RESEARCH ARTICLE / ARAŞTIRMA

DOI: 10.4274/mjima.galenos.2022.2021.25
Mediterr J Infect Microb Antimicrob 2022;11:25
Erişim: http://dx.doi.org/10.4274/mjima.galenos.2022.2021.25

Outcomes of COVID-19 in Patients with Inflammatory Bowel Disease: A Tertiary Center Experience

COVID-19'un Enflamatuvar Bağırsak Hastalarındaki Sonuçları: Üçüncü Basamak Merkez Deneyimi

Batuhan BAŞPINAR[1], İbrahim Ethem GÜVEN[1], İlhami YÜKSEL[1,2]

[1]*Ankara City Hospital, Clinic of Gastroenterology and Hepatology, Ankara, Turkey*
[2]*Ankara Yıldırım Beyazit University Faculty of Medicine, Department of Gastroenterology, Ankara, Turkey*

Abstract

Introduction: The frequency, risk factors, and outcome of Severe acute respiratory syndrome-Coronavirus-2 (SARS-CoV-2) infection in patients with inflammatory bowel disease (IBD) remain unclear. This study aimed to investigate the incidence and effects of SARS-CoV-2 infection in IBD.
Materials and Methods: Patients with IBD were recruited retrospectively between March 2020 and March 2021, and those with SARS-CoV-2 infection were analyzed.
Results: A total of 894 patients with IBD were identified during the study period. SARS-CoV-2 was detected in 18 (2.0%) patients, including five (1.2%) of the 430 patients with Crohn's disease (CD), 12 (2.8%) of 428 patients with ulcerative colitis (UC) and, one (2.8%) of 36 with unclassified IBD. The mean age was 42.2 years. Twelve (66.7%) of the patients were men. None of the patients was vaccinated for Coronavirus disease-2019. Five (27.8%) patients were hospitalized for a median of 10 days; the remaining patients were isolated at home. No intensive care unit admission or mortality occurred. Although a disease flare was not observed, a patient with UC who was on steroids demonstrated temporary terminal ileitis, pneumonitis intestinalis, and recto-vaginal fistulae. Six (33.3%) patients were on biologic agents, with one having concomitant immunomodulator and steroid therapy. The main gastrointestinal (GI) symptom was diarrhea in six (33.3%) patients.
Conclusion: The incidence of SARS-CoV-2 infection was 2.0% (n=18) in patients with IBD. Diarrhea is the most common GI symptom and should not be confused with IBD flare.
Keywords: COVID-19, Crohn's disease, inflammatory bowel diseases, SARS-CoV-2, ulcerative colitis

Öz

Giriş: Şiddetli akut solunum yolu sendromu-Koronavirüs-2 (SARS-CoV-2) enfeksiyonunun enflamatuvar bağırsak hastalığında (İBH) sıklığı, risk faktörleri ve sonucu hala belirsizliğini korumaktadır. Bu çalışma, İBH'de SARS-CoV-2 enfeksiyonunun insidansını ve etkilerini araştırmayı amaçlamaktadır.
Gereç ve Yöntem: İBH hastaları Mart 2020 ile Mart 2021 arasında geriye dönük olarak dahil edildi. SARS-CoV-2 enfeksiyonu olan hastalar analiz edildi.
Bulgular: Çalışma süresinde 894 İBH hastası başvurdu. SARS-CoV-2, 18 (%2,0) hastada tespit edildi: Crohn hastalığı (CH) olan 430 hastanın beşi (%1,2), ülseratif kolit (ÜK) olan 428 hastanın 12'si (%2,8) ve 36 sınıflandırılmamış-İBH (İBH-U) olan hastanın birinde (%2,8) ortalama yaş 42,2 yıldı. Hastaların 12'si (%66,7) erkekti. Hastaların hiçbirinde Koronavirüs hastalığı-2019'a karşı aşılanma öyküsü yoktu. Beş (%27,8) hasta ortanca 10 gün hastanede yattı, geri kalan hastalar evde izole edildi. Yoğun bakım ünitesine yatış veya ölüm olmadı. Hastalık alevlenmesi gözlenmemesine rağmen, steroid kullanan ÜK'li bir hastada geçici terminal ileit, pnömonitis intestinalis ve rekto-vajinal fistül görüldü. Altı (%33,3) hasta biyolojik ajan kullanıyordu ve bir hastada eş zamanlı immünomodülatör ve steroid tedavisi vardı. Başlıca gastrointestinal (Gİ) semptom altı (%33,3) hastada ishaldi.
Sonuç: İBH hastalarında SARS-CoV-2 enfeksiyonunun insidansı %2.0 (n=18) bulunmuş olup ishal en sık görülen Gİ semptomdur ve hastalık alevlenmesi ile karıştırılmamalıdır.
Anahtar Kelimeler: COVID-19, Crohn hastalığı, enflamatuvar bağırsak hastalığı, SARS-CoV-2, ülseratif kolit

Cite this article as: Başpınar B, Güven İE, Yüksel İ. Outcomes of COVID-19 in Patients with Inflammatory Bowel Disease: A Tertiary Center Experience. Mediterr J Infect Microb Antimicrob. 2022;11:25.

Address for Correspondence/Yazışma Adresi: Batuhan Başpınar MD, Ankara City Hospital, Clinic of Gastroenterology and Hepatology, Ankara, Turkey
Phone: +90 555 883 37 67 **E-mail:** batuhanbaspinar@gmail.com **ORCID ID:** orcid.org/0000-0003-3143-2642
Received/Geliş Tarihi: 23.01.2022 **Accepted/Kabul Tarihi:** 29.03.2022

Presented in: The presented study was presented as a poster (P1080) in United European Gastroenterology Week Virtual October 3-5, 2021.

Published: 10 April 2022

Introduction

The world has been struggling with novel Coronavirus disease-2019 (COVID-19) since December 2019 when Severe acute respiratory syndrome-Coronavirus-2 (SARS-CoV-2) was first identified in Wuhan, China[1,2]. Although the disease is mostly characterized by pneumonia leading to respiratory insufficiency, many other organ systems are involved. The pathophysiology and risk factors for COVID-19 have not been well understood yet. Thus far, literature data suggest that increasing age and comorbidities are the main risk factors for COVID-19 outcomes[2-4].

Inflammatory bowel disease (IBD) is a spectrum of immune-mediated bowel disorders that mainly consist of Crohn's disease (CD) and ulcerative colitis (UC)[5]. Although patients with IBD at risk of opportunistic infections, particularly of viral or bacterial etiology, are treated with immunosuppressors, immunomodulators, or biologic agents[6,7], available data showed that in elderly patients with IBD with comorbidities and steroid use appear to be an increased risk of SARS-CoV-2 infection and mortality[4]. However, data regarding the frequency, risk factors, and outcome of SARS-CoV-2 infection in patients with IBD revealed conflicting results[8-15]. Moreover, gastrointestinal (GI) symptoms are common among patients with COVID-19; specifically, diarrhea and abdominal pain have been reported in half of the patients, which can mimic primary GI conditions or exacerbation of IBD[16]. In this study, we aimed to investigate the incidence and outcomes of SARS-CoV-2 infection in patients with IBD followed at our tertiary referral center.

Materials and Methods

This retrospective, single-center, and observational study was conducted to investigate the incidence and outcomes of SARS-CoV-2 infection in patients with IBD in a tertiary referral teaching center. The study was approved by a Ankara City Hospital Local Scientific Research Assessment and Ethics Committee (protocol no: 671, decision date: 20.01.2021).

Adult patients followed in the IBD unit of our department were employed in the study for incidence calculation. Among them, patients with confirmed SARS-CoV-2 infection defined by a positive test result of nasopharyngeal swab sample on real-time reverse transcriptase-polymerase chain reaction between March 1, 2020 and March 31, 2021 were evaluated for outcome analysis. Patients with symptoms suggesting COVID-19 but had negative RT-PCR results were excluded from the study.

Patients' demographic data and IBD history were collected from the IBD database of our clinic. Symptoms, medication, and outcomes regarding SARS-CoV-2 infection were obtained by phone interview. Laboratory and radiological test results were obtained from the electronic file of the patients. Crohn's disease activity index (CDAI) and Partial Mayo Score were used to assess CD and UC activity, respectively. Patients were also asked for discontinuation of IBD treatment, worsening of IBD symptoms, characteristics and duration of the GI symptoms, and relation with COVID-19 therapies. Diarrhea was defined as ≥4 loose stools (Bristol stool scale 6 or 7) in a day for at least three days. Stool analysis was performed in all patients presenting with diarrhea to rule out infectious pathologies.

Statistical Analysis

Statistical analysis was performed using IBM Statistical Package for the Social Sciences Statistics for Windows, version 26 (IBM Corp., Armonk, NY, USA). Categorical data are presented as numbers and percentages. Continuous variables that were normally scattered are presented as mean and standard deviation (SD); otherwise, the median and interquartile range (IQR) were used. Pearson's chi-square or Fisher's exact test was performed for percentage comparisons. An independent sample t-test was performed for parametric data, whereas Mann-Whitney U test was used for nonparametric data.

Results

A total of 894 patients with IBD have been followed in our gastroenterology department, and the characteristics are presented in Table 1. Among those, SARS-CoV-2 infection was detected in 18 (2.0%) patients, five (1.2%) of 430 patients with CD, 12 (2.8%) of 428 patients with UC, and one (2.8%) of 36 with IBD-unclassified (IBD-U) had SARS-CoV-2 infection. The mean age (SD) of the patients with SARS-CoV-2 infection was 42.2 (11.5) years, and 12 (66.7%) patients were male. Of the patients with IBD and SARS-CoV-2 infection, six (33.3%) had at least one underlying comorbidity, with diabetes being the most common, and three (16.7%) were active smokers. The median interval between the onset of SARS-CoV-2 infection symptoms and PCR test confirmation of infection was 0 days (range, 0-3 days). Six (33.3%) of all patients with SARS-CoV-2 infection were taking biologic agents (two adalimumab, two infliximab, and two vedolizumab), of which one was taking concomitant immunomodulator and low-dose (4 mg/day) steroid therapy. Of the patients with SARS-CoV-2 infection, three (16.7%) have used immunomodulators, eight (44.4%) have used mesalazine, and one has used steroid (prednisolone 20 mg/day) with mesalazine. The clinical characteristics and treatments of patients with IBD and SARS-CoV-2 infection are provided in Table 2. None of the patients with SARS-CoV-2 infection, whose details were presented in Table 2, were vaccinated for COVID-19 during the follow-up period. The most frequent non-GI symptom was myalgia (nine patients) followed by fever and arthralgia (eight patients each), and cough (seven patients) (Table 3).

The main GI symptom was diarrhea in six (33.3%) patients, followed by nausea and vomiting in two (11.1%). The median duration of GI symptoms was five (range, 4-8) days. Diarrhea was painless, non-bloody, and lasted for a median of five (range, 4-8) days. In patients five and 12, diarrhea started with the onset of the COVID-19 treatment. Five (27.8%) of the patients with COVID-19 were hospitalized for a median of 10 (range, 5-19) days, whereas the remaining patients were isolated at home. No intensive care unit admission or mortality was observed. The laboratory data of patients with SARS-CoV-2 infection are given in a supplementary table. The mean (SD) values for hemoglobin, leucocyte, lymphocyte, and platelet count were 13.9 g/dl (1.9), 6448 10^6/L (2320), 1342 10^6/L (712), and 237 10^9/L (78), respectively. The median (IQR) levels of C-reactive protein, procalcitonin, and ferritin were 9.9 mg/dl (12), 0.03 µg/L (0.02), and 52 µg/L (163), respectively. The mean (SD) aspartate aminotransferase (AST), alanine aminotransferase, and creatinine values were 24.2 U/L (9.8), 33.0 U/L (18.7), and 0.81 mg/dl (0.22), respectively. The median (IQR) D-dimer level was 0.75 (1.38), whereas mean (SD) values for fibrinogen 3 and lactate dehydrogenase were 7 g/L (1.2) and 261 U/L (78), respectively.

Table 1. Demographic characteristics of all patients with IBD

	CD n=430	UC n=428	IBD-U n=36	Total n=894
Age at diagnosis	33.2±12.2	37.7±12.8	34.3±14.1	35.4±12.8
Disease duration, median years (IQR)	8.0 (9.0)	8.0 (10.0)	8.5 (10.75)	8.0 (10.0)
Female/Male	176 (40.9%)/254 (59.1%)	156 (36.4%)/272 (63.6%)	13 (36.1%)/23 (63.9%)	345 (38.6%)/549 (61.4%)
Smokers (current/ex)	129 (30.0%)/112 (26.0%)	45 (10.5%)/165 (38.6%)	6 (16.7%)/10 (27.8%)	180 (20.1%)/287 (32.1%)
UC extension				
Proctitis		49 (11.4%)		
Left-sided		232 (54.2%)		
Extensive		147 (34.3%)		
CD localization				
Ileal (L1)	186 (43.3%)			
Colonic (L2)	56 (13.0%)			
Ileocolonic (L3)	184 (42.8%)			
Isolated upper GI disease (L4)	4 (0.9%)			
CD behavior				
Inflammatory disease (B1)	319 (74.2%)			
Stenosing (B2)	36 (8.4%)			
Penetrating (B3)	75 (17.4%)			
P (perianal disease)	136 (31.6%)			
Prior major abdominal surgery	188 (43.7%)	24 (5.6%)	8 (22.2%)	220 (24.6%)
Current medication				
Mesalazine	117 (27.2%)	336 (78.5%)	22 (61.1%)	475 (53.1%)
Sulphapyridine	31 (7.2%)	26 (6.1%)	5 (13.9%)	62 (6.9%)
Azathioprine	104 (24.2%)	67 (15.7%)	5 (13.9%)	176 (19.7%)
Methotrexate	26 (6.1%)	2 (0.5%)	2 (5.6%)	30 (3.4%)
Budesonide	9 (2.1%)	0 (0.0%)	0 (0.0%)	9 (1.0%)
Steroids	7 (1.6%)	3 (0.7%)	0 (0.0%)	10 (1.1%)
Adalimumab	103 (24.0%)	28 (6.5%)	5 (13.9%)	136 (15.2%)
Infliximab	109 (25.3%)	32 (7.5%)	5 (13.9%)	146 (16.3%)
Vedolizumab	35 (8.1%)	18 (4.2%)	0 (0.0%)	53 (5.9%)
Ustekinumab	6 (1.4%)	0 (0.0%)	1 (2.8%)	7 (0.8%)
Sertolizumab	6 (1.4%)	0 (0.0%)	1 (2.8%)	7 (0.8%)
Positive SARS-CoV-2	5 (1.2%)	12 (2.8%)	1 (2.8%)	18 (2.0%)

Montreal classification of CD. Disease location (L): L1, terminal ileum; L2, colon; L3, ileocolon; L4, upper gastrointestinal tract, Disease behavior (B): B1, non-stricturing non-penetrating; B2, stricturing; B3, penetrating.

IBD: Inflammatory bowel diseases, CD: Crohn's disease, UC: Ulcerative colitis, IBD-U: IBD-unclassified, SARS-CoV-2: Severe acute respiratory syndrome-Coronavirus-2

Table 2. Clinical characteristics and treatments of patients with inflammatory bowel diseases and SARS-CoV-2 infection

Patient no	Sex, current age, IBD type	Disease duration (years)	CD (location/ behavior)	Perianal disease	UC extension	CDAI (CD)	Partial mayo score (UC)	Current IBD-related therapy	Smoking	Comorbidities
1	M, 53, UC	21	–	No	Extensive	–	1	Mesalazine	Ex-smoker	Diabetes
2	M, 38, UC	5	–	No	Extensive	–	8	Mesalazine	Never smoker	None
3	F, 43, CD	14	L3/B1	No	–	203	–	Mesalazine, CS, methotrexate	Ex-smoker	Ankylosing spondylitis
4	F, 34, CD	9	L1/B2	yes	–	65	–	Mesalazine, azathioprine	Never smoker	None
5	M, 46, UC	11	–	No	Left-sided	–	4	Mesalazine	Ex-smoker	None
6	F, 25, CD	8	L3/B1	Yes	–	52	–	Adalimumab	Daily smoker	None
7	M, 34, UC	2	–	No	Extensive	–	7	Mesalazine	Ex-smoker	None
8	M, 49, IBD-U	15	–	yes	–	–	–	Mesalazine, vedolizumab	Never smoker	Diabetes
9	M, 77, UC	21	–	No	Left-sided	–	4	Mesalazine	Ex-smoker	Hypertension, diabetes, cardiovascular disease
10	F, 37, UC	10	–	No	Extensive	–	3	Mesalazine, azathioprine, CS, adalimumab	Never smoker	Familial mediterranean fever
11	M, 39, UC	2	–	No	Left-sided	–	2	Mesalazine	Ex-smoker	None
12	F, 32, UC	7	–	No	Extensive	–	9	Mesalazine, CS	Daily smoker	None
13	M, 47, UC	12	–	No	Extensive	–	2	Mesalazine, infliximab	Ex-smoker	None
14	M, 39, CD	9	L2/B1	No	–	86	–	Mesalazine, infliximab	Never smoker	None
15	M, 47, CD	8	L1/B2	No	–	98	–	Vedolizumab	Ex-smoker	Ankylosing spondylitis, renal cell carcinoma, COPD
16	F, 35, UC	15	–	No	Left-sided	–	6	Mesalazine	Never smoker	None
17	M, 34, UC	8	–	No	Extensive	–	3	Mesalazine, azathioprine	Ex-smoker	None
18	M, 51, UC	16	–	No	Left-sided	–	2	Mesalazine	Daily smoker	None

Montreal classification of CD: Disease location (L): L1, terminal ileum; L2, colon; L3, ileocolon; L4, upper gastrointestinal tract. Disease behavior (B): B1, nonstricturing non-penetrating; B2, structuring; B3, penetrating.

CD: Crohn's disease, COPD: Chronic obstructive pulmonary disease, CS: Corticosteroid, IBD: Inflammatory bowel disease, UC: Ulcerative colitis, IBD-U: IBD-unclassified, CDAI: Crohn's disease activity index

Table 3. Clinical characteristics, treatments, and outcomes of patients with inflammatory bowel diseases and SARS-CoV-2 infection

Patient no	Sex, current age, IBD type	Date of first symptoms	Date of + SARS-CoV-2	Discontinued IBD therapy	Common symptoms	GI symptoms	IBD flare	Duration of GI symptoms, (days)	Treatment of COVID-19	Radiological findings	Complications	Hospitalization, length of stay (days)	Intensive care follow	Outcomes
1	M, 53, UC	12.11.2020	14.11.2020	No	Fever, fatigue, headache	Nausea, vomiting	No	8	HQ, favipiravir	Normal	None	Yes/10	No	Discharged
2	M, 38, UC	12.12.2020	12.12.2020	No	Fatigue	Diarrhea	No	6	Favipiravir	Normal	None	No	No	Isolated at home
3	F, 43, CD	14.09.2020	17.09.2020	No	Fever, cough, myalgia, arthralgia	Diarrhea	No	4	Favipiravir	Bilateral pneumonia	None	No	No	Isolated at home
4	F, 34, CD	–	25.08.2020	No	None	None	No	–	HQ	Normal	None	No	No	Isolated at home
5	M, 46, UC	01.04.2020	01.04.2020	No	Fever	Diarrhea*	No	5	HQ, favipiravir	Normal	None	No	No	Isolated at home
6	F, 25, CD	–	06.04.2021	No	None	None	No	–	Favipiravir	Normal	None	No	No	Isolated at home
7	M, 34, UC	01.04.2020	01.04.2020	Yes	Fever, cough, myalgia, arthralgia	Diarrhea, nausea, vomiting	No	5	None	Normal	None	No	No	Isolated at home
8	M, 49, IBD-U	10.09.2020	10.09.2020	No	Myalgia, arthralgia	None	No	–	Favipiravir	Normal	None	No	No	Isolated at home
9	M, 77, UC	24.07.2020	24.07.2020	No	Fever, myalgia	None	No	–	HQ	Normal	None	Yes/5	No	Discharged
10	F, 37, UC	14.12.2020	14.12.2020	No	Cough, myalgia, arthralgia	None	No	–	Favipiravir	Normal	None	No	No	Isolated at home
11	M, 39, UC	12.08.2020	12.08.2020	No	Arthralgia	None	No	–	HQ	Normal	None	No	No	Isolated at home
12	F, 32, UC	15.09.2020	15.09.2020	Yes	Fever, fatigue	Diarrhea*	No	6	Favipiravir	Bilateral pneumonia	Pneumatosis intestinalis, Recto-vaginal fistulae	Yes/19	No	Discharged
13	M, 47, UC	10.08.2020	10.08.2020	No	Cough, dyspnea, myalgia, arthralgia,	None	No	–	Favipiravir	Bilateral pneumonia	None	No	No	Isolated at home
14	M, 39, CD	19.08.2020	19.08.2020	No	Fever	None	No	–	Favipiravir	Normal	None	Yes/10	No	Discharged
15	M, 47, CD	22.09.2020	23.09.2020	No	Fever, cough, dyspnea, myalgia, arthralgia, anosmia	Diarrhea	No	5	HQ, favipiravir	Normal	None	No	No	Isolated at home
16	F, 35, UC	31.01.2021	31.01.2021	No	Cough, myalgia,	None	No	–	Favipiravir	Normal	None	No	No	Isolated at home
17	M, 34, UC	25.04.2020	25.04.2020	No	Cough, myalgia, arthralgia	None	No	–	HQ	Normal	None	Yes/5	No	Discharged
18	M, 51, UC	–	6.04.2021	No	None	None	No	–	Favipiravir	Normal	None	No	No	Isolated at home

*Diarrhea was observed with the onset of COVID-19 treatment.

CD: Crohn's disease, IBD: Inflammatory bowel disease, COPD: Chronic obstructive pulmonary disease, CS: Corticosteroid, HQ: Hydroxychloroquine, UC: Ulcerative colitis, IBD-U: IBD-unclassified, COVID-19: Coronavirus disease-2019, SARS-CoV-2: Severe acute respiratory syndrome-Coronavirus-2, GI: Gastrointestinal

Five (27.8%) of the 18 patients with SARS-CoV-2 infection had CD with a median CDAI of 86 (range, 52-203). Diarrhea was observed in two of them with one concomitant abdominal pain. One patient (20.0%) with CD was hospitalized, whereas the remaining patients were isolated at home. No complication occurred despite steroid and biologic usage. Patient 8 followed for IBD-U was isolated at home and did not develop any GI symptoms or complications. Seven (58.3%) of the 12 patients with SARS-CoV-2 infection and UC had extensive colitis, whereas the remaining had left-sided colitis. The median Partial Mayo Score was 3.5. Moreover, 5 (41.7%) of the patients with UC had GI symptoms, with diarrhea as the most common. In addition, four (33.3%) of the patients with SARS-CoV-2 infection and UC needed hospitalization. One of them (patient 10) having concomitant immunomodulator and low-dose (4 mg/day) steroid therapy did not require hospitalization. A complication was observed in only patient 12 among those with UC who were using steroids (prednisolone 20 mg/day) at the time of SARS-CoV-2 infection and demonstrated temporary terminal ileitis, pneumonitis intestinalis, and recto-vaginal fistulae. The patient was admitted to the COVID-19 unit at our hospital and received favipiravir, methylprednisolone intravenously, and low-molecular-weight heparin. Stool analysis was not positive for parasites or *Clostridioides difficile*, and stool cultures were negative. Real-time polymerase chain reaction was performed to analyze Cytomegalovirus presence in the serum samples and yielded negative. The patient improved progressively, and recto-vaginal symptoms resolved within one week. After 10 days of hospitalization, she was discharged with a tapered prednisolone schedule. The patient has remained asymptomatic with only mesalazine after steroid treatment.

Discussion

Literature data regarding the course of SARS-CoV-2 infection in patients with IBD are accumulating. Different results have been reported regarding the frequency and outcomes of SARS-CoV-2 infection in patients with IBD[3,13,17-20]. In our study, the incidence of SARS-CoV-2 infection in patients with IBD was 2.0%, higher than the incidence in the normal population, as reported between 0.02% and 0.7% in previous studies[3,13,19]. Our findings contradict those demonstrating similar[17,18,20] or decreased[3,13,19] incidence of SARS-CoV-2 infection in patients with IBD.

The increased incidence can be explained by the fact that patients with IBD are more sensitive to SARS-CoV-2 infection because they think their immune systems are weakened. Moreover, because GI symptoms in patients with IBD can also be seen in COVID-19, doctors tend to screen these patients for the presence of SARS-CoV-2 infection more frequently than the normal population[8,21]. Finally, since our hospital is a referral center, the incidence may have been high because of the high suspicion of SARS-CoV-2 infection in patients who presented to our clinic.

The most common GI symptom was painless and nonbloody diarrhea (33.3%) in patients with SARS-CoV-2 infection and IBD, which is consistent with the previously reported studies in which diarrhea was observed in up to 37.1% of the patients with IBD and SARS-CoV-2 infection[3,22-27]. Diarrhea can be an admission complaint of patients with SARS-CoV-2 infection[22,28] or can be the sole manifestation of COVID-19 independent of IBD. SARS-CoV-2 RNA isolation from the stool samples demonstrated intestinal tropism of the virus[29-31]; thus, GI symptoms may arise with COVID-19 even in the absence of IBD. Gupta et al.[32] reported two cases of previously healthy adolescents who presented with severe enteritis as the sole manifestation of COVID-19. Moreover, diarrhea can start with the onset of COVID-19 treatment. In our study, diarrhea started in patients 5 and 12 with the onset of hydroxychloroquine combined with favipiravir and favipiravir treatment alone, respectively, which was supported by several studies in the literature[33-35]. Other rare GI symptoms were nausea and vomiting, which were detected in 11.1% of patients with IBD and SARS-CoV-2 infection. In the present study, the median duration of all-GI symptoms was five (range, 4-8) days, which was consistent with the literature[36]. The short duration of GI symptoms caused by SARS-CoV-2 infection may indicate that COVID-19 does not cause an IBD flare. The duration of the symptoms may differentiate IBD remission from activation.

Patients with IBD tend to have a mild course of COVID-19 despite the presence of immunosuppressive treatment[3,13-15,17,37]. This situation could be explained by the hampered hyperactivity of the immune response with anti-inflammatory treatments such as anti-tumor necrosis factor (anti-TNF) agents[13,38]. However, not all drugs used in IBD treatment were associated with decreased COVID-19 severity. Corticosteroid use was also associated with severe COVID-19[3,4,15,17,38]. Although several studies have reported the safe use of 5-aminosalicylic acid (ASA) in COVID-19[15,39,40], Brenner et al.[38] reported a more severe COVID-19 course in patients with IBD using 5-ASA preparations. Khan et al.[15] reported an increased risk of SARS-CoV-2 infection with vedolizumab treatment. In the present study, 16 (88.9%) patients were on 5-ASA therapy (nine patients only have 5-ASA treatment). Three (16.7%) patients were using steroid therapy combined with 5-ASA and methotrexate in patient 3; 5-ASA, azathioprine, and adalimumab in patient 10; and 5-ASA only in patient 12. Four (22.2%) patients were on anti-TNF therapy, whereas two (11.1%) patients were on vedolizumab therapy. A complication was observed only in patient 12 who was on steroid and 5-ASA treatments for UC and experienced temporary terminal ileitis, pneumonitis intestinalis, and recto-vaginal fistulae that improved with COVID-19 treatment. This

case shows that, in line with the literature, caution is necessary for the management of complications related to SARS-CoV-2 infection in patients using steroids[38].

Previous studies have demonstrated that COVID-19 complications were mainly observed in older people and those with comorbidities[1,13,17,38]. The young age and therefore low incidence of comorbidities enable milder disease course in patients with SARS-CoV-2 infection and IBD. Nevertheless, complications regarding GI systems reported with COVID-19 can be mistaken for IBD flare. Coronavirus disease-2019 may lead to severe small bowel and colorectal inflammation, which may mimic an IBD exacerbation. Therefore, during the pandemic, COVID-19-related enteritis should be considered when evaluating patients with IBD with suspected acute IBD flare. A recently published study revealed that the most common abdominal computed tomography imaging features of patients with SARS-CoV-2 infection are colorectal and small bowel wall thickening, intestinal distension, gastritis, and small bowel pneumatosis with portal venous gas and intestinal perforation[41]. An example of GI complication was ileal perforation following SARS-CoV-2 infection in an inactive CD, which was reported by Santana et al.[42]. In the present study, six (33.3%) patients had comorbidities such as diabetes, hypertension, cardiovascular disease, and renal cell carcinoma (not on chemotherapy). Despite the increased severity and complication risk of COVID-19, none of our patients had comorbidities and such outcomes.

Study Limitations

The major limitation of this study was the low number of patients with IBD and SARS-CoV-2 infection. This situation precluded further statistical analysis for safety investigations of the drugs used in IBD therapy.

Conclusion

In conclusion, SARS-CoV-2 infection was found in 18 (2.0%) of all patients with IBD. GI symptoms are common and may be the only manifestation in patients with IBD and SARS-CoV-2 infection. During the pandemic, new or exacerbated GI symptoms in patients with IBD should raise the suspicion of COVID-19. Ongoing treatments of IBD should be continued in such patients with COVID-19. Concerns that steroid use may cause a worse prognosis in patients with IBD should be investigated with larger studies.

Ethics

Ethics Committee Approval: The study was approved by a Ankara City Hospital Local Scientific Research Assessment and Ethics Committee (protocol no: 671, decision date: 20.01.2021).

Informed Consent: Not applicable since the presented study was conducted retrospectively.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: B.B., İ.E.G., İ.Y., Concept: B.B., İ.E.G., İ.Y., Design: B.B., İ.E.G., İ.Y., Data Collection or Processing: B.B., İ.E.G., İ.Y., Analysis or Interpretation: B.B., İ.E.G., İ.Y., Literature Search: B.B., İ.E.G., İ.Y., Writing: B.B.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, Liu L, Shan H, Lei CL, Hui DSC, Du B, Li LJ, Zeng G, Yuen KY, Chen RC, Tang CL, Wang T, Chen PY, Xiang J, Li SY, Wang JL, Liang ZJ, Peng YX, Wei L, Liu Y, Hu YH, Peng P, Wang JM, Liu JY, Chen Z, Li G, Zheng ZJ, Qiu SQ, Luo J, Ye CJ, Zhu SY, Zhong NS; China Medical Treatment Expert Group for Covid-19. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med. 2020;382:1708-20.
2. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, Wu Y, Zhang L, Yu Z, Fang M, Yu T, Wang Y, Pan S, Zou X, Yuan S, Shang Y. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med. 2020;8:475-81.
3. Taxonera C, Sagastagoitia I, Alba C, Mañas N, Olivares D, Rey E. 2019 novel coronavirus disease (COVID-19) in patients with inflammatory bowel diseases. Aliment Pharmacol Ther. 2020;52:276-83.
4. Onder G, Rezza G, Brusaferro S. Case-Fatality Rate and Characteristics of Patients Dying in Relation to COVID-19 in Italy. JAMA. 2020;323:1775-6.
5. Kaser A, Zeissig S, Blumberg RS. Inflammatory bowel disease. Annu Rev Immunol. 2010;28:573-621.
6. Wisniewski A, Kirchgesner J, Seksik P, Landman C, Bourrier A, Nion-Larmurier I, Marteau P, Cosnes J, Sokol H, Beaugerie L; the Saint-Antoine IBD network. Increased incidence of systemic serious viral infections in patients with inflammatory bowel disease associates with active disease and use of thiopurines. United European Gastroenterol J. 2019;8:303-13.
7. Osterman MT, Sandborn WJ, Colombel JF, Peyrin-Biroulet L, Robinson AM, Zhou Q, Lewis JD. Crohn's Disease Activity and Concomitant Immunosuppressants Affect the Risk of Serious and Opportunistic Infections in Patients Treated With Adalimumab. Am J Gastroenterol. 2016;111:1806-15.
8. Attauabi M, Poulsen A, Theede K, Pedersen N, Larsen L, Jess T, Rosager Hansen M, Verner-Andersen MK, V Haderslev K, Berg Lødrup A, Molazahi A, Neumann A, Wase A, Seidelin JB, Burisch J. Prevalence and Outcomes of COVID-19 Among Patients With Inflammatory Bowel Disease-A Danish Prospective Population-based Cohort Study. J Crohns Colitis. 2021;15: 540-50.
9. Aziz M, Fatima R, Haghbin H, Lee-Smith W, Nawras A. The Incidence and Outcomes of COVID-19 in IBD Patients: A Rapid Review and Meta-analysis. Inflammatory Bowel Dis. 2020; 26:132-3.
10. Derikx LAAP, Lantinga MA, de Jong DJ, van Dop WA, Creemers RH, Römkens TEH, Jansen JM, Mahmmod N, West RL, Tan ACITL, Bodelier AGL, Gorter MHP, Boekema PJ, Halet ERC, Horjus CS, van Dijk MA, Hirdes MMC, Epping Stippel LSM, Jharap B, Lutgens MWMD, Russel MG, Gilissen LPL, Nauta S, van Bodegraven AA, Hoentjen F. Clinical Outcomes of Covid-19 in Patients With Inflammatory Bowel Disease: A Nationwide Cohort Study. J Crohns Colitis. 2021;15:529-39.

11. Singh S, Khan A, Chowdhry M, Bilal M, Kochhar GS, Clarke K. Risk of Severe Coronavirus Disease 2019 in Patients With Inflammatory Bowel Disease in the United States: A Multicenter Research Network Study. Gastroenterology. 2020;159:1575-8.

12. Axelrad JE, Malter L, Hong S, Chang S, Bosworth B, Hudesman D. From the American Epicenter: Coronavirus Disease 2019 in Patients with Inflammatory Bowel Disease in the New York City Metropolitan Area. Inflamm Bowel Dis. 2021;27:662-6.

13. Allocca M, Fiorino G, Zallot C, Furfaro F, Gilardi D, Radice S, Danese S, Peyrin-Biroulet L. Incidence and Patterns of COVID-19 Among Inflammatory Bowel Disease Patients From the Nancy and Milan Cohorts. Clin Gastroenterol Hepatol. 2020;18:2134-2135.

14. Gubatan J, Levitte S, Balabanis T, Patel A, Sharma A, Habtezion A. SARS-CoV-2 Testing, Prevalence, and Predictors of COVID-19 in Patients with Inflammatory Bowel Disease in Northern California. Gastroenterology. 2020;159:1141-4.

15. Khan N, Patel D, Xie D, Pernes T, Lewis J, Yang YX. Are Patients With Inflammatory Bowel Disease at an Increased Risk of Developing SARS-CoV-2 than Patients Without Inflammatory Bowel Disease? Results From a Nationwide Veterans' Affairs Cohort Study. Am J Gastroenterol. 2021;116:808-10.

16. Anikhindi SA, Kumar A, Arora A. COVID-19 in patients with inflammatory bowel disease. Expert Rev Gastroenterol Hepatol. 2020;14:1187-93.

17. Lukin DJ, Kumar A, Hajifathalian K, Sharaiha RZ, Scherl EJ, Longman RS; Jill Roberts Center Study Group Study Group; Weill Cornell Medicine-Gastrointestinal Study Group. Baseline Disease Activity and Steroid Therapy Stratify Risk of COVID-19 in Patients With Inflammatory Bowel Disease. Gastroenterology. 2020;159:1541-4.

18. Mao R, Liang J, Shen J, Ghosh S, Zhu LR, Yang H, Wu KC, Chen MH; Chinese Society of IBD, Chinese Elite IBD Union; Chinese IBD Quality Care Evaluation Center Committee. Implications of COVID-19 for patients with pre-existing digestive diseases. Lancet Gastroenterol Hepatol. 2020;5:425-7.

19. Norsa L, Indriolo A, Sansotta N, Cosimo P, Greco S, D'Antiga L. Uneventful Course in Patients With Inflammatory Bowel Disease During the Severe Acute Respiratory Syndrome Coronavirus 2 Outbreak in Northern Italy. Gastroenterology. 2020;159:371-2.

20. Rodríguez-Lago I, Ramírez de la Piscina P, Elorza A, Merino O, Ortiz de Zárate J, Cabriada JL. Characteristics and Prognosis of Patients With Inflammatory Bowel Disease During the SARS-CoV-2 Pandemic in the Basque Country (Spain). Gastroenterology. 2020;159:781-3.

21. Ludvigsson JF, Axelrad J, Halfvarson J, Khalili H, Larsson E, Lochhead P, Roelstraete B, Simon TG, Söderling J, Olén O. Inflammatory bowel disease and risk of severe COVID-19: A nationwide population-based cohort study in Sweden. United European Gastroenterol J. 2021;9: 177-92.

22. Luo S, Zhang X, Xu H. Don't Overlook Digestive Symptoms in Patients With 2019 Novel Coronavirus Disease (COVID-19). Clin Gastroenterol Hepatol. 2020;18:1636-7.

23. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z, Yu T, Xia J, Wei Y, Wu W, Xie X, Yin W, Li H, Liu M, Xiao Y, Gao H, Guo L, Xie J, Wang G, Jiang R, Gao Z, Jin Q, Wang J, Cao B. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395:497-506.

24. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, Qiu Y, Wang J, Liu Y, Wei Y, Xia J, Yu T, Zhang X, Zhang L. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020;395:507-13.

25. Xu XW, Wu XX, Jiang XG, Xu KJ, Ying LJ, Ma CL, Li SB, Wang HY, Zhang S, Gao HN, Sheng JF, Cai HL, Qiu YQ, Li LJ. Clinical findings in a group of patients infected with the 2019 novel coronavirus (SARS-Cov-2) outside of Wuhan, China: retrospective case series. BMJ. 2020;368: m606.

26. Mao R, Qiu Y, He JS, Tan JY, Li XH, Liang J, Shen J, Zhu LR, Chen Y, Iacucci M, Ng SC, Ghosh S, Chen MH. Manifestations and prognosis of gastrointestinal and liver involvement in patients with COVID-19: a systematic review and meta-analysis. Lancet Gastroenterol Hepatol. 2020;5:667-78.

27. Elmunzer BJ, Spitzer RL, Foster LD, Merchant AA, Howard EF, Patel VA, West MK, Qayed E, Nustas R, Zakaria A, Piper MS, Taylor JR, Jaza L, Forbes N, Chau M, Lara LF, Papachristou GI, Volk ML, Hilson LG, Zhou S, Kushnir VM, Lenyo AM, McLeod CG, Amin S, Kuftinec GN, Yadav D, Fox C, Kolb JM, Pawa S, Pawa R, Canakis A, Huang C, Jamil LH, Aneese AM, Glamour BK, Smith ZL, Hanley KA, Wood J, Patel HK, Shah JN, Agarunov E, Sethi A, Fogel EL, McNulty G, Haseeb A, Trieu JA, Dixon RE, Yang JY, Mendelsohn RB, Calo D, Aroniadis OC, LaComb JF, Scheiman JM, Sauer BG, Dang DT, Piraka CR, Shah ED, Pohl H, Tierney WM, Mitchell S, Condon A, Lenhart A, Dua KS, Kanagala VS, Kamal A, Singh VK, Pinto-Sanchez MI, Hutchinson JM, Kwon RS, Korsnes SJ, Singh H, Solati Z, Willingham FF, Yachimski PS, Conwell DL, Mosier E, Azab M, Patel A, Buxbaum J, Wani S, Chak A, Hosmer AE, Keswani RN, DiMaio CJ, Bronze MS, Muthusamy R, Canto MI, Gjeorgjievski VM, Imam Z, Odish F, Edhi AI, Orosey M, Tiwari A, Patwardhan S, Brown NG, Patel AA, Ordiah CO, Sloan IP, Cruz L, Koza CL, Okafor U, Hollander T, Furey N, Reykhart O, Zbib NH, Damianos JA, Esteban J, Hajidiacos N, Saul M, Mays M, Anderson G, Wood K, Mathews L, Diakova G, Caisse M, Wakefield L, Nitchie H, Waljee AK, Tang W, Zhang Y, Zhu J, Deshpande AR, Rockey DC, Alford TB, Durkalski V; North American Alliance for the Study of Digestive Manifestations of COVID-19. Digestive Manifestations in Patients Hospitalized With Coronavirus Disease 2019. Clin Gastroenterol Hepatol. 2021;19:1355-65.

28. Song Y, Liu P, Shi XL, Chu YL, Zhang J, Xia J, Gao XZ, Qu T, Wang MY. SARS-CoV-2 induced diarrhoea as onset symptom in patient with COVID-19. Gut. 2020;69:1143-4.

29. Wang W, Xu Y, Gao R, Lu R, Han K, Wu G, Tan W. Detection of SARS-CoV-2 in Different Types of Clinical Specimens. JAMA. 2020;323:1843-4.

30. Xiao F, Tang M, Zheng X, Liu Y, Li X, Shan H. Evidence for Gastrointestinal Infection of SARS-CoV-2. Gastroenterology. 2020;158:1831-3.

31. Wu Y, Guo C, Tang L, Hong Z, Zhou J, Dong X, Yin H, Xiao Q, Tang Y, Qu X, Kuang L, Fang X, Mishra N, Lu J, Shan H, Jiang G, Huang X. Prolonged presence of SARS-CoV-2 viral RNA in faecal samples. Lancet Gastroenterol Hepatol. 2020;5:434-35.

32. Gupta S, Kaushik A, Kest H, Charles AK, De Bruin W, Colletti M, Goldberg D. Severe Enteritis as the Sole Manifestation of Novel Coronavirus Disease 2019 (COVID-19) in Adolescent Patients. Case Rep Infect Dis. 2020;2020:8823622.

33. Cai Q, Yang M, Liu D, Chen J, Shu D, Xia J, Liao X, Gu Y, Cai Q, Yang Y, Shen C, Li X, Peng L, Huang D, Zhang J, Zhang S, Wang F, Liu J, Chen L, Chen S, Wang Z, Zhang Z, Cao R, Zhong W, Liu Y, Liu L. Experimental Treatment with Favipiravir for COVID-19: An Open-Label Control Study. Engineering (Beijing). 2020;6:1192-8.

34. Sanders JM, Monogue ML, Jodlowski TZ, Cutrell JB. Pharmacologic Treatments for Coronavirus Disease 2019 (COVID-19): A Review. JAMA. 2020;323:1824-36.

35. Ivashchenko AA, Dmitriev KA, Vostokova NV, Azarova VN, Blinow AA, Egorova AN, Gordeev IG, Ilin AP, Karapetian RN, Kravchenko DV, Lomakin NV, Merkulova EA, Papazova NA, Pavlikova EP, Savchuk NP, Simakina EN, Sitdekov TA, Smolyarchuk EA, Tikhomolova EG, Yakubova EV, Ivachtchenko AV. AVIFAVIR for Treatment of Patients with Moderate COVID-19: Interim Results of a Phase II/III Multicenter Randomized Clinical Trial. Clin Infect Dis. 2021;73:531-4.

36. Maslennikov R, Poluektova E, Ivashkin V, Svistunov A. Diarrhoea in adults with coronavirus disease-beyond incidence and mortality: a systematic review and meta-analysis. Infect Dis (Lond). 2021;53:348-60.

37. Marafini I, Salvatori S, Sena G, Calabrese E, Biancone L, Monteleone G. Low frequency of COVID-19 in inflammatory bowel diseases. Dig Liver Dis. 2020;52:1234-5.

38. Brenner EJ, Ungaro RC, Gearry RB, Kaplan GG, Kissous-Hunt M, Lewis JD, Ng SC, Rahier JF, Reinisch W, Ruemmele FM, Steinwurz F, Underwood

FE, Zhang X, Colombel JF, Kappelman MD. Corticosteroids, But Not TNF Antagonists, Are Associated With Adverse COVID-19 Outcomes in Patients With Inflammatory Bowel Diseases: Results From an International Registry. Gastroenterology. 2020;159:481-91.

39. Kirchgesner J, Lemaitre M, Carrat F, Zureik M, Carbonnel F, Dray-Spira R. Risk of Serious and Opportunistic Infections Associated With Treatment of Inflammatory Bowel Diseases. Gastroenterology. 2018;155:337-46.

40. Rubin DT, Ananthakrishnan AN, Siegel CA, Sauer BG, Long MD. ACG Clinical Guideline: Ulcerative Colitis in Adults. Am J Gastroenterol. 2019;114:384-413.

41. Bhayana R, Som A, Li MD, Carey DE, Anderson MA, Blake MA, Catalano O, Gee MS, Hahn PF, Harisinghani M, Kilcoyne A, Lee SI, Mojtahed A, Pandharipande PV, Pierce TT, Rosman DA, Saini S, Samir AE, Simeone JF, Gervais DA, Velmahos G, Misdraji J, Kambadakone A. Abdominal Imaging Findings in COVID-19: Preliminary Observations. Radiology. 2020;297:207-15.

42. Santana GO, de Santana AC, Pfeilsticker VB. Ileum Perforation in Crohn's Disease Patient During SARS-Cov-2 Infection. Inflamm Bowel Dis. 2021;27:e42.