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Original Article

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Predictive Factors of Non-Inflammatory Small Bowel Obstruction After Bowel Resection in Crohn's Patients

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Abstract

Background: The aim of the study was to investigate the risk factors associated with the development of small bowel obstruction (SBO) in Crohn's disease (CD) after small bowel resection (SBR) that are not due to active/recurrent inflammation.

Methods: We conducted a retrospective cohort study of patients who had SBR for active or complicated CD. Abstracted data included demographics, phenotype, therapies for CD, endoscopic disease recurrence, and several surgical variables. The primary outcome was the development of non-inflammatory SBO (NI-SBO) within 5 years after SBR.

Results: A total of 335 patients were included. The cumulative rates of NI-SBO at 6 months, 1 year, and 5 years were 5 (1.5%), 8 (2.4%), and 29 (8.9%), respectively. Variables associated with the development of NI-SBO were active macroscopic or microscopic inflammation in the surgical margins (13 (56%) vs. 65 (27%), P = 0.004), open resection (vs. laparoscopic resection) (12 (41.4%) vs. 60 (19.5%), P = 0.0006) and a higher median number of previous resections (2 (interquartile range (IQR) 2 - 3) vs. 1 (IQR 1 - 2), P = 0.0002). Only 21% of patients who developed NI-SBO required surgical intervention.

Conclusions: The incidence of NI-SBO after SBR in CD is low and associated with inflammation at the margins of the resected bowel, previous bowel resections, and an open laparotomy approach. Most NI-SBOs resolve with medical management.

Keywords: Crohn's disease; Small bowel resection; Small bowel obstruction; Crohn's disease recurrence

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Introduction

Crohn's disease (CD) is an inflammatory bowel disease (IBD) that can involve any area of the gastrointestinal tract and most commonly affects the terminal ileum and/or colon [1]. Up to 80% of patients with ileal disease require surgical intervention at some point in their lives [2]. The common risk factors for surgical intervention include aggressive penetrating phenotype, fibro-stenotic strictures, and/or refractoriness to medical therapy [3, 4]. In patients with small bowel CD, one of the main surgical indications for small bowel resection (SBR) is bowel obstruction, followed by intestinal fistula and abscess [5, 6]. Although a significant number of patients develop disease recurrence commonly at the anastomosis [7-9], some develop small bowel obstruction (SBO) without evidence of inflammation at the transition point [9-11]. In the general population, SBOs are common surgical emergencies, occurring in 9% of patients who have undergone abdominal surgery [1, 2]. Most SBOs are believed to result from adhesions (56-73%), but other etiologies include hernias (10%), neoplasms (5%), and inflammation due to active CD (5%) [4, 12]. Although several studies have explored postoperative adhesive SBO in the general population, these studies have often excluded patients with CD. The incidence and risk factors for the development of SBO after SBR in ileal CD are poorly described in the literature. While many studies have investigated CD recurrence after SBR [5, 12-20], to the best of our knowledge, none have examined the incidence of SBOs unrelated to CD recurrence. This is important as while it is a common practice to proactively use medications to prevent the recurrence of CD and its complications, many patients may still present with obstructions that are not induced disease recurrence but by other etiologies such as intra-abdominal adhesions. Stratifying the risk of these complications and describing the

natural history can aid in managing CD and help make informed decisions as surgical resection for CD may be an option. Many clinicians assume that ileal resections dramatically increase the risk of future SBOs, but no significant evidence is available. The primary aim of our study was to assess the risk factors associated with the development of SBO in CD after SBR not induced by active intestinal inflammation. We also sought to explore the short-term outcomes associated with this entity.

Materials and Methods

Patients and settings

We conducted a retrospective cohort study at Froedtert Hospital and The Medical College of Wisconsin in Milwaukee, Wisconsin. We included patients 18 years and older with a confirmed diagnosis of CD who underwent open or laparoscopic ileocecal resection with ileocolonic anastomosis or segmental SBR between 2004 and 2014. Patients who received part of their IBD or colorectal surgery care outside the Froedtert Hospital System were excluded from the analysis. We also excluded patients with ostomies, a history of total or sub-total colectomy, a history of non-IBD intra-abdominal surgeries, those who lost to follow-up, and those with missing or incomplete operative and/or pathology reports.

Clinical and surgical predictive variables

The data collected included patient demographics such as age and gender, CD phenotype (according to the Montreal classification), smoking status (stratified as a former smoker, current smoker, or never smoker), and medical therapies patients received after index surgery for CD, including biologics, thiopurines, methotrexate, mesalamine, and corticosteroids. In addition, we extracted several surgical variables, including the type of surgical anastomosis (end-to-end, side-to-side, or end-to-side), history of previous SBRs, presence of active macroscopic and microscopic inflammation in the surgical specimen, stricture at the time of surgery (determined by imaging, endoscopic, or intraoperative assessment), length of resected bowel, and presence of active CD in areas other than the surgical specimen. Patients were followed longitudinally until the development of SBO, the need for a new SBR, recurrence of CD, or loss to follow-up. Postoperative variables collected included endoscopic recurrence of CD at postoperative surveillance colonoscopy, graded using the Rutgeerts endoscopic score [21]. The Rutgeerts score was developed to classify postoperative changes after ileocecal resection. It includes the assessment of inflammatory lesions in the anastomotic area, which predicts the likelihood of disease recurrence [21].

The primary outcome was the development of non-inflammatory SBO (NI-SBO), defined as the presence of abdominal distention and pain, nausea, and/or vomiting, confirmed by cross-sectional imaging showing bowel dilatation without radiographic evidence of inflammation at the transition point level. SBO was stratified as partial or complete obstruction. The medical record was reviewed to retrospectively determine the etiology of NI-SBO based on the physician's impression at the time of presentation and through a retrospective review of endoscopic and imaging studies.

Statistical analysis

Descriptive statistics were used to examine the baseline characteristics of the study population. Continuous variables were compared using Student's *t*-test or Mann-Whitney U-test (for nonparametric variables). The Chi-square test was used to evaluate distributions of categorical variables. Variables for inclusion in the multivariate model were selected based on the results of univariate regression analysis. In the univariate analysis, each variable was individually assessed for its effect on the primary outcome. Variables with a two-tailed probability value < 0.05 were considered statistically significant and were candidates for inclusion in the multivariate model via stepwise forward method.

Institutional review board approval and ethical compliance

An institutional review board has reviewed and approved this project. The study was conducted in compliance with the ethical standards of the responsible institution on human subjects as well as with the Helsinki Declaration.

Results

Patients characteristics

Three hundred and thirty-five patients met the inclusion criteria. Baseline characteristics of the patient population at the time of index surgery are presented in Table 1. The mean age was 33 years, and the vast majority of patients (98.5%) had a stricturing CD phenotype. The median number of lifetime bowel resections, including index resection, was one (interquartile range (IQR) 1 - 2). The vast majority of patients (325 (96.7%)) underwent an end-to-end anastomosis (versus to a side-to-side or end-to-side anastomosis). The mean length of bowel resection was 23 cm, and most surgeries were performed laparoscopically (78.6%). Fifty-four patients (16%) developed postoperative complications: one patient with perforated anastomosis, two with infected hematoma, three with postoperative ileus, eleven with wound infections, two deep vein thrombosis (DVT) cases, seven cases of intra-abdominal abscess, one portal vein thrombosis, one intra-abdominal hematoma, one pelvic abscess and one case of anastomotic bleeding. In the overall study group, 274 (81.6%) patients remained on or started biological therapy after surgery. Of the study population, 326 patients (97.3%) underwent postoperative surveillance colonoscopy after a median of 10 months (IQR: 7 - 19). The median Rutgeerts score at postoperative surveillance colonoscopy was 0 (IQR: 0 - 2).

Table 1. Baseline Characteristics of the Study Population

Baseline characteristics	
Age at the time of surgery, years, mean (SD)	33 (16)
End-to-end anastomosis, n (%)	324 (96.7)
Surgery performed through laparoscopy, n (%)	266 (79)
Median number of life-long bowel resections, median (IQR)	1 (1 - 2)
Receiving a biologic post-surgery, n (%)	274 (81.6)
Receiving combination (biologic and immunomodulator) therapy post-surgery, n (%)	171 (51.4)
Receiving 5-ASA post-surgery, n (%)	8 (2.4)
Received a course of metronidazole post-surgery, n (%)	91 (27)
Active smoker at the time of surgery, n (%)	104 (31.5)
Active inflammation in the surgical specimen, n (%)	327 (98.5)
Stricture at the time of surgery, n (%)	300 (90)
Length of bowel resected, cm, mean (SD)	23 (17)
Post-operative complication, n (%)	54 (16)
Active Crohn's disease other than the surgical specimen	35 (10.5)
Body mass, kg, mean (SD)	78 (21)
Active smoker, n (%)	104 (31)
Crohn's disease phenotype	
Stricturing disease, n (%)	331 (98.5)
Presence of fistulas, n (%)	157 (47)
Perianal disease, n (%)	91 (27.3)

5-ASA: 5-aminosalicylic acids; SD: standard deviation; IQR: interquartile range.

Rate and baseline variables associated with the development of NI-SBO

The cumulative rates of NI-SBO not attributed to active CD at 6 months, 1 year, and 5 years were 5 (1.5%), 8 (2.4%), and 29 (8.9%), respectively. NI-SBOs were most commonly attributed to adhesions (26 patients), followed by incisional hernias (three patients). Patients who developed NI-SBO had a higher median number of prior resections compared to patients who did not develop (2 (IQR: 2 - 3) vs. 1 (IQR: 1 - 2), P = 0.0002). In addition, a higher number of patients in the group who developed NI-SBO had active macro- or microscopic inflammation at the surgical margins compared to those who did not develop obstruction (13 (56%) vs. 65 (27%), P = 0.004) and had more open resection (compared to laparoscopic bowel resection) (12 (41.4%) and 60 (19.5%), P = 0.0006). No other differences were found between the groups (Table 2). A univariate analysis showing factors associated with the development of NI-SBO is presented in Table 3. In a multivariate analysis adjusting for all variables, the presence of active inflammation in the surgical margin, bowel resection prior to the index surgery, and using an open laparotomy as the surgical approach for index surgery remained statistically significant (Table 4).

Outcomes of NI-SBO

Of the 29 patients who developed SBO due to adhesions or incisional hernias, only six (20.7%) required reoperation, while the remaining responded to conservative medical management. One of these six patients, who had an initially complicated 68 cm resection due to a proximal ileal perforation, developed SBO requiring exploratory laparoscopy. This revealed a ventral hernia, adhesions, and a small bowel loop adherent to a small abscess. Another of the six patients, who had closed-loop obstruction secondary to adhesion from a previous uncomplicated SBR, also had resolution of her SBO after undergoing adhesion lysis. Two of the six patients eventually developed a second SBO, which again required surgical intervention. The immediate postoperative surgical complications from the repeat surgical procedure for SBO were few, with only one patient experiencing delayed healing and abdominal pain.

Bowel obstruction secondary to active CD

Of the total population included in the study, 326 patients underwent surveillance colonoscopy to assess CD recurrence. The median time between surgery and colonoscopy was 10 months (IQR: 7 - 19 months). The median Rutgeerts score was 0 (IQR 0 - 2). During the entire follow-up, six patients required a revised anastomosis due to recurrent inflammation in the anastomosis (two, one, and three patients at the 1-, 3-, and 5-year time points).

Discussion

In this study, we found that the rates of SBO after ileal resec-

Table 2. Differences in Baseline Variables Between Patients Who Had NI-SBO Within 5 Years of Ileal Resection vs. Those Without

	NI-SBO within 5 years	No NI-SBO within 5 years	P-value
Rutgeerts score at post-resection colonoscopy, median (IQR)	1 (0 - 2)	0 (0 - 2)	0.12
Total number of bowel resections, median (IQR)	2 (2 - 3)	1 (1 - 2)	0.0002*
Body mass, kg, mean (SD)	74 (21)	78 (21)	0.29
Length of resected bowel, cm, median (IQR)	18 (12 - 28)	17 (12 - 29)	0.79
History of perianal CD, n (%)	6 (21)	83 (28.2)	0.39
Active smoker, n (%)	9 (31)	92 (31.1)	0.95
Age at the time of surgery, years, mean (SD)	38 (18)	33 (16)	0.16
Complete SBO at the time of surgery, n (%)	25 (86.2)	266 (89.6)	0.58
Active inflammation in the surgical specimen, n (%)	28 (96.6)	289 (98.6)	0.39
Active inflammation in the surgical margins, n (%)	13 (56.5)	65 (27)	0.004*
Post-operative complication (30-day) at the time of surgery, n (%)	8 (28)	43 (14.5)	0.064
Active CD in an area other than the resected bowel, n (%)	4 (13.8)	31 (10.5)	0.58
Index surgery performed through laparoscopy (vs. open), n (%)	17 (58.6)	247 (80.5)	0.006*

*Statistically significant. CD: Crohn's disease; IQR: interquartile range; NI-SBO: non-inflammatory small bowel obstruction; SD: standard deviation.

Table 3. Univariate Analysis Showing Variables Associated With the Development of a Non-Inflammatory Small Bowel Obstruction Within 5 Years or Ileocolonic Resections

Variable	OR	95% CI	P-value
Female gender	1.1	0.51 - 2.34	0.83
Age > 40 years	1.7	0.76 - 3.6	0.2
On biologic therapy after the index surgery	1.1	0.39 - 2.92	0.9
Active inflammation in the surgical margins (index surgery)	3.4	1.44 - 8.23	0.004*
Active Crohn's disease in areas other than the resected bowel (index surgery)	1.4	0.5 - 4.3	0.55
Bowel stricture at the time of index surgery	1.0	0.29 - 3.53	0.99
History of bowel resection previous to the index surgery	5.1	2.03 - 13.0	0.0002*
Development of a complication after index surgery	2.2	0.9 - 5.2	0.1
Rutgeerts score > i1 on surveillance colonoscopy after index surgery	1.5	0.63 - 3.4	0.38
Active smoker	1.0	0.44 - 2.3	0.99
Index surgery performed through open laparotomy (versus laparoscopy)	2.9	1.3 - 6.4	0.01*

*Statistically significant. CI: confidence interval; OR: odds ratio.

Table 4. Multivariable Analysis Showing Variables Independently Associated With the Development of a Non-Inflammatory Small Bowel Obstruction Within 5 Years or Ileocolonic Resections

Variable	aOR	95% CI	P-value
Female gender	1.0	0.3 - 3.3	0.94
Age > 40 years	0.7	0.2 - 2.1	0.51
On biologic therapy after the index surgery	2.2	0.4 - 12.8	0.37
Active inflammation in the surgical margins (index surgery)	5.0	1.7 - 14.8	0.003*
Active Crohn's disease in areas other than the resected bowel (index surgery)	1.7	0.4 - 6.8	0.43
Bowel stricture at the time of index surgery	0.8	0.1 - 4.6	0.76
History of bowel resection previous to the index surgery	4.8	1.4 - 16.8	0.015*
Development of a complication after index surgery	1.6	0.4 - 6.5	0.54
Rutgeerts score > i1 on surveillance colonoscopy after index surgery	1.5	0.5 - 4.4	0.51
Active smoker	0.8	0.2 - 2.7	0.73
Index surgery performed through open laparotomy (versus laparoscopy)	6.1	1.9 - 19.7	0.002*

*Statistically significant. aOR: adjusted odds ratio; CI: confidence interval.

tion not due to CD recurrence were low. We also found that most of these patients respond to medical therapy, and a minority require additional surgical intervention. The only three baseline variables that were independently associated with the development of NI-SBO were a history of SBR prior to index surgery, the presence of active inflammation at the margins of the surgical specimen, and performing the surgery through an open laparotomy. These results have several implications. Even though drug therapy is the mainstay of treatment for CD, some patients develop strictures, fistulas, and/or refractory inflammation and would be better off undergoing surgical resection and avoiding the futile use of pharmacological therapies. In many cases, physicians delay surgical treatment of CD because of concerns about short and long-term complications. These include potential bowel obstructions resulting from adhesions, which, unlike CD recurrence, cannot be prevented.

We identified three variables associated with a higher risk of developing NI-SBO, which could potentially help stratify patients before considering surgery. As shown in our study, the risk of developing NI-SBO was higher in patients with a history of SBR. This is consistent with previous studies that have examined adhesive SBOs and found that the number of previous laparotomies, bowel injuries, operative times, perioperative bleeding, and diffuse adhesions (or matted adhesions) were all significantly associated with recurrent hospitalizations for SBO [22-24]. The results of this study suggest that while the probability of developing NI-SBO after a first resection is low, prevention of CD recurrence after a first resection is critical, and clinicians should likely start/optimize therapy to avoid the need for repeat resection.

In our analysis, performing an open laparotomy (as opposed to a laparoscopic surgical approach) was also independently associated with the development of NI-SBO. The potential shared mechanism between a history of multiple resections and undergoing an open laparotomy is a potential increased tissue damage, scarring, and adhesion formation from repeated and more extensive surgical manipulation. The existing literature provides conflicting data regarding the incidence of SBO after laparoscopic vs. open procedures. A previous study compared adhesion formation in 13 patients who underwent laparoscopic colectomy and 33 patients who underwent open colectomy [16]. Intraoperative adhesions were assessed because these patients underwent laparoscopy for tumor staging prior to liver resection. The researchers found a statistically significant lower "adhesion score" compared to the open surgery group [16]. Another study retrospectively assessed adhesion-related readmissions in over 70,000 patients who underwent open and laparoscopic abdominal or pelvic surgeries. In the study, of 21,519 patients who had undergone laparoscopic surgery, 359 were readmitted for causes directly related to adhesions, compared to 2,168 of 50,751 patients in the open surgery arm [12]. Nakamura et al reported a higher risk of recurrence with laparotomy than with laparoscopy [25].

On the other hand, although laparoscopy has been shown to be associated with decreased adhesion formation, it has not been associated with a lower incidence of SBO in colorectal surgery [16]. Two other meta-analyses found no benefit with regard to reoperation for adhesion in patients undergoing laparoscopic procedures compared to those undergoing open procedures [24, 26]. Furthermore, no significant benefits were found between the two approaches in the "conventional vs. laparoscopic-assisted surgery in colorectal cancer" trial, which compared the incidence of adhesion-related complications, particularly SBO, after laparoscopic and open colorectal surgery [27]. Although the results of our study in a population with CD support the use of laparoscopy when possible to limit long-term complications, this should be interpreted cautiously. It is crucial to mention that our results could be confounded by the fact that patients requiring an open laparotomy may have more complicated anatomy, higher inflammatory burden, more complications (such as fistulas), and are therefore at a higher risk of developing SBO in the future. Further randomized controlled trials (RCTs) are essential to determine whether laparoscopy has a lesser risk of recurrence than laparotomy for operative management of adhesive SBO.

The third factor we found associated with a higher risk of postoperative NI-SBO was the presence of microscopic inflammation at the surgical margins of index surgery. Even if the surgeon attempts to remove the intestinal segment with active disease, it is sometimes not possible to intraoperatively assess the presence of histological inflammation, which is only confirmed at postoperative pathological examination. Although many studies have investigated resection margin inflammation associated with CD recurrence and postoperative complications, none have specifically addressed the development of adhesions and NI-SBO. The existing literature provides conflicting evidence regarding the association between inflammation at the resection margins and CD recurrence (defined as a recurrent disease requiring repeat resection), with recent studies supporting an association between the two [15, 28-31]. It is, however, unclear why residual (even minimal) inflammation might lead to NI-SBO. One explanation may be found in the pathophysiology of adhesion formation. Although adhesions are caused by prior surgical procedures in more than 90% of cases, a small percentage (< 10%) can also occur without prior abdominal surgery [32]. The formation of adhesions has been attributed to reactive oxygen species that can be overproduced in injured peritoneal surfaces due to various triggers such as surgical trauma, ongoing acute or chronic infection or inflammation, cancer, or radiation [33]. We suggest that the residual inflammation at the margins (even if minimal) might lead to adhesions, which in turn could explain the increased rate of adhesive SBO found in our study. This association and the more recent data regarding increased CD recurrence with positive margins may help clinicians to stratify these patients and consider closer follow-up and more aggressive medical management for those who have histological evidence of inflammation at the resection margins. Potentially, the use of real-time intraoperative assessment of histological activity could help to determine resection margins. In some cases, the absence of inflammation may not necessarily exclude the possibility of SBO, as other factors could contribute to obstruction, such as adhesions or strictures. Conversely, the presence of inflammation may not always lead to obstruction, as the severity and location of inflammation can vary, and other factors like

bowel motility play a role in the development of obstruction. Therefore, while inflammation at the margin is a significant risk factor, its presence or absence alone may not definitively determine the occurrence of SBO. It is essential to consider multiple factors comprehensively when evaluating the risk and likelihood of SBO in clinical practice.

Our study is not free from limitations. First, the study's retrospective design inherently introduces bias since most data were extracted from remote surgical, radiological, and pathological notes. Second, the etiology of SBO considered in the analysis was based on a review of the medical record based on the clinical judgment of the treating physician and not necessarily on an objective factor. However, cross-sectional imaging confirmed the absence of active inflammation. In addition, the incidence and risk of SBOs can vary between surgical practices and depend on the surgeon's experience. In addition, surgeries were performed at a tertiary referral center, where more complex patients are usually seen. These factors must be considered when extrapolating the results to the general population. Additionally, we did not evaluate the remission status of these patients, which could potentially influence the development of NI-SBO. We suggest that future investigations concentrate on examining the correlation between remission status and NI-SBO to gain a comprehensive understanding of these factors. Furthermore, we did not conduct subgroup analyses on patients receiving metronidazole, advanced therapies post-resection for CD, and those on prophylactic treatment, which could have provided additional insights into recurrence rates and the development of SBO.

Conclusions

The incidence of NI-SBO after ileal resection in CD is low and resolves with medical management in most cases. Inflammation at the margins of the resected bowel, previous bowel resections, and an open laparotomy approach were all independently associated with the development of SBO within 5 years of index surgery. The results support the use of conservative management in these patients in hopes of avoiding repeated resections and surgeries, which in turn could result in more long-term complications.

Learning points

The incidence of NI-SBO after ileal resection in CD is low.

Predictive factors for the development of SBO within 5 years of index surgery include: inflammation at the margins of the resected bowel, previous bowel resections, and an open laparotomy approach.

Our results support the use of conservative management in Crohn's patients with NI-SBO and avoid repeated resections and surgeries.

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Conflict of Interest

M. Zulqarnain: no conflict; F. Jaber: no conflict, V. Jahagirdar: no conflict; S. Alsakarneh: no conflict; A. Stanton: no conflict; N. Patel: no conflict; J. Gomez: no conflict; P. Beniwal-Patel: no conflict; D. Stein: AbbVie: consulting, speaking and teaching; Allergan: speaking; Bristol Myers Squibb: speaking and teaching; Pfizer: speaking and teaching; Takeda: speaking and teaching; M. F. Otterson: no conflict; A. Yarur: consultant Takeda, Bristol Myers Squibb, Pfizer, Arena.

Informed Consent

Not applicable.

Author Contributions

M. Zulqarnain: conceptualization, supervision, validation, writing-original draft, writing-review and editing. F. Jaber: conceptualization, resources, data curation, validation, investigation, visualization, writing-review and editing. V. Jahagirdar: validation, investigation, visualization, writing-review and editing. S. Alsakarneh: validation, visualization, writing-review and editing. J. Gomez: conceptualization, resources, data curation, software, formal analysis, methodology, writing-original draft and editing. A. Stanton: writing-review and editing. N. Patel: data curation, writing-review and editing. P. Beniwal-Patel: conceptualization, resources, data curation, software, formal analysis and supervision, D. Stein: validation, investigation, visualization, methodology, writing-original draft, project administration, writing-review and editing. M. Otterson: validation, investigation, writing-original draft, project administration, writing-review. A. Yarur: project administration, writing-review, conceptualization, resources, supervision and editing.

Data Availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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