Journal of Coloproctology

Original Article

Risk factors for postoperative complications in Crohn disease: analysis of 173 patients ☆

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ARTICLE INFO

ABSTRACT

Background and objectives: Surgery for Crohn disease has a wide range of factors that are being studied as possible risk factors for postoperative complications. The later are a major problem in those patients and are associated with longer hospital stays and increased mortality and morbidity. Despite the debate regarding the influence of patients' characteristics, preoperative and operative details, the risk factors are not fully identified. The debate has been focused on the new medical therapy and the time of surgery. Our goal was to help identify and confirm risk factors for postoperative complications.

Materials and methods: A retrospective cohort study including all patients operated due to Crohn disease in São João Hospital Center from 2010 to 2015. We analyzed patient, preoperative and surgical characteristics. For postoperative complications data only those occurring within 30 days were included.

Results: Neither age at diagnosis or previous corticotherapy/anti-TNF/ustekinumab was significantly associated with an increased risk in postoperative complications. Only age at surgery >40 years (Montreal Classification A1 + A2 vs. A3; OR = 4.12; $p < 0.05$) and the group others (occlusion vs. others [combination of intestinal perforation, mesenteric ischemia and postoperative complications] vs. fistula/abscess as indication for surgery; OR = 4.12; $p < 0.05$) remained as independent risk factors after multivariable regression analysis.

Conclusions: We described clear associations between age at surgery >40 years and the group others (intestinal perforation, mesenteric ischemia and postoperative complications) and overall postoperative complications in Crohn disease. These results may suggest that surgery does not need to be delayed and, in some cases, should be anticipated.

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Fatores de risco para complicações pós-operatórios na Doença de Crohn: análise de 173 pacientes

R E S U M O

Palavras-chave:
Crohn disease
Risk factors
Postoperative complications
Anti-TNF

Introdução e objetivos: Vários fatores têm sido estudados como possíveis fatores de risco para complicações pós-operatórias na doença de Crohn. Estas complicações estão associadas a estadias mais prolongadas no hospital e a um aumento da mortalidade. Apesar do debate relativo à influência das características dos pacientes, pré-operatórias e operatórias, os fatores de risco ainda não estão completamente identificados. Atualmente, o debate centra-se nos avanços da terapia médica e no melhor momento para realizar a operação. O objetivo era identificar os fatores de risco para complicações pós- operatórias.

Materiais e métodos: Realizamos um estudo retrospectivo incluindo todos os pacientes operados devido à doença de Crohn no Hospital São João desde 2010 até 2015. Analisamos as características dos doentes, as pré e as pós-operatórias. Apenas foram incluídos os dados relativos a complicações no período de 30 dias após a cirurgia.

Resultados: A idade ao diagnóstico e o uso prévio de corticoterapia/anti-TNF/ustekinumab não foram associados a um aumento no risco de complicações pós-operatórias. Apenas a idade na cirurgia superior aos 40 anos (Classificação de Montreal A1 + A2 vs. A3; OR = 4.12; p < 0.05) e o grupo 'outros' (oclusão vs. outros [combinação de perfuração intestinal, isquemia mesentérica e complicações pós-operatórias] vs. fistula/abscesso como indicação para cirurgia; OR = 4.12; p < 0.05) são fatores de risco independentes.

Conclusões: Descrevemos uma associação clara entre a idade na cirurgia superior aos 40 anos e o grupo 'outros' e a existência de complicações pós-operatórias na doença de Crohn. A cirurgia não deve ser adiada e, em alguns casos, seria benéfico antecipá-la.

Introduction

Crohn disease (CD) is a relapsing and progressive autoimmune disorder mainly affecting the gastrointestinal tract with abnormal transmural granulomatous inflammation.[1–3] It is slightly more incident in women and Caucasians and it has a bimodal distribution, appearing especially in the second and thirds decades and then between sixth and seventh.[1] The prevalence of CD has been increasing for the past several decades, as well as its severity.[4] In Portugal, 4% of patients with CD refer limitations in their daily life, 10% refer they lost their jobs because of the diseases' complications and 16% of students failed one or more years.[5]

Clinical features vary according the location where it occurs (terminal ileum, colon, ileocolonic or upper gastrointestinal tract) and the phenotype (structuring, penetrating or nonstricturing/nonpenetrating).[1,6] Till 10% of the patients can have extra intestinal symptoms (especially arthropathy) or perianal complications.[1] Major clinical complications such as strictures, abscesses or fistulas appear in 33.7% of the patients at 5 years and 50.8% at 20 years after the diagnosis.[3] The diagnostic gold standard is full ileocolonoscopy with biopsies but image exams like CR and MRI should also be performed to study the disease and its complications and decide the treatment.[1,2]

The disease's management is firstly medical. The goal of medical treatment is to induce remission with Corticosteroids (CCT) or biological treatment (anti-TNFα) and maintain it with immunomodulators and/or biological treatment.[1,6–8] Surgery is reserved for failure of medical treatment, neoplasia and complications (such as perforation or fistulas).[6] The most common site of CD is terminal ileum so ileocolonic resection is the most common surgery performed in these patients, whether by laparotomy or laparoscopy.[9,10] About one third of patients need a surgery within 5 years after the diagnosis.[2] Post-operative complications are a major problem in patients with CD and are associated with longer hospital stays and increased mortality and morbidity. Within all, intra-abdominal septic complications such as dehiscence, abscesses or enterocutaneous fistulas, are those that most concern.[11] A wide range of risk factors have been related to early postoperative complications, within the first 30 days.[9] Those risks include patients' characteristics such as use of CCT, penetrating phenotype, previous abdominal surgery or surgical specificities such as age at surgery, indication for surgery or type of operation.[9,12–14] Currently one of the main focus of investigation is whether the new medical treatment based on immunomodulators/biologic agents can be considered a risk factor.[3,14,15]

The aim of the present study was to study the risk factors for postoperative complications in patients who underwent surgery due to CD at Centro Hospital de São João (Porto, Portugal) from 2010 to 2015.

Material and methods

This study was approved by the Ethic Commission for Health of Centro Hospital de São João and Faculty of Medicine,

University of Porto (number 28-18). In this retrospective study, all patients operated due to CD at HSJ between 1st January 2010 and 31st December 2015 was included. Patients were identified by the diagnosis code for CD in the hospital registries and all the data was obtained through the electronic health registries.

Data collection

All electronic health registries were reviewed for the following patient characteristics: birth date, sex, age at diagnosis, method of diagnosis, Montreal classification and history of previous abdominal surgery. We also analyzed surgical characteristics at the time of surgery, including smoking habits, preoperative medication (within 12 weeks before surgery), surgical indication, surgical approach, rate of conversion from laparotomy to laparoscopic and type of anastomosis. Postoperative complications data occurring within 30 days were also collected.

Endpoint

The outcome was postoperative complications, which included peritonitis, surgical-site infections, anastomotic leakage, prolonged postoperative ileus, post-operative occlusion due to flanges and meningeal syndrome. Surgical-site infections included both superficial and deep abscess.

Statistical analysis

Descriptive statistics were performed depending on the variables' type and distribution. Continuous variables were described as medians and Inter-Quartile Ranges (IQR) if they showed a skewed distribution. Categorical variables were described with absolute frequencies and percentages. Student t-tests or Mann–Whitney tests were used to compare continuous values between groups. For categorical variables, these comparisons were performed using Pearson χ^2 test or Fisher's Exact test, when the assumptions of the first test were not warranted. To define variables included for the multivariate analysis, we selected factors with a p-value lower than 0.1 and with major clinical relevance. For multivariate analysis, a logistic regression was performed using the Enter selection procedure and their results were presented as Odds Ratio (OR) with 95% Confidence Interval (95% CI).

Results

During the six-year period, 173 patients with CD were operated in this hospital.

Median age at the time of diagnosis was 27 years ($n = 173$). Diagnoses were obtained mostly by colonoscopy (97 patients; 56.1%). The most common location was ileum with 81 patients (46.8%). Regarding phenotype, the most frequent (69 patients) was stricturing CD ($n = 69$; 39.9%). Sixty patients had concomitant perianal disease (34.7%). Patients included in this study had a median age of 35 years at the time of surgery. 67 patients (38.7%) underwent corticotherapy before surgery but the majority of patients (100) were being treated with azathioprine (57.8%). Other therapeutic regimens included anti-TNF

(62 patients; 35.8%) or ustekinumab (5 patients; 2.9%). More than half of the surgeries were performed by laparoscopy ($n = 89$; 51.4%). 11 started as a laparoscopy but required conversion to laparotomy (6.4%). Significantly more anastomosis were laterolateral ($n = 114$; 87.0%). All patient and surgical characteristics are summarized in Table 1.

The postoperative complication rate was 12.1% (21 patients). 2 patients had peritonitis (1.2%), 7 patient had surgical site infections (4.0%), 2 patients had postoperative occlusion due to flanges (1.2%), 4 patients had anastomotic leakage (2.3%), 5 had prolonged postoperative ileus (2.9%) and one patient developed meningeal syndrome (0.6%).

A significant association was found between age at surgery, age at diagnosis, use of CCT, anti-TNF and ustekinumab and indication for surgery and post-operative complications in the univariate analysis. In this multivariate analysis, only the age at surgery and indication for surgery was independent risk factors for post-operative complications. Those aged 40 or more at surgery (Montreal Classification A3) had higher probability of postoperative complications comparing to those under 40 years (Montreal Classification A1 + A2) (OR = 4.12; $p < 0.05$). The composite group of other indications for surgery (intestinal perforation, mesenteric ischemia and postoperative complications) were also associated with an increase of postoperative complications comparing to the ones who underwent surgery due to occlusion or fistula/abscess (OR = 4.12; $p < 0.05$). Neither age at diagnosis or previous CCT/anti-TNF/ustekinumab was significantly associated with an increased risk in postoperative complications.

Discussion

In this retrospective study, we assessed the risk factors for postoperative complications in CD which have not been fully identified yet but can be grouped in three main categories: patient characteristics, characteristics at the time of the surgery and specificities of surgery itself.

From the 21 patients who had postoperative complications, 8 were men (38.1%) and 13 were women (61.9%). These results are not significant ($p = 0.280$), similar to what happened in other studies.[9] Yamamoto T et al.[9] and Huang W et al.[11] found that previous abdominal surgery is a significant risk factor for postoperative complications. In our cohort, difference was not statistically significant but 47.6% of the cases of postoperative complications happened in patients with history of previous abdominal surgery ($n = 10$; $p = 0.310$).

Postoperative complications were more common when diagnosis was made in older ages (median of age of patients with complications was 33 vs. 26 without complications; $p = 0.053$). The difference was not statistically significant and, when evaluated by multivariable regression analysis, A3 category of Montreal classification was not an independent risk factor. Unlike the results of several studies, the location of CD did not appear as a risk factor (Table 1).[14,16] Regarding phenotype, stricturing CD seemed to be a risk factor but it was not significant (12 with complications – 57.1% and 57 without – 37.5%; $p = 0.214$). These results go in the opposite direction of the results obtained in other studies, stating that penetrating phenotype is an independent risk factor.[9,17]

Table 1 – Characteristics of patients and surgery.

	With complications (n = 21)	Without complications (n = 152)	Total (n = 173)	p-Value	Test
Age at diagnosis, median (IQR)	33 (17)	26 (16)	27 (15)	0.053	Mann–Whitney U
Age at surgery, median (IQR)	43 (14)	34.5 (18)	35 (17)	0.009	Mann–Whitney U
Male sex, n (%)	8 (38.1)	77 (50.7)	85 (49.1)	0.280	Chi-square
Method of diagnosis, n (%)				–	–
Colonoscopy	14 (66.7)	83 (54.6)	97 (56.1)		
EnteroMR	3 (14.3)	34 (22.4)	37 (21.4)		
EnteroCT	4 (19.0)	34 (22.4)	38 (22.0)		
Phase-contrast X-ray	0 (0.0)	1 (0.7)	1 (0.6)		
Montreal classification A, n (%)				0.013	Fisher's Exact test (A1/A2 vs. A3)
A1 (≤16 yo)	2 (9.5)	21 (13.8)	23 (13.3)		
A2 (17–40 yo)	12 (57.1)	114 (75.0)	126 (7212.8)		
A3 (>40 yo)	7 (33.3)	17 (11.2)	24 (13.9)		
Montreal classification L, n (%)				0.616	Chi-square L2/L3 (colonic) vs. L1/L4 (non-colonic)
L1 (ileal)	9 (42.9)	72 (47.4)	81 (46.8)		
L2 (colonic)	4 (19.0)	16 (10.5)	20 (11.6)		
L3 (ileocolonic)	8 (38.1)	62 (40.8)	70 (40.5)		
L4 (isolated upper disease)	0 (0.0)	2 (1.3)	2 (1.2)		
Montreal classification B, n (%)				0.214	Chi-square
B1 (non stricturing, non penetrating)	4 (19.0)	36 (23.7)	40 (23.1)		
B2 (stricturing)	12 (57.1)	57 (37.5)	69 (39.9)		
B3 (penetrating)	5 (23.8)	59 (38.8)	64 (37.0)		
P (perianal disease), n (%)	4 (19.0)	56 (36.8)	60 (34.7)	0.108	Chi-square
Tobacco use/consume, n (%)	11 (55.0)	50 (45.5)	61 (46.9)	0.431	Chi-square
Previous abdominal surgery, n (%)	10 (47.6)	55 (36.2)	65 (37.6)	0.310	Chi-square
Preoperative medication (Y/N)					
Corticotherapy, n (%)	4 (19.0)	63 (41.4)	67 (38.7)	0.048	Chi-square
Azathioprine, n (%)	10 (47.6)	90 (59.2)	100 (57.8)	0.313	Chi-square
Mesalazines, n (%)	7 (33.3)	40 (26.3)	47 (27.2)	0.498	Chi-square
Anti-TNF, n (%)	2 (9.5)	60 (39.5)	62 (35.8)	0.007	Chi-square
Ustekinumab, n (%)	2 (9.5)	3 (2.0)	5 (2.9)	0.053	Chi-square
Indication for surgery, n (%)				0.008	Chi-square (Occlusion vs. Fistula/abscess vs. Other)
Intestinal occlusion	12 (57.1)	75 (49.3)	87 (50.3)		
Fistulas	4 (19.0)	43 (28.3)	47 (27.2)		
Abscesses	1 (4.8)	28 (18.4)	29 (16.8)		
Intestinal perforation	3 (14.3)	4 (2.6)	7 (4.0)		
Mesenteric ischemia	0 (0.0)	1 (0.7)	1 (0.6)		
Other postoperative complications	1 (4.8)	1 (0.7)	2 (1.2)		
Surgical approach, n (%)				0.429	Chi-square
Laparotomy	10 (47.6)	63 (41.4)	73 (42.2)		
Laparoscopy	11 (52.4)	78 (51.3)	89 (51.4)		
Conversion	0 (0.0)	11 (7.2)	11 (6.4)		
Type of anastomosis, n (%)				0.180	Fisher's Exact test (laterolateral/end-to-end vs. stoma)
Laterolateral	15 (75.0)	99 (89.2)	114 (87.0)		
End-to-end	1 (5.0)	1 (0.9)	2 (1.5)		
Colostomy	2 (10.0)	6 (5.4)	8 (6.1)		
Ileostomy	2 (10.0)	5 (4.5)	7 (5.3)		

There were 43 missing data for smoking habits (n = 130).

EnteroMR, Magnetic Resonance Enterography; EnteroCT, Computed Tomography Enterography; MLNR, Metastatic Lymph Node Ratio.

As previously mentioned, the major focus of the debate regarding risk factors for postoperative complications in CD is the influence that the advances in medical therapy have. The majority of studies have identified steroid intake before surgery as an important risk factor.[3,13,18,19] In our cohort, less than a quarter of patients with complications were under therapy with CCT ($n = 4$; 19%; $p < 0.05$). From the patients with no postoperative complications, 41.4% history of CCT therapy ($n = 63$; $p < 0.05$). Although the difference was significant in the univariate analysis, after the multivariable logistic analysis, the use of CCT did not prove to be a modifying factor (Table 2). Nevertheless, these results may arise due to the use of multiple medication that results in confounding factors and a bigger cohort would be more capable to exclude the use of CCT as a risk factor.

Unlike the studies regarding the use of CCT, conflicting results exist about the impact of preoperative immunomodulators/biologic therapy as risk factors for complications, specifically septic complications.[3,9,13–15,18,20,21] In some studies, preoperative anti-TNFα was associated with more postoperative infections and influence on wound healing[14] or considered a significant risk factor for anastomotic leakage.[20] In one meta-analyses, it was associated with an increased risk of infectious complications (i.e. abscess and sepsis) (OR = 1.50, 95% CI 1.08–2.08).[22] In contrast, one meta-analyses reported that preoperative biological treatment did not increase the risk of major complications (i.e. sepsis, anastomotic leak, peritonitis, local fistula or abscess, wound infection, wound failure, stoma complications, bowel perforation, severe anemia and hemorrhage) for CD patients (OR = 1.59, 95% CI 0.89–2.86).[15] In a review article, cumulative incidence suggests that there is no increment in postoperative complications in those patients, although they point out that their conclusion is only based in retrospective studies.[3] In our cohort, the majority of postoperative complications appeared in patients who did not use anti-TNFα (only 9.5% of patients taking anti-TNFα had postoperative complications; $p < 0.05$). These values did not reach statistically significant when subject to multivariable logistic analysis (Table 2). For that purpose, a multicenter prospective study (the PUCCINI trial) is being carried out aiming to evaluate the association of preoperative use of immunosuppressive and biologic agents with the incidence of complications after resection.[23] The results for the use of ustekinumab, azathioprine or mesalazine did not led to

significant differences in the postoperative complications in these patients.

Similar to the age of diagnosis, postoperative complications were more common when surgeries were performed in older patients (median of age of patients with complications was 43 vs. 34.5 without complications; $p = 0.009$). When multivariable logistic analysis, age of surgery >40 years remained as an important and independent risk factor for postoperative complications (OR = 4.12, 95% CI 1.20–14.15). Argeny S et al. also concluded that major complications (especially anastomotic leakage) were increased in older patients (>50 years).[24] Other studies confirm these results[11,14] that can be attributed to different surgical characteristics of older patients compared to younger ones. These results raise the issue of the anticipation of the timing of operation that should be subject of further studies.

The majority of studies correlate smoking habits with recurrence and not with postoperative complications. Although we had 43 missing data due to lack of information in the clinical files, the majority (55.0%) of patients with postoperative complications were reported as smokers ($p = 0.431$). One study reached similar conclusions, with a OR = 1.45 (0.63–3.35), although it was also not statistically significant.[9]

The frequency of the several surgical indications are in accordance with the literature, being that intestinal occlusion is the main indication (Table 1).[13,14] The majority (57.1%) of patients with postoperative complications were operated due to intestinal occlusion ($p < 0.05$). Almost half (49.3%) of patients who did not have any postoperative complications had also intestinal occlusion as indication for surgery ($p < 0.05$). We had to join abscesses and fistulas in one group and intestinal perforation, mesenteric ischemia and postoperative complications in other. Then, we compared these groups to the reference (i.e. intestinal occlusion) that is the main indication. Several studies refer abscesses and fistulas as major risk factors for postoperative septic complication in patients with CD.[9,17,21] In our cohort, although not statistically significant, the results do not appear to match the conclusion of these studies (Table 2). Regarding the results obtained by the composite outcome of intestinal perforation, mesenteric ischemia and postoperative complications, we found a significant association with postoperative complications. After multivariable logistic analysis, this group was considered an independent risk factor for postoperative complications in CD patients (OR = 4.12; 95%

Table 2 – Multivariate logistic regression analysis of risk factors for all complications.		
Variable	Adjusted OR (95% CI)	*p*-Value
Age at diagnosis >40 years	1.52 (0.39–6.02)	0.548
Age at surgery >40 years	4.12 (1.20–14.15)	0.024
Previous CCT	0.18 (0.002–15.79)	0.456
Previous anti-TNF	0.81 (0.01–69.16)	0.928
Previous ustekinumab	20.54 (0.15–2767.90)	0.227
Surgical indication		
Intestinal occlusion	(reference)	(reference)
Fistula/abscess a	0.46 (0.14–1.51)	0.202
Other	4.12 (1.23–41.08)	0.028

Univariate selected by those with <0.1.

CI 1.23–41.08). We might attribute this relation to intestinal perforation, which would be in agreement with the conclusions of other studies.[9] Nevertheless, to better correlate these variables we would benefit from a bigger cohort.

Several studies defend that different surgical approaches (laparotomy vs. laparoscopy) do not influence the outcome.[9,12,25] Although not significant, our results appear to be similar to their conclusions (Table 1). The rate of conversion of laparoscopic surgery into laparotomy in our hospital (6.4%) is lower than reported in other studies (varies between 11.2%[26] and 42%[27]), reflecting the experience of surgeons.

Regarding the type of anastomosis, the results were not statistically significant (Table 2). Despite this, the fact that 87% of surgeries had latero-lateral anastomosis is accordingly the conclusions of several studies that defend that lateralateral anastomosis has a significantly lower risk of postoperative complications comparing to end-to-end anastomosis.[9,12]

This study had some limitations. The fact that it is a retrospective and observational study, without a fixed perioperative management protocol, may always lead to some bias. The size of the sample was quite small and there was not a sample size calculation based on a primary statistical endpoint. Also, due to the need in relying exclusively on hospital health records we had some variables with missing values.

For the complete analysis of all the important variables for the established outcome, we should have collected data on preoperative nutritional status and C-Reactive Protein (CRP) and history of blood transfusions. Lately, some studies have analyzed the importance of these variables as potential risk factors for postoperative complications, with some significant results.[3,9,11,14,28,29]

Conclusion

In conclusion, age at surgery >40 years and the group others (intestinal perforation, mesenteric ischemia and postoperative complications) as surgical indication are significant risk factors for overall postoperative complications on CD. These results may suggest that surgery should not need to be delayed. Mostly, previous medical treatment was not conclusive.

A large-scale prospective study should be performed to better define the influence of medical treatment (e.g., CCT or biologics) in postoperative complications.

Conflicts of interest

The authors declare no conflicts of interest.

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