# SARS-Cov-2 Infection in Patients with Inflammatory Bowel Disease: A Single-Center Study

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## ABSTRACT

**Objective:** Inflammatory bowel diseases (IBDs) are polygenic disorders. Patients with IBD, especially ulcerative colitis (UC), are more vulnerable to infections because of medications. Key COVID-19-related factors/risks have not been well-researched in IBD patients. In this study, we compared IBD patients with control patients who presented to our clinic with COVID-19 infection suspicion regarding COVID-19 PCR test positivity, COVID-19 pneumonia, hospitalization, and need for treatment at the intensive care unit (ICU).

**Material and Methods:** Thiscohort study included 480 IBD patients as cases and 9,269 age- and gender-matched control patients who came to our hospital for complaints/checkups and were tested for COVID-19 PCR.

Results: Covid-19 positivity was higher in IBD patients than in controls. COVID-19 pneumonia rates were higher in IBD compared to the pneumonia rate of Turkey — mainly due to the high prevalence of COVID-19 pneumonia in UC as none of the Crohn's disease (CD) patients experienced COVID-19 pneumonia. Hospitalization was significantly higher in UC than in CD and higher in IBD than in controls. Hospitalization at ICU was significantly higher in UC than in the controls. There were no IBD patients who died because of COVID-19 infection.

**Conclusion:** IBD patients have a significantly higher rate of COVID-19 PCR positivity, COVID-19 pneumonia, hospitalization, and the need for ICU than the controls; however, mortality is comparable.

**Keywords:** COVID-19, Crohn disease, inflammatory bowel diseases, ulcerative colitis

## INTRODUCTION

Inflammatory bowel diseases (IBDs) (Crohn's disease (CD) and ulcerative colitis (UC)) are polygenic disorders caused primarily by intestinal microbiome contributions, defects in barrier function, and irregular host responses to microbial stimulation (1). Most IBD patients can be treated with aminosalicylates, antibiotics and corticosteroids, or a proper combination of these medications. Many, however, will need immunomodulators such as 6-mercaptopurine (Excella GmbH & Co. Feucht, Germany), as well as biologic treatment such as infliximab, when necessary (2). CD is chronic, affecting the entire gastrointestinal tract, and can cause extraintestinal complications. Patients with CD are at high risk for diseases such as cancer and should take biological drugs with/without immunomodulators (3).

UC is idiopathic and chronic with an unpredictable course, with exacerbation and remission periods. In patient with severe UC, in addition to aminosalicylates, topical or systemic corticosteroids, immunosuppressives, and biological agents are used (4). An excessive immune response is triggered against the target organ in IBD pathogenesis. This is also linked to a weakened immune system. Moreover, due to immunosuppressive, these patients are more vulnerable to infections.

COVID-19 has become one of the world's most serious public health crises and causes of death globally. The research for therapeutic and preventive options against the new SARS-CoV-2 is still ongoing. Two of the current priorities in this field are the active use of already-approved pharmacological agents, and the development of new treatments to reduce virus-related morbidity/mortality. Another is the production and spreading of safe and effective vaccines (5). In IBD, COVID-19 transmission rates, viral pneumonia prevalence in COVID-19 sufferers, hospitalization owing to severe disease, intensive care (IC) needs, and illness management have not been well-researched. Our study has the distinction of being Turkey's first study on the subject. It is also one of the most comprehensive studies, with the most cases reported in English literature.

## MATERIAL and METHODS

This study was conducted to collect data on COVID-19 infection in 954 IBD patients followed up on at our center from 2014 to 2021. It is based on analysis of data from patients with IBD who were followed up by our center and underwent the COVID-19 PCR test because of complaints for Covid-19-like symptoms.

As a control group, 9,269 patients were age- and gender-matched to our IBD patients from 14,520 patients who presented to our center for various complaints or checkup purposes and underwent COVID-19 PCR testing between December 2020 and March 2021. The aim was to compare the IBD patients (i.e., cases) with the control cohort in terms of COVID-19 test positivity, COVID-19 pneumonia frequency, hospitalization due to COVID-19, need for IC and intubation, and, if applicable, fatality rates. COVID-19 pneumonia rates could be detected in the IBD group but not in the controls because not all patients testing positive had lung computed tomography (CT) scans. Therefore, the pneumonia rates in IBD were compared to the general average reported by the Turkish Ministry of Health as Turkey's overall Covid-19-related pneumonia status.

Ethical approval was provided by the Ethics Committee of Istanbul Medipol University Hospitals, on 10 March 2021 (decision No:267). Moreover, permission was received from the Turkish Ministry of Health for anonymous analysis of recorded patient data. All procedures were in accordance with the ethical standards of the committee on human experimentation and with the Helsinki Declaration of 1964 and later versions.

**Statistical Analysis**

Data were analyzed using SAS ®Version 9.4 (Carry, North Carolina, USA). Continuous variables were presented as mean±standard deviation, and categorical variables as overall or subgroup-specific frequencies and percentages. Relations between pairs of categorical factors were analyzed through Chi-Square/Fisher's Exact Test as appropriate. Distributions of continuous variables among categorical variable levels were compared through Wilcoxon-Mann-Whitney/Kruskal-Wallis test as appropriate.

Cases were matched with controls using the propensity score approach in SAS PSMATCH procedure with exact gender match. P-values are not adjusted for multiplicity; therefore, the results must be considered in the context of generating research hypotheses for future prospective studies. A p value <.05 was considered statistically significant.

## RESULTS

The IBD cohort involved 954 patients (75.4% had UC, 24.6% had CD). Mean follow-up time was 5.2±4.0, 6.0±4.9 and 4.8±3.3 years among the entire cohort, females, and males, respectively. Regarding gender, 430 (44.61%) were female, and 534 (55.39%) were male. Of these, 480 (49.79%) were tested for COVID-19 through RT-PCR. Therefore, our case group consisted of 480 patients, while our control group consisted of 9,269 age- and gender-matched control cases tested for COVID-19 through RT-PCR at our center. Nearly all IBD patients were monitored in remission with or without the treatments available at the time.

The groups have compatible age and gender distribution as expected through matching. The average age was 40.4±11.6 years for the cases and 40.1±11.7 years for the controls (p=0.53); 64.4% of the cases and 63.1% of the controls were male (p=0.57).

Covid-19 test positivity (**Table 1**) was significantly higher in the IBD patients (34.38%) compared to the controls (28.97%) (p=0.011). CD patients had compatible Covid-19 positivity rate with the controls (p=0.73), whereas UC patients had a significantly greater proportion of COVID-19 positive cases than the controls (p=0.001).

**Table 2** compares COVID-19 PCR test results per disease location. There were significantly higher COVID-19 PCR test positivity rates in UC involving the left colon (p=0.005), pancolitis (p=0.003), and CD involving the colon and terminal ileum (p=0.002) compared to the controls according to Montreal classification. The rate was significantly lower than the controls only in CD involving the terminal ileum (19.4%, p=0.041).

**Table 1.** COVID-19 PCR test data of IBD subgroups and control group. *Chi-Square test results against the controls

| | COVID-19 PCR Test | | | | | | |
|---|---|---|---|---|---|---|---|
| | Negative | | Positive | | Total | | *p** |
| | n | Row% | n | Row% | n | Row% | |
| **Ulcerative Colitis** | 213 | 62.83 | 126 | 37.17 | 339 | 100.00 | 0.001 |
| **Crohn's Disease** | 102 | 72.34 | 39 | 27.66 | 141 | 100.00 | 0.730 |
| **Controls** | 6584 | 71.03 | 2685 | 28.97 | 9269 | 100.00 | |

**Table 2.** Comparison of COVID-19 PCR test data with control group by IBD localization zones.

| | COVID-19 PCR Test | | | | | |
|---|---|---|---|---|---|---|
| | Negative | | Positive | | Total | |
| | n | Row% | n | Row% | n | *p** |
| **Ulcerative Colitis** | | | | | | |
| **Rectum** | 63 | 72.41 | 24 | 27.59 | 87 | 0.780 |
| **Left Colon** | 93 | 60.78 | 60 | 39.22 | 153 | 0.005 |
| **Pancolitis** | 57 | 57.58 | 42 | 42.42 | 99 | 0.003 |
| | | | | | | |
| **Crohn's Disease** | | | | | | |
| **Terminal ileum** | 75 | 80.65 | 18 | 19.35 | 93 | 0.041 |
| **Colon** | 6 | 100.00 | . | . | 6 | 0.120 |
| **Colon+Terminal ileum** | 21 | 50.00 | 21 | 50.00 | 42 | 0.002 |
| **Controls** | 6584 | 71.03 | 2685 | 28.97 | 9269 | |

Among the all IBD patients who tested positive for COVID-19 PCR, 5.45% were those who did not receive treatment, 60% received mesalazine (Dr. Falk Pharma GmbH, Neuenburg, Germany) only, 30.91% received mesalazine and azathioprine, and 3.64% received anti-TNF. Compared to the control group, statistically significantly greater proportion of those receiving mesalazine and azathioprine tested positive for COVID-19 (43.6%, p=0.0005). Because of insufficient number of cases, no significant difference could be found between other subgroups and the controls.

Overall, the incidence of COVID-19 pneumonia in IBD patients was greater than the national Covid-19 related pneumonia incidence in Turkey (23.63% vs. 5.28%, respectively, p<0.0001) (see **Table 3 and Figure 1**). However, this difference was interestingly attributed to the high incidence of COVID-19 pneumonia found in UC patients (30.95% vs. 5.28%, respectively). None of the CD patients had COVID-19 pneumonia. Hospitalization due to Covid-19 also differed significantly among the groups.

In terms of admission to ICU and intubation, there was a significant difference between the IBD and control groups (p<0.0001) and between the UC and control groups (p<0.0001).

All nine patients who were admitted to ICU and were intubated had ulcerative pancolitis, and three were taking anti-tumor necrosis factor (anti-TNF) drugs, three were taking mesalazine, and azathioprine, and three were taking mesalazine only. There were significant differences in terms of gender between the UC, CD, and control groups among those with COVID-19; 34.55% of IBD patients with COVID-19 were female, and 65.45% were male. Moreover, males and females were significantly different regarding hospitalization, ICU treatment, and pneumonia (p<0.05).

Hospitalized patients were divided into treatment subgroups. Statistical analysis was not possible for those followed without treatment and those receiving anti-TNF because of insufficient numbers of patients. Patients receiving mesalazine only and those receiving mesalazine and azathioprine were not significantly different from the controls in hospitalization (6.25% vs. 4.84%, p=0.53, and 6.30% vs. 0.65, p=0.65), but more frequently required IC and intubation than the controls (3.13% vs. 0.6%, p=0.0031, and 6.28% vs 0.6%, p<0.0001). The disease was not lethal in any of our patients diagnosed with IBD and tested positive for COVID-19, resulting in a mortality rate of 0%.

**Table 3.** Pneumonia, hospitalization and IC statistics in IBD and control groups

| | IBD | | | | | | CONTROL | | |
| | Ulcerative Colitis (UC) | | Crohn's Disease (CD) | | Total | | Total | | |
| | n | Col% | n | Col% | n | Col% | n | Col% | p* |
|---|---|---|---|---|---|---|---|---|---|
| **COVID-19's pneumonia** | | | | | | | | | |
| Yes | 39 | 30.95 | 0 | 0.00 | 39 | 23.64 | N/A | 5.28** | <0.0001[a], <0.0001[b], |
| No | 87 | 69.05 | 39 | 100.00 | 126 | 76.36 | N/A | 94.72** | <0.0001[c], 0.14[d] |
| **Hospitalization** | | | | | | | | | |
| Yes | 15 | 11.90 | 0 | 0.00 | 15 | 9.09 | 130 | 4.84 | 0.0008[a], 0.0373[b], |
| No | 111 | 88.10 | 39 | 100.00 | 150 | 90.91 | 2555 | 95.16 | 0.0005[c], 0.20[d] |
| **ICU Treatment** | | | | | | | | | |
| Yes | 9 | 7.14 | 0 | 0.00 | 9 | 5.45 | 16 | 0.60 | <0.0001[a], 0.11[b], |
| No | 117 | 92.86 | 39 | 100.00 | 156 | 94.55 | 2669 | 99.40 | <0.0001[c], 0.66[d] |
| **OVERALL TOTAL** | 126 | 100.00 | 39 | 100.00 | 165 | 100.00 | 2685 | 100.00 | |

*Chi-Square test results against the controls

**The percentage is the average data for the whole of Turkey.

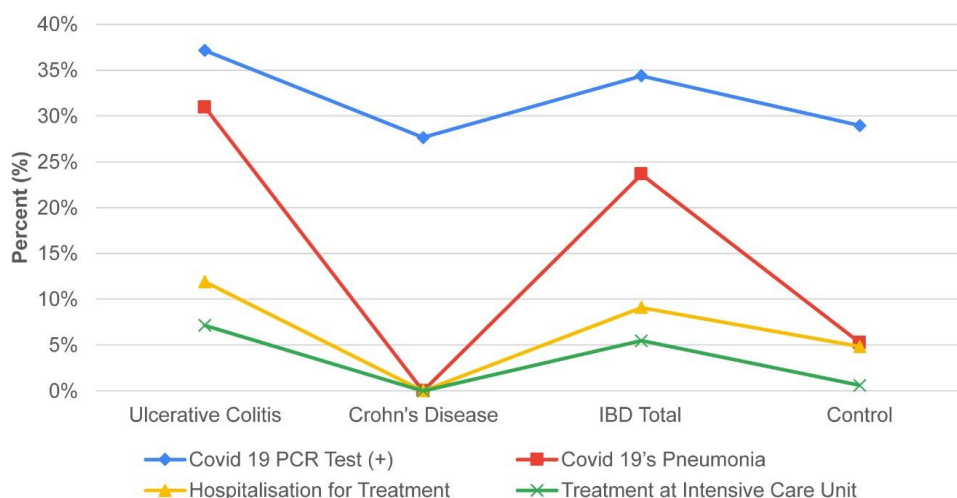[a] Case Group (IBD) vs. Control Group, bUC vs. CD, cUC vs. Control Group, dCD vs. Control Group



**Figure 1.** COVID-19 related results of case and control group participants.

# DISCUSSION

Although the specific origin of IBD is unknown, most experts believe it is tissue damage caused by an overactive immune response to luminal bacteria in the intestines through various environmental effects in genetically susceptible people (6). IBDs affect millions of people and cause several symptoms/conditions, necessitating drug use, but they also put patients at risk of developing other complications (7). Coronaviruses bind to their targets in cells via angiotensin-converting enzyme-2 (ACE2) (8). Morphologically, epithelial cells in the lungs, intestines, kidneys, and blood vessels secrete ACE2 with the highest concentrations in the terminal ileum and colon (9). In studies on different biological samples of SARS-Cov-2 in COVID-19 patients, the virus was isolated from approximately 50% of fecal samples. Moreover, approximately 1/5 of patients continue to test positive through fecal samples after testing negative through respiratory tract samples (10). These findings explain why COVID-19 patients develop GIS symptoms and how SARS-Cov-2 also spreads through the fecal route. ACE2 secretion is increased in the inflamed bowel of IBD patients (11). Moreover, proteomics studies on IBD tissue samples revealed that ACE2 secretion increase was more pronounced in CD than UC (12). Aside from binding to ACE2, coronavirus envelope must also fuse with the host cell membrane for infection to occur. This is aided by specific fusion or "spike" proteins known to be up-regulated in IBD (13). These findings indicate that IBD patients' inflamed intestinal mucosa is an ideal entry point for the virus into tissues. However, the thesis that the GIS mucosa, apart from the respiratory tract mucosa, is another entry point for SARS-Cov-2 to the body has yet to be proven.

A study from Italia (14) reported a significant link of increased risk between active IBD and COVID-19 pneumonia and death from COVID-19; while deaths due to COVID-19 were not significantly related to corticosteroid and anti-TNF use, being older than 65 was the strongest predictor of death (14). A new IBD series reported a 5% mortality rate from Spain (15). COVID-19 infection rate was lower in IBDs than in controls, while the mortality rates were similar in another study from Spain (16). However, there are some issues with determining and accurately comparing data from IBD and control groups in all these study series. The limitation of our study is that not all IBD patients we followed were tested for COVID-19 PCR, but it is important to note that the control and case group cohorts were from the same center and were similar in age and gender.

# CONCLUSION

We found that while IBD patients had an increased risk of COVID-19 infection and associated pneumonia, hospitalization, and ICU treatment, their mortality rates did not rise. There was no particular mortality risk regarding the prevalence and type of treatment, either. Therefore, it is recommended not to discontinue IBD patients' ongoing treatment during COVID-19 infection and to closely monitor the symptoms/signs of patients taking immunosuppressants. However, according to the guidelines, IBD patients over the age of 60 and/or those with comorbidity are at a higher risk of COVID-19 pneumonia and, therefore should avoid activities that increase the risk of disease transmission (17).

Although IBD patients have a higher risk of COVID-19 infection, we believe that the lack of a parallel increase in mortality is due to the immunomodulatory treatments, which protect them from "cytokine storm" — thought to be the main cause of COVID-19 infection-related mortality.

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