Indian Journal of Forensic Medicine and Toxicology
Volume 16 No. 3, July-September 2022
DOI: http://dx.doi.org/xxxxx/ijfmt.xxxx.16322.30

The Occurrence and the Characteristics of Liver Injury, and its Impactamong Hospitalized Covid-19 Patients in Basrah City-Iraq

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How to cite this article: EFateh Al-khaqani, Yasser Alaa Sabeeh, Ali Raheem Hashim et al. The Occurrence and the Characteristics of Liver Injury, and its Impactamong Hospitalized Covid-19 Patients in Basrah City-Iraq. Indian Journal of Forensic Medicine and Toxicology 2022;16(3):165-172.

Abstract

Background: The respiratory system is most affected by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV2). However, COVID-19 can appear in a variety of ways. It has found a link between higher liver enzymes and COVID-19 infection, implying that the virus can induce liver damage through direct hepatotoxic injury, medication toxicity, or an immune-mediated response.

Materials and Methods: In the southern Iraqi province of Basra, a cross-sectional observational study is being conducted in a single center (Basra teaching hospital) to estimate the prevalence of liver damage among hospitalized patients and identify those at risk.

Results: The study found that most of the patients have a normal liver function test at the time of diagnosis and or admission, but after hospitalization, there is a statistically significant increase in the liver enzymes that is positively related to the disease severity and cytokine storm and also lead to more extended hospital staying and further mortality. Fortunately, the degree of liver damage is of mild severity in the majority of patients. Still, the severe form of liver damage was also noticed in some patients, especially those with a higher degree of lung involvement and severely desaturates with raised inflammatory markers.

Conclusions: Elevated liver enzymes are prevalent, but the majority is mild with COVID-19 disease. Liver function abnormalities, particularly increased levels of AST and ALT, are not only common in COVID-19, but they are also linked to poor outcomes, mainly if severe liver damage has occurred.

Keywords: Liver injury; liver Enzymes; COVID-19.

Introduction

The "severe acute respiratory syndrome coronavirus-2" (SARS-CoV-2) has posed new health risks and difficulties in the world since December 2019, according to the International Classification Committee of Viruses. The World Health Organization (WHO) labeled the coronavirus disease 2019 (COVID-19) a global pandemic on March 11, 2020.[1] The respiratory system is most affected by the severe acute respiratory syndrome coronavirus

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2 (SARS-CoV2); however, as we learn more about this novel disease, several published research have revealed its organotropism and multisystem organ inflammatory nature.[2,3]

COVID-19 can appear in a variety of ways, ranging from mild cases with minimal symptoms like a sore throat and loss of smell or taste to disease those results in death.[4] Other organ injuries, such as acute kidney injury, liver damage, cerebrovascular stroke, and gastroenteritis, have been recorded in addition to respiratory tract involvement.[5] Although the liver has been implicated in adult patients with COVID-19 infection, the actual prevalence of hepatic abnormalities, the kind of liver enzyme derangement, and its association to outcomes are yet unknown.[6]

Researchers have found a link between COVID-19 infection and higher liver enzymes, suggesting the virus may damage the liver either directly or through medication toxicity, or through an immune response. The SARS epidemic has been linked to 60 percent of patients developing liver damage in the past.[7] We believe SARS-CoV-2 may induce liver impairment since it belongs to the same coronavirus family as SARS-CoV-1. The angiotensin-converting enzyme (ACE-2) receptor, which is also the binding site for SARS-CoV-2, is expressed in the biliary epithelium.[8] The expression of the ACE2 receptor in hepatocytes has been found to be increased.[9,10]

It is unclear whether liver enzyme abnormalities are a prevalent symptom of COVID-19. The prevalence, extent, and rate of progression to liver failure in patients who have a simultaneous liver enzyme derangement with COVID-19 are unknown. In light of the fact that the evidence isn't conclusive. Many of the COVID-19 patients had abnormal liver enzymes to variable degrees. Most of the injuries were minor, and they seemed to be related to the severity of the COVID-19 infection. It is uncommon for a severe liver injury, to result in major liver damage, liver failure, or death.[11] Furthermore, In the current COVID-19 clinical trials, mild to moderate liver injury has been recorded, including increased aminotransferases, hypoproteinaemia, and prothrombin time lengthening.[12]

Regarding liver injury, Acute liver failure occurs when significant complications arise soon after the initial signs of liver disease (such as jaundice) and suggests that the liver has been severely damaged (80–90 percent of liver cells have lost function). Hepatic encephalopathy and decreased protein synthesis are two of the side effects (as measured by the levels of serum albumin and the prothrombin time in the blood). The 1993 categorization defines hyperacute as occurring within one week, acute as occurring between eight to twenty-eight days, and subacute as occurring from four to twelve weeks, both the speed with which the disease develops, and the underlying cause have a significant impact on prognosis.[13]

Many clinical investigations on the effects of hepatic involvement in COVID-19 have been reported recently. However, the majority of them differ due to differences in the definition of liver injury, clinical presentations, and disease severity in separate research.[14]Furthermore, Acute liver injury and liver function abnormalities, particularly high AST and ALT values are not only common in COVID-19 but are also linked to poor outcomes.[15]

Objective

This study aims to estimate the prevalence of liver damage among hospitalized COVID -19 patients and try to identify those who are at risk.

Methods

This cross-sectional observational study took place in a single center in the Basra governorate in southern Iraq (Basra teaching hospital, which specializes centre for the treatment of COVID 19 patients) from March 15, 2020, to August 15, 2021. The study covers 280 hospitalized patients who have been diagnosed with COVID 19 on clinical, radiological, and laboratory levels. The training and human development center in the Basra health directorate gave its permission.Information was gathered through medical records in hospitals and intensive care units, direct interviews, and examinations of patients, and then plotted on a standardized questionnaire.

The variables used in the study include:[16]

- The **age** (which is further categorized into three groups: <35, 35–65, and above 65 years).
- The **sex** (male and female).
- The **comorbidities**: "diabetes mellitus, hypertension, cerebrovascular disease, ischemic heart diseases, heart failure, atrial fibrillation, chronic kidney disease, bronchial

asthma, or chronic obstructive pulmonary disease, hemoglobinopathies, malignancy, and immunocompromised patients” and are plotted as absent if the patient has no comorbidities or present if the patient has any.

- The **ward** in which the patients were admitted (Intensive care unit and infectious ward).
- The **duration** of hospitalization (less than five days, from five to ten days, more than ten days).
- The presence of **cytokine storm** or release syndrome, which is measured clinically and biochemically, and plotted as present or absent.
- The extent of **lung involvement** as determined by a chest CT (below 50 percent and higher than 50 percent).
- The **oxygen saturation**, which is divided into three categories (below 70 percent, from 70 percent to 93 percent, and above 93 percent).
- The **clinical manifestation,** which includes epigastric pain, jaundice, hepatomegaly, nausea or vomiting, diarrhea and was plotted as present or absent.
- The levels of **liver enzymes** were taken on two occasionsin this study: At admission prior, on the first day of hospitalization prior to any medical intervention, and onthe last day of admission after receiving the full course of medical treatment.
- The **pattern of liver damage** was classified into three categories according to the degree of elevation of liver enzymes: No elevation: if the readings are within the normal laboratory reference range. Mild to moderate elevation: if the readings are less than three times of the standard laboratory reference range.Severe elevation: if the readings are more than three to five times of the normal laboratory reference range.
- In this study, the **patient’s outcome** was evaluated and classified as follows: Respiratory failure or another COVID-19-related consequence caused death. Alternatively, patients may be discharged with full recovery (as measured by improvements in O2 saturation, respiratory rate, general condition, and inflammatory biomarkers such as C-reactive protein, ESR, Ferritin, and LDH) or with morbidity (for those who are infection-free but still have respiratory problems due to lung fibrosis).

All patients involved in this study have received the COVID-19 protocol, which includes steroids, the antiviral drug, remdesivir, and antibiotics in a particular situation with supplemental oxygen in addition to other supportive therapy.

The statistical analysis was done by using SPSS (Statistical Package for the social sciences) version 20. The quantitative variables were calculated by the mean, and the standard deviation and one-sample t-test was used for the two-group comparison while the categorized variables were expressed by count and percentage.The results were expressed in the form of tables, the association between the variables were assessed by using Chi-square test (or fissure exact test) and the significance threshold was set at a P value less than 0.05.

Results

The total number of patients involved in this study is (280); their mean age is (57.1) years, with a standard deviation of (1.28). regarding sex distribution, they were 161 (57.5%) male and 119 (42.5%) females. while 66 (27.5%) have no comorbidities, the other 203 (72.5%) patients have comorbidities. Moreover, the degree of lung involvement was less than 50% in 66 (23.6%) only. In comparison, it was more than 50% in 214 (76.4%) of patients. for oxygen saturation, 158 (65.4%) of patients their SP02 ranging from 70 – 90% but 122 (43.6) their average oxygen saturation was below 70%. Finally, concerning the presence of cytokine storm, the result shows that 272 (93.6) of patients have clinical and laboratory evidence of cytokine storm, while the remaining 18 (6.4%) have no such evidence.

The gastrointestinal manifestation of patients enrolled in the study showed that the most frequently reported complaint is anorexia that presented in 169 (60.4%) followed by abdominal pain (epigastric and right hypochondria pain) in 154 (55%). Vomiting was the 3rd most common symptom in 150 (53.5%). Regarding the altered bowel motion, diarrhea was found in 57 (20.4%) patients, while constipation was found in 40 (14.2%) patients. Regarding jaundice, it was presented in 14 (5%) patients, and hepatomegaly by clinical examination was detected in 19 (6.8%) patients. Malena is reported only in two patients (0.7%), while hematemesis and hematochezia were not reported during this survey.

For the total number of patients, eighty-seven (31.1%) have liver damage through the evaluation of liver enzymes and total serum bilirubin at the time of admission. Moreover,one hundred ninetytwo patients (68.6%) have liver damage through the evaluation of liver enzymes and total serum bilirubin at time discharge, the majority have only mild elevation in the liver function test, and the degree of liver damage at admission and discharge is summarized in the Table 1 below.

Table 1: The degree of liver damage at time of admissionand discharge

The Pattern of liver damageat admission	The frequency	
	No.	%
No evidence of liver injury	193	68.9
Mild liver damage	84	30.0
Moderate liver damage	1	0.4
Severe liver damage	2	0.7
The Pattern of liver damageat discharge	**The frequency**	
	No.	**%**
No evidence of liver injury	88	31.4
Mild liver damage	162	57.9
Moderate liver damage	17	6.1
Severe liver damage	13	4.6

The mean difference between the level of liver enzyme and total serum bilirubin at time of admission and time of discharge are summarized in the Table 2 below and the significance of difference was calculated by using one sample t test.

Table 2: The difference between liver function test at admission and discharge

The parameter		Statistical numbers				95% Confidence Interval of the Difference	
		Mean	SD	SE	P value	Lower	Upper
ALT	Admission	47.85	21.8	1.30	0.001	44.85	49.99
	Discharge	83.62	58.99	3.52		76.68	90.56
AST	Admission	52.14	34.08	2.03	0.001	48.13	56.15
	Discharge	101.16	75.55	4.51		92.27	110.05
TSB	Admission	0.84	0.36	0.02	0.001	0.80	0.88
	Discharge	1.88	6.01	0.35		1.17	2.58
ALP	Admission	39.71	19.79	1.18	0.001	37.38	42.04
	Discharge	54.43	19.95	1.19		52.09	56.78

The relationship between liver injury at the time of discharge and the study variables (sex, age, medical illnesses, severity of respiratory disease, cytokine storm) are summarized in Table 3 below.

Table 3: The association between the liver injury and patients' characteristics

The variables		Liver injury				Total
		Absent (%)	Mild (%)	Moderate (%)	Sever (%)	
Sex	**Male**	51 (31.7)	97 (60.2)	8 (5.0)	5 (3.1)	161
	Female	37 (31.1)	65 (54.6)	9 (7.6)	8 (6.7)	119
Statistical numbers		**P value: 0.387**				
Age	**<35**	8 (57.1)	6 (42.9)	Zero	Zero	14
	35-65	64 (36.8)	97 (55.7)	7 (4.0)	6 (3.4)	174
	>65	16 (17.4)	59 (64.1)	10 (10.9)	7 (6.7)	

Contd... Table 3: The association between the liver injury and patients' characteristics						
Statistical numbers		**P value: 0.002 (Chi Square) / P value: 0.003 (Fishers exact)**				
Medical illnesses	**Absent**	41 (53.2)	34 (44.2)	Zero	2 (2.6)	77
	Present	47 (23.2)	128 (61.1)	17 (8.4)	11 (5.4)	203
Statistical numbers		**P value: 0.001 (Chi Square) / P value: 0.001 (Fishers exact)**				
Saturation	**70-93**	77 (48.7)	79 (50.0)	2 (1.3)	Zero	158
	<70	11 (9.0)	83 (68.0)	15 (12.3)	13 (10.7)	122
Statistical numbers		**P value: 0.001 (Chi Square) / P value: 0.001 (Fishers exact)**				
CT	**<50 %**	41 (62.1)	25 (37.9)	Zero	Zero	66
	1. **>50%**	47 (22.0)	137 (64.0)	17 (7.9)	13 (6.1)	214
Statistical numbers		**P value: 0.001 (Chi Square) / P value: 0.001 (Fishers exact)**				
Cytokine storm	**Absent**	13 (72.2)	5 (27.8)	Zero	Zero	18
	2. **Present**	75 (28.6)	157 (59.9)	17 (6.5)	13 (5.0)	262
Statistical numbers		**P value: 0.001 (Chi Square) / P value: 0.005 (Fishers exact)**				
Site of admission	**ICU**	18 (12.9)	92 (66.2)	16 (11.5)	13 (9.4)	139
	Ward	70 (49.6)	70 (49.6)	1 (0.7)	Zero	141
Statistical numbers		**P value: 0.001 (Chi Square) / P value: 0.001 (Fishers exact)**				
Total		88	162	17	12	280

The impact of liver damage on the survival and the duration of hospitalization are shown in Table 4 below.

Table 4: The association of the liver injury with the outcome and the duration of hospitalization

The variables		**Outcome**		**Duration of hospitalization**			**Total**
		Discharge	**Death**	**<5**	**5-10**	**>10**	
Liver injury	**Absent**	87 (98.9)	1 (1.1)	33 (37.5)	51 (58.0)	4 (4.5)	88
	Mild	141 (87.0)	21 (13.0)	32 (19.8)	110 (67.9)	20 (12.3)	162
	Moderate	11 (64.7)	6 (35.3)	Zero	12 (70.6)	5 (29.4)	17
	Sever	4 (30.8)	9 (69.2)	Zero	6 (46.2)	7 (53.8)	13
Total		243	37	179	36	36	20
Statistical numbers		**P value (Chi & Fisher): 0.001**		**P value(Chi & Fisher): 0.001**			

Discussion

To start with, COVID-19-related hepatic damage is defined as alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels above three times the upper limit of normal, and alkaline phosphatase (ALP) or total bilirubin levels exceeding two times the upper limit of normal.[17] This was referred to in our study as severe elevation of liver enzyme or liver damage.

As it was shown in our study, the gastrointestinal symptoms are common suffering or common complaint in hospitalized patients with COVID-19, especially the Anorexia followed by abdominal pain, nausea, and vomiting, and diarrhea, then constipation, to a lesser extent to other GIT complaints as jaundice or Malena. These results were consistent with the results of many studies, which showed that COVID-19 patients have GIT signs in a range of 11.4–61.1 percent of cases. Also stated, is that Anorexia, diarrhea, nausea, vomiting, and abdominal pain/discomfort are among the COVID-19-related GI symptoms that are minor and self-limiting.[18]

Regarding the demographic features of the patients enrolled in the study, our results found high severe liver injury among females. In contrast, the mild elevation of the liver enzyme was higher among males, but both these findings are not statistically significant. Nevertheless, regarding the age group categories, a significant association was shown between the severity of the liver injury and advancing age, while no reported case of severe liver injury was under 35 years. Our finding is not similar to other studies regarding gender distribution as it is shown that male patients were more likely to have a liver function injury than females.[19]

Both hollow and solid gut organs express the ACE2 receptor. The neutral amino acid transporter B0AT1 (SLC6A19) present in the intestinal epithelium stabilizes ACE2 messenger RNA (mRNA), which is abundantly expressed in the GI tract (Xiao et al. 2020). As a result, one idea for COVID-19 patient's liver impairment is that the SARS-CoV-2 virus destroys Cholangiocytes via ACE 2 receptors. Furthermore, it was discovered that in cases of liver injury, the expression of ACE 2 in hepatocytes increased.[20] Therefore, it is expected to find elevation of liver enzyme and some sort of lover damage even at the initial days of diagnosis or hospitalization in which the virus its self is blame as a cause of liver injury due to ACE2 receptor effect and according to our results, we found that the majority of patients about 70% has no evidence of liver damage but, approximately 30% show elevation of liver enzyme and despite the majority is mild to moderate, but severe liver damage is found in one patient also.

It is worthy to note that liver damage is increased during the days of hospitalization. As shown in the results above, there is a noticeable increase in the percentage of mild to moderate liver damage, which reaches up to 60%. Furthermore, the rate of severe liver injury also increases to reach up to 5% compared with less than 1% at the time of admission. These findings are of close similarity to a large cohort study that shows at the time of entry, 41.0 percent of the patients showed abnormal liver function tests and liver damage, but those Patients with abnormal liver function tests and liver injury climbed to 76.3 percent after two weeks in the hospital.[21] Many ways may explain this. The first of them is increasing the progression of diseases and respiratory disease severity in addition to the cytokine storm, and our results show a significant difference in the manifestation of liver injury and its severity among those with severe respiratory disease; ICU admitted patients who severely desaturated and among those with a high level of inflammatory markers who labelled as patients with cytokine storm or release syndrome. It was known that cytokine storm frequently results in a rapid deterioration of the patient's condition when the patient enters multiple organ failures, and the systemic inflammation generated by it might result in additional liver injury.[22,23] The other mechanism that might explain the progression of liver damage during hospitalization is the side effects of the commonly used drug during admission, such as the antiviral and paracetamol, or maybe the antibiotics that might be used for the secondary bacterial infections in addition to tocilizumab that used in the treatment for the cytokine storm. As a result, one of the reasons for COVID-19-related liver impairment could be pharmacological activities. Therefore, monitoring changes in liver function and medication timing in COVID-19 patients throughout hospitalization may help determine the causal association between medicines and liver harm.[24]

In addition to what was mentioned above, this study also showed a highly significant difference between the levels of the enzyme at the time of admission comparison with their levels at times of discharge as well as there is an obvious increase in the level of AST higher than the level of ALT and this is consistent with the findings of the majority of research that have found raised AST and ALT are the most common causes of abnormal liver function tests, with elevated AST being more common than ALT. Increased GGT and total bilirubin are less prevalent than elevated AST and ALT.[25]

Finally, according to our findings, the higher level of liver enzymes and the more severe liver injury is associated with increased mortality and poorer outcome in addition to more extended hospital stays. This might be related to the higher severity of infection that resulted in a liver injury which may exaggerate the occurrence of poorer outcomes. Also, this may give a hint to monitor the liver function test frequently during hospitalization. In addition, the clinician may depend on the liver enzyme as mortality predictors. This finding is argued with Henry and colleagues. They did a meta-analysis to see if liver function and coagulation function were considerably more significant in severe and critical patients than in non-severe patients. It was hypothesized that liver injury could be linked to severe COVID-19 infection. Also, the clinical features of individuals with and without liver function damage were compared. The findings revealed that those with liver injury spent much more time in the hospital.[26] Furthermore, Increased AST values are related to 3 times more risk of bad outcomes in COVID-19 patients, according to a meta-analysis of 12 studies that presented data on raising AST and outcomes, resulting in a total sample size of 5135 patients for evaluation.[15]

Conclusions

1. Elevated liver enzymes are prevalent, but the majority is mild with COVID-19 disease.
2. Liver function abnormalities, particularly increased levels of AST and ALT, are not only common in COVID-19, but they are also linked to poor outcomes, mainly if severe liver damage has occurred.
3. The etiology of the liver injury is unknown, although it appears to be complex, with a cytokine storm and immunological dysregulation playing a role. Hypoxia, sepsis, numerous medications, direct viral action, and ICU-related infections are all possibilities.

Recommendations

1. Future research should focus on determining the etiology of liver impairment during COVID-19 infection, particularly if it is caused by a therapeutic medicine.
2. In clinical practice, it's essential to know whether the aberrant liver function appears at the time of diagnosis or later on during treatment.
3. Regular follow-up for the patients is required for the liver function test to avoid serious complications.

Limitations

This study is an only cross-sectional study and involves a small sample size. In addition, it did not include the evaluation of the levels of coagulation profile or protein levels that may give more idea about the state of liver injury. Moreover, there are differences in how liver dysfunction and acute liver injury are classified. There are different cutoff values for increased liver enzymes and varied definitions of Covid-19 disease severity and outcomes among studies.

Additional Information

The authors declare that they have no competing interests (financial AND nonfinancial interests)

Ethical clearance

It is taken from the college of medicine ethical committee in Basrah university and the development and training committee in Basrah health directorate.

Source of funding: It was self-funding from the budget of the researchers.

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