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REVIEW

Risk of adverse outcomes in inflammatory bowel disease patients infected with SARS-CoV-2: a systematic review and meta-analysis

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Abstract

Background Between people with and without inflammatory bowel disease (IBD), there was no statistically significant difference in the probability of contracting the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). However, the risk of adverse outcomes in IBD patients after virus infection remains unclear.

Methods Eligible studies conducted from January 1, 2020 to March 17, 2022 were obtained by searching PubMed, Embase, and Web of Science. Information was collected in tables from the included studies. Random-effects and fixed-effects models were used as measures for the pooled estimates. All data were estimated by R version 4.1.3.

Results Twenty-four studies were included. The risk ratio (RR) of adverse outcomes in COVID-19 patients with IBD increased by 32% (RR 1.32; 95% CI 1.06–1.66) relative to COVID-19 patients without IBD. The RR of mortality was higher in COVID-19 patients with IBD from Europe (RR 1.72; 95% CI 1.11–2.67) than in those that were not from Europe (RR 1.00; 95% CI 0.79–1.26; $\chi^2 = 4.67$; $P = 0.03$). Patients with ulcerative colitis were at higher risk of adverse outcomes after SARS-CoV-2 infection than patients with Crohn's disease patients (RR1.38; 95% CI 1.27–1.50). The IBD drugs treatment was associated with the risk of adverse outcomes, the pooled odds ratio (OR) of mesalazine (1.79; 95% CI 1.59–2.02), immunomodulators (1.30; 95% CI 1.10–1.53), and anti-TNF (0.47; 95% CI 0.41–0.53) were assessed.

Conclusion COVID-19 patients with IBD had an increased risk of adverse outcomes than those without IBD, whereas anti-TNF treatment might reduce the risk.

Keywords SARS-CoV-2 · Adverse outcome · IBD · IBD drug · Meta-analysis

Introduction

The coronavirus disease 2019 (COVID-19) has exerted the most significant impact on human health among the epidemics in the last 100 years [1, 2]. As of May 29, 2022, more than 526 million people had been infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and over six million died due to the virus [3]. Preliminary studies have shown that advanced age, being male, high BMI, and pre-existing chronic diseases increase the risk of developing adverse forms and fatal outcomes [4, 5]. The entry of SARS-CoV-2 into host cells depend on the interactions of viral spike protein and angiotensin-converting enzyme 2 (ACE-2) [6, 7]. Thus, high ACE-2 expression levels in intestinal epithelial cells and SARS-CoV-2 may cause intestinal symptoms or results in poor prognosis in patients with chronic intestinal diseases [8–11].

Inflammatory bowel disease (IBD) refers to a group of disabling chronic and immune-mediated inflammatory disorders including ulcerative colitis (UC) and Crohn's disease (CD) and is associated with human immune system [12]. In 2017, approximately 6.8 million patients with IBD were recorded worldwide [13], including 2 million from Europe and 1.5 million from North America [14]. Notably, ACE-2 expression increases in patients with IBD, particularly in the colonic tissue of patients with UC [8, 15], which might enable SARS-CoV-2 infection and cause poor outcomes

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[16]. The intestine might serve as an entry point for serious COVID-19 complications, such as endotoxemia and thrombosis [17]. In addition, a significant proportion of patients with IBD are treated with IBD drugs, including mesalazine, corticosteroids, immunomodulators (IMs), and anti-TNF, which may be associated with low immunity in patients and increased risk of COVID-19 infection and adverse outcomes [18–21].

Given these premises, a much-debated question is whether patients with IBD are at increased risk of being infected by COVID-19 and developing adverse outcomes [22–27]. Currently, the world is going through massive waves of infections by the omicron and delta variants of SARS-CoV-2, and the vast majority of people seem to be susceptible to the omicron variant [28]. Although the virulence of this variant has weakened and disease severity has been reduced through vaccination [29], the vast waves of omicron infections have indicated increasing number of adverse outcomes [28], especially in people with underlying diseases [30–32]. Therefore, focusing on adverse outcomes, such as hospitalization, intensive care unit (ICU), and mortality in COVID-19 patients with IBD in the context of high infectivity of SARS-CoV-2 is critical.

To date, the risk of adverse outcomes in patients with IBD after SARS-CoV-2 infection is contradictory in different studies [25–27, 33], and a meta-analysis assessed this risk in COVID-19 patients with and without IBD has not been conducted. Therefore, we performed the meta-analysis. Then, the association between adverse outcomes and IBD drug treatment in COVID-19 patients with IBD was explored.

Materials and methods

Search strategy

We systematically searched electronic databases (PubMed, Embase, and Web of Science) from January 1, 2020 to March 17, 2022 by three independent authors (CL, HK, and CC). The following combined free-text terms and MeSH terms with no language limitation were used: COVID-19 (such as "COVID-19," "SARS-CoV-2," "2019 Novel Coronavirus," "2019-nCoV," "Coronavirus Disease-19," "2019-nCoV Disease," or "severe COVID-19") and IBD (such as "inflammatory bowel disease," "ulcerative colitis," "Crohn disease," "enteritides," "bowel disease," "IBD," "UC," or "CD") were adopted in the search strategies. In addition, we manually searched the lists of references of relevant articles to prevent omission. This meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Selection criteria

We used the PECO strategy (patient, exposure, comparison, outcome) in constructing research questions and searching evidence. The meta-analysis adopted the following inclusion criteria: (a) prevalence of adverse outcomes in COVID-19 patients with and without IBD can be calculated; (b) prevalence of adverse outcomes in patients suffering from different types of IBD (UC and CD) and infected with SARS-CoV-2 can be calculated; or (c) provided medication status (mesalazine, corticosteroids, IMs, and anti-TNF) in adverse and mild cases.

Adverse outcomes were defined as requiring hospitalization, invasive ventilation, or intensive care unit (ICU) admission, or death [34], and mild outcomes were defined as presenting with mild or no symptoms of COVID-19 and without adverse outcomes. The study included cross-sectional, cohort, case–control, and case series studies. Animal experiments, literature without complete original data and no access to original data, and single case reports were excluded.

Data extraction and quality assessment

First, two authors (CL and HK) independently analyzed the titles and abstracts to exclude irrelevant studies. Subsequently, the full texts of the included studies were further reviewed. In the case of any disagreement, a third reviewer was consulted (CC).

The following pieces of information were extracted from the included studies: first author, study name, type of study design, publication year, country, number of COVID-19 patients with IBD, number of adverse outcomes in patients with IBD, number of comparators (COVID-19 patients without IBD), number of comparators with adverse outcomes, type of IBD (UC and CD), demographic information (age, gender, and comorbidity), and ongoing IBD treatments, including mesalazine, corticosteroids, IMs (including azathioprine, mercaptopurine, and methotrexate), and anti-TNF. The Newcastle–Ottawa scale (NOS) was used in evaluating the quality of eligible studies [35]. Each study has a maximum score of nine (highest quality), and a NOS score of ≥ 6 indicated high quality.

Data analysis

The RR was used as a unified effect size for assessing the risk of adverse outcomes in COVID-19 patients with IBD and those without and in patients with UC or CD. And the odds ratio (OR) was used in estimating the association between IBD drugs and adverse outcomes. Random-effects models ($I^2 > 50\%$) and common-effects models ($I^2 \leq 50\%$)

were used in estimating the pooled adjusted effect, and Q test and I^2 statistics were used in assessing heterogeneity among the studies. An I^2 value of < 25% demonstrated no heterogeneity among the studies, 25–50% indicated low heterogeneity, and > 50% indicated moderate-to-high heterogeneity. For subgroup analyses, the studies were stratified by region, the source of the population, gender, age, disease type, and sample size. We further conducted sensitivity analysis by sequentially eliminating each study to assess the stability of the results. Egger's test and funnel plots were used in evaluating publication bias.

A two-tailed $P < 0.05$ was considered statistically significant in all the analyses, which were performed with R version 4.1.3 and RStudio (the integrated development environment of R) with meta-packages.

Results

Study selection and characteristics

The exclusion and inclusion processes for articles are presented in Fig. 1. A total of 2638 articles were identified in the databases. After duplicates were excluded, titles and abstracts of 2121 articles were screened, and full-text reading was performed in 223 studies. Finally, 24 articles met the inclusion criteria, and data from the SECURE-IBD registry were included (date of last update: January 25, 2022). Nine studies evaluated the risk of adverse outcomes in patients with IBD and COVID-19 and comparative population, and 14 studies evaluated the risk in patients with UC or CD. a total of 15 studies analyzed IBD drug exposure in adverse

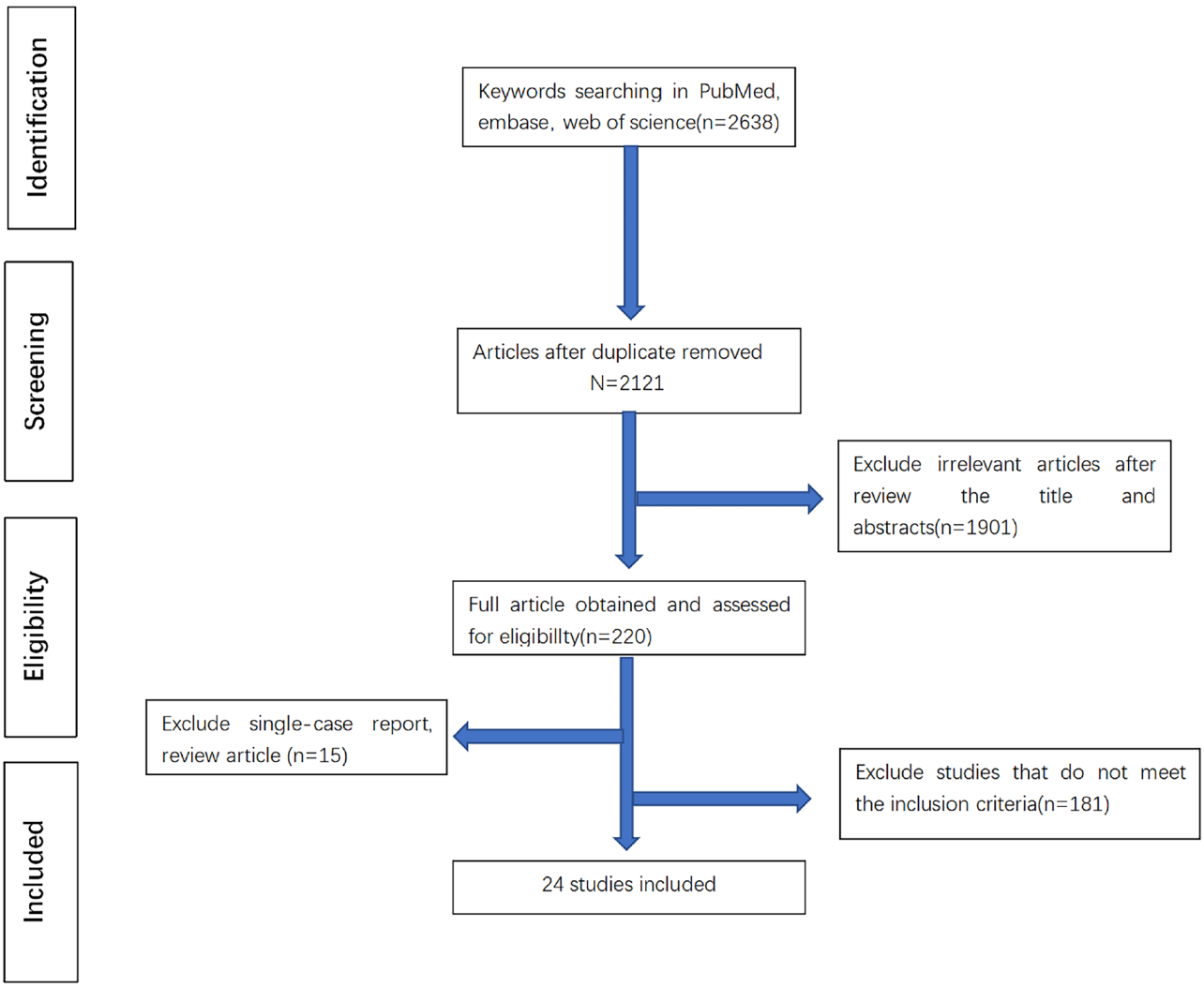


Fig. 1 Study selection flowchart. A total of 2638 studies were obtained from three databases: PubMed ($N = 886$), Embase ($N = 901$), and Web of Science ($N = 871$), by keyword search

Table 1 Demographics of the patients in the included studies

Authors	Location	Type of study	COVID-19 patients with IBD, *N*	Age(years)	Female, *N* (%)	Compare population, *N*	Patients with adverse outcomes, *N*		IBD drugs	Comorbidities, *N*	Inclusion criteria	NOS
							IBD	Comparators				
Ardizzone et al. [18]	Italy	Retrospective Cohort	7 (4 UC, 3 CD)	56 (26–78)	4(57.1)	85,481	4 (2 UC, 2 CD) Death: 2	42,942 Death:15,597	5-ASA 1 Steroid 1 Biologicals 7	2	a and c	7
Maconi et al. [22]	Italy	Case control	2	NA	NA	10	1	6	NA	NA	a	6
Singh et al. [25]	multiple health care organizations (HCOs) globally	Retrospective Cohort	232	51.2 ± 18.1	147 (63.4)	232	56	60	5-ASA 32 Steroid 111 IMS 62 Biologicals 37	Essential hypertension: 121 COPD and asthma: 91 DM: 62	a	7
Attauabi et al. [26]	Denmark	Prospective Cohort	516 (319 UC, 197 CD)	UC 48 (35–61) CD 44 (30–59)	270 (52.3)	230,087	70 (46 UC, 24 CD) Death:15	13,306 Death: 516	NA	365	a and c	6
Curtis et al. [37]	USA	Retrospective cohort	811	52 (18–89)	428 (52.8)	311,563	155 Death: 23	48,423 Death: 7937	Steroid 198 Anti-TNF 76 JAK 11 Tofacitinib 11	Hypertension: 1088 Hyperlipidemia:827 DM: 479 Coronary artery disease: 356 COPD: 288	a	7
Hadi et al. [38]	USA	Retrospective cohort	4310 (2082 UC, 2190 CD)	49.7 ± 18.19	2503 (58.1)	4310	515 (272 UC,235 CD) Death: 90	441 Death: 95	NA	Hypertension: 1934 Heart failure: 464 Chronic lower: 1499 DM: 868	a and c	7
Ludvigsson et al. [39]	Sweden	Prospective cohort	811	NA	NA	2890	IBD 202 Death:53	558 Death: 122	NA	NA	a	7
Attauabi et al. [36]	Denmark	Prospective cohort	76 (45 UC, 31 CD)	UC 51 (39–70) CD 54 (38–62)	31 (40.8)	7945	Death: 4	Death: 460	5-ASA 37 Steroid 6 IMS 16 Biologicals 18	26	a	6
Sima et al. [40]	Iran	Prospective cohort	84 (60 UC, 24 CD)	43.35 ± 14.1	35 (41.6)	49	36 (28 UC, 8 CD) Death: 1	8 Death: 1	5-ASA 59 Steroid 13 IMS 28 Anti-TNF 20	Hypertension: 11 Chronic Liver disease:8 DM: 7 COPD: 6	a, b and c	7
Allocca et al. [23]	France, Italy	Retrospective cohort	15 (6 UC,9 CD)	39 (26–61)	11 (73.3)	NA	5 (3 UC, 2 CD)	NA	5-ASA 1 Steroid 2 IMS 3 Biologicals 11	9	b and c	6
Axelrad et al. [41]	USA	Case series	84 (27 UC, 56 CD)	35 (27–45)	39 (47)	NA	5 (1 UC, 4 CD)	NA	5-ASA 13 Steroid 10 IMS 6 Biologicals 58 (anti-TNF 44)	Organ transplantation: 2 Kidney disease: 1 Hypertension: 3 DM: 1 COPD: 1	b and c	NA
Bezzio et al. [50]	Italy	Prospective cohort	11	NA	101 (41.6)	NA	2	NA	Steroid 9 Biologicals 2	93	c	7
Burke et al. [42]	USA	Retrospective cohort	39 (22 UC, 17 CD)	45.6 ± 18.8	24 (62)	NA	7 (5 UC, 2 CD)	NA	5-ASA 12 IMS 3 Biologicals 20 (anti-TNF 13)	Obesity: 11 DM: 3 Hypertension: 7 Asthma: 4	b and c	7
Conley et al. [48]	UK	Prospective cohort	42 (28 UC, 14 CD)	NA	NA	NA	0	NA	NA	NA	b	6
Kornbluth et al. [43]	USA	Retrospective cohort	65 (24 UC, 41 CD)	39 (17–71)	NA	NA	3 (3 UC, 0 CD)	NA	5-ASA 5 Steroid 2 IMS 1 Biologicals 37 Antibiotics 2	NA	b	6

Table 1 (continued)

Authors	Location	Type of study	COVID-19 patients with IBD, *N*	Age(years)	Female, *N* (%)	Compare population, *N*	Patients with adverse outcomes, *N*		IBD drugs	Comorbidities, *N*	Inclusion criteria	NOS
							IBD	Comparators				
Lamb et al. [44]	UK	Retrospective cohort	211 (109UC, 86 CD)	NA	94 (44.6)	NA	56 (37UC,16 CD)	NA	5-ASA 91 Steroid 10 IMS 34 Biologicals 95 (Anti-TNF 32)	COPD: 15 Hypertension: 52 DM: 31 Obesity: 11	b and c	7
Lee et al. [49]	South Korea	Case series	9 (7 UC, 2 CD)	42 (21–64)	3 (33.3)	NA	0	NA	5-ASA 7 Steroid 1 IMS 2, Biologicals 2	1	b	NA
Rizzello et al. [46]	Italy	Cross-sectional	26 (11 UC, 15 CD)	49 (24–86)	14 (53.8)	NA	7 (4 UC, 3 CD)	NA	5-ASA 19 Steroid 4 IMS 1 Biologicals 4	10	b and c	NA
Taxonera et al. [33]	Spain	Case series	12 (5 UC, 7 CD)	51 (20–76)	9 (75.0)	NA	8 (5 UC, 3 CD)	NA	5-ASA 4 IMS 6 Biologicals 5	5	b and c	NA
Wetwittayakhlang et al. [47]	Canada	Retrospective cohort	82 (19 UC, 63 CD)	39 (27–48)	41 (50.0)	NA	6 (2 UC, 4 CD)	NA	5-ASA 18 Steroid 9 IMS 3 Biologicals 59 Antibiotics 3	CVD: 8 Chronic lung disease: 7 DM: 5 Obesity (BMI > 30 kg/m^2): 14 Malignancies: 2	b and c	6
Nakase et al. [45]	Japan	Retrospective cohort	187 (104 UC, 74 CD)	42.0 ± 15.6	72 (38.5)	NA	12 (11 UC,1 CD)	NA	5-ASA 144 Steroid 14 IMS 57 Anti-TNF 74	DM: 5 CKD: 4 Liver diseases: 8 CVD: 4 All: 56	b and c	7
Bezzio et al. [34]	Italy	Prospective cohort	937 (446 UC, 491 CD)	44 (10–86)	424 (45.3)	NA	165 (83 UC, 82 CD)	NA	5-ASA 492 Steroid 122 IMS 101 Biologicals 512 (anti-TNF 346)	376	b	7
Khan et al. [51]	USA	Retrospective cohort	649	NA	NA	NA	149	NA	5-ASA 247 Steroid 61 IMS 92 Biologicals 173	NA	c	6
Zabana et al. [52]	Spain	Prospective cohort	482 (221 UC, 247 CD)	52 (42–61)	231 (48)	NA	167	NA	5-ASA 202 Steroid 26 IMS 113 Biologicals 117 (anti-TNF 117)	NA	b	7

The values of age are median (interquartile range, IQR) or mean ± standard deviation (SD)

NA data not available, *5-ASA* mesalazine, *IMS* immunomodulators including azathioprine, mercaptopurine and methotrexate, *JAK* JAK inhibitor, *DM* diabetes mellitus, *CKD* chronic kidney disease, *BMI* body mass index, *COPD* chronic obstructive pulmonary disease, *CVD* cardiovascular disease, *NOS* Newcastle–Ottawa scale

and mild cases. Among these studies, 13 were conducted in European countries, seven in North American countries (six in the USA and one in Canada), three in Asia, and one in multiple healthcare organizations.

Table 1 provides the included studies' main characteristics, including type of research, location, publication date, number of subjects, use of IBD drugs, comorbidities, types of inclusion criteria (a, b, and c), and NOS score. Among the included studies, 20 respected the NOS for good-quality research, and three case series and one cross-sectional study had unclear answers.

Risk of adverse outcomes in COVID-19 patients with IBD versus comparative population

Nine studies regarded IBD as the exposure factor in COVID-19 patients and adverse effects as outcomes [18, 22, 25, 26, 36–40]. A total of 7280 COVID-19 patients with IBD and 635,363 COVID-19 patients without IBD served as the comparative populations, including a matched population adjusted for age, gender, and comorbidities and the general population in the same period. In the comparison of the risk of adverse outcomes in COVID-19 patients with IBD and comparators, the pooled RR was 1.32 (95% CI 1.06–1.66), and heterogeneity was high ($I^2=81\%$; $P<0.01$; Fig. 2). The results of Egger's test indicated no evidence of publication bias ($P=0.72$). In subgroup analyses performed according to the source of comparators (matched and general population), the pooled RRs of adverse outcomes were 1.20 (95% CI 1.12–1.29; $I^2=40\%$; $P=0.13$) in the control population group and 1.74 (95% CI 0.87–3.50; $I^2=77\%$; $P=0.04$; Fig. 2) in the general population group.

In the analysis of the risk of mortality in COVID-19 patients with IBD, the pooled RR values were 1.35 (95% CI 0.95–1.92; $I^2=63\%$; $P=0.01$), 1.72 (95% CI 1.11–2.67) with mild heterogeneity ($I^2=47\%$; $P=0.13$) in the European studies, and 1.00 (95% CI 0.79–1.26; $I^2=0\%$; Supplementary Fig. 1) in the non-European studies. The difference in the risk of mortality between the two groups was statistically significant ($\chi^2=4.67$; $P=0.03$). The RR of mortality in European patients with IBD was higher than that in non-European patients with IBD after SARS-CoV-2 infection.

Risk of adverse outcomes between UC and CD patients infected with SARS-CoV-2

Information from 16 studies and the SECURE-IBD registry were used in evaluating the risk of adverse outcomes in UC and CD patients infected with SARS-CoV-2, including 6243 UC patients and 7308 CD patients [18, 23, 33, 34, 36, 38, 40–49]. The pooled RR was 1.38 (95% CI 1.27–1.50), with no evidence of heterogeneity ($I^2=13\%$; $P=0.31$; Fig. 3) or publication bias (Egger's test, $P=0.36$). On the risk of mortality in UC and CD patients infected with SARS-CoV-2, the summary RR was 1.35 (95% CI 1.04–1.75; $I^2=0\%$; Supplementary Fig. 2).

Association between adverse outcomes and IBD drugs in COVID-19 patients with IBD

Data used in evaluating the association between adverse outcomes and IBD drugs were obtained from the 12 included studies and the SECURE-IBD registry, including 1474 adverse and 7445 mild cases [23, 33, 41, 42, 44–47, 50–52]. The pooled OR of mesalazine (1.79; 95% CI 1.59–2.02; $I^2=44\%$; $P=0.05$), corticosteroids (1.66; 95% CI 0.99–2.78; $I^2=64\%$; $P<0.01$), IMS (1.30; 95% CI 1.10–1.53; $I^2=45\%$; $P=0.04$), anti-TNF (0.47; 95% CI 0.41–0.53; $I^2=0\%$; $P=0.59$) are shown in Fig. 4). No publication bias was observed (Egger's test, $P_{\text{mesalazine}}=0.83$, $P_{\text{corticosteroids}}=0.11$, $P_{\text{IMS}}=0.09$, $P_{\text{anti-TNF}}=0.46$).

Subgroup and sensitivity analyses

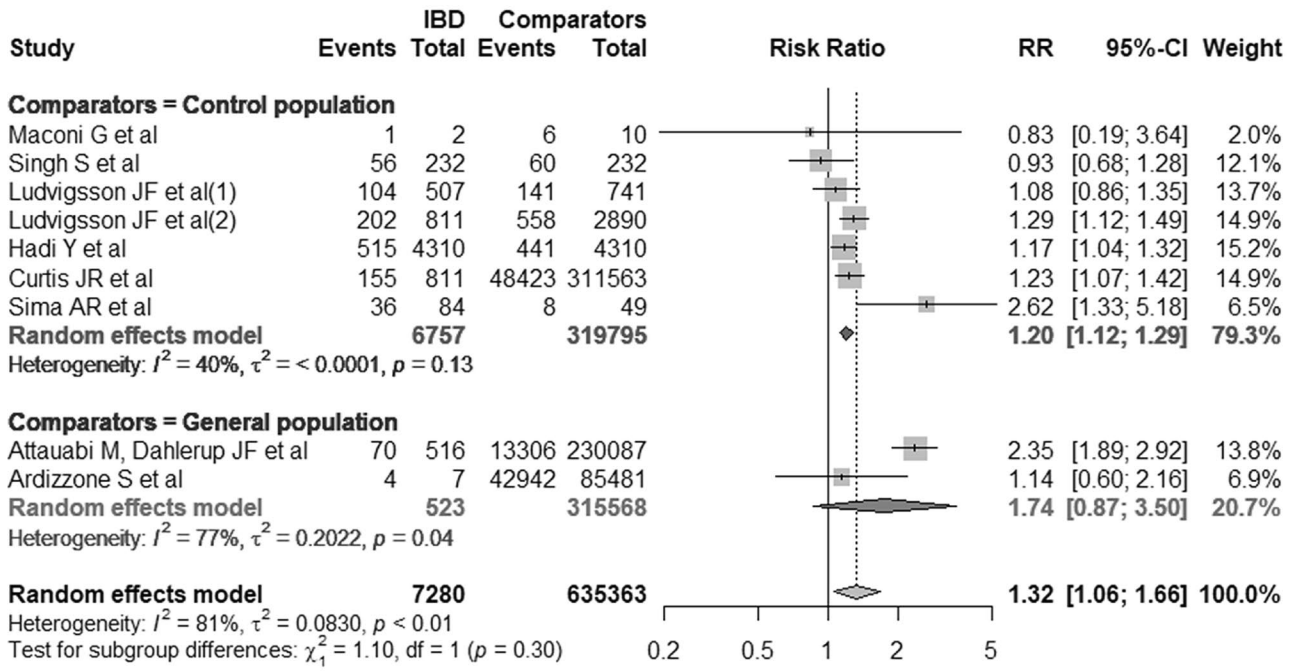
Subgroup analyses defined by age, region, sample size, source of comparators (control and general population), gender, and type of IBD were associated with the risk of adverse outcomes (Table 2). In subgroup analyses of the source of the comparators, the pooled RR was 1.20 (95% CI 1.12–1.29) with mild heterogeneity ($I^2=40\%$; $P=0.13$) in the control population group, and the pooled RR was 1.74 (95% CI 0.87–3.50) with high heterogeneity ($I^2=77\%$; $P=0.04$) in the general population group. Therefore, the different sources of comparators may account for the high heterogeneity.

In sensitivity analysis, none of the individual studies led to a substantial change in pooled risk in the leave-one-out analysis removing one study in turn (Supplementary Fig. 3).

Discussion

During the SARS-CoV-2 pandemic, IBD patients, as immune-mediated disease patients, should be treated more carefully than the general population. Until now, many patients with IBD did not receive or complete vaccines because of concerns about adverse reactions to vaccines, and the effectiveness of vaccines may wane more rapidly in patients with IBD [53–55]. Accumulating evidence of poor prognosis in patients with other diseases accompanied by IBD and increased risk of developing malignancies in these patients has been obtained, such as myocardial infarction and hematological malignancies [56–58]. Therefore, the risk of hospitalization, death, and other adverse outcomes in patients suffering from IBD and infected with SARS-CoV-2 should be an ongoing concern.

To the best of our knowledge, this study is the first meta-analysis to evaluate the risk of adverse outcomes between COVID-19 patients with and without IBD. In this study, we found that COVID-19 patients with IBD were at increased



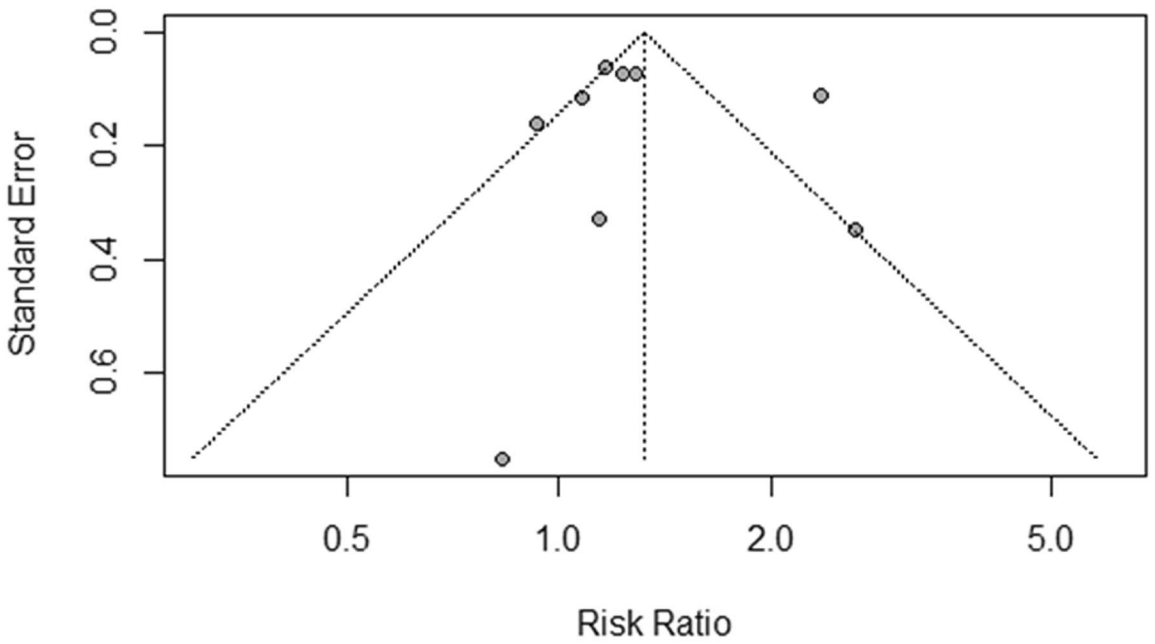


Fig. 2 Risk of adverse outcomes in COVID-19 patients with IBD versus comparative population. The comparison population includes the control population infected with SARS-CoV-2 adjusted for age, gender, and comorbidities and the general population infected with SARS-CoV-2 during the same period

risk for adverse outcomes than those without IBD. Furthermore, patients with UC have an increased risk than those with CD. Moreover, COVID-19 may intersect with the pathogenesis of IBD and extend treatment. As a result, mesalazine (5-ASA) and IMS treatment might be risk factors for adverse outcomes in COVID-19 patients with IBD. By contrast, anti-TNF treatment might provide protection against the development of negative outcomes.

On subgroup analyses of the source of comparators (control and general population group), there is a pooled RR with low heterogeneity in control population group adjusted for age, gender, and comorbidities. Inconsistency

in the distribution of these confounders may account for the heterogeneity.

The increased risk of adverse outcomes in patients with IBD may be associated with increased SARS-CoV-2

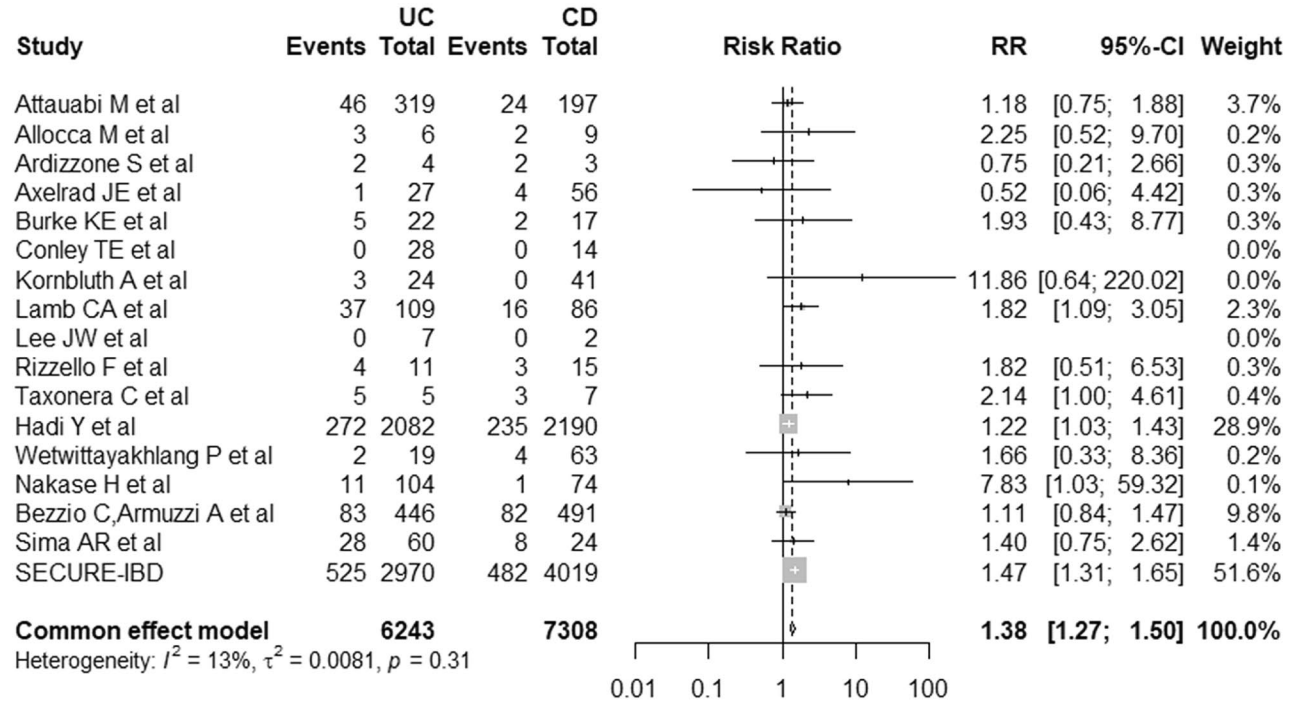


Fig. 4 Exposure to IBD drugs in adverse and mild cases. The study compared exposure to IBD drugs, including mesalazine; corticosteroids; immunomodulators (IMS), including azathioprine, mercaptopurine, and methotrexate; and anti-TNF in adverse and mild cases

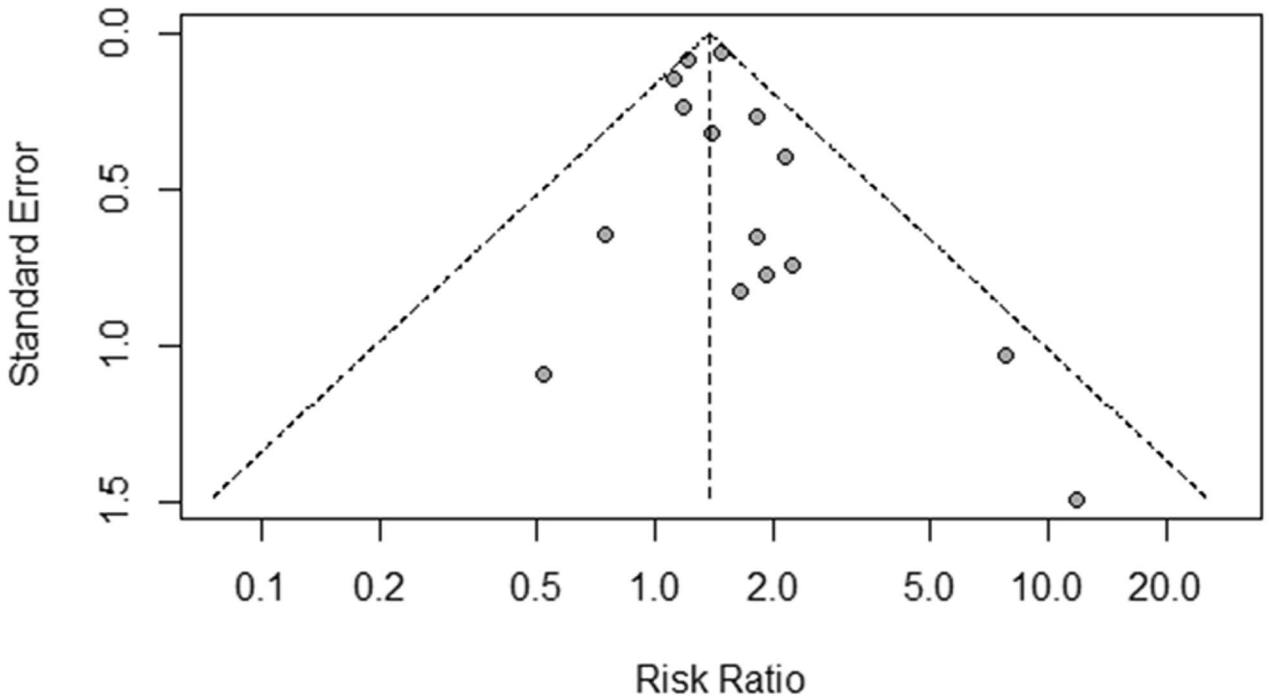
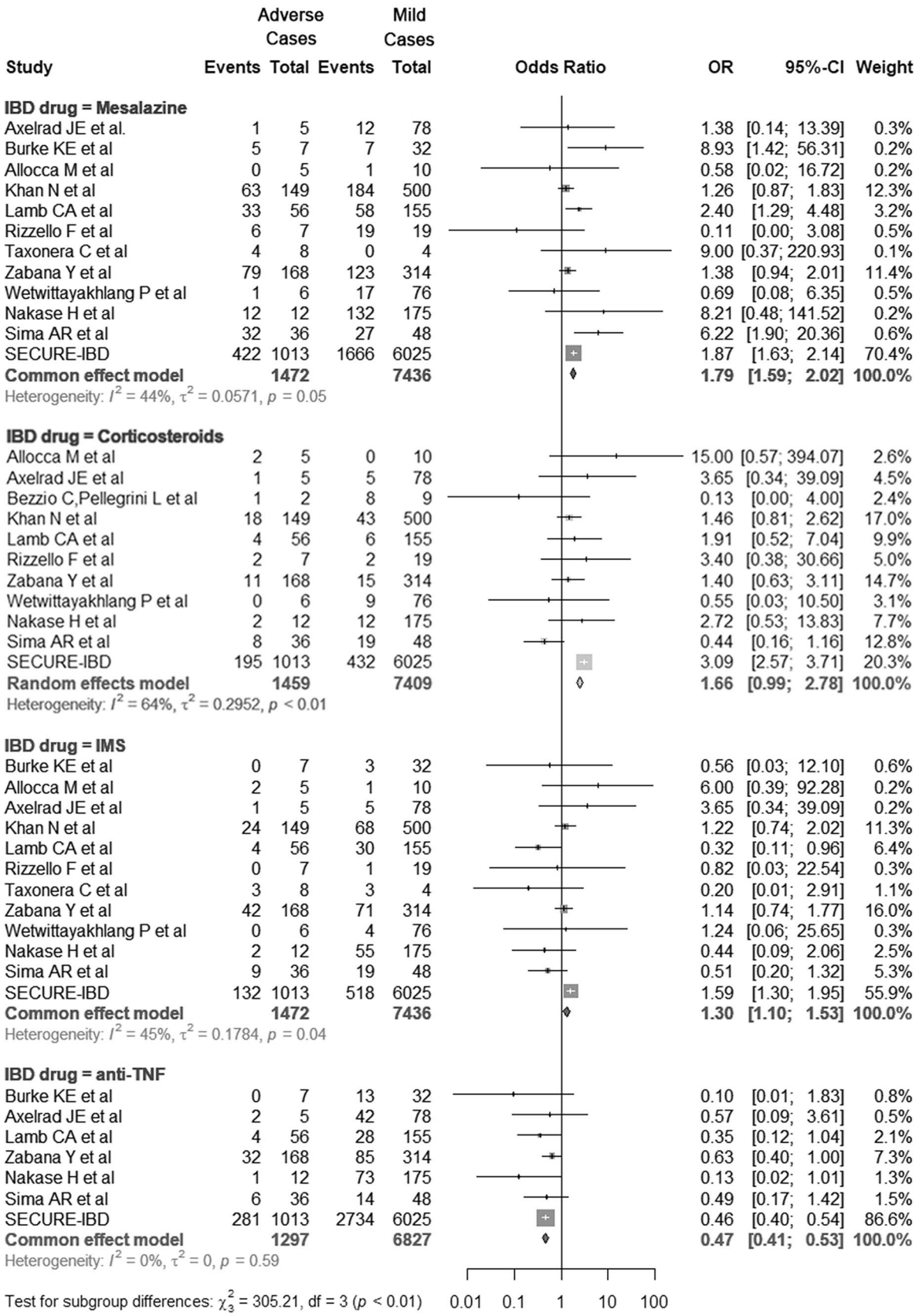


Fig. 3 Risk of adverse outcomes in COVID-19 patients with UC and CD


Adverse Cases
Mild Cases
Study Events Total Events Total Odds Ratio OR 95%-CI Weight
IBD drug = Mesalazine
Axelrad JE et al. 1 5 12 78 1.38 [0.14; 13.39] 0.3%
Burke KE et al 5 7 7 32 8.93 [1.42; 56.31] 0.2%
Allocca M et al 0 5 1 10 0.58 [0.02; 16.72] 0.2%
Khan N et al 63 149 184 500 1.26 [0.87; 1.83] 12.3%
Lamb CA et al 33 56 58 155 2.40 [1.29; 4.48] 3.2%
Rizzello F et al 6 7 19 19 0.11 [0.00; 3.08] 0.5%
Taxonera C et al 4 8 0 4 9.00 [0.37; 220.93] 0.1%
Zabana Y et al 79 168 123 314 1.38 [0.94; 2.01] 11.4%
Wetwittayakhlang P et al 1 6 17 76 0.69 [0.08; 6.35] 0.5%
Nakase H et al 12 12 132 175 8.21 [0.48; 141.52] 0.2%
Sima AR et al 32 36 27 48 6.22 [1.90; 20.36] 0.6%
SECURE-IBD 422 1013 1666 6025 1.87 [1.63; 2.14] 70.4%
Common effect model 1472 7436 1.79 [1.59; 2.02] 100.0%
Heterogeneity: I^2 = 44%, τ^2 = 0.0571, p = 0.05
IBD drug = Corticosteroids
Allocca M et al 2 5 0 10 15.00 [0.57; 394.07] 2.6%
Axelrad JE et al 1 5 5 78 3.65 [0.34; 39.09] 4.5%
Bezzio C,Pellegrini L et al 1 2 8 9 0.13 [0.00; 4.00] 2.4%
Khan N et al 18 149 43 500 1.46 [0.81; 2.62] 17.0%
Lamb CA et al 4 56 6 155 1.91 [0.52; 7.04] 9.9%
Rizzello F et al 2 7 2 19 3.40 [0.38; 30.66] 5.0%
Zabana Y et al 11 168 15 314 1.40 [0.63; 3.11] 14.7%
Wetwittayakhlang P et al 0 6 9 76 0.55 [0.03; 10.50] 3.1%
Nakase H et al 2 12 12 175 2.72 [0.53; 13.83] 7.7%
Sima AR et al 8 36 19 48 0.44 [0.16; 1.16] 12.8%
SECURE-IBD 195 1013 432 6025 3.09 [2.57; 3.71] 20.3%
Random effects model 1459 7409 1.66 [0.99; 2.78] 100.0%
Heterogeneity: I^2 = 64%, τ^2 = 0.2952, p < 0.01
IBD drug = IMS
Burke KE et al 0 7 3 32 0.56 [0.03; 12.10] 0.6%
Allocca M et al 2 5 1 10 6.00 [0.39; 92.28] 0.2%
Axelrad JE et al 1 5 5 78 3.65 [0.34; 39.09] 0.2%
Khan N et al 24 149 68 500 1.22 [0.74; 2.02] 11.3%
Lamb CA et al 4 56 30 155 0.32 [0.11; 0.96] 6.4%
Rizzello F et al 0 7 1 19 0.82 [0.03; 22.54] 0.3%
Taxonera C et al 3 8 3 4 0.20 [0.01; 2.91] 1.1%
Zabana Y et al 42 168 71 314 1.14 [0.74; 1.77] 16.0%
Wetwittayakhlang P et al 0 6 4 76 1.24 [0.06; 25.65] 0.3%
Nakase H et al 2 12 55 175 0.44 [0.09; 2.06] 2.5%
Sima AR et al 9 36 19 48 0.51 [0.20; 1.32] 5.3%
SECURE-IBD 132 1013 518 6025 1.59 [1.30; 1.95] 55.9%
Common effect model 1472 7436 1.30 [1.10; 1.53] 100.0%
Heterogeneity: I^2 = 45%, τ^2 = 0.1784, p = 0.04
IBD drug = anti-TNF
Burke KE et al 0 7 13 32 0.10 [0.01; 1.83] 0.8%
Axelrad JE et al 2 5 42 78 0.57 [0.09; 3.61] 0.5%
Lamb CA et al 4 56 28 155 0.35 [0.12; 1.04] 2.1%
Zabana Y et al 32 168 85 314 0.63 [0.40; 1.00] 7.3%
Nakase H et al 1 12 73 175 0.13 [0.02; 1.01] 1.3%
Sima AR et al 6 36 14 48 0.49 [0.17; 1.42] 1.5%
SECURE-IBD 281 1013 2734 6025 0.46 [0.40; 0.54] 86.6%
Common effect model 1297 6827 0.47 [0.41; 0.53] 100.0%
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.59
Test for subgroup differences: χ^2_3 = 305.21, df = 3 (p < 0.01)
0.01 0.1 1 10 100

replication and imbalance of ACE-2 levels in the intestine. On the one hand, the intestines of IBD patients with high ACE-2 expression may provide favorable sites for virus replication. On the other hand, ACE-2 not only is a SARS-CoV-2 binding receptor but also acts as an enzyme in the renin–angiotensin system to reduce inflammatory response [59, 60]. The renin–angiotensin system functions in inflammation, fibrosis, and cell proliferation in opposite roles regulated through two complementary pathways (classical and alternative) [61, 62]. The ACE-2/Ang 1–7/MasR axis can reduce proinflammatory response and cytokine storm in the renin–angiotensin system [63]. Recent studies have revealed that the key enzymes of the system (ACE and ACE-2) were expressed and active in the human intestine [62, 64]. As a result of binding to virus, ACE-2 in the guts of patients with IBD may be severely depleted [65], and this effect may result in an imbalance in the renin–angiotensin system that promotes fibrosis and inflammatory response and has negative effects.

Similarly, differences in ACE-2 expression levels in the guts of patients with UC or CD may account for differences in the risk of developing adverse outcomes. In contrast to the results of our study, UC patients without COVID-19 were not at increased risk of developing adverse outcomes in contrast to CD patients without COVID-19 [66, 67]. These findings were consistent with the meta-analysis results. In addition to the above reason, UC patients may prefer 5-ASA [68], an IBD drug associated with high risk of developing adverse outcomes. In our study, 5-ASA and IMS treatments might be risk factors for adverse outcomes in COVID-19 patients with IBD. By contrast, anti-TNF treatment might protect against the development of negative outcomes. Notably, reduced small bowel but elevated colonic ACE-2 levels in IBD patients were associated with adverse outcomes but returned to normal after anti-TNF therapy [69]. Although evidence showing the risk of adverse outcomes in IBD patients treated wtih corticosteroids is insufficient, previous studies have shown that corticosteroids should be selected carefully [70, 71].

Our study has some limitations. Nevertheless, it has offered a comprehensive review of the risk of adverse outcomes in IBD patients after being infected with SARS-CoV-2, in patients with UC or CD, and in patients using different IBD treatment drugs. First, many small case series were included in our meta-analysis, including four studies with quality not evaluated using the NOS. Second, heterogeneity in our meta-analysis was high, which is a general limitation of all published COVID-19 studies. Third, some studies showed data duplication in reporting adverse outcomes, such as hospitalization, ICU admission, and death. In these studies, the number of patients hospitalized or admitted to ICUs was the number of patients with adverse outcomes, and some patients who died but were not hospitalized may have been not included.

In conclusion, this systematic review and meta-analysis shows that COVID-19 patients with IBD have a higher risk of developing adverse outcomes than patients without IBD.

Table 2 Subgroup analysis on the risk of adverse COVID-19 outcomes in IBD patients

Subgroup	Studies, *n*	RR (95%CI)	I^2(%)	*P*
Source of the comparators				
Comparators = matched population	7	1.20 (1.12–1.29)	40	0.13
Comparators = general population	2	1.74 (0.87–3.50)	77	0.04
Geographic area				
Europe	5	1.38 (0.97–1.98)	86	< 0.01
Non-Europe	4	1.19 (1.09–1.29)	61	0.05
Sample size				
≥ 100	6	1.29 (1.01–1.64)	87	< 0.01
< 100	3	1.52 (0.77–3.00)	48	0.14
Gender (male, %)				
≥ 55	1	2.62 (1.33–5.18)		
< 55	5	1.31 (0.95–1.81)	89	< 0.01
NA	3	1.20 (1.01–1.43)	4	0.35
Type of IBD (UC, %)				
≥ 55	3	1.44 (0.94–2.21)	57	0.10
< 55	3	1.37 (0.80–2.36)	94	< 0.01
NA	3	1.20 (1.01–1.43)	4	0.35
Age				
≥ 50	3	1.13 (0.92–1.39)	18	0.29
< 50	3	1.84 (1.09–3.10)	94	< 0.01
NA	3	1.20 (1.01–1.43)	4	0.35

NA data not available, *RR* risk ratio

The 5-ASA and IMS treatments may be associated with high risk of adverse outcomes in COVID-19 patients with IBD, whereas anti-TNF treatment can reduce this risk.

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Declarations

Competing interests The authors declare no competing interests.

Conflict of interest The authors declare no competing interests.

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