



Risk of postoperative morbidity in patients having bowel resection for colonic Crohn's disease

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Abstract

Background The aim of the present multicenter study was to analyze the incidence and risk factors associated with postoperative morbidity in patients who had colorectal resection for colonic Crohn's disease.

Methods Consecutive patients undergoing colorectal resection for colonic Crohn's disease at seven surgical units in 1992–2017 were included. Exclusion criteria were: proctectomy for perianal disease, surgery for cancer, previous colectomies, surgery before 1998. Abdominal colectomy and proctocolectomy were defined as extended resections; all other operations were classified as segmental resections. Postoperative intraabdominal septic complications (IASC) were: anastomotic leaks, peritonitis and abscess.

Results One hundred ninety-nine patients met the inclusion criteria: 116 patients had segmental resections and extended resections were performed in 83 patients. An anastomosis was constructed in 122 patients and an additional stoma was formed in 15 of those cases. Segmental resections were performed significantly more frequently in stricturing or penetrating disease (93% vs. 61%, $p < 0.001$) and were completed by an anastomosis more often than extended resections (78% vs. 37%, $p < 0.001$). The overall IASC rate was 17%. On multivariate analysis, formation of an anastomosis (Hazard ratio 2.9; 95% CI 1.1–7.7; $p = 0.036$) and preoperative hemoglobin level of < 10 g/dl (Hazard ratio 3.1; 95% CI 1.1–9.1; $p = 0.034$) were associated with an increase of postoperative IASC rate. Preoperative medication did not influence postoperative outcome.

Conclusions Severe preoperative anemia is associated with an increased postoperative morbidity. Resections completed by an anastomosis pose an increased postoperative complication risk in patients with colonic Crohn's disease as compared to resections without an anastomosis.

Keywords Crohn's disease · Surgery · Colonic disease, postoperative morbidity

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Introduction

Numerous studies examine the risk of postoperative complications in patients having intestinal resection for Crohn's disease (CD). Factors associated with an increased complication risk have been well described and include preoperative weight loss, low albumin level, penetrating disease (presence of fistula or abscess), steroid intake, and use of anti-tumor necrosis factor (TNF)-alpha medication. Other factors such as intake of immunosuppressive agents, preoperative C-reactive protein (CRP)-level, preoperative opioid intake, length of the resected specimen and anemia are a matter of controversy [1–7]. However, the vast majority of intestinal operations for CD are ileocolic resections for complicated disease at the distal ileum [8]. Results of morbidity studies are dominated by factors determining postoperative risk in those having ileocolic resection and it maybe that risk factors for complications after ileocolic resection are not the same as risk factors for complications after other colonic resections for CD.

There are few of studies addressing intestinal resections for colonic CD. Most of the published papers analyze the risk of postoperative recurrence or the outcome of ileal pouch–anal anastomosis (IPAA) in patients with CD [9–14]. Only few studies have addressed postoperative complication risk in patients with Crohn's colitis [15–17]. They include almost exclusively patients who had surgery in the pre-infliximab era, and predictors of postoperative morbidity are not addressed by multivariate comparisons. The aim of this study was to determine the risk factors for postoperative complications in a multicenter retrospective consecutive series of patients who had resection for colonic CD.

Materials and methods

This was a retrospective analysis including a consecutive series of patients who had bowel resection for colonic CD at seven surgical units: three in Germany (University of Regensburg 1998–2013, $n = 102$; Marien Hospital Gelsenkirchen 2009–2014, $n = 7$; and Bogenhausen Hospital 2014–2017; $n = 18$), one in Denmark (2009–2013, $n = 16$), one in Italy (2011 to 2016, $n = 37$), one in Spain (1998–2011, $n = 21$) and one in Israel (2008–2015, $n = 10$).

The following exclusion criteria were applied: age below 15 years, surgery before 1998 (i.e., during the pre-anti-TNF era), extensive anal disease requiring proctectomy, restorative proctocolectomy with IPAA, previous colorectal resection, surgery for cancer and ileocolic resection for stricturing or penetrating ileitis even if a concomitant colitis was present.

The disease localization was defined according to the Montreal classification [18] as ileal disease (L1), colonic disease (L2) or ileocolonic disease (L3). The extent of the colonic disease was defined as: (a) pancolitis (i.e., diffuse disease) (b) right-sided colitis (ascending and/or transverse colon); (c) left-sided colitis (descending and/or sigmoid colon and rectum).

Disease behavior was also classified according to the Montreal classification: non-stricturing/non-penetrating (B1), stricturing (B2), and penetrating (B3). Penetrating disease was defined as the presence of an intraabdominal abscess, intraabdominal fistula or inflammatory mass. B2-disease and B3-disease were exclusive, i.e., the disease was classified as B3 when an intestinal stricture and penetrating complications were present at the same time [18].

Definition of postoperative intraabdominal septic complications (IASC) was: presence of an anastomotic leak, intraabdominal abscess, any intestinal leaks (also leaks of colonic stumps), or any postoperative peritonitis. The following variables were included to calculate the risk of postoperative morbidity: age, sex, the presence of extraintestinal disease, preoperative weight loss, smoking, the presence of intraabdominal abscess, the presence of anal fistula, extent of disease, the presence of ileal disease, clinical behavior, preoperative medication, hemoglobin level, albumin level, urgency of surgery, extent of resection, construction of intestinal anastomosis, formation of a diverting ileostomy, and laparoscopy. Patients were considered to have been treated with TNF-alpha inhibitors if they had received infliximab infusion within the 8 weeks prior to surgery or adalimumab injection within 2 weeks prior the surgery. Any intake of steroid medication on the day before the surgery was defined as “steroid use”. Immunosuppressive drugs—methotrexate and azathioprine—were considered to potentially affect postoperative morbidity when taken within a month before surgery.

Right colectomies, transversal colon resections, left colectomies and extended left colectomies were grouped together as segmental resections. Abdominal colectomy and proctocolectomy were classified as extended resections.

Statistical analysis

Association between pre-/intra-operative variables and IASC was analyzed with the Mann–Whitney test (continuous variables) or Fisher's exact test (categorical variables). Variables associated with postoperative IASC at univariate analysis with a $p < 0.2$ were included in a multivariate analysis using a stepwise logistic regression model with backward elimination. $p < 0.05$ was considered to indicate statistical significance (two-tailed test). The Pearson's correlation coefficient was used as a measure of bivariate correlation between

variables. The Statistical Package for the Social Sciences version 20 (IBM, Chicago, IL, USA) was used.

Results

Of 260 patients identified, 199 met the inclusion criteria (male patients $n=73$, 37%) and had their first segmental or extended bowel resection for colonic Crohn's disease between 1998 and 2017. Eighty-eight patients (44%) presented with ileocolonic disease (L3) and 111 (56%) with colonic disease (L2). Anal fistula was found in 96 of 196 patients with available data (49%). Perianal disease was present significantly more frequently in patients with L3 than those with L2 disease (59% vs. 41%, $p=0.014$). The mean age at the time of the surgery was 39.0 years (median 37.0; range 15–80 years). A pancolitis (diffuse colitis) as opposed to left-sided or right-sided colitis was observed in 99 patients (50%). Clinical disease behavior was non-stricturing/non-penetrating in 40 patients (20%), stricturing in 67 patients (34%) and penetrating in 92 patients (46%). An intraabdominal abscess was noted preoperatively in 37 patients (19%); 11 of whom underwent percutaneous drainage of the abscess before surgery.

Abnormal preoperative hemoglobin levels (<13 g/dl in males and <12 g/dl in females) were noted in 61% of patients with pertinent data (117 out of 192). Twenty-eight patients (15%) presented with a hemoglobin level of less than 10 g/dl. There was a significant positive correlation between hemoglobin levels of <10 g/dl and emergency colectomy ($r=0.22$, $p=0.002$) and the presence of other extraintestinal manifestations ($r=0.153$, $p=0.039$). Thirty-one percent of patients having emergency colectomy presented with a hemoglobin level of <10 g/dl compared to 11% of patients having elective surgery ($p=0.007$). Smoking correlated significantly with higher hemoglobin levels ($r=-0.155$, $p=0.033$).

Emergency resections were performed in 39 patients (20%). Only 17 were completed by an anastomosis. Altogether, 34 right colectomies, 15 transversal colon resections, 67 left-sided colectomies, 66 total colectomies, and 17 proctocolectomies were performed. Thus, according to the study definition, there were 116 segmental and 83 extended resections. There were some significant differences between resection groups (Table 1). Of note, there were significantly more patients with penetrating disease undergoing segmental resections than extended resections ($p<0.001$).

An intestinal anastomosis was constructed in 122 patients (61%) and an additional diverting ileostomy in 15 of them. Laparoscopic colonic resection was performed in 57 patients (26%) with a 19% conversion rate.

Postoperative complications occurred in 62 patients (31%); 1 patient (0.5%) died on postoperative day 9 from

septic shock following proctocolectomy. Generalized peritonitis was revealed at autopsy. IASC occurred in 34 patients (17%). In particular, IASC was observed in 25 of 122 patients with an anastomosis (21%). Median length of postoperative hospital stay was 10 days (range, 4–130 days). The length of postoperative hospital stay was prolonged in patients with preoperative anemia (15.5 days vs. 11.6 days, $p=0.047$) and it was even longer in patients with preoperative hemoglobin levels of less than 10 g/dl (21.3 days, $p=0.003$).

Table 2 shows the results of the univariate analysis of factors affecting occurrence of postoperative IASC. Factors affecting the IASC incidence at the significance level of $p<0.2$ were included in multivariate regression analysis. On the multivariate analysis, colonic resection followed by a formation of an anastomosis (HR 2.9; 95% CI 1.1–7.7; $p=0.036$) and preoperative hemoglobin levels of <10 g/dl (HR 3.1; 95% CI 1.1–9.1; $p=0.034$) were associated with an increased postoperative IASC rate (Table 3).

Discussion

We found that formation of an anastomosis and low hemoglobin were significant risk factors for complications after resection for colonic CD, with no significant effect of other factors, including medical treatment. A recent meta-analysis performed by Angriman et al. [19] which included a few studies addressing postoperative morbidity in patients with colonic CD having segmental or extended colectomies, respectively, demonstrated an increased risk of postoperative complications (OR 2.84) but a decreased risk of stoma formation after segmental resections. Segmental colonic resections were associated with the increased likelihood of developing postoperative IASC as opposed to extended colectomies, as in our study. However, the difference was not statistically significant on univariate, or multivariate analysis. Segmental resections were performed mostly for strictures or fistulae/abscesses in the descending or sigmoid colon and there were almost no segmental resections performed for a non-stricturing/non-penetrating disease in this particular group. In addition, more segmental resections were completed by an anastomosis (78% vs. 37%). Many extended resections were performed for non-stricturing/non-penetrating disease (39%), and were more often completed by stoma formation (69%). In our study, anastomosis construction was associated with an increased likelihood of developing postoperative IASC, both after segmental and extended resections. Utilizing a diseased colon and rectum for anastomotic reconstruction might be a risk factor. The presence and extent of proctitis should be taken into account especially when planning left-sided resections. Strategies to reduce rectal inflammation preoperatively (e.g., steroid

Table 1 Differences between patients undergoing right-sided, left-sided or extended colonic resections

Variable	Segmental resections, N (%)	Extended resections, N (%)	<i>p</i>
Age at surgery, years	38.3	39.9	0.42
Age at diagnosis, years	22.4	13.6	<0.001
Sex, male	44/116 (38%)	29/83 (35%)	0.77
Disease localization			
Colonic (L2)	61/116 (53%)	50/83 (60%)	
Ileocolonic (L3)	55/116 (47%)	33/83 (40%)	0.31
Anal disease*	53/113 (47%)	43/83 (52%)	0.56
Disease behavior			
Non-penetrating/non-stricturing (B1)	8/116 (7%)	32/83 (39%)	
Stricturing (B2)	38/116 (33%)	29/83 (35%)	
Penetrating (B3)	70/116 (60%)	22/83 (26%)	<0.001
Preoperative intraabdominal abscess	29/116 (25%)	8/83 (10%)	0.006
Preoperative hemoglobin level, g/dl	11.8	11.1	0.038
Preoperative albumin level, g/dl	3.4	3.4	0.99
Extraintestinal disease*	39/108 (36%)	25/80 (31%)	0.53
Smoking*	32/114 (28%)	31/83 (37%)	0.22
Azathioprine intake*	29/111 (26%)	25/83 (30%)	0.63
Methotrexate intake*	5/111 (4%)	3/82 (4%)	1.0
Steroid intake*	58/115 (50%)	26/82 (32%)	0.013
Biologicals intake	112/115 (10%)	25/83 (30%)	0.001
Presence of pancolitis*	38/116 (33%)	61/83 (74%)	<0.001
Preoperative weight loss*	36/92 (39%)	47/79 (59%)	0.009
Formation of an anastomosis	91/116 (78%)	31/83 (37%)	<0.001
Additional fecal diversion	10/91 (11%)	5/31 (16%)	
Length of resected specimen, cm	26.9	63.4	<0.001
Emergency surgery	25/116 (22%)	14/83 (17%)	0.47
Laparoscopic resections	25/116 (22%)	32/83 (39%)	0.011
Converted to open	2/25 (8%)	9/32 (22%)	0.09

*There were missing data for some variables

enemas) should be taken into consideration. Preoperative optimization [20] with antibiotics, nutritional support, percutaneous drains, optimization of the medical treatment—should be discussed with patients about to undergo colonic resection with a planned anastomosis. Unfortunately, the number of patients receiving a diverting ileostomy in addition to an anastomosis was very low in our study ($n = 15$), since most patients had either surgery without anastomosis or had unprotected anastomoses. Thus, we are not able to draw any conclusions regarding the usefulness of diverting ileostomy. Resection without an anastomosis should be considered in patients estimated to be at highest risk of complications.

Anemia is one of the most frequent extraintestinal manifestations of inflammatory bowel disease (IBD) and is present in up to 50% of patients [21]. It seems to occur even more often in a surgical population of colonic CD patients and 61% of patients in our study had abnormal hemoglobin levels. There are several pathophysiological mechanisms

that cause anemia in IBD patients including intestinal bleeding, iron deficiency, myelosuppression induced by immunosuppressive treatment, chronic inflammation and hemolysis. In patients presenting with colonic CD intestinal blood loss develops significantly more often than in those with ileal CD [22]. Anemic patients are more likely to present with malnutrition, weight loss, a history of recent blood transfusions, preoperative sepsis, and are more often on steroids and immunosuppressants [21]. There is a correlation between anemia and endoscopic bowel damage, and between anemia and disease activity indices [23]. Low hemoglobin was an independent predictor of disease complications and need for surgery in a German population-based study [24]. Moreover, as shown by our study and other data [21], anemic patients also have an increased risk of undergoing emergency surgery. We were able to demonstrate that severe anemia, commonly defined as a hemoglobin level of < 10 g/dl, is strongly associated with postoperative IASC in patients having intestinal resection for colonic CD. Increased IASC

Table 2 Association between pre-/intra-operative variables and post-operative IASC: on univariate analysis

Variable	IASC rate, <i>N</i> (%)	<i>p</i>
Sex		
Male	13 of 73 (18%)	0.85
Female	21 of 126 (17%)	
Age		
≥ 35 years	17 of 104 (16%)	0.85
< 35 years	17 of 95 (18%)	
Clinical disease behavior		
B1–2 (non-penetrating)	12 of 107 (11%)	0.023
B3 (penetrating)	22 of 92 (24%)	
Perianal disease		
Yes	14 of 96 (15%)	0.45
No	19 of 100 (19%)	
Intraabdominal abscess		
Yes	9 of 37 (24%)	0.23
No	25 of 162 (15%)	
Diffuse colitis (pancolitis)		
Yes	14 of 99 (14%)	0.35
No	20 of 100 (20%)	
Disease localization		
L2	21 of 111 (19%)	0.46
L3	13 of 88 (15%)	
Extraintestinal disease		
Yes	11 of 64 (17%)	0.84
No	20 of 124 (16%)	
Preoperative weight loss		
Yes	14 of 83 (17%)	0.67
No	12 of 88 (14%)	
Smoking		
Yes	7 of 63 (11%)	0.16
No	26 of 134 (19%)	
Hemoglobin level		
≥ 10 g/dl	23 of 164 (14%)	0.16
< 10 g/dl	8 of 28 (25%)	
Albumin level		
< 3.0 g/dl	2 of 19 (11%)	0.66
≥ 3.0 g/dl	5 of 62 (8%)	
Systemic steroid intake		
Yes	13 of 84 (15%)	0.70
No	21 of 113 (19%)	
Azathioprine intake		
Yes	6 of 54 (11%)	0.21
No	27 of 140 (19%)	
Methotrexate intake		
Yes	2 of 8 (25%)	0.63
No	31 of 185 (17%)	
Intake of biologicals		
Yes	6 of 37 (16%)	1.0
No	28 of 161 (17%)	

Table 2 (continued)

Variable	IASC rate, <i>N</i> (%)	<i>p</i>
Emergency surgery		
Yes	6 of 39 (16%)	1.0
No	28 of 160 (17%)	
Formation of an anastomosis		
Yes	25 of 122 (21%)	0.13
No	9 of 77 (9.5%)	
Fecal diversion		
Yes	13 of 91 (14%)	0.35
No	21 of 108 (19%)	
Extent of colectomy		
Segmental resections	25 of 116 (22%)	0.057
Extended resections	9 of 83 (11%)	
Laparoscopic surgery		
Yes	9 of 57 (16%)	0.84
No	25 of 142 (18%)	

IASC intraabdominal septic complications

Table 3 Association between pre-/intra-operative variables and post-operative IASC, the multivariate analysis

Variable	Hazard ratio (95% confidence interval)	<i>p</i>
Penetrating disease	2.1 (0.9–4.8)	0.072
Segmental resection	1.0 (0.4–2.9)	0.93
Anastomosis	2.9 (1.1–7.7)	0.036
Smoking	0.42 (0.15–1.2)	0.11
Hemoglobin level < 10 g/dl	3.1 (1.1–9.1)	0.034

IASC intraabdominal septic complications

risk in patients with lower preoperative hemoglobin levels has been demonstrated by Bruewer et al. in a population consisting predominantly of patients with ileocolic disease [25]. However, in many other studies, there were no differences between patients with normal and low hemoglobin levels [2, 26]. As mentioned above, ileocolic resections dominated all of these studies, thus the results should probably not be compared to the current analysis. A recent large population-based study from the United States of 15,761 patients demonstrated a significant correlation between anemia and postoperative morbidity, prolonged hospital stay, postoperative transfusions and mortality in patients with CD and ulcerative colitis [21]. Further studies are needed to demonstrate whether preoperative iron substitution could reduce the postoperative complication risk in IBD patients as has been suggested for patients undergoing gastrointestinal cancer surgery [27]. In our study, smokers presented with higher preoperative hemoglobin levels and developed less, although not significantly less, postoperative IASC.

Low serum albumin levels have been shown to be a predictor of postoperative morbidity [28] and also a strong indicator of severe colonic disease [29, 30]. In the present study, the difference in IASC rate was not statistically different between patients with normal and reduced serum albumin levels. Unfortunately, the serum albumin level is not measured routinely at German hospitals; therefore, those data were missing in more than half of the study patients. Again, patients with severe anemia, and probably, hypoalbuminemia should be strongly considered for preoperative optimization strategies or even for resection without anastomosis.

Treatment with TNF-alpha inhibitors, azathioprine and especially steroids has been suggested to be a factor affecting postoperative morbidity in Crohn's disease patients in numerous studies [1, 5, 6, 26]. Moreover, most international guidelines strongly recommend stopping treatment with TNF-alpha inhibitor preoperatively or to use a staged approach [6, 31, 32]. The present study did not demonstrate any association between preoperative intake of any of those medications and the risk of IASC. The attempt to achieve mucosal healing in colonic segments later utilized for the formation of the anastomosis might have a positive role in patients undergoing surgery for colonic disease and might counterbalance some risks of the immunosuppression.

The present study has several limitations. There might be some discrepancies in interpretation of variables and definitions between countries, especially regarding the definition of clinical disease behavior, disease localization and postoperative IASC. In addition, some differences in surgical strategies, patient selection or even surgical techniques might have affected the results of our study. Moreover, data about some important variables which might have affected the results, e.g., serum albumin level, extent of proctitis, preoperative mechanical bowel preparation, and preoperative weight loss, were incomplete or could not be obtained at all. However, to the best of our knowledge, this is the first study analyzing the risk factors for postoperative morbidity—especially, anastomotic and other septic complications—in patients undergoing intestinal resection for colonic CD.

Conclusions

Preoperative risk assessment might be different in patients undergoing colonic resection for colonic Crohn's disease and in patients undergoing ileocolic resection for ileal Crohn's disease. Resections completed by formation of an anastomosis seem to be associated with an increased complication risk. Severe anemia (hemoglobin level < 10 g/dl) is a strong indicator of postoperative risk. Preoperative optimization strategies—nutritional support, antibiotics, bowel rest—should be considered in patients at risk. Further studies are necessary to define the role of preoperative iron substitution.

Unfortunately, the present study could not provide any recommendations regarding the use of diverting ileostomy.

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Data Availability Data have been generated as part of the routine work.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent For this type of retrospective cohort study, an informed consent is not required.

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