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Alimentary Tract

Risk of COVID 19 in patients with inflammatory bowel diseases compared to a control population



Giovanni Maconi^{a,*}, Cristina Bosetti^b, Alberta De Monti^a, Ray Kiran Boyapati^c, Edward Shelton^c, Nicole Piazza^{d,m}, Anna Maria Carolhas Gabrielli^a, Marco Vincenzo Lenti^e, Cristina Bezzio^f, Chiara Ricci^{g,n}, Salvatore Greco^h, Samanta Romeoⁱ, Francesco Giangregorio^j, Daniele Gridavilla^a, Fabio Tagliani^a, Alessandro Massari^a, Luca Pastorelli^m, Antonio Di Sabatino^e, Simone Saibeni^f, Saverio Alicanteⁱ, Francesca Ferretti^a, Giuliano Rizzardini^k, Massimo Galli^l, Sandro Ardizzone^a

^a Gastroenterology Unit, ASST Fatebenefratelli Sacco, Department of Biomedical and Clinical Sciences "L.Sacco" University of Milan, Italy

^b Department of Oncology, Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Milan, Italy

^c Department of Gastroenterology, Monash Health. Faculty of Medicine, Nursing & Health Sciences, Monash University, Clayton, Victoria, Australia

^d Gastroenterology Unit, IRCCS Policlinico San Donato, San Donato Milanese, Italy

^e Department of Internal Medicine, Fondazione IRCCS Policlinico San Matteo, Università degli Studi di Pavia, Pavia, Lombardia, Italy

^f Gastroenterology Unit, Rho Hospital, Rho (MI), ASST Rhodense, Garbagnate Milanese, Italy

^g Department of Clinical and Experimental Sciences, University of Brescia, Brescia, Italy

^h Papa Giovanni XXIII Hospital, Gastroenterology and Digestive Endoscopy Units, Bergamo, Italy

ⁱ Department of Gastroenterology and Endoscopy, Maggiore Hospital, ASST Crema, Crema, Italy

^j Internal Medicine and Gastroenterology, Codogno Hospital, Italy

^k I Division of Infectious Diseases, ASST Fatebenefratelli-Sacco, L. Sacco Hospital, Milan, Italy

^l III Division of Infectious Diseases, ASST Fatebenefratelli-Sacco, Department of Biomedical and Clinical Sciences, University of Milan, Italy

^m Department of Biomedical Sciences for Health, University of Milan, Milan, Italy

ⁿ Division of Gastroenterology, ASST Spedali Civili, Brescia, Italy

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ABSTRACT

Background: It is unclear whether patients with inflammatory bowel disease (IBD) are at increased risk of COVID-19.

Objectives: This observational study compared the prevalence of COVID-19 symptoms, diagnosis and hospitalization in IBD patients with a control population with non-inflammatory bowel disorders.

Methods: This multicentre study, included 2733 outpatients (1397 IBD patients and 1336 controls), from eight major gastrointestinal centres in Lombardy, Italy. Patients were invited to complete a web-based questionnaire regarding demographic, historical and clinical features over the previous 6 weeks. The prevalence of COVID-19 symptoms, diagnosis and hospitalization for COVID-19 was assessed.

Results: 1810 patients (64%) responded to the questionnaire (941 IBD patients and 869 controls). IBD patients were significantly younger and of male sex than controls. NSAID use and smoking were more frequent in controls. IBD patients were more likely treated with vitamin-D and vaccinated for influenza. Highly probable COVID-19 on the basis of symptoms and signs was less frequent in the IBD group (3.8% vs 6.3%; OR:0.45, 95%CI:0.28–0.75). IBD patients had a lower rate of nasopharyngeal swab-PCR confirmed diagnosis (0.2% vs 1.2%; OR:0.14, 95%CI:0.03–0.67). There was no difference in hospitalization between the groups (0.1% vs 0.6%; OR:0.14, 95%CI:0.02–1.17).

Conclusion: IBD patients do not have an increased risk of COVID-19 specific symptoms or more severe disease compared with a control group of gastroenterology patients.

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1. Introduction

The novel coronavirus (SARS CoV-2) was first reported in Wuhan in December 2019 and quickly evolved into a global pandemic [1–3]. The outbreak rapidly spread to Europe in February

* Corresponding author.

E-mail address: giovanni.maconi@unimi.it (G. Maconi).

2020 with Italy becoming the most impacted country and Lombardy, the most affected area [4]. Shortly following the outbreak, the region went into lockdown and the population was instructed to self-isolate at home. Patients with inflammatory bowel disease (IBD) were advised to isolate and take routine precautions against coronavirus disease 2019 (COVID-19) as recommended by the World Health Organization, but to continue their medical therapy, including immunosuppressives or biologics [5,6,7].

Infection with SARS CoV-2 leading to COVID-19 can manifest with minor symptoms often mimicking the common influenza and usually managed at home with isolation. More severe cases are characterized by respiratory function impairment and multi organ failure that require hospitalization and intensive care admission with a current estimate for infection fatality rate of 0.5–1% [8,9]. Severe and fatal manifestations of COVID-19 are associated with advanced age and pre-existing comorbidities including cardiovascular disease, diabetes, obesity, respiratory illnesses and cancer [1,2].

It remains uncertain whether IBD patients are more susceptible to COVID-19 or more prone to severe disease. Consequently, there has been significant anxiety among IBD patients and clinicians regarding potential increased susceptibility. This is in part related to IBD management which involves immunosuppression, potentially placing patients at increased risk of opportunistic infections and respiratory illnesses [10,11]. However, whether immunomodulators and biologics increase the risk of infection or of developing severe forms of COVID-19, is currently undefined [12].

Initial reports from China demonstrated that the incidence of severe disease might be lower in IBD patients compared with rates in the general population [13]. Similarly, early reports from Italy demonstrated no cases in their IBD population despite continuation of immunosuppressive therapy [14]. Furthermore, there have been reports on the safety of IBD therapy demonstrating no association between treatment with biologics and/or immunomodulators [15]. The recently published series from the SECURE-IBD registry of 525 IBD COVID-19 cases noted no increased severity with TNF antagonists but a significant association with corticosteroids and the traditional risk factors of increased age and comorbidities [16].

These early reports are reassuring and suggest that IBD patients may be at decreased risk of COVID-19. However, the mechanisms underpinning this observation in the absence of large case-control studies is uncertain. More data is needed to inform patients and healthcare providers regarding their risk and how to manage it during the COVID-19 pandemic. We thus conducted a study to compare the prevalence of COVID-19 symptoms, formal diagnosis and hospitalization for COVID-19 in IBD patients versus general gastroenterology controls.

2. Methods

This was a multicentre observational study conducted in Lombardy, a region in the northwest of Italy, which has a population of 10 million and a high prevalence of IBD (96.2 cases per 100,000) [17]. The 14 major gastroenterology units in the region and 1 in the nearby region Emilia, were invited to participate. The case population consisted of all IBD patients who attended these units in the 3 months prior to study commencement. The matched controls were referred as outpatients with non-inflammatory bowel disorders (functional gastrointestinal disorders, gastroesophageal reflux disease, diverticular disease or colonoscopy surveillance patients) who visited the same units in the same period. Controls were matched for age (clusters of 5 years), sex and area of residence.

Cases and controls were contacted between April 4, 2020 and April 12, 2020, shortly following the peak of the COVID-19 pandemic in Lombardy. They were initially invited by text message to complete a web-based questionnaire regarding COVID-19 risk

factors, symptoms and diagnosis that occurred in the previous 6 weeks which corresponded to the beginning of the outbreak in Lombardy. Non-responders were followed up with two further text messages, email or phone call by their usual treating team. The questionnaire was accessible in a web-based form by smartphone or email, and remained active until April 25, 2020. The questionnaire included demographic variables, social factors, medications, comorbidities, contact history, COVID-19 symptoms, confirmed COVID-19 diagnosis and hospitalization (Appendix 1).

Prior to its use, the questionnaire was tested twice for validation. Initially it was sent to 20 IBD patients and their responses gathered on two different days and compared. This was then repeated in 40 IBD patients. Intra-patient concordance in responses between days was >90% and specifically regarding demographic, historical and clinical variables, 96%, 94% and 94% respectively. Responses stating a diagnosis and hospitalization for COVID-19 were verified by each center via phone calls and cross checking with hospital records.

During the study period, most study participants with symptoms of COVID-19 were not investigated with a nasopharyngeal swab due to the limited availability of diagnostic tests. Furthermore, with advice to self-isolate, there was an understandable reluctance to present for testing in milder cases. We therefore considered it probable that there was a large proportion of symptomatic patients with COVID-19 not formally diagnosed by nasopharyngeal swab-PCR. To capture these patients we reported highly probable COVID-19 based on the combination of fever and ageusia or anosmia and at least one other common symptom (either cough, dyspnea, fatigue or myalgia).

The endpoints of the study were to compare in IBD and controls:

- i) the prevalence of highly probable COVID-19 based on suggestive symptoms
- ii) the diagnosis of COVID-19 confirmed by PCR nasopharyngeal swab
- iii) the prevalence of severe COVID-19 requiring hospitalization
- iv) the clinical and demographic variables associated with COVID-19 risk

2.1. Ethics approval

The study was approved by Luigi Sacco University Hospital ethics committee (Code. n. 2020/ST/062). The identity and privacy of each patient was secured and response to each questionnaire was anonymised.

2.2. Statistical analysis

Results for continuous data are presented as median and interquartile range and analysed using Mann Whitney U-Test. Categorical data are presented as absolute and relative frequencies, and analysed using a chi-square test.

The prevalence of likely symptoms, diagnosis and hospitalization for COVID-19 were compared using multivariate logistic regression models, estimating odds ratios (OR) and their 95% confidence intervals (CI). The models were adjusted for socio-demographic variables, i.e., age, sex, area of residence. Moreover, additional models were also adjusted for variables which were significantly different on univariate analysis. All tests were 2-tailed and a *p* value of less than 0.05 was considered statistically significant.

The statistical analysis was performed using software SAS, version 9.4 (SAS Institute, Cary, NC).

3. Results

3.1. Study population

The study initially planned to include 8000 participants from 15 gastroenterology units. Due to the overwhelming nature of the COVID-19 pandemic and the recruitment of gastroenterology unit staff for COVID-19 units, 7 institutions were unable to contribute. The 8 remaining gastroenterology units (Luigi Sacco University Hospital in Milan, Policlinico San Matteo University Hospital in Pavia, and the Hospitals of San Donato, Bergamo, Brescia, Crema, Rho and Piacenza) identified 2829 patients that met inclusion criteria (1394 IBD cases and 1435 gastroenterology controls). 1810 patients (64%) responded to the questionnaire, with rate of responses varying widely among centres (20–71%). Respondents were more likely to be IBD patients (52% vs 44.5%, $p < 0.0001$), female (51.4% vs 43.4%, $p = 0.009$) and residents in Milan and surrounds compared to elsewhere in Lombardy (73.8% vs 26.2%; $p < 0.0001$).

Respondents included an IBD population of 941 patients (517 Crohn's disease and 424 ulcerative colitis) and a control group of 869 patients (143 gastroesophageal reflux disease, 60 with colorectal polyps, 53 diverticular disease, 217 patients with abdominal complaints and a large group of patients with no specific disease (268) or miscellaneous disorders (128)) (Table 2).

3.2. Demographic & clinical characteristics

IBD patients (50 yrs, IQR 39–60) were significantly younger than controls (54 years, IQR 44–63, $p < 0.0001$), of male sex (51.5% vs 45.3%, $p = 0.0084$) and never or past smokers (78.7% vs 75.2%, $p = 0.001$). There were differences in occupation between groups, with a greater prevalence of managers and professionals among controls, and more craft and trade workers in the IBD group. Educational level, BMI and physical, social and religious activity were not significantly different between groups (Table 1). IBD patients were mainly in clinical remission (77%), and treatment was predominantly with mesalamine (47.6%) or biologic therapies (43.5%), with 10.5% on corticosteroids (Supplementary Table 3).

Prevalence of comorbidities, namely hypertension (including treatment with ACE inhibitors), diabetes, hepatic, cardiovascular and respiratory diseases was similar between groups. Oncologic diseases were less frequent in the IBD group (3.7% vs 8.6%, $p < 0.0001$) while rheumatic diseases were more frequent in the IBD group (14.7% vs 8.6%, $p < 0.0001$). Current use of aspirin and non-steroidal anti-inflammatory drugs (NSAIDs) was more frequent in the control group (64.0% vs 34.9% $p < 0.00001$), while intake of vitamin D (38.7% vs 31.8%, $p < 0.007$) and vaccination for influenza (28.7% vs 21.9%, $p < 0.0009$) were more prevalent in IBD patients (Table 2).

3.3. Response to the COVID-19 lockdown

The majority of patients (>90%) in both groups responded appropriately to the lockdown by staying at home, socially isolating, wearing mask in public settings and using hand hygiene (Supplementary Table 4). IBD patients were more likely to cease or markedly reduce time spent at work compared to controls (56.7% vs 63.2%, $p = 0.024$).

3.4. COVID-19 symptoms

IBD patients more frequently reported no symptoms (43.8% vs 37.9%) although this was not statistically significant ($p = 0.06$) (Table 3). Fewer patients reported arthralgia and myalgia in the IBD group compared to controls (26.9% vs 34.0%, $p = 0.001$), but there

was no significant difference on univariate analysis of other symptoms. IBD patients and controls reported the same rate (16.1%) of family members with one or more of the above-mentioned symptoms.

3.5. Diagnosis of COVID-19

COVID-19 was diagnosed by PCR swab in 2 (0.2%) IBD patients and 10 (1.2%) controls ($p = 0.018$; Table 4). No data were available regarding the overall rate of PCR swab testing in the groups. There was no difference in the numbers who were not investigated or where data was missing from the completed questionnaire. On logistic regression analysis adjusting for age, sex, area of residence and education, there was a lower rate of COVID-19 diagnosis in the IBD cohort compared to the control group (OR 0.15, 95% CI 0.03–0.68). The lower rate of COVID-19 diagnosis in the IBD cohort was also found on a different logistic regression model adjusting for smoking, oncologic diseases, rheumatologic diseases, use of acetaminophen, aspirin and NSAIDs, vitamin D intake and vaccination for seasonal influenza (OR 0.14, CI 0.03–0.67).

3.6. Highly probable COVID-19 based on symptoms

Highly probable COVID-19 was less frequent in the IBD group compared to the control group (3.8% vs 6.3%, $p = 0.006$). The lower rates of highly probable COVID-19 in the IBD group persisted after logistic regression analysis adjusting for age, sex, area of residence and education (OR 0.53; 95% CI 0.33–0.84) and in another model adjusting for smoking, oncologic diseases, rheumatologic diseases, use of acetaminophen, aspirin and NSAIDs, vitamin D intake and vaccination for seasonal influenza (OR 0.45; 95% CI 0.28–0.75).

Alternative definitions of highly probable COVID-19, including fever, ageusia/anosmia and respiratory symptoms such as cough or dyspnea (OR 0.52; 95% CI 0.30–0.90) or fever, ageusia/anosmia and systemic symptoms such as fatigue or myalgia (OR 0.42; 95% CI 0.26–0.70) provided very similar results, even after adjusting for smoking, oncologic diseases, rheumatologic diseases, use of acetaminophen, aspirin and NSAIDs, vitamin D intake and vaccination for seasonal influenza. IBD patients treated with biologic therapy showed a comparable rate (15/409; 3.67%) of COVID-19 symptoms compared with patients treated with other therapies (21/532; 3.95%). Prevalence of COVID-19 symptoms in active IBD patients was not significantly different from that of patients in clinical remission (3.7% vs 4.1%).

3.7. Hospitalization for COVID-19

One (0.1%) IBD patient and 6 (0.7%) controls were hospitalised for COVID-19 ($p = 0.08$), and the IBD patient died (Table 4). There was no difference in the numbers where data was missing from the completed questionnaire. There was no difference found between the groups on logistic regression analysis adjusting for age, sex, area of residence and education (OR 0.15, 95% CI 0.02–1.26) or in another model adjusting for smoking, oncologic diseases, rheumatologic diseases, use of acetaminophen, aspirin and NSAIDs, vitamin D intake and vaccination for seasonal influenza (OR 0.14, 95% CI 0.02–1.17).

4. Discussion

This study is the largest to date examining the risk of IBD patients developing COVID-19 compared to a cohort of patients with digestive complaints/disorders. The diagnosis of COVID-19 by nasopharyngeal swab-PCR and highly suspected diagnosis based on

Table 1
Characteristics of 941 IBD patients and 869 controls.

Characteristics	IBD patients n. (%)	Controls n. (%)	p-value
Age (years)			
Median, IQR	50 (39–60)	54 (44–63)	<0.0001
<40	244 (25.9)	162 (18.6)	<0.0001
40–59	457 (48.6)	412 (47.4)	
≥60	240 (25.5)	295 (34.0)	
Sex			0.0084
Male	485 (51.5)	394 (45.3)	
Female	456 (48.5)	475 (54.7)	
Educational level			0.071
Primary education	35 (3.7)	36 (4.1)	
Lower secondary education	228 (24.2)	189 (21.7)	
Upper secondary education	451 (47.9)	386 (44.4)	
Post-secondary education	207 (22.0)	229 (26.3)	
Missing	20 (2.1)	29 (3.3)	
Area of residence			0.047
Milan	544 (57.8)	531 (61.1)	
Bergamo	40 (4.3)	35 (4.0)	
Monza Brianza	63 (6.7)	49 (5.6)	
Pavia	98 (10.4)	89 (10.2)	
Other	184 (19.6)	139 (16.0)	
Unknown	12 (1.4)	26 (3.0)	
Type of occupation [41,42]			0.063
Managers	31 (3.3)	40 (4.6)	
Professionals	97 (10.3)	115 (13.2)	
Technicians and associate	32 (3.4)	38 (4.4)	
Office employers	243 (25.8)	221 (25.4)	
Services and sales workers	117 (12.4)	103 (11.9)	
Skilled agricultural / forestry workers	14 (1.5)	8 (0.9)	
Craft and related trades workers	107 (11.4)	60 (6.9)	
Plant and machine operators and assemblers	9 (1.0)	6 (0.7)	
Elementary occupations	50 (5.31)	43 (5.0)	
Armed forces	5 (0.5)	7 (0.8)	
Retired or unemployed	142 (15.1)	133 (15.3)	
Missing	94 (10.0)	95 (10.9)	
Body mass index (kg/m ²)			0.88
<25	581 (61.7)	543 (62.5)	
25–30	260 (27.6)	231 (26.6)	
>30	100 (10.6)	95 (10.9)	
Smoking habit			0.001
No smoker	580 (61.6)	553 (63.6)	
Past smoker	161 (17.1)	101 (11.6)	
Current smoker	185 (19.7)	186 (21.4)	
Missing	15 (1.6)	29 (3.3)	
Physical activity [43]			0.32
Less than three times per week	603 (64.1)	527 (60.64)	
Three times or more per week	244 (25.9)	249 (28.7)	
Missing	94 (10.0)	93 (10.7)	
Social activity [43]			0.67
Less than once per week	488 (51.9)	437 (50.3)	
Once or more per week	377 (40.1)	353 (40.6)	
Missing	76 (8.1)	79 (9.1)	
Religious activity [43]			0.096
Less than once per week	675 (71.7)	584 (67.2)	
Once or more per week	196 (20.8)	204 (23.5)	
Missing	70 (7.4)	81 (9.3)	
Sharing home with one or more symptomatic family members (fever and other symptoms)	151 (16.1)	141 (16.1)	0.97

IQR: interquartile range.

symptoms was lower in IBD patients compared to the control group. Furthermore, the rate of COVID-19 with severe manifestations requiring hospitalization was less frequent in the IBD group. We identified a number of possible modifiable protective factors including influenza vaccination, lower smoking rate, vitamin D intake and higher vigilance.

The low risk of COVID-19 in IBD patients has already been reported in China, Italy and Spain [13,14,18]. In a Spanish study only 12 of 1918 IBD patients were diagnosed with COVID-19, with lower adjusted incidence ratio of COVID-19 (OR 0.74) compared with the general population, but a similar mortality ratio (OR 0.95) [18]. In addition, severe sequelae of COVID-19 may be less frequent in IBD patients than in control subjects [19].

In our study, both groups were well matched for comorbidities for severe COVID-19 including BMI, hypertension, diabetes, and hepatic, cardiovascular and respiratory diseases. There were differences in some of the demographic and clinical features between the groups which may have contributed to the risk of acquiring SARS-CoV2 and developing more severe clinical manifestations. The control cohort was older and there were significantly more males in the IBD cohort. Increasing age is a well-established risk factor and male gender is associated with worse outcomes [8]. The control group included a greater proportion of managers and professionals, while IBD patients had more craft and trade workers. These different occupations, and likely a greater concern about the condition in the IBD cohort, may have led different exposures

Table 2
Comorbidities and drug use among 941 patients with inflammatory bowel diseases (IBD) and 869 controls.

Comorbidities and drug use	IBD patients n. (%)	Controls n. (%)	p-value
Diabetes	45 (4.8)	50 (5.8)	0.35
Type 1	8 (0.9)	7 (0.8)	
Type 2	37 (3.9)	43 (5.0)	0.53
Hypertension	194 (21.1)	200 (24.0)	0.22
Treatment with ACE inhibitors	52 (5.5)	51 (5.9)	0.71
Cardiovascular diseases	58 (6.2)	53 (6.1)	0.95
Liver disease	29 (3.1)	28 (3.2)	0.86
Respiratory diseases	52 (5.5)	57 (6.6)	0.36
Oncologic diseases	35 (3.7)	76 (8.6)	<0.0001
Rheumatic diseases	138 (14.7)	75 (8.6)	<0.0001
Current use of anti-inflammatory drugs			
Acetaminophen	603 (64.1)	444 (51.1)	<0.0001
Aspirin	80 (8.5)	145 (16.7)	<0.0001
Diclofenac	99 (10.5)	137 (15.8)	0.0009
Ibuprofen	150 (15.9)	274 (31.5)	<0.0001
Current use of vitamin D	364 (38.7)	276 (31.8)	0.007
Vaccination for seasonal influenza	270 (28.7)	190 (21.9)	0.0009

Table 3
Respiratory and other symptoms among 941 patients with inflammatory bowel diseases (IBD) and 869 controls since late-February 2020.

Symptoms	IBD patients n. (%)	Controls n. (%)	p-value
Fever	184 (19.6)	157 (18.1)	0.42
<38 °C	128 (13.6)	105 (12.1)	0.63
≥38 °C	56 (6.0)	52 (6.0)	
Cough	185 (20.0)	177 (20.4)	0.71
dyspnea	53 (5.6)	65 (7.5)	0.11
Sore throat	195 (20.7)	211 (24.3)	0.07
Arthralgia and myalgia	253 (26.9)	295 (34.0)	0.001
Headache	287 (30.5)	283 (32.6)	0.34
Fatigue	250 (26.6)	254 (29.2)	0.21
Unusual diarrhea	167 (17.8)	159 (18.3)	0.76
Nausea and vomiting	96 (10.2)	92 (10.6)	0.79
Ageusia	59 (6.3)	66 (7.6)	0.27
Anosmia	48 (5.1)	56 (6.4)	0.22
Number of symptoms			
0	412 (43.8)	329 (37.9)	0.06
1	134 (14.2)	140 (16.1)	
2	105 (11.2)	117 (13.5)	
3 or more	290 (30.8)	283 (32.6)	

Table 4

Association between diagnosis, hospitalization, and highly probable COVID-19 based on signs and symptoms, over the previous 6 weeks in 941 IBD patients and 869 corresponding controls.

COVID-19	IBD patients (%)	Controls (%)	Odds ratio, 95% confidence interval ^a	p-value	Odds ratio, 95% confidence interval ^b	p-value
Diagnosis of COVID-19						
No	393 (41.8)	366 (42.1)	1 ^c		1 ^c	
Yes	2 (0.2)	10 (1.2)	0.19 (0.02–0.88)	0.030	0.14 (0.03–0.67)	0.024
Not investigated	545 (57.9)	489 (56.3)				
Missing	1 (0.1)	4 (0.5)				
Hospitalization for COVID-19						
No	938 (99.7)	859 (98.9)	1 ^c		1 ^c	
Yes	1 (0.1)	6 (0.7)	0.15 (0.00–1.26)	0.099	0.14 (0.02–1.17)	0.07
Missing	2 (0.2)	4 (0.5)				
Likely COVID-19 based on fever, ageusia/anosmia, and cough/myalgia						
No	905 (96.2)	815 (93.8)	1 ^c		1 ^c	
Yes	36 (3.8)	54 (6.3)	0.53 (0.33–0.84)	0.006	0.54 (0.34–0.86)	0.0018

^a Estimated from a logistic regression model adjusted for age, sex, area of residence, and education.

^b Estimated from a logistic regression model further adjusted for BMI, smoking, oncologic diseases, rheumatologic diseases, use of acetaminophen, aspirin and Nonsteroidal anti-inflammatory drugs, vitamin D intake and vaccination for seasonal flu.

^c Reference category.

to COVID-19 and could explain why IBD patients were more likely to stop work during the lockdown.

There were additional clinical features that may explain the higher rate of COVID-19 observed in the control cohort including a higher rate of oncologic diseases and more frequent use of NSAIDs. The potentially detrimental effect of NSAIDs on COVID-19 has been widely reported, although uncertainty exists regarding causation [20–24]. A large proportion of IBD patients in this study was on biological therapies and this is likely a reflection of the study design (recruitment of patients who had visited the gastroenterology department in the last 3 months). TNF antagonist treatment, unlike mesalamine or corticosteroids, is not associated with adverse COVID-19 outcomes and may be protective by blunting the cytokine storm associated with severe disease. This phenomenon may help explain the lack of any significant difference in the prevalence of COVID-19 symptoms between patients treated with biologics compared to other treatments. [16,25,26]. However, due to the small number of IBD patients with adverse outcomes, we could not verify these data.

There were other protective factors evident in the IBD population including a greater intake of vitamin D and higher rate of vaccination for influenza. The potential beneficial impact of vitamin D in the prevention of COVID-19 and mortality has been reported [27–29]. Likewise, the adjuvant benefit of influenza vaccination to minimize COVID-19 has been suggested, including in IBD patients [30–32]. Moreover, we observed a lower rate of active smoking in IBD patients. Systematic reviews and meta-analysis have found that active smoking is associated with progression and severity of COVID-19 [33–35].

We acknowledge a number of limitations in this study. Data were collected retrospectively through a web-based questionnaire and thus prone to recall bias. Hospitalization rates and death may have been underreported as patients may not have been able to complete the questionnaire. This effect should be balanced in both groups, although IBD patients under regular surveillance may be more likely to have notified their treating team in the event of significant illness. The methodology, with a focus on recall of symptoms, was appropriate for the period of early 2020 in Lombardy when patients were advised to isolate at home. There was a low initial response rate (35–40%) to the text message invitation to complete the questionnaire. This may have been related to the numerous unsolicited messages received by the population during the pandemic (including fundraising campaigns, some fraudulent). We found personal reminders by doctors were the most effective mechanism to increase participation. The higher response rate of IBD patients reflects the established and trusted relationship with their treating team. The response rate also differed by age and sex and among IBD patients and controls. This affected the proportion of responders between the groups and required a logistic regression - adjusted for age and sex - to properly estimate the risks.

Overall the response rate was acceptable considering the survey included a consecutive and unselected series of patients who had visited in the months prior to the lockdown, in all recruiting centers. This with the intent to obtain best representative results, generalizable to all IBD patients. However, the overall response rate to the questionnaire was affected by geographical reasons (place of the recruiting unit) and responses slightly differed in IBD and controls according to the place of residence. Therefore, odds of COVID-19, have been estimated by logistic regression analysis adjusted also for the area of residence. We acknowledge that a random sample of the general population would have been the ideal control group for this kind of study. This study included a control group of general gastroenterology patients matched for sex, age and geographical areas which represented a reasonable and convenient alternative.

Another limitation of the study is the low rate of nasopharyngeal swab-PCR based diagnosis and the lack of clear data on the number of swabs performed. Selection bias is thus possible, and any furthermore interpretation of PCR positivity rate should be made with caution. Although we acknowledge that an ideal study of prevalence should have tested all patients for COVID-19, the limited testing capability in Lombardy during early 2020 meant that most patients were unable to be tested despite symptoms. This has been reflected elsewhere in the world in the early phases of this pandemic [8]. With this in mind, we could not assess the confirmed diagnoses of COVID-19, but considered only the “highly suspected COVID-19” based on symptoms. Without confirmation by swab-PCR, this analysis potentially misdiagnosed a proportion of patients as COVID-19 who actually had other respiratory conditions. However, nasopharyngeal swab-PCR has suboptimal sensitivity, as low as 60% in some reports [36]. We incorporated fever (common but not specific for COVID-19) with change in sense of smell and taste (less common but much more specific for COVID-19) and another symptom (pulmonary or systemic) to optimize the accuracy of highly suspected COVID [37–40]. It is likely that asymptomatic or pauci-symptomatic patients have been overlooked in this analysis and this might have underestimated the real prevalence of the infection. In our region (10 million of habitants) at that time there were only 72,000 (0.72%) cases diagnosed with PCR swab, and 13,000 (0.13%) hospital admissions, a percentage quite similar to that seen in our study [44].

There are a number of strengths in this study. This is the largest cohort study of COVID-19 reporting symptoms, diagnosis and outcomes in IBD to date. It was conducted in Lombardy at the time when it was the worldwide epicenter of the COVID-19 pandemic. The high rate of community risk for COVID-19 during this period provided a suitable environment for a case-control study of this type. The large number of patients in this study allowed identification of modifiable protective factors accounting for the lower rate of COVID-19 in IBD patients including higher use of vitamin D and influenza vaccination, less NSAID use, lower smoking rates and increased vigilance.

This study found that IBD patients have a lower risk of COVID-19 by highly probable symptomatic criteria and do not have a higher risk of hospitalization compared to controls. It also identifies modifiable protective factors. This is reassuring for patients and clinicians and supports the emerging data that IBD patients are not at increased risk of contracting COVID-19 or more severe disease [13,14,18].

Declaration of Competing Interest

All authors have indicated they have no potential conflicts of interest relevant to this article to disclose.

Contributors' statements

Giovanni Maconi, MD: Conceptualized and designed the study, collected and analysed the data, drafted the work and approved the final manuscript as submitted.

Cristina Bosetti, MD, PhD: Conceptualized and designed the study, performed the statistical analysis, critically reviewed the manuscript and approved the final manuscript as submitted.

Alberta De Monti, MD: collected the data, interpreted the data, revised and approved the final manuscript as submitted.

Ray Kiran Boyapati, MBBS, MD: interpreted the data, revised the manuscript critically for important intellectual content and approved the final manuscript as submitted.

Edward Shelton, MBBS, MD: interpreted the data, revised the manuscript critically for important intellectual content and approved the final manuscript as submitted.

Nicole Piazza, MD: collected the data, interpreted the data, revised and approved the final manuscript as submitted.

Anna Maria Carvalhas Gabrielli, MD: collected the data, interpreted the data, revised and approved the final manuscript as submitted.

Marco Vincenzo Lenti, MD, PhD: collected the data, interpreted the data, revised and approved the final manuscript as submitted.

Simone Saibeni, MD: collected the data, interpreted the data, revised and approved the final manuscript as submitted.

Chiara Ricci, MD: collected the data, interpreted the data, revised and approved the final manuscript as submitted.

Salvatore Greco, MD: collected the data, interpreted the data, revised and approved the final manuscript as submitted.

Samanta Romeo, MD: interpreted the data, revised the manuscript critically for important intellectual content and approved the final manuscript as submitted.

Francesco Giangregorio, MD: collected the data, interpreted the data, revised and approved the final manuscript as submitted.

Daniele Gridavilla, MD: collected the data, interpreted the data, revised and approved the final manuscript as submitted.

Fabio Tagliani: Conceptualized and designed the study, collected the data, interpreted the data, and approved the final manuscript as submitted.

Alessandro Massari, MD: collected the data, interpreted the data, revised and approved the final manuscript as submitted.

Luca Pastorelli, MD, PhD: interpreted the data, revised the manuscript critically for important intellectual content and approved the final manuscript as submitted.

Antonio Di Sabatino, MD, PhD: interpreted the data, revised the manuscript critically for important intellectual content and approved the final manuscript as submitted.

Cristina Bezzio, MD: collected the data, interpreted the data, revised and approved the final manuscript as submitted.

Saverio Alicante, MD: collected the data, interpreted the data, revised and approved the final manuscript as submitted.

Giuliano Rizzardini, MD: interpreted the data, revised the manuscript critically for important intellectual content and approved the final manuscript as submitted.

Massimo Galli, MD: interpreted the data, revised the manuscript critically for important intellectual content and approved the final manuscript as submitted.

Sandro Ardizzone, MD: interpreted the data, revised the manuscript critically for important intellectual content and approved the final manuscript as submitted.

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