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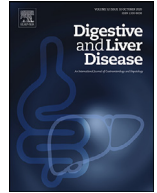
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Alimentary Tract

## COVID-19 in IBD: The experience of a single tertiary IBD center<sup>☆</sup>

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### ABSTRACT

**Background:** Italy has been one of the most affected countries in the world by COVID-19. There has been increasing concern regarding the impact of COVID-19 on patients with inflammatory bowel disease (IBD), particularly in patients treated with immunosuppressants or biologics. The aim of our study is to understand the incidence of COVID-19 in a large cohort of patients with IBD. Furthermore, we analyzed possible risk factors for infection and severity of COVID-19.

**Methods:** This was an observational study evaluating the impact of COVID-19 on IBD patients in a single tertiary center. A 23 multiple-choice-question anonymous survey was administered to 1200 patients with IBD between March 10th and June 10th 2020.

**Results:** 1158 questionnaires were analyzed. The majority of patients had Crohn's disease (CD) (60%) and most of them were in clinical remission. Among the 26 patients (2.2%) who tested positive for COVID-19, only 5 (3CD) were on biological treatment and none required hospitalization. Two patients died and were on treatment with mesalazine only. Of the 1158 patients, 521 were on biological therapy, which was discontinued in 85 (16.3%) and delayed in 195 patients (37.4%). A worsening of IBD symptoms was observed in 200 patients on biological therapy (38.4%). Most of these patients, 189 (94.5%), had stopped or delayed biological treatment, while 11 (5.5%) had continued their therapy regularly ( $p < 0.001$ ).

**Conclusions:** Our data are in line with the current literature and confirm a higher incidence compared to the general population. Biological therapy for IBD seems to not be a risk factor for infection and should not be discontinued in order to avoid IBD relapse.

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## 1. Introduction

In December 2019, the novel coronavirus SARS-CoV-2 surfaced from Wuhan, central Hubei Province, China [1]. After rapid spread across the world, the World Health Organization (WHO) declared coronavirus disease 2019 (COVID-19) a pandemic on 11 March 2020 [2]. There are currently more than 7 million confirmed cases across more than 200 countries and there have been almost 400,000 deaths at the time of writing. Italy has been one of the most affected countries with Lombardy, Piedmont and Emilia-Romagna being among the regions with the highest number of confirmed cases and deaths.

The clinical presentation of COVID-19 is quite variable. A large study from the Chinese Center for Disease Control and Prevention showed that among 72,314 affected patients, severity was reported as mild in 81.4%, severe in 13.9%, and critical in 4.7% [3]. The clinical characteristics of mild COVID-19 include symptoms common to other viral infections such as fever, cough, dyspnea, myalgia, fatigue, and diarrhea. In severe cases, COVID-19 may lead to acute respiratory distress syndrome (ARDS), multiple organ failure and death [4].

Risk factors for contracting COVID-19 have not been fully understood. Healthcare professionals are at greater risk due to increased exposure [5] and there are conflicting data regarding smoking as a risk factor [6].

Severity and mortality of COVID-19 are associated with age, underlying cardiovascular disease, hypertension, chronic pulmonary disease, diabetes and cancer. The fatality rate appears higher in males and smokers [7].

<sup>☆</sup> The authors declare their willingness to publicly release the data of their published article.

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Moreover, angiotensin-converting enzyme 2, used by coronaviruses to penetrate target cells, is expressed by vascular endothelial and intestinal epithelial cells, mainly in the terminal ileum and colon, especially when inflamed [8,9].

As the pandemic expands, there has been increasing concern regarding the impact of COVID-19 on patients with inflammatory bowel disease (IBD), particularly in patients treated with immunosuppressants or biologics. Specific risk factors for developing COVID-19 in IBD patients are yet to be determined, however the greatest risk factors for other infections in patients with IBD are nutritional status, age, co-morbidities, disease activity and pharmacological treatment.

Indeed, malnutrition deprives the immune system of the components needed to generate an effective immune response. Nutritional deficiency is associated with impaired cell-mediated immunity as well as decreased phagocyte function, cytokine production, secretory antibody affinity and response, and impairment of the complement system [10]. Furthermore, early reports suggest that low vitamin D levels, common in IBD patients, may be associated with an increased risk and/or severity of COVID-19 [11].

Disease activity is a significant non-pharmacological risk factor for infections, therefore medical treatment aiming for disease control should be optimized [12]. On the other hand, IBD treatments include corticosteroids, immunosuppressants (such as thiopurines) and immunomodulators (such as TNF-antagonists, non-TNF-targeted biologics and targeted small molecule therapies), which may weaken the immune system and potentially place IBD patients at increased risk of infections and infectious complications [13].

Age is associated with a higher risk of infections in IBD patients [14], and comorbidities have been described in general as an independent risk factor for infection-related hospitalizations [15]. Consequently, there is a concern that IBD patients are at greater risk of both developing COVID-19 and of a more severe clinical course compared to the general population.

With this in mind, the aim of our study is to understand the incidence of COVID-19 in a large cohort of patients with IBD from a single Italian tertiary referral IBD center. Furthermore, we analyzed possible risk factors for infection and severity of COVID-19 and the impact of the pandemic on IBD management.

## 2. Materials and methods

This was an observational study evaluating the impact of COVID-19 on IBD patients in a single tertiary IBD center.

A 23 multiple-choice-question anonymous survey (Supplementary Table 1) was administered to a total of 1200 patients with Crohn's disease (CD) or Ulcerative Colitis (UC) who had scheduled visits in our IBD center in Bologna between March 10th and June 10th, 2020. The survey was administered in-person to 680 patients who underwent an outpatient visit and by telephone or email to 520 patients who missed a scheduled visit during the period under review. The follow-up was mainly conducted face-to-face and, only in a minority of patients, by e-mail or telephone. Telephone triage before patients' access to the outpatient clinic was performed to check for possible symptoms and/or contact with infected persons and for promotion of basic protective measures. A rigorous protocol to avoid infection outbreaks was adopted for patient access to the outpatient clinic and, particularly, checkpoints to investigate suspected symptoms and signs of COVID-19, to test body temperature, and to provide personal protective equipment (PPE) were posted at every public entrance of the hospital. All patients and the entire staff wore PPE and strictly followed the WHO recommendations to prevent infection.

We used REDCap (Research Electronic Data Capture), a secure, web-based electronic data capture tool hosted at the University of Bologna, DIMEC, to collect and manage study data. Health care

providers recorded the following information: age, city and region of residence, sex, BMI, type of IBD (CD, UC), disease activity (clinical Mayo score in UC patients, Harvey Bradshaw Index in CD patients), IBD treatment at the time of COVID-19 diagnosis, date of COVID-19 test (polymerase chain reaction on nasopharyngeal swab), hospitalization, symptoms related to COVID-19, COVID-19 treatment, and complications or death related to COVID-19.

If patients were on biological therapy, they were asked to report if treatment was discontinued or delayed due to the pandemic. All patients were asked to describe if they experienced subjective worsening of IBD symptoms during the health emergency. For hospitalized patients, length of stay and need for ventilation support were also recorded.

We removed all known duplicates or erroneous reports. We identified additional potential duplicate records based on matching age, sex, IBD disease type, and place of residence, and reviewed these manually.

The study was approved by the local ethics committee (Comitato Etico Area Vasta Emilia Centro – AVEC c/o Azienda Ospedaliero-Universitaria di Bologna Policlinico S. Orsola-Malpighi 534/2020/Oss/AOUBo). Written, informed consent was obtained from each patient included in the study. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee.

### 2.1. Statistical analysis

We used descriptive statistics to summarize the basic demographic and clinical characteristics of the study population. We summarized continuous variables using means and standard deviations. We expressed categorical variables as proportions. Comorbidities recorded were hypertension, diabetes, heart disease (ischemic or congestive), and other diseases.

We analyzed a variety of COVID-19 outcomes, including outpatient care only, hospitalization, ventilator requirement, and death from COVID-19 or related complications. Simple data are provided for the overall study population.

Multivariable logistic regression estimated the independent effects of age, sex, disease (CD vs UC), disease activity, smoking, IBD therapy, BMI  $\geq 30$ , and number of comorbidities (0, 1,  $\geq 2$ ) on the primary outcome of severe COVID-19. A secondary outcome was the composite of any hospitalization and/or death.

All statistical analyses were performed with a statistical software package (SPSS-20). Two-sided *p* values < 0.05 were considered statistically significant.

## 3. Results

Of 1200 questionnaires, 1158 were analyzed. 42 questionnaires were discarded due to missing data. Demographic, clinical, and IBD treatment-related characteristics are summarized in Table 1. The mean age was 44.5 years (range 18–86), and there was a slight predominance of males (55.62%).

The majority of patients had CD (60%) and were in clinical remission (56.7%).

Of the overall population, 521 patients (45%) were on biological treatment for refractory active IBD, 83 (7.2%) were on non-systemic steroids, 77 (6.65%) were on systemic steroids, 787 (67.9%) were on sulfasalazine/mesalazine and 46 (3.9%) were on thiopurines (Table 1).

In all 521 (45%) patients on biological treatment the indication was refractory IBD.

As stated in Table 1, 292 (25.2%) patients also had spondyloarthritis and 25 (2.2%) had psoriasis.

**Table 1**  
Demographics and clinical characteristics of general population.

	All	UC	CD	p
Number (%)	1158	463 (39.98%)	695 (60.02%)	
Mean Age (+/- SD, range)	44.48 (14.56, 18–81)	45.15 (14.58, 18–75)	44.4 (14.55, 18–81)	NS
Sex, n (%):				
Male	644 (55.6%)	354 (76.4%)	290 (41.7%)	NS
Female	514 (44.4%)	109 (25.6%)	405 (58.3%)	
IBD disease activity (%):				
Remission	56.7%	56%	57.2%	NS
Mild	27.5%	26.6%	28.2%	NS
Moderate	14.6%	15.8%	13.8%	NS
Severe	1.2%	1.5%	1%	NS
Mean BMI (+/- SD)	23.15 (3.71)	23.54 (3.62)	22.89 (3.75)	NS
IBD therapy, n (%):				
Sulfasalazine/mesalazine	786 (67.9%)	377 (81.4%)	409 (58.8%)	0.012
Budesonide	82 (7.1%)	40 (8.6%)	42 (7.3%)	NS
Oral/parenteral steroids	76 (6.6%)	39 (8.4%)	37 (5.4%)	NS
6MP/azathioprine	45 (3.9%)	22 (4.8%)	23 (3.2%)	NS
Anti-TNF	285 (24.6%)	103 (22.3%)	182 (26.2%)	NS
Anti-integrin	198 (17.1%)	76 (16.5%)	122 (17.3%)	NS
IL-12/23 inhibitor	38 (3.3%)	0 (0%)	38 (5.5%)	0.048
Therapy discontinuation, n (%)	102 (8.8%)	37 (8%)	65 (9.3%)	NS
Delay in biological administration (%)	244 (21.1%)	90 (19.5%)	154 (22.1%)	NS
Worsening of symptoms, n (%)	204 (17.6%)	86 (18.5%)	118 (17%)	NS
COVID +, n	26	11	15	NS
Coronavirus swab (%)	32.1%	31%	33%	NS
Coronavirus serology (%)	6.8%	5%	7.2%	NS
Region, n (%):				
High risk <sup>a</sup>	874 (75.5%)	352 (76.2%)	522 (75.1%)	NS
Low risk	284 (24.5%)	110 (23.8%)	174 (24.9%)	NS
Comorbidity, n (%):				
Any condition	555 (47.9%)	237 (51.1%)	318 (43.9%)	NS
Cardiovascular disease	63 (5.4%)	25 (5.4%)	38 (5.4%)	NS
Diabetes	63 (5.4%)	33 (7.1%)	30 (4.3%)	NS
Hypertension	311 (26.9%)	126 (27.2%)	185 (26.8%)	NS
Arthritis	292 (25.2%)	98 (21.2%)	194 (27.9%)	NS
Skin diseases (psoriasis)	25 (2.2%)	7 (1.5%)	18 (2.7%)	NS
Hospitalizations, n	9	5	4	NS
Death due to COVID-19, n	2	1	1	NS

<sup>a</sup> Lombardy, Piedmont, Veneto, and Emilia-Romagna.

No comorbidities were present in 555 patients (47.9%); 336 (29%) had a single comorbidity, 148 (12.78%) had two, and 64 (5.52%) had three or more (Table 1). The most common comorbidity was hypertension, present in 311 patients (26.86%). Of the 521 patients on biological therapy, 109 were on infliximab, 198 were on vedolizumab, 176 were on adalimumab and 38 on ustekinumab.

No patients were in combo-therapy.

Treatment was autonomously discontinued by 85 (16.3%) of the 521 patients on biologics. Of these, 31 patients had CD and 54 had UC. In addition, treatment was autonomously delayed in 195 patients (37.4%), 73 with CD and 122 with UC. The main reasons for discontinuation or delay were the impossibility to reach the IBD center in 226 patients (80.7%); fear of COVID-19 in 47 patients (16.8%), and difficulty with drug supplying in 7 patients (2.5%). The remaining 241 (46.3%) patients continued the scheduled biological treatment. No patient changed biological therapy nor, particularly, switched from intravenous to subcutaneous treatment. Mean (SD) delay of therapy was of 72.8 (17.5) days.

A worsening of IBD symptoms was observed in 200 patients on biological therapy (38.4%): 84 with CD and 116 with UC. Most of these patients, 189 (94.5%), had stopped or delayed biological treatment during the national lockdown period, while the remaining 11 (5.5%) had continued their therapy regularly ( $p < 0.001$ ). No patients required hospitalization for IBD reactivation during the observation period.

Of the 637 patients not in biological therapy, worsening of symptoms and reactivation was observed in 219 (34.4%). Of these patients, 32 (14.6%) had spontaneously discontinued therapy, all of them treated with immunosuppressors, because of fear of COVID-19.

A total of 26 patients (2.2%) tested positive for COVID-19 detected by PCR from nasopharyngeal swab. Most of our patients spent the lockdown in high-risk regions (92.3%).

Among the 26 IBD patients who tested positive for COVID-19, 4 (15.4%) were asymptomatic, 15 (57.7%) presented with mild symptoms and did not need hospitalization, while 7 (35%) were hospitalized. Two of these patients died (7.7%). Both patients who died (1 with UC and 1 with CD) were male, 78 and 86 years of age respectively, with at least 3 comorbidities, in IBD clinical remission at the time of COVID-19 infection and only on mesalazine therapy.

Of the 26 patients who tested positive for COVID-19, 15 had CD and 11 had UC. Five patients (3 CD and 2 UC) were on biological treatment (2 with anti-TNF agents, 2 with anti-integrin and 1 with IL-12/23 inhibitor), all on monotherapy; 16 (7 CD and 9 UC) were only on mesalazine, 5 (3 CD and 2 UC) on systemic steroids and 1 (UC) on thiopurines (Table 2). No patient on biological treatment required hospitalization, 3 were asymptomatic and 2 presented with only a low-grade fever. No patients underwent surgery.

In our cohort, the cumulative incidence observed was 22.4 cases per 1000 persons (versus 4.5 cases per 1000 persons potentially expected). Through June 10, 2020, cumulative incidence of laboratory-confirmed COVID-19 in the general Italian population was 3.91 cases per 1000 (235,763 reported cases among an overall population of 60,360,000) with a mortality rate of 0.57 per 1000 (34,114 deaths). In the high-risk regions of Lombardy, Emilia-Romagna and Piedmont, the incidence was 9.01, 6.27, and 7.10 cases per 1000 inhabitants respectively [16].

On multivariable analysis, age above 70 years (OR 1.08, 95% CI 1.02–1.09) and the presence of  $\geq 2$  comorbidities (OR 3.1, 95% CI

**Table 2**  
Clinical characteristics, treatments and outcomes of inflammatory bowel diseases patients with COVID-19 infection.

N	Sex	Age	Smoking	BMI	IBD	Activity	IBD-Therapy	Delayed or discontinued	Worsening	Comorbidity	Common symptoms	Hospitalization	Outcomes
1	F	50	No	24	CD	Moderate	Steroids	No	Yes	None	None	Yes	Discharged
2	F	32	No	22	CD	Mild	Mesalazine	No	No	None	None	No	Isolated at home
3	M	41	No	26.9	CD	Remission	Mesalazine	No	No	Hypertension	Cough, dyspnea, diarrhea	No	Isolated at home
4	F	58	No	21	CD	Remission	Mesalazine	No	No	None	No	No	Isolated at home
5	F	69	No	21.5	CD	Moderate	Mesalazine	No	Yes	Lymphoma	Fever, diarrhea, dyspnea	No	Isolated at home
6	M	86	No	22	CD	Remission	Mesalazine + steroids	No	No	Hypertension, cardiovascular disease	Respiratory failure	Yes	Discharged
7	F	63	No	26.6	CD	Remission	Mesalazine	No	No	Hypertension, psoriasis	Fever	No	Isolated at home
8	M	38	No	21.2	CD	Mild	Ustekinumab	Yes	No	None	No	No	Isolated at home
9	F	36	No	28.2	CD	Remission	Mesalazine	Yes	Yes	Arthritis	Diarrhea	No	Isolated at home
10	M	89	No	24	CD	Remission	Mesalazine	No	No	Hypertension, cardiovascular disease, diabetes	Respiratory failure	Yes	Death
11	F	48	No	24	CD	Remission	Mesalazine	No	Yes	None	Fever, diarrhea, dyspnea, cough	No	Isolated at home
12	M	24	No	18.3	CD	Moderate	Adalimumab	Yes	Yes	None	Fever, diarrhea, dyspnea, cough	No	Isolated at home
13	M	28	No	20.6	CD	Moderate	Mesalazine	Yes	No	None	Fever	No	Isolated at home
14	F	29	No	24.2	CD	Remission	Vedolizumab	Yes	Yes	None	Diarrhea	No	Isolated at home
15	F	52	No	20.9	CD	Remission	Mesalazine	No	No	Hypertension	Fever, asthenia	No	Isolated at home
16	M	78	No	21	UC	Remission	Mesalazine	No	No	Hypertension, Diabetes, cardiovascular disease	Respiratory failure	Yes	Death
17	F	50	No	18.6	UC	Moderate	Mesalazine + steroid	No	No	None	Fever, diarrhea	No	Isolated at home
18	F	26	No	19.6	UC	Mild	Mesalazine + steroid	No	No	None	Fever, diarrhea, cough	No	Isolated at home
19	F	72	No	29	UC	Remission	Mesalazine	Yes	Yes	Hypertension	Fever, diarrhea, cough	Yes	Discharged
20	M	58	No	23	UC	Remission	Azathioprine	Yes	No	None	No	No	Isolated at home
21	F	59	Yes	25.6	UC	Mild	Infliximab	Yes	No	None	Fever, cough	No	Isolated at home
22	M	33	No	27.4	UC	Mild	Mesalazine	No	No	None	Fever, cough	Yes	Discharged
23	M	40	Yes	24.9	UC	Remission	Vedolizumab	No	No	None	Fever, headache	No	Isolated at home
24	M	57	No	27.4	UC	Remission	Mesalazine	No	No	None	Fever, Headache	No	Isolated at home
25	M	40	No	26.5	UC	Remission	Mesalazine	No	Yes	None	Headache	No	Isolated at home
26	F	48	No	31.1	UC	Remission	Mesalazine	No	No	Hypertension	Fever, cough	Yes	Discharged

1.2–7.6) were positively associated with a more aggressive COVID-19 course. No significant association was seen between biological treatment and a more severe COVID-19 course.

#### 4. Discussion

There are only limited data on the incidence of COVID-19 in the IBD population. In our study, the incidence of COVID-19 is 22.4 per 1000 patients, higher than that of the overall population [16]. Among the 26 patients who tested positive, 4 were asymptomatic. These data can be explained by the fact that most of our patient cohort came from high-risk regions for COVID-19, where preliminary data from serology studies show that the prevalence of the infection seems to be much higher than that known to date due to an uncountable number of asymptomatic patients [5,17].

In very early reports from China, no patients with IBD were reported to be infected with SARS-CoV-2 in the IBD Elite Union, which incorporates the seven largest IBD referral centers in China with more than 20,000 patients with IBD [18].

An and colleagues described a very low incidence of SARS-CoV-2 infection in 318 patients followed in a prospective database at the Regional Medical IBD Center of China, Renmin Hospital of Wuhan University, Wuhan, China. Patients were educated about virus transmission and invited to strictly avoid non-familiar contact. All drugs were stopped except mesalazine and thalidomide. Flares were treated with enteral nutrition and/or low-dose steroids. None of the 318 patients living in the high-risk area but closely adherent to the indications developed symptoms suggesting COVID-19 [19].

Taxonera et al. reported a cumulative incidence of 6.1 per 10,000 patients among IBD patients followed at a large IBD unit in the Madrid Region, lower than that of the overall population [20].

In a very early study, among 522 patients followed in a single IBD center in Bergamo, no case of COVID-19 was reported [21].

Due to the variable presentation of COVID-19, these early reports highlight the need for studies on the prevalence of the disease based on serology.

In our study, 44.8% of patients were on maintenance treatment with biologics and 6.6% were on systemic steroid therapy. Among the 26 patients who tested positive for COVID-19, 5 were on maintenance therapy with biologics (19%) and 4 were in treatment with systemic steroids (15.4%). Patients on biologics who tested positive did not have a more severe COVID-19 course, and the only two patients who died were on mesalazine monotherapy. Risk factors for a more aggressive course of the disease were in line with current literature: advanced age, male sex and the presence of more than 2 comorbidities.

Examining the risk of severe infection related to the ongoing treatment, Bezzio and colleagues evaluated COVID-19 outcome in 79 patients with IBD. In their study, twenty-two patients (28%) with COVID-19-related pneumonia required hospitalization, 9 (11%) non-invasive ventilation support, 2 (3%) endotracheal intubation and 6 patients (8%) died. Multivariate analysis demonstrated that age over 65 years old, UC diagnosis and disease activity, but not concomitant treatment, were significantly associated with the risk of pneumonia and death [22].

In the Surveillance Epidemiology of Coronavirus Under Research Exclusion for Inflammatory Bowel Disease (SECURE-IBD), a large international registry that monitors the outcomes of IBD patients with COVID-19, severe infection (defined as intensive care unit admission, ventilator use and death) correlated with age, presence of  $\geq 2$  comorbidities, steroids and sulfasalazine/mesalazine use, but not with anti-TNF drugs [23,24].

Furthermore, patients in our study who discontinued or delayed therapy with anti-TNF agents or other biologics showed higher rates of relapse, and in 41% of cases steroid treatment was needed.

On the other hand, patients on systemic steroid therapy during the lockdown seemed to be at higher risk for infection, although due to the small sample size no conclusion can be drawn.

These data suggest that TNF antagonists may reduce the severity of COVID-19 infection, while IBD recurrence is a negative prognostic factor. This has led the various scientific societies to advise not to stop therapy with biologics in patients in stable remission for fear of COVID-19 infection [25].

Furthermore, our data seem to confirm the results of early studies results that indicate that continuous steroid treatment could be a risk factor for infection in IBD patients [26].

This study has several limitations. First, the heterogeneity of the clinical presentation of COVID-19 and the small sample size of our cohort of patients prevent us from drawing any final conclusions on the incidence and the risk factors of COVID-19 in the IBD population. Second, the limited number of COVID-19 positive patients in our cohort does not allow us to identify risk factors for severe COVID-19 illness related to the IBD treatment. Large multicenter studies are necessary to evaluate the association between IBD characteristics and COVID-19.

#### 5. Conclusions

The present study recorded a higher incidence of COVID-19 infection in our IBD cohort than in the general population. These data were probably due to the variable incidence among different regions and to the different methods of diagnosis in asymptomatic subjects in the general population. Current treatment should not be discontinued, particularly biological therapy, in order to avoid IBD relapse.

#### Conflict of Interest

None declared.

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#### Supplementary material

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.dld.2020.12.012.

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