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Research paper

Risk factors for the development of hepatic manifestations in COVID-19 patients with digestive symptoms

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ABSTRACT

Background: Abnormalities in liver function tests (LFTs) are found in 14%–53% of hospitalized COVID-19 patients. These could occur in patients with or without previous chronic liver diseases. Knowing the risk factor of liver manifestations in COVID-19 subjects is crucial for the proper management of these patients.

Objectives: We aimed to identify the risk factors for liver manifestations as well as other risk factors in COVID-19 subjects who complained of digestive manifestations.

Materials and Methods: COVID-19 patients with and without liver manifestations at the Emergency Department of Al Fallujah Teaching Hospital were enrolled in this study. This study covered a period from September 15, 2022, to April 22, 2022. Comparisons between patients with or without abnormal LFTs were made. The possible risk variables connected to abnormal LFTs and hepatic manifestation were investigated using univariable and multivariable logistic regression analysis.

Results: Out of 100 COVID-19 patients, there were 64 suffering from mild gastrointestinal (GI) symptoms. There were 26 mild cases with abnormal LFTs (40.6%). Although there were nine (total number 22) and seven (total number 14) of the moderate and severe cases with liver involvement, there was no statistically significant difference between the digestive manifestations severity and liver involvement. Increased alanine aminotransferase (ALT) levels were linked to a greater incidence of LFTs, according to multivariable analysis (odds ratio [OR]: 45.05; $P < 0.0001$), elevated aspartate aminotransferase (AST; OR: 3.462; $P = 0.00041$), elevated direct bilirubin (DBIL) (OR: 3.643; $P < 0.001$), and elevated d-dimer levels [OR]: 2.690; $P < 0.0137$) in liver involvement group compared with non-involvement patients.

Conclusions: Elevated ALT, AST, DBIL, and d-dimer are potential risk factors for liver manifestations in COVID-19 patients with digestive symptoms.

Keywords: COVID-19, digestive symptoms, liver manifestations, liver functions tests, SARS-CoV-2

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INTRODUCTION

Coronavirus Interactive Disease 2019 is a worldwide pandemic outbreak caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). This virus binds to the angiotensin-converting enzyme 2 (ACE2) receptor in the host cells.[1,2] SARS-CoV-2 mainly infects the respiratory system, and the most frequent symptoms are fever, cough, and dyspnoea. Respiratory failure, and possibly, death might be complications of the disease.[2]

The immune and neurological systems as well as the digestive tract, liver, lung, skeletal or smooth muscle, heart, kidney, and brain are affected by this virus.[3,4] In addition to the lungs, the liver is one of the organs that is most commonly damaged.[4] Moreover, there is a wide range of COVID-19 manifestations including, but not limited to, cough, fever, shortness of breath, smell, and taste dysfunctions, sore throat, dysphonia, deafness, and gastrointestinal tract (GIT) symptoms like diarrhea and vomiting.[5–7]

The abnormality for liver manifestation is composed of rises in the serum enzymes, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), and bilirubin, which impair the hepatocytes' capacity to carry out their typical functions and eventually result in bile duct cells' dysfunction.[8]

According to a case study, abnormal liver function was detected in 55 (37.2%) of 148 hospitalized COVID-19 patients. Liver involvement occurs in patients with or without previous history of liver injury.[9]

Although the exact mechanism of liver involvement in COVID-19 patients is not known, certain mechanisms include the direct effect of the virus on the liver, hypoxic effect, previous chronic liver diseases, etc.[10]

To our best knowledge, there is no previous study on this subject in Iraq, hence we conducted this study to investigate the risk factors for liver manifestation such as changes in liver function tests (LFTs) and hematological parameters with other risk factors in COVID-19 who showed digestive signs and compares the results with similar studies around the world.

MATERIALS AND METHODS

Study Design

A prospective descriptive cross-sectional study included hospitalized individuals from one specific medical facility (Emergency Department in Fallujah Teaching Hospital), Anbar Governorate, Iraq, between September 15 and April 22, 2022.

The severity of digestive symptoms in COVID-19 patients was performed by two physicians according to the following criteria: severe diarrhea, more than 10 loose, watery stools in a day (24 hours); moderate diarrhea, more than a few but not more than 10 diarrhea stools in a day; and mild diarrhea, a few diarrhea stools in a day (https://2u.pw/5EuYu). While severe vomiting means vomiting everything, nearly everything or eight or more times/day, moderate vomiting means vomiting 3 to 7 times/day; and mild vomiting means vomiting 1 to 2 times/day (https://2u.pw/AQfmU).

In this study, throughout the hospitalization period, the LFTs were assessed and recorded for each subject.

All confirmed cases of COVID-19 patients with no gastrointestinal (GI) or hepatic symptoms, negative RT-PCR results, younger than 15 years, concurrent GI or hepatic symptoms prior to COVID-19 infection, or solely respiratory symptoms, and pregnant women were excluded from the investigation.

The current investigation included all COVID-19 cases who were positively identified by nasopharyngeal swab PCR and had GI and hepatic manifestations in patients between the ages of 15 and 96 years, regardless of gender, and who had no prior history of these symptoms. This study was approved by the Ethical Approval Committee of the University of Anbar, Iraq, on June 1, 2022. Informed consent was obtained from all patients before enrolment in this study.

Expert opinion as endorsed by the "Hepatology Chinese Civilization" and Chinese Clinical Association, liver biochemical abnormalities (LBA) is defined as elevated levels of specific parameters that exceed the normal value upper limitation. These parameters include ALT, AST, total bilirubin (TBIL), direct bilirubin (DBIL), ALP, GGT, and lactate dehydrogenase (LDH).

Data Collection

Age, gender, primary signs including cough, fever, anorexia diarrhea, and weakness, as well as cases of comorbidities such as hypertension, were all part of the medical history collection. Besides, all

patients had laboratory tests performed at the laboratory center upon admission to the hospital, including ALT, AST, DBIL, TBIL, ALP, and GGT, as well as d-dimer, leukocyte count, albumin, amylase, ferritin, C-reactive protein (CRP), and procalcitonin (PT).

Statistical Analysis

The Kruskal–Wallis and Mann–Whitney *t*-tests were used to compare continuous data. Continuous variables were presented as mean and standard deviation (SD). The categorical variables were represented as frequency (%), and χ^2 or Fisher's exact tests were used to compare categorical variables. Risk factors linked to LBA, hematological parameters, other risk factors, and hepatic manifestation were investigated using univariable and multivariable logistic regression tests. Risk variables linked to the emergence of COVID-19 hepatic manifestations are presented as a forest plot for ORs. A two-sided tail value of less than 0.05 was considered statistically significant. SPSS version 26.0 (IBM, Armonk, NY) and GraphPad Prism version 8.0 (GraphPad Prism Software) were used to conduct the statistical analyses.

RESULTS

Out of 407 COVID-19 cases, 100 patients fulfilled the inclusion criteria and were enrolled in this study. About two-thirds of the patients were with mild digestive symptoms (Figure 1).

Liver Manifestation Frequency and the Severity of GIT Symptoms in COVID-19 Patients

Of the total 100 COVID-19 patients, 64 had mild GI illness and 38 of them were without liver manifestation. Out of the total 22 patients with moderate digestive symptom severity, nine patients had liver manifestations. Out of the 14 patients with severe GI symptoms, seven were with liver manifestations. There is no statistically significant variance between COVID-19 patients with or without liver manifestation according to the COVID-19 digestive manifestations severity (Figure 2).

Risk Factors of Biochemistry Abnormality for Hepatic Impairment in COVID-19 Patients with Digestive Symptoms

Patients who had hepatic manifestation had a higher chance of developing LBA, according to a univariable study. Increased ALT levels were shown to be substantially linked with the development of COVID-19's hepatic manifestation in univariate and multivariate analyses (OR: 45.05; $P < 0.0001$). Furthermore, elevated AST (OR: 3.462; $P = 0.00041$) and elevated DBIL (OR: 3.643; $P < 0.001$) were found to be significantly associated with the liver manifestation development of COVID-19, whereas elevated ALP (OR: 3.462; $P > 0.001$), elevated TBIL (OR: 1.714; $P > 0.001$), and elevated GGT

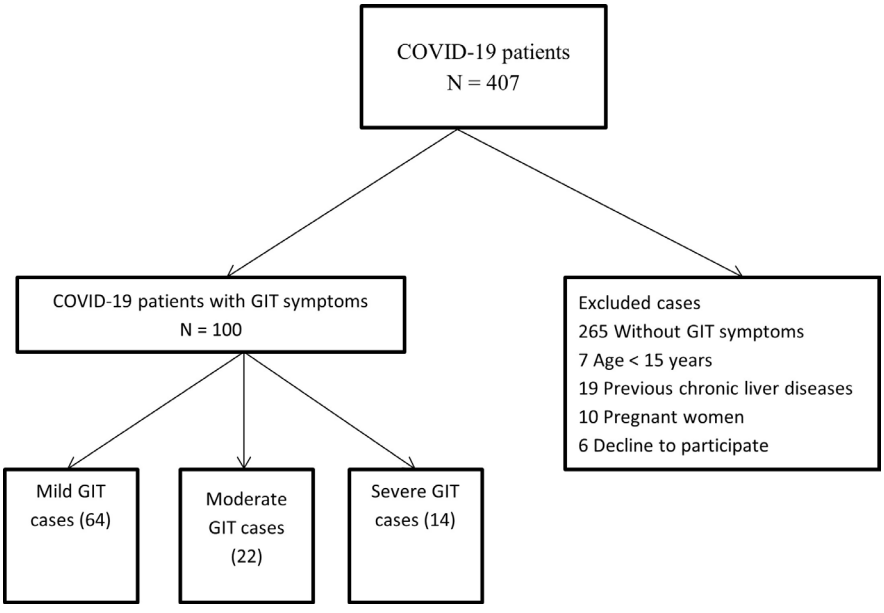


Figure 1. Flow chart of 407 COVID-19 patients.

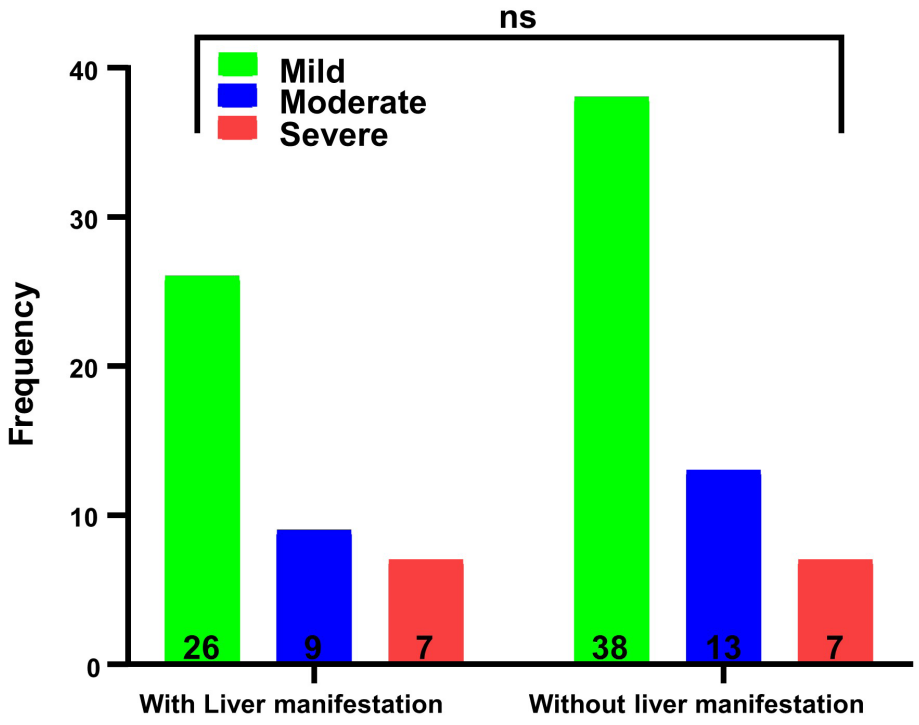
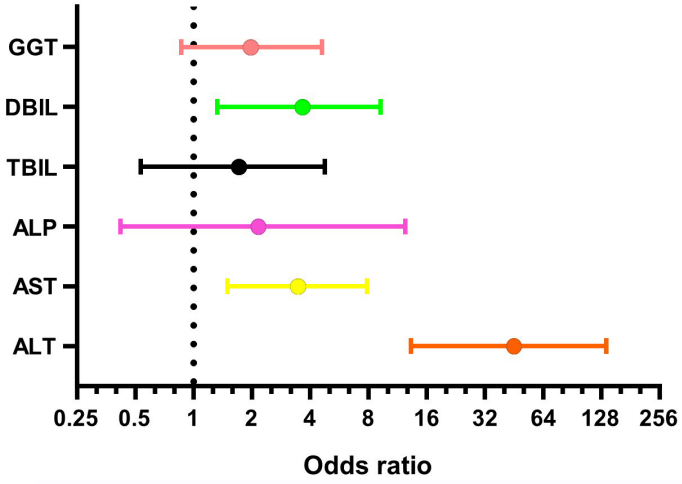


Figure 2. Liver manifestation frequency according to the COVID-19 digestive manifestations severity.



	ALT	AST	ALP	TBIL	DBIL	GGT
Lower CL	13.29	1.492	0.4206	0.5316	1.330	0.8664
Odds ratio	45.05	3.462	2.154	1.714	3.643	1.969
Higher CL	136.3	7.857	12.48	4.756	9.239	4.617
P Value	<0.0001****	0.0041***	ns	ns	0.0100**	ns

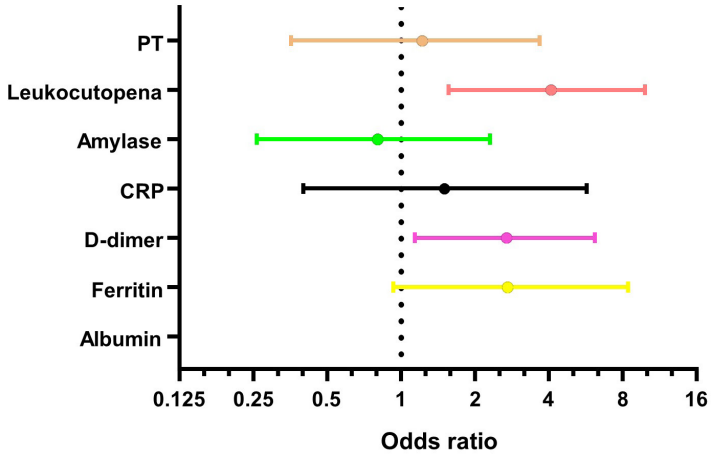
Figure 3. Forest plot presentation of the OR of AST, AST, ALP, TBIL, DBIL, and GGT risk factors related to COVID-19 liver manifestation development of those suffering from digestive symptoms.

(OR: 1.969; $P > 0.001$) were found to be significantly nonrelated with the COVID-19 liver manifestation development (Figure 3).

Depending on univariate and multivariate analyses, increased D-dimer levels (OR: 2.690; $P < 0.0137$) and elevated leukocyte levels are significantly related to liver manifestation development in COVID-19 patients (OR: 4.083; $P < 0.0024$), whereas raised albumin (OR: 0.000; $P < 0.05$) and amylase levels (OR: 0.8000; $P > 0.05$) are significantly not related to liver manifestation development

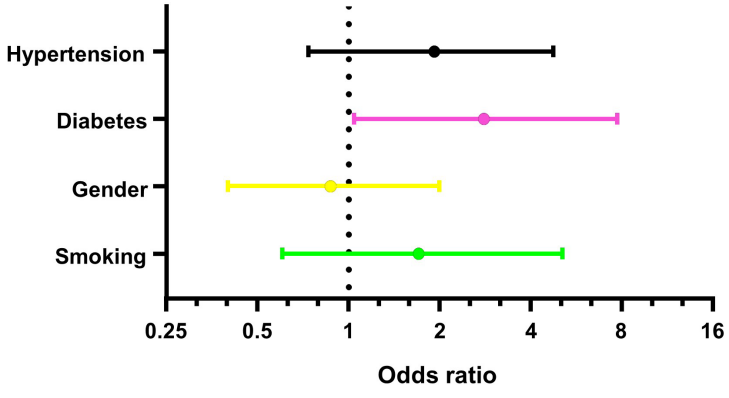
in COVID-19 patients, also increased ferritin (OR: 2.708; $P > 0.05$), CRP (OR: 1.500; $P > 0.05$), and PT (OR: 1.214; $P > 0.05$) are significantly not related to liver manifestation development in COVID-19 patients (Figure 4).

Depending on the univariate and multivariate analyses, diabetes was significantly related to liver manifestation development in COVID-19 patients suffering from digestive symptoms (OR: 2.802; $P = 0.0376$), whereas gender (OR: 0.8710; $P > 0.05$), smoking (OR: 1.705; $P > 0.05$), and hypertension (OR: 1.920; $P > 0.05$) were not related to liver manifestation development in COVID-19 patients suffering from digestive symptoms (Figure 5).



	Albumin	Ferritin	D-dimer	CRP	Amylase	Leukocutopenia	PT
Lower CL	0.000	0.9314	1.139	0.4001	0.2576	1.555	0.3550
Odds ratio	0.000	2.708	2.690	1.500	0.8000	4.083	1.214
Higher CL	2.976	8.425	6.163	5.722	2.307	9.842	3.674
P Value	ns	ns	0.0173*	ns	ns	0.0024**	ns

Figure 4. Forest plot presentation of the OR of albumin, ferritin, D-dimer, CRP, amylase, leukocytopenia, and PT risk factors related to liver manifestation development in COVID-19 patients suffering from a digestive infection.



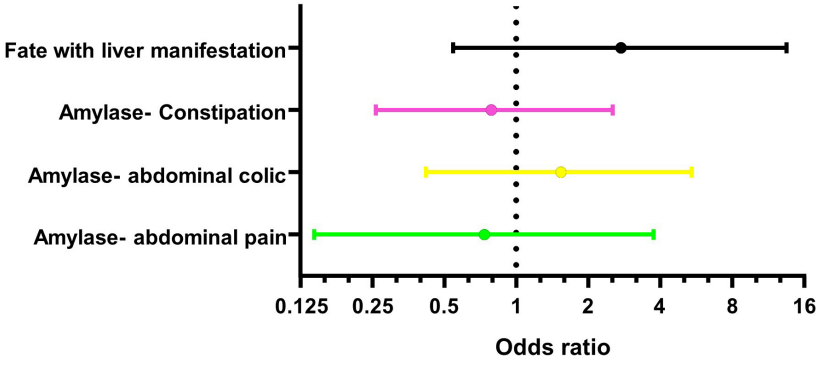
	Smoking	Gender	Diabetes	Hypertension
Lower CL	0.6059	0.3993	1.042	0.7373
Odds ratio	1.705	0.8710	2.802	1.920
Higher CL	5.090	1.993	7.725	4.747
P Value	ns	ns	0.0376*	ns

Figure 5. Forest plot presentation of the OR of smoking, gender, diabetes, and hypertension risk factors related to liver manifestation development in COVID-19 patients suffering from a digestive infection.

Increased amylase levels were not related to the onset of abdominal discomfort in COVID-19 patients with digestive symptoms according to univariate and multivariate analyses (OR: 2.802; $P > 0.05$). Furthermore, abdominal colic development in COVID-19 patients was not substantially correlated with elevated amylase levels (OR: 1.538; $P > 0.05$). Also, increased amylase levels were not significantly related to the constipation development in COVID-19 patients suffering from digestive symptoms (OR: 0.7867; $P > 0.05$), and mortality rate in COVID-19 patients with digestive infections was not substantially correlated with increased amylase levels (OR: 2.745; $P > 0.05$) as shown in Figure 6.

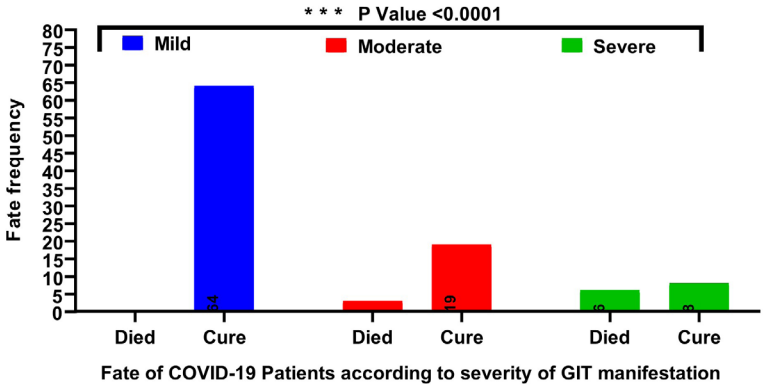
Mortality Rate in COVID-19 Patients according to GI Manifestation Severity

There were nine deceased patients, three due to moderate digestive symptoms and six due to severe cases. No statistically significant differences were found between the mortality rate and severity of digestive symptoms in COVID-19 patients (Figure 7).



	Amylase-abdominal pain	Amylase-abdominal colic	Amylase-Constipation	Fate-with liver manifestation
Lower CL	0.1431	0.4188	0.2582	0.5458
Odds ratio	0.7368	1.538	0.7867	2.745
Higher CL	3.752	5.430	2.536	13.53
P Value	ns	ns	ns	ns

Figure 6. Forest plot presentation of OR for amylase levels related to abdominal pain, abdominal colic, constipation developments, and mortality rate in COVID-19 patients with digestive infections.



Fate	Severity of GIT			Total
	Mild	Moderate	Severe	
Died	0	3	6	9
	0.0%	3.0%	6.0%	9.0%
Cure	64	19	8	91
	64.0%	19.0%	8.0%	91.0%
Total	64	22	14	100
	64.0%	22.0%	14.0%	100.0%

Figure 7. The mortality rate of COVID-19 patients according to the severity of the digestive signs.

DISCUSSION

In this descriptive cross-sectional investigation, 42% of the COVID-19 patients showed mild, moderate, and severe biochemistry problems with liver symptom development. In hospitalized COVID-19 patients, we reported that several risk factors for liver diseases including excessively high ALT, AST, DBIL, or D-dimer levels were all linked to increased chances of liver abnormality with hepatic manifestation in COVID-19 patients at the time of admission. This study showed that the frequency of liver impairment was consistent with other studies, which indicated that hepatic LBA increases more than twofold from normal values.[8]

With a minor influence on hepatocytes, the findings of the present investigation had been analogous to community-acquired pneumonia patients. However, it has been demonstrated that in COVID-19 patients, abnormal liver test findings with liver damage are linked to developing severe pneumonia.[4]

Despite the possibility of elevated D-dimer levels in severe cases, uncertainty still exists regarding the precise connection between liver damage and attacks on the kidney, heart, or coagulation system in COVID-19 patients with digestive and hepatic manifestations. Complications associated with COVID-19, such as "multiple organ failure" or "respiratory distress syndrome" may cause liver ischemia or hypoxia-reperfusion dysfunction.[11]

In Chinese meta-analysis study consisting of 6,686 patients, it had shown that patients with severe illnesses had significantly higher ALT and AST levels than those who were not very ill (OR: 1.89, 95% confidence interval: 1.30–2.76, $P = 0.0009$ and OR: 3.08, 95% confidence interval: 2.14–4.42, $P = 0.00001$, respectively).[12]

Smokers and those with chronic obstructive pulmonary disease (COPD) also have a greater expression of ACE2 receptors, according to Leung et al.[13] Additionally, ACE2 gene polymorphisms have been linked to diabetes and hypertension.[14]

In disagreement with the present study, ACE inhibitors (ARI) and angiotensin receptor blockers (ARB), two medications used to treat hypertension, work by lowering cytokines to decrease inflammation. Furthermore, they might boost ACE2 expression;[15] however, there is no evidence linking the usage of ACE and ARB to a poorer clinical course in COVID-19 patients. Potential but unconfirmed risk factors for COVID-19 in adults and children may include hypertension, cardiovascular disease, and chronic kidney disease, as well as the medications commonly prescribed for these conditions, ARI and ARB. Consequently, it is advised that hypertension patients continue to take these medications.[16,17]

GGT level was somewhat greater in severe COVID-19 cases paralleled to those with mild or moderate symptoms, even though in this study there were no appreciable variances in whole bilirubin between mild and severe COVID-19 cases.

In the most severe cases of COVID-19, there were high levels of ALT, AST, and GGT, more than twice the reference value indicated in previous research.[9] This could help to partially explain how the AST/ALT ratio increased as the illness developed.

Increased AST/ALT ratio in chronic hepatitis patients was associated with progressive functional liver impairment, according to two earlier investigations.[15] As a result, to more accurately determine the condition of liver injury, the AST/ALT ratio should be reserved into account, combined with AST and ALT levels.

Our research showed that in those with severe COVID-19, CRP was a risk factor, but non-significantly associated with developing hepatic impairment. This difference in results may be due to the differences between the two studies on bacterial complications associated with an increase in CRP.[18]

A fascinating Canadian meta-analysis study concerning 3,615 COVID-19 patients from 15 trials found an elevated death rate following acute liver damage (RR = 4.02 [1.51, 10.68], $P = 0.005$).[19] According to a prior study, individuals with liver impairment at admission would require lengthier hospital stays than those with good liver function. Besides, it leads to a higher death rate.[9]

According to Lippi et al.,[20] the progression of COVID-19 chronic liver disease was not always correlated with the severity of the condition or death and this may be due to immune response development in those patients.

Patients with COVID-19 may have toxicity from medications, liver issues, a rise in blood levels of cytolysis biomarkers, an infection-related inflammatory storm, hepatic ischemia, reperfusion dysfunction, or an infection-related inflammation storm.[21]

This study regarding the prevalence of COVID-19 in the Anbar governorate was consistent with previous studies in the same area.[22–24]

It must be mentioned that this study does have certain restrictions. First, asymptomatic individuals were not admitted to hospitals during the COVID-19 epidemic, which might lead to biases in how clinical observations are analyzed. Second, the patients were exclusively chosen from one specified center in the Fallujah Teaching Hospital emergency room in the Iraqi Province of Anbar. Since the descriptive cross-sectional study's sample size was very limited, it would be preferable to add patients from other hospitals in the Governorate of Anbar, other cities in Iraq, and even other nations to produce a substantial dataset.

A large size of COVID-19 patients with digestive and hepatic manifestations is essential for a well understanding of the pathophysiology in the liver, given the great prevalence of SARS-CoV-2 transmission among persons and the equivocal incidence of liver impairment and damage.

CONCLUSION

According to our findings, individuals with COVID-19 commonly display liver problems. Smoking, elevated AST, AST, D-dimer, and COVID-19 with stomach symptoms are all possible risk factors for liver involvement.

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CONFLICT OF INTEREST

No disclosed conflicts of interest for the writers.

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