

ORIGINAL ARTICLE

Perioperative management and early complications after intestinal resection with ileocolonic anastomosis in Crohn's disease: analysis from the PRACTICROHN study

Ana Gutiérrez¹, Montserrat Rivero², Maria Dolores Martín-Arranz³, Valle García Sánchez⁴, Manuel Castro⁵, Jesús Barrio⁶, Ruth de Francisco⁷, Manuel Barreiro-de Acosta⁸, Berta Juliá^{9,*}, Luis Cea-Calvo⁹, Cristina Romero⁹, Natalia Borrueal Sainz¹⁰ and Eugeni Domènech¹¹

¹Gastroenterology Department, General University Hospital of Alicante and Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBERehd), Carlos III Health Institute, Madrid, Spain; ²Gastroenterology Department, Marques de Valdecilla General University Hospital, Santander, Spain; ³Gastroenterology Department, La Paz General University Hospital, Instituto de Investigación Biomédica La Paz (IdiPaz), Madrid, Spain; ⁴Clinical Management of Gastrointestinal Tract Diseases Unit, Reina Sofia University Hospital, Maimonides Institute of Biomedical Research of Cordoba (IMIBIC), Cordoba University, Cordoba, Spain; ⁵Gastroenterology Department, Valme University Hospital, Sevilla, Spain; ⁶Gastroenterology Department, University Hospital, Río Hortega, Valladolid, Spain; ⁷Gastroenterology Department, University Hospital Central de Asturias, Oviedo, Spain; ⁸Gastroenterology Department, Inflammatory Bowel Disease Unit, University Hospital Complex of Santiago de Compostela, Santiago de Compostela, Spain; ⁹Medical Department, Merck Sharp and Dohme, Madrid, Spain; ¹⁰Crohn-Colitis Care Unit (UACC), Digestive Tract Service, Hospital Universitari Vall d'Hebron, Barcelona, Spain; ¹¹Gastroenterology Department, Germans Trias i Pujol University Hospital and CIBERehd, Badalona, Spain

*Corresponding author. Merck Sharp and Dohme, C/Josefa Valcárcel 38, Madrid, Spain. Tel: +34696943120; Email: berta_julia@merck.com

Abstract

Background: This study is aimed at describing the prevalence of and risk factors associated with early post-operative complications after Crohn's disease-related intestinal resection.

Methods: This was a retrospective analysis of data from the PRACTICROHN cohort. Adult Crohn's disease patients who underwent ileocolonic resection with ileocolonic anastomosis between January 2007 and December 2010 were included. The complications evaluated included death, ileus, anastomotic leak, abscess, wound infection, catheter-related infection, digestive bleeding and other extra-abdominal infections that occurred in the 30 days after surgery.

Submitted: 6 August 2018; Revised: 7 November 2018; Accepted: 20 December 2018

© The Author(s) 2019. Published by Oxford University Press and Sixth Affiliated Hospital of Sun Yat-sen University

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/4.0/>), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact journals.permissions@oup.com

Results: A total of 364 patients (median age at surgery 38 years and 50% men) were included. Indication for surgery was: stricturing disease (46.4%), penetrating disease (31.3%), penetrating and stricturing disease (14.0%) or resistance to medical treatment (5.8%). Early complications were recorded in 100 (27.5%) patients, with wound infection, intra-abdominal abscess and anastomotic leakage being the most frequent complications. Median hospitalization duration was 16 days for patients with complications vs. 9 days without complications ($P < 0.001$). Complications were more common among patients with penetrating disease (36/114, 31.6%) and those refractory to treatment (9/21, 42.9%) compared with stricturing disease (45/169, 26.6%) or stricturing + penetrating disease (6/51, 11.8%) ($P = 0.040$). The rate of complications was higher among patients with diagnosis made at the time of surgery (15/31, 48.4%) compared with the rest (85/331, 25.7%) ($P = 0.013$). Medication received at the time of surgery did not affect the rate of complications.

Conclusions: Almost a quarter of patients developed early complications after intestinal resection. Penetrating disease and urgent surgery were associated with an increased risk of complications.

Key words: Ileocolonic resection; Crohn's disease; post-operative complications; risk factors

Introduction

Crohn's disease (CD) is an inflammatory bowel disease (IBD) that affects the ileum, colon or both and may involve other parts of the gastrointestinal tract and/or have extra-intestinal manifestations. It is a progressive, destructive and currently incurable condition that is more prevalent in Europe and North America, where it affects between 10 and 150 in 100,000 persons, with a higher prevalence in women than in men [1].

Treatment is aimed at achieving sustained clinical remission and preventing cumulative tissue damage and subsequent disease-related complications [2]. Medical treatment is the primary therapeutic approach [3], though surgical management is essential in patients who fail to respond to medical therapy and in those who present intra-abdominal abscesses, perianal or internal fistulas, bowel obstruction or cancer [4]. Intestinal resection rates in CD range between 19% and 61% in the first 5 years after diagnosis and can reach 80% in the first 20 years after diagnosis, with recent studies suggesting a decline in the frequency of surgery [5–8]. The risk factors for surgery in CD are current smoking, penetrating and stricturing disease, early treatment with corticosteroids, ileal or jejunal disease and young age at diagnosis [1, 9]. Relapses are common, with post-operative recurrence affecting about 30% of patients despite prophylaxis [10]; approximately 14% of patients require re-intervention in the first 5 years after surgery and 30% in the first 10 years after surgery [11].

Surgery is associated with post-operative complications (POCs), the risk of which depends on several factors, such as disease pattern (perforating disease is associated with a higher risk of POCs), type of anastomosis, surgeon's experience, type of surgery (elective vs. urgent, open vs. laparoscopic) and other factors [12]. The aim of our study was to describe the prevalence of and the risk factors associated with early POCs (ePOCs) in a cohort of patients who underwent intestinal resection for CD.

Methods

Study design

We retrospectively reviewed the records of patients at 26 Spanish IBD units. No data were collected prospectively. The study was approved by the corresponding Research Ethics Committees.

Patient selection

We identified patients from IBD outpatient clinics aged more than 18 years who underwent ileocolonic resection with

ileocolonic anastomosis for CD between January 2007 and December 2010. Those who signed an informed consent authorizing the use of their clinical data for research were included. For this analysis, patients' data from diagnosis of CD to the index surgery and until 5 years after the index surgery were collected from medical records. All surgeries were performed with anastomosis; no surgeries with stomas were included. When the patient had undergone more than one procedure, the index surgery was considered that closest to December 2010. Data collected from the medical records included demographic data (age, sex, smoking status and family history) and clinical data (date of diagnosis, Montreal classification at diagnosis and at time of surgery [13], extra-intestinal manifestations, immune-mediated inflammatory diseases, IBD-related treatments received before surgery [from diagnosis to surgery] and at the time of surgery, approach [open or laparoscopic], previous surgeries, reason for current surgery [penetrating or stricturing disease or resistance to treatment], length of resection and hospital stay). We evaluated the rate of ePOCs during the 30 days after surgery, including death, ileus, anastomotic leak, digestive bleeding, abscess, wound infection, catheter-related infection and other extra-abdominal infections. We performed a separate analysis of infectious complications (wound infections, intra-abdominal abscesses, extra-abdominal infections and catheter-related infections). Finally, we analyzed the number of surgeries performed at each site during the study period and the influence of IBD drugs on ePOCs at the time of surgery. The rate of post-operative recurrence in this sample of patients has been reported elsewhere [10].

Statistical analysis

The sample size was calculated based on the primary endpoint of the PRACTICROHN study, namely the rate of disease recurrence at 52 weeks after surgery, and has been published elsewhere [10]. The *t*-test, analysis of variance or nonparametric tests (Mann-Whitney test) were used to compare continuous variables. Categorical variables were compared using the χ^2 test or Fisher's exact test, if needed.

Missing values and their frequency were tabulated but included in calculating the percentages. In all cases, the distribution of variables according to theoretical models was verified with the Kolmogorov-Smirnov test and the assumption of homogeneity of variance was contrasted using Levene's test.

Logistic-regression analysis was performed to study which baseline characteristics correlated with the variables of interest (primary and secondary objectives). Models were compared based on baseline clinical variables and surgical characteristics

using a maximum-likelihood test, with an evaluation of possible interactions. Variables with $P < 0.15$ in the bivariate analysis were selected for the multivariate analysis. Statistical significance was set at $P < 0.05$.

Results

Baseline characteristics

Data from 364 CD patients were analyzed with a median age at time of surgery of 38 years (interquartile range [IQR] 30–48). The patients' demographic and clinical characteristics are summarized in Table 1. At the time of surgery, 90 (24.7%) patients had been exposed to corticosteroids, 165 (45.3%) to immunomodulators and 64 (17.6%) to biological treatments. Median time of hospitalization was 10 days (interquartile range

[IQR] 7–14). After surgery, 27 patients had residual disease (7.4%). All patients underwent open surgery, except for 2 patients who underwent laparoscopy (data available for 300 patients).

Early POCs

At least one ePOC was recorded in 100 patients (27.5%). Wound infection ($n = 33$, 9.1%), intra-abdominal abscess ($n = 28$, 7.7%) and anastomotic leak ($n = 27$, 7.4%) were the most common ePOCs (Table 2). There were no deaths within 30 days after surgery. Median hospital stay for patients with ePOCs was 16 days (IQR 10–28) compared with 9 days (IQR 7–11) for patients without ePOCs ($p < 0.001$). As for the experience of the centres in IBD-related surgery, only 20 out of 26 centres had data on the number of IBD-related surgeries performed during 2007–10. We

Table 1. Patients' demographic and clinical characteristics

Characteristic	All patients ^a ($n = 364$)	Without ePOCs ($n = 263$)	With ePOCs ($n = 100$)	P-value
Male gender	182 (50.0)	126 (47.9)	55 (55.0)	0.276
Age at time of diagnosis, years	28 (22–39)	28 (22–38)	30 (24–44)	0.042
Time between diagnosis and surgery, years	6 (1–12)	7 (1–12)	5 (0.8–12)	0.197
Age at time of resection, years	38 (30–48)	37 (29–47)	39 (31–51)	0.119
Active smokers at time of resection	128 (35.2)	97 (36.9)	30 (30.0)	0.836
Number of previous surgeries				0.745
0	290 (79.7)	211 (80.2)	78 (78.0)	
≥ 1	74 (20.3)	52 (19.8)	22 (22.0)	
Location at time of resection				0.474
L1 \pm L4	199 (54.7)	145 (55.1)	53 (53.0)	
L2 \pm L4	6 (1.6)	3 (1.1)	3 (3.0)	
L3 \pm L4	159 (43.7)	115 (43.7)	44 (44.0)	
Behaviour at time of resection				0.883
B1	32 (8.8)	22 (8.4)	10 (10.0)	
B2	184 (50.5)	134 (51.0)	50 (50.0)	
B3	145 (39.8)	105 (39.9)	39 (39.0)	
Perianal disease at time of resection	37 (10.2)	25 (9.5)	12 (12.0)	0.607
Perianal disease at any time during the disease	65 (17.9)	49 (18.6)	16 (16.0)	0.603
Length of resection				0.243
≤ 50 cm	248 (68.1)	177 (67.3)	71 (71.0)	
> 50 cm	38 (10.4)	23 (8.7)	15 (15.0)	
Extra-intestinal manifestations between diagnosis and surgery	45 (12.4)	31 (11.8)	14 (14.0)	0.651
Indication for surgery				0.018
Penetrating	114 (31.3)	77 (29.3)	36 (36.0)	
Stricturing	169 (46.4)	124 (47.1)	45 (45.0)	
Penetrating + stricturing	51 (14.0)	45 (17.1)	6 (6.0)	
Resistance to treatment	21 (5.8)	12 (4.6)	9 (9.0)	
Medication prior to surgery				
Corticosteroids	174 (47.8)	134 (51.0)	39 (39.0)	0.043
Immunomodulators	73 (20.1)	57 (21.7)	16 (16.0)	0.305
Anti-TNF	68 (18.7)	51 (19.4)	17 (17.0)	0.736
More than 1 medication	81 (22.3)	62 (23.6)	19 (19.0)	0.379
Medication at the time of surgery				
Corticosteroids	90 (24.7)	62 (23.6)	28 (28.0)	0.493
Immunomodulators	165 (45.3)	119 (45.2)	46 (46.0)	0.937
Anti-TNF	64 (17.6)	42 (16.0)	22 (22.0)	0.218
More than 1 medication	90 (24.7)	62 (23.6)	28 (28.0)	0.434
Time from diagnosis to surgery				0.013
< 1 month	31 (8.5)	16 (6.1)	15 (15.0)	
≥ 1 month	331 (90.9)	245 (93.2)	85 (85.0)	
Length of hospitalization, days	10 (7–14)	9 (7–11)	16 (10–28)	< 0.001

ePOCs, early post-operative complications; TNF, tumour necrosis factor.

^aThere is one patient with missing data regarding having ePOC or not.

Values presented as median (interquartile range) or number (%).

found no difference in the rate of ePOCs related to the number of surgeries performed in each hospital (32% in hospitals with <30 surgeries, 25% in hospitals with 31–60 surgeries and 26% in hospitals with >60 surgeries; $P=0.40$). The only type of ePOC that was more frequent in hospitals with a lower number of IBD-related surgeries was anastomotic leak (15.2% in hospitals with <30 surgeries performed vs. 5.9% in hospitals with 31–60 surgeries and 3.5% in hospitals with >60 surgeries; $P=0.001$) (Table 2).

There were no associations between the incidence of ePOCs and the length of intestinal resection, sex, age at time of surgery, history of previous surgeries, location of disease, presence of perianal disease, disease behaviour or smoking status (Table 1). Regarding treatments received before surgery, we found that patients without ePOC more frequently received corticosteroids before surgery than patients with ePOC 39 (51.0% vs. 39.0%, $P=0.043$), with no difference in the rate of ePOCs found with other treatments. Nevertheless, at the time of surgery, we found no differences in the rate of ePOCs with any of the treatments received (Table 1). The main reason for surgery was stricturing disease, both in patients with ePOCs (45.0%) and without ePOCs (47.1%); however, the incidence of ePOCs was

higher in patients with intestinal perforation as the indication for surgery (36/114, 31.6%), as was being refractory to treatment (9/21, 42.9%), than in those with stricturing disease (alone or in combination with penetrating disease), which was associated with a lower risk of ePOCs (45/169, 26.6% and 6/51, 11.8%, respectively) ($P=0.040$) (Figure 1). We also analyzed the relationship between time from diagnosis to surgery and the presence of ePOCs and found that ePOCs were more common in patients with surgery performed in the month following the diagnosis of CD (15/31, 48.4%) than in patients who were operated on when the diagnosis of CD had been already established (85/331, 25.7%; $P=0.013$) (Figure 1).

Multiple logistic-regression analysis showed no association between the risk of ePOCs and the following independent variables: age at time of surgery, sex, reason for surgery, emergency surgery and number of surgeries performed at each site (Table 3).

Treatments prescribed at discharge and follow-up after surgery are summarized in Table 4. Patients with ePOCs were prescribed immunomodulators at discharge less frequently ($P=0.025$) and were monitored with imaging techniques (computed tomography or magnetic resonance imaging) more frequently ($P=0.047$). No other differences were found regarding

Table 2. Number of patients with early post-operative complications (ePOCs)

Event	All patients (n = 364)	Number of IBD surgeries performed between 2007 and 2010			P-value
		≤30 (n = 105)	31–60 (n = 85)	>60 (n = 170)	
Any complication	100 (27.5) ^a	34 (32.4)	21 (24.7)	44 (25.9)	0.404
Death	0 (0)	0 (0)	0 (0)	0 (0)	–
Ileus	11 (3.0)	6 (5.7)	1 (1.2)	3 (1.8)	0.122
Digestive bleeding	11 (3.0)	3 (2.9)	2 (2.4)	6 (3.5)	0.927
Anastomotic leak	27 (7.4)	16 (15.2)	5 (5.9)	6 (3.5)	0.001
Intra-abdominal abscess	28 (7.7)	11 (10.5)	5 (5.9)	12 (7.1)	0.446
Wound infection	33 (9.1)	10 (9.5)	6 (7.1)	17 (10.0)	0.737
Catheter-related sepsis	4 (1.1)	0 (0)	2 (2.4)	2 (1.2)	0.270
Other extra-abdominal infections	12 (3.3)	2 (1.9)	3 (3.5)	7 (4.1)	0.693

^aThere is one patient with ePOC missing data regarding number of surgeries performed on this site.

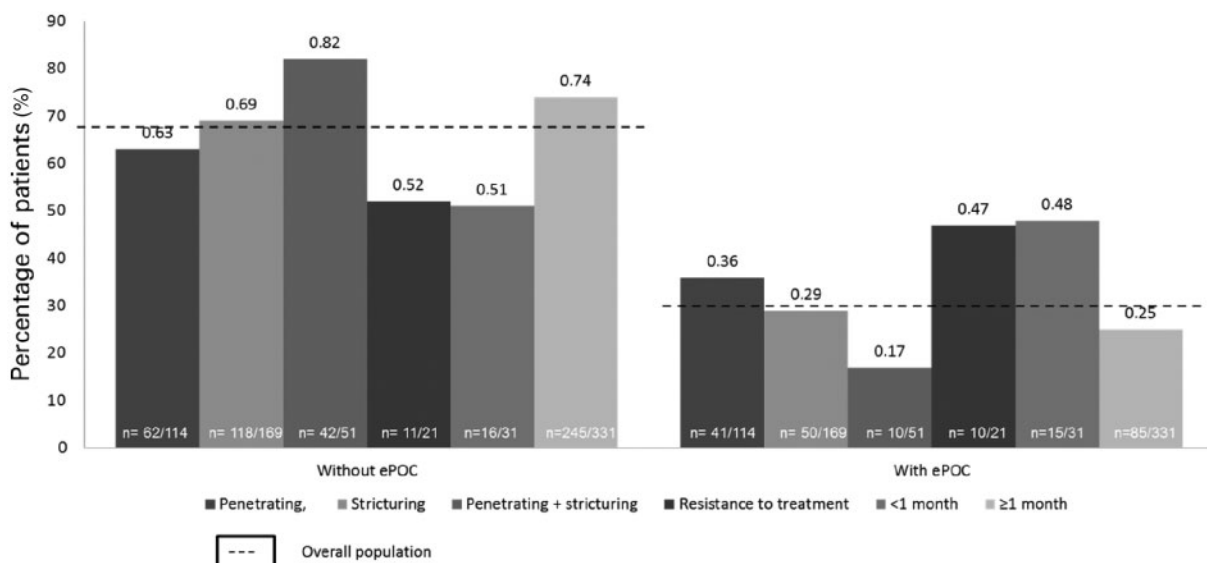


Figure 1. Percentage of patients with and without early post-operative complications (ePOCs) according to cause for surgery and time from diagnosis to surgery. The dotted lines correspond to the percentages of patients without and with ePOCs in the overall study population (68.4% and 31.6%, respectively).

Table 3. Logistic-regression results

Explicative variables	Coefficient (95% confidence interval)	Odds ratio	Z-value	P-value
Intercept	-0.42 (-1.51, 0.67)	0.65	-0.760	0.447
Age at surgery	0.02 (0, 0.04)	1.02	1.818	0.069
Gender: female	-0.30 (-0.8, 0.2)	0.74	-1.164	0.244
Indication for surgery: stricturing	-0.16 (-0.72, 0.41)	0.86	-0.546	0.585
Indication for surgery: penetrating + stricturing	-1.05 (-2.1, -0.14)	0.35	-2.120	0.034
Indication for surgery: resistance to treatment	0.61 (-0.41, 1.62)	1.85	1.196	0.232
Number of surgeries performed at each site: 31–60	-0.29 (-0.98, 0.38)	0.75	-0.839	0.401
Number of surgeries performed at each site: >60	-0.26 (-0.82, 0.31)	0.77	-0.887	0.375
Time from diagnosis to surgery ≥ 1 month	-0.90 (-1.7, -0.09)	0.41	-2.183	0.029

Table 4. Medication at discharge and follow-up after surgery

Treatment	All patients ^a (n = 364)	Without ePOC (n = 263)	With ePOC (n = 100)	P-value
Medication at discharge				
Oral corticosteroids	70 (19.2)	47 (17.9)	23 (23.0)	0.364
Immunomodulators	117 (32.1)	94 (35.7)	23 (23.0)	0.025
Antibiotics	77 (21.2)	52 (19.8)	25 (25.0)	0.324
Anti-TNF	31 (8.5)	19 (7.2)	12 (12.0)	0.213
Aminosalicylates	43 (11.8)	32 (12.2)	11 (11.0)	0.881
More than 1 medication	79 (21.7)	59 (22.4)	20 (20.0)	0.722
Follow-up after surgery				
Days until the following visit	46.9 \pm 59.9	45.8 \pm 52.1	46.2 \pm 68.4	0.992
Colonoscopy in the first year	140 (38.5)	102 (38.8)	38 (38.0)	0.987
Imaging technique in the first year	59 (16.2)	36 (13.7)	23 (23.0)	0.047
Blood test in the first year	300 (82.4)	214 (81.4)	86 (86.0)	0.376
Biomarker test in the first year	44 (12.1)	30 (11.4)	14 (14.0)	0.620

ePOCs, early post-operative complications; TNF, tumour necrosis factor.

^aThere is one patient with missing data regarding having ePOC or not.

Values presented as mean \pm standard deviation or number (%).

the treatments received or the follow-up between patients with and without ePOCs.

Infectious complications

During the first month after surgery, 69 patients (19.0%) presented with at least one infectious complication; the median length of hospital stay was 19 days (IQR 10–30) for patients with infectious complications compared with 9 days (IQR 7–12) for the remaining patients ($P < 0.001$). The most frequent infectious complications were wound infections ($n = 33$), intra-abdominal abscesses ($n = 28$), extra-abdominal infections ($n = 12$) and catheter-related infections ($n = 4$). No differences in the incidence of infectious complications were observed regarding age, sex, smoking status, disease location or length of intestinal resections. There was no association between medication received at surgery and the rate of infectious complications.

Discussion

Surgery carries risks, including mortality and POCs. Serious POCs, such as anastomotic leak and intra-abdominal sepsis, develop more frequently after surgery for CD than other intestinal resections [14, 15]. Incidence varies with the type of complication, as follows: 0%–18.8% for wound sepsis, 3.1%–18.7% for abdominal abscess, 0%–12.7% for anastomotic leak [8, 16, 17] and 0.6%–3.6% for post-operative death [17].

In the present observational study, which was based on data from routine practice in a large sample of patients from Spain, we evaluated the rate of ePOCs following surgery for CD. We

found that 27.5% of patients developed ePOCs after intestinal resection, with wound infection, abscess and anastomotic leak being the most frequent complications. Our results are in line with those of previous studies, which reported an incidence of ePOCs of 15%–30% after bowel resection in patients with CD [18–21].

It is worth mentioning that hospital experience in IBD-related surgery was not related to the rate of ePOCs, except for anastomotic leak, which was more common in hospitals with <30 surgeries performed between 2007 and 2010 than in hospitals with >60 surgeries performed during the same time period ($P = 0.001$). This finding is similar to that of previous studies, where surgeon experience was associated with better outcomes [22, 23]. In our study, most of the surgeries were performed by specialized colorectal surgeons, thus explaining the low rate of differences found.

Analysis of the risk factors for ePOCs revealed that surgery performed at the time of diagnosis (probably an urgent surgery) and stricturing disease as the indication for surgery were both significantly associated in the bivariate analyses, with an increased risk of complications, and penetrating + stricturing disease (more specifically, perforation, data not shown) associated with a lower risk. The potential impact of previous medication, in particular, anti-tumour necrosis factor (TNF) drugs or corticosteroids, on the risk of ePOCs after bowel resection in CD is a matter of debate. While some studies and meta-analyses suggest that anti-TNF treatment before surgery is associated with a higher rate of ePOCs, especially infectious complications [24–26], others find no increased risk [20, 27, 28]. In our study, we found no association between the risk of ePOCs and the use

of anti-TNF drugs. In that sense, the number of patients receiving anti-TNF treatment at surgery 64 (17.6%) is similar to the study of Colombel *et al.* [29], with 19% of patients receiving anti-TNF treatment at surgery. In Colombel's study, no difference was found either in the number of patients presenting ePOC between those with and without anti-TNF treatment at surgery. During the study period, no other biologics were allowed for CD treatment, hence no comparisons with vedolizumab could be made. A comparison with vedolizumab would have been interesting, given that treatment with this agent, which targets $\alpha 4\beta 7$ integrin, has been associated with a greater risk of ePOCs (53%) than treatment with TNF inhibitors (33%) or no biological therapies (28%) [30].

Several observational studies identified pre-operative corticosteroid treatment as a risk factor for POCs [28, 31, 32]; however, high-quality studies on the subject are lacking. We found that treatment with corticosteroids at the time of surgery was not associated with a higher risk of early POCs. Though the number of patients may have been insufficient to detect differences, we concomitantly found that corticosteroid use before surgery was associated with a lower rate of ePOCs. This could be explained by the fact that, while, during the treatment, 47.8% of patients received treatment with corticosteroids, at the exact time point of the surgery, only 24.7% of patients were receiving treatment with steroids. That reflects an important withdrawal of corticosteroid use and the patients who remained on corticosteroids likely used the minimum dose possible. Unfortunately, we did not collect information on the dose of corticosteroid used, so we cannot assure this point.

Other factors have been linked to POCs after CD-related intestinal resection. Thus, several studies and meta-analyses focused on the surgical approach and technique: 3 meta-analyses of up to 15 studies showed the post-operative benefits of the laparoscopic approach [33–35], including a decreased rate of POCs and shorter hospital stay, faster return to normal activity and diet, better cosmesis and improved social and sexual interaction. Another meta-analysis concluded that stapled side-to-side anastomosis was linked to fewer overall POCs and a lower recurrence and re-operation rate than end-to-end hand-sewn anastomosis [36]. In our sample, only two patients underwent laparoscopy, thus implying that our results only apply to open abdominal surgery. Furthermore, since information on the type of anastomosis was not collected in our study, we cannot compare the frequencies of ePOC associated with the different techniques. Given that the laparoscopic approach is widely used in Spain today, the prevalence of ePOCs would probably be lower than that reported in this analysis.

Emergency surgery is seldom necessary in CD. However, when required, it is associated with higher rates of post-operative mortality (3.6%; 95% confidence interval [CI], 1.8%–6.9%) than elective surgery (0.6%; 95% CI, 0.2%–1.7%) [17]. We recorded no POC-related deaths, but 31 (8.5%) patients underwent surgery within 1 month of the diagnosis of CD, probably reflecting a more severe and complex disease, or emergency surgeries. In these patients, the number of ePOCs was significantly higher than in patients who had undergone surgery at least 1 month after the diagnosis. Although we cannot rule out the possibility that there were no emergency procedures in the latter group of patients, our data agree with previous reports that associate emergency surgery with an increased risk of POCs [37] and stress the importance of the surgeon's experience for better outcomes.

Observational studies like this one use statistical methods to identify risk factors; however, the results are more difficult to

compare due to differences in study design, available information and possible confounding effects. Thus, in an observational study of 131 patients with CD, Heimann *et al.* [18] found that 30% experienced complications early after surgical intervention and septic complications were more common in patients with extensive resections and in those with multiple previous operations. In our study, there was no statistically significant association between length of resection and risk of POCs, though there was a trend toward a higher incidence of ePOCs among patients with extensive resections (>50 cm). We found no additional risk of ePOCs associated with a history of previous surgeries, but the number of patients with repeat surgeries was low. A total of 74 patients had previously undergone surgery (one procedure in 70, two procedures in 2 and three procedures in 3). The number of patients with previous surgeries may have been insufficient to detect significant differences in ePOCs between them and the patients who underwent primary surgery.

In an observational study on 161 consecutive patients with CD, Alves *et al.* [38] found that pre-operative corticosteroids, poor nutritional status and the presence of abscess at the time of surgery significantly increased the risk of septic abdominal complications after the first ileocecal resection for CD. Similarly, in a pooled analysis of 343 patients who underwent 566 operations for primary or recurrent CD, Yamamoto *et al.* [39] found that intra-abdominal septic complications were significantly associated with low pre-operative albumin levels (<30 g/L), pre-operative corticosteroids and abscess or fistula at the time of laparotomy. In the present sample, as mentioned above, therapy with corticosteroids at the time of surgery was not associated with a higher risk of POCs, whereas perforation was. Unfortunately, we recorded no data on nutritional status or albumin levels at the time of surgery. Consistently with our results, Yamamoto *et al.* found that age, duration of symptoms, number of previous bowel resections and site of disease had no effect on the risk of infectious complications. In contrast, in a large study of 2638 patients with CD and 559 patients with ulcerative colitis, Frolkis *et al.* [37] reported that predictors for in-hospital POCs for both diseases included older age, comorbidities, open laparotomy for CD, emergency admission, stoma surgery and concurrent resection of both the small and the large bowels. Further, well-designed, large studies with wide-ranging data are needed to better characterize the risk factors associated with POC in CD-related bowel resection.

Our study presents a series of limitations. First, owing to its retrospective design, the only data available were those from patients' medical records. Several relevant variables were not collected, including type of anastomosis (stapled vs. hand-sewn), configuration of anastomosis (end-to-end vs. side-to-side), patients' nutritional status, serum albumin levels, creatinine levels and microscopically positive resection margin, which have been recognized as risk factors for complications. Second, the complications were not classified, such as using the Clavien–Dindo classification [40]. As a result, we can only draw conclusions about the scope of the complications but not about their severity or impact on the patient beyond length of hospital stay. Third, the insufficient size of certain subgroups of patients may have hindered the detection of differences and precluded the identification of additional risk factors for POCs. Finally, analysing surgeries between 2007 and 2010 may not accurately reflect current management of CD, though the choice of these dates for the index surgeries did allow us to assess long-term outcomes, such as recurrence and hospital admissions over 5 years of follow-up after surgery. The study reflects clinical practice during the years when the surgeries were performed and, although

clinical practice has evolved since then, our findings highlight the importance of ePOC as an event leading to longer hospital stay and thus potentially higher related health-care costs.

In conclusion, one-quarter of patients who underwent ileo-colonic resection for CD experienced ePOCs. The indication for surgery and emergency surgery were the most important predictors of ePOCs.

Authors' contributions

All of the authors fulfilled all four criteria for authorship as stated in section 2 of the recommendations of the ICMJE, and approved the final manuscript.

Funding

This study was supported by Merck Sharp and Dohme, Spain.

Acknowledgements

The authors are grateful to all the participating researchers for their work in obtaining the study data: Dr Guillermo Alcaín (Hospital Virgen de la Victoria, Málaga), Dr María Rosario Gómez García (Hospital Virgen de las Nieves, Granada), Dr Sabino Riestra Menéndez (Hospital Central de Asturias, Oviedo), Dr Daniel Ginard (Hospital Son Espases, Palma de Mallorca), Dr Jesús Barrio (Hospital Río Ortega, Valladolid), Dr Angel Sierra Hernández (Hospital Insular de Canarias, Las Palmas), Dr Ingrid Ordás (Hospital Clinic, Barcelona), Dr Natalia Borrue (Hospital Vall d'Hebrón, Barcelona), Dr María Esteve Comas (Hospital Mútua de Terrassa, Barcelona), Dr Montserrat Rivero (Hospital Marqués de Valdecilla, Santander), Dr Luis Menchén (Hospital General Universitario Gregorio Marañón, Madrid), Dr Javier P Gisbert and Dr María Chaparro (Hospital de la Princesa, Madrid), Dr José Luis Mendoza (Hospital Clínico San Carlos, Madrid), Dr Olga Merino (Hospital de Cruces, Bilbao) and Dr Jose Luis Cabriada and Dr Iago Rodríguez (Hospital de Galdakao, Bilbao). They are also grateful to the patients for their participation. Editorial assistance during manuscript preparation was provided by Content Ed Net (Madrid, Spain) and funded by Merck Sharp and Dohme, Spain.

Conflict of interests

A.G. has served as a speaker, consultant and advisory board member for or has received research funding from Merck Sharp and Dohme, AbbVie, Hospira, Takeda, Janssen, Kern, Ferring, FaesFarma, ShirePharmaceuticals and Dr Falk Pharma. M.R. has served as a speaker, consultant and advisory board member for Merck Sharp and Dohme, AbbVie and Janssen. V.G.S. has served as a speaker, consultant and advisory board member for or has received research funding from MSD, AbbVie, Hospira, Pfizer, Kern Pharma, Biogen, Takeda, Faes Farma, Shire Pharmaceuticals, Dr Falk Pharma and Otsuka Pharmaceutical. J.B. has served as a speaker and consultant for MSD, AbbVie, Hospira and Janssen. M.B.A. has served as a speaker, consultant and advisory board member for or has received research funding from Merck Sharp and Dohme, AbbVie, Hospira, Takeda, Janssen, Kern, Ferring, Faes Farma, Shire Pharmaceuticals, Dr Falk Pharma, Chiesi, Gebro Pharma, Otsuka Pharmaceuticals and Tillotts Pharma. E.D. has served as a speaker, consultant and

advisory board member for or has received research funding from Merck Sharp and Dohme, AbbVie, Pfizer, Takeda, Janssen, Otsuka Pharmaceuticals, Grifols, Shield Therapeutics and Tillotts Pharma.

References

1. Hovde Ø, Moum BA. Epidemiology and clinical course of Crohn's disease: results from observational studies. *World J Gastroenterol* 2012;**18**:1723–31.
2. Baumgart DC, Sandborn WJ. Crohn's disease. *Lancet* 2012;**380**: 1590–605.
3. Gomollón F, Dignass A, Annesse V et al. 3rd European Evidence-based Consensus on the Diagnosis and Management of Crohn's Disease 2016: Part 1: diagnosis and medical management. *J Crohns Colitis* 2017;**11**:3–25.
4. Larson DW, Pemberton JH. Current concepts and controversies in surgery for IBD. *Gastroenterology* 2004;**126**:1611–9.
5. Ramadas AV, Gunesh S, Thomas GA et al. Natural history of Crohn's disease in a population-based cohort from Cardiff (1986–2003): a study of changes in medical treatment and surgical resection rates. *Gut* 2010;**59**:1200–6.
6. Rungoe C, Langholz E, Andersson M et al. Changes in medical treatment and surgery rates in inflammatory bowel disease: a nationwide cohort study 1979–2011. *Gut* 2014;**63**:1607–16.
7. Cosnes J, Gower-Rousseau C, Seksik P et al. Epidemiology and natural history of inflammatory bowel diseases. *Gastroenterology* 2011;**140**:1785–94.
8. de Buck van Overstraeten A, Eshuis EJ, Vermeire S et al. Short- and medium-term outcomes following primary ileocaecal resection for Crohn's disease in two specialist centres. *Br J Surg* 2017;**104**:1713–22.
9. Gionchetti P, Dignass A, Danese S et al. 3rd European Evidence-based Consensus on the Diagnosis and Management of Crohn's Disease 2016: Part 2: Surgical Management and Special Situations. *ECCOJC* 2017;**11**:135–49.
10. Domenech E, Garcia V, Iborra M et al. Incidence and management of recurrence in patients with Crohn's disease who have undergone intestinal resection: the PRACTICROHN study. *Inflamm Bowel Dis* 2017;**23**:1840–6.
11. Margagnoni G, Aratari A, Mangone M et al. Natural history of ileo-caecal Crohn's disease after surgical resection: a long term study. *Minerva Gastroenterol Dietol* 2011;**57**:335–44.
12. Kirchhoff P, Clavien PA, Hahnloser D. Complications in colorectal surgery: risk factors and preventive strategies. *Patient Saf Surg* 2010;**4**:5.
13. Silverberg MS, Satsangi J, Ahmad T et al. Toward an integrated clinical, molecular and serological classification of inflammatory bowel disease: report of a Working Party of the 2005 Montreal World Congress of Gastroenterology. *Can J Gastroenterol* 2005;**19** (Suppl A):5A–36A.
14. Latchis KS, Rao CS, Colcock BP. The complications of enterocolitis. *Am J Surg* 1971;**121**:418–25.
15. Lipska MA, Bissett IP, Parry BR et al. Anastomotic leakage after lower gastrointestinal anastomosis: men are at a higher risk. *ANZ J Surg* 2006;**76**:579–85.
16. Waterland P, Athanasiou T, Patel H. Post-operative abdominal complications in Crohn's disease in the biological era: systematic review and meta-analysis. *WJGS* 2016;**8**: 274–83.
17. Singh S, Al-Darmaki A, Frolkis AD et al. Postoperative mortality among patients with inflammatory bowel diseases: a systematic review and meta-analysis of population-based studies. *Gastroenterology* 2015;**149**:928–37.

18. Heimann TM, Greenstein AJ, Mechanic L et al. Early complications following surgical treatment for Crohn's disease. *Ann Surg* 1985;**201**:494–8.
19. Jacobson S. Early postoperative complications in patients with Crohn's disease given and not given preoperative total parenteral nutrition. *Scand J Gastroenterol* 2012;**47**:170–7.
20. Rosenfeld G, Qian H, Bressler B. The risks of post-operative complications following pre-operative infliximab therapy for Crohn's disease in patients undergoing abdominal surgery: a systematic review and meta-analysis. *J Crohns Colitis* 2013;**7**: 868–77.
21. Zhu W, Guo Z, Zuo L et al. CONSORT: different end-points of preoperative nutrition and outcome of bowel resection of Crohn disease: a randomized clinical trial. *Medicine (Baltimore)* 2015;**94**:e1175.
22. Jan S, Slap G, Dai D et al. Variation in surgical outcomes for adolescents and young adults with inflammatory bowel disease. *Pediatrics* 2013;**131**:S81–9.
23. Chowdhury MM, Dagash H, Pierro A. A systematic review of the impact of volume of surgery and specialization on patient outcome. *Br J Surg* 2007;**94**:145–61.
24. Billioud V, Ford AC, Tedesco ED et al. Preoperative use of anti-TNF therapy and postoperative complications in inflammatory bowel diseases: a meta-analysis. *J Crohns Colitis* 2013;**7**:853–67.
25. Kopylov U, Ben-Horin S, Zmora O et al. Anti-tumor necrosis factor and postoperative complications in Crohn's disease: systematic review and meta-analysis. *Inflamm Bowel Dis* 2012;**18**:2404–13.
26. Yang ZP, Hong L, Wu Q et al. Preoperative infliximab use and postoperative complications in Crohn's disease: a systematic review and meta-analysis. *Int J Surg* 2014;**12**:224–30.
27. Canedo J, Lee SH, Pinto R et al. Surgical resection in Crohn's disease: is immunosuppressive medication associated with higher postoperative infection rates? *Colorectal Dis* 2011;**13**:1294–8.
28. Kotze PG, Saab MP, Saab B et al. Tumor necrosis factor alpha inhibitors did not influence postoperative morbidity after elective surgical resections in Crohn's disease. *Dig Dis Sci* 2017;**62**:456–64.
29. Colombel JF, Loftus EV Jr, Tremaine WJ et al. Early postoperative complications are not increased in patients with Crohn's disease treated perioperatively with infliximab or immunosuppressive therapy. *Am J Gastroenterology* 2004;**99**:878–83.
30. Lightner AL, Tse CS, Potter DD Jr et al. Postoperative outcomes in vedolizumab-treated pediatric patients undergoing abdominal operations for inflammatory bowel disease. *J Pediatr Surg* 2018;**53**:1706–9.
31. Aberra FN, Lewis JD, Hass D et al. Corticosteroids and immunomodulators: postoperative infectious complication risk in inflammatory bowel disease patients. *Gastroenterology* 2003;**125**:320–7.
32. Fumery M, Seksik P, Auzolle C et al. Postoperative complications after ileocecal resection in Crohn's disease: a prospective study from the REMIND group. *Am J Gastroenterol* 2017;**112**:337–45.
33. Dasari BV, McKay D, Gardiner K. Laparoscopic versus open surgery for small bowel Crohn's disease. *Cochrane Database Syst Rev* 2011:CD006956.
34. Eshuis EJ, Slors JF, Stokkers PC et al. Long-term outcomes following laparoscopically assisted versus open ileocolic resection for Crohn's disease. *Br J Surg* 2010;**97**:563–8.
35. Stocchi L, Milsom JW, Fazio VW. Long-term outcomes of laparoscopic versus open ileocolic resection for Crohn's disease: follow-up of a prospective randomized trial. *Surgery* 2008;**144**: 622–8.
36. He X, Chen Z, Huang J et al. Stapled side-to-side anastomosis might be better than handsewn end-to-end anastomosis in ileocolic resection for Crohn's disease: a meta-analysis. *Dig Dis Sci* 2014;**59**:1544–51.
37. Frolkis A, Kaplan GG, Patel AB et al. Postoperative complications and emergent readmission in children and adults with inflammatory bowel disease who undergo intestinal resection: a population-based study. *Inflamm Bowel Dis* 2014;**20**: 1316–23.
38. Alves A, Panis Y, Bouhnik Y et al. Risk factors for intra-abdominal septic complications after a first ileocecal resection for Crohn's disease: a multivariate analysis in 161 consecutive patients. *Dis Colon Rectum* 2007;**50**:331–6.
39. Yamamoto T, Allan RN, Keighley MR. Risk factors for intra-abdominal sepsis after surgery in Crohn's disease. *Dis Colon Rectum* 2000;**43**:1141–5.
40. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg* 2004;**240**: 205–13.