# COVID-19 Susceptibility and Clinical Outcomes in Inflammatory Bowel Disease: An Updated Systematic Review and Meta-Analysis

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**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, tumor-necrotizing factor; BMI, body mass index.

## Summary

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 1st 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), tumor necrosis factor antagonists, biologics, systemic corticosteroids, or immunomodulators for IBD. 35 studies were eligible for our analysis. Pooled odds ratio of COVID-19-related hospitalization, intensive care unit (ICU) admission, or death in IBD compared to in non-IBD were 0.58 (95% CI=0.28-1.18), 1.09 (95% CI=0.27-4.47), and 0.67 (95% CI=0.32-1.42), respectively. IBD was not associated with increased hospitalization, ICU admission, or death. Susceptibility to COVID-19 did not increase with any drugs for IBD. Hospitalization, ICU admission, and death were more likely with 5-ASA and corticosteroid use. COVID-19-related hospitalization (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. In conclusion, IBD does not increase the mortality and morbidity of COVID-19. However, physicians should be aware that additional monitoring is needed in ulcerative colitis patients or in patients taking 5-ASA or systemic corticosteroids.

## 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 GI physicians and the referred infected patients.(2) IBD, which refers to Crohn's disease (CD) and ulcerative colitis (UC), is associated with significant morbidity and a high burden of hospitalization, 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 industrialized 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) ACE-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 gastrointestinal (GI) symptoms such as diarrhea 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 tumor-necrotizing factor (TNF) 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.

## Materials and methods

*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 (PRISMA) 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 January 2, 2021. Thereafter, we manually searched for eligible studies in the databases until June 1st, 2022.

Studies using an observational or case-control design and describing the prevalence and outcomes of COVID-19 (namely, hospitalization, 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 hospitalized 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 inflammatory bowel disease, ulcerative colitis, 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).

*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)

*Outcome assessment*

The primary outcomes included the prevalence of severe COVID-19 outcomes in IBD and general population groups, including hospitalization, 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 analyzed the susceptibility of COVID-19 for the use of each IBD medication use.

*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 visualize 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

157 packages. Excluding Cochran's Q and Egger's test, all other statistical tests used a two-sided p-
158 value of 0.05 as a marker for significance.

159

160 **Results**

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

169 *Morbidity and mortality in IBD patients with COVID-19*

170 The odds of developing severe COVID-19 in COVID-19 patients with versus without IBD were
171 analyzed. Our meta-analysis found that severe COVID-19 hospitalizations (odds ratio (OR)=0.83;
172 95% confidence interval (CI)=0.36-1.89), severe COVID-19 ICU admissions (OR=1.36; 95%
173 CI=0.48-3.88), and combined severe COVID-19 hospitalizations and ICU admissions (OR=0.90;
174 95% CI=0.41-1.96) were not significantly different between IBD and non-IBD cohorts (Figure 2).
175 Five studies provided information on COVID-19-related mortality in IBD patients and non-IBD
176 patients. The odds of COVID-19-related death were also found to not be significantly different
177 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 hospitalization, $I^2$=51% with ICU admission, and $I^2$=79% with hospitalization 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 several variables (Table 3). Among them, no variable was associated statistically significantly with COVID-19 hospitalization, ICU admission, and death. The remaining results of the meta-regression are shown in Supplementary Table S3.

*IBD 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 analyzed 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 analyzing the morbidity and mortality of COVID-19 patients on IBD drugs, there were significant differences based on treatment. IBD patients who were not treated with 5-ASA had significantly lower odds of having severe COVID-19 hospitalization (OR=0.41; 95% CI=0.24-0.72) and ICU admission (OR=0.46; 95% CI=0.24-0.85) (Table S4). IBD patients who were not treated with steroids had both lower odds of having severe COVID-19 hospitalization

(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 hospitalization (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 ASA use ($I^2$=0%). No publication bias was found with Egger's test and funnel plots (Table 2 and Supplementary Figure S1).

*Morbidity and mortality in CD and UC 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 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 hospitalization (Egger's p=0.094) (Table 2).

*Quality assessment and risk of bias*

The quality of each study was evaluated using the Newcastle-Ottawa scale. Those results are summarized 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 summarized in Supplementary Figure S3.

## Discussion

Considerable discussion centers 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 toward 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 hospitalization, 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 (BMI), 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 hospitalization and death. In addition, our findings showed that the use of 5-ASA and corticosteroids within IBD patients were associated with both hospitalization 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 hospitalization, 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 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 hospitalization, 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 hospitalization, 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. ACE-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-analyzed 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:**

MH Lee, L Smith and JI Shin formulated the research question and reviewed the report. MH Lee, HJ Li, P Wasuwanich and SE Kim did the literature search, extracted and selected articles. JY Kim, GH Jeong, and MS Kim did the meta-analysis. All authors (M.H.L, H.J.L, P.W, S.E.K, J.Y.K, G.H.J, S.P., J.W.Y, M.S.K, D.K.Y, S.W.L, A.K, L.J, J.I.S, and L.S) 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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**Data availability:** 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.

## Figure legends

**Figure 1. PRISMA flow chart showing selection process of the studies**

**Figure 2. Summary of the overall meta-analyses on association between COVID-19 and IBD patients**

OR: odds ratio; N: number of; CI: confidence interval; COVID: coronavirus disease; ASA, aminosalicylic acid; ICU: intensive care unit; UC: ulcerative colitis; CD, Crohn's disease

**Figure 3. Meta-analysis of clinical outcomes of COVID-19 in patients with IBD compared to general population**

COVID: coronavirus disease; IBD: inflammatory bowel disease; ICU: intensive care unit; OR: odds ratio; CI: confidence interval.

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## 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 | Hospitalization | ICU | Ventilation | Death | |
| Derikx et al., 2020 | Netherlands | 59 | 36 | Cohort (Multi center) | 34763 | 100 | ● | | | ● | NA |
| Ungaro et al., 2020 | International registry | NA | NA | Case control (Multi center) | 1439 | 1439 | | ● | ● | ● | Age, Sex, IBD disease type, Country and state |
| Attauabi et al., 2020 | Denmark | 45 | 31 | Cohort (Multi center) | 76 | 76 | ● | ● | ● | ● | NA |
| Attaway et al., 2020 | USA | NA | NA | Case control (Multi Center) | 338 | 27 | ●* | ●* | | | Age, Race, Sex, BMI, Comorbidities |
| Guerra et al., 2020 | Spain | 14 | 11 | Cohort (Single Center) | 805 | 28 | | ● | | ● | NA |
| Burke et al., 2020 | USA | 17 | 22 | Cohort (Multi Center) | 5302 | 39 | ● | ● | | ● | Age, Sex, Race, IBD-type, Comorbidities |
| Allocca et al., 2020 | France/Italy | 6 | 9 | Cohort (Multi center) | 6000 | 15 | ● | ● | | ● | NA |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Norsa et al., 2020 | Italy | NA | NA | Cohort (Single center) | 522 | 0 | | | | | NA |
| Taxonera et al., 2020 | Spain | 5 | 7 | Cohort (Single center) | 1918 | 12 | ● | ● | ● | ● | Age, Sex |
| An et al., 2020 | China | NA | NA | Cohort (Single Center) | 318 | 0 | | | | | NA |
| Grassia et al., 2020 | Italy | NA | NA | Cohort (Single center) | 251 | 1 | | | | | NA |
| Gubatan et al., 2020 | USA | 3 | 2 | Cohort (Single Center) | 168 | 5 | ● | ● | ● | ● | NA |
| Singh et al., 2020 | USA | 131 | 101 | Cohort (Multi center) | 196403 | 232 | ● | | | | Propensity score matched |
| Khan et al., 2020 | USA | NA | NA | Cohort (Multi Center) | 37857 | 36 | | | | | Age, Comorbidities |
| Mak et al., 2020 | Hongkong / Taiwan | NA | NA | Cohort (Multi Center) | 5508 | 0 | | | | | Corticosteorids, anti-TNF |
| Marafini et al., 2020 | Italy | NA | NA | Cohort (Single Center) | 672 | 3 | ● | | | ● | Therapy |
| Turner et al., 2020 | China/ South Korea | NA | NA | Cohort (Multi Center) | 272 | 0 | ● | ● | ● | ● | NA |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Scaldaferri et al., 2020 | Italy | NA | NA | Cohort (Single Center) | 1451 | 5 | | | | | NA |
| Bodini et al., 2020 | Italy | 0 | 0 | Cohort (Single Center) | 48 | 0 | | | | | NA |
| Martinelli et al., 2020 | Italy | 0 | 0 | Cohort (Single Center) | 180 | 0 | | | | | NA |
| Lukin et al., 2020 | USA | 14 | 15 | Cohort (Multi Center) | 119 | 29 | ● | ● | ● | ● | Age, Sex |
| Bezzio et al., 2020 | Italy | 47 | 32 | Cohort (Multi Center) | NA | 79 | ● | ● | ● | ● | Steroid use |
| Rodriguez et al., 2020 | Spain | 27 | 13 | Cohort (Multi Center) | NA | 40 | ● | ● | ● | ● | NA |
| Brenner et al., 2020 | International registry | 203 | 312 | Cohort (Multi Center) | NA | 525 | ● | ● | ● | ● | Clinical and demographic variables, Systemic Corticosteroid use and 5-ASA/Sulfasalazine use |
| Axelrad et al., 2020 | USA | 27 | 56 | Cohort (Single Center) | NA | 83 | ● | ● | ● | ● | NA |
| Hormati et al., 2020 | Iran | NA | NA | Cohort (Single Center) | 150 | 8 | | | | | NA |
| Haberman et al., 2020 | USA | 17 | 20 | Cohort | NA | 37 | ● | ● | | | NA |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | (Single Center) | | | | | | | |
| Mosli et al., 2020 | Saudi Arabia | 1 | 5 | Cohort (Multi Center) | 1156 | 6 | | | | | NA |
| Grunert et al., 2020 | Germany | 0 | 0 | Cohort (Single Center) | 415 | 0 | | | | | Propensity score matched |
| Yu et al., 2020 | China | 0 | 0 | Cohort (Multi Center) | 102 | 0 | | | | | NA |
| Fonteinogiannopoulou et al., 2020 | Greece | NA | NA | Cohort (Single Center) | 78 | 0 | | | | | NA |
| Sima et al., 2022 | Iran | 60 | 24 | Cohort (Multi Center) | 2159 | 84 | ● | ● | ● | ● | NA |
| Richter et al., 2021 | Israel | 44 | 60 | Cohort (Multi Center) | 2,152 | 104 | | | | | NA |
| Macaluso et al., 2022 | Italy | 46 | 76 | Cohort (Multi Center) | 15,000 | 122 | ● | ● | ● | ● | NA |
| Queiroz et al., 2021 | Latin America | 114 | 115 | Cohort (Multi Center) | NA | 229 | ● | ● | ● | ● | NA |

Abbreviations - IBD: inflammatory bowel disease, TNF: tumor necrosis factor, ASA: 5-aminosalicylic acid;BMI: body mass index, N/A: not applicable
*: p-value < 0.05

| Outcomes | Random effects estimate and 95% CI | Random effects p value | Fixed effects estimate and 95% CI | Fixed effects p value | I2 and p value for Q test | Metric | Egger p value | Number of studies |
|---|---|---|---|---|---|---|---|---|
| Severe COVID-19 - hospitalization | 0.83 (0.36 to 1.89) | 0.65 | 0.89 (0.65 to 1.21) | 0.46 | 82% (< 0.001) | OR | 0.8 | 5 |
| Severe COVID-19 - ICU | 1.36 (0.48 to 3.88) | 0.56 | 1.89 (1.02 to 3.52) | 0.043 | 51% (0.088) | OR | 0.2 | 5 |
| COVID-19 related death | 0.66 (0.32 to 1.37) | 0.27 | 0.66 (0.32 to 1.37) | 0.27 | 0% (0.79) | OR | **0.051** | 6 |
| Severe COVID-19 – hospitalization & ICU | 0.90 (0.41 to 1.96) | 0.79 | 1 (0.74 to 1.34) | 0.98 | 79% (< 0.001) | OR | 0.73 | 7 |
| Susceptibility to COVID-19 according to steroid | 0.52 (0.24 to 1.1) | 0.088 | 0.52 (0.24 to 1.1) | 0.088 | 0% (0.50) | OR | 0.1 | 3 |
| Susceptibility to COVID-19 according to immunomodulator | 0.62 (0.3 to 1.26) | 0.18 | 0.62 (0.3 to 1.26) | 0.18 | 0% (0.68) | OR | 0.64 | 5 |
| Susceptibility to COVID-19 according to anti-TNF | 1.09 (0.59 to 2.01) | 0.79 | 1.09 (0.59 to 2.01) | 0.79 | 0% (0.74) | OR | 0.48 | 6 |
| Susceptibility to COVID-19 according to ASA | 0.62 (0.27 to 1.38) | 0.24 | 0.79 (0.48 to 1.29) | 0.34 | 49% (0.12) | OR | **0.018** | 4 |
| Susceptibility to COVID-19 according to Vedolizumab | 0.46 (0.21 to 1.04) | 0.062 | 0.46 (0.21 to 1.04) | 0.062 | 0% (0.50) | OR | 0.4 | 5 |
| Susceptibility to COVID-19 according to Ustekinumab | 0.18 (0.02 to 1.33) | 0.094 | 0.53 (0.23 to 1.23) | 0.14 | 76% (< 0.001) | OR | **0.064** | 6 |
| Severe COVID-19 hospitalization (vs non-ASA users) | 0.41 (0.24 to 0.72) | **0.002** | 0.5 (0.41 to 0.62) | < 0.001 | 19% (0.29) | OR | 0.37 | 5 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Severe COVID-19 hospitalization (vs non-Steroid users) | 0.35 (0.26 to 0.46) | **< 0.001** | 0.35 (0.26 to 0.46) | < 0.001 | 0% (0.74) | OR | 0.9 | 5 |
| Severe COVID-19 hospitalization (vs non-Immunomodulator users) | 0.96 (0.46 to 1.98) | 0.9 | 0.83 (0.65 to 1.05) | 0.12 | 42% (0.14) | OR | 0.81 | 5 |
| Severe COVID-19 ICU (vs non-ASA users) | 0.46 (0.24 to 0.85) | **0.013** | 0.51 (0.34 to 0.76) | < 0.001 | 5% (0.37) | OR | 0.026 | 4 |
| Severe COVID-19 ICU (vs non-Steroid users) | 0.21 (0.10 to 0.42) | **< 0.001** | 0.23 (0.15 to 0.34) | < 0.001 | 30% (0.23) | OR | 0.89 | 4 |
| Severe COVID-19 ICU (vs non-Immunomodulator users) | 1.40 (0.82 to 2.37) | 0.22 | 1.4 (0.82 to 2.37) | 0.22 | 0% (0.58) | OR | **0.13** | 4 |
| COVID-19 related death (vs non-ASA users) | 0.37 (0.23 to 0.59) | **< 0.001** | 0.37 (0.23 to 0.59) | < 0.001 | 0% (0.84) | OR | 0.83 | 5 |
| COVID-19 related death (vs non-Steroid users) | 0.43 (0.10 to 1.97) | 0.28 | 0.64 (0.4 to 1.01) | 0.055 | 84% (< 0.001) | OR | 0.72 | 5 |
| COVID-19 related death (vs non-Immunomodulator users) | 0.99 (0.25 to 3.94) | 0.99 | 1.21 (0.65 to 2.28) | 0.55 | 40% (0.16) | OR | 0.71 | 5 |
| Severe COVID-19 between UC and CD - hospitalization | 0.55 (0.40 to 0.75) | **< 0.001** | 0.55 (0.4 to 0.75) | < 0.001 | 0% (0.79) | OR | **0.094** | 8 |
| Severe COVID-19 between UC and CD - ICU | 0.60 (0.29 to 1.24) | 0.17 | 0.6 (0.29 to 1.24) | 0.17 | 0% (0.83) | OR | 0.71 | 4 |
| COVID-19 related death between UC and CD | 0.35 (0.16 to 0.75) | **0.007** | 0.35 (0.16 to 0.75) | 0.007 | 0% (0.91) | OR | 0.47 | 7 |

**Table 2. Outcomes of meta-analyses including heterogeneity and Egger's test**

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

**Table 3. Meta-regression of the variables potentially associated with the severe outcomes of COVID-19**

| | Hospitalization | | | ICU admission | | | Hospitalization & 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 | 0.9999969 | 0.66 | 3 | 1.00011 | 0.062 | 4 | 0.9999988 | 0.84 | 5 | 0.9997 | 0.24 | 4 |
| Number of COVID19 (n) | 0.999951 | 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) | 0.999964 | 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 |

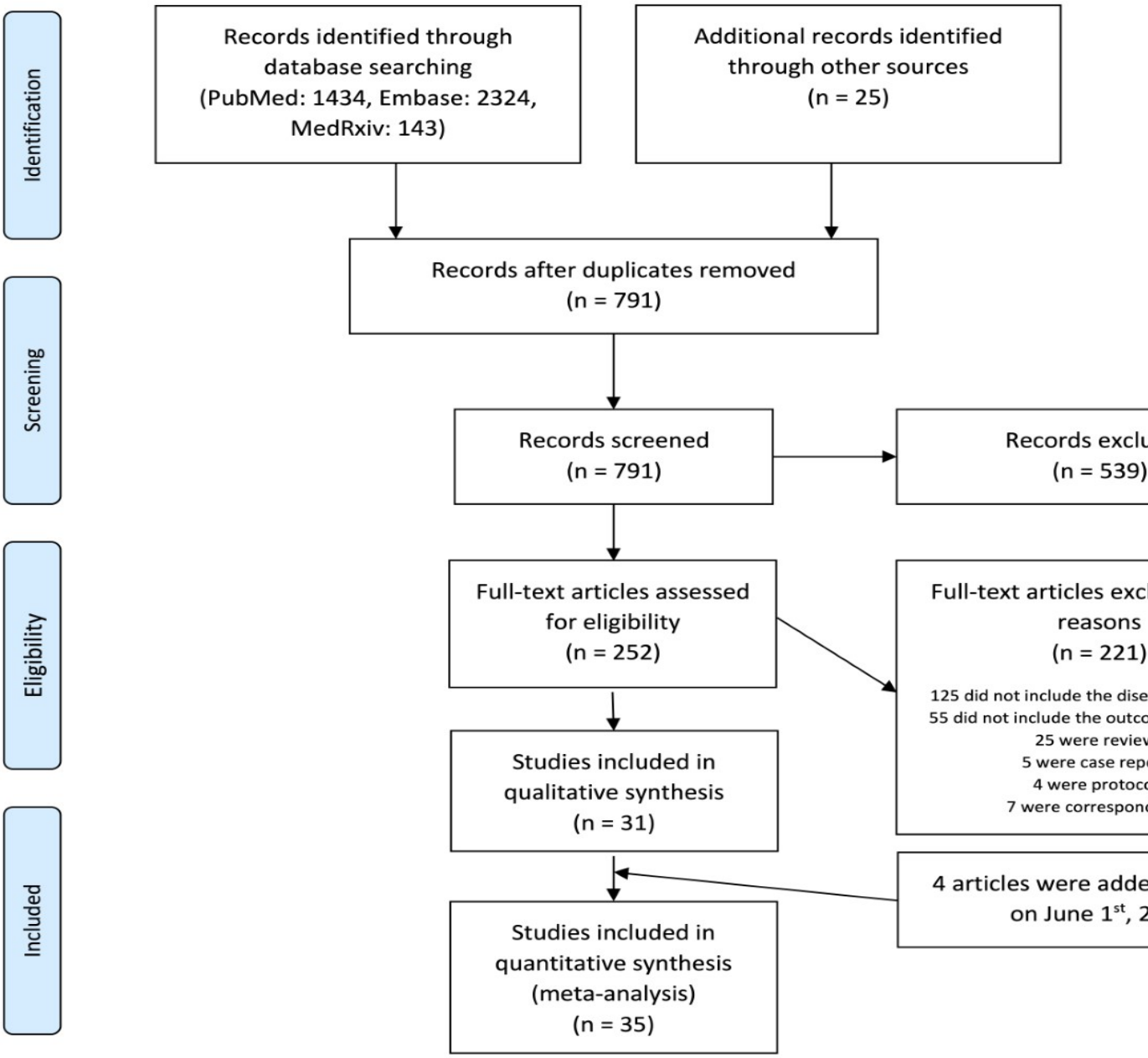
Abbreviations - COVID: coronavirus disease; ICU: intensive care unit; GC: glucocorticoid; DMARD: disease-modifying antirheumatic drug; cs-DMARD: conventional synthetic DMARD; b/ts-DMARD: biologic/target synthetic DMARD.

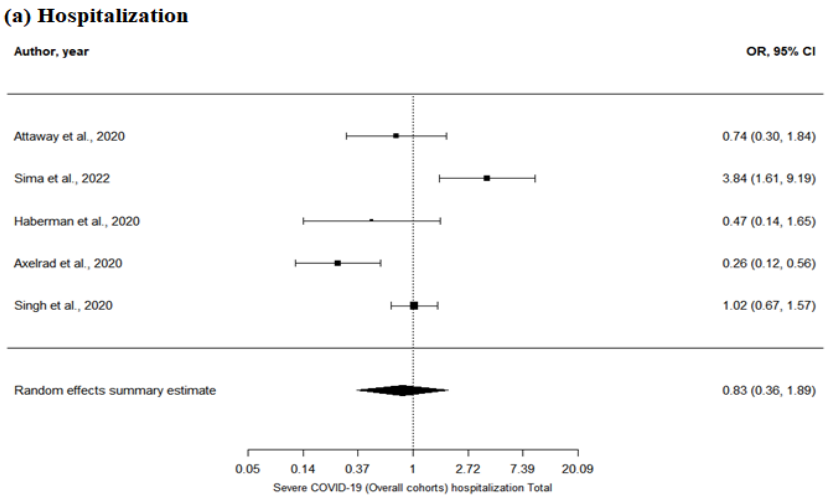
**Table 4. Meta-analysis of susceptibility of COVID-19 in patients with IBD according to drug use**

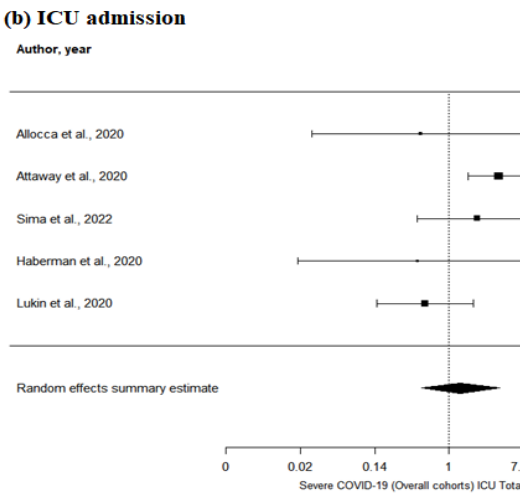
| **Steroid** | | | | | |
|---|---|---|---|---|---|
| Study | Steroid user | | Non-steroid user | | OR, 95% CI |
| | Event | Total | Event | Total | |
| Gubatan et al., 2020 | 1 | 34 | 4 | 134 | 1.01 [0.11; 9.38] |
| Lukin et al., 2020 | 13 | 35 | 16 | 84 | 0.40 [0.17; 0.96] |
| Mosli et al., 2020 | 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 | 35466 | 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 | 32937 | 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]** |

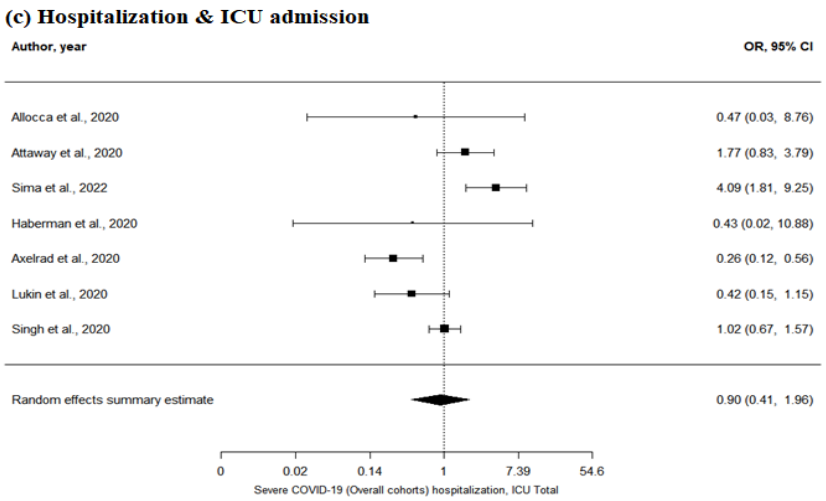
| Ustekinumab | | | | | |
|---|---|---|---|---|---|
| | Ustekinumab user | | Non-Ustekinumab user | | |
| Taxonera et al., 2020 | 1 | 23 | 11 | 1895 | 0.13 [0.02; 1.03] |
| Grassia et al., 2020 | 0 | 1 | 1 | 250 | 0.02 [0.00; 0.65] |
| Gubatan et al., 2020 | 0 | 4 | 5 | 164 | 0.31 [0.01; 6.50] |
| Lukin 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]** |

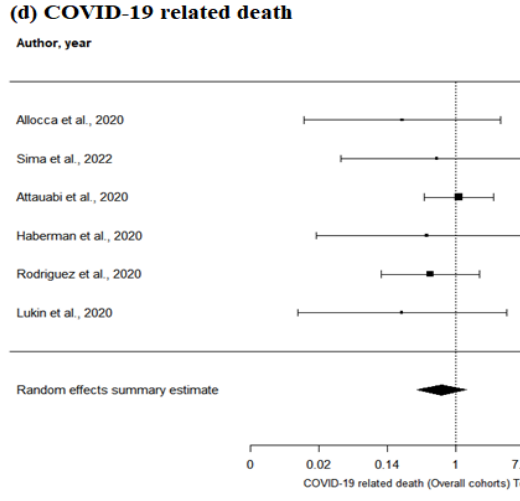
Abbreviations - IBD: inflammatory bowel disease; CI: confidence interval; TNF: tumor necrosis factor; ASA: 5-aminosalicylic acid; odds ratio: OR.


Identification
Screening
Eligibility
Included
Records identified through database searching (PubMed: 1434, Embase: 2324, MedRxiv: 143)
Additional records identified through other sources (n = 25)
Records after duplicates removed (n = 791)
Records screened (n = 791)
Records exclu (n = 539)
Full-text articles assessed for eligibility (n = 252)
Full-text articles exc reasons (n = 221)
125 did not include the dise
55 did not include the outco
25 were reviev
5 were case rep
4 were protoc
7 were correspon
Studies included in qualitative synthesis (n = 31)
4 articles were adde on June 1st, 2
Studies included in quantitative synthesis (meta-analysis) (n = 35)




**Supplementary Table S1. Databases searched for relevant studies**

| |
|---|
| **PubMed Search Strategy (319 hits)**<br><br>Years/Issue Searched: 2019 to 2020<br><br>Search date: 2 Jan 2021<br><br>(“inflammatory bowel disease” OR IBD OR “ulcerative col*” OR UC OR “colitis ul*” OR “colitis ulcerosa” OR “crohn” OR CD) AND (“COVID-19” OR “SARS-CoV-2” OR coronavirus OR 2019-nCoV’ OR (novel AND cov) OR (wuhan AND virus) OR wuhan coronavirus OR “covid 2019”) AND (prevalence OR susceptibility OR “outcome*” OR “clinical feature*” OR prognosis OR “severity” OR “risk factor*” OR mortality OR death OR hospitali?ation OR ICU OR ventilation OR ventilator OR incidence OR intubation)Filters: English, from 2019 – 2020 |

**Embase Search Strategy (520 hits)**

#1. 'severe acute respiratory syndrome'/exp
#2. 'severe acute respiratory syndrome'
#3. 'coronavirus disease 2019'/exp
#4. 'covid-19' OR 'sars-cov-2' OR coronavirus OR '2019-ncov' OR (novel AND cov) OR (wuhan AND virus) OR 'wuhan coronavirus' OR 'covid 2019'
#5. 'inflammatory bowel disease*' OR ibd
#6. 'crohn*' OR cd
#7. 'ulcerative col*'
#8. 'colitis ul*' OR 'colitis ulcerosa' OR uc
#9. mortality OR death OR hospitalization OR ventilation OR ventilator OR icu OR 'clinical' OR 'outcome*' OR prevalence OR prognosis OR 'risk factor*' OR incidence OR intubation
#10. (#1 OR #2 OR #3 OR #4) AND (#5 OR #6 OR #7 OR #8) AND #9 AND [english]/lim AND [2019-2020]/py

**MedRxiv Search Strategy (110 hits)**

Years/Issue Searched: 2019 to 2020

Search date: 2 Jan 2021

("inflammatory bowel" OR "Crohn" OR "Ulcerative") AND ("COVID-19" OR "CoV")" and full text or abstract or title "COVID or inflammatory or Crohn or ulcerative" (match whole any) and posted between "01 Dec, 2019 and 01 Nov, 2020"

**Manual Search (including MedRxiv, Embase, PubMed)**

Years Seached: 2021 to 1st June 2022

Search date: 1st June 2022

**Supplementary Table S2. Characteristics of studies included in the meta-analysis**

| Study | Study location | Total number of patients# | Diagnosis | Demographics of patients with IBD | | | | | | | COVID-19 | | Demographics of patients with IBD and COVID-19 | | | | | | | COVID-19 outcomes## | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Mean/ Median Age (y/o) | Male (%) | Comorbidities (%) | GCs (%) | csDMARDs (%) | b/tsDMARDs monotherapy (%) | b/tsDMARDs – csDMARDs combination therapy (%) | Number of COVID 19 (n) | Number of Confirmed COVID-19 with positive PCR (n) | Mean/ Median Age (y/o) | Male (%) | Comorbidities (%) | GCs (%) | csDMARDs (%) | b/tsDMARDs monotherapy (%) | b/tsDMARDs –csDMARDs combination therapy (%) | Hospitalization (n) | ICU admission (n) | Ventilation (n) | Death (n) |
| Derikx et al | Netherlands | 34763 | IBD | NA | NA | NA | NA | NA | NA | NA | 100 | 100 | 62.5 | 46.0 | 59.0 | 22.2 | NA | NA | NA | 40 | NA | NA | 13 |
| Ungaro et al | International registry | 1439 | IBD | NA | NA | NA | NA | NA | NA | NA | 1439 | 1439 | 44.1 | 51.4 | 37.2 | NA | NA | NA | NA | NA | 82 | 66 | 49 |
| Attauabi et al | Denmark | 76 | IBD | NA | NA | NA | NA | NA | NA | NA | 76 | 76 | 51 | 59.0 | 57.0 | NA | NA | NA | NA | 19 | 5 | 3 | 4 |
| Attaway et al | USA | 15586 | IBD | NA | NA | NA | NA | NA | NA | NA | 2527 | 2527 | NA | NA | NA | NA | NA | NA | NA | 6 | 8 | NA | NA |
| Guerra et al | Spain | 805 | IBD | NA | NA | NA | NA | NA | NA | NA | 28 | 28 | 54 | 53.6 | 60.7 | NA | NA | NA | NA | NA | 1 | NA | 1 |
| Burke et al | USA | 5302 | IBD | 45.6 | 38.0 | NA | 21.0 | NA | NA | NA | 39 | 39 | 46.6 | 49.0 | NA | 20.0 | NA | NA | NA | 7 | 3 | NA | 1 |
| Allocca et al | France/ Italy | 6000 | IBD | NA | NA | NA | NA | NA | NA | NA | 15 | 15 | 39.1 | 26.7 | 60.0 | 13.3 | 20.0 | 60.0 | 13.3 | 5 | 0 | NA | 0 |
| Norsa et al | Italy | 522 | IBD | 46 | 58.0 | NA | 3.1 | 19.2 | 15.7 | NA | 0 | 0 | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| Taxonera et al | Spain | 1918 | IBD | NA | NA | NA | NA | NA | NA | NA | 12 | 12 | 52.3 | 25.0 | 41.7 | 0.0 | 50.0 | 8.3 | 33.3 | 8 | 1 | 1 | 2 |
| An et al | China | 318 | IBD | 39.2 | NA | 15.4 | NA | NA | NA | NA | 0 | 0 | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| Grassia et al | Italy | 251 | IBD | NA | NA | NA | NA | NA | 16.3 | NA | 1 | NA | NA | NA | NA | NA | 100.0 | 0.0 | 0.0 | NA | NA | NA | NA |
| Gubatan et al | USA | 168 | IBD | 47.7 | 47.6 | NA | 20.2 | 8.9 | 28.6 | NA | 5 | 5 | 70.6 | 40.0 | NA | 20.0 | 20.0 | 20.0 | NA | 1 | 1 | 1 | 1 |
| Singh et al | USA | 196403 | IBD | NA | NA | NA | NA | NA | NA | NA | 232 | 232 | 51.2 | 36.6 | NA | 47.8 | 14.7 | 15.9 | NA | 56 | NA | NA | NA |
| Khan et al | USA | 37857 | IBD | NA | NA | NA | NA | NA | NA | NA | 36 | NA | 63 | NA | NA | NA | 5.6 | 8.3 | NA | NA | NA | NA | NA |
| Mak et al | Hong Kong/ Taiwan | 5508 | IBD | 46.9 | 67.8 | NA | 30.6 | 43.4 | 19.2 | NA | 0 | 0 | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| Marafini et al | Italy | 672 | IBD | 46 | 53.7 | NA | 4.3 | 6.4 | 35.9 | NA | 3 | 3 | NA | NA | NA | NA | NA | NA | NA | 2 | NA | NA | 1 |
| Turner et al | China/ South Korea | 272 | IBD | NA | NA | NA | NA | NA | NA | NA | 8 | 6 | 16.1 | 62.5 | NA | 12.5 | 50.0 | 37.5 | 25.0 | 0 | 0 | 0 | 0 |
| Scaldaferri et al | Italy | 1451 | IBD | 44 | 58.0 | NA | NA | NA | 85.1 | NA | 5 | 5 | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| Bodini et al | Italy | 48 | IBD | NA | NA | NA | NA | NA | NA | NA | 0 | 0 | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| Martinelli et al | Italy | 180 | IBD | 15.3 | 53.3 | NA | 5.0 | 33.3 | 12.2 | 11.1 | 0 | 0 | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| Lukin et al* | USA | 1386 | IBD | NA | NA | NA | NA | NA | NA | NA | 80 | NA | 48.3 | 56.3 | NA | 12.5 | NA | 47.5 | NA | 17 | 3 | 2 | 0 |
| Bezzio et al | Italy | NA | IBD | NA | NA | NA | NA | NA | NA | NA | 79 | 49 | 47 | 55.7 | 38.0 | 11.4 | NA | 59.5 | NA | 22 | 11 | 11 | 6 |
| Rodriguez et al | Spain | NA | IBD | NA | NA | NA | NA | NA | NA | NA | 40 | 40 | 58.5 | 60.0 | 62.5 | 10.0 | 32.5 | 17.5 | 5.0 | 21 | 0 | 0 | 2 |
| Brenner et al | International registry | NA | IBD | NA | NA | NA | NA | NA | NA | NA | 525 | 525 | 42.9 | 52.6 | 33.1 | 7.0 | NA | 55.0 | 9.9 | 161 | 24 | 21 | 16 |
| Axelrad et al | USA | NA | IBD | NA | NA | NA | NA | NA | NA | NA | 83 | 45 | 35 | 53.0 | NA | 7.2 | 7.2 | 74.7 | NA | 5 | 1 | 1 | 1 |
| Hormati et al | Iran | 200 | IBD | 48.4 | NA | NA | NA | NA | NA | NA | 11 | 11 | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |

| | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Haberman et al | USA | NA | IBD | NA | NA | NA | NA | NA | NA | NA | 86 | 59 | 46 | 43 | NA | NA | NA | NA | NA | 14 | 1 | NA | 1 |
| Mosli et al | Saudi Arabia | 1156 | IBD | NA | 52.5 | NA | NA | NA | NA | NA | 6 | 6 | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| Grunert et al | Germany | 415 | IBD | 45 | 45.3 | 49.8 | 13 | NA | NA | NA | 0 | 0 | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| Yu et al | China | 102 | IBD | 34 | 66.7 | NA | 3.9 | NA | NA | NA | 0 | 0 | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| Foteinogiannopoulou et al | Greece | 890 | IBD | NA | NA | NA | NA | NA | NA | NA | 0 | 0 | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| Sima et al | Iran | 2159 | IBD | NA | NA | NA | NA | NA | NA | NA | 84 | 84 | 43.4 | 41.6 | 40.4 | 9.8 | NA | 15 | 8.3 | 36 | 7 | 4 | 1 |
| Richter et al | Israel | 2152 | IBD | 39 | 39.5 | 24.4 | NA | NA | NA | NA | 104 | 104 | 37 | 45.2 | 21.2 | NA | NA | NA | NA | NA | NA | NA | NA |
| Macaluso et al | Italy | 15000 | IBD | NA | NA | NA | NA | NA | NA | NA | 122 | 122 | 43.9 | 50 | 30.3 | 21.7 | NA | NA | NA | 12 | NA | 3 | 4 |
| Queiroz et al | Latin America | NA | IBD | NA | NA | NA | NA | NA | NA | NA | 230 | 230 | 40.47 | 40 | 34.3 | 13 | NA | NA | NA | 47 | 15 | 7 | 4 |

# If the parent population of autoimmune diseases was not available, an analysis for the prevalence of COVID-19 was not conducted.
## If all of clinical outcomes regarding COVID-19 were not available, we declined an analysis of COVID-19 outcomes.
* These studies were excluded for an analysis of the prevalence as all of included patients were COVID-19.
Abbreviations - GC: use of glucocorticoid, IBD: inflammatory bowel disease, b/ts-DMARD: biological DMARDs or targeted synthetic DMARDs, c-DMARD: conventional synthetic DMARDs, DMARD: Disease-modifying antirheumatic drugs, ICU: intensive care unit, N/A: not applicable

## Supplementary Table S3. Meta-regression of the variables potentially associated with susceptibility and severe outcome of COVID-19

| | **Hospitalization** | | | **ICU admission** | | | **COVID-19 related death** | | | **Hospitalization and ICU** | | | **Susceptibility to COVID-19 according to immunomodulator** | | | **Susceptibility to COVID-19 according to anti-TNF** | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **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** | **Coefficient** | **P value** | **Number of studies** | **Coefficient** | **P value** | **Number of studies** |
| Total number of patients | 0.999969 | 0.66 | 3 | 1.00011 | 0.062 | 4 | 0.9997 | 0.24 | 4 | 0.999988 | 0.84 | 5 | 0.9918 | 0.41 | 3 | 1.000022 | 0.33 | 5 |
| IBD group Male (%) | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| Number of COVID19 (n) | 0.999951 | 0.93 | 5 | 1.00064 | **0.02** | 5 | 1.016 | 0.37 | 6 | 1.00036 | 0.46 | 7 | 0.986 | 0.24 | 3 | 1.00089 | 0.95 | 5 |
| Number of Confirmed COVID-19 with positive PCR (n) | 0.999964 | 0.95 | 5 | 1.00047 | 0.14 | 4 | 1.022 | 0.23 | 5 | 1.00031 | 0.56 | 6 | NA | NA | NA | 0.912 | 0.54 | 3 |
| IBD with COVID19 group Mean/ Median Age (y/o) | 1.076 | 0.5 | 4 | 0.91 | 0.56 | 4 | 1.025 | 0.74 | 6 | 1.058 | 0.54 | 6 | NA | NA | NA | 1.029 | 0.58 | 4 |
| IBD with COVID19 group Male (%) | 0.901 | 0.25 | 4 | 0.981 | 0.72 | 4 | 1.036 | 0.38 | 6 | 0.949 | 0.31 | 6 | NA | NA | NA | 1.004 | 0.91 | 3 |
| IBD with COVID19 group Comorbidities (%) | NA | NA | NA | NA | NA | NA | 0.978 | 0.76 | 4 | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| IBD with COVID19 group GCs (%) | 1.0043 | 0.94 | 3 | 0.61 | 0.17 | 3 | 0.75 | 0.49 | 4 | 1.0099 | 0.8 | 5 | NA | NA | NA | 1.0011 | 0.98 | 3 |
| Hospitalization (n) | 1.027 | 0.21 | 5 | 1.0011 | 0.98 | 5 | 1.028 | 0.66 | 6 | 1.021 | 0.35 | 7 | NA | NA | NA | 1.014 | 0.88 | 3 |
| ICU admission (n) | 1.25 | 0.15 | 4 | 1.4 | **0.006** | 5 | 1.18 | 0.28 | 6 | 1.39 | **< 0.001** | 6 | NA | NA | NA | 1.083 | 0.88 | 3 |
| Ventilation (n) | NA | NA | NA | NA | NA | NA | 1.25 | 0.43 | 4 | 2.6 | **< 0.001** | 3 | NA | NA | NA | 1.17 | 0.88 | 3 |
| Death (n) | NA | NA | NA | 3 | 0.25 | 4 | 1.45 | 0.13 | 6 | 2 | 0.62 | 5 | NA | NA | NA | 0.941 | 0.91 | 3 |
| | **Susceptibility to COVID-19 according to ASA** | | | **Susceptibility to COVID-19 according to Vedolizumab** | | | **Susceptibility to COVID-19 according to Ustekinumab** | | | **Hospitalization (vs non-ASA users)** | | | **Hospitalization (vs non-Steroid users)** | | | **Hospitalization (vs non-Immunomodulator users)** | | |
| **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** | **Coefficient** | **P value** | **Number of studies** | **Coefficient** | **P value** | **Number of studies** |
| Total number of patients | 1.00027 | 0.079 | 4 | 0.99961 | 0.68 | 5 | 1.00085 | 0.55 | 5 | 1.00058 | 0.22 | 3 | NA | NA | NA | 0.99923 | 0.05 | 3 |
| IBD group Male (%) | 0.88 | **0.046** | 3 | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| Number of COVID19 (n) | 1.016 | 0.33 | 4 | 1.014 | 0.23 | 5 | 0.9934 | 0.16 | 6 | 1.0017 | 0.097 | 5 | 0.99982 | 0.86 | 5 | 0.99946 | 0.81 | 5 |
| Number of Confirmed COVID-19 with positive PCR (n) | 1.054 | **0.019** | 3 | 0.74 | 0.2 | 3 | 0.993 | **0.024** | 4 | 1.0017 | 0.1 | 5 | 0.9998 | 0.84 | 5 | 0.99956 | 0.85 | 5 |
| IBD with COVID19 group Mean/ Median Age (y/o) | 0.91 | 0.057 | 3 | 1.021 | 0.84 | 3 | 1.066 | 0.66 | 4 | 0.925 | 0.46 | 5 | 0.964 | 0.75 | 5 | 1.2 | 0.08 | 5 |
| IBD with COVID19 group Male (%) | 1.093 | 0.41 | 3 | 1.057 | 0.13 | 3 | 1.024 | 0.84 | 4 | 1.051 | 0.15 | 5 | 1.0092 | 0.75 | 5 | 0.975 | 0.49 | 5 |
| IBD with COVID19 group Comorbidities (%) | NA | NA | NA | NA | NA | NA | NA | NA | NA | 1.015 | 0.84 | 4 | 0.961 | 0.44 | 4 | 0.938 | 0.39 | 4 |
| IBD with COVID19 group GCs (%) | 0.956 | 0.85 | 3 | 1.13 | 0.12 | 3 | 1.13 | 0.53 | 4 | 1.059 | 0.73 | 5 | 0.991 | 0.9 | 5 | 0.84 | 0.25 | 5 |
| Hospitalization (n) | 1.07 | 0.57 | 3 | 1.036 | 0.79 | 3 | 0.973 | 0.086 | 4 | 1.0053 | 0.15 | 5 | 0.9993 | 0.83 | 5 | 0.9993 | 0.93 | 5 |

| | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | | | 8 | | | 2 | | |
| ICU admission (n) | 2.8 | 0.075 | 3 | 1.82 | 0.34 | 3 | 0.83 | 0.097 | 4 | 1.033 | 0.25 | 5 | 0.9952 | 0.85 | 5 | 0.99934 | 0.99 | 5 |
| Ventilation (n) | NA | NA | NA | 3.3 | 0.34 | 3 | 0.81 | 0.075 | 4 | 1.051 | 0.065 | 4 | 0.988 | 0.61 | 4 | 0.959 | 0.096 | 4 |
| Death (n) | 0.71 | 0.85 | 3 | 0.42 | 0.13 | 3 | 0.73 | **0.013** | 4 | 1.054 | 0.098 | 5 | 0.9944 | 0.84 | 5 | 0.9901 | 0.89 | 5 |
| | **ICU admission (vs non-ASA users)** | | | **ICU admission (vs non-Steroid users)** | | | **ICU admission (vs non-Immunomodulator users)** | | | **COVID-19 related death (vs non-ASA users)** | | | **COVID-19 related death (vs non-Steroid users)** | | | **COVID-19 related death (vs non-Immunomodulator users)** | | |
| **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** | **Coefficient** | **P value** | **Number of studies** | **Coefficient** | **P value** | **Number of studies** |
| Total number of patients | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| IBD group Male (%) | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| Number of COVID19 (n) | 1.0035 | 0.087 | 4 | 0.99989 | 0.97 | 4 | 1.0012 | 0.46 | 4 | 1.00019 | 0.9 | 5 | 0.998 | 0.67 | 5 | 1.00053 | 0.91 | 5 |
| Number of Confirmed COVID-19 with positive PCR (n) | 1.0035 | 0.084 | 4 | 0.99983 | 0.95 | 4 | 1.0012 | 0.44 | 4 | 1.00015 | 0.92 | 5 | 0.9983 | 0.7 | 5 | 1.00093 | 0.83 | 5 |
| IBD with COVID19 group Mean/ Median Age (y/o) | 1.041 | 0.8 | 4 | 1.13 | 0.53 | 4 | 0.9965 | 0.98 | 4 | 0.914 | 0.44 | 5 | 1.05 | 0.84 | 5 | 1.33 | **0.028** | 5 |
| IBD with COVID19 group Male (%) | 1.05 | 0.46 | 4 | 1.062 | 0.38 | 4 | 1.033 | 0.53 | 4 | 1.049 | 0.4 | 5 | 0.961 | 0.76 | 5 | 0.92 | 0.25 | 5 |
| IBD with COVID19 group Comorbidities (%) | 0.84 | 0.23 | 3 | 1.11 | 0.6 | 3 | 0.958 | 0.68 | 3 | 0.96 | 0.74 | 4 | 1.43 | 0.18 | 4 | 1.11 | 0.47 | 4 |
| IBD with COVID19 group GCs (%) | 1.035 | 0.89 | 4 | 0.84 | 0.083 | 4 | 1.16 | 0.44 | 4 | 1.14 | 0.39 | 5 | 0.77 | 0.48 | 5 | 0.86 | 0.48 | 5 |
| Hospitalization (n) | 1.012 | 0.081 | 4 | 1.0017 | 0.84 | 4 | 1.0045 | 0.41 | 4 | 1.00051 | 0.92 | 5 | 0.9981 | 0.9 | 5 | 1.0049 | 0.73 | 5 |
| ICU admission (n) | 1.083 | 0.082 | 4 | 0.982 | 0.79 | 4 | 1.034 | 0.38 | 4 | 1.0077 | 0.85 | 5 | 0.932 | 0.51 | 5 | 1.042 | 0.68 | 5 |
| Ventilation (n) | 1.092 | 0.082 | 4 | 1.0073 | 0.91 | 4 | 1.033 | 0.42 | 4 | 1.008 | 0.86 | 5 | 0.95 | 0.66 | 5 | 1.044 | 0.7 | 5 |
| Death (n) | 1.12 | 0.083 | 4 | 1.01 | 0.9 | 4 | 1.034 | 0.5 | 4 | 1.0039 | 0.95 | 5 | 0.937 | 0.65 | 5 | 1.057 | 0.71 | 5 |
| | **Hospitalization between UC and CD** | | | **ICU admission between UC and CD** | | | **COVID-19 related death between UC and CD** | | | | | | | | | | | |
| **Continuous variable** | **Coefficient** | **P value** | **Number of studies** | **Coefficient** | **P value** | **Number of studies** | **Coefficient** | **P value** | **Number of studies** | | | | | | | | | |
| Total number of patients | 1.000046 | 0.45 | 4 | NA | NA | NA | 1.000059 | 0.62 | 3 | | | | | | | | | |
| IBD group Male (%) | NA | NA | NA | NA | NA | NA | NA | NA | NA | | | | | | | | | |
| Number of COVID19 (n) | 1.00061 | 0.42 | 8 | 1.00075 | 0.71 | 4 | 0.99923 | 0.66 | 7 | | | | | | | | | |
| Number of Confirmed COVID-19 with positive PCR (n) | 1.00061 | 0.41 | 8 | 1.00068 | 0.73 | 4 | 0.99923 | 0.65 | 7 | | | | | | | | | |
| IBD with COVID19 group Mean/ Median Age (y/o) | 0.932 | 0.32 | 8 | 0.89 | 0.39 | 4 | 0.945 | 0.49 | 7 | | | | | | | | | |
| IBD with COVID19 group Male (%) | 1.024 | 0.4 | 8 | 1.046 | 0.43 | 4 | 1.024 | 0.66 | 7 | | | | | | | | | |
| IBD with COVID19 group Comorbidities (%) | 0.962 | 0.27 | 6 | 0.912 | 0.49 | 3 | 0.995 | 0.92 | 6 | | | | | | | | | |
| IBD with COVID19 group GCs (%) | 1.018 | 0.67 | 7 | 1.075 | 0.73 | 4 | 1.056 | 0.44 | 7 | | | | | | | | | |
| Hospitalization (n) | 1.0017 | 0.48 | 8 | 1.002 | 0.76 | 4 | 0.9971 | 0.59 | 7 | | | | | | | | | |

| | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ICU admission (n) | 1.02 | 0.31 | 7 | 1.014 | 0.77 | 4 | 0.984 | 0.71 | 6 | | | | | | | | |
| Ventilation (n) | 1.0051 | 0.81 | 6 | 1.016 | 0.75 | 4 | 0.973 | 0.53 | 7 | | | | | | | | |
| Death (n) | 1.016 | 0.52 | 8 | 1.02 | 0.75 | 4 | 0.963 | 0.53 | 7 | | | | | | | | |

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

**Supplementary Table S4. Meta-analysis of severe outcomes of COVID-19 in patients with IBD according to drug use**

| **Severe COVID-19 Hospitalizations: 5-ASA Use** | | | | | |
|---|---|---|---|---|---|
| Study | ASA user | | Non-ASA user | | Odds Ratio, 95% CI |
| | Event | Total | Event | Total | |
| Allocca et al., 2020 | 0 | 1 | 4 | 13 | 1.42 [0.05; 42.23] |
| Taxonera et al., 2020 | 4 | 4 | 4 | 8 | 0.11 [0.00; 2.72] |
| Brenner et al., 2020 | 213 | 572 | 299 | 1258 | 0.52 [0.42; 0.65] |
| Axelrad et al., 2020 | 2 | 13 | 5 | 70 | 0.42 [0.07; 2.46] |
| Sima et al., 2022 | 32 | 59 | 4 | 25 | 0.16 [0.05; 0.53] |
| **Total (95% CI)** | | | | | **0.41 [0.24; 0.73]** |
| **Severe COVID-19 ICU Admissions: 5-ASA Use** | | | | | |
| Study | ASA user | | Non-ASA user | | Odds Ratio, 95% CI |
| | Event | Total | Event | Total | |
| Taxonera et al., 2020 | 1 | 4 | 0 | 8 | 0.14 [0.00; 4.25] |
| Brenner et al., 2020 | 44 | 572 | 55 | 1258 | 0.55 [0.36; 0.83] |
| Axelrad et al., 2020 | 1 | 13 | 0 | 70 | 0.06 [0.00; 1.53] |
| Sima et al., 2022 | 7 | 59 | - | 25 | 0.13 [0.01; 2.50] |
| **Total (95% CI)** | | | | | **0.46 [0.24; 0.85]** |
| **COVID-19 Related Deaths: 5-ASA Use** | | | | | |
| Study | ASA user | | Non-ASA user | | Odds Ratio, 95% CI |
| | Event | Total | Event | Total | |
| Taxonera et al., 2020 | 2 | 4 | 0 | 8 | 0.06 [0.00; 1.67] |
| Bezzio et al., 2020 | 3 | 24 | 3 | 55 | 0.40 [0.08; 2.16] |
| Brenner et al., 2020 | 34 | 572 | 29 | 1258 | 0.37 [0.22; 0.62] |
| Axelrad et al., 2020 | 0 | 13 | 1 | 70 | 0.58 [0.02; 15.09] |
| Sima et al., 2022 | 1 | 59 | 0 | 25 | 0.76 [0.03; 19.41] |
| **Total (95% CI)** | | | | | **0.37 [0.23; 0.59]** |
| **Severe COVID-19 Hospitalizations: Steroid Use** | | | | | |
| Study | Steroid user | | Non-steroid user | | Odds Ratio, 95% CI |
| | Event | Total | Event | Total | |
| Allocca et al., 2020 | 2 | 2 | 2 | 12 | 0.05 [0.00; 1.33] |
| Brenner et al., 2020 | 98 | 197 | 414 | 1633 | 0.34 [0.25; 0.46] |
| Axelrad et al., 2020 | 1 | 10 | 6 | 73 | 0.81 [0.09; 7.48] |
| Sima et al., 2022 | 8 | 13 | 28 | 71 | 0.41 [0.12; 1.37] |
| Queiroz et al., 2021 | 10 | 32 | 28 | 198 | 0.36 [0.15; 0.85] |
| **Total (95% CI)** | **101** | **209** | **422** | **1718** | **0.34 [0.25; 0.46]** |
| **Severe COVID-19 ICU Admissions: Steroid Use** | | | | | |
| Study | Steroid user | | Non-steroid user | | Odds Ratio, 95% CI |
| | Event | Total | Event | Total | |
| Brenner et al., 2020 | 29 | 197 | 70 | 1633 | 0.26 [0.16; 0.41] |
| Axelrad et al., 2020 | 0 | 10 | 1 | 73 | 0.43 [0.02; 11.36] |
| Sima et al., 2022 | 2 | 13 | 5 | 71 | 0.42 [0.07; 2.42] |
| Queiroz et al., 2021 | 9 | 32 | 6 | 198 | 0.08 [0.03; 0.24] |
| **Total (95% CI)** | | | | | **0.26 [0.17; 0.41]** |
| **COVID-19 Related Death: Steroid Use** | | | | | |

| Study | Steroid user | | Non-steroid user | | Odds Ratio, 95% CI |
|---|---|---|---|---|---|
| | Event | Total | Event | Total | |
| Bezzio et al., 2020 | 2 | 9 | 4 | 70 | 0.21 [0.03; 1.37] |
| Brenner et al., 2020 | 15 | 197 | 48 | 1633 | 0.37 [0.20; 0.67] |
| Axelrad et al., 2020 | 0 | 10 | 1 | 73 | 0.43 [0.02; 11.36] |
| Sima et al., 2022 | 8 | 49 | 36 | 84 | 3.84 [1.61; 9.19] |
| Queiroz et al., 2021 | 3 | 32 | 1 | 198 | 0.05 [0.00; 0.49] |
| **Total (95% CI)** | | | | | **0.43 [0.10; 1.97]** |
| **Severe COVID-19 Hospitalizations: Immunomodulator Use** | | | | | |
| Study | Steroid user | | Non-steroid user | | Odds Ratio, 95% CI |
| | Event | Total | Event | Total | |
| Allocca et al., 2020 | 2 | 3 | 2 | 11 | 0.11 [0.00; 1.92] |
| Taxonera et al., 2020 | 3 | 6 | 5 | 6 | 5.00 [0.34; 72.72] |
| Brenner et al., 2020 | 115 | 360 | 397 | 1470 | 0.79 [0.61; 1.01] |
| Axelrad et al., 2020 | 1 | 6 | 6 | 77 | 0.42 [0.04; 4.23] |
| Sima et al., 2022 | 9 | 28 | 27 | 58 | 1.84 [0.71; 4.74] |
| **Total (95% CI)** | | | | | **0.96 [0.46; 1.98]** |
| **Severe COVID-19 ICU Admissions: Immunomodulator Use** | | | | | |
| Study | Steroid user | | Non-steroid user | | Odds Ratio, 95% CI |
| | Event | Total | Event | Total | |
| Taxonera et al., 2020 | 1 | 6 | 0 | 6 | 0.28 [0.01; 8.42] |
| Brenner et al., 2020 | 14 | 360 | 85 | 1470 | 1.52 [0.85; 2.70] |
| Axelrad et al., 2020 | 0 | 6 | 1 | 77 | 0.26 [0.01; 6.91] |
| Sima et al., 2022 | 4 | 56 | 3 | 28 | 1.56 [0.32; 7.51] |
| **Total (95% CI)** | | | | | **1.40 [0.82; 2.37]** |
| **COVID-19 Related Deaths: Immunomodulator Use** | | | | | |
| Study | Steroid user | | Non-steroid user | | Odds Ratio, 95% CI |
| | Event | Total | Event | Total | |
| Taxonera et al., 2020 | 0 | 6 | 2 | 6 | 7.22 [0.28; 189.09] |
| Bezzio et al., 2020 | 0 | 6 | 6 | 73 | 1.25 [0.06; 24.83] |
| Brenner et al., 2020 | 10 | 360 | 53 | 1470 | 1.31 [0.66; 2.60] |
| Sima et al., 2022 | 0 | 28 | 1 | 56 | 1.54 [0.61; 39.04] |
| **Total (95% CI)** | | | | | **0.99 [0.25; 3.94]** |

Abbreviations - IBD: inflammatory bowel disease; CI: confidence interval; ICU: intensive care unit; ASA: aminosalicylic acid.

## Supplementary Table S5. Meta-analysis of severe COVID-19 outcomes according to CD and UC

| **Severe COVID-19 Hospitalizations: UC vs CD** | | | | | |
|---|---|---|---|---|---|
| Study | UC with COVID-19 | | CD with COVID-19 | | Odds Ratio, 95% CI |
| | Event | Total | Event | Total | |
| Allocca et al., 2020 | 3 | 6 | 2 | 9 | 0.29 [0.03; 2.70] |
| Taxonera et al., 2020 | 5 | 5 | 3 | 7 | 0.07 [0.00; 1.76] |
| Bezzio et al., 2020 | 17 | 46 | 5 | 32 | 0.32 [0.10; 0.98] |
| Brenner et al., 2020 | 77 | 203 | 83 | 312 | 0.59 [0.41; 0.87] |
| Axelrad et al., 2020 | 3 | 27 | 4 | 56 | 0.61 [0.13; 2.96] |
| Haberman et al., 2020 | 3 | 17 | 1 | 20 | 0.25 [0.02; 2.62] |
| Sima et al., 2022 | 28 | 60 | 8 | 24 | 0.57 [0.21; 1.53] |
| Macaluso et al., 2022 | 5 | 46 | 7 | 76 | 0.83 [0.25; 2.79] |
| **Total (95% CI)** | | | | | **0.53 [0.38; 0.74]** |
| **Severe COVID-19 ICU Admissions: UC vs CD** | | | | | |
| Study | UC with COVID-19 | | CD with COVID-19 | | Odds Ratio, 95% CI |
| | Event | Total | Event | Total | |
| Taxonera et al., 2020 | 1 | 5 | 0 | 7 | 0.20 [0.01; 6.04] |
| Brenner et al., 2020 | 12 | 203 | 12 | 312 | 0.64 [0.28; 1.45] |
| Axelrad et al., 2020 | 0 | 27 | 1 | 56 | 1.49 [0.06; 37.69] |
| Sima et al., 2022 | 6 | 60 | 1 | 24 | 0.39 [0.04; 3.44] |
| **Total (95% CI)** | | | | | **0.60 [0.29; 1.24]** |
| **COVID-19 Related Deaths: UC vs CD** | | | | | |
| Study | UC with COVID-19 | | CD with COVID-19 | | Odds Ratio, 95% CI |
| | Event | Total | Event | Total | |
| Taxonera et al., 2020 | 2 | 5 | 0 | 7 | 0.09 [0.00; 2.51] |
| Bezzio et al., 2020 | 5 | 46 | 1 | 32 | 0.26 [0.03; 2.38] |
| Rodriguez et al., 2020 | 2 | 27 | 0 | 13 | 0.38 [0.02; 8.45] |
| Brenner et al., 2020 | 11 | 203 | 5 | 312 | 0.28 [0.10; 0.83] |
| Axelrad et al., 2020 | 0 | 27 | 1 | 56 | 1.49[0.06; 37.69] |
| Sima et al., 2022 | 1 | 60 | 0 | 24 | 0.81 [0.03; 20.57] |
| Macaluso et al., 2022 | 2 | 46 | 2 | 76 | 0.59 [0.08; 4.37] |
| **Total (95% CI)** | | | | | **0.35 [0.16; 0.75]** |

Abbreviations – CD: Chron's disease; UC: ulcerative colitis; CI: confidence interval; ICU: intensive care unit.

## Supplementary Table S6. Quality assessment

| Cohort studies | Selection | | | | Comparability | Outcome | | | Total quality score |
|---|---|---|---|---|---|---|---|---|---|
| **Author, year** | **Representativeness of the exposed cohort** | **Selection of the non-exposed cohort** | **Ascertainment of exposure** | **Demonstration that the current outcome of interest was not present at start of study** | **Comparability of cohorts on the basis of the design or analysis** | **Assessment of outcome** | **Was follow-up long enough for outcomes to occur** | **Adequacy of follow up of cohorts** | |
| Derikx et al., 2020 | * | * | * | | ** | * | | * | **7** |
| Ungaro et al., 2020 | * | * | * | | ** | * | | * | **7** |
| Attauabi et al., 2020 | * | * | * | | ** | * | | | 6 |
| Attaway et al., 2020 | * | * | * | | ** | * | | * | **7** |
| Guerra et al., 2020 | | * | | | * | * | | | 3 |
| Burke et al., 2020 | | * | * | | ** | * | | * | 6 |
| Allocca et al., 2020 | | * | * | | ** | * | | * | 6 |
| Norsa et al., 2020 | | * | * | | * | * | | | 4 |
| Taxonera et al., 2020 | | * | * | | ** | * | | * | 6 |
| An et al., 2020 | | * | | | ** | * | | | 4 |
| Grassia et al., 2020 | | * | * | | | * | | | 3 |
| Gubatan et al., 2020 | | * | * | | ** | * | | | 5 |
| Singh et al., 2020 | * | * | * | | ** | * | | * | **7** |
| Khan et al., 2020 | * | * | * | | ** | * | | * | **7** |
| Mak et al., 2020 | * | * | * | | ** | * | | * | **7** |
| Marafini et al., 2020 | | * | * | | ** | * | | | 5 |
| Turner et al., 2020 | * | * | * | | ** | * | | | 6 |
| Scaldaferri et al., 2020 | | * | * | | ** | * | | | 5 |
| Bodini et al., 2020 | | * | * | | * | * | | | 4 |
| Martinelli et al., 2020 | | * | * | | * | * | | | 4 |
| Lukin et al., 2020 | * | * | * | | ** | * | | * | **7** |
| Bezzio et al., 2020 | * | * | * | | ** | * | | | 6 |
| Rodriguez et al., 2020 | * | * | * | | * | * | | | 5 |
| Brenner et al., 2020 | * | * | * | | ** | * | | * | **7** |
| Axelrad et al., 2020 | * | * | * | | ** | * | | * | **7** |
| Hormati et al., 2020 | | * | * | | ** | * | | * | 6 |
| Haberman et al., 2020 | | * | * | | ** | * | | * | 6 |
| Mosli et al., 2020 | | * | * | | * | * | | * | 5 |

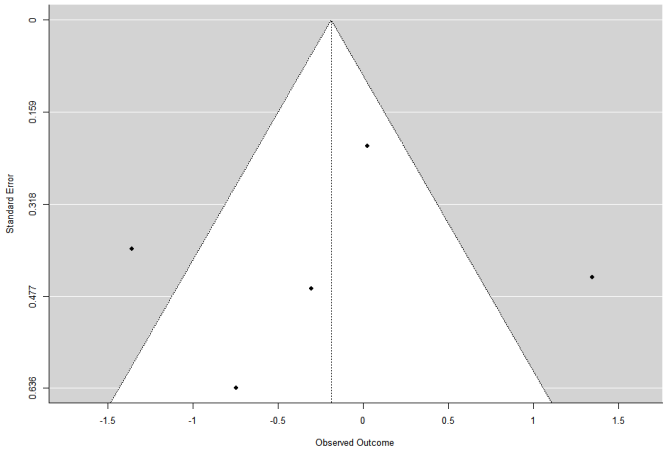
| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Grunert et al., 2020 | | * | * | | ** | * | | * | 6 |
| Yu et al., 2020 | | * | * | | * | * | | * | 5 |
| Fonteinogiannopoulou et al., 2020 | | * | * | | * | * | | | 4 |
| Sima et al., 2022 | | * | * | | ** | * | | * | 6 |
| Richter et al., 2021 | | * | * | | ** | * | | * | 6 |
| Queiroz et al., 2021 | * | * | * | | * | * | | | 5 |
| Macaluso et al., 2022 | * | * | * | | * | * | | * | 6 |

**Supplementary Table S7. Comparison of the results of studies of good quality and studies with low risk of bias.**

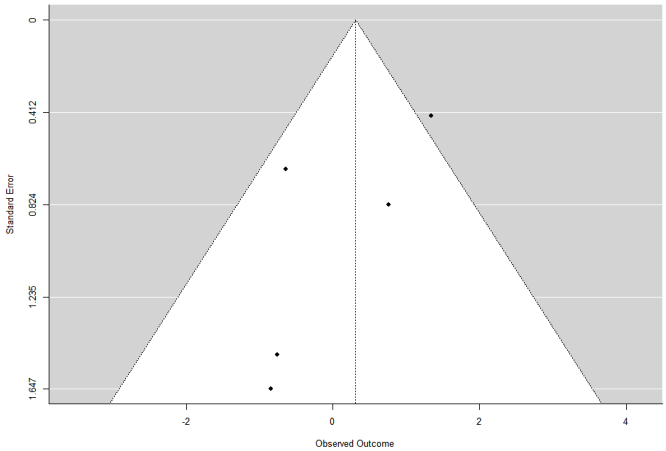
| | All studies | | | Studies of good quality | | | Studies with low risk of bias | | |
|---|---|---|---|---|---|---|---|---|---|
| **Outcomes** | **Random effects estimate and 95% CI** | **Random effects p value** | **Number of studies** | **Random effects estimate and 95% CI** | **Random effects p value** | **Number of studies** | **Random effects estimate and 95% CI** | **Random effects p value** | **Number of studies** |
| Severe COVID-19 - hospitalization | 0.83 (0.36 to 1.89) | 0.65 | 5 | 0.78 (0.15 to 4.05) | 0.77 | 3 | 0.60 (0.26 to 1.39) | 0.23 | 3 |
| Severe COVID-19 - ICU | 1.36 (0.48 to 3.88) | 0.56 | 5 | 1.55 (0.37 to 6.57) | 0.55 | 2 | 1.52 (0.22 to 10.57) | 0.67 | 2 |
| COVID-19 related death | 0.66 (0.32 to 1.37) | 0.27 | 6 | 0.51 (0.06 to 4.22) | 0.53 | 2 | 0.21 (0.02 to 8.30) | 0.55 | 1 |
| Severe COVID-19 – hospitalization & ICU | 0.90 (0.41 to 1.96) | 0.79 | 7 | 0.86 (0.12 to 6.13) | 0.88 | 3 | 0.98 (0.49 to 1.95) | 0.95 | 3 |
| Severe COVID-19 hospitalization (vs non-ASA users) | 0.41 (0.24 to 0.72) | **0.002** | 5 | 0.35 (0.16 to 0.76) | **0.01** | 4 | 0.52 (0.42 to 0.65) | **<0.001** | 2 |
| Severe COVID-19 hospitalization (vs non-Steroid users) | 0.35 (0.26 to 0.46) | **< 0.001** | 5 | 0.35 (0.27 to 0.46) | **<0.001** | 4 | 0.35 (0.26 to 0.47) | **<0.001** | 2 |
| Severe COVID-19 hospitalization (vs non-Immunomodulator users) | 0.96 (0.46 to 1.98) | 0.9 | 5 | 1.06 (0.54 to 2.08) | 0.86 | 4 | 0.78 (0.61 to 1.00) | 0.053 | 2 |
| Severe COVID-19 ICU (vs non-ASA users) | 0.46 (0.24 to 0.85) | **0.013** | 4 | 0.46 (0.24 to 0.85) | **0.013** | 4 | 0.33 (0.05 to 2.06) | 0.24 | 2 |
| Severe COVID-19 ICU (vs non-Steroid users) | 0.21 (0.10 to 0.42) | **< 0.001** | 4 | 0.21 (0.10 to 0.42) | **< 0.001** | 4 | 0.26 (0.17 to 0.42) | **<0.001** | 2 |
| Severe COVID-19 ICU (vs non-Immunomodulator users) | 1.40 (0.82 to 2.37) | 0.22 | 4 | 1.40 (0.82 to 2.37) | 0.22 | 4 | 1.34 (0.62 to 2.91) | 0.46 | 2 |
| COVID-19 related death (vs non-ASA users) | 0.37 (0.23 to 0.59) | **< 0.001** | 5 | 0.37 (0.23 to 0.59) | **< 0.001** | 5 | 0.38 (0.23 to 0.62) | **<0.001** | 2 |
| COVID-19 related death (vs non-Steroid users) | 0.43 (0.10 to 1.97) | 0.28 | 5 | 0.43 (0.10 to 1.97) | 0.28 | 5 | 0.37 (0.20 to 0.67) | **<0.001** | 2 |
| COVID-19 related death (vs non-Immunomodulator users) | 0.99 (0.25 to 3.94) | 0.99 | 5 | 0.88 (0.13 to 5.97) | 0.89 | 4 | 0.25 (0.01 to 11.94) | 0.48 | 2 |
| Severe COVID-19 between UC and CD - hospitalization | 0.55 (0.40 to 0.75) | **< 0.001** | 8 | 0.55 (0.41 to 0.76) | **<0.001** | 7 | 0.59 (0.41 to 0.86) | **0.006** | 2 |
| Severe COVID-19 between UC and CD - ICU | 0.60 (0.29 to 1.24) | 0.17 | 4 | 0.60 (0.29 to 1.24) | 0.17 | 4 | 0.67 (0.30 to 1.48) | 0.32 | 2 |
| COVID-19 related death between UC and CD | 0.35 (0.16 to 0.75) | **0.007** | 7 | 0.35 (0.16 to 0.77) | **0.009** | 6 | 0.33 (0.12 to 0.93) | **0.04** | 2 |

**Supplementary Figure S1. Funnel plots of meta-analyses**

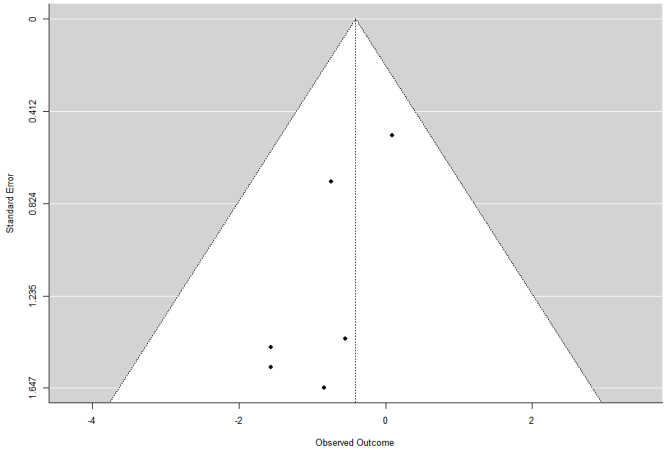
Hospitalization



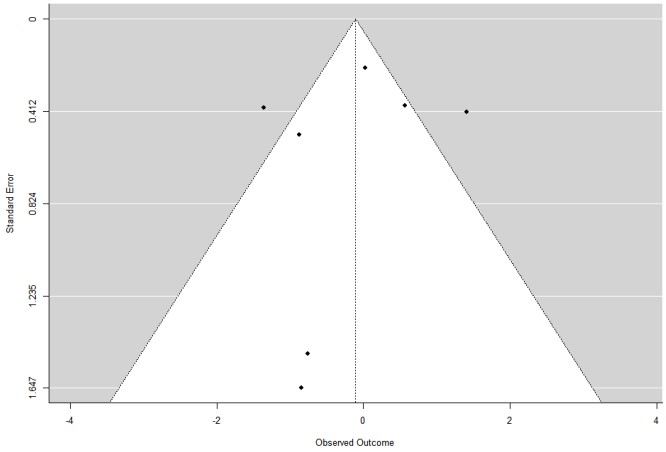

ICU admission



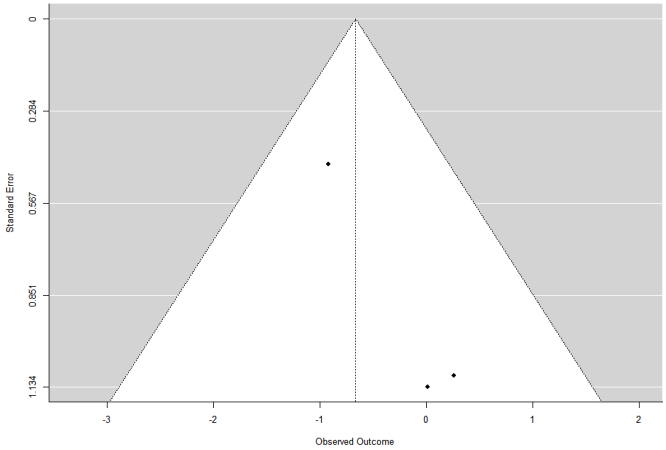

COVID-19 related death



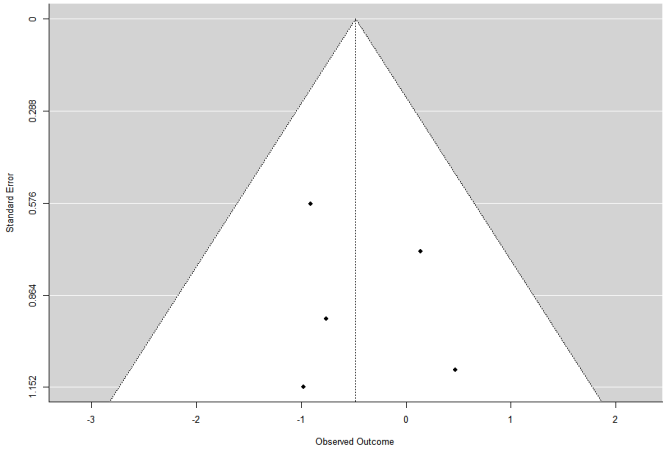

Hospitalization and ICU



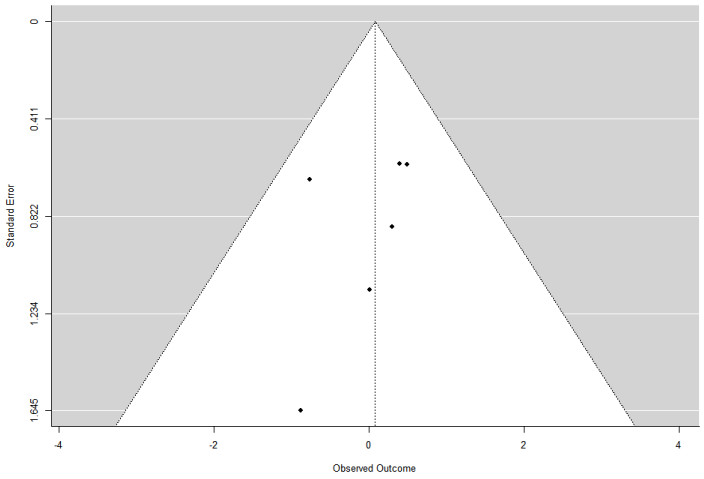

Susceptibility to COVID-19 according to steroid



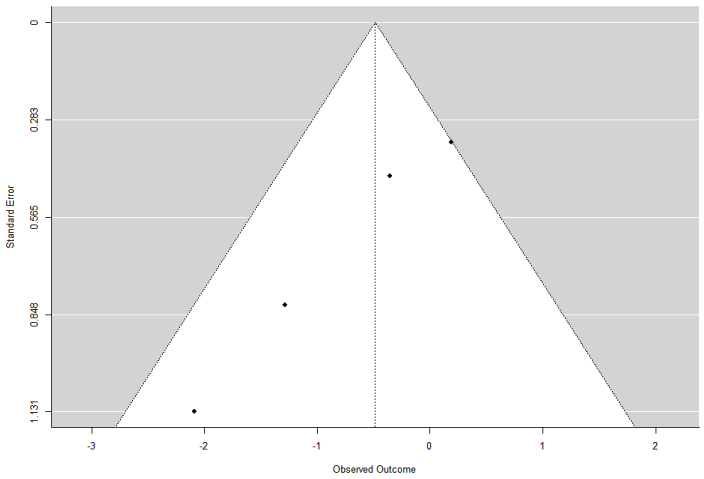

Susceptibility to COVID-19 according to immunomodulator



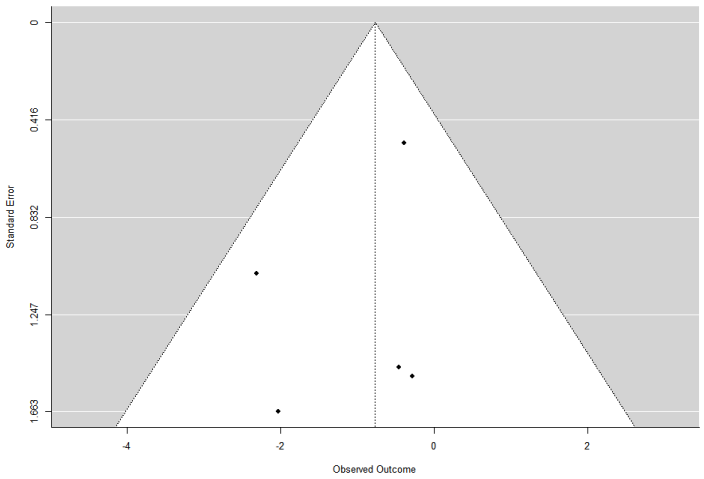
Susceptibility to COVID-19 according to anti-TNF



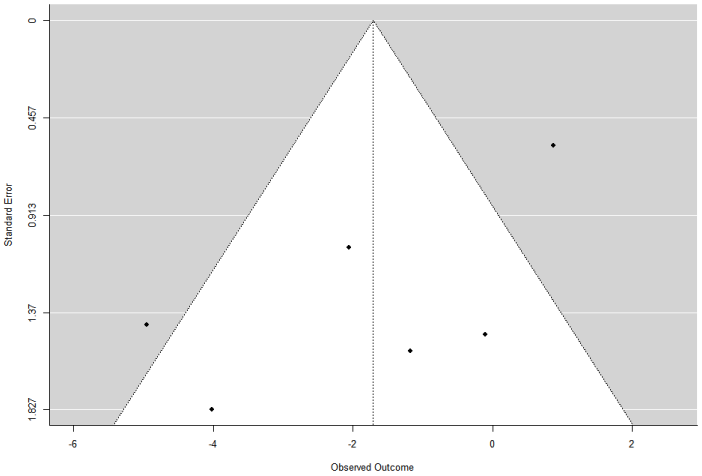

Susceptibility to COVID-19 according to ASA



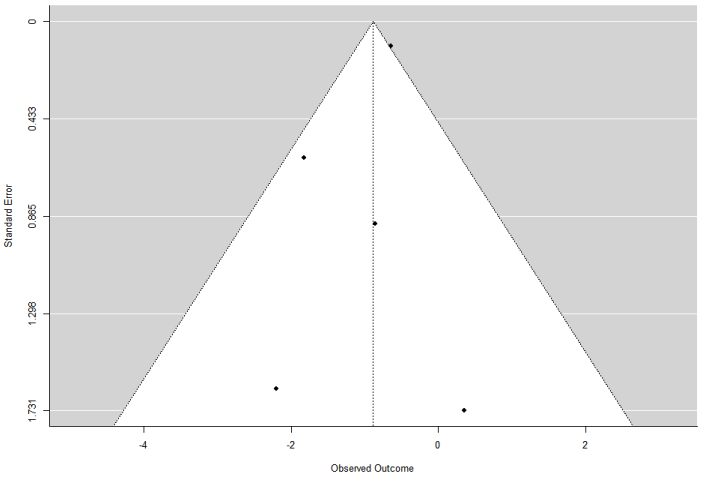

Susceptibility to COVID-19 according to Vedolizumab



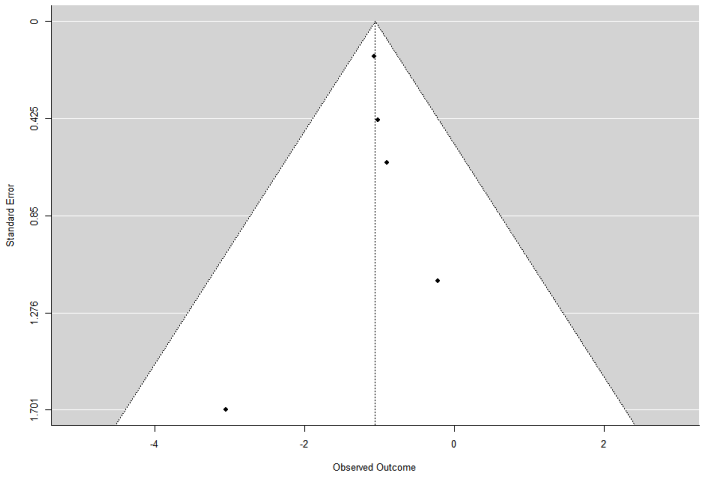

Susceptibility to COVID-19 according to Ustekinumab



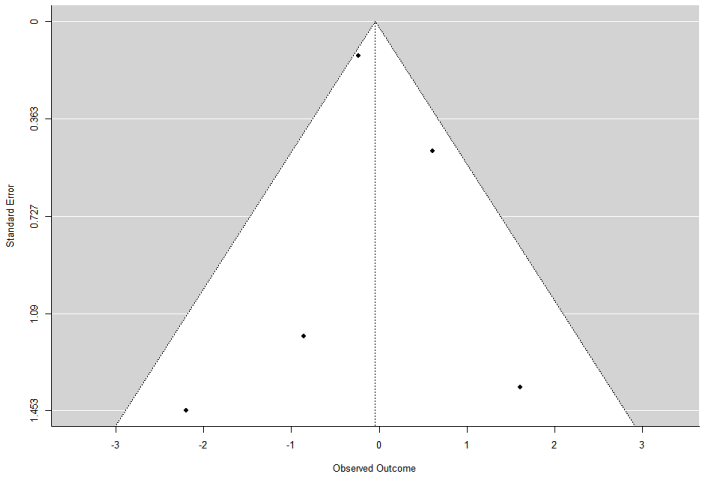

Hospitalization (vs non-ASA users)



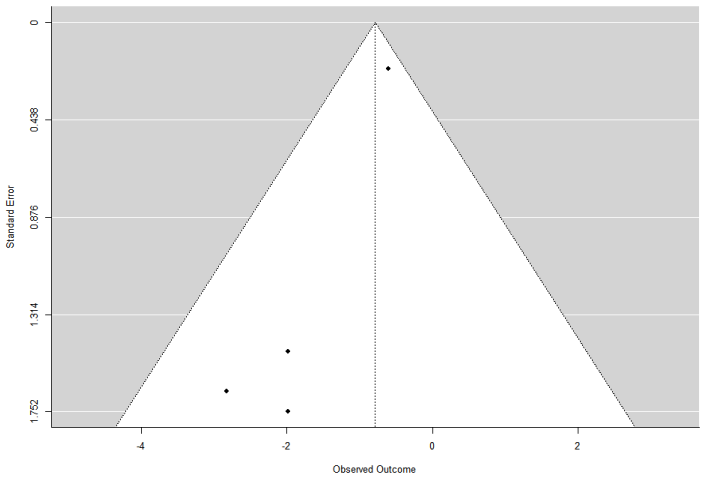

Hospitalization (vs non-Steroid users)


Standard Error
0
0.425
0.85
1.276
1.701
-4
-2
0
2
Observed Outcome

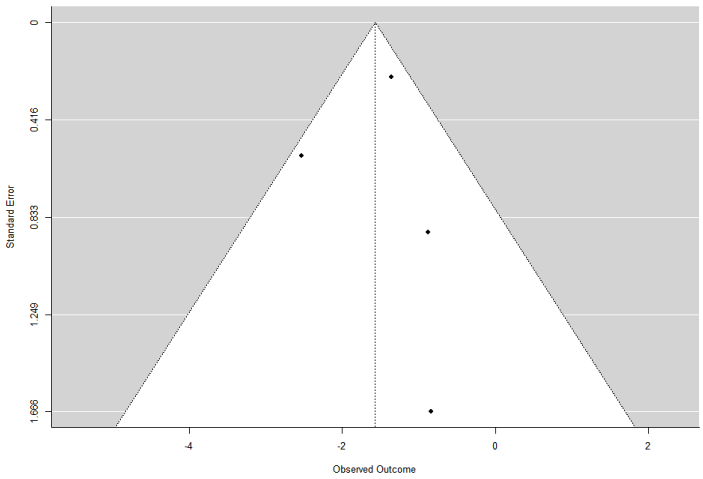
Hospitalization (vs non-Immunomodulator users)



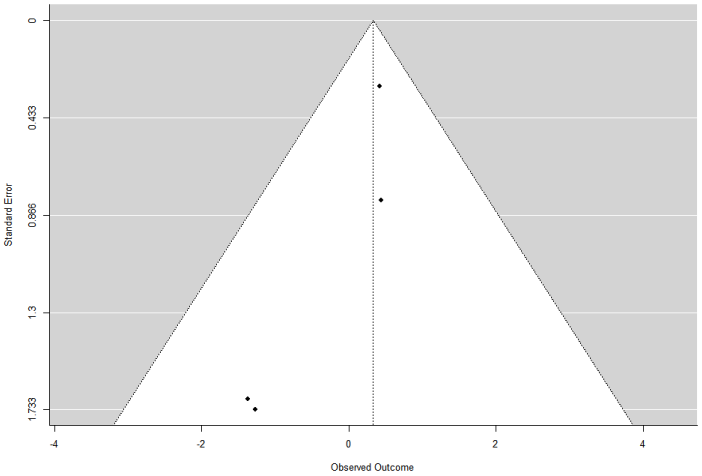

ICU admission (vs non-ASA users)



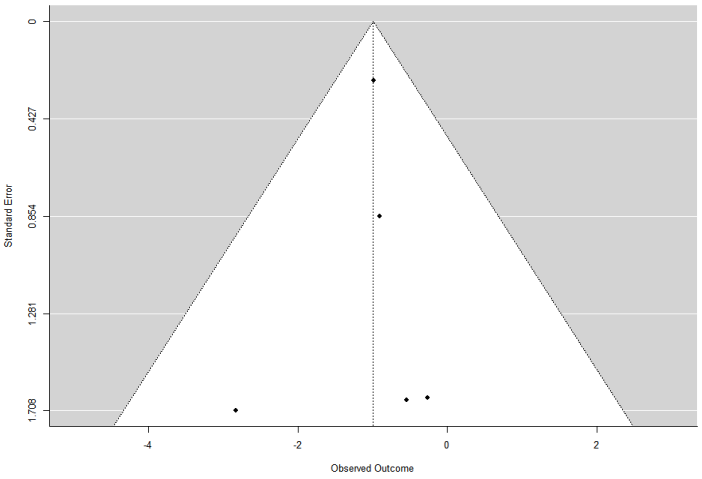

ICU admission (vs non-Steroid users)



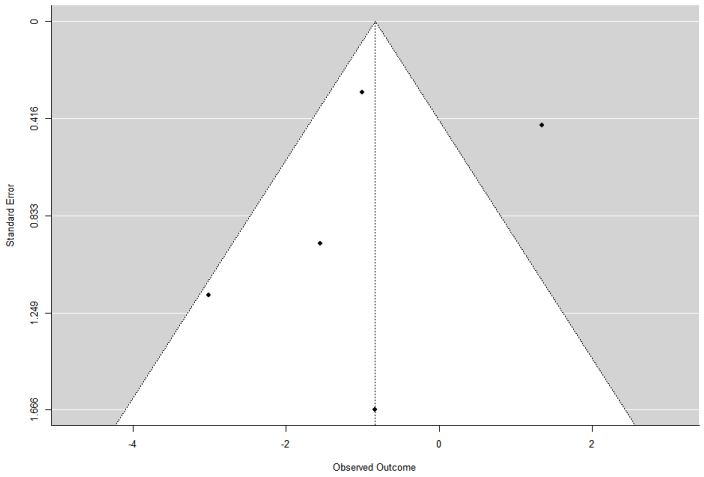

Hospitalization (vs non-Immunomodulator users)



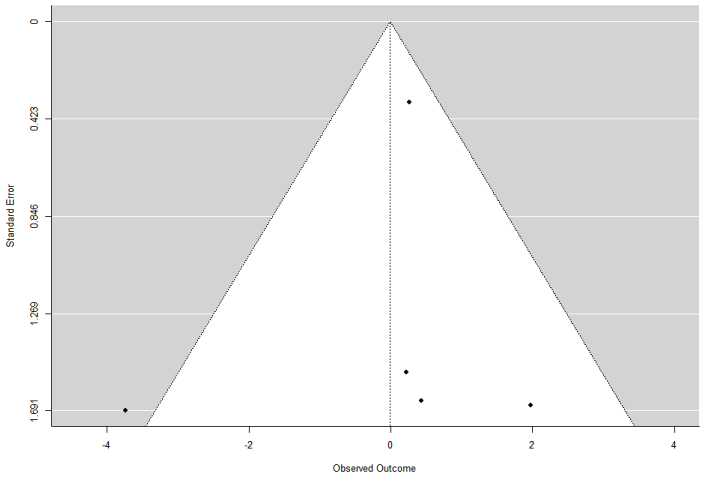

COVID-19 related death (vs non-ASA users)



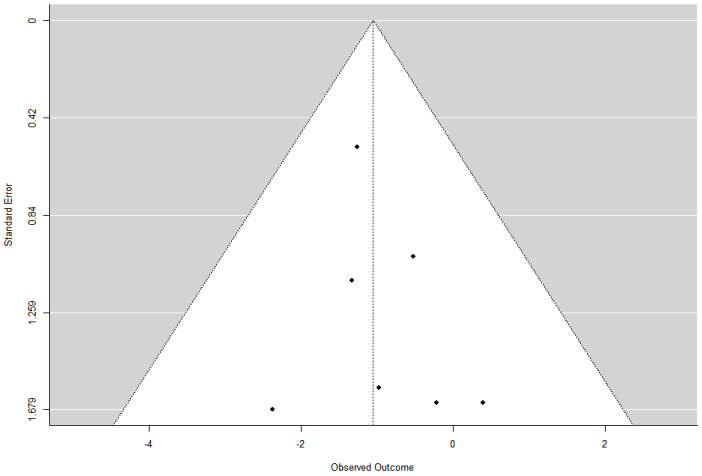

COVID-19 related death (vs non-Steroid users)


Standard Error
0
0.416
0.833
1.249
1.666
-4
-2
0
2
Observed Outcome

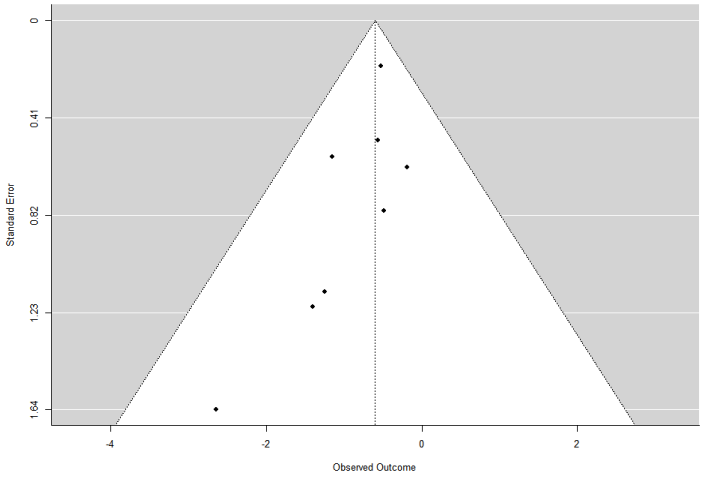
COVID-19 related death (vs non-Immunomodulator users)



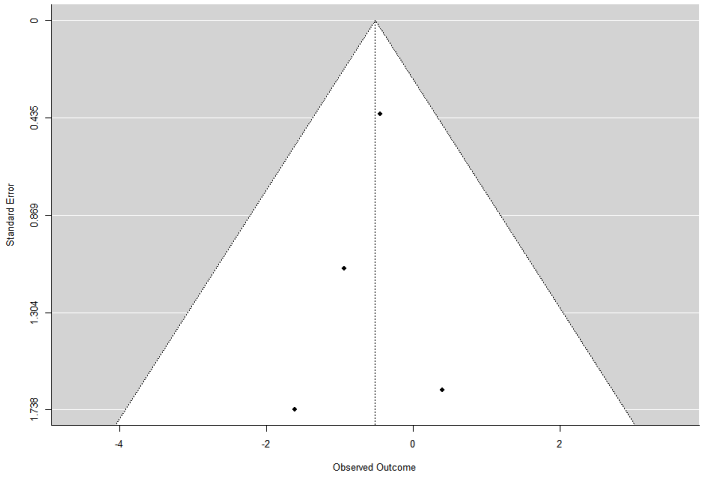

COVID-19 related death between UC and CD




Hospitalization between UC and CD

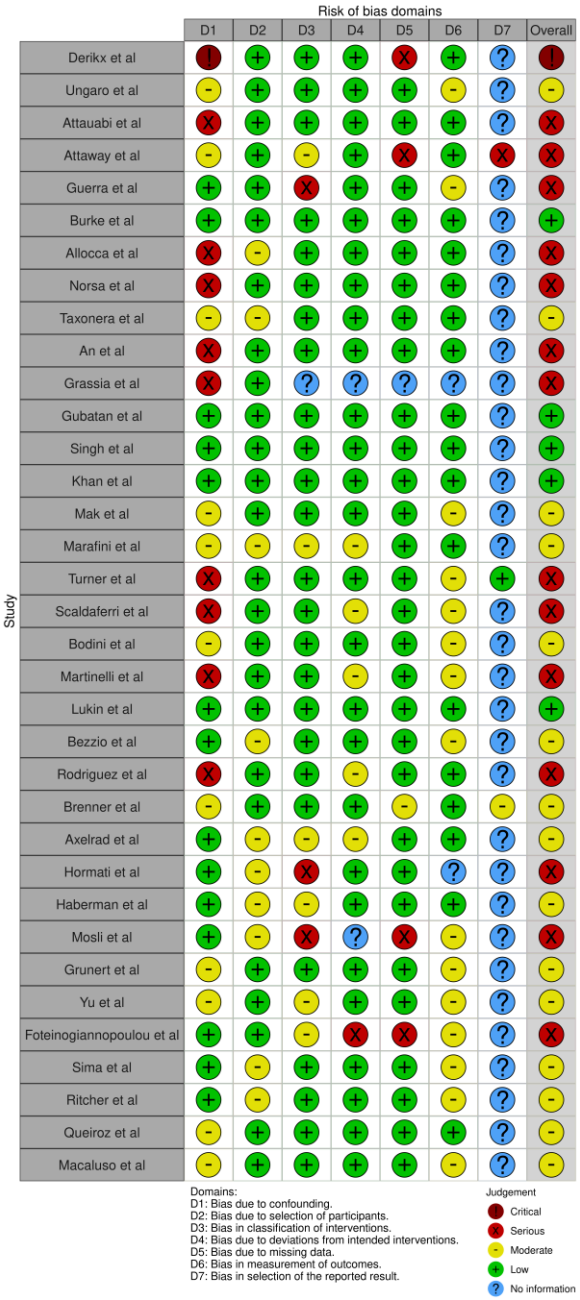



ICU admission between UC and CD

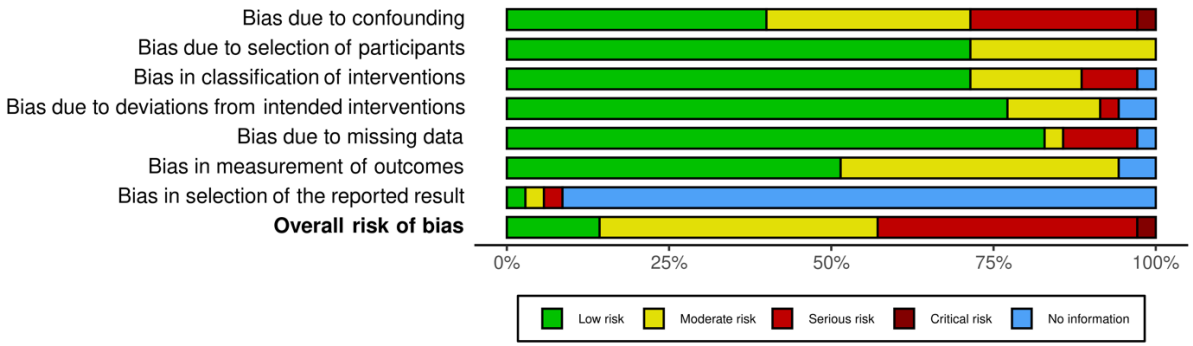


## Supplementary Figure S2. Risk of Bias Assessment

**(a) Risk of Bias ROBINS-I Traffic Light Plot**


Risk of bias domains
D1
D2
D3
D4
D5
D6
D7
Overall
Study
Derikx et al
Ungaro et al
Attauabi et al
Attaway et al
Guerra et al
Burke et al
Allocca et al
Norsa et al
Taxonera et al
An et al
Grassia et al
Gubatan et al
Singh et al
Khan et al
Mak et al
Marafini et al
Turner et al
Scaldaferri et al
Bodini et al
Martinelli et al
Lukin et al
Bezzio et al
Rodriguez et al
Brenner et al
Axelrad et al
Hormati et al
Haberman et al
Mosli et al
Grunert et al
Yu et al
Foteinogiannopoulou et al
Sima et al
Ritcher et al
Queiroz et al
Macaluso et al
Domains:
D1: Bias due to confounding.
D2: Bias due to selection of participants.
D3: Bias in classification of interventions.
D4: Bias due to deviations from intended interventions.
D5: Bias due to missing data.
D6: Bias in measurement of outcomes.
D7: Bias in selection of the reported result.
Judgement
Critical
Serious
Moderate
Low
No information

**(b) Risk of Bias ROBINS-I Weighted Summary Plot**



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