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Risk factors for postoperative infection after gastrointestinal surgery among adult patients with inflammatory bowel disease: Findings from a large observational US cohort study

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Abstract

Background and Aim: Postoperative infection (POI) is a major source of morbidity and prolongation of hospitalization in inflammatory bowel disease (IBD) patients. This large observational study was conducted to further describe risk factors and to quantify the proportion of POIs that are preventable.

Methods: We conducted a retrospective cohort analysis of the Optum US health insurance claims database. The study population included adults with ulcerative colitis (UC) or Crohn’s disease (CD) who underwent lower gastrointestinal (GI) surgery of small intestine, colon, rectum, or anus during September 2014 to September 2016. Multiple logistic regression was used to identify and quantify risk factors and determine the proportion of infections that are preventable.

Results: A total of 3360 adult IBD patients with lower GI surgery were included in the study. Their mean age was 51 years, 52.5% were women, and 59.5% had CD. The 30-day POI incidence was 15.1% (95% confidence interval: 14.0–16.4%). We identified the following nonmodifiable or procedural risk factors: history of POI, open procedure, red blood cell transfusion within 6 months, preoperative hospital stay of at least 4 days, lower GI ostomy surgery, lower GI resection surgery, and a history of chronic obstructive pulmonary disease. Modifiable risk factors included corticosteroid use and anemia prior to surgery, but few infections were attributable to these modifiable factors.

Conclusions: This large, observational, real-world evidence study from the US found that the majority of the observed risk factors were nonmodifiable or procedure-related. Corticosteroid use and anemia before surgery were identified as modifiable risk factors.

Introduction

Inflammatory bowel disease (IBD) is a relapsing and chronic inflammatory disorder of the gastrointestinal (GI) tract where Crohn’s disease (CD) and ulcerative colitis (UC) are two predominant forms of this debilitating disease. It has been estimated that up to 75% of patients with CD and approximately 25–45% of UC patients will eventually require a surgery.3 It has been reported that 6.9–31.4% of IBD patients have surgical site infections (SSIs).2–7 Postoperative infections (POIs) including SSIs are a major source of morbidity, prolongation of hospitalization, and increased medical costs and are associated with increased risk of mortality in IBD patients.8,9

Multiple risk factors for POIs have been identified in studies of non-IBD patients, including greater length of preoperative hospital stay,10 comorbidities such as diabetes, rheumatoid arthritis, anemia, HIV, hematoma, and cirrhosis; and preoperative use of corticosteroids and anticoagulants.11,12 In patients with IBD, apart from systemic disease (i.e. history of cancers, chronic obstructive pulmonary disease [COPD]), IBD severity, IBD surgery-related procedures such as open surgery,13 and intraoperative red blood cell (RBC) transfusion14 were identified as risk factors for POIs.

Previous studies of POIs in IBD patients were relatively small in size and therefore identified only a limited number of independent risk factors.13–16 Moreover, none of the previous IBD studies have an estimated population-attributable risk,17 which may be used to bring a perspective of population prevention strategies or impact on public health. In this study, we analyzed a large US health-care claims database in a commercially health-insured population to further describe risk factors and to quantify the proportion of POIs that are preventable in IBD patients.

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**Patients and methods**

**Study design and data source.** This was an observational retrospective cohort study.

The study population was selected from the US Optum Clinformatics DataMart (CDM). The CDM comes from a database of administrative health-care insurance claims for members of a large national managed care company affiliated with Optum and includes approximately 16 million annual covered lives for a total of over 48 million unique lives. The CDM is statistically deidentified under the Expert Determination method consistent with the Health Insurance Portability and Accountability Act (HIPAA). The claims data comprise both commercial and Medicare Advantage health plan data. The population is geographically diverse, spanning all 50 states. In addition to medical claims and pharmacy claims, the claims data include tables with member eligibility and inpatient confinement.

**Study population.** The analysis focused on IBD patients having lower GI surgery within the 2-year period, 1 September 2014 through 30 September 2016.

We defined lower GI surgery as having a claim for resection, repair, ostomy surgery, or drainage procedure of the small intestine, colon, rectum, or anus as defined by ICD-10 during the study period (Table 1). Enterolysis was grouped under drainage procedures, although typically, enterolysis may not include surgical drainage per se. If a patient had multiple lower GI surgeries during the study period, the analysis focused on the first surgery. Patients were required to have at least two medical claims on different dates for UC or CD on or before their surgery. Patients with only one prior medical claim were not included to minimize misclassification of other disease as IBD. If patients had only two IBD medical claims, and one had UC diagnosis and the other had CD diagnosis, then these patients were also excluded to minimize misclassification. Other selection criteria included: adults (age ≥ 18 years) at time of the index surgery, having both medical and pharmacy claims benefits from the start of the study period, and being continuously enrolled in an insurance plan for at least 6 months before and 30 days after lower GI surgery.

**Variables.** POIs included postoperative wound infection, peritonitis, retroperitoneal infection, and sepsis coded using ICD-9 and ICD-10. Infections occurring elsewhere, such as urinary tract and respiratory infections, were not included. POIs occurring 2–30 days after the lower GI surgery were identified from inpatient and outpatient facility claims and provider claims. POIs are likely to require antibiotic therapy, extension of hospitalization, or additional surgical procedures and would be captured in the insurance claims database as a reason for a claim. Minor infections that did not require antibiotics or did not result in an insurance claim were not captured.

Patients were classified as having UC or CD. Patients with both UC and CD diagnoses in their claim records were classified as follows: the IBD diagnosis closest to the surgery was used; if both diagnoses were used on the closest diagnosis date, then the diagnosis with a higher frequency in the patient’s claims record was used.

Demographics included gender, age at time of surgery, calendar year of surgery, and duration of insurance enrollment before surgery. IBD-related characteristics included claim histories for Clostridium difficile infection, GI abscess or fistula, lower GI surgery, POI, IBD-related hospital or physician visits, IBD-related hospitalizations, and emergency room visits prior to lower GI surgery. No information was available on UC/CD disease activity status at the time of surgery.

Other medical claim histories included: other bacterial infections (other than Clostridium difficile infection), any cancer other than basal cell carcinoma, cirrhosis, COPD, type 1/2 diabetes, deep venous thrombosis (DVT) in lower limbs, hematoma, HIV or use of antiretroviral therapy, and rheumatoid arthritis.

Surgery-related information included open or nonopen surgical procedure, type of lower GI surgery (resection, repair, ostomy surgery, drainage), duration of preoperative hospital stay, anemia within 14 days prior to surgery, and intraoperative RBC transfusion.

Medical and pharmacy claims for dispensing of the following medications in the 12 weeks before surgery were extracted, except corticosteroids where a 14-day period before surgery was used: 5-aminosalicylates (sulfasalazine, mesalamine/mesalazine, balsalazide, and olsalazine), systemic corticosteroids (defined as AHFS drug class 68 040 000 or 680 400 and included beclomethasone, budesonide, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, and prednisone), immunosuppressants (6-mercaptopurine, azathioprine, cyclosporin A, methotrexate, tacrolimus, thalidomide, mycophenolate mofetil, cyclophosphamide, and sirolimus), anti-TNF-α (adalimumab, certolizumab, golimumab, infliximab, including biosimilars of these agents), vedolizumab, and ustekinumab.

**Table 1** The most frequent lower gastrointestinal surgeries

| GI resection                | Ostomy surgery                  | Repair                      | Drainage procedure       |
|-----------------------------|---------------------------------|-----------------------------|--------------------------|
| Colectomy (n = 339)         | Ileostomy (n = 365)             | Surgical treatment of anal fistula (n = 191) | Enterolysis (n = 179)    |
| Resection of small intestine (n = 226) | Closure of stoma of small intestine (n = 80) | Anastomosis to anus (n = 42) | Placement of seton (n = 156) |
| Resection of small intestine, single resection and anastomosis (n = 198) | Revision of stoma of small intestine (n = 55) | Closure of fistula of small intestine (n = 38) | Incision and drainage, perianal abscess, superficial (n = 126) |
| Right hemicolectomy (n = 101) | Colostomy (n = 47)             | Repair of pericolostomy hernia (n = 33) | NA                       |

Note: Some patients had more than one procedure.
Information on use of non-IBD biologicals (alemtuzumab, belatacept, brentuximab vedotin, efalizumab, etanercept, natalizumab, ofatumumab, rituximab, abatacept, anakinra, tocilizumab) or anticoagulants during the 12 weeks before surgery and antibiotics during the 30 days before surgery was extracted. The antibiotics examined were those listed on the Centers for Disease Control and Prevention (CDC)’s SSI Form (CDC 57.120) or the Crohn’s and Colitis Foundation of America’s antibiotic fact sheet and included amoxicillin, amoxicillin with clavulanic acid, azithromycin, cephalosporin, ciprofloxacin, clarithromycin, clindamycin, fidaxomicin, gentamicin, metronidazole, rifaximin, trimethoprim, and vancomycin.

The study protocol was approved by the sponsor’s Protocol Review Committee before commencement of the analyses. No Institutional Review Board approval was required.

Statistical analyses. An unmatched cohort analysis was used to enable all potential risk factors to be quantified and risk modifiers to be assessed. Descriptive statistics were calculated for continuous and categorical variables, with all continuous variables classified into categorical variables as necessary. The 30-day cumulative incidence of POI and 95% confidence intervals (CIs) were calculated. Crude odds ratios (ORs) and 95% CIs for the risk of POI were calculated for each variable examined. Stepwise multiple logistic regression modeling was performed to generate ORs while adjusting for the effects of all other variables in the model. Covariates with a P < 0.1 in the crude analyses were entered into the regression model, and those maintaining a maximum likelihood ratio (P < 0.05) were retained in the model using a stepwise approach. Modeling was undertaken for all IBD patients and separately for UC and CD patients. Women tended to have lower risk of surgery-related infection compared with men, but in preliminary analysis, no gender effect was found, so separate analyses for males and females were not required.

To estimate the relative contribution of each risk factor, the population-attributable fraction (PAF) was calculated for each variable retained in the multiple logistic regression model. PAF provides an estimate of the proportion of cases of POI attributable to each of the risk factors and is based on the magnitude of the relative risk (adjusted OR was used as its estimate in this study) and the prevalence of the risk factor in the study population. All data management and analyses were performed using SAS version 9.4 (SAS Institute Inc.; Cary, NC, USA).

Results

Eligible patients. The patient attrition is presented in Table 2. Of 5341 adult patients with at least one UC or CD claim and with a lower GI surgery during 1 September 2014 to 30 September 2016, 4264 (79.8%) had two diagnostic claims for UC or CD before/on the index surgery date. After applying study inclusion and exclusion criteria, 3360 (62.9%) of the 5341 UC and CD patients having lower GI surgery were included in the analysis. There were slightly more females (52.5%), and the majority had CD (59.5%). The mean age at time of surgery was 51.2 years (SD = 17.9), and the surgeries were undertaken at 1269 hospitals (n = 3161, 94.1%) and 162 nonhospital facilities or providers (n = 199, 5.9%) across the United States.

Table 2. Patient attrition in the Optum Clinformatics DataMart (1 September 2014 through 30 September 2016)

| Inclusion criteria | Patients remained (%) | Patients excluded (%) |
|--------------------|----------------------|----------------------|
| Adult patients with one claim with UC or CD diagnosis code and with a lower GI surgery during 01 September 2014 to 30 September 2016 | 5471 (100) | NA |
| Adult patients with a lower GI surgery at index surgery date | 5341 (97.6) | 130 (2.4) |
| Patients with two diagnoses of UC or CD before/on the index surgery | 4264 (79.8) | 1077 (20.2) |
| Patients who were continuously enrolled for at least 6 months before the surgery | 3605 (84.6) | 659 (15.4) |
| Patients who were continuously enrolled for at least 30 days after the surgery | 3360 (93.2) | 245 (6.8) |

The most frequent surgeries were lower GI resection (60.8%), ostomy surgery, (30.3%), drainage procedure (23.5%), and repair (17.5%), with some patients having surgery involving more than one procedure (Table 1).

Incidence of POIs. A total of 509 IBD patients had a POI within 30 days after their surgery, yielding a POI rate of 15.1% (95% CI 14.0–16.4%), which was similar to the rates for UC (14.4%, 95% CI: 12.6–16.4%) and CD patients (15.7%, 95% CI: 14.1–17.3%).

The incidence of POI was highest in the group of patients, defined in Table 1 as those having open surgery (27.2%, 95% CI 24.3–30.2%) then those who had ostomy surgery (23.7%, 95% CI: 21.1–26.4%) followed by resection surgery (18.5%, 95% CI: 16.8–20.2%), repair surgery (12.4%, 95% CI: 9.8–15.3%), and laparoscopic or other lower GI surgery (10.9%, 95% CI 9.7–12.2%). The incidence of POI was lowest for GI drainage procedures (7.6%, 95% CI: 5.8–9.7%).

Univariate analyses. In unadjusted univariate analyses (Tables 3–6), increased risk of infection was associated with age ≥ 60 years (OR 1.49, 95% CI: 1.17–1.88); payer type, specifically Medicare insurance (OR 1.42, 95% CI: 1.17–1.73); prior history of POIs (OR 5.53, 95% CI: 4.41–6.95); history of Clostridium difficile infections (OR 3.17, 95% CI: 2.25–4.47); history of other bacterial infections (OR 3.38, 95% CI: 2.68–4.25); and two or more prior IBD-related hospitalizations (OR 2.27, 95% CI: 1.54–3.37). Use of 5-aminosalycilates, immunosuppressants, anti-TNF-α agents, or vedolizumab in the 12 weeks before surgery did not increase the risk of POI. Conversely, corticosteroids use within 14 days before surgery was associated with an increased risk of POI (OR 2.11, 95% CI: 1.71–2.60). Preoperative hospital stay ≥ 4 days (OR 2.80, 95% CI: 1.98–3.96), anemia within 14 days before surgery (OR 3.12, 95% CI 2.45–3.96), and intraoperative RBC transfusion (OR 2.38, 95% CI: 1.47–3.87) were associated with increased risk of POI. Other factors associated with risk of infection were cirrhosis (OR 2.11, 95% CI: 1.11–4.01), COPD (OR 2.28, 95% CI: 1.69–3.07), type 1 or...
Risk factors for postoperative infection

2 diabetes (OR 1.69, 95% CI: 1.29–2.22), DVT in lower limbs (OR 2.13, 95% CI: 1.45–3.15), rheumatoid arthritis (OR 2.13, 95% CI: 1.31–3.47), and RBC transfusion within 6 months before the index date (OR 4.33, 95% CI: 1.17–1.33). Reduced risk of infection was associated with >24 months of insurance enrollment before surgery (OR 0.78, 95% CI: 0.64–0.95).

Multiple logistic regression analyses. Two factors doubled the risk of a POI in the study population: prior history of POI (OR 4.21, 95% CI: 3.3–5.37) and having an open procedure (OR 2.31, 95% CI: 1.86–2.87) (Table 7). In addition, for UC patients, an RBC transfusion within 6 months and preoperative hospital stay (≥24 days) also doubled the risk, as did having GI ostomy surgery for CD patients.

Other statistically significant risk factors included anemia in 14 days before surgery (OR 1.89, 95% CI: 1.43–2.48), having GI resection (OR 1.65, 95% CI: 1.3–2.09), history of COPD (OR 1.63, 95% CI: 1.17–2.28), and use of systemic corticosteroids in 14 days before surgery (OR 1.52, 95% CI: 1.21–1.92).

The risk factors with the highest PAF were lower GI resection surgery (PAF 28.3%, 95% CI 15.5–39.8%), history of POI (PAF 27.9%, 95% CI 21.7–34.5%), and open procedure (PAF 25.6%, 95% CI 18.4–32.9%). Other risk factors such as RBC transfusion within 6 months, preoperative hospital stay ≥24 days, and history of COPD had relatively low PAF because of the low prevalence of the risk factors in the IBD population.

Discussion

Currently, this is the largest population-based observational US study to generate new real-world evidence on POI rates in patients with IBD. Several studies reported the POI rate in IBD patients after GI surgery.6–7 Among these, only two studies were completed in the United States on IBD patients.6,7 Bhakta et al. found an SSI incidence of 18% in IBD patients, and Lightner et al. reported a POI rate of 19.1% (derived using 75 patients with SSI or nonabdominal sepsis/392).6,7 In our study, we found that the 30-day POI incidence was 15.1% and was similar for patients with UC or CD. The difference in infection rates across studies in part reflects differences in the sample size, study population, study period, GI surgeries, and types of infections assessed. For example, Bhakta et al.’s study included 7570 IBD patients in the American College of Surgeons National Surgical Quality Improvement Project (ACS NSQIP) database, twice the size of our study, which included 3600 patients, and much larger than the study by Lightner et al. (n = 392). Moreover, Bhakta et al. also included UC, CD, and indeterminate colitis patients, but the percentage of IBD subtype was not reported. The percentage of patients with CD was 59.5% in our study versus 73% in Lightner et al.’s study. In addition, comparing the mean age of 51 years of adult IBD patients in our study, the IBD patients were younger in both Bhakta et al.’s study (mean age 43.7 years) and Lightner et al.’s study (median age 33 years). In addition, the Bhakta et al. study included only surgeries from 2008 through 2012, and all IBD patients underwent elective colectomy. Among them, open surgery procedure was performed in 52.1% of patients.7 Lightner’s study included patients with major GI surgeries performed between 20 May 2014 and 31 December 2015 at the Mayo Clinic Rochester, with the surgery data based on medical chart review. The present US cohort study included a broader span of surgeries between 1 September 2014 and
30 September 2016, and an open surgery procedure was performed on 26.3% patients.

We identified several independent risk factors for POI in IBD patients undergoing lower GI surgery. Although these risk factors for infection have been reported in other surgery populations, to the best of our knowledge, this is the first large observational US cohort study to report these risk factors in an IBD surgical cohort. Open procedures are recognized risk factors for infection and an open surgery procedure was performed on 26.3% patients.

Table 4 Inflammatory bowel disease-related characteristics and risk of postoperative infection

| IBD-related characteristics | All patients (n = 3360) | Postoperative infection |
|-----------------------------|------------------------|------------------------|
| IBD type                    |                        |                        |
| UC                          | 1362 (40.5)            | 196 (14.4)             | 1166 (85.6) | Reference |
| CD                          | 1998 (59.5)            | 313 (15.7)             | 1685 (84.3) | 1.10 (0.91, 1.34) |
| Abscess/fistula              |                        |                        |
| No                          | 3170 (94.4)            | 481 (15.2)             | 2689 (84.8) | Reference |
| Yes                         | 190 (5.6)              | 28 (14.7)              | 162 (85.3)  | 0.97 (0.64, 1.46) |
| Previous lower GI surgery   |                        |                        |
| No                          | 3224 (96.0)            | 494 (15.3)             | 2730 (84.7) | Reference |
| Yes                         | 136 (4.0)              | 15 (11.0)              | 121 (89.0)  | 0.69 (0.40, 1.18) |
| History of postoperative infections |                   |                        |
| No                          | 2956 (88.0)            | 340 (11.5)             | 2616 (88.5) | Reference |
| Yes                         | 404 (12.0)             | 169 (41.8)             | 235 (58.2)  | 5.53 (4.41, 6.95) |
| History of Clostridium difficile infection |                   |                        |
| No                          | 3203 (95.3)            | 455 (14.2)             | 2748 (85.8) | Reference |
| Yes                         | 157 (4.7)              | 54 (34.4)              | 103 (65.6)  | 3.17 (2.25, 4.47) |
| History of other bacterial infections |                  |                        |
| No                          | 2939 (87.5)            | 371 (12.6)             | 2568 (87.4) | Reference |
| Yes                         | 421 (12.5)             | 138 (32.8)             | 283 (67.2)  | 3.38 (2.68, 4.25) |
| Number of IBD-related physician visits |                 |                        |
| 0–3                         | 2822 (84.0)            | 417 (14.8)             | 2405 (85.2) | Reference |
| ≥4                          | 539 (16.0)             | 92 (17.1)              | 446 (82.9)  | 1.19 (0.93, 1.52) |
| Number of IBD-related hospitalizations |                 |                        |
| 0–1                         | 3229 (96.1)            | 472 (14.6)             | 2756 (85.4) | Reference |
| ≥2                          | 132 (3.9)              | 37 (28.0)              | 95 (72.0)   | 2.27 (1.54, 3.37) |
| Number of IBD-related emergency room visits |                |
| 0–1                         | 3225 (99.3)            | 508 (15.2)             | 2827 (84.8) | Reference |
| ≥2                          | 25 (0.7)               | 1 (4.0)                | 24 (96.0)   | 0.23 (0.03, 1.72) |
| IBD medications use before surgery |                      |
| Anti-TNF-alpha              |                        |                        |
| No                          | 2674 (79.6)            | 399 (14.9)             | 2275 (85.1) | Reference |
| Yes                         | 686 (20.4)             | 110 (16.0)             | 576 (84.0)  | 1.09 (0.87, 1.37) |
| Vedolizumab                 |                        |                        |
| No                          | 3246 (96.6)            | 492 (15.2)             | 2754 (84.8) | Reference |
| Yes                         | 114 (3.4)              | 17 (14.9)              | 97 (85.1)   | 0.98 (0.58, 1.66) |
| Ustekinumab                 |                        |                        |
| No                          | 3352 (99.8)            | 508 (15.2)             | 2844 (84.8) | Reference |
| Yes                         | 8 (0.2)                | 1 (12.5)               | 7 (87.5)    | 0.80 (0.10, 6.51) |
| 5-Aminosalicylates          |                        |                        |
| No                          | 2627 (78.2)            | 388 (14.8)             | 2239 (85.2) | Reference |
| Yes                         | 733 (21.8)             | 121 (16.5)             | 612 (83.5)  | 1.14 (0.91, 1.43) |
| Corticosteroids             |                        |                        |
| No                          | 2666 (79.9)            | 348 (13.0)             | 2388 (87.0) | Reference |
| Yes                         | 674 (20.1)             | 161 (23.9)             | 513 (76.1)  | 2.11 (1.71, 2.60) |
| Immunosuppressants          |                        |                        |
| No                          | 2978 (88.6)            | 450 (15.1)             | 2528 (84.9) | Reference |
| Yes                         | 382 (11.4)             | 59 (15.4)              | 323 (84.6)  | 1.03 (0.76, 1.38) |

CD, Crohn’s disease; GI, gastrointestinal; IBD, inflammatory bowel disease; UC, ulcerative colitis.

Immunosuppressants = 6-mercaptopurine, azathioprine, cyclosporin A, methotrexate, tacrolimus, thalidomide, mycophenolate mofetil, cyclophosphamide, and sirolimus.
Intraoperative red blood cell transfusion and risk factors for postoperative infection in patients with ulcerative colitis or Crohn’s disease

| Procedure type            | All patients (n = 3360) | Yes (n = 509) | No (n = 2851) | Odds ratio | 95% confidence interval |
|---------------------------|-------------------------|---------------|---------------|------------|-------------------------|
|                          | N (%)                   | N (%)         | N (%)         |            |                         |
| Procedure type            |                          |               |               |            |                         |
| Nonopen                    | 2477 (73.7)             | 269 (10.9)    | 2208 (69.1)   | Reference  |                         |
| Open                      | 883 (26.3)              | 240 (27.2)    | 643 (72.8)    | 3.06       | (2.52, 3.72)            |
| Resection                 |                          |               |               |            |                         |
| No                        | 1318 (39.2)             | 131 (9.9)     | 1187 (90.1)   | Reference  |                         |
| Yes                       | 2042 (60.8)             | 378 (18.5)    | 1664 (81.5)   | 2.06       | (1.66, 2.54)            |
| Repair                    |                          |               |               |            |                         |
| No                        | 2771 (82.5)             | 436 (15.7)    | 2335 (84.3)   | Reference  |                         |
| Yes                       | 589 (17.5)              | 73 (12.4)     | 516 (87.6)    | 0.76       | (0.58, 0.99)            |
| Ostomy surgery            |                          |               |               |            |                         |
| No                        | 2341 (69.7)             | 268 (11.4)    | 2073 (88.6)   | Reference  |                         |
| Yes                       | 1019 (30.3)             | 241 (23.7)    | 778 (76.4)    | 2.40       | (1.98, 2.90)            |
| Drainage procedure        |                          |               |               |            |                         |
| No                        | 2569 (76.5)             | 449 (17.5)    | 2120 (82.5)   | Reference  |                         |
| Yes                       | 791 (23.5)              | 60 (7.6)      | 731 (92.4)    | 0.39       | (0.29, 0.51)            |
| Preoperative hospital stay (days) |                  |               |               |            |                         |
| 0–3 days                  | 3200 (95.2)             | 458 (14.3)    | 2742 (85.7)   | Reference  |                         |
| ≥4 days                   | 160 (4.8)               | 51 (31.9)     | 109 (68.1)    | 2.80       | (1.98, 3.96)            |
| Anemia 14 days before surgery |                      |               |               |            |                         |
| No                        | 2976 (88.6)             | 387 (13.0)    | 2589 (87.0)   | Reference  |                         |
| Yes                       | 384 (11.4)              | 122 (31.8)    | 262 (68.2)    | 3.12       | (2.45, 3.96)            |
| Intraoperative red blood cell transfusion |              |               |               |            |                         |
| No                        | 3278 (97.6)             | 485 (14.8)    | 2793 (85.2)   | Reference  |                         |
| Yes                       | 82 (2.4)                | 24 (29.3)     | 58 (70.7)     | 2.38       | (1.47, 3.87)            |

POIs possible due to microbial dysbiosis.18,23,24 Laparoscopic surgeries have been demonstrated to reduce POIs. Lower GI ostomy creation and resection surgeries, which included the most common IBD surgeries of colectomy and fistula repair, were associated with increased POIs, possibly related to the complexity of these surgeries.

In our study, we also found a preoperative hospital stay for at least 4 days to be an independent predictor for POI. A pre-surgical hospital stay of more than 4 days has been reported to be associated with higher risk of POI in inpatients recovering from trauma (OR 1.58, 95% CI 1.1–2.35)25 as well as in orthopedic patients (OR 3.3, 95% CI 2.5–4.0).26,27 While appropriate to minimize surgical delay in hospitalized IBD patients, this may not be clinically feasible. Although other risk factors including history of POI, history of COPD, and RBC transfusion within 6 months are not modifiable, surgeons may consider patients with these risk factors at a higher risk of POI.

We found that the use of systemic corticosteroids was an independent risk factor for POIs. Several studies suggest that preoperative use of corticosteroids is associated with an increased risk of systemic and wound infections.28 A meta-analysis of studies from 1965 to October 2006 also identified corticosteroids to be associated with postoperative infectious complications in IBD patients (OR 1.68, 95% CI: 1.24–2.28).29 Systemic immune suppression with oral or intravenous corticosteroids may predispose a patient to infection.30 Corticosteroid use has also been found to be an independent risk factor for increased hospital resource utilization.31 Minimizing systemic corticosteroid use in IBD patients when possible may reduce the cost as well as the risk of POI. In this study, biological therapies such as anti-TNF-α and vedolizumab did not increase the risk of POI.

Anemia 14 days before surgery was also an independent risk factor for POIs among both UC and CD patients. Caused by multiple pathogenic mechanisms in UC and CD,32 anemia is common in both UC and CD patients. Low hemoglobin concentrations in anemia predispose the patient to acute bacterial infection, probably by means of reduced oxygen saturation at potentially infected sites.33 Preoperative correction of anemia through interventions according to relevant guidelines is needed to achieve a safe hemoglobin level before surgery.34,35

We found that the majority of the observed risk factors were nonmodifiable or procedure-related. For example, lower GI resection surgery, history of POI, and open procedure each had PAF greater than 25%. Considering the estimated prevalent cases of 780 000 CD and 907 000 UC in the United States36 and that up to 75% of patients with CD and approximately 25–45% of UC patients will eventually require a surgery,1 assuming 50% of CD patients and 30% of UC patients had a lower GI surgery and the lifespan in the United States is 80 years, the estimated number of lower GI surgeries per year is estimated to be 8276 surgeries in IBD patients. Assuming a 30-day POI is 15.1% and a PAF of 9% for both use of corticosteroids and anemia before surgery in the surgery population, the number of POI cases that may be prevented would be around 112 per year if each of these two modifiable risk factors could be first eliminated alone. Considering none of the previous studies in IBD have reported PAFs, our
findings provide important information for the prevention and control of POI.

Our study exhibits several strengths. In this large study, we used a US database that included all medical and pharmacy information on claims for all morbidities, all medical facilities, and physicians treating the patient. Through the use of a geographically diverse US database, we had access to detailed patient information, including patient’s diagnoses and use of medications. Including the most current data, a broader group of surgeries, and a large sample size gave us a more recent and representative estimate of POI; thus, this analysis significantly advances the existing literature on POIs in US patients with IBD.

There are a few limitations to note. The proportion of elderly patients in this database was slightly lower than in the general population. This might bias the results toward a lower incidence of POI. Information was based on events and procedures for which medical claims were paid; thus, minor morbidities may not have been captured in medical claims data.

### Table 6 Medical histories and non-IBD medication use and risk of postoperative infection in patients with ulcerative colitis or Crohn’s disease

| Medical History / Medication Use                                                                 | All patients (n = 3360) | Postoperative infection | Odds ratio  | 95% confidence interval |
|-------------------------------------------------------------------------------------------------|-------------------------|-------------------------|-------------|-------------------------|
|                                                                                                 | N (%)                   | Yes (n = 509)          | No (n = 2851) |                       |
|                                                                                                 | N (%)                   | N (%)                  | N (%)       |                         |
| Cancer                                                                                          |                         |                        |             |                         |
| No                                                                                              | 3007 (89.5)             | 446 (14.8)             | 2561 (85.2) | Reference               |
| Yes                                                                                             | 353 (10.5)              | 63 (17.8)              | 290 (82.2)  | 1.25                    | (0.93, 1.67) |
| Cirrhosis                                                                                       |                         |                        |             |                         |
| No                                                                                              | 3312 (98.6)             | 496 (15.0)             | 2816 (85.0) | Reference               |
| Yes                                                                                             | 48 (1.4)                | 13 (27.1)              | 35 (72.9)   | 2.11                    | (1.11, 4.01) |
| Chronic obstructive pulmonary disease                                                            |                         |                        |             |                         |
| No                                                                                              | 3115 (92.7)             | 442 (14.2)             | 2673 (85.8) | Reference               |
| Yes                                                                                             | 245 (7.3)               | 67 (27.4)              | 178 (72.6)  | 2.28                    | (1.69, 3.07) |
| Diabetes (type 1 or 2)                                                                          |                         |                        |             |                         |
| No                                                                                              | 3002 (89.4)             | 430 (14.3)             | 2572 (85.7) | Reference               |
| Yes                                                                                             | 356 (10.6)              | 79 (22.1)              | 279 (77.9)  | 1.69                    | (1.29, 2.22) |
| Deep vein thrombosis in lower limbs                                                             |                         |                        |             |                         |
| No                                                                                              | 3222 (95.9)             | 472 (14.6)             | 2750 (85.4) | Reference               |
| Yes                                                                                             | 138 (4.1)               | 37 (26.8)              | 101 (73.2)  | 2.13                    | (1.45, 3.15) |
| Hematoma                                                                                        |                         |                        |             |                         |
| No                                                                                              | 3358 (99.9)             | 509 (15.2)             | 2849 (84.8) | Reference               |
| Yes                                                                                             | 2 (0.1)                 | 0 (0.0)                | 2 (100.0)   | NA                      | NA          |
| HIV or use of ART                                                                               |                         |                        |             |                         |
| No                                                                                              | 3343 (99.5)             | 509 (15.2)             | 2834 (84.8) | Reference               |
| Yes                                                                                             | 17 (0.5)                | 0 (0.0)                | 17 (100.0)  | NA                      | NA          |
| Low gastrointestinal surgery                                                                     |                         |                        |             |                         |
| No                                                                                              | 3224 (96.0)             | 494 (15.3)             | 2730 (84.7) | Reference               |
| Yes                                                                                             | 136 (4.0)               | 15 (11.0)              | 121 (89.0)  | 0.69                    | (0.40, 1.18) |
| Postprocedural hemorrhage                                                                       |                         |                        |             |                         |
| No                                                                                              | 3348 (99.6)             | 505 (15.1)             | 2843 (84.9) | Reference               |
| Yes                                                                                             | 12 (0.4)                | 4 (33.3)               | 8 (66.7)    | 2.82                    | (0.85, 9.38) |
| Rheumatoid arthritis                                                                            |                         |                        |             |                         |
| No                                                                                              | 3275 (97.5)             | 486 (14.8)             | 2789 (85.2) | Reference               |
| Yes                                                                                             | 85 (2.5)                | 23 (27.1)              | 62 (72.9)   | 2.13                    | (1.31, 3.47) |
| Red blood cell transfusion                                                                      |                         |                        |             |                         |
| No                                                                                              | 3299 (98.2)             | 483 (14.6)             | 2816 (85.4) | Reference               |
| Yes                                                                                             | 61 (1.8)                | 26 (42.6)              | 35 (57.4)   | 4.33                    | (2.58, 7.26) |
| Other non-IBD medication use before surgery                                                      |                         |                        |             |                         |
| Other biologics therapy                                                                         |                         |                        |             |                         |
| No                                                                                              | 3354 (99.8)             | 508 (15.2)             | 2846(84.8)  | Reference               |
| Yes                                                                                             | 6 (0.2)                 | 1 (16.7)               | 5 (83.3)    | 1.12                    | (0.13, 9.61) |
| Antibiotics                                                                                     |                         |                        |             |                         |
| No                                                                                              | 3007 (89.5)             | 444 (14.8)             | 2563 (85.2) | Reference               |
| Yes                                                                                             | 353 (10.5)              | 65 (18.4)              | 288 (81.6)  | 1.30                    | (0.98, 1.74) |
| Anticoagulants                                                                                  |                         |                        |             |                         |
| No                                                                                              | 3106 (92.4)             | 460 (14.8)             | 2645 (85.2) | Reference               |
| Yes                                                                                             | 255 (7.6)               | 49 (19.2)              | 206 (80.8)  | 1.37                    | (0.99, 1.90) |

ART, antiretroviral therapy; HIV, human immunodeficiency virus; IBD, inflammatory bowel disease.
Residual confounding is possible as information on some risk factors, such as duration of surgery, experience of the surgeon, smoking, alcohol use, and poor hygiene, was not available in the database, and we were not able to adjust for the effects of these factors. One potential protective factor we were not able to study was prophylactic antibiotic use as it was rarely captured as a separate insurance claim and was instead bundled with surgical procedure claims. We assume that, per practice guidelines, most patients would have had prophylactic antibiotics. Another limitation is that we were unable to separate out emergency versus elective surgeries in a claims database without electronic medical records data. Emergency surgeries in IBD include surgeries for toxic colitis, hemorrhage, perforation, intra-abdominal abscess or mass with sepsis, and intestinal obstruction.

Conclusions

This large real-world evidence study from the United States found that the majority of the observed risk factors for POI were nonmodifiable or procedure-related. Corticosteroid use and anemia before surgery were identified as modifiable risk factors. The study findings could provide further guidance for physicians caring for IBD patients.

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Table 7  Multiple logistic regression analysis of risk factors for postoperative infection and prevalence in the study cohort

| Variable                                      | Adjusted odds ratio | 95% confidence interval of aOR | Prevalence of risk factor in study population (%) | Population attributable fraction (PAF) | 95% confidence interval of PAF |
|------------------------------------------------|---------------------|--------------------------------|--------------------------------------------------|---------------------------------------|---------------------------------|
| All IBD (n = 3360)                             |                     |                                |                                                  |                                       |                                 |
| History of postoperative infection             | 4.21                | (3.3, 5.37)                    | 12                                               | 27.9                                  | (21.7, 34.5)                    |
| Open procedure                                 | 2.31                | (1.86, 2.87)                   | 26.3                                             | 25.6                                  | (18.4, 32.9)                    |
| Red blood cell transfusion                     | 1.9                 | (1.06, 3.39)                   | 1.82                                             | 1.6                                   | (0.1, 4.2)                      |
| Anemia in 14 days before surgery               | 1.89                | (1.43, 2.48)                   | 11.4                                             | 9.2                                   | (4.7, 14.5)                     |
| Lower GI ostomy surgery                        | 1.76                | (1.42, 2.18)                   | 30.3                                             | 18.8                                  | (11.4, 26.3)                    |
| Lower GI resection surgery                     | 1.65                | (1.3, 2.09)                    | 60.8                                             | 28.3                                  | (15.5, 39.8)                    |
| History of COPD                                | 1.63                | (1.17, 2.28)                   | 7.29                                             | 4.4                                   | (1.2, 8.5)                      |
| Preoperative hospital stay (≥4 days)           | 1.61                | (1.07, 2.42)                   | 4.76                                             | 2.8                                   | (0.3, 6.3)                      |
| Corticosteroids use in 14 days before surgery  | 1.52                | (1.21, 1.92)                   | 20.1                                             | 9.5                                   | (4.1, 15.6)                     |
| Ulcerative colitis (n = 1362)†                 |                     |                                |                                                  |                                       |                                 |
| History of postoperative infection             | 5.54                | (3.67, 8.36)                   | 10.4                                             | 32                                    | (21.7, 43.2)                    |
| Red blood cell transfusion                     | 3.46                | (1.56, 7.66)                   | 2.5                                              | 5.8                                   | (1.4, 14.3)                     |
| Preoperative hospital stay (≥4 days)           | 2.29                | (1.24, 4.21)                   | 4.92                                             | 5.9                                   | (1.2, 13.6)                     |
| Open procedure                                 | 2.22                | (1.56, 3.18)                   | 25.8                                             | 24                                    | (12.6, 36)                      |
| Lower GI resection surgery                     | 1.93                | (1.29, 2.67)                   | 63.4                                             | 37                                    | (15.5, 54.3)                    |
| Anemia in 14 days before surgery               | 1.78                | (1.13, 2.81)                   | 10.6                                             | 7.6                                   | (1.3, 16.1)                     |
| History of COPD                                | 1.71                | (1.03, 2.83)                   | 8.3                                              | 5.6                                   | (0.3, 13.2)                     |
| Corticosteroids use in 14 days before surgery  | 1.37                | (0.91, 2.06)                   | 17.3                                             | 6.1                                   | —                               |
| Lower GI ostomy surgery                        | 1.27                | (0.89, 1.81)                   | 40.2                                             | 9.8                                   | —                               |
| Crohn’s disease (n = 1998)†                    |                     |                                |                                                  |                                       |                                 |
| History of postoperative infection             | 3.53                | (2.59, 4.81)                   | 13.2                                             | 25                                    | (17.3, 33.4)                    |
| Open procedure                                 | 2.36                | (1.79, 3.12)                   | 26.6                                             | 26.5                                  | (17.3, 36)                      |
| Lower GI ostomy surgery                        | 2.3                 | (1.73, 3.05)                   | 23.6                                             | 23.5                                  | (14.7, 32.6)                    |
| Anemia 14 days before surgery                  | 2                   | (1.41, 2.83)                   | 12                                              | 10.7                                  | (4.7, 18)                       |
| Corticosteroids use in 14 days before surgery  | 1.64                | (1.23, 2.19)                   | 21.9                                             | 12.3                                  | (4.8, 20.7)                     |
| Lower GI resection surgery                     | 1.6                 | (1.19, 2.16)                   | 59                                               | 26.2                                  | (9.9, 40.7)                     |
| History of COPD                                | 1.58                | (1.01, 2.49)                   | 6.61                                             | 3.7                                   | (0.9)                           |
| Preoperative hospital stay (≥4 days)           | 1.41                | (0.8, 2.48)                    | 4.65                                             | 1.9                                   | —                               |
| Red blood cell transfusion                     | 1.02                | (0.41, 2.54)                   | 1.35                                             | 0                                     | —                               |

†For comparability, the UC and CD model included the same variables as the all IBD model. COPD, chronic obstructive pulmonary disease; IBD, inflammatory bowel disease; PAF, population attributable fraction.
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