

## Hepatology and Gastroenterology | Research article

# Gastrointestinal Manifestations can be the only expression of COVID-19; A Report of hotpoint area in Middle East

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## Abstract

**Background:** COVID-19 is a worldwide public health problem that has attracted much attention due to its clinical and para-clinical findings. In the western Asia, Qom was the first city to report COVID-19 cases on a large scale. We report gastrointestinal (GI) manifestations, as the only primary signs of COVID-19 infection have been reported.

**Methods:** Data were obtained from patients, referred to GI clinics in Qom city, from February 25th to March 15th, 2020 who had refractory GI symptoms but there was no detection of digestive diseases after typical medical examinations. They were requested to do follow up tests, eventually the patients were tested for COVID-19. The presence of COVID-19 was confirmed based on the WHO guidelines.

**Results:** 25 patients were enrolled in our study, of which 14 subjects were male. The average age of patients was  $43.4 \pm 14$  years. The mean BMI  $\pm$  SD was  $19.4 \pm 1.8$  Kg. The main presentations were nausea, abdominal pain, and diarrhea in 16 (64%), 11 (44%) and 4 (16%) patients, respectively. Hematemesis was observed in two patients. In addition, recent loss of appetite, partial anosmia and dry mouth were reported in 3 (13%), 1 (4%) and 1 (4%) patients respectively. In the follow up, all of the cases demonstrated main symptoms of COVID-19.

**Conclusions:** GI symptoms can be the solitary complaint of patients with COVID-19 which may cause late diagnosis and lead to the virus spreading more broadly. Consequently, in GI clinics the disease must be considered a serious issue, and appropriate protection and surveillance of staff are recommended.

**Keywords:** COVID-19, Infection, Gastrointestinal, Epidemiology

## Introduction

The novel Coronavirus outbreak was reported in December 2019 in China. It was later affirmed as a global health emergency by the World Health Organization (WHO). The new viral infection was caused by SARS-CoV-2 and named COVID-19 [1]. The virus then spread to all of the countries in the world and became a pandemic health problem.

In mid-February 2020, the first case of the virus in Iran was reported in Qom. Subsequently, this city was considered as the hotspot of infection in Iran and also in the Middle East.

Based on recent studies in the literature the virus mainly attacks the respiratory system and subsequently causes respiratory illnesses such as acute respiratory syndrome [2, 3]. Also, the spectrum of clinical presentations of COVID-19 varies from asymptomatic infections to mild upper respiratory tract illnesses, severe viral pneumonia with respiratory failure and eventually death [4]. Although the respiratory symptoms of COVID-19 are the most common manifestations, other less common presentations may also be seen [4, 5]. Gastrointestinal (GI) manifestations including nausea, vomiting, diarrhea and abdominal discomfort may be observed at the onset of the disease or together with respiratory symptoms [6]. In a recent publication from the United States, it was indicated that nausea and vomiting accompanied a dry cough 2 days before admission of patients testing positive for COVID-19 [7]. However, to our knowledge, GI symptoms have not been reported as the sole signs of COVID-19 as of yet. In such circumstances, it can be assumed that a silent transmission of the virus occurred in the abovementioned patients. Indeed, former studies proposed that viruses can spread via fecal-oral routes even before classic presentations [6, 8].

Qom is a city in the centre of Iran with expanded communication with other cities due to its religious site and industrial centres. This city is located on the main route connecting north to south and west to east. The COVID-19 outbreak occurred and was identified from February to March 2020. During this period Qom also faced an increasing number of outpatients in adult gastroenterology clinics and healthcare workers had to deal with patients with refractory gastrointestinal symptoms and resistance to typical medical treatment. The result of all diagnostic approaches was negative. There were neither viral, nor respiratory manifestations. Indeed, a high rate of coronavirus infection among gastroenterologists and their staff was observed compared to other physicians in this area. Therefore, it was hypothesized that the personnel of these clinics may have had contact with asymptomatic patients with digestive tract problems and this clinical presentation was the only presentation of COVID-19.

## Method

### Patient Selection

The patients who have been referred to the three gastrointestinal clinics in Qom between February 25th to March 15th were considered. Each of them, based on presenting complaints, underwent appropriate standard medical and laboratory interventions including upper or lower endoscopy, abdominal ultrasonography and assessment of complete blood count (CBC), liver enzyme and pancreatic tests. The patients with confirmed digestive tract diseases treated accordingly.

The patients with refractory symptoms without definitive abnormalities in para-clinical findings were followed up. During the follow-up, the patients who complained of respiratory problems referred to COVID-19 centers for more evaluations. Other patients were monitored by visiting or communications via social networking or by phone. Due to the remarkable COVID-19 epidemic statistics, we suspected about the infection. These patients, with only gastrointestinal problems, were screened for COVID-19 by the means of PCR and chest CT scan. The confirmed COVID-19 patients based on WHO guidelines were selected. These patients invited for new interview and the data of them was collected.

## Laboratorial Evaluations

Venous blood samples were obtained from each participant. Serum separator tube was used for blood clotting and the sera were obtained after centrifugation. Ethylene Diamine Tetra Acetic acid (EDTA)-containing tubes were used for CBC analysis by an Auto-Analyzer BS200 (Mindray, Shenzhen, China). Diagnostic kits have been made by Pars Azmoon Company (Pars Azmoon Co., Tehran, Iran) for alanine aminotransferase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase (ALP).

An automated blood cell counter (Sysmex K1000, Hamburg, Germany) used for CBC and differential blood counts including hemoglobin concentration, mean corpuscular volume, red blood cell count and morphology, platelet count, and white blood cell count and types.

The BMI (body mass index) calculated by using square of the height (kg/m<sup>2</sup>) measurement. One-step Real-time PCR was performed by referral diagnostic laboratory which confirmed by the Qom University of Medical Sciences, Qom, Iran based on universal protocols. A nasopharyngeal swab into viral transport media (VTM) was used for commercial RNA extraction according to manufacturer's instructions.

## Statistical Analysis

The results analysis by SPSS version 20 (IBM, SPSS ver.20). Continuous variables were expressed as Mean  $\pm$  SD or simple ranges, as appropriate. Categorical variables were state as counts and percentages.

## Results

Totally 25 patients were selected in this study, 14 (56%) males and 11 (44%) females. The average age was 43.4  $\pm$  14 years old. The mean BMI was 19.4  $\pm$  1.8 Kg. Table 1 represents the basic characteristics of patients. Of all patients, 7 were recalled that had history of contact with suspected subject. There was no history of contact with animal or seafood market or travel to China. However, two

of them were not citizen of Qom and travel to other cities by public transport. Two patients had diabetes and other two patients were smoker.

The main gastrointestinal symptoms were nausea, abdominal pain, and diarrhea with 16 (64%), 11 (44%) and 4 (16%) patients, respectively. Gastrointestinal bleeding including hematemesis was reported in three (13%) patients. One of them had the history of ulcerative colitis. In addition, recent loss of appetite, partial anosmia and dry mouth were also reported in 3 (13%), 1 (4%) and 1 (4%) patients, respectively.

During their follow-up, the patients presented the COVID-19 signs and symptoms. This period takes 8  $\pm$  2 days. In this time, the main clinical and diagnostic presentations were partial shortness of breath, fever, and also nausea and abdominal pain. The patients complained of abdominal pain located on umbilical and epigastric area (Table 2).

A positive RT-PCR result was recorded in all patients. Table 3 shows the laboratorial data of patients during undiagnosed and diagnosed periods. The acquired data was almost different in all items including white blood cell, lymphocytes and neutrophil. Lymphopenia (<1500) was stated in 13 (52%) patients but the lung involvement in chest CT scan was illustrated in 23 (92%) patients.

Of all patients, 7 patients had contact with a suspected subject. There was no history of contact with animal or seafood, wholesale Market or travel to China. However, three of them travel to other cities by public transports. Details of underlying diseases including diabetes, hypertension etc. and another clinical data are shown in Table 1.

## Discussion

In the present study, we have provided evidence of solely gastrointestinal presentations of the infection by COVID-19 which could be the initial manifestation of disease. Of these patients, 7 (28%) had a history of contact with suspected coronavirus cases and the others had no history of exposure and had not travelled to areas with a high risk of disease. In fact, at the beginning of the outbreak of COVID-19 the diagnosis of disease was more difficult and the significant alarming signs and symptoms of the disease were obscure. Hence, its diagnosis was clinically more complicated, until classic signs occurred; similar information was also indicated in reports from China [2, 9].

Nevertheless, in current reports, a few patients complained of certain symptoms that may be related to viral infections but these were not the chief complaint of patients. Furthermore, the patients did not complain of any respiratory symptoms. Moreover, laboratory data

did not give us further clues for identification of the virus. Along with these facts, our findings may support the hypothesis that many of patients may have been contaminated person to person by asymptomatic patients or during an incubation period. Therefore, asymptomatic patients can be considered as a source of infection and they can spread the virus and consequently large-scale transmission in this city from asymptomatic patients is suspected. Clearly, pathogenicity and transmission of COVID 19 is more powerful than severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS). Therefore, rapid transmission of the virus can be assumed where there is close contact in crowded places. Similar results were reported in South Korea during the MERS outbreak [10]. Furthermore, COVID-19 can be transmitted in cluster form that can cause the transmission in 80% of cases that outweighs MERS or SARS [10-12]. This rate in MERS and SARS were about 20%-30% [13]. Chan JF et al. reported a familial cluster of SARS-CoV-2 infection. In this paper, the author introduced family members with a history of travel to Wuhan, China. One of whom did not travel, but became infected later on. This patient had no symptoms but ground-glass lung opacities were detected in radiography [14]. Also, in a report from Germany, transmission of COVID-19 after probable direct contact with asymptomatic subjects was mentioned [15]. In previous reports about SARS and MERS, asymptomatic patients reached 7.5 % and 25% respectively [16, 17]. Weak immune response or other routes of transmission may possibly influence asymptomatic presentation of COVID-19 [15, 18]. Whether the fecal-oral route plays a role in this respect calls for further investigation. Previous studies in the literature on the coronavirus family indicated the possibility of transmission via fecal-oral routes and actually isolated COVID-19 virus from stools too [19, 20]. Therefore, it is of utmost importance that asymptomatic patients be identified and warnings be given, concerning these carriers to control the epidemic. Indeed, some studies have revealed that viral load plays a key role in the spreading of infection. Interestingly, viral load was not significantly different between symptomatic and asymptomatic patients in more recent studies [21]. The asymptomatic patients may develop symptoms during the course of disease. What was observed in Qom was in accordance with this means.

The majority of our patients were young male. These findings are comparable with reports from China [4]. Our patients had only gastrointestinal symptoms of whom the majority complained of abdominal pain and nausea. Additionally, the related COVID-19 symptoms developed more than one week later, after the first visit.

In many studies gastrointestinal symptoms are considered as part of the manifestations of COVID-19. In a study by J. J. Zhang et al., the characteristics of 140 symptomatic patients in which gastrointestinal symptoms were the most reported common symptoms presenting in 39.6% of cases and out of those nausea was the most common symptom [22]. Furthermore, Wang D et al. reported that gastrointestinal symptoms were not common in COVID-19 patients [23]. In this context, Liang W et al. emphasized on subjects presenting with diarrhea as an initial complaint [24]. Also, Huang C et al. stated that among all the COVID-19 positive patients in Wuhan, gastroenteric problems were also reported in a small number of patients and the main symptom was diarrhea [25]. The same result was mentioned in a report from Chen N et al. [5]. These findings indicated that gastrointestinal symptoms are an uncommon presentation of COVID-19 that may occur in the early stages of the disease or as the disease progresses and may require modification in the screening algorithm. In this regard, patients and medical staff are at risk of contamination [26].

Regarding liver injuries, liver enzyme alteration was observed. Our finding was compatible with previous reports indicating that liver injury may not be determined as a considerably significant problem at the onset of the disease, although it could occur in the course of the disease, relating to direct or indirect virus invasion or side effects of medications as MERS or SARS [27-29].

Altogether, it can be assumed that the digestive system may be an alternative route for the spread of infection. Hence, physicians across the different disciplines, especially those in gastrointestinal clinics, must take particular care to identify the patients whose only symptoms are gastrointestinal problems.

Our study limitation was the sample size which it was due to the recent emergence of the disease.

## Conclusion

In the present study, we have illustrated that a gastrointestinal (GI) manifestation can be the sole presenting clinical presentation of COVID-19. In this regard, the diagnosis of disease is more complicated and spread of the virus would be easier and even extensive via different transmission routes. In these circumstances, a high rate of contamination by other clients and medical staff particularly within gastrointestinal clinics could occur. Therefore, all patients referring to medical centers especially gastrointestinal and endoscopy centers should be considered as suspected cases of COVID-19 and appropriate protection and surveillance should be employed. Also, modification of screening criteria may be required.

## Abbreviations

BMI: Body Mass Index

COVID-19: Coronavirus Disease-2019

GI: Gastrointestinal

SARS: Severe Acute Respiratory Syndrome

MERS: Middle East Respiratory Syndrome

WHO: World Health Organization

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Variable	Total Patients=25 N, (%)
Mean age(year)± SD	43.4± 14
Gender(M/F)	14/11
BMI; Mean	19.4± 1.8
15-29 yr.	4, (16)
30-49 yr.	11, (44)
50-69 yr.	9, (36)
≥70 yr.	1, (4)
Smoking	2, (8)
Opium	1, (4)
Diabetes	2, (8)
Neurologic Disease	2, (8)
Chronic GI Diseases	1, (4)
Usage of immune suppressive drug	1, (4)

**Table 1: The basic characteristic of COVID-19 patients who have been admitted to Corona-hospitals**

Variable	Before Diagnosis (First Visit)	Diagnosis of COVID19
Temperature; Mean	<37.4	>37.8
<37.5	18(72%)	6(24%)
37.5-37.9	7(28%)	12(48%)
38.0-38.9	0	6
>39.0	0	1
Conjunctiva Congestion	N*	N
Nasal Congestion	N	N
Sore Throat	N	3
Headache	3	6
Coughing	N	5
Sputum Production	N	N
Fatigue	2	6
Myalgia /Arthralgia	N	2
Weight Loss	N	2
Chills	2	6
Chest Pain (Non-Cardiac)	N	1
Sweating	N	2
Anosmia	N	3
Shortness of Breath	N	18
Dizziness	N	N
Globus sensation	1	3
Nausea and Vomiting	11	20
Abdominal pain (Epigastria)	10	13
Constipation	1	2
Diarrhea	4	6

Table 2: The clinical presentation of COVID-19 patients before and in beginning of viral infection. \*Negative

Variables	Normal range	First visit	After 7-10days	<i>P value</i>
WBC (Mean $\pm$ SD)	4-9.5 Cell count $\times 10^9/L$	5.8 $\pm$ 1.6	6.35 $\pm$ 5.4	0.01
>10.0		N	4	
<4.0		N	6	
Neutrophil (Mean $\pm$ SD)	1.8-7.4 Cell count $\times 10^9/L$	5 $\pm$ 1.6	5.3 $\pm$ 4.3	0.01
Lymphocyt (Mean $\pm$ SD)	1.0-4.4 Cell count $\times 10^9/L$	2.2 $\pm$ 1.0	2.0 $\pm$ 1.8	0.01
<1500(N)		6	13	
plat (Mean $\pm$ SD)	150-400 Cell count $\times 10^9/L$	200 $\pm$ 180	190 $\pm$ 140	0.01
<150000(N)		4	10	
Protrombin Time	13 second			
Creatinin (Mean $\pm$ SD)	0.6-1.4 mg/dl	1.1 $\pm$ 0.26	1.1 $\pm$ 0.3	0.05
Bilirubin Total (Mean $\pm$ SD)	0.1-1.1 mg/dl	1.1 $\pm$ 0.2	1.25 $\pm$ 0.21	0.6
ALT (Mean $\pm$ SD)	15-40 IU/L	27.8 $\pm$ 28.2	28 $\pm$ 27	0.1
AST (Mean $\pm$ SD)	15-40 IU/L	27.3 $\pm$ 30	29.42 $\pm$ 32	0.1

**Table 3: Laboratories results of COVID-19 patients who have been admitted to Corona-hospitals**