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Immunosuppressed Patients with Crohn's Disease Are at Increased Risk of Postoperative Complications: Results from the ACS-NSQIP Database

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Abstract

Background The impact of immunosuppressants on postoperative complications following colon resections for Crohn's disease remains controversial. This study aimed to compare postoperative outcomes between immunosuppressed and immunocompetent patients with Crohn's disease undergoing elective colon resection.

Methods Analysis of 30-day outcomes using a cohort from the American College of Surgeons National Surgical Quality Improvement Program colectomy-specific database was performed. The database is populated by trained clinical reviewers who collect 30-day postoperative outcomes for patients treated at participating North-American institutions. Adult patients who underwent an elective colectomy between 2011 and 2015 were included. Immunosuppression for Crohn's disease was predefined as use of regular corticosteroids or immunosuppressants within 30 days of the operation. Patients who received chemotherapy within 90 days of surgery, and patients who had disseminated cancer, preoperative shock, or emergency surgery were excluded. Primary outcome was infectious complications.

Results Three thousand eight hundred sixty patients with Crohn's disease required elective colon resection and met the inclusion criteria. Of these, 2483 were immunosuppressed and 1377 were immunocompetent. On multivariate analysis, the odds of infectious complications [OR 1.25; 95% CI (1.033–1.523)], overall surgical site infection [1.40; (1.128–1.742)], organ space surgical site infection [1.47; (1.094–1.984)], and anastomotic leak [1.51; (1.018–2.250)] were significantly higher for immunosuppressed compared to immunocompetent patients with Crohn's disease.

Conclusions Patients with Crohn's disease who were on immunosuppressant medications within 30 days of elective colectomy had significantly increased rates of infectious complications, overall surgical site infection, organ space surgical site infection, and anastomotic leak compared to patients who were not on immunosuppressive agents.

Keywords Crohn's disease · Inflammatory bowel disease · Immunosuppression · Colectomy · Infection

Abbreviations

CD	Crohn's disease
IBD	Inflammatory bowel disease
ACS-NSQIP	American College of Surgeons National Surgical Quality Improvement Program
ICD-9	Internal Classification of Diseases, Ninth Revision
CPT	Current Procedural Terminology
IMS	Immunosuppressed
IMC	Immunocompetent
UC	Ulcerative colitis
ASA	American Society of Anesthesiologists
SSI	Surgical site infection
OSI	Organ space surgical site infection
BMI	Body mass index
COPD	Chronic obstructive pulmonary disease

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Introduction

The management of Crohn's disease (CD) has significantly changed over the past two decades. Whereas, in the past, surgery was considered to be the mainstay of treatment, immunosuppressive medications that target inflammatory pathways have emerged as the cornerstone of contemporary management of CD.[1] Despite this shift towards more conservative treatment modalities, most patients with CD will eventually require an operative procedure at some point in their future.[2–5]

The key pharmacological agents employed in the current management of CD namely corticosteroids, biologics, and immunomodulators have been reported to be associated with increased rates of postoperative infectious complications probably as a consequence of their immunomodulating effect which targets the same pathways involved in wound healing and pathogen clearance.[6–9] Conversely, the association of infectious complications and immunosuppressive agents has been refuted by other studies.[10,11] Notwithstanding the large body of existing literature that has attempted to address this question, there remains much equipoise regarding the impact of biologic agents on postoperative outcomes in inflammatory bowel diseases (IBD). This is especially apparent since the majority of reported studies that have attempted to address this issue have been mostly non-randomized, underpowered small-retrospective studies, which limited conclusions that could be drawn from systematic reviews and meta-analyses.[8,12–16] Thus, the aim of the present study was to evaluate the impact of preoperative immunosuppression on the development of postoperative infectious complications following elective colorectal resections in CD patients using a large prospective validated database.

Materials and Methods

Study Population

The study population consisted of adults (≥ 18 years of age) with CD who underwent elective colon resections from 2011 to 2015 from the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP). ACS-NSQIP is a nationally validated prospective, comprehensive database made up of over 400 institutions aimed to improve the quality of surgical care. This study received institutional ethics review board approval.

Inclusion Criteria

Patients with CD were identified according to International Classification of Diseases, Ninth Revision (ICD-9) codes 555.0, 555.1, 555.2, and 555.9. CD patients who underwent colon resections were captured using the appropriate Current Procedural Terminology (CPT) codes (Table 1). The ACS-NSQIP definition for immunosuppression in IBD further subdivided these patients into immunosuppressed (IMS) or immunocompetent (IMC). According to this definition, individuals who received intravenous or oral corticosteroids for

Table 1 CPT codes for patients who underwent colon resections in this study

Procedure	CPT codes	Proportion (%)
Partial colectomy with anastomosis	44,140	8.08
Partial colectomy with skin level cecostomy or colostomy	44,141	0.65
Partial colectomy with end colostomy and closure of distal segment (Hartmann type procedure)	44,143	1.71
Partial colectomy with resection with colostomy or ileostomy and creation of mucofistula	44,144	1.35
Partial colectomy with coloproctostomy (low pelvic anastomosis)	44,145	2.41
Partial colectomy with coloproctostomy (low pelvic anastomosis) with colostomy	44,146	0.34
Partial colectomy by abdominal and transanal approach	44,147	0.05
Total abdominal colectomy, without proctectomy, with ileostomy or ileoproctostomy	44,150	3.99
Partial colectomy with removal of terminal ileum and ileocolostomy	44,160	27.36
Laparoscopic partial colectomy with anastomosis	44,204	11.84
Laparoscopic partial colectomy with removal of terminal ileum and ileocolostomy	44,205	35.39
Laparoscopic partial colectomy with end colostomy and closure of distal segment (Hartmann type procedure)	44,206	0.88
Laparoscopic partial colectomy with anastomosis with coloproctostomy (low pelvic anastomosis)	44,207	1.19
Laparoscopic partial colectomy with anastomosis with coloproctostomy (low pelvic anastomosis) with colostomy	44,208	0.31
Laparoscopic total abdominal colectomy without proctectomy, with ileostomy or ileoproctostomy	44,210	4.46

more than 10 days or immunosuppressant medications in the 30 days prior to surgery or at evaluation for surgery for IBD were considered immunosuppressed. Immunosuppressant medications included in this definition were mycophenolate mofetil, adalimumab, etanercept, azathioprine, cyclosporine, tacrolimus, sirolimus, infliximab, natalizumab, methotrexate, and certolizumab pegol.

Exclusion Criteria

Patients who underwent an emergency procedure were excluded. Emergency surgery was defined by ACS-NSQIP as operations that occurred within a short interval of time between diagnosis or symptomatology implying the patient's well-being was threatened by the unnecessary delay of surgical intervention. Also excluded were patients who received chemotherapy within 90 days of surgery, patients who had evidence of preoperative septic shock or intubated preoperatively, patients with an American Society of Anesthesiologists (ASA) classification 5, and patients with disseminated cancer.

Outcomes

The primary outcome was infectious complications, a composite outcome defined as all surgical site infection (SSI), urinary tract infection, pneumonia, sepsis, and septic shock. Overall SSI (superficial, deep, and organ space surgical site infection), organ space infection surgical site infection, and anastomotic leak comprised secondary outcomes. Superficial, deep, and organ space infections surgical site infection (OSI) were defined by NSQIP as an occurrence of infection that manifests in the skin or subcutaneous tissues of the incision, deep soft tissues of the incision and organs or spaces other than the incision, which was opened or manipulated during the operation, respectively. Reoperation was defined by NSQIP as unplanned return to the operating room within 30 days of surgery for any surgical procedure.

Statistical Analysis

On univariate analysis, normally distributed and categorical variables were compared using a two-tailed Student's *t* test and Pearson's chi-square test, respectively. We used Wilcoxon rank sum test for continuous variables that were not normally distributed. Patients with significant missing data (> 20%) were excluded from the analysis. The association between immunosuppression and risk of postoperative complications was evaluated by means of multivariate logistic regression. The regression models were adjusted for known confounders as well as variables found to be statistically significant on univariate analysis. A two-tailed *p* value less than 0.05 was considered to indicate statistical significance. Statistical analyses were performed using Stata software version14.1 (StataCorp. 2015. *Stata Statistical Software: Release 14*. College Station, TX: StataCorp LP.)

Results

Of the 94,055 patients in the colectomy-specific ACS-NSQIP database from 2011 to 2015, a total of 3860 patients with CD required elective colon resections and met the inclusion criteria (Fig. 1). Of those, 2483 (64.33%) patients were IMS and 1377 patients (35.67%) were IMC. Preoperative and demographic variables in both groups are detailed in Table 2.

On univariate analysis, there were significant differences amongst both groups. IMS patients had increased rates of infectious complications (16.23% vs. 13.58%, $p = 0.028$), SSI (13.09% vs. 9.94% $p = 0.004$), OSI (7.17% vs. 4.79%, $p = 0.004$), and anastomotic leak (4.07% vs. 2.55%, $p = 0.014$) (Table 3). The odds of infectious complications on multivariate logistic regression were 25% higher for IMS compared to IMC patients (odds ratio, OR 1.25; 95% CI 1.033–1.523) (Table 4). The increase in odds in IMS relative to IMC patients remained true for all SSI (OR 1.49; 1.128–1.742), OSI (OR 1.47; 1.094–1.984), and anastomotic leak (OR 1.51; 1.018–2.250) (Tables 5, 6, and 7). In addition to immunosuppression, the multivariate regressions performed identified other independent predictors of postoperative complications including open surgery, smoking status, and wound contamination (Tables 5, 6, and 7). In a subgroup of 3216 patients with an anastomosis and without any diversion, the odds of infectious complications, all SSI, and OSI (1.28, 1.31, and 1.38, respectively) remained significantly greater for IMS compared to IMC; however, the anastomotic leak rate was not significantly greater in IMS (OR 1.26, 95% CI 0.86 to 1.98).

Discussion

In the present study, a significant association between immunosuppression for CD and postoperative infectious complications was identified in a cohort of 3860 CD patients who underwent elective colectomies. This increased risk was observed for a composite outcome of infectious complications, all SSI, OSI, and anastomotic leak. In fact, the odds of all SSI were 40% greater in IMS compared to IMC patients, which could be explained by the finding that the odds of OSI were 47% higher in IMS CD patients. Likewise, a parallel increased risk of anastomotic leak was also observed in IMS compared to IMC patients. The results of increased risk of OSI and anastomotic leak are clinically significant as these infections result in morbidity, prolong hospital length of stay, and often necessitate re-intervention. These findings were observed despite controlling for important confounders including age, body mass index, preoperative weight loss, diabetes, smoking,

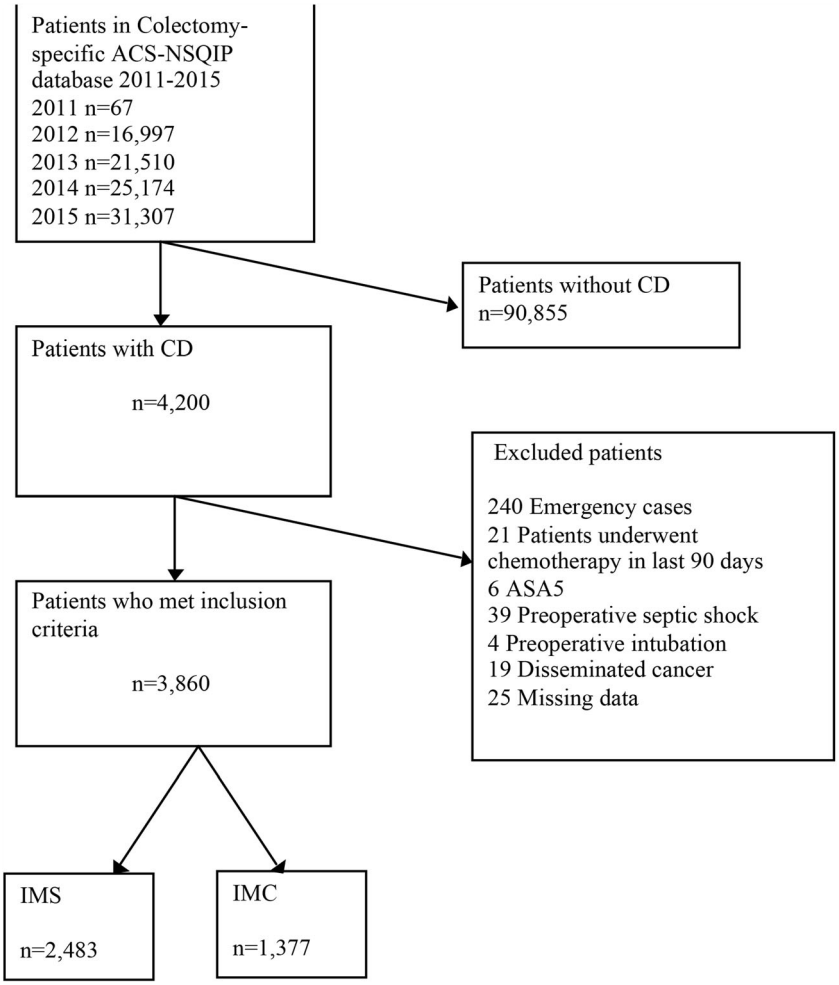

Fig. 1 Patients who met inclusion criteria (IMS, immunosuppressed; IMC, immunocompetent; PUF, patient user file)

chronic obstructive pulmonary disease, hypertension, wound contamination, laparoscopic approach, presence of a stoma, and type of colonic resection.

The assumption that immunosuppressant medications may predispose to postoperative complications is rooted in their role in inhibiting the inflammatory cascade, a key component of the wound healing process and remodeling phase.[17] Although several studies have examined the association between immunosuppression and postoperative complications in patients with CD, the literature is fraught with heterogeneity with regard to exposure to different immunosuppressive agents. Using results from a longitudinal CD database of ileocolic resections, Appau et al.[18] compared 60 patients who had received infliximab to 389 controls. The authors observed a heightened risk of intra-abdominal sepsis, intra-abdominal abscess, anastomotic leak, and readmissions in those patients who had received anti-TNF-α prior to surgery compared to those who had not. Other studies, however, failed to demonstrate a significant association between perioperative treatment with biological agents and/or other immunosuppressants and postoperative complications.[17,19–21] In a retrospective review of 413 patients with CD, UC, or indeterminate colitis who underwent a variety of abdominal procedures, preoperative infliximab ($n = 101$) was not found to increase crude postoperative complications (16.8% vs. 15.7%, $p = 1$). Similarly, on multivariate regression, the use of infliximab (OR 2.5, $p = 0.14$) or steroids (OR 1.2, $p = 0.74$) was not shown to be associated with increased risk of postoperative infections after adjusting for potential confounders.[19] In addition, a case-control study that matched patients on operative procedure, IBD subtype, exposure to steroids, and patient age (195 cases on anti-TNF-α and 278 matched controls) did not find any difference between the two groups with regard to postoperative outcomes on multivariate analysis.[21] In another study, Canedo et al.[10] assessed 225 patients with CD reviewing their comorbidities, type of operations, and postoperative complications. Patients were grouped based on having received immunosuppressive medications within 90 days of the surgery (infliximab group, group having received steroids and other immunosuppressive drugs, and controls receiving no drugs). The authors did not observe a statistically significant difference in the rates of postoperative infectious complications amongst the groups. Furthermore, a recent meta-analysis that included 21 studies comparing CD patients

Table 2 Univariate comparison of preoperative and operative characteristics of IMS vs. IMC patients with CD

	IMS ($n = 2483$)	IMC ($n = 1377$)	p
Patient characteristics			
Age (mean ± SD, years)	38.96 ± 14.59	43.50 ± 16.30	< 0.001
Race (%)			0.45
White	88.60	87.95	
Asian	0.81	0.86	
African American	9.19	9.08	
Hispanic	1.40	2.11	
Female (%)	53.28	54.68	0.40
ASA (%)			0.25
No disturbance	1.37	2.11	
Mild disturbance	64.16	62.04	
Severe disturbance	33.87	35.20	
Life-threatening disturbance	0.60	0.65	
Body mass index (kg/m^2 ± SD)	25.05 ± 6.3	25.42 ± 6.5	0.04
Albumin (g/dL ± SD)	3.60 ± 0.69	3.62 ± 0.70	0.18
Diabetic (%)	3.06	4.28	0.047
Smoker (%)	23.44	23.89	0.75
COPD (%)	1.13	1.82	0.08
Hypertension (%)	14.70	17.86	0.01
> 10 weight loss/6 months (%)	9.8	8.8	0.32
Operative characteristics			
Wound classification (%)			0.001
Clean-clean/contaminated	62.38	66.73	
Contaminated	24.65	19.32	
Dirty	12.97	13.94	
Open wound/drain at the time of operation (%)	2.66	3.12	0.40
Laparoscopic approach (%)	64.16	60.42	0.02
Colon resection (%)			< 0.001
Ileocolic resection	63.83	60.78	
Partial colonic resection	26.38	33.19	
Subtotal colectomy	9.79	6.03	
Stoma (%)	18.32	13.73	< 0.001

COPD, chronic obstructive pulmonary disease; CD, Crohn's disease; IMS, immunosuppressed; IMC, immunocompetent; ASA, American Society of Anesthesiologists

Table 3 Univariate comparison of outcomes in IMS vs. IMC patients with CD following elective colon resections

Variable	IMS	IMC	p value
SSI (%)	13.09	9.94	0.004
Superficial SSI	5.72	4.28	0.06
Deep SSI	1.17	1.01	0.67
Organ space SSI	7.17	4.79	0.004
Postoperative pneumonia (%)	1.25	1.10	0.66
Unplanned reintubation (%)	0.44	0.58	0.56
Pulmonary embolism (%)	0.44	0.44	0.97
Postoperative urinary tract infection (%)	1.49	1.60	0.79
Sepsis (%)	6.04	4.65	0.07
Unplanned reoperation (%)	4.95	4.00	0.17
Infectious complications (%)	16.23	13.58	0.03
Major morbidity (%)	36.17	35.58	0.71
Anastomotic leak (%)	4.07	2.55	0.01
Length of stay (mean ± SD, days)	6.19 ± 4.78	6.36 ± 5.05	0.15
Median operative time (1st quartile; 3rd quartile, min)	154 (114; 206)	153 (113; 209)	0.64

SSI, surgical site infection; CD, Crohn's disease; IMS, immunosuppressed; IMC, immunocompetent

who received preoperative immunosuppressive agents with those who had not clearly highlighted the heterogeneity of available data.[8] Of these, six studies compared outcomes for patients with CD who received a varied combination of immunosuppressive agents including steroids, immunomodulators, and anti-TNF-α medications. In this subgroup of 1264 patients, no significant difference in infectious complications or overall morbidity was observed.[8] However, when the authors limited the analysis to studies that included exposure to only anti-TNF-α ($n = 14$ studies, RR 1.29; 95% CI 1.07–1.55) or steroids ($n = 13$ studies, OR 1.55; 95% CI 1.23–1.95), they observed an increased risk of infectious complications. As noted by the authors of the review, the quality of included studies remained suboptimal as most were underpowered, retrospective, and unmatched. Although a randomized controlled trial would be ideal in resolving this issue, such a study design would be difficult due to the required large sample size and obvious barriers in the feasibility of randomizing critically symptomatic patients with CD who are awaiting surgery. Thus, the use of a large prospectively validated dataset such as the ACS-NSQIP is helpful in filling some of these gaps.

In a recent publication by Valizadeh et al.[22] looking at the impact of immunosuppression on 30-day postoperative outcomes for patients with CD who underwent emergency or elective colectomy using the ACS-NSQIP database for the years 2012–2013, the authors found that IMS patients were at increased risk of anastomotic leak, sepsis, and septic shock. Despite the significance of these results, the data are difficult to translate into clinical practice as this heterogeneous cohort included emergent and elective colectomies, without taking diversion or type of resection into consideration. Many patients who undergo emergency surgery for CD are significantly more ill than elective patients, have preoperative intra-abdominal sepsis, have more extensive resections, and are most often best managed with concomitant diversion.[1,23–25] In fact, emergency surgery for IBD has been repeatedly shown to be a significant risk factor for such complications and death.[26,27] For this reason, in the present study, we chose to

Table 4 Multivariate logistic regression for infectious complications following elective surgery in IMS patients with CD

Infectious complications		Odds ratio	*p* value	[95% CI]
IMS for patients with CD		1.25	0.02	1.033–1.523
Age		1.00	0.78	0.992–1.006
BMI		1.01	0.10	0.997–1.028
Preoperative weight loss		1.11	0.49	0.822–1.495
Diabetic		1.57	0.05	1.001–2.463
Smoker		1.50	< 0.001	1.230–1.833
COPD		0.90	0.78	0.425–1.910
Hypertension		1.03	0.84	0.780–1.359
Wound contamination	Clean/contaminated	Reference	Reference	Reference
	Contaminated	1.30	*0.02*	1.041–1.613
	Dirty	2.39	< 0.001	1.881–3.037
Laparoscopic		0.62	< 0.001	0.514–0.740
Surgery type	Ileocolic resection	Reference	Reference	Reference
	Partial colectomy	1.13	0.24	0.921–1.395
	Subtotal colectomy	1.31	0.10	0.950–1.811
Stoma		1.07	0.61	0.835–1.360

BMI, body mass index; COPD, chronic obstructive pulmonary disease

include a larger cohort of patients (from 2012 to 2015) and to limit the study group to a more homogeneous CD population, without decreasing the power of the hypothesis testing. Indeed, to create a clear and homogeneous cohort from which conclusions applicable to clinical practice could be obtained, patients with evidence of emergency surgery, preoperative septic shock, intubation, or ASA 5 scores, in addition to patients with preoperative chemotherapy/radiotherapy or disseminated cancer, were excluded.

Interestingly, in addition to the significantly greater risk of infectious complications observed in the IMS group, we observed that the types of operations performed differed in both groups. IMS patients were observed to have had significantly greater rates of subtotal colectomies and concomitant stomas compared to IMC patients who had increased rates of segmental colectomies. This is intuitive as the patients on immunosuppressive medications may have had more advanced disease requiring a total colectomy, diversion, or no anastomosis, or it may reflect surgeons' reluctance to create an anastomosis in this immunosuppressed population. In addition, we observed higher rates of laparoscopy for IMS compared to IMC patients as did Canedo et al.[10] They described a

Table 5 Multivariate logistic regression for all SSI following elective surgery in IMS patients with CD

All SSI		Odds ratio	*p* value	[95% CI]
IMS for patients with CD		1.40	0.002	1.128–1.742
Age		1.00	0.71	0.994–1.009
BMI		1.01	0.071	0.999–1.031
Preoperative weight loss		0.96	0.86	0.687–1.366
Diabetic		1.61	0.06	0.984–2.640
Smoker		1.46	0.001	1.176–1.822
COPD		0.78	0.58	0.322–1.878
Hypertension		0.85	0.31	0.622–1.165
Wound contamination	Clean/clean-contaminated	Reference	Reference	Reference
	Contaminated	1.27	0.053	0.997–1.617
	Dirty	2.26	< 0.001	1.734–2.936
Laparoscopic		0.66	< 0.001	0.536–0.805
Surgery type	Ileocolic resection	Reference	Reference	Reference
	Partial colectomy	1.09	0.44	0.869–1.378
	Subtotal colectomy	1.32	0.13	0.924–1.880
Stoma		0.92	0.55	0.696–1.211

BMI, body mass index; COPD, chronic obstructive pulmonary disease

Table 6 Multivariate logistic regression for organ space SSI following elective surgery in IMS patients with CD

Organ space infections		Odds ratio	*p* value	[95% CI]
IMS for patients with CD		1.47	0.01	1.094–1.984
Age		0.99	*0.04*	0.979–0.999
BMI		0.98	0.11	0.957–1.004
Preoperative weight loss		0.97	0.88	0.629–1.487
Diabetic		1.24	0.59	0.570–2.704
Smoker		1.40	*0.03*	1.042–1.870
COPD		0.66	0.57	0.155–2.802
Hypertension		1.18	0.46	0.763–1.827
Wound contamination	Clean/clean-contaminated	Reference	Reference	Reference
	Contaminated	1.65	0.002	1.194–2.271
	Dirty	3.14	< 0.001	2.260–4.366
Laparoscopic		0.82	0.15	0.622–1.074
Surgery type	Ileocolic resection	Reference	Reference	Reference
	Partial colectomy	1.10	0.53	0.812–1.503
	Subtotal colectomy	1.40	0.16	0.876–2.226
Stoma		0.86	0.43	0.600–1.243

BMI, body mass index; COPD, chronic obstructive pulmonary disease

higher rate of laparoscopic surgery in the group that was treated with infliximab, steroids, or other immunosuppressive agents compared to the group that received no drugs (47.7% vs. 45.9% vs. 29.3% $p = 0.04$). This may reflect referral bias as IMS patients may be more likely to be referred to tertiary care centers with advanced minimally invasive colorectal expertise. Given that IMS patients are at increased odds of infectious complications, laparoscopy, an independent protective factor for the latter, may help mitigate significant morbidity in this subgroup.[28,29] Thus, the importance of a minimally invasive approach in minimizing complications following resections for patients with CD should be highlighted. Moreover, risk factors for complications identified such as smoking should be considered when counseling patients for surgery and for preoperative risk adjustment.

The major strength of this study lies in its use of a large, multi-institutional nationally validated database that allows for increased generalizability. The quality of this dataset has been repeatedly validated through regular stringent audits, making the longitudinal database a strong base for hypothesis

Table 7 Multivariate logistic regression for anastomotic leak following elective surgery in IMS patients with CD

Anastomotic leak		Odds ratio	*p* value	[95% CI]
IMS for patients with CD		1.51	0.04	1.018–2.250
Age		0.99	0.05	0.972–1.001
BMI		0.98	0.33	0.954–1.016
Preoperative weight loss		1.31	0.31	0.779–2.206
Diabetic		1.55	0.38	0.583–4.132
Smoker		1.66	0.008	1.142–2.394
COPD		0.60	0.61	0.079–4.473
Hypertension		1.00	0.99	0.553–1.817
Wound contamination	Clean/clean-contaminated	Reference	Reference	Reference
	Contaminated	1.28	0.25	0.846–1.924
	Dirty	1.48	0.11	0.918–2.381
Laparoscopic		0.89	0.52	0.621–1.274
Surgery type	Ileocolic resection	Reference	Reference	Reference
	Partial colectomy	0.97	0.87	0.639–1.458
	Subtotal colectomy	1.30	0.40	0.706–2.379
Stoma		0.93	0.79	0.574–1.520

BMI, body mass index; COPD, chronic obstructive pulmonary disease

testing. Moreover, due to the breadth of available data within the database and the large sample size, many possible confounders could be accounted for in the multivariate analysis. In addition, the individual effect of these confounders on each of the outcomes of interest was clearly highlighted in the different logistic regression models outlined in this article (which is information lacking in a similar study evaluating 30-day postoperative outcomes for IMS compared to IMC patients with CD).[22] While nutritional status, an important variable that has been associated with postoperative complications in CD, was not available, we used preoperative weight loss and albumin level to gauge the overall nutritional status of our patient population.[30] Furthermore, we used stringent inclusion and exclusion criteria to create a well-characterized study population. By excluding those who required emergency surgery, our study population was made more homogeneous ultimately representing patients with CD who underwent elective surgery.

Nonetheless, several limitations from this study merit attention. Though this is a large multicenter database, it remains a limited sample which makes the subgroup analyses on the outcome of leak for patients without a diverting stoma underpowered thus limiting the conclusions drawn in this subset of patients. In addition, we were unable to evaluate the role of different kinds of immunosuppressant medications individually as this information was not available in this database. Patients with CD are often on multimodal agents and the risk of postoperative wound infections cannot be attributed to a specific immunosuppressant medication. Furthermore, whether the patients had adequate drug levels at the time of operation to actually cause immunosuppression is also unknown. Lau et al. evaluated 30-day postoperative outcomes in patients with CD and ulcerative colitis (UC) who underwent abdominal surgery by a single surgeon and analyzed their level of anti-TNF-α levels from stored serum samples within 7 days prior to their operation.[7] Almost 50% of patients treated with anti-TNF-α therapy preoperatively failed to have detectable anti-TNF-α levels at the time of surgery. In patients with CD, an increased rate of overall postoperative infectious complications and readmissions was found in the detectable serum anti-TNF-α drug level group. Although they showed a dose relationship with higher levels of detected anti-TNF-α drug levels being associated with higher rates of adverse postoperative outcomes, their results were not statistically significant.[7] The paucity of data regarding the severity and extent of CD in our patient population is another limitation. Patients with complex CD including fistulas and abscesses are at greater risk of OSI; however, this could not be accounted for in the database.[30] Thus, while we attempted to adjust for potential confounders when reporting postoperative complications, we acknowledge that we might not have accounted for all of them. This, too, applies to intraoperative and postoperative antibiotic use, as these details were also not available. In a similar vein, we were unable to clearly account for the presence of a fistula. Thus, "wound classification" which we adjusted for in the multivariate analysis was used as a surrogate due to its high correlation with this variable. Along those lines, another limitation to be highlighted is the possible selection bias between patients who are on immunosuppressant medications and those who are not. While it remains probable that some patients may have been on immunosuppressive agents but had their surgery delayed because of the timing of administration of these agents, the inability to accurately account for patient's disease severity and the indication for immunosuppression should be noted.

Conclusion

There is currently no consensus on the perioperative management of patients with CD on immunosuppressive agents. In this multicenter, nationally validated database with rigorous, standardized data collection, a significantly increased rate of infectious complications, anastomotic leak, SSI, and OSI was observed following colectomies in IMS patients with CD compared to IMC patients. When possible, consideration for a laparoscopic approach and allowing a washout period for these agents prior to surgery may decrease this associated risk. Given the inability to accurately study the effect of diversion on decreasing the risk of postoperative complications because of sample size limitations, we are unable to specifically recommend diversion or not in this patient population. However, as we observed higher rates of leak and OSI in the IMS, consideration for diversion in this group is important to mitigate the clinical sequelae of these complications.[31,32] Prospective studies are needed to better design recommendations on the need for preoperative discontinuation of immunosuppressive agents in patients with CD. Furthermore, future studies are needed to determine the risk of complications due to each type of immunosuppressive agent. IMS patients should be referred to tertiary care centers with specialized IBD teams for a multidisciplinary approach and access to minimally invasive techniques.

Authors' Contributions Abou Khalil, M.: Substantial contributions to the conception and design of the work, acquisition, analysis, and interpretation of data for the work; AND primary author of the work; AND gave final approval of the version to be published; AND agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Abou-Khalil, J.: Substantial contribution to the conception and design of the work, acquisition, analysis and interpretation of data for the work; AND revised the work for important intellectual content; AND gave final approval of the version to be published; AND agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Compliance with Ethical Standards

The American College of Surgeons National Surgical Quality Improvement Program and the hospitals participating in the ACS-NSQIP are the source of the data used herein; they have not verified and are not responsible for the statistical validity of the data analysis or the conclusions derived by the authors.

Conflict of Interest The authors declare that they have no conflicts of interest.

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