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Gastrointestinal Symptoms in Patients with Coronavirus Disease 2019: A Single-Center Observational Study

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Keywords:

Coronavirus-infected pneumonia; Diarrhea; Gastrointestinal symptoms; Novel coronavirus 2019

Abbreviations:

ACE2: angiotensin-converting enzyme II; AIDS: acquired immunodeficiency syndrome; ALB: albumin; ALT: alanine aminotransferase; AST: aspartate aminotransferase; COVID-19: coronavirus disease 2019; CT: computed tomography; GI: gastrointestinal; HIV: human immunodeficiency virus; INR: international normalization ratio; LOS: length of stay; nCoV: novel coronaviruses; PLA: People's Liberation Army; PT: prothrombin time; TBIL: total bilirubin

1. Abstract

1.1. Background: The first case of novel coronavirus 2019 (COVID-19) was reported in Wuhan, China in December 2019, and the disease has rapidly spread globally. This study aimed to determine the characteristics and functioning of the Gastrointestinal (GI) system in patients admitted to our center with COVID-19 and to provide guidance on the prevention and treatment of this disease.

1.2. Methods and Material: This observational study included 64 patients hospitalized with coronavirus disease 2019 within the age range of 18-85 years. We analyzed data on patient characteristics, disease severity, incubation period, initial symptoms and GI manifestations, timing of positive testing, duration of symptoms, and duration of antiviral therapy. Analysis involved continuity-adjusted chi-square test for independent samples.

1.3. Results: The mean incubation period was 7.7±6.5 days, and the mean duration of hospitalization was 18.84±9.75 days. Key symptoms were fever (84.37%), cough (57.8%), fatigue (20.3%), diarrhea (18.75%), muscle aches (17.18%), dyspnea (14%), sore throat (12.5%), decreased appetite, and headache (10.9%). Sixty percent of patients developed GI symptoms 1–30 days after disease onset, including diarrhea (69.2%), nausea (23.07%), abdominal distension (7.69%), and hematochezia (2.56%). Among patients with GI symptoms, 33.33% had symptoms before receiving therapy, of whom 92.3% had diarrhea; 66.67% of patients developed GI symptoms, primarily diarrhea (57.69%), after receiving therapy.

1.4. Conclusions: Most NCIP patients had diarrhea and abnormal transaminase levels. Severe complications such as GI bleeding should be anticipated in this patient group. Data presented herein can serve as a reference for COVID-19 prevention and treatment.

2. Introduction

Since the first reported case of novel coronavirus 2019 (COVID-19) in Wuhan in December 2019, the disease has spread rapidly throughout China and other countries worldwide, including Singapore, Japan, and the United States. The COVID-19 outbreak has triggered global concern [1, 2]. COVID-19, which was caused by the infection of 2019 novel coronaviruses (2019-nCoV), has now been included as a Class B infectious disease in the Law of the

People's Republic of China on Prevention and Treatment of Infectious Diseases [2], while preventive and control measures designated for Class A infectious diseases have been adopted to deal with the outbreak.

Coronavirus is an enveloped, positive-sense RNA virus that belongs to the family of beta nCoV. The World Health Organization named the virus the "2019 novel coronavirus" and the related disease "coronavirus disease 2019" [3]. Studies have found that 2019-nCoV enters cell primarily through the angiotensin-converting enzyme II (ACE2) receptor [4]. ACE2 is expressed in respiratory organs and in the small intestine, duodenum, colon, and liver [5, 6], suggesting that the Gastrointestinal (GI) system may also be a target of 2019-nCoV. Indeed, a research group showed that some of the infected patients in that study had GI symptoms, including diarrhea (3.7%) and vomiting (5.0%) and reported the incidence of increased levels of transaminases at 21%-22% [5]. The virus 2019-nCoV exhibits high infectivity. In fact, patients infected with 2019-nCoV and even asymptomatic carriers can be sources of infection. The main route of virus transmission is through respiratory droplets and close contact. However, it has been reported that viral nucleic acid testing of stool specimens and rectal swabs was positive [7]. Viable 2019-nCoV has been detected in stool specimens [8]. One report showed that patients with confirmed infection who later tested negative during nucleic acid retesting of specimen from pharyngeal swabs, nonetheless, had positive test results from their stool specimens [9]. These findings suggest that this virus can be transmitted through environments contaminated by stool.

During clinical diagnosis and treatment performed at the Fifth Medical Center of Chinese People's Liberation Army (PLA) General Hospital in China, we also noted that some patients developed GI symptoms, whose clinical manifestations might be of great significance for the prevention and treatment of COVID-19. The present study has summarized GI manifestations among patients with COVID-19 admitted to our center, with the aim of providing evidence and guidance for the prevention and treatment of this disease.

3. Methods

3.1. Study Population

Data of patients with COVID-19 admitted to the Fifth Medical Center of Chinese PLA General Hospital in China were collected from Jan 25 to Feb 29, 2020.

The inclusion criteria were based on the Guidelines for Diagnosis and Treatment of Novel Coronavirus Pneumonia (provisional version 7), issued by the National Health Commission of China [10], and included: 1) patients with fever and cough-related symptoms; 2) patients with positive results of 2019-nCoV nucleic acid testing, whose chest Computed Tomography (CT) scans indicated changes associated with viral pneumonia, and who had a clinical diagnosis of COVID-19.

3.2. Study Methods

We analyzed data on patients' general condition, severity of disease, and incubation period, as well as the initial symptoms, manifestations, timing, and duration of GI symptoms. We estimated the time of disease onset from the time of contact with an individual with suspected COVID-19 or visit to a venue that might have been exposed to COVID-19.

3.3. Statistical Analysis

Data were analyzed using the SPSS 23.0 statistical software (IBM SPSS statistics). Quantitative data were expressed as $\bar{x}\pm SD$, and qualitative data were expressed as count (percentage). P-values <0.05 were considered statistically significant.

4. Results

4.1. Patient Characteristics and Disease Conditions

The study included 36 males (56.25%) and 28 females (43.75%), within the age range of 18-85 (49±18) years. Thirty-two patients (50%) had history of contact with someone infected with COVID-19. The mean incubation period was 7.7±6.5 days, and the mean length of stay (LOS) in the hospital was 18.84±9.75 days. Key disease manifestations were fever (84.37%), cough (57.8%), fatigue (20.3%), diarrhea (18.75%), myalgia (17.18%), dyspnea (14%), sore throat (12.5%), and others, including decreased appetite, headache, nausea, and hematochezia (10.9%) (Table 1). All the patients were treated with antiviral therapy by lopinavir/ritonavir.

Table 1: Summary of patient characteristics (N=64)

General Characteristics		Frequency (%)
Gender	Male	36 (56.25)
	Female	28 (43.75)
Age (years)	Mean	49 ±18
LOS (in days)	Mean	18.84±9.75
Main clinical manifestation	Fever	54 (84.37)
	Cough	37 (57.8)
	Fatigue	13 (20.3)
	Diarrhea	12 (18.75)
	Muscular soreness	11 (7.18)
	Dyspnea	9 (14)
	Sore throat	8 (12.5)

4.2. Key GI Manifestations

A total of 60.9% (39/64) of patients developed GI symptoms at the time of disease onset and during the treatment course. These symptoms appeared 1-30 days after disease onset and lasted for 1-15 days, with a mean of 3.9±3.1 days. The GI symptoms reported were diarrhea (69.2%; 27/39), nausea (23.07%; 9/39), abdominal distension (7.69%; 3/39), and hematochezia (2.56%; 1/39) (Table 2).

Among patients who had GI symptoms, 33.33% (13/39) had GI symptoms before receiving treatment; among these patients, 92.3% (12/13) had diarrhea. GI symptoms developed after therapy

in 66.67% (26/39) of patients, primarily diarrhea (57.69%; 15/26). Among patients who developed GI symptoms after therapy, 7 (26.9%; 7/26) developed symptoms after discontinuation of anti-viral drugs. The GI symptoms reported among these patients were nausea (26.9%; 7/26), abdominal distension (11.54%; 3/26), and hematochezia (3.85%; 3.85) (Table 3).

Moreover, 28.1% (18/64) of patients had abnormal liver function on the day of admission, with mean levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) at 96.7±22.6 and 107.2±35.2 U/L, respectively. Approximately 10.8±8.6 days after receiving therapy, 31.25% (20/64) of patients had mean AST and ALT levels at 102.5±66.3 and 119.6±60.2 U/L, respectively. However, the increase in bilirubin level was not significant, with a mean value of 12.06±6.29 umol/L. Concurrently, the mean albumin level was 38.23±5.26 g/L, prothrombin time (PT) was 12.28±1.29 seconds, and International Normalized Ratio (INR) was 1.23±0.59 (Table 4).

Table 2: Summary of gastrointestinal symptoms of COVID-19 (60.9%)

General Characteristics		Frequency (%)
GI manifestation	Diarrhea	27(69.2)
	Nausea	9(23.07)
	Abdominal distention	3(7.69)
	Hematochezia	1(2.56)

Table 3: Summary of gastrointestinal symptom before and after anti-viral therapy

	Prior to treatment	Post treatment	Duration of symptoms (d)
	n (%)	n (%)	
GI manifestation	13 (33.33)	26 (66.67)	3.9±3.1
Diarrhea	12 (92.3)	15 (57.69)	
Nausea	1 (7.69)	7 (26.9)	
Abdominal distention	0	3 (11.54)	
Hematochezia	0	1 (3.85)	

Table 4: Summary of gastrointestinal symptom data

	Prior to treatment		Post-treatment	
	mean±SD		mean±SD	
ALT (U/L)	107.2±35.2	18 (28.1%)	119.6±60.2	20 (31.25%)
AST (U/L)	96.7±22.6	18 (28.1%)	102.5±66.3	20 (31.25%)
TBIL (umol/L)	12.06±6.29			
ALB (g/L)	38.23±5.26			
PT (S)	12.28±1.29			
INR	1.23±0.59			

4.3. Adjunct Testing

Patients with GI bleeding underwent emergency gastroscopy and colonoscopy. Gastroscopy revealed no discernable bleeding mucosal lesions. Colonoscopy revealed old blood and local diverticula that were visible in the intestinal lumen (Figure 1). The base of the mucous membrane appeared smooth after washing. We observed no erosion, ulcers, or bleeding lesions in the washed mucosa. Lung CT scans showed multiple bilateral ground-glass opacities (Figure 2).

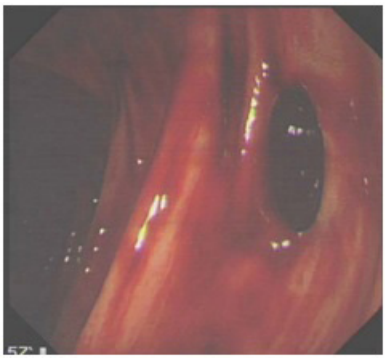

Figure 1: Colonoscopy noted fresh blood throughout the colon and a few diverticula

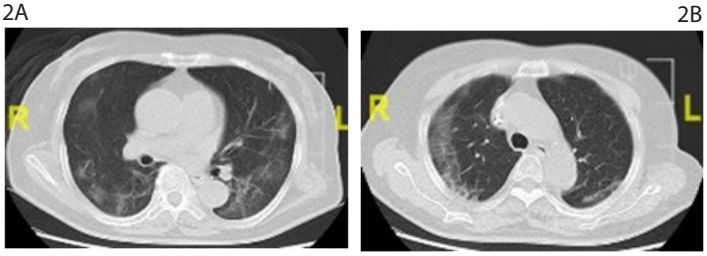

Figure 2: Progressive diffuse interstitial opacities and consolidation in the bilateral lower lung fields on CT scan

5. Discussion

Current epidemiological investigations show that the incubation period of the 2019-nCoV is 1–14 days, with the majority being 3-7 days [10]. The key manifestations are fever, dry cough, and fatigue, while some patients also have symptoms such as nasal congestion, rhinorrhea, sore throat, and diarrhea [10, 11]. The present study has found that 60.9% of infected patients displayed GI symptoms at disease onset and during diagnosis and treatment, among which 33.33% had GI symptoms at the time of disease onset. Among these patients, the most common GI symptom was diarrhea (92.3%). GI symptoms developed in 66.67% of the patients after receiving therapy, which primarily manifested as diarrhea (57.69%). As such, it is possible that disease-related factors and GI symptoms might be therapy-related.

Lopinavir/ritonavir is a compound formulation. Lopinavir is a protease inhibitor for the treatment of acquired immunodeficiency syndrome (AIDS) caused by human immunodeficiency virus (HIV) infection. It blocks the cleavage of Gag-Pol polyprotein, leading to the production of immature, non-infectious viral particles. Ritonavir is an active peptidomimetic inhibitor against the aspartyl proteases HIV-1 and HIV-2. The inhibition of HIV proteases by ritonavir in turn inhibits the processing of the Gag-Pol polyprotein precursor. This results in production of immature HIV particles that fail to initiate a new infection cycle. The most common treatment-related adverse reactions during the use of lopinavir/ritonavir are diarrhea, nausea, vomiting, hypertriglyceridemia, and hypercholesterolemia. The risk of diarrhea may be higher in patients who receive their drugs once daily [12, 13].

Studies have shown that adverse reactions associated with lopinavir/ritonavir are mainly GI reactions and reactions that affect liver and kidney functions, bone metabolism, blood glucose, and blood lipid levels [13, 14]. Among patients who developed GI symptoms after treatment in the present study, 7 (26.9%) developed symptoms after discontinuation of antiviral drugs. Thus, we cannot rule out the fact that the cause of the observed GI symptoms was viral virulence. Symptomatic support and other treatments alleviated the GI symptoms. The mean duration of symptoms was 3.9±3.1 days.

By comparison, diarrhea, nausea, and vomiting may occur at the beginning of treatment [12]. Many research groups have detected viable 2019-nCoV in patients' intestines and stools. The virus enters the cells in the small intestine, duodenum, and colon through ACE2, thereby reaching the GI tract, which becomes the target organ. This can partially explain symptoms such as diarrhea and abdominal distension. In addition, analyses have shown that stools of infected patients are free of red or white blood cells, which is consistent with the characteristics of diarrhea caused by viruses. In addition to therapy and disease-related factors, the GI symptoms experienced by patients in the present study might be related to fever and digestive disorders associated with a particular stage of the disease.

Guidelines on Diagnosis and Treatment of Novel Coronavirus Pneumonia (provisional version 7), issued by the National Health Commission of China, stipulate that elevated levels of liver enzymes, lactate dehydrogenase, muscle enzymes, and myoglobin may occur in certain patients [10]. Relevant observations from cases in the present study included: hepatomegaly, degeneration and focal necrosis of hepatocytes with neutrophil infiltration, hepatic sinusoidal dilatation, lymphocyte and monocyte infiltration in the portal area, and micro thrombosis. The pathogenesis of COVID-19-related liver injury is related to multiple organ insufficiency syndrome, drug-induced liver injury, microcirculation disorder, and direct liver injury caused by novel coronavirus. As ACEII is also expressed in the liver [15], it cannot be ruled out that 2019-nCoV may also act on the liver, leading to elevated levels of liver enzymes. Liver injury incurred or aggravated in the treatment of COVID-19 may be related to liver injury caused by antiviral therapy and other drug therapy, and it could be the result of successive or joint action of various mechanisms. In the present study, 28.1% of patients had increased AST and ALT levels at admission. Their condition improved after receiving symptomatic treatments, such as hepatoprotection and therapies that reduced the levels of liver enzymes. In contrast, there was no significant changes in TBIL, ALB, and PT levels, which are indicators of synthesis and metabolic function of the liver. As most patients had received antivirals or other drugs in the early stages of disease onset, they are prone to drug-induced elevation of liver enzymes.

One of the patients with severe disease with GI symptoms treated at our center developed hematochezia and hemorrhagic shock due to bleeding, which might have been the effect of viral virulence. SARS-CoV-2 shares more than 85% homology with bat SARS-like coronavirus. It has been reported that GI bleeding in patients with SARS is caused by the SARS virus itself, which leads to vasodilation and hyperemia of the GI mucosa and bleeding in specific GI segments [16]. A previous study has reported that a critically ill patient with COVID-19 infected with 2019-nCoV also had coagulopathy [7]. It is possible that the severe condition of the patient was due to the direct action of 2019-nCoV on the target organ that led to coagulation abnormalities. Concurrently, treatment with steroids and mental stress due to illness may induce acute GI bleeding [17]. The attenuated defense mechanism of the GI tract may lead to the development of stress ulcers in some patients. Finally, stress and viral infection might cause colonic diverticular bleeding. More case support is needed in the study of COVID-19 with GI bleeding.

In summary, most patients with COVID-19 admitted to our center had GI symptoms, which primarily manifested as diarrhea and abnormal transaminase levels. All patients were followed up for more than 6 months without digestive and respiratory symptoms or recurrence. There is a need for further research to unveil the mechanism of diarrhea caused by COVID-19 and its significance in the transmission of the disease. Furthermore, severe complications such as GI bleeding at disease onset and during treatment should be anticipated in this patient group. It is hoped that this article can draw attention to the gastrointestinal symptoms in patients with COVID-19. Data presented in this study may guide in the development of COVID-19 prevention and treatment strategies.

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