Diseases of the Colon & Rectum Publish Ahead of Print

DOI: 10.1097/DCR.0000000000002446

ORIGINAL CONTRIBUTION

Postoperative Complications Are Associated With Early and Increased Rate of Disease Recurrence After Surgery for Crohn's Disease

Running head: Recurrence in Crohn's disease

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Funding/Support: None reported.

Financial Disclosures: AS acted as speaker for Johnson and Johnson and Takeda, MC acted as speaker for Takeda and Pfizer, ADH, GB, AM, CC, SV, and SD have nothing to disclose.

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ABSTRACT

BACKGROUND: Several potential risk factors for Crohn's disease recurrence after surgery have been identified, including age at diagnosis, disease phenotype, and smoking. Despite the clinical relevance, few studies investigated the role of postoperative complications as a possible risk factor for disease recurrence.

OBJECTIVE: To investigate the association between postoperative complications and recurrence in Crohn's disease patients after primary ileocolic resection.

DESIGN: This was a retrospective case-control study.

SETTING: This study was conducted at two tertiary academic centers.

PATIENTS: We included 262 patients undergoing primary ileocolic resection for Crohn's disease between January 2008 and December 2018 and allocated the patients into *recurrent* (145) and *non-recurrent* (117) groups according to endoscopic findings.

MAIN OUTCOME MEASURES: Postoperative complications were assessed as possible risk factors for endoscopic recurrence after surgery by univariable and multivariable analysis. The effect of postoperative complications on endoscopic and clinical recurrence was evaluated by Kaplan-Meier and Cox regression analyses.

RESULTS: At multivariable analysis, smoking (OR = 1.84; 95% CI: 1.02-3.32; $p = 0.04$), penetrating phenotype (OR = 3.14; 95% CI: 1.58-6.22; $p < 0.01$), perianal disease (OR = 4.03; 95% CI: 1.75-9.25; $p = 0.001$), and postoperative complications (OR = 2.23; 95% CI: 1.17; $p = 0.01$) were independent risk factors for endoscopic recurrence. Postoperative complications (HR = 1.45; 95% CI: 1.02-2.05; $p = 0.03$) and penetrating disease (HR = 1.73; 95% CI: 1.24-2.40; $p = 0.001$) significantly reduced the time to endoscopic recurrence; postoperative complications (HR= 1.6; 95% CI: 1.02-2.88; $p = 0.04$) and penetrating disease (HR = 207.10; 95%CI: 88.41-542.370; $p < 0.0001$) significantly shortened the time to clinical recurrence.

LIMITATIONS: This study was limited by its retrospective design.

CONCLUSIONS: Postoperative complications are independent risk factors for endoscopic recurrence after primary surgery for Crohn's disease, affecting the rate and timing of endoscopic and clinical disease recurrence. See **Video Abstract** at http://links.lww.com/DCR/C48 .

LAS COMPLICACIONES POSOPERATORIAS ESTÁN ASOCIADAS CON UNA TASA TEMPRANA Y AUMENTADA DE RECURRENCIA DE LA ENFERMEDAD DESPUÉS DE LA CIRUGÍA PARA LA ENFERMEDAD DE CROHN

ANTECEDENTES: Se han identificado varios factores de riesgo potenciales para la recurrencia de la enfermedad de Crohn después de la cirugía, incluida la edad en el momento del diagnóstico, el fenotipo de la enfermedad y el tabaquismo. A pesar de la relevancia clínica, pocos estudios investigaron el papel de las complicaciones postoperatorias como posible factor de riesgo para la recurrencia de la enfermedad.

OBJETIVO: Investigar la asociación entre las complicaciones postoperatorias y la recurrencia en pacientes con enfermedad de Crohn después de la resección ileocólica primaria.

DISEÑO: Este fue un estudio retrospectivo de casos y controles.

AJUSTE: Este estudio se realizó en dos centros académicos terciarios.

PACIENTES: Incluimos 262 pacientes sometidos a resección ileocólica primaria por enfermedad de Crohn entre enero de 2008 y diciembre de 2018 y los asignamos en grupos recurrentes (145) y no recurrentes (117) según los hallazgos endoscópicos.

PRINCIPALES MEDIDAS DE RESULTADO: Las complicaciones posoperatorias se evaluaron como posibles factores de riesgo de recurrencia endoscópica después de la cirugía mediante análisis univariable y multivariable. El efecto de las complicaciones posoperatorias sobre la recurrencia endoscópica y clínica se evaluó mediante análisis de regresión de Kaplan-Meier y Cox.

RESULTADOS: En el análisis multivariable, tabaquismo (OR = 1,84; IC 95%: 1,02-3,32; p = 0,04), fenotipo penetrante (OR = 3,14; IC 95%: 1,58-6,22; p < 0,01), enfermedad perianal (OR = 4,03; IC 95%: 1,75-9,25; p = 0,001) y las complicaciones postoperatorias (OR = 2,23; IC 95%: 1,17; p = 0,01) fueron factores de riesgo independientes para la recurrencia endoscópica. Las

complicaciones posoperatorias (HR= 1,45; IC 95%: 1,02-2,05; p = 0,03) y la enfermedad penetrante (HR= 1,73; IC 95%: 1,24-2,40; p = 0,001) redujeron significativamente el tiempo hasta la recurrencia endoscópica; las complicaciones posoperatorias (HR= 1,6; IC 95%: 1,02-2,88; p = 0,04) y la enfermedad penetrante (HR = 207,10; IC 95%: 88,41-542,370; p < 0,0001) acortaron significativamente el tiempo hasta la recurrencia clínica.

LIMITACIONES: Este estudio estuvo limitado por su diseño retrospectivo.

CONCLUSIONES: Las complicaciones postoperatorias son factores de riesgo independientes para la recurrencia endoscópica después de la cirugía primaria para la enfermedad de Crohn, lo que afecta la tasa y el momento de la recurrencia endoscópica y clínica de la enfermedad. Consulte **Video Resumen** en http://links.lww.com/DCR/C48 . *(Pre-proofed version)*

KEY WORDS: Crohn's disease; Endoscopic recurrence; Postoperative complications; Postoperative recurrence.

INTRODUCTION

Despite the significant improvement in diagnosis and advances in medical treatment, up to 80% of Crohn's disease (CD) patients may require surgical treatment during their life.[1,2] Surgery plays a crucial role in the treatment of CD and is indicated for complicated disease featuring stricture, fistula, or abscess.[3] However, endoscopic recurrence may occur in about two/thirds of patients within a year after surgery.[4,5] As a result, half of the patients at 10 years may require further surgical treatment for disease recurrence.[6,7] Several potential risk factors for disease recurrence have been identified, including age at diagnosis, disease phenotype, and smoking.[8–13] In the light of the evolution of prevention and management of postoperative recurrence, including early immunosuppressive and biologic treatments, the identification of potential risk factors is pivotal.[14–20] Despite the clinical relevance, few studies investigated the role of postoperative complications as a possible risk factor for disease recurrence.[21–23] Moreover, as postoperative complications might be driven by modifiable perioperative risk factors such as impaired nutritional status or delayed surgery, it is of paramount importance to address this issue.[24,25]

This study aimed to investigate the association between postoperative complications and disease recurrence in CD patients after primary ileocolonic resection.

MATERIALS AND METHODS

This was a retrospective multicentric case-control study. The study was approved by the medical ethical boards of the Institutions involved and the patients gave informed consent. The surgical registries of two tertiary referral centers for inflammatory bowel disease (IBD) were screened to collect patients with a proven diagnosis of CD who underwent ileocolic resection between January 2008 and December 2018. Patients were excluded from the primary analyses if meeting one of the following exclusion criteria: repeated ileocolic resections for disease recurrence; follow-up less than 24 months. Patients receiving stoma at index surgery were added to the study sample and evaluated in a separate analysis. The subjects were ~~included~~ allocated as cases (*recurrent*) and controls (*non-recurrent*) according to the endoscopic findings. Controls were selected in the absence of any

endoscopic, clinical, or surgical evidence of disease recurrence during the follow-up. Demographics and clinical data were retrieved from the prospectively collected databases. Details of medical and surgical treatments were obtained by the review of electronic records. The following data were collected for each patient: gender, age at surgery, disease phenotypes (according to the Montreal classification, depicted in Table 2), level of hemoglobin and serum albumin before surgery, smoking status at surgery, ASA score, BMI, Charlson Comorbidity Index (CCI), previous therapies (including steroids, anti-TNF-α, and monoclonal antibodies), surgical approach (laparotomy or laparoscopy), conversion rate, surgical setting (elective/emergency), detailed postoperative complications and classification according to Clavien-Dindo scale.[26] Patients experiencing at least one complication were classified as *outcome-positive* (1) in the multivariable models. For patients experiencing multiple complications, the most severe one was reported and detailed in Table 3. Furthermore, postoperative medical prophylactic treatment (defined as any treatment starting within three-four weeks from surgery),[27] and endoscopic, clinical, and surgical recurrence data were collected.

The list of all variables collected is detailed in Table S1 at http://links.lww.com/DCR/C49 .

Prophylactic medical treatment policy has been progressively adopted since 2014 and selection criteria were: smoking, penetrating phenotype, perianal disease, and young age onset.

The categorization of patients, according to the Montreal classification, was performed according to the patients' symptoms, endoscopic findings, and preoperative imaging. Multidisciplinary meetings- including a dedicated gastroenterologist, surgeon, pathologist, and radiologist- were performed routinely to determine the treatment course of patients.

Definition of recurrence

Endoscopic recurrence was defined according to the evidence of endoscopic disease recurrence (Rutgeerts' score equal to or higher than i_2[4]) during regular follow-up performed at 6 months (median time: 6 [5-7] months) after surgery. Endoscopy units of both centers routinely performed colonoscopy in IBD patients and were fully trained with regards to Rutgeerts' score assessment.

The non-recurrent group included patients with a Rutgeerts' less than i_2 at each endoscopic assessment throughout the follow-up and without any symptoms of recurrence. Clinical recurrence was defined as a Crohn's Disease Activity Index (CDAI) score > 150. Surgical recurrence was defined as the need for further resection for complicated disease.

Statistical analysis

Categorical and dichotomous variables are presented as percentages over the total and were compared using a χ-test, with Yates' correction or Fisher exact test, where needed. The odd's ratio (OR) and relative 95% confidence intervals (95% CI) were reported. Continuous data were tested for normal distribution, using the Shapiro-Wilk test (with $p < 0.05$ indicating non-normal distribution), and are presented as mean ± standard deviations or median and interquartile range [IQR], according to the distribution. Continuous data were analyzed using a two-sided unpaired T-test or a Mann-Whitney unpaired test, depending on the distribution. The results were considered statistically significant for p value less than 0.05 or if the 95% CI did not include the null value. A binary logistic regression model was used to identify possible risk factors for endoscopic disease recurrence. The cumulative recurrence-free survival rates and median recurrence-free survival for endoscopic, clinical, and surgical recurrence were calculated using the Kaplan-Meier analysis. Categorical variables were compared using a log-rank Mantel-Cox test. The Cox proportional hazard model was used for multivariate analysis, reporting the hazard ratio (HR) and 95% CI. Statistical analyses were performed with IBM SPSS Statistics for Windows, Version 24.0. (IBM Corp, Armonk, NY). Reported graphs were obtained using GraphPad Prism 5 Software (GraphPad Software, Inc., La Jolla, CA, USA).

RESULTS

Demographics and clinical characteristics

Data from 305 eligible patients were retrieved from both the institutional prospectively maintained databases. After excluding 6 patients for missing data, 299 were included in the study; 37 patients received a stoma during the index surgery and were evaluated in a separate analysis. Recurrence

was endoscopically diagnosed in 145 over 262 (55%) patients which constituted the recurrent group. The non-recurrent group comprised 117 patients. The mean age at surgery was 33.88 ± 12.74 years for the non-recurrent group and 35.61 ± 13.60 for the recurrent ($p = 0.29$). Gender was equally distributed between the two groups (58% versus 48% of female patients, respectively; $p = 0.09$). At the time of surgery there were 29 active smokers (25%) in the non-recurrent group versus 51 (35%) in the recurrent (OR = 1.65; 95% CI: 1.02-2.83; $p = 0.04$). ASA classification grade, CCI, preoperative hemoglobin and albumin level, and BMI did not differ between the 2 groups (Table 1). Reduced time from diagnosis to surgery was associated with a higher risk of developing endoscopic disease recurrence (non-recurrent: 5 [2-11] years versus recurrent: 3 [1-8] years; $p = 0.04$). Penetrating disease phenotype was more frequent in the recurrent group: 23% (27) versus 49% (71) (OR= 3.19; 95% CI: 1.86-5.48; $p < 0.0001$). A higher percentage of concomitant perianal disease was registered in the recurrent group: 31 (21%) versus 10 (8%) (OR= 2.91; 95% CI: 1.36-6.22; $p = 0.004$). There were no differences with regards to preoperative medical therapy including steroids, anti-TNF-α, and monoclonal antibodies. No difference was registered with regards to postoperative early medical treatment, defined as any prophylactic treatment starting within four weeks from surgery (17% versus 16%; $p = 0.88$) (Table 2).

Surgical characteristics and postoperative outcomes

The majority of patients underwent surgery on an elective basis and with a minimally invasive approach in both groups (Table 3). The proportion of laparoscopic approach, duration of surgery, and blood loss were comparable between the recurrent and non-recurrent groups. Overall, postoperative complications rates (within 30-days from surgery) were significantly higher for the recurrent group (65% versus 51%; OR= 1.80; 95% CI: 1.09-2.97; $p = 0.02$). Septic complication rates did not differ (18% versus 15%; $p = 0.55$). Anastomotic leak was diagnosed in 6 (6%) patients in the non-recurrent group and 8 (5%) in the recurrent group. Non-recurrent patients had a significantly shorter follow-up compared with recurrent patients (56 [26-80] versus 63 [41-88]; $p = 0.04$) (Table 3).

Risk factors associated with postoperative disease recurrence

According to the findings of the univariable analysis, a logistic regression model was performed to ascertain the effect of smoking, disease duration, stricturing and penetrating disease, concomitant perianal disease, and postoperative complications on the likelihood of developing endoscopic disease recurrence. Smoking (OR = 1.84; 95% CI: 1.02-3.32; $p = 0.04$), penetrating phenotype (OR = 3.134; 95% CI: 1.58-6.22; $p < 0.01$), perianal disease (OR = 4.03; 95% CI: 1.75-9.25; $p = 0.001$), and postoperative complications (OR = 2.23; 95% CI: 1.17; $p = 0.01$)were independently associated with an increased risk of developing endoscopic disease recurrence. Shorter time from diagnosis to surgery was associated with an increased likelihood of exhibiting disease recurrence (OR = 0.98; 95% CI: 0.95-1.02; $p = 0.45$), however not statistically significant (Table 4).

Factors influencing the rate and timing of postoperative disease recurrence

Within the study population, 145 (55%) patients had endoscopic disease recurrence, while 65 patients (25%) experienced clinical recurrence, and 11 patients (4%) had surgical recurrence during the follow-up (Table S2 at http://links.lww.com/DCR/C49). At Kaplan-Meier analysis, the median time to endoscopic disease recurrence was 37 months (95% CI: 15-58 months) and the cumulative proportion of endoscopic disease-free survival at 24 months was 57%; the cumulative proportions of clinical and surgical disease-free survival at 24 months were 85% and 99%, respectively (Figure S1 at http://links.lww.com/DCR/C49). A Mantel-Cox log-rank analysis was performed to explore the factors associated with reduced time of endoscopic and clinical disease remission. The results of the univariable analysis are presented in Table S3 at http://links.lww.com/DCR/C49 . Postoperative complications (HR= 1.54; 95% CI: 1.09-2.17; $p = 0.01$) (Fig. 1A) and penetrating disease behavior (HR = 1.78; 95% CI: 1.28-2.47; $p = 0.001$) influenced endoscopic recurrence; postoperative complications (HR= 1.91; 95% CI: 1.13-3.26; $p = 0.02$) (Fig. 1B) and penetrating disease (HR = 191.65; 95% CI: 18.63-1960.71; $p < 0.0001$) significantly affected clinical recurrence. The multivariable Cox proportional hazard regression analysis confirmed postoperative complications (HR = 1.45; 95% CI: 1.02-2.05; $p = 0.03$) and penetrating disease (HR = 1.73; 95% CI: 1.24-2.40; p

= 0.001) to be independent risk factors for endoscopic recurrence. Postoperative complications (HR = 1.6; 95% CI: 1.02-2.88; $p = 0.04$) and penetrating disease (HR = 207.10; 95%CI: 88.41-542.370; $p < 0.0001$) resulted as risk factors for clinical recurrence (Table 5).

Analysis on diverted and non-diverted patients

In the study period, 37 patients underwent ileocolic resection with stoma diversion: 17 of those patients developed endoscopic disease recurrence. An additional analysis was performed to explore the factors affecting endoscopic and clinical recurrence in the study population including also diverted patients (n = 299). Recurrence was endoscopically diagnosed in 162 over 299 (54%) patients which constituted the recurrent group. At univariable analysis, the factors affecting endoscopic recurrence were smoking (OR = 1.85; 95% CI: 1.12-3.07; $p = 0.02$), reduced time from diagnosis to surgery (non-recurrent: 5 [2-10] years versus recurrent: 3 [1-8] years; $p = 0.04$), penetrating phenotype (OR= 3.10; 95% CI: 1.87-5.13; $p < 0.0001$), perianal disease (OR = 2.25; 95% CI: 1.15-4.40; $p = 0.02$), and postoperative complications (OR= 1.80; 95% CI: 1.13-2.88; $p = 0.01$). Stoma construction did not influence endoscopic recurrence (OR= 0.68; 95%CI: 0.34-1.37; $p = 0.29$). At multivariable analysis, smoking (OR= 2.17; 95% CI: 1.25-3.75; $p = 0.006$), penetrating disease (OR = 3.22; 95% CI: 1.89-5.50; $p < 0.0001$), perianal disease (OR= 3.01; 95% CI: 1.44-6.30; $p = 0.003$), and postoperative complications (OR = 2.06; 95% CI: 1.22-3.48; $p = 0.007$) were confirmed as independent risk factors of endoscopic disease recurrence (Table S3). The multivariable Cox proportional hazard regression analysis confirmed postoperative complications (HR = 1.42; 95% CI: 1.02-1.97; $p = 0.03$), penetrating disease (HR= 1.69; 95% CI: 1.23-2.32; $p = 0.001$), and smoking (HR = 1.43; 95% CI: 1.03-1.97; $p = 0.03$) to be independent risk factors for endoscopic recurrence. Postoperative complications (HR = 1.90; 95% CI: 1.12-3.24; $p = 0.02$) and reduced time from diagnosis to surgery (HR = 0.94; 95% CI: 0.90-0.99; $p = 0.03$) resulted as risk factors for clinical recurrence (Table S4 at http://links.lww.com/DCR/C49).

DISCUSSION

Our study showed a negative impact of postoperative complications on long-term outcomes after primary ileocolonic resection for CD. Along with smoking, perianal disease, and penetrating phenotype, postoperative complications resulted as independent risk factors for endoscopic disease recurrence. Furthermore, postoperative complications ~~rate~~ significantly shortened the time to endoscopic and clinical recurrence. These results strengthen the importance of preventing postoperative complications after surgery for CD as they are detrimental for both short- and long-term outcomes.

A postoperative endoscopic recurrence rate of 70% within one year has been reported by previous studies with almost all patients developing clinical recurrence at three years follow up.[4,28] The rate of recurrence in our cohort was similar to the abovementioned reports.

To date, several risk factors of early disease recurrence after surgery have been identified.[8–11] Specifically, smoking habit, penetrating phenotype, and perianal disease at the time of the surgical resection are associated with an increased risk of disease recurrence.[11–13] Our results are consistent with these previous findings. However, while smoking habit is a patients-dependent modifiable risk factor, penetrating phenotype and perianal disease strictly depend on the disease itself. On the clinical side, the presence of these risk factors simply allows ~~to~~ stratifying patients depending on their specific recurrence risk and it is common practice to tailor postoperative therapy accordingly, including early postoperative medical treatment.[14–20]

Conversely, in our cohort, we identified postoperative complications as a risk factor for postoperative recurrence, which is a potentially modifiable variable by the clinician through different possible pathways. On one hand, the rate of complications might be lowered by the centralization of surgical treatment at referral centers. On the other, as postoperative complications might be driven by delayed surgery and poor nutritional status,[24] much effort has to be undertaken in choosing the right timing for surgery along with prehabilitation and perioperative optimization of nutritional status.

Scarpa et al. identified postoperative complications rate as an independent risk factor for recurrence in a retrospective analysis of 141 patients. However, the primary study aim was the comparison of different surgical techniques for intestinal anastomosis- including end-to-side and side-to-side fashion- and the study also included patients undergoing surgery for recurrent disease, which might constitute a selection bias affecting the recurrence rate.[21,29] Given that the young age of onset was also associated with early recurrence, the authors concluded that postoperative complications were arguably due to a more aggressive disease pattern.

Similarly, Iesalnieks et al. found that the incidence of intra-abdominal septic complications was strongly associated with surgical disease recurrence.[30] Moreover, they further correlated the presence of postoperative complications with preoperative disease severity. Indeed, preoperative risk factors impacted the rate of postoperative septic complications which, in turn, negatively affected long-term outcomes of CD patients in terms of surgical recurrence rate. However, this study was limited by the inhomogeneous case-mix including surgical recurrence, colectomies, resection with colo-colonic anastomosis. Conversely, in our study, we have included only primary ileocolic resection and excluded potential confounding factors by including penetrating and stricturing phenotype in the multivariable analysis confirming postoperative complications as independent risk factors for recurrence. Furthermore, preoperative nutritional status and operative characteristics (proxy of complicated disease) in our cohort did not directly impact postoperative complications rate, being comparable between recurrent and non-recurrent groups.

More recently, Guo et al analyzed a consecutive series of 237 patients undergoing surgical resection with primary anastomosis for complicated CD.[23] They found an association between postoperative infectious complications and early clinical recurrence. However, the study also included ~~in the analysis~~ patients undergoing surgery for recurrent disease and failed to report data on endoscopic assessment, which is a well-recognized mainstay of diagnostic follow-up after surgery for CD especially for tailoring postoperative treatment.

In our study, septic complications did not significantly correlate with postoperative recurrence. Additionally, a further comparison taking into account specific types of septic and non-septic complications did not find a significant correlation with disease recurrence. Notably, a low incidence of septic complications, including reoperations and anastomotic leaks, was registered in our cohort. Arguably, the relatively low rate of the events along with the small sample size could explain the weak statistical correlation. Interestingly, a higher postoperative ileus rate was found for recurrent versus non-recurrent patients (28 versus 16%). A possible explanation might be found in the causes leading to postoperative ileus, especially considering that standard perioperative measures (ERP, opioid-sparing analgesia, MIS) were used. Postoperative ileus is known to be associated with postoperative septic complications. We could assume that, in those patients, a subclinical anastomotic complication did not produce an effect detectable by the current clinical tests, except for postoperative ileus as a related epiphenomenon.

Conversely, the overall complications rate, including non-infectious events, correlated with disease recurrence. Arguably, this could be explained by the fact that every deviation from an uneventful postoperative course could generate an alteration of CD patients' immune profile, possibly triggering the immune system and altering the course of disease remission.[31] As shown by De Buck et al., a significantly increased level of postoperative immune response can be appreciated in CD patients when compared to colorectal cancer patients testifying the marked susceptibility of CD patients to surgical trauma.[31] Furthermore, we have recently shown that any grade of postoperative complications, including non-infectious ones, ~~are~~ is associated with a consistent increased level of CRP in CD patients.[32]

Even though our study was limited by its retrospective nature, only patients undergoing primary resection for complicated CD were included. The cohort of patients has undergone standard management, including a multidisciplinary meeting to define the optimal treatment pathway with full adherence to current guidelines in terms of medical treatment and surgical indication. Furthermore, the patients underwent standard follow-up including regular endoscopic evaluation.

Both institutions are referral centers for IBD and have a dedicated colorectal surgery division having also adopted a long-established enhanced recovery program. The strength of our study laid in the fact that a reliable cohort has been taken into account. Indeed, in our analysis, well-recognized risk factors for disease recurrence- such as smoking habit, penetrating, and perianal disease- were confirmed with regards to the most recent literature. This consistency has made our cohort reliable for further investigation.

Some limitations have to be acknowledged. Firstly, our study is limited by its retrospective nature. Overall, many factors might have influenced the treatment course, especially considering the timeline of the study, crossing about 10 years. The implementation of the multidisciplinary approach over time might have impacted the timing of surgery leading to early intervention when indicated. Conversely, the improvement of medical treatment with biologics and the introduction of novel effective drugs might have produced a delay in the surgical management of some patients. Secondly, the recurrent group had a significantly longer follow-up. However, endoscopic recurrence was mostly found at the first endoscopy performed 6 months after surgery according to the standard policy, and survival analyses allowed for the minimization of the bias, confirming the occurrence of postoperative complications as a significant risk factor for endoscopic and clinical recurrence. As a consequence of the short follow-up, we could not identify a possible correlation between postoperative complications and the risk of surgical recurrence. Our study lacked an analysis of early biohumoral markers which could corroborate the concept of immune system alteration as a trigger for disease recurrence. Finally, even though special attention was given to the nutritional status of patients undergoing surgery in the two Institutions, a standardized preoperative nutritional assessment has not been adopted.

To date, this is the largest case-control study specifically addressing the correlation between postoperative complication rate and disease recurrence after primary surgery for Crohn's disease.

CONCLUSION

Postoperative complications affect long-term outcomes after surgery possibly leading to an increased and early disease recurrence rate. Further larger prospective studies are needed to corroborate our findings and to better stratify the specific risk of postoperative complication types.

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LEGEND

Figure 1: Recurrence-free survival. A) Kaplan-Meier analysis of endoscopic recurrence-free survival comparing non-complicated (black line) and complicated (red line) patients (HR = 1.54; 95% CI: 1.09-2.17; $p = 0.01$). B) Kaplan-Meier analysis of clinical recurrence-free survival comparing non-complicated (black line) and complicated (red line) patients (HR = 1.91; 95% CI: 1.13-3.26; $p = 0.02$).

Table 1. Baseline and demographic characteristics, mean ± standard deviation, % (n)

Characteristics	Non-recurrent (117)	Recurrent (145)	*p* value
Age at surgery, years	33.88 ± 12.74	35.61 ± 13.60	0.29
Gender, females	58% (68)	48% (69)	0.09
ASA classification			0.74
ASA I	18% (21)	19% (28)	
ASA II	74% (86)	70% (101)	
ASA III	8% (10)	11% (16)	
BMI, Kg/m^2	21.80 ± 4.08	21.81 ± 3.39	0.98
Hemoglobin, g/dL	12.83 ± 1.57	12.92 ± 1.53	0.63
Albumin, g/dL	4.02 ± 0.49	4.43 ± 3.82	0.35
Smoking	25% (29)	35% (51)	0.04
CCI			0.97
CCI=0	78% (91)	80% (113)	
CCI=1	12% (14)	11% (18)	
CCI=2	6% (8)	7% (10)	
CCI=3	2% (2)	1% (2)	
CCI≥4	2% (2)	1% (2)	

Abbreviations: ASA, American Society of Anesthesiologists; BMI, Body Mass Index; CCI, Charlson Comorbidity Index.

Categorical and dichotomous variables are analyzed using a χ-test with Yates' correction. Continuous variables are analyzed using a two-sided unpaired T-test.

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Table 2. Clinical characteristics, mean ± standard deviation, median [IQR], % (n)

Characteristics	Non-recurrent (117)	Recurrent (145)	*p* value
Time from diagnosis to surgery, years	5 [2-11]	3 [1-8]	0.04
Montreal classification, disease location			0.06
L1 (ileal)	46% (54)	62% (90)	
L2 (colonic)	6% (6)	5% (7)	
L3 (ileocolonic)	48% (57)	33% (48)	
Montreal classification, disease behavior			<0.0001
B1 (nonstricturing, nonpenetrating)	30% (35)	24% (35)	
B2 (stricturing)	47% (55)	27% (39)	
B3 (penetrating)	23% (27)	49% (71)	
'p' (concomitant perianal disease)	8% (10)	21% (31)	0.004
Previous therapies			
Steroids	67% (78)	68% (99)	0.44
Anti-TNF-α	48% (56)	37% (53)	0.06
Monoclonal antibodies	8% (10)	10% (15)	0.67
Postoperative prophylactic treatment	17% (20)	16% (23)	0.88

Abbreviations: IQR, Interquartile range; TNF-α, Tumor Necrosis Factor- α.
Categorical and dichotomous variables are analyzed using a χ-test with Yates' correction. Continuous variables are analyzed using an unpaired Mann-Whitney test. Statistical significance: $p<0.05$.

Table 3. Operative characteristics and postoperative outcomes, median [IQR], % (n)			
Operative outcomes	**Non-recurrent (117)**	**Recurrent (145)**	***p* value**
Surgical setting			0.57
Elective	97% (113)	95% (138)	
Emergency	3% (4)	5% (7)	
Surgical approach			0.22
Laparoscopic	72% (99)	84% (130)	
Open	15% (18)	10% (15)	
Conversion*	4% (4)	5% (6)	0.83
Anastomosis type			0.23
Handsewn	8% (10)	5% (8)	
Stapled	92% (107)	95% (137)	
Anastomosis Configuration			0.43
Side-to-side	91% (106)	95% (138)	
Side-to-end	2% (3)	1% (1)	
End-to-end	5% (5)	2% (3)	
Kono-S	2% (3)	2% (3)	
Operative time, minutes	140.70 ± 72.42	140.80 ± 65.10	0.98
Estimated blood loss, mL	2 [0-50]	10 [0-50]	0.73
Length of hospital stay, days	7 [5-8]	6 [5-8]	0.12
Postoperative complications	51% (60)	65% (95)	0.02
Clavien-Dindo I	25% (29)	34% (49)	
Clavien-Dindo II	17% (20)	25% (37)	
Clavien-Dindo IIIa	--	1% (2)	
Clavien-Dindo IIIb	8% (10)	4% (6)	
Clavien-Dindo IVa	--	1% (1)	
Clavien-Dindo IVb	--	--	
Clavien-Dindo V	1% (1)	--	
Septic complications	18% (21)	15% (22)	0.55
Anastomotic leak	6% (6)	5% (8)	1.00
SSI	9% (11)	7% (11)	0.65
Other infectious complications	3% (4)	3% (3)	0.70
Non-infectious complications	33% (39)	50% (73)	0.01
Type of complication			
Gastrointestinal	37% (43)	47% (68)	0.10
Anastomotic leak	6% (6)	5% (8)	
Ileus	16% (19)	28% (41)	
Wound infection	1% (1)	1% (2)	
Rectal bleeding	11% (13)	7% (11)	
Bowel obstruction	3% (4)	4% (6)	
Cardiovascular	2% (2)	4% (6)	1.00
Neurological	1% (1)	3% (4)	0.38
Pulmonary	2% (2)	--	0.19
Urinary	1% (1)	3% (5)	0.22
Fever	6% (7)	4% (6)	0.58
Anemia	3% (4)	1% (1)	0.18
Other	--	3% (5)	NA
Thirty-days reintervention	8% (10)	4% (6)	0.09
Follow-up, months	56 [26-80]	63 [41-88]	0.04

Abbreviations: IQR, Interquartile Range; SSI, Surgical Site Infections.
*Percentages calculated over laparoscopic interventions: Non-recurrent (n=99) versus Recurrent (n=130).
Categorical and dichotomous variables are analyzed using a χ-test with Yates' correction. Continuous variables are analyzed using a two-sided unpaired T-test. Statistical significance: $p<0.05$.

Table 4. Binary logistic regression model for endoscopic Crohn's disease recurrence

Variables	OR (95% CI)	*p* value
Smoking	1.84 (1.02-3.32)	0.04
Time from diagnosis to surgery, years	0.98 (0.95-1.02)	0.45
Disease behavior (vs non-stricturing/non-penetrating)		
Stricturing disease	1.01 (0.49-2.07)	0.98
Penetrating disease	3.14 (1.58-6.22)	0.01
Perianal disease	4.03 (1.75-9.26)	0.001
Postoperative complications	2.23 (1.19-4.17)	0.01

Abbreviations: OR, Odds Ratio; CI, Confidence Intervals.

The statistical analysis is performed using a multivariable binary logistic regression model. The model was statistically significant ($\chi^2(6) = 40.22$; $p<0.0001$) and explained 19% (Nagelkerke R^2) of the variance of the endoscopic disease recurrence, correctly classifying 55% of cases. The Hosmer-Lemeshow test indicated a good model fitness ($\chi^2(8) = 23.78$; $p= 0.12$).

Table 5. Multivariable survival analysis on endoscopic and clinical disease recurrence

	Endoscopic disease recurrence	
Variables	**HR (95% CI)**	***p* value**
Age, years	1.01 (0.99-1.02)	0.13
BMI, Kg/m^2	1.00 (0.96-1.04)	0.93
Time from diagnosis to surgery, years	0.97 (0.95-1.00)	0.12
Penetrating disease behavior (B3)	1.73 (1.24-2.40)	0.001
Postoperative complications	1.45 (1.02-2.05)	0.03
	Clinical disease recurrence	
	HR (95% CI)	***p* value**
Age, years	1.02 (0.99-1.04)	0.15
BMI, Kg/m^2	0.99 (0.93-1.05)	0.74
Time from diagnosis to surgery, years	0.97 (0.93-1.01)	0.18
Penetrating disease behavior (B3)	207.10 (88.41-542.37)	<0.0001
Postoperative complications	1.65 (1.02-2.88)	0.04

Abbreviations: HR, Hazard Ratio; CI: Confidence Intervals; BMI, Body Mass Index.
The statistical analysis is performed using a multivariable Cox proportional hazard model. Statistical significance: $p<0.05$.

Figure 1