

■ **ARTHROPLASTY**

# Inflammatory bowel disease is associated with an increased risk of adverse events in patients undergoing joint arthroplasty

## A META-ANALYSIS OF OBSERVATIONAL STUDIES

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### Aims

The present study aimed to investigate whether patients with inflammatory bowel disease (IBD) undergoing joint arthroplasty have a higher incidence of adverse outcomes than those without IBD.

### Methods

A comprehensive literature search was conducted to identify eligible studies reporting postoperative outcomes in IBD patients undergoing joint arthroplasty. The primary outcomes included postoperative complications, while the secondary outcomes included unplanned re-admission, length of stay (LOS), joint reoperation/implant revision, and cost of care. Pooled odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using a random-effects model when heterogeneity was substantial.

### Results

Eight retrospective studies involving 29,738 patients with IBD were included. Compared with non-IBD controls, patients with IBD were significantly more likely to have overall complications (OR 2.11 (95% CI 1.67 to 2.66),  $p < 0.001$ ), medical complications (OR 2.15 (95% CI 1.73 to 2.68),  $p < 0.001$ ), surgical complications (OR 1.43 (95% CI 1.21 to 1.70),  $p < 0.001$ ), and 90-day readmissions (OR 1.42 (95% CI 1.23 to 1.65),  $p < 0.001$ ). The presence of IBD was positively associated with the development of venous thromboembolism (OR 1.60 (95% CI 1.30 to 1.97),  $p < 0.001$ ) and postoperative infection (OR 1.95 (95% CI 1.51 to 2.51),  $p < 0.001$ ). In addition, patients with IBD tended to experience longer LOS and higher costs of care.

### Conclusion

The findings suggest that IBD is associated with an increased risk of postoperative complications and readmission after joint arthroplasty, resulting in longer hospital stay and greater financial burden. Surgeons should inform their patients of the possibility of adverse outcomes prior to surgery and make appropriate risk adjustments to minimize potential complications.

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**Keywords:** Joint arthroplasty, Orthopaedic surgery, Crohn's disease, Ulcerative colitis, Inflammatory bowel disease, Postoperative complication, Cost of care

### Article focus

■ This study evaluated the relationship between coexisting inflammatory bowel diseases (IBD) (Crohn's disease, ulcerative

colitis) and adverse outcomes after joint arthroplasty.

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## Key messages

- Current evidence suggests that IBD increases the risk of postoperative complications and readmission in patients undergoing joint arthroplasty.
- This meta-analysis also found that patients with IBD have longer length of stay and higher costs of care.

## Strengths and limitations

- The advantage of this study is that it is the first meta-analysis of the relationship between IBD and postoperative outcomes after joint arthroplasty.
- Most of the studies included were from nationally representative databases with a large sample size, which can maximize the detection of the association between IBD and adverse events following arthroplasty.
- This is a meta-analysis of the currently available literature, including eight retrospective cohort studies. Therefore, residual confounding by unmeasured variables, such as the frequency and severity of active disease, could not be well controlled.
- Due to the low quality of the study design and the high risk of bias, the results of the pooled data should be interpreted with great caution.

## Introduction

Inflammatory bowel disease (IBD), which encompasses Crohn's disease (CD) and ulcerative colitis (UC), is a condition characterized by chronic inflammation in the gastrointestinal tract.<sup>1</sup> The pathogenesis of IBD remains elusive, but it is thought to result from a complex interplay of genetic susceptibility, environmental exposures, and host immunity.<sup>2,3</sup> According to data from the Centres for Disease Control and Prevention in the USA, approximately 3.1 million individuals (1.3% of the total population) have been diagnosed with IBD, with a higher incidence observed among those aged 45 years and older.<sup>4</sup> In the coming decade, the demand for major orthopaedic surgery among IBD patients is expected to increase due to the ageing population.<sup>5,6</sup>

In addition to the intestinal lesions, extraintestinal manifestations usually involve the liver, skin, eyes, and joints in a substantial proportion (6% to 48%) of IBD patients.<sup>7,8</sup> Musculoskeletal manifestations, including peripheral and axial arthritis, frequently result in joint pain and adversely affect the patient's quality of life.<sup>9-12</sup> Additionally, immunomodulatory treatments for IBD may interfere with normal bone metabolism, worsening the risk of osteoporosis, osteonecrosis, and fragility fracture in the elderly.<sup>2,13-15</sup> Due to reduced absorption of micro-nutrients and uncontrolled inflammation in the gut, patients with IBD often suffer from malnutrition and bone loss, which can be detrimental to rapid postoperative recovery.<sup>16,17</sup>

Recently, several studies have been published investigating the potential impact of IBD on postoperative outcomes in patients undergoing joint arthroplasty.<sup>5,18-25</sup> These studies produced conflicting results, making it

essential to take an evidence-based approach to synthesize the cohort data and draw more concrete conclusions in the context of modern surgical practice. To the best of our knowledge, no systematic review or meta-analysis has been performed to date to evaluate the impact of coexisting IBD on the clinical outcomes in joint arthroplasty patients. In light of this, we proposed a systematic review and meta-analysis of observational studies to address this gap in knowledge and provide a more comprehensive understanding of the relationship between IBD and postoperative outcomes in joint arthroplasty patients. Specifically, we examined: postoperative complications; mortality; readmission; length of stay (LOS); joint reoperation/implant revision; and cost of care.

## Methods

This meta-analysis was conducted according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines. We have registered this study protocol in the International Prospective Register of Systematic Reviews database (registration number: CRD42022336042).

**Search strategy.** The following electronic databases were searched from inception to May 2022: PubMed; Embase; Scopus; and the Cochrane Library. No language restriction was applied. Titles and abstracts were searched using the terms "inflammatory bowel disease", "Crohn's disease", "ulcerative colitis", "replacement", "arthroplasty", "orthopaedic surgery", and their associated synonyms and abbreviations. All search terms were combined with Boolean operators and Medical Subject Headings to ensure completeness of search and maximize retrieval. A bibliographic review of included articles was also undertaken to identify additional relevant studies.

**Study selection.** A study was deemed potentially eligible if it met all of the following criteria: observational studies (e.g. prospective cohort studies, retrospective cohort studies, and case-control studies) evaluating the influence of IBD on postoperative outcomes in joint arthroplasty patients; original publications in peer-reviewed journals; reports on at least one outcome of interest; and studies involving human subjects. We excluded review articles, case series, case reports, comments, letters, and protocols; any study whose participants were less than 18 years of age; studies with no or an inappropriate control group; and animal studies. After removing duplicate articles, two authors (DX and CD) independently reviewed titles and abstracts. Following this screening, the full texts of eligible articles were retrieved and assessed according to predefined criteria. In the case of overlapping patient data, only the study with the largest sample size was included.

**Data extraction.** Two authors (DX and CD) independently extracted the following data: first author; country of origin; year of publication; journal of publication; study design; study period; patient characteristics; IBD subtype; number of participants; surgical modality; length of follow-up; and outcomes of interest. Primary outcomes

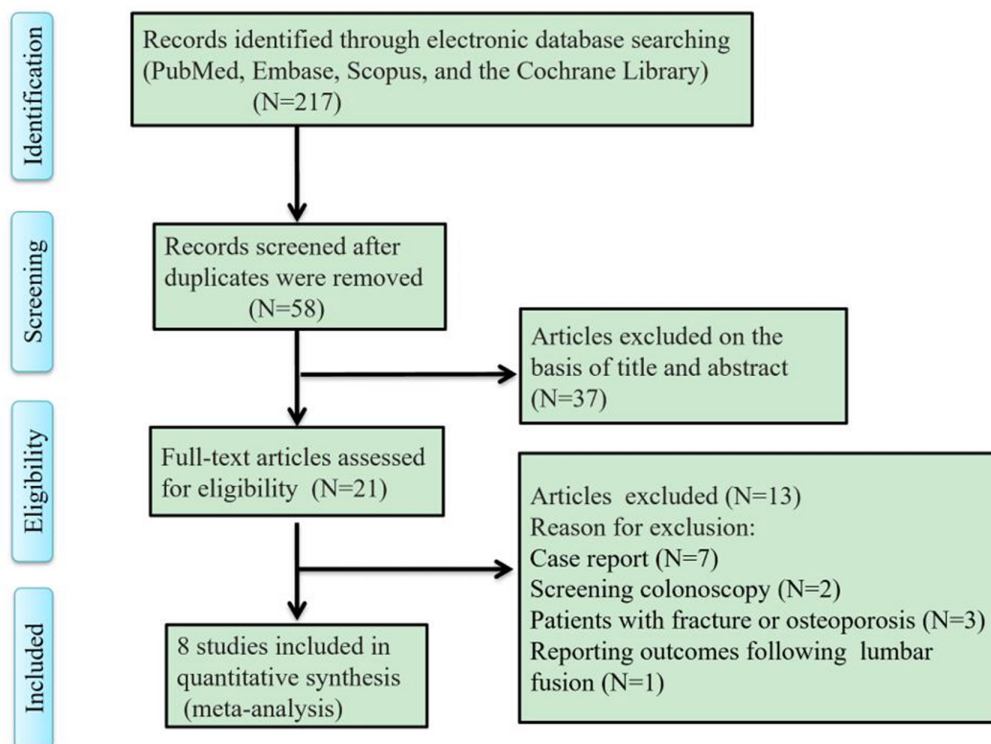


Fig. 1

The full search strategy is shown in the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) flowchart.

included postoperative complications (medical complications and surgical complications). Secondary outcomes included all-cause mortality, unplanned readmission, joint reoperation, implant revision, LOS, and cost of care.

**Quality assessment.** The Newcastle-Ottawa Scale (NOS) was used to assess the methodological quality of observational studies. The instrument assessed the risk of bias in three categories: selection of study groups; comparability between study groups; and ascertainment of the exposure or outcome of interest. All the included studies were classified as good quality (seven to nine stars), fair quality (four to six stars), or poor quality (zero to three stars). Disagreements were resolved through consensus meetings.

**Statistical analysis.** A meta-analysis was performed for each outcome if at least three studies could be identified. For dichotomous outcomes, we pooled the individual study data into an odds ratio (OR) with 95% confidence intervals (CIs) using the Cochran-Mantel-Haenszel (CMH) test. The level of heterogeneity was assessed using the  $I^2$  statistic. We intended to use a random-effects model for substantial heterogeneity ( $I^2 \geq 50\%$ ) and a fixed-effects model without such heterogeneity. A funnel plot was used to visually assess the publication bias of the primary outcomes. The robustness of the results was assessed by performing sensitivity analyses (i.e. restricted to studies with a low risk of bias). We also performed subgroup analyses according to type of surgery and IBD subtype. A  $p$ -value  $< 0.05$  was considered statistically significant

for all outcomes. All meta-analyses were performed using Review Manager version 5.3 (Nordic Cochrane Centre, Cochrane Collaboration, Denmark).

## Results

**Search results.** A search of electronic databases identified 217 citations. After eliminating duplicate citations, 58 citations were screened based on titles and abstracts, and 21 citations were selected for detailed full-text review. A total of 13 studies were then excluded from the analysis: one reported immediate postoperative outcomes following lumbar fusion;<sup>6</sup> two enrolled colonoscopy cases;<sup>26,27</sup> three included fracture or osteoporosis cases;<sup>2,14,28</sup> and seven were case reports.<sup>29-35</sup> Overall, eight studies comprising 407,462 patients were included in this meta-analysis. The study selection process is shown in Figure 1.

**Characteristics of included studies.** The included studies were all conducted in the USA. Six studies collected data from nationwide administrative databases,<sup>5,18,19,21-23</sup> and two from a single-centre hospital database.<sup>20,24</sup> Five studies reported mixed cohorts of patients suffering from IBD<sup>5,19-21,24</sup> and three included patients with CD only.<sup>18,22,23</sup> One study investigated hip, knee, and shoulder arthroplasty,<sup>21</sup> two investigated hip and knee arthroplasty,<sup>5,24</sup> two investigated total knee arthroplasty only,<sup>22,23</sup> and three investigated total hip arthroplasty only.<sup>18-20</sup> The International Classification of Diseases, Ninth/Tenth Revision (ICD-9/10) diagnosis codes were used to diagnose IBD in seven studies.<sup>5,18,19,21-24</sup> Five studies used ICD-9

**Table I.** Summary of characteristics of included studies.

First author (year, country, journal)	Study design (level of evidence)	Data source (study period)	Patient demographics	IBD type (diagnostic code)	Sample size (IBD vs control)	Surgery type (procedural code)	Duration of follow-up	Postoperative outcomes
Chisari <sup>24</sup> (2022, USA, JBJS)	Observational study (retrospective, III)	Single institution (2000 to 2018)	Age, sex, BMI, year of surgery, comorbidities (CCI)	CD, UC, RNC (ICD-9/10)	152; 456	THA, TKA	2 years	PJI, aseptic revision, discharge to rehabilitation facility, complication, readmission
Ehrenpreis <sup>5</sup> (2017, USA, WJG)	Observational study (retrospective, III)	NIS (2005 to 2011)	Age, sex, race, comorbidities, insurance, income, admission type, hospital status	CD, UC (ICD-9)	2,968; 12,012	Knee/hip arthroplasty (ICD-9)	Inpatient	LOS, mortality, cost of hospitalization
Gregory <sup>21</sup> (2019, USA, JCC)	Observational study (retrospective, III)	THAMCCE (2006 to 2014)	Age, sex, comorbidities (ECI), smoker, opioid use	CD, UC, IC (ICD-9)	1,455; 14,550	Hip/knee/shoulder arthroplasty (CPT, ICD-9)	90 days	Serious infection, CDI, UTI, VTE, haemorrhage/haematoma, prosthesis malfunction, mechanical complication, LOS, total charge, readmission, joint reoperation, joint survival
Hadid <sup>23</sup> (2023, USA, JKS)	Observational study (retrospective, III)	PearlDiver (2005 to 2014)	Age, sex, comorbidities (ECI)	CD (ICD-9)	16,037; 80,176	TKA (CPT, ICD-9)	90 days	Medical complication, LOS, cost of care
Kapadia <sup>20</sup> (2014, USA, JOA)	Observational study (retrospective, III)	Single institution (2001 to 2010)	Age, sex, BMI, corticosteroid use, nutritional status	CD, UC, MC	17; 51	THA	47 months (24 to 94)	Postoperative complication, HSS, implant survivorship, radiological evaluation
Kim <sup>22</sup> (2022, USA, Knee)	Observational study (retrospective, III)	NYSPRCS (2009 to 2013)	Age, sex, race, insurance, BMI, comorbidities (Deyo score)	CD (ICD-9)	244; 88,890	TKA (ICD-9)	2 years (minimum)	Medical complication, surgical complication, in-hospital mortality, readmission, reoperation, LOS, surgical charge
Moran <sup>19</sup> (2021, USA, PO)	Observational study (retrospective, III)	SHAR, SNPR (1999 to 2017)	Age, sex, comorbidities (ECI)	CD, UC, RNC (ICD-9/10)	2,604; 147,469	THA	8.9 years (mean)	All-cause mortality, implant revision (septic and aseptic)
Voyvodic <sup>18</sup> (2021, USA, JOA)	Observational study (retrospective, III)	PearlDiver (2005 to 2014)	Age, sex, comorbidities (ECI)	CD (ICD-9)	9,229; 46,132	THA (CPT, ICD-9)	90 days	Medical complication, LOS, cost of care

IC, indeterminate colitis; CCI, Charlson Comorbidity Index; CD, Crohn's disease; CDI, *Clostridium difficile* infection; CPT, Current Procedural Terminology; ECI, Elixhauser Comorbidity Index; HSS, Harris Hip Score; IBD, inflammatory bowel disease; ICD, International Classification of Diseases; JBJS, The Journal of Bone and Joint Surgery; JCC, Journal of Crohn's and Colitis; JKS, The Journal of Knee Surgery; JOA, The Journal of Arthroplasty; LOS, length of stay; MC, microscopic colitis; NIS, National Inpatient Sample; NYSPRCS, New York Statewide Planning and Research Cooperative System; PJI, periprosthetic joint infection; PO, PLoS One; RNC, regional non-specific colitis; SHAR, Swedish Hip Arthroplasty Register; SNPR, Sweden National Patient Register; THA, total hip arthroplasty; THAMCCE, Truven Health Analytics MarketScan Commercial Claims and Encounters; TKA, total knee arthroplasty; UC, ulcerative colitis; UTI, urinary tract infection; VTE, venous thromboembolism; WJG, World Journal of Gastroenterology.

procedural codes or Current Procedural Terminology codes to identify patients undergoing joint arthroplasty.<sup>5,18,21-23</sup> Three preoperative risk assessment tools were used, including the Charlson Comorbidity Index,<sup>24</sup> Charlson Deyo Index,<sup>22</sup> and Elixhauser Comorbidity Index.<sup>18,19,21,23</sup> Postoperative follow-up period was within 90 days of surgery in four studies,<sup>5,18,21,23</sup> whereas medium-term or long-term follow-up (2 to 8.9 years) was reported in four studies.<sup>19,20,22,24</sup> The characteristics of the included studies are shown in Table I.

**Risk of bias assessment.** All eight studies were considered retrospective cohort designs (sample sizes ranged from 68 to 89,134). Of these, two applied propensity score

matching,<sup>5,24</sup> three used Cox proportional hazards models,<sup>19,21,24</sup> and five evaluated multivariable regression analyses.<sup>5,18,22-24</sup> The majority of the included articles (n = 6) were rated as “good” in terms of methodological quality,<sup>5,18,19,21-23</sup> and two articles were rated as “fair”.<sup>20,24</sup> A summary of the NOS criteria scores per study is shown in Figure 2.

**Postoperative complications.** In total, six studies were included to evaluate postoperative complications (27,134 patients with IBD and 230,255 patients without IBD).<sup>18,20-24</sup> Pooled results showed that patients with IBD had higher odds of overall complications (OR 2.11 (95% CI 1.67 to 2.66), p < 0.001, CMH test) (Figure 3), medical

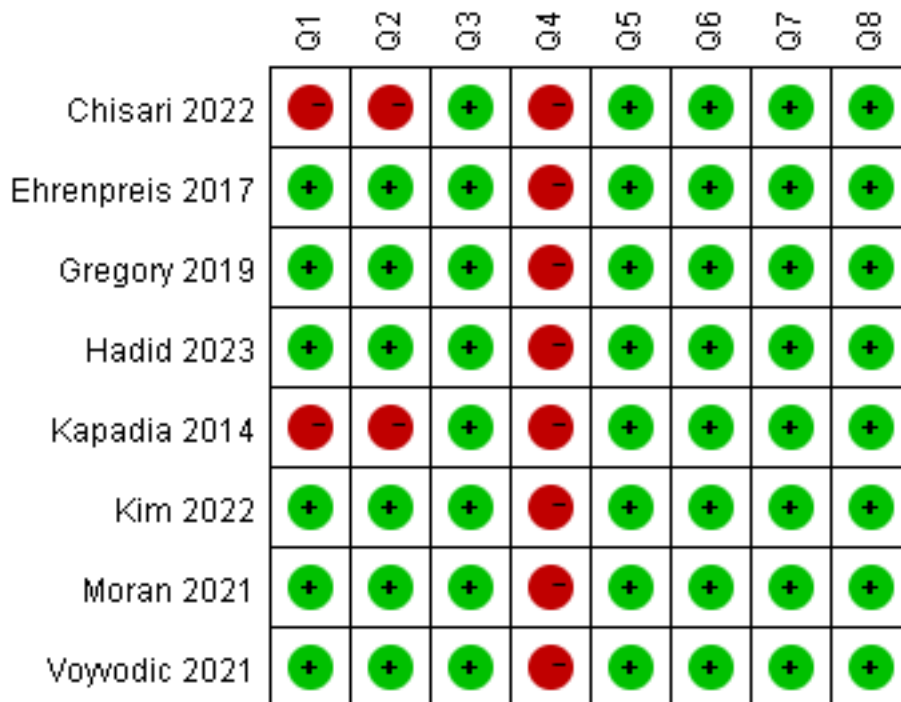


Fig. 2

Methodological quality of the included studies according to the Newcastle-Ottawa Scale criteria.

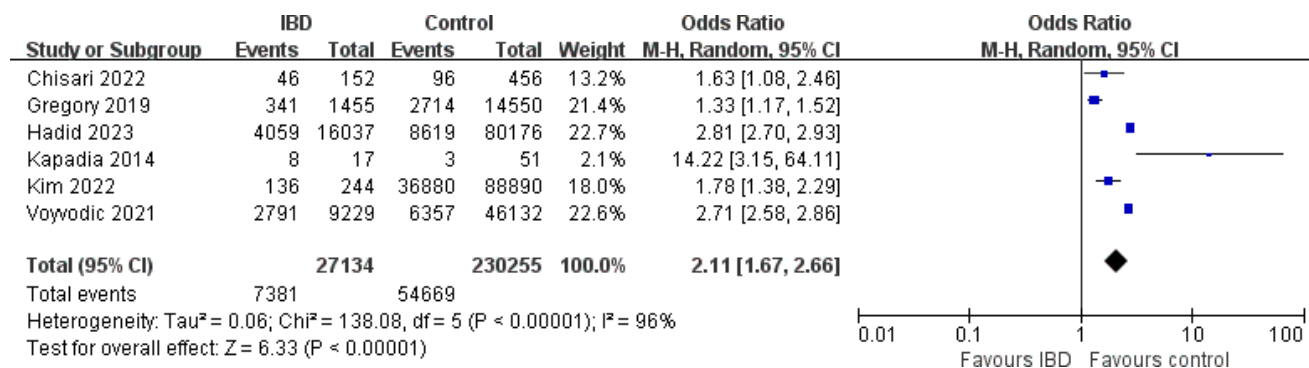


Fig. 3

Forest plot of overall complications. CI, confidence interval; IBD, inflammatory bowel disease; M-H, Mantel-Haenszel.

complications (OR 2.15 (95% CI 1.73 to 2.68),  $p < 0.001$ , CMH test), and surgical complications (OR 1.43 (95% CI 1.21 to 1.70),  $p < 0.0001$ , CMH test) than non-IBD patients (Supplementary Figure a and Supplementary Table i).

Data concerning postoperative infections were available from seven studies.<sup>18–24</sup> According to the pooled results, IBD was positively associated with serious infections (OR 1.95 (95% CI 1.51 to 2.51),  $p < 0.001$ , CMH test). Specifically, IBD patients experienced more pneumonia (OR 2.08 (95% CI 1.47 to 2.96),  $p < 0.001$ , CMH test), joint infection (OR 1.47 (95% CI 1.25 to 1.73),  $p < 0.001$ , CMH test), and urinary tract infection (OR

2.09 (95% CI 1.69 to 2.58),  $p < 0.001$ , CMH test) than non-IBD patients (Supplementary Table i and Supplementary Figure b). The incidence of venous thromboembolism (VTE), including pulmonary embolism (PE) and deep vein thromboembolism (DVT), was recorded in three studies (26,721 IBD patients and 140,858 non-IBD patients).<sup>18,21,23</sup> Patients with IBD were found to have a significantly higher risk of VTE (OR 1.60 (95% CI 1.30 to 1.97),  $p < 0.001$ , CMH test).

A pooled analysis of three studies (3,344 IBD patients and 101,358 non-IBD controls) found that the odds of all-cause mortality after surgery were not significantly



**Table II.** Summary of care costs and hospital charges of included studies.

First author	Term	IBD type	Surgery site	Sample size (IBD vs control)	Mean cost, \$		p-value
					IBD	Control	
Ehrenpreis <sup>5</sup>	Cost of hospitalization	IBD	Hip	1,484; 4,452	50,074.72	33,161.78	0.732
	Cost of hospitalization	IBD	Knee	1,484; 7,560	45,319.13	25,714.03	0.441
	Total charge	CD	Hip	847; 2,539	48,941.9 (SD 28,236.1)	48,596 (SD 27,763.6)	0.630
	Total charge	UC	Hip	596; 1,799	52,620.7 (SD 34,203.1)	50,966.2 (SD 29,412.4)	0.761
	Total charge	CD	Knee	1,317; 3,965	44,975.6 (SD 26,145.8)	45,161 (SD 27,971.7)	0.574
	Total charge	UC	Knee	1,145; 3,465	46,681.3 (SD 27,892.7)	46,545.8 (SD 28,108)	0.727
Gregory <sup>21</sup>	Index total charge	IBD	Hip, knee, shoulder	1,455; 14,550	30,220	29,894	0.930
Hadid <sup>23</sup>	90-day EOC cost	CD	Knee	16,037; 80,176	15,401.63	14,241.15	< 0.001
Kim <sup>22</sup>	Total surgical charge	CD	Knee	244; 88,890	45,870 (SD 38,537)	43,851 (SD 25,324)	0.360
Voyvodic <sup>18</sup>	Cost of care (day of surgery)	CD	Hip	9,229; 46,132	12,662 (SD 6,321.84)	12,193.16 (SD 6,676.01)	< 0.001
	90-day EOC cost	CD	Hip	9,229; 46,132	16,933.18 (SD 12,330.55)	15,670.32 (SD 2,617.33)	< 0.001

CD, Crohn's disease; EOC, episode of care; IBD, inflammatory bowel disease; SD, standard deviation; UC, ulcerative colitis.

different between IBD patients and non-IBD controls (OR 1.04 (95% CI 0.39 to 2.78),  $p = 0.930$ , CMH test).<sup>5,22,24</sup>

**Unplanned readmission and length of stay.** Three studies provided data on readmission rate (1,851 patients with IBD and 103,896 patients without IBD).<sup>21,22,24</sup> The result of the pooled analysis indicated that patients with IBD were more likely to undergo an unplanned readmission at 90 days than patients without IBD (OR 1.42 (95% CI 1.23 to 1.65),  $p < 0.001$ , CMH test).

Five studies involving 271,693 patients reported in-hospital LOS, with 29,933 and 241,760 patients in the IBD and control groups, respectively.<sup>5,18,21-23</sup> The mean LOS for patients with IBD was 3.85 days, while the mean LOS for patients without IBD was 3.42 days. The LOS in the non-IBD cohort was shorter (0.43 days), resulting in earlier discharge from hospital. Nevertheless, Chisari et al<sup>24</sup> reported that patients with IBD had similar rates of discharge to rehabilitation facility as those in the control group (34.9% vs 30.9%,  $p = 0.431$ ).

**Joint reoperation and implant revision.** Due to considerable heterogeneity regarding the definition of reoperation/revision and the duration of follow-up, meta-analysis was not suitable. Gregory et al<sup>21</sup> reported no difference in the occurrence of joint failure per patient-year between IBD patients and controls following hip, knee, or shoulder arthroplasty (all  $p \geq 0.340$ ). Kim et al<sup>22</sup> found that no significant differences were observed in univariate or multivariate analysis for 90-day and overall reoperation in patients with CD (all  $p \geq 0.380$ ). In contrast, Kapadia et al<sup>20</sup> reported that patients with IBD had a lower overall survivorship of 87% (three joint failures) compared with 98.5% (one joint failure) in the control group with a mean follow-up of 47 months, but the difference reached borderline statistical significance ( $p = 0.040$ ). At two years post-operatively, Chisari et al<sup>24</sup> found that patients with IBD had a higher rate of aseptic revisions (5.92% vs 1.54%). When comparing the cumulative incidence of aseptic

revision, the log-rank test showed a significant difference ( $p = 0.003$ ). The most common cause was periprosthetic fracture (50%), followed by aseptic loosening (25%). A Cox regression analysis showed that the risk of aseptic revision was significantly associated with pre-existing IBD (hazard ratio (HR) 4.02 (95% CI 1.50 to 10.79),  $p = 0.006$ ). A registry-based study from Sweden also reported that patients with a history of IBD had a higher risk of revision surgery for septic causes. In comparison, non-IBD patients had a higher likelihood of revision surgery for aseptic reasons ( $p = 0.004$ ).<sup>19</sup>

**Care cost and hospital charge.** The definitions of costs varied considerably between the included studies and were not considered suitable for meta-analysis. Table II summarizes the full details of the included studies. Voyvodic et al<sup>18</sup> and Hadid et al<sup>23</sup> used reimbursements as a surrogate for the cost of care by using Medicare claims for the PearlDiver platform. Following hip and knee arthroplasty, patients with CD had significantly higher costs for day of surgery and 90-day episode of care.<sup>18,23</sup> Three other studies found similar hospital or surgical charges for joint arthroplasty in patients with IBD and controls.<sup>5,21,22</sup> However, healthcare costs tended to be higher in the IBD group.

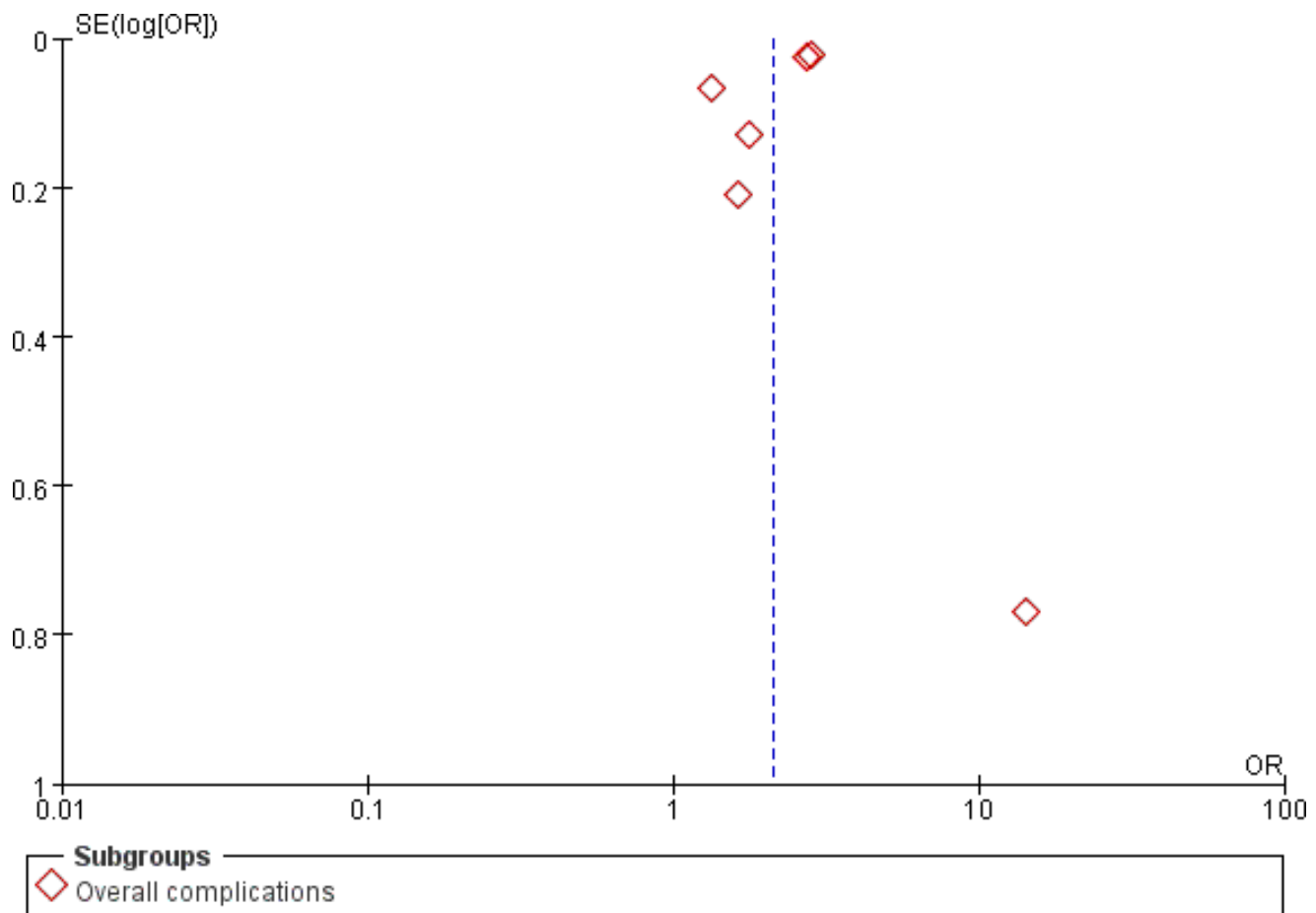
**Sensitivity and subgroup analyses.** Our conclusions were not affected by restricting the analysis to high-quality studies (NOS > 6) or patients with CD (Table III). In addition, a subgroup analysis of patients by type of surgery suggested that IBD patients had an increased risk of joint infection compared with non-IBD patients undergoing hip surgery (OR 1.37 (95% CI 1.19 to 1.58),  $p < 0.001$ , CMH test).

**Publication bias.** Publication bias of the included studies was detected by a visual inspection of the funnel plot, which showed a marked asymmetry (Figure 4).

**Table III.** Sensitivity and subgroup analyses of postoperative outcomes.

Postoperative outcome	NOS > 6	CD patients
<b>Overall complication</b>	2.09 (1.64 to 2.68), < 0.001	1.99 (1.57 to 2.52), < 0.001
Medical complication	2.13 (1.71 to 2.65), < 0.001	2.66 (2.37 to 2.98), < 0.001
Surgical complication	1.38 (1.19 to 1.61), < 0.001	1.52 (1.36 to 1.69), < 0.001
<b>Postoperative infection</b>	2.03 (1.65 to 2.49), < 0.001	2.20 (1.88 to 2.57), < 0.001
Pneumonia	2.08 (1.47 to 2.96), < 0.001	2.19 (1.55 to 3.08), < 0.001
Joint infection	1.46 (1.29 to 1.65), < 0.001	1.53 (1.37 to 1.71), < 0.001
UTI	2.09 (1.69,2.58), < 0.001	2.33 (2.04,2.66), < 0.001

All results are given as Mantel-Haenszel odds ratios (95% confidence intervals) and p-values of the inflammatory bowel disease (IBD) group developing complications compared with the non-IBD group. All p-values were calculated using the Cochran-Mantel-Haenszel test. CD, Crohn's disease; NOS, Newcastle-Ottawa Scale; UTI, urinary tract infection.

**Fig. 4**

Funnel plot of all studies included examining the association between inflammatory bowel disease and overall complications. OR, odds ratio; SE, standard error.

## Discussion

As the IBD population ages, the number of patients requiring joint arthroplasty is expected to rise. Consequently, it is essential to clarify the role of IBD in postoperative complications so that orthopaedic surgeons can take measures to prevent such complications from arising. Nonetheless, the relationship between IBD and the risk of severe infection and VTE after surgery remains controversial, and there have been no other meta-analyses of this topic to date. To our knowledge, this is

the first systematic review and meta-analysis to address these issues.

Recent studies have shown that IBD patients are more likely to experience serious infections than the general population.<sup>21,36,37</sup> This is consistent with our findings that IBD patients are at higher risk of postoperative infections following joint arthroplasty, including pneumonia, joint infection, and urinary tract infection. A retrospective cohort and nested-control study using administrative data from the LifeLink Health Plan Claims Database

demonstrated that the risk of pneumonia was higher in IBD patients compared with non-IBD patients (HR 1.54), with an increased risk in patients with both CD (HR 1.71) and UC (HR 1.41).<sup>37</sup> It is well known that epithelial immunity plays a prominent role in both IBD and pneumonia, and that many of the susceptibility genes for IBD are associated with the microbial immune response.<sup>36</sup> Similar to the gut, an impairment in the barrier function of pulmonary epithelium has also been reported in patients with IBD.<sup>36</sup>

Moran et al<sup>19</sup> used the Swedish Arthroplasty Register<sup>38</sup> and the Sweden National Patient Register<sup>39</sup> to evaluate implant survival in a retrospective analysis. The authors reported that IBD patients had a higher prevalence of sepsis (2.7%) as a cause of implant failure compared with non-IBD controls (2.1%). Periprosthetic joint infection (PJI), a devastating complication of arthroplasty, can occur due to intraoperative contamination, local extension of surgical incision infection, or haematogenous seeding.<sup>40,41</sup> In several case reports of implant failure, normal intestinal flora was isolated in joint aspiration cultures from patients with IBD.<sup>32-34</sup> A prospective, case-control study by Coelho-Prabhu et al<sup>42</sup> found that patients undergoing esophagogastroduodenoscopy with biopsy were at increased risk of PJI. The investigators suggested that this finding may be related to transient bacteraemia during endoscopic procedures. The above observations have led some researchers to propose the 'Trojan horse' hypothesis, whereby bacteria that pass through a disrupted gut membrane and are engulfed by immune cells (e.g. neutrophils and macrophages) are transported intracellularly to other sites in the body.<sup>24,43</sup> This may partially explain the association between gut health and postoperative infections. Given the increased risk of postoperative infections reported in this study, we believe that prophylactic antibiotic regimens may need to be more aggressive in patients with IBD, particularly when they are immunocompromised.

Our study demonstrates that patients with IBD are also at increased risk of VTE. The presence of moderate-to-severe disease activity with upregulated inflammatory cytokines induces a hypercoagulable state, resulting in local microthrombi and systemic thrombotic events.<sup>44,45</sup> Evidence from one study has shown that the local inflammatory response in the gut and peripheral blood of individuals with active IBD is characterized by the presence of neutrophil extracellular traps containing bioactive interleukin-1 $\beta$  and thrombogenic tissue factor, which may account for the higher rates of thrombosis in these individuals than in healthy individuals.<sup>46</sup> In a meta-analysis of 11 observational studies assessing the incidence of VTE in patients with IBD, Arvanitakis et al<sup>44</sup> found a statistically significant twofold increase in rates compared with matched cohorts. It has been shown that major orthopaedic surgery itself is a notable risk factor for VTE, which may be associated with an inflammatory stress response.<sup>47</sup> Moreover, hypercoagulability is further exacerbated by the altered immune activity present in patients with

IBD.<sup>3,44</sup> The study by Voyvodic et al<sup>18</sup> has also revealed that corticosteroid users are more likely to develop PE and DVT than non-corticosteroid users in IBD.<sup>18</sup> There is evidence that glucocorticoids may alter fibrinolysis, resulting in increased clotting factor and plasminogen activator inhibitor-1, thus contributing to hypercoagulability.<sup>44,48</sup> It is essential to consider corticosteroid-sparing agents and anticoagulants suitable for extended thromboprophylaxis in patients with IBD.

Our meta-analysis shows that patients diagnosed with IBD exhibit a greater probability of all-cause readmission in comparison with patients without IBD. This disparity can potentially be attributed to several factors, including differences in the patient population and their overall fitness level. Specifically, IBD patients may tend to be more self-selected and less physically fit than the non-IBD group, factors that could contribute to inferior outcomes, both with and without surgical intervention. As healthcare costs continue to escalate, there may be a disincentive for hospital systems to treat IBD patients within bundled payment programmes unless appropriate risk adjustment is implemented.

We acknowledge the limitations of the literature contributing to our meta-analysis. First, as all eligible studies have a retrospective cohort design, it is possible that residual confounding from unmeasured variables has not been fully addressed. To gain a deeper understanding from a clinician's perspective, it would be valuable to examine any specific factors associated with adverse outcomes in patients with IBD who have undergone joint arthroplasty. It is laudable that most of the included studies have taken steps to adjust for confounders through the use of propensity score matching and multivariable regression. Second, the limited number of studies included in the present meta-analysis makes it challenging to conduct meta-regression analyses. Therefore, we recommend further exploration of the relationship between study-level characteristics (such as sample size, study design, or study quality) and effect size estimates using statistical techniques in future studies. Third, there was variability in the surgical methods and pathological subtypes used in the studies. As expected, surgical procedures with higher complexity and inflammatory burden are associated with a higher risk of postoperative adverse events.<sup>47,49</sup> To reduce clinical heterogeneity, we attempted to quantify the relationship between IBD and postoperative outcomes by performing subgroup analyses. Finally, the information on concurrent medication use was reported inconsistently across the studies. In a clinical setting, patients with IBD may require a combination of treatments based on the activity level of their disease or their immune response.<sup>50</sup> It would be useful for further research to specifically examine and compare patients receiving biologics, immunotherapy, or a combination of both.

In conclusion, our study suggests that IBD may be a risk factor for developing postoperative complications and all-cause readmission following joint arthroplasty.



Patients with IBD also tend to have longer LOS and higher healthcare costs. Orthopaedic surgeons should therefore consider a patient's IBD status in preoperative decision-making and improve risk adjustment performance. While our study provides some clarity on the impact of IBD, it is important to note that our findings should be interpreted with caution due to the limitations of the study. Larger, prospective, long-term studies that take into account disease severity and concurrent medication use would be highly beneficial to determine more accurately the impact of IBD on the risk of postoperative complications and implant failure.

## Supplementary material



Table and forest plots showing the detailed data of postoperative complications.

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