Influence of Inflammatory Bowel Disease on Patients Undergoing Primary Total Joint Arthroplasty

A Systematic Review and Meta-analysis of Cohort Studies

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Background: Inflammatory bowel disease (IBD) is recognized as a global disease. Although IBD is commonly diagnosed in the young male population, it also occurs in patients aged >60 years. With the advent of an aging society, it is expected that an increasing number of patients with IBD will undergo total joint arthroplasty (TJA).

Purpose: To assess the impact of IBD on the risk of complications and revision as well as the length of stay (LOS) and treatment costs after TJA.

Study Design: Systematic review; Level of evidence, 4.

Methods: Utilizing PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines, articles were searched in the PubMed/MEDLINE, Embase, and Cochrane Library databases from the date of inception to August 31, 2022, using the following search terms: (1) ''Inflammatory Bowel Diseases''[MeSH] and (2) ''Arthroplasty, Replacement''[MeSH]. The study quality was scored according to the Newcastle-Ottawa Scale. A fixed-effects or random-effects model was used to calculate odds ratios or mean differences with 95% confidence intervals.

Results: Of 232 studies initially retrieved, 8 retrospective cohort studies consisting of 33,758 patients with IBD and 386,238 patients without IBD were included. Patients with IBD had a higher incidence of complications ($P < .05$), readmission and revision ($P < .05$), experienced a longer LOS ($P < .01$), and paid higher treatment costs after TJA compared with patients without IBD .

Conclusion: The results of our review demonstrated that IBD increased the risk of postoperative complications, prolonged the LOS, and increased treatment costs.

Keywords: inflammatory bowel disease; total joint arthroplasty; complication; revision; length of stay; hospitalization costs

Inflammatory bowel disease (IBD) is a chronic idiopathic disorder. Ulcerative colitis (UC) and Crohn's disease (CD) are the 2 most common pathological subtypes. It is generally considered to be influenced by multiple factors such as genetic susceptibility, environmental factors, and abnormal immune responses to microorganisms.[11] IBD is commonly diagnosed in the young male population, but it also occurs in patients aged >60 years.[9,27] The incidence of IBD has been showing a gradual upward trend and became a global disease in the 21st century.[24] The clinical manifestations of IBD are complex, accompanied by a protracted course, repeated attacks, and a variety of complications, which result in physiological and economic burdens on patients. Furthermore, IBD affects not only the gastrointestinal tract but also other organs.[20] Inflammatory articular disease is the most common extraintestinal manifestation, which affects approximately 5% to 14% of patients with UC and 10% to 20% of patients with CD.[7]

Total joint arthroplasty (TJA), as a final treatment option for end-stage osteoarthrosis, is usually applied to patients who have failed nonoperative treatment. With the advent of an aging society, it is expected that increasing numbers of patients with IBD will undergo TJA. Over the past decade, several studies with short-term follow-up data have been published on the effects of IBD

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in patients treated with TJA.[5,8,15-17,19,22,29] Some studies have suggested that patients with IBD have a higher risk of complications and revision after TJA,[5,16,17,19,22,29] while other studies have not found a significant increase in the incidence of postoperative complications.[8,15]

The aim of this systematic review and meta-analysis was to assess the impact of IBD on the risk of complications and revision as well as length of stay (LOS) and treatment costs after TJA. Our hypothesis was that IBD would have a negative effect on TJA in terms of both postoperative complications and treatment costs.

METHODS

Search Strategy

We performed this systematic review and meta-analysis according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines and registered the study with the International Prospective Register of Systematic Reviews (No. CRD42022352996). The electronic PubMed/MEDLINE, Embase, and Cochrane Library databases were searched from the date of inception to August 31, 2022, using the following search terms: (1) "Inflammatory Bowel Diseases"[MeSH] and (2) "Arthroplasty, Replacement"[MeSH]. A manual search of references from relevant articles was also performed. There were 2 independent reviewers (S.Z. and Z.W.) who separately conducted the search process by title and abstract. If the title and abstract of each study contained insufficient information to identify its appropriateness for inclusion, the full article was reviewed. Any inconsistency between the 2 reviewers was resolved by a discussion.

Inclusion criteria for the meta-analysis were as follows: (1) cohort or case-control study design; (2) evaluated the impact of IBD on complications and revision, LOS, and treatment costs after TJA; (3) provided sufficient data; and (4) articles in English. Exclusion criteria were as follows: (1) non–English-language articles, (2) animal experiments, (3) narrative review articles, (4) case reports, (5) studies without a non-IBD control group, (6) studies with incomplete data, and (7) study objective or intervention measures that failed to meet the inclusion criteria.

Data Extraction

Another 2 independent reviewers (S.Y. and Z.D.) objectively analyzed the included studies and extracted relevant data into a form made in advance by Excel software (Version 2019; Microsoft). The following data were extracted: (1) name of first author, (2) year of publication, (3) country of publication and data sources, (4) study design, (5) number of patients in each group, (6) quality scores, (7) duration of follow-up, and (8) all results.

Quality Assessment

There were 2 reviewers (X. Zhang and X. Zhou) who independently assessed the methodological quality of each study using the Newcastle-Ottawa Scale, as recommended by the Cochrane Non-Randomized Studies Methods Group. The scale contains 8 items, divided into 3 dimensions: selection, comparability, and outcome measurement. Disagreements on scores were resolved through a discussion with a third senior reviewer (B.L.).

Statistical Analysis

All statistical analyses and related graphics were performed with Review Manager (Version 5.4 for Windows; Cochrane). Dichotomous variables were assessed with odds ratios (ORs) and their related 95% confidence intervals, and continuous variables were evaluated using mean differences (MDs) or standardized MDs. The heterogeneity of the included studies was calculated with the I^2 and Q statistics. When I^2 was $\geq$50%, we used a random-effects model instead of a fixed-effects model. When there was high heterogeneity, sensitivity analysis was conducted. This means that 1 study was removed at each turn, and the data from the remaining studies were summarized to explore potential reasons for high heterogeneity. The overall effects of each study are shown by forest plots, and publication bias is displayed by funnel plots. A P value of $<.05$ was considered statistically significant.

RESULTS

Results of Literature Search

A total of 232 studies were retrieved after searching the databases: PubMed (n = 28)/MEDLINE (n = 22), Cochrane Library (n = 0), and Embase (n = 182). Of these studies, 8 retrospective cohort studies[5,8,15-17,19,22,29] were included, consisting of 33,758 patients with IBD and 386,238 patients without IBD. The flowchart of literature retrieval is shown in Figure 1.

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TABLE 1
Characteristics of Included Studies[a]

Lead Author (Year)	Country	Source of Data	Newcastle-Ottawa Quality Score	Minimum Follow-up
Kapadia[17] (2014)	USA	Single high-volume institution	7	49 mo
Ehrenpreis[8] (2017)	USA	National Inpatient Sample database	7	NR
Gregory[15] (2019)	USA	Truven Health Analytics MarketScan Commercial Claims and Encounters Database	7	NR
Voyvodic[29] (2021)	USA	PearlDiver	9	90 d
Hadid[16] (2023)	USA	PearlDiver	9	90 d
Moran[22] (2021)	Sweden	Swedish Hip Arthroplasty Register and Swedish National Patient Register	8	4.4 y
Kim[19] (2022)	USA	Statewide Planning and Research Cooperative System	7	NR
Chisari[5] (2022)	USA	Prospectively collected arthroplasty database at Thomas Jefferson University	8	2 y

[a]NR, not reported.

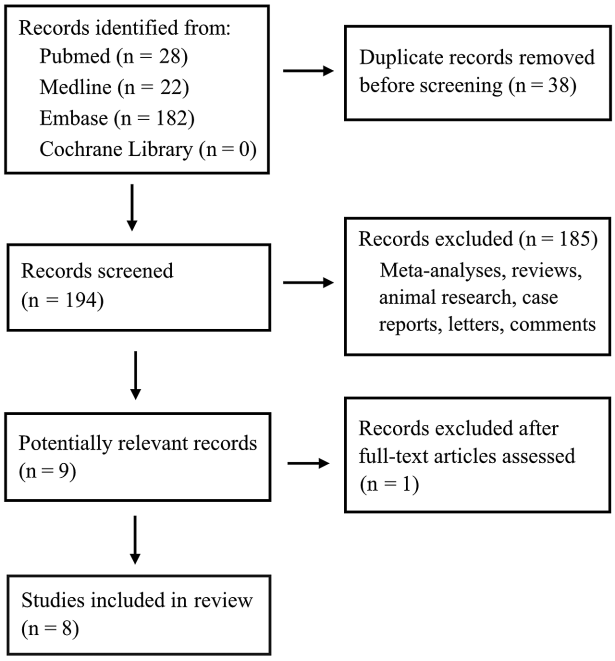

Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowchart of the assessment and selection of studies for the review and meta-analysis.

Characteristics of Included Studies

Of the 8 included retrospective cohort studies, 7 articles[5,8,15-17,19,29] were published in the United States, and 1 study[22] was published in Sweden. In addition, 6 studies[8,15,16,19,22,29] involved research data extracted from large medical databases, and 2 studies[5,17] were from single-center electronic medical record systems. The years of publication ranged from 2014 to 2023, and the duration of follow-up ranged from 90 days to 4.4 years. Detailed study characteristics and the quality scores are summarized in Table 1.

There were 7 studies[5,15-17,19,22,29] that recorded the number of revision procedures and postoperative complications. Complications were divided into medical and surgical complications. Additionally, 5 studies[5,8,15,16,29] recorded the mean LOS and treatment costs (Table 2).

Postoperative Surgical Complications

Surgical complications included periprosthetic joint infection (PJI), surgical site infection (SSI), and aseptic loosening. Forest plots comparing the studies that included these complications are presented in Figure 2.

Periprosthetic Joint Infection. A total of 4 studies[5,15,17,22] reported PJI events after total hip arthroplasty (THA) or total knee arthroplasty (TKA). Based on the results of heterogeneity testing (I^2 = 53%), we chose a random-effects model (OR, 1.56 [95% CI, 0.98-2.49]; P = .06). We discovered that the study by Chisari et al[5] had a significant impact on heterogeneity. After removing this study, the results showed no heterogeneity in the remaining 3 studies (OR, 1.30 [95% CI, 1.05-1.60]; I^2 = 0%; P = .02). However, this study was still retained because of its high quality, low risk of bias, and control for other confounding factors.

Surgical Site Infection. SSI events were observed in 4 studies,[15-17,29] and the results showed statistically significant differences between the IBD and non-IBD groups. The incidence of an SSI was 1.50 times higher in the IBD group than in the non-IBD group (OR, 1.50 [95% CI, 1.33-1.68]; I^2 = 31%; $P < .01$) (Figure 2B). For this meta-analysis, we chose a fixed-effects model because heterogeneity analysis indicated insignificant heterogeneity ($I^2 < 50\%$).

Aseptic Loosening. There were 4 studies,[5,15,17,22] with 166,778 patients, that were included in this subgroup analysis. A random-effects model was employed in the meta-analysis because the heterogeneity was significant (I^2 = 78%). We found that there were no statistical differences between the 2 groups in terms of aseptic loosening events (OR, 1.33 [95% CI, 0.74-2.40]; P = .35). A sensitivity analysis was also conducted, which found that the

TABLE 2
Patients and Outcomes of Included Studies[a]

Lead Author (Year)	Patients, n				Outcomes
	Crohn's Disease	Ulcerative Colitis	Other Type of Colitis	Control	
Kapadia[17] (2014)	11	5	7	69	(1) Implant survivorship, (2) clinical outcomes as measured by Harris Hip Score, (3) complication rate (wound drainage, superficial or deep infection, DVT, pulmonary embolism, *Clostridioides difficile* infection, and acute pancreatitis), (4) nutritional status as measured by preoperative albumin and total protein levels, (5) corticosteroid use, and (6) radiographic results
Ehrenpreis[8] (2017)	2211	1803	NR	8496	LOS, costs, and mortality rate
Gregory[15] (2019)	631	727	97	14,550	Primary outcome was serious infection (composite of joint infection, SSI, pneumonia, and sepsis) within 90 d of surgery. Secondary outcomes included *C difficile* infection, UTI, VTE, hemorrhage/hematoma, mechanical complications, index LOS, total charge for index admission, and readmission.
Voyvodic[29] (2021)	9229	NR	NR	46,132	90-d medical complications, in-hospital LOS, and costs of care
Hadid[16] (2023)	16,037	NR	NR	80,176	In-hospital LOS, medical complications, and episode-of-care costs
Moran[22] (2021)	2604	NR	NR	147,469	Risk of revision surgery
Kim[19] (2022)	244	NR	NR	88,890	90-d and overall medical complications, surgical complications, and readmission
Chisari[5] (2022)	34	90	28	456	PJI at 2 y postoperatively, aseptic revision at 2 y postoperatively, discharge to rehabilitation facility, complications up to 30 d postoperatively, and readmission up to 90 d postoperatively

[a]DVT, deep vein thrombosis; LOS, length of stay; NR, not reported; PJI, periprosthetic joint infection; SSI, surgical site infection; UTI, urinary tract infection; VTE, venous thromboembolism.

heterogeneity was large, and the exclusion of any study did not reduce heterogeneity or alter the outcomes.

Postoperative Medical Complications

Medical complications included deep vein thrombosis (DVT), urinary tract infection (UTI), and pneumonia. Figure 3 shows the forest plots for studies that included these complications.

Deep Vein Thrombosis. Overall, 3 studies[15,16,29] described the incidence of DVT. A random-effects model was used because obvious heterogeneity was found (OR, 1.53 [95% CI, 1.25-1.89]; I^2 = 74%; $P < .01$). The sensitivity analysis showed that except for the study by Gregory et al,[15] there was no heterogeneity, and the result was statistically significant (OR, 1.76 [95% CI, 1.59-1.95]; I^2 = 0%; $P < .01$). However, given Gregory et al's[15] work with a large sample size and long follow-up time, this study was still retained.

Urinary Tract Infection. The incidence of UTI events was reported in 4 studies,[15,16,19,29] including a total of 255,227 patients. Because of high heterogeneity ($I^2 >$ 50%), we used a random-effects model. The meta-analysis suggested that the incidence of a UTI was 2.04 times higher in the IBD group than in the control group (OR, 2.04 [95% CI, 1.64-2.54]; $P < .01$). The sensitivity analysis showed that after excluding Gregory et al's[15] study, the heterogeneity was greatly reduced (OR, 2.51 [95% CI, 2.39-2.63]; I^2 = 0%; $P < .01$).

Pneumonia. There were 4 studies[15,16,19,29] recording pneumonia that were included in this subgroup analysis using a random-effects model ($I^2 > 50\%$). The result indicated that IBD increased the risk of pneumonia after TJA (OR, 1.96 [95% CI, 1.30-2.93]). We conducted a sensitivity analysis and concluded that the heterogeneity was caused by different aspects, and deleting a certain study did not reduce the heterogeneity.

Readmission and Revision

Forest plots for the incidence of readmission and revision are presented in Figure 4.

Readmission. A total of 3 studies[5,15,19] compared readmission rates. The results revealed a slightly increased risk of readmission in patients with IBD relative to those without IBD (OR, 1.42 [95% CI, 1.22-1.65]; I^2 = 0%; $P <$ .01). A fixed-effects model was used because no evidence of heterogeneity was found.

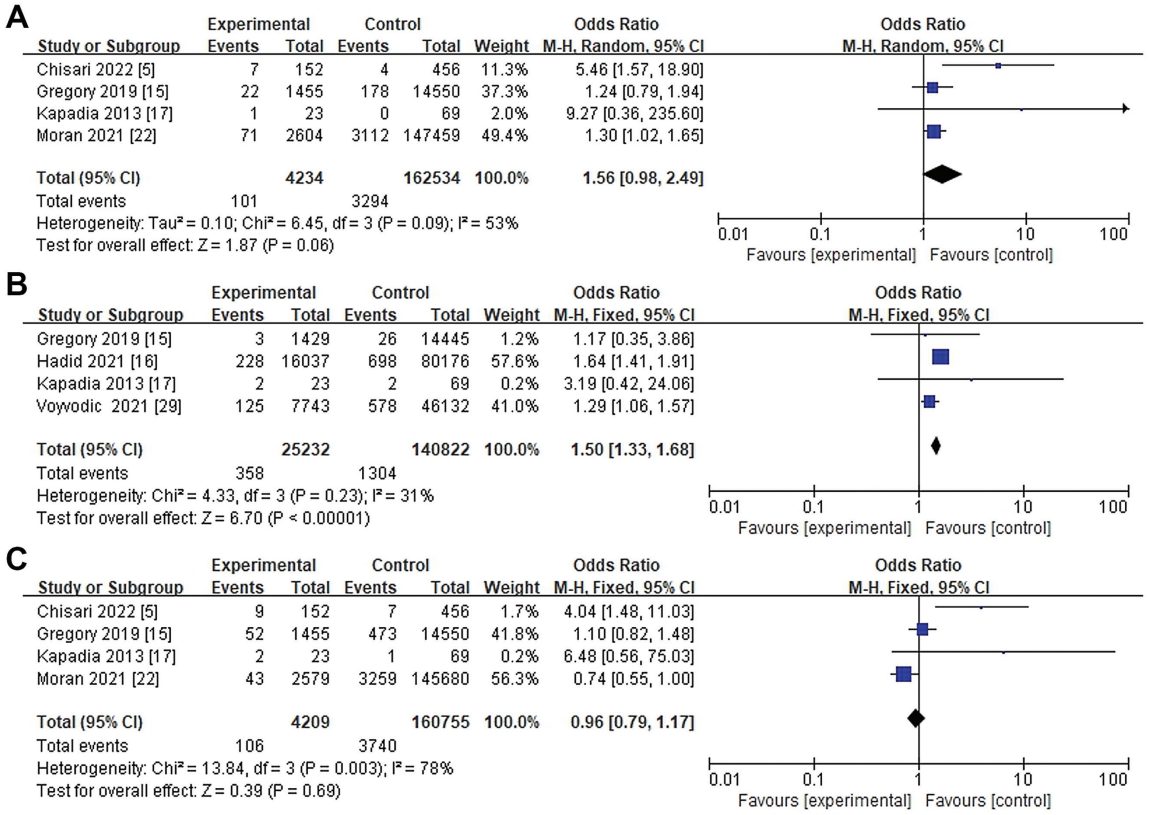

Figure 2. Forest plots for postoperative surgical complications: (A) periprosthetic joint infection, (B) surgical site infection, and (C) aseptic loosening. M-H, Mantel-Haenszel.

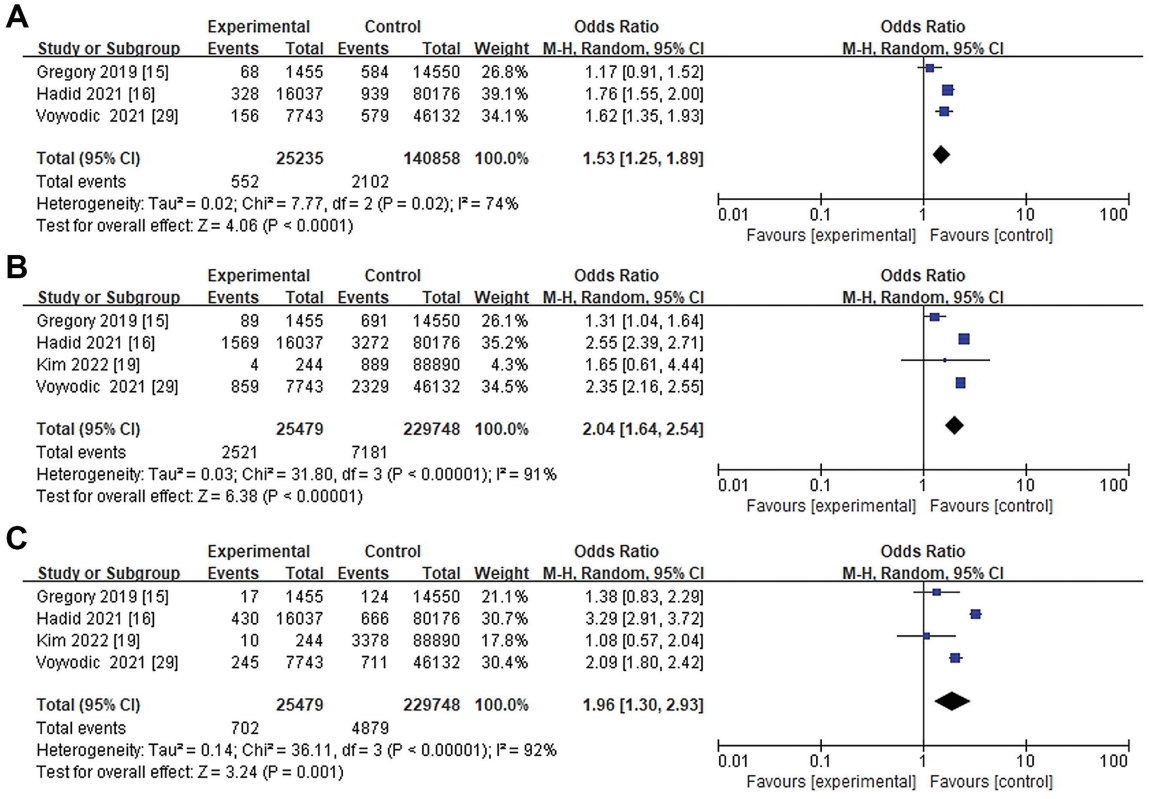

Figure 3. Forest plots for postoperative medical complications: (A) deep vein thrombosis, (B) urinary tract infection, and (C) pneumonia. M-H, Mantel-Haenszel.

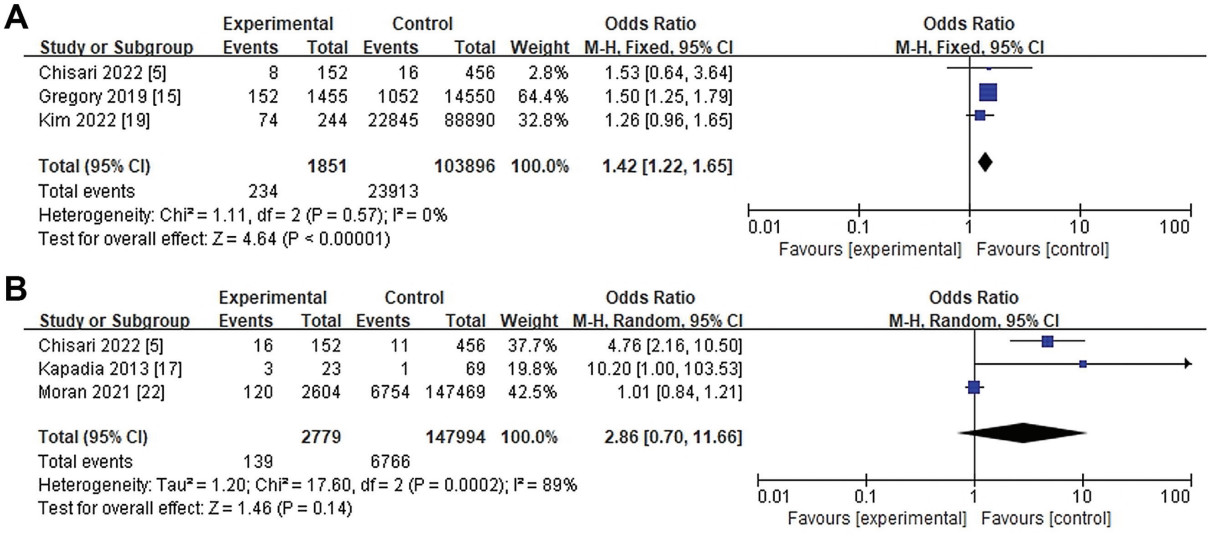

Figure 4. Forest plots for (A) readmission and (B) revision. M-H, Mantel-Haenszel.

Revision. The revision rate after TJA was reported in 3 studies.[5,17,22] Because of strong heterogeneity, a random-effects model was employed. The meta-analysis indicated that there were no statistical differences between the 2 groups (OR, 2.86 [95% CI, 0.70-11.66]; I^2 = 89%; P = .14). Then, we performed a sensitivity analysis and found that the heterogeneity was caused by Moran et al's[22] study. Excluding Moran et al's[22] work resulted in greatly reduced heterogeneity (I^2 = 0%) and a significant difference between the IBD and non-IBD groups in revision rates (OR, 5.15 [95% CI, 2.44-10.90]; I^2 = 0%; P < .01).

Length of Hospitalization and Treatment Costs

Forest plots for LOS and treatment costs are shown in Figure 5.

Length of Hospitalization. Overall, 3 studies[8,15,29] reported that IBD prolonged the LOS after TKA (MD, 0.18 [95% CI, 0.14-0.22]; I^2 = 79%; random-effects model), and 2 studies[8,29] showed that IBD prolonged the LOS after THA (MD, 0.20 [95% CI, 0.14-0.25]; I^2 = 0%; fixed-effects model).

Treatment Costs. A total of 3 studies[8,16,17] showed that IBD increased costs after TKA (MD, 1150.67 [95% CI, 943.28-1358.07]; I^2 = 0%; fixed-effects model), and 2 studies[8,29] showed that treatment costs for patients with IBD were significantly higher than those for control patients after THA (MD, 468.32 [95% CI, 325.98-610.66]; I^2 = 0%; fixed-effects model).

Publication Bias

The funnel plots of the subgroup analyses were asymmetric, indicating a potential risk of publication bias (Appendix Figure A1).

DISCUSSION

Our systematic review demonstrated that patients with IBD had a higher risk of postoperative PJI (OR, 1.30; P < .05), SSI (OR, 1.50; P < .05), DVT (OR, 1.76; P < .05), UTI (OR, 2.51; P < .05), pneumonia (OR, 1.96; P < .05), readmission (OR, 1.42; P < .05), and revision (OR, 5.15; P < .05) than the non-IBD group. In addition, patients with IBD experienced a longer LOS after TKA (MD, 0.18; P < .05) or THA (MD, 0.20; P < .05) and paid higher treatment costs after TKA (MD, 1150.67; P < .05) or THA (MD, 468.32; P < .05).

An infection is currently the leading cause of failure for TJA.[13] Our results demonstrated that the incidence of PJI events was 1.30 times higher in the IBD group than in the non-IBD group. Contributory factors to the higher rate of deep infections include the immunocompromised status of patients with IBD,[26] disturbance of intestinal flora,[1] and long-term treatment with glucocorticoids or immunomodulators.[6,10] However, the studies by Hadid et al,[16] Voyvodic et al,[29] and Chisari et al[5] excluded the relevant possible effects of biological agents and found that IBD remained an independent risk factor for surgical infections.

Recently, an interesting theory suggested that the bacterial translocation process is not only mediated by blood but also may be mediated by neutrophils or macrophages .[2,23] Immune cells transport internalized bacteria to other sites in the body like a Trojan horse and thus result in an infection at that site.[28] Because of enhanced permeability and existent dysbiosis, IBD is seen as the cause of enterogenous bacterial translocation.[12] Several scholars[3,4] cultured pathogens from patients with PJI and found that a considerable number of bacteria came from the digestive tract (such as *Enterococcus faecalis* and *Escherichia coli*), which undoubtedly confirmed the above hypothesis.

At present, there is no unified conclusion on whether patients with IBD have an increased risk of aseptic loosening. Chisari et al[5] revealed that patients with IBD carried a considerably higher risk of aseptic failure after TJA. A similar result was seen in research by Kapadia et al.[17] However, Gregory et al[15] reported that there was no

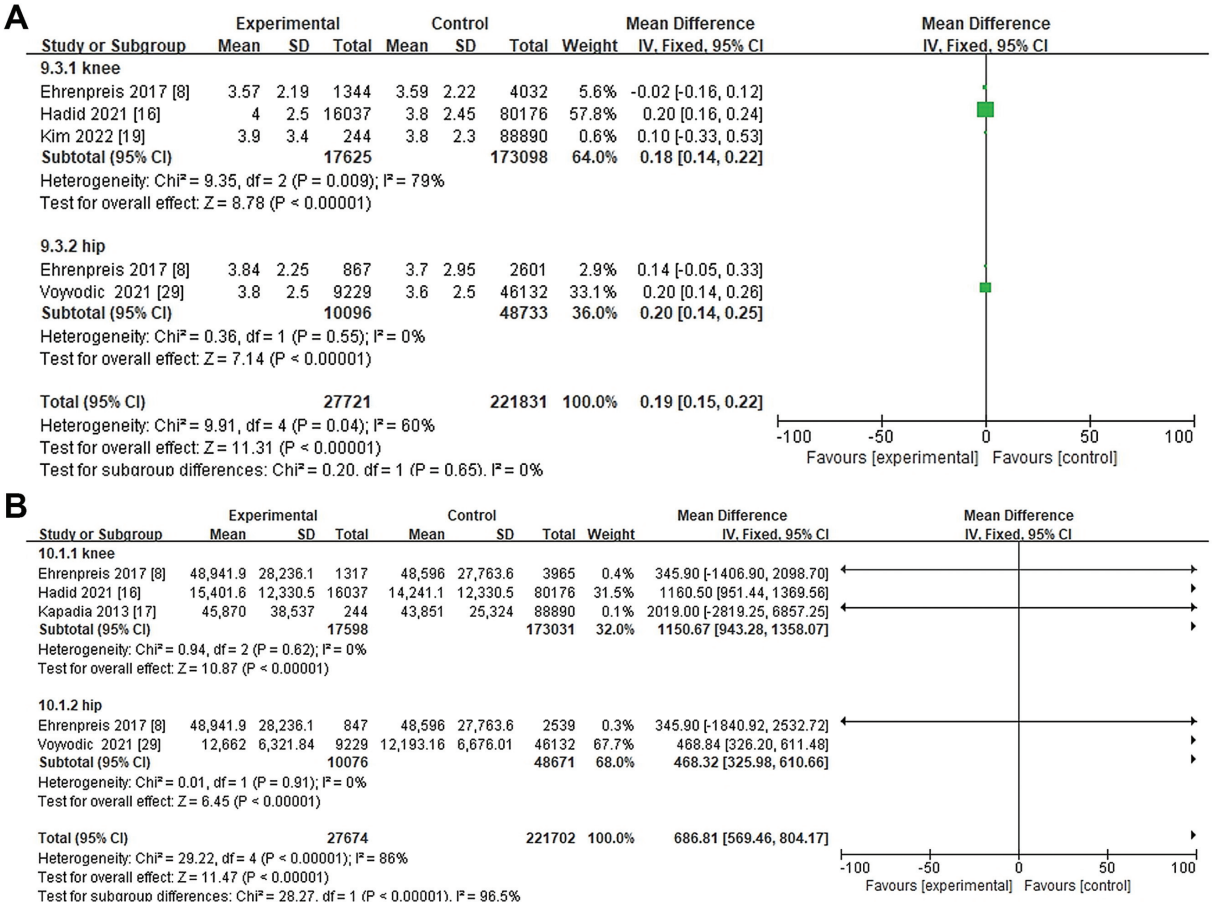

Figure 5. Forest plots for (A) length of hospitalization and (B) treatment costs. IV, inverse variance.

difference in mechanical complications between the IBD and control groups. In addition, Moran et al[22] found that patients with a history of IBD had a relatively higher risk of revision surgery for septic causes, while the non-IBD group had a relatively higher risk of revision for aseptic causes. Because of the large heterogeneity, we could not synthesize the results. More studies are needed to address this controversy.

Hypercoagulability observed in patients with IBD possibly leads to thromboembolic events, which is an important factor in patient morbidity and mortality.[21,25] Our results found that the risk of venous thromboembolism (VTE) in patients with IBD was 1.76 times higher than that in the non-IBD control group.[14] Another study reported that patients with IBD had a 2.03-fold increased risk of VTE after intestinal resection compared to patients without IBD.[30] These results provide reasonable evidence to support more active anticoagulant therapy to reduce the incidence of VTE events after surgery in patients with IBD.

Our study demonstrated that patients with IBD had a higher risk of early readmission (OR, 1.42) and long-term revision (OR, 5.15). The heterogeneity came from Moran et al's[22] study, but the final conclusion was not affected. Additionally, our study also found that patients with IBD had a significantly longer LOS and higher treatment costs compared with their non-IBD counterparts. This was consistent with previous findings of other surgical procedures in patients with IBD.[18]

There are certain limitations to our study. First, all studies included were retrospective cohort or case-control studies with inherent limitations. Some studies with a large amount of data cannot obtain specific information in detail, which possibly resulted in variability in the definitions for endpoints and thus only relied on the ICD-9 (International Classification of Diseases–9th Revision) diagnosis code. There is an urgent need for better quality prospective studies. Second, some outcome indicators are highly heterogeneous, which may result in low credibility of the results. UC and CD are 2 main subtypes of IBD. Unfortunately, we did not perform further subgroup analysis to explore the differences between UC and CD. Finally, there are confounding factors other than IBD, such as whether immunosuppressive therapy was performed, that affect the results. Some studies have not ruled out the interference of relevant factors, causing results to be exaggerated.

CONCLUSION

The current systematic review demonstrated that IBD increased the risk of postoperative complications and revision, prolonged the LOS, and increased treatment costs. The surgeon should pay more attention to the perioperative management of patients with IBD, fully outline the increased risks during the consent process, and make personalized adjustments to reduce related complications.

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APPENDIX

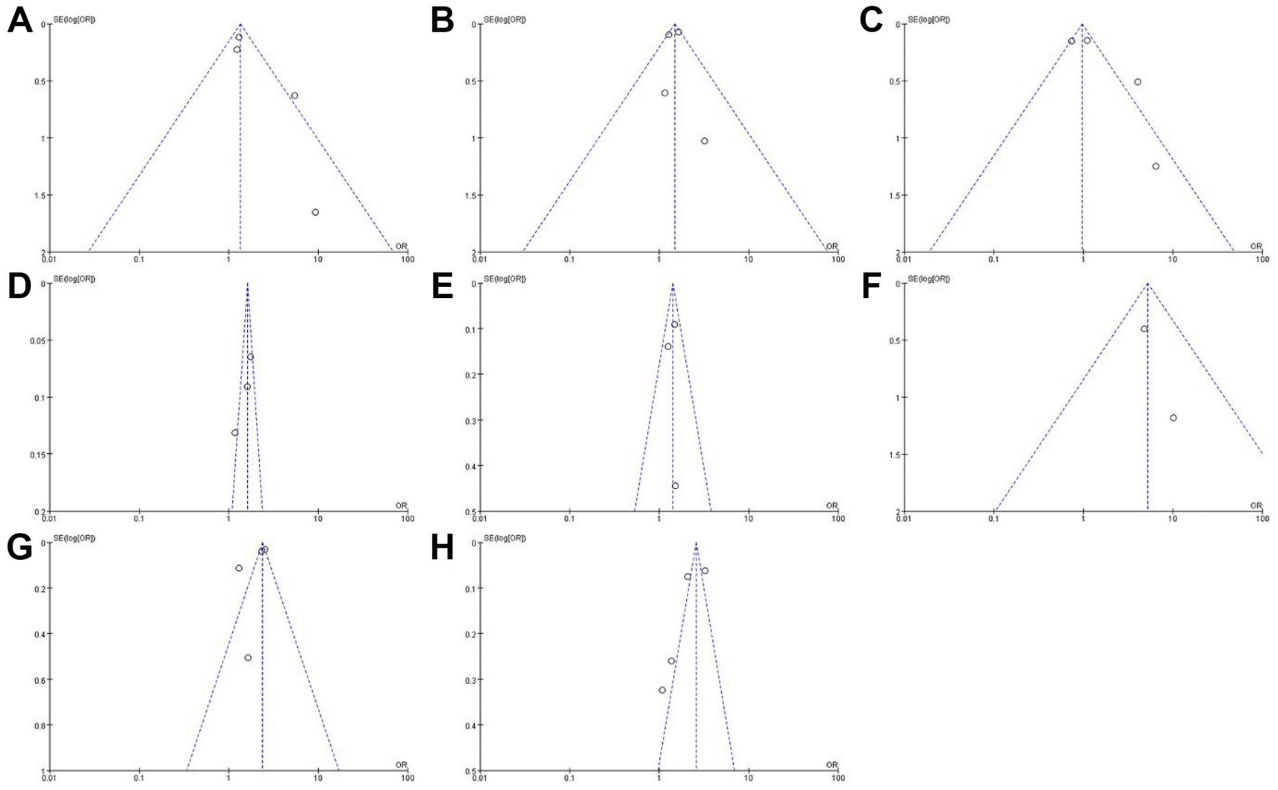

Figure A1. Funnel plots showing publication bias according to subgroup analyses: (A) periprosthetic joint infection, (B) surgical site infection, (C) aseptic loosening, (D) deep vein thrombosis, (E) readmission, (F) revision, (G) urinary tract infection, and (H) pneumonia. The circles represent the included studies, the dashed vertical line represents the pooled effect size, and the diagonal lines represent the 95% confidence interval. OR, odds ratio.