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.

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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

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This article has an accompanying continuing medical education activity, also eligible for MOC credit, on page e12. Learning Objective: Upon completion of this CME activity, successful learners will be able to discuss how steroids are associated with severe outcomes from COVID-19 among patients with inflammatory bowel disease (IBD).

See Covering the Cover synopsis on page 407.

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 patients with IBD and evaluate the association among 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 patients with IBD with confirmed COVID-19. We calculated age-standardized mortality ratios and used 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). Standardized mortality ratios for patients with IBD 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 United States, respectively. Risk factors for severe COVID-19 among patients with IBD 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). Tumor necrosis factor 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 patients with IBD, although a causal relationship cannot be definitively established. Notably, tumor necrosis factor antagonists do not appear to be associated with severe COVID-19.

Keywords: Inflammatory Bowel Disease; Crohn's Disease; Ulcerative Colitis; COVID-19.

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

***Authors share co-first authorship**

Abbreviations used in this paper: **aOR, adjusted odds ratio; CD, Crohn's disease; CI, confidence interval; COVID-19, Coronavirus disease 2019; IBD, inflammatory bowel disease; ICU, intensive care unit; 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.**

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CLINICAL AT

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.

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 1 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-interleukin-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 1099 patients in China included only 2 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[20] reported a case of COVID-19 pneumonia leading to death in a patient with severe acute UC treated with systemic corticosteroids.

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 patients with IBD. SECURE-IBD is an international, collaborative effort, endorsed and promoted by the International Organization for the Study of Inflammatory Bowel Disease, the Crohn's & Colitis Foundation (United States), the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition, the European Crohn's and Colitis Organisation, the Pan American Crohn's and Colitis Organization, the Asian Organization of Crohn's & Colitis, and several regional/national organizations (Supplementary Table 1).

Physicians and other health care providers were encouraged to voluntarily report all cases of polymerase chain reaction–confirmed COVID-19 occurring in patients with IBD, regardless of severity. To foster international collaboration and promote transparency, we developed a project Web site (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), medications at time of COVID-19 diagnosis, whether the patient was hospitalized, gastrointestinal 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 4 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

implemented a parallel reporting system at 102 affiliated sites. Recently reported preliminary data from this consortium are included in the analyses described as follows.[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 (United States only), and reviewed these manually. Reports from nonvalid e-mail 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) using published age-stratified COVID-19 case fatality rates from China and Italy[2,23] and publically available data from the United States.[24,25]

Multivariable logistic regression estimated the independent effects of age, sex, disease (CD vs UC/IBD-U), disease activity, smoking, body mass index $\geq$30, and number of comorbidities (0, 1, $\geq$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 (vs not) as these were the 2 most commonly reported medication classes and systemic corticosteroid use (vs 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, 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 subanalysis to directly compare the effects of TNF antagonists vs 5-ASA/ sulfasalazine, controlling for the preceding 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, NC). Two-sided P values $<$ .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 institutional review board approval.

Results

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; Supplementary Tables 2 and 3). Demographic, clinical, and IBD treatment related characteristics are summarized in Table 1. The median age was 41 years, with a range from 5 to $\geq$ 90 years, and there was a slight predominance of male individuals (52.6%). Most cases were reported in white individuals (84.2%). Ethnicity was reported as Hispanic/Latino in 14.3% of cases (Table 1).

Most patients had CD (59.4%), and IBD disease activity by physician global assessment 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 1, 6.7% had 2, and 5.5% had 3 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 (7%) of 525 patients. Of these, 20 (20%) of 101 occurred in patients $\geq$60 years of age vs 0 of 29 pediatric cases ($<$ 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 (24%) of 37 patients on systemic corticosteroids experienced the primary endpoint. Additional outcome data, stratified by medication use, are shown in Table 2.

Sixteen deaths (3% of reported cases) are summarized in Supplementary Table 4. Eight deaths (50%) occurred in patients $\geq$70 years of age. No deaths occurred in patients $<$30 years of age. Most deaths had comorbidities, including 8 with cardiovascular disease. The age-standardized SMRs for the SECURE-IBD population relative to China, Italy, and the United States were 1.8 (95% 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), $\geq$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

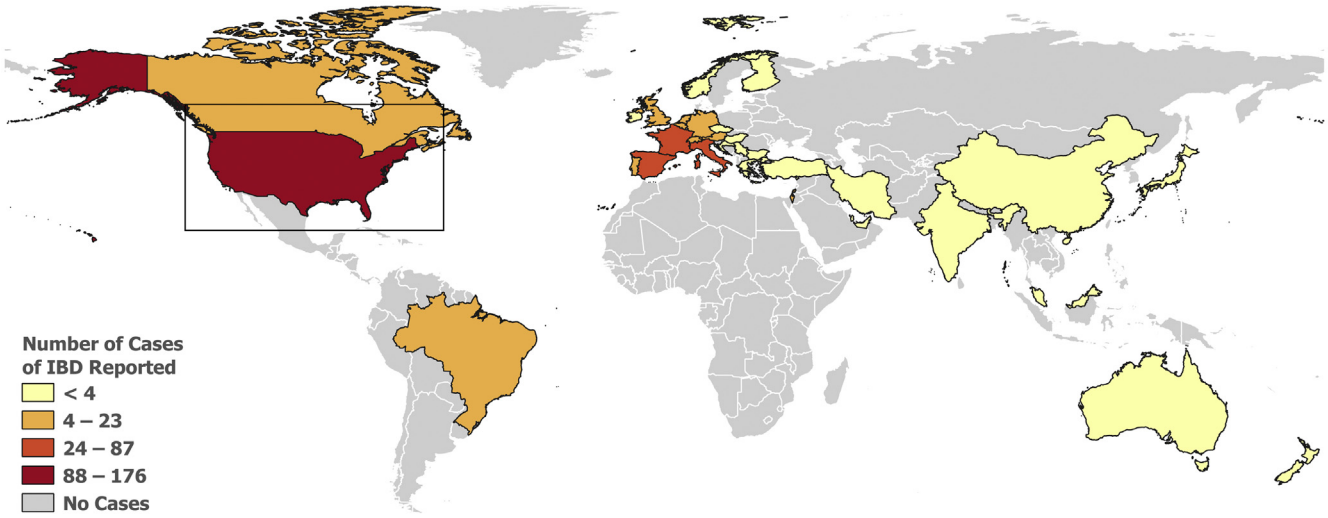

Figure 1. World map depicting cases of COVID-19 among patients with IBD reported to the SECURE-IBD database. Interactive web-based map: http://covidibd.org/map/

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 with 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 with 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 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 patients with IBD 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.

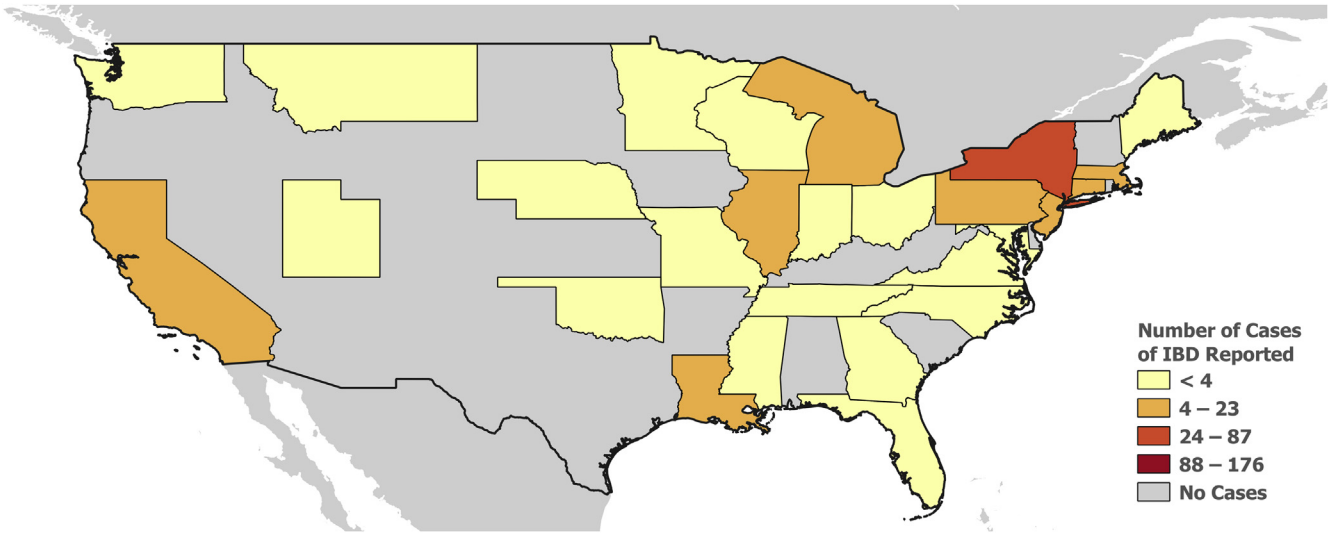

Figure 2. US map depicting cases of COVID-19 among patients with IBD reported to the SECURE-IBD database. Interactive web-based map: http://covidibd.org/map/

Table 1. Demographics and Clinical Characteristics of SECURE-IBD Cohort (Total N = 525)

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 (%)	
CD	312 (59.4)
UC	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 (eg, CAD, heart failure, arrhythmia)	38 (7.2)
Diabetes	29 (5.5)
Lung disease (eg, asthma, COPD)	44 (8.4)
Hypertension	63 (12.0)
Cancer	10 (1.9)
History of stroke	4 (0.8)
Chronic renal disease (eg, CKD)	10 (1.9)
Chronic liver disease (eg, PSC, NAFLD, cirrhosis)	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)

Table 1. Continued

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)

AZA, azathioprine; CAD, coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; GI, gastrointestinal; MTX, methotrexate; NAFLD, non-alcoholic fatty liver disease; PSC, primary sclerosing cholangitis; SECURE-IBD, Surveillance Epidemiology of Coronavirus Under Research Exclusion for Inflammatory Bowel Disease; 6MP, 6-mercaptopurine.
[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 $\geq$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

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 with the general populations of China, Italy, and the United States with CIs 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 older than 70 years 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 (eg, Middle East respiratory syndrome, severe acute respiratory syndrome).[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

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, y							
0–9	3	3 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
10–19	26	23 (88)	3 (12)	0 (0)	0 (0)	0 (0)	0 (0)
20–29	116	93 (80)	23 (20)	2 (2)	1 (1)	0 (0)	2 (2)
30–39	108	87 (81)	20 (19)	4 (4)	2 (2)	1 (1)	4 (4)
40–49	95	64 (67)	31 (33)	4 (4)	3 (3)	2 (2)	5 (5)
50–59	74	45 (61)	29 (39)	3 (4)	5 (7)	2 (3)	6 (8)
60–69	54	30 (56)	24 (44)	10 (19)	9 (17)	3 (6)	11 (20)
70–79	24	7 (29)	17 (71)	1 (4)	1 (4)	2 (8)	3 (13)
>=80	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							
CD	312	228 (73)	83 (27)	12 (4)	9 (3)	5 (2)	16 (5)
UC/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)

AZA, azathioprine; IL, interleukin; MTX, methotrexate; 6MP, 6-mercaptopurine.
[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

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 vs 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.

Table 3. Observed and Expected Deaths by Age and SMRs for SECURE-IBD Cohort vs China and Italy[a] (IBD Overall)

Age (y)	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	3	0	0.0%	0	0	0	0
10–19	26	0	0.0%	0.2	0.052	0	0
20–29	116	0	0.0%	0.2	0.232	0	0
30–39	108	1	0.9%	0.2	0.216	0.3	0.324
40–49	95	2	2.1%	0.4	0.38	0.4	0.38
50–59	74	2	2.7%	1.3	0.962	1	0.74
60–69	54	3	5.6%	3.6	1.944	3.5	1.89
70–79	24	2	8.3%	8	1.92	12.8	3.072
>=80	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]Based on references 23 and 2, respectively.

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 (93%) of 55 patients treated with anti-interleukin12/23 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 patients with IBD 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 overrepresent patients with more severe COVID-19 who come to the attention of their provider and patients in areas with readily available COVID-19 testing. Conversely, our sample may underrepresent 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] although 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-SMRs using case fatality rates reported from China, Italy, and the United States, 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 US data suggest 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.

Table 4. Observed and Expected Deaths by Age and SMRs for SECURE-IBD Cohort vs United States[a] (IBD Overall)

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

[a]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)	.002	1.03 (1.01–1.04)	<.001	1.07 (1.03–1.11)	<.001
Male (Female[b])	1.20 (0.55–2.60)	.65	1.38 (0.89–2.15)	.15	2.78 (0.76–10.14)	.12
Diagnosis						
Crohn's disease (ulcerative colitis/IBD unspecified)	0.76 (0.31–1.85)	.54	0.84 (0.51–1.38)	.49	1.64 (0.42–6.43)	.48
Disease severity[c] (remission)						
Active disease	1.14 (0.49–2.66)	.76	1.96 (1.23–3.11)	.005	0.97 (0.26–3.62)	.96
Systemic corticosteroid (none)	6.87 (2.30–20.51)	<.001	6.46 (2.74–15.23)	<.001	11.62 (2.09–64.74)	.005
TNF antagonist (none)	0.90 (0.37–2.17)	.81	0.60 (0.38–0.96)	.03	0.99 (0.23–4.23)	.99
Current smoker	0.55 (0.06–4.94)	.59	2.38 (0.92–6.16)	.07	1.47 (0.12–17.53)	.76
BMI ≥ 30	2.00 (0.72–5.51)	.18	1.18 (0.61–2.31)	.63	1.58 (0.28–8.80)	.60
Comorbidities (none)						
1	1.22 (0.45–3.26)	.70	1.29 (0.76–2.20)	.34	1.64 (0.35–7.67)	.53
≥2	2.87 (1.05–7.85)	.04	4.42 (2.16–9.06)	<.001	2.51 (0.56–11.24)	.23
5-ASA/sulfasalazine (none)	3.14 (1.28–7.71)	.01	1.77 (1.00–3.12)	.05	1.71 (0.46–6.38)	.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

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2020.05.032.

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Supplementary Table 1. Acknowledgement of Additional Organizations That Supported or Promoted the SECURE-IBD 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)

Supplementary Table 2. Number of Cases Reported to the SECURE-IBD 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

Supplementary Table 3. Number of Cases Reported to the SECURE-IBD Database by State

State	Number of cases
California	9
Connecticut	7
District of Columbia	2
Florida	4
Georgia	2
Illinois	13
Indiana	2
Louisiana	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

Supplementary Table 4. Description of Deaths Reported to SECURE-IBD Cohort[a]

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

CMV, cytomegalovirus; COPD, chronic obstructive pulmonary disease; Meds, medications.

[a]Note that 1 of these deaths was described in a previous case report (Mazza S, Sorce A, Peyvandi F, et al. A fatal case of COVID-19 pneumonia occurring in a patient with severe acute ulcerative colitis. Gut 2020;69:1148–1149).