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## Impact of COVID-19 on the digestive system: A descriptive cross-sectional study

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### ABSTRACT

**Background:** Various digestive symptoms caused by COVID-19 are frequently reported. This study aims to describe the most frequent digestive signs in patients with COVID-19, the relationship between the severity of digestive symptoms and some serological markers associated with liver manifestation, the detection of SARS-CoV-2 in a stool sample, and the mortality rate of those patients.

**Materials and Methods:** A descriptive cross-sectional study on 100 confirmed COVID-19 cases with digestive and hepatic manifestation in one center (Fallujah Teaching Hospital), Anbar governorate, Iraq, during a period of study. Questioner's data were formed for all patients regarding age, sex, and comorbidities such as diabetes and hypertension. Liver function enzymes such as alanine aminotransferase (ALT), aspartate aminotransferase, alkaline phosphatase, total bilirubin (TBIL), and direct bilirubin and haematological parameters such as ferritin D-dimer, C-reactive protein (CRP), albumin, amylase, leukocyte count, and prothrombin time were used. SARS-CoV-2 prevalence in stool is determined using reverse transcription polymerase chain reaction according to manufacturer's instructions. The mortality rate of patients with COVID-19 was also determined. Data were followed up until April 22, 2022.

**Results:** Patients with digestive symptoms who had COVID-19 had an average age of 45.03 (SD 20.078), 52 (52%) were men, and 48 (48%) were women. No statistically significant variances were observed in the severity of digestive symptoms among age groups. The three digestive symptoms that patients with COVID-19 experienced most frequently were fatigue, fever, and abdominal colic. SARS-CoV-2 was detected in the stool of 11% of the patients with COVID-19 with digestive signs. The COVID-19 mortality rate was 9%. Statistically, significant variance was observed in ALT ( $P$  value 0.01) and TBIL ( $P$  value 0.0027) levels between mild, moderate, and severe gastrointestinal (GI) diseases. The levels of CRP varied considerably among those with mild, moderate, and severe GI conditions ( $P$  value 0.0182, according to the findings). In mild, moderate, and severe GI disorders, ferritin levels differed considerably ( $P$  value 0.05).

**Conclusions:** The faecal sample with a nasopharyngeal swab is needed to confirm COVID-19 diagnosis; hepatic manifestations are connected with increased COVID-19 mortality in individuals with digestive symptoms.

**Keywords:** COVID-19, digestive symptoms, haematological parameters, SARS-CoV-2, stool, Anbar governorate, Iraq

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## INTRODUCTION

SARS-CoV-2, which refers to severe acute respiratory syndrome corona virus, is the cause of coronavirus disease-19 (COVID-19). Although a wide range of treatment modalities are being used and effective vaccines are available, the disease still affecting has already killed millions of people globally since it first emerged in China<sup>1,2</sup>. The respiratory symptoms of COVID-19, such as coughing and shortness of breath, were most often seen<sup>3</sup>. However, it can also manifest with non-respiratory symptoms, including gastrointestinal (GI) symptoms like diarrhoea, nausea, and lack of appetite<sup>4</sup>.

A meta-analysis consists of sexton trials, which includes 4243 patients with COVID-19. Of those, 17.6% reported digestive signs including diarrhoea (12.5%), anorexia (26.8%), nausea with vomiting (10.2%), and abdominal pain (9.2%)<sup>3</sup>.

Notably, there were only a few sporadic SARS-CoV-2 infections that occurred through faeces, indicating that contagious virions were likely released into the GI system and suggesting the faecal-oral transmission as an alternative method of viral transmission<sup>5</sup>. According to one investigation, long after the virus had disappeared from the respiratory system, SARS-CoV-2 continued to be present in faeces of 40.5% patients<sup>4</sup>.

Patients with COVID-19 frequently experience abnormal hepatic function due to “hepatocellular” and “cholangiocellular” damage, having a total frequency of 24.4% throughout the illness; this affected up to 76.3% of hospitalized patients<sup>6</sup>. A recent meta-analysis study established that decreased levels of albumin and aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (GGT), total bilirubin, and lactate dehydrogenase elevated levels are common indicators of abnormalities<sup>7</sup>.

## PATIENTS AND STUDY DESIGN

A descriptive cross-sectional research included hospitalized individuals in one specific centre (Emergency Department in Fallujah Teaching Hospital), Anbar governorate, Iraq, and it was conducted between September 15, 2021, and April 22, 2022. According to the interim WHO recommendations, a positive case of COVID-19 was determined based on positive results for SARS-CoV-2 utilizing the reverse transcription polymerase chain reaction (RT-PCR) technique using nasopharyngeal swab. According to the WHO ordinary criteria, at least two specialized medical consultants confirmed digestive and hepatic manifestations during COVID-19 infection.

## EXCLUSION CRITERIA

All the patients who were COVID-19-positive who did not develop digestive or hepatic manifestation (with only respiratory symptoms), patients under 15 years old, and patients with concomitant digestive or hepatic manifestations before COVID-19 infection were excluded from the study.

The current investigation included all COVID-19 confirmed cases (confirmed positive by nasopharyngeal swab PCR) with GI hepatic manifestation infections and was from either sex or age (15–96). The severity of COVID-19 digestive signs was classified into mild, moderate, and severe. Family consent was obtained for every patient, and the research was approved by the Scientific Committee of the College of Medicine, University of Anbar.

This study aims to describe the most frequent digestive symptoms, the relationship between the severity of digestive symptoms and means of liver function enzymes (ALT, AST, ALP, TBIL and DBIL), and haematological parameters as ferritin D-dimer, C-reactive protein (CRP), albumin, amylase, leukocyte count, prothrombin time (PT), SARS-CoV-2 detection in the stool sample, and mortality rate of patients with COVID-19.

Questioner’s data were formed for all patients regarding age, sex, and comorbidities such as diabetes and hypertension. Patients’ serological markers, including ALT, AST, ALP, TBIL, DBIL, ferritin D-dimer, CRP, albumin, amylase, leukocyte count, and PT, were detected based on the manufacturer’s instructions. SARS-CoV-2 RNA detection in COVID-19 stool samples by RT-PCR was done according to the manufacturer’s instructions using specific primers.

## STATISTIC EVALUATION

Version 26 of IBM SPSS software was used to evaluate the data. The results, frequencies, and percentages are shown in tables. Cross-tabulations were performed to compare the variables using the  $\chi^2$  test, and statistically significant variance was defined as one with a *P* value less than 0.05. Data were analyzed using a graph pad prism through frequency, descriptive statistics,  $\chi^2$  test, independent sample t-test, one-way ANOVA, and two-way ANOVA to show mean, standard deviation, and *P* value. One-way ANOVA and box plot compare the severity of digestive and hepatic

manifestation with different quantitative data regarding liver function enzymes and haematological and serological parameters associated with COVID-19 infection.

**RESULTS**

**Severity of Digestive Symptoms According to Age Group**

The mean age of patients with COVID-19 with digestive manifestation was 45.03 ± SD 20.078. Of them, 52 (52%) were men, and 48 (48%) were women. Out of 64 patients with COVID-19 with mild GI infections, roughly half (31 patients) were in the age range of 18–40 years, followed by 16 in the 41–60-year range. Similarly, of 22 patients with moderate infections, roughly half (10 patients) were in the 18–40-year range, and of the 14 severely infected patients, half (7 patients) were in the 18–40-year range. There is no statistically significant difference in the severity of GI symptoms between age groups, as shown in Figure 1.

**Clinical Symptoms of COVID-19**

Clinical GI symptoms of patients with COVID-19 are summarized in Figure 2.

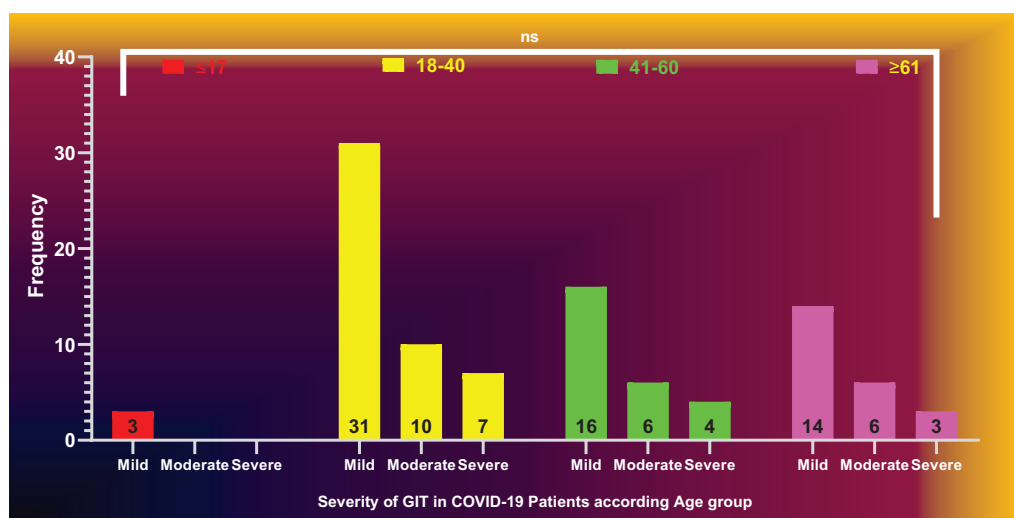


Figure 1. Severity of digestive symptoms according to the age group.

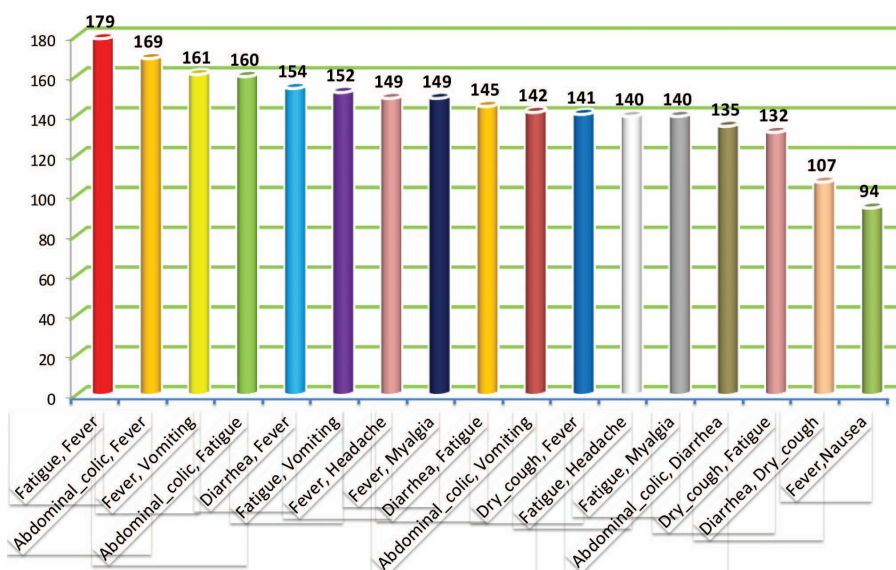


Figure 2. Two of the most typical digestive signs in patients with COVID-19.

### Positivity of SARS-CoV-2 using RT-PCR of Patients with Gastrointestinal Tract (GIT) in Stools

Out of the 64 patients with COVID-19 with mild GI, 58 patients had negative RT-PCR results and 6 patients had positive RT-PCR results, and out of the 22 patients with moderate GI, 3 patients had positive RT-PCR data. Two of the 14 seriously afflicted individuals had positive RT-PCR findings; 11 of the 100 patients who underwent the test had positive results. According to the degree of digestive signs. There was no statistically significant difference between negative and positive RT-PCR results for patients with COVID-19, as shown in Figure 3.

### Patients with COVID-19 Mortality Depending on GI Manifestation Severity

None of the 64 patients with COVID-19 who had mild GI symptoms died, but 3 of the 22 patients who had significant GI symptoms also perished. Six of the 14 severely afflicted patients died, making the total number of patients who died 9. Depending on the degree of GI illness, there was no statistically significant difference between cured and deceased patients with COVID-19, as shown in Figure 4.

### ALT, AST, ALP, GGT, TBIL, and DBIL Means According to the Severity of GIT Infection in Patients with COVID-19

According to the findings, there was statistically significant variance in ALT levels in mild, moderate, and severe GI illnesses ( $P$  value 0.01), but not in the levels of AST in mild and moderate GI infections. ALP levels did, however, differ statistically significantly ( $P$  value 0.01) across mild, moderate, and severe GI illnesses. Furthermore, the levels of GGT differed to a statistically significant extent in COVID-19 patients with mild, moderate, and severe GI illnesses ( $P$  value 0.01), as shown in Figure 5.

The findings demonstrated that the levels of TBIL in patients with mild, moderate, and severe GI illnesses differed statistically significantly ( $P$  value 0.0027). In addition, statistically significant variance in DBIL levels was observed in patients with COVID-19 with mild, moderate, and severe GI illnesses ( $P$  value 0.02), as shown in Figure 5.

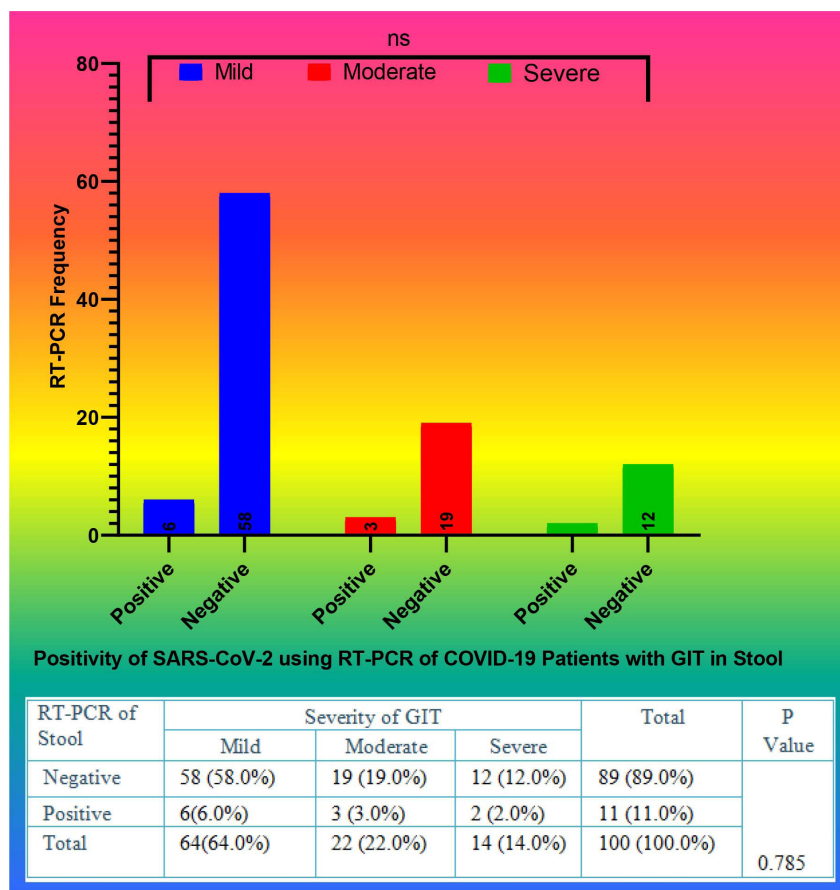


Figure 3. SARS-CoV-2 positivity detected by RT-PCR in stools of patients with COVID-19.

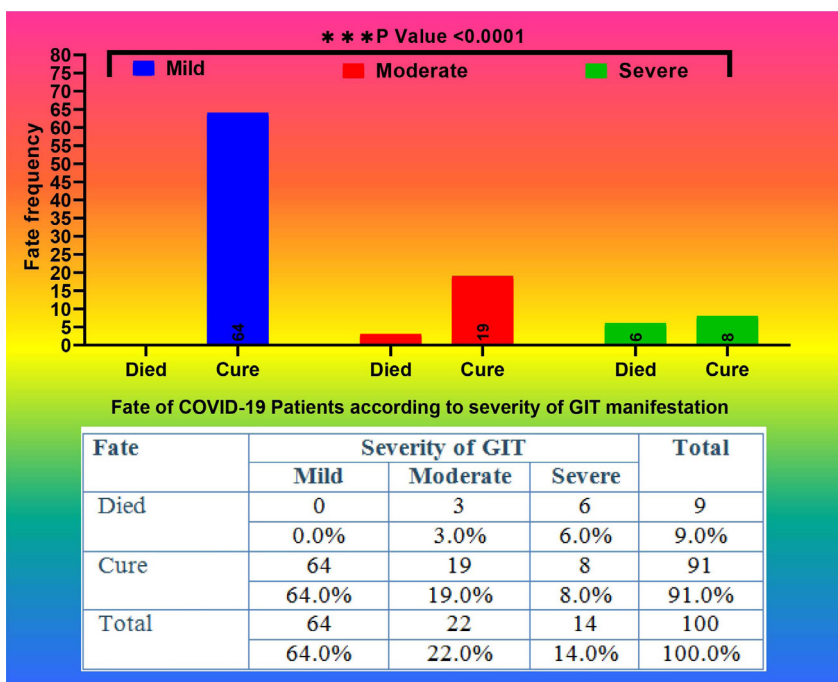


Figure 4. Mortality of patients with COVID-19 depending on GI manifestation severity.

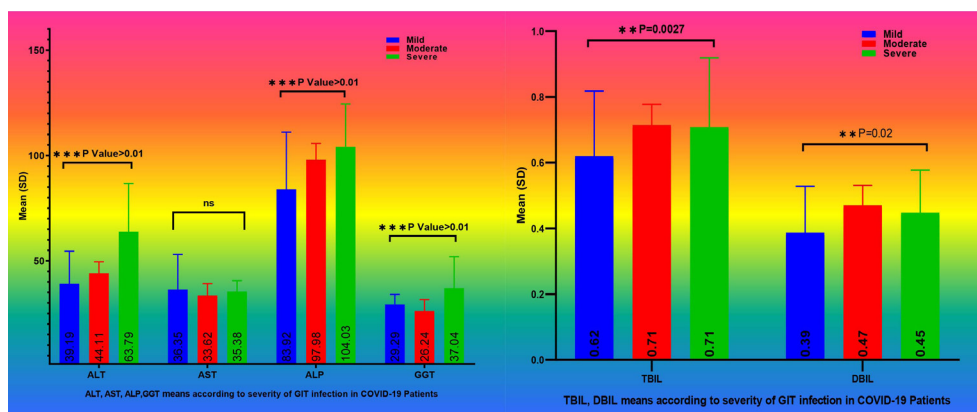


Figure 5. ALT, AST, ALP, GGT, TBIL and DBIL means depending on GI manifestation severity of patients with COVID-19.

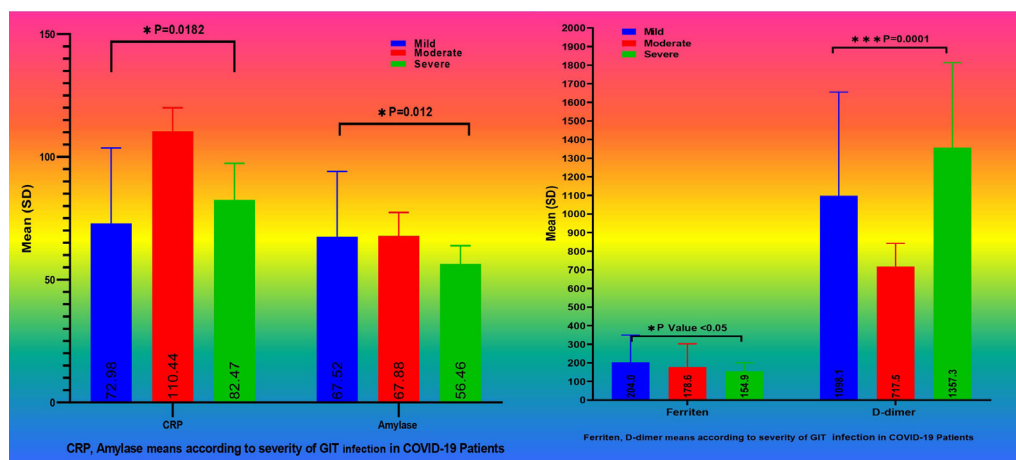


Figure 6. CRP, amylase, ferritin, and D-dimer means according to the severity of GIT infection in patients with COVID-19.

### **CRP and Amylase, Ferritin, and D-dimer Means depending on GI Manifestation Severity of Patients with COVID-19**

The levels of CRP were significantly different ( $P$  value 0.0182) according to the findings in patients with mild, moderate, and severe GI illnesses. In addition, statistically significant variance was observed in the amylase levels of patients with COVID-19 with mild, moderate, and severe GI illnesses ( $P$  value 0.012), as shown in Figure 6.

The findings demonstrated that ferritin levels differed significantly in patients with mild, moderate, and severe GI illnesses ( $P$  value 0.05). In addition, a statistically significant difference in D-dimer levels was observed in patients with COVID-19 with mild, moderate, and severe digestive signs ( $P$  value 0.0001), as shown in Figure 6.

## **DISCUSSION**

### **Severity of Digestive Symptoms in Patients with COVID-19 according to Age Group**

No statistical significance was observed in the severity of digestive symptoms between various age groups in the current study. This result contradicts the data that showed that GI symptoms and progressive age were associated with the severity of GI signs without defining whether participants had digestive problems; another study linked increasing age with sickness severity<sup>8</sup>.

The age group (18–40) with the most significant percentage of COVID-19 infections during the current investigation may be the explanation because the sample was gathered over a short time and most patients fell within this age range. It might be because most people in this age group work in occupations that expose them to more sick people and the outside world, while also putting them in closer contact with those individuals.

This investigation's findings contradict those of another study that found that Italian patients over the age of 70 had the highest prevalence of COVID-19 infections<sup>9</sup>.

### **Clinical Symptoms of COVID-19**

The current study's findings on the digestive symptoms of patients with COVID-19 were in line with research that discovered a connection between tiredness, myalgia, dyspnoea, sore throat, anosmia, ageusia, temperature over 38.5°C, exhaustion, dyspnoea, and headache with digestive symptoms<sup>10</sup>.

The results of the current study on the GI symptoms of COVID-19 were in agreement with those of other studies, including those by Borges do Nascimento et al.,<sup>11</sup> who stated that 9% of patients in a meta-analysis of 59,254 individuals from 11 countries had GI problems, and Parasa et al.<sup>4</sup> According to a review of 23 published studies and 6 preprints, out of 4805 individuals, 7.4% of patients with COVID-19 experienced diarrhoea and 4.6% of them had nausea or vomiting. According to our findings, anorexia and diarrhoea were the most frequent digestive symptoms reported by hospitalized patients with COVID-19, which is consistent with other research<sup>12</sup>.

Some of the previous studies found that most hospitalized patients had respiratory symptoms, and other studies reported that out of 103 hospitalized patients with COVID-19, 50.5% of them reported having digestive symptoms, such as abdominal pain in 2 (1.9%) patients, loss of appetite in 81 (78.6%), diarrhoea in 35 (34%) and vomiting in 4 (3.9%) cases<sup>12</sup>.

### **SARS-CoV-2 Positivity in Stools of Patients with COVID-19 with Digestive Signs using the RT-PCR Technique**

Our study found that the prevalence of the virus' RNA in faeces was 11.0%; it was contrast to a previous meta-analysis study that included 4,243 patients, which reported 48.1% prevalence. This disparity might result from using different primers in each study, variances in the SARS-CoV-2 virus, or SARS-CoV-2 circulating in each region.

According to previous studies, 70.3% of these samples tested positive for viral RNA in the faeces, which may persist for up to 33 days after the onset of symptoms even after the respiratory system produced a negative result<sup>13</sup>.

Due to the fact that there was no obvious variance among two groups in current research ( $P$  value 0.31), it was concluded that the existence of SARS-CoV-2 RNA in faeces does not always predict severity of GI signs<sup>13</sup>.

In contrast to the current study, 53.42% of stool samples from 73 hospitalized patients in the prior study were SARS-CoV-2-positive<sup>14</sup>; it suggests the likelihood of GI SARS-CoV-2 infection and faecal–oral transmission.

The results of the present study were consistent with those of a previous cohort study, which demonstrated that in a group of 59 patients with the illness, viral RNA was found in the faeces of 9 (15.3%) patients and the stool of 38.5% of those patients and 8.7% of the patients who had diarrhoea ( $P = 0.019$ ).

In one study, while the respiratory tract was negative for the virus, 23.29% of the faeces samples remained positive<sup>14</sup>. In another study, 48.1% of the faeces samples that were positive for the virus continued to be positive even after clearing their respiratory system<sup>15</sup>.

The current study was different from earlier studies, such as that by Chen et al.<sup>16</sup> Researchers found that despite pharyngeal swabs being negative for the illness, 18 (64.29%) of the 42 patients with COVID-19 had viral RNA in their faeces for roughly 7 days, and Zhou et al.,<sup>10</sup> who discovered that faecal SARS-CoV-2 RNA was isolated in 47% of patients with COVID-19.

Studies could not, however, distinguish whether the RNA in faeces is a virus that can infect or is simply a viral remnant that cannot. These results make us doubt the need for routine PCR testing of faeces of patients with COVID-19. Further study should be conducted to investigate this matter since possible faecal–oral transmission may significantly affect underdeveloped countries with poor sanitation.

### **Fate or Mortality Rate of Patients with COVID-19 According to the GI Manifestation Severity**

The mortality rate for patients with COVID-19 with digestive symptoms was 9% in the current study, while previous results from Anbar showed a higher mortality of hospitalized patients with high disease severity (63.4%)<sup>17</sup>. However, this result was consistent with a fascinating meta-analysis research conducted in Canada, which included 3,615 adult patients with COVID-19 and discovered that acute liver damage was connected to high mortality rate (relative risk = 4.02 [1.51, 10.68],  $P = 0.005$ )<sup>18</sup>.

The elevated levels of cytokine biomarkers in the blood of patients with COVID-19 may be due to an inflammatory storm brought on by an infection, hepatic ischemia, dysfunctional reperfusion, or medication toxicity. This mortality rate may also be related to digestive symptoms linked to liver abnormalities<sup>19</sup>.

### **Severity of Digestive Symptoms and Some Serological Markers Associated with the Liver Manifestation**

The results of the current study are inconsistent with those of other studies on the severity of patients with COVID-19 with or without GI symptoms, which reported a low mortality rate<sup>20</sup>. Patients with GI symptoms had significant levels of CRP, ALT, AST, and bilirubin than those who did not have GI symptoms, which is in line with prior research.

A comprehensive evaluation of 128 papers found that severe illness was associated with higher rates of hypo-albuminemia, aberrant GGT, and AST<sup>21</sup>.

Notably, multiple studies indicate that patients with COVID-19 with transaminases were more likely to experience severe illness and an increase in mortality, and the current study's findings supported these findings<sup>22</sup>.

As was already established, liver damage may occur as a side effect of SARS-CoV-2 infection, which might lead to hepatic manifestation and multi-organ failure<sup>23</sup>.

Patients with COVID-19 are likely affected by a variety of factors, including the virus directly, immune system damage due to significant systemic inflammatory response, ischemic injury from hypoxia or hypo perfusion due to comorbidities associated with COVID-19, and iatrogenic reasons such as drug-induced mechanical ventilation<sup>23</sup>.

The results regarding the distribution of COVID-19 were described in previous studies in the same area<sup>24–27</sup>.

We concluded that a faecal sample with a nasopharyngeal swab is needed to confirm COVID-19 diagnosis. The severity of digestive symptoms in patients with COVID-19 is associated with increased liver function, enzymes, and other haematological parameters.

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