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REVIEW

COVID-19 susceptibility and clinical outcomes in inflammatory bowel disease: An updated systematic review and meta-analysis

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Abstract

The susceptibility, risk factors, and prognosis of COVID-19 in patients with inflammatory bowel disease (IBD) remain unknown. Thus, our study aims to assess the prevalence and clinical outcomes of COVID-19 in IBD. We searched PubMed, EMBASE, and medRxiv from 2019 to 1 June 2022 for cohort and case-control studies comparing the prevalence and clinical outcomes of COVID-19 in patients with IBD and in the general population. We also compared the outcomes of patients receiving and not receiving 5-aminosalicylates (ASA), tumour necrosis factor antagonists, biologics, systemic corticosteroids, or immunomodulators for IBD. Thirty

Abbreviations: IBD, inflammatory bowel disease; ASA, aminosalicylates; ICU, intensive care unit; OR, odds ratio; CI, confidence interval; CD, Crohn's disease; UC, ulcerative colitis; ACE-2, Angiotensin-converting enzyme 2; GI, gastrointestinal; TNF, tumour-necrotising factor; BMI, body mass index..

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five studies were eligible for our analysis. Pooled odds ratio of COVID-19-related hospitalisation, intensive care unit (ICU) admission, or death in IBD compared to in non-IBD were 0.58 (95% confidence interval (CI) = 0.28–1.18), 1.09 (95% CI = 0.27–4.47), and 0.67 (95% CI = 0.32–1.42), respectively. Inflammatory bowel disease was not associated with increased hospitalisation, ICU admission, or death. Susceptibility to COVID-19 did not increase with any drugs for IBD. Hospitalisation, ICU admission, and death were more likely with 5-ASA and corticosteroid use. COVID-19-related hospitalisation (Odds Ratio (OR): 0.53; 95% CI = 0.38–0.74) and death (OR: 0.13; 95% CI = 0.13–0.70) were less likely with Crohn's disease than ulcerative colitis (UC). In conclusion, IBD does not increase the mortality and morbidity of COVID-19. However, physicians should be aware that additional monitoring is needed in UC patients or in patients taking 5-ASA or systemic corticosteroids.

KEYWORDS
COVID-19, Crohn's disease, inflammatory bowel disease, meta-analysis, ulcerative colitis

1 | INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of coronavirus disease 2019 (COVID-19), continues to spread worldwide with no clear signs of diminishing, despite the release of multiple effective vaccines.[1] It has become apparent that the disease will likely follow humanity for years to come. This pandemic is particularly fearful for patients with weakened immunity, including those with inflammatory bowel disease (IBD) who frequently receive immunosuppressive therapy. Suitable therapeutic or diagnostic methods were needed to reduce close contact between gastrointestinal (GI) physicians and the referred infected patients.[2] Inflammatory bowel disease, which refers to Crohn's disease (CD) and ulcerative colitis (UC), is associated with significant morbidity and a high burden of hospitalisation, surgery, and use of immunosuppressive agents.[3] Additionally, the prevalence of IBD is over 0.3% in North America and the incidence has been rising in some newly industrialised countries.[4] As some studies revealed that combination therapies for patients with IBD increase the risk of serious infection, it is of prime importance to study the incidence and clinical prognosis of COVID-19 according to IBD and immunosuppressive agents.[5]

While COVID-19 is known to cause increased morbidity and mortality in populations with chronic diseases such as diabetes and coronary heart disease, its effect on patients with IBD and the immunosuppressive drugs is still unclear.[6] Angiotensin-converting enzyme 2 (ACE-2) is the cell receptor that SARS-CoV-2 binds to in order to enter the host cell.[7] Angiotensin-converting enzyme 2 is expressed on pneumocytes of the lower respiratory tracts, which may explain the high frequency of pneumonia in COVID-19 patients. Intestinal cells also express ACE-2. As GI symptoms such as diarrhoea are increasingly reported in mild COVID-19 patients, several studies support direct infection of SARS-CoV-2 via ACE-2 in intestinal cells.[8] There are conflicting data, but several studies support that IBD could increase ACE-2 activity and expression in the GI tract and that its therapeutic agents have the opposite effect.[9,10] Taken together, these findings suggest that IBD patients may be vulnerable to COVID-19. However, there have been some studies reporting that IBD and related therapies are not likely to increase susceptibility to COVID-19.[11,12] In addition, in COVID-19 patients from China, immunodeficiency was not found to be related to the severity of COVID-19.[13] As for drug-related risk factors, some studies argue that corticosteroids are associated with adverse COVID-19 outcomes in patients with IBD, but tumour-necrotising factor antagonists are not.[14] However, most current evidence has not been evaluated by systematic reviews or is outdated. There has been one meta-analysis on COVID-19 in patients with IBD.[15] However, since its publication, many new studies on COVID-19 in IBD patients have been published, therefore there is a need for an updated meta-analysis on this subject.

In this systematic review and meta-analysis, we aim to not only investigate the morbidity and mortality of IBD patients to SARS-CoV-2 infection, but also the effects of the drugs used to treat IBD, in light of newly published evidence.

2 | MATERIALS AND METHODS

2.1 | Search strategy and study selection

This meta-analysis was performed according to previously defined protocols registered in PROSPERO (CRD42021223504) and in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[16] We searched for studies in PubMed/MEDLINE, EMBASE, and medRxiv that compared the

prevalence and clinical outcomes of COVID-19 in IBD and in the general population from 2019 to 2 January 2021. Thereafter, we manually searched for eligible studies in the databases until 1 June 2022.

Studies using an observational or case-control design and describing the prevalence and outcomes of COVID-19 (namely, hospitalisation, intensive care unit (ICU)-admission, and death) in patients with IBD were deemed eligible and included. No language or geographic restrictions were enacted prior to inclusion. Articles were excluded if they included only patients with COVID-19, included only hospitalised patients, or excluded deceased patients. Articles were also excluded if they were reviews, case reports, protocols, or correspondence. We searched the databases using keywords such as IBD, UC, Crohn's disease, and COVID-19 (full search strategy is shown in Supplementary Table S1). Two investigators (MHL, SEK) independently performed the initial search and subsequent full-text screening. Disagreements were resolved by reaching the consensus by a third investigator (JYL).

2.2 | Data extraction and quality assessment

Two investigators (MHL, SEK) independently extracted data from eligible studies. Using a standardized extraction form, investigators recorded author name(s), publication date, study design, study duration, location, sample size, diagnostic method, and types of IBD (UC and CD), undergoing IBD medications such as anti-TNF and steroid, patient mean age, patient gender, the prevalence of comorbidities among patients including hypertension, diabetes, obesity, and clinical outcomes of COVID-19. The quality of each eligible study was evaluated using the Newcastle-Ottawa Scale (NOS) by two independent investigators (PW, HJL), and the risk of bias was assessed using the Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool for non-randomized studies of interventions.[17,18]

2.3 | Outcome assessment

The primary outcomes included the prevalence of severe COVID-19 outcomes in IBD and general population groups, including hospitalisation, ICU admission, or COVID-19-related death. Subgroup analyses for primary outcomes were performed based on medication use (corticosteroids, immunomodulators, anti-TNF biologics, aspirin, vedolizumab, and ustekinumab) and IBD classification (UC or CD) within the IBD population. Finally, we analysed the susceptibility of COVID-19 for the use of each IBD medication use.

2.4 | Statistical analysis

We performed our meta-analysis using random effects models. The random-effects model was deemed appropriate due to a high expected heterogeneity amongst studies. Heterogeneity was assessed using Higgins' I^2, with $I^2 < 25\%$ indicating low heterogeneity, 25%–75% indicating moderate heterogeneity, and >75% indicating high heterogeneity.[19] A Cochran's Q test $p < 0.10$ was taken to indicate significant heterogeneity.[20] Egger's test was used to evaluate publication bias, and funnel plots were constructed to visualise evidence of bias for each outcome analysis when three or more studies were available.[21] Publication bias was claimed at Egger's p-value <0.1 or when there was visual asymmetry in the funnel plot.

We performed mixed effect meta-regression models to evaluate the effects of the percentage of medication usage, percentage of patient characteristics and comorbidities, and the number of patients on the outcome effect estimates. Analyses were performed in *R* version 4.0.4 and its packages. Excluding Cochran's Q and Egger's test, all other statistical tests used a two-sided p-value of 0.05 as a marker for significance.

3 | RESULTS

A total of 949 titles were identified through a search of the PubMed, Embase, and MedRxiv databases, with an additional 25 titles identified through other sources. After the removal of duplicates, 791 titles were screened, and exclusion criteria were applied. Ultimately, 35 studies were included in this meta-analysis (Figure 1).[14,22–55] Characteristics of the 35 studies analysed are presented in Table 1 and Supplementary Table S2. The outcomes of overall meta-analyses with the between-study heterogeneity and small study effects are presented in Table 2 and Figure 2. All studies included in the meta-analysis were weighted based on the random-effects model.

3.1 | Morbidity and mortality in inflammatory bowel disease patients with COVID-19

The odds of developing severe COVID-19 in COVID-19 patients with versus without IBD were analysed. Our meta-analysis found that severe COVID-19 hospitalizations (odds ratio (OR) = 0.83; 95% confidence interval (CI) = 0.36–1.89), severe COVID-19 ICU admissions (OR = 1.36; 95% CI = 0.48–3.88), and combined severe COVID-19 hospitalizations and ICU admissions (OR = 0.90; 95% CI = 0.41–1.96) were not significantly different between IBD and non-IBD cohorts (Figure 2). Five studies provided information on COVID-19-related mortality in IBD patients and non-IBD patients. The odds of COVID-19-related death were also found to not be significantly different between IBD and non-IBD cohorts (OR = 0.66; 95% CI = 0.32–1.37) (Figure 3). Heterogeneity was low with COVID-19-related death ($I^2 = 0\%$) but was moderate or high with other analyses ($I^2 = 82\%$ with hospitalisation, $I^2 = 51\%$ with ICU admission, and $I^2 = 79\%$ with hospitalisation and ICU admission). No publication bias was detected by Egger's test and funnel plots (Table 2 and Supplementary Figure S1).

The results of meta-regression analysis showed a statistically significant association between severe outcomes of COVID-19 and

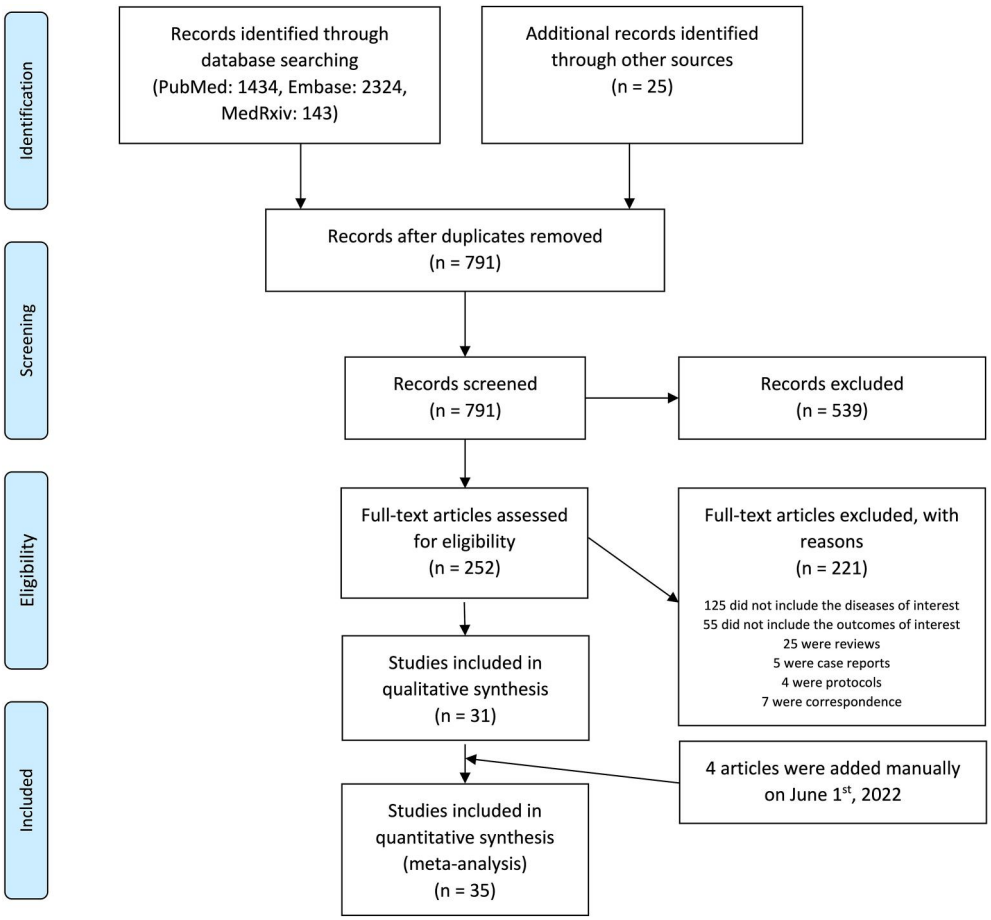

FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart showing selection process of the studies

several variables (Table 3). Among them, no variable was associated statistically significantly with COVID-19 hospitalisation, ICU admission, and death. The remaining results of the meta-regression are shown in Supplementary Table S3.

3.2 | Inflammatory bowel disease drugs and COVID-19

A total of six drugs used to treat IBD (steroids, immunomodulators, anti-TNF, 5-aminosalicylic acid (5-ASA), vedolizumab, and ustekinumab) were analysed for their association with COVID-19 infection. In this meta-analysis, none of the six drugs were found to significantly increase or decrease the odds of COVID-19 infection in IBD patients (Table 4). Most of the analyses showed low heterogeneity (I^2 = 0%) except two (I^2 = 49% with 5-ASA and I^2 = 76% with ustekinumab). Publication bias was found with 5-ASA (Egger's p = 0.018) and ustekinumab (Egger's p = 0.064) (Table 2).

However, when analysing the morbidity and mortality of COVID-19 patients on IBD drugs, there were significant differences based on treatment. Inflammatory bowel disease patients who were not treated with 5-ASA had significantly lower odds of having severe COVID-19 hospitalisation (OR = 0.41; 95% CI = 0.24–0.72) and ICU admission (OR = 0.46; 95% CI = 0.24–0.85) (Supplementary Table S4). Inflammatory bowel disease patients who were not treated with steroids had both lower odds of having severe COVID-19 hospitalisation (OR = 0.35; 95% CI = 0.26–0.46) and ICU admission (OR = 0.21; 95% CI = 0.10–0.42). In contrast, IBD patients not treated with immunomodulators had similar odds of severe COVID-19 hospitalisation (OR = 0.96; 95% CI = 0.46–1.98) and ICU admission (OR = 1.40; 95% CI = 0.82–2.37) compared to IBD patients treated with immunomodulators.

The odds of COVID-19-related death were lower in IBD patients not treated with 5-ASA compared to IBD patients treated with 5-ASA (OR = 0.37; 95% CI = 0.23–0.59) (Table S4). In the contrast, the odds of COVID-19-related death were not significantly different in IBD patients not treated with steroids (OR = 0.43; 95% CI = 0.10–1.97). Similarly, there were no significant differences in the odds of COVID-19-related death between IBD patients treated with immunomodulators versus those not treated with immunomodulators (OR = 0.87; 95% CI = 0.15–5.08). Heterogeneity was mostly high except for COVID-19-related death according to aminosalicylates use (I^2 = 0%). No publication bias was found with Egger's test and funnel plots (Table 2 and Supplementary Figure S1).

TABLE 1 Characteristics of the included studies

Author, year	Country	IBD type (with COVID)		Study design	No. of population		Outcome				Adjustment of outcome
		UC	CD		IBD	IBD with COVID19	Hospitalisation	ICU	Ventilation	Death	
Derikx et al., 2020	Netherlands	59	36	Cohort (multi centre)	34,763	100	●			●	NA
Ungaro et al., 2020	International registry	NA	NA	Case control (multi centre)	1439	1439		●	●	●	Age, sex, IBD disease type, Country and state
Attauabi et al., 2020	Denmark	45	31	Cohort (multi centre)	76	76	●	●	●	●	NA
Attaway et al., 2020	USA	NA	NA	Case control (multi Centre)	338	27	●*	●*			Age, race, sex, BMI, Comorbidities
Guerra et al., 2020	Spain	14	11	Cohort (single Centre)	805	28		●		●	NA
Burke et al., 2020	USA	17	22	Cohort (multi Centre)	5302	39	●	●		●	Age, sex, race, IBD-type, comorbidities
Allocca et al., 2020	France/Italy	6	9	Cohort (multi centre)	6000	15	●	●		●	NA
Norsa et al., 2020	Italy	NA	NA	Cohort (single centre)	522	0					NA
Taxonera et al., 2020	Spain	5	7	Cohort (single centre)	1918	12	●	●	●	●	Age, sex
An et al., 2020	China	NA	NA	Cohort (single Centre)	318	0					NA
Grassia et al., 2020	Italy	NA	NA	Cohort (single centre)	251	1					NA
Gubatan et al., 2020	USA	3	2	Cohort (single Centre)	168	5	●	●	●	●	NA
Singh et al., 2020	USA	131	101	Cohort (multi centre)	196,403	232	●				Propensity score matched
Khan et al., 2020	USA	NA	NA	Cohort (multi Centre)	37,857	36					Age, comorbidities
Mak et al., 2020	Hongkong/ Taiwan	NA	NA	Cohort (multi Centre)	5508	0					Corticosteorids, anti-TNF
Marafini et al., 2020	Italy	NA	NA	Cohort (single Centre)	672	3	●			●	Therapy

(Continues)

TABLE 1 (Continued)

Author, year	Country	IBD type (with COVID)		Study design	No. of population		Outcome				Adjustment of outcome
		UC	CD		IBD	IBD with COVID19	Hospitalisation	ICU	Ventilation	Death	
Turner et al., 2020	China/South Korea	NA	NA	Cohort (multi Centre)	272	0	•	•	•	•	NA
Scaldaferri et al., 2020	Italy	NA	NA	Cohort (single Centre)	1451	5					NA
Bodini et al., 2020	Italy	0	0	Cohort (single Centre)	48	0					NA
Martinelli et al., 2020	Italy	0	0	Cohort (single Centre)	180	0					NA
Lukin et al., 2020	USA	14	15	Cohort (multi Centre)	119	29	•	•	•	•	Age, sex
Bezzio et al., 2020	Italy	47	32	Cohort (multi Centre)	NA	79	•	•	•	•	Steroid use
Rodriguez et al., 2020	Spain	27	13	Cohort (multi Centre)	NA	40	•	•	•	•	NA
Brenner et al., 2020	International registry	203	312	Cohort (multi Centre)	NA	525	•	•	•	•	Clinical and demographic variables, systemic Corticosteroid use and 5-ASA/ Sulfasalazine use
Axelrad et al., 2020	USA	27	56	Cohort (single Centre)	NA	83	•	•	•	•	NA
Hormati et al., 2020	Iran	NA	NA	Cohort (single Centre)	150	8					NA
Haberman et al., 2020	USA	17	20	Cohort (single Centre)	NA	37	•	•			NA
Mosli et al., 2020	Saudi Arabia	1	5	Cohort (multi Centre)	1156	6					NA
Grunert et al., 2020	Germany	0	0	Cohort (single Centre)	415	0					Propensity score matched
Yu et al., 2020	China	0	0	Cohort (multi Centre)	102	0					NA
Fonteinogiannopoulou et al., 2020	Greece	NA	NA	Cohort (single Centre)	78	0					NA

TABLE 1 (Continued)

Author, year	Country	IBD type (with COVID) UC	CD	Study design	No. of population IBD	IBD with COVID19	Outcome Hospitalisation	ICU	Ventilation	Death	Adjustment of outcome
Sima et al., 2022	Iran	60	24	Cohort (multi Centre)	2159	84	●	●	●	●	NA
Richter et al., 2021	Israel	44	60	Cohort (multi Centre)	2152	104					NA
Macaluso et al., 2022	Italy	46	76	Cohort (multi Centre)	15,000	122	●	●	●	●	NA
Queiroz et al., 2021	Latin America	114	115	Cohort (multi Centre)	NA	229	●	●	●	●	NA

Note: *: *p*-value <0.05.

Abbreviations: ASA, 5-aminosalicylic acid; BMI, body mass index; IBD, inflammatory bowel disease; N/A, not applicable; TNF, tumour necrosis factor.

3.3 | Morbidity and mortality in CD and ulcerative colitis patients with COVID-19

The odds of having severe COVID-19 hospitalizations were significantly lower in patients with CD compared to patients with UC (OR = 0.55; 95% CI = 0.40–0.75) (Table 2 and Supplementary Table S5). Additionally, the odds of COVID-19-related death were significantly lower in patients with CD compared to patients with UC (OR = 0.35; 95% CI = 0.16–0.75). However, there were no significant differences in the odds of having severe COVID-19 ICU admissions between CD and UC patients (OR = 0.60; 95% CI = 0.29–1.24). There was low heterogeneity in each analysis ($I^2 = 0\%$). Publication bias was found with hospitalisation (Egger's $p = 0.094$) (Table 2).

3.4 | Quality assessment and risk of bias

The quality of each study was evaluated using the NOS. Those results are summarised in Supplementary Table S6. Of 35 studies, 10 studies were of good quality (7 points or more). Bias was evaluated using ROBINS-I for all 35 studies included in this meta-analysis. The results of the bias evaluation are summarised in Supplementary Figure S2. In addition, subgroup analyses performed to compare the results of studies of good quality and low risk of bias studies were presented in Supplementary Table S7.

4 | DISCUSSION

Considerable discussion centres around the susceptibility of IBD patients to COVID-19 since the discovery of ACE-2 in the intestinal lumen and of SARS-CoV-2 virions shedding in stool even after elimination from the lungs.[56,57] On the other hand, conflicting findings exist on whether ACE-2 expression increases with IBD in both animal and clinical models.[10,12,58] Soluble ACE-2 serum levels are elevated in IBD, which may act as competitive inhibition for viral entry and impart protection from SARS-CoV-2.[59] As IBD is a multifaceted illness, predisposing patients towards infection, malnutrition, and immunomodulating treatment, it is of particular interest to describe not only susceptibilities but also outcomes of COVID-19 in this population. Corticosteroids, 5-ASAs, and anti-TNF are commonly prescribed to reduce inflammation in IBD. Case reports described patients on anti-TNFs who proceeded to develop severe COVID-19-related respiratory complications or death.[60] Although preliminary results of the RECOVERY trial show mortality benefits of dexamethasone for COVID-19 in the general population, corticosteroid use is associated with poor clinical outcomes in the IBD population.[15,61] Previous systematic reviews have thus far found no increased susceptibilities to COVID-19 but increased hospitalisation, ICU admission, and mortality with 5-ASA or corticosteroids.[15,62,63]

However, one limitation of the current systematic reviews is the possibility for age, sex, and other patient demographics to confound results. To our knowledge, no systematic review has yet performed a meta-analysis including only observational data that have adjusted for factors such as age, sex, race, body mass index, or comorbidities. Thus, it is unknown whether UC or CD remain risk factors for COVID-19 susceptibility or clinical outcomes independent of these factors. Furthermore, the most recent systematic reviews have only included studies up to July 2020. Accordingly, this systematic review and meta-analysis evaluated IBD as a risk factor for COVID-19 while including studies up to June 2022 and performed distinct analyses based on adjusted, unadjusted, or total studies. We found that patients with UC were more likely than those with CD to suffer hospitalisation and death. In addition, our findings showed that the use

TABLE 2 Outcomes of meta-analyses including heterogeneity and Egger's test

Outcomes	Random effects estimate and 95% CI	Random effects *p* value	Fixed effects estimate and 95% CI	Fixed effects *p* value	I^2 and *p* value for *Q* test	Metric	Egger *p* value	Number of studies
Severe COVID-19 - hospitalisation	0.83 (0.36–1.89)	0.65	0.89 (0.65–1.21)	0.46	82% (<0.001)	OR	0.8	5
Severe COVID-19 - ICU	1.36 (0.48–3.88)	0.56	1.89 (1.02–3.52)	0.043	51% (0.088)	OR	0.2	5
COVID-19 related death	0.66 (0.32–1.37)	0.27	0.66 (0.32–1.37)	0.27	0% (0.79)	OR	0.051	6
Severe COVID-19—hospitalisation & ICU	0.90 (0.41–1.96)	0.79	1 (0.74–1.34)	0.98	79% (<0.001)	OR	0.73	7
Susceptibility to COVID-19 according to steroid	0.52 (0.24–1.1)	0.088	0.52 (0.24–1.1)	0.088	0% (0.50)	OR	0.1	3
Susceptibility to COVID-19 according to immunomodulator	0.62 (0.3–1.26)	0.18	0.62 (0.3–1.26)	0.18	0% (0.68)	OR	0.64	5
Susceptibility to COVID-19 according to anti-TNF	1.09 (0.59–2.01)	0.79	1.09 (0.59–2.01)	0.79	0% (0.74)	OR	0.48	6
Susceptibility to COVID-19 according to ASA	0.62 (0.27–1.38)	0.24	0.79 (0.48–1.29)	0.34	49% (0.12)	OR	0.018	4
Susceptibility to COVID-19 according to vedolizumab	0.46 (0.21–1.04)	0.062	0.46 (0.21–1.04)	0.062	0% (0.50)	OR	0.4	5
Susceptibility to COVID-19 according to ustekinumab	0.18 (0.02–1.33)	0.094	0.53 (0.23–1.23)	0.14	76% (<0.001)	OR	0.064	6
Severe COVID-19 hospitalisation (vs. non-ASA users)	0.41 (0.24–0.72)	0.002	0.5 (0.41–0.62)	<0.001	19% (0.29)	OR	0.37	5
Severe COVID-19 hospitalisation (vs. non-steroid users)	0.35 (0.26–0.46)	< 0.001	0.35 (0.26–0.46)	<0.001	0% (0.74)	OR	0.9	5
Severe COVID-19 hospitalisation (vs. non-immunomodulator users)	0.96 (0.46–1.98)	0.9	0.83 (0.65–1.05)	0.12	42% (0.14)	OR	0.81	5
Severe COVID-19 ICU (vs. non-ASA users)	0.46 (0.24–0.85)	0.013	0.51 (0.34–0.76)	<0.001	5% (0.37)	OR	0.026	4
Severe COVID-19 ICU (vs. non-steroid users)	0.21 (0.10–0.42)	<0.001	0.23 (0.15–0.34)	<0.001	30% (0.23)	OR	0.89	4
Severe COVID-19 ICU (vs. non-immunomodulator users)	1.40 (0.82–2.37)	0.22	1.4 (0.82–2.37)	0.22	0% (0.58)	OR	0.13	4
COVID-19 related death (vs. non-ASA users)	0.37 (0.23–0.59)	<0.001	0.37 (0.23–0.59)	<0.001	0% (0.84)	OR	0.83	5
COVID-19 related death (vs. non-steroid users)	0.43 (0.10–1.97)	0.28	0.64 (0.4–1.01)	0.055	84% (<0.001)	OR	0.72	5
COVID-19 related death (vs. non-immunomodulator users)	0.99 (0.25–3.94)	0.99	1.21 (0.65–2.28)	0.55	40% (0.16)	OR	0.71	5
Severe COVID-19 between UC and CD - hospitalisation	0.55 (0.40–0.75)	<0.001	0.55 (0.4–0.75)	<0.001	0% (0.79)	OR	0.094	8
Severe COVID-19 between UC and CD - ICU	0.60 (0.29–1.24)	0.17	0.6 (0.29–1.24)	0.17	0% (0.83)	OR	0.71	4
COVID-19 related death between UC and CD	0.35 (0.16–0.75)	0.007	0.35 (0.16–0.75)	0.007	0% (0.91)	OR	0.47	7

Abbreviations: ASA, 5-aminosalicylic acid; CD, Chron's disease; CI, confidence interval; ICU, intensive care unit; TNF, tumour necrosis factor; UC, ulcerative colitis.

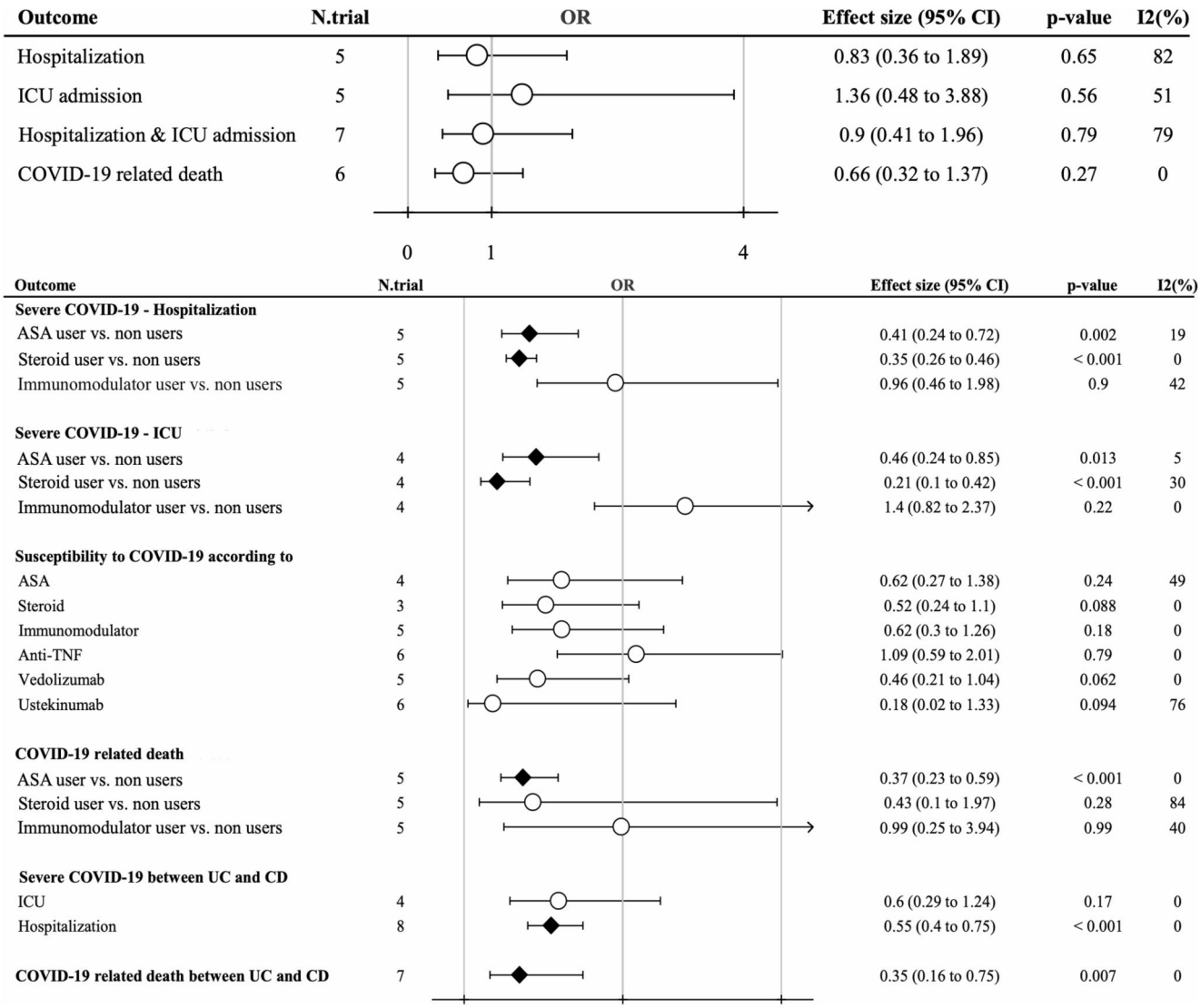

FIGURE 2 Summary of the overall meta-analyses on association between COVID-19 and inflammatory bowel disease (IBD) patients. ASA, aminosalicylic acid; CD, Crohn's disease; CI, confidence interval; COVID, coronavirus disease; ICU, intensive care unit; N, number of; OR, odds ratio; UC, ulcerative colitis.

of 5-ASA and corticosteroids within IBD patients were associated with both hospitalisation and ICU usage, and the use of 5-ASA was associated with death. However, not all IBD drugs, including anti-TNF, vedolizumab, and ustekinumab increased susceptibility to COVID-19.

It was explained in earlier studies that corticosteroid use represented higher disease activity or severity, explaining the higher rates of hospitalisation, ICU admission, and death.[15,62] However, one recent adjusted study found poor corticosteroid outcomes adjusted for disease severity amongst other factors such as smoking, age, sex, disease type, BMI, comorbidities, and concomitant anti-TNF or 5-ASA use.[14] It is possible that poor clinical outcomes may instead be a result of prolonged corticosteroid use or the inability to mount an immune response against the initial stages of SARS-CoV-2 infection. 5-ASA was also associated with poor outcomes, which Singh et al.[15] attributed to 5-ASA proxying for more severe baseline IBD. Of the three adjusted studies evaluating 5-ASA use, Brenner et al.[14] controlled for disease severity and numerous other factors, while Bezzio et al. and Taxonera et al. controlled for corticosteroid use and age/sex, respectively. The mechanisms of action of 5-ASA are diverse, but it is believed to be primarily through repression of nuclear factor B through activation of peroxisome proliferator-activated receptor (PPAR)-gamma. Suppression of lipoxygenases and cyclooxygenases, as well as cytokine production, are also contributing mechanisms.[64] Similar to corticosteroids, 5-ASA may impair the initial immune response to COVID-19, leading to adverse outcomes.[65]

However, there are several aspects to consider evaluating whether the negative effects of 5-ASA or corticosteroids are real. First, COVID-19 has a large difference in mortality rate according to the age factor. It is well understood from the worldwide data that age over 50 could be the determinant effect on COVID-19 mortality.[66] Since 5-ASA medication is widely used in IBD patients with mild to

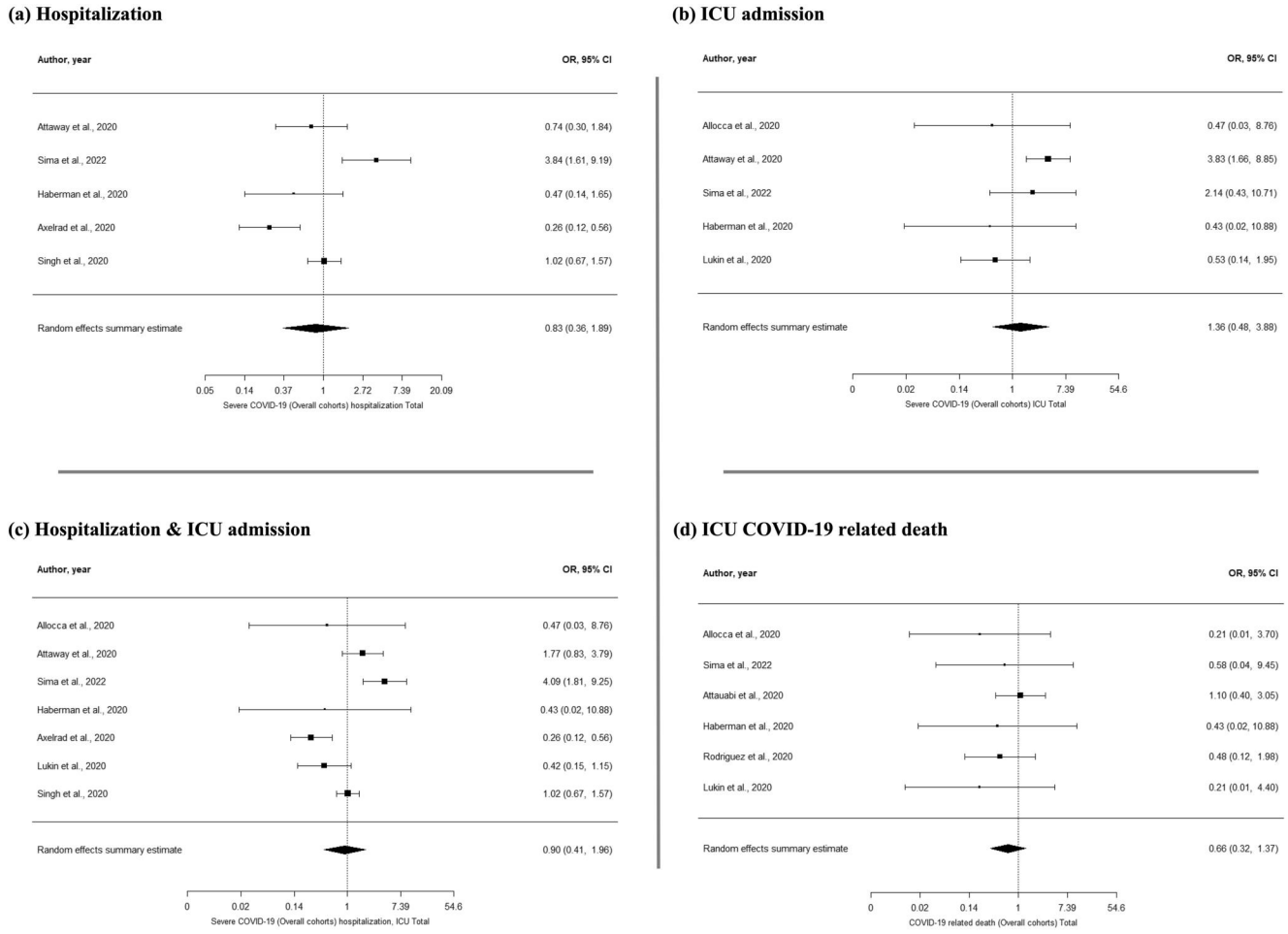

FIGURE 3 Meta-analysis of clinical outcomes of COVID-19 in patients with inflammatory bowel disease (IBD) compared to general population. CI, confidence interval; COVID, coronavirus disease; IBD, inflammatory bowel disease; ICU, intensive care unit; OR, odds ratio.

TABLE 3 Meta-regression of the variables potentially associated with the severe outcomes of coronavirus disease 2019 (COVID-19)

	Hospitalisation			ICU admission			Hospitalisation & ICU admission			COVID-19 related death		
Continuous variable	Coefficient	*p* value	Number of studies	Coefficient	*p* value	Number of studies	Coefficient	*p* value	Number of studies	Coefficient	*p* value	Number of studies
Total number of patients	0.9,999,969	0.66	3	1.00011	0.062	4	0.9,999,988	0.84	5	0.9997	0.24	4
Number of COVID19 (*n*)	0.999,951	0.93	5	1.00064	0.02	5	1.00036	0.46	7	1.016	0.37	6
Number of PCR-confirmed COVID-19 (*n*)	0.999,964	0.95	5	1.00047	0.14	4	1.00031	0.56	6	1.022	0.23	5
Mean/Median age (y/o)	1.076	0.5	4	0.91	0.56	4	1.058	0.54	6	1.025	0.74	6
Male (%)	0.901	0.25	4	0.981	0.72	4	0.949	0.31	6	1.036	0.38	6
Comorbidities (%)	NA	NA	NA	NA	NA	NA	NA	NA	NA	0.978	0.76	4
GCs (%)	1.0043	0.94	3	0.61	0.17	3	1.0099	0.8	5	0.75	0.49	4
Ventilation (*n*)	NA	NA	NA	NA	NA	NA	2.6	< 0.001	3	1.25	0.43	4

Abbreviations: b/ts-DMARD, biologic/target synthetic DMARD; COVID, coronavirus disease; cs-DMARD, conventional synthetic DMARD; DMARD, disease-modifying antirheumatic drug; GC, glucocorticoid; ICU, intensive care unit.

TABLE 4 Meta-analysis of susceptibility of coronavirus disease 2019 (COVID-19) in patients with inflammatory bowel disease (IBD) according to drug use

	Steroid user		Non-steroid user		
Study	**Event**	**Total**	**Event**	**Total**	**OR, 95% CI**
Steroid					
Gubatan et al., 2020	1	34	4	134	1.01 [0.11; 9.38]
Lukin et al., 2020	13	35	16	84	0.40 [0.17; 0.96]
Mosli et al., 2020	1	238	5	918	1.30 [0.15; 11.16]
Total (95% CI)	1	307	25	1136	0.52 [0.24; 1.10]
Immunomodulator					
	Immunomodulator user		**Non-immunomodulator user**		
Taxonera et al., 2020	6	553	6	1365	0.40 [0.13; 1.26]
Gubatan et al., 2020	1	15	4	153	0.38 [0.04; 3.60]
Khan et al., 2020	2	2391	34	35,466	1.15 [0.28; 4.77]
Lukin et al., 2020	2	5	27	114	0.47 [0.07; 2.94]
Mosli et al., 2020	1	280	5	876	1.60 [0.19; 13.78]
Total (95% CI)					0.62 [0.30; 1.26]
Anti-TNF					
	Anti-TNF user		**Non-anti-TNF user**		
Burke et al., 2020	3	582	36	4720	1.48 [0.46; 4.8]
Taxonera et al., 2020	3	260	9	1658	0.47 [0.13; 1.74]
Grassia et al., 2020	0	30	1	221	0.41 [0.02; 10.43]
Gubatan et al., 2020	1	34	4	134	1.01 [0.11; 9.38]
Khan et al., 2020	3	4920	33	32,937	1.64 [0.50; 5.36]
Mosli et al., 2020	2	466	4	690	1.35 [0.25; 7.41]
Total (95% CI)					1.09 [0.59; 2.01]
ASA					
	ASA user		**Non-ASA user**		
Burke et al., 2020	12	1854	27	3448	1.21 [0.61; 2.40]
Gubatan et al., 2020	4	58	1	110	0.12 [0.01; 1.14]
Lukin et al., 2020	11	38	18	81	0.70 [0.29; 1.68]
Mosli et al., 2020	3	252	3	904	0.28 [0.06; 1.38]
Total (95% CI)					0.62 [0.27; 1.38]
Vedolizumab					
	Vedolizumab user		**Non-vedolizumab user**		
Taxonera et al., 2020	1	18	11	1900	0.10 [0.01; 0.81]
Grassia et al., 2020	0	10	1	241	0.13 [0.01; 3.41]
Gubatan et al., 2020	0	10	5	158	0.75 [0.04; 14.54]
Lukin et al., 2020	7	23	22	96	0.68 [0.25; 1.86]
Mosli et al., 2020	0	53	6	1103	0.63 [0.04; 11.41]
Total (95% CI)					0.46 [0.21; 1.04]

(Continues)

TABLE 4 (Continued)

Ustekinumab					
	Ustekinumab user		Non-ustekinumab user		
Taxonera et al., 2020	1	23	11	1895	0.13 [0.02; 1.03]
Grassia et al., 2020	0	1	1	250	0.02 [0.00; 0.65]
Gubatan et al., 2020	0	4	5	164	0.31 [0.01; 6.50]
Lukin et al., 2020	4	29	25	90	2.40 [0.76; 7.61]
Brenner et al., 2020	37	37	169	488	0.01 [0.00; 0.12]
Mosli et al., 2020	0	74	6	1082	0.90 [0.05; 16.13]
Total (95% CI)					0.18 [0.02; 1.33]

Abbreviations: ASA, 5-aminosalicylic acid; CI, confidence interval; IBD, inflammatory bowel disease; OR, odds ratio; TNF, tumour necrosis factor.

moderate symptoms due to fewer side effects, it is widely used in elderly patients with other underlying diseases. In addition, patients with IBD on other biologics are relatively more cared for, and there would be selection or reporting biases that could influence the outcome values. Finally, some studies have argued that the use of immunosuppressants for IBD patients helps to suppress the disease activity of COVID-19 by avoiding the cytokine storm.[42,67] To get the undistorted effect of these medications, additional research adjusting for disease severity, duration of corticosteroid/5-ASA use, and other patient demographics are warranted to evaluate corticosteroids and 5-ASA as risk factors. Likewise, since 5-ASA is mostly used as an induction and maintenance therapy for UC patients rather than CD patients, it is difficult to accurately determine whether the high rate of hospitalisation, ICU admission, and the death rate is due to the type of IBD or the medication. The analysis of medication use by the type of IBD is beyond the scope of our study, but future studies are needed.

In adjusted studies, UC was a risk factor for COVID-19-related hospitalisation, ICU admission, and death. This finding is shared by previous works, which attributed the increased age of UC patients as the underlying cause. Two of the three studies comparing UC and CD in our analysis adjusted for age and sex, and only one additionally adjusted for disease severity. Angiotensin-converting enzyme 2 is expressed to a higher degree in UC, which may cause a higher likelihood of disease progression.[58]

Our findings suggest that patients with IBD and at high risk of COVID-19 infection might be cautious when using corticosteroid or 5-ASA therapy. Moreover, UC patients are at higher risk for COVID-19 complications, necessitating more aggressive monitoring and management. However, our study has several limitations that should be considered. First, our meta-analysis includes observational cohort or case-control studies, which predispose our study to possible selection or recall biases. Furthermore, some studies were of considerably larger samples than the average, and studies varied in location, which increased heterogeneity. Since pooling the outcomes from studies with large heterogeneity could distort the true effects, it is important to consider the results of individual studies as well as the meta-analysed outcomes. Because of the observational nature of included studies, it was not possible to distinguish whether the poor aspirin- and corticosteroid-associated outcomes resulted as a marker of more severe IBD or from underlying pathophysiology. Second, differences in study definitions and protocols may increase heterogeneity in our findings. When outcomes were adjusted, differing studies did not always adjust for the same variables (e.g. one study may account for age and sex only while another may account for age, sex, and race), allowing for unaccounted heterogeneity amongst adjusted studies. Not all studies shared information concerning patient comorbidities or medication history, which forced some subgroup analyses to include smaller samples and prevented some adjusted subgroup analyses. Washout periods were not reported if 5-ASAs were stopped to prevent severe COVID-19 outcomes. Moreover, each study had a different definition of the severity of COVID-19, which should be considered when readers interpret the outcomes. Third, the diagnosis of COVID-19 was confirmed by the nucleic acid amplification test, which has a 71% sensitivity.[68] It is possible that significant proportions of the COVID-19-infected population with lower viral loads were not included in the study as a result. Patients on immunomodulating drugs may have been tested earlier and more often in the disease course, selecting for falsely elevated susceptibilities.

This systematic review and meta-analysis confirm that six medications for IBD patients are not at risk of higher COVID-19 susceptibility using studies adjusting for age, sex, etc. Recent observational studies adjusting for age, sex, and disease severity confirm the association of 5-ASA, corticosteroids, and UC with poor COVID-19 outcomes. Further studies are needed that could support the evidence of our study and also consider the influence of confounding variables such as sex, age, and whether the patients are vaccinated or not.

AUTHOR CONTRIBUTIONS

Min Ho Lee, Lee Smith and Jae Il Shin formulated the research question and reviewed the report. Min Ho Lee, Han Jacob Li, Paul Wasuwanich and Sung Eun Kim did the literature search, extracted

and selected articles. Jong Yeob Kim, Gwang Hun Jeong, and Min Seo Kim did the meta-analysis. All authors (Min Ho Lee, Han Jacob Li, Paul Wasuwanich, Sung Eun Kim, Jong Yeob Kim, Gwang Hun Jeong, Seoyeon Park, Jae Won Yang, Min Seo Kim, Dong Keon Yon, Seung Won Lee, Ai Koyanagi, Louis Jacob, Jae Il Shin, and Lee Smith) contributed to the writing of the paper. The corresponding authors had the final responsibility for the decision to submit for publication.

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CONFLICT OF INTEREST

All authors have no conflict of interest to declare.

DATA AVAILABILITY STATEMENT

The data supporting the findings of the study are available within the article and its supplementary materials. Additional data are available from the corresponding author upon reasonable request.

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REFERENCES

1. Arif TB. The 501.V2 and B.1.1.7 variants of coronavirus disease 2019 (COVID-19): a new time-bomb in the making? *Infect Control Hosp Epidemiol*. 2021;43(3):1-2. https://doi.org/10.1017/ice.2020.1434
2. Hormati A, Ghadir MR, Zamani F, Khodadadi J, Afifian M, Ahmadpour S. Preventive strategies used by GI physicians during the COVID-19 pandemic. *New Microbes New Infect*. 2020;35:100676. https://doi.org/10.1016/j.nmni.2020.100676
3. Nguyen NH, Khera R, Ohno-Machado L, Sandborn WJ, Singh S. Annual burden and costs of hospitalization for high-need, high-cost patients with chronic gastrointestinal and liver diseases. *Clin Gastroenterol Hepatol*. 2018;16(8):1284-1292.e30. https://doi.org/10.1016/j.cgh.2018.02.015
4. Ng SC, Shi HY, Hamidi N, et al. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. *Lancet*. 2017;390(10114):2769-2778. https://doi.org/10.1016/s0140-6736(17)32448-0
5. Singh S, Facciorusso A, Dulai PS, Jairath V, Sandborn WJ. Comparative risk of serious infections with biologic and/or immunosuppressive therapy in patients with inflammatory bowel diseases: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol*. 2020;18(1):69-81.e3. https://doi.org/10.1016/j.cgh.2019.02.044
6. Tian W, Jiang W, Yao J, et al. Predictors of mortality in hospitalized COVID-19 patients: a systematic review and meta-analysis. *J Med Virol*. 2020;92(10):1875-1883. https://doi.org/10.1002/jmv.26050
7. Ning L, Shan G, Sun Z, et al. Quantitative proteomic analysis reveals the deregulation of nicotinamide adenine dinucleotide metabolism and CD38 in inflammatory bowel disease. *BioMed Res Int*. 2019;2019:3950628. https://doi.org/10.1155/2019/3950628
8. Wong SH, Lui RN, Sung JJ. Covid-19 and the digestive system. *J Gastroenterol Hepatol*. 2020;35(5):744-748. https://doi.org/10.1111/jgh.15047
9. Neurath MF. COVID-19 and immunomodulation in IBD. *Gut*. 2020;69(7):1335-1342. https://doi.org/10.1136/gutjnl-2020-321269
10. Burgueno JF, Reich A, Hazime H, et al. Expression of SARS-CoV-2 entry molecules ACE2 and TMPRSS2 in the gut of patients with IBD. *Inflamm Bowel Dis*. 2020;26(6):797-808. https://doi.org/10.1093/ibd/izaa085
11. Al-Ani AH, Prentice RE, Rentsch CA, et al. Review article: prevention, diagnosis and management of COVID-19 in the IBD patient. *Aliment Pharmacol Ther*. 2020;52(1):54-72. https://doi.org/10.1111/apt.15779
12. Monteleone G, Ardizzone S. Are patients with inflammatory bowel disease at increased risk for Covid-19 infection? *J Crohns Colitis*. 2020;14(9):1334-1336. https://doi.org/10.1093/ecco-jcc/jjaa061
13. Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med*. 2020;382(18):1708-1720. https://doi.org/10.1056/nejmoa2002032
14. 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(2):481-491.e3. https://doi.org/10.1053/j.gastro.2020.05.032
15. Singh AK, Jena A, Kumar MP, Sharma V, Sebastian S. Risk and outcomes of coronavirus disease (COVID-19) in patients with inflammatory bowel disease: a systematic review and meta-analysis. *United Eur Gastroenterol J*. 2020;9(2):159-176. https://doi.org/10.1177/2050640620972602
16. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ*. 2009;339(jul21 1):b2700. https://doi.org/10.1136/bmj.b2700
17. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol*. 2010;25(9):603-605. https://doi.org/10.1007/s10654-010-9491-z
18. Sterne JA, Hernan MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ*. 2016;355:i4919. https://doi.org/10.1136/bmj.i4919
19. Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343(oct18 2):d5928. https://doi.org/10.1136/bmj.d5928
20. Cumpston M, Li T, Page MJ, et al. Updated guidance for trusted systematic reviews: a new edition of the Cochrane Handbook for Systematic Reviews of Interventions. *Cochrane Database Syst Rev*. 2019;10:ED000142. https://doi.org/10.1002/14651858.ed000142
21. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315(7109):629-634. https://doi.org/10.1136/bmj.315.7109.629
22. Singh S, Khan A, Chowdhry M, Bilal M, Kochhar GS, Clarke K. Risk of severe coronavirus disease 2019 in patients with inflammatory bowel disease in the United States: a multicenter research network study. *Gastroenterology*. 2020;159(4):1575-1578.e4. https://doi.org/10.1053/j.gastro.2020.06.003
23. Khan N, Patel D, Xie D, Lewis J, Trivedi C, Yang YX. Impact of anti-tumor necrosis factor and thiopurine medications on the development of COVID-19 in patients with inflammatory bowel disease: a nationwide veterans administration cohort study. *Gastroenterology*. 2020;159(4):1545-1546.e1. https://doi.org/10.1053/j.gastro.2020.05.065
24. Rodriguez-Lago I, Ramirez de la Piscina P, Elorza A, Merino O, Ortiz de Zarate J, Cabriada JL. Characteristics and prognosis of patients with inflammatory bowel disease during the SARS-CoV-2 pandemic in the Basque country (Spain). *Gastroenterology*. 2020;159(2):781-783. https://doi.org/10.1053/j.gastro.2020.04.043
25. Guerra I, Algaba A, Jimenez L, et al. Incidence, clinical characteristics, and evolution of SARS-CoV-2 infection in patients with

inflammatory bowel disease: a single-center study in Madrid, Spain. *Inflamm Bowel Dis*. 2021;27(1):25-33. https://doi.org/10.1093/ibd/izaa221
26. An P, Ji M, Ren H, et al. Prevention of COVID-19 in patients with inflammatory bowel disease in Wuhan, China. *Lancet Gastroenterol Hepatol*. 2020;5(6):525-527. https://doi.org/10.1016/s2468-1253(20)30121-7
27. Ungaro RC, Brenner EJ, Gearry RB, et al. Effect of IBD medications on COVID-19 outcomes: results from an international registry. *Gut*. 2021;70(4):725-732. https://doi.org/10.1136/gutjnl-2020-322539
28. Taxonera C, Sagastagoitia I, Alba C, Manas N, Olivares D, Rey E. 2019 novel coronavirus disease (COVID-19) in patients with inflammatory bowel diseases. *Aliment Pharmacol Ther*. 2020;52(2):276-283. https://doi.org/10.1111/apt.15804
29. Lukin DJ, Kumar A, Hajifathalian K, et al. Baseline disease activity and steroid therapy stratify risk of COVID-19 in patients with inflammatory bowel disease. *Gastroenterology*. 2020;159(4):1541-1544.e2. https://doi.org/10.1053/j.gastro.2020.05.066
30. Grassia R, Soro S, Conti CB. Inflammatory bowel diseases and biological treatment in SARS-CoV-2 era. Why not? *Inflamm Bowel Dis*. 2020;26(7):e71. https://doi.org/10.1093/ibd/izaa110
31. Yu M, Ye Z, Chen Y, et al. Questionnaire assessment helps the self-management of patients with inflammatory bowel disease during the outbreak of Coronavirus Disease 2019. *Aging*. 2020;12(13):12468-12478. https://doi.org/10.18632/aging.103525
32. Norsa L, Indriolo A, Sansotta N, Cosimo P, Greco S, D'Antiga L. Uneventful course in patients with inflammatory bowel disease during the severe acute respiratory syndrome coronavirus 2 outbreak in northern Italy. *Gastroenterology*. 2020;159(1):371-372. https://doi.org/10.1053/j.gastro.2020.03.062
33. Mak JWY, Weng MT, Wei SC, Ng SC. Zero COVID-19 infection in inflammatory bowel disease patients: findings from population-based inflammatory bowel disease registries in Hong Kong and Taiwan. *J Gastroenterol Hepatol*. 2021;36(1):171-173. https://doi.org/10.1111/jgh.15164
34. Scaldaferri F, Pugliese D, Privitera G, et al. Impact of COVID-19 pandemic on the daily management of biotechnological therapy in inflammatory bowel disease patients: reorganisational response in a high-volume Italian inflammatory bowel disease centre. *United Eur Gastroenterol J*. 2020;8(7):775-781. https://doi.org/10.1177/2050640620929133
35. Grunert PC, Reuken PA, Stallhofer J, Teich N, Stallmach A. Inflammatory bowel disease in the COVID-19 pandemic - the patients' perspective. *J Crohns Colitis*. 2020.
36. Derikx L, Lantinga MA, de Jong DJ, et al. Clinical outcomes of Covid-19 in patients with inflammatory bowel disease: a nationwide cohort study. *J Crohns Colitis*. 2021;15(4):529-539. https://doi.org/10.1093/ecco-jcc/jjaa215
37. Mosli M, Alourfi M, Alamoudi A, et al. A cross-sectional survey on the psychological impact of the COVID-19 pandemic on inflammatory bowel disease patients in Saudi Arabia. *Saudi J Gastroenterol*. 2020;26(5):263-271. https://doi.org/10.4103/sjg.sjg_220_20
38. Martinelli M, Strisciuglio C, Fedele F, Miele E, Staiano A. Clinical and psychological issues in children with inflammatory bowel disease during COVID-19 pandemic. *Inflamm Bowel Dis*. 2020;26(9):e95-e6. https://doi.org/10.1093/ibd/izaa136
39. Axelrad JE, Malter L, Hong S, Chang S, Bosworth B, Hudesman D. From the American epicenter: coronavirus disease 2019 in patients with inflammatory bowel disease in the New York City metropolitan area. *Inflamm Bowel Dis*. 2020.
40. Allocca M, Fiorino G, Zallot C, et al. Incidence and patterns of COVID-19 among inflammatory bowel disease patients from the Nancy and Milan cohorts. *Clin Gastroenterol Hepatol*. 2020;18(9):2134-2135. https://doi.org/10.1016/j.cgh.2020.04.071
41. Haberman RH, Castillo R, Chen A, et al. COVID-19 in patients with inflammatory arthritis: a prospective study on the effects of comorbidities and disease-modifying antirheumatic drugs on clinical outcomes. *Arthritis Rheumatol* 2020;72(12):1981-1989. https://doi.org/10.1002/art.41456
42. Hormati A, Ghadir MR, Zamani F, et al. Are there any association between COVID-19 severity and immunosuppressive therapy? *Immunol Lett*. 2020;224:12-13. https://doi.org/10.1016/j.imlet.2020.05.002
43. Bodini G, Demarzo MG, Casagrande E, et al. Concerns related to COVID-19 pandemic among patients with inflammatory bowel disease and its influence on patient management. *Eur J Clin Invest*. 2020;50(5):e13233. https://doi.org/10.1111/eci.13233
44. Attaway AA, Zein J, Hatipoglu US. SARS-CoV-2 infection in the COPD population is associated with increased healthcare utilization: an analysis of Cleveland clinic's COVID-19 registry. *EClinicalMedicine*. 2020;26:100515. https://doi.org/10.1016/j.eclinm.2020.100515
45. Gubatan J, Levitte S, Balabanis T, Patel A, Sharma A, Habtezion A. SARS-CoV-2 testing, prevalence, and predictors of COVID-19 in patients with inflammatory bowel disease in northern California. *Gastroenterology*. 2020;159(3):1141-1144.e2. https://doi.org/10.1053/j.gastro.2020.05.009
46. Foteinogiannopoulou K, Orfanoudaki E, Koutroubakis IE. Keeping on the high quality of health care in Greek inflammatory bowel disease patients in the SARS-CoV-2 era. *Clin Gastroenterol Hepatol*. 2020;18(10):2380-2381. https://doi.org/10.1016/j.cgh.2020.04.076
47. Burke KE, Kochar B, Allegretti JR, et al. Immunosuppressive therapy and risk of COVID-19 infection in patients with inflammatory bowel diseases. *Inflamm Bowel Dis*. 2021;27(2):155-161. https://doi.org/10.1093/ibd/izaa278
48. Attauabi M, Poulsen A, Theede K, et al. Prevalence and outcomes of COVID-19 among patients with inflammatory bowel disease-A Danish prospective population-based cohort study. *J Crohns Colitis*. 2021;15(4):540-550. https://doi.org/10.1093/ecco-jcc/jjaa205
49. Bezzio C, Saibeni S, Variola A, et al. Outcomes of COVID-19 in 79 patients with IBD in Italy: an IG-IBD study. *Gut*. 2020;69(7):1213-1217. https://doi.org/10.1136/gutjnl-2020-321411
50. Marafini I, Salvatori S, Sena G, Calabrese E, Biancone L, Monteleone G. Low frequency of COVID-19 in inflammatory bowel diseases. *Dig Liver Dis*. 2020;52(11):1234-1235. https://doi.org/10.1016/j.dld.2020.06.007
51. Turner D, Huang Y, Martin-de-Carpi J, et al. Corona virus disease 2019 and paediatric inflammatory bowel diseases: global experience and provisional guidance (March 2020) from the paediatric IBD Porto group of European society of paediatric gastroenterology, hepatology, and nutrition. *J Pediatr Gastroenterol Nutr*. 2020;70(6):727-733. https://doi.org/10.1097/mpg.0000000000002729
52. Sima AR, Saberzadeh-Ardestani B, Vahedi H, et al. Outcomes of COVID-19 in patients with inflammatory bowel disease: comparison with household members and the role of IBD medications. *Arch Iran Med*. 2022;25(1):17-25. https://doi.org/10.34172/aim.2022.04
53. Richter V, Bermont A, Cohen DL, Broide E, Shirin H. Effect of inflammatory bowel disease and related medications on COVID-19 incidence, disease severity, and outcome: the Israeli experience. *Eur J Gastroenterol Hepatol*. 2022;34(3):267-273. https://doi.org/10.1097/meg.0000000000002239
54. Queiroz NSF, Martins CA, 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;36(11):3033-3040. https://doi.org/10.1111/jgh.15588
55. Macaluso FS, Giuliano A, Fries W, et al. Severe activity of inflammatory bowel disease is a risk factor for severe COVID-19. *Inflamm Bowel Dis*. 2022.

56. Xiao F, Tang M, Zheng X, Liu Y, Li X, Shan H. Evidence for gastrointestinal infection of SARS-CoV-2. *Gastroenterology*. 2020;158(6):1831-1833.e3. https://doi.org/10.1053/j.gastro.2020.02.055
57. Hamming I, Timens W, Bulthuis ML, Lely AT, Navis G, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. *J Pathol*. 2004;203(2):631-637. https://doi.org/10.1002/path.1570
58. Nowak JK, Lindstrom JC, Kalla R, Ricanek P, Halfvarson J, Satsangi J. Age, inflammation, and disease location are critical determinants of intestinal expression of SARS-CoV-2 receptor ACE2 and TMPRSS2 in inflammatory bowel disease. *Gastroenterology*. 2020;159(3):1151-1154.e2. https://doi.org/10.1053/j.gastro.2020.05.030
59. Garg M, Burrell LM, Velkoska E, et al. Upregulation of circulating components of the alternative renin-angiotensin system in inflammatory bowel disease: a pilot study. *J Renin Angiotensin Aldosterone Syst*. 2015;16(3):559-569. https://doi.org/10.1177/1470320314521086
60. Brito CA, Paiva JG, Pimentel FN, Guimaraes RS, Moreira MR. COVID-19 in patients with rheumatological diseases treated with anti-TNF. *Ann Rheum Dis*. 2020;80(5):e62. https://doi.org/10.1136/annrheumdis-2020-218171
61. Group RC, Horby P, Lim WS, et al. Dexamethasone in hospitalized patients with Covid-19. *N Engl J Med*. 2021;384(8):693-704. https://doi.org/10.1056/nejmoa2021436
62. Macaluso FS, Orlando A. COVID-19 in patients with inflammatory bowel disease: a systematic review of clinical data. *Dig Liver Dis*. 2020;52(11):1222-1227. https://doi.org/10.1016/j.dld.2020.09.002
63. Lee MH, Ng CH, Chin YH, Muthiah M, Foo FJ, Chong CS. Incidence of SARS-CoV-2 infection in inflammatory bowel disease. *J Gastroenterol Hepatol*. 2020;35(11):2021-2022. https://doi.org/10.1111/jgh.15191
64. Iacucci M, de Silva S, Ghosh S. Mesalazine in inflammatory bowel disease: a trendy topic once again? *Can J Gastroenterol*. 2010;24(2):127-133. https://doi.org/10.1155/2010/586092
65. Stevens C, Lipman M, Fabry S, et al. 5-Aminosalicylic acid abrogates T-cell proliferation by blocking interleukin-2 production in peripheral blood mononuclear cells. *J Pharmacol Exp Ther*. 1995;272(1):399-406.
66. Bonanad C, Garcia-Blas S, Tarazona-Santabalbina F, et al. The effect of age on mortality in patients with COVID-19: a meta-analysis with 611, 583 subjects. *J Am Med Dir Assoc*. 2020;21(7):915-918. https://doi.org/10.1016/j.jamda.2020.05.045
67. Mehta P, McAuley DF, Brown M, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet*. 2020;395(10229):1033-1034. https://doi.org/10.1016/s0140-6736(20)30628-0
68. Fang Y, Zhang H, Xie J, et al. Sensitivity of chest CT for COVID-19: comparison to RT-PCR. *Radiology*. 2020;296(2):E115-E7. https://doi.org/10.1148/radiol.2020200432

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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