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COVID-19 and related gastrointestinal symptoms: An observational study

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ABSTRACT

Objective: COVID-19 pandemic has infected the entire world and causes obsolete morbidity and mortality. While respiratory symptoms are the most frequently reported, several recent studies revealed that gastrointestinal symptoms are not uncommon. Our aim in this observational study is to reveal the gastrointestinal symptoms of COVID-19 patients.

Patients and Methods: Data of COVID-19 patients with gastrointestinal symptoms were recorded and retrospectively analyzed during their hospital follow-up period. 82 patients participated in the study and later on had a positive polymerase chain reaction (PCR) test. Gender, age, systemic and gastrointestinal complaints, medical and surgical disease history, laboratory results, thorax computer tomography (CT) findings, and characteristics of gastrointestinal system (GIS) symptoms of patients were also recorded. Data were analyzed by statistical software.

Results: The most common typical symptoms of COVID-19 patients were cough, anosmia, debility, and shortness of breath. Further, most of the gastrointestinal symptoms found in COVID-19 patients were nonspecific abdominal pain.

Lymphopenia and elevated liver transaminases were the most common findings of the tests. Patients with diarrhea indicated watery diarrhea. Two patients also had ileus, they healed spontaneously without surgical intervention. Furthermore, all patients were discharged without any problems.

Conclusion: Gastrointestinal symptoms are typical in COVID-19 patients. However, these symptoms do not seem to have a detrimental effect on the progression of the disease. In our study group, there was no need for surgical intervention, but COVID-19 patients with gastrointestinal symptoms should be treated by a multidisciplinary approach.

Keywords: COVID-19, Gastrointestinal symptom, Diarrhea, Intestinal obstruction

1. INTRODUCTION

The COVID-19 pandemic has resulted in several new challenges for the global healthcare system. Mostly recognized as a respiratory pathogen and with major symptoms thought to be fever and cough, gastrointestinal symptoms of the global pandemic were identified shortly thereafter, and emerging data revealed that the gastrointestinal system (GIS) is one of the eventual targets of the pathogenic SARS-COV-2 virus, which enters lung cells via the angiotensin-converting-enzyme (ACE-2) receptor, which is highly abundant and reproductive on GIS epithelial cells [1].

SARS-COV-2 RNA was found in the feces in 83.3% of patients, and these patients still have viral RNA particles in their stools even after elimination from the respiratory tract. So, there was concern about the likelihood of fecal to oral transmission [2, 3].

Moreover, 50% of patients experience GIS symptoms such as nausea, vomiting, diarrhea, and abdominal pain. Typically, these

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symptoms were seen after respiratory findings. The severity of the gastrointestinal symptoms is related to COVID-19 general disease severity [3]. The pathophysiology can be specifically linked to direct damage of the GIS by inflammatory response in addition to the ACE-2 receptor-related mechanism. Enterocytes might also be destroyed by viral particles, resulting in malabsorption and unbalanced intestinal secretion presented by symptoms such as diarrhea [2, 3].

Some studies revealed that patients might have GIS symptoms just before the advent of respiratory manifestations of COVID-19, meaning that patients with these symptoms at the height of the pandemic may need to be carefully assessed according to status of outpatients and inpatients [4].

In this study, COVID-19 patients were hospitalized and later had GIS symptoms. The patients were analyzed according to the characteristics of their symptoms. The possible effects of the GIS on the COVID-19 disease were observed. Our aim in this observational study is to reveal the GIS symptoms of COVID-19 patients in Kutahya, Turkey.

2. PATIENTS and METHODS

After local ethical committee approval (Kutahya Health Sciences University, Local Ethical Committee approval number: 2020/10-02), the data of COVID-19 patients with gastrointestinal symptoms were recorded and retrospectively analyzed during their hospital follow-up period between June 2020-September 2020 in Kutahya Health Sciences University, Evliya Çelebi Research and Education Hospital. Eighty-two patients who had a positive finding for polymerase chain reaction (PCR) test and were hospitalized due to COVID-19 disease and who later had gastrointestinal symptoms participated in the study.

Patients who were hospitalized for another disease and later diagnosed with COVID-19 and also those with chronic GIS symptoms were excluded from the study.

Gender, age, systemic and GIS complaints, medical and surgical disease history, thorax computer tomography (CT) findings, and characteristics of GIS symptoms of patients were also recorded.

The major GIS symptoms addressed in this study include diarrhea, dyspepsia, abdominal pain, nausea, vomiting, epigastric pain, and constipation. Characteristics of diarrhea were also recorded. These patients were hospitalized by an infectious disease clinician and regularly consulted in our general surgery unit for gastrointestinal complaints

Statistical Analysis

While evaluating the findings obtained in the study, the IBM SPSS (Statistical Package for Social Sciences) Statistics 20 software was used for statistical analysis. For descriptive data in the study, frequency tables, descriptive statistics, and pie and bar charts were used.

3. RESULTS

Forty-three patients were female and 39 were male. The median age of the patients was 52 years (20-87). Moreover, the most common symptoms linked to COVID-19 were cough, cough and debility, and cough and high temperature (24.4 %, 18.3 %, and 14.6 %, respectively). Patients' general complaints during hospitalization are shown in Table I.

Table I. *Patients' general symptoms at hospitalization*

Variables	Symptoms	Number (n)	Percentage (%)
Patient Complaints	Anosmia, Abdominal pain	**19**	**23.1**
	Fever	1	1.2
	Fever, Cough	3	3.7
	Headache, Anosmia	9	11.0
	Muscle pain	1	1.2
	Myalgia, Cough	2	2.4
	Dyspnea, Cough	**12**	**14.6**
	Cough	**20**	**24.4**
	Cough, Weakness	**15**	**18.3**
	Anosmia	1	1.2
Other system findings	Fever	3	3.7
	Fever, Cough	**23**	**28.0**
	Headache	7	8.5
	Myalgia, Cough	1	1.2
	Cough	**47**	**57.3**

Hypertension was the most common medical comorbidity, and chronic obstructive pulmonary disease (COPD) and diabetes mellitus (DM) accompanied patients' illnesses (15.9 %, 6.1 %, and 6.1 %, respectively). Cholecystectomy was the most common condition (8.5 %) among the patients' surgical experience. The medical and surgical history of patients is shown in Table II.

Laboratory investigations revealed that lymphopenia was the most common finding with 41.5 %, while normal functions had 29.3%. Further, 18.3% of patients underwent abnormal liver function examinations. Almost all patients had a thorax CT except for one patient. Bilateral typical pulmonary infiltration was observed in 69.5 %. The laboratory and radiological properties of the patients are shown in Table III.

Nausea, abdominal pain, and vomiting were the most common complaints among patients (74.4 %, 65.9 %, and 50 %). The characteristics of the gastrointestinal symptoms are shown in Table IV.

While 14 patients had diarrhea, two had constipation related to intestinal obstruction. In addition, 71.4% of the patients with diarrhea (n:10) had watery diarrhea.

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Table II. *Medical and Surgical History of COVID 19 Patients*

Characteristics		Number (n)	Percentage (%)
Medical History	Asthma	1	1.2
	Bipolar Disorder	1	1.2
	Diabetes Mellitus	**5**	**6.1**
	Gestational Diabetes	1	1.2
	Pregnancy	1	1.2
	Hypertension	**13**	**15.9**
	Hypertension, Diabetes Mellitus	5	6.1
	Congestive Heart Failure	2	2.4
	Chronic renal disease	2	2.4
	Chronic obstructive pulmonary disease	**5**	**6.1**
	Coronary Heart Disease	1	1.2
	Malignity	1	1.2
	Cerebrovascular disease	1	1.2
	Ulcerative Colitis	1	1.2
	None	42	51.2
Surgical History	Appendectomy	3	3.7
	Inguinal Hernioplasty	2	2.4
	Cholecystectomy	**7**	**8.5**
	Coronary Bypass	2	2.4
	Peripheral Arterial Disease	1	1.2
	Thyroidectomy	1	1.2
	None	66	80.5

Table III. *Radiological and laboratory results of COVID 19 Patients with gastrointestinal symptoms*

	Pathology	Number	Percentage (%)
Thorax CT findings	**Bilateral pulmonary infiltration**	**57**	**69.5**
	Not ordered	1	1.2
	Normal	7	8.5
	Unillateral pulmonary infiltration	17	20.7
Laboratory Results	High D-Dimer Level	2	2.4
	High Liver Transanimases	**15**	**18.3**
	Lymphopenia	**34**	**41.5**
	Leucopenia, lymphopenia	6	7.3
	Normal	**24**	**29.3**
	High Urea/Creatinine Levels	1	1.2

Table IV. *Gastrointestinal symptoms of COVID-19 Patients*

Categories	Patient (n)	Percentage (%)
Abdominal Pain	54	65.9
Nausea	61	74.4
Vomiting	41	50.0
Epigastric Pain	20	24.4
Diarrhea	14	17.1
Dyspepsia	19	23.2

Moreover, 69.5 % of the patients (n: 57) did not require additional GIS investigations. Also, 19.5 % of the patients (n:16) had an occult blood test, while 8.5 % (n:7) had a stool culture. Two patients also had additional abdominal CT due to intestinal obstruction (Figure 1).

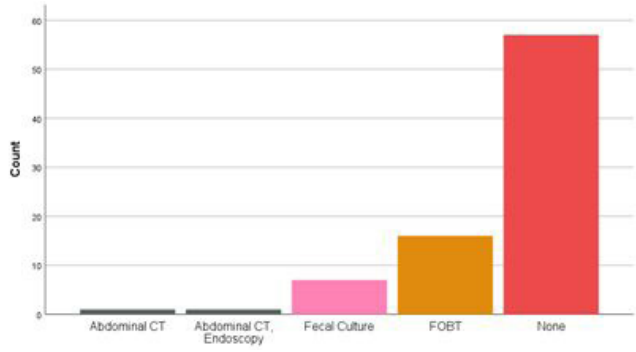

Figure 1. *Investigations for GIS symptoms*

These two patients encountered intestinal obstruction during the follow-up period. One of these patients was an 82-year-old male with prior stroke and history of upper gastrointestinal surgery with gastric outlet obstruction, which was spontaneously resolved following nasogastric decompression and supportive treatment. The other patient was a 55-year-old male, who had had inguinal hernioplasty before and had small intestinal fluids with gaseous fluids, and the ileus was also spontaneously resolved after supportive treatment and nasogastric decompression. Ranitidine was used in 85.4 % of the cases (n:70), followed by proton pump inhibitors (PPIs) (13 %). Metoclopramide, ranitidine, and PPIs were administered together to one patient with recurrent vomiting (Figure 2).

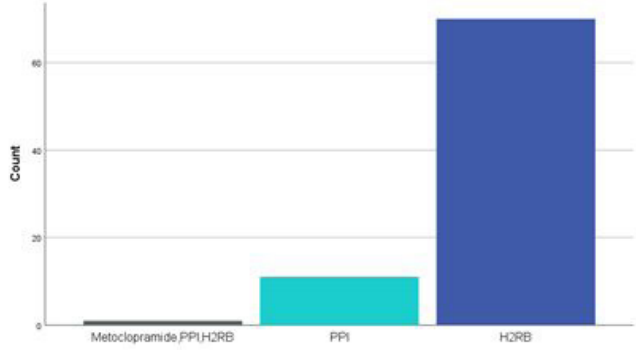

Figure 2. *GIS Treatment Agents*

4. DISCUSSSION

This prospective observational study is one of the high numbers of patient series demonstrating GIS manifestations in COVID-19 patients and Turkey's first case series.

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This study has some limitations, such as its retrospective nature and which data was obtained from the data set of the patients. Some of the information may be misleading, since symptoms may not have been assessed objectively. Patients who were added to the data were only those from the COVID-19 facilities, so patients in intensive care units were not included in the study.

In addition to respiratory tract findings, GIS symptoms are common with COVID-19 infection. As previously reported in such epidemic infections as SARS (severe acute respiratory syndrome), diarrhea, was frequently noted in 40% of patients. In those patients with gastrointestinal findings, respiratory assistance and intensive care follow-up ratios were increased. Also, some GIS symptoms were typical in patients with Middle East respiratory syndrome (MERS) [5].

In a review article, anorexia was found to be the most common GIS correlated with inflammation. Symptoms such as loss of appetite were difficult to assess and may be subjective, making diarrhea more objective [6]. In our study, we also did not ask patients about lack of appetite.

Diarrhea was seen in 17.1% (n:14) of our patients, and 71.4% of the patients with diarrhea (n:10) had watery diarrhea. Viral infection is thought to alter the intestinal permeability that causes enterocyte damage, so unbalanced intestinal activity leads to diarrhea. Lately, symptoms of diarrhea were increasingly reported in the literature [6].

One of the mechanisms linked to gastrointestinal manifestations is intestinal dysbiosis that was correlated with diminished species of *Lactobacillus* and *Bifidobacterium* [7]. Viral lung infection induces increased inflammatory response and viral translocation to the circulatory system, and sequentially altered microbiota results in increased intestinal permeability and inflammatory cytokines associated with secondary infections and multiple-organ failure [8]. Hence, the Chinese health commission recommends the use of probiotics [7]. In comparison to the literature reports, our patients had fewer GIS symptoms, but for a general assumption larger patient cohort is required.

Another proposed mechanism related to GIS is the cytokine storm, which causes severe systemic infection and multiple-organ failure, including the digestive system. Many cytokines may be dysregulated, resulting in abnormal immunity and drastic increase in disease severity. It is still unclear if the involvement of the gastrointestinal system is secondary to systemic inflammation or if primary intestinal infection may lead to disease [9]. Our patients did not need to be referred to an intensive care unit, so in mild disease condition, GIS may not contribute to disease severity.

The most common symptoms of our patients were nausea, abdominal pain, and vomiting (74.4%, 65.9%, and 50 %, respectively). In the literature, disease severity was significantly related to patients with COVID-19 who had abdominal pain, nausea, or vomiting [10]. However, there was no adverse event in our patients with GIS.

Epigastric pain and dyspepsia were also a common finding in these patients (24.4 % and 23.2 %, respectively). During our observations, these symptoms were spontaneously resolved.

In our analysis of seven patients with watery diarrhea, feces culture was requested, but no pathogens were found. For 16 patients, fecal occult blood tests were done, but none of them had positive results. In the literature, fecal-oral transmission is clearly indicated, and fecal viral shedding may continue even after respiratory tract infections have been resolved. There is still no consensus in clinical use to prevent fecal-oral transmission. However, great care must be taken against fecal-oral transmission in order to support the control of the infection resource [2].

Although, diarrhea is a prominent symptom related to unbalanced intestinal secretion, intestinal obstruction experienced by two of our patients was resolved spontaneously. These two patients underwent abdominal surgery, and possible related abdominal adhesions may lead to ileus symptoms. They did not have peritonitis during physical examination. In our study, patients had no signs of constipation. In literature, constipation is not a typical finding in COVID-19 patients; however, a recent study showed that critically ill patients with COVID-19 had higher gastrointestinal findings compared with similar patients who did not have COVID-19. High ACE-2 receptor expression might be responsible for this finding [11].

In our study, lymphopenia was the most common laboratory finding with 41.5%, while the normal range of laboratory results was 29.3%. Moreover, 18.3% of patients underwent abnormal liver function examinations. Abnormal liver function tests have been documented in a variety of studies. Persistent high levels of aspartate transferase, alanine transferase, and bilirubin were associated with serious illnesses. Several proposed mechanisms are contributing to liver injury. Direct damage to SARS-COV-2 hepatocytes, drug hepatotoxicity, systemic inflammation related to cytokine storm and hypoxic injury are the potential causes of liver injury [2, 3, 12]. In our patients, liver function tests resolved spontaneously during the follow-up period.

The management of GIS symptoms in patients with COVID-19 is supportive, so treatment must be tailored to the patients' characteristics and comorbidities. For patients with diarrhea and vomiting, adequate oral or intravenous hydration is essential [13]. ACE-2 inhibitors were associated with lower digestive symptoms by blocking potential ACE-2 receptors on the gastrointestinal system. However, its partial blockage may lead to a malfunction in the transport of amino acids in the intestine, which adversely leads to malnutrition, so its use is not widely accepted [14, 15].

In our patients, histamine-2 receptor antagonists were used in 85.4% of cases (n:70), while PPIs (13.4%) were rarely required. As recently stated in the literature, patients who are actively using PPIs are at increased risk for severe clinical outcomes related to COVID-19, so treatment for GIS gastrointestinal symptoms of COVID-19 patients must be individualized by weighing the benefits and risks [16].

Conclusion

Gastrointestinal symptoms are not rare in patients with COVID-19. In addition to taking care of respiratory symptoms

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in COVID-19 patients, gastrointestinal assessment and physical examination are essential.

Compliance with Ethical Standards

Ethical approval:

The approval was obtained from Kutahya Health Sciences University, Local Ethics Committee (approval number: 2020/10-02)

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Conflict of Interest: The authors have no conflicts of interest to declare

Authors' Contributions: ACY, SA and SZ: Drafting of the work, ACY and SA: Concept and design of the study, SZ and MFE: Data acquisition, OA: Statistical analysis, ACY,SA,SZ,MFE,FY, MCA: Medical practices. All authors critically revised the manuscript, approved the final version to be published, and agreed to be accountable for all aspects of the work.

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