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RESEARCH

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Prevalence of GIT symptoms in patients of COVID 19 and role of rectal PCR in detecting COVID 19 with GIT symptoms

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Abstract

Background In December 2019, a cluster of patients with pneumonia of undetermined etiology was recognized in Wuhan, Hubei, China. Subsequently, a novel coronavirus (Severe Acute Respiratory Distress Syndrome- related Coronavirus) (SARS-CoV-2) was identified from lower respiratory tract samples obtained from affected patients. The clinical manifestation of Coronavirus disease 2019 (COVID 19) is broad and ranges from asymptomatic and mild upper respiratory tract symptoms to severe illnesses with multi-organ failure and death. Furthermore, it is challenging to predict the clinical course or determine patients at risk of deterioration.

Aim of the work The aim of our study is to assess prevalence of gastrointestinal tract (GIT) symptoms in COVID 19 infected patients and to assess significance of rectal PCR in detecting COVID 19 patients with gastrointestinal symptoms.

Patients and methods This study was conducted on 100 adult COVID 19 patients recently diagnosed by polymerase chain reaction (PCR). All patients were submitted to clinical examination, laboratory testing for Erythrocyte Sedimentation Rate (ESR), C-Reactive Protein,(CRP), Complete Blood Count (CBC), and D-dimer. Radiological investigations in the form of Computed Tomography Chest were reported by radiologist for all patients (High resolution computed tomography). Nasopharyngeal, oropharyngeal and rectal swabs were collected for COVID-19 (PCR) test. All patients received COVID-19 treatment according to protocols of World Health Organization (WHO) and Ministry of Health and Population, Egypt.

Results We found that GI symptoms are prevalent among COVID-19 Egyptian patients (64%). The most common GIT symptoms were Nausea, vomiting and diarrhea. We observed that 25 patients (25%) had positive viral RiboNucleic Acid (RNA) in rectal swab. Nausea was manifested in 38 patients (38%), Vomiting was manifested in 24 patients (24%), diarrhea was manifested in 21 patients (21%), pain was manifested in 22 patients (22%), hematemesis was manifested in 3 patients (3%) and melena was manifested in 2 patients (2%).

Conclusion The results of current study demonstrated that GIT symptoms are prevalent among COVID-19 Egyptian patients (64%) with Nausea, vomiting and diarrhea to be most common symptoms. Rectal PCR was found in 25 patients, all of them had GIT symptoms but it was statistically non-significant result when compared to the overall number of COVID-19 infected patients. Severe COVID-19 was more frequent in older age.

Keywords GIT Symptoms, COVID 19

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Introduction

In December 2019, a cluster of patients with pneumonia of undetermined etiology was recognized in Wuhan, Hubei, China [1]. Subsequently, a novel coronavirus (SARS-CoV-2) was identified from lower respiratory tract samples obtained from affected patients [2, 3].

The clinical manifestation of COVID-19 is broad and ranges from asymptomatic and mild upper respiratory tract symptoms to severe illnesses with multi-organ failure and death [4]. Furthermore, it is challenging to predict the clinical course or determine patients at risk of deterioration [5, 6].

Importantly, significant differences have been noted in the clinical and demographic features of COVID-19 patients in different regions of the world [7]. People with co-morbidities are at risk for COVID-19 pneumonia Furthermore, blood biomarkers differ significantly among COVID- 19 patients with different disease severities [8].

Extra-pulmonary clinical manifestations of COVID-19 affect multiple other organs including cardiovascular (*e.g.*, arrhythmias, myocarditis, pericarditis, acute coronary syndrome, and heart failure), renal (*e.g.,* acute kidney injury and acute tubular necrosis), hepatic [*e.g.,* elevated alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin], gastrointestinal (*e.g.*, diarrhea, nausea, vomiting, and abdominal pain), ocular (*e.g.,* epiphora, conjunctivitis, and chemosis), dermatologic (*e.g.*, erythematous rash, urticaria, and chickenpox-like vesicles), and neurological systems (*e.g.,* headache, neuropathy, encephalopathy, cerebrovascular disorders, and dizziness) [9].

The GI and hepatobiliary tracts mechanism of injury is not entirely clear and is mostly attributed to multiple factors. COVID-19–associated injury potential mechanisms include direct consequences of viral replication, systemic inflammatory and immune-mediated effects, and vascular changes resulting in ischemia, drug-induced injury, and exacerbation of underlying disease [10].

Toll like receptors (TLRs) play a considerable role in the host defense against microorganism [11, 12]. Activation of the TLRs in COVID-19 infection could lead to the production of pro-inflammatory cytokines [13]. Serum levels of Programmed death-ligand 1 (PD-L1) have a prognostic role in COVID-19 patients and associated to COVID-19 pathogenesis [14]. PD-L1 is responsible for T cell activation, proliferation, and cytotoxic secretion in cancer to produce anti-tumor immune responses [15]. Transforming growth factor-beta 1 (TGF-β1) [16] and interleukin-10 (IL-10) are key regulators of immune homeostasis [17]. TGF-β is a prominent regulator of immune reactions [18] and it causes a comorbidity of severe COVID-19 patients [19]. Mean platelet volume (MPV), and platelet distribution width (PDW) were increased in non-survivors of COVID-19 [20]. Also, MPV and PDW are valuable diagnostic markers for diagnosis of Spontaneous bacterial peritonitis (SBP) [16].

Mechanistically, the interaction between the S protein and Angiotensin converting enzyme 2 (ACE2) is likely to have a central role in disease pathogenesis. The high burden of systemic inflammation associated with COVID-19 has been proposed to accelerate the development of subclinical disorders or cause de novo systemic damage**.** Studies have shown that GI epithelial cells are expressed in the COVID-19 receptor, i.e., an angiotensin convertor enzyme 2 (ACE2) [2, 3].

The COVID-19 related liver and gastroenterological dysfunction may be attributed to direct infection of the virus via ACE2 receptors and secondary tissue damage caused mainly by; systemic inflammatory response (cytokine storm), medication of potentially hepatotoxic drugs, and respiratory distress syndrome-induced hypoxia [21].

Many gastrointestinal symptoms affected COVID-19 infected patients, but diarrhea followed by nausea and vomiting - especially in younger vaccinated age groups – were the most common when compared to the non-vaccinated group [22].

Matsubara et al., concluded that in COVID-19 patients, diarrhea was associated with better clinical outcomes. The prevalence of diarrhea, nausea/vomiting, abdominal pain, and melena were 16.6%, 8.9%, 3.5%, and 0.7%, respectively. Results showed reduced admission to intensive care unit (ICU) and requirement for mechanical ventilation in patients with diarrhea when compared to those not having diarrhea [23].

Conclusions

Diarrhea was associated with better clinical outcomes in COVID-19 patients.

Aim of the work

To assess prevalence of GIT symptoms in COVID 19 infected patients and to assess significance of rectal PCR in detecting COVID patients with GIT symptoms.

Patients and methods

The study was carried out on in quarantine departments at Luxor International Hospital and Ain Shams University hospitals.

Study design

A cross-Sectional analytical study.

Patients

This cross-Sectional analytical study was conducted on 100 subjects who were infected with COVID-19 and

recently diagnosed by polymerase chain reaction (PCR) using oro-nasopharyngeal swab. This study took place in the period from November 2021 to June 2022.

Inclusion criteria

Patients infected with COVID-19, either male or female, 18 years of age or more.

Exclusion criteria

Patients < 18 years, patients with chronic GIT disorders as Inflammatory Bowel Disease, any advanced malignancy, patients with autoimmune diseases, pregnant women and non-compliant patients.

Methodology

All patients were subjected to the following:

History and Clinical Examination: Complete history taking: included age, sex, Residence, Occupation, Special Habits, marital state, Menstrual History: (Premenstrual/ Menstruating/ Menopausal), (Pregnant/ Lactating). Symptoms of cardiac, renal, chest diseases and other comorbid conditions such as hypertension, thyroid dysfunction and malignancy were noted. History taking included a questionnaire for the study group about occurrence of GI symptoms (nausea, vomiting, diarrhea, abdominal pain, hematemesis or melena).

Full clinical examination: Full Clinical Examination include assessment of general condition with stress on vital signs (pulse, blood pressure, respiratory rate and temperature). Abdominal, chest and heart examination were assessed with focus on manifestations of chest disease. Blood pressure equal or more than 140/90 mmHg defined as hypertension. Anthropometric parameters were obtained. Height and weight were measured, and body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters.

Laboratory Investigations:- Blood samples were collected from patients and submitted to the following: Complete blood picture (CBC): hemoglobin concentration (Hb %), red blood cells (RBCs), white blood cells (WBCs), neutrophilic count, lymphocytic count, platelet count, fasting blood glucose level and HbA1c. The diagnosis of Diabetes was defined as fasting blood glucose ≥ 126 mg/dl and/or glycosylated hemoglobin >6.5% or by the use of hypoglycemic agents or by self-reported history of diabetes, liver profile: alanine aminotransferase (ALT), aspartate aminotransferase (AST), serum total bilirubin, and serum albumin, CRP, ESR and ferritin, D Dimer, LDH with nasopharyngeal , oropharyngeal and rectal swab for PCR.

Sampling and details of laboratory investigations: Seven milliliters of venous blood were collected from each participant by the use of disposable sterilized plastic syringes. The needle of the syringe was then removed and each sample was divided as follows: Five milliliters of blood were allowed to pass gently along the wall of a clean dry centrifuge tube labeled with the patient name. The blood was allowed to clot for half an hour in a water bath at 37°C, and then it was centrifuged for 15 min at 3000 rpm for separation of serum by means of a clean dry Pasteur pipette. The serum was fractionated into two clean dry tubes for measuring the following:

Erythrocyte sedimentation rate (ESR) by the Westergren method.

Latex agglutination slide test for qualitative and semiquantitative determination of C-reactive protein in non-diluted serum.

D-dimer level by immune turbidimetry assay with the coagulational laboratory auto-analyzer (ACL 2000; Instrumentation Laboratory, Milan, Italy). The D-dimer level was graded according to the level of estimation Graded as normal level, when less than 200 ngm/ml, slightly elevated when 200-500 ngm/ml, moderate elevation when 500-1000 ngm/ml and severely elevated when 1000-2000 ngm/ml.

Serum ferritin (TOSOH AIA-360 Automated Immunoassay Analyzer, JAPAN).

Aspartate aminotransferase (AST), alanine aminotransferase (ALT), serum bilirubin, serum creatinine, CRP, lactate dehydrogenase (LDH), and D-dimer by using a photometric unit of the auto-analyzer the Cobas 6000 analyzer (c501 module).

The remaining two milliliters of blood were put on Ethylenediaminetetraacetic acid (EDTA) (1mg/ml blood) and mixed thoroughly to perform complete blood picture by Erma Automated Blood Count Machine (Tokyo, Japan).

Nasopharyngeal, oropharyngeal and rectal swabs were collected for COVID-19 (PCR) test by using Rotor Gene real-time PCR with fluorescence system (QIAGEN, GmbH, Germany) before or soon after admission to the assigned hospitals.

Rectal swab for PCR was done by careful insertion of the swab into the rectum for 3 cm past the anal margin, then gentle rotation of the swab clockwise for 5 – 10 seconds, and then the swab was withdrawn without touching the skin. For the samples loaded by heavy stools they were rejected and substituted with

another samples to get not fecal material for analysis.

Radiological investigations: in the form of X-ray Chest and CT Chest reported by radiologist for all patients. On CT chest, each of the Five lung lobes was visually scored from 0 to 5 as follows: 0, no involvement; 1, < 5% involvement; 2, 5% - 25% involvement; 3, 26%–49% involvement; 4, 50%-75% involvement; and 5, > 75% involvement [24].

Assessment of disease severity: Disease severity on admission was classified according to the report of the WHO-China Joint Mission on COVID-19 [25]. Patients with COVID- 19 were divided into mild (laboratory confirmed, without pneumonia), moderate (clinical and laboratory confirmed with pneumonia oxygen saturation≥ 94%), severe (oxygen saturation ≤ 93% at rest,dyspnea with a respiratory rate ≥ 30 breath/min and/or lung infiltrates >50% of the lung field within 24–48 h) and critical (respiratory failure requiring mechanical ventilation, shock, or other organ failure that requires intensive care).

All patients received medical treatment according to protocols of Ministry of Health and Population, Egypt.

Consent form: All subjects involved in the study were informed about the nature and details of the work and a written consent was obtained for each participant. The study was approved by the local Ethics Committee, Faculty of Medicine, and Ain Shams University.

Statistical analysis: Data was analyzed using Statistical Program for Social Science (SPSS) version 24. Quantitative data was expressed as mean ±Standard Deviation. Qualitative data were expressed as frequency and percentage. Mean (average): the central value of a discrete set of numbers, specifically the sum of values divided by the number of values. Standard deviation (SD): is the measure of dispersion of a set of values. A low SD indicates that the values tend to be close to the mean of the set, while a high SD indicate that the values are spread out over a wider range.

The following tests were done:

Mann-Whitney U test: was used when comparing between two means (for abnormal distributed data).

Chi-square test: was used when comparing between non-parametric data.

Multivariate logistic regression analysis: was used to demonstrate the factors predictive for severe disease in studied patients.

Table 1 Description of demographic data in all studied patients

		Studied patients (*N* = 100)	
Age (years)	**Mean ±SD**	46.7 ± 9.9	
	Min – Max	30 – 81	
Sex	**Male**	50	50%
	Female	50	50%
BMI (kg/m^2)	**Mean ±SD**	31.3 ± 4.8	
	Min – Max	25.3 – 46.7	
Residence	**Rural**	54	54%
	Urban	36	36%
Social Economic state	**Low**	70	70%
	Moderate	30	30%
Smoking	**No**	79	79%
	Yes	21	21%

Table 2 Description of symptoms in all studied patients

		Studied patients (*N* = 100)	
General symptoms	**Fever**	76	76%
	Malaise	76	76%
	Loss of smell	9	9%
Pulmonary symptoms	**Cough**	61	61%
	Dyspnea	60	60%
	Chest pain	11	11%

Probability (*P*-value): *P*-value < 0.05 was considered significant, *P*-value < 0.001 was considered as highly significant and *P*-value > 0.05 was considered insignificant.

Results

Fifty of the studied patients were diabetic, 12 with mild disease severity, 17 with moderate disease severity and 21 with severe disease.

Total number of COVID-19 patients with positive rectal PCR who had diarrhea was 7 (28%), which is not significant when compared to the overall number of COVID-19 infected patients (21 %). There was no significant difference in the other GIT manifestations (Nausea, vomiting, abdominal pain, hematemesis and melena), when rectal PCR-positive cases compared to the overall number of patients included in the study Tables 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 and 16.

Discussion

In December 2019, a group of patients with pneumonia of unknown etiology was recognized in Wuhan, Hubei, China. Subsequently, a novel coronavirus (SARS-CoV-2)

Table 3 Description of GIT manifestations in all studied patients

		Studied patients (*N* = 100)	
GIT manifestations	**Vomiting**	24	24%
	Diarrhea	21	21%
	Nausea	38	38%
	Abdominal Pain	22	22%
	Hematemesis	3	3%
	Melena	2	2%

was identified from lower respiratory tract samples obtained from affected patients [1].

Extra-pulmonary clinical manifestations of COVID-19 affect multiple other organs including cardiovascular (*e.g.*, arrhythmias, myocarditis, pericarditis, acute coronary syndrome, and heart failure), renal (*e.g.,* acute kidney injury and acute tubular necrosis), hepatic [*e.g.,* elevated alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin], gastrointestinal (*e.g.*, diarrhea, nausea, vomiting, and abdominal pain), ocular (*e.g.,* epiphora, conjunctivitis, and chemosis), dermatologic (*e.g.*, erythematous rash, urticaria, and

Table 4 Description of laboratory data in all studied patients

(*n* = 100)	Minimum	Maximum	Mean	±SD
Dimer (mg/L)	0.1	70.7	4.7	15.1
LDH (U/L)	67	1276	297.3	204.5
Ferritin (ng/mL)	58	935	347.4	217.5
CRP (mg/dL)	1.8	192	32.1	42.5
ALT (U/L)	10	156	39.7	31.4
AST (U/L)	15	176	46.1	32.7
Hb (g/dL)	0.9	16.8	12.5	2.0
Platelets (10*3/UL)	64	651	246.8	88.9
White Blood Counts (10*3/UL)	1	34.5	8.0	5.2
Absolute lymphocytic count (10*3/UL)	0.3	3.3	1.5	0.7
Neutrophil Count (10*3/UL)	0.2	32	6.2	5.0
Lymphocyte Neutrophil Ratio	0.04	4	0.4	0.6
Prothrombin Time (Seconds)	12	16	13.0	0.9
International Normalized Ratio	1	1.4	1.1	0.1
Creatinine (mg/dL)	0.4	8	1.1	0.7

Table 5 Description of CT findings in all studied patients

		Studied patients (*N* = 100)	
CT findings	**Normal**	22	22%
	Bilateral Ground Glass Opacities (GGO)	70	70%
	Crazy-paving appearance	27	27%
CO-RAD classification (COVID-19 Reporting and Data System)	**CO-RAD 1**	18	18%
	CO-RAD 3	11	11%
	CO-RAD 4	33	33%
	CO-RAD 5	38	38%

Table 6 Description of PCR results in all studied patients

		Studied patients (*N* = 100)	
Nasal swab	**Negative**	0	0%
	Positive	100	100%
Rectal swab	**Negative**	75	75%
	Positive	25	25%

Table 7 Description of disease severity in all studied patients

		Studied patients (*N* = 100)	
Disease severity	**Mild, moderate**	68	68%
	Severe	32	32%

Table 8 Relation between disease severity and demographic data in studied patients

		Disease severity				Stat. test	*P*-value
		Mild: Mod (*N* = 68)		Severe (*N* = 32)			
Age (years)	**Mean**	42.7		55.2		**T = 7.3**	**< 0.001**
	±SD	5.02		12.2			
Sex	**Male**	34	50%	16	50%	$X^2 = 0.0$	1.0
	Female	34	50%	16	50%		
BMI (kg/m^2)	**Mean**	31.02		31.9		MW = 976.5	0.409
	±SD	4.8		5.1			
Residence	**Rural**	36	52.9%	18	56.2%	$X^2 = 0.09$	0.757
	Urban	32	47.1%	14	43.8%		
SES	**Low**	49	72.1%	21	65.6%	$X^2 = 0.42$	0.513
	Moderate	19	27.9%	11	34.4%		
Smoking	**No**	55	80.9%	24	75%	$X^2 = 0.45$	0.501
	Yes	13	19.1%	8	25%		

Abbreviation: T Independent sample T test, HS *p*-value < 0.001 is considered highly significant, *MW* Mann Whitney U test, NS *p*-value > 0.05 is considered non-significant

Table 9 Relation between disease severity and symptoms in studied patients

		Disease severity				X^2	*P*-value
		Mild, Mod (*N* = 68)		Severe (*N* = 32)			
General Symptoms	**Fever**	48	70.6%	28	87.5%	3.4	0.065
	Malaise	48	70.6%	28	87.5%	3.4	0.065
	Loss of smell	9	13.2%	0	0%	**4.6**	**0.031**
Pulmonary Symptoms	**Cough**	38	55.9%	23	71.9%	2.33	0.126
	Dyspnea	36	52.9%	24	75%	**4.4**	**0.036**
	Chest pain	10	14.7%	1	3.1%	2.98	0.084

Abbreviation: S *p*-value < 0.05 is considered significant, X2 Chi-square test, NS *p*-value > 0.05 is considered non-significant

Table 10 Relation between disease severity and GIT manifestations in studied patients

		Disease severity				X^2	*P*-value
		Mild: Mod (*N* = 68)		Severe (*N* = 32)			
GIT manifestations	**Vomiting**	16	23.5%	8	25%	0.02	0.872
	Diarrhea	16	23.5%	5	15.6%	0.82	0.365
	Nausea	26	38.2%	12	37.5%	0.005	0.944
	Pain	17	25%	5	15.6%	1.11	0.291
	Hematemesis	1	1.5%	2	6.3%	1.7	0.191
	Melena	0	0%	2	6.3%	**4.3**	**0.037**

Abbreviation: S *p*-value < 0.05 is considered significant, X2 Chi-square test, NS *p*-value > 0.05 is considered non-significant

chickenpox-like vesicles), and neurological systems (*e.g.*, headache, neuropathy, encephalopathy, cerebrovascular disorders, and dizziness) [9].

The interaction between the S protein and ACE2 is likely to have a central role in disease pathogenesis. The high burden of systemic inflammation associated with COVID-19 has been proposed to accelerate the development of subclinical disorders or cause de novo systemic damage (Zheng et al., 2020). Studies have shown that GI epithelial cells are expressed in the COVID-19 receptor [2].

Table 11 Relation between disease severity and laboratory data in studied patients

		Disease severity		MW	*P*-value
		Mild: Mod (*N* = 68)	Severe (*N* = 32)		
D-Dimer (mg/L)	Mean	0.8	13.0	555	< 0.001
	±SD	0.5	25.0		
LDH (U/L)	Mean	238.7	421.8	528	< 0.001
	±SD	152.3	244.7		
Ferritin (ng/mL)	Mean	287.2	475.3	547	< 0.001
	±SD	186.0	227.0		
CRP (mg/dL)	Mean	19.1	59.9	328.5	< 0.001
	±SD	31.6	49.3		
ALT (U/L)	Mean	33.6	52.7	837.5	0.064
	±SD	23.5	41.4		
AST (U/L)	Mean	39.6	59.8	711	0.005
	±SD	26.5	40.2		
Hb (g/dL)	Mean	12.6	12.1	981	0.428
	±SD	1.6	2.7		
PLTs (10*3/UL)	Mean	240.6	259.9	979.5	0.423
	±SD	77.1	110.2		
WBCs (10*3/UL)	Mean	8.2	7.6	795.5	0.031
	±SD	3.7	7.5		
Absolute Lymphocytic Count (10*3/UL)	Mean	1.7	1.0	433	< 0.001
	±SD	0.7	0.4		
NC (10*3/UL)	Mean	6.2	6.4	953	0.318
	±SD	3.7	7.1		
LNR	Mean	0.4	0.5	849.5	0.078
	±SD	0.3	1.0		
PT (Seconds)	Mean	13.0	13.03	955	0.489
	±SD	1.0	0.8		
INR	Mean	1.1	1.12	892	0.132
	±SD	0.1	0.07		
Creat (mg/dL)	Mean	1.08	1.01	961	0.341
	±SD	0.9	0.1		

Abbreviation: S *p*-value < 0.05 is considered significant, HS *p*-value < 0.001 is considered highly significant, MW Mann Whitney U test, NS *p*-value > 0.05 is considered non-significant

This study was conducted on 100 adult COVID 19 patients recently diagnosed by polymerase chain reaction (PCR) of oropharyngeal and nasopharyngeal swabs.

The results of current study demonstrated that GI symptoms are prevalent among COVID-19 Egyptian patients (64%). The most common GI symptoms were Nausea, vomiting and diarrhea. Nausea was manifested in 38 patients (38%), Vomiting was manifested in 24 patients (24%), diarrhea was manifested in 21 patients (21%), pain was manifested in 22 patients (22%), hematemesis was manifested in 3 patients (3%) and melena was manifested in 2 patients (2%).

Teima et al assessed 860 patients with COVID-19 infection. The mean age of studied patients was 46.1 ± 11.8 and ranged from 17 to 81 years old, 45.8% of the studied patients were males and 54.2% were females. The most common symptoms were cough (33%), dyspnea (21.9%) and fever (20%). The most common GIT symptoms were vomiting (40.1%), diarrhea (37.6%) then abdominal and gastric pain (29.1%). COVID-19 severity was distributed as 32.6% mild, 30% moderate and 37.4% severe. GIT symptoms present in 27.2% of studied patients [26].

Among 204 COVID-19 patients in Hubei China, only 99 (48.5%) had gastrointestinal signs as their chief complaint. These COVID-19 patients had a diversity of digestive symptoms, including abdominal pain (0.4%), anorexia (83.8%), diarrhea (29.3%), and vomiting (0.8%) [24].

A retrospective study conducted by Guan et al reported that among 1099 COVID-19 patients from 552 centers across China, 5% of cases had nausea and vomiting, and 3.8% of cases had diarrhea [8]. A further study indicated that 32.5% of COVID-19 patients had at least one gastrointestinal tract symptom. These symptoms included diarrhea (37.8%), anorexia (56.7%), abdominal pain (10.4%), nausea (16.5%), and vomiting (7.9%) [27].

Additionally, Luo *et al* documented that 16% of 1141 cases, had at least one GIT symptom including, anorexia (98%), nausea, vomiting (66%), diarrhea (37%), and abdominal pain (25%) [28].

In New York, GIT symptoms have been identified in a single-center-case series, which included 892 cases. The most common symptom was diarrhea (19.8%), accompanied by nausea (16.6%), abdominal pain (7.8%), vomiting (10.2%), and anorexia (11.8%) [29].

An additional retrospective study conducted in New York showed that of 1059 COVID-19 patients, 22% had diarrhea, 6% had nausea, 19% had vomiting, and 7% had abdominal pain [30].

In addition to these studies, the pooled prevalence of GI symptoms was found to be 17.6 % in a meta-analysis of 60 studies involving 4243 cases in 6 countries. The most frequent symptom was anorexia (26.8%), accompanied by diarrhea (12.5%), nausea/vomiting (10.2%) and stomach pain/discomfort (9.2%) [31].

The study by Gadiparthi et al showed that the higher Glasgow Blatchford bleeding score was 7 and 11 in 2 of 3 patients on admission and represents a high risk of gastrointestinal bleeding (GIB) with a need for intervention of more than 50%. However, both young patients responded by carefully controlling hemodynamic parameters, levels of hematocrit or hemoglobin, transfusion of packed red blood cells as needed and medical therapy.

Table 12 Relation between disease severity and CT findings in studied patients

		Disease severity				X^2	*P*-value
		Mild: Mod (*N* = 68)		Severe (*N* = 32)			
CT findings	**GGO**	43	63.2%	27	84.4%	**4.6**	**0.031**
	Crazy-paving appearance	12	17.6%	15	46.9%	**9.4**	**0.002**
	Normal	22	32.4%	0	0%	**13.2**	**< 0.001**
CORAD class	**CORAD 1**	18	26.5%	0	0%	**15.1**	**0.002**
	CORAD 3	9	13.2%	2	6.3%		
	CORAD 4	22	32.4%	11	34.4%		
	CORAD 5	19	27.9%	19	59.4%		

Abbreviation: S *p*-value < 0.05 is considered significant, X2 Chi-square test, HS *p*-value < 0.001 is considered highly significant

Table 13 Relation between disease severity and PCR results in studied patients

		Disease severity				X^2	*P*-value
		Mild: Mod (*N* = 68)		Severe (*N* = 32)			
Nasal swab	**Negative**	0	0%	0	0%	---	---
	Positive	68	100%	32	32%		
Rectal swab	**Negative**	52	76.5%	23	71.9%	0.24	0.621
	Positive	16	23.5%	9	28.1%		

X2: Chi-square test

NS: *p*-value > 0.05 is considered non-significant

Although GIB was resolved, two patients died due to respiratory failure [32].

In a meta-analysis of 4,243 COVID-19 patients, the prevalence of gastrointestinal symptoms was 17.6%, with anorexia as the commonest symptom (26.8%), diarrhea (12.0%), nausea or vomiting (10.0%), and abdominal pain (9.0%) [33].

The results of current study showed that 25 patients (25%) had positive viral RNA in rectal swab.

A meta-analysis that included 436 patients with established diagnoses by Wong et al. showed that the stool detection rate among them was 43.7% [34].

Wang et al revealed that of 153 patients with COVID-19, 44 (29%) showed positive stool virus [4]. Moreover, Xiao *et al* indicated that of 73 COVID-19 patients hospitalized in China, 17 (23.29%) showed SARS-CoV-2 RNA in stools. Xiao et al demonstrated that infectious SARS-CoV-2 may be secreted from virus-infected gastrointestinal cells [35].

Our study results revealed that severe COVID-19 was more frequent in older age. There was statistical significant (p-value < 0.001) increased age in severe patients (55.2 ± 12.2 years) when compared with mild: moderate patients (42.7 ± 5.02 years).

The results of current study were supported by Zhou et al who confirmed that increased age of patients with COVID-19 was associated with death [6]. Petrilli et al. described characteristics of 4103 patients in New York City with laboratory-confirmed COVID-19 disease, 1999 of them needed hospital admission while 650 of them needed ICU, respiratory support, were discharged to hospital and/or died. They found that older age was one of the most important predictors of hospitalization and a vital predictor of severe outcomes [36].

Khan et al. evaluated 648 COVID-19-positive patients with definitive outcomes to explore risk factors for critical outcomes. 11.9% of them were critical while 88.1% were non-critical. Out of the 77 critical patients, 15.6% (n=12) patients have died and 84.4% (n=65) have recovered. They stated that old age was independent risk factors for critical *outcomes* [37].

Similarly, Ghweil et al. involved 36 patients with mild to moderate COVID-19 and 30 patients with severe/critical infection. There was a significant older age among severe (62.6 years old±10.1SD) than mild to moderate infection (55.5 ± 10.1) (p<0.05) [38]. Taha et al. revealed that the severity and mortality of COVID-19 were significantly predominant in the older age groups [39]. Also Teima et al noticed that age significantly differed as regarding COVID-19 severity where old age patients (53.03 ± 8.87) had severer disease symptoms [26].

Table 14 Multivariate logistic regression analysis for factors predictive of severe patients

	B	SE	*p*-value	Odds	95% CL	
Age	**0.19**	**0.43**	**< 0.001**	**1.21**	**1.11**	**1.32**
Sex	0.0	0.42	1.0	1.0	0.43	2.3
BMI (Kg/m2)	0.035	0.044	0.423	1.03	0.95	1.12
Residence	- 0.13	0.43	0.757	0.87	0.37	2.03
SES	0.3	0.46	0.513	1.35	0.54	3.3
Smoking	0.34	0.51	0.502	1.4	0.51	3.8
Fever	1.07	0.59	0.073	2.9	0.9	9.4
Malaise	1.07	0.59	0.073	2.9	0.9	9.4
Loss of smell	- 20.5	13397	0.999	0.0		
Cough	0.7	0.46	0.129	2.01	0.81	4.9
Dyspnea	**0.98**	**0.47**	**0.039**	**2.7**	**1.05**	**6.7**
Chest pain	- 20.6	12710	0.999	0.0		
Vomiting	0.08	0.49	0.872	1.08	0.4	2.8
Diarrhea	- 0.5	0.56	0.368	0.6	0.19	1.8
Nausea	- 0.03	0.44	0.944	0.96	0.4	2.3
Pain	- 0.58	0.56	0.295	0.55	0.18	1.67
Hematemesis	1.49	1.24	0.229	4.6	0.39	51.1
Melena	22.02	28420	0.999			
D-Dimer (mg/L)	**1.09**	**0.4**	**0.007**	**2.9**	**1.35**	**6.5**
LDH (U/L)	**0.005**	**12.7**	**< 0.001**	**1.0**	**1.0**	**1.01**
Ferritin (ng/mL)	**0.004**	**0.001**	**< 0.001**	**1.0**	**1.0**	**1.01**
CRP (mg/dL)	**0.03**	**0.009**	**0.001**	**1.03**	**1.01**	**1.05**
ALT (U/L)	**0.019**	**0.007**	**0.008**	**1.01**	**1.0**	**1.03**
AST (U/L)	**0.019**	**0.007**	**0.007**	**1.01**	**1.0**	**1.03**
Hb (g/dL)	- 0.12	0.1	0.241	0.88	0.71	1.08
PLTs (10*3/UL)	0.002	0.002	0.312	1.0	0.99	1.01
WBCs (10*3/UL)	- 0.021	0.044	0.637	0.979	0.89	1.06
ALC (10*3/UL)	**- 2.2**	**0.54**	**< 0.001**	**0.11**	**0.038**	**0.31**
NC (10*3/UL)	0.008	0.042	0.855	1.01	0.92	1.09
LNR	0.34	0.34	0.315	1.4	0.72	2.7
PT (Seconds)	0.41	0.21	0.051	1.5	0.99	2.3
INR	1.02	1.82	0.573	2.7	0.07	99.9
Creat (mg/dL)	0.3	0.32	0.344	1.35	0.72	2.55

Table 15 Multivariate logistic regression analysis for factors predictive of severe patients

	B	SE	*p*-value	Odds	95% CL	
GGO	**1.14**	**0.54**	**0.037**	**3.1**	**1.07**	**9.2**
Crazy-paving app	**1.41**	**0.47**	**0.003**	**4.1**	**1.6**	**10.5**
Nasal swab	0.91	0.49	0.063	2.5	0.95	6.5
Rectal swab	0.24	0.48	0.621	1.27	0.49	3.2

B Regression coefficient, *SE* Standard error, *CL* Confidence interval

In agreement with our findings, Liu et al reported that elderly patients with COVID-19 are more likely to progress to severe COVID-19 disease in comparison with young and middle aged COVID-19 patients [40]. Also, Mahase et al and Yang et al reported similar findings. This could be explained by the age-dependent decline in cell-mediated immune function and reduced humoral immune function [41, 42].

Table 16 Description of GIT manifestations in all rectal PCR positive studied patients

		Studied patients (*N* = 25)				
		Disease severity				
		Mild *N*=10	Moderate *N*=6	Severe *N*=9	X^2	*p*-value
GIT manifestations	**Vomiting**	5	3	4	0.71	0.965
	Diarrhea	4	3	0	5.6	0.59
	Nausea	9	4	4	4.5	0.104
	Abdominal Pain	1	1	1	0.16	0.919
	Hematemesis	0	0	0	---	---
	Melena	0	0	0	---	---
	No symptoms	1	0	3	3.4	0.181

Abbreviation: *X2* Chi-square test, *NS p*-value > 0.05 is considered non-significant

Our study results revealed that dyspnea was associated with severity of COVID 19 infection. We found statistically significant (p-value = 0.036) increased percentage of dyspnea in severe patients (24 patients, 75%) when compared with mild: moderate patients (36 patients, 52.9%).

Our data are in accordance with those of Ghweil et al. who revealed that only dyspnea rather than other presenting manifestations was significantly associated with COVID-19 severity [38]. In accordance, Zheng et al reported a significant positive association of shortness of breath/dyspnea with COVID-19 progression to severe illness and death [43]. Additionally, In a recent meta-analysis, Shi et al. reported similar findings and recommended dyspnea rather than fever as an indicator of poor outcome in COVID-19 patients [44].

In our study, patients with severe infection were indicated to have a higher percentage of leukocytosis and lymphopenia when compared with mild and moderate cases. We found Statistically significant (p-value = 0.006) increased WBCs in severe group (Median = 10, IQR = 6.7 - 12.5 x10^3/ul) when compared with moderate group (Median = 6.35, IQR = 4.9 - 8.6 x10^3/ul) and mild group (Median = 6.6, IQR = 4.5 - 9.7 x10^3/ul), and highly statistical significant (p-value < 0.001) decreased % of lymphocytes in severe group (Median = 0.9, IQR = 0.7 - 1.5 %) when compared with moderate group (Median = 1.45, IQR = 1.1 - 1.7 %) and mild group (Median = 2.1, IQR = 1.37 - 2.9 %).

Taha et al. [39] revealed that the severity and mortality of COVID-19 were significantly associated with lower median absolute lymphocyte counts and higher median absolute neutrophil counts, among severe patients and non-survivors. Also, lymphopenia < 1 x 10^3/μL was an independent predictor of disease severity. Additionally, Ghweil et al. [38] analyzed the hematological indices of the included COVID-19-patients and revealed significantly lower mean values of lymphocytic count among severely infected patients than those had mild to moderate COVID-19.

We observed statistically significant increased AST in severe group when compared with moderate group and mild group.

Hepatic dysfunction in SARS-CoV-2 infection was reported by Chen et al., who noticed increased serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) serum levels in 43.4% of COVID-19 cases from Wuhan, with mild elevation in most of them [45]. Then, a strong reasonable relation between abnormal liver biochemistries and SARS-CoV-2 infection severity has been highlighted [46]. In a study by Lu et al., severe to critical cases exhibited significantly higher serum ALT and AST levels than those who had mild to moderate COVID-19 [47].

Our study results revealed that increased CRP and high serum levels of ferritin and lactate dehydrogenase were significantly associated with COVID-19 severity. We observed statistical significant (p-value < 0.001) increased LDH in severe patients (421.8 ± 244.7) when compared with mild: moderate patients (238.7 ± 152.3). Also we observed statistical significant (p-value < 0.001) increased ferritin in severe patients (475.3 ± 227) when compared with mild: moderate patients (287.2 ± 186).

In Ghweil et al., there were significantly higher mean values of CRP, ESR, and ferritin among patients with severe/critical COVID-19 when compared with those having mild to moderate COVID-19, p<0.05 for all [38]. Also, Taha et al. revealed significantly higher inflammatory and tissue damage markers (CRP, ESR, ferritin, PCT, and LDH) among severe COVID-19 patients and those who died from the disease. Also, ferritin ≥ 350 ng/mL was an independent predictor of COVID-19 severity with an odds ratio of 11.08 [39]. Li et al identified 269 (49.1%)

of 548 patients as severe cases on admission. The authors reported that high CRP, high serum ferritin, and high lactate dehydrogenase level were significantly associated with severe COVID-19 on admission (Li et al., 2020). Another recent study from our locality evaluated 116 confirmed patients with COVID 19 infection revealed that CRP was associated with disease severity and clinical outcome [48].

The results of current study showed significantly higher serum values of D-dimer among severely infected than those who had mild or moderate COVID-19 infection. We found statistical significant (p-value < 0.001) increased D-Dimer in severe patients (13 ± 25) when compared with mild: moderate patients (0.8 ± 0.5).

Results obtained in this study were in agreement with Zhou et al. [6] who found D-dimer more than 1 μg/mL is associated with mortality of COVID-19. Petrilli et al reported striking findings regarding the predictive value of inflammatory markers to distinguish future critical from non-critical illness. Early elevation in D-dimer level had the strongest association with prolonged hospitalization and the need for mechanical ventilation or death [36].

The results of the current study showed a significantly high frequency of bilateral peripheral GGO among patients with mild to moderate COVID- 19, while in those with severe/critical infection, their CT chest revealed a crazy-paving appearance. Additionally, CT chest findings were a significant predictor for the severity of COVID-19 infection.

Pan et al reviewed 21 confirmed COVID-19 patients. They noticed the rapid growth of GGOs into crazy-paving appearance as the disease progresses, with its disappearance in the absorption stage, concluding that crazy-paving pattern could be considered as one of the indices that could be used to evaluate the course of the disease [24].

Similar findings were reported by Ghweil et al., in which normal CT chest was recorded in 12 cases (33.3%) with mild to moderate infection and the remaining 24 patients (66.6%) exhibited focal or multifocal ground glass opacities (GGO) with patchy consolidations and distributed peripherally (subpleural), involving mostly the posterior part or lower lung lobes, while all included cases (30 patients, 100%) with severe COVID-19 showed crazy-paving appearance (in the form of reticular and/or interlobular septal thickening) with or without GGO [38].

Our study had some limitations like the retrospective design, single center study, and lack of outpatient representation. We are willing to conduct future studies with an increased sample size, include mild outpatient cases for comparison and to conduct multicenter study with cooperation with other research centers and universities for broader generalizability, this could not be done due to limitations we faced during the study due to the sudden unexpected pandemic with deficiency in personnel and equipment, including many acquired infections in the medical team for which they were isolated and temporarily banned from offering medical services. Future studies with proper arrangements and anticipation can overcome these limitations and complete our work in a wider range.

Conclusion

GI manifestations are frequent in COVID -19 patients (Nausea: 38%, Vomiting: 24%, abdominal pain: 22%, diarrhea: 21%, hematemesis: 3% and melena: 2%), and vary in severity among patients.

Rectal PCR is not significant to detect patients with COVID-19 even in those with GI symptoms. Based on our study results we recommend to evaluate GI patients for the presence of GI symptoms, while we are not recommending to routinely check rectal PCR for COVID-19 patients even if they are symptomatic with GI symptoms.

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None.

Authors' contributions

WM formulated the research idea and shared in data analysis, and manuscript revision. SS supervised data analysis and manuscript drafting. SA shared in data collection, statistical analysis, and manuscript drafting. AA shared in the formulation of the research hypothesis, data processing, statistical analysis, and drafting of the final manuscript. All authors have read and approved the final manuscript.

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Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

All subjects involved in the study signed an informed consent to participate. The study was approved by the Ethical Review Board of Ain Shams University. The study protocol conforms to the ethical guidelines of the Declaration of Helsinki as reflected in a priori approval by the institution's human research committee.

Consent for publication

Participants provided a consent for the study findings to be published.

Competing interests

All authors declare they have no competing interests.

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