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ORIGINAL ARTICLE

Impact of biologics and small molecules for inflammatory bowel disease on COVID-19-related hospitalization and mortality: A systematic review and meta-analysis

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biologics, COVID-19, hospitalization, inflammatory bowel disease, janus kinase-1 inhibitor.

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Abstract

Background and Aim: The use of biologics and small molecules has been a concern for patients with inflammatory bowel disease (IBD) during the COVID-19 pandemic. We aimed to assess the association between the risk of COVID-19-related hospitalization and these agents.

Methods: We made a systematic review and meta-analysis of all published studies from December 2019 to September 2021 to identify studies that reported COVID-19-related hospitalization in IBD patients receiving biologic therapies or tofacitinib. We calculated the risk ratio (RR) to compare the relative risk of COVID-19-related hospitalization in patients receiving these medications to those who were not, at the time of the study.

Results: Eighteen studies were included. The relative risk of hospitalization was significantly lower in patients with IBD and COVID-19 who were receiving biologic therapy (RR = 0.47 [95% confidence interval, CI: 0.42–0.52, $P < 0.00001$]) compared to patients not receiving biologics. The RR was lower in patients receiving anti-tumor necrosis factors (TNFs) compared to those who were not (RR = 0.48 [95% CI: 0.41–0.55, $P < 0.00001$]). A similar finding was observed in patients taking ustekinumab (RR = 0.55 [95% CI: 0.43–0.72, $P < 0.00001$]). Combination therapy involving anti-TNF and an immunomodulator did not lower the risk of COVID-19-related hospitalization (RR = 0.98 [95% CI: 0.82–1.18, $P = 0.84$]). The use of vedolizumab (RR = 1.13 [95% CI: 0.75–1.73, $P = 0.56$]) or tofacitinib (RR = 0.81 [95% CI: 0.49–1.33, $P = 0.40$]) was not associated with a lower risk of COVID-19-related hospitalization.

Conclusion: Regarding COVID-19-related hospitalization in IBD, anti-TNFs and ustekinumab were associated with decreased risk of hospitalization. In addition, vedolizumab and tofacitinib were not associated with COVID-19-related hospitalization.

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a global pandemic that had evolved shortly after emerging from Wuhan, China, in December 2019.[1,2]A significant number of patients are at risk of hospitalization as a result of disease complications, who include vulnerable patients such as elderly and immunocompromised individuals as well as those with active malignancy and cardiopulmonary diseases.[3,4] SARS-CoV-2 is known to be transmitted through air droplets and aerosols, although airborne transmission can also be considered as a source.[2] The ability of SARS-CoV-2 to affect almost any organ of the body is due to the presence of a receptor called the angiotensin converting enzyme 2 (ACE2).[5] It is mainly expressed in the alveolar epithelial type II cells in the lungs, the brush border of gut enterocytes, and along the ciliated cells. The intestinal

ACE2 receptor is involved in regulating the expression of antimicrobial peptides and promoting the homeostasis of the gut microbiome.[5] Gastrointestinal (GI) manifestations are common in patients with the coronavirus disease (COVID-19). Additionally, a recent study showed that GI manifestations of COVID-19 are also common in patients with inflammatory bowel disease (IBD).[6] However, current data show that patients with IBD are not at any higher risk for COVID-19 infection.[7]

Patients with IBD often require long-term maintenance medical therapy. Biologics and janus kinase (JAK) inhibitors are commonly used to maintain remission in patients with IBD.[8] The effect of these medications on COVID-19 outcome is still not fully understood. The Surveillance Epidemiology of Coronavirus Under Research Exclusion (SECURE-IBD) database is an international registry that was established at the beginning of the pandemic to report the outcomes of COVID-19 in patients with IBD.[9] To date, it includes the outcomes of COVID-19 infection in more than 6000 patients with IBD from 72 countries worldwide. In addition, multiple studies have been performed to evaluate the safety of IBD medications during COVID-19 pandemic with conflicting data.[7,10,11] Furthermore, there is a lack of up-to-date data because of the rapidity of emerging studies and diverging evidence. To our knowledge, there has been no systematic review so far that looked at individual biologic therapy and the risk of COVID-19-related hospitalization. Therefore, we performed a systematic review and meta-analysis to assess the impact of biologics and JAK-1 inhibitors on COVID-19-related hospitalization.

Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[12] was used to conduct this systematic review, and the meta-analysis was carried out as

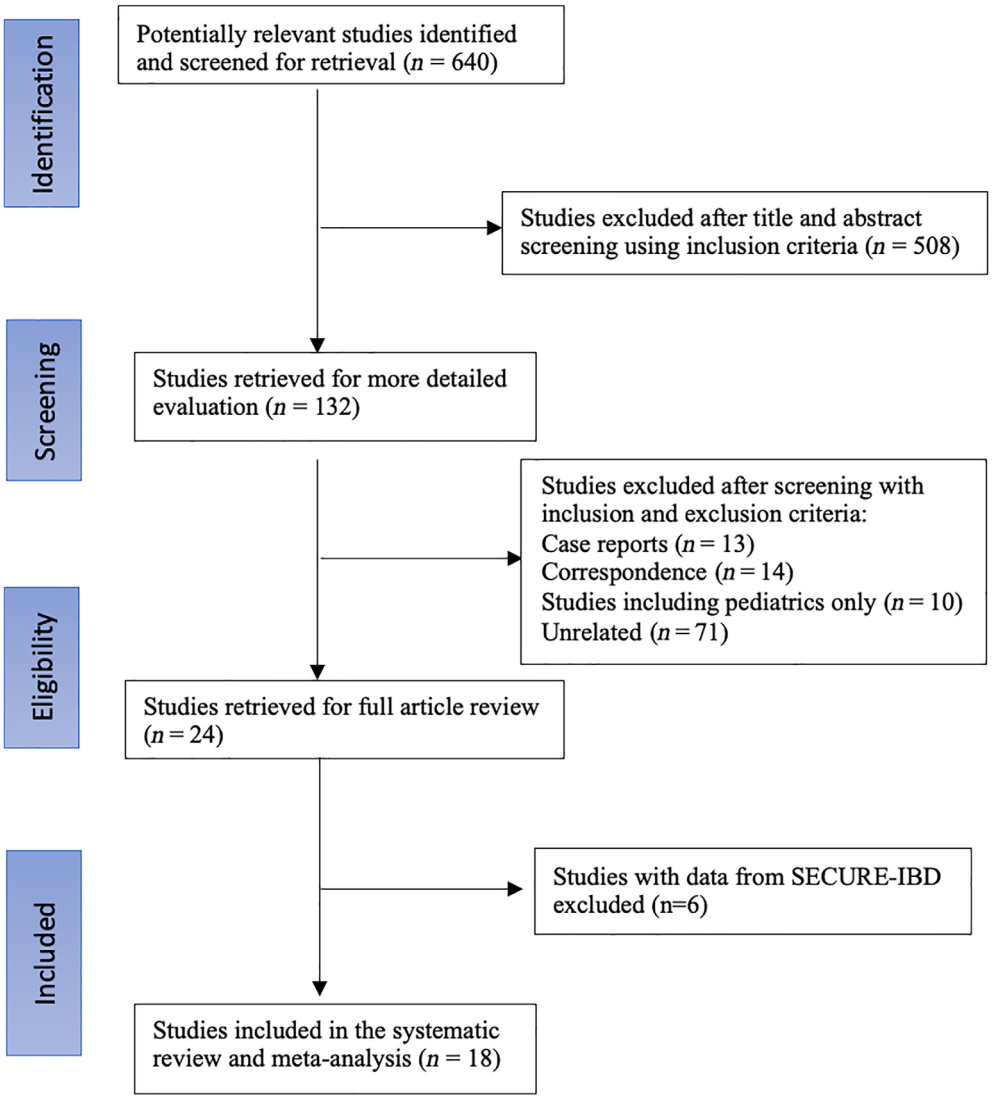

Figure 1 PRISMA diagram showing search strategy. SECURE-IBD, Surveillance Epidemiology of Coronavirus Under Research Exclusion.

Table 1 Summary of included studies and patient characteristics

Study	Total number of patients with IBD + COVID-19 (*n*)	Study design	Country	Mean age	Male sex (*n*)	Ulcerative colitis (*n*)	Crohn's disease (*n*)	IBD undetermined
Allocca *et al.*	15	Observational	France and Italy	39	4	9	6	NA
Annapureddy *et al.*	464	Observational	United States	48	26	Not specified	Not Specified	NA
Attauabi *et al* .	76	Observational	Denmark	52.5	45	45	31	NA
Axerlrad *et al.*	83	Observational	United States	35	44	27	56	NA
Bezzio et al.	79	Observational	Italy	45	44	47	32	NA
Bezzio *et al.*	24	Observational	Italy	45.9	79	Not specified	Not specified	NA
Burke *et al.*	39	Observational	United States	45.5	15	21	18	NA
Conley *et al.*	203	Observational	United Kingdom	42	65	98	105	NA
Derikx *et al.*	100	Observational	Netherlands	62.5	46	59	36	NA
Gubatan *et al.*	5	Observational	United States—California	70.6	2	3	2	0
Kennedy *et al.*	590	Observational	United Kingdom	Not specified	Not specified	Not specified	Not specified	NA
Khan *et al.*	649	Observational	United States	65	Not specified	Not specified	Not specified	NA
Lamp *et al.*	211	Observational	United Kingdom	59.5	116	109	86	16
Lukin *et al.*	80	Observational	United States—New York	48.3	45	26	38	NA
Rizzello *et al.*	26	Observational	Italy	Not specified	Not specified	11	15	NA
SECURE-IBD	6438	Database	Multiple countries	Not specified	2699	2597	3539	NA
Taxonera *et al.*	12	Observational	Spain	52	3	5	7	NA
Vadan *et al.*	7	Observational	Italy	44.5	5	4	3	NA

IBD, inflammatory bowel disease; NA, not applicable; SECURE-IBD, Surveillance Epidemiology of Coronavirus Under Research Exclusion.

described in the Cochrane Handbook of Systematic Reviews. MOOSE guidelines were also followed.[13]

Inclusion and exclusion criteria. We included all relevant studies based on predetermined inclusion and exclusion criteria. In terms of the types of studies, we included randomized controlled trials, observational studies, and letters to the editor. Furthermore, data from SECURE-IBD were included. In terms of population, only adult patients (age ≥ 18 years) with IBD and confirmed SARS-CoV-2 infection were included. As for outcomes, any study that reported hospitalization data in IBD patients infected with SARS-CoV-2 and receiving biologic therapy or small-molecule JAK inhibitors at the time of the study were included.

Based on the modified Newcastle–Ottawa Scale (mNOS), we excluded low-quality studies such as case series and case reports as well as any study that did not have relevant outcome data. In addition, to avoid duplication, any study that reported data from the SECURE-IBD database was excluded. Finally, we also excluded studies that included only pediatric patients (age < 18 years).

Definitions and outcome measures. The primary outcome measure was the risk of COVID-19-related hospitalization in patients taking biologic therapy or small-molecule JAK inhibitors. Biologic agents included the tumor necrosis factor antagonists (anti-TNFs) adalimumab and infliximab, vedolizumab, and ustekinumab. The association between COVID-19-related hospitalization and individual biologic agents was explored when available. If data on individual biologic agents were not available, we grouped the anti-TNFs vedolizumab and ustekinumab under such agents. Data on the concurrent use of anti-TNF agents and an immunomodulator (combination therapy) were also extracted. For secondary outcomes, we explored the association of biologic therapies and JAK inhibitors with intensive care unit (ICU) admission and mortality, when data were available. Mortality was defined as the number of patients who died within the study observation period. We also collected information on baseline characteristics of patients such as age, gender, and type of IBD in addition to the number of patients from each country when available.

Search strategy. MEDLINE, Embase, Scopus, and Cochrane Central Register of Controlled Trials databases were searched from December 1, 2019 to September 1, 2021 using predetermined search terms (Table S1, Supporting information). The only restriction applied was that the reports be in English language. In addition, the SECURE-IBD database was searched for relevant data, as well as clinical trials databases (www.clinicaltrials.gov and International Randomized Standard Clinical Trial [IRSCT] Register).

English conference proceedings were searched. These included the Canadian Digestive Disease Week, the Digestive Disease Week, the World Congress of Gastroenterology, the American College of Gastroenterology, the European Crohn's and Colitis Organization Congress, and the United European Gastroenterology Week. Furthermore, Google Scholar was used to search for unindexed studies. Finally, systematic reviews were also reviewed for relevant studies.

Any relevant titles and abstracts were appraised independently by two authors (Fatema Alrashed and Hajer Alasfour) and data extraction was also performed by the same authors.

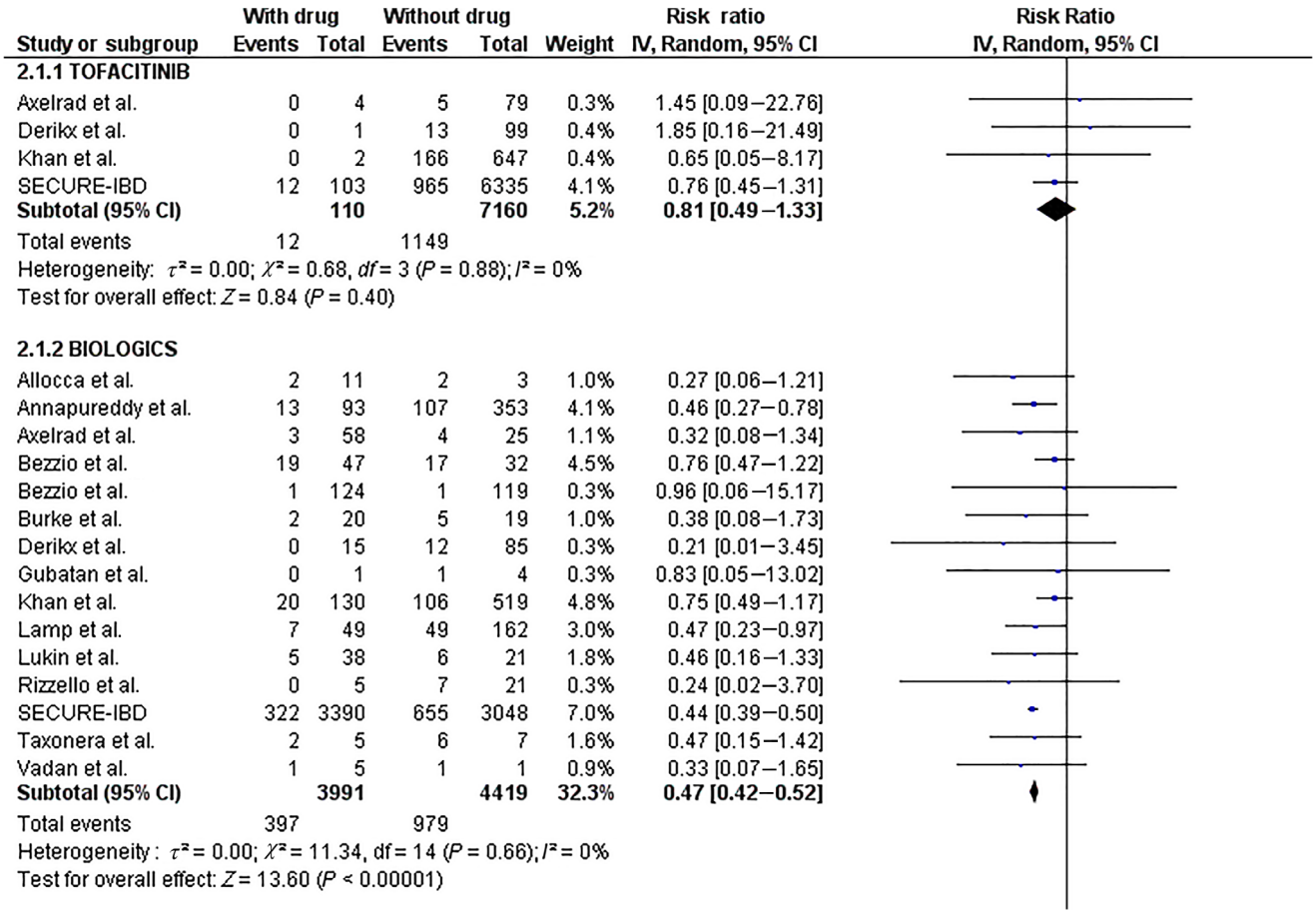

Figure 2 Forest plot showing the risk of COVID-19-related hospitalization in patients receiving biological agents and small molecules. CI, confidence interval.

Differences, if any, were resolved after discussion with a third reviewer (Mohammad Shehab).

Risk of bias and study quality. The mNOS[14] was used to evaluate the quality of all included studies (see Table S2). This tool allows us to use a scoring system to quantify the quality of studies. A score of 0–3 means the study is of a low quality, whereas a score of 4–6 means a study of moderate quality. Finally, any study scoring 7 or 8 is deemed to be of high quality. This assessment tool uses three domains to appraise the quality of observational studies. These domains are selection, compatibility, and outcome.

ROBINS-I was used for assessing the risk of bias in non-randomized studies of interventions[15] for observational studies, whereas the Cochrane Risk of Bias tool (RoB-2)[16] was used for randomized controlled trials. To evaluate the quality and risk of bias, two authors (Mohammad Shehab and Fatema Alrashed) worked independently.(see Table S3).

Statistical analysis. The risk ratio (RR) was calculated to compare the relative risk of COVID-19 hospitalization in patients taking biologic therapy and JAK inhibitors with those who were not receiving those medications at the time of the study. Statistical analysis was conducted using the Review Manager (RevMan) version 5.3.5 (The Cochrane Collaboration). Random-effects models were used to estimate the 95% confidence interval (CI) given that studies differed in their designs and approach to the research question. Heterogeneity was determined by I^2 and the *P*-value of heterogeneity. An I^2 value of less than 30% was selected to indicate low heterogeneity, whereas as an I^2 value of 30–75% indicated moderate heterogeneity. Finally, an I^2 value of >75% was chosen to define high heterogeneity.

Results

Search results. From the initial 811 studies identified in the search, 18 studies[17–33] met the inclusion criteria (Fig. 1). These also include the data extracted from the SECURE-IBD database. To avoid duplicating patients, six studies were excluded, as these studies reported data from SECURE-IBD only.[7,10,11,34–36] All included studies were observational. Six studies were conducted in the United States, five in Italy, three in the United Kingdom,

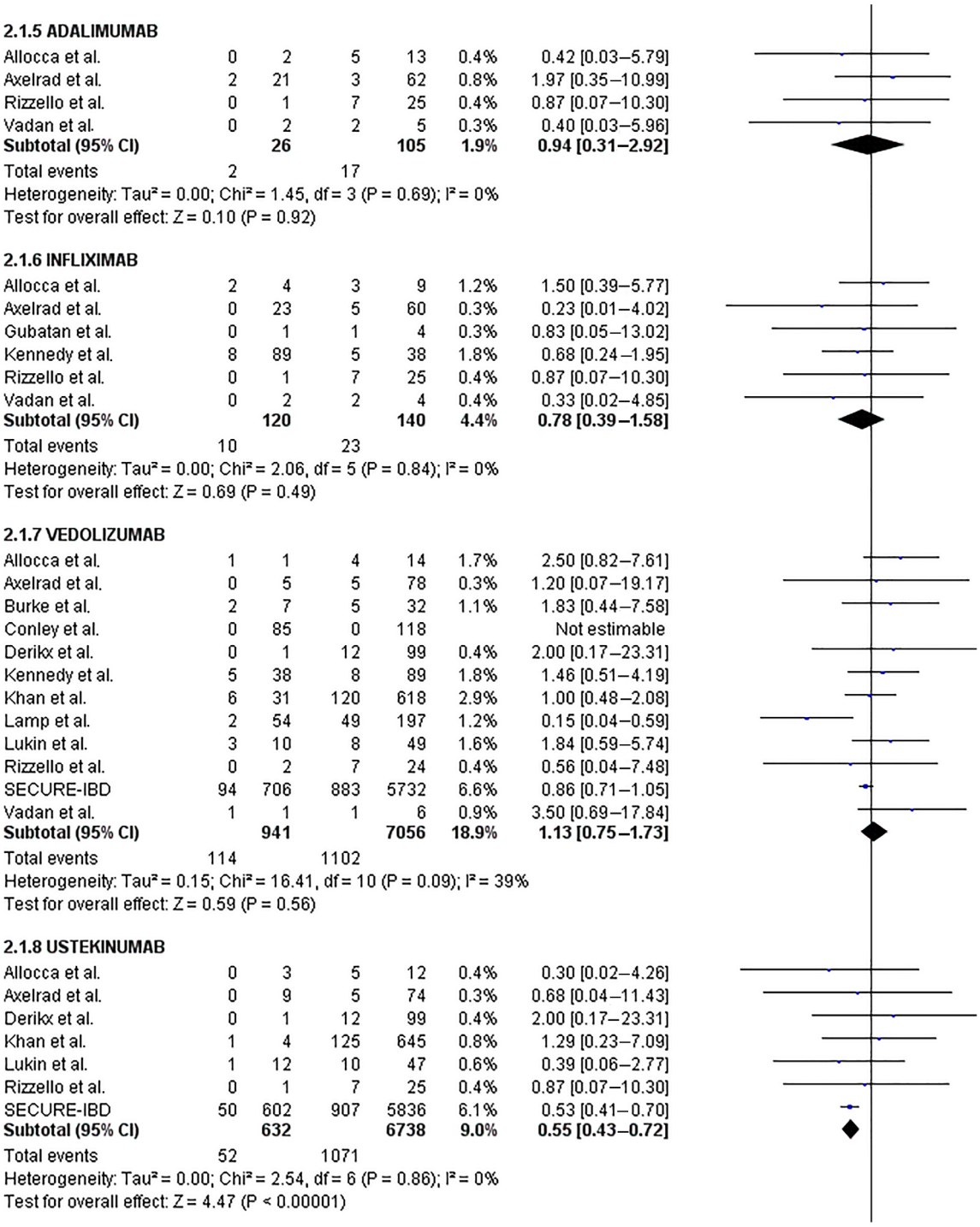

Figure 3 Forest plot showing the risk of COVID-19-related hospitalization in patients receiving different biologic therapies. CI, confidence interval.

and the rest in multiple countries including France, Spain, and Denmark. The main characteristics and findings of the 18 studies are shown in Table 1.

In total, 9101 patients with IBD and confirmed COVID-19 diagnosis were included. The mean age was 42 (±10.3), and 3283 (36%) patients were male. Of these, 1320 (14.5%) patients were from the United States, 1004 (11.3%) from the United Kingdom, 151 (1.6%) from Italy, and the remaining from different countries such as France and the Netherlands. However, information about the majority of the patients (6438) was extracted from the SECURE-IBD database (70.7%). Among the included patients, 3061 (33.6%) had ulcerative colitis, 3974

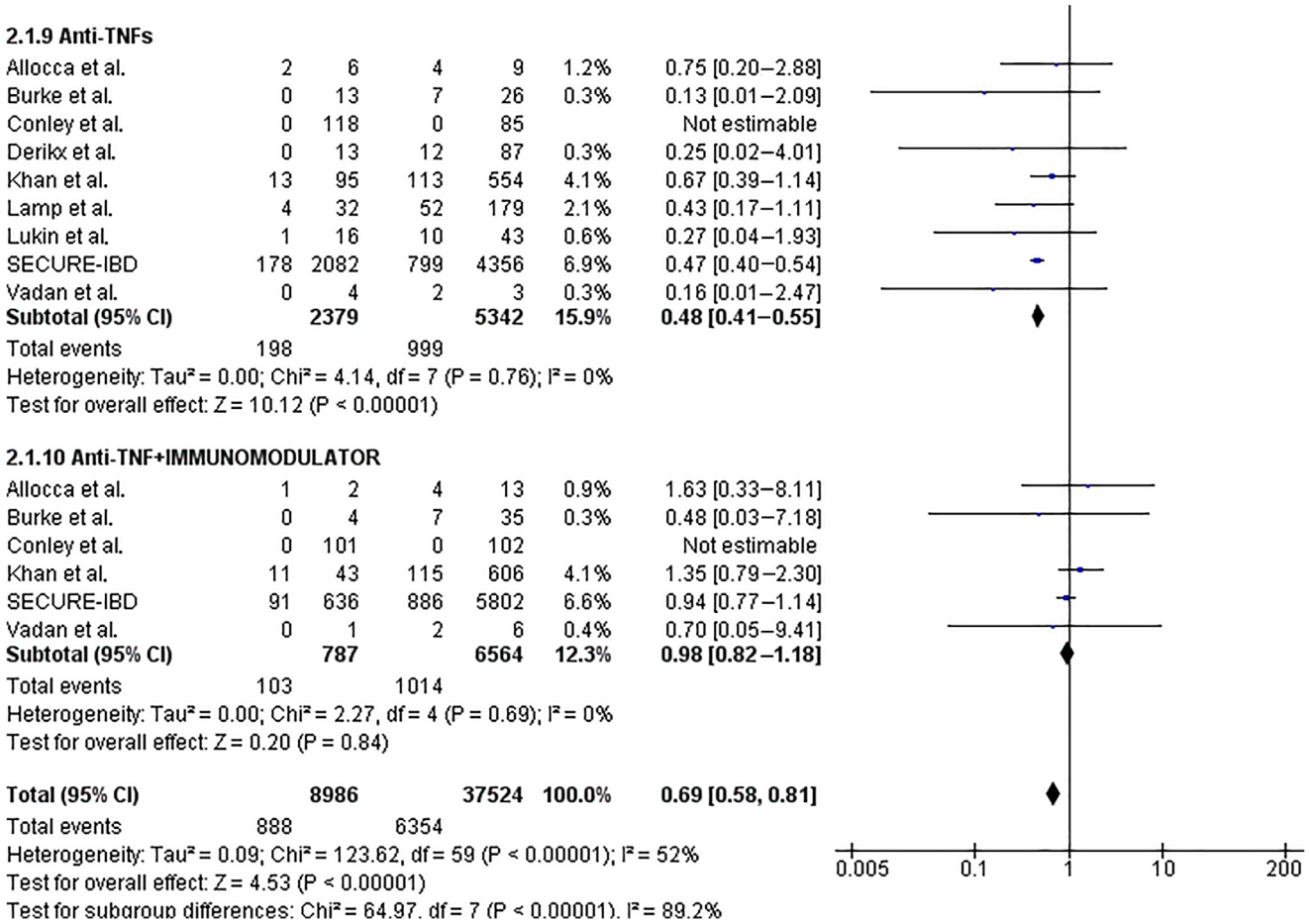

Figure 4 Forest plot showing the risk of COVID-19-related hospitalization in patients receiving tumor necrosis factors inhibitors (anti-tumor necrosis factorss) with or without an immunomodulator. CI, confidence interval.

(43.6%) had Crohn's disease, and the remainder did not specify the IBD type. Six-hundred and thirteen (6.7%) patients were receiving corticosteroids. Most patients were on anti-TNFs without immunomodulators (2379; 26.1%) and 787 (8.6%) patients were receiving combination therapy of anti-TNF and an immunomodulator. The number of patients on vedolizumab and ustekinumab was 941 (10.3%) and 632 (6.9%), respectively, whereas 110 (1.2%) patients were receiving tofacitinib.

In terms of hospitalization per each country, 201 (15.2%) out of 1320 patients from the United States, 69 (6.8%) out of 1004 patients from the United Kingdom, 39 (25.8%) out of 151 patients from Italy, 19 patients from Denmark, 12 patients from the Netherlands, and 8 patients from Spain were hospitalized, as reported by each study. The remaining hospitalization data were extracted from the SECURE-IBD database.

Main outcomes. The relative risk of hospitalization was significantly lower in patients with IBD and COVID-19 who were receiving biologic therapy (Fig. 2). Specifically, the RR was 0.47 (95% CI: 0.42–0.52, $P < 0.00001$). When looking at specific biologic therapy (Fig. 3), the RR of COVID-19-related hospitalization was lower in patients receiving anti-TNFs compared to those who did not (RR = 0.48 [95% CI: 0.41–0.55, $P < 0.00001$]). A similar finding was observed in patients taking ustekinumab (RR = 0.55 [95% CI: 0.43–0.72, $P < 0.00001$]). On the other hand, the combination therapy of anti-TNF and an immunomodulator (Fig. 4) did not increase the risk of COVID-19-related hospitalization (RR = 0.98 [95% CI: 0.82–1.18, $P = 0.84$]). Similarly, the use of vedolizumab (RR = 1.13 [95% CI: 0.75–1.73, $P = 0.56$]) and tofacitinib (RR = 0.81 [95% CI: 0.49–1.33, $P = 0.40$]) was not associated with favorable outcomes in relation to COVID-19-related hospitalization (Fig. 2).

Secondary outcomes. Among the total number of hospitalized patients, 1432 were admitted to the ICU, 5.3% were receiving anti-TNFs, 1.7% were on vedolizumab, and less than 1% were on ustekinumab. None of the patients receiving tofacitinib was admitted to the ICU. When looking at the number of deaths at the time of each study, mortality was significantly lower in patients taking biologics (RR = 0.32 [95% CI: 0.23–0.44, $P < 0.00001$]) compared to those not receiving biologics (Fig. 5). Data related to mortality in patients taking tofacitinib were not reported by the studies.

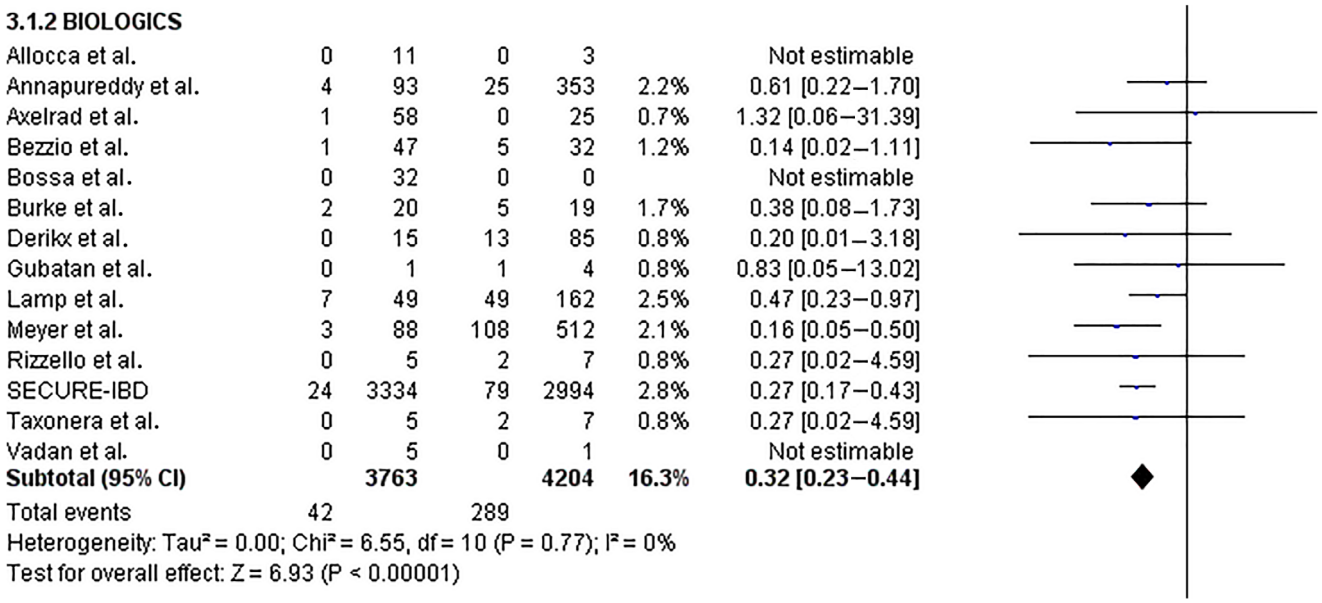

Figure 5 Forest plot showing the risk of COVID-19 mortality in patients receiving biological agents. CI, confidence interval.

Heterogeneity assessment, risk of bias, and quality of studies. After assessing each study independently, the median mNOS score was 4 (range 4–6; see Table S2). In addition, using the ROBINS-I tool, most studies were judged to have low risk of bias (see Table S3). Using the random-effects model, the heterogeneity (I^2 was low (less than 30%) except for studies evaluating vedolizumab where the heterogeneity was medium (39%).

Discussion

In this meta-analysis, 18 studies were identified evaluating a total of 9101 patients with IBD and COVID-19. Patients were receiving different biologic therapies including anti-TNFs, vedolizumab, ustekinumab, and tofacitinib. Our analysis showed that the risk of COVID-19-related hospitalization was significantly decreased in patients taking anti-TNFs and ustekinumab, whereas tofacitinib, vedolizumab, and immunomodulators in combination with anti-TNFs were not associated with any negative outcomes. Our study indicated that the percentage of hospitalization differed in each country. This observed variation can be explained by the different thresholds of hospitalization among different countries.[37,38]

Our study also showed that biologics without immunomodulators were associated with decreased COVID-19-related hospitalization in patients with IBD. Several studies[11,39,40] described the rationale for trying anti-TNF therapies in COVID-19. In summary, the mechanism of action of these medications ultimately leads to the neutralization of TNF, which plays a major part in the body cytokine response. This response leads to hyperimmune reaction and inflammation in some patients infected with SARS-CoV-2.[41] Furthermore, the excess inflammatory phase in COVID-19 is characterized by elevated concentrations of serum TNF, interleukin (IL)-6, and IL-8, but relatively little IL-1.[42] Therefore, it is possible that TNF blockade can reduce COVID-19 hyperinflammation and prevent the need for hospitalization or ICU care. A randomized control trial (CATALYST) is under way in the United Kingdom assessing the use of infliximab in patients hospitalized with severe COVID-19. Additionally, another phase II trial conducted in Boston by the Tufts Medical Center is also examining the hypothesis that early initiation of TNFα inhibitor therapy in patients with severe COVID-19 infections will prevent further clinical deterioration (NCT04425538).

Another notable finding of this meta-analysis is that ustekinumab, but not vedolizumab, is associated with decreased COVID-19-related hospitalization. Ustekinumab binds to the p40 subunit of IL-12 and IL-23. The binding of this subunit prevents their interaction and attachment with the cell surface, preventing IL-12- and IL-23-mediated cell signaling and cytokine production.[43] Current data propose that interfering with cytokine production will result in dampening of the systemic inflammation caused by SARS-CoV-2 infection, which can lead to multiorgan failure and death.[44] One report described a case where ustekinumab might have exerted a protective action in COVID-19 and attributed this action to the anti-inflammatory effect of the double neutralization of IL-12 and IL-23.[45] On the other hand, vedolizumab did not exert the same protective effect; however, it was not associated with increased risk of COVID-19-related hospitalization. Given its gut-specific mechanism of action, vedolizumab does not lead to a significant impact on systemic immunity and therefore cytokine production may not be significantly reduced to prevent the complications arising from the hyperimmune response caused by SARS-CoV-2 infection described previously. Interestingly, one study compared COVID-19 outcomes among patients on vedolizumab monotherapy with those on anti-TNF monotherapy. Although the difference between the two groups was not significant in terms of severe COVID-19 outcomes, this

study found that the risk of hospitalization was 38% more with vedolizumab monotherapy compared to anti-TNF monotherapy.[35] These findings further support the hypothesis that anti-TNF therapy can be protective against severe COVID-19. Furthermore, one study, which enrolled 234 patients,[29] provided evidence for the protective role of biologics against SARS-CoV-2 infection in IBD. The study found that patients taking biologics were 5 times less likely to be diagnosed with the infection, supporting the hypothesis that immunomodulating drugs that dampen cytokine activity have a protective role against COVID-19.

Our study also showed that mortality was significantly lower in patients taking biologics, defined as the number of patients who died within the study observation period. As discussed previously, possible rationale for the benefits of biologic therapies can be explained by the mechanism of action of these medications. Furthermore, as disease activity is associated with worse COVID-19 outcomes,[28] it is possible that use of effective agents, such as biologics, reduces the risk by reducing intestinal disease activity.

Our findings regarding biologic therapy support their continued use and should be reassuring to the large number of IBD patients receiving these agents. Currently, experts agree that active IBD disease leads to more adverse outcomes in patients with SARS-CoV-2 infection compared to medication-related immunosuppression, and therefore different professional organizations of gastroenterology are endorsing continuing IBD therapies during the COVID-19 pandemic.[46] Other recommendations include avoiding immunomodulators if possible, minimizing corticosteroid exposure, and giving preference to subcutaneous route of drug delivery for initiation of biologic therapy.[47,48]

In this meta-analysis we also found that tofacitinib was not associated with increased risk of COVID-19-related hospitalization. Similarly, a study by Agrawal *et al*. found that the risk of hospitalization or ICU admission did not differ between tofacitinib-treated patients and other patients.[10] In addition, a recent randomized controlled trial found that tofacitinib reduces the incidence of death.[49] The observed difference between the effect of tofacitinib and anti-TNF agents on COVID-19 outcomes in our study can be attributed to the neutralization of TNF and subsequent reduction of hyperimmune response by anti-TNFs. However, it can be argued that the functional selectivity of tofacitinib for JAK-2, which blocks cytokine intracellular transduction pathways and reduces the release of cytokines[49] that are implicated in the pathogenesis of the acute respiratory distress syndrome, can lead to favorable COVID-19-related outcomes. Ongoing trials with tofacitinib (NCT04415151 and NCT04750317) may give further insights related to the impact of JAK inhibitors on Covid-19 outcomes. Furthermore, the small sample size of patients receiving tofacitinib could have led to statistically insignificant results.

This study is the first to comprehensively explore the role of all biological therapies, anti-TNF combination therapy, and small-molecule inhibitors in COVID-19-related hospitalization. The current study summarizes the significantly increased available data overall and for individual biological therapies. A previous systematic review and meta-analysis earlier in the pandemic, which included studies up to July 2020,[50] also found that biological agents have favorable outcomes in severe COVID-19 disease. However, all biologic therapies were grouped together, and hence it was difficult to draw any conclusion on the role of different biological agents individually. With a larger sample size, our study found that ustekinumab, but not vedolizumab, has a protective role against COVID-19-related hospitalization. Furthermore, this larger sample of IBD patients infected with SARS-CoV-2 gives a more precise estimation of the risk of COVID-19-related hospitalization. In addition, because of the specific and strict outcome measure we have chosen, heterogeneity was low among all studies. Finally, this study was performed by adhering to the highest of standards including the MOOSE guideline and PRISMA statement. Inclusion of good-quality studies with detailed extraction of data and rigorous evaluation of study quality lend great credibility and strength to our systematic review and meta-analysis.

Our study limitations include the observational nature of the included studies with risk of confounding and selection bias. Furthermore, patient-level data were lacking, and insufficient data were available to stratify patients by different factors, including the age, disease activity, and socioeconomic assessments of the patients. Additional research is needed to ascertain which risk factors play significant roles in causing COVID-19-related hospitalization. Finally, the majority of patients included in our study were from the SECURE-IBD database. One disadvantage of this database is that it may be subject to reporting bias, which means that severe cases tend to be documented by physicians while the milder cases may remain underreported. Additional research is needed to further evaluate the causality between the use of biologic therapies and COVID-19 outcomes.

In conclusion, regarding COVID-19-related hospitalization in patients with IBD, anti-TNFs and ustekinumab were associated with decreased risk of hospitalization. Furthermore, vedolizumab and tofacitinib were not associated with COVID-19-related hospitalization. In addition, mortality was lower in patients receiving biologic therapy.

Data availability statement. The data that support the findings of this study are openly available.

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Supporting information

Additional supporting information may be found in the online version of this article at the publisher's website:

Appendix S1. Supporting information.