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ORIGINAL ARTICLE

Hepatic affection associated with COVID-19

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ABSTRACT

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Background; By the end of December 2019, a single- stranded ribonucleic acid (RNA) virus, Coronavirus, was said to be responsible for an outbreak of respiratory infections of unknown origin in Wuhan, China. Some of the reported studies revealed that those patients who were affected with this virus had hepatic affection in form of raised transaminases. **Aim and objectives;** to study the hepatic disorders in coronavirus-19 (COVID-19) patients in Aswan and its relationship to covid-19 severity and impact on prognosis. **Subjects and methods;** A cross sectional study, was carried out on patients presented with COVID-19 infection in Aswan University Hospital, through a period between 2020 to 2022. Up to 152 patients were enrolled. Detailed history and examination was performed to all patients. Laboratory data was done in patients especially liver function test. **Result;** median age of the patients was 60 years old with range between 54-70 years. Majority of those patients were males. Majority of patients were critically ill representing 44% ,while only 31% were mild or moderate. Up to 61% of the patients (N=92) had hepatic affection. Patients with hepatic affection had higher age, male predominance and severe form of COVID-19 disease. Also, diabetes mellitus, hypertension, cardiac disease, asthma and dyspnea were more frequent among those with hepatic affection. Based on the current study, the predictors for hepatic affection in those patients were severe or critical disease. **Conclusion;** patients with COVID-19 could be liable to hepatic affection especially in case of severe form of the disease. Hepatic affection in those patients may lead to poor outcomes, so future studies with large number of participants are warranted about this point.

INTRODUCTION

Corona virus disease 2019 (COVID-19) is a viral infectious disease caused by severe acute respiratory syndrome coronavirus2 (SARS-CoV-2).

Some patients are more prone to serious outcomes, including pneumonia, acute respiratory distress syndrome (ARDS), and even death. Recent reports have summarized the clinical presentation of COVID-19, which commonly presents as fever, cough, dyspnea, and myalgia or fatigue [1].

Many clinical studies suggested that patients with COVID-19 have elevation of liver chemistries, including aspartate transferase (AST), alanine transferase (ALT) and total bilirubin [2].

The mentioned parameters and albumin were correlated with disease severity after

severe acute respiratory syndrome coronavirus-2 infection [3].

Also, clinical studies based on single or multiple centers have shown significant increase in number of COVID-19 patients who have liver injury, indicating that liver injury is relatively common among COVID-19 patients[3-5].

.The incidence of liver injury in patients with critical COVID-19 disease is higher than that in patients with mild disease [7].

Patients with abnormal liver tests were at increased risk of progressing to severe COVID-19 disease [6] Also, Patients they had longer mean hospital stays[7,8].

We aim to study the hepatic changes in COVID-19 patients and identify the value of it in diagnosis and prognosis.

Aim of the work

This was conducted to study the hepatic disorders in COVID-19 patients in Aswan and its effect on severity and prognosis of the disease.

PATIENTS &METHODS

Informed consent was obtained from all patients after being informed about the aims and process of the study as well as applicable objectives.

Study setting and design

A cross-sectional study was conducted at the Department of Internal Medicine, Aswan University Hospital. It was done in the period between 2020 and 2022.

Inclusion criteria

Patients with confirmed positive COVID-19 with no restriction of race, gender, or occupation, patient age > 18 years.

Exclusion criteria

- Alcholic patients.
- Pregnant women.
- Patients with history of liver diseases.

Methodology

All patients were subjected to full history taking; the data include demographic criteria (age, gender, and smoking history) and history of symptoms of COVID-19 (cough,dyspnea,diarrhea…. etc.).

Thorough clinical examination was done. The following investigations were performed; polymerase chain reaction (PCR) for COVID-19 , liver function (AST, ALT, serum albumin, serum bilirubin), international normalized ratio(INR) and complete blood count. In addition to abdominal ultrasound.

Statistical analysis

All statistics were performed using SPSSversion25 (BMCorp.Released 2017.IBMSPSS Statistics for Windows , Version 25.0 Armonk ,NY : IBM Corp.) .Continuous data were presented as mean ± SD and range .Qualitative variables were expressed as frequency (percentage). Analysis of continuous data with normal distribution were analyzed by appropriate parametric test and non-normally distributed data by appropriate non-parametric test . Categorical data was analyzed by chi-square test or Fischerexact where applicable. P value of <0.05 defined as statistically significant.

RESULTS

Baseline data of the studied patients (table 1):

A total of 152 COVID-19 patients were included. The median age of participants was 60 years with range between 54-70 years. Out of them 53% were males. Moreover, 40 % of the included participants were smokers.

Most of patients develop cough, dyspnea, and fever. The majority of included patients in hepatic affection group had comorbidities with a percentage reaching 74%: most of them were diabetes or hypertension or both representing 57% and 62 % respectively.

Disease severity and baseline laboratory data in the studied patients (table 2):

The majority of patients were critical representing 44% while only 31% were mild or moderate and 25% were severe . Up to 92 (61%) patients had hepatic affection& the perecentage of severity in COVID-19 patients who had liver dieases was 5,4%(N=5) mild&moderate, 25%(N=23) severe & 70%(N=64) critical patients . Laboratory data are summarized at table 2.

Characteristics of the studied patients based on hepatic affection (table 3):

There were significant differences between both groups as regard different characteristics with exception of frequency of chronic kidney disease. The differences in severity in both groups are obvious where most of patients who developed hepatic diseases were in critical state of COVID-19. On the other hand, patients with mild or moderate state represented the majority of patients with no hepatic affection.

Symptoms and laboratory investigations for patients with and without hepatic affection (table 4):

There were significant differences between both groups as regard frequency of dyspnea, ALT, AST and platelets count. Other data showed no significant difference as regard other data ($p > 0.05$).

Predictors of hepatic affection among the studied patients (table 5):

Based on the current study, the predictors for hepatic affection in those patients were severe or critical disease .

DISCUSSION

According to recent reports, 2%–11% of COVID-19 patients had liver comorbidities, and 14%–35% of cases with abnormal levels of alanine amino transferase (ALT) and aspartate amino transferase (AST) during disease progression have been reported.Our study is across sectional study that included 152 COVID -19 patients .The median age of participants was 60 IQR (54, 70) years, of them 53% were males. Moreover, 40 % of the included participants were smoker.

In our study, the severity of the disease differed among patients which was classified into three categories as follows: mild or moderate, severe, and critical. The majority of patients were critical representing 44% while only 31% were mild or moderate &25% were severe [9].

Our study revealed that regarding presenting characteristics and symptoms, most of patients develop cough, dyspnea, and fever. The majority of included patients had comorbidities with a percentage reaching 74%. These comorbidities varied for each patient. For instance, most of patients who are positive hepatic affection developed diabetes or hypertension representing 57% and 62 % respectively but patients who are negative hepatic affection developed diabetes or hypertention representing 32% and 25% respectively . In contrast, small proportion of patients suffered from cardiac, renal or asthmatic problems

Chen et al. (2020) showed that 50 (51%) patients had chronic diseases, including cardiovascular and cerebro vascular diseases, endocrine system disease, digestive system, respiratory disease, malignant tumor, and nervous system disease. On admission, most patients had fever or cough and a third of patients had shortness of breath[9].

This study illustrated that up to 92 (61%) patients had hepatic affection. Males represented

the majority of patients with hepatic affection reaching 59%, females reached 55% in patients with no hepatic affection. This study showed that the differences in severity in both groups are obvious where most of patients who developed hepatic diseases were in critical state of COVID-19.

On the other hand, patients with mild or moderate state represented the majority of patients with no hepatic affection. These differences were highly statistically significant with a p-value < 0.001. The majority of patients with hepatic affection suffered from different comorbidities.

The percentage of patients with hepatic affection suffered from different comorbidities was the same in the group who did not develop hepatic diseases. This comparison was highly statistically significant with a p-value < 0.001. The results of all comorbidities were statistically significant except for chronic kidney disease. Also, the study demonstrated that there are no statistical differences in albumin and bilirubin. ALT and AST showed apparent differences in both groups. Additionally, the differences in ALT and AST were highly statistically significant with a p-value <0.001.

Zou et al. (2021) showed that elevated levels of liver tests were observed in several patients at admission, with elevated ALT, AST, TBIL, ALP, and γ-GT in 22 (20.95%), 29 (27.62%), 7 (6.67%), 1(0.95%), and 7 (6.67%) patients, respectively. Among the patients with liver test abnormalities, most were mildly elevated within 1– 2× ULN at admission. Fourteen patients (13.33%) presented with reduced prothrombin activity and prolonged INR at admission [10].

Cai et al. (2020) showed the presence of abnormal liver tests and liver injury were associated with the progression to severe pneumonia.

Many reasons may explain this. First, the 2 studies used different criteria for liver injury. Previous study defined ALT and/or AST over 3× ULN and/or TBIL over 2× ULN as liver injury according to the protocol for prevention, diagnosis, and treatment of liver injury in COVID-19, whereas liver injury was defined as ALT and/or AST over 3× ULN and ALP, γ-GT, and/or TBIL over 2× ULN in the study of Cai et al [6].

Second, the interval from onset of COVID-19 affection to admission of patients in the present study was 10 days, which may lead to missed diagnosis of early liver injury for lack of data before admission. Furthermore, there is heterogeneity in the population characteristics included in the 2 studies [11].

Based on the current study, the predictors for hepatic affection in those patients were severe or critical disease while other variables were not considered predictors

This study has several limitations. First, only 152 patients with confirmed 2019-nCoV were included; suspected but undiagnosed cases were ruled out in the analyses. Second, more detailed information, particularly regarding clinical outcomes, was unavailable at the time of analysis; however, the data in this study permit an early assessment of the epidemiological and clinical characteristics of 2019-nCoV pneumonia.

In conclusion; patients with severe form of covid-19 are more liable to hepatic affection with poor out comes. Hence, future studies should carefully investigate the cause of liver injury during COVID-19 infection.

From a clinical perspective, these findings may help in early triage, close monitoring of the occurrence of liver injury, and careful use of drugs which can cause liver toxicity in COVID-19 patients

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Legend of Tables:

Table 1: Baseline characteristics of the studied patients

Variable	**N = 152**
Age **(years)**	60 (54 - 70)
Gender	
Female	71 (47%)
Male	81 (53%)
Smoking	60 (40%)
Clinical presentations	
Cough	104 (68 %)
Dyspnea	130 (86 %)
Anorexia	86 (57 %)
Vomiting	67 (44 %)
Diarrhea	6 (3.9 %)
Fever	148 (97 %)
Overall	113 (74%)
Comorbidities	
Diabetes mellitus	86 (57%)
Hypertension	94 (62%)
Cardiac disease	18 (12%)
Chronic kidney disease	13 (8.6%)
Asthma	16 (11%)

Data expressed as frequency (percentage), median (range)

Table 2: Disease severity and baseline laboratory data in the studied patients

Variables	**N= 152**
Hepatic affection	
With hepatic affection	92 (61%)
No hepatic affection	60 (39%)
Severity of covid-19	
Mild or moderate	47 (31%)
Severe	38 (25%)
Critical	67 (44%)
Laboratory investigation	
Hemoglobin (g/dl)	11.75 (10.1- 12.8)
Bilirubin (mg/dl)	0.8 (0.6- 0.9)
ALT (U/L)	72 (37- 129)
AST (U/L)	116 (48- 145)
Albumin (g/dl)	3.2 (3- 3.5)
Platelets (×109/L)	228 (148- 306)
INR	1.3 (1.1- 1.4)

Data expressed as frequency (percentage), median (range). ALT; alanine transaminase; AST: aspartate transaminase; INR: international randomized ratio

Table 3: Characteristics of the studied patients based on hepatic affection

Variable	Combined (n= 152)	Hepatic affection (n= 92)	No hepatic affection (n= 60)	p-value
	Median (IQR); n (%)			
Age	60 (54 - 70)	62 (55- 71)	60 (50- 70)	< 0.001
Gender				< 0.001
Female	71 (47%)	38 (41%)	33 (55%)	
Male	81 (53%)	54 (59%)	27 (45%)	
Smoking	60 (39.5%)	45	15	< 0.001
Severity				< 0.001
Mild	47 (31%)	5 (5.4%)	42 (70%)	
Severe	38 (25%)	23 (25%)	15 (25%)	
Critical	67 (44%)	64 (70%)	3 (5.0%)	
Comorbidities	113 (74.3%)	83 (90%)	30 (50%)	
Diabetes	86 (57%)	67 (73%)	19 (32%)	<0.001
Hypertension	94 (62%)	69 (75%)	25 (42%)	<0.001
Cardiac	18 (12%)	15 (16%)	3 (5%)	0.035
CKD	13 (8.6%)	7 (7.6%)	6 (10%)	0.69
Asthma	16 (11%)	14 (15%)	2 (3.3%)	0.02

Data expressed as frequency (percentage), median (range). *P* value was significant if < 0.05. CKD: chronic kidney disease

Table 4: Symptoms and laboratory data based on hepatic affection

Variable	Combined (n= 152)	Hepatic affection (n= 92)	No hepatic Affection (n= 60)	p-value
Dyspnea	130 (86 %)	89 (96.7%)	41 (68.3%)	<0.001
Cough	104 (68 %)	65 (70.7%)	39 (65%)	0.44
Anorexia	86 (57 %)	49 (53.3%	37 (61.7%)	0.39
Vomiting	67 (44 %)	37 (40.2%)	30 (50%)	0.21
Diarrhea	6 (3.9 %)	1 (1.8%)	5 (8.3%)	0.06
Fever	148 (97 %)	90 (97.8%)	58 (96.7%)	0.65
Bilirubin	0.8 (0.6- 0.9)	0.8 (0.6- 0.9)	0.8 (0.6- 1)	0.64
ALT	72 (37- 129)	120 (80-143)	31 (20- 46)	<0.001
AST	116 (48- 145)	136 (122- 163	38 (28- 62)	<0.001
Albumin	3.2 (3- 3.5)	3.2 (2.89-3.5)	3.2 (3- 3.52)	0.29
Platelets	228 (148-306)	216 (136- 273	246 (176- 348)	0.015
INR	1.3 (1.1- 1.4)	1.3 (1.1- 1.4)	1.2 (1.1- 1.4)	0.76

Data expressed as frequency (percentage), median (range). P value was significant if < 0.05
ALT; alanine transaminase; AST: aspartate transaminase; INR: international randomized ratio

Table 5: Logistic regression for prediction of hepatic affection

Characteristic	OR [95% CI]	p-value
(Intercept)	0.6 (0.05- 6.20)	0.7
Age	0.96 (0.92- 1.01)	0.10
Gender (Male)	0.84 (0.28- 2.33)	0.7
Severity		
Critical	155 (35.3- 958)	<0.001
Severe	11.1 (3.42- 42.3)	<0.001
Comorbidities	3.11 (0.72- 13.6)	0.12

P value was significant if < 0.05. CI: confidence interval; OR: odd's ratio