Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Journal Pre-proof

Corticosteroids, but not TNF Antagonists, are Associated with Adverse COVID-19 Outcomes in Patients With Inflammatory Bowel Diseases: Results from an International Registry

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Corticosteroids, but not TNF Antagonists, are Associated with Adverse COVID-19 Outcomes in Patients With Inflammatory Bowel Diseases: Results from an International Registry

SHORT TITLE

COVID-19 and IBD

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ABBREVIATIONS

AZA (azathioprine)*

CAD (coronary artery disease)*

CKD (chronic kidney disease)*

COPD (chronic obstructive pulmonary disease)*

COVID-19 (Coronavirus disease 2019)

CD (Crohn's disease)

GI (Gastrointestinal)

IBD (inflammatory bowel disease)

ICU (intensive care unit)

MERS (Middle East Respiratory Syndrome)

MTX (Methotrexate)*

NAFLD (non-alcoholic fatty liver disease)*

PSC (primary sclerosing cholangitis)*

SARS (Severe Acute Respiratory Syndrome)

SMR (standardized mortality ratio)

SECURE-IBD (Surveillance Epidemiology of Coronavirus Under Research Exclusion for Inflammatory Bowel Disease)

TNF (Tumor Necrosis Factor)

UC (ulcerative colitis)

5-ASA (5-aminosalicylate)

6-MP (6-Mercaptopurine)

*Abbreviations used in tables only

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ABSTRACT

Background and Aims: The impact of Coronavirus disease 2019 (COVID-19) on patients with inflammatory bowel disease (IBD) is unknown. We sought to characterize the clinical course of COVID-19 among IBD patients and evaluate the association between demographics, clinical characteristics, and immunosuppressant treatments on COVID-19 outcomes.

Methods: Surveillance Epidemiology of Coronavirus Under Research Exclusion for Inflammatory Bowel Disease (SECURE-IBD) is a large, international registry created to monitor outcomes of IBD patients with confirmed COVID-19. We calculated age-standardized mortality ratios (SMRs) and utilized multivariable logistic regression to identify factors associated with severe COVID-19, defined as intensive care unit admission, ventilator use, and/or death.

Results: 525 cases from 33 countries were reported (Median age 43 years, 53% men). Thirty-seven patients (7%) had severe COVID-19, 161 (31%) were hospitalized, and 16 patients died (3% case fatality rate). SMRs for IBD patients were 1.8 (95% confidence interval [CI] 0.9-2.6), 1.5 (95% CI 0.7-2.2), and 1.7 (95% CI 0.9-2.5) relative to data from China, Italy, and the US, respectively. Risk factors for severe COVID-19 among IBD patients included increasing age (adjusted odds ratio [aOR] 1.04, 95% CI 1.01-1.02), ≥2 comorbidities (aOR 2.9, 95% CI 1.1-7.8), systemic corticosteroids (aOR 6.9, 95% CI 2.3-20.5), and sulfasalazine or 5-aminosalicylate use (aOR 3.1, 95% CI 1.3-7.7). TNF antagonist treatment was not associated with severe COVID-19 (aOR 0.9, 95% CI 0.4-2.2).

Conclusions: Increasing age, comorbidities, and corticosteroids are associated with severe COVID-19 among IBD patients, although a causal relationship cannot be definitively established. Notably, TNF antagonists do not appear to be associated with severe COVID-19.

Keywords: inflammatory bowel disease, Crohn's disease, ulcerative colitis, COVID-19

INTRODUCTION

Coronavirus Disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first reported in December 2019 and has rapidly spread throughout the world leading to an international pandemic.[1] Although most cases of COVID-19 are mild, the disease can become severe and result in hospitalization, respiratory failure, or death with reported case fatality rates ranging from 2.3% to 7.2%.[2, 3] To date, the most frequently identified risk factors for severe COVID-19 have been age, cardiovascular disease, chronic lung conditions, obesity, and diabetes.[2, 4] In a recent report from the United States, 78% of patients requiring intensive care unit (ICU) admission had at least one underlying comorbidity.[4]

Inflammatory bowel diseases (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), are chronic inflammatory conditions of the gastrointestinal tract affecting millions of people worldwide.[5-7] Patients with IBD and related rheumatologic, dermatologic, and neurologic auto-inflammatory conditions frequently require treatment with immunosuppressant medications which can increase the risk of infection.[6-10] Corticosteroids, immunomodulators (thiopurines, methotrexate), biologics, and janus-kinase inhibitors, commonly used to treat chronic auto-inflammatory conditions, have been associated with higher rates of serious viral and bacterial infections including influenza and pneumonia.[11-15] Yet, it is also possible that some forms of immune suppression may blunt the excessive immune response/cytokine storm characteristic of severe COVID-19 infection and consequently reduce mortality, as suggested by emerging case reports of anti-IL-6 therapy.[16, 17]

Little is known about the impact of COVID-19 on patients with chronic auto-inflammatory diseases such as IBD, particularly those who require systemic immunosuppressant medications. An initial report of COVID-19 among 1,099 patients in China included only two persons with immune deficiency.[18] A subsequent report found that cancer patients had a higher risk of severe COVID-19, but this conclusion was based on only 16 patients.[19] In Italy, Mazza et al reported a case of COVID-19 pneumonia leading to death in a patient with severe acute ulcerative colitis treated with systemic corticosteroids.[20]

In order to provide better guidance to patients and their health care providers and to inform strategies for prevention of COVID-19 and medication management, more data are urgently needed regarding the impact of IBD and treatments on COVID-19 outcomes. In the present work, we report on the clinical course of COVID-19 and risk factors for adverse outcomes in a large cohort of patients with IBD collected through an international registry.

MATERIALS AND METHODS

Case identification and data collection

We created the Surveillance Epidemiology of Coronavirus Under Research Exclusion for Inflammatory Bowel Disease (SECURE-IBD) database to monitor outcomes of COVID-19 occurring in pediatric and adult IBD patients. SECURE-IBD is an international, collaborative effort, endorsed and promoted by the International Organization for the Study of Inflammatory Bowel Disease (IOIBD), the Crohn's & Colitis Foundation (US), the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN), the European Crohn's and Colitis Organisation (ECCO), the Pan American Crohn's and Colitis Organization (PANCCO),

the Asian Organization of Crohn's & Colitis (AOCC) and several regional/national organizations (Table S4).

Physicians and other health care providers were encouraged to voluntarily report all cases of Polymerase Chain Reaction (PCR)-confirmed COVID-19 occurring in IBD patients, regardless of severity. To foster international collaboration and promote transparency, we developed a project website (www.covidibd.org) to acknowledge the contributions of individual reporters and share crude, aggregate data along with an interactive web-based map displaying the geographic location of reported cases (https://covidibd.org/map/).

We instructed health care providers to report cases after a minimum of 7 days from symptom onset and sufficient time had passed to observe the disease course through resolution of acute illness or death. In the event that a patient's status changed after reporting or if there were concerns about data accuracy, we instructed reporters to re-report and contact the research team to remove their initial entry.

We utilized REDCap (Research Electronic Data Capture), a secure, web-based electronic data capture tool hosted at the University of North Carolina at Chapel Hill to collect and manage study data. Health care providers recorded the following information: age, country of residence, state of residence (if applicable), year of COVID-19 diagnosis, name of center/practice/physician providing care, sex, race, ethnicity, height, weight, patient's diagnosis (CD, UC, or inflammatory bowel disease unclassified, IBD-U), disease activity (as defined by physician global assessment [PGA]), medications at time of COVID-19 diagnosis, whether the patient was hospitalized, gastrointestinal (GI) symptoms related to COVID-19, COVID-19 treatments used, and whether the patient died of COVID-19 or complications related to COVID-

19. For hospitalized patients, the name of hospital, length of stay, need for ICU, and need for a ventilator were additionally recorded.

QGIS 3.4.4 (www.osgeo.org) was used to create a choropleth map of the number of reported cases of IBD stratified by four classes using Jenks Natural Breaks.[21] ArcGIS Pro 2.4.1 and ArcGIS Online (www.esri.com/en-us/home) were used to create an interactive global map (https://covidibd.org/map/) that visualizes patients with IBD diagnosed with COVID-19, as well as their clinical course and characteristics.

The Pediatric IBD Porto group of the European Society of Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) implemented a parallel reporting system at 102 affiliated sites. Recently reported preliminary data from this consortium are included in the analyses described below.[22]

Quality control

We removed all known duplicate or erroneous reports. We identified additional potential duplicate records based on matching age, sex, IBD disease type, country, and state (U.S. only), and reviewed these manually. Reports from non-valid email addresses were flagged as potential errors and we performed a Google search of reporters and practice locations to confirm legitimacy of reports.

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 were collapsed into the following categories: cardiovascular disease, diabetes, hypertension, stroke, lung disease, kidney disease, liver disease, and cancer.

We analyzed a variety of COVID-19 outcomes, including outpatient care only, hospitalization, ICU or ventilator requirement, and death from COVID-19 or related complications. Crude data are provided for the overall study population, and stratified by a variety of demographic and clinical characteristics. To understand the impact of IBD on case fatality, we computed expected and observed deaths and age-standardized mortality ratios (SMR) utilizing published age-stratified COVID-19 case fatality rates from China and Italy [2, 23] and publically available data from the U.S.[24, 25]

Multivariable logistic regression estimated the independent effects of age, sex, disease (CD vs UC/IBD-U), disease activity, smoking, BMI ≥30, and number of comorbidities (0, 1, ≥2) on the primary outcome of severe COVID-19, defined as a composite of ICU admission, ventilator use, and/or death, consistent with existing COVID-19 literature.[18] Models also included tumor necrosis factor (TNF) antagonist use (versus not) and sulfasalazine/5-aminosalicylate (5-ASA) use (versus not) as these were the two most commonly reported medication classes and systemic corticosteroid use (versus not) based on increased risk of infectious complications based on prior literature and crude data. A secondary outcome was the composite of any hospitalization and/or death. We also analyzed death as a separate endpoint. We reported adjusted odds ratios (aOR) and 95% confidence intervals (CI) for each demographic or disease characteristic.

We also performed a series of exploratory sub-analyses. We compared TNF antagonist monotherapy versus combination therapy with immunomodulators (6-mercaptopurine [6MP],

azathioprine, or methotrexate), controlling for the above demographic and clinical factors as well as the use of systemic corticosteroids and 5-ASA/sulfasalazine. In addition, given the surprising association between 5-ASA/sulfasalazine use and more severe COVID outcomes in our main analyses, we performed a sub-analysis to directly compare the effects of TNF antagonists versus 5-ASA/ sulfasalazine, controlling for the above factors as well as use of immunomodulators. The primary outcome of these exploratory analyses was the composite of any hospitalization and/or death. The number of events was too sparse to evaluate other outcomes. All data were prepared and analyzed using SAS v 9.3 (SAS Institute, Cary, North Carolina). Two-sided p values < 0.05 were considered statistically significant.

Ethical Considerations

Each SECURE-IBD survey item met criteria for de-identified data, in accordance with the HIPAA Safe Harbor De-Identification standards. The UNC-Chapel Hill Office for Human Research Ethics has determined that the storage and analysis of de-identified data for this project does not constitute human subjects research as defined under federal regulations [45 CFR 46.102 and 21 CFR 56.102] and does not require IRB approval.

FINDINGS

At the time of this writing, a total of 525 cases were reported to the SECURE-IBD database from 33 different countries and 28 states within the United States (Figures 1 and 2; Tables S1 and S2). Demographic, clinical, and IBD treatment related characteristics are summarized in Table 1. The median age was 41 years, with a range from 5 to ≥ 90 years, and there was a slight predominance of males (52.6%). Most cases were reported in whites (84.2%). Ethnicity was reported as Hispanic/Latino in 14.3% of cases (Table 1).

The majority of patients had CD (59.4%), and IBD disease activity by PGA was classified as remission in 58.9% of cases. The most common class of IBD treatment was TNF antagonist therapy (43.4% overall, 33.5% monotherapy and 9.9% combination therapy with azathioprine, 6-mercaptopurine, or methotrexate). Use of other medications is described in Table 1. Most patients (63.4%) had no comorbidities other than IBD; 21.0% had one, 6.7% had two, and 5.5% had three or more. Four percent of the cohort reported using tobacco and/or electronic cigarettes (Table 1).

Crude outcome data are summarized in Table 2 for the overall study population, stratified by a variety of demographic and clinical characteristics. Overall, 161 patients required hospitalization (31%), 24 stayed in an ICU (5%), and 21 used a ventilator (4%). The primary outcome (ICU/ventilator/death) was observed in 37/525 (7%) of patients. Of these, 20/101 (20%) occurred in patients ≥ 60 years of age versus 0/29 pediatric cases (< 20 years). Only 3 pediatric patients (10%) required hospitalization; none required ICU or ventilator support. Patients with more comorbidities also experienced a higher proportion of adverse outcomes. Nine of 37 patients on systemic corticosteroids (24%) experienced the primary endpoint. Additional outcome data, stratified by medication use, is shown in Table 2.

Sixteen deaths (3% of reported cases) are summarized in Table S3. Eight deaths (50%) occurred in patients ≥ 70 years of age. No deaths occurred in patients < 30 years of age. Most deaths had comorbidities, including eight with cardiovascular disease. The age-standardized SMRs for the SECURE-IBD population relative to China, Italy, and the U.S. were 1.8 (95%

confidence interval [CI] 0.9-2.6), 1.5 (95% CI 0.7-2.2), and 1.7 (95% CI 0.9-2.5) respectively (Tables 3 and 4).

On multivariable analysis, increasing age (aOR 1.04, 95% CI 1.01-1.06), ≥ 2 comorbidities (aOR 2.9, 95% CI 1.1-7.8), systemic corticosteroids (aOR 6.9, 95% CI 2.3-20.5), and 5-ASA/sulfasalazine use (aOR 3.1, 95% CI 1.3-7.7) were positively associated with the primary endpoint after controlling for all other covariates listed in Table 5. No significant association was seen between TNF antagonist use and the primary endpoint (aOR 0.9, 95% CI 0.4-2.2). Similar associations were observed for our secondary outcomes, although TNF antagonist use was inversely associated with the outcome of hospitalization or death while only age and systemic corticosteroid use were positively associated with the outcome of death.

In our exploratory analyses, we found that TNF antagonist combination therapy, compared to monotherapy, was positively associated with the outcome of hospitalization or death (aOR 5.0, 95% CI 2.0-12.3), after adjusting for clinical and demographic variables and use of systemic corticosteroids and 5-ASA/sulfasalazine. Compared to TNF antagonists, 5-ASA/sulfasalazine was positively associated with the outcome of hospitalization or death (aOR 3.8, 95% CI 1.7-8.5).

DISCUSSION

We report the development of an international, physician-driven, reporting system to study the natural history of COVID-19 in pediatric and adult patients with IBD. Given the expanding knowledge that persons with comorbidities are disproportionately affected by COVID-19, there

is an urgent need to evaluate this emerging infection on patients with systemic, auto-inflammatory conditions such as inflammatory bowel disease (IBD), many of whom are treated with immunosuppressive medications. To date, no large, international reports describing the clinical course of COVID-19 in these patient populations have been published. Based on results from 525 IBD patients from 33 countries, we observed an overall case fatality rate of 3% with 7% of reported cases experiencing a composite outcome of ICU admission, ventilator support, and/or death. Strong risk factors for adverse COVID-19 outcomes were older age, number of comorbidities, and use of systemic corticosteroids. Unexpectedly, use of 5-ASA/sulfasalazine was also associated with more severe COVID-19. Reassuringly, TNF antagonist biologic therapy was not an independent risk factor for more severe COVID-19.

In this international IBD population, we observed an age-standardized mortality ratio of approximately 1.5 to 1.8, as compared to the general populations of China, Italy, and the U.S. with confidence intervals crossing the null. We note no deaths occurred in the 29 reported cases occurring in patients <20 years of age, extending the findings of an earlier case series suggesting a milder course of COVID-19 in pediatric patients.[22] In contrast, 50% of deaths occurred in patients over 70 years of age and 50% of patients who died had cardiovascular comorbidities.

The strong positive association between systemic corticosteroid use and our primary and secondary outcomes is consistent with extensive prior literature in IBD and other auto-inflammatory conditions describing the infectious complications of corticosteroid use as well as more recent data indicating that corticosteroids are not beneficial, and may even be harmful, in the treatment of coronavirus and similar viruses (MERS, SARS, etc.).[26] Forty-three percent of

our cohort was exposed to TNF antagonist medications. In the adjusted analysis of our primary outcome, we observed no association between TNF antagonist use and severe COVID-19. As TNF antagonists are the most commonly prescribed biologic therapy for patients with IBD, these initial findings should be reassuring to the large number of patients receiving TNF antagonist therapy and support their continued use during this current pandemic. In our exploratory subgroup analysis, we observed a higher risk of hospitalization and/or death with TNF antagonist combination therapy versus monotherapy, consistent with prior studies of other infectious complications.[12] Given the overall effect estimate of TNF antagonists (combination and monotherapy combined) in our primary model was 0.9, one can hypothesize that TNF antagonist monotherapy may have a protective effect against severe COVID-19, as suggested in a recent commentary.[27]

We observed a higher risk of our primary outcome in patients exposed to 5-ASA/sulfasalazine. This finding persisted after controlling for age, comorbidities, IBD disease characteristics, corticosteroid use, and other factors. Furthermore, in a direct comparison, we observed that 5-ASA/sulfasalazine treated patients fared worse than those treated with TNF inhibitors. Although we cannot exclude unmeasured confounding, further exploration of biological mechanisms is warranted. Conversely, although the number of reported cases exposed to other IBD treatments is currently small, it is worth noting that 51/55 (93%) patients treated with anti-IL12/23 required outpatient care only and none died.

The strengths of this study include the robust, worldwide collaboration that enabled us to assemble clinical data on a large, geographically diverse sample of pediatric and adult IBD patients and rapidly define the course of COVID-19 in this population. The reporting directly by

physicians or their trained medical staff strengthens the validity of these data. Although our study sample is diverse in terms of age, geography, race, and other factors, we acknowledge the possibility of reporting bias. Reported cases may over-represent more severe COVID-19 patients who come to the attention of their provider and patients in areas with readily available COVID-19 testing. Conversely, our sample may under-represent those severely ill patients who may be hospitalized at an outside hospital or die without their physician's awareness. The registry includes only confirmed cases of COVID-19 in accordance with other reporting initiatives from national authorities and the World Health Organization,[2, 4, 18] though we recognize many patients with suspected infection are never tested. Although we adjusted for many factors such as age, comorbidities, and IBD disease type and severity, we acknowledge the possibility of unmeasured confounding. Additional research is needed to further evaluate causality between the use of corticosteroids and other medications and COVID-19 outcomes. Finally, we computed age-standardized mortality ratios using case fatality rates reported from China, Italy, and the U.S., yet our study sample arose from 31 different countries. Given the profound effects of age on COVID-19 related mortality, we believe it was useful to standardize to existing data. That our SMR estimates were roughly equivalent when standardizing to Chinese, Italian, or U.S. data suggests the overall validity of this approach.

In summary, older age, increased number of comorbidities and systemic corticosteroid use among patients with IBD are strong risk factors for adverse COVID-19 outcomes. Maintaining remission with steroid-sparing treatments will be important in managing patients with IBD through this pandemic. It appears that TNF antagonist therapy is not associated with severe COVID-19, providing reassurance that patients can continue TNF antagonist therapy.

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Author names in bold designate shared co-first authorship.

TABLES

Table 1. Demographics and clinical characteristics of SECURE-IBD cohort (Total N = 525)1

Characteristic[a,b]	
Age in years, mean (SD)	42.9 (18.2)
Sex, n (%)[c]	
Male	276 (52.6)
Female	243 (46.3)
Missing	6 (1.1)
Race, n (%)[d]	
Reported at least selected one race (including other/unknown)	523 (99.6)
White	442 (84.2)
Black or African American	26 (5.0)
American Indian/Native Alaskan	1 (0.2)
Asian	14 (2.7)
Native Hawaiian/Pacific Islander	0 (0.0)
Other	47 (9.0)
Unknown	13 (2.5)
Hispanic/Latino, n (%)	
Yes	75 (14.3)
No	350 (66.7)
Unknown	45 (8.6)
Missing	55 (10.5)
Disease type, n (%)	
Crohn's disease	312 (59.4)
Ulcerative Colitis	203 (38.7)
IBD-unspecified	7 (1.3)
Missing	3 (0.6)
IBD disease activity, n (%)[e]	

Remission	309 (58.9)
Mild	100 (19.0)
Moderate	76 (14.5)
Severe	24 (4.6)
Unknown	4 (0.8)
Missing	12 (2.3)
IBD Medication, n (%)[f]	
Any medication	494 (94.1)
Sulfasalazine/mesalamine	117 (22.3)
Budesonide	18 (3.4)
Oral/parenteral steroids	37 (7.0)
6MP/azathioprine monotherapy[g]	53 (10.1)
Methotrexate monotherapy[g]	5 (1.0)
Anti-TNF without 6MP/AZA/MTX	176 (33.5)
Anti-TNF + 6MP/AZA/MTX	52 (9.9)
Anti-integrin	50 (9.5)
IL-12/23 inhibitor	55 (10.5)
JAK inhibitor	8 (1.5)
Other IBD medication	22 (4.2)
Comorbid conditions, n (%)	
Any condition	192 (36.6)
Cardiovascular disease (CAD, heart failure, arrhythmia, etc.)	38 (7.2)
Diabetes	29 (5.5)
Lung disease (asthma, COPD, etc.)	44 (8.4)
Hypertension	63 (12.0)
Cancer	10 (1.9)
History of stroke	4 (0.8)
Chronic renal disease (CKD, etc.	10 (1.9)
Chronic liver disease (PSC, NAFLD, cirrhosis, etc.)	26 (5.0)
Other	53 (10.1)

Current smoker[h]	23 (4.4)
Gastrointestinal symptoms, n (%)	
Any increase in baseline IBD symptoms	161 (30.7)
Abdominal pain	44 (8.4)
Diarrhea	134 (25.5)
Nausea	30 (5.7)
Vomiting	17 (3.2)
Other	13 (2.5)
Medications and/or investigational therapies used in COVID-19 treatment, n (%)	
Any medication	146 (27.8)
Remdesivir	2 (0.4)
Chloroquine	14 (2.7)
Hydroxychloroquine	98 (18.7)
Oseltamivir	6 (1.1)
Lopinavir/ritonavir	28 (5.3)
Tocilizumab	5 (1.0)
Corticosteroids[i]	12 (2.3)
Other	67 (12.8)
No medications and/or investigational therapies were used	321 (61.1)
Unknown	16 (3.0)
Died of COVID-10 or other complications caused by or contributed to by COVID-19, n (%)	
Yes	16 (3.0)
No	498 (94.9)
Unknown	8 (1.5)
Missing	3 (0.6)
Emergency Room, n (%)	
Yes	199 (37.9)
No	312 (59.4)
Unknown	9 (1.7)

Missing	5 (1.0)
Hospitalized, n (%)	
Yes	161 (30.7)
No	363 (69.1)
Unknown	1 (0.2)
Hospital length of stay in days, mean (SD)	8.5 (6.9)
ICU, n (%)	24 (4.6)
Ventilator, n (%)	21 (4.0)
ICU and/or ventilator use, n (%)	27 (5.1)

[a]Unless otherwise specified, percentages do not include missing values or "unknown." For all characteristics, less than 4% of data was missing and unknown, respectively, for each category.
[b]Percentages and n from each subcategory may not add up to the exact number of total reported cases due to missing values and/or non-mutually exclusive variables.
[c]No individuals identifying as other sex were reported to the database.
[d]Individual cases could belong to ≥1 race, so percentages may sum to >100%.
[e]By physician global assessment (PGA) at time of COVID-19 infection
[f]At time of COVID-19 infection. Medication categories are not mutually exclusive unless otherwise noted.
[g]Monotherapy indicates no concomitant TNF antagonist, anti-integrin, anti-IL12/23, or JAK inhibitor
[h]Current smoker defined as current tobacco and/or e-cigarette use
[i]Started specifically for COVID-19 treatment, not for IBD care

Abbreviations: SECURE-IBD = Surveillance Epidemiology of Coronavirus Under Research Exclusion for Inflammatory Bowel Disease; COVID-19 = Coronavirus Disease 2019; TNF = Tumor Necrosis Factor; 6MP = 6-mercaptopurine; AZA = azathioprine; MTX = methotrexate; CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; CKD = chronic kidney disease; PSC = primary sclerosing cholangitis; NAFLD = non-alcoholic fatty liver disease; GI = gastrointestinal

Table 2. Outcomes by demographic, clinical, and treatment characteristics of SECURE-IBD cohort

Characteristic[a,b]	Total N	Outpatient only, n (%)	Hospitalized, n (%)	ICU, n (%)	Ventilator, n (%)	Death, n (%)	ICU/Ventilator/ Death, n (%)
Overall	525	363 (69)	161 (31)	24 (5)	21 (4)	16 (3)	37 (7)
Age							
0-9 years	3	3 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
10-19 years	26	23 (88)	3 (12)	0 (0)	0 (0)	0 (0)	0 (0)
20-29 years	116	93 (80)	23 (20)	2 (2)	1 (1)	0 (0)	2 (2)
30-39 years	108	87 (81)	20 (19)	4 (4)	2 (2)	1 (1)	4 (4)
40-49 years	95	64 (67)	31 (33)	4 (4)	3 (3)	2 (2)	5 (5)
50-59 years	74	45 (61)	29 (39)	3 (4)	5 (7)	2 (3)	6 (8)
60-69 years	54	30 (56)	24 (44)	10 (19)	9 (17)	3 (6)	11 (20)
70-79 years	24	7 (29)	17 (71)	1 (4)	1 (4)	2 (8)	3 (13)
>=80 years	23	9 (39)	14 (61)	0 (0)	0 (0)	6 (26)	6 (26)
Sex							
Male	276	183 (66)	93 (34)	12 (4)	9 (3)	11 (4)	21 (8)
Female	243	175 (72)	67 (28)	12 (5)	12 (5)	5 (2)	16 (7)
Disease type							
Crohn's disease	312	228 (73)	83 (27)	12 (4)	9 (3)	5 (2)	16 (5)
Ulcerative Colitis/unspecified	210	133 (63)	77 (37)	12 (6)	12 (6)	11 (5)	21 (10)
IBD Disease Activity[c]							
Remission	309	232 (75)	76 (25)	12 (4)	14 (5)	8 (3)	19 (6)
Mild	100	70 (70)	30 (30)	2 (2)	1 (1)	4 (4)	5 (5)
Moderate/Severe	100	52 (52)	48 (48)	9 (9)	5 (5)	3 (3)	12 (12)
Unknown	16	9 (56)	7 (44)	1 (6)	1 (6)	1 (6)	1 (6)
Smoking							
Current smoker	23	12 (52)	11 (48)	0 (0)	0 (0)	1 (4)	1 (4)
Non-smoker	502	351 (70)	150 (30)	24 (5)	21 (4)	15 (3)	36 (7)
Comorbidities							
0	351	272 (77)	79 (23)	11 (3)	8 (2)	4 (1)	13 (4)

1	110	74 (67)	35 (32)	4 (4)	4 (4)	4 (4)	8 (7)
2	35	10 (29)	25 (71)	4 (11)	5 (14)	3 (9)	7 (20)
3+	29	7 (24)	22 (76)	5 (17)	4 (14)	5 (17)	9 (31)
IBD medication[d]							
Sulfasalazine/ mesalamine	117	60 (51)	57 (49)	12 (10)	12 (10)	9 (8)	20 (17)
Budesonide	18	9 (50)	9 (50)	3 (17)	3 (17)	1 (6)	3 (17)
Oral/parenteral steroids	37	11 (30)	26 (70)	6 (16)	5 (14)	4 (11)	9 (24)
6MP/azathioprine monotherapy[e]	53	29 (55)	24 (45)	3 (6)	3 (6)	1 (2)	3 (6)
Methotrexate monotherapy[e]	5	2 (40)	3 (60)	0 (0)	0 (0)	0 (0)	0 (0)
Anti-TNF without 6MP/AZA/MTX	176	150 (85)	25 (14)	3 (2)	1 (1)	1 (1)	4 (2)
Anti-TNF + 6MP/AZA/MTX	52	32 (62)	20 (38)	4 (8)	2 (4)	2 (4)	5 (10)
Anti-integrin	50	34 (68)	16 (32)	2 (4)	3 (6)	0 (0)	3 (6)
IL-12/23 inhibitor	55	51 (93)	4 (7)	1 (2)	0 (0)	0 (0)	1 (2)
JAK inhibitor	8	7 (88)	1 (13)	1 (13)	1 (13)	1 (13)	1 (13)
Other IBD medication	22	13 (59)	9 (41)	1 (5)	1 (5)	0 (0)	1 (5)

[a]Unless otherwise specified, percentages do not include missing values or "unknown." For all characteristics, less than 4% of data was missing and unknown, respectively, for each category.
[b]Percentages and n from each subcategory may not add up to the exact number of total reported cases due to missing values and/or non-mutually exclusive variables.

[c]By physician global assessment (PGA) at time of COVID-19 infection
[d]At time of COVID-19 infection. Medication categories are not mutually exclusive unless otherwise noted.
[e] Monotherapy indicates no concomitant TNF antagonist, anti-integrin, anti-IL12/23, or JAK inhibitor

Abbreviations: COVID-19 = Coronavirus Disease 2019; ICU = Intensive Care Unit; TNF = Tumor Necrosis Factor; 6MP = 6-mercaptopurine; AZA = azathioprine; MTX = methotrexate

Table 3. Observed and expected deaths by age and standardized mortality ratios for SECURE-IBD[a] Cohort versus China and Italy[b] (IBD overall)

Age (years)	SECURE-IBD (n)	SECURE-IBD observed number of deaths	SECURE-IBD fatality rate (%)	China case fatality rate (%)	China expected number of deaths	Italy case fatality rate (%)	Italy expected number of deaths
0-9 years	3	0	0.0%	0	0	0	0
10-19 years	26	0	0.0%	0.2	0.052	0	0
20-29 years	116	0	0.0%	0.2	0.232	0	0
30-39 years	108	1	0.9%	0.2	0.216	0.3	0.324
40-49 years	95	2	2.1%	0.4	0.38	0.4	0.38
50-59 years	74	2	2.7%	1.3	0.962	1	0.74
60-69 years	54	3	5.6%	3.6	1.944	3.5	1.89
70-79 years	24	2	8.3%	8	1.92	12.8	3.072
>=80 years	23	6	26.1%	14.8	3.404	20.2	4.646
All	523	16		2.3	9.11	7.2	11.052
SMR (96% CI)					1.76 (0.90-2.62)		1.45 (0.74-2.16)

[a]SECURE-IBD = Surveillance Epidemiology of Coronavirus Under Research Exclusion for Inflammatory Bowel Disease
[b]Based on references 23 and 2, respectively

Table 4. Observed and expected deaths by age and standardized mortality ratios for SECURE-IBD[a] Cohort versus United States[b] (IBD overall)

Age (years)	SECURE-IBD (n)	SECURE-IBD observed number of deaths	United States case fatality rate (%)	United States expected number of deaths
0-14 years	10	0	0	0
15-44 years	295	1	0.2	0.052
45-64 years	149	5	0.2	0.232
65+ years	69	10	0.2	0.216
All	523	16	0.4	0.38
SMR (95% CI)				1.66 (0.85-2.47)

[a]SECURE-IBD = Surveillance Epidemiology of Coronavirus Under Research Exclusion for Inflammatory Bowel Disease
[b]Based on references 24 and 25

Table 5. Multivariable regression for primary and secondary outcomes from SECURE-IBD cohort

Variable (Referent group)[a]	ICU/Vent/Death Odds Ratio (95% CI) (n = 517)	p	Hospitalization or Death Odds Ratio (95% CI) (n =517)	p	Death Odds Ratio (95% CI) (n = 513)	p
Age	1.04 (1.01-1.06)	0.002	1.03 (1.01-1.04)	<0.001	1.07 (1.03-1.11)	<0.001
Male (Female[b])	1.20 (0.55-2.60)	0.65	1.38 (0.89-2.15)	0.15	2.78 (0.76-10.14)	0.12
Diagnosis Crohn's disease (ulcerative colitis/IBD unspecified)	0.76 (0.31-1.85)	0.54	0.84 (0.51-1.38)	0.49	1.64 (0.42-6.43)	0.48
Disease severity[c] (remission) Active disease	1.14 (0.49-2.66)	0.76	1.96 (1.23-3.11)	0.005	0.97 (0.26-3.62)	0.96
Systemic corticosteroid (none)	6.87 (2.30-20.51)	<0.001	6.46 (2.74-15.23)	<0.001	11.62 (2.09-64.74)	0.005
TNF antagonist (none)	0.90 (0.37-2.17)	0.81	0.60 (0.38-0.96)	0.03	0.99 (0.23-4.23)	0.99
Current smoker	0.55 (0.06-4.94)	0.59	2.38 (0.92-6.16)	0.07	1.47 (0.12-17.53)	0.76
BMI ≥ 30	2.00 (0.72-5.51)	0.18	1.18 (0.61-2.31)	0.63	1.58 (0.28-8.80)	0.60
Comorbidities (none) 1 ≥2	 1.22 (0.45-3.26) 2.87 (1.05-7.85)	 0.70 0.04	 1.29 (0.76-2.20) 4.42 (2.16-9.06)	 0.34 <0.001	 1.64 (0.35-7.67) 2.51 (0.56-11.24)	 0.53 0.23
5-ASA/sulfasalazine (none)	3.14 (1.28-7.71)	0.01	1.77 (1.00-3.12)	0.05	1.71 (0.46-6.38)	0.43

[a]We adjusted each odds ratio for all other variables listed in this table.
[b]Other sex excluded from analysis due to low numbers
[c]By physician global assessment (PGA) at time of COVID-19 infection

Abbreviations: SECURE-IBD = Surveillance Epidemiology of Coronavirus Under Research Exclusion for Inflammatory Bowel Disease; TNF = Tumor Necrosis Factor; 5-ASA = 5-aminosalicylate

FIGURE LEGEND

Figure 1. World map depicting cases of COVID-19 among patients with inflammatory bowel disease reported to the SECURE-IBD[a] database

Footnote:

Interactive web-based map: http://covidibd.org/map/

[a]SECURE-IBD = Surveillance Epidemiology of Coronavirus Under Research Exclusion for Inflammatory Bowel Disease

Figure 2. United States map depicting cases of COVID-19 among patients with inflammatory bowel disease reported to the SECURE-IBD[a] database

Footnote:

Interactive web-based map: http://covidibd.org/map/

[a]SECURE-IBD = Surveillance Epidemiology of Coronavirus Under Research Exclusion for Inflammatory Bowel Disease

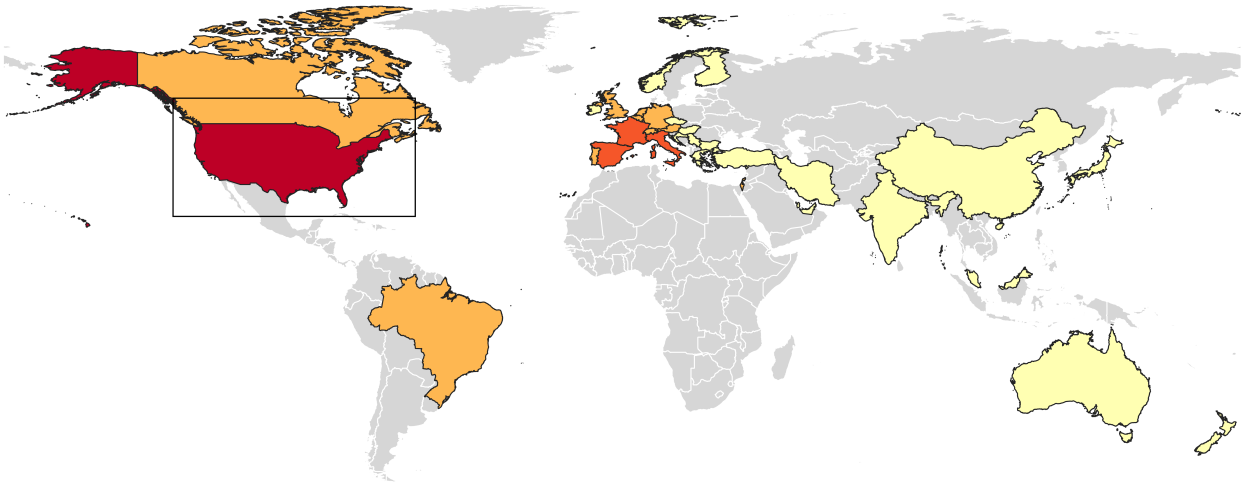
STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

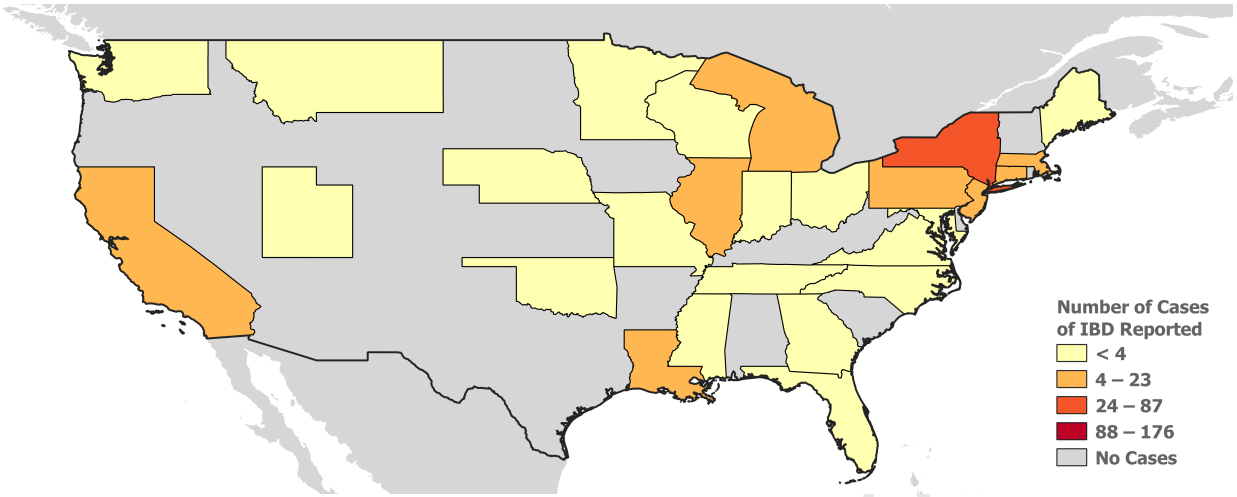
	Item No	Recommendation
☑ **Title and abstract**	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
☑Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
☑ Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
☑Study design	4	Present key elements of study design early in the paper
☑ Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
☑Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed
☑Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
☑Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
☑Bias	9	Describe any efforts to address potential sources of bias
☑Study size	10	Explain how the study size was arrived at
☑Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
☑Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, explain how loss to follow-up was addressed
		(*e*) Describe any sensitivity analyses
Results		
☑Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers

		potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
☑Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) Summarise follow-up time (eg, average and total amount)
☑Outcome data	15*	Report numbers of outcome events or summary measures over time
☑Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
☑Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
☑Key results	18	Summarise key results with reference to study objectives
☑Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
☑Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
☑Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
☑Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.





Supplementary Appendix

Table S1. Number of cases reported to the SECURE-IBD[a] database by country

Country	Number of cases
Australia	3
Austria	8
Bahrain	1
Belgium	19
Brazil	7
Bulgaria	1
Canada	10
China	1
Croatia	1
Czech Republic	4
Finland	1
France	52
Germany	10
Greece	2
Hungary	1
India	1
Iran, Islamic Republic of	3
Ireland	4
Israel	11
Italy	39
Japan	1
Malaysia	1
Netherlands	17
New Zealand	1
Norway	2
Portugal	8
Qatar	2
Serbia	1
Spain	88
Switzerland	16
Turkey	4
United Arab Emirates	1

[a]Surveillance Epidemiology of Coronavirus Under Research Exclusion for Inflammatory Bowel Disease

Table S2. Number of cases reported to the SECURE-IBD[a] database by state

State	Number of cases
California	9
Connecticut	7
District of Columbia	2
Florida	4
Georgia	2
Illinois	13
Indiana	2
Lousiana	8
Maine	2
Maryland	2
Massachusetts	7
Michigan	5
Minnesota	1
Mississippi	2
Missouri	4
Montana	1
Nebraska	1
New Jersey	12
New York	71
North Carolina	2
Ohio	1
Oklahoma	1
Pennsylvania	8
Tennessee	2
Utah	1
Virginia	1
Washington	2
Wisconsin	3

[a]Surveillance Epidemiology of Coronavirus Under Research Exclusion for Inflammatory Bowel Disease

Table S3. Description of deaths reported to SECURE-IBD cohort[a]

Age group	Sex	Diagnosis	Disease activity	Medications	Comorbidities	Hospital stay?	ICU?	Ventilator use?
>=80 years	Male	Ulcerative colitis	Mild	Mesalamine	Cardiovascular disease, Alzheimer	Yes	No	No
>=80 years	Male	Crohn's disease	Remission	Adalimumab	Cardiovascular disease	No	Unknown	Unknown
40-49 years	Male	Ulcerative colitis	Severe	Prednisone or prednisolone, JAK inhibitor	None reported	Yes	Yes	Yes
70-79 years	Male	Ulcerative colitis	Remission	Mesalamine	Cardiovascular disease, Diabetes, COPD, Hypertension, Cancer, Chronic liver disease	Yes	No	No
50-59 years	Male	Crohn's disease	Remission	Adalimumab, Methotrexate	None reported	Yes	No	No
>=80 years	Male	Crohn's disease	Mild	None reported	Cardiovascular disease, Hypertension, Chronic renal disease	Yes	No	No
30-39 years	Female	Crohn's disease	Mild	Adalimumab, Azathioprine, Prednisone or prednisolone	Familial mediteranean fever, juvenile rheumatoid arthritis	Yes	Yes	Yes
>=80 years	Female	Ulcerative colitis	Remission	Mesalamine	Cardiovascular disease, epilepsy, recent orthopedic surgery	Yes	No	No
>=80 years	Male	Ulcerative colitis	Remission	Mesalamine	Cardiovascular disease, COPD, Hypertension, Current cigarette smoker	Yes	No	No
>=80 years	Female	Ulcerative colitis	Severe	Mesalamine, Prednisone or prednisolone	Hypertension	Yes	No	No
60-69 years	Male	Ulcerative colitis	Moderate	Mesalamine	Cancer	Yes	No	No
70-79 years	Male	Ulcerative colitis	Mild	Prednisone or prednisolone	Cardiovascular disease, Hypertension, CMV infection	Yes	No	No
60-69 years	Male	Ulcerative colitis	Unknown	Mesalamine, Azathioprine	Cardiovascular disease, Diabetes, Hypertension	Yes	Yes	Yes
40-49 years	Female	Crohn's disease	Remission	None reported	Asthma	Yes	Yes	Yes
60-69 years	Female	Ulcerative colitis	Remission	Sulfasalazine, Budesonide	None reported	Yes	Yes	Yes
50-59 years	Male	Ulcerative colitis	Remission	Mesalamine	None reported	Yes	Yes	Yes

[a]Note that one of these deaths was described in a previous case report[1]

Abbreviations: SECURE-IBD = Surveillance Epidemiology of Coronavirus Under Research Exclusion for Inflammatory Bowel Disease; Meds = medications

Table S4. Acknowledgement of additional organizations who supported or promoted the SECURE-IBD[a] database

Professional organization
Agrupación Chilena de Trabajo en Enfermedad de Crohn y Colitis Ulcerosa (ACTECCU)
American College of Gastroenterology (ACG)
American Gastroenterological Association (AGA)
Asia-Pacific Association of Gastroenterology (APAGE)
BRICS IBD Consortium
Canadian Association of Gastroenterology
Crohn's and Colitis Australia (CCA)
Crohn's and Colitis Canada (CCC)
Crohn's and Colitis India (CCI)
Crohn's and Colitis New Zealand (CCNZ)
Grupo Argentino de Estudio de Enfermedad de Crohn y Colitis Ulcerosa
Grupo de Estudio de Crohn y Colitis Colombiano
Grupo de Estudos de Doenca Inflamatória Intestinal do Brasil (GEDIIB)
Grupo uruguayo de trabajo en enfermedad inflamatoria intestinal (GUTEII)
Grupo Venezolano de Trabajo en Enfermedad Inflamatoria Intestinal
Hong Kong IBD Society (HKIBS)
Improve Care Now (ICN)
Indian Society of Gastroenterology
Japanese IBD Society
Korean Society for the Study of Intestinal Diseases
Malaysia Society of Gastroenterology
National Taiwan GI society
Pediatric Inflammatory Bowel Disease Network (PIBD-NET)
Taiwan IBD society
The Gastroenterological Society of Australia (GESA)
The New Zealand Society of Gastroenterology (NZSG)
United European Gastroenterology (UEG)

[a]Surveillance Epidemiology of Coronavirus Under Research Exclusion for Inflammatory Bowel Disease

References

1. Mazza S, Sorce A, Peyvandi F, Vecchi M, Caprioli F. A fatal case of COVID-19 pneumonia occurring in a patient with severe acute ulcerative colitis. *Gut.* 2020:gutjnl-2020-321183.

WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT: The impact of Coronavirus disease 2019 (COVID-19) on patients with inflammatory bowel disease (IBD) is unknown. We sought to characterize the clinical course of COVID-19 among IBD patients.

NEW FINDINGS: Of 525 reported cases, 31% were hospitalized and 3% died. Risk factors for severe COVID-19 included increasing age, other comorbidities, systemic corticosteroids, and sulfasalazine/5-aminosalicylate use but not anti-TNF antagonist treatment.

LIMITATIONS: Possibility of reporting bias and unmeasured confounding.

IMPACT: Maintaining remission with steroid-sparing treatments is important in managing IBD patients through this pandemic. TNF antagonist therapy does not appear to be a risk factor for severe COVID-19.

LAY SUMMARY

We created an international registry of IBD patients who developed COVID-19. Corticosteroids, but not TNF antagonists, were associated with adverse outcomes. Other risk factors were similar to the general population.