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Hepatic and gastrointestinal manifestations in patients with COVID-19 and relationship with disease severity: a single-centre experience

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ABSTRACT

Background and aims: Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), emerged in late 2019. While the infection is commonly perceived as a respiratory disease, gastrointestinal complaints have been described in a significant number of patients since the beginning of the pandemic. This study investigated the prevalence of hepatic and gastrointestinal manifestations among patients with COVID-19 in terms of symptoms and biochemical findings, and the relationship with disease severity and outcomes.

Methods: Patients admitted to a tertiary medical centre in Dubai, United Arab Emirates, between March and June 2020, with COVID-19 were analysed retrospectively. Patients were stratified into two main groups based on the presence or absence of hepatic and gastrointestinal manifestations.

Results: Among 521 eligible patients, 119 patients (22.8%) had gastrointestinal manifestations, and the majority of patients were middle-aged males (90%). The most common symptom was diarrhoea, followed by vomiting and abdominal pain. The most commonly observed biochemical abnormality was raised alanine transferase. No differences in the severity of COVID-19 pneumonia or overall mortality rate were found between the two groups. However, patients with COVID-19 pneumonia, even those without hepatic or gastrointestinal manifestations, had longer hospital stays ($P < 0.05$) and other infection-related complications.

Conclusion: This paper adds to the literature on the extrapulmonary manifestations of SARS-CoV-2 with a focus on the hepatic and gastrointestinal systems. The presence of hepatic and gastrointestinal manifestations in patients with COVID-19 at hospital admission was not associated with increased severity of COVID-19 pneumonia or overall mortality.

Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), emerged in late 2019, and spread globally, resulting in millions of deaths (Wong et al., 2020). While the infection is commonly perceived as a respiratory disease with typical presentation consisting of fever, cough and shortness of breath, recent studies have explored its effects on other systems, such as the gastrointestinal, cardiovascular, neurological, endocrine, immunological and dermatological systems.

Gastrointestinal symptoms are of particular significance in patients with COVID-19 because, in contrast to other coronaviruses, they appear

early and may worsen during the course of disease. In some patients, gastrointestinal symptoms could be the only manifestation of SARS-CoV-2 infection. In patients presenting solely with gastrointestinal symptoms, there is usually a delay in diagnosis and time to first respiratory symptoms, which renders these patients as sources of viral dissemination.

In a meta-analysis by Cheung et al. (2020), gastrointestinal symptoms such as anorexia, diarrhoea, nausea, vomiting and abdominal pain were described in 12% of patients with non-severe COVID-19, and this increased to 17% in patients with severe COVID-19. Interestingly, Han et al. (2020) showed that gastrointestinal symptoms may be the only manifestation in patients with COVID-19, not necessarily concomitant with any respiratory symptoms, and may be associated with longer

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hospital stay. The mechanism of gastrointestinal involvement has been attributed to the widespread expression of angiotensin-converting enzyme II (ACE2) receptors throughout the gastrointestinal tract, which facilitates viral entry to the cells (Cheung et al., 2020).

This study investigated the prevalence of hepatic and gastrointestinal manifestations in terms of symptoms and biochemical findings, and the relationship with severity of disease and outcomes among patients admitted to the study hospital over a 4-month study period.

Methods

Study design and participants

This analytical cross-sectional study included 521 patients with COVID-19 who were admitted to Rashid Hospital, Dubai between March and June 2020. Demographic data, clinical presentation and laboratory data were extracted from the hospital electronic medical records (EPIC system) after obtaining ethical approval from Dubai Health Authority Ethical Review Board. All patients aged >18 years admitted with COVID-19 [confirmed by reverse transcription polymerase chain reaction (RT-PCR)] between March and June 2020 were included in this study. Pregnant women, and patients known to have inflammatory bowel disease or chronic liver disease were excluded from the study. Patients were divided into two groups based on the presence or absence of gastrointestinal symptoms upon initial assessment and hospital admission.

Statistical analyses

Statistical analysis was performed using SPSS Version 26 (SPSS Inc., Armonk, NY, USA). Descriptive summary statistics have been presented as mean and standard deviation (SD) for continuous variables, and frequency and percentage for categorical variables. Categorical and continuous variables were tested for statistical significance using Chi-squared test and Student’s *t*-test, respectively. If the continuous variable was not

normally distributed, a non-parametric test, such as the Mann–Whitney *U*-test, was used to compare the groups.

On univariate analyses, Student’s *t*-test and Fisher’s exact test were used for continuous variables and categorical variables, respectively. Multi-variate analyses were performed using logistic regression, with covariates chosen a priori based on clinical judgement. Two-tailed *P*-values ≤0.05 were considered to indicate statistical significance.

Results

Demographic and epidemiological characteristics

In total, 521 patients hospitalized with confirmed COVID-19 during the study period met the inclusion criteria and were included in the data analysis. There were 469 (90%) males and 52 (10%) females. Ages ranged from 20 to 85 years [mean 45.35 (SD 11.21) years], and the 25th, 50th and 75th percentiles were 37, 45 and 53 years, respectively.

One hundred and nineteen (22.8%) patients had gastrointestinal symptoms (cases), and 402 (77.2%) patients did not have gastrointestinal symptoms (controls) upon initial assessment at hospital admission. Of note, isolated respiratory symptoms were documented in the majority of patients [*n*=387 (74.3%)], a minority of patients had isolated gastrointestinal symptoms [*n*=9 (1.7%)], and the rest had both respiratory and gastrointestinal symptoms [*n*=110 (21.1%)]. Fifteen patients were asymptomatic, and underwent COVID-19 RT-PCR at hospital admission for other reasons (Figure 1).

The predominant diagnosis on hospital admission was COVID-19 pneumonia [*n*=465 (89.3%)], followed by upper respiratory tract infection [*n*=43 (8.3%)], and surgical diagnoses such as pancreatitis and appendicitis [*n*=6, 1.2%]. Other diagnoses requiring hospital admission occurred less frequently [*n*=13 (2.5%)] (Table 1).

The most common comorbidities associated with admitted patients in order of frequency were: diabetes mellitus [*n*=200 (38.4%)]; hypertension [*n*=126 (24.2%)]; ischaemic heart disease [*n*=24 (4.6%)]; and

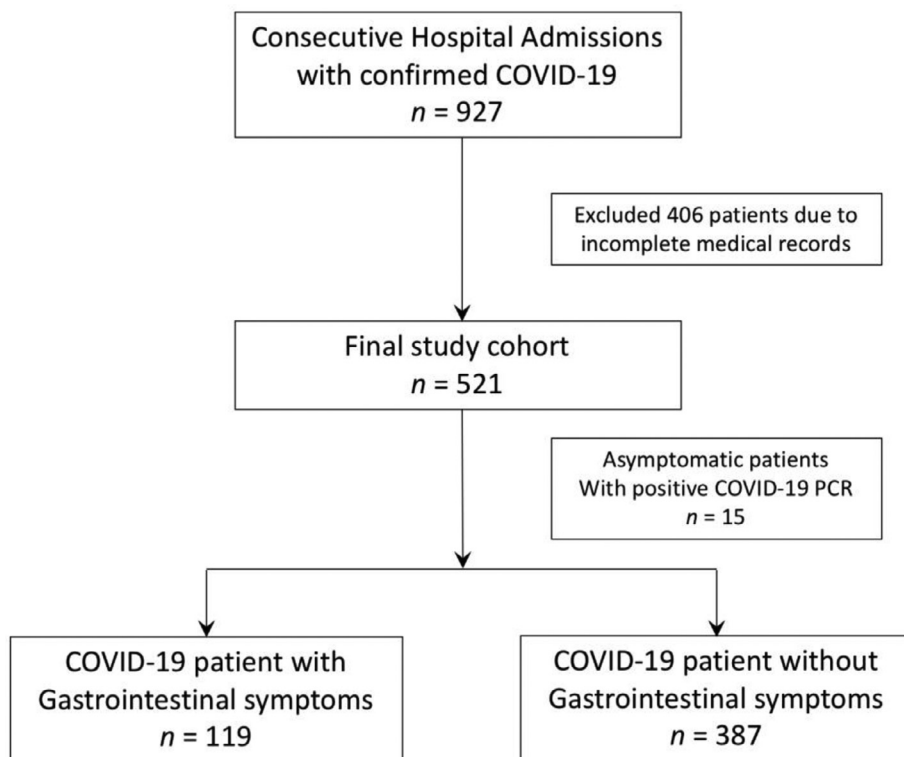


Figure 1. Study flowchart.

Table 1
Baseline demographics of the study population

Variable	Patients without gastrointestinal symptoms (n=402)	Patients with gastrointestinal symptoms (n=119)	P-value
Gender: n (%)			
Male 469 (90%)	364 (90.5%)	105 (88.2%)	
Female 52 (10%)	38 (9.5%)	14 (11.8%)	
Age, mean (SD) 45.35 ± 11.21	45.8 ± 11.1	43.7 ± 11.4	
Comorbidities, n (%)			
Diabetes mellitus	153 (38.1%)	47 (39.5%)	0.830
Hypertension	99 (24.6%)	27 (22.7%)	0.716
Ischaemic heart disease	16 (4%)	8 (6.7%)	0.217
Heart failure	2 (0.5%)	1 (0.8%)	1.000
Arrhythmias	16 (4%)	8 (6.7%)	0.217
Chronic kidney disease	1 (0.2%)	1 (0.8%)	0.942
Asthma	7 (1.7%)	3 (2.5%)	0.870
Dyslipidaemia	11 (2.7%)	4 (3.4%)	0.963
Thyroid disease	8 (2%)	1 (0.8%)	0.656
Stroke	3 (0.7%)	1 (0.8%)	1.000
Other comorbidities	21 (5.2%)	9 (7.6%)	0.370
Admission diagnosis			
COVID-19 pneumonia	359 (89.3%)	106 (89.1%)	1.000
Upper respiratory tract infection	32 (8%)	11 (9.2%)	0.704
Other	11 (2.7%)	2 (1.7%)	0.742
Gastrointestinal symptoms			
Diarrhoea	0 (0)	57 (47.9%)	
Vomiting	0 (0)	48 (40.3%)	
Abdominal pain	0 (0)	33 (33.0%)	
Anorexia	0 (0)	30 (24.4%)	
Nausea	0 (0)	25 (21.0%)	
Other symptoms			
Respiratory	366 (91%)	100 (84%)	0.040 ^a
Fever	365 (90.8%)	105 (88.2%)	0.386

SD, standard deviation; COVID-19, coronavirus disease 2019.

^a Statistical significance ($P < 0.05$).**Table 2**
Presenting symptom on admission among the study population

First symptom	n (%)
Asymptomatic	15 (2.9%)
Respiratory	41 (7.8%)
Gastrointestinal	10 (1.9%)
Fever	37 (7.1%)
Respiratory + gastrointestinal	29 (5.6%)
Respiratory + fever	337 (64.7%)
Gastrointestinal + fever	12 (2.3%)
Combined + fever	40 (7.7%)

bronchial asthma [$n=10$ (1.9%)] (Table 1). Comorbidities were evenly distributed between the two groups ($P > 0.05$) (Table 1).

Clinical, laboratory and radiographic characteristics

Of the 521 patients, 119 (22.8%) had gastrointestinal manifestations. The most common symptom was diarrhoea [$n=57$ (10.9%)], followed by vomiting [$n=48$ (9.2%)], abdominal pain [$n=33$ (6.3%)], anorexia [$n=30$ (5.8%)] and nausea [$n=25$ (4.8%)] (Table 1). The duration of gastrointestinal symptoms ranged from 1 to 14 days [mean 4.27 (SD 2.68) days], with a median of 4 days, predominantly during the first week of illness.

The first presenting symptoms among the study patients were fever and respiratory complaints [$n=337$ (64.7%)]. Isolated gastrointestinal symptoms presented first in only 1.9% ($n=10$) of patients (Table 2).

Regarding biochemical abnormalities, almost half of the patients (248/521 46.6%) had a mild increase in serum alanine transferase (ALT), and two patients had a moderate increase in ALT level. Forty-two (8.1%) patients had elevated serum bilirubin, and 36 patients (6.9%) had elevated alkaline phosphatase. There was no significant association

between disturbed liver function and overall mortality, intensive care unit (ICU) admission or rate of viral clearance (Tables 4 and 5).

In terms of the severity of pneumonia based on chest x-ray, patients without gastrointestinal symptoms had mild-to-moderate pneumonia [$n=288$ (71.6%)], and a smaller percentage had severe pneumonia [$n=69$ (17.2%)]. A similar pattern was observed in patients with gastrointestinal symptoms with mild-to-moderate [$n=91$ (76.5%)] and severe [$n=16$ (13.4%)] pneumonia.

Among the tested prognostic markers of COVID-19 severity upon hospital admission, procalcitonin and C-reactive protein (CRP) were found to be significantly associated with gastrointestinal symptoms ($P < 0.05$) (Table 3).

Other analysed variables, including ferritin, lactate dehydrogenase, absolute lymphocyte count and d-dimer, were similar between the two study groups, with $P > 0.05$ for all tested variables.

Hospital stay, ICU admission and outcomes

The majority of patients were hospitalized for <3 weeks [$n=452$ (86.8%)], although 69 (13.2%) patients had a longer hospital stay for the management of severe COVID-19 or related complications. The 25th, 50th and 75th percentiles for hospital stay were 4, 10 and 16 days, respectively. Length of stay was significantly associated with the presence of pneumonia on chest x-ray and isolated respiratory symptoms ($P < 0.05$), but was not associated with abnormal liver function tests, or combined gastrointestinal and respiratory symptoms ($P > 0.05$).

The prevalence of ICU admission among all patients was 16.7% ($n=87$). Most patients admitted to ICU were aged between 45 and 65 years [$n=56$ (64.4%)], and seven (8.0%) patients were aged >65 years [$n=7$ (8.0%)]. Among the patients admitted to ICU with severe COVID-19 pneumonia, 24 (27.6%) were aged <45 years. The mortality rate reached 60% ($n=52$) in cases with severe COVID-19 admitted to ICU over the study period, which matched other regional and global reports over the same period. In addition, mortality rates corresponded to the

Table 3
Laboratory data and outcomes of both cohorts.

Variable	Patients without gastrointestinal symptoms (n=402)	Patients with gastrointestinal symptoms (n=119)	P-value
Elevated liver enzymes at admission			
ALT (>41 U/L)	190 (47.4%)	58 (49.2%)	0.754
Bilirubin (>1 mg/dL)	35 (8.7%)	7 (5.9%)	0.443
ALP (>129 U/L)	31 (7.7%)	5 (4.2%)	0.221
Prognostic markers of severity at admission			
Ferritin (>300 ng/mL)	293 (72.9%)	85 (71.4%)	0.815
LDH (>222 U/L)	308 (76.6%)	94 (79%)	0.621
Lymphopenia (<1*10 ³ /μL)	158 (39.3%)	46 (38.7%)	0.915
D-dimer (0.5 μg/ml)	257 (63.9%)	79 (66.4%)	0.664
Procalcitonin (> 0.05 mg/L)	343 (85.3%)	114 (95.8%)	0.001
CRP (>5 mg/L)	355 (88.3%)	115 (96.6%)	0.005
Severity of pneumonia on CXR			
Normal	45 (11.2%)	12 (10.1%)	0.555
Mild to moderate	288 (71.6%)	91 (76.5%)	
Severe	69 (17.2%)	16 (13.4%)	
Hospital stay			
ICU admission	66 (16.4%)	21 (17.6%)	0.780
CRRT	11 (2.7%)	4 (3.4%)	0.963
Overall mortality	38 (9.5%)	14 (11.8%)	0.487

ALT, alanine aminotransferase; ALP, alkaline phosphatase; LDH, lactate dehydrogenase; CRP, C-reactive protein; CRRT, continuous renal replacement therapy.

All laboratory values are represented as n (%).

Table 4
Bivariate analysis of intensive care unit (ICU) admission and liver function tests.

Liver function tests	ICU admission n (%)	χ^2	P-value ^a
Bilirubin	Normal 82 (17.1%)	0.755	0.385
	Abnormal 5 (11.9%)		
Alkaline phosphatase	Normal 78 (16.1%)	1.916	0.166
	Abnormal 9 (25%)		
ALT	Normal 39 (14.4%)	2.696	
	Mild 48 (19.4%)		
	Moderate 0 (0.0%)		

ALT, alanine aminotransferase.

^a Statistical significance ($P < 0.05$).

age distribution of ICU cases, with 35 deaths (67.3%) in patients aged 45–65 years, 13 deaths (25.5%) in patients aged <45 years, and four deaths (7.7%) in patients aged >65 years. As observed in other studies, age alone contributed to higher rates of ICU admission and subsequent

mortality ($P < 0.05$). Patients aged >65 years were at seven-fold higher risk of ICU admission and six-fold higher risk of mortality.

There was no significant association between the presence of gastrointestinal manifestations and ICU admission among the study patients, with a similar distribution found between the two groups (17.6% in patients with gastrointestinal manifestations and 16.4% in patients without gastrointestinal manifestations).

The presence of other medical comorbidities, mainly diabetes mellitus and hypertension, was associated with a longer time for viral clearance ($P < 0.005$), but this was not significant in patients with gastrointestinal manifestations ($P > 0.05$).

Unadjusted and adjusted odds ratios

None of the comorbidities were significantly associated with gastrointestinal manifestations, whether adjusted for covariates or not, as indicated by almost all of the P -values being > 0.05 .

Only procalcitonin and CRP were significantly related to gastrointestinal manifestations ($P < 0.05$). These ORs were found from significant models (equations of estimation) with $P < 0.05$. The same was also seen for adjusted results (Table 6).

Male gender and dyslipidaemia were found to be associated with significant risk of hepatic manifestations: OR 2.5 ($P = 0.003$) and OR 0.13

Table 5
Laboratory data and outcomes of both cohorts (mean \pm standard deviation)

Variable	Patients without gastrointestinal symptoms(n=402)	Patients with gastrointestinal symptoms(n=119)	P-value
Elevated liver enzymes at admission			
Bilirubin	0.61 \pm 0.32	0.62 \pm 0.58	0.880
ALT	48.46 \pm 40.47	50.32 \pm 45.34	0.731
ALP	79.66 \pm 34.22	76.73 \pm 28.4	0.351
Prognostic markers of severity at admission			
Ferritin	1075.57 \pm 2164.07	922.08 \pm 1004.01	0.349
LDH	352.52 \pm 170.14	326.32 \pm 137.53	0.111
Lymphopenia	1.2 \pm 0.57	1.22 \pm 0.55	0.675
D-dimer	1.37 \pm 2.88	1.24 \pm 2.1	0.588
Procalcitonin	0.37 \pm 1.43	4.67 \pm 28.68	0.255
CRP	90.71 \pm 96.09	83.01 \pm 90.46	0.449
Hospital stay			
Total length of stay	12.92 \pm 13.13	11.74 \pm 12.86	0.409
Time for viral clearance	16.63 \pm 9.69	16.77 \pm 8.55	0.889

ALT, alanine aminotransferase; ALP, alkaline phosphatase; LDH, lactate dehydrogenase; CRP, C-reactive protein.

Table 6
Odds ratios (OR) for gastrointestinal involvement.

Variable	Unadjusted results (1-variable model)			Adjusted results		
	Overall model of significance	OR	P-value	Overall model of significance	OR	P-value
Comorbidities						
Diabetes mellitus	0.777	1.062	0.777	0.571	1.198	0.621
Hypertension	0.663	0.898	0.665	0.571	0.935	0.830
Chronic kidney disease	0.402	3.398	0.388	0.571	3.585	0.429
Ischaemic heart disease	0.230	1.739	0.215	0.431	2.260	0.116
Asthma	0.598	1.459	0.588	0.658	1.351	0.675
Dyslipidaemia	0.725	1.236	0.721	0.644	1.419	0.581
Thyroid disease	0.703	0.746	0.711	0.631	0.596	0.539
Laboratory tests						
D-dimer (0.5 µg/mL)	0.622	1.114	0.623	0.575	1.245	0.342
Procalcitonin (>0.05 mg/L)	0.001	3.922	0.004	0.010	4.895	0.001
C-reactive protein (>5 mg/L)	0.003	3.806	0.012	0.014	5.713	0.002

Table 7
Odds ratios (OR) for hepatic involvement.

Variable	Unadjusted results (1-variable model)			Adjusted results		
	Overall model of significance	OR	P-value	Overall model of significance	OR	P-value
Demographics						
Gender	0.002	2.498	0.003	0.000	2.396	0.006
Age	0.172	0.989	0.173	0.000	0.988	0.164
Comorbidities						
Diabetes mellitus	0.219	1.249	0.220	0.000	1.410	0.091
Hypertension	0.090	0.706	0.090	0.000	0.809	0.363
Chronic kidney disease	0.941	0.901	0.941	0.000	3.408	0.999
Ischaemic heart disease	0.272	0.630	0.276	0.000	1.062	0.905
Asthma	0.258	2.132	0.277	0.000	2.563	0.205
Dyslipidaemia	0.001	0.132	0.008	0.000	0.166	0.023
Thyroid disease	0.632	0.746	0.633	0.000	1.531	0.532

Table 8
Severity of pneumonia.

Predictor	Unadjusted results			Adjusted results		
	Model of significance	OR	P-value	Model of significance	OR	P-value
Gastrointestinal involvement	0.614	1.123	0.617	0.000	0.987	0.955
Diarrhoea	0.456	0.797	0.463	0.000	0.677	0.215
Hepatic involvement	0.059	0.691	0.060	0.000	0.726	0.117

OR, odds ratio.

($P=0.001$), respectively. The adjusted results were similar to the unadjusted results in terms of size and indication for both of these variables (Table 7).

Gastrointestinal manifestations, diarrhoea and hepatic manifestations were not significantly associated with severity of COVID-19 pneumonia, as all P -values for the unadjusted results were >0.05 . For the adjusted results, the contribution to the OR of severity was not significant for all three predictors (all P -values >0.05). However, the models from which these three adjusted contributions to the OR came from were significant (models of significance <0.05), and this is because the adjusted covariates had a considerable effect on severity (more than gastrointestinal manifestations, diarrhoea or hepatic manifestations) (Table 8).

Discussion

COVID-19 can be viewed as a multi-system inflammatory condition with a spectrum of clinical manifestations, ranging from totally asymptomatic infection to acute respiratory distress syndrome and multi-organ failure. This is interpreted as the way that the immune system reacts to this novel virus, underlying genetic composition, and other underlying comorbidities and risk factors (Zaim et al., 2020).

Being a respiratory pathogen, it is not uncommon to see the lungs as the main target of SARS-CoV-2, with pathophysiological manifestations affecting respiratory system airways as well as vessels, leading ultimately to pneumonia and pulmonary emboli as the most serious com-

plications of infection. However, other organ systems have also been reported to be affected in COVID-19 with variable degrees of severity and involvement. This includes the central nervous system (embolic or haemorrhagic stroke), viral encephalitis, acute cardiovascular events, myocarditis, cardiac arrhythmias, thyroid gland abnormalities, mucocutaneous manifestations, acute kidney injury, acute pancreatitis, hepatic and gastrointestinal manifestations. Different mechanisms have been proposed, as discussed in detail by Mokhtari et al. (2020).

The focus of this study was to investigate hepatic and gastrointestinal manifestations among a group of adult patients admitted to hospital with COVID-19 of varying severity over a 4-month study period.

Recent information in the literature from multiple studies and meta-analyses have shown that the pathophysiology of hepatic and gastrointestinal manifestations is multi-factorial, and can be summarized as follows:

- The presence of active viral replication in the hepatocytes and gastrointestinal tract (gastric, duodenal and rectal glandular epithelial cells) of infected patients has been detected via electronic microscopy and viral culture (Cha et al., 2020).
- SARS-CoV-2 enters and replicates in cells by binding to ACE2 receptors in epithelial cells throughout the gastrointestinal tract and cholangiocytes (Mao et al., 2020).
- SARS-CoV-2 may trigger a massive release of pro-inflammatory cytokines, leading to cardiopulmonary manifestations, tissue hypoxia

and thrombosis with subsequent gastrointestinal and hepatic complications.

- SARS-CoV-2 can lead to severe hypoxaemic respiratory failure with multi-organ tissue hypoxia, loss of cell integrity, cell injury and cell death.
- Drugs used in managing COVID-19 can induce gastrointestinal adverse events and/or acute hepatic injury, such as Acetaminophen, Favipiravir and Remdesivir.

The differential diagnoses of hepatic and gastrointestinal manifestations in patients with COVID are broad and can be divided into two main clinical presentations:

- Gastrointestinal manifestations. Diarrhoea can be caused by other infectious illnesses such as concomitant bacterial or *Clostridium difficile* infection; ischaemic colitis, especially in elderly patients with multiple comorbidities; and patients with underlying inflammatory bowel disease exacerbation. Abdominal pain can be caused by acute or chronic pancreatitis, acute cholecystitis or gastric/duodenal ulcers.
- Hepatic manifestations. Abnormal liver function tests can be secondary to underlying chronic hepatitis B or C infection; concomitant acute hepatitis A, cytomegalovirus, Epstein–Barr virus or herpes simplex virus infection; Acetaminophen overdose; autoimmune hepatitis; primary biliary cirrhosis; drug-induced liver injury; portal vein thrombosis; or Budd–Chiari syndrome.

Gastrointestinal complaints are common in patients with COVID-19, and have been described in up to 26% of patients in some populations (Zhou et al., 2020).

The exact incidence of hepatic and gastrointestinal involvement in patients with COVID-19 has not been confirmed, especially with the emergence of new variants. At the time of writing, the Wuhan variant was predominant in the study population, and this may explain differences between patient groups and publications.

In addition, various clinical presentations and gastrointestinal symptoms have been reported. Studies looking at the association between the severity of COVID-19 and concurrent gastrointestinal symptoms have also yielded mixed results.

Pan et al. (2020) showed that the presence of gastrointestinal symptoms was associated with higher liver enzyme levels, lower monocyte count and longer prothrombin time. None of the liver function tests conducted in this study, including ALT, alkaline phosphatase and bilirubin, were significantly associated with mortality; ICU admission; viral clearance; or the presence of isolated respiratory symptoms, gastrointestinal symptoms or both combined ($P > 0.05$).

The most common gastrointestinal system in patients with COVID-19 is diarrhoea (3.8–34%), followed by nausea and/or vomiting (3.9–10.1%) and abdominal pain (1.1–2.2%) (Huang et al., 2020; Guan et al., 2020). Anorexia was reported to be the most common symptom in one study (39.9–50.2%), with diarrhoea reported to be the most common symptom in both adult and paediatric populations in other studies (2–49.5%) (Pan et al., 2020; Tian et al., 2020). Liang et al. (2020) found that more than half of their patients with COVID-19 developed diarrhoea following hospitalization and introduction of antiviral medication, which is one of the mechanisms explained above.

A meta-analysis of 60 studies involving 4243 patients with COVID-19 from six countries found gastrointestinal symptoms in 17.6% of patients (Cheung et al., 2020). Anorexia was observed in 26.8% of patients, followed by diarrhoea (12.5%), nausea/vomiting (10.2%) and abdominal pain/discomfort (9.2%).

A larger meta-analysis by Borges do Nascimento et al. (2020) included data from 59,254 patients with COVID-19 from 11 countries. Their review showed that 9% of all included patients had gastrointestinal symptoms.

In another large-scale systematic review and meta-analysis, data of 78,798 patients with COVID-19 from 158 studies were analysed in

detail. The most common gastrointestinal manifestations were diarrhoea [16.5%, 95% confidence interval (CI) 14.2–18.4%], nausea (9.7%, 95% CI 9.0–13.2%) and elevated hepatic enzymes (5.6%, 95% CI 4.2–9.1%). Overall mortality was 23.5% (95% CI 21.2–26.1%), and mortality among patients with gastrointestinal manifestations was 3.5% (95% CI 3.1–6.2%). On subgroup analysis, non-significant associations were found between gastrointestinal symptoms/elevated liver enzymes and ICU admission [odds ratio (OR) 1.01, 95% CI 0.55–1.83]. Mortality among patients with gastrointestinal manifestations was 10.8% (95% CI 7.8–11.3%) in the USA and 0.9% (95% CI 0.5–2.2%) in China (Shehab et al., 2021).

Gastrointestinal symptoms tend to worsen with disease progression, and this can be explained by several pathophysiological mechanisms.

Other reported gastrointestinal symptoms in patients with COVID-19 are anosmia and dysgeusia (Giacomelli et al., 2020), upper gastrointestinal bleeding, haemorrhagic colitis and acute pancreatitis.

An important infection control and diagnostic measure is related to the fact that the presence of diarrhoea in patients with COVID-19 is associated with a higher SARS-CoV-2 viral load in stool, as well as higher positivity rates. In one study, SARS-CoV-2 viral RNA was detected in almost 50% of patients with COVID-19, with stool RNA positivity lasting for 33–47 days post initial diagnosis, and lasting beyond clearance of nasopharyngeal RT-PCR samples (Walsh et al., 2020).

In comparison with the gastrointestinal manifestations described above, abnormal liver function tests have been described in patients with more severe COVID-19. Most patients were found to have mild hepatitis, with normalization of liver enzymes tending to match clinical and radiological recovery. In the study hospital, in alignment with national COVID-19 treatment guidelines, liver function tests are performed on hospital admission and repeated every 3–5 days according to the patient's clinical data.

Mild-to-moderate increases in transaminases were observed after treatment initiation. No cases of fulminant hepatitis or acute hepatic failure were associated with COVID-19, or drugs used to manage COVID-19, in the study patients.

To date, few cases of COVID-19 have been reported with presentation of acute liver failure. Melquist et al. (2020) reported a 35-year-old female patient, and Orandi et al. (2021) reported a 15-year-old female patient with acute liver failure. Ihlow et al. (2021) presented a case report of rapidly progressive fatal fulminant hepatic failure in a patient with underlying liver cirrhosis. Autopsy revealed severe chronic and acute liver damage with bile duct infestation by SARS-CoV-2 that was accompanied by higher expression of ACE2, cathepsin L and transmembrane serine protease 2. Of note, all three patients had isolated acute fulminant hepatitis without concomitant COVID-19 pneumonia.

Patients who exceeded a five-fold increase in transaminases were managed by adjusting the dose of Favipiravir (e.g. 50% reduction in the dose) or stopping it if the transaminase level was >10% upper limit of normal.

The present study found that 22.8% ($n=119$) of patients admitted with COVID-19 presented with gastrointestinal manifestations. Diarrhoea was the most common gastrointestinal symptom [10.9% ($n=57$)], followed by nausea/vomiting, anorexia and abdominal pain. Rarely, patients with COVID-19 can present with isolated gastrointestinal symptoms without respiratory symptoms (Pan et al., 2020), as reported in the present study cohort [1.9% ($n=9$)]. The incidence of gastrointestinal symptoms in patients with COVID-19 found in the present study (22.8%) was lower than incidence rates reported in other studies in the USA and China (50.5–61.3%) (Han et al., 2020; Pan et al., 2020). In the present study, abnormal ferritin levels were significantly associated with isolated respiratory symptoms ($P=0.038$), but not with isolated gastrointestinal symptoms ($P=0.069$). Abnormal procalcitonin and CRP levels were significantly associated with combined respiratory and gastrointestinal symptoms ($P=0.001$ and 0.005 , respectively).

The majority of patients admitted to ICU had isolated respiratory symptoms [$n=62$ (71.3%)], a minority presented with isolated gastroin-

testinal symptoms [$n=5$ (5.7%)], and 14.9% ($n=13$) had combined respiratory and gastrointestinal symptoms.

Among the study population, a lower mortality rate was observed in patients with gastrointestinal symptoms [$n=14$, (2.68%)] compared with those without gastrointestinal symptoms [$n=38$ (7.29%)]. This supports results from the USA and Spain with large cohorts which showed similar lower mortality rates among patients with gastrointestinal manifestations (Borobia et al., 2020; Hajifathalian et al., 2020).

In terms of the severity of pneumonia based on chest x-ray, patients with combined respiratory and gastrointestinal symptoms showed a similar pattern of mild-to-moderate [$n=86$ (78.2%)] and severe [$n=16$ (14.5%)] pneumonia to isolated respiratory symptoms.

Study limitations

Limitations of this study include the retrospective design, small sample size and single-centre design. This could have introduced selection bias, and limited the reliability and generalizability of the results.

Conclusion

Patients with COVID-19 can show a variety of hepatic and gastrointestinal manifestations, which may pre-date or may not be accompanied by active respiratory complaints. Diarrhea was the most common GI presentation observed in this study. Patients with GI or hepatic manifestations were not found to have longer hospital stays or poorer outcomes, in terms of pneumonia severity, ICU admission and overall mortality.

Further research is required to better describe the true incidence and prevalence of hepatic and gastrointestinal manifestations in patients with COVID-19, as well as the association with disease outcome and long-term prognosis.

Conflict of interest statement

None declared.

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Ethical approval

The Dubai Health Authority Ethical Review Board approved this study while utilizing anonymized and de-identified retrospective data, and waived the requirement for informed consent.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Author contributions

HK and HF: Conception and design.

HK, HF, OB, MH and HA: Data collection.

HK and HF: Drafting manuscript and literature review.

LA: Critical revision, and final approval of the manuscript.

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