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ORIGINAL ARTICLE

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.[1] 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) transfusion[14] 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.

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 confinements.

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.[18] 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.[19]

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[11] 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)[20] 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.[21]

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,[22] 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.[17] 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/or on the index surgery. 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-aminosalicylates, 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

Table 3 Demographics and patient characteristics and risk of postoperative infection

	All patients (n = 3360) N (%)	Postoperative infection			
		Yes (n = 509) N (%)	No (n = 2851) N (%)	Odds ratio	95% confidence interval
Gender					
Female	1764 (52.5)	263 (14.9)	1501 (85.1)	Reference	
Male	1596 (47.5)	246 (15.4)	1350 (84.6)	1.04	(0.86, 1.26)
Age at surgery (years)					
18–39	1023 (30.4)	131 (12.8)	892 (87.2)	Reference	
40–59	1153 (34.3)	166 (14.4)	987 (85.6)	1.15	(0.90, 1.46)
≥60	1184 (35.2)	212 (17.9)	972 (82.1)	1.49	(1.17, 1.88)
Region, n (%)					
West	549 (16.3)	91 (16.6)	458 (83.4)	Reference	
Midwest	981 (29.2)	142 (14.5)	839 (85.5)	0.85	(0.64, 1.13)
Northeast	453 (13.5)	72 (15.9)	381 (84.1)	0.95	(0.68, 1.33)
South	1374 (40.9)	204 (14.9)	1170 (85.2)	0.88	(0.67, 1.15)
Unknown	3 (0.1)	0 (0)	3 (100.0)	0.00	NA
Payer type, n (%)					
Commercial	2340 (69.6)	321 (13.7)	2019 (86.3)	Reference	
Medicare	1020 (30.4)	188 (18.4)	832 (81.6)	1.42	(1.17, 1.73)
Year of surgery					
2014–2015	2285 (68.0)	333 (14.6)	1952 (85.4)	Reference	
2016	1075 (32.0)	176 (16.4)	899 (83.6)	1.15	(0.94, 1.40)
Enrollment duration before surgery (months)					
6 to <24	1214 (36.1)	209 (17.2)	1005 (82.8)	Reference	
≥24	2146 (63.9)	300 (14.0)	1846 (86.0)	0.78	(0.64, 0.95)

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: 2.58–7.26). 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 (≥4 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 ≥4 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.[2–7] 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

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

	All patients (n = 3360) N (%)	Postoperative infection		Odds ratio	95% confidence interval
		Yes (n = 509) N (%)	No (n = 2851) N (%)		
IBD-related characteristics					
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	538 (16.0)	92 (17.1)	446 (82.9)	1.19	(0.93, 1.52)
Number of IBD-related hospitalizations					
0–1	3228 (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	3325 (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	2686 (79.9)	348 (13.0)	2338 (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.

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

Table 5 Surgery-related variables and risk of postoperative infection in patients with ulcerative colitis or Crohn's disease

	All patients (n = 3360) N (%)	Postoperative infection			
		Yes (n = 509) N (%)	No (n = 2851) N (%)	Odds ratio	95% confidence interval
Procedure type					
Nonopen	2477 (73.7)	269 (10.9)	2208 (89.1)	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 presurgical 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 States[36] 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

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

		Postoperative infection			
	All patients (n = 3360) N (%)	Yes (n = 509) N (%)	No (n = 2851) N (%)	Odds ratio	95% confidence interval
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	358 (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	3105 (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.

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 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, 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, 2.87)	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.

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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HL, DB, and PD participated in the design of the study and development of protocol. HL, SM, and BJ conducted analyses. TL served as a scientific advisor. All authors participated in the data and results interpretation. HL wrote the first manuscript draft. All authors critically reviewed, revised for important intellectual content, and approved the final manuscript. The authors acknowledge that Hari Patel, Shashi Adsul, Raquel Rogers, and Biplob Dass from Takeda Pharmaceutical Company Limited reviewed the manuscript and provided valuable comments.

References

1 *Surgery for Crohn's Disease & Ulcerative Colitis.* Cited 8 May 2017. Available from URL: http://www.crohnscolitisfoundation.org/resources/surgery-for-crohns-uc.html?referrer=https://www.google.com/.

2 Uchino M, Ikeuchi H, Matsuoka H, Takahashi Y, Tomita N, Takesue Y. Surgical site infection and validity of staged surgical procedure in emergent/urgent surgery for ulcerative colitis. *Int. Surg.* 2013; **98**: 24–32.
3 Maeda K, Nagahara H, Shibutani M *et al*. A preoperative low nutritional prognostic index correlates with the incidence of incisional surgical site infections after bowel resection in patients with crohn's disease. *Surg. Today*. 2015; **45**: 1366–72.
4 Uchino M, Ikeuchi H, Tsuchida T, Nakajima K, Tomita N, Takesue Y. Surgical site infection following surgery for inflammatory bowel disease in patients with clean-contaminated wounds. *World J. Surg.* 2009; **33**: 1042–8.
5 Guo K, Ren J, Li G *et al*. Risk factors of surgical site infections in patients with crohn's disease complicated with gastrointestinal fistula. *Int. J. Colorectal Dis.* 2017; **32**: 635–43.
6 Lightner AL, Raffals LE, Mathis KL *et al*. Postoperative outcomes in vedolizumab-treated patients undergoing abdominal operations for inflammatory bowel disease. *J. Crohns Colitis*. 2017; **11**: 185–90.
7 Bhakta A, Tafen M, Glotzer O *et al*. Increased incidence of surgical site infection in ibd patients. *Dis. Colon Rectum*. 2016; **59**: 316–22.
8 Ban KA, Minei JP, Laronga C *et al*. Executive summary of the american college of surgeons/surgical infection society surgical site infection guidelines-2016 update. *Surg. Infect. (Larchmt.)*. 2017; **18**: 379–82.
9 Shepard J, Ward W, Milstone A *et al*. Financial impact of surgical site infections on hospitals: the hospital management perspective. *JAMA Surg.* 2013; **148**: 907–14.
10 Gibbons C, Bruce J, Carpenter J *et al*. Identification of risk factors by systematic review and development of risk-adjusted models for surgical site infection. *Health Technol. Assess.* 2011; **15**: 1–156 iii–iv.
11 Marmor S, Kerroumi Y. Patient-specific risk factors for infection in arthroplasty procedure. *Orthop. Traumatol. Surg. Res.* 2016; **102**: S113–9.
12 Deleuran T, Vilstrup H, Overgaard S, Jepsen P. Cirrhosis patients have increased risk of complications after hip or knee arthroplasty. *Acta Orthop.* 2015; **86**: 108–13.
13 Wilson MZ, Connelly TM, Hollenbeak CS, Messaris E. Organ space infection following ileocolectomy for crohn's disease: a national surgical quality improvement project study. *Am. J. Surg.* 2014; **208**: 749–55.
14 Coakley BA, Divino CM. Identifying factors predictive of surgical-site infections after colectomy for fulminant ulcerative colitis. *Am. Surg.* 2012; **78**: 481–4.
15 Araki T, Okita Y, Uchino M *et al*. Risk factors for surgical site infection in japanese patients with ulcerative colitis: a multicenter prospective study. *Surg. Today*. 2014; **44**: 1072–8.
16 Uchino M, Ikeuchi H, Bando T *et al*. Does pre-operative multiple immunosuppressive therapy associate with surgical site infection in surgery for ulcerative colitis. *Digestion*. 2015; **92**: 121–9.
17 Levin ML. The occurrence of lung cancer in man. *Acta Unio Int. Contra Cancrum.* 1953; **9**: 531–41.
18 Olsen MA, Nickel KB, Wallace AE, Mines D, Fraser VJ, Warren DK. Stratification of surgical site infection by operative factors and comparison of infection rates after hernia repair. *Infect. Control Hosp. Epidemiol.* 2015; **36**: 329–35.
19 Stemkowski S, Bailey RA, McKenzie RS, Piech CT. Evaluation of blood transfusion utilization in patients undergoing elective total knee replacement surgery. *Transfusion*. 2009; **49**: 2256–7.
20 Centers for Disease Control and Prevention (CDC)'s National Healthcare Safety Network. *Surgical Site Infection Form (CDC 57.120).* Cited 30 November 2016. Available from URL: www.Cdc.Gov/nhsn/forms/57.120_ssi_blank.pdf
21 CCFA. Crohn's and Colitis Foundation of America (CCFA) fact sheet. News from the IBD help center. Updated: January 2015. Cited 31 Aug 2015. Available from URL: http://www.ccfa.org/assets/pdfs/antibiotics.pdf
22 Cohen B, Choi YJ, Hyman S, Furuya EY, Neidell M, Larson E. Gender differences in risk of bloodstream and surgical site infections. *J. Gen. Intern. Med.* 2013; **28**: 1318–25.
23 Ohigahsi S, Sudo K, Ode S, Takahashi O, Sakamoto F, Onodera H. Factors affecting the risk of surgical site infection after surgery for colorectal cancer - association between causative bacteria and postoperative changes of microbiota. *Nippon Daicho Komonbyo Gakkai*. 2014; **67**: 158–67.
24 Sheka AC, Tevis S, Kennedy GD. Urinary tract infection after surgery for colorectal malignancy: risk factors and complications. *Am. J. Surg.* 2016; **211**: 31–9.
25 Herruzo-Cabrera R, Lopez-Gimenez R, Diez-Sebastian J, Lopez-Acinero MJ, Banegas-Banegas JR. Surgical site infection of 7301 traumatologic inpatients (divided in two sub-cohorts, study and validation): Modifiable determinants and potential benefit. *Eur. J. Epidemiol.* 2004; **19**: 163–9.
26 de Boer AS, Mintjes-de Groot AJ, Severijnen AJ, van den Berg JM, van Pelt W. Risk assessment for surgical-site infections in orthopedic patients. *Infect. Control Hosp. Epidemiol.* 1999; **20**: 402–7.
27 Pereira HO, Rezende EM, Couto BR. Length of preoperative hospital stay: A risk factor for reducing surgical infection in femoral fracture cases. *Rev. Bras. Ortop.* 2015; **50**: 638–46.
28 Kurz A, Saager L, Dalton J, Turner P, Turan A. Preoperative chronic steroid use is associated with increased wound and systemic infection in non-cardiac surgical patients. *Anesth. Analg.* 2010; **1**: S182.
29 Subramanian V, Saxena S, Kang JY, Pollok RC. Preoperative steroid use and risk of postoperative complications in patients with inflammatory bowel disease undergoing abdominal surgery. *Am. J. Gastroenterol.* 2008; **103**: 2373–81.
30 Leung DY, Bloom JW. Update on glucocorticoid action and resistance. *J. Allergy Clin. Immunol.* 2003; **111**: 3–22 quiz 3.
31 Click B, Ramos Rivers C, Koutroubakis IE *et al*. Demographic and clinical predictors of high healthcare use in patients with inflammatory bowel disease. *Inflamm. Bowel Dis.* 2016; **22**: 1442–9.
32 Kaitha S, Bashir M, Ali T. Iron deficiency anemia in inflammatory bowel disease. *World J Gastrointest. Pathophysiol.* 2015; **6**: 62–72.
33 Musher DM. Anemia and infection. *Clin. Infect. Dis.* 2004; **39**: 1731–2 author reply 2.
34 Gasche C, Berstad A, Befrits R *et al*. Guidelines on the diagnosis and management of iron deficiency and anemia in inflammatory bowel diseases. *Inflamm. Bowel Dis.* 2007; **13**: 1545–53.
35 DeBellis RJ. Anemia in critical care patients: Incidence, etiology, impact, management, and use of treatment guidelines and protocols. *Am. J. Health-Syst. Pharm.* 2007; **64**: S14–21 quiz S8–30.
36 Crohn's & Colitis Foundation of America. *The Facts about Inflammatory Bowel Diseases.* Accessed 6 Sept 2017. 2014 Nov. http://www.ccfa.org/assets/pdfs/updatedibdfactbook.pdf