SYSTEMATIC REVIEWS AND META-ANALYSIS

A Systematic Review and Meta-Analysis: Adverse Inflammatory Bowel Disease Outcomes Following Acute COVID-19

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BACKGROUND AND AIMS: Respiratory viral infections have been implicated in the exacerbation of immune-mediated inflammatory diseases such as inflammatory bowel disease (IBD). To understand the impact of early SARS-CoV-2 variants on the risk of adverse IBD outcomes, we aimed to perform a meta-analysis of high-quality studies. **METHODS:** Cohort studies investigating adverse IBD outcomes (IBD flares, change in disease activity, change in medication, IBD-related hospitalization, and surgery) following COVID-19 were retrieved from MEDLINE and Embase. The Risk Of Bias In Nonrandomized Studies—of Exposure tool was used to assess risk of bias. Random effects model meta-analysis was used to calculate the hazard ratio (HR) for risk of adverse outcomes. Subgroup analysis was performed to estimate risk of outcomes for ulcerative colitis and Crohn's disease patients. Metaregression was performed for sex and duration of follow-up. **RESULTS:** Of the 3119 identified studies, 5 were included in the meta-analysis. A total of 34,977 IBD patients with COVID-19 and 53,270 IBD patients without recorded COVID-19 infection were identified. Two of the studies showed a high risk of bias. The random effects model did not show a statistically significant increase in the risk of adverse IBD outcomes following COVID infection (HR:1.05 [0.75–1.46]). There was no significant difference in adverse outcomes between Crohn's disease (HR: 0.91 [0.82–1.02]) and ulcerative colitis patients (HR: 0.83 [0.76–0.90]). Neither the proportion of male participants nor the mean duration of follow-up were found to be significant predictors of effect size. **CONCLUSION:** In this systematic review and meta-analysis, we find that COVID-19 did not increase the risk of adverse IBD outcomes.

Keywords: Inflammatory Bowel Disease (IBD); COVID-19 Infection; IBD Flares

Introduction

Inflammatory bowel diseases (IBD), Crohn's disease (CD), and ulcerative colitis (UC) are immune-mediated inflammatory diseases (IMID) characterized by inflammation of the gastrointestinal tract.[1,2] Both CD and UC are recurrent in nature in that the patients experience alternating episodes of flares and remissions.[3–5] Patients are often treated with immunosuppressive or biologic medication to control disease flares.[6] Certain factors including discontinuation of medication, smoking, stress, infections and other environmental factors are associated with disease flares.[4,7] Infections with enteric pathogens such as Salmonella, Campylobacter, Clostridium difficile, Norovirus and Toxoplasma gondii have been shown to induce or exacerbate IBD[8–11] and viral infections have long been implicated in the induction and exacerbation of various immune-mediated inflammatory diseases.[12–14] The COVID-19 pandemic has therefore raised questions over the impact of the infection on the disease course of IBD.

SARS-CoV-2 enters the host cell by attachment to the ACE-2 receptor which is highly expressed not only in the alveolar pneumocytes but also in the gastrointestinal tract. Although the infection is predominantly localized in the respiratory tract, the virus also colonizes the gastrointestinal tract.[15] The already compromised intestinal epithelium in IBD patients might lead to additional complications including viral invasion of the lamina propria ultimately resulting in a substantial increase in proinflammatory cytokines.[16] In a study carried out by Zollner et al., antigen persistence was reported in around 70% of IBD patients until after 7 months postinfection.[17] In addition to the role of the disease, the broad-spectrum immunosuppressants

Abbreviation used in this paper: **CD, Crohn's disease; HR, hazard ratio; IBD, inflammatory bowel disease; IRR, incidence rate ratio; OR, odds ratio; PCR, polymerase chain reaction; PMS, Partial Mayo Score; REM, random effects model; ROBINS-E, Risk Of Bias In Nonrandomized Studies—of Exposure; RR, risk ratio; UC, ulcerative colitis.**

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used in the treatment of IBD could impair immune responses to the infection, thereby potentially elevating the risk of long-term consequences of the infection. Treatment with infliximab has been shown to be associated with reduced serum antibody levels in IBD patients who contracted COVID-19.[18] Pediatric and young adult IBD patients undergoing biologic treatments were also found to mount lower and short-lasting antibody responses upon infection.[19] Antigen persistence and improper viral clearance has been hypothesized as a potential driver of long-term consequences.[17] One or the combination of the above-mentioned mechanisms could potentially lead to IBD flare, hospitalization, or medication switch following COVID-19.

Studies have been carried out to investigate the outcomes of SARS-CoV-2 infection in patients with IBD.[20,21] However, the impact of COVID-19 on patients with IBD, including the influence on the disease course, has not been studied to the same extent and results are conflicting. The current evidence on the impact of COVID-19 on IBD during and following the acute phase of the disease is limited by small sample size, short follow-up time, and inconsistent findings with respect to the risk of adverse IBD outcomes. To understand the impact of infection with early SARS-CoV-2 variants on the disease course of IBD and to be better prepared to tackle future variants of the virus, we aimed to carry out a meta-analysis of the available evidence. To our knowledge, no meta-analysis exploring this question has been performed.

Methods

Literature Search

A systematic literature search for studies investigating the impact of COVID-19 on adverse IBD outcomes was conducted in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) reporting guidelines.[22] MEDLINE and Embase were searched for all relevant articles published between 2020 and 2023. The following Medical Subject Headings terms were used to retrieve the articles: (Inflammatory Bowel Disease OR IBD OR Crohn* disease OR CD OR Ulcerative Colitis OR UC) AND (SARS-CoV-2 OR coronavirus disease) AND (COVID-19 OR nCOVID-19). All terms were searched as both keywords and exploded subject headings (Table A1). The search was performed on May 1, 2023.

Inclusion and Exclusion Criteria

The inclusion and exclusion criteria were defined a priori, and the protocol was registered in PROSPERO (ID: CRD42023421797). The included observational studies had to involve a comparator group to serve as a negative control for SARS-CoV-2 infection. The studies had to require a registered polymerase chain reaction (PCR) or antigen test to be part of the study group. Only studies that reported adverse IBD outcomes including IBD flares, change in disease activity, change in medication, IBD-related hospitalization, and IBD-related surgery were eligible for inclusion. The reference lists of the included articles and other systematic reviews were screened manually for prospective inclusions. We did not include any articles in languages other than English. The PRISMA flow diagram for inclusion and exclusion of articles is shown in Figure 1. Only published studies were included; gray literature including conference abstracts and preprints were excluded from systematic review and meta-analysis to ensure only high-quality peer-reviewed evidence was included.

Data Collection

Two reviewers (EV and SM) performed the title and abstract screen independently, and a third reviewer (RE) settled discrepancies in study inclusion. Following this, full article screening was carried out. Data extracted included study publication year, country, participant demographics (including age and sex), duration of follow-up and adverse IBD outcomes (IBD flares, change in disease activity, change in medication, IBD-related hospitalization, and surgery). The number of individuals included in each study and the number of events in the COVID and non-COVID group was also extracted. The overall effect size for adverse IBD outcome following COVID-19 infection compared to the uninfected matched control group (eg, hazard ratio (HR), risk ratio, odds ratio (OR)) was also extracted for each study.

Risk of Bias Assessment

The included studies were assessed for bias using Risk Of Bias In Nonrandomized Studies—of Exposure (ROBINS-E),[23] a tool for assessing the risk of bias in observational epidemiological studies. The tool evaluates the studies in 7 domains of bias, each provided with a set of signaling questions designed to assess the elements of the study. An overall judgment of the risk of bias (high, some concerns or low risk of bias) is generated based on the results from the 7 domains.

Statistical Analysis

The adjusted overall summary effect size measuring the risk of adverse IBD outcomes following COVID-19, either adjusted HR or analogous risk estimates along with the 95% confidence intervals (CIs) were extracted. The standard errors were calculated from the 95% CI of the effect size using the log of lower and upper limits of the CIs of the individual study effect size. The different measures of adverse outcomes in the studies were pooled together as one single composite outcome. Random effects model (REM) meta-analysis was then carried out using the generic inverse variance method with DerSimonian Laird estimator used for the calculation of τ^2. REM was chosen due to the a priori assumption of the presence of both interstudy and intrastudy heterogeneity. The generic inverse variance method was chosen as precalculated effect sizes were extracted and used to undertake REM meta-analysis. Subgroup meta-analysis was carried out to assess the risk of adverse IBD outcomes following COVID-19, by IBD subtype. Metaregression was carried out for sex as the males have been shown to have increased adverse outcomes related to COVID-19[24], and for the duration of follow-up since it varied between studies. Publication bias was formally assessed using Egger's test with a funnel plot for visual interpretation. All statistical analyses were performed in R, using the "meta" package.[25]

All authors had access to the study data and reviewed and approved the final manuscript.

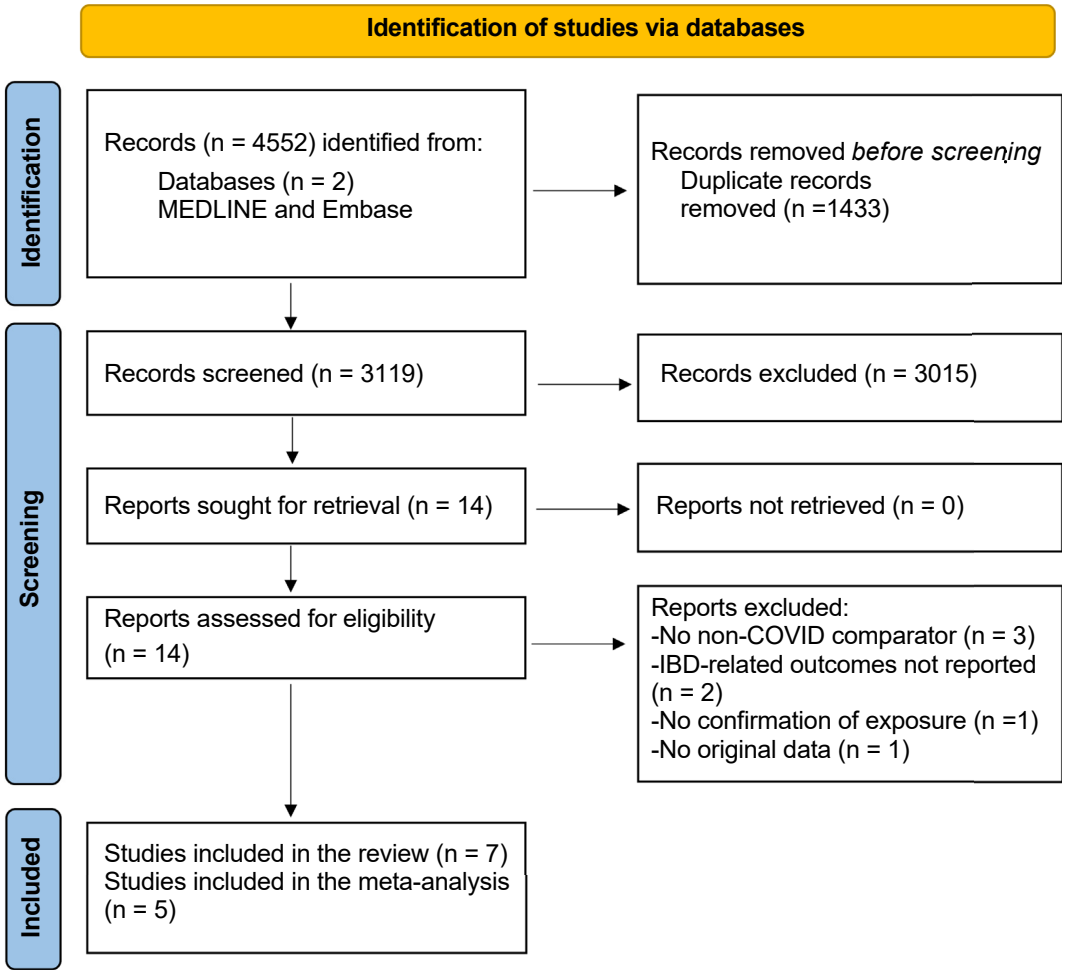

Figure 1. Preferred Reporting Items for Systematic reviews and Meta-Analyses flowchart illustrating article inclusions.

Results

Search Results and Study Selection

A total of 3119 articles were retrieved from the initial systematic literature search, of which 3015 were excluded following the title and abstract screen. Of the 14 articles that were included for full review, 7 fulfilled the inclusion criteria (Figure 1). The studies were based on cohorts from Denmark, Italy, the US, and a cohort from a consortium of the EU (Belgium, Denmark, France, Germany, Greece, Hungary, Ireland, Israel, Italy, the Netherlands, Poland, Portugal, Spain, Sweden, and United Kingdom) comprising a total of 34,977 SARS-CoV-2 positive IBD patients and 53,270 IBD patients without the infection as controls. All the studies included both CD (25,162 patients) and UC (62,857 patients) patients.

Four of the studies measured disease flares and 3 measured disease activity. Lukin et al. and Norgard et al.[26,27] adopted a self-controlled design whereas Amiot et al., Papa et al., Hadi et al., Hong et al., and Bezzio et al., carried out cohort studies.[28–32] Four of the studies used a PCR test as confirmation of exposure and 2 of the studies used antigen tests. Lukin et al. did not present evidence of infection confirmation. Papa et al.[29] only included IBD patients who were under biologics therapy as this group of patients are at an increased risk of developing flares and are closely monitored. All the studies included in the meta-analysis identified treatment exposure at baseline in their cohorts. The characteristics of the included studies are summarized in Table 1.

The impact of SARS-CoV-2 infection on the disease course of IBD was the primary outcome in 5[26,27,29,31,32] and the secondary outcome in 2 of the included studies.[28,30] Three of the studies[26,28,32] compared the disease activity, measured using Harvey-Bradshaw Index for CD and Simple Clinical Colitis Activity Index/Partial Mayo Score for UC, between the groups. The other studies measured IBD flares as IBD-related hospitalization, surgery, need for corticosteroids or intensification of current therapy.[27,29–31]

Only 2 of the 5 included studies, Hadi et al.[30] and Norgard et al.,[27] showed a statistically significant result albeit in opposite directions. The study carried out by Hadi et al.[30] using the TriNetX research network, comprising of over 40 US health-care organizations showed an increased risk of adverse IBD outcomes in the COVID group. On comparing 4310 COVID-positive IBD patients to 22,508 COVID-negative

Table 1. Characteristics of the Included Studies on the Risk of Long-Term Impact of COVID-19 on Adverse IBD Outcomes

Author	Country	Source population	Study period	COVID-19 cohort			Reference cohort size			Summary estimates with 95% CI: type of relative estimate	Covariates	Adverse IBD outcome	ROBINS-E overall risk of bias (RoB)[b]
				Overall	CD	UC	Overall	CD	UC				
Papa et al., (2022)	Italy	IBD patients from 5 Italian treatment centers	Oct 2020 -Mar 2021 (6)	95	64	31	190	128	62	0.42 (0.08–2.15): HR	Age, sex, IBD subtype, disease duration, CD localization, UC extension, previous surgery, active smoker, extraintestinal manifestations, biological therapeutic agents, steroids, mesalazine, immunosuppressants, CRP level at the start of follow-up, CRP level at the end of follow-up, difference in the level of CRP	Need for therapy intensification	High RoB
Hadi et al., (2022)	USA	TriNetX (40+ US Health Care organizations)	Jan 2020 – Mar 2021 (3)	4310	2190	2082		22,508		1.33 (1.18–1.51): RR		Inpatient hospitalization along with a collection of stool studies, intravenous methylprednisolone requirement or flexible sigmoidoscopy	High RoB
Hong et al., (2022)	USA	5 academic medical centers within New York's Crohn's & colitis organization	Feb 2020 – Dec 2021 (11)	251	139	112	251	139	112	0.84 (0.44–1.42): HR	COVID-19 severity, indicators of IBD disease severity (prior IBD hospitalization or surgery, disease duration), disease activity(current steroids or biologic use), and delays in care(time to first follow-up or postponement of biologics)	IBD-related hospitalization/ surgery	Low RoB
Bezzio et al., (2022)	Italy	IG-IBD Italian cohort	Mar 2020 – Dec 2020(7)	219	92	127	219	92	127	1.48 (0.90–2.42): OR	Sex, age, IBD subtype, therapy and disease activity	Change in HBI or PMS	Some concerns
Nørgård et al., (2023)	Denmark	Danish National IBD cohort	Mar 2020 – Jul 2022(6)	30,102	11,159	18,943	30,102	11,159	18,943	0.85 (0.79–0.91): IRR	Sex, age, CCI 10 y before start, disease duration, biologics & thiopurine uses during pandemic, corticosteroids.	Corticosteroid prescription	Some concerns
Amiot et al., (2022)	EU I-CARE cohort[a]	I-CARE European prospective longitudinal multicenter cohort	Apr 2020 – Dec (9)	233	142	85	5224	3192	1935			Change in HBI or SCCAI	Some concerns

Table 1. Continued

Author	Country	Source population	Study period	COVID-19 cohort			Reference cohort size			Summary estimates with 95% CI: type of relative estimate	Covariates	Adverse IBD outcome	ROBINS-E overall risk of bias (RoB)[b]
				Overall	CD	UC	Overall	CD	UC				
Lukin et al., (2021)	USA	I-CARE European prospective longitudinal multicenter cohort	(6 mo)	118	73	40	118	73	40			Change in HBI or PMS	Some concerns

CCI, Charlson Comorbidity Index; CRP, C-reactive protein; HBI, Harvey Bradshaw Index; IRR, incidence rate ratio; SCCAI, Simple Clinical Colitis Activity Index; PMS, Partial Mayo Score; RoB: risk of bias; RR, relative risk.
[a]Belgium, Denmark, France, Germany, Greece, Hungary, Ireland, Israel, Italy, the Netherlands, Poland, Portugal, Spain, Sweden and United Kingdom.
[b]The studies are rated as having a high risk of bias, some concerns or low risk of bias.

counterparts, the IBD patients who had contracted COVID-19 showed an increased risk of developing IBD flares characterized by IBD-related hospitalization. Moreover, 7.36% and 2.10% of the patients with and without a history of biologic use switched to or started a new biologic therapy. This US cohort studied by Hadi et al.,[30] which showed a significantly increased risk of adverse IBD outcomes following COVID-19 had a high risk of bias, whereas the Danish cohort studied by Norgard et al.[27] which showed a lower risk of the outcome following COVID-19, had some concerns of bias when assessed with the ROBINS-E tool.

Hong et al.[31] showed a numerically increased risk of adverse IBD outcomes in the case of severe COVID-19. Papa et al.[29] and Bezzio et al.[32] included discontinuation of IBD therapy as a variable in the multivariate analysis and it was found to be significantly associated with an increased risk of flare in both these studies (HR: 7.27 [1.17–45.18] $P = .03$; OR: 4.18 [2.12–8.25] $P < .0001$, respectively).

Meta-Analysis of Risk of Flare following COVID-19

Out of the 7 studies included (22–28), 5 were suitable for meta-analysis. Amiot et al., (25) and Lukin et al., (26) were not eligible for the meta-analysis as only the statistical significance (P value) for the difference between the incidence of adverse IBD outcomes in the case and control groups were reported and not the effect sizes. Two of the included studies reported the risk as adjusted HR, 1 study reported it as incidence rate ratio, another as relative risk and 1 study as an OR. Meta-analysis of the 5 included studies did not show any significant difference between the risk of adverse IBD outcomes in the presence and absence of COVID-19 (HR: 1.05, CI: 0.76–1.47, $P = .77$). The heterogeneity in the main analysis was 91%, $P < .01$ indicating substantial differences in the included studies (Figure 2).

Only 2 studies reported risk estimates by IBD subtype.[27,32] The subgroup analysis by IBD subtype did not show any significant difference between the CD and UC patients in terms of IBD-related outcomes following COVID-19 (CD HR: 0.91, CI: 0.82–1.02; UC HR: 0.83, CI: 0.76–0.90).

Metaregression

Metaregression was carried out for sex and duration of follow-up. The follow-up period for the studies ranged between 3 to 13 months. The sex of the participants was not a significant predictor of the risk of adverse IBD outcomes following a SARS-CoV-2 infection. The duration of follow-up accounted for 23.1% of the heterogeneity observed in study effect size. It was not, however, a significant predictor of the effect size of the study ($P = .45$).

Risk of Bias Assessment

The ROBINS-E tool for risk of bias revealed that 2 of the studies had a high risk of bias, 4 had some concerns of bias, and 1 had a low risk of bias (Figure 3). The detailed domain-specific analysis is summarized in Table 2 and the complete

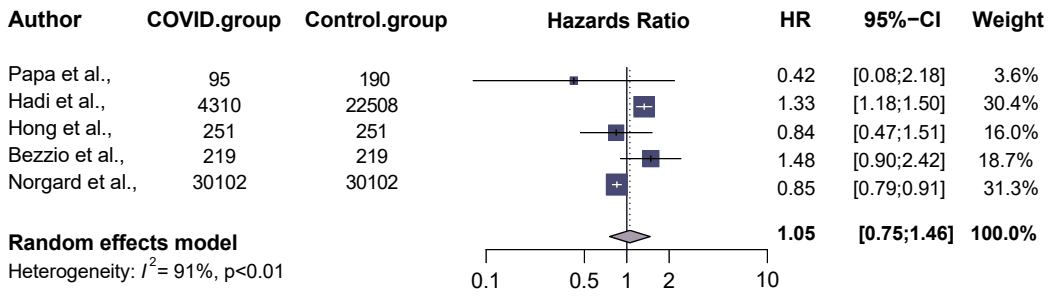

Figure 2. Forest plot of the random effects model meta-analysis on the overall risk of adverse IBD outcomes in 34,977 patients with IBD following a SARS-CoV-2 infection compared to 53,270 IBD patients without a recorded infection.

ROBINS-E used for risk of bias assessment is available in the Table A2. One of the studies that showed a high risk of bias only included IBD patients who were treated with biologics and did not control for comorbidities and body mass index and excluded patients with severe IBD.[29] In the other study with a high risk of bias, the authors do not mention controlling for confounders in the cohort.[30] Domain 1 (bias due to confounding) and domain 5 (bias due to missing data) were the highest contributors to bias in the included studies.

Egger's regression test returned an intercept of 1.014 ($P = .69$) indicating a possibility of publication bias and funnel plot generated for the included studies was deemed symmetric on visual inspection (Figure A1).

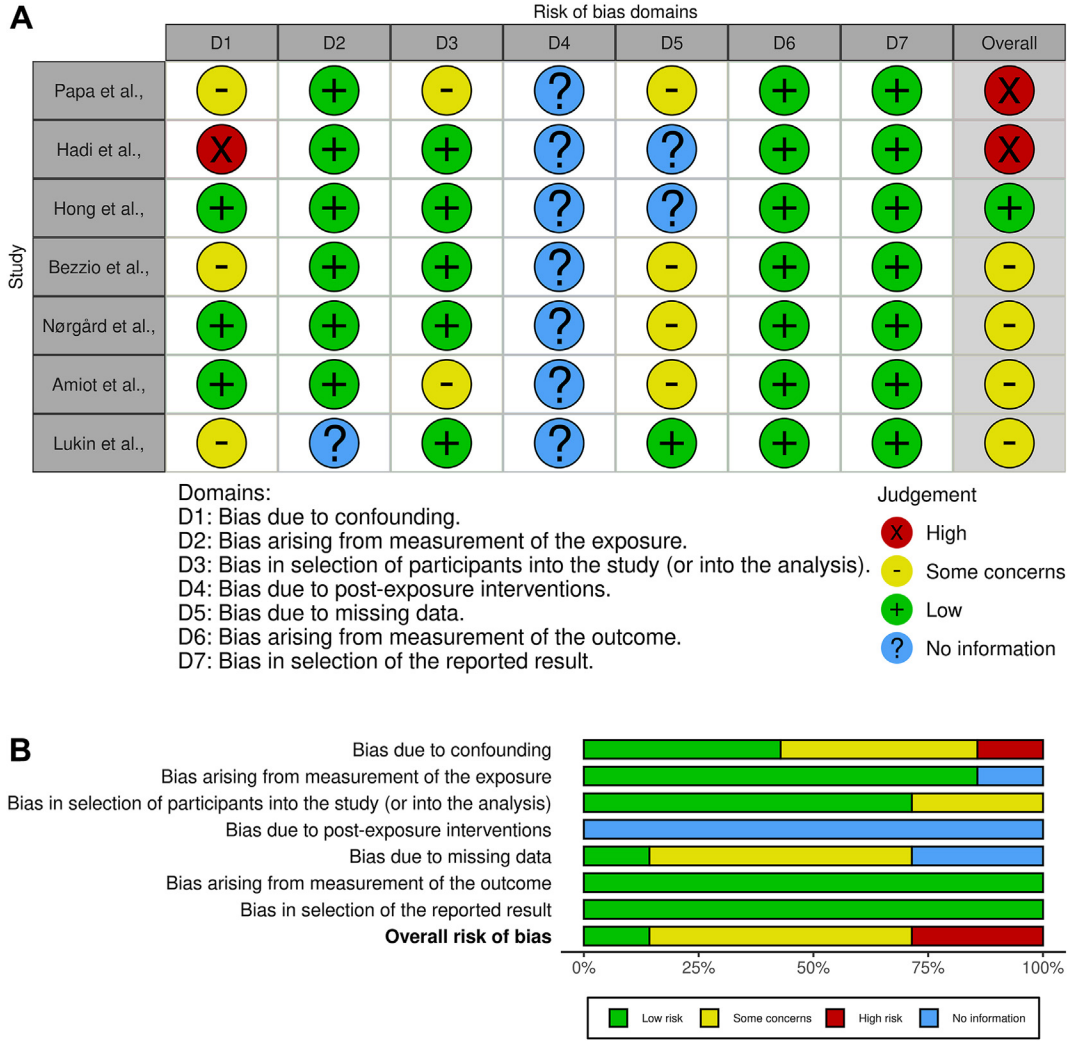

Figure 3. (A) Study-wise summary of risk of bias in each of the 7 domains assessed in ROBINS-E tool for observational studies presented as a traffic light plot. (B) Domain-wise summary of risk of bias of the included studies using the ROBINS-E tool for observational studies.

Table 2. Detailed Summary of the Quality Assessment of the Studies Using the ROBINS-E Tool. The ROBINS-E Tool has 7 Domains Across Which Risk of Bias Is Evaluated

Study	Domain	Risk
Papa et al.,	Confounding	Some concerns. Not controlled for comorbidities.
	Measurement of exposure	Low risk. A positive nasopharyngeal swab test was required for inclusion in the case group.
	Participant selection	Some concerns. Only patients undergoing biologics therapy were included.
	Postexposure interventions	No information.
	Missing data	Some concerns. Only patients with stable, inactive IBD were included. Data missing—Retrospective.
	Measurement of outcome	Low. Need for therapy intensification was used as proxy for IBD recurrence rate.
	Selection of reported result	Low. No issue of selection of reported results was identified.
Hadi et al.,	Confounding	High risk.
	Measurement of exposure	Low risk. Selection based on diagnostic codes.
	Participant selection	Low risk. Patients with COVID-19 on the TriNetX (>40 HCOs) were included.
	Postexposure interventions	No information.
	Missing data	No information. No information about missing data.
	Measurement of outcome	Low risk. IBD flare was measured as inpatient hospitalization along with stool studies, intravenous methylprednisolone requirement or flexible sigmoidoscopy.
	Selection of reported result	Low risk. No issue of selection of reported results was identified.
Hong et al.,	Confounding	Low risk.
	Measurement of exposure	Low risk. Controls were individuals with negative PCR and IgG tests.
	Participant selection	Low. IBD patients from 5 academic medical centers within NY Crohn's & colitis.
	Postexposure interventions	No information.
	Missing data	No information. Missing variables were excluded from the analysis.
	Measurement of outcome	Low risk. Composite of IBD-related hospitalization or surgery.
	Selection of reported result	Low risk. No issue of selection of reported results was identified.
Bezzio et al.,	Confounding	Some concerns. Not controlled for BMI.
	Measurement of exposure	Low risk. A positive PCR test is required for inclusion of cases.
	Participant selection	Low risk. Patients from the Italian IG-IBD cohort were included in the study.
	Postexposure interventions	No information.
	Missing data	Some concerns. Patients with severe disease at baseline were excluded in the final analysis.
	Measurement of outcome	Low risk. IBD disease activity was measured using HBI or PMS.
	Selection of reported result	Low. No issue of selection of reported result was identified.
Nørgård et al.,	Confounding	Some concerns. Not controlled for BMI and smoking status.
	Measurement of exposure	Low risk. A positive PCR test is required for inclusion of cases.
	Participant selection	Low risk. Patients from the Danish National IBD cohort were included.
	Postexposure interventions	No information.
	Missing data	Some concerns. No data on antigen test results.
	Measurement of outcome	Low risk. Corticosteroid prescription used as proxy for disease flares.
	Selection of reported result	Low. No issue of selection of reported result was identified.
Amiot et al.,	Confounding	Low risk.
	Measurement of exposure	Low risk. A positive PCR, Ag or serological test is required for inclusion of cases.
	Participant selection	Some concerns. Some participants included were selected by their physicians(I-CARE).
	Postexposure interventions	No information.
	Missing data	Some concerns. Missing data on the comparison.
	Measurement of outcome	Low. Change in disease activity by comparing HBI or SCCAI.
	Selection of reported result	Low. No issue of selection of reported results was identified.
Lukin et al.,	Confounding	Some concerns. Not controlled for baseline disease activity.
	Measurement of exposure	No information.
	Participant selection	Low risk. Patients from the I-CARE cohort were included in the study.
	Postexposure interventions	No information.
	Missing data	Low risk.
	Measurement of outcome	Low. IBD disease activity was measured using HBI or SCCAI.
	Selection of reported result	Low. No issue of selection of reported results was identified.

BMI, body mass index; HBI, Harvey Bradshaw Index; HCO, health care organizations; PMS, Partial Mayo Score; SCCAI, Simple Clinical Colitis Activity Index.

Discussion

In this systematic review and meta-analysis, we assessed the impact of SARS-CoV-2 infection on adverse IBD outcomes. We identified 7 studies including a total of 34,977 SARS-CoV-2 positive IBD patients and 53,270 IBD patients without a recorded SARS-CoV-2 infection. We find no significantly increased risk of adverse IBD outcomes following the acute phase of COVID-19 infection, and this was true for both CD and UC patients.

Meta-analyses have explored the incidence of COVID-19 in IBD patients and the effect of IBD on the outcomes of the infection. A comprehensive meta-analysis carried out by Abdulla et al.[33] shows that IBD is not significantly associated with increased risk of COVID-related hospitalization or death. However, the risk of adverse IBD outcomes following COVID-19 have not been explored through a meta-analysis.

The primary findings from this meta-analysis are in keeping with the results from most other studies exploring this question. In a cohort study carried out in Canada by Wetwittayakhlang et al., only 8 out of 82 IBD patients (9.8%) experienced a flare 3 months following an infection.[34] In another study by Guerra et al., only 1 out of 805 (0.12%) patients developed a flare post-COVID.[35] The above-mentioned studies did not include a control group and were therefore deemed to be of insufficient robustness to be included in the meta-analysis. However, in a long COVID study in an Italian IBD cohort by Salvatori et al., 30% of the participants were reported as having experienced an IBD flare following infection.[36] Interestingly, both the Canadian and the Italian study recruited participants from a tertiary referral center. It is important to note that some of the studies report discontinuation of therapy in these patients.

Several factors might be driving the observed absence of increased risk of adverse IBD outcomes in COVID-infected IBD patients. Vaccination could be a potential contributor to preventing an increased risk of adverse IBD outcomes. In a cohort study carried out by Al-Aly et al., vaccination against COVID-19 was associated with reduced risk of developing postacute sequelae of COVID-19 (HR: 0.85, 95% CI: 0.82–0.89).[37] By reducing the severity of COVID-19 disease,[38] vaccination might lower the risk of adverseIBD events. The impact of vaccination could not be analyzed in this meta-analysis as the vaccination status of the individual participants has not been presented in the included studies. The cohort studied by Papa et al.,[29] did not include any vaccinated individuals due to unavailability of vaccines to IBD patients in Italy during the subject recruitment. Hong et al.,[31] and Norgard et al.,[27] mention that their cohort included both vaccinated and unvaccinated individuals. Since IBD patients were among the prioritized groups for vaccination, a large portion of them would have been vaccinated once available.

Another possible reason for the observed results might be the definition used for the reference group in these studies. Most of the studies did not require a recorded negative COVID-19 test to be classified as non-COVID comparators. This could mean that asymptomatic and perhaps even symptomatic COVID-19 patients who did not get tested would be classified as non-COVID comparators thereby leading to bias towards the null. The duration of follow-up might not explain the absence of an increased risk of the outcome since it was not a significant predictor of the outcome in our analysis. The longest duration of follow-up in the included studies is 11 months.[31] Interestingly, the only study where an IBD flare was significantly associated with a SARS-CoV-2 infection had the least amount of follow-up.[30]

Factors like therapy discontinuation might also be contributing toward the risk of the outcome. Discontinuation of IBD therapy has been shown to be associated with IBD flares in 2 of the included studies.[29,32] Not all included studies report information on treatment adherence after contraction of the infection. Turner et al.[39] showed that 22% of pediatric IBD patients without COVID-19 developed a flare after discontinuation of IBD therapy. Therefore, failure to adhere to medication and not COVID-19 might be implicated in triggering disease flares in some cases. Existing evidence is not sufficient to establish therapy discontinuation as the sole or primary contributor of flares in IBD patients with COVID-19.

This meta-analysis has several strengths but also a few limitations. This is the first meta-analysis studying the impact of the infection on IBD disease outcomes. This meta-analysis is well-powered with a total of 34,977 SARS-CoV-2 positive IBD patients and 53,270 IBD patients without recorded COVID-19. Robust statistical methods have been used for the analysis and data are reported in line with PRISMA guidelines. There are, however, a few limitations to the study. Most studies on COVID-19 are prone to misclassification bias due to the change in testing strategies at different periods. Most of the included studies did not require a negative PCR or antigen test to be part of the control group. Some studies only considered a registered PCR test for inclusion in the study group and therefore did not capture the patients who tested positive in an antigen test and those who acquired the infection but did not get tested. Some of the studies did not include information about adherence to IBD therapy after infection with COVID-19. Also, the studies used different indicators to measure adverse IBD outcomes. Although the different outcomes were pooled as one composite outcome, we acknowledge that the 5 outcomes have different grades of clinical importance. No thorough accountability for vaccination has been provided in the studies. These methodological limitations might be contributing to the observed insignificant result. However, due to our stringent inclusion and exclusion criteria, these are among the most reliable high-quality studies available for the exploration of this question of the present study.

In conclusion, in this systematic review and meta-analysis, we did not find a significantly increased risk of adverse IBD outcomes following acute COVID-19. While this is reassuring for clinicians and patients, all studies lacked

individual-level vaccination status; hence, studies with better methodological robustness are needed to predict the impact of the more novel variants of the virus on the disease course of IBD.

Supplementary Materials

Material associated with this article can be found in the online version at https://doi.org/10.1016/j.gastha.2024.10.021.

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Evangelin Shaloom Vitus: Study conceptualization and design, review, data analysis, data interpretation.Simran Mann: Study conceptualization and design, writing – original draft, data interpretation, review, critical revision. Rahma Elmahdi: Study conceptualization and design, data interpretation, critical revision. Charlie W Lees: Study conceptualization and design, data interpretation, critical revision. Tine Jess: Study conceptualization and design, data interpretation, critical revision.

Conflicts of Interest:
These authors disclose the following: Professor Charlie Lees has acted as a speaker and/or consultant to AbbVie, Janssen, Takeda, Pfizer, Galapagos, GSK, Gilead, Vifor Pharma, Ferring, Dr Falk, BMS, Boehringer Ingelheim, Novartis, Sandoz, Celltrion, Cellgene, Amgen, Samsung Bioepis, Fresenius Kabi, Tillotts, Trellus Health and Iterative Health. Professor Tine Jess has acted as a consultant to Pfizer and Ferring Pharmaceuticals. The remaining authors disclose no conflicts.

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Ethical Statement:
Since this is a meta-analysis of published studies, ethical approval was not required.

Data Transparency Statement:
Data extraction templates, data extracted and used for analysis, analysis codes may be made available upon request. All data used in the study are publicly available.

Reporting Guidelines:
PRISMA.