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Gastrointestinal and Liver Manifestations in Patients with COVID-19

Nasser Elhamshary MD[1], Islam Abdel-Mawla Ammar MD[2], Ahmed Mohamed Shaaban Ahmed Abdelgalil[3]

Department of Hepatogastroenterology and Infectious Diseases, Faculty of Medicine, Al-Azhar University
Corresponding author: Ahmed Mohamed Shaaban Ahmed Abdelgalil,
Email: *drahmadshaaban3[at]gmail.com*

Abstract: ***Background: As the outbreak of COVID-19, It has rapidly spread over the world, the World Health Organization had declared the outbreak of COVID-19 as an international public health emergency. Besides typical respiratory symptoms and signs of COVID-19, digestive symptoms and liver injury had been frequently reported during the course of the disease. Aim and objectives: To explore the available evidences on liver and GI involvement in patients with COVID-19 infection and to provide a comprehensive understanding of the phenomenon, and to anticipate effective follow-up. Subjects and methods: This study will be conducted on two hundreds of COVID-19 infected patients who had positive COVID-19 PCR as an outpatients and admitted in Abu Hommos Central Hospital from January to the end of June 2021. Patients were divided into 2 groups. Group 1 has GIT symptoms only (abdominal pain, Anorexia, nausea, vomiting, diarrhea….)-Group 2 has GIT and respiratory symptoms as difficulty of breathing, cough….) (Mild to moderate cases) guided with Egyptian protocol. Result: There was statistically significant difference between two groups regarding CT scan as group who had GIT symptoms and respiratory symptoms was higher positive in CT scan than group with GIT symptoms only, there were slight increase in laboratory investigations as ALT, AST, Lymphopenia, CRP, ESR in group 1 more than group 2. Conclusion: Digestive symptoms are common in patients with COVID-19, and in some cases digestive symptoms may occur in the absence of any respiratory symptoms. COVID-19 patients with digestive symptoms have worse clinical outcomes. Attention should also be paid to monitor liver function during the course of COVID-19, especially in patients with higher disease severity.***

Keywords: COVID-19, Liver, Gastrointestinal and Liver Manifestations

1. Introduction

A novel coronavirus was reported to World Health Organization on Dec 30, 2019, as the cause of a cluster of pneumonia cases in China, city of Wuhan. The first name of 2019-nCoV (human) was adopted on Jan 7, 2020, lately changed to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). COVID-19 infection became an outbreak throughout China on Feb 11, 2020 and subsequently was identified as a global pandemic on March 11, 2020, spreading to more than 120 countries, as a major threat to public health [1, 2].

COVID-19 may manifest in different ways. Many subjects may remain asymptomatic, but the exact number is still unknown. [3]

Although the most frequent and critical clinical presentation is secondary to the involvement of the lung (fever, cough), the infection by SARS-CoV-2 virus may lead to a systemic and multi-organ disease [4], also involving the gastrointestinal tract (nausea/vomiting, or diarrhea) [5, 6]. The liver appears to be the second organ involved, after the lung [7, 8].

As SARS-CoV-2 RNA was detected in stool of reported COVID-19 cases who presented with the digestive symptoms of nausea, vomiting, and diarrhea, 3 more attentions have been paid to the gastrointestinal manifestations of SARSCoV-2 [9].
Liver injury was common in the patients infected by the other two highly pathogenic coronavirus—SARS-CoV and the Middle East respiratory syndrome coronavirus—and associated with the severity of diseases. In patients with COVID-19, several studies have reported the incidence of liver injury, liver comorbidities and abnormal LFTS [10].

2. Aim of the Work

Explores the available evidences on liver and GI involvement in patients with COVID-19 infection. Provide a comprehensive understanding of the phenomenon, and to anticipate effective follow-up.

Patients and Methods

Type of study: Prospective study.

Patients: This study was conducted on two hundreds of COVID-19 infected patients who had positive COVID-19 PCR as an outpatients and admitted in Abu Hommos Central Hospital from January to the end of June 2021.

Study Populations:-

Inclusion Criteria: All inclusion criteria were added according to the Egyptian COVID-19 Protocol program. The age range was between 18-75 years. All patients tested positive for COVID-19 PCR (mild and moderate cases).

Exclusion Criteria: severe critically ill patients infected with COVID-19 admitted In ICU. Patients on Mechanical ventilator. Patients with chronic liver diseases. Patients with chronic GIT disorders as IBD. Patient with multi organ failure

Methods

Patients were divided into 2 groups: Group 1 has GIT symptoms only (abdominal pain, Anorexia, nausea, vomiting, diarrhea….). Group 2 has GIT and respiratory symptoms as difficulty of breathing, cough….) (Mild to moderate cases) guided with Egyptian protocol.

All studied patients subjected to the following:-

Full history taking: Which includes history of anorexia, nausea, vomiting, diarrhea, travelling outside, dealing with documented COVID-19 patients, Past history of chronic GIT or hepatic diseases

Clinical examination: Including vital data, general and local examination, head & neck, chest and extremities.

Laboratory investigations: Complete blood count (CBC). Coagulation profile (Prothrombin time (PT), International normalization Ratio (INR). Partial thromboplastin time (PTT). Liver function tests (LFTs) and they include: Serum bilirubin level {Total bilirubin (T. Bil.), Direct bilirubin (D. Bil.). ALT, AST. Alkaline phosphatase (ALP) level. Gamma glutamyl transpeptidase (GGT) level. Total protein. Albumin. Viral Markers {Hepatitis C Virus Antibody (HCV Ab), Hepatitis B surface Antigen. (HBsAg) and Human Immunodeficiency virus (HIV Ab) }. ESR. CRP. LDH. S. ferritin. D –Dimer

Imaging: CT chest were done for all patients

Statistical analysis

Data was collected, formulated and tabulated using appropriate tests.

3. Results

Table 1: Basic characteristics among the patients

Variables	Total n= 200	Group 1 GIT symptoms only n= 96	Group 2 GIT+ respiratory n= 104	p value
Age Mean± SD	42.5± 3.5	40± 1.2	46.2± 3.1	0.003*
Gender Male n (%) Female n (%)	106 (58) 84 (42)	64 (66.7) 32 (33.3)	52 (50) 52 (50)	0.017*

Student t test; Chi square test; *p is significant at <0.05

Table 2: Gastrointestinal symptoms among the participants

Variables	Total n= 200	Group 1 GIT symptoms only n= 96	Group 2 GIT+ respiratory n= 104	p value
Abdominal pain Yes No	44 (22) 156 (78)	24) 25.0) 72 (75.0)	20 (19.2) 84 (80.8)	0.325
Anorexia Yes No	70 (35) 130 (65)	45 (46.7) 51 (53.3)	25 (24.1) 79 (74.9)	<0.0001*
Nausea Yes No	82 (41) 118 (59)	60 (62.5) 36 (37.5)	22 (21.4) 82 (78.6)	<0.0001*
Vomiting Yes No	110 (55) 90 (45)	64 (66.6) 32 (33.3)	46 (44.2) 58 (55.7)	<0.0001*
Diarrhea Yes No	102 (51) 98 (49)	68 (70.8) 28 (29.2)	34 (32.7) 70 (67.3)	<0.0001*

Student t test; *p is significant at <0.05

Table 3: Laboratory findings among the participants

Variables	Total (n. =200) Mean± SD	Group 1 GIT symptoms only (n. =96) Mean± SD	Group 2 GIT+ respiratory (n. =104) Mean± SD	p value
Hb (g/dl) Male: 13.8 to 17.2 g/dl Female: 12.1 to 15.1 g/dL	11.4 ± 0.2	11.5± 0.3	11.2 ± 0.2	0.218
WBC (*10^9/L) 4.5 to 11.0 × 10^9/L	6.8± 1.2	6.5± 1.5	7.6± 0.7	<0.001*
Lymphocytes (*10^9/L) 1.00-4.80 x 10^9/L	0.9 ± 0.1	0.9 ± 0.1	0.8 ± 0.1	<0.001*
Neutrophils (*10^9/L) 1.70-7.00 x 109/L	4.6± 1.2	3.7± 1.4	5.3± 2.1	0.001*
Platelet (*10^9/L) 150-450 x 109/L	227± 7.8	247± 5.6	208± 8.2	<0.001*
D-Dimer (mg/L) (0-0.5 mg/L)	0.8±0.01	0.7±0.01	1.2 ±0.1	<0.001*

Student t test; *p is significant at <0.05

Table 4: Liver function tests among the participants

Variables	Group 1 GIT symptoms only (n. =96) Mean± SD	Group 2 GIT+ respiratory (n. =104) Mean± SD	p value
ALT (U/L) 10 to 40 IU/L	89.1± 10.3	106± 12.1	<0.001*
AST (U/L) 10 to 40 IU/L	105± 7.5	126± 16	<0.001*
GGT (IU/L) 0 to 30 IU/L	32.5± 6	36.2± 8.7	0.01*
ALP (IU/L) 44 to 147 IU/L	69.5± 13.1	73.4± 12.5	0.714
Albumin (g/dl) 3.5-5.5 g/dL	33.2± 4.3	34.9± 2.7	0.001*
Total bilirubin (mg/dl) 0.1 to 1.2 mg/dL	0.5±0.01	1.3±0.2	<0.0001*

Student t test; *p is significant at <0.05

Table 5: Relevant laboratory parameters among the participants

Variables	Group 1 GIT symptoms only (n. =96) Mean± SD	Group 2 GIT+ respiratory (n. =104) Mean± SD	p value
ESR (mm/hr) 1–13 mm/hr for male 1-20 mm/ hr for female	22± 1.5	27± 3.1	<0.0001*
CRP (mg/dl) below 3.0 mg/L	8.2± 0.2	11.6± 0.8	<0.0001*
LDH (IU/L) 105 – 333 IU/L	352.86±25.1	458±36	<0.0001*

Student t test; *p is significant at <0.05

Table 6: CT scan among the participants

Variables	Total n= 200	Group 1 GIT symptoms only n= 96	Group 2 GIT+ respiratory n= 104	p value
CT scan Positive n (%) Negative n (%)	 98 (49) 102 (51)	 6 (6.3) 90 (93.8)	 92 (88.5) 12 (11.5)	 <**0.001***

Fisher Exact test; *p is significant at <0.05

4. Discussion

Coronaviruses are enveloped viruses with positive-sense single-stranded RNA genomes, which infect both humans and animals. There are currently 7 known coronaviruses, which infect humans, including the Middle East Respiratory Syndrome (MERS) and severe acute respiratory syndrome (SARS). The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the most recently identified human coronavirus, which can cause the coronavirus disease 2019 (COVID-19). SARS-CoV-2 has been known to spread through respiratory droplets and possibly through fecal-oral route ([11]).

The main aim of this study was to explore the available evidences on liver and GI involvement in patients with COVID-19 infection and provide a comprehensive understanding of the phenomenon, and to anticipate effective follow-up.

This Prospective study was conducted on 200 hundreds of COVID-19 infected patients who had positive COVID-19 PCR outpatient clinic and admitted in Abu Hommos Central Hospital from January to the end of June 2021. Patients were divided into 2 groups: Group 1 has GIT symptoms only (abdominal pain, Anorexia, nausea, vomiting, diarrhea….) Group 2 has GIT and respiratory symptoms as difficulty of breathing, cough….) (Mild to moderate cases) guided with Egyptian protocol.

The main results of this study were as following:

In the study we found that the mean age was 45.1± 7.8 among the participants, it was 42.4± 8.3 among group with GIT symptoms only and it was 46.2± 3.1 among group with GIT and respiratory symptoms. There was no statistically significant difference between two groups regarding age. Regarding gender there were 58% males and 42% females among the participants. There were 66.7% males and 33.3% females among group with GIT symptoms only while there 50% males and 50% females among group with GIT and respiratory symptoms. There was no statistically significant difference between the two groups regarding gender.

However, in the study of **Lin et al., ([12])** they reported that a total of 95 patients (50 women and 45 men) were included in this study with an average age of 45.3±18.3 years. There was no statistically significant difference between groups with and without GIT symptoms regarding age and gender.

Studies of airplane transmission are commonly biased by contacts sharing exposure risks before boarding the aircraft ([13]). In the investigation of **Schwartz et al., ([14])** transmission may have been mitigated by mild symptoms and masking during the flight. However, the lack of secondary cases after prolonged air travel exposure supports droplet transmission, not airborne, as the likely route of spread of the COVID-19.

The leading hypothesis for the mechanism of transmission of SARS-CoV-2 is through aerosolized respiratory droplets. When an individual comes into contact with the pathogen, the virus binds to the angiotensin-converting enzyme 2 (ACE2) receptors in the lungs. The spike glycoprotein of SARS-CoV-2 attaches to the ACE2 receptor and enables efficient viral entry into the cells, leading to viral replication and spread throughout the body. The intestinal (principally absorptive enterocytes of the ileum and colon) and esophageal epithelium also highly express ACE2 receptors. Further, the glandular cells of both the stomach and duodenum are reported to express ACE2, so SARS-CoV-2 may be able to infect intestinal epithelial cells via ACE2 receptors. The ACE2 receptors in the GI tract maintain a regulatory role in amino acid homeostasis, gut microbiome, and innate immunity ([15]).

Consequently, the binding of SARS-CoV-2 to ACE2 receptors in the GI tract may result in GI symptoms such as abdominal pain and diarrhea.

In the study, there were 22% had abdominal pain, 35% had anorexia, 41% had nausea, 55% had vomiting and 51% had diarrhea among the participants. There was no statistically significant difference between the two groups regarding gastrointestinal symptoms.

In accordance with our results, study of **Lin et al., ([12])** they reported that diarrhea (2–10 loose or watery stools a day, 24.2%), anorexia (17.9%) and nausea (17.9%) were the most frequently observed manifestations.

Similarly, **Song et al., ([16])** revealed that in patients with COVID-19, diarrhea is also a common digestive symptom, with the incidence ranging from 1.3% to 29.3%. In addition, SARS-CoV-2–induced diarrhea could be the onset symptom in patient with COVID-19.

Nevertheless, the incidence of diarrhea varied widely among different reports, suggesting that the criteria for diagnosing diarrhea may differ in different hospitals. Clinicians might underestimate the value of digestive symptom in clinical practice, and it may affect the preliminary diagnostic accuracy ([17]).

In contrast to our study, another study of 1099 patients from China carried out by **Guan et al., (**[18] showed that the most common symptoms on admission were fever (43.8%) and cough (67.8%). Less common were gastrointestinal symptoms with 5% (55/1099) of patients presenting with nausea or vomiting and 3.8% (42/1099) of patients presenting with diarrhea. Similarly, in a single-center case series of 138 hospitalized patients with COVID-19 in China held by **Wang et al., (**[19], 10.1% (14/138) of patients had diarrhea and/or nausea, but the proportion of patients with only digestive symptoms was not outlined.
It is believed that the prevalence of GI symptoms is underestimated because the majority of studies included in the study of **Shehab et al., (**[20] reported GI symptoms only on the day of admission but not throughout the disease course. Furthermore, many earlier studies did not report on other GI symptoms except for diarrhea ([21]. Based on these findings, clinicians must be aware that digestive symptoms, such as diarrhea, may be a presenting feature of COVID-19 that can arise before respiratory symptoms and, on rare occasions, may be the only presenting manifestation of COVID-19 ([22].

In our study, there were some changes in laboratory investigations of total population of study in the form of slight anemia Hb level 11.4 g/dl, WBC was normal, lymphopenia 0.9 ± 0.1 10^9/L, D-dimer increased above normal around 0.8±0.01mg/l. There were abnormalities in LFTs as ALT and AST increased between 2-3 folds above normal limit, Albumin was slightly decreased 33.2± 4.3 g/dl but all other lab are normal including neutrophil, platelets, bilirubin, ALP. ESR and CRP elevated in total number of patient slightly elevated in group 2 more than 1. There was no statistically significant difference between the two groups regarding liver function tests.

While, **Lin et al., (**[12] revealed that 32.6% of the patients developed hepatic function impairment during hospitalization with elevated bilirubin, aspartate transaminase or alanine aminotransferase.

In the studies of **Zhang et al., (**[15], **Huang et al., (**[21], patients with severe forms of COVID-19 requiring ICU care exhibited a higher prevalence of ALT, AST, and total bilirubin elevations compared to patients with non-severe COVID-19 cases. In most cases of COVID-19, transient elevation of liver enzymes occurs and improves as the patient recovers ([23].

Furthermore, **Guan et al., (**[18] showed that elevated AST levels were observed in 18.2% of patients with non-severe disease and 39.4% of patients with severe disease, whereas elevated ALT levels were observed in 19.8% of patients with non-severe disease and 28.1% of patients with severe disease. **Wang et al., (**[19] also showed that patients admitted to ICU had significantly higher ALT (35 vs 23, p = 0.007) and AST (52 vs 29, p < 0.001) levels. These data suggest that liver injury is more prevalent in severe cases than in mild cases of COVID-19.

In the study of **Xiong et al., (**[24], the majority of the patients had a normal white blood cell count (26/37, 70%), neutrophil count (26/37, 70%), and lymphocyte count (19/37, 51%). Some patients had reduced white blood cell count (10/37, 27%), reduced lymphocyte count (18/37, 49%).

According to **Zheng et al., (**[25], the median lymphocyte count was significantly higher in the non-GI group (1.99 vs 1.76; P = .038). However, there were no significant intergroup differences in hematological parameters, including leukocyte, neutrophil, and platelet count, hemoglobin, and C-reactive protein (CRP).

In the study of **Xiong et al., (**[24], some patients had increased CRP (27/32, 84%), increased ESR (10/22, 46%), and increased LDH (15/26, 58%).

Our results showed that there was statistically significant difference between two groups regarding CT scan as group who had GIT symptoms and respiratory symptoms was higher positive in CT scan than group with GIT symptoms only.

Our results were supported by study of **Zheng et al., (**[25], as they reported that of the total patients, the vast majority (66.1%) showed typical ground-glass opacities on chest CT. Bilateral lesions on chest CT were found in 884 patients and were more common in the GI group (78.1% vs 65.1%; P < .001).

5. Conclusion

Digestive symptoms are common in patients with COVID-19, and in some cases digestive symptoms may occur in the absence of any respiratory symptoms. COVID-19 patients with digestive symptoms have worse clinical outcomes. Attention should also be paid to monitor liver function during the course of COVID-19, especially in patients with higher disease severity.

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