Case Report:

Clinical Case Series of Gastrointestinal Symptoms in Patients With Novel Coronavirus 2019 Infection

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ABSTRACT

Background: Various digestive symptoms have been frequently reported in a significant portion of patients infected with the virus since the outbreak of Coronavirus Disease 2019 (COVID-19). Most patients with COVID-19 have a fever accompanied by respiratory signs and symptoms, such as cough and dyspnea. We present 36 cases with a chief complaint of Gastrointestinal (GI) symptoms along with respiratory symptoms. In this study, we aimed at investigating the prevalence and outcomes of COVID-19 patients with digestive symptoms.

Methods: A variety of observed GI symptoms included nausea and vomiting (72.2%), diarrhea (25%), abdominal pain (19.4%), loss of appetite (14%), and anosmia (14%). The most non-GI symptoms were dyspnea (66.7%), fever (66.7%), dry cough (58.3%), myalgia (52.4%), and others. Six patients (16.6%) were critically ill, 7 (19.4%) were in stable condition, and 23 patients (64%) showed moderate symptoms. Among the patients, 7 (19.5%) needed critical care and were admitted to ICU. Leucopenia, lymphopenia, and elevated acute-phase proteins were other features observed in these patients. The most common antiviral regimen was hydroxychloroquine and oseltamivir. Finally, 32 patients (89%) were discharged, and 4 (11%) died.

Conclusion: This case series study highlights that patients with COVID-19 are prone to GI symptoms along with fever and respiratory symptoms. Patients may even present with digestive symptoms and without any respiratory symptoms. Hence, clinicians should pay more attention to these patients and help diagnose COVID-19 earlier to start prompt treatment before the occurrence of severe disease.

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Introduction

In December 2019, a cluster of acute respiratory illness, now known as a Novel Coronavirus–Infected Pneumonia (NCIP), occurred in Wuhan, Hubei, China [1]. Full-genome sequencing and phylogenic analysis indicated that 2019-nCoV is a distinct clade of beta coronaviruses associated with human Severe Acute Respiratory Syndrome (SARS) and the Middle East Respiratory Syndrome (MERS) [2]. This pneumonia was called Coronavirus Disease 2019 (COVID-19) by the World Health Organization on February 11, 2020.

The first confirmed case of the disease in Iran was reported from Qom City (the assumed source of COVID-19 in Iran) on February 19, 2020 [3]. Then, it was disseminated all over the country. It is well established that most patients with COVID-19 have a fever accompanied by respiratory signs and symptoms, such as cough and dyspnea [4, 5]. In addition to fever and respiratory problems that seem to be the initial and major symptoms, Gastrointestinal symptoms (GI symptoms) are observed in many patients [6].

Recent studies have shown that the ACE2 receptor (angiotensin-converting enzyme), essential for cells infected by COVID-19, is highly expressed not only in lung AT2 cells but also in absorptive enterocytes of the ileum and colon [7, 8]. Therefore, digestive symptoms like diarrhea and abdominal discomfort will occur by the invaded enterocytes malabsorption, which theoretically indicates that the digestive system might be vulnerable to COVID-19 infection. The results of our study further confirm that the digestive system may be a potential route for COVID-19 infection.

In this study, we enrolled 36 out of 100 COVID-19 cases with a chief complaint of GI symptoms and respiratory manifestations in Razi Hospital located in Mazandaran Province, north of Iran, between February 25 and March 10, 2020. It is worth mentioning that the current research was approved by the Mazandaran University of Medical Sciences Ethics Committee (approval code of IR.MAZUMS.REC.1398.1436).

Cases Report

This research included 36 hospitalized patients with confirmed COVID-19 who were admitted to Razi Hospital (the referral center of novel coronavirus 2019) in the north of Iran. They all showed gastrointestinal symptoms, including diarrhea, nausea, vomiting, loss of appetite, abdominal pain, and anosmia. Among the patients, 17(47.2%) were male, and 19(52.8%) were female. The Mean±SD age of the patients was 55.3±15 (50.2-60.4) years, and half of them (~50%) were 31-59 years old. Among the patients, 24(66.7%) had close contact with confirmed COVID-19 patients, 4(11.1%) had a history of travel to areas with a high rate of COVID-19, and 8(22.2%) had hospital-related transmission (they were either the health-care worker or those who had referred to hospital to receive care). The median time from appearing the first symptoms on admission to hospital and discharge was 5 days (IQR, 4) and 7 days (IQR, 3), respectively (Table 1). As presented in Table 1, 21 patients (58.3%) had one or more comorbidities: hypertension (10, 47.6%), diabetes (9, 43%), cardiovascular disease (7, 33.3%), and respiratory disease (5, 23.8%).

According to Table 1, a variety of observed Gastrointestinal (GI) symptoms included nausea and vomiting (26 cases, 72.2%), diarrhea (9 cases, 25%), abdominal pain (7 cases, 19.4%), loss of appetite (5 cases, 14%), and anosmia (5 cases, 14%). The most non-GI symptoms were dyspnea (24 cases, 66.7%), fever (24 cases, 66.7%), dry cough (21 cases, 58.3%), myalgia (19 cases, 52.4%), and others (headache, fatigue, etc.). Seven patients (19.5%) who needed critical care were admitted to ICU, but 29 patients (80.5%) did not require intensive therapy, so they were hospitalized in non-ICU rooms. Among the patients, 6(16.6%) were critically ill (severe condition), 7(19.4%) were in stable condition, and 23 patients (64%) showed moderate symptoms. As reflected in Table 1, 12 patients had multi-organ dysfunction: 9 (25%) with heart injury, 3(8.4%) with ARDS, 2(5.6%) with acute liver injury, and 1(2.8%) with acute renal injury. Among the 4 patients (11%) who died, 3 belonged to ICU-hospitalized patients, and 1 was in the non-ICU section.

The blood counts of patients on admission showed leucopenia (white blood cell count less than 4×10^9/L) in 5 patients (13.8%) and lymphopenia (lymphocyte count $<1.0\times10^9$/L) in 16 patients (44.4%). Twenty-two patients (61.1%) had neutrophils above the normal range.

As Table 2 indicates, hemoglobin was below the normal range in 16 patients (44.5%), so do the platelets. The Median of prothrombin time was 14 seconds (IQR, 2). The level of aspartate aminotransferase (AST) increased in 9 patients (25%), alanine aminotransferase (ALT) increased in 3 patients (8.3%), and alkaline phosphatase (ALP) level raised only in one patient (2.7%). Creatine phosphokinase (CPK) increased in 12 patients (34%), among whom the virus-related cardiac injury was diagnosed. Moreover, Table 2 demonstrates laboratory data in detail. The most common antiviral regimens were

Table 1. Demographics, clinical characteristics, and clinical outcomes of 36 COVID-19 patients with GI symptoms

Variabels		Mean±SD/No. (%)
Age, y		55.3±15 (range: 50.2-60.4)
Age group, y	18-30	3 (8.3)
	31-59	18 (50)
	60-69	9 (25)
	≥ 70	6 (16.7)
Sex	Male	17 (47.2)
	Female	19 (52.8)
Risk factor	Close contact	24 (66.7)
	Health-care workers	8 (22.2)
	History of traveling	4 (11.1)
Admission setting	ICU	7 (19.5)
	Non-ICU	29 (80.5)
Co-morbidity, n=21	Hypertension	10 (47.6)
	Diabetes	9 (43)
	Cardiovascular disease	7 (33.3)
	Respiratory disease	5 (23.8)
Hospitalized days	Median (IQR)	7 (3)
Digestive Symptoms	Nausea/vomiting	26 (72.2)
	Diarrhea	9 (25)
	Abdominal pain	7 (19.4)
	Loss of appetite	5 (14)
	Anosmia	5 (14)
Non-digestive Symptoms	Fever	24 (66.7)
	Dyspnea	24 (66.7)
	Dry cough	1 (58.3)
	Myalgia	61 (61)
	Fatigue	8 (22.2)
	Others (headache, diaphoresis, productive cough, diaphoresis, faintness)	10 (28)
The onset of symptoms to admission (d)	Median (IQR)	5 (4)
Comorbidity, n=21	Hypertension	10 (47.6)
	Diabetes	9 (43)
	Cardiovascular disease	7 (33.3)
	Chronic respiratory disease	5 (23.8)

Variabels		Mean±SD/No. (%)
Organ dysfunction, n=12	Heart dysfunction	9 (25)
	ARDS	3 (8.4)
	Acute liver injury	2 (5.6)
	Acute renal injury	1 (8.4)
Clinical outcome	Death	4 (11)
	Improvement	32 (89)
History of smoking, substance and alcohol abuse	None of the patients	

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GI: Gastrointestinal; ARDS: Acute Respiratory Distress Syndrome; ICU: Intensive Care Unit; SD: Standard Deviation; IQR: Interquartile Range.

hydroxychloroquine and oseltamivir for 13 patients (36.1%), and hydroxychloroquine, oseltamivir, and lopinavir-ritonavir for 6 patients (16.7%). Approximately all patients (33, 91.6%) received antibiotics, and the most prescribed antibiotics were levofloxacin (15, 45.4%), ceftriaxone (13, 39.4%), vancomycin (11, 33.3%) followed by imipenem, tazocin, azithromycin, teicoplanin, and meropenem, respectively (Table 3).

Table 3 indicates that Heart Rate (HR), Respiratory Rate (RR), Temperature (T), and mean arterial pressure (MAP) of all patients were recorded on the first day of their admission in the hospital (with a median of HR: 88 (IQR, 24); RR: 19 (IQR, 2); Temperature: 37 (IQR, 1) and MAP: 93 (IQR, 14). The median oxygen saturation of patients was 92.5% (IQR, 17.5).

Discussion

This study is a case series of 36 out of 100 patients hospitalized with COVID-19 in the north of Iran. We included all confirmed cases of 2019-nCoV in Razi Hospital with gastrointestinal discomfort as the chief complaint. Among the patients recruited in this study, 32(89%) were discharged, and 4(11%) died. The common symptoms at the onset of illness were dyspnea and fever [4-6].

Although in clinical practice, the patients' respiratory systems are mainly affected by COVID-19, damage to other organs of the patients has also been reported [9, 10], especially in critical patients who are susceptible to multiple organ dysfunction [11]. We found that digestive symptom is a common complaint among patients with COVID-19 [12], along with nausea/vomiting, abdominal pain, diarrhea, and loss of appetite. Clinicians mostly focus on respiratory symptoms to label cases as a definite COVID-19 so that they may miss or underestimate cases, initially referring with non-respiratory symptoms. Patients with digestive symptoms usually do not go to a hospital, and the disease may not be diagnosed until respiratory symptoms occur. Therefore, they have a longer onset of illness than other patients. Among the 36 patients with COVID-19 we enrolled, the rate of GI symptoms was higher than the reported data of 3% from Wuhan [5] and the findings of the study conducted by Jin et al. [13]. However, a recent report from Wuhan revealed that 10.1% experienced nausea/diarrhea, and 3.6% suffered from vomiting [4].

We can suggest many explanations for why COVID-19 appears to cause digestive symptoms. One answer is the similarity of COVID-19 and SARS-CoV that can attack the human body by binding to the human angiotensin-converting enzyme 2 receptor. This reaction causes liver tissue injury by upregulation of ACE2 expression in liver tissue caused by a compensatory proliferation of hepatocytes derived from bile duct epithelial cells [14]. The other theory is that COVID-19 causes direct and indirect damages to the digestive system by an inflammatory response. Several studies revealed that viral nucleic acid was detected in stool samples in up to 53.4% of patients [15-17]. The intestinal flora plays an essential physiological role in the body, like regulating the body's nutritional metabolism, regulating the development and maturation of the body's immune system, and antibacterial effects [18].

Our data indicated that patients with digestive symptoms had no underlying gastrointestinal diseases. Unlike other studies [9, 10], we found only 2 patients with liver dysfunction, so there was no significant liver injury in this study, similar to the research conducted by Wu et al. [19]. Initially, we suggested that COVID-19 patients with GI symptoms have elevated liver function test, such as aminotransferases (AST and ALT). In contrast to the

Table 2. Laboratory data of 36 COVID-19 patients with GI symptoms

Evaluated Components	No. (%)
	Median (IQR)
White blood cell count, $\times 10^9$/L (normal range 4-10)	6.05 (3.65)
● *Leucopenia*	5 (13.8)
● *Leukocytosis*	4 (11.1)
Hemoglobin, g/L (normal range 12-15)	12.25 (2.07)
Hematocrit ratio, % (normal range 35-50)	36.4 (5.63)
Neutrophil ratio, % (normal range 40-66)	70.7 (24.35)
● *Increased*	22 (61.1)
Lymphocyte ratio, % (normal range 20-40)	22 (25.1)
● *Lymphopenia*	16 (44.5)
Monocyte ratio, % (normal range 2-8)	6.3 (4.48)
Platelet count, ×109/L (normal range 150-450)	160 (88)
● *Decreased*	16 (45.7)
Prothrombin time, s (normal range 11-14)	14.1 (1.88)
Increased	17 (53.1)
International normalized ratio (normal range 0.9-1.5)	1.26 (0.28)
● *Increased*	2 (8.3)
Alanine aminotransferase, U/L (normal range <34)	28 (16)
● Increased	3 (8.3)
Aspartate aminotransferase, U/L (normal range 5-40)	35 (15)
● *Increased*	9 (25)
Alkaline phosphatase, U/L (normal range 46-306)	131 (59)
● *Increased*	1 (2.7)
Creatine phosphokinase, U/L (normal range <145)	115.5 (107.5)
● *Increased*	12 (34)
Blood urea nitrogen, mg/dL (normal range 13-43)	27.5 (17.5)
● *Increased*	8 (22.2)
Lactate dehydrogenase, U/L (normal range 345-470)	626 (254)
● *Increased*	34 (94.4)
Blood glucose, mg/dL	110.5 (26)
Estimated sedimentation rate, mm/h (normal range <14)	59 (40.5)
Increased	36 (100)
C-reactive protein (Positive, %)	87
Creatinine, mg/dL (normal range 0.6-1.2)	0.9 (0.3)
● *Increased*	6 (16.6)
Serum sodium, mmol/L (normal range 135-145)	139 (7)
● *Increased*	3 (8.3)
Serum potassium, mmol/L (normal range 3.5-5.5)	4.4 (0.7)

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Increased means over the upper limit of the normal range and decreased means below the lower limit of the normal range.

Table 3. Clinical findings, vital signs, and treatment of 36 COVID-19 patients with GI symptoms

Vital Sgns			Median (IQR)/No. (%)
Heart rate (beats/minute)			88 (24)
Respiratory rate (breaths/minute)			19 (2)
Temperature (°C)			37 (1)
Mean arterial pressure (mm Hg)			93 (14)
O2 saturation (%)			92.5 (17.5)
Body mass index, kg/m² *Overweight (BMI>24)*			50 (55.5)
Severity	*Mild*		7 (19.4)
	Moderate		23 (64)
	Severe		6 (16.6)
Treatment	Antiviral regimen		13 (36.1)
	● *HCQ+Oseltamivir*		6 (16.7)
	● *HCQ+Oseltamivir+Kaletra®*		33 (91.6)
	Antibiotics	*Levofloxacin*	15 (45.4)
		Ceftriaxone	13 (39.4)
		Vancomycin	11 (33.3)

HCQ: Hydroxychloroquine; Kaletra: Lopinavir/Ritonavir.

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study done by Jin et al. [13], there were no significant abnormalities in our research to prove that. Hence, it requires further studies to find an exact correlation between them.

Like other studies, our study had some limitations. First, the sample size was small, and it might limit the validity of the results. Moreover, we did not have stool samples, so we could not correlate digestive symptom prevalence and severity with the presence of viral RNA in stool specimens. Thus, further studies need to be done to determine the prognostic value of stool testing as both a diagnostic and prognostic indicator in COVID-19.

This case series study highlights that patients with COVID-19 are prone to GI symptoms, along with fever and respiratory symptoms. In particular, patients may present digestive symptoms without respiratory symptoms. Hence, clinicians should pay more attention to these patients and help diagnose COVID-19 earlier to start treatment promptly before the occurrence of severe disease.

Ethical Considerations

Compliance with ethical guidelines

All ethical principles were considered in this article.

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Authors' contributions

All authors equally contributed to preparing all parts of the research.

Conflict of interest

The authors declared no conflict of interest.

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