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Liver enzymes among COVID-19 patients in Al-Ahsa region of Saudi Arabia

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ABSTRACT

Background Hepatic damage is one of the common forms of extra pulmonary organ destructions among patients with COVID-19 infections.

Aim To evaluate the prognosis of liver damage among COVID-19 patients based on their liver enzymes profile.

Methods A retrospective study was done to evaluate the records of the hospitably admitted patient due to COVID-19 infection.

Retrieved data included clinical presentation and investigation either imaging or laboratory with special investing in liver function tests.

Result We reviewed 442 patients who were diagnosed with COVID-19 infection.

They were 64.5% of female patients and 35.5% of male patients. Their mean age was 54.5%, most of them were Saudi (76.7%) and the overall mortality reached up to (20.4%).

Conclusion This large cohort of 442 patients has shown that liver damage may be an independent prognostic factor for morbidities and mortality among COVID-19 patients. It also showed the importance of liver function enzymes screening as a predictor for the outcome of those patients.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ There are multiple studies in the literature assessing the impact of the COVID-19 pandemic on the patient's pulmonary and extrapulmonary pathologies and their manifestations.

⇒ Hepatic damage and abnormal liver functions are one of these important affections of COVID-19 that may lead to a different degree of liver damage.

⇒ Many studies suggested that COVID-19-related hepatic injuries might have a poor prognosis.

WHAT THIS STUDY ADDS

⇒ This study has shown that liver damage may be an independent prognostic factor for morbidities and mortality among COVID-19 patients in Saudi Arabia.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study suggests liver function enzymes screening as a predictor for the outcome of COVID-19 patients mainly hospitalised patients with severe infection.

⇒ Perhaps a long-term follow-up may have raised the mortality potential.

⇒ Hence, a long-term follow-up study is going on to realistically evaluate the-outcome.

INTRODUCTION

Infection by SARS-CoV-2 was initially reported to not only induce sever pneumonia but also multisystemic pathologies. The common manifestations of this devastating viral infection are fever and cough plus extrapulmonary symptoms, such as vomiting and diarrhoea.[1] However, abnormal liver functions were reported among COVID-19 patients that may lead to a different degree of liver damage.[2]

The mechanism for such liver dysfunction among those patients is still uncertain. Nonetheless, ACE-2, which is a receptor of SARS-CoV-2, is proven to be pronounced in cholangiocytes as well as hepatocytes.[3]

Such a notion supports the concept of SARS-CoV-2 invading liver cells resulting in liver injury.[4] Moreover, postmortem histopathological assessment of COVID-19 patients has shown microvesicular steatosis with mild to moderate portal activities supporting the previous concept.[5] On the other hand, some reports suggested the cytokine storm syndrome of COVID-19 to be accused of such damage.[6–8]

Although, the reason for liver damage among COVID-19 patients is still obscure, it was clearly pronounced among severely infected patients who stayed for a prolonged time in the hospital. Those admitted to the intensive care unit show higher pathological levels of liver enzymes compared with their peers in the general ward.[9 10]

Many studies suggested that COVID-19-related hepatic injuries might have a poor prognosis.[10 11]

The current study aims to evaluate the level of liver enzymes as a predictor of morbidities and mortalities among COVID-19 hospitalised patients.

Table 1 Baseline characteristics of the patients (n=442)

Study variables	N (%)
Age in years (mean±SD)	54.3±14.9
Gender	
Male	157 (35.5%)
Female	285 (64.5%)
Nationality	
Saudi	339 (76.7%)
Non-Saudi	103 (23.3%)
Prognosis outcome	
Died	90 (20.4%)
Alive	352 (79.6%)
X-ray	
Normal	85 (19.2%)
Abnormal	357 (80.8%)
CT scan	
Normal	87 (19.7%)
Bilateral ground glass opacity	12 (02.7%)
More than one type	25 (05.7%)
Not done	318 (71.9%)
Length of hospital stay (days) (median (min–max))	8.00 (1–155)

Table 2 Laboratory characteristics of the patients (n=442)

Parameters	N (%)
Hb	12.9±2.20
Platelets	250.7±93.5
WCC	7.71±6.76
Lymphocytes	19.8±15.2
Neutrophils	63.2±26.7
ALT	60.2±117.0
AST	59.0±90.6
Total bilirubin	13.0±36.5
Direct bilirubin	4.02±6.19
Albumin	31.7±6.68
PTT	34.7±10.9
PT	13.2±6.72
INR	1.07±0.52
Urea	7.47±6.95
Creatinine	131.2±148.7
RBS	10.6±6.80
ESR	73.5±54.9
CRP	11.5±11.2
LDH	426.8±440.4
Ferritin	1139.9±1367.9
D-dimer	3.27±6.31

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C reactive protein; ESR, Erythrocyte Sedimentation Rate; HB, Hemoglobin; INR, International Normalised Ratio; LDH, Lactate Dehydrogenase; PT, Prothrombin Time; PTT, Partial Thromboplastin Time; RBS, Random Blood Sugar; WCC, white cell count.

PATIENTS AND METHODS

A 6-month retrospective study was done in the periods from July 2020 to January 2021. This was within the first peak of COVID-19 infection in Saudi Arabia. Records of patients who underwent admission and treatment because of this infection were thoroughly studied to retrieve the sociodemographic variance of patients, as well as all their clinical presentations. Performed investigation including laboratory and imaging types was reported.

Collected data were statistically analysed by using the SPSS V.21, IBM.

A p<0.05 (two sided) was used to indicate statistical significance.

RESULTS

We reviewed 442 patients who were diagnosed with COVID-19 (64.5% males vs 35.5% females). As described in table 1, the mean age of the patients was 54.5 (SD 14.5%) years old. Most patients were Saudis (76.7%). The prevalence of patients who had died due to COVID-19 was 20.4%. The majority had abnormal X-rays (80.8%) while 19.7% were normal in CT scans. The median days of hospital stay were 8 with a range of 1–155 days.

The details of the laboratory characteristics of the patients have been described in table 2. It can be observed that the mean values of Hemoglobin (Hb), platelets, white cell count (WCC), lymphocytes, neutrophils, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, direct bilirubin, albumin, Partial Thromboplastin Time (PTT), Prothrombin Time (PT), The International Normalised Ratio (INR), urea, creatinine, Random Blood Sugar (RBS), Erythrocyte Sedimentation Rate (ESR), C-reactive protein (CRP), Lactate Dehydrogenase (LDH), ferritin and D-dimer were 12.9, 250.7, 7.71, 19.8, 63.2, 60.2, 59, 13, 4.02, 31.7, 34.7, 13.2, 1.07, 7.47, 131.2, 10.6, 73.5, 11.5, 426.8, 1139.9 and 3.27, respectively.

In table 3, a high level of the liver enzyme was significantly more common among females (p=0.006), Saudi nationality (p=0.004), those who survived (p=0.033) and those with abnormal X-rays (p=0.001). In addition, the median days of length of stay (LOS) were statistically significantly longer among those with the higher level of liver enzyme (p<0.001).

We also conducted a statistical test to measure the differences in laboratory parameters between high and normal liver enzymes. Based on the results, we noted that a high level of the liver enzyme was more associated with increased Hb (p=0.001), WCC (p=0.027), CRP (p=0.032), LDH (p<0.001) and ferritin (p=0.042) while it was positively associated with a lower mean value of D-dimer (p=0.022) (see table 4).

Table 3 Association between liver enzyme level and the baseline characteristics of the patients (n=442)

Factor	Level of liver enzyme		P value*
	High N (%) (n=313)	Normal N (%) (n=113)	
Age in years (mean±SD)†	53.6±14.9	56.8±14.9	0.051
Gender			
Male	94 (30.0%)	50 (44.2%)	**0.006‡**
Female	219 (70.0%)	63 (55.8%)	
Nationality			
Saudi	226 (72.2%)	97 (85.8%)	**0.004‡**
Non-Saudi	87 (27.8%)	16 (14.2%)	
Prognosis outcome			
Died	71 (22.7%)	15 (13.3%)	**0.033‡**
Alive	242 (77.3%)	98 (86.7%)	
X-ray			
Normal	44 (14.1%)	32 (28.3%)	**0.001‡**
Abnormal	269 (85.9%)	81 (71.7%)	
CT scan§			
Normal	66 (69.5%)	17 (68.0%)	0.931
Bilateral ground glass opacity	09 (09.5%)	03 (12.0%)	
More than one type	20 (21.1%)	05 (20.0%)	
LOS in days (median (min–max))¶	9.00 (1.00–155.0)	6.00 (1.00–64.00)	**<0.001‡**

*P value has been calculated using χ^2 test.
†P value has been calculated using independent sample t-test.
‡Significant at p<0.05 level.
§Patients who did not undergo with CT scan were excluded from the analysis.
¶P value has been calculated using Mann-Whitney U test.
LOS, length of stay.

When conducting multivariate estimates, we have known that a higher level of the liver enzyme was independently associated with a decreased level of CRP (adjusted OR, AOR 0.904; 95% CI 0.828 to 0.987; p=0.024) and LDH (AOR 0.989; 95% CI 0.983 to 0.995; p=0.001). On the other hand, age in years, gender, prognosis outcome, LOS, Hb, WCC and creatinine were not statistically significant after adjustments to confounders (p>0.05) (see table 5).

DISCUSSION

COVID-19 proved to highly influence liver functions.

They are considered as an important predictor for higher morbidities and mortality rates due to liver cell insufficiency.

Such damage may occur when there is hepatocellular or biliary-type hepatic dysfunction.[4 11–13]

Hepatocellular type of liver injury is usually presented with elevated ALT, and or AST with normal alkaline phosphatase (ALP) level while the biliary injuries present with an elevated ALP.

This may help in the grading of liver functions from grade 0 to 2.[4]

Little is known about the relationship between COVID-19 infection and liver functions.

Therefore, the current study included a large cohort study of 442 patients who have been diagnosed with COVID-19 infection without any previous liver cell insufficiency.

Many factors that could have affected liver function do exist.

They include the viral infection itself and other comorbidities, such as hypertension, coronary heart disease, diabetes mellitus, chronic renal insufficiency as well as malignancy.

Nevertheless, other associated infections on top of COVID-19 infection may have also participated in the morbidities and mortality.

Different treatment modalities such as antiviral and antibiotics can have there own side effect in the liver.

Moreover, immunoglobulin and corticosteroids may have also contributed to the effect of COVID-19-related liver pathology.

Out of the 442 studied patients in the current cohort, 157 (35.5%) were male and 285 (64.5%) were female.

Table 4 Association between liver enzyme level and the laboratory characteristics of the patients (n=442)

Factor	Level of liver enzyme: High Mean±SD (n=313)	Level of liver enzyme: Normal Mean±SD (n=113)	P value*
Hb	13.1±2.17	12.5±2.23	**0.018**†
Platelets	252.0±98.4	246.8±80.5	0.611
WCC	8.12±7.64	6.48±2.99	**0.027**†
Lymphocytes	16.2±13.8	24.4±17.7	0.456
Neutrophils	63.5±33.9	62.7±14.9	0.963
Total bilirubin	14.4±42.9	9.93±7.33	0.278
Direct bilirubin	4.26±4.54	3.53±9.63	0.299
Albumin	31.6±6.85	32.3±5.99	0.380
PTT	35.1±11.7	32.5±7.37	0.162
PT	13.5±7.51	12.0±1.29	0.210
INR	1.09±0.58	0.97±0.09	0.165
Urea	7.21±6.59	7.56±6.73	0.633
Creatinine	119.9±119.5	143.5±169.9	0.113
RBS	10.3±5.91	11.1±8.60	0.315
ESR	75.9±61.6	69.7±34.5	0.543
CRP	13.1±12.3	7.83±6.78	**0.032**†
LDH	491.5±504.0	279.8±124.9	**<0.001**†
Ferritin	1253.3±1413.3	859.6±1237.3	**0.042**
D-dimer	2.59±4.36	6.06±10.8	**0.022** †

*P value has been calculated using independent sample t-test.
†Significant at p<0.05 level.
CRP, C reactive protein; ESR, Erythrocyte Sedimentation Rate; HB, Hemoglobin; INR, International Normalised Ratio; LDH, Lactate Dehydrogenase ; PT, Prothrombin Time; PTT, Partial Thromboplastin Time; RBS, Random Blood Sugar; WCC, white cell count.

Table 5 Multivariate regression analysis to determine the predictor of high-level liver enzyme among patients who had been diagnosed with COVID-19 (n=442)

Factor	AOR	95% CI	P value
Age in years	1.003	0.964 to 1.043	0.886
Gender			
Male	Ref		
Female	1.857	0.547 to 6.298	0.321
Prognosis outcome			
Died	Ref		
Alive	0.538	0.079 to 3.685	0.528
LOS	1.054	0.979 to 1.134	0.162
Hb	0.916	0.700 to 1.198	0.521
WCC	1.095	0.901 to 1.331	0.363
CRP	0.904	0.828 to 0.987	**0.024***
LDH	0.989	0.983 to 0.995	**0.001***

*Significant at p<0.05 level.
AOR, adjusted OR; CRP, C reactive protein; HB, Hemoglobin; LDH, Lactate Dehydrogenase; LOS, length of stay; WCC, white cell count.

A similar study showed a percentage of (55.4%) male and (44.6%) female contradicting the high female percentage in our cohort. This may be explained by the fact that males in our society may have not always sought early medical services; therefore, they may have been expired before they hospitalised carried out including 502 patients with 278 males (55.4%) and 224 female (44.6%).[4]

The mean age of our included patients was 54.3±14.9.

This is relatively lower than what is reported previously for a mean age of 61.[4]

The reason may be due to the lower health parameters in our setting.

Most of our studied patients were Saudi (76.7%) the overall mortality rate was 20.4% is similar to the previously published data of 20.9%.

The laboratory parameters in our series were relatively similar to what was previously published such as mean serum albumen 31.6 compared with 30.7 in published data yet a high distinctive discrepancy in serum creatinine (119.9) in our series compared with 69 in the literature.

In addition, d-dimer was 2.59 in our series compared with 0.66 in the literature.

The current study results clearly described changes in the liver enzymes level among patients with COVID-19. The reason may be bile duct and liver injury due to the viral infection.

This is supported by previously published data.[4 12 13]

The current result also revealed a positive relationship between the higher liver enzymes, liver injury and the severity of COVID-19-related pneumonia simulating what was previously published.[9 10 14]

Although, the literature revealed high mortality among COVID-19-infected patients due to liver injuries[15 16] reaching up to 58% or even 78%, our study revealed a mortality rate of 20.4%.

Perhaps a long-term follow-up may have raised the mortality potential.

Hence, a long-term follow-up study is going on to realistically evaluate the obtain result in relation to previously published data.

In conclusion, this large cohort of 442 patients has shown that liver damage may be an independent prognostic factor for morbidities and mortality among COVID-19 patients. It also showed the importance of liver function enzymes screening as a predictor for the outcome of those patients.

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