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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; $P < .01$; $I^2 = 0\%$) 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; $P = .13$; $I^2 = 39\%$). 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.[5–7] 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

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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 adult 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 χ^2 and I^2 statistics. An I^2 <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).

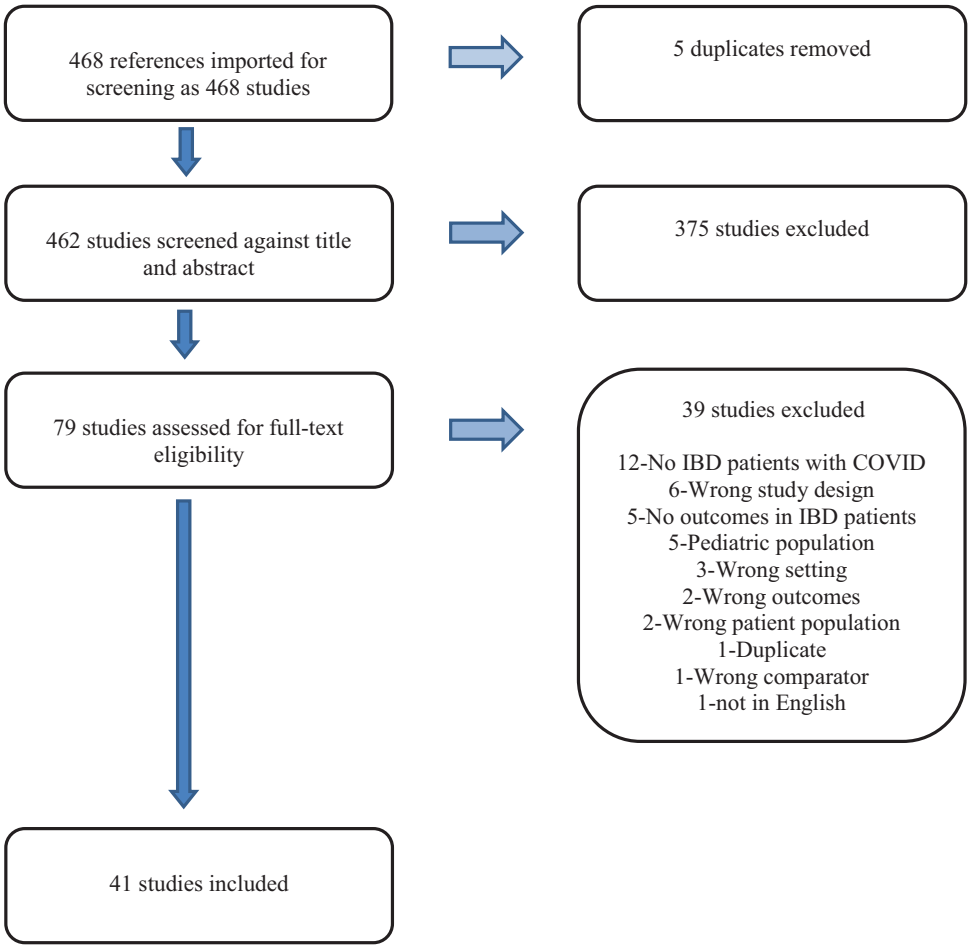

Figure 1. PRIMSA flow chart.

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).[12,15,17–21,26,30,32,33] 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).[12,15,18–20,26,30,31,34] Oral and rectal mesalamine was used in 23.4% of patients, with 44.1% requiring hospitalization, 8.7% ICU admission, and 6.8% deaths. Immunomodulators (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; I^2 = 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; I^2 = 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; I^2 = 3%) and ICU admission (RR, 0.20; 95% CI, 0.07-0.58; P < .01; I^2 = 0%) and similar risk of death (RR, 0.21; 95% CI, 0.04-1.00; P = .05; I^2 = 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; I^2 = 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; I^2 = 0%; Supplementary

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

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: Hospitalization	ICU	Deaths
Allocca[12]	Retrospective cohort study	Italy and France	6000	15	9	6	73.3% (11)	39.1	Renal transplantation, Primary Sclerosing Cholangitis, chronic paranoid psychosis, arthrosis, muscular dystrophia, HTN, obesity, arthritis, ankylosing spondylitis, Mitral Valve Prolapse	NA	Anti-TNF, 8 (53.3%); Ustekinumab, 3 (20.0%); steroids, 2 (13.3%); thiopurines, 2 (13.3%); mesalamine, 1 (6.7%); Vedolizumab, 1 (6.7%); investigational drugs, 1 (6.7%); calcineurin inhibitors, 1 (6.7%)	5 (33.3%)	0	0
Allocca[13]	Prospective case series	Italy	21	21	9	12	NA	NA	NA	NA	NA	NA	NA	NA
Attauabi[14]	Prospective cohort study	Denmark	76	76	31	45	41% (31)	Median UC- 51, CD- 54	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	NA	Represented in ODDS ratio: Topical ASA, 2.13[0.28-16.08] p=0.46, Systemic 5-ASA 11.67 [0.81-167.49 *P* = .07
Axelrad[15]	Case series	United States	83	83	56	27	47% (39)	Median 35	Organ transplantation, kidney disease, pregnancy, current malignancy, HTN, DM, COPD, Asthma	Fever 55(66%), cough 46 (55%), pharyngitis 21 (25%), rhinorrhea 15 (18%), diarrhea 26 (31%), ageusia 18 (22%), anosmia 25 (30%), SOB 21 (25%)	5-ASA 13 (16%), Azathioprine/MCP 2(2%), MTX 4(5%), Prednisone 6 (6%), Budesonide 4 (6%), Vedolizumab 5 (6%), Infliximab 23 (28%), Adalimumab 21(25%), Tofacitinib 4 (5%) Ustekinumab 9 (11%)	6% (5)	1% (1)	1% (1)
Bezzio[16]	Prospective cohort study	Italy	243	11	NA	NA	NA	47.5±15	93 (38%) had at least CAD, HTN, DM, COPD, CKD, IMID	NA	unspecified	2 (0.8%)	NA	NA

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: Hospital-ization	ICU	Deaths
Bezzio[17]	Prospective cohort study	Italy	79	79	32	47	44%(35)	Median 45	None- 49 (62%) 2, Hypertension 9 (11%),Coronary heart disease 5 (6%), COPD 5 (6%), CMV colitis 2 (3%), Hypothyroidism 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%)
Brenner[18]	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)	Sulfasalazine/ 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%)

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: Hospitalization	ICU	Deaths
Garrido[19]	Retrospective cohort study	Portugal	11	11	9	2	54.5% (6)	44.1	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[20]	Retrospective cohort study	United States	168	5	2	3	60% (3)	70.6	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[21]	Cross-sectional observational study	Spain	805	82	42	35	53.7% (44)	46	CKD, COPD, CHF, CHD, Cerebrovascular disease, DM, HTN, dyslipidemia, malignancy, chornic 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[22]	Case series	United States	37	37	20	17	NA	NA	NA	NA	NA	10.8% (4)	0	0
Hormati[23]	Retrospective cohort study	Iran	150	8	NA	NA	NA	NA	NA	fever, cough, sore throat	Unclear exactly the specific tx. because this info is not provided for patients with COVID.	NA	NA	NA
Khan[24]	Retrospective cohort study	United States	37857	36	0	0	NA	60.9 (17.1)	NA	NA	Thiopurine (2), Anti TNF (3)	NA	NA	NA
Kornbluth[25]	Retrospective cohort study	United States	65	65	41	24	NA	39 (17-71)	NA	NA	Adalimumab (11), Infliximab (10), Golimumab (1), AntiTNF and thiopurine (1), Vedolizumab (5), Ustekinumab (9), Upabacitinib RCT (1), Mesalamine/sulfasalazine (5), Antibiotics (2), prednisone 20mg and MTX (1), Prednisone 10mg (1), No medications (5)	4.6% (3)	3% (2)	0

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: Hospitalization	ICU	Deaths
Lukin[26]	Case control	United States	119	29	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, dyspnea, anosmia, and diarrhea	TNF alpha antagonist (16), vedolizumab (10), ustekinumab (12), Tofacitinib (1), vedolizumab + Tofacitinib (1), trial drug (1), Thiopurines (4), methotrexate (3), combination (4), aminosalicilates (20), steroid (13)	NA	NA	NA
Marafini[27]	Retrospective cohort study	Italy	672	3	NA	NA	NA	NA	NA	NA	NA	66.7% (2)	NA	33.3% (1)
Norsa[28]	Retrospective cohort study	Italy	103	19	14	5	68.4% (13)	Median 50.0 (28-57)	NA	Fever (7), Cough (3), Dysgeusia/ Anosmia (5)	Adalimumab (10), infliximab (5), Vedolizumab (1), Ustekinumab (3)	NA	NA	NA
Rodríguez-Lago[29]	Retrospective cohort study	Spain	40	40	13	23	40% (16)	59 (48-68)	CKD, chronic pulmonary disease, CHF, CAD, DM, cerebrovascular disease, hypertension, dementia, neoplasia	Fever (77%), cough (67%, diarrhea (21%)	Infliximab (2), Adalimumab (1), Vedolizumab (1), Ustekinumab (3), mesalamine (26), systemic steroids (4), thiopurines (8), methotrexate (3), thiopurine + anti-TNF (1), thiopurine + ustekinumab (1	53% (21)	0	5% (2)
Taxonera[30]	Case series	Spain	1918	12	7	5	75% (9)	52.3	Hypertension (3), diabetes (2), Chronic liver disease (2), CKD (1), cardiovascular disease (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)
Eltabbakh[31]	Case series	Egypt	11	2	0	2	100% (2)	38	NA	fever, dry cough, generalized fatigue	None	100% (2)	0	0

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: Hospitalization	ICU	Deaths
Singh[32]	Retrospective cohort study	United States	1901	232	101	93	63.4 (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[33]	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/ mtx (8), high dose systemic corticoids (2), anti TNF (8), Vedolizumab (1), Ustekinumab (1)	NA	NA	NA
Waggershauser[34]	Prospective cohort study	Germany	55	5	0	0	NA	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
Abdullah[35]	Case report	Germany	1	1	0	1	Female	18	NA	dry cough	Y - infliximab	N	N	N
Bezzio[36]	Case report	Italy	1	1	0	1	Male	36	NA	12 bowel movements with blood on presentation.	Topical and oral Mesalazine	Y	N	Pt improved with infliximab for 7 days
DiRuscio[37]	Case report	Italy	1	1	0	1	Female	60	NA	Fever, dry cough, dyspnea	Patient was treatment with corticosteroids for active flare	Patient was hospitalized initially for UC flare, but was found to be COVID+ while hospitalized	Yes, d/t septic shock from central venous catheterNArelated infection	N

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: Hospitalization	ICU	Deaths
Dimopoulos[38]	Case report	United States	1	1	1	0	Male	24	NA	Asymptomatic	Y - adalimumab (ADA) and ustekinumab (UST) combination therapy	N	N	N
Garcia[39]	Case report	Brazil	1	1	0	1	Female	33	PSC	Abdominal pain and diarrhea	sulfasalazine, topical mesalamine, corticosteroids for flare	Y	N	N
Gutin[40]	Case report	United States	1	1	0	1	Male	40	NA	Fever, mild cough	mesalamine (azathioprine was held)	N	N	N
Jacobs[41]	Case report	United States	1	1	0	1	Female	33	NA	fever, chills, cough, myalgias, sore throat, fatigue, night sweats	Tofacitinib	N	N	N
Kunisaki[42]	Case report	Japan	1	1	0	1	Male	60	NA	High fever	Infliximab, azathioprine, mesalamine	N	N	N
Lenti[43]	Case report	Italy	1	1	1	0	Male	25	NA	Dry cough, mild fever, elevated creatinine, hypoalbuminemia and hypercholesterolemia (acute kidney injury/nephrotic syndrome)	adalimumab	Y	0	0
Mansoor[44]	Case report	United States	1	1	1	0	Male	60	Hypertension	Diarrhea, cough, abdominal pain and weakness	AZA	Y	N	N
Mayer[45]	Case report	France	1	1	0	1	Female	20	Multidrug resistant miliary tuberculosis	UC pancolitis flare	No	Y	N	N
Mazza[46]	Case report	Italy	1	1	0	1	Female	80	NA	High fever, dry cough	Mesalamine	Y	Y	Y
Navaneethan[47]	Case report	United States	1	1	1	0	Female	43	Bronchial asthma, congenital heart disease	cough, nonbloody diarrhea, SOB, fever, fatigue	Ustekinumab, 6MP	Y	N	N
Okeke[48]	Case report	United States	1	1	1	0	Female	60	Rheumatoid arthritis, SLE	Fever, generalized myalgias, fatigue, nonbloody diarrhea, vomiting, abdominal cramping	Adalimumab, methotrexate	Y	N	N

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: Hospital-ization	ICU	Deaths
Rosen[49]	Case report	United States	1	1	0	1	Female	26	Pregnancy	Diarrhea, hematochezia, abdominal pain. Developed pleuritic chest pain 5 days after	None	Y	N	N
Tursi[50]	Case report	Italy	1	1	1	0	0	30	NA	High fever, chest pain during breaths	mesalamine 3g/day, adalimumab 40mg sc	Y	N.	N
Tursi[51]	Case reports	Italy	2	1	1	1	One male and one female	Median age of 55	NA	NA	Adalimumab (1)	100% (2)	50% (1)	50% (1)
Wolf[52]	Case report	United States	1	1	1	0	0	85	NA	Diarrhea, cough	N	N	N	N

Abbreviations: NA, data not available; HTN, Hypertension; MTX, Methotrexate; MCP, 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.

Table 2. COVID-19 prevalence of IBD patients.

Study author	Total No. IBD Patients in the Study (IBD population n)	IBD Patients With COVID 19 (%)
Allocca[12]	6000	15 (0.25%)
Bezzio[16]	243	11 (4.5%)
Gubatan[20]	168	5 (2.9%)
Guerra[21]	805	82 (10.1%)
Hormati[23]	150	8 (5.3%)
Khan[24]	37857	36 (0.1%)
Lukin[26]	119	29 (24.3%)
Marafini[27]	672	3 (0.45%)
Norsa[28]	103	19 (18.4%)
Taxonera[30]	1918	12 (0.6%)
Eltabbakh[31]	11	2 (18.1%)
Singh[32]	1901	232 (12.2%)
Viganò[33]	704	53 (7.5%)
Waggershauser[34]	55	5 (9.1%)
Total	50,706	512 (1.0%)

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 heterogenous from different parts of the world. All included studies were retrospective and were similar in methodologies.

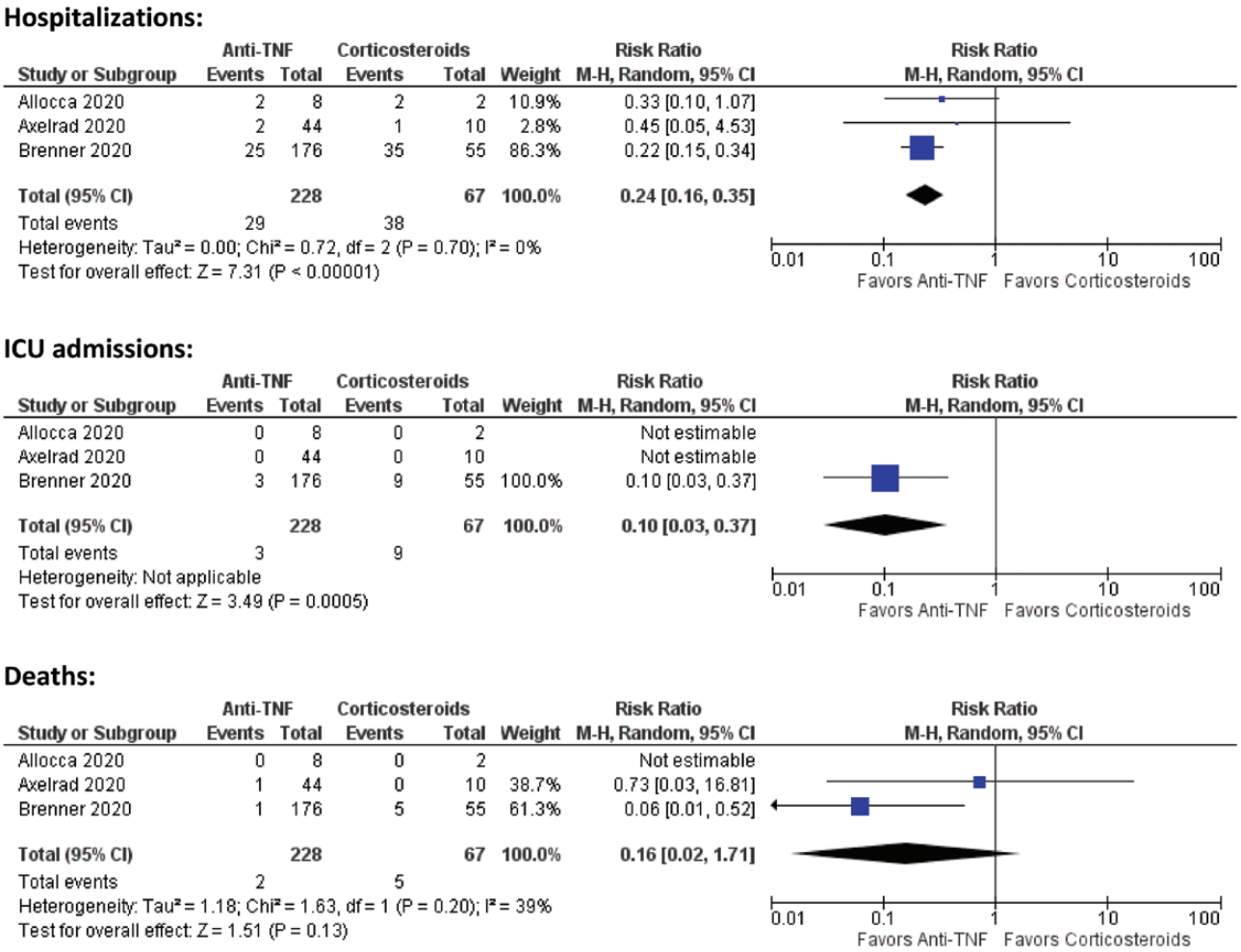

Figure 2. Outcomes in IBD patients on corticosteroids when compared with those on anti-TNF therapy.

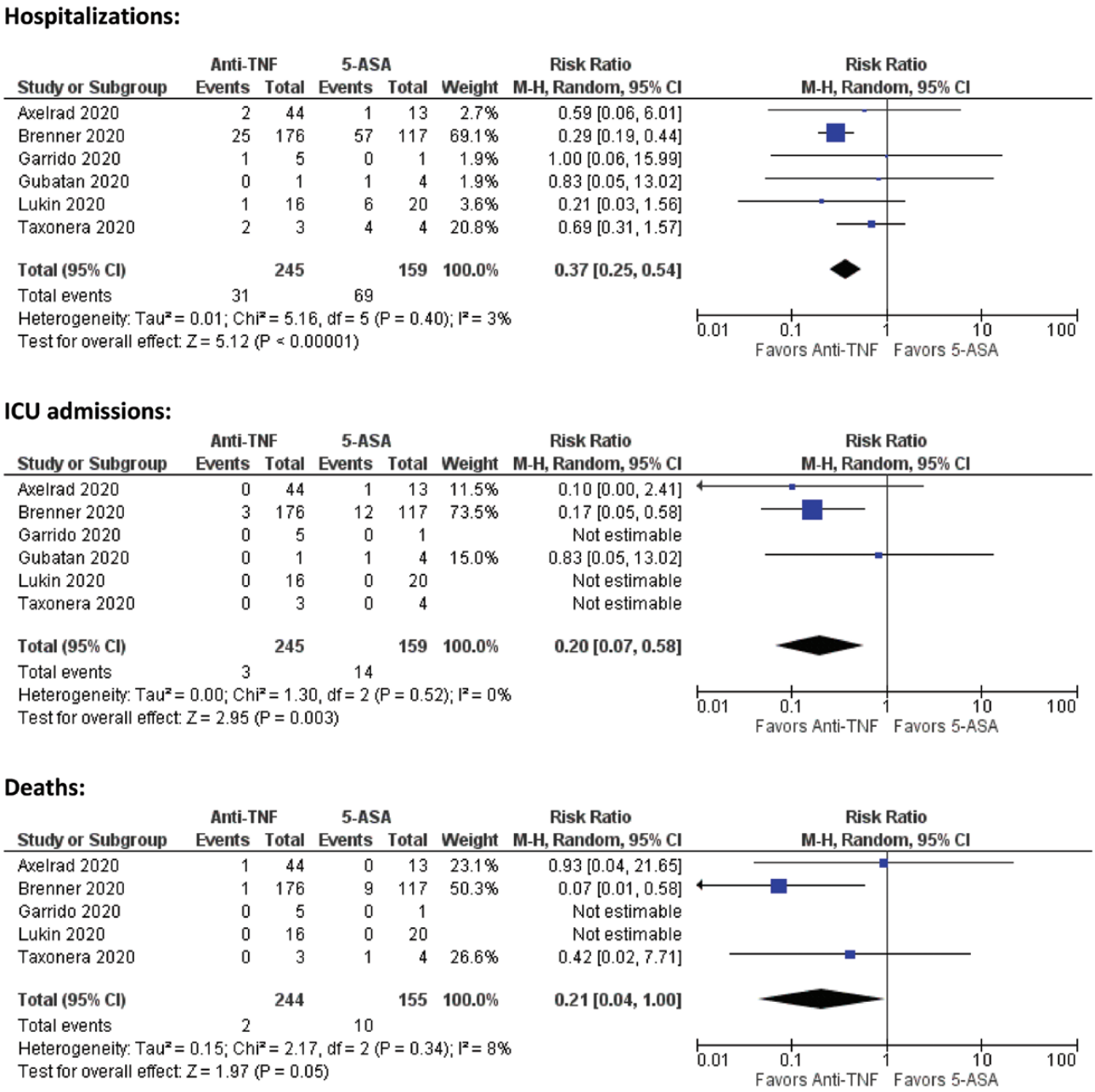

Figure 3. Outcomes in IBD patients on mesalamine when compared with those on anti-TNFs.

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.[20,26] There were 4 studies with moderate quality that scored 7 points; of these, 3 were included.[15,18,34] There were 9 studies with low quality that scored 6 points; of these, 4 were included in the analyses.[12,19,30,31] Studies scoring 5 and lower were not included due to lack of outcome of interest (Table 3).

Discussion

This systematic review aimed to investigate the epidemiology and outcomes of COVID-19 among IBD patients. Across studies that provided data on patients with and without COVID-19, the pooled infection prevalence was 1%. The prevalence is variable depending on a given time point, but to provide context, varied from 0.4% to 0.7% in earlier studies.[53,54] 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.[55] With this anecdotal evidence from the SECURE-IBD registry, Feldman et al proposed to use anti-

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	Outcome (2) Was Follow-up Long Enough for Outcome to Occur	Outcome (3) Adequacy of Follow-up Cohorts	Score
Allocca[12]	*		*	*		*	*	*	6
Allocca[13]	*		*	*					3
Attauabi[14]	*		*	*		*	*	*	6
Axelrad[15]	*		*	*	*	*	*	*	7
Bezzio[16]	*	*	*	*		*	*	*	7
Bezzio[17]	*		*	*		*	*	*	6
Brenner[18]	*		*	*	*	*	*	*	7
Garrido[19]	*		*	*		*	*	*	6
Gubatan[20]	*	*	*	*	*	*	*	*	8
Guerra[21]	*		*	*				*	4
Haberman[22]	*		*	*		*	*	*	6
Hormati[23]	*		*			*			3
Khan[24]	*	*	*						3
Kornbluth[25]	*		*			*	*	*	5
Lukin[26]	*	*	*	*	**	*	*	*	9
Marafini[27]	*		*	*		*	*	*	6
Norsa[28]	*	*	*	*					4
Rodríguez-Lago[29]	*		*	*		*	*	*	6
Taxonera[30]	*		*	*		*	*	*	6
Eltabbakh[31]	*		*	*		*	*	*	6
Singh[32]	*	*	*	*	*				5
Viganò[33]	*								1
Waggershauser[34]	*	*	*	*		*	*	*	7

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-y) 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-

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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