



Postoperative Crohn's Disease and Relapse Risk Factors: A Single Centre Experience

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Abstract

Introduction and Aim: Surgical intervention is an unavoidable companion for majority of patients with Crohn's Disease (CD). In this study we determine with Crohn's Disease (CD).

Methods: 50 CD patients with at least one surgical resection were assessed retrospectively. Patients underwent clinical (CDAI) and endoscopic (Rutgeerts) assessments at the Department of Gastroenterology and Hepatology, University Hospital "Zvezdara" on average 36 months after their operation. Age at diagnosis, gender, smoking status, duration of CD before resection, presence of perianal disease, colonic involvement, length of resected segment, type of anastomosis, concomitant immunomodulators and biologics (anti-TNF) were reviewed as potential risk factors for clinical and endoscopic recurrence. Data were analysed using univariate and multivariate logistic regression analyses.

Results: 74% of patients had clinical remission and 40% of patients had endoscopic remission. Patients in clinical remission were significantly younger than patients that relapsed. Termino-lateral anastomosis resulted in higher remission rates, 66% compared to 25% of patients with termino-terminal anastomosis. Anti-TNF therapy was crucial for maintenance of clinical remission. Older age at diagnosis and extensive small bowel resection were risk factors for endoscopic recurrence based on multivariate logistic regression analysis.

Conclusion: Older age at the time of diagnosis, lack of biologics postoperatively, latero-lateral or termino-terminal anastomosis as well as extensive resection were high risk factors for relapse in postoperative CD patients.

Keywords: Anastomosis; Anti-TNF Therapy; Crohn's Disease; Postoperative Course; Resection; Risk Factors

Abbreviations

CD: Crohn's Disease; IBD: Inflammatory Bowel Disease; NA: Not Applicable

Introduction

Around 80% of patients with Crohn's Disease (CD) will need surgery at some stage and 70% of these patients will need more

than one surgical intervention [1]. Clinical and endoscopic relapses are common and are estimated at 10-38% and 35-85% in the first year, respectively [2].

Identifying CD patients at risk of relapse in the first 36 months post operation is a great challenge. Risk factors can be classified

into: patient related (i.e. gender, smoking, family history of inflammatory bowel disease), disease related (disease duration, extensiveness and localisation, perianal disease, penetrant disease, NOD2/CARD 15/IBD1 status, presence of granuloma and myenteric plexitis, previous resection, elevated levels of TGF-β) and operation related (i.e. extensive resection of > 50 cm, marginal resection, stricturoplasty, need for transfusion, and postoperative complications) [3,4]. The Rutgeerts score is most commonly used tool to assess endoscopic relapses, typically one year postoperatively (Table 1) [5,6].

Scale	Lesion	Assessment of clinical relapse
i0	No lesions	<10% for 10 years
i1	<5 aphthous ulceration	
i2	>5 aphthous lesions on IC anastomosis	20% for 5 years
i3	Diffuse aphthous ileitis	50-100% during five years with increased possibility of reoperation
i4	Diffuse inflammation with large ulceration and narrowing of anastomosis	

Table 1: Rutgeerts` score.

A number of medications can be used for postoperative prophylaxis depending on the risk of relapse as well as the pharmacokinetic panel of the medication [7]. Mesalazines, imidazole antibiotics [8,9], thiopurines and tumour necrosis factor (TNF) blockers [10,11] are the medications of choice.

The main goal of the study was to identify postoperative risk factors for clinical and endoscopic relapses in CD patients. The secondary goal was to assess the role of immunosuppressive and biological therapy on maintaining remission. Identifying these risk factors may be used to stratify high from low relapse risk patients and monitor the high-risk patients closely as they may need more aggressive treatment. In this study, we compare our results with published European guides.

Materials and Methods

50 patients with CD who underwent at least one surgical resection in the 2009-2015 period were examined retrospectively. All patients were treated at the Department of Gastroenterology and

Hepatology of the University Clinical Center "Zvezdara", Belgrade. CD diagnosis was determined based on clinical, laboratory, radiological and histological criteria [12]. The Montreal classification was used to determine CD localisation and behaviour [13].

Inclusion criteria for this study were: 1. Age 18- 65 years; 2. patients with at least one small bowel resection, and/or colon resection; 3. A postoperative immunosuppressive protocol: a. azathioprine (AZA, 2-2.5mg/kg) for up to three months after surgery, b. methotrexate (MTX, 25mg intramuscular or subcutaneously) weekly for 12 weeks, then decreased to 15 mg weekly followed by mandatory folic acid (10mg/24h) for three days; c. biological therapy, i.e. TNF-α blockers: adalimumab in the standard induction protocol (160mg subcutaneously in the first week, 80mg subcutaneously in the second week, 40mg subcutaneously in the third week), then according to the protocol of maintenance (40 mg fortnightly), or infliximab in the standard induction protocol (5mg/kg at 0, 2 and 6 weeks) and thereafter continuation with maintenance (5mg/kg every eight weeks), d. combined therapy: adalimumab + azathioprine/methotrexate or infliximab + azathioprine/methotrexate, e. patients without maintenance therapy or f. mesalazine (3g/daily).

Clinical remission and relapse were evaluated based on the value of Crohn's Disease Activity Index (CDAI): a. Remission was defined as CDAI <150; b. Relapse was defined as a CDAI> 150. Endoscopic activity was assessed by total colonoscopy and terminal ileoscopy based on Rutgeerts score (RS, i.e., 0-4; table 1): a. endoscopic remission for RS values of i0 and i1. b. Endoscopic relapse for RS values of i2, i3 and i4.

We analysed patients demographics, disease progression (age at diagnosis, first operation, consecutive resections), smoking status, Montreal Classification (age at diagnosis, location of disease, illness behaviour), family history, type of preoperative and postoperative therapy, number of resections, type of resection and the length of the resected segment.

Statistical analysis

SPSS Statistics 20 (Chicago, IL, USA) was used for statistical analysis. Descriptive statistics - for parametric variables arithmetic mean and standard deviation or median (according to the type of distribution data), while non-parametric characteristics

frequency percentages were used. Student T-test/Mann - Whitney or Kruskal-Wallis test (based on type data distribution) were used to check for differences between means variables or median c. χ^2 and Fisher's test were used to determine differences in frequency. Univariate analysis and multivariate binary logistic regression (methods Backward stepwise) was used to analyse the risk factors for clinical and endoscopic, postoperative relapse.

The study was approved by the local ethics committee.

Results and Discussion

Table 2 shows the demographic characteristics of 50 CD patients with at least one surgical resection. The average age of patients was 43 years with a relatively equal gender distribution (46% women, 54% men). 36% of patients were smokers, while 10% had positive family history for IBD. The average age at diagnosis was 31 and the disease on average lasted 11 years. The most common complications were stricture (64%), penetration (28%) and inflammation (8%). Perianal disease was found in a third of the patients.

Demographics	N = 50
Age (years), mean ± SD	43 ± 11
Females, n (%)	23 (46%)
Disease duration (years), Med+IQR	11 ± 10
Positive IBD family history, n (%)	5 (10%)
Smokers	18 (36%)
Age at diagnosis (years), Med+IQR	30.5 ± 18.0
Montreal Age at diagnosis - A, n (%)	
A1&A2,	37 (74%)
A3	13 (26%)
Montreal disease localization - L, n (%)	
L1	24 (48%)
L3	26 (52%)
Montreal behaviour - B, n (%)	
B1 - non-stricturing, non-penetrating	4 (8%)
B2 - stricturing	32 (64%)
B3 - Penetrating	14 (28%)
Perianal disease present, n (%)	17 (34%)
Immunomodulators (IMD); n (% of 50 patients)	33 (66%)
Azathioprine (AZA)	28 (85%)
Methotrexate (MTX)	5 (15%)
Combined therapy (Anti-TNFα +AZA/MTX); n (% of 50 patients)	21 (42%)
Infliximab (IFX)	9 of 21 (42%)
Adalimumab (ADA)	12 of 21 (58%)

Other therapies, n (%):	17 (34%)
Mesalamine	7 (41%)
Metronidazole	0
Without therapy (% of other)	10 (59%)

Table 2: Demographic characteristics of patients with CD.

33 out of 50 patients (66%) were treated with immunomodulator (IMD) therapy - azathioprine or methotrexate, 21(42%) out of which were treated with a combined biological agent protocol (adalimumab or infliximab). 14% (7/50) of patients were treated with mesalazine (3g/d), while 20% (10/50) of patients did not receive any treatment. The number and type of surgical interventions are shown in table 3. 72% of patients had only one surgical resection, 24% had two, while only two patients (4%) were operated three times. Median time from the last resection was 1.5 years (IQR 5), while the median time between resections was 5.5 years (IQR 8). 56% of patients had termino-lateral (TL) anastomosis, 32% termino-terminal (TT) and 12% had latero-lateral (LL) anastomosis. Resected segments varied greatly in length (10-150 cm).

Resections, n (%)	
One	36 (72%)
Two	12 (24%)
Three	2 (4%)
Time from last resection, Med + IQR	1.5 ± 5 (0-20)
First resection	3 ± 7 (0-10)
Second resection	2.5 ± 9 (0-20)
Time between resections	5.5 ± 8.0 (0-13)
Resected segments length (cm), Med +IQR	45 ± 41 (10-150)
Resected segment length (cm), n (%):	
>50 cm	35 (70%)
<50 cm	15 (30%)
Anastomosis type, n (%):	
Termino-Lateral (TL)	28 (56%)
Termino-Terminal (TT)	16 (32%)
Latero-Lateral (LL)	6 (12%)

Table 3: Number and type of surgical resections, length of the resected segment in 50 resected patients with CD.

Tables 4-6 show the risk of relapse depending on the number/type of resection, the length of resection, the clinical properties of

patients with one or more resections and the postoperative status. 74% of patients were in clinical remission, in contrast to the 40% of patients in endoscopic remission (table 5). We identified four favourable factors: single resection (patient had significantly shorter disease duration; table 4, $P < 0.01$; OR 5.76, CI 1.7-24.4), younger age (41 ± 2 years vs. 49 ± 3 years for relapsed patients, $P < 0.05$, table 6), type of anastomosis (66% of patients with TL anastomosis were in clinical remission compared to 25% in relapse; $P < 0.05$; OR 3.84; CI 1:39 to 10:58) and anti-TNF α therapy (clinical remission maintained even after 3 years; $P < 0.05$, CI 3:58; 1:22 to 10:42). Multivariate logistic regression analysis revealed older age at diagnosis and extensive small bowel resection as risk factors for endoscopic recurrence. While, the ileum was most commonly affected (55% patients with any L1 were in clinical remission, while 25% were in the deterioration of the 3 years after operations), it was not statistically significant compared to other sites ($P = 0.06$; OR 3.67, CI 0.86-15.87).

Characteristics	One resection	Two or more resections	Odds ratio	P value
Age (years)	41.8 \pm 11.0	45.9 \pm 12.4	NA	0.26
Disease duration (<10y); n %	22 (61%)	3 (21%)	5.8 CI 1.4-24.4	0.01*
Females; n %	16 (44%)	7 (50%)	1.3 CI 0.4-4.3	0.72
Smokers, n %	12 (33%)	6 (43%)	1.50 CI 0.4-5.3	0.5
Age at diagnosis (A1, A2), n %	24 (67%)	13(92%)	6.5 CI 0.7-5.6	0.06
Montreal L1; n %	16 (44%)	8 (57%)	0.6 CI 0.2-2.1	0.4
Montreal B2; n %	22(36%)	10 (71%)	1.6 CI 0.4-6.1	0.5
Perianal disease; n %	13(36%)	4 (29%)	1.4 CI 0.4-5.4	0.6
Immunosuppressive therapy; n %	25 (70%)	8 (57%)	1.7 CI 0.4-6.1	0.41
IT duration; (Median \pm IQR)	2 \pm 5	4.5 \pm 6	NA	0.40

Endoscopic remission; n, %	15(42%)	5 (38)	1.3 CI 0.4-4.6	0.70
Clinical remission	28 (77%)	10 (71%)	1.4 CI 0.3-5.7	0.63
Termino-lateral anastomosis	22 (61%)	6 (42%)		0.34

Table 4: Clinical characteristics of two groups of patients with one or more resections.

Postoperative status	N = 50
Clinical remission (CDAI <150); n, (%)	38 (74%)
Clinical relapse (CDAI >150), n, (%)	12 (26%)
Endoscopic remission (i0, i1), n, (%)	20 (40%)
Endoscopic relapse (i2, i3, i4), n, (%)	30 (60%)
Rutgeerts' score i0	9 (18%)
Rutgeerts' score i1	11 (22%)
Rutgeerts' score i2	8 (16%)
Rutgeerts' score i3	15 (30%)
Rutgeerts' score i4	7 (14%)

Table 5: Postoperative status after 36 months (Median follow-up of the last operation).

Characteristics	Clinical remission	Clinical relapse	Odds ratio	P value
Age (mean \pm SE)	41 \pm 2	49 \pm 3	NA	0.024*
Age at diagnosis (median \pm IQR)	30 \pm 17	37 \pm 14	NA	0.21
Disease duration (median \pm IQR)	11 \pm 11	15 \pm 13	NA	0.83
Resections >1; n %	28 (74%)	8(66%)	1.40 CI 0.34-5.68	0.64
T-L anastomosis; n %	25 (66%)	3 (25%)	3.84 CI 1.3910.58	0.03*

Resected segment <50cm; n %	26 (68%)	9 (75%)	1.38 CI 0.31-6.06	0.66
Non-smokers; n %	25 (66%)	7(58%)	1.37 CI 0.36-5.18	0.64
Age at diagnosis (A1, A2) n %	30 (79%)	7(58%)	2.69 CI 0.66-10.72	0.156
L1 Montreal category	21(55%)	3(25%)	3.67 CI 0.86-15.87	0.06
B2/B Montreal category	25(66%)	7(58%)	1.37 CI 0.36-5.18	0.64
Perianal disease	14 (37%)	3(25%)	0.89 CI 0.65-1.19	0.450
Immunosuppressive therapy (IT), n%	27 (71%)	6(50%)	2.45 CI 0.64-9.25	0.18
IT duration in years (median ± IQR)	3 ± 5	2 ± 4	NA	0.73
Biological therapy (BT), n %	20(52%)	1(8%)	1.26 CI 1.44-10.0	0.007*
BT duration in years (median ± IQR)	1 ± 1	1 ± 1	NA	0.99
Endoscopic remission n %	20 (52%)	0 (0%)	1.66 CI 1.24-2.32	0.001*

Table 6: Differences in clinical characteristics of patients in clinical relapse or remission, 36 months (median) from surgery.

Immunosuppressive and biological therapies have improved the outcomes for postoperative patients with Crohn's Disease [4]. The European Crohn's and Colitis Organisation (ECCO) recommends a minimum of two years therapy with azathioprine and methotrexate for postoperative patients [14], particularly since azathioprine is good in the prevention of clinical and endoscopic relapses [15]. Biologic therapy with anti-TNFα is superior to immunosuppressive therapy and is considered most effective in preventing postoperative relapse [4,16]. While infliximab is superior to azathioprine

and monotherapy with infliximab alone can achieve high rates in endoscopic remissions [4,5,16], ECCO recommends supplemental treatment with thiopurines for patients with high risk for postoperative relapse [17]. In our study, 21 (42%) patients were treated with biological therapy in combination with azathioprine or methotrexate protocol (table 2). 20 patients achieved clinical remission 36 months after surgery as a result of biological therapy, while only one patient had clinical deterioration (P < 0.05). Univariate and multivariate analyses suggested biological therapy as a significant predictor of clinical remission, but not for achieving endoscopic remission. Several reasons arise: first, the criteria for the introduction of biological therapies are heterogeneous. In particular, while ECCO recognises previous surgery, smoking and penetrating phenotype as risk factors, the second European evidence-based Consensus did not follow suit [3]. Secondly, inadequate early endoscopic surveillance and treatment can affect the postoperative results at the 36-month mark. Finally, when patients in this study had their operations six years ago, there were no specific postoperative follow-up guides established and implemented in any major IBD European centre. The POCER study defined the protocols of postoperative follow-up for patients with Crohn's Disease and emphasised endoscopy as the pivotal tool for postoperative follow-up [4,18]. A 1990 prospective cohort study showed that patients with minimal endoscopic lesions (i0 and i1) had a very favorable postoperative clinical course [4], in contrast to patients with RS> i1. An Italian prospective cohort study demonstrated relapse in 48% of studied patients, with 38% of the patients relapsing only after six months [19]. The high rates of clinical and endoscopic remission in at 36 months follow up in our study may be due to the fact that 42% of patients were receiving biological therapy concurrently.

There are conflicting reports about the preventative efficacy when thiopurines are combined with imidazoles, specifically metronidazole. Some authors have demonstrated greater preventative effect [20], while others have shown endoscopic deterioration as high as 44% and 82% in the first and fifth follow up year, respectively [21]. In our study, biological therapy was essential in achieving remission, and neither immunosuppressive therapy nor the length of IMD therapy had an effect on this. The finding cannot not be generalised due to the small number of participants along with lack of pre-selection criteria.

The 2010 ECCO guide stressed the role of smoking, previous intestinal resection (including appendectomy), extensive intestinal

resection, penetrating phenotype and perianal disease as risk factors [3]. In our study, with 35% of smokers in endoscopic remission and 37% of non-smokers with endoscopic relapse, smoking was not identified as a risk factor for prediction of clinical or endoscopic relapse. The small cohort and the short follow up period may explain why smoking was not a risk factor in our study.

Age at diagnosis is not a clearly defined risk factor for relapse and surgical interventions as studies are conflicting [4,22]. Our study did not show that younger age at diagnosis is a risk factor for relapse. In fact, our patients in clinical and endoscopic remission were significantly younger than the group with clinical relapse. This may be explained by the fact that older patients who have a long disease history may have a poorer response to biological therapy.

The impact of disease location was investigated in previous studies with varied results [6]. In a European study, the upper segments of the digestive tract (L4) were identified as a risk factor for postoperative relapse [23]. Only one study identified the colon (L2) as a predictive factor for clinical relapse however the study had a small number of participants [24]. In our study, relapses favored the ileocolic region but the difference was not significant relapses (L3; 75% vs 45%). Penetrating phenotype is an independent factor for postoperative relapse [3,4]. A meta-analysis of 13 studies showed that perianal fistula is a risk factor for clinical and endoscopic relapse (HR 1.5, 95% CI: 1.16-1.93) [25]. In our cohort, B3 phenotype was found in 50% of patients with an endoscopic deterioration compared to 20% who were in endoscopic remission. In the postoperative period, endoscopic relapse develops proximal to the anastomosis. Although it is believed that the causes are multifactorial, it is assumed that faecal stream plays an important role [26]. In addition to this, luminal size may contribute to disease relapse as it may be a ground for obstruction or secondary bacterial contamination. Because of this, many authors proposed "side to side" anastomosis over "end to end" anastomosis. Meta-analysis showed that "side to side" anastomosis was associated with a lower degree of postoperative relapse [27]. In our cohort, most patients had termino-lateral (TL) anastomosis and 66% of these patients were in clinical remission ($P < 0.05$). Multivariate analysis suggested TL anastomosis as an independent factor associated with the clinical remission. However, the type of anastomosis did not affect the occurrence of endoscopic relapse.

Conclusion

In summary, our results show that after a median of 36 months, 60% of patients had endoscopic relapse, while significantly smaller number, 26% were in clinical deterioration. These results are surprisingly positive compared to other studies, probably due to the fact that almost half the cohort was treated with TNF blockers postoperatively. Older age, termino-terminal, latero-lateral anastomosis and the absence of biological therapies were identified as risk factors for postoperative relapse. Our study is limited by its retrospective design and the small to moderate number of patients. Patients were selected from the 2009 – 2015 electronic database and complete documentation in electronic form exists only for 2015. Despite the limitations, we believe that this study contributes to everyday clinical practice.

Conflict of Interest

The authors declare no conflicts of interest.

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