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Risk Factors Associated with *Clostridium difficile* Infection in Inflammatory Bowel Disease: A Systematic Review and Meta-Analysis

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Abstract

Background and Aim: *Clostridium difficile* infection [CDI] is a significant concern in inflammatory bowel disease [IBD]. Risk factors and consequences associated with CDI in inflammatory bowel disease [IBD] patients are important to characterize. The aim of this research was to perform a systematic review and meta-analysis on risk factors and outcomes associated with CDI in IBD patients.

Methods: Multiple databases were searched for studies investigating risk factors, colectomy and mortality risk in IBD patients with and without CDI. This was stratified by short [<3 months] and long-term [>1 year] outcomes. Summary estimates were calculated using a random-effects model. Quality assessment used the Newcastle–Ottawa scale.

Results: Twenty-two studies met inclusion criteria. Antibiotics use within 30 days of diagnosis was associated with CDIs (odds ratio [OR]: 1.85, 95% confidence interval [CI]:1.36, 2.52). Colonic involvement in Crohn's disease patients was associated with significantly higher CDI rates [OR: 2.76, 95% CI: 1.75, 4.35]. There was a significant association between biologic medication use and CDI [OR: 1.65, 95% CI: 1.18, 2.30], with minimal heterogeneity [I^2 = 4.0%]. The long-term colectomy risk was significantly higher for IBD patients with CDI compared with that for IBD patients without CDI [OR: 2.22, 95% CI: 1.17, 4.18]. Significantly higher mortality was found for CDI in IBD patients both short-term [OR: 3.84, 95% CI: 2.62, 5.61] and long-term [OR: 3.65, 95% CI: 1.58, 8.44]. Substantial heterogeneity existed. Most studies were of moderate quality.

Conclusion: Colonic involvement, and biologic and antibiotic use appear to be risk factors associated with CDI among IBD patients. CDI is associated with increased short- and long-term mortality.

Key Words: inflammatory bowel disease, Clostridium difficile infection, risk factors, mortality, colectomy, meta-analysis

1. Introduction

Clostridium difficile is a common cause of nosocomial diarrhea, associated with substantial morbidity and mortality. In the past two decades, there has been a considerable rise in the incidence and severity of *Clostridium difficile* infections [CDIs] and CDI has surpassed methicillin-resistant *Staphylococcus* as the leading cause of nosocomial infections.[1]

There is a growing recognition of the impact of CDI on patients with inflammatory bowel disease (IBD; Crohn's disease [CD],

ulcerative colitis [UC]), even in the absence of traditional risk factors such as hospitalization and antibiotic exposure.[2–5] IBD is a chronic relapsing disorder and these patients have increased exposure to health-care facilities. IBD patients have altered gut microbiomes and are frequently on immunosuppressive medications, conferring them to additional risk of CDI. Furthermore, the overlap in symptomatology between CDI and IBD flares complicates the diagnosis of CDI in IBD patients, and CDI management in IBD is not clearly delineated.[6]

Studies have demonstrated that the incidence of CDI in IBD is higher than in that of the general population. However, there is conflicting evidence in the literature when examining potential risk factors for CDI among IBD patients. While some studies have reported antibiotic use is an independent risk factor for CDI,[7–10] others have shown that there is no effect.[11–13] Similarly, individual studies have reported no effect of proton pump inhibitors [PPIs] on CDI,[7,11,14] while others have shown that there may be an increased risk of CDI among patients using PPIs.[8,15] Immunosuppression is a known risk factor for the development of *C. difficile*–associated disease.[16–18] However, the role of immunomodulator use in the development of CDI in IBD is controversial. Studies have shown that there is an increased risk of CDI in IBD patients taking immunosuppressive medications [i.e. thiopurines, methotrexate, infliximab, systemic corticosteroids],[9,19] whereas others have demonstrated that there is no effect or a protective effect of certain immunomodulators.[11,15,20,21]

There is also conflicting evidence on the risk of mortality and colectomy among IBD patients with CDI. While individual studies have found that IBD patients with CDI have a higher rate of colectomy[3,9,22,23] and a greater mortality[4,22,24,25] than non-CDI-IBD controls, certain other studies have demonstrated that there is no effect or an inverse relationship.[11,20,24,26–28] A recent meta-analyses showed that there is an increased risk of colectomy and mortality among IBD patients with CDI.[29] These findings were confirmed by two other meta-analyses.[30,31]

To our knowledge, there has been no meta-analysis published on the risk factors that contribute to CDI among IBD patients. The objectives of this meta-analysis were to assess the risk factors associated with CDI in IBD patients, as well as to confirm the previous findings of the risk of colectomy and mortality in IBD with CDI.

2. Methods

2.1. Data sources and search strategy

This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines [PRISMA].[32] We searched the Cumulative Index to Nursing and Allied Health Literature, Medline, Embase, BIOSIS, and Web of Science between January 1, 1980, and August 1, 2017. Conference proceedings were searched [World Congress of Gastroenterology, American College of Gastroenterology, Canadian Digestive Disease Week, Digestive Disease Week and United European Gastroenterology Week] between January 1, 1980, and August 1, 2017. We searched study references and review articles and contacted authors for additional data. Abstracts and brief reports were included. The search strategies for CDI risk factors and outcomes in IBD are outlined in Supplemental Table 1. Studies were independently selected by two reviewers [BB and AK]; disagreements were resolved by a third reviewer [TB].

2.2. Study selection

We included studies analyzing adult IBD populations [diagnosis of UC or CD as per conventional definitions]; and any of the following: [i] risk factors associated with CDI in IBD patients compared with non-CDI IBD controls, [ii] mortality rates in CDI patients compared with non-CDI controls, and [iii] colectomy rates in CDI patients compared with non-CDI controls. We excluded studies if: [i] they lacked CDI-negative IBD controls, [ii] they were not written in English, and [iii] they involved surgeries other than colectomies. We accepted cohort, case–control and cross-sectional studies.

2.3. Data extraction and study quality

We used a standardized data extraction form. Variables extracted included: [i] study characteristics—primary author, and study time period, location, and design, [ii] patient characteristics—age, gender, IBD subtype [UC or CD], [iii] risk factors—IBD location, PPI use, antibiotic use, IBD medications [steroids, immunomodulators, and biologic therapy], and [iv] outcomes—mortality and colectomy rates.

The methodological quality of the included studies was assessed using the Newcastle–Ottawa Scale [NOS].[33] Studies were scored across three categories: selection [four questions], comparability of study groups [two questions], and ascertainment of the outcome of interest [three questions], with a maximum of two points per questions in certain categories [Supplemental Tables 2 and 3]. Study quality was defined as low, moderate, or high, based on scores of 0–3, 4–6, or 7–10, respectively. Two reviewers [BB and AK] extracted data and assessed quality independently.

2.4. Risk factors and clinical outcomes assessed

The primary objective was to identify the risk factors and outcomes associated with CDI in IBD patients, either hospitalized or in ambulatory clinic settings, compared with non-CDI IBD controls. We investigated patient demographic data and disease-related risk factors to ascertain risk factors that could be included in the meta-analysis. We also assessed the risk of colectomy in IBD patients with CDI compared with non-CDI IBD controls, as well as risk of mortality in IBD patients with CDI compared with non-CDI IBD controls. Risk of colectomy and mortality were stratified by follow-up time. Short-term follow-up was defined as within the index hospitalization or within three months of diagnosis of CDI. Long-term follow-up was defined as having follow-up of 1 year or greater since the diagnosis of CDI.

Subgroup and sensitivity analyses were performed to identify potential sources of heterogeneity. Subgroups included: [i] UC patients only, [ii] country where study was performed [within North America vs outside], [iii] age subgroup [<40 years vs >40 years], and [iv] study period [<2005 or ≥2005]. We performed subgroup analysis of studies before and after 2005 because infliximab was approved for treatment of UC in the USA in 2005, which resulted in a significant change in the management of UC. Sensitivity analyses included: [i] hospitalized patients only and [ii] high-quality study [NOS > 6].

2.5. Statistical analyses

Statistical analysis was performed using STATA [version 12.1]. Reported odds ratios [ORs] or adjusted ORs, when available, were used in the analysis. Weighted summary estimates were calculated using a generalized inverse variance with random effects model.[34] Summary estimates are presented as ORs with 95% confidence intervals [CIs]. We used the I^2 statistic to estimate the proportion of total variation across studies due to heterogeneity rather than chance. Values of <30%, 30–59%, 60–75%, and >75% were suggestive of low, moderate, substantial, and considerable heterogeneity, respectively.[35] We explored sources of heterogeneity with a predetermined

subgroup analysis [as described above]. Qualitative estimation of publication bias was performed through visual inspection of funnel plots. Tests for funnel plot asymmetry were only used if there were more than 10 studies evaluating the same risk factor or outcome.[36]

3. Results

3.1. Search results

Our search identified 436 citations. Twenty-four studies met inclusion criteria [Figure 1]. All studies were performed retrospectively. Eleven of these studies were case–control studies and thirteen were retrospective cohort studies. Five studies were in abstract form. Fifteen studies were published in North America, six in Europe and three in Asia.

3.2. Patient characteristics

We extracted data from a total of 38 336 IBD patients with a diagnosis of CDI and 1 199 752 IBD controls without CDI. The majority of studies investigated hospitalized patients [n = 20], and four studies also included patients from ambulatory clinics. Eleven studies included both CD and UC patients, while eleven studies included only UC patients. The baseline characteristics of these patients are outlined in Table 1.

3.3. CDI diagnosis

Twelve studies diagnosed CDI by stool enzyme-linked immunosorbent assay or enzyme immunoassay [ELISA/EIA] and two studies used polymerase chain reaction [PCR].[37] The remaining studies [n = 10] used ICD9/ICD10 codes to identify CDI-positive patients. Short-term patient follow-up of patients, i.e. within index hospitalization or 3 months of CDI diagnosis, was assessed in five studies. Long-term follow-up, i.e. within at least 1 year of follow-up after CDI diagnosis was assessed in eleven studies, and four studies evaluated both long- and short-term follow-up.

3.4. Risk factors for CDI in IBD patients

The clinical parameters listed in Table 1 were analyzed to evaluate risk factors for developing CDI in IBD patients. The demographic data and risk factors that were included in the meta-analysis were: gender, colonic involvement, antibiotic use, proton-pump inhibitor use, immunomodulatory therapy, and biologic therapy. IBD patients who used antibiotics within 30 days of *C. difficile* testing [number of studies, n = 7], were more likely to develop CDIs than those who did not [OR: 1.85, 95% CI: 1.36, 2.52] [I^2 = 18.1%] [Figure 2]. Patients with colonic involvement were more likely to develop CDIs [OR: 2.76, 95% CI: 1.75, 4.35] [n = 4] with moderate heterogeneity in the overall analysis [I^2 = 31.9%] [Figure 3]. We did not find any significant association between the use of proton-pump inhibitors and CDI in IBD patients [OR: 0.98, 95% CI: 0.54, 1.78] [n = 7, I^2 = 70.0%] [Figure 4]. There was also no association between gender and CDI in IBD patients [OR: 0.98, 95% CI: 0.70, 1.37] [n = 10, I^2 = 96.0%] [Figure 5]. Among patients using immunosuppressive medication, there was a significant association between biologics medication use and CDI [OR: 1.65, 95% CI: 1.18, 2.30] [n = 6], with minimal heterogeneity [I^2 = 4.0%] [Figure 6]. Of note, the majority of studies [n = 4] included patients on TNF-α inhibitors [infliximab or adalimumab], while the remaining did not specify. However, there was no association between 5-ASA [OR: 1.05, 95% CI: 0.51, 2.14] [n = 5, I^2 = 69.4%], systemic steroids [OR: 0.96, 95% CI: 0.55, 1.69] [n = 8, I^2 = 72%], or immunomodulators use [OR: 1.25, 95% CI: 0.82, 1.93] [n = 7, I^2 = 39.2%] [Figure 6].

3.5. Outcomes of CDI

3.5.1. Short- and long-term risk of colectomy

Data from 17 individual time points from 15 studies reported the rates of colectomy during index hospitalization or within 3 months of CDI diagnosis. There was no statistically significant difference between the risk of colectomy in IBD patients with CDI compared with the risk in those without CDI [OR: 1.52, 95% CI: 0.84, 2.81] [Figure 7]. There was also considerable heterogeneity in the overall analysis [I^2 = 98.5]. Data from five studies reported the long-term rates of colectomy in IBD patients who were followed up for one or more years since the diagnosis of CDI. On the pooled analysis, the risk of colectomy was significantly higher for IBD patients with CDI compared with for those without CDI [OR: 2.22, 95% CI: 1.17, 4.18] [Figure 8]. However, there was substantial heterogeneity between the studies included in the analysis [I^2: 74.7%].

3.6. Short- and long-term mortality risk

Data from 12 time points from 10 studies reported short-term mortality rates, i.e. during index hospitalization or within 3 months of CDI diagnosis. There was a significant mortality risk for IBD patients with CDI compared with the risk for those without CDI [OR: 3.84, 95% CI: 2.62, 5.61] [Figure 9]. There was also considerable heterogeneity in the overall analysis [I^2 = 97.2]. Data points from three studies reported long-term rates of mortality in IBD patients who were followed up for one or more years since the diagnosis of CDI. On the pooled analysis, the mortality risk was significantly higher for IBD patients with CDI compared with the risk for those without CDI [OR: 3.65, 95% CI: 1.58, 8.44] [Figure 10]. However, there was substantial heterogeneity between the studies included in the analysis [I^2: 90.5%].

3.7. Subgroup and sensitivity analyses

Our conclusions were not affected by restricting the analysis to UC patients, studies performed in North America, study period, or high-quality studies [NOS > 6] [Table 2]. When patients were stratified by age [<40 vs 40 years or older], there was an increased risk of short-term colectomy among IBD patients with CDI who were younger than 40 years of age [OR: 1.71, 95% CI: 1.14, 2.55].

3.7.1. Study quality and publication bias

The quality of studies was assessed by a modified NOS [Supplemental Tables 2 and 3]. Abstracts were excluded from qualitative assessment.[8,22,23,26,38] The majority of the studies had a high-quality score [n = 10]. The median modified NOS score was 6, with scores ranging from 3 to 9. Ten studies used the International Classification of Diseases [ICD] code 9/10 for the definition of the study population with IBDs including UC and CD.[3,4,20,24,25,27,39–41] Only four studies reported an exclusion criteria of patients with a history of previous colectomy.[20,21,25,27,39] There was evidence of publication bias on visual examination of the funnel plots [Supplemental Figure 1].

4. Discussion

Our study shows that recent use of antibiotics or biologics, and colonic involvement are important risk factors for the development of CDI in patients with IBD. This is the first meta-analysis to investigate potential risk factors that could be implicated in CDIs among IBD patients. This is also the first study to combine both colectomy and mortality as end points in assessing the impact of CDI and IBD.

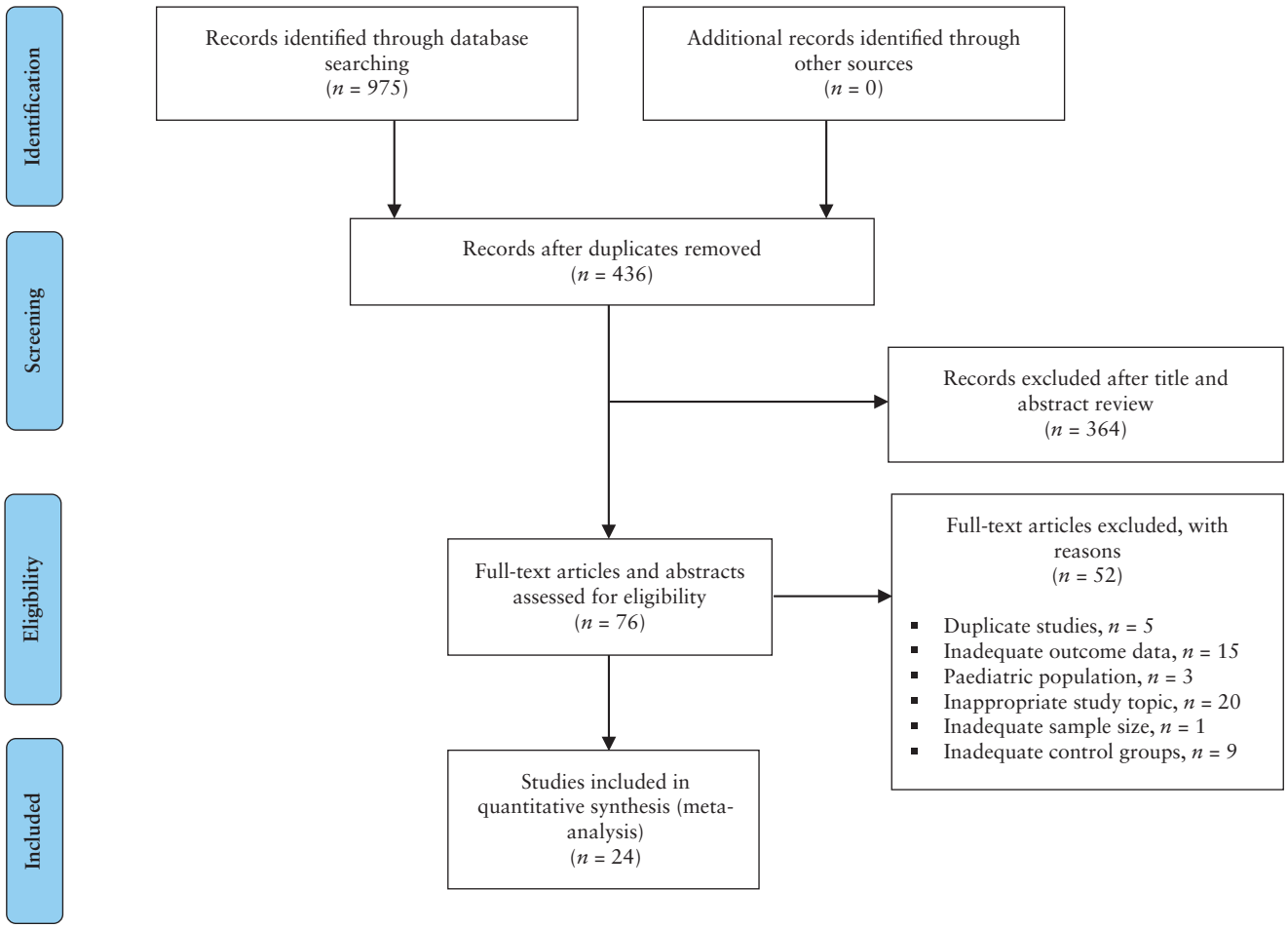

Figure 1. Flow chart of study selection.

Historically, antibiotic use remains the most widely recognized risk factor associated with the development of *C. difficile*–associated diarrhea in the general population.[42] *C. difficile* is implicated in 20–30% of patients with antibiotic-associated diarrhoea, in 50–70% of those with antibiotic-associated colitis, and in >90% of those with antibiotic-associated pseudomembranous colitis.[43,44] Antimicrobials may disrupt the normal gastrointestinal flora, causing reduced colonization resistance, enough to allow toxigenic strains of *C. difficile* to initiate disease. In our pooled analysis, antibiotic use nearly doubled the odds of acquiring CDI among IBD patients, which is consistent with the risk of acquiring *C. difficile* with antibiotic exposure in the general population.[45] Given that IBD patients frequently receive antibiotics as part of the treatment of their IBD exacerbations or complications from immunosuppressive therapy, they are a particularly high-risk subgroup for acquiring CDI. Therefore, routine use of empiric broad-spectrum antibiotics in the treatment of IBD flare-ups should be considered with caution.

Previous studies have identified immunosuppression in oncology and transplant patients to be a significant risk factor for the development of a CDI.[46] In our analysis, biologic therapy, the majority of which involved TNFα inhibitors, doubled the odds of a CDI among IBD patients. This is in keeping with findings in the literature that demonstrate that biologics, specifically infliximab, were associated with opportunistic bacterial infections, including CDI.[47,48] Among the studies included in the analysis, five studies did not find any association between biologic use and CDI, compared with one study, by Zhang *et al.*, that showed there was increased risk of CDI in patients on biologic therapy [OR: 2.19, 95% CI: 1.40, 3.40]. However, it should be noted that these five studies had smaller sample sizes and together were assigned 50% of the weight when calculating weighted effect size. Biologics like infliximab are effective treatments for IBD because, in various ways, these drugs inhibit activity of the immune system. Therefore, their association with opportunistic infections can be viewed as an extension of their normal, intended pharmacologic activity. Interestingly, in our analysis, the use of steroids and immunomodulators did not correlate with increased risk for CDI. These findings suggest that specific regimens of immunosuppression might carry different risk for the acquisition of a CDI. Our arsenal of biologic therapy is expanding, with newer and more selective biologics, such as the novel humanized monoclonal antibody, vedolizumab, which is hypothesized to be gut-selective, acting on key components of the gut mucosal immunity and inflammation. Given its gut-selective mechanism, the possibility exists that there may be an increase in enteric infections such CDI with vedolizumab. In fact, data from phase 2 and phase 3 trials report that all CDIs have occurred in the vedolizumab group rather than in the placebo group.[49] In our meta-analysis, we could not evaluate the association between vedolizumab and CDI because the majority of studies evaluated TNF-α inhibitors [infliximab or adalimumab].

Table 1. Study characteristics.

Author	Study period	Location	Study design	IBD	CDI + IBD	%UC	Outcomes	Risk factors
Ananthakrishnan *et al.*[3]	2003	USA	Case–control	77366	2 804	NA	Short-term colectomy and mortality	
Ananthakrishnan *et al.*[41]	NA	USA	Case–Control	3153	35	45		Steroid use
Ananthakrishnan *et al.*[59]	1998	USA	Case–control	143143	2 004	38.2%	Short-term colectomy and mortality	
Ananthakrishnan *et al.*[59]	2004	USA	Case–control	208739	4 801	36.4%	Short-term colectomy	
Ananthakrishnan *et al.*[59]	2007	USA	Case–control	238207	69 081	36.3%	Short-term colectomy	
Gu *et al.*[11]	2013–2015	China	Cohort	247	13	32%	Short-term colectomy and mortality	Abx; CI; PPI
Issa *et al.*[19]	2000–2005	USA	Cohort	953	46	NA		CI; gender; biologics; immunomodulators
Jen *et al.*[25]	2003–2008	UK	Cohort	239076	2 185	NA	Short-term colectomy Short- and long-term mortality	Gender
Jodorkovsky *et al.*[39]	2004–2005	USA	Cohort	52	47	100%	Short- and long-term colectomy	
Joshi *et al.*[28]	2007–2013	UK	Case–control	47	47	71%	Short-term colectomy and mortality Long-term colectomy	Abx
Kaneko *et al.*[14]	2006–2009	Japan	Cohort	82	55	100%	Short-term colectomy	PPI; systemic steroids; immunomodulators
Kariv *et al.*[7]	2000–2006	USA	Case–control	39	39	100%	Short-term colectomy	Abx; PPI
Khanna *et al.*[38]	2005–2009	USA	Cohort	4301	138	NA	Short-term mortality	
Morrison *et al.*[22]	2007–2011	USA	Cohort	288808	19 090	100%	Short-term colectomy and mortality	
Murthy *et al.*[27]	2002–2008	Canada	Cohort	1835	181	100%	Short-term colectomy and mortality Long-term colectomy and mortality	Gender
Navaneethan *et al.*[20]	2002–2007	USA	Cohort	101	45	100%	Short- and long-term colectomy	Gender;5-ASA; biologics; systemic steroids; immunomodulators
Negron *et al.*[40]	2003–2010	Canada	Cohort	1873	81	100%	Long-term colectomyand mortality	
Nguyen *et al.*[4]	1998–2004	USA	Case–control	42017	1 628	100%	Short-term colectomy and mortality	CI
Ramos-Martinez *et al.*[15]	2005–2014	Spain	Case–control	15	15	50%	Short-term mortality	Gender; Abx; CI; 5-ASA; biologics; systemic steroids;
Regnault *et al.*[21]	2008–2010	France	Cohort	443	34	58%		Gender; Abx; CI biologics; systemic steroids; immunomodulators
Reinglas *et al.*[23]	2011–2013	Canada	Cohort	180	20	65%	Short-term colectomy	
Saffouri *et al.*[24]	2005–2009	USA	Cohort	357000	16 633	100%	Short-term colectomy and mortality	Gender
Smith *et al.*[26]	2007–2009	UK	Case–control	74	12	100%	Short-term colectomy	
Stoica *et al.*[8]	2012–2014	Romania	Case–control	52	26	NA		PPI
Wang *et al.*	2004–2011	Canada	Case–control	28	9	100%		Gender
Zhang *et al.*[9]	NA	China	Case–control	547	99	40%	Short-term colectomy	Gender; Abx; PPI; 5-ASA; biologics; systemic steroids; immunomodulators

Abx: antibiotic use, CI: colonic involvement, PPI: proton-pump inhibitor use

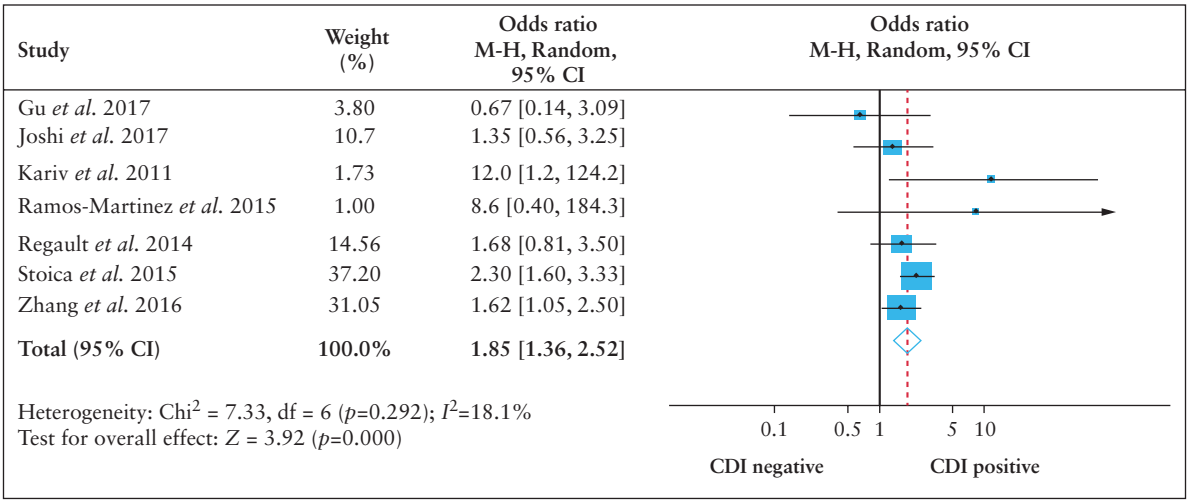

Figure 2. Antibiotic use in IBD patients and *Clostridium difficile* infection.

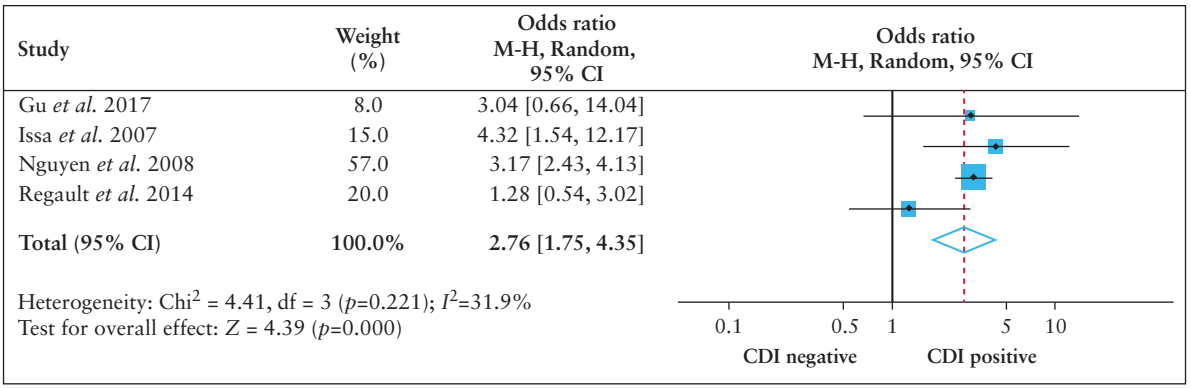

Figure 3. Colonic involvement in IBD patients and *Clostridium difficile* infection.

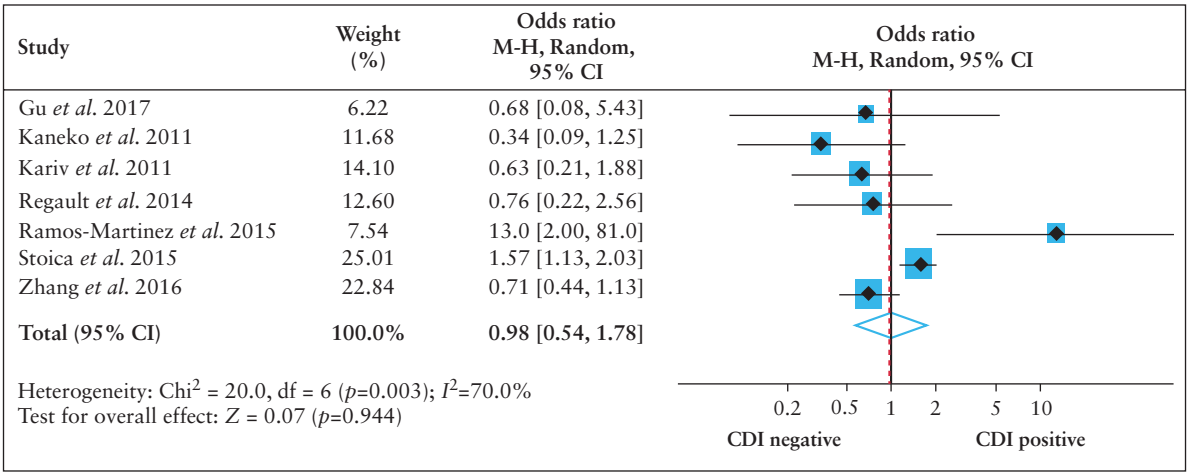

Figure 4. Proton pump inhibitor use in IBD patients and *Clostridium difficile* infection.

Furthermore, our study also demonstrated that, compared with isolated small bowel disease, any colonic involvement with IBD is a significant risk factor for CDI. It is unclear whether this increased risk is attributable to the chronic inflammation of the colonic mucosa, an altered gut microbiome, or some other mechanism. One possible explanation is that the larger the area of colon affected by IBD, the greater the impairment in mucosal barrier function and immunity to colonic pathogens. Furthermore, patients with more

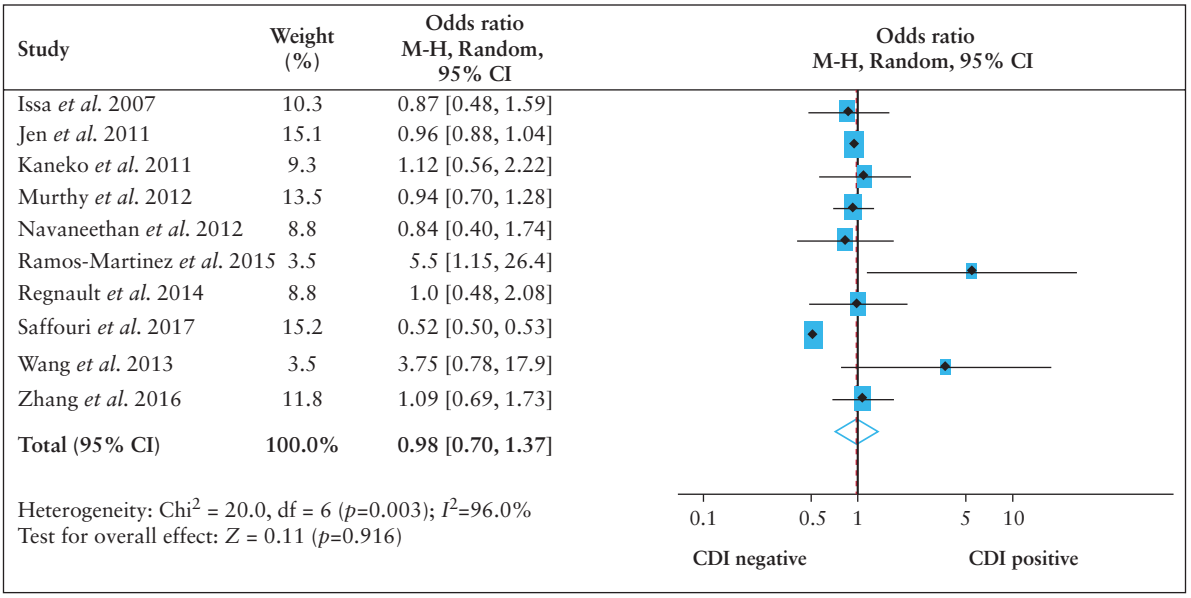

Figure 5. Male gender and C*lostridium difficile* infection in IBD patients.

extensive disease are at increased risk of progressing to severe disease, of requiring systemic corticosteroids and immunomodulators, and possibly of prolonged hospital admissions, which in turn puts them at risk of acquiring a CDI.[2]

Finally, our pooled analysis showed no association between proton-pump inhibitor use and CDI in IBD patients, which is in contrast to the mounting evidence implicating PPIs in the exacerbation or prolongation of CDI among the general population.[50–55] It has been postulated that PPIs increase the proliferation of spores and permit the spores to survive intraluminally by reducing the acidic environment of the stomach.[56] However, we hypothesize that, given IBD patients already have altered intestinal flora, perhaps gastric suppression does not alter the susceptibility to CDI.

This meta-analysis subsequently analyzed clinical outcomes, colectomy, and mortality, stratified by short- and long-term follow-up in IBD patients with CDI. Our report shows that CDI was not associated with a short-term risk of colectomy, which is in contrast to the findings for the general population, in which CDI has been associated with increased risk of colectomy.[57,58] In contrast to short-term follow-up, our findings suggest that CDI more than doubled the odds of having a colectomy in the long term. These results are consistent with a previous meta-analysis that also demonstrated that CDI is a significant risk factor for colectomy in the long term, but not the short term.[29] Our results are also compatible with the findings of Chen *et al*., who demonstrated that CDI is a significant risk factor for colectomy in IBD patients.[30] However, their meta-analysis included only six studies and did not stratify outcomes by short- and long-term risk. It should be noted that there was substantial heterogeneity between studies, and possible confounding within individual studies, that precludes identifying any causal relationship between *C. difficile* and long-term colectomy risks.

Our report also demonstrated that IBD patients with a CDI have a nearly 4-fold increase in the risk of both in-hospital and long-term mortality. These findings suggest that an episode of CDI is a potential risk factor for mortality, possibly as a result of recurrent CDIs or by altering long-term IBD behaviour. Our findings are consistent with two other meta-analyses that reached similar conclusions.[29,31] These conclusions, consistent amongst the meta-analyses, further justify the need for rapid diagnosis and aggressive treatment of CDI in IBD patients.

This meta-analysis also demonstrated that the results were stable within our sensitivity analysis and most of the subgroups. When controlled for studies within North America, there was no change in the results. Similarly, when restricting the analysis to UC patients only, a study time period before 2005, and studies of high quality, the results remained consistent. Notably, sensitivity analysis showed that there was an increase in short-term colectomy rates when restricting analysis to patients <40 years of age. Further studies are needed to confirm this finding and to investigate whether certain subgroups of IBD patients are at increased risk of colectomy.

There are notable limitations in this meta-analysis. Although we performed an exhaustive and systematic search of the literature, publication bias could have resulted in the selective publication of those studies showing a positive association between CDI and clinical outcomes or risk factors. It is plausible that the actual risk between CDI and colectomy/mortality or the risk factors associated with CDI are less than what is demonstrated in this meta-analysis. Second, the studies included in the meta-analysis were observational studies, blurring the sequence of exposures and outcomes. Thus, results have to be interpreted with caution. The studies also contained substantial heterogeneity, which could be explained by differences in patient populations, hospital settings, trends in CDI management, antibiotic therapy, and use of immunosuppressive medications. Next, certain study populations were recruited from subspecialty IBD clinics, which might have resulted in referral bias. Furthermore, most studies did not compare clinical severity or endoscopic severity, which may have introduced a detection bias if a disproportionate number of patients with severe IBD underwent testing for CDI. Notably, several studies did not control for patients admitted for elective colectomies, thus falsely increasing the rates of colectomy in non-CDI patients.

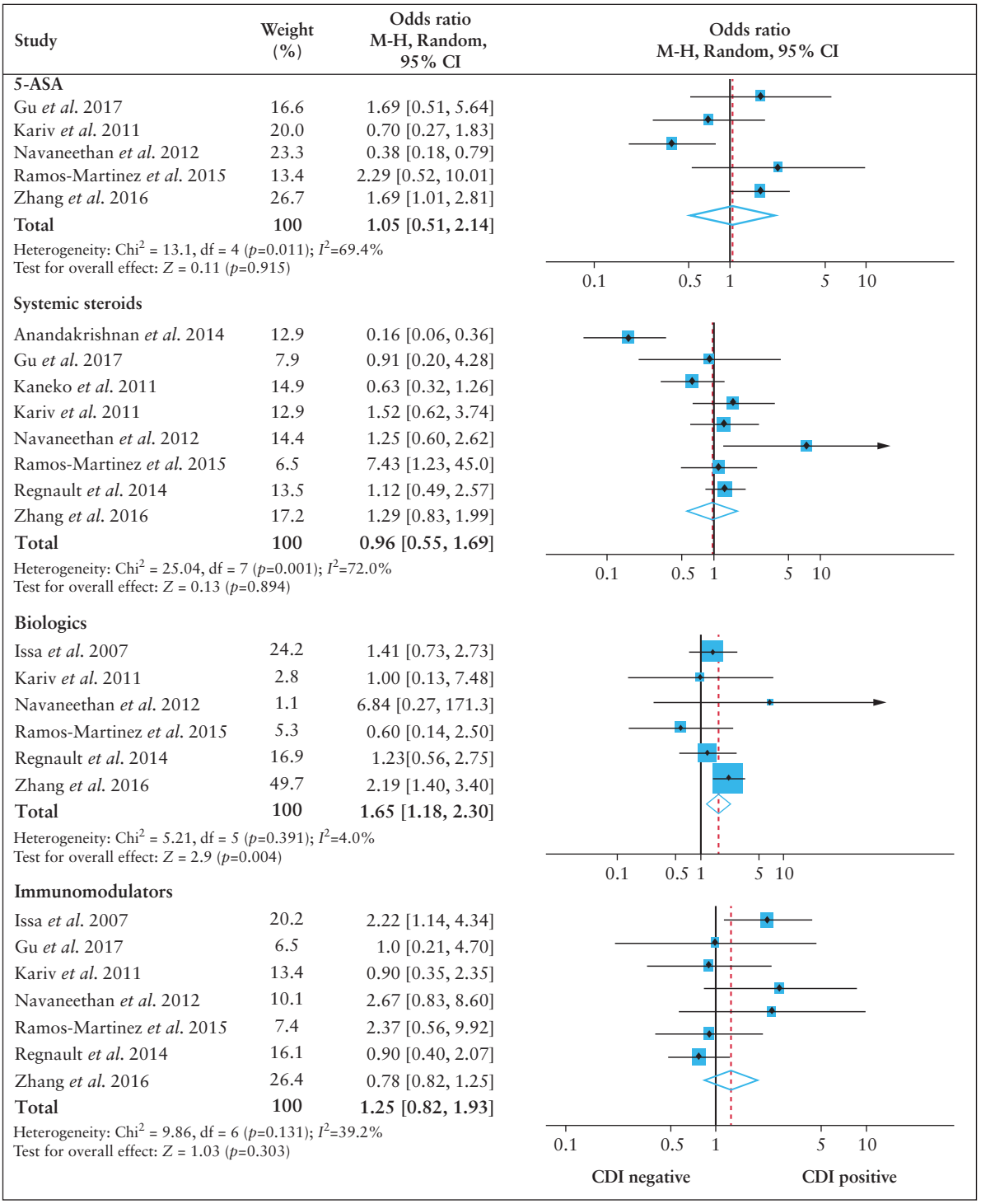

Figure 6. IBD medications [5-ASA, systemic steroids, biologics, immunomodulators] and C*lostridium difficile* infection in IBD patients.

Another limitation is in using administrative databases, which rely upon diagnostic codes for case ascertainment, rather than direct laboratory confirmation.

In summary, this meta-analysis suggests that colonic involvement, biologic therapy, and prior antibiotic use are significant risk factors for developing CDI among IBD patients. Furthermore, while CDI does not appear to increase the short-term risk of colectomy in IBD patients, it is a significant risk factor for mortality and long-term colectomy in these patients. Future prospective studies are necessary to validate these findings, to determine which risk factors play causative roles in acquiring CDI in IBD patients, to identify preventive strategies, and to help guide optimal management of CDI in IBD.

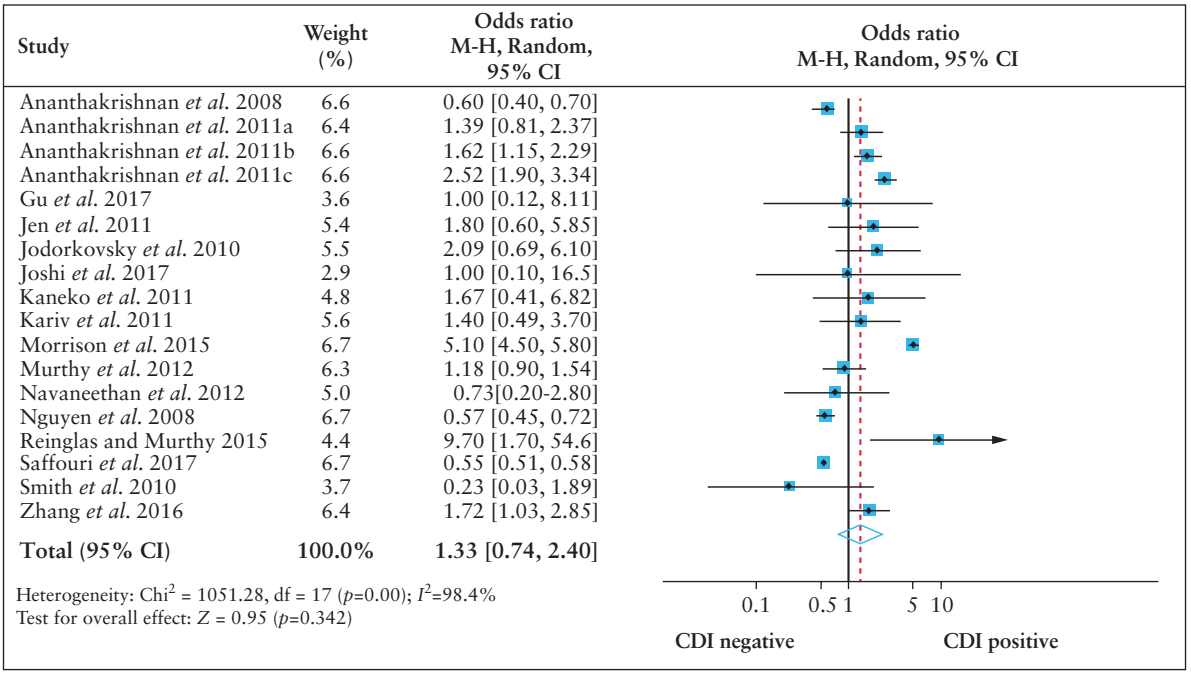

Figure 7. Short-term risk of colectomy in IBD patients and *Clostridium difficile* infection.

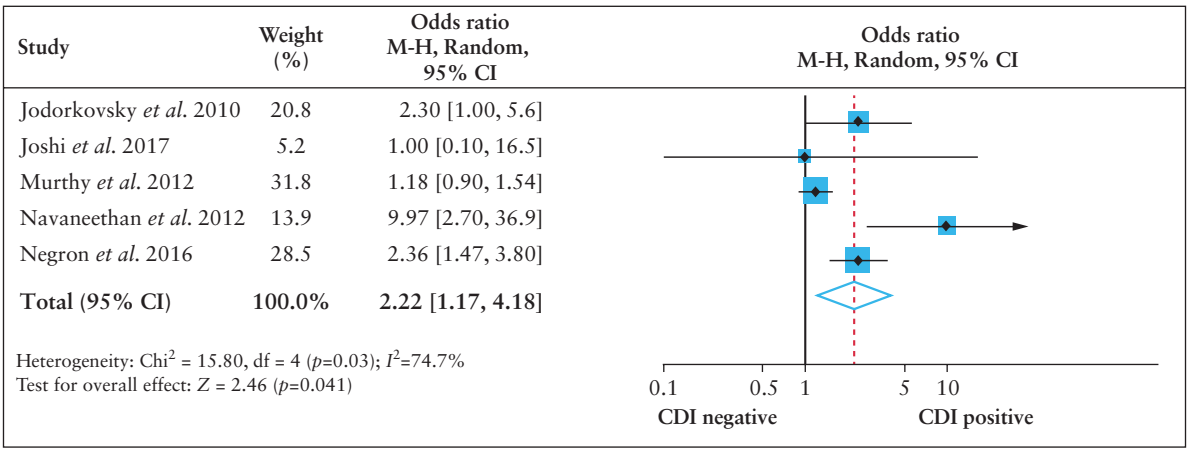

Figure 8. Long-term risk of colectomy in IBD patients and *Clostridium difficile* infection.

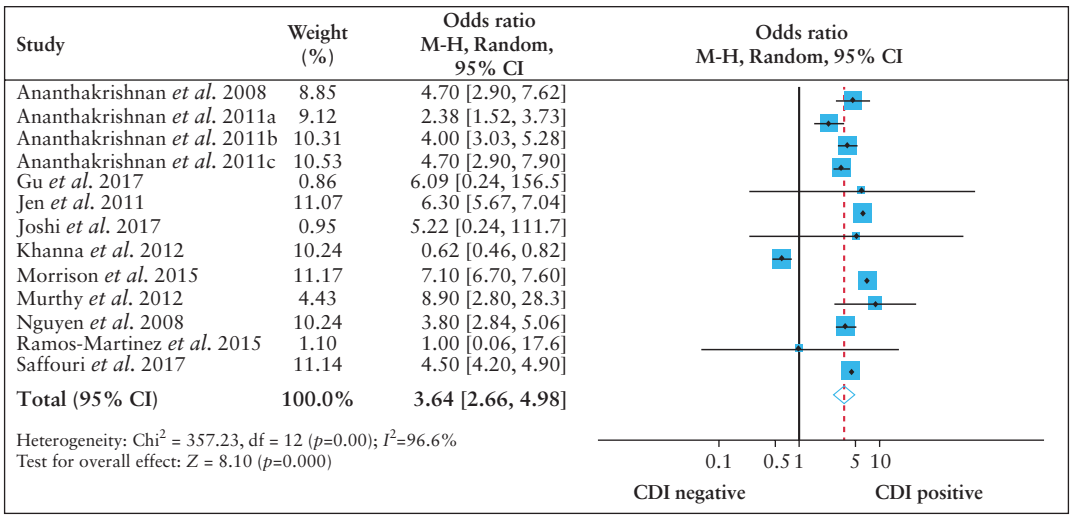

Figure 9. Risk of in-hospital mortality in IBD patients and *Clostridium difficile* infection.

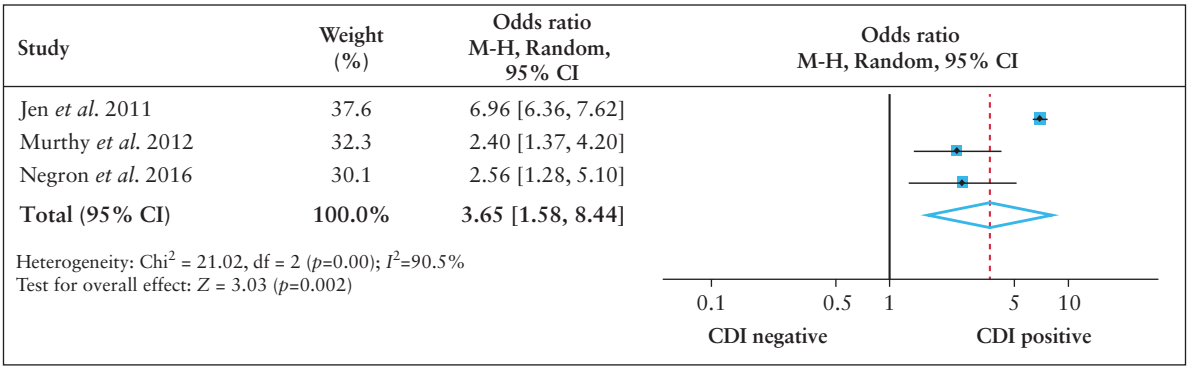

Figure 10. Risk of long-term mortality in IBD patients and *Clostridium difficile* infection.

Table 2. Subgroup and sensitivity analysis for short-term risk of colectomy associated with CDI in IBD patients.

Subgroups	Values	OR [95% CI]	I^2
UC patients only	9	1.07 [0.42, 2.73]	99.2%
North American patients only	12	1.40 [0.70, 2.82]	98.9%
Age subgroup			
<40 years	4	1.71 [1.14, 2.55]	0%
>40 years	8	1.16 [0.46, 2.96]	99.3%
High-quality study [NOS > 6]	9	1.31 [0.84, 2.04]	83.9%
Study period			
<2005	7	0.963 [0.64, 1.45]	83.1%
≥2005	10	1.62 [0.60, 4.37]	99.1%
Subgroup and sensitivity analysis for long-term risk of colectomy associated with CDI in IBD patients			
Subgroups	Values	OR [95% CI]	I^2
UC patients only	4	2.34 [1.19, 4.60]	80.9%
North American patients only	4	2.34 [1.19, 4.60]	80.9%
High-quality study [NOS > 6]	4	2.34 [1.20, 4.60]	80.9%
Subgroup and sensitivity analysis for short-term risk of mortality associated with CDI in IBD patients			
Subgroups	Values	OR [95% CI]	I^2
UC patients only	4	5.25 [3.66, 7.43]	96.7%
North American patients only	9	3.44 [2.34, 5.04]	97.7%
High-quality study [NOS > 6]	7	4.15 [2.93, 5.90]	85.7%
Study period			
<2005	4	3.67 [2.92, 4.62]	39.8%
≥2005	7	2.92 [1.68, 5.08]	98.2%
Subgroup and sensitivity analysis for long-term risk of mortality associated with CDI in IBD patients			
Subgroups	Values	OR [95% CI]	I^2
UC patients only	2	2.46 [1.60, 3.80]	0.00%
North American patients only	2	2.46 [1.60, 3.80]	0.00%
High-quality study [NOS > 6]	3	3.65 [1.58, 8.44]	90.5%

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Conflict of Interest

TB has received honoraria and acted as a consultant for Janssen, AbbVie, Takeda, and Pfizer and acted as speaker for Janssen, Abbvie, Takeda, Ferring, Actavis, PendoPharm, and Shire. TB has served as a speaker, a consultant, and an advisory board member for Janssen, AbbVie, Takeda, Pfizer, Ferring, Pendopharm, and Shire, and has received research funding from AbbVie and Janssen. PLL has been a speaker and/or advisory board member for AbbVie, EGIS, Falk Pharma, GmbH, Ferring, Genetech, Jansen, Kyowa, Hakko Kirin Pharma, Mitsubishi Tanabe Pharma Corporation, MSD, Otsuka Pharma, Oharmacosmos, Pfizer, Roche, Shire, and Takeda, and has received unrestricted grants from AbbVie, MSD, and Pfizer. WA has served as a speaker and/or advisory board member for AbbVie, Janssen, Takeda, Merck, Pfizer, Ferring, and Shire, and received research grants from AbbVie, Theradiag, and Prometheus. AB has received honoraria for participation in advisory boards from Allergan. AB has served as a consultant or advisory board member for AbbVie, Janssen, Shire, Warner Chilcott, and Takeda, and as a speaker for AbbVie, Janssen, Shire, Warner Chilcott, and Aptalis. BB, RB, JD'a, and A.Al-K have no conflicts of interest to report.

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Author Contributions

BB: data collection, statistical analysis, methodological quality assessment, and manuscript writing; TB: study design, data analysis, and manuscript writing and editing; AA: manuscript writing and editing, and methodological quality assessment; RB: data collection, and manuscript writing; JD: data collection and manuscript writing; WA: manuscript writing and editing; AB: data analysis, and manuscript writing and editing; PLL: study design, statistical analysis, and manuscript writing and editing.

Supplementary Data

Supplementary data are available at *ECCO-JCC* online.

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