مرضى أنزيمات الكبد الطبيعية (38.92 ± 13.47 سنة). في الحالات الشديدة ، كان 45.65٪ من المرضى لديهم ارتفاع في إنزيم الكبد مقارنة بـ 24.24٪ في الحالات المتوسطة و 33.04٪ في الحالات الخفيفة ، وبفرق معنوي.
الاستنتاجات: يمكن أن تترافق الحالات الشديدة من كوفيد 19مع وظائف غير طبيعية للكبد كما يتجلى من تركيز إنزيمات الكبد في المصل .المرضى الاكبر عمرا المصابون بالحالات الشديدة من كوفيد 19هم أكثر عرضة لوظائف الكبد غير الطبيعية.
مفتاح الكلمات: كوفيد 19- ارتفاع انزيمات الكبد- نسبة الحدوث-التهاب الكبد