

Anti-TNF Therapy Is Associated With an Increased Risk of Postoperative Morbidity After Surgery for Ileocolonic Crohn Disease

Results of a Prospective Nationwide Cohort

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Objective: To determine the risk factors of morbidity after surgery for ileocolonic Crohn disease (CD).

Summary Background Data: The risk factors of morbidity after surgery for CD, particularly the role of anti-TNF therapy, remain controversial and have not been evaluated in a large prospective cohort study.

Methods: From 2013 to 2015, data on 592 consecutive patients who underwent surgery for CD in 19 French specialty centers were collected prospectively. Possible relationships between anti-TNF and postoperative overall morbidity were tested by univariate and multivariate analyses. Because treatment by anti-TNF is possibly dependent on the characteristics of the patients and disease, a propensity score was calculated and introduced in the analyses using adjustment of the inverse probability of treatment-weighted method.

Results: Postoperative mortality, overall and intra-abdominal septic morbidity rates in the entire cohort were 0%, 29.7%, and 8.4%, respectively; 143 (24.1%) patients had received anti-TNF <3 months prior to surgery. In the multivariate analysis, anti-TNF <3 months prior to surgery was identified as an independent risk factor of the overall postoperative morbidity (odds-ratio [OR] = 1.99; confidence interval [CI] 95% = 1.17–3.39, $P = 0.011$), with preoperative hemoglobin <10 g/dL (OR = 4.77; CI 95% = 1.32–17.35, $P = 0.017$), operative time >180 min (OR = 2.71; CI 95% = 1.54–4.78, $P < 0.001$) and recurrent CD (OR = 1.99; CI 95% = 1.13–3.36, $P = 0.017$). After calculating the propensity score and adjustment according to the inverse probability of treatment-weighted method, anti-TNF <3 months prior to surgery remained associated with a higher risk of overall (OR = 2.98; CI 95% = 2.04–4.35, $P < 0.0001$) and intra-abdominal septic postoperative morbidities (OR = 2.22; CI 95% = 1.22–4.04, $P = 0.009$).

Conclusions: Preoperative anti-TNF therapy is associated with a higher risk of morbidity after surgery for ileocolonic CD. This information should be considered in the surgical management of these patients, particularly with regard to the preoperative preparation and indication of temporary defunctioning stoma.

Keywords: anti-TNF, Crohn disease, morbidity, surgery

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Despite major advances in the medical therapy for Crohn disease (CD), with the sequential introduction of immunomodulators and monoclonal antibodies targeting TNF α ^{1–3} (anti-TNF), up to 60% of patients with ileocolonic CD eventually require surgical treatment during the course of their disease, predominantly because of CD complications or resistance to medical therapy.⁴ Over the past 2 decades, the short-term outcomes after surgery for ileocolonic CD have been markedly improved by better perioperative management^{5–8} and the introduction of the laparoscopic approach.^{9–11} However, postoperative morbidity, including infectious complications, could occur in up to 40% of patients after surgery for ileocolonic CD.^{12–14} Several retrospective studies have attempted to identify risk factors for morbidity after ileocolonic CD surgery and reported that preoperative steroid therapy, poor preoperative nutritional status, or complicated forms of CD (ie, perforating form with abscess and/or fistula, or recurrent CD) were associated with an increased risk of postoperative morbidity.^{13,15,16} No prospective evaluation or validation of these possible risk factors for postoperative morbidity after surgery for ileocolonic CD has been reported. In particular, the possible effect of the preoperative administration of anti-TNF on postoperative results remains controversial.^{17–22} However, better knowledge of these risk factors for morbidity after surgery for ileocolonic CD would be helpful in defining a high-risk population in whom prevention for postoperative complications including a temporary ileocolostomy could be proposed.

The aim of this study was to identify risk factors of postoperative complications after surgery for ileocolonic CD in a nationwide prospective cohort.

METHODS

Patients and Data Collection

From September 1, 2013, to September 1, 2015, all patients who underwent surgery for ileocolonic CD at 19 French academic centers of the GETAID Chirurgie group, which specializes in inflammatory bowel disease (IBD) management, were prospectively included. The inclusion criteria were as follows: age >18 years, ileocolonic CD and elective or emergency intestinal resection. The patients who had surgery for CD limited to a perianal or a colonic location were excluded. The indications for surgery and perioperative management were discussed in each institutional multidisciplinary IBD team, which included local gastroenterologists, radiologists, pathologists, and surgeons based on the current guidelines.^{23–25} Variables including demographics, disease type and severity, previous treatment of CD, intraoperative findings, and surgical procedures were prospectively collected on an electronic dedicated clinical research form (Cleanweb). No specific recommendation was provided with regard to previous medical treatment or steroid cessation before surgery, preoperative nutritional support, or preoperative treatment of infectious complications. The indications for these steps of the preoperative preparation were left to the discretion of each participating surgical team. This observational cohort study was conducted according to the ethical standards of the institutional committee on human experimentation and reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.²⁶

Surgical Procedure and Postoperative Outcome

A laparoscopic approach was proposed as the preferred option as frequently as possible at all participating centers. A complete exploration of the peritoneal cavity was performed, and the entire length of the bowel was run with atraumatic forceps to ensure that no lesion had been missed during the preoperative workup. The bowel targeted for resection was extracted through a 5 to 6 cm incision in a right lower quadrant or midline incision. A conversion to open surgery was defined as any unplanned incision or a planned incision that was made longer than necessary for simple exteriorization of the resected specimen and fashioning of the anastomosis. Management of an internal fistula was decided according to the type of structures and the presence or absence of CD on the intestinal segment involved in the fistula. In addition to the CD resection, upfront repair of the bladder was used in patients with an enterovesical fistula. In those patients with a fistula involving a different part of the bowel, a combined resection was proposed in patients with ileocolonic CD and associated CD on the intestinal segment involved (eg, colonic or jejunal CD), whereas suture of the fistula was preferred in cases presenting no CD on the “victim” intestinal segment. The decision to perform a primary anastomosis or temporary ileocolostomy was made on a per-patient basis and left to the discretion of the surgeon, according to the preoperative clinical data and intraoperative findings.

The in-hospital or 30-day postoperative morbidity and mortality were recorded prospectively starting from the date of the surgery. Postoperative morbidity was defined as any deviation from the normal postoperative course, graded according to the Clavien–Dindo classification.²⁷ Intraabdominal septic morbidity included postoperative peritonitis, anastomotic leakage with or without peritonitis and intra-abdominal abscess. In addition, the reoperation rate, length of hospital stay, and readmission rate were prospectively recorded.

TABLE 1. Characteristics of 592 Patients With Crohn Disease Undergoing Ileocolonic Resection

	n = 592
Age, yrs*	34 (18–85)
Sex (male/female)	261/331
Body mass index, kg/m ² *	21 (12.8–43)
Weight loss >10%	149 (25)
Smoking history†	
Never smoked	334 (56)
Past smoker	92 (16)
Current smoker	166 (28)
ASA status >2‡	32 (5)
Duration of the Crohn disease before surgery, yrs	7.6 (0–52)
Acute episode <3 mo†	36 (6)
Disease behavior†	
Stricturing CD	343 (58)
Inflammatory CD	42 (7)
Perforating CD	207 (35)
Recurrent CD†	156 (26)
Multifocal intestinal CD†	102 (17)
Associated colorectal CD†	106 (18)
Associated Perianal CD†	86 (15)
Preoperative biologic parameters†	
Hemoglobin level <10 g/dL	20 (3)
Albumin serum level <30 g/L	75 (13)
C reactive protein serum level >10 mg/L	253 (43)

*Values are median (range).

†% are in parentheses.

‡ASA indicates American Society of Anesthesiology.

Statistical Analysis

The quantitative and qualitative variables were expressed as the mean \pm the standard deviation (SD), median (range), and frequency. The primary endpoint was the overall 30-day or in-hospital postoperative morbidity. To identify the risk factors of the overall postoperative morbidity, univariate and multivariate analyses were used to examine the relationship between the occurrence of postoperative morbidity and 44 variables related to the patient characteristics and comorbidities, the type and severity of the CD, preoperative treatment targeting CD, preoperative biological parameters, and intraoperative findings and surgical procedures. All variables associated with a *P* value <0.1 were subsequently included in a binary logistic regression model. A *P* value <0.05 was considered statistically significant. A risk score of postoperative morbidity was calculated according to the risk factors identified in the multivariate analysis. In those patients undergoing surgery, the prescription of anti-TNF is a confounding factor because it is linked to the severity of the disease. Because anti-TNF is possibly dependent on the patient and disease characteristics, a propensity score was calculated and introduced into the analyses of the effect of anti-TNF therapy <3 months on overall and intraabdominal septic morbidity using adjustment of the inverse probability of treatment-weighted (IPTW) method. The statistical analysis was performed using SAS software, version 9.4 (SAS Institute Inc, Cary, NC).

RESULTS

Patient Characteristics

From September 1, 2013, to September 1, 2015, 592 underwent surgery for ileocolonic CD. The patient characteristics are summarized in Table 1.

Regarding the preoperative physical status and comorbidities, 96 patients (16%) had a body mass index (BMI) <18, whereas 27 patients (4.5%) were overweight with a BMI >30, and 223 (37.6%)

TABLE 2. Previous Medical of Crohn Disease in 592 Patients Undergoing Surgery for Ileocolonic Crohn Disease

	n = 592
Previous medical treatment exposure*	457 (77)
Budesonide	71 (12)
Mesalazine	62 (10)
Thiopurin	155 (26)
Adalimumab	174 (29)
Infliximab	136 (23)
Other anti-TNF	22 (4)
Methotrexate	26 (4)
Vedolizumab	8 (2)
Number of lines of medical treatment \geq 2*	202 (34)
Medical treatment <3 months before surgery	
Systemic steroids	27 (5)
Budesonide	20 (3)
Mesalazine	13 (2)
Thiopurin	42 (7)
Methotrexate	8 (1)
Adalimumab	78 (13)
Infliximab	62 (10)
Other anti-TNF	3 (0.5)

*% are in parentheses.

had poor preoperative nutritional status defined as a BMI <18 and/or weight loss >10% of the body weight within 6 months before surgery and/or preoperative serum albumin <30 g/dL. A minority of patients (*n* = 32, 5.4%) had marked comorbidities with an ASA status >2. The most common comorbidities were hypertension and cardiac disease, in 23 and 11 patients, respectively.

The majority of patients (*n* = 457, 77%) had been diagnosed with CD more than 2 years before surgery. One hundred fifty-six patients (26.3%) had already had an intestinal resection for CD, and 44 (7%) had more than 1 prior intestinal resection. Eighty-five patients (14.3%) had at least 3 acute episodes of CD before surgery. During the preoperative workup, the perforating form of CD was diagnosed in 207 (35%) patients, including 47 (7.9%) patients presenting with an intraabdominal abscess, 100 (16.8%) with an internal fistula, and 60 patients (10.1%) with both an abscess and an internal fistula. Among the 207 patients with perforating CD, 192 patients (32.4%) had received antibiotics before surgery, and 31 (5.2%) had required preoperative percutaneous drainage of an abscess. The 385 remaining patients (65%) had stricturing or inflammatory ileocolonic CD.

The vast majority of patients (*n* = 457, 77.2%) had received at least 1 line of medical therapy targeting CD before surgery; among these, 145 received 2 lines of treatment, 41 received 3 lines, and 17 received more than 4 lines. Two hundred fifty-three patients (42.9%) received treatment within 3 months before the surgery; the details of these treatments are reported in Table 2. Overall, the median time interval between cessation of medical therapy for CD and surgery was 5.5 weeks (0–725). Forty-seven patients received steroids, including either systemic steroids or budesonide, within 3 months before surgery. Among these 47 patients, the median time interval between the cessation of treatment and surgery was 3.9 weeks (0–12), and 15 patients remained on steroid therapy at the time of surgery (<14 days before surgery). One hundred forty-three patients (24.1%) had received anti-TNF therapy within 3 months before surgery. Among these 143 patients, the median time interval between the cessation of the anti-TNF therapy and surgery was 4.4 weeks (0–12). One patient received concomitant treatment with anti-TNF therapy and steroids within the 3 months prior to surgery.

TABLE 3. Preoperative Management and Surgical Procedures in 592 Patients Undergoing Ileocolonic Resection for Crohn Disease

	n = 592
Preoperative nutritional support	
Oral/enteral	88/50
Total parenteral nutrition	92
Intraoperative findings†	
Internal fistula	208 (35)
Abscess	106 (18)
CD length >50 cm	68 (11)
Emergency surgery†	57 (10)
Surgical approach†	
Laparoscopy	432 (73)
Conventional	160 (27)
Type of resection†	
Ileocecal resection	423 (71.5)
Redo ileocolonic resection	144 (24.5)
Intestinal resection	25 (4)
Associated procedures†	
Strictureplasty	19 (3)
Additional intestinal resection	45 (7)
Length of resected bowel, cm*	25 (2–99)
Intraoperative complications†	
Bowel injury	2 (0.3)
Bleeding	2 (0.3)
Primary anastomosis†	465 (79)
Type of anastomosis†	
End to side/end to end/side to side	88/51/316
Hand-sewn/stapled	276/189
Operative time, min	135 (50–370)

*Values are median (range).

†% are in parentheses.

Surgical Procedure and Postoperative Outcome

The operative characteristics of the 592 patients undergoing surgery for ileocolonic CD are summarized in Table 3.

Among the 156 patients undergoing surgery for recurrent ileocolonic CD, 144 underwent an iterative ileocolonic resection, and 12 had an iterative intestinal resection with preservation of the previous ileocolonic anastomosis. Fourteen additional patients underwent a primary intestinal resection with preservation of the ileocolonic junction for isolated ileal CD with no lesion of the caecum. Among the 57 patients undergoing emergency surgery, 31 had a perforating form of CD with an intraabdominal abscess. Other indications for emergency surgery were small bowel obstruction in 14 patients and localized peritonitis in 12 patients.

The majority of the patients (n = 465, 79%) had primary anastomosis. A temporary defunctioning ileocolostomy was performed in the other 127 patients (23%). The characteristics of these 127 patients differed from those of the patients undergoing primary anastomosis, with a higher prevalence of known risk factors of intraabdominal septic complications such as poor preoperative nutritional status and the perforating form of CD (Table 4). A temporary ileocolostomy was preferred to primary anastomosis in patients undergoing emergency surgery ($P < 0.001$), a BMI < 18 ($P = 0.002$), with preoperative weight loss $> 10\%$ ($P < 0.001$), in the patients with the perforating form of CD detected on the preoperative workup ($P < .001$) and in the patients with intraoperative findings of an abscess ($P < 0.001$).

The postoperative results of the 592 patients undergoing surgery for ileocolonic CD are summarized in Table 5. Postoperative mortality was nil. Postoperative complications occurred in 176 patients (30%), including severe complications (Dindo-Clavien

grade III/IV) in 53 patients (9%). Reoperation was required in 25 patients (4%), predominantly for intraabdominal septic morbidity requiring a resection of the anastomosis and temporary ileocolostomy creation in 20 patients (3%). The median postoperative hospital stay was 7 days (2–272).

Univariate and Multivariate Analyses of the Risk Factors of Overall Postoperative Morbidity

The results of the univariate and multivariate analyses of the risk factors for overall postoperative morbidity in 592 patients undergoing surgery for ileocolonic CD are reported in Table 6.

In the multivariate analysis, anti-TNF < 3 months prior to surgery was identified as an independent risk factor for the overall postoperative morbidity (odds-ratio [OR] = 1.99; confidence interval [CI] 95% = [1.17–3.39], $P = 0.011$), with preoperative hemoglobin < 10 g/dL (OR = 4.77; CI 95% = [1.32–17.35], $P = 0.017$), operative time > 180 min. (OR = 2.71; CI 95% = [1.54–4.78], $P < 0.001$) and recurrent CD (OR = 1.95; CI 95% = [1.13–3.36], $P = 0.017$). The risk of postoperative complications increased significantly according to the number of risk factors present in the same patient. The postoperative complication rate was 18% among the 262 patients with no risk factor for postoperative morbidity, 33% among the 233 patients with 1 risk factor, and 52% among the 97 patients with 2 risk factors or more (Fig. 1).

To better assess the role of anti-TNF on overall postoperative morbidity, a propensity score was calculated using the inverse probability weighted method. After adjustment, anti-TNF therapy < 3 months remained associated with an increased risk of postoperative morbidity (OR = 2.98; CI 95% = [2.04–4.35], $P < 0.0001$). Using the same method, anti-TNF therapy was associated with an increased risk of intraabdominal septic morbidity (OR = 2.22; CI 95% = [1.22–4.04], $P = 0.009$).

Concerning the risk of overall morbidity and intraabdominal septic morbidity according to the time of last infusion of anti-TNF therapy, among 143 patients who underwent surgery for ileocolonic CD and who received anti-TNF therapy within 3 months before surgery, overall morbidity rates in patients who received last infusion more or less than 5 weeks prior to surgery were 49% (31/63) and 41% (33/80) respectively (NS). Septic intraabdominal morbidity rates in patients who received last infusion more or less than 5 weeks prior to surgery were 7.9% (5/63) and 16% (13/80) respectively ($P = 0.203$).

DISCUSSION

This study is the first to prospectively evaluate the risk factors of complications after surgery for ileocolonic CD. In the era of modern multimodal management of CD, our results indicate that preoperative anti-TNF therapy increases the risk of morbidity after surgery for ileocolonic CD. In addition, we identified new risk factors of morbidity, including recurrent CD, low preoperative hemoglobin, and prolonged operative time.

Anti-TNF antibodies have gained wide acceptance in the management of CD. Their efficacy on the induction and the maintenance of remission of CD has been demonstrated in several randomized controlled trials.^{1–3} As a consequence, patients who are candidates for surgery have frequently been previously treated with anti-TNF, and failure of this treatment reflects the disease severity. This relationship explains why it is so difficult to address the effect of anti-TNF on the risk of postoperative complications after the surgical treatment of ileocolonic CD and the discrepancies among the studies that have been previously reported.^{17–22} Additionally, the evaluation of the effect of anti-TNF on morbidity in a randomized study might not be feasible because anti-TNF therapy is indicated according to the severity of the disease rather than to the need for

TABLE 4. Preoperative Characteristics and Operative Findings of 592 Patients Undergoing Surgery for Ileocolonic CD

	Primary Anastomosis n = 465	Temporary Ileocolostomy n = 127	P
From centers with more than 20 inclusions*	419 (90)	123 (97)	0.012
Age >65 yrs*	29 (6)	5 (4)	0.222
Male sex*	190 (41)	71 (56)	0.002
Body mass index >30 kg/m ² *	23 (5)	4 (3)	0.284
Body mass index <18 kg/m ² *	64 (14)	32 (25)	0.002
Weight loss >10%*	101 (22)	48 (38)	<0.001
Active smoking history*	134 (29)	32 (25)	0.384
ASA status >2*	17 (4)	15 (12)	<0.001
Duration of the Crohn disease before surgery >2 yrs*	366 (79)	92 (72)	0.168
Acute episode <3 mo*	31 (7)	5 (4)	0.177
Disease behavior*			
Stricturing CD	309 (66)	34 (27)	<0.001
Inflammatory CD	17 (4)	25 (20)	<0.001
Perforating CD	139 (30)	68 (54)	<0.001
Recurrent CD*	123 (26)	33 (26)	0.507
Multifocal intestinal CD*	83 (18)	19 (15)	0.314
Associated colorectal CD*	75 (16)	31 (24)	0.025
Perianal CD*	56 (12)	30 (24)	0.001
Preoperative biologic parameters*			
Hemoglobin level <100 g/dL	9 (2)	11 (9)	0.001
Albumin serum level <30 g/L	34 (7)	41 (32)	<0.001
C-reactive protein serum level >10 mg/L	166 (36)	87 (69)	<0.001
Previous medical treatment exposure*	359 (77)	98 (77)	0.982
Number of lines of medical treatment ≥ 2*	159 (34)	43 (34)	0.964
Preoperative nutritional support*	150 (32)	53 (42)	0.045
Enteral	109 (23)	29 (23)	0.503
Total parenteral nutrition	61 (13)	31 (24)	0.002
Intraoperative findings*			
Internal fistula	140 (30)	68 (54)	<0.001
Abscess	61 (13)	45 (35)	<0.001
CD length >50 cm	49 (11)	19 (15)	0.138
Emergency surgery*	17 (4)	40 (31)	<0.001
Operative time >180 min*	90 (19)	38 (30)	0.007

*% are in parentheses.

ASA indicates American Society of Anesthesiology.

surgery. In our prospective study, we aimed to eliminate the possible bias related to the link between the severity of the disease and prescription of anti-TNF by adjusting the analysis with a propensity score (IPTW method). Our results showed that regardless of the disease severity, preoperative anti-TNF therapy increased the risk of morbidity after surgery for ileocolonic CD. These results are in accordance with 3 recent meta-analyses of retrospective studies showing that anti-TNF could increase the risk of morbidity and, in particular, infectious complications.^{21,22,28} Our results confirm that anti-TNF therapy could increase the risk of overall morbidity and intraabdominal septic complications. Overall, we did not show a significant difference in overall morbidity rates according to the time of last infusion. We observed a trend toward an increase in the rate of septic intraabdominal morbidity according to the time of last infusion of anti-TNF, but this difference did not reach a statistically significant level. This may be explained by the sample size.

In this study, the deleterious effect of preoperative steroids, preoperative poor nutritional status, and the perforating CD phenotype was not found to be prominent. These factors have been identified as being potentially associated with an increased risk of morbidity in several retrospective studies in the past.^{13,15,16} However, the discrepancy between previous retrospective series and this prospective study could be explained. Our results show that the rate of temporary ileocolostomy was significantly increased in patients presenting 1 or several of these known factors. This finding strongly

TABLE 5. Postoperative Outcome in 592 Patients Undergoing Ileocolonic Resection for Crohn Disease

	n = 592
Postoperative mortality*	0 (0)
Overall postoperative morbidity*	176 (30)
Intraabdominal septic complications*	50 (8)
Anastomotic leakage with peritonitis	15 (3)
Anastomotic leakage without peritonitis	12 (2)
Intraabdominal abscess	23 (4)
Other complications*	
Intraabdominal bleeding	7 (1)
Intestinal bleeding	13 (2)
Ileus	33 (6)
Wound infection	23 (4)
Urinary tract infection	11 (2)
Pneumonia	2 (0.3)
Pulmonary embolism	1 (0.1)
Catheter infection	9 (2)
Urinary retention	4 (0.7)
Acute renal failure	7 (1.1)
Others	21 (4)
Severe postoperative complications (Dindo-Clavien grade III/IV)*	53 (9)
Reoperation for complications*	25 (4)

*% are in parentheses.

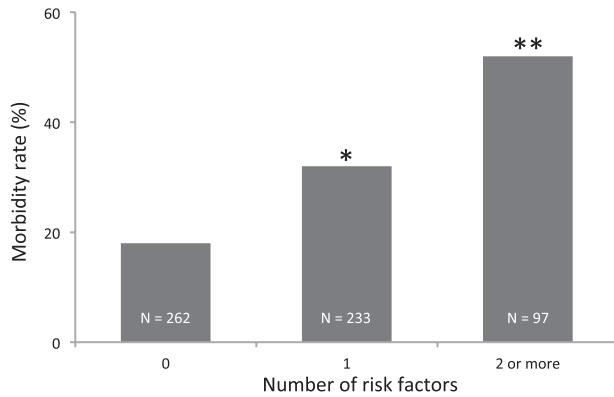
TABLE 6. Univariate and Multivariate Analysis of Risk Factors of Overall Postoperative Morbidity in 592 Patients Undergoing Ileocolonic Resection for Crohn Disease

	Univariate Analysis	Multivariate Analysis
	<i>P</i>	OR, Confidence Interval 95%, <i>P</i>
From centers with more than 20 inclusions	0.430	—
Sex	0.430	—
Age >65 yrs	0.219	—
BMI <18 kg/m ²	0.449	—
BMI >30 kg/m ²	0.651	—
Weight loss >10%	0.754	—
CD evolution >2 yrs	0.010	—
Active smoking	0.470	—
Hypertension	0.023	NS
Cardiac disease	0.102	—
ASA ^a score >2	0.339	—
Acute episode	0.135	—
Number of acute episodes >3	0.014	NS
Acute episode <3 mo before surgery	0.224	—
Number of treatment lines ≥2	0.393	—
Medical treatment within 3 months before surgery		
Systemic steroids	0.068	NS
Budesonide	0.004	NS
Mesalazine	0.362	—
Anti-TNF therapy	<0.001	1.99 [1.17–3.39], <i>P</i> = 0.011
Thiopurin	0.342	—
Methotrexate	1	—
Vedolizumab	0.330	—
Recurrent CD	0.008	1.95 [1.13–3.36], <i>P</i> = 0.017
Type of CD on preoperative workup		
Multifocal CD	0.039	NS
Perforating CD	0.584	—
Strictureing CD	0.598	—
Associated colonic CD	0.638	—
Associated perianal CD	0.005	—
Extradigestive symptoms	0.885	—
Preoperative biologic parameters		
Serum albumin serum level <30 g/dL	0.257	—
Hemoglobin level <10 g/dL	<0.001	4.77 [1.32–17.35], <i>P</i> = 0.017
C-reactive protein serum level >10 mg/L	0.801	—
Preoperative nutritional support		
Total parenteral nutrition	0.011	NS
Enteral nutrition	0.737	—
Emergency surgery	0.624	—
Laparoscopic approach	0.050	NS
Intraoperative findings		
Abscess	0.722	—
Internal fistula	0.773	—
Associated procedures		
Intestinal resection	0.552	—
Strictureplasty	0.348	—
Primary anastomosis	0.561	—
Intraoperative bleeding >300 mL	0.522	—
Intraoperative bowel injury	0.095	—
Operative time >180 min	<0.001	2.71 [1.54–4.78], <i>P</i> <0.001

ASA indicates American Society of Anesthesiology.

supports the hypothesis that participating surgeons working at IBD centers have anticipated an increased risk of complications in these high-risk patients. In this study, the absence of the effect of these well-known risk factors on postoperative morbidity in the multivariate analysis suggests that a temporary ileocolostomy probably limited the negative effect of these factors on the postoperative outcome. As such, we could not conclude that these factors are useless; on the contrary, we hypothesize that they should be still considered. Furthermore, our results show that recurrent CD,

operative time >180 min, and preoperative anemia <10 g/dL are additional risk factors for postoperative complications. The finding that recurrent CD is associated with an increased risk of postoperative morbidity was previously reported in a case-controlled study.¹⁴ Surgical resection of recurrent CD is not always feasible laparoscopically^{14,29} and could require additional procedures¹⁴ that might increase the risk of postoperative complications. Prolonged operative time has been shown to increase the risk of anastomotic leakage after colorectal surgery.^{30,31} More recently, an operation time >180 min



* 0 vs 1 risk factor, $p < 0.001$

** 1 vs 2 or more risk factors, $p = 0.002$; 0 vs 2 or more risk factors, $p < 0.001$

FIGURE 1. Morbidity rate according to the number of risk factors in 592 patients undergoing surgery for ileocolonic Crohn's disease.

was shown to increase the risk of intraabdominal septic morbidity in a retrospective series of 550 patients undergoing surgery for CD.¹³ Finally, preoperative anemia has been consistently reported as a potential risk factor of postoperative morbidity after noncardiac surgery.^{32–35}

In this study, we could not evaluate the possible effect of perioperative actions targeting specifically the risk factors to limit postoperative morbidity after surgery for ileocolonic CD. The fact that preoperative anti-TNF increases the risk of postoperative morbidity raises the question of whether the treatment should be discontinued 3 months before surgery whenever possible. In other cases, different types of perioperative or operative measures could be proposed, including preoperative preparation (iron therapy and/or nutritional support) or temporary defunctioning stoma in the subgroup of patients at high risk of postoperative complications. Based on our results, prevention should probably be discussed in patients with 2 or more risk factors that have a >50% postoperative morbidity risk. In CD patients undergoing surgery, the beneficial effect of preoperative nutritional support has been evaluated in only a few studies.^{5,6} These studies suggest that preoperative nutritional support could limit the risk of postoperative complications and the need for temporary stoma.

This study shows that in the era of modern ileocolonic CD management, new risk factors for postoperative morbidity could be proposed, including recurrent CD, preoperative anemia, operative time >180 min and preoperative anti-TNF therapy within 3 months before the surgery. At this time, in patients with ileocolonic CD, surgery is frequently proposed only after failure of previous anti-TNF therapy. That anti-TNF therapy is associated with an increased risk of postoperative morbidity is important for determining the optimal treatment strategy when 2 treatment options, that is, introduction of anti-TNF or surgery, are available.^{23–25} If in patients with recent anti-TNF therapy and other associated risk factors, preoperative preparation and/or temporary stoma could be a reasonable solution, and the choice of surgery as an alternative to anti-TNF therapy could be discussed.

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