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Risk factors for postoperative endoscopic recurrence in Crohn's disease: a Brazilian observational study ☆

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ABSTRACT

Introduction: Postoperative endoscopic recurrence (PER) is the initial event after intestinal resection in Crohn's disease (CD), and after a few years most patients present with progressive symptoms and complications related to the disease. The identification of risk factors for PER can help in the optimization of postoperative therapy and contribute to its prevention.
Methods: Retrospective, longitudinal, multicenter, observational study involving patients with CD who underwent ileocolic resections. The patients were allocated into two groups according to the presence of PER and the variables of interest were analyzed to identify the associated factors for recurrence.
Results: Eighty-five patients were included in the study. The mean period of the first postoperative colonoscopy was 12.8 (3–120) months and PER was observed in 28 patients (32.9%). There was no statistical difference in relation to gender, mean age, duration of CD, family history, previous intestinal resections, smoking, Montreal classification, blood transfusion, residual CD, surgical technique, postoperative complications, presence of granulomas at histology, specimen extension and use of postoperative biological therapy. The preoperative use of corticosteroids was the only variable that showed a significant difference between the groups in univariate analysis, being more common in patients with PER (42.8% vs. 21%; *p* = 0.044).
Conclusions: PER was observed in 32.9% of the patients. The preoperative use of corticosteroids was the only risk factor associated with PER in this observational analysis.

Fatores de risco para recorrência endoscópica pós-operatória na doença de Crohn: um estudo observacional brasileiro

R E S U M O

Palavras-chave:
Doença de Crohn
Recorrência
Fatores de risco

Introdução: Recorrência endoscópica pós-operatória (REP) é evento inicial após ressecções intestinais na doença de Crohn (DC) e grande parte dos pacientes progride com sintomas e complicações relacionados à doença em alguns anos. A identificação dos fatores de risco para REP pode auxiliar na otimização da terapia pós-operatória e contribuir para sua prevenção.

Método: Estudo retrospectivo, longitudinal, multicêntrico e observacional, realizado com pacientes portadores de DC, submetidos à ressecção ileocólica. Os pacientes foram alocados em dois grupos de acordo com a presença de REP e as variáveis de interesse foram analisadas a fim de se identificar os fatores associados à recorrência.

Resultados: Oitenta e cinco pacientes foram incluídos no estudo. O tempo médio da primeira colonoscopia pós-operatória foi de 12,8 (3-120) meses e REP foi observada em 28 pacientes (32,9%). Não houve diferença estatística entre os grupos em relação a gênero, média de idade, duração da DC, história familiar, ressecção intestinal prévia, tabagismo, classificação de Montreal, transfusão sanguínea, DC residual, técnica cirúrgica, complicações pós-operatórias, presença de granuloma, extensão do espécime e utilização de biológicos após a cirurgia. O uso pré-operatório de corticosteroides foi a única variável que apresentou significativa diferença na análise univariada, sendo mais frequente nos pacientes que apresentaram REP (42.8% vs. 21%, p = 0.044).

Conclusões: REP foi observada em 32.9% dos pacientes. A utilização pré-operatória de corticosteroides foi o único fator associado à REP nesta análise observacional.

Introduction

Despite the progress in the medical therapy of Crohn's disease (CD), with better results after the use of immunosuppressive drugs and antagonists of tumor necrosis factor alpha (anti-TNFs), about 70% of patients will require surgery throughout their lives, often due to complications associated with the disease, such as fistulae, abscesses and fibrotic strictures.[1–3] Once undergoing intestinal resection, these patients are at increased risk of future reoperations and 30–70% will require a new procedure in a 10-year interval.[1]

Postoperative recurrence can be defined by different findings, including clinical, endoscopic, histological, radiological and surgical Characteristics.[4] The time to recurrence follows a definite pattern, with endoscopic recurrence being a precursor of symptomatic (clinical) recurrence.[5] Upon endoscopic recurrence, about 20% of patients have concomitant clinical relapse within 1 year and above 50% at 5 years.[2,5,6]

Besides preceding the symptoms, the severity of endoscopic lesions predicts the likelihood of subsequent development of clinical recurrence and the need for another operation.[7] Accordingly, the use of the classification of endoscopic recurrence described by Rutgeerts et al.[8] plays an important role in the standardization of postoperative endoscopic findings.

Some publications have suggested the stratification of postoperative endoscopic recurrence (PER) risk, based on patient-related characteristics, on surgical findings and on the CD itself, in order to determine the best type of postoperative prophylaxis.[6,7] The factors commonly used for this stratification are those with the highest level of evidence: prior bowel resection, penetrating disease and smoking.[7,9,10]

In Brazil, there is scarce published data on factors associated with postoperative endoscopic recurrence. There is a need to determine which risk factors for PER recognized in the international literature can be applied to patients and at referral centers in our country, in order to properly stratify the risks of recurrence, with subsequent improvement in postoperative management.

Thus, the aim of this study was to examine rates of PER and determine which risk factors would be associated with its occurrence in a cohort of Brazilian patients undergoing ileocolic resections for CD.

Method

This study was approved by the Ethics Committee on Research, Center for Bioethics, Pontifícia Universidade Católica do Paraná (PUCPR), based on Opinion of Presentation Certificate for Ethics Assessment (CAAE) nr. 19923413.1.0000.0020 (second version), performed by the *Plataforma Brasil* website.

This was a retrospective, longitudinal, multicenter, observational study involving patients with CD undergoing ileocolic resections in the period from January 2002 to December 2012, from four referral centers in the management of inflammatory bowel diseases (IBD) in southern and southeastern Brazil.

Table 1 – Detailed description of the Rutgeerts' score (adapted from Rutgeerts et al.)[8].

Rutgeerts score	Endoscopic description of findings
i0	No lesions
i1	≤5 aphthous ulcerations
i2	>5 aphthous ulcerations with normal mucosa between them, or normal areas between larger ulcerations, or ulcerations limited to the ileocolic anastomosis
i3	Diffuse aphthous ileitis with diffusely inflamed mucosa
i4	Diffuse inflammation with large ulcerations, nodules or stenoses

Patients with CD, aged between 14 and 80 years, who underwent ileocolic resection with primary anastomosis and with postoperative ileocolonoscopy during the evaluation period were included in the study. Patients with undetermined inflammatory bowel disease, aged under 14 and over 80 years; patients undergoing other types of surgical procedures (enterectomies, enteroplasties, colectomies, ileostomies or other procedures without anastomosis) or who did not undergo postoperative ileocolonoscopy; and patients with no follow-up after surgery in their respective institution were excluded.

Collection and processing of data

Patients were previously identified in databases of IBD operations conducted at the four referral units. After confirmation of the inclusion criteria, data were collected by reviewing electronic medical records and filling a pre-established protocol. In the absence of data recorded in medical records, phone calls to patients, when necessary to supplement the information, were performed.

Definition of recurrence and study groups

The occurrence of PER was assessed by the first postoperative colonoscopic examination after ileocolic resection. The definition of PER was based on the Rutgeerts' score,[8] defined as i2, i3 or i4 at ileocolonoscopy. The Rutgeerts' score is illustrated in Table 1.

Patients were allocated into two groups according to the presence or absence of endoscopic recurrence: group without recurrence (Rutgeerts i0/i1) and group with recurrence (Rutgeerts ≥ i2). From these groups, the variables of interest were tested in order to identify possible factors associated with PER, which would be designated as risk factors if statistical significance was reached.

Statistical analysis

For statistical analysis the SPSS v.20 software was used. For qualitative variables, we used Fisher exact test or chi-squared test. For quantitative variables, the Student's t test or non-parametric Mann–Whitney test was used. Univariate analysis was performed to determine the association between each independent variable and the presence or absence of PER. Statistical significance was defined as $P < 0.05$.

Results

During the study period, 94 patients with CD underwent ileocolic resection in the four referral units. Of these, nine were excluded because they had not undergone colonoscopy postoperatively. Thus, the series consisted of 85 patients (Fig. 1).
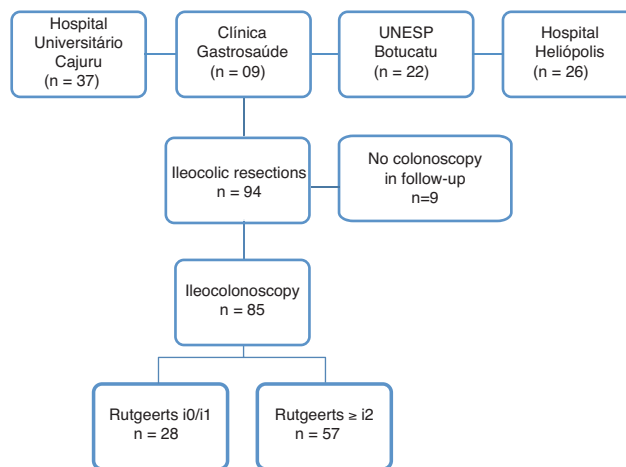

Fig. 1 – Study design and group division for evaluation according to the presence or absence of PER, defined as Rutgeerts' score ≥ i2.

The average time for the first postoperative ileocolonoscopy was 12.8 (3–120) months. Considering recurrence as the presence of a Rutgeerts' score ≥ i2, the PER rate was 32.9% (n = 28). Table 2 illustrates in details the findings in relation to the Rutgeerts' score individually, showing the division of the study groups.

Table 2 – Identification of the groups according to the Rutgeerts' score at the first post-operative colonoscopy in 85 patients. Recurrence defined as a Rutgeerts score ≥ i2.

Group	Rutgeerts'	n (%)	n (%)
W/o PER	i0	25 (29.4)	57 (67.1)
	i1	32 (37.6)	
With PER	i2	10 (11.8)	28 (32.9)
	i3	15 (17.6)	
	i4	3 (3.5)	
Total	–	85 (100)	85 (100)

Patient-related factors were compared between groups (Table 3) and only the preoperative use of corticosteroids was statistically significant, being observed in a significantly higher number of patients in the group with PER compared to the group without PER (42.8% vs. 21% $P = 0.044$).

Tables 4 and 5 illustrate the analysis among the variables related to CD and to surgical procedures *per se*, respectively, and to study groups. As noted, none of these factors were associated with PER in this study.

Table 3 – Univariate analysis among factors related to patient and study groups regarding the presence of PER. Only preoperative use of corticosteroids was statistically significant.

Variable	w/o PER (n = 57)	With PER (n = 28)	P value
Gender			0.487
Male	34 (59.7)	14 (50.0)	
Female	23 (40.3)	14 (50.0)	
Average age (years)	32.8 (14–63)	33.7 (15–57)	0.753
Family history of IBD	1 (1.7)	2 (7.1)	0.251
Previous resections for CD	17 (29.8)	8 (28.5)	1.000
Smoking status	10 (17.5)	7 (25.0)	0.565
Preoperative medications			
Corticosteroids	**12 (21.0)**	**12 (42.8)**	**0.044**
AZA/6MP	30 (52.6)	17 (60.7)	0.498
Biologicals	15 (26.3)	4 (14.2)	0.129
Blood transfusion	8 (14.0)	4 (14.2)	1.000
Biologicals in the postoperative period	39 (68.4)	17 (60.7)	0.627
Type of postoperative biological			1.000
Adalimumab	20 (35.0)	8 (28.5)	
Infliximab	19 (33.3)	9 (32.1)	

Table 4 – Univariate analysis among factors related to CD and study groups regarding the presence of PER.

Variable	w/o PER (n = 57)	With PER (n = 28)	P value
CD Duration (months)	92.8 (2–300)	67.6 (10–192)	0.193
Montreal classification			
Age at diagnosis			0.594
A1	7 (12.2)	3 (10.7)	
A2	41 (71.9)	18 (64.2)	
A3	9 (15.7)	7 (25.0)	
Location			0.792
L1	22 (38.5)	12 (42.8)	
L2	4 (7.0)	1 (3.5)	
L3	31 (54.3)	15 (53.5)	
L4	0	0	
Phenotype of the disease			0.329
B1	4 (7.0)	1 (3.5)	
B2	30 (52.6)	11 (39.2)	
B3	23 (40.3)	16 (57.1)	
Perianal (p)	11 (19.2)	5 (17.8)	1.000
Residual CD	8 (14.0)	6 (21.4)	0.535
Extension of the specimen (cm)	36.8 (10–150)	31.4 (12–67)	0.536
Granuloma	23 (40.3)	11 (39.2)	1.000

Discussion

The occurrence of PER is not an uncommon event in CD, because of the recurring nature of this disease. It is known that endoscopic recurrence precedes the clinical recurrence, which in turn precedes surgical recurrence. About 20% of patients with PER will have symptoms within a year, and over 50% in five years, making these people vulnerable to further complications and possibly reoperations.[6] Based on these data, the main issue in the current management of postoperative recurrence of CD is to identify strong predictors of recurrence, in order to establish if patients would benefit from postoperative prophylaxis.[11]

The scarcity of national data is an obstacle to better define the behavior of postoperative CD in our country. To date, this is the first study including a large number of Brazilian patients with CD, which sought to identify risk factors for endoscopic recurrence.

The PER rate observed in this study was 32.9%, notwithstanding the postoperative therapy used. Earlier studies showed PER rates over 90% in 1 year.[5] Currently, these values remain high, but with greater variations in referral centers (48–93%).[5] In a retrospective study, De Cruz et al. observed PER in 37.1% of 70 patients who underwent colonoscopy within 1 year after surgery,[12] a figure similar to the number found in this series. Standardization in the prevention of postoperative recurrence therapy, as well as the use of biological agents, may have contributed to the reduction of PER in more recent publications.

Only nine patients did not undergo postoperative ileocolonoscopy in this study, demonstrating a better attention in

Table 5 – Univariate analysis among factors related to surgical procedures *per se* and study groups regarding the presence of PER.

Variable	w/o PER (*n* = 57)	With PER (*n* = 28)	P value
Isolated intestinal resection	50 (87.7)	23 (82.1)	0.519
Type of operation			1.000
Open	49 (85.9)	25 (89.2)	
Laparoscopic	8 (14.0)	3 (10.7)	
Anastomosis			1.000
stapled	43 (75.4)	22 (78.5)	
hand-sewn	14 (24.5)	6 (21.4)	
Anastomosis type			0.274
side-to-side	42 (73.6)	24 (85.7)	
end-to-end	15 (26.3)	4 (14.2)	
Early complications	13 (22.8)	8 (28.5)	0.599
Abdominal sepsis	5 (8.7)	4 (14.2)	0.469
Anastomotic dehiscence	4 (7.0)	3 (10.7)	0.679

the follow-up of patients after surgical resection. However, in some cases the endoscopic examination was performed later, which may have influenced the finding of luminal lesions, since the longer the waiting time, the greater the risk of endoscopic recurrence.[2] The mean postoperative ileocolonoscopy time was of 12.8 (3–120) months, and the Mann–Whitney test adapted an exclusion of the more disparate findings of the study, limiting this bias.

Comparing observationally the groups with PER (*n* = 27) versus without PER (*n* = 58), it was noted that there was no statistical difference in relation to gender and age of patients at surgery. Gender does not seem to be a risk factor for recurrence[7,13]; on the other hand, the age factor at the time of surgery presents conflicting data.[2] Ryan et al.,[14] in a Californian database, described an increased risk of surgical recurrence in patients previously operated when with less than 20 years old (RR = 1.98, 95% CI 1.6–2.4).

Despite the shorter duration of CD in PER group, there was no statistical difference between groups; thus, this variable was not established as a risk factor in this observational study. CD of shorter duration may indicate a more aggressive behavior, with rapid progression to complications and consequent reoperations. Some studies suggest that CD of short duration is associated with postoperative recurrence,[15,16] while others have failed to demonstrate such a relationship.[8,17] This lack of consistency between studies may be linked to the definition of the term "short" duration, making it difficult to compare studies.[7]

Despite the higher proportion of smokers in the group with PER (25%, *n* = 7), there was no statistical difference between groups. Although not associated with PER in this study, smoking is the only modifiable independent factor for postoperative recurrence described with consistent evidence in the literature.[2,6,10] Besides increasing the risk of clinical and surgical recurrence, cigarette smoking is responsible for the elevation of PER rates. According to Cottone et al.[18] in a study involving 182 patients, PER was described in 70% of smokers, compared with 35% in nonsmokers. Thus, it is essential to stop smoking in patients with CD because, in addition to reducing

disease activity, this may also reduce the risk of endoscopic, clinical and postoperative surgical recurrence.[7]

Another consistent factor associated with recurrence is the presence of previous bowel resection. In a study conducted by Ng et al.,[19] symptomatic recurrence was more frequent in patients with previous resection (*p* = 0.06). Other publications also describe this association, mostly with clinical and surgical recurrence.[20,21] In the present study, there was no correlation between the history of previous intestinal resection and endoscopic recurrence. Approximately 30% of patients in both groups had prior intestinal surgery. Although there is consistent data in the literature on high risk for clinical and surgical recurrence, previous bowel resections were not considered a risk factor for endoscopic recurrence, maybe due to the limited number of patients in this sample.

Regarding the Montreal classification, none of the items showed statistical difference with respect to PER. Nevertheless, patients with PER presented mainly with penetrating CD (57.1%, *n* = 16), which is considered one of the factors with scientific evidence for postoperative recurrence of CD. A meta-analysis by Simillis et al.[22] described the penetrating phenotype of the disease as associated with clinical and surgical recurrence, although significant heterogeneity was observed in the 13 studies included. Again, few studies address this behavior of CD as a risk factor for PER, there is no consensus in the literature, and in our study this variable lacks statistical significance.

A cohort study of 907 patients in Sweden found an association of postoperative recurrence with perianal CD (OR = 1.6, P = 0.003) in patients undergoing ileocolic resection.[23] Yang et al.[24] also demonstrated this association with clinical recurrence (P = 0.007). However, other studies failed to demonstrate this relationship, being few the trials published with high level of evidence to support perianal CD as a risk factor for recurrence.[7,10] In our study, a relationship between perianal CD and PER also was not identified.

Regarding the medications used before surgery, patients on immunosuppressive and biologic drugs had similar rates of PER. On the other hand, patients on corticosteroids had higher PER rates (21%) compared to those without PER (42.8%), with statistical significance (P = 0.044). Although reported in some studies,[1,25] the use of corticosteroids in the preoperative period presents no scientific evidence as a risk factor for recurrence, which goes against the observational findings of this study. However, many patients with surgical indication are steroid-dependents, despite the immunosuppressive and biologic therapy, assuming an aggressive behavior and possibly establishing a higher rate of recurrence. It is not known exactly whether this association is a coincidence (patients with a more severe disease, who find in corticosteroids a medication for stabilization of symptoms before their operations), or represent a pharmacological effect of this medication on the occurrence of higher rates of PER.

There was no difference between the association of procedures with ileocolic resection, as well as the presence of residual CD on the findings of this observational study. Few patients required procedures of stricturoplasty (*n* = 3) and enterectomy (*n* = 2), which may have hampered the analysis of this variable. In a systematic review by Yamamoto et al.,[26] in 90% of the patients the postoperative recurrence occurred

in areas without stricturoplasty and only in 3% at the sites of plastic procedures.

Residual CD was observed in a higher percentage (21.4%) in the group with PER compared to those patients without PER (14%). This finding is closely related to areas in which it was decided to perform the stricturoplasty. However, studies suggest that the recurrence rates are low after the permanence of residual CD in areas of plastic procedures.[27,28] There is no evidence to support stricturoplasty and residual CD as risk factors for PER.

Regarding the surgical procedure *per se*, although the laparoscopic procedures reduce the systemic inflammatory response, there is no evidence to suggest a reduction in the risk of PER. Three retrospective studies[29–31] and three randomized clinical trials[32–34] showed no difference in rates of early or late recurrence between open and laparoscopic procedures. The configuration and type of anastomosis have also been tested as a risk factor for PER. In a randomized clinical trial with a mean follow-up of 12 months, the rates of PER and clinical recurrence were similar between groups with side-to-side and end-to-end anastomoses.[20] As observed in the current scientific evidence, in the present study, the data related to the surgical technique used were not considered as risk factors, considering that differences between groups regarding PER were not identified.

The presence of granulomas in the surgical specimens occurred in approximately 40% in both groups, with no association with PER. Data regarding the predictive value of granulomas in the surgical specimens are conflicting.[2,7,13] In a prospective 20-year study, Cullen et al.[35] found an association between granulomas and increased clinical and surgical recurrence. In a meta-analysis including 21 studies and a total of 2236 patients with CD, the number of recurrences and reoperations was significantly higher in patients with versus without granulomas.[36] However, other publications[37,38] and more recently a German study did not reveal this association.[39]

Krause et al. followed 173 patients operated for CD for over 27 years.[40] Extended resections with normal margins (10 cm) were associated with lower rates of reoperation, compared with economic resections (31% vs. 83%). On the other hand, Fazio et al. found no difference in postoperative recurrence in patients undergoing resection with limited (2 cm) or enlarged (12 cm) macroscopic margins.[27] The extent of CD influences the length of resection, but both have an indefinite impact in the postoperative recurrence.[7,10] Considering the fact that extended surgical margins do not represent clear benefits in preventing recurrence, an economic resection of the macroscopically affected segment may be the best strategy in patients with CD, given the likely need for future reoperations, as well as the risk of short bowel syndrome.[7] In our study, the mean length of the specimen was slightly larger in the group without PER (36.8 cm vs. 31.4 cm), but with no difference between groups (P = 0.536).

It is known that biological therapy currently presents good results in the prevention of postoperative recurrence and is indicated for patients classified as high risk for recurrence.[10] According to the literature, the postoperative use of anti-TNFs was not related to PER in the present study, and a lower utilization rate was observed in the group with PER (60.7%), compared to the group without PER (68.4%), but with no

statistical difference between their use or the type of drug (infliximab or adalimumab).

This study has clear limitations that must be taken into account in the data analysis. In some patients the colonoscopy was performed 12 months after ileocolic resection, a fact that influences the rate of PER, since the risk of postoperative recurrence is directly proportional to the time of postoperative colonoscopy. In addition to the limitations inherent to a retrospective study, data from different units can influence the results, especially because this is an observational study, with no use of a fixed prospective protocol. Although the institutions involved in this study are considered referral centers in IBD, there is some variability in relation to the medical therapy and surgical technique used and in the interpretation of endoscopic findings between centers. On the other hand, the small number of patients analyzed in some variables and the absence of a multivariate analysis also contributed to the adoption of a cautious interpretation of the results obtained in this series.

In summary, in this first study on the subject on Brazilian patients, PER was observed in 32.9% of the patients. Preoperative corticosteroid use was the only variable that was related to PER, establishing the use of these drugs as a possible risk factor for the occurrence of endoscopic recurrence after ileocolic resection.

Conflicts of interest

The authors declare no conflicts of interest.

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