COVID-19 and Outcomes in Patients With Inflammatory Bowel Disease: Systematic Review and Meta-Analysis

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Background: Our understanding of coronavirus disease 2019 (COVID-19) and its implications for patients with inflammatory bowel diseases (IBD) is rapidly evolving. We performed a systematic review and meta-analysis to investigate the epidemiology, clinical characteristics, and outcomes in IBD patients with COVID-19.

Methods: We searched PubMed, EMBASE, Cochrane Central, Clinicaltrials.gov, Web of Science, MedRxiv, and Google Scholar from inception through October 2020. We included studies with IBD patients and confirmed COVID-19. Data were collected on the prevalence, patient characteristics, pre-infection treatments for IBD, comorbidities, hospitalization, intensive care unit (ICU), admission, and death.

Results: Twenty-three studies with 51,643 IBD patients and 1449 with COVID-19 met our inclusion criteria. In 14 studies (n = 50,706) that included IBD patients with and without COVID-19, the prevalence of infection was 1.01% (95% confidence interval [CI], 0.92-1.10). Of IBD patients with COVID-19, 52.7% had Crohn’s disease, 42.2% had ulcerative colitis, and 5.1% had indeterminate colitis. Nine studies (n = 687) reported outcomes according to IBD therapy received. Compared with patients on corticosteroids, those on antitumor necrosis factor (anti-TNF) therapy had a lower risk of hospitalization (risk ratio [RR], 0.24; 95% CI, 0.16-0.35; P < .01; I² = 0%) and ICU admission (RR, 0.10; 95% CI, 0.03-0.37; P < .01) but not death (RR, 0.16; 95% CI, 0.02-1.71; P = .33; I² = 39%). Compared with patients on mesalamine, those on antitumor necrosis factor therapy had a lower risk of hospitalizations (RR, 0.37; 95% CI, 0.25-0.54), ICU admissions (RR, 0.20; 95% CI, 0.07-0.58), and death (0.21; 95% CI, 0.04-1.00). Comparing patients on immunomodulators vs mesalamine or anti-TNF therapy, there was no difference in these outcomes.

Conclusions: The prevalence of COVID-19 in IBD patients was low. Use of corticosteroids or mesalamine was significantly associated with worse outcomes, whereas use of anti-TNFs was associated with more favorable outcomes. Further investigation clarifying the mechanisms of these disparate observations could help identify risk and adverse outcome-mitigating strategies for patients with IBD.

Key Words: COVID-19, IBD, UC, CD, antitumor necrosis factors

Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the novel coronavirus that caused the coronavirus disease 2019 (COVID-19) outbreak. In December 2019, the first reported case of SARS-CoV-2 presented as pneumonia of unknown etiology in Wuhan, Hubei province, China.1,2 Since then, it has spread rapidly leading to a large number of infections and deaths worldwide. The World Health Organization (WHO) declared a pandemic state that led to various national and international authorities to impose restrictions, including total lockdown, to prevent the spread of the virus.3 The infection with the virus ranges from asymptomatic to a wide range of clinical manifestations including fevers, chills, gastrointestinal manifestations, pneumonia, respiratory distress, and death. As of July 2021, there were over 190 million cases with over 4 million deaths worldwide. In the United States alone, there are over 600,000 deaths due to COVID-19.4

Inflammatory bowel diseases (IBD), predominantly comprising Crohn’s disease (CD) and ulcerative colitis (UC), are chronic, idiopathic, immune-mediated inflammatory disorders of the digestive tract affecting nearly 3 million Americans and over 3 million people in Europe.5,6 The pathogenesis of both CD and UC is thought to be driven by dysregulated immune response towards gut mucosa and intestinal flora in a genetically susceptible host.7 Treatment of IBD is aimed at controlling an overactive immune response, which may involve use of immune modifying therapies including immunomodulators or biologic drugs. Many of these treatments are associated with known increased risks of infections, potentially posing an increased risk of infection with SARS-CoV-2, as well.8 Since the beginning of the pandemic, immunocompromised individuals were deemed at risk of acquiring the infection and possibly a more severe form of it.9

However, the actual risk of infection or development of COVID-19 in these at-risk patients with IBD or those
on immunosuppressive treatments for IBD is not clear. Additionally, it is not known whether any dose adjustments are appropriate to mitigate these risks without altering the maintenance of remission leading to complications from the disease.8,10 Throughout the ongoing COVID-19 pandemic, the International Organization for the Study of Inflammatory Bowel Diseases (IOIBD) has provided guidance on the management of IBD, such as the encouragement to continue biologic therapies and only temporarily holding them when infected.10 However, as more data emerge, our understanding on COVID-19 and its clinical implications in IBD are rapidly evolving. We performed a systematic review and meta-analysis to investigate the evolving epidemiology, clinical characteristics, therapeutic options, and outcomes in IBD patients with COVID-19.

Methods
We conducted a systematic review with a predefined protocol in accordance with the Cochrane Handbook and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.11

Search Strategy
We searched PubMed, EMBASE, Cochrane Central, Clinicaltrials.gov, Web of Science, MedRxiv, and Google Scholar from inception through October 2020 to identify studies that had IBD patients with confirmed COVID-19. The medical subject heading (MeSH) terms used were coronavirus disease 19, COVID-19, SARS-CoV-2, inflammatory bowel disease, ulcerative colitis, Crohn’s disease, IBD, UC, CD, in conjunction with operators AND or OR. Studies from search results were uploaded to Covidence for screening and inclusion. Two investigators independently screened titles and abstracts of the studies and included them for full-text review. Subsequently, full text studies were reviewed independently by 1 reviewer, with confirmation and review by another reviewer. Conflicts were resolved through adjudication by consensus discussion with a third reviewer.

Selection Criteria
All studies and case series that met the following criteria were included: (1) any patient with a confirmed diagnosis of IBD; and (2) any patient in the study population with a confirmed COVID-19 diagnosis with positive diagnostic test. Literature reviews, systematic reviews and/or meta-analyses, studies that included pediatric population (younger than 18 years old), and editorials were excluded. There were no language or geographic restrictions.

Data Extraction
Data were independently abstracted by 2 authors. Data were collected for first author of the study, year of publication, study design, country of origin, number of participants, total number of patients with IBD, total number of IBD patients with COVID-19, patient demographics (age, sex), type of IBD, comorbidities, active smoking, ongoing treatment for IBD at the time of COVID-19 infection (eg, corticosteroids, 5-aminosalicylate [5-ASA], immunomodulator, biologic therapy), symptom at presentation, treatment offered for COVID-19, and clinical outcomes (hospitalizations, intensive care unit [ICU] admissions, or deaths). Case reports were included in the initial search but were excluded in the meta-analyses.

Assessment of Study Quality
All included studies were cohort, nonrandomized studies. Hence, the Newcastle-Ottawa Scale (NOS) was used to assess the quality of the studies. The NOS score ranged from 0 to 9 based on 8 items that included selection (representativeness of the exposed cohort, selection of nonexposed cohort, ascertainment of exposure, the demonstration that outcome of interest was not present at the start of study); comparability (comparability of the cohort on the basis of design or analysis); and outcome (assessment of outcome, whether follow-up was long enough for outcomes to occur, adequacy of follow-up cohorts). For each criterion fulfilled, 1 star can be awarded to the study in question, except for comparability where a maximum of 2 stars can be awarded. The NOS score of 6 and higher were high-quality studies, and 3 and lower were low-quality studies.

Statistical Analysis
The prevalence of COVID-19 infections was estimated using the total number of COVID-19 infections divided by the total number of individuals. Studies that reported only COVID-19-positive patients were excluded from prevalence estimations. Meta-analyses using random effects models were performed to compare therapeutic classes (corticosteroids, 5-ASA, immunomodulator, biologic agent) and their relative risk of the primary outcomes (hospitalization, ICU admission, death). For comparability within the same study population, each meta-analysis only included studies that fully reported data on the compared medications and particular outcome of interest. Heterogeneity was assessed qualitatively and quantitatively using χ² and I² statistics. An I² <25% was considered low heterogeneity, 25% to 50% moderate heterogeneity, and >50% substantial heterogeneity. Statistical analyses were performed using R 4.0 and RevMan 5.4.

Results
Study Characteristics
The PRISMA flowchart of the search results is detailed in the Figure 1. A total of 5393 articles were identified through the search with PubMed Medline resulting in 260 results, Embase with 339 results, Cochrane Central with 6 results, Clinicaltrials.gov with 13, Web of Science with 116, MedRxiv with 29, and Google Scholar with 4630—results out of which the first 200 were saved for screening. After excluding duplicates, 468 were included for title and abstract review, and 85 studies were included for full-text review. After full-text review, an additional of 39 studies were excluded (Figure 1). Finally, 41 studies were included for abstraction, including the SECURE-IBD registry and 18 individual case reports that were not included in the meta-analysis.

Patient Demographics and Characteristics
A total of 23 studies with 51,643 IBD patients and 1449 with confirmed COVID-19 met our inclusion criteria (Table 1). Additionally, there were 18 case reports with a total of 19 IBD patients with confirmed COVID-19 cases (Table 1).
Of IBD patients with COVID-19, 763 (52.7%) had CD, 612 (42.2%) had UC, and 74 (5.1%) had indeterminate colitis. Mean ages for patients ranged from 18 to 85 years. Eight studies provided information on gender, and 60.7% were females (Supplemental Table 1). 12,20,21,28,30–33 Fourteen studies (n = 50,706) provided the information on prevalence that included IBD patients with and without COVID-19 (Table 2).12,16,20,21,23,24,26–28,30–34 The pooled prevalence of infection was 1.0% (95% confidence interval [CI], 0.92-1.10).

Risk Factors, Comorbidities, and Symptoms
Five studies provided smoking data (Supplemental Table 2).18,20,21,32,33 Of the IBD patients with COVID-19, 8.9% were active smokers. Eleven studies reported comorbidities, with a total of 1177 COVID-19 patients with IBD (Supplemental Tables 3, 4).12,13,17–21,26,30,32,33 Out of these, 245 (20.8%) had hypertension, 105 (8.9%) had diabetes mellitus, 107 (9.1%) patients had coronary artery disease, 65 (5.5%) had chronic lung diseases, and 3 (0.25%) had obesity. Thirteen studies described COVID 19 symptoms in IBD patients.14,15,17–21,23,26,28,30–32 Fevers and cough were the most common presenting symptoms: 488 (41.9%) patients reported fever, and 427 (36.7%) reported cough. Diarrhea was the most common gastrointestinal symptom: 160 (13.8%) patients reported diarrhea; 78 (6.7%) patients reported nausea and vomiting; and 57 (4.9%) patients reported abdominal pain (Supplemental Table 5).

Outcomes With IBD Therapy Received
Nine studies (n = 687) reported outcomes in patients who received IBD maintenance therapy (Supplemental Table 6).12,13,19–20,26,30,31,34 Oral and rectal mesalamine was used in 23.4% of patients, with 44.1% requiring hospitalization, 8.7% ICU admission, and 6.8% deaths. Immunosuppressive agents (methotrexate, azathioprine, 6-mercaptopurine) were used in 12.4% of patients, with 37.6% requiring hospitalization, 3.5% ICU admission, and 2.4% deaths. Antitumor necrosis factor (TNF) therapies were used in 37.2% patients, with 12.9% requiring hospitalization, 1.2% ICU admission, and 0.8% deaths.

Compared with patients on corticosteroids, those on anti-TNF therapy had a lower risk of hospitalization (risk ratio [RR], 0.24; 95% CI, 0.16-0.35; P < .01; F = 0%) and ICU admission (RR, 0.10; 95% CI, 0.03-0.37; P < .01) but not death (RR, 0.16; 95% CI, 0.02-1.71; P = .13; F = 39%; Figure 2). Compared with patients on mesalamine, those on anti-TNF therapy had a lower risk of hospitalization (RR, 0.37; 95% CI, 0.27-0.54; P < .01; F = 3%) and ICU admission (RR, 0.20; 95% CI, 0.07-0.58; P < .01; F = 0%) and similar risk of death (RR, 0.21; 95% CI, 0.04-1.00; P = .05; F = 8%; Figure 3). Compared with patients on immunomodulators, those on anti-TNF therapy had similar risk of hospitalization (RR, 0.56; 95% CI, 0.26-1.21; P = .14; F = 37%), ICU admission (RR, 0.33; 95% CI, 0.07-1.59; P = .17), and death (RR, 0.21; 95% CI, 0.03-1.40; P = .11; F = 0%; Supplementary
| Author       | Study Design          | Country                  | Total No. IBD Patients | IBD Patients With COVID-19 | CD UC Female % (n) | Mean/median age (yrs) | Comorbidities/smoking | Symptoms at Presentation | Ongoing IBD Therapy | Outcomes: ICU Hospitalization | Deaths |
|--------------|-----------------------|--------------------------|------------------------|----------------------------|--------------------|------------------------|------------------------|------------------------|------------------------|-------------------------------|--------|
| Allocca12    | Retrospective cohort study | Italy and France        | 6000                   | 15                         | 9                  | 67.3% (11)             | Renal transplantation, Primary Sclerosing Cholangitis, chronic paranoid psychosis, arthrosis, muscular dystrophy, HTN, obesity, arthritis, ankylosing spondylitis, Mitral Valve Prolapse | NA                     | Anti-TNF, 8 (53.3%); 5 (33.3%) | 0                |
| Alloc13      | Prospective case series | Italy                    | 21                     | 21                         | 9                  | 12 NA                  | NA                     | NA                     | NA                     | NA                             | NA     |
| Attauabi14   | Prospective cohort study | Denmark                 | 76                     | 76                         | 31                 | 45.41% (31)            | Asthma, Type 1 Diabetes, Sarcoidosis | NA                     | None 19 (25%); Topical 5-ASA 18 (20%); Systemic 5-ASA 25 (29%); Topical steroids 3 (3%); Systemic steroids 3 (3%); Immunomodulators 16 (18%); Biologic therapies 18 (20%) | NA     |
| Axelrad15    | Case series            | United States            | 83                     | 83                         | 56                 | 27.47% (39)           | Median UC-51, CD-54 | NA                     | 5-ASA 13 (16%); Azathioprine/MCP 2 (1%); MTX 4 (5%); Prednisone 6 (6%); Budesonide 4 (6%); Vedolizumab 5 (6%); Infliximab 3 (28%); Adalimumab 21 (25%); Tofacitinib 4 (5%); Ustekinumab 9 (11%) | 6% (5) | 1% (1)                          | 1% (1) |
| Bezzio16     | Prospective cohort study | Italy                    | 243                    | 11                         | NA                 | NANA                   | Fever 55 (66%); cough 46 (55%); pharyngitis 21 (25%); rhinorrhea 15 (18%); diarrhea 26 (31%); anemia 18 (22%); anosmia 25 (30%); SOB 21 (25%) | NA                     | unspecified                     | 2 (0.8%) | NA                             | NA     |

Table 1. Patient demographics and baseline characteristics of cohort studies and case series.
### Table 1. Continued

| Author     | Study Design      | Country   | Total No. IBD Patients | IBD Patients With COVID-19 | CD UC Female % (n) | Mean/median age (yrs) | Comorbidities/smoking | Symptoms at Presentation | Ongoing IBD Therapy | Outcomes: ICU Hospitalization | Deaths |
|------------|-------------------|-----------|------------------------|----------------------------|---------------------|-----------------------|------------------------|--------------------------|----------------------|---------------------------|--------|
| Bezzio17   | Prospective cohort study | Italy     | 79                     | 79                         | 32                  | 47 444% (35) Median 45 | None 49 (62%) | Hypertension 9 (11%), Coronary heart disease 5 (6%), COPD 5 (6%), CMV colitis 2 (3%), Hyperthyroidism 1 (1%), Psoriasis 2 (3%), Ankylosing spondylitis 2 (3%), Rheumatoid arthritis 1 (1%), Multiple sclerosis 1 (1%), Undifferentiated connective tissue disease 1 (1%), Hypothyroidism 1 (1%), Kaposi's sarcoma 1 (1%) | Fever (90%), Cough (66%), Dysosmia/ dysgeusia (24%), Arthralgia/myalgia (23%), Dyspnoea (19%), Diarrhoea (15%) and Rhinopharyngitis (16%) | None 5 (6%), Aminosalicylates 24 (30%), Thiopurines 6 (8%), Systemic corticosteroids 9 (11%), Calcineurin inhibitors 1 (1%), Anti-TNF 29 (37%), Vedolizumab 15 (20%), Ustekinumab 3 (4%) | 22 (27%) | 18 (22%) | 6 (7.5%) |
| Brenner18  | Retrospective cohort study | United States | 525                    | 525                        | 312 203 243 (46.3) | 42.9 | CAD 38 (7.2%) | DM 29 (5.5%) | Lung disease 44 (8.4%), Hypertension 63 (12.0%), Cancer 10 (1.9%) | History of stroke 4 (0.8%), CKD 10 (1.9%), Chronic liver disease 26 (5.0%) | 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%) | Sulphasalazine/mesalamine 117 (22.3%), Budesonide 37 (7%), Oral/parenteral steroids 37 (7%), 6MP/azathioprine monotherapy 53 (10.1%), Methotrexate monotherapy 5 (1), 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%) | 161 (30.7%) | 24 (4.6%) | 16 (3.0%) |
| Author     | Study Design      | Country          | Total No. IBD Patients | IBD Patients With COVID-19 | CD UC Female | Mean/median age (yrs) | Comorbidities/smoking | Symptoms at Presentation | Ongoing IBD Therapy | Outcomes: ICU Hospitalization | Deaths |
|------------|-------------------|------------------|------------------------|---------------------------|--------------|-----------------------|------------------------|-------------------------|----------------------|-------------------------------|---------|
| Garrido    | Retrospective cohort study | Portugal    | 11                     | 11                         | 9            | 254.5% (6)            | HTN, HLD, Asthma, Diabetes, CV disease, PCT | fever, cough, fatigue, myalgia, sore throat, headache, anosmia, dysgeusia, rhinorrhea, n/v, diarrhea | Azathioprine 27% (3), Infliximab 27% (3), MCP 9% (1), ADA 18% (2), Mesalazine 9% (1) | 9% (1) | 0                              | 0       |
| Gubatan    | Retrospective cohort study | United States | 168                   | 5                          | 2            | 360% (3)              | HTN 80% (4), DM 40% (2), Fever, cough, fatigue, dyspnea | Steroids 20% (1), 5-ASA 80% (4), 6MP/Azathioprine 20% (10), infliximab 20% (1) | 20% (1) | 20% (1)                        | 20% (1) |
| Guerra     | Cross-sectional observational study | Spain     | 805                   | 82                         | 42           | 35 53.7% (44)        | CKD, COPD, CHF, CHD, Cerebrovascular disease, DM, HTN, dyslipidemia, malignancy, chronic liver disease | Cough, fever, dyspnea, fatigue, myalgia, headache, dysgeusia/dysosmia, sore throat, rhinorrhea, diarrhea, n/v, abdominal pain | Mesalazine 50% (41), Azathioprine 29.3% (24), MCP 3.7% (3), MTX 2.4% (2), Infliximab 7.3% (6), ADA 9.8% (8), golimumab 3.7% (3), Ustekinumab 3.7% (3) | 20.7% (17) | 1.2% (1)                       | 0       |
| Haberman   | Case series        | United States   | 37                    | 37                         | 20           | 17 NA                | NA                     | NA                      | NA                   | NA                            | 10.8% (4) | 0                              | 0       |
| Hormati    | Retrospective cohort study | Iran         | 150                   | 8                          | NA NANA      | NA                   | fever, cough, sore throat | Unclear exactly the specific tx. because this info is not provided for patients with COVID. | NA | NA                            | NA       |
| Khan       | Retrospective cohort study | United States | 37857                 | 36                         | 0            | 0 NA                 | 60.9 (17.1) NA         | NA                      | Thiopurine (2), AntiTNF (3) | NA | NA                            | NA       |
| Kornbluth  | Retrospective cohort study | United States | 65                    | 65                         | 41           | 24 NA                | 39 (17-71) NA          | NA                      | Adalimumab (11), Infliximab (10), Golimumab (1), AntiTNF and thiopeurine (1), Vedolizumab (5), Ustekinumab (9), Upabactim RCT (1), Mesalazine/sulfasalazine (5), Antibiotics (2), prednisone 20mg and MTX (1), Prednisone 10mg (1), No medications (5) | 4.6% (3) | 3% (2)                         | 0       |
| Author          | Study Design   | Country       | Total No. IBD Patients | IBD Patients With COVID-19 | CD UC Female % (n) | Mean/median age (yrs) | Comorbidities/smoking | Symptoms at Presentation | Ongoing IBD Therapy | Outcomes: ICU Hospitalization (%) | Deaths (%) |
|-----------------|----------------|---------------|------------------------|---------------------------|-------------------|-----------------------|------------------------|------------------------|----------------------|---------------------------------|----------|
| Lukin26         | Case control   | United States | 119                    |                           | 38                | 26 NA                | NA                     | HTN, DM, CKD, CVD, COPD/asthma, OSA, VTE, cancer, chronic liver disease | High fever, more than 1 new symptom including cough, sore throat, (12), Tofacetinib dyspnea, anosmia, and diarrhea | TNF alpha antagonist (16), vedolizumab (10), ustekinumab (12), Tofacetinib + Vedolizumab (1), trial drug (1), Thiopurines (4), methotrexate (3), combination (4), aminosalicylates (20), steroid (13) | NA      |
| Marafini27      | Retrospective cohort study | Italy       | 672                    |                           | 3                 | NA NANA              | NA                     | Fever (7), Cough (3), Dysgeusia/Anosmia (5) | NA | 66.7% (2) | NA | 33.3% (1) |
| Norsa28         | Retrospective cohort study | Italy       | 103                    |                           | 19                | 14 568.4% (13)       | Median 50.0 (28-57)   | Fever (77%), cough (67%), diarrhea (21%) | Adalimumab (10), infliximab (5), Vedolizumab (1), Ustekinumab (3) | NA | NA | NA | 5% (2) |
| Rodríguez-Lago29 | Retrospective cohort study | Spain       | 40                     |                           | 40                | 13 2340% (16)        | 59 (48-68)             | CKD, chronic pulmonary disease, CHF, CAD, DM, cerebrovascular disease, hypertension, dementia, neoplasia | Infliximab (2), Adalimumab (1), Vedolizumab (1), Ustekinumab (3), mesalamine (26), systemic steroids (4), thiopurines (8), methotrexate (3), thopurine + anti-TNF (1), thopurine + ustekinumab (1) | 53% (21) | 0 | 5% (2) |
| Taxonera30      | Case series    | Spain         | 1918                   |                           | 12                | 7 575% (9) 52.3      | Hypertension (3), diabetes (2), Chronic liver disease (2), CKD (1), cardiovasculardisease (1) | Fever, cough, dyspnea, myalgia, ageusia, fatigue, headache, sore throat, diarrhea, nausea, vomiting | Azathioprine (1), mesalazine (3), azathioprine + mesalazine (1), adalimumab (1), golimumab + methotrexate (1), ustekinumab + 6MP (1), Vedolizumab + MTX (1) | 66.7% (8) | 8.3% (1) | 16.6% (2) |
| Elhabakh31      | Case series    | Egypt          | 11                     |                           | 2                 | 0 2100% (2)          | NA                     | fever, dry cough, generalized fatigue | None | 100% (2) | 0 | 0 |
| Author          | Study Design          | Country  | Total No. of IBD Patients | IBD Patients With COVID-19 | CD UC Gender | CD UC Female % (n) | Mean/median age (yrs) | Comorbidities/smoking                                                                 | Symptoms at Presentation                                                                 | Ongoing IBD Therapy                                                                 | Outcomes: Hospitalization | ICU Deaths | Deaths |
|----------------|-----------------------|----------|---------------------------|---------------------------|--------------|-------------------|----------------------|------------------------|----------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|------------------------|----------|
| Singh          | Retrospective cohort study | United States | 1901                     | 232                       | 101          | 95.634 (147)      | 51.2 +/- 18.1        | Essential hypertension (121), COPD (91), DM (62), Ischemic heart disease (49), CKD (38), Heart failure (37), cerebrovascular diseases (3), nicotine dependence (35), alcohol related disorders (11) | Cough 56 (24.14), Fever 38 (16.37), Dyspnea 30 (12.93), Nausea 25 (10.77), Malaise 20 (8.62), Diarrhea 19 (8.19), Abdominal pain 18 (7.75), Sore throat 14 (6.03), Hypoxemia 12 (5.17) | Biologics (37), immunomodulators (34), aminosalicylate therapy (32), corticosteroids (111) | 24.1% (56)   | NA       | NA     |
| Viganò         | Retrospective observational cohort study | Italy | 704                      | 53                        | 20           | 33.49% (26)       | 50 (42-62)          | Systemic hypertension (9), cardiac disease (5), COPD (2), CKD (3), any comorbidity (18) | Diarrhea                                                                    | Aminosalicylates (30), thiopurines/mxt (8), high dose systemic corticoids (2), anti TNF (8), Vedolizumab (1), Ustekinumab (1) | NA                  | NA       | NA     |
| Waggershauser  | Prospective cohort study | Germany | 55                       | 5                         | 0            | 0 NA              | NA                   | Fevers, chills, anosmia                                                        | Infliximab (3), ustekinumab + azathioprine (1), none (1)                                                                 |                                                                      | 0                  | 0        | 0      |

| Author          | Study design          | Country  | Total number of IBD patients | IBD patients with COVID-19 | CD UC Gender | Age (yrs) | Comorbidities/smoking | Symptoms at presentation                                                                 | Ongoing IBD therapy                                                                 | Outcomes: Hospitalization | ICU Deaths | Deaths |
|----------------|-----------------------|----------|-----------------------------|---------------------------|--------------|-----------|-------------------|----------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|------------------------|----------|
| Abdullah       | Case report           | Germany  | 1                           | 1                         | 0            | 1 Female   | 18                | dry cough                                                                                           | Y - infliximab                                                                 | N                      | N        | N      |
| Bezzio         | Case report           | Italy    | 1                           | 1                         | 0            | 1 Male     | 36                | 12 bowel movements with blood on presentation.                                                        | Topical and oral Mesalazine                                                                 | Y                      | N        | N      |
| DiRuscio       | Case report           | Italy    | 1                           | 1                         | 0            | 1 Female   | 60                | Fever, dry cough, dyspnea                                                                                     | Patient was treated with corticosteroids for active flare                          | Patient was hospitalized initially for UC flare, but was found to be COVID+ while hospitalized | Yes, d't sep. shock from central venous catheter NARelated infection | N        |

**Table 1.**
| Author       | Study Design | Country       | Total No. IBD Patients | IBD Patients With COVID-19 | CD UC Female % (n) | Mean/median age (yrs) | Comorbidities/smoking | Symptoms at Presentation | Ongoing IBD Therapy | Outcomes: ICU Hospitalization | Deaths |
|-------------|--------------|---------------|------------------------|---------------------------|--------------------|------------------------|-----------------------|------------------------|-----------------------|-------------------------------|---------|
| Dimopoulos | Case report  | United States | 1                      | 1                         | 1                  | 0 Male                 | 24                    | NA                    | Asymptomatic             | Y - adalimumab (ADA) and ustekinumab (UST) combination therapy sulfasalazine, topical mesalamine, corticosteroids for flare mesalmine (azathioprine was held) | N      |
| Garcia      | Case report  | Brazil        | 1                      | 1                         | 0                  | 1 Female               | 33                    | PSC                   | Abdominal pain and diarrhea | N                                | N      |
| Gutin       | Case report  | United States | 1                      | 1                         | 0                  | 1 Male                 | 40                    | NA                    | Fever, mild cough         | mesalmine (azathioprine was held)                         | N      |
| Jacobs      | Case report  | United States | 1                      | 1                         | 0                  | 1 Female               | 33                    | NA                    | Fever, chills, cough, Tofacitinib myalgias, sore throat, fatigue, night sweats | N      |
| Kunisaki    | Case report  | Japan         | 1                      | 1                         | 0                  | 1 Male                 | 60                    | NA                    | High fever               | Infliximab, azathioprine, mesalmine                           | N      |
| Lenti       | Case report  | Italy         | 1                      | 1                         | 1                  | 0 Male                 | 25                    | NA                    | Dry cough, mild fever, elevated creatinine, hypoalbuminemia and hypercholesterolemia (acute kidney injury/nephrotic syndrome) | Y      |
| Mansoor     | Case report  | United States | 1                      | 1                         | 1                  | 0 Male                 | 60                    | Hypertension           | Diarrhea, cough, abdominal pain and weakness                 | Y      |
| Mayer       | Case report  | France        | 1                      | 1                         | 0                  | 1 Female               | 20                    | Multidrug resistant miliary tuberculosis | UC pancolitis flare | No                       | Y      |
| Mazza       | Case report  | Italy         | 1                      | 1                         | 0                  | 1 Female               | 80                    | NA                    | High fever, dry cough | Mesalmine                      | Y       |
| Navaneethan | Case report  | United States | 1                      | 1                         | 1                  | 0 Female               | 43                    | Bronchial asthma, congenital heart disease | Nonbloody diarrhea, SOB, fever, fatigue | Y      |
| Okeke       | Case report  | United States | 1                      | 1                         | 1                  | 0 Female               | 60                    | Rheumatoid arthritis, SLE | Fever, generalized myalgias, fatigue, trexate nonbloody diarrhea, vomiting, abdominal cramping | Y      |
| Author     | Study Design | Country    | Total No. IBD Patients | CD UC Female % (n) | Mean/median age (yrs) | Comorbidities/smoking | Symptoms at Presentation | Ongoing IBD Therapy | Outcomes: ICU Hospitalization | Deaths |
|------------|--------------|------------|------------------------|--------------------|-----------------------|-----------------------|------------------------|----------------------|--------------------------|--------|
| Rosen49    | Case report  | United States | 1                      | 1                  | 0                     | 1 Female 26           | Pregnancy             | None                 | Y                         | N      |
| Tursi50    | Case report  | Italy       | 1                      | 1                  | 00                   | 30                    | NA                    | mesalamine 3g/day, adalimumab 40mg sc | Y                  | N.                        | N      |
| Tursi51    | Case reports | Italy       | 2                      | 1                  | One male and one female | Median age of 55      | NA                    | NA                  | Adalimumab (1)            | 100% (2) | 50% (1) | 50% (1) |
| Wolf52     | Case report  | United States | 1                      | 1                  | 00                   | 85                    | NA                    | Diarrhea, cough        | N                        | N      | N      | N      |

Abbreviations: NA, data not available; HTN, Hypertension; MTX, Methotrexate; MRP, mercaptopurine; CAD, coronary artery disease; DM, diabetes mellitus; COPD, chronic obstructive lung diseases; PCT, porphyria cutanea tarda; n/v, nausea and vomiting; IMID, immune-mediated immune deficiency; OSA, obstructive sleep apnea; VTE, venous thromboembolism; CKD, chronic kidney disease; CHF, congestive heart failure; CHD, coronary heart disease; IFX, infliximab; ADA, adalimumab.
Figure 1). Compared with patients on corticosteroids, those on mesalamine and immunomodulators had similar risk of hospitalization, ICU admission, and death (Supplementary Figure 2). Compared with patients on mesalamine, those on immunomodulators also had similar risk of hospitalization, ICU admission, and death (Supplementary Figure 3).

Subgroup meta-analysis comparing thiopurines and methotrexate did not reveal any differences in risk of hospitalization, ICU admission, or death; although the comparisons were limited by sparse data (Supplementary Figure 4). Data on ustekinumab and vedolizumab were sparse, so meta-analysis could not be performed.

**Heterogeneity**

In the meta-analyses, there was no evidence of significant statistical heterogeneity, and most had low to moderate degree of heterogeneity, except for substantial heterogeneity ($I^2 = 65\%$) in the comparison between immunomodulators and corticosteroids for the outcome of death. Qualitatively, included studies were similar in demographics; however, study population was heterogeneous from different parts of the world. All included studies were retrospective and were similar in methodologies.

| Study author | Total No. IBD Patients in the Study (IBD population n) | IBD Patients With COVID-19 (%) |
|--------------|-------------------------------------------------------|-------------------------------|
| Allocca      | 6000                                                  | 15 (0.25%)                    |
| Bezzio       | 243                                                   | 11 (4.5%)                     |
| Gubatan      | 168                                                   | 5 (2.9%)                      |
| Guerra       | 805                                                   | 82 (10.1%)                    |
| Hormati      | 150                                                   | 8 (5.3%)                      |
| Khan         | 37857                                                 | 36 (0.1%)                     |
| Lukin        | 119                                                   | 29 (24.3%)                    |
| Marafini     | 672                                                   | 3 (0.45%)                     |
| Norsa        | 103                                                   | 19 (18.4%)                    |
| Taxonera     | 1918                                                  | 12 (0.6%)                     |
| Eltabbakh    | 11                                                    | 2 (18.1%)                     |
| Singh        | 1901                                                  | 232 (12.2%)                   |
| Viganò       | 704                                                   | 53 (7.5%)                     |
| Waggershauser| 55                                                    | 5 (9.1%)                      |
| Total        | 50,706                                                | 512 (1.0%)                    |

Table 2. COVID-19 prevalence of IBD patients.
Hospitalizations:

| Study or Subgroup | Anti-TNF Events | 5-ASA Events | Risk Ratio M-H, Random, 95% CI |
|-------------------|----------------|--------------|--------------------------------|
| Axelrad 2020      | 2              | 1            | 0.59 [0.06, 6.01] |
| Brenner 2020      | 25             | 57           | 0.29 [0.19, 0.44] |
| Garrido 2020      | 1              | 1            | 1.00 [0.06, 15.99] |
| Gubatan 2020      | 0              | 1            | 0.83 [0.05, 13.02] |
| Lukin 2020        | 1              | 6            | 0.21 [0.03, 1.56] |
| Taxonera 2020     | 2              | 4            | 0.69 [0.31, 1.57] |
| **Total**         | **245**        | **159**      | **0.37 [0.25, 0.54]** |

Total events: 31
Heterogeneity: Tau² = 0.01; Chi² = 5.18, df = 6 (P = 0.40); I² = 3%
Test for overall effect: Z = 5.12 (P < 0.00001)

ICU Admissions:

| Study or Subgroup | Anti-TNF Events | 5-ASA Events | Risk Ratio M-H, Random, 95% CI |
|-------------------|----------------|--------------|--------------------------------|
| Axelrad 2020      | 0              | 1            | 0.10 [0.00, 2.41] |
| Brenner 2020      | 3              | 12           | 0.17 [0.05, 0.58] |
| Garrido 2020      | 0              | 1            | Not estimable |
| Gubatan 2020      | 0              | 1            | 0.83 [0.05, 13.02] |
| Lukin 2020        | 0              | 0            | Not estimable |
| Taxonera 2020     | 0              | 4            | Not estimable |
| **Total**         | **245**        | **159**      | **0.20 [0.07, 0.58]** |

Total events: 2
Heterogeneity: Tau² = 0.00; Chi² = 1.30, df = 2 (P = 0.52); I² = 0%
Test for overall effect: Z = 2.95 (P = 0.003)

Deaths:

| Study or Subgroup | Anti-TNF Events | 5-ASA Events | Risk Ratio M-H, Random, 95% CI |
|-------------------|----------------|--------------|--------------------------------|
| Axelrad 2020      | 1              | 1            | 0.93 [0.04, 21.65] |
| Brenner 2020      | 1              | 9            | 0.07 [0.01, 0.55] |
| Garrido 2020      | 0              | 1            | Not estimable |
| Lukin 2020        | 0              | 0            | Not estimable |
| Taxonera 2020     | 0              | 1            | 0.42 [0.02, 7.71] |
| **Total**         | **244**        | **155**      | **0.21 [0.04, 1.00]** |

Total events: 2
Heterogeneity: Tau² = 0.15; Chi² = 2.17, df = 2 (P = 0.34); I² = 8%
Test for overall effect: Z = 1.97 (P = 0.05)

Figure 3. Outcomes in IBD patients on mesalamine when compared with those on anti-TNFs.

Discussion

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Study Quality

All included studies were assessed for quality using the NOS. Two studies scored 8 and above (high quality for assessing outcomes) and were included. There were 4 studies with moderate quality that scored 7 points; of these, 3 were included. There were 9 studies with low quality that scored 6 points; of these, 4 were included in the analyses. Studies scoring 5 and lower were not included due to lack of outcome of interest (Table 3).

The prevalence is variable depending on a given time point, but to provide context, varied from 0.4% to 0.7% in earlier studies. A third of IBD patients who contracted COVID-19 required hospitalization, and fewer than 4% required admission to the ICU. Mortality in this specific population was also low at 2.5%. Our study also found an association between use of 5-ASA compounds and increased risk of adverse outcomes, including hospitalization, ICU admission, and death. By contrast, use of biologic therapy was associated with lower risk of these adverse outcomes.

The SECURE-IBD trial recently showed that combination therapy and thiopurines may be associated with an increased risk of severe COVID-19; however, there was no significant difference in severe infections when comparing different classes of biologics. With this anecdotal evidence from the SECURE-IBD registry, Feldman et al proposed to use anti-
TNFs under clinical trials in patients who are at high risk of developing severe infection to prevent worse outcomes. 56 The findings from our meta-analysis is consistent with those published by Burke et al in January 2021, which states that the use of biologics is associated with preferable outcomes in patients with COVID-19 infection, most likely due to reduction in the cytokine storm.53 Of patients receiving anti-TNFs, 12.9% required hospitalization, with less than 1% deaths. Hence, it appears safe to continue biologics in IBD patients who are in remission or in process of achieving remission. This would prevent disease-related adverse outcomes and possibly prevent loss of drug from the therapeutic armamentarium for the patient, as discontinuation and missed doses can lead to formation of antibodies.57

The use of 5-ASA leading to worse clinical outcomes in IBD patients with COVID-19 is not well understood. The 5-ASA compounds act on peroxisome proliferator-activator gamma receptors (PPAR-γ) to alleviate the ongoing inflammatory response. COVID-19 infection is typically accompanied by an aggressive inflammatory response, with the release of large amount of pro-inflammatory cytokines, known as the “cytokine storm.” 58 This cytokine storm directly correlates with lung injury, multi-organ failure, and ultimately, unfavorable outcomes due to severe disease.58,59 Although immunomodulators and biologic medications are linked to an increased risk of infections, their suppressive effect on the cytokines involved during inflammation in IBD might help suppress the hyperactivation of T cells and the cytokine storm that occurs during COVID-19.60 Alternatively, it is possible that patients on biologic therapies have been much more cautious about infection precautions than those on less immunosuppressive therapies. In our recent multicenter survey of 323 adults with IBD during the COVID-19 pandemic, use of biologic therapy was associated with increased perception of risk and decreased activity when compared with those not on biologic therapy.61 Additionally, reporting bias remains a concern for patients on 5-ASA, as these patients may not report mild/early symptoms of COVID-19 when compared with those on immunosuppressive medications such as anti-TNFs. These factors may have led to less outdoor activity, less physical interaction with others, and increased precautions with socializing in this subset of population.

This study is thus far the most extensive and up-to-date systematic review with meta-analysis evaluating the epidemiology and outcomes of IBD patients with COVID-19. We nonetheless acknowledge several limitations. First, not every study reported the outcome of interest. Second, we were unable to control for potential selection bias or unmeasured confounders, such as smoking, corticosteroid use, or med-

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**Table 3.** Quality of studies included in systematic review and meta-analysis according to Newcastle-Ottawa Scale

| Study Author | Selection (1) Representativeness of Exposed Cohort | Selection (2) Selection of Nonexposed Cohort | Selection (3) Ascertainment of Exposure | Selection (4) Demonstration that Outcome of Interest Was Not Present at the Start of the Study | Comparability (1) Comparability of Cohorts on the Basis of Design and Analysis | Outcome (1) Assessment of Outcome (2) Was Follow-up Long Enough for Outcome to Occur | Outcome (3) Adequacy of Follow-up Cohorts | Score |
|--------------|--------------------------------------------------|---------------------------------------------|----------------------------------------|------------------------------------------------------------------------------------------------|-----------------------------------------------------------------|--------------------------------------------------------------------------------|---------------------------------------------|-------|
| Allocca12    | *                                                 | *                                           | *                                      | *                                                                                              | *                                                               | *                                                                              | *                                           | 6     |
| Allocca13    | *                                                 | *                                           | *                                      | *                                                                                              | *                                                               | *                                                                              | *                                           | 3     |
| Attuabi14    | *                                                 | *                                           | *                                      | *                                                                                              | *                                                               | *                                                                              | *                                           | 6     |
| Axelrad15    | *                                                 | *                                           | *                                      | *                                                                                              | *                                                               | *                                                                              | *                                           | 7     |
| Bezzio16     | *                                                 | *                                           | *                                      | *                                                                                              | *                                                               | *                                                                              | *                                           | 7     |
| Bezzio17     | *                                                 | *                                           | *                                      | *                                                                                              | *                                                               | *                                                                              | *                                           | 6     |
| Brenner18    | *                                                 | *                                           | *                                      | *                                                                                              | *                                                               | *                                                                              | *                                           | 7     |
| Garrido19    | *                                                 | *                                           | *                                      | *                                                                                              | *                                                               | *                                                                              | *                                           | 6     |
| Gubatan20    | *                                                 | *                                           | *                                      | *                                                                                              | *                                                               | *                                                                              | *                                           | 8     |
| Guerra21     | *                                                 | *                                           | *                                      | *                                                                                              | *                                                               | *                                                                              | *                                           | 4     |
| Haberman22   | *                                                 | *                                           | *                                      | *                                                                                              | *                                                               | *                                                                              | *                                           | 6     |
| Horman23     | *                                                 | *                                           | *                                      | *                                                                                              | *                                                               | *                                                                              | *                                           | 3     |
| Khan24       | *                                                 | *                                           | *                                      | *                                                                                              | *                                                               | *                                                                              | *                                           | 3     |
| Kornbluth25  | *                                                 | *                                           | *                                      | *                                                                                              | *                                                               | *                                                                              | *                                           | 5     |
| Lukin26      | *                                                 | *                                           | *                                      | *                                                                                              | *                                                               | *                                                                              | *                                           | 9     |
| Marafini27   | *                                                 | *                                           | *                                      | *                                                                                              | *                                                               | *                                                                              | *                                           | 6     |
| Norsa28      | *                                                 | *                                           | *                                      | *                                                                                              | *                                                               | *                                                                              | *                                           | 4     |
| Rodríguez-Lago29 | *                                           | *                                           | *                                      | *                                                                                              | *                                                               | *                                                                              | *                                           | 6     |
| Taxonera30   | *                                                 | *                                           | *                                      | *                                                                                              | *                                                               | *                                                                              | *                                           | 6     |
| Eltabbakh31  | *                                                 | *                                           | *                                      | *                                                                                              | *                                                               | *                                                                              | *                                           | 6     |
| Singh32      | *                                                 | *                                           | *                                      | *                                                                                              | *                                                               | *                                                                              | *                                           | 5     |
| Viganò33     | *                                                 | *                                           | *                                      | *                                                                                              | *                                                               | *                                                                              | *                                           | 1     |
| Waggershauser34 | *                                           | *                                           | *                                      | *                                                                                              | *                                                               | *                                                                              | *                                           | 7     |
ical practices. Third, at the time of the review, there were no randomized trials on medications with our outcomes of interest. Fourth, given that the SECURE-IBD registry aggregates data worldwide, there is a chance of data duplication, which cannot be eliminated. Some estimates may thus be inappropriately strengthened. However, the included studies are reported from a very diverse and heterogenous population from different parts of the world, which may inherently have different disease characteristics and outcomes based on the native population or regional practices. This diversity in study population improves generalizability of our findings.

In conclusion, the prevalence of COVID-19 in IBD patients was low; however, our ability to obtain an accurate denominator for global prevalence is limited due to limitations in available studies and their respective regions. The use of mesalamine was significantly associated with worse outcomes including higher hospitalization rates, ICU admissions, and deaths, though the use of anti-TNFs was associated with favorable hospitalization and mortality outcomes. Although more data are needed to clarify the validity of these differential effects, our findings at least indicate that anti-TNF therapy is not associated with increased risk of adverse outcomes, and in general, patients with IBD should continue their maintenance biologic therapies. No recommendations regarding mesalamine therapies can be made at this time until the significance is better understood. Further investigation clarifying the mechanisms of these disparate observations could help identify risk and adverse outcome-mitigating strategies for patients with IBD.

Supplementary Data
Supplementary data is available at Inflammatory Bowel Diseases online.

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Author Contributions
K.T., A.M.P., and B.N.L. were involved in study concept and design. K.T., G.G.B., M.T.N., Y.S., M.S.I., J.S.S., A.M.P., and B.N.L. participated in title and abstract screening, full-text review, assessment of study eligibility for inclusion, and double data abstraction. K.T. and G.G.B. performed the study quality assessment. K.T. and B.N.L. performed the analyses. K.T. and B.N.L. drafted the original manuscript. All authors critically reviewed the manuscript and approved the final version.

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Conflicts of Interest
No conflicts of interest to disclose.

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