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Impact of medical therapies for inflammatory bowel disease on the severity of COVID-19: a systematic review and meta-analysis

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ABSTRACT

Background During COVID-19 pandemic, the safety of medical therapies for inflammatory bowel disease (IBD) in relation to COVID-19 has emerged as an area of concern. This study aimed to evaluate the association between IBD therapies and severe COVID-19 outcomes.

Method We performed a systematic review and metaanalysis of all published studies from December 2019 to August 2021 to identify studies that reported severe COVID-19 outcomes in patients on current IBD therapies including 5-aminosalicylic acid (5-ASA), immunomodulators, corticosteroids, biologics, combination therapy, or tofacitinib. Results Twenty-two studies were identified. Corticosteroids (risk ratio (RR) 1.91 (95% CI 1.25 to 2.91, p=0.003)) and 5-ASA (RR 1.50 (95% Cl 1.17 to 1.93, p=0.001)) were associated with increased risk of severe COVID-19 outcomes in patients with IBD patients. However, possible confounders for 5-ASA use were not controlled for. Sub-analysis showed that corticosteroids increased the risk of intensive care unit (ICU) admission but not mortality. Immunomodulators alone (RR 1.18 (95% CI 0.87 to 1.59, p=0.28)) or in combination with anti-TNFs ((RR 0.96 (95% CI 0.80 to 1.15, p=0.63)), tofacitinib (RR 0.81 (95% Cl 0.49 to 1.33, p=0.40)) and vedolizumab ((RR 1.02 (95% Cl 0.79 to 1.31, p=0.89)) were not associated with severe disease. Anti-TNFs (RR 0.47 (95% CI 0.40 to 0.54, p<0.00001)) and ustekinumab (RR 0.55 (95% CI 0.43 to 0.72, p<0.00001)) were associated with decreased risk of severe COVID-19.

Conclusion In patients with IBD, the risk of severe COVID-19 is higher among patients receiving corticosteroids. Corticosteroid use was associated with ICU admission but not mortality. The risk is also higher among patients receiving 5-ASAs. However, patientlevel data were lacking and insufficient data existed for meta-regression analyses to adjust for confounding. Vedolizumab, tofacitinib, and immunomodulators alone or in combination with anti-TNF were not associated with severe disease. Anti-TNFs, and ustekinumab were associated with favourable outcomes.

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in Wuhan, China in December 2019 and shortly after, it evolved into a global pandemic.^{1 2'} SARS-CoV-2 is primarily transmitted through air droplets and aerosols. Airborne transmission is also a likely source of transmission.² A significant number of patients develop severe respiratory symptoms requiring hospitalisation, intensive care admission, and death. In addition, vulnerable groups include elderly individuals, those with active malignancy and cardiopulmonary diseases, and immunocompromised individuals.^{3 4} While gastrointestinal (GI) manifestations of COVID-19 are also common, they are not associated with increased intensive care unit (ICU) admissions or mortality.⁵ Furthermore, a recent study found that while GI symptoms are common in patients with IBD with COVID-19, they are not associated with an increased risk of death due to COVID-19.6

SARS-CoV-2 enters human cells by binding to ACE2 and other receptors.⁷ Intestinal ACE2 is involved in the uptake of dietary amino acids, regulating the expression of antimicrobial peptides and promoting the homeostasis of the gut microbiome.⁷ Inflammatory bowel disease (IBD) is a chronic inflammatory condition of the gastrointestinal tract. Despite the use of gastrointestinal tract. Despite the use of gastrointestinal ACE2 receptors by SARS-CoV-2 to infect individuals, current data show patients with IBD were not at higher risk for COVID-19 infection.⁸

Patients with IBD often require longterm maintenance medical therapy such as 5-aminosalicylic acid (5-ASA), immunomodulators, janus kinase (JAK) inhibitors, biologic therapies, or corticosteroids.⁸ The effect of these medications on COVID-19 outcome is not fully understood. The Epidemiology of Coronavirus Under Research Exclusion (SECURE-IBD)⁹ database is an international registry that was established at the beginning of the COVID-19 pandemic, for reporting outcomes of COVID-19 in patients with IBD. To date, it includes outcomes of more than 6000 patients with IBD with COVID-19 infection from 72 countries worldwide. In addition, multiple studies have been performed to evaluate the safety of IBD medications during COVID-19 pandemic with conflicting data.^{6 10 11} Due to the rapidity of emerging data, up-to-date summary data are lacking. To our knowledge, there was no previous systematic review that looked at individual biologic therapy and risk of severe COVID-19. Moreover, this is the first and largest systematic review to include anti-TNF combination therapy and janus kinase inhibitors.

METHODS

This systematic review and meta-analysis were conducted using the methods described in the Cochrane Handbook of Systematic Reviews and reported according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement.¹² MOOSE guidelines were also followed.¹³

Eligibility criteria

Randomised, placebo-controlled, or active comparatorcontrolled trials, cohort studies, observational studies, and editorial were included. Furthermore, Surveillance Epidemiology of Coronavirus Under Research Exclusion (SECURE-IBD) data were included. Adult patients (age ≥ 18 years) with IBD and confirmed SARS-CoV-2 infection were included. Specifically, we included any study that reported hospitalisation, ICU admission or mortality data in patients with IBD infected with SARS-CoV-2, and IBD medical therapy taken at the time of the study. Our study analysed outcomes stratified by pharmacological treatments alone or in combination with other agents. We excluded case series, and case reports and any studies that did not have relevant outcome data. In addition, to avoid duplication, any study that reported data from the SECURE-IBD database was excluded. Finally, we also excluded studies that included paediatric patients only (age <18 years).

Definitions and outcome measures

The primary outcome measure was the risk of severe COVID-19 in patients taking IBD medications. For the purpose of this study, we defined severe COVID-19 as infection resulting in hospitalisation, ICU admission, or mortality. Mortality was defined as the number of patients who died within the study observation period. In addition, we performed a sub-analysis by exploring the risk of ICU admission and mortality separately with the use of specific IBD medications. Data on current use of IBD medications were extracted for 5-ASA, immunomodulators (thiopurines and methotrexate), calcineurin inhibitors, steroids, biological agents (tumour necrosis factor antagonists (anti-TNF), vedolizumab, ustekinumab), or janus kinase (JAK) inhibitors (tofacitinib). We looked at the association of severe COVID-19 and individual biologic agents when available. If data on individual biologic agent were not available, we grouped tumour necrosis factor antagonists (anti-TNF), vedolizumab, and ustekinumab under biologic agents, whereas methotrexate and thiopurines were grouped under immunomodulators. Data on concurrent use of anti-TNF agents and an immunomodulator (combination therapy) were also extracted.

Search strategy and data extraction

Literature searches were conducted by two authors (FA and IA) using MEDLINE, Embase, Scopus, and Cochrane Central Register of Controlled Trials databases from 1 December 2019 to 10 August 2021, using predefined strategies (online supplemental table 1). Our search strategies were designed with the help of a librarian. The search was restricted to English-language publications involving humans. English conference proceedings were searched (World Congress of Gastroenterology, American College of Gastroenterology, Canadian Digestive Disease Week, Digestive Disease Week, European Crohn's and Colitis Organization congress, and United European Gastroenterology Week). Furthermore, clinical trials databases (www.clinicaltrials.gov and International Randomized Standard Clinical Trial (IRSCT) Register) were searched. Google Scholar was also searched for unindexed studies. In addition, SECURE-IBD database was searched for relevant data. The bibliographies of included studies and reviews were searched for additional eligible studies. Systematic reviews were also reviewed for relevant studies. The search terms used are outlined in online supplemental material.

Data extraction and quality control were done independently by two reviewers (FA and IA). Discrepancies were resolved on discussion with a third reviewer (MS). The same two authors extracted information from the studies. Extracted information included baseline characteristics, type of IBD (ulcerative colitis vs Crohn's disease), study design, country of publication, risk of bias, IBD medications, and outcomes using standardised Excel spreadsheet.

Risk of bias and study quality

To assess risk of bias and quality of the included studies, two authors (MS and FA) independently used the Cochrane risk of bias tool for randomised controlled trial (RoB 2)¹⁴ and ROBINS-I for assessing risk of bias in non-randomised studies of interventions.¹⁵ By using these assessment tools, studies were classified as being of unclear or low or high risk of bias. Seven domains random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other potential sources of bias are included in this tool.

The quality of all included studies was assessed using the modified Newcastle-Ottawa Scale (mNOS).¹⁶ Three

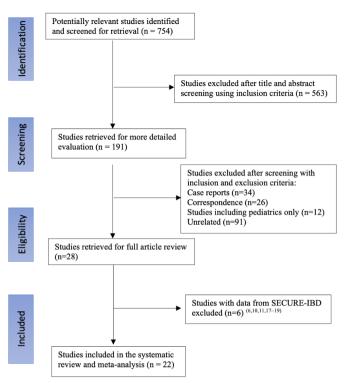


Figure 1 PRISMA flow chart outlining the search process for selecting the studies included in this systematic review with meta-analysis.

domains were assessed by using mNOS: selection, compatibility, and outcome. Study quality was defined as low (score of 0–3), moderate (score of 4–6), and high (score of 7 and 8).

Statistical analysis

The risk ratio (RR) was calculated to compare outcomes in patients taking specific IBD medications to those who were not receiving those medications at the time of the study. Statistical analysis was conducted using Review Manager (RevMan) V.5.3.5 (The Cochrane Collaboration). Prevalence and 95% CI were estimated using random-effects models assuming between and within study variability. I² statistic, which ranges from 0% to 100%, was used to quantify the relative amount of observed heterogeneity. An I² value less than 30% indicates low heterogeneity, whereas a range of 30%–75% indicates moderate heterogeneity and high heterogeneity was defined as I²>75%.

RESULTS Search results

From the initial 754 studies identified in the search, 22 studies met criteria for inclusion (figure 1). This also includes the data extracted from the SECURE-IBD database. All included studies were observational, except for one study that was a randomised controlled trial. Six studies were conducted in Italy and the USA, three were done in the UK, and the rest were done in multiple countries including France, Spain, and Denmark. Table 1

provides details of the included studies and patients' demographics. To avoid duplication of the same population, six studies were excluded as these studies reported data from SECURE-IBD only.^{6 10 11 17-19} In total, 10391 patients with IBD and confirmed COVID-19 diagnosis were included in the main analysis. Mean age was 48.7 (\pm 11.7) and 3864 (36%) were male. Among these patients, 4284 (30.5%) had ulcerative colitis, 5217 (48.6%) had Crohn's disease, and the remainder did not specify IBD type.

Primary outcome

When comparing patients with IBD infected with SARS CoV-2 receiving corticosteroids with patients who did not receive corticosteroids, the analysis showed significantly higher risk of severe COVID-19 with a RR of 1.91 (95% CI 1.25 to 2.91, p=0.003). Patients receiving 5-ASA had increased risk of severe COVID-19 compared with those not receiving 5-ASA (RR 1.50 (95% CI 1.17 to 1.93, p=0.001)). Whereas immunomodulators alone (RR 1.18 (95% CI 0.87 to 1.59, p=0.28)) or in combination with anti-TNFs ((RR 0.96 (95% CI 0.80 to 1.15, p=0.63)), were not associated with severe outcomes. Similarly, in patients using adalimumab ((RR 0.94 (95% CI 0.31 to 2.92, p=0.92)), infliximab ((RR 0.78 (95% CI 0.39 to 1.58, p=0.49)), vedolizumab ((RR 1.02 (95% CI 0.79 to 1.30, p=0.90)), or tofacitinib (RR 0.81 (95% CI 0.49 to 1.33, p=0.40)), no significant association was observed between their use and severe outcomes. Interestingly, the use of biologics (RR 0.45 (95% CI 0.40 to 0.50, p<0.00001)) was associated with favourable outcomes. Specifically, anti-TNFs (RR 0.47 (95% CI 0.40 to 0.54, p<0.00001)) and ustekinumab (RR 0.55 (95% CI 0.43 to 0.72, p<0.00001) were associated with significantly lower risk of severe COVID-19 (figure 2).

Sub-analyses

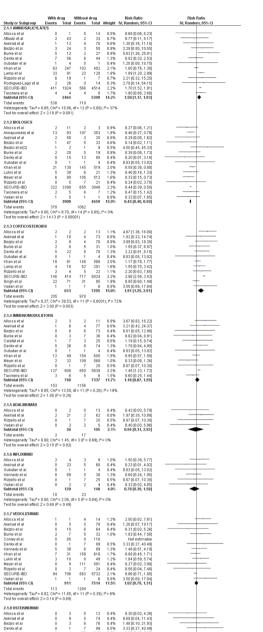
ICU admissions

The number of patients in the sub-analyses was different among the drug groups. The number of patients included in this sub-analysis who were receiving 5-ASA was 2015, whereas the numbers of patients receiving corticosteroids and immunomodulators were 435 and 681, respectively. The total number of patients receiving biologic therapies was 3686. Specifically, 2365 patients were taking anti-TNF monotherapy; 28 patients were taking infliximab. Finally, the numbers of patients receiving vedolizumab and ustekinumab included in this sub-analysis were 731 and 610, respectively. The risk of ICU admission was significantly higher in patients with IBD taking corticosteroids compared with patients who did not (RR 2.38 (95% CI 1.17 to 4.84, p=0.02; $I^2=50\%$)). The risk was also higher in patients taking 5-ASA (RR 1.91 (95% CI 1.50 to 2.43, p<0.00001; $I^2=0\%$)). Conversely, the use of biologics (RR 0.38 (95%) CI 0.29 to 0.48, p<0.00001; $I^2=0\%$) was associated with lower risk of ICU admission. Specifically, anti-TNFs (RR 0.32 (95% CI 0.23 to 0.45, p<0.00001; $I^2=0\%$)) and ustekinumab (RR 0.53 (95% CI 0.28 to 0.99, p=0.05; $I^2=0\%$))

Table 1 Summar	Summary of included studies and patients' characteristics	es and patients'	characteristics						
Study	Total number of patients with IBD+COVID-19 (n)	Study Design	Country	Mean age	Male sex (n)	Ulcerative colitis (n)	Crohn's disease (n)	IBD undetermined	IBD drug
Allocca <i>et al</i>	15	Observational	France and Italy	68	4	თ	ω	NA	Corticosteroids, tacrolimus, everolimus, infliximab, vedolizumab, ustekinumab, adalimumab, mesalamine, azathioprine
Annapureddy <i>et al</i>	464	Observational	USA	48	26	Not specified	Not Specified	NA	Biologics
Attauabi <i>et al</i>	76	Observational	Denmark	52.5	45	45	31	NA	5-ASA, topical steroids
Axerirad et al	83	Observational	USA	35	44	27	56	NA	Corticosteroids methofrexate, infliximab, vedolizumab, ustekinumab, adalimumab, mesalamine, azathioprine
Bezzio et al	26	Observational	Italy	45	44	47	32	ИА	Corticosteroids methofrexate, infliximab, vedolizumab, ustekinumab, adalimumab, mesalamine, azathioprine
Bezzio et al ²	24	Observational	Italy	45.9	79	Not specified	Not specified	NA	Biologics
Burke <i>et al</i>	39	Observational	USA	45.5	15	21	0	NA	Corticosteroids, biologics, aminosalicylates, immunomodulators, tofacitinib
Calafat <i>et al</i>	418	Observational	Spain	73	218	290	117	11	Immunomodulators
Conley <i>et al</i>	203	Observational	UK	42	65	98	105	NA	Corticosteroids, biologics, immunomodulators
Derikx <i>et al</i>	100	Observational	Netherlands	62.5	46	59	36	NA	Corticosteroids, biologics, 5-ASA, immunomodulators, tofacitinib
Gubatan <i>et al</i>	ى	Observational	USA – California	70.6	N	ო	N	0	Corticosteroid, 5-ASA, 6MP/ azathiprine, methotrexate, vedolizumab, ustekinumab, tofacitinib, anti-TNF
Kennedy <i>et al</i>	590	Observational	UK	Not specified	Not specified	Not specified	Not specified	NA	Infliximab, vedolizumab
Khan <i>et al</i>	649	Observational	NSA	65	Not specified	Not specified	Not specified	NA	5-ASA, prednisolone, thiopurine, biologics
Lamp <i>et al</i>	211	Observational	UK	59.5	116	109	86	16	5-ASA, prednisolone, thiopurine, biologics
Lukin <i>et al</i>	8	Observational	USANew York	48.3	45	26	38	Ą	Biologics (anti-TNF, vedolizumab, ustekinumab), non biologics (tofacitinib), dual (vedolizumab +tofacitinib), 6MP, azathioprine, methotrexate, corticosteroids, 5-ASA
									Continued

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Total									
of pa Study IBD+	Total number of patients with IBD+COVID-19 (n) Study Design	Study Design	Country	Mean age	Male sex (n)	Ulcerative colitis (n)	Crohn's disease (n)	IBD undetermined IBD drug	IBD drug
Meyer <i>et al</i> 600		Observational	France	50	Not specified	Not specified	Not specified	AN	Biologics, immunomodulators
Rizzello et al 26	(0	Observational	Italy	Not specified	Not specified	1	15	NA	Biologics and 5-ASA
Rodríguez-Lago 40 et al	6	Observational	Spain	59	24	23	13	4	5-ASA
SECURE-IBD 6438		Database	Multiple countries Not spe	is Not specified	2699	2597	3539	AA	Corticosteroids methofrexate, infliximab, vedolizumab, ustekinumab, adalimumab, 5- ASA, azathioprine, tofacitnib
Singh <i>et al</i> 232	~	Observational	NSA	51.2	85	93	101	38	Corticosteroids
Taxonera et al 12	0	Observational	Spain	52	ო	ъ	7	NA	Biologics, 5-ASA, immunomodulators
Vadan et al 7	2	Observational	Italy	44.5	ß	4	ę	AN	Corticosteroids, biologics, immunomodulators



2.1.1 AMINOSALIC Allocca et al Attauti et al Axeirad et al Bezzio et al Burke et al Derrike et al Gubatan et al Lamp et al Rizzelio et al Rodriguez-Lago et SECURE-IBD Taxonera et al Subtrata (95% CU Hebrogeneity, Tau Test for overall effe

Test for overall effect: 2.1.2 BUOLOGICS Allocca et al Annapuredly et al Annapuredly et al Bezzio et al Meyer et al Rizzello et al SECUFE-IBD Total events Hederogeneity, Tau⁺e Test for overall effect.

Test for overall effect Z = 1 2.1.3 CORTICOSTERNIDS Allocca et al Avetra det al Burke et al Denko et al Denko et al Cubatan et al Lamp et al Burke et al Singh et al Vadan et al Statiotal (95% C) Total events

 Subtotal (95% CI)

 Total events
 205

 Heterogeneity: Tau² = 0.27; Chi²

 Test for overall effect Z = 3.00 (P

DULATORS

Test for overall effect 2.1.4 MMUNOMOL Allocca et al Austrad et al Burske et al Calafat et al Deriko et al Gubatan et al Mayer et al Rizzello et al SECURF.eIDD Taxonera et al Statiotal (9% C) Total events Heterogenenky: Tau"

2.1.5 ADALIM Allocca et al Axeirad et al Rizzello et al

Test for overall effec 2.1.6 INFLIXIMAB Allocca et al Avaelrad et al Gubatan et al Kennedy et al Nizzello et al Vadan et al Subtotal (95% CI) Total events Heterogeneity: Tau²: Test for overall effect

Vadan et al 0 Vadan et al 0 Subtotal (95% CI) Total events 2 Heterogeneity: Tau^a = 0.00; Chi^a : Test for overall effect. Z = 0.10 (P

153 Chi#:

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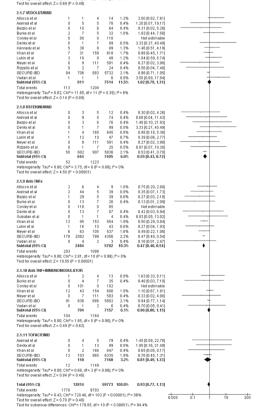


Figure 2 Forest plot showing the risk of severe COVID-19 in patients taking 5-ASA, immunomodulators, steroids, tofacitinib, and biological agents.

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	with dr Events		without Events		Weight	Risk Ratio IV, Random, 95% Cl	Risk Ratio IV, Random, 95% Cl
.1.1 AMINOSALICYLAT	res						
diocca et al	0	1	0	14		Not estimable	
xelrad et al	0	13	0	70		Not estimable	
Burke et al	5	12	2 0	27	2.6% 1.3%	5.63 [1.26, 25.01] 1.20 [0.08, 18.75]	
∋ubatan et al .amp et al	1 33	4 91	23	1 120	4.1%	1.20 [0.08, 18.75] 1.89 [1.20, 2.99]	
ECURE-IBD	33 79	1894	100	4434	4.1%	1.85 [1.38, 2.47]	+
Subtotal (95% CI)	75	2015	100	4666	12.3%	1.91 [1.50, 2.43]	•
otal events	118		125				-
Heterogeneity: Tau ² = 0 Test for overall effect: Z				= 0.54);	I= 0%		
.1.2 BIOLOGICS	(,				
diocca et al	0	11	0	3		Not estimable	
Annapureddy et al	5	93	52	353	3.5%	0.36 [0.15, 0.89]	
Axeirad et al	3	58	4	25	2.7%	0.32 [0.08, 1.34]	
Bossa et al	1	32	0	0		Not estimable	
Burke et al	2	20	5	19	2.5%	0.38 [0.08, 1.73]	
Bubatan et al	0	1 49	1 49	4 162	1.3% 3.8%	0.83 [0.05, 13.02] 0.47 [0.23, 0.97]	
_amp et al viever et al	6	49	105	512	3.7%	0.33 [0.15, 0.73]	
SECURE-IBD	52	3334	127	2994	4.3%	0.37 [0.27, 0.51]	-
Subtotal (95% CI)	52	3686	121	4072	21.7%	0.38 [0.29, 0.48]	•
otal events	76		343				•
leterogeneity: Tau ² = 0				= 0.99);	I ² = 0%		
est for overall effect: Z		P < 0.00	001)				
1.1.3 CORTICOSTEROIE		2		40		higttime - / '	
Niocca et al Axeirad et al	0	2 10	0	12 73	1.0%	Not estimable 2.24 (0.10, 51.67)	
Burke et al	2	8	5	31	2.6%	2.24 [0.10, 51.67]	
Subatan et al	Ó	1	1	4	2.0%	0.83 [0.05, 13.02]	
_amp et al	4	10	52	201	3.7%	1.55 [0.70, 3.42]	
BECURE-IBD	41	404	138	5924	4.3%	4.36 [3.12, 6.08]	
Subtotal (95% CI)		435		6245	12.9%	2.38 [1.17, 4.84]	•
Fotal events	47		197				
Heterogeneity: Tau² = 0 Fest for overall effect: Z			df = 4 (P	= 0.09);	I²= 50%		
.1.4 IMMUNOMODULA							
Viocca et al	0	3	0	11		Not estimable	
velrad et al	0	6	1	77	1.1%	3.71 [0.17, 82.93]	
Burke et al	0	3	7	36	1.3%	0.62 [0.04, 8.91]	
Calafat et al	1	7	3	25	1.8%	1.19 [0.15, 9.74]	
Gubatan et al	0	1	1	4	1.3%	0.83 [0.05, 13.02]	
_amp et al	4	34	52	177	3.4%	0.40 [0.16, 1.03]	
	2	32	109	568	2.8%	0.33 [0.08, 1.26]	
Meyer et al SECURE-IBD	27	589	152	5739	4.2%	1.73 [1.16, 2.58]	
BECURE-IBD Taxonera et al					4.2% 1.1%	1.73 [1.16, 2.58] 3.00 [0.15, 61.74]	
BECURE-IBD Taxonera et al Subtotal (95% CI)	27	589 6	152 0	5739 6	4.2%	1.73 [1.16, 2.58]	
SECURE-IBD Taxonera et al Subtotal (95% CI) Total events Heterogeneity: Tau* = 0.	27 1 35 .40; Chiª	589 6 681 = 13.02	152 0 325 1, df = 7 (F	5739 6 6643	4.2% 1.1% 17.0 %	1.73 [1.16, 2.58] 3.00 [0.15, 61.74] 0.89 [0.43, 1.86]	
SECURE-IBD	27 1 35 .40; Chiª	589 6 681 = 13.02	152 0 325 1, df = 7 (F	5739 6 6643	4.2% 1.1% 17.0 %	1.73 [1.16, 2.58] 3.00 [0.15, 61.74] 0.89 [0.43, 1.86]	•
SECURE-IBD Taxonera et al Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0 Test for overall effect: Z 1.1.5 INFLIXIMAB	27 1 35 .40; Chi ^a = 0.30 (F	589 6 81 = 13.02 P = 0.76	152 0 325 2, df = 7 (F	5739 6643 9 = 0.07	4.2% 1.1% 17.0 %	1.73 [1.16, 2.58] 3.00 [0.15, 61.74] 0.89 [0.43, 1.86]	-
BECURE-IBD Taxonera et al Subtotal (95% CI) Total events Heterogeneity: Tau ^a = 0. Test for overall effect: Z 1.1.5 INFLIXIMAB Allocca et al	27 1 35 .40; Chl ^a = 0.30 (f	589 6 81 = 13.02 P = 0.76	152 0 325 2, df = 7 (F	5739 6643 P = 0.07 9	4.2% 1.1% 17.0 %); I [*] = 469	1.73 [1.16, 2.58] 3.00 [0.15, 61.74] 0.89 [0.43, 1.86]	
SECURE-IBD Taxonera et al Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0. Test for overall effect: Z: 1.1.5 INFLIXIMAB Allocca et al	27 1 .40; Chl ^a = 0.30 (F 0 0	589 6 81 = 13.02 P = 0.76 4 23	152 0 325 2, df = 7 (F 0 1	5739 6643 P = 0.07 9 60	4.2% 1.1% 17.0 %); I* = 469 1.0%	1.73 [1.16, 2.58] 3.00 [0.15, 61.74] 0.89 [0.43, 1.86] 6 Not estimable 0.85 [0.04, 20.08]	
SECURE-IBD Taxonera et al Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0 Test for overall effect: Z 1.1.5 INFLIXIMAB Allocca et al Axelrad et al Gubatan et al	27 1 35 .40; Chl ^a = 0.30 (f	589 6 81 9 = 0.76 4 23 1	152 0 325 2, df = 7 (F	5739 6643 9 = 0.07 9 60 4	4.2% 1.1% 17.0 %); I [≈] = 469 1.0% 1.3%	1.73 (1.16, 2.58) 3.00 (0.15, 61, 74) 0.89 [0.43, 1.86] 6 Not estimable 0.85 (0.04, 20.08) 0.83 (0.05, 13.02]	
SECURE-IBD Taxonera et al Subtorat (95% Cf) Total events Heterogeneity: Tau ² = 0 Test for overall effect: Z T.5. INFLIXIMAB Allocca et al Aveirad et al Subtorat (95% Cf)	27 1 35 .40; Chi ^a = 0.30 (F 0 0 0	589 6 81 = 13.02 P = 0.76 4 23	152 0 325 2, df = 7 (F) 0 1 1	5739 6643 P = 0.07 9 60	4.2% 1.1% 17.0 %); I* = 469 1.0%	1.73 [1.16, 2.58] 3.00 [0.15, 61.74] 0.89 [0.43, 1.86] 6 Not estimable 0.85 [0.04, 20.08]	
SECURE-IBD Taxonera et al Subtotal (95% CI) Total events Heterogeneity. Tau ² = 0 Test for overall effect: Z 1.1.5 INFLDXIMAB Allocca et al Aveirad et al Subtotal (95% CI) Total events	27 1 .40; Chi ^a = 0.30 (f 0 0 0	589 681 9 = 13.02 9 = 0.76 4 23 1 28	152 0 325 t, df = 7 (F) 0 1 1 2	5739 6643 9 = 0.07 9 60 4 73	4.2% 1.1% 17.0%); I*= 469 1.0% 1.3% 2.3%	1.73 (1.16, 2.58) 3.00 (0.15, 61, 74) 0.89 [0.43, 1.86] 6 Not estimable 0.85 (0.04, 20.08) 0.83 (0.05, 13.02]	
SECURES-IBD Faxonera et al Subtortal (95% CI) Total events Heterogeneity: Tau* = 0 Fest for overall effect. Z: I.1.5 INFLIXIMAB Valocca et al Valotata et al Subtortal (95% CI) Total events Heterogeneity: Tau* = 0	27 1 35 40; Chi ^a = 0.30 (f 0 0 0 0 .00; Chi ^a	589 681 = 13.02 = 0.76 4 23 1 28 = 0.00,	152 0 325 c, df = 7 (f) 0 1 1 2 df = 1 (P	5739 6643 9 = 0.07 9 60 4 73	4.2% 1.1% 17.0%); I*= 469 1.0% 1.3% 2.3%	1.73 (1.16, 2.58) 3.00 (0.15, 61, 74) 0.89 [0.43, 1.86] 6 Not estimable 0.85 (0.04, 20.08) 0.83 (0.05, 13.02]	
SECURE-IBD Taxonera et al Subtotal (95% CI) Fotal events Heterogenethy. Tau" = 0 Fest for overall effect. Z I.1.5 INFLIXIMB Viorca et al Subtotal (95% CI) Total events Heterogenethy. Tau" = 0 Fest for overall effect. Z	27 1 35 40; Chi ^a = 0.30 (f 0 0 0 0 .00; Chi ^a	589 681 = 13.02 = 0.76 4 23 1 28 = 0.00,	152 0 325 c, df = 7 (f) 0 1 1 2 df = 1 (P	5739 6643 9 = 0.07 9 60 4 73	4.2% 1.1% 17.0%); I*= 469 1.0% 1.3% 2.3%	1.73 (1.16, 2.58) 3.00 (0.15, 61, 74) 0.89 [0.43, 1.86] 6 Not estimable 0.85 (0.04, 20.08) 0.83 (0.05, 13.02]	
SECURE-IBD Taxonera et al Subtota (95% C) Fotal events Heterogeneity Tau*= 0 Fest for overall effect Z L.1.5.INFLUCIMAB Valcaca et al Subtatan et al Subtatan et al Subtatan et al Subtatan (95% C)) Total events Heterogeneity: Tau*= 0 Fest for overall effect Z L.1.6 VEDOLIZUMAB	27 1 35 40; Chi ^a = 0.30 (f 0 0 0 0 .00; Chi ^a	589 681 = 13.02 = 0.76 4 23 1 28 = 0.00,	152 0 325 c, df = 7 (f) 0 1 1 2 df = 1 (P	5739 6643 9 = 0.07 9 60 4 73	4.2% 1.1% 17.0%); I*= 469 1.0% 1.3% 2.3%	1.73 (1.16, 2.58) 3.00 (0.15, 61, 74) 0.89 [0.43, 1.86] 6 Not estimable 0.85 (0.04, 20.08) 0.83 (0.05, 13.02]	
SECURE-BD Taronera et al Subtotal (95% C) Total events Tearopare, tau" = 0 Teart for overall effect Z I.1.5 INFLIDMINB Unocca et al Subtotal (95% C) Total events Heterogeneity: Tau" = 0 Teat for overall effect Z I.1.6 VEDOLIZUMBB Unocca et al	27 1 35 .40; Chi ^a = 0.30 (f 0 0 0 .00; Chi ^a = 0.17 (f	589 681 = 13.02 = 0.76 4 23 1 28 = 0.00, P = 0.87	152 0 325 2, df = 7 (F) 0 1 1 1 2 df = 1 (P	5739 6643 9 = 0.07 9 60 4 73 = 0.99);	4.2% 1.1% 17.0%); I*= 469 1.0% 1.3% 2.3%	1.73 (1.6, 2.8) 0.09 (0.43, 1.86) 0.89 (0.43, 1.86) 0.89 (0.43, 1.86) 0.85 (0.42, 20.08) 0.83 (0.04, 20.08) 0.83 (0.05, 13.02) 0.84 (0.11, 6.69)	
SECURE-IBD Taxonera et al Subtotal (9% C) Total events Helerogeneity: Tau" = 0 Test for overall effect Z Total events Valocca et al Valocca et al Valoca et al Valora et al Valora et al Valora et al Valora et al Valora et al	27 1 35 40; Chi ² = 0.30 (f 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	589 681 9 = 0.76 4 23 1 28 5 = 0.00, 9 = 0.87 1	152 0 325 2, df = 7 (f) 0 1 1 2 df = 1 (P) 0 1 5	5739 6643 P = 0.07 9 60 4 73 = 0.99); 14	4.2% 1.1% 17.0%); *= 469 1.0% 1.3% 2.3% *= 0%	1.73 [1.16, 2.58] 3.00 [0.15, 0.43, 1.86] 0.89 [0.43, 1.86] 0.65 [0.44, 20.89] 0.83 [0.05, 1.302] 0.84 [0.11, 6.69] Not estimable	
SECURE-IBD Taxonera et al Subtotal (9% C) Total events Helerogeneity: Tau* = 0 Test for overall effect Z Total events Volcca et al Subtotal (9% C) Otal events Helerogeneity: Tau* = 0 Volca et al Venta et al Subtotal effect Z Helerogeneity: Tau* = 0 Venta et al Subtota et al Subta et al Surke et al Lamp et al	27 1 35 .40; Chi ^a = 0.30 (f 0 0 0 .00; Chi ^a = 0.17 (f 0 0 2 2	589 681 9 = 0.76 4 23 1 28 9 = 0.00, 9 = 0.87 1 5 7 14	152 0 325 t, df = 7 (F) 0 1 1 2 df = 1 (P) 0 1 5 54	5739 66643 9 = 0.07 9 60 4 73 = 0.99); 14 78 32 197	4.2% 1.1% 17.0%); *= 469 1.0% 1.3% 2.3% *= 0% 1.1% 2.7% 2.8%	1.73 (1.6, 2.8) 3.00 (0.15, 6.74) 0.89 (0.43, 1.86) 0.85 (0.43, 1.86) 0.85 (0.04, 20.08) 0.83 (0.05, 13.02) 0.84 (0.05, 13.02) 0.84 (0.11, 6.69) 1.83 (0.44, 7.82) 0.52 (0.14, 1.92)	
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SECURE-IBD axanorea et al subtotal (95% C) folal events relatoropeneity: Tau* = 0 fest for overall effect Z substan et al substan et a	27 1 35 40; Chi ^a = 0.30 (f 0 0 0 .00; Chi ^a = 0.17 (f 0 0 2 2 0 20	589 6 681 2 = 13.02 2 = 0.76 4 23 1 28 2 = 0.00, 2 = 0.87 1 5 7 14 9	152 0 325 c, df = 7 (f) 0 1 1 2 df = 1 (P) 0 1 5 54 111 159	5739 6643 9 = 0.07 9 60 4 73 = 0.99); 14 78 322 197 591	4.2% 1.1% 17.0% 17.0% 1.0% 1.3% 2.3% 1*= 0% 1.1% 2.8% 2.8% 1.3%	1.73 (1.16, 2.67) 3.00 (0.15, 6.7) 0.89 (0.43, 1.86) 6 Not estimable 0.85 (0.04, 20.08) 0.83 (0.05, 13.02) 0.84 (0.11, 6.69) Not estimable 1.83 (0.44, 7.58) 0.52 (0.14, 1.92) 0.27 (0.02, 3.88)	
SECURE-BD aronera et al subtotal (95% C) otal events teterogeneity: Tau* = 0 est for overall effect Z substant et al substant et al su	27 1 35 .40; Chi ^a = 0.30 (f 0 0 0.00; Chi ^a = 0.17 (f 0 0 2 2 0 20 20 24	589 6 681 = 13.02 1 28 = 0.00, 7 14 9 695 7 71 = 3.46,	152 0 325 , df = 7 (f) 0 1 1 2 df = 1 (P) 0 1 5 54 111 159 330 df = 4 (P	5739 6 6643 9 = 0.07 9 60 4 73 = 0.99); 14 78 = 0.99); 14 78 32 197 591 5633 6545	4.2% 1.1% 17.0%); *= 469 1.0% 1.3% 2.3% *= 0% 1.1% 2.8% 1.3% 4.1% 12.0%	1.73 (1.6, 2.8) 3.00 (0.15, 6.74) 0.89 (0.43, 1.86) 0.65 (0.4, 3, 1.86) 0.83 (0.05, 13.02) 0.83 (0.05, 13.02) 0.84 (0.11, 6.69) 0.83 (0.05, 13.02) 0.84 (0.11, 6.69) 1.83 (0.44, 7.58) 0.52 (0.14, 1.92) 0.52 (0.14, 1.92) 0.20 (0.64, 1.61)	
SECURE-IBD aronera et al subtotal (95% C) ofal events rest or overall effect est or overall effect Z substant et al substant et al sub	27 1 35 .40; Chi ^a = 0.30 (f 0 0 0.00; Chi ^a = 0.17 (f 0 0 2 2 0 20 20 24	589 6 681 = 13.02 1 28 = 0.00, 7 14 9 695 7 71 = 3.46,	152 0 325 , df = 7 (f) 0 1 1 2 df = 1 (P) 0 1 5 54 111 159 330 df = 4 (P	5739 6 6643 9 = 0.07 9 60 4 73 = 0.99); 14 78 = 0.99); 14 78 32 197 591 5633 6545	4.2% 1.1% 17.0%); *= 469 1.0% 1.3% 2.3% *= 0% 1.1% 2.8% 1.3% 4.1% 12.0%	1.73 (1.6, 2.8) 3.00 (0.15, 6.74) 0.89 (0.43, 1.86) 0.65 (0.4, 3, 1.86) 0.83 (0.05, 13.02) 0.83 (0.05, 13.02) 0.84 (0.11, 6.69) 0.83 (0.05, 13.02) 0.84 (0.11, 6.69) 1.83 (0.44, 7.58) 0.52 (0.14, 1.92) 0.52 (0.14, 1.92) 0.20 (0.64, 1.61)	
SECURE-BED amonera et al subtotal (95% C) ofal events teterogeneity: Tau* = 0 fest or overall effect Z L.1.6 MELLDMAB Viocca et al viorad et al vio	27 1 35 40; Chi ² = 0.30 (f 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	589 6 681 = 13.02 9 = 0.76 4 4 23 1 28 = 0.00, 9 = 0.87 1 5 7 7 1 4 9 695 731 = 3.46, 9 = 0.99	152 0 325 2, df = 7 (f 1 2 df = 1 (P 0 1 1 54 111 159 330 df = 4 (P	5739 6643 9 = 0.07 9 0 0 4 73 = 0.99); 14 78 32 197 591 5633 6545 = 0.48);	4.2% 1.1% 17.0% 1.0% 1.3% 2.3% 1*= 0% 1.1% 2.7% 2.8% 1.3% 4.1% 12.0%	1.73 (1.16, 2.84 3.00 (0.15, 6.74) 0.89 (0.43, 1.86) 0.85 (0.04, 20.08) 0.83 (0.05, 13.02) 0.83 (0.05, 13.02) 0.84 (0.11, 6.69) 1.83 (0.44, 7.53) 0.54 (0.14, 1.92) 0.54 (0.14	
SECURE-IBD axanorea et al subtotal (95% C) Cotal events reletrogeneity: Tau* = 0 Fest for overall effect Z substant et al substant et a	27 1 35 40; Chi ^a = 0.30 (f 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	589 6 681 = 13.02 P = 0.76 4 4 23 1 28 = 0.000, P = 0.87 1 1 5 7 7 1 4 9 695 5 7 71 1 = 3.46, 9 = 0.99 3	152 0 325 (, df = 7 (f 1 1 1 1 5 5 5 (df = 1 (P 0 1 1 5 5 5 330 330 df = 4 (P) 0 0 0 1 1 5 9 0 1 1 1 1 1 5 5 0 0 0 1 1 1 1 1 1 5 0 0 0 0	5739 6 66643 9 9 60 4 73 = 0.090; 144 78 32 197 5913 6545 = 0.48); 12	4.2% 1.1% 17.0% 1.0% 1.3% 2.3% 1.3% 2.3% 1.1% 2.8% 4.1% 12.0%	1.73 (1.16, 2.67) 3.00 (0.15, 6.7) 0.89 (0.43, 1.86) 0.45 (0.04, 20.08) 0.45 (0.04, 20.08) 0.43 (0.05, 13.02) 0.83 (0.05, 13.02) 0.84 (0.11, 6.69) 1.83 (0.44, 7.58) 0.52 (0.14, 1.92) 0.27 (0.02, 9.856) 1.02 (0.64, 1.61) 1.00 (0.66, 1.50)	
SECURE-IBD Taxonera et al Subtotal (9%) C() Total events Heterogeneity: Tau" = 0 Test for overall effect 2 Total events Nitocca et al Vocca et al Vocca et al Vocca et al Vocca et al Subtotal (9%) C() Total events Heterogeneity: Tau" = 0 Vocca et al Vocca et al Vocca et al Vocca et al Subtotal (9%) C() Total events Es for overall effect 2 Subtotal (9%) C() Total events Heterogeneity: Tau" = 0 Vocta et al Vocca et al Vocca et al Vocca et al Vocca et al Vocca et al	27 1 35 36 36 36 36 37 36 37 37 37 37 37 37 37 37 37 37	589 6 681 = 13.02 = 0.76 4 23 1 28 = 0.00, 9 = 0.87, 1 5 7 7 14 9 9695 731 = 3.46, 9 = 0.99 3 9	152 0 325 2, df = 7 (F 1 2 df = 1 (P) 0 1 1 5 5 4 4 111 159 330 0 df = 4 (P) 0 1	5739 6643 2 = 0.07 9 80 4 73 = 0.99); 14 78 32 197 591 5633 6545 = 0.48); 12 74	4.2% 1.1% 1.1% 1.0% 2.3% ₽ = 0% 1.1% 2.7% 2.8% 4.1% 12.0%	1.73 (1.16, 2.67) 3.00 (0.15, 6.74) 0.89 (0.43, 1.86) 0.85 (0.04, 20.08) 0.83 (0.05, 13.02) 0.83 (0.05, 13.02) 0.84 (0.11, 6.69) 1.83 (0.41, 7.50) 0.54 (0.14, 1.92) 0.54 (0.14, 1.92) 0.54 (0.14, 1.92) 0.71 (0.02, 9.84, 1.61) 1.00 (0.66, 1.50) Not estimable 2.50 (0.11, 57.29)	
SECURE-IBD subtotal (95% C) folal events relation events relation events relation events relation events substant et al substant et al	27 1 35 35 40; Chi ^a 0 0 0 0 0 0 0 0 0 0 0 0 0	589 6 681 = 13.02 = 0.76 4 23 1 28 = 0.00, 7 = 0.87 1 5 7 7 14 4 9 695 7 7 1 1 5 7 7 1 1 5 7 7 1 1 5 7 7 1 2 8 9 9 9 9	152 0 325 0 0 1 1 1 1 2 0 0 1 5 4 111 159 330 0 0f = 4 (P) 0 0 1 111 159 330 0 0f = 4 (P 1 111 159 330 0 0 1 111 111 159 159 159 159 159 159 159 1	5739 6643 9 = 0.07 9 80 4 73 = 0.99); 14 78 32 197 591 14 78 12 197 5633 6545 = 0.48); 12 74 591	4.2% 1.1% 17.0% 17.0% 1.3% 2.3% 2.7% 2.7% 2.7% 1.1% 1.3% 1.3% 1.3%	1.73 (1.16, 2.68) 3.00 (0.15, 64) 0.89 (0.43, 1.86) 0.65 (0.04, 20.08) 0.63 (0.05, 13.02) 0.83 (0.05, 13.02) 0.84 (0.11, 6.69) Not estimable 1.83 (0.44, 7.58) 0.52 (0.14, 1.52) 1.02 (0.64, 1.61) 1.00 (0.66, 1.50) Not estimable 2.50 (0.11, 57.22) 0.27 (0.02, 3.88)	
SECURF-BD Samorera et al Subtotal (95% C) Total events Teletrogeneity: Tau" = 0 Test for overail effect Z Lis (FWLDMAR Vorca et al Vorca et	27 1 35 36 36 36 36 37 36 37 37 37 37 37 37 37 37 37 37	589 6 681 = 13.02 = 0.76 4 23 1 28 = 0.00, 9 = 0.87, 1 5 7 7 14 9 9695 731 = 3.46, 9 = 0.99 3 9	152 0 325 2, df = 7 (F 1 2 df = 1 (P) 0 1 1 5 5 4 4 111 159 330 0 df = 4 (P) 0 1	5739 6643 9 = 0.07 9 80 4 73 = 0.99); 14 78 32 197 591 5633 6545 = 0.48); 12 74	4.2% 1.1% 1.1% 1.0% 2.3% ₽ = 0% 1.1% 2.7% 2.8% 4.1% 12.0%	1.73 (1.16, 2.84 3.00 (0.15, 6.74 0.89 (0.43, 1.86) 0.85 (0.04, 20.08) 0.83 (0.05, 13.02) 0.83 (0.05, 13.02) 0.84 (0.11, 6.69) 1.83 (0.41, 7.54) 0.54 (0.14, 1.92) 0.27 (0.02, 9.96 1.83 (0.44, 7.54) 0.54 (0.14, 1.92) 0.27 (0.02, 9.96) 1.83 (0.44, 7.54) 1.00 (0.66, 1.50) Not estimable 2.50 (0.11, 57.29) 0.27 (0.02, 3.98) 0.54 (0.26, 1.00)	
SECURCE-IBD subtotal (95% C) folal events relation events relation events relation events relation events substant et al substant et a	27 1 35 35 40; Chi ^a 0 0 0 0 0 0 0 0 0 0 0 0 0	589 661 = 13.02 = 0.76 4 23 1 2 = 0.00, 7 4 23 2 = 0.00, 7 1 5 7 3 1 5 7 3 4 9 9 9 9 589	152 0 325 0 1 1 1 1 2 0 0 1 5 4 111 159 330 0 0 1 4 (P) 0 0 1 1 11 1 159 330 0 0 1 1 111 1 159 330 0 0 1 1 111 1 159 159 159 159 159 159 159 159	5739 6643 P = 0.07 9 60 4 73 = 0.99); 14 78 32 197 591 5633 6545 6545 12 74 55715	4.2% 1.1% 1.7.0% 1.0% 1.3% 2.3% 1.1% 2.7% 2.8% 1.3% 2.8% 1.3% 1.3% 3.3%	1.73 (1.16, 2.68) 3.00 (0.15, 64) 0.89 (0.43, 1.86) 0.65 (0.04, 20.08) 0.63 (0.05, 13.02) 0.83 (0.05, 13.02) 0.84 (0.11, 6.69) Not estimable 1.83 (0.44, 7.58) 0.52 (0.14, 1.52) 1.02 (0.64, 1.61) 1.00 (0.66, 1.50) Not estimable 2.50 (0.11, 57.22) 0.27 (0.02, 3.88)	
SECURE-BED amonera et al subtotal (95% C) Total events teterogeneity: Tau* = 0 Test for overall effect Z teterogeneity: Tau* = 0 verta det al verta	27 1 3 40; Chi ^a 0 0 0 0 0 0 0 0 0 0 0 0 0	589 681 = 13.02 9 = 0.76 4 23 1 28 = 0.00, 7 1 4 9 = 0.87 7 1 4 9 9 695 5 7 31 9 9 9 9 5 89 610	152 0 325 3, cf = 7 (f 1 0 1 1 2 0 1 1 1 2 0 1 1 1 5 4 (f) 1 1 1 0 1 1 1 1 0 0 1 1 1 1 0 0 1 1 1 0 0 1 1 0 0 1 0 0 1 0 1 0 0 1 0 0 0 1 0 0 0 1 0 0 0 0 0 0 0 0 0 0 0 0 0	5739 6 6643 2 = 0.07 9 9 8 0 4 73 = 0.99); 14 78 32 197 591 5633 6545 = 0.48); 12 74 5715 6392	4.2% 1.1% 1.7.0% 1.0% 1.3% 2.3% 1.1% 2.7% 2.8% 1.3% 1.3% 3.3% 6.2%	1.73 (1.16, 2.84 3.00 (0.15, 6.74 0.89 (0.43, 1.86) 0.85 (0.04, 20.08) 0.83 (0.05, 13.02) 0.83 (0.05, 13.02) 0.84 (0.11, 6.69) 1.83 (0.41, 7.54) 0.54 (0.14, 1.92) 0.27 (0.02, 9.96 1.83 (0.44, 7.54) 0.54 (0.14, 1.92) 0.27 (0.02, 9.96) 1.83 (0.44, 7.54) 1.00 (0.66, 1.50) Not estimable 2.50 (0.11, 57.29) 0.27 (0.02, 3.98) 0.54 (0.26, 1.00)	
SECURCHED Ganorera et al subtotal (95% C) Colal events relation events relation events relation events relation events relation et al subtotal (95% C) Colal events relation e	27 1 3.40; Chi ^m ie = 0.30 (f 0 0 0 0 0 0 0 0 0 0 0 0 0	589 6 681 = 13.02 1 28 = 0.00, 7 = 0.87, 731 = 3.46, 9 = 0.99 3 9 589 610 = = 1.20,	152 0 325 c, df = 7 (f 0 1 1 2 0 0 1 1 1 5 4 (f) = 1 (P 0 0 1 1 1 5 4 (f) = 7 (f 0 1 1 1 5 4 (f) = 7 (f) (f) = 1 (f) (f) = 1 (f)	5739 6 6643 2 = 0.07 9 9 8 0 4 73 = 0.99); 14 78 32 197 591 5633 6545 = 0.48); 12 74 5715 6392	4.2% 1.1% 1.7.0% 1.0% 1.3% 2.3% 1.1% 2.7% 2.8% 1.3% 1.3% 3.3% 6.2%	1.73 (1.16, 2.84 3.00 (0.15, 6.74 0.89 (0.43, 1.86) 0.85 (0.04, 20.08) 0.83 (0.05, 13.02) 0.83 (0.05, 13.02) 0.84 (0.11, 6.69) 1.83 (0.41, 7.54) 0.54 (0.14, 1.92) 0.27 (0.02, 9.96 1.83 (0.44, 7.54) 0.54 (0.14, 1.92) 0.27 (0.02, 9.96) 1.02 (0.64, 1.61) 1.00 (0.66, 1.50) Not estimable 2.50 (0.11, 57.29) 0.27 (0.02, 3.98) 0.54 (0.26, 1.00)	
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SECURE-IBD Taxonera et al Subtotal (9%) C() Total events Heterogeneity: Tau" = 0 Test for overall effect Z Lis (WFLOMMA World et al Subatan et al Subtotal (9%) C() Total events Heterogeneity: Tau" = 0 Test for overall effect Z Lis (WEDOLIZUMAB World et al Subtotal (9%) C() Total events Heterogeneity: Tau" = 0 SecURE-IBD Subtotal (9%) C() Total events Heterogeneity: Tau" = 0 Subtotal (9%) C() Subtotal events Heterogeneity: Tau" = 0 Subtotal events	27 1 35 40; Chi ^a = 0.30 (f 0 0 0 0 0 0 0 0 0 0 0 0 0	589 681 23 23 24 23 24 23 24 25 25 25 25 25 25 25 25 25 25 25 25 25	152 2 0 325 2 2, df = 7 (f 0 1 1 5 5 4 111 159 34 (f 111 159 34 (f 2 22 2 4 111 159 34 (f 2 2 2 2 2 2 2 5 5 4 11 1 1 1 1 1 1 1 1 1 1 1 1	5739 6643 6643 9 8 0 9 8 0 9 8 0 9 8 0 9 8 0 4 7 3 2 197 591 5635 5715 6535 2 7 4 5715 6545 3 2 9 9 8 12 7 4 5 12 7 4 5 12 7 4 5 12 7 4 5 5 12 5 7 4 5 5 12 5 7 4 5 5 12 5 7 4 5 5 12 5 7 4 5 5 12 5 7 4 5 5 12 5 7 4 5 5 12 5 7 7 5 1 5 5 12 5 7 7 5 1 5 5 1 5 5 1 5 5 1 5 5 1 5 5 1 5 5 1 5 5 1 5 5 1 5 5 1 5 5 1 5 5 1 5 5 1 5 5 1 5 5 1 5 5 1 5 5 1 5 5 5 5 5 5 5 5 5 5 5 5 5	4.2% 1.1% 1.1% 1.7.0% 1.3% 2.3% 2.3% 2.8% 2.8% 2.8% 2.8% 2.8% 2.8% 2.8% 2.8	1.73 (1.16, 2.8) 3.00 (0.15, 6.74) 0.89 (0.43, 1.86) 0.85 (0.04, 20.08) 0.83 (0.05, 13.02) 0.83 (0.05, 13.02) 0.83 (0.05, 13.02) 0.84 (0.11, 6.69) 1.83 (0.20, 96 56) 1.83 (0.20, 96 56) 1.83 (0.24, 75 0) 0.52 (0.14, 9.22) 0.52 (0.23, 9.03) 0.53 (0.28, 0.99) Not estimable 0.28 (0.09, 0.94) 0.13 (0.01, 2.09) 0.43 (0.17, 1.11)	
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SECURCHED Ganorer et al subtotal (95% C) Colal events relationer entry Tau" = 0 fest for overall effect Z substant et al substant et al subst	27 35 36 40; Chi'i 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	589 681 28 28 29 20 20 20 20 20 20 20 20 20 20 20 20 20	152 2 0 325 2 0 1 1 1 1 1 1 1 1 1 1 1 1 1	5739 6643 9 = 0.07 9 600 4 73 = 0.990; 14 78 32 197 591 512 5545 591 5545 591 5715 6533 6545 591 5715 6392 = 0.55; 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9	4.2% 1.1% 1.1% 1.1% 1.3% 2.3% 2.3% 2.2% 2.2% 4.1% 1.3% 2.2% 4.1% 1.3% 2.2% 2.8% 2.2% 4.1% 1.3% 3.9% 3.2% 3.2% 3.3% 3.3%	1.73 (1.16, 2.68) 3.00 (0.15, 6.14) 0.89 (0.43, 1.86) 0.45 (0.04, 20.08) 0.45 (0.04, 20.08) 0.43 (0.05, 13.02) 0.83 (0.05, 13.02) 0.84 (0.11, 6.69) 1.83 (0.44, 7.58) 0.52 (0.14, 9.52) 0.27 (0.02, 3.88) 1.02 (0.64, 1.61) 1.00 (0.66, 1.50) 0.53 (0.28, 0.99) 0.51 (0.26, 1.00) 0.53 (0.28, 0.99) 0.51 (0.26, 1.00) 0.53 (0.28, 0.99) 0.43 (0.01, 0.24) 0.13 (0.01, 2.09) 0.43 (0.17, 0.11) 0.33 (0.15, 0.73)	
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SECURCE-IED aconora et al subtotal (95% C) Cola events rest or overall effect 2 subtotal (95% C) ide storoverall effect 2 subtotal (95% C) ide sevents rest or overall effect 2 sevents rest or overall effect 2 set or overall effect 2 set or overall effect 2 set or overall effect 2 set of overall effect 2 set or overall effect 2 set of overall effect 2 set or overall effect 2 set of overall e	27 35 36 4.0; Chi'i 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	589 681 = 13.02 = 0.76 4 23 1 28 = 0.00, - 28 - 28 	152 2 0 325 2 0 0 1 1 2 0 1 1 2 0 1 1 1 1 2 0 1 1 1 1 1 1 1 1 1 1 1 1 1	5739 6643 2 = 0.07 9 60 4 73 = 0.99); 14 78 = 0.99); 14 78 = 0.99); 591 563 5715 563 5715 5755	4.2% 1.1% 1.1% 1.1% 1.3% 2.3% 2.2% 2.8% 1.3% 2.8% 1.3% 2.8% 1.3% 5.8% 6.2% 1.1% 6.2% 1.1% 5.2% 1.2% 5.2% 1.2% 5.2% 1.2% 5.2% 1.2% 5.2% 1.2% 5.2% 1.2% 5.2% 1.2% 5.2% 1.2% 5.2% 1.2% 5.2% 1.2% 5.2% 1.2% 1.3% 5.2% 1.2% 1.3% 1.3% 1.3% 1.3% 1.3% 1.3% 1.3% 1.3	1.73 (1.16, 2.68) 3.00 (0.15, 64) 0.433, 1.86] 0.433, 1.86] 0.433, 1.86] 0.433, 0.43, 1.86] 0.441, 0.49, 0.433, 1.86] 0.45 (0.04, 20.08) 0.43 (0.05, 13.02) 0.83 (0.04, 20.08) 0.44, 7.68] 0.52 (0.24, 9.68) 1.83 (0.44, 7.68) 0.52 (0.24, 9.68) 1.02 (0.64, 1.61) 1.00 (0.66, 1.50) 0.55 (0.26, 1.00) 0.55 (0.26, 1.00) 0.55 (0.28, 0.99) 0.55 (0.28, 0.99) 0.55 (0.28, 0.99) 0.43 (0.17, 1.11) 0.33 (0.15, 0.73) 0.33 (0.20, 0.48) 0.32 (0.23, 0.45)	
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SECURE-BED amonera et al subtotal (95% C). Total events teterogeneity: Tau* = 0 Test for overall effect Z Substan et al substan et al substant et al	27 1 35 40; Chim 0 0 0 0 0 0 0 0 0 0 0 0 0	$580 \\ 6681 \\ = 13.00 \\ = 0.766 \\ 4 \\ 233 \\ 1 \\ 288 \\ = 0.00, 7 \\ 1 \\ 577 \\ 731 \\ = 3.46, 2 \\ 0.95 \\ 610 \\ = 1.20, 0 \\ 39 \\ 610 \\ = 1.20, 0 \\ 133 \\ 32 \\ 2050 \\ = 0.87, 2 \\ 360 \\ = 0.00, 10 \\ 10 \\ 10 \\ 10 \\ 10 \\ 10 \\ 10 \\ 1$	152 0 325 2 (aff = 7 (fr 1 1 2 aff = 1 (P 1 1 1 1 1 1 1 1 1 1 1 1 1	5739 6643 9 = 0.07 9 600 4 73 = 0.99); 14 73 = 0.99); 12 74 591 5533 6545 5715 65392 = 0.55); 9 9 26 12 74 5715 5715 5715 5715 5715 5755 39989	4.2% 1.1% 1.1% 1.1% 1.1% 1.3% 2.3% P = 0% 1.1% 2.7% 2.8% 2.8% 2.8% P = 0% 3.0% 7.2% 2.8% 2.8% 2.8% 2.8% 2.8% 2.8% 2.8% 2	1.73 (1.16, 2.68) 3.00 (0.15, 6.14) 0.89 (0.43, 1.86) 0.65 (0.04, 20.08) 0.63 (0.04, 20.08) 0.63 (0.05, 13.02) 0.83 (0.05, 13.02) 0.84 (0.11, 6.69) 1.83 (0.44, 7.68) 0.52 (0.14, 9.29) 0.52 (0.14, 9.29) 0.52 (0.14, 9.29) 0.52 (0.14, 5.29) 0.52 (0.14, 5.29) 0.52 (0.14, 5.29) 0.52 (0.14, 5.29) 0.52 (0.14, 5.29) 0.55 (0.26, 1.61) 0.55 (0.26, 1.00) 0.55 (0.28, 0.99) 0.43 (0.17, 0.11) 0.33 (0.15, 0.73) 0.31 (0.20, 0.48) 0.32 (0.23, 0.45] 0.78 (0.54, 1.13)	

Figure 3 Forest plot showing the risk of intensive care unit (ICU) admission in patients taking 5-ASA, immunomodulators, steroids, and biological agents.

were protective against severe COVID-19 outcomes. No difference was observed in the risk of ICU admission in patients receiving immunomodulators (RR 0.89 (95% CI 0.43 to 1.86, p=0.76; I²=46%)), infliximab (RR 0.84 (95% CI 0.11 to 6.69, p=0.87; I²=0%)), or vedolizumab (RR 1.00 (95% CI 0.66 to 1.50, p=0.99; I²=0%)) (figure 3).

Mortality

The number of patients who were eligible to be included in this sub-analysis was different among the drug groups. The number of patients included in this sub-analysis who were receiving 5-ASA was 2434, whereas the numbers of patients receiving corticosteroids and immunomodulators were 604 and 762, respectively. The total number of patients who were receiving biologic was 3763. Specifically, 2288 patients were taking anti-TNF monotherapy, 26 patients were taking adalimumab and 31 patients were taking infliximab. Finally, the numbers of patients receiving vedolizumab and ustekinumab included in this sub-analysis were 774 and 617, respectively. The risk of mortality in patients with IBD taking 5-ASA was significantly higher than patients not taking 5-ASA (RR 2.08 $(95\% \text{ CI } 1.64 \text{ to } 2.65, \text{ p} < 0.00001; \text{ I}^2 = 0\%))$. No difference was observed in risk of mortality between patients with IBD who received immunomodulators and those patients who did not (RR 0.84 (95% CI 0.48 to 1.48, p=0.54; $I^2=36\%)$). Furthermore, corticosteroid use was not associated with mortality (RR 1.82 (95% CI 0.93 to 3.57, p=0.08; $I^2=75\%$)). Mortality was significantly lower in patients taking biologics (RR 0.32 (95% CI 0.23 to 0.44, p<0.00001; I²=0%)); specifically, in patients taking anti-TNFs the RR was 0.26 (95% CI 0.17 to 0.41, p<0.00001; $I^2=0\%$). Finally, neither the use of vedolizumab nor ustekinumab were associated with mortality. (figure 4).

Heterogeneity assessment, risk of bias, and quality of studies

Median mNOS score was 4, with scores ranging from 4 to 6 (see online supplemental table 2). In terms of risk of bias, most studies were judged to have low risk of bias using the Risk of Bias in Non-Randomized Studies – of Interventions (ROBINS-I) tool, while three studies had moderate risk of bias (see online supplemental table 3). Using random-effect model, heterogeneity I^2 ranged from 0% to 72%. In all studied medications, heterogeneity was low (less than 30%) except for corticosteroids where it was medium (72%).

Publication bias

Online supplemental figure 1 shows a funnel plot of publication bias. Based on visual examination of the plot, symmetrical distribution of the studies on the funnel plot suggests low risk of publication bias.

DISCUSSION

In this systematic review and meta-analysis, we analysed the risk of severe COVID-19 in patients with IBD who are receiving different medical therapies. Our analysis showed that the risk of severe disease significantly increases in patients taking 5-ASA and corticosteroids. Conversely, tofacitinib, vedolizumab, immunomodulators alone or in combination with anti-TNFs were not associated with any negative outcomes. In addition, anti-TNFs and ustekinumab were associated with favourable outcomes.

Surprisingly, the current study demonstrated an increased risk of severe COVID-19 in patients taking 5-ASA. As 5-ASA has very mild immunosuppressive

Study or Subgroup E S.1.1 AMINOSALICYLATE	with dr Events		without Events	drug Total	Weight	Risk Ratio IV, Random, 95% Cl	Risk Ratio IV, Random, 95% Cl
llocca et al	0	1	0	14		Not estimable	
ttaubiet al kxelrad et al	2	43 13	2	33 70	1.3% 0.7%	0.77 [0.11, 5.17] 1.69 [0.07, 39.40]	
Bezzio et al	3	24	3	55	1.7%	2.29 [0.50, 10.55]	
Burke et al Derikx et al	5	12 56	2 6	27 44	1.7% 2.2%	5.63 [1.26, 25.01] 0.92 [0.33, 2.53]	
Bubatan et al	í	4	0	1	0.8%	1.20 [0.08, 18.75]	
(han et al	23	247 91	18 23	402	2.7% 2.8%	2.08 [1.15, 3.77]	
ampetal Rizzelloetal	33 2	91 19	23	120 7	2.8%	1.89 [1.20, 2.99] 2.00 [0.11, 37.22]	
Rodriguez-Lago et al	2	26	0	14	0.7%	2.78 [0.14, 54.15]	
ECURE-IBD axonera et al	52 2	1894	51 0	4434 8	2.9% 0.8%	2.39 [1.63, 3.50] 9.00 [0.53, 152.93]	
ubtotal (95% CI)		2434		5229	19.0%	2.08 [1.64, 2.65]	•
otal events leterogeneity: Tau² = 0.0 lest for overall effect: Z =	132 10; Chi² = 5.95 (P	= 7.17, d < 0.000	106 f=11 (P 01)	= 0.79); I	²= 0%		
1.2 BIOLOGICS							
llocca et al innapureddy et al	0	11 93	0 25	3 353	2.2%	Not estimable 0.61 [0.22, 1.70]	
xelrad et al	1	58	0	25	0.7%	1.32 [0.06, 31.39]	
lezzio et al	1	47	5	32 0	1.2%	0.14 [0.02, 1.11]	
ossa et al urke et al	0	32 20	0 5	19	1.7%	Not estimable 0.38 [0.08, 1.73]	
ierikx et al	0	15	13	85	0.8%	0.20 [0.01, 3.18]	
iubatan et al amp et al	0	1 49	1 49	4 162	0.8%	0.83 [0.05, 13.02] 0.47 [0.23, 0.97]	
leyer et al	3	88	108	512	2.1%	0.16 [0.05, 0.50]	
Rizzello et al ECURE-IBD	0 24	5 3334	2 79	7 2994	0.8% 2.8%	0.27 [0.02, 4.59] 0.27 [0.17, 0.43]	
'axonera et al	0	5	2	7	0.8%	0.27 [0.02, 4.59]	
adan et al ubtotal (95% CI)	0	5 3763	0	1 4204	16.3%	Not estimable 0.32 [0.23, 0.44]	•
otal events	42		289			01012 [01120] 01111]	•
leterogeneity: Tau ² = 0.0 est for overall effect: Z =	10; Chi ² = 6.93 (P	= 6.55, d < 0.000	f=10(P: 01)	= 0.77); I	²= 0%		
1.3 CORTICOSTEROIDS							
llocca et al	0	2	0	13		Not estimable	
ttaubiet al xelrad et al	1	6 10	3	70 73	1.2% 0.7%	3.89 [0.47, 31.88] 2.24 [0.10, 51.67]	
ezzio et al	2	9	4	70	1.6%	3.89 [0.83, 18.30]	<u> </u>
urke et al Ierikx et al	2 5	8 22	5 8	31 78	1.7% 2.2%	1.55 [0.37, 6.57] 2.22 [0.81, 6.10]	
Bubatan et al	0	1	1	4	0.8%	0.83 [0.05, 13.02]	
(han et al	1	61	40	588	1.3%	0.24 [0.03, 1.72]	
amp et al ECURE-IBD	4 27	10 404	52 76	201 5924	2.5% 2.8%	1.55 [0.70, 3.42] 5.21 [3.40, 7.99]	Ť
ingh et al	22	71	31	95	2.8%	0.95 [0.60, 1.49]	+
ubtotal (95% CI) otal events	64	604	221	7147	17.7%	1.82 [0.93, 3.57]	
leterogeneity: Tau ² = 0.6	6; Chi ² =	35.99	df= 9 (P	< 0.0001); I² = 759	16	
est for overall effect: Z =		= U.08)					
.1.4 IMMUNOMODULAT(ORS 0	3	0	11		Not estimable	
xeirad et al	1	6	0	77		33.43 [1.50, 746.35]	
lezzio et al lurke et al	0	6 3	6 7	73 36	0.8% 0.9%	0.81 [0.05, 12.98] 0.62 [0.04, 8.91]	
alafat et al	1	7	6	25	1.3%	0.60 [0.09, 4.16]	
Derikx et al	5	26	8	74	2.2%	1.78 [0.64, 4.95]	
Rubatan et al Chan et al	0	1 49	1 39	4 600	0.8% 1.8%	0.83 [0.05, 13.02] 0.63 [0.16, 2.52]	
amp et al	4	34	52	177	2.3%	0.40 [0.16, 1.03]	
leyer et al ECURE-IBD	2 13	32 589	109 90	568	1.8% 2.7%	0.33 [0.08, 1.26] 1.41 [0.79, 2.50]	
axonera et al				5739			
	0	6	2	6	0.8%	0.20 [0.01, 3.46]	
Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0.2	28 8; Chi ² =	762	2	6 7390	0.8% 16.1%	0.20 [0.01, 3.46] 0.84 [0.48, 1.48]	•
Subtotal (95% CI) Total events Heterogeneity: Tau ^a = 0.2 Test for overall effect: Z =	28 8; Chi ² =	762	2	6 7390	0.8% 16.1%	0.20 [0.01, 3.46] 0.84 [0.48, 1.48]	•
Subtotal (95% CI) Fotal events Heterogeneity: Tau ² = 0.2 Fest for overall effect: Z = S.1.5 ADALIMUMAB Wlocca et al	28 8; Chi ^a = 0.61 (P	762 = 15.71, = 0.54) 2	2 320 df = 10 (F	6 7390 = 0.11)	0.8% 16.1% P= 36%	0.20 (0.01, 3.46) 0.84 (0.48, 1.48) Not estimable	•
Subtotal (95% CI) Total events Heterogeneity: Tau ^a = 0.2 Test for overall effect: Z = k.1.5 ADALIMUMAB Nocca et al	28 8; Chi ² = 0.61 (P 0 1	762 = 15.71, = 0.54) 2 21	2 320 df = 10 (F 0 0	6 7390 = 0.11) 13 62	0.8% 16.1% P= 36% 0.7%	0.20 [0.01, 3.46] 0.84 [0.48, 1.48] Not estimable 8.59 [0.36, 203.22]	•
Subtotal (95% CI) Fotal events Heterogeneity: Tau ² = 0.2 Fest for overall effect: Z = S.1.5 ADALIMUMAB Wlocca et al	28 8; Chi ^a = 0.61 (P	762 = 15.71, = 0.54) 2 21 1 2	2 320 df = 10 (F 0 2	6 7390 = 0.11) 13 62 25 5	0.8% 16.1 % P = 36% 0.7% 0.9%	0.20 [0.01, 3.46] 0.84 [0.48, 1.48] Not estimable 8.59 [0.36, 203.22] 2.60 [0.18, 37.70] Not estimable	
subtotal (95% CI) Total events deterogeneity: Tau ² = 0.2 Test for overall effect: Z = i.1.5 ADALIMUMAB Ulocca et al vorirad et al Vizzello et al Vizzello et al Viabtotal (95% CI)	28 8; Chi ^a = 0.61 (P 0 1 0 0	762 = 15.71, = 0.54) 2 21	2 320 df = 10 (F 0 2 0	6 7390 = 0.11) 13 62 25	0.8% 16.1% P= 36% 0.7%	0.20 [0.01, 3.46] 0.84 [0.48, 1.48] Not estimable 8.59 [0.36, 203.22]	
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subtotal (95% CI) Total events Test for overall effect Z = 1.1.5 ADALIMUMAB Juocca et al veirad et al Xazzello et al Yadan et al Subtotal (95% CI) Total events Heterogeneily: Tau ² = 0.0 Fest for overall effect: Z = 1.6 INFLIXIMAB	28 (8; Chi ^a = 0.61 (P 1 0 1 0; Chi ^a = 1.40 (P	762 = 15.71, = 0.54) 2 21 1 2 26 = 0.32, d = 0.16)	2 320 df = 10 (F 0 2 0 f = 1 (P =	6 7390 '= 0.11) 13 62 25 5 105 0.57); P	0.8% 16.1% I ^a = 36% 0.7% 0.9% 1.5%	0.20 (0.01, 3.46) 0.84 (0.48, 1.48) Not estimable 6.59 (0.36, 203.22) 2.60 (0.18, 37.70) Not estimable 4.28 (0.56, 32.98)	
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Figure 4 Forest plot showing risk of mortality in patients taking 5-ASA, immunomodulators, steroids, and biological agents.

activity, further studies are required to explore this association. One study found that compared with methotrexate monotherapy, sulfasalazine was associated with higher risk of death (OR 3.60, 95% CI 1.66 to 7.78) in patients with rheumatic diseases.²⁰ Recent data from the SECURE-IBD registry demonstrated that 5-ASA use was associated with severe COVID-19 outcomes in univariable but not in multivariable analyses.¹⁷ However, individual patient-level data were lacking. Factors controlled for in multivariable analyses were age, sex, race, disease type, medications used, disease activity, comorbidities, and when patients were enrolled in the registry. Although it is unclear if any specific factor explained the finding, the use of these together provide a possible explanation for this surprising finding. Not being an immunosuppressive drug, and being widely available and less costly than biologics, 5-ASA might be used more often in more vulnerable populations, such as the elderly, patients with low socioeconomic status, or patients with multiple comorbidities. In addition, patients using 5-ASA may have been under-treated, resulting in more active intestinal inflammation. For example, a significant proportion of patients with CD were on 5-ASA, despite data demonstrating similar efficacy to placebo.²¹ ²² Furthermore, 5-ASA use in moderate to severe ulcerative colitis or Crohn's disease is less likely to control luminal inflammation and active IBD could be the driver of the observed adverse outcomes in patients on 5-ASA. Finally, patients on biologic therapies are usually followed more often by their treating physicians and get tested for SARS-CoV-2 more frequently than those on 5-ASAs leading to reporting bias.²³ Some of the included studies cited few other reasons for the increased risk of severe COVID-19 in patients with IBD taking 5-ASA. Meyer *et al*²⁴ postulated that closer follow-up of patients taking other therapies such as biologics by physicians and over-reporting of most serious outcomes led to the introduction of several biases. It is important to recognise that some studies found that the risk of severe COVID-19 is associated with older age (>65 years), cardiovascular, pulmonary, and renal diseases. $^{25-27}$ It is likely that these factors are associated with severe COVID-19 more than 5-ASA use itself.

Another finding of this meta-analysis was that corticosteroids use was associated with an increased risk of severe COVID-19, while the use of biologics was associated with a reduction in these outcomes. This finding has been described in the literature before with other types of infection.^{28 29} The strong positive association between systemic corticosteroid use and our severe COVID-19 outcomes is consistent with extensive prior literature in IBD. Brenner *et al* found that corticosteroids use but not anti-TNFs were associated with severe COVID-19.¹¹ It is important to note that in our sub-analysis, we found that corticosteroids use was associated with ICU admission but not mortality.

The RECOVERY trial³⁰ reported mortality benefits in patients with severe COVID-19 treated with dexamethasone. It is important to understand that the impact of corticosteroids depends on the stage of infection.²⁸ It is likely that the degree of the benefit of corticosteroid treatment is related to the level of disease severity. At the onset of infection, corticosteroids may weaken the immune response and delay viral clearance; however, during the advanced stage of severe COVID-19, the blunting of the hyperimmune response by corticosteroids improves prognosis and reduces mortality.³¹ Furthermore, available evidence suggest that the benefits of corticosteroids depends on other factors such as level of respiratory support.³² Results from different studies^{31–33} indicate that among patients requiring low-flow oxygen, corticosteroid use did not lower mortality or ICU admission. However, patients with advance level of respiratory support requirement, such as invasive mechanical ventilation, benefited the most in terms of reduction in mortality.³⁴ In addition, one study found that critically ill patients with COVID-19 were five times more likely to get corticosteroids compared with non-ICU patients.³⁵ Therefore, the aforementioned reasons present a possible explanation of the association of corticosteroid use with ICU admission but not mortality.

Finally, the level of heterogeneity found among the studies in the corticosteroid group can be explained by the inclusion of large, heterogenous, and diverse group of patients receiving corticosteroids. It is unlikely that all patients will benefit from corticosteroid use, for some receiving corticosteroids might lead to harmful effects. The duration of corticosteroids use could also have a considerable impact on heterogeneity. Other circumstances that may give rise to clinical heterogeneity include differences in selection of patients, severity of disease, and management.³⁶ For example, patients with acute exacerbations of their IBD may have got infected with COVID-19 while being on corticosteroids for couple of weeks leading to worse COVID-19 outcome. On the other hand, patients with IBD who were not on corticosteroids and were admitted to ICU with severe COVID-19 were given steroids for a shorter period of time to improve their outcome. Therefore, the diversity of the included patients who received corticosteroids can contribute to the level of heterogeneity observed.

The present data are consistent with previous data showing immunomodulators are not associated with an increased risk of severe infection. For example, data reported on 1099 patients from China did not observe immunomodulator use as a risk factor for severe disease.³⁷ Consistent with this, an Italian prospective observational cohort of 79 patients with a diagnosis of IBD and COVID-19 found no association between thiopurine and COVID-19–related pneumonia.³⁸ This might be explained by the cytokine storm syndrome, which predisposes patients to a severe form of COVID-19.³⁹ Patients with IBD on immunomodulatory treatments, particularly those who directly interfere with cytokine action and production, may be protected even against the severe forms of COVID-19.

Our study also showed that biologics, without immunomodulators, have a protective effect against severe COVID-19 in IBD. Previous studies^{11 40 41} suggested possible rationale for the benefits of biologic therapies, particularly anti-TNFs, in COVID-19. This can be explained by the mechanism of action of these medications. Anti-TNFs inactivate the proinflammatory cytokine TNF by direct neutralisation, thus resulting in suppression of inflammation.⁴² This suppression interferes with the cytokine storm mentioned previously and prevents need for hospitalisation or ICU admission.⁴³ Importantly, this was consistent with anti-TNF agents, and ustekinumab but not vedolizumab. Ustekinumab binds to the p40 subunit of interleukin (IL)-12 and IL-23, which ultimately prevents cell signalling and cytokine production. This again interferes with systemic inflammation and prevents severe disease by stopping multiorgan failure that can lead to death in patients infected with SARS-CoV-2.44 On the other hand, vedolizumab is gut specific and does not significantly affect systemic immune reaction.¹⁸ Finally, as disease activity is associated with worse COVID-19 outcomes,³⁸ it is possible that use of effective agents, such as biologic therapy, reduces risk by reducing intestinal disease activity.

With regards to tofacitinib use in patients with IBD infected with SARS-CoV-2, we found that tofacitinib was not associated with severe disease. A recent randomised controlled trial found that tofacitinib reduces the incidence of death.⁴⁵ Another study, which included 86 patients with COVID-19 in the USA, suggests that being on tofacitinib did not appear to increase the risk of developing SARS-CoV-2 features that led to serious infection or death.⁴⁶ Finally, a study by Agrawal *et al* reported no significant differences between tofacitinib-treated patients and other patients in the occurrence of hospitalisation or admission to the ICU.¹⁰

Finally, the most recently published studies recruited patients up to March 2021 and did not report vaccination status among the included patients. It would be interesting to know if vaccination would alter the outcomes of COVID-19 in relation to IBD medications.

This systematic review has several clinical implications. It provides guidance regarding the continuation of most IBD medications in the setting of the COVID-19 pandemic. Our study showed that continuing biologic therapies, small molecule inhibitors, and immunomodulators, alone or in combination with anti-TNFs, are safe and should not be discouraged. Furthermore, initiation of corticosteroids should be minimised in areas with high prevalence of SARS-CoV-2 infection. If needed, it should be continued and tapered down in the shortest period, weighing benefits and risks. This practice is also recommended by both the British Society of Gastroenterology and the International Organization for the Study of Inflammatory Bowel Diseases guidelines.^{47 48} Finally, as discussed previously, active IBD disease has been shown to worsen COVID-19 outcome; therefore, clinicians should continue to treat patients targeting clinical and endoscopic remission. Clinicians should also encourage patients to comply with their medications and clarify any misgivings patients may have regarding the safety of their IBD medications.

This study is the first to include summary data on individual biological therapies, anti-TNF combination therapy, and small molecule inhibitors. The current study summarises significantly increased available data overall and for individual medications. A previous systematic review and meta-analysis earlier in the pandemic,⁴⁹ which included studies up to July 2020, also found that both 5-ASA and corticosteroids, but not immunomodulators, increased the risk of severe disease in patients infected with SARS-CoV-2. With a larger sample size, our study found that corticosteroids were associated with ICU admission, but not mortality. Furthermore, the inclusion of more than 10000 patients with IBD infected with SARS-CoV-2 gives more precise estimation of the risk of severe COVID-19 in this patient population. Our study limitations include the observational nature of included studies with risk of confounding and selection bias. Furthermore, the majority of patients included in our study were extracted from the SECURE-IBD database. Even though the validity of the data is reinforced by the physician-reported nature of this database, it is still subject to reporting bias, which may lead to documentation of the more severe cases that come to the attention of healthcare providers, while the milder cases may remain undiagnosed or underreported. In addition, patient-level data were lacking, and insufficient data existed for metaregression analyses to adjust for confounding. Larger prospective studies are necessary to validate the findings of our study, to ascertain which risk factors play significant roles in causing severe COVID-19 outcomes, and to stratify patients by different factors, including age, disease activity, and socio-economic assessments of the patients.

CONCLUSION

In patients with IBD, the risk of severe COVID-19 is higher among patients receiving corticosteroids. Corticosteroid use was associated with ICU admission but not mortality. The risk is also higher among patients receiving 5-ASAs. However, patient-level data were lacking and insufficient data existed for meta-regression analyses to adjust for confounding. In contrast, tofacitinib, vedolizumab, immunomodulators alone or in combination with anti-TNFs were not associated with severe disease. Finally, anti-TNFs, and ustekinumab were associated with favourable outcomes.

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REFERENCES

- 1 CDC. Human Coronavirus Types [Internet]. COVID-19. Available: https://www.cdc.gov/coronavirus/types.html
- 2 WHO. Coronavirus disease (COVID-19), 2020. Available: https:// www.who.int/emergencies/diseases/novel-coronavirus-2019/ guestion-and-answers-hub/g-a-detail/coronavirus-disease-covid-19
- 3 WHO. WHO Director-General's opening remarks at the media briefing on COVID-19 [Internet], 2020. Available: https://www. who.int/director-general/speeches/detail/who-director-general-sopening-remarks-at-the-media-briefing-on-covid-19-3-march-2020
- 4 CDC. Provisional Death Counts for Coronavirus Disease 2019 (COVID-19) [Internet], 2021. Available: https://www.cdc.gov/nchs/ covid19/mortality-overview.htm
- 5 Shehab M, Alrashed F, Shuaibi S, et al. Gastroenterological and hepatic manifestations of patients with COVID-19, prevalence, mortality by country, and intensive care admission rate: systematic review and meta-analysis. BMJ Open Gastroenterol 2021;8:e000571.
- 6 Ungaro RC, Brenner EJ, Gearry RB, et al. Effect of IBD medications on COVID-19 outcomes: results from an international registry. Gut 2021;70:725–32.
- 7 Ahlawat S, Asha SKK, Sharma KK. Immunological co-ordination between gut and lungs in SARS-CoV-2 infection. *Virus Res* 2020;286:198103.
- 8 Monteleone G, Ardizzone S. Are patients with inflammatory bowel disease at increased risk for Covid-19 infection? *J Crohns Colitis* 2020;14:1334–6.
- 9 Brenner EJ, Ungaro RC, Colombel JF KM. SECURE-IBD [Internet], 2021. Available: covidibd.org
- 10 Agrawal M, Brenner EJ, Zhang X, et al. Characteristics and outcomes of IBD patients with COVID-19 on tofacitinib therapy in the SECURE-IBD registry. *Inflamm Bowel Dis* 2021;27:585–9.
- 11 Brenner EJ, Ungaro RC, Gearry RB, et al. Corticosteroids, but not TNF antagonists, are associated with adverse COVID-19 outcomes in patients with inflammatory bowel diseases: results from an international registry. *Gastroenterology* 2020;159:481–91.
- 12 Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71.

- 13 Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA 2000;283:2008-12.
- Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 2019;366:I4898-8.
- 15 Sterne JA, Hernán MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ 2016:355:i4919-10.
- Lo CKL MD, Loeb M. Newcastle-Ottawa Scale: comparing 16 reviewers' to authors' assessments. BMC Med Res Methodol 2014:14:1-5
- 17 In:. Ungaro RC. The impact of COVID-19 on IBD patients lessons from SECURE-IBD registry. Oral Presentation Presented at: 16th Congress of ECCO.
- 18 Agrawal M, Zhang X, Brenner EJ, et al. The impact of vedolizumab on COVID-19 outcomes among adult IBD patients in the SECURE-IBD registry. J Crohns Colitis 2021:1-8.
- 19 Queiroz NSF, Martins CdeA, Quaresma AB, et al. COVID-19 outcomes in patients with inflammatory bowel diseases in Latin America: results from SECURE-IBD registry. J Gastroenterol Hepatol 2021:1-8.
- 20 Strangfeld A, Schäfer M, Gianfrancesco MA, et al. Factors associated with COVID-19-related death in people with rheumatic diseases: results from the COVID-19 Global Rheumatology Alliance physician-reported registry. Ann Rheum Dis 2021;80:930-42.
- 21 Lim WC, Wang Y, Macdonald JK. Aminosalicylates for induction of remission or response in Crohn's disease. Cochrane Database Syst Rev 2016;7.
- Ak A, Zhang D, Gordon M, et al. Remission in Crohn's disease 22 (Review), 2016.
- 23 Khan N, Mahmud N, Trivedi C. Risk factors for SARS-CoV-2 infection and course of COVID-19 disease in patients with IBD in the Veterans affair healthcare system. Gut 2021:1-8.
- 24 Meyer A, Semenzato L, Zureik M, et al. Risk of severe COVID-19 in patients treated with IBD medications: a French nationwide study. Aliment Pharmacol Ther 2021;54:160–6
- 25 Fagni F, Simon D, Tascilar K, et al. COVID-19 and immunemediated inflammatory diseases: effect of disease and treatment on COVID-19 outcomes and vaccine responses. Lancet Rheumatol 2021;3:e724-36.
- 26 Rizzello F, Calabrese C, Salice M, et al. COVID-19 in IBD: the experience of a single tertiary IBD center. Digestive and Liver Disease 2021;53:271-6.
- Gubatan J, Levitte S, Balabanis T, et al. SARS-CoV-2 testing, 27 prevalence, and predictors of COVID-19 in patients with inflammatory bowel disease in northern California. Gastroenterology 2020:159:1141-4.
- Kirchgesner J, Lemaitre M, Carrat F, et al. Risk of serious and 28 opportunistic infections associated with treatment of inflammatory bowel diseases. Gastroenterology 2018;155:e10:337-46.
- Seksik P, Cosnes J, Sokol H, et al. Incidence of benign upper respiratory tract infections, HSV and HPV cutaneous infections in inflammatory bowel disease patients treated with azathioprine. Aliment Pharmacol Ther 2009;29:1106–13.
- 30 The RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with Covid-19. N Engl J Med 2021:384:693-704.

- 31 Fadel R. Morrison AR. Vahia A. et al. Early short-course corticosteroids in hospitalized patients with COVID-19. Clin Infect Dis 2020;71:2114-20.
- 32 Tortajada C, Colomer E, Andreu-Ballester JC, et al. Corticosteroids for COVID-19 patients requiring oxygen support? Yes, but not for everyone: effect of corticosteroids on mortality and intensive care unit admission in patients with COVID-19 according to patients' oxygen requirements. J Med Virol 2021;93:1817-23.
- 33 Villar J, Ferrando C, Martínez D, et al. Dexamethasone treatment for the acute respiratory distress syndrome: a multicentre, randomised controlled trial. Lancet Respir Med 2020;8:267-76.
- 34 Keller MJ, Kitsis EA, Arora S, et al. Effect of systemic glucocorticoids on mortality or mechanical ventilation in patients with COVID-19. J Hosp Med 2020;15:489–93.
- 35 Budhathoki P. Shrestha DB. Rawal E. et al. Corticosteroids in COVID-19: is it rational? A systematic review and meta-analysis. SN Compr Clin Med 2020;2:2600-20.
- 36 Fletcher J. What is heterogeneity and is it important? BMJ 2007:334:94-6.
- Guan W-J, Ni Z-Y, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med* 2020;382:1708–20. Bezzio C, Saibeni S, Variola A, *et al*. Outcomes of COVID-19 in 79
- 38 patients with IBD in Italy: an IG-IBD study. Gut 2020;69:1213-7.
- 39 Tang Y, Liu J, Zhang D, et al. Cytokine storm in COVID-19: the current evidence and treatment strategies. Front Immunol 2020:11:1-13.
- 40 Bezzio C, Pellegrini L, Manes G, et al. Biologic therapies may reduce the risk of covid-19 in patients with inflammatory bowel disease. Inflamm Bowel Dis 2020;26:e107-9.
- 41 Feldmann M, Maini RN, Woody JN, et al. Trials of anti-tumour necrosis factor therapy for COVID-19 are urgently needed. Lancet 2020:395:1407-9
- Lees CW, Irving PM, Beaugerie L. COVID-19 and IBD drugs: should 42 we change anything at the moment? Gut 2021;70:632-4.
- 43 Henderson LA, Canna SW, Schulert GS, et al. On the alert for cytokine storm: immunopathology in COVID-19. Arthritis Rheumatol 2020:72:1059-63.
- 44 Messina F, Piaserico S. SARS-CoV-2 infection in a psoriatic patient treated with IL-23 inhibitor. J Eur Acad Dermatol Venereol . 2020:34:e254–5.
- 45 Guimarães PO, Quirk D, Furtado RH, et al. Tofacitinib in patients hospitalized with Covid-19 pneumonia. N Engl J Med 2021;385:406-15.
- 46 Haberman R, Axelrad J, Chen A, et al. Covid-19 in immunemediated inflammatory diseases - case series from New York. N Engl J Med 2020;383:85-8.
- 47 Kennedy NA, Jones G-R, Lamb CA, et al. British Society of Gastroenterology guidance for management of inflammatory bowel disease during the COVID-19 pandemic. Gut 2020;69:984-90.
- 48 Rubin DT, Abreu MT, Rai V, et al. Management of patients with Crohn's disease and ulcerative colitis during the coronavirus disease-2019 pandemic: results of an international meeting. Gastroenterology 2020;159:6-13.
- 49 Singh AK, Jena A, Kumar-M P, et al. Risk and outcomes of coronavirus disease in patients with inflammatory bowel disease: a systematic review and meta-analysis. United European Gastroenterol J 2021;9:159-76.