Received: 8 August 2023 | Revised: 25 January 2024 | Accepted: 8 March 2024

DOI: 10.1111/codi.17056

ORIGINAL ARTICLE

Short-term outcomes of surgical treatment for primary ileocaecal Crohn's disease: Results of the Crohn's(urg) study, a multicentre, retrospective, comparative analysis between inflammatory and complicated phenotypes

Nicolas Avellaneda[1,2] | Gianluca Pellino[3,4] | Annalisa Maroli[5,6] | Anders Tottrup[1] | Gabriele Bislenghi[7] | Jan Colpaert[7] | Andre D'Hoore[7] | Michele Carvello[5,6] | Lorenzo Giorgi[5] | Patrizia Juachon[5] | Sanne Harsløf[1] | Anthony de Buck Van Overstraeten[8] | Pablo A. Olivera[9,10,11] | Javier Gomez[8] | Stefan D. Holubar[12] | Eddy Lincango Naranjo[12] | Scott R. Steele[12] | Amit Merchea[13] | Andrew Shaker[13] | Marc Marti Gallostra[4] | Miquel Kraft[4] | Paulo Gustavo Kotze[14] | Beatriz Yuki Maruyama[14] | Steven D. Wexner[15] | Zoe Garoufalia[15] | Zhihui Chen[16] | Dieter Hahnloser[17] | Djana Rrupa[17] | Christianne Buskens[18] | Anouck Haanappel[18] | Janindra Warusavitarne[19] | Katherine J. Williams[19] | Peter Christensen[1] | Albert Wolthuis[7] | Analia Potolicchio[20] | Antonino Spinelli[5,6]

Correspondence
Nicolas Avellaneda, General Surgery Department, CEMIC, Callao Av. 1620, Buenos Aires, Capital Federal, Argentina.
Email: n.avellaneda86@gmail.com

Abstract

Aim: Recent evidence challenges the current standard of offering surgery to patients with ileocaecal Crohn's disease (CD) only when they present complications of the disease. The aim of this study was to compare short-term results of patients who underwent primary ileocaecal resection for either inflammatory (luminal disease, earlier in the disease course) or complicated phenotypes, hypothesizing that the latter would be associated with worse postoperative outcomes.

Method: A retrospective, multicentre comparative analysis was performed including patients operated on for primary ileocaecal CD at 12 referral centres. Patients were divided into two groups according to indication of surgery for inflammatory (ICD) or complicated (CCD) phenotype. Short-term results were compared.

Results: A total of 2013 patients were included, with 291 (14.5%) in the ICD group. No differences were found between the groups in time from diagnosis to surgery. CCD patients had higher rates of low body mass index, anaemia (40.9% vs. 27%, $p < 0.001$) and low albumin (11.3% vs. 2.6%, $p < 0.001$). CCD patients had longer operations, lower rates of laparoscopic approach (84.3% vs. 93.1%, $p = 0.001$) and higher conversion rates (9.3%

For affiliations refer to page 1425.

vs. 1.9%, $p < 0.001$). CCD patients had a longer hospital stay and higher postoperative complication rates (26.1% vs. 21.3%, $p = 0.083$). Anastomotic leakage and reoperations were also more frequent in this group. More patients in the CCD group required an extended bowel resection (14.1% vs. 8.3%, p: 0.017). In multivariate analysis, CCD was associated with prolonged surgery (OR 3.44, $p = 0.001$) and the requirement for multiple intraoperative procedures (OR 8.39, $p = 0.030$).

Conclusion: Indication for surgery in patients who present with an inflammatory phenotype of CD was associated with better outcomes compared with patients operated on for complications of the disease. There was no difference between groups in time from diagnosis to surgery.

KEYWORDS
Crohn, early, inflammatory, surgery, uncomplicated

INTRODUCTION

A significant proportion of patients diagnosed with Crohn's disease (CD) have limited active disease in the terminal ileum [1]. For patients with inflammatory disease behaviour (without structural bowel damage such as fibrotic strictures or fistulas, namely category B1 of the Montreal Classification for CD), biological agents comprise the standard initial escalating treatment after failure of conventional therapy. Surgery is mainly reserved for patients with complicated disease (stricture/fistulas/abscess) or those refractory to optimized medical therapy [2].

Unfavourable postoperative outcomes have been reported when surgery is delayed and performed for CD complications [3, 4]. Recently, the LIR!C group presented evidence suggesting that surgery could be a reasonable alternative to biologicals in patients with a limited (<40 cm) inflammatory phenotype at the terminal ileum in terms of 5-year recurrence rate, quality of life and costs to the healthcare system [5–7]. Furthermore, there is ongoing research looking at the short- and long-term outcomes after ileocaecal resection for purely luminal disease [8, 9].

Increasingly, evidence is being published calling for reconsideration of the timing of surgery in patients with CD limited to the ileocaecal region [10, 11]. Authors highlight the fact that the current indication of waiting for structural damage also implies that patients have additional CD-related complications (e.g. malnutrition) and might end up facing surgery in a suboptimal condition, with a negative impact on surgical outcomes.

Even though earlier surgery is emerging as an alternative to medical therapy, there is no international consensus on what *early* is, with some authors suggesting the use of timing from diagnosis to surgery to define the character of surgery [12], while others include a definition based on exposure to biological drugs [5]. A study from Denmark demonstrated that ileocaecal resection can be considered as a first-line therapy [13], challenging the current paradigm of leaving surgery as a last resort. Hence, literature assessing surgical outcomes earlier in the disease course (prior to complications) is scarce.

What does this paper add to the literature?

After the LIR!C trial, the concept of early surgery for ileocaecal Crohn's disease (CD) has gained popularity. This paper provides a unique insight into this matter by providing a comparative analysis between a large cohort of (early) uncomplicated and complicated ileocaecal CD patients from worldwide tertiary referral centres.

This study aimed to compare short-term results of patients who underwent primary ileocaecal resection for either inflammatory (luminal disease, earlier in the disease course) or complicated CD phenotypes, hypothesizing that the latter would be associated with worse postoperative outcomes.

METHOD

This paper was written following STROBE guidelines for the reporting of scientific publications.

Study type

Crohn's(urg) is a retrospective, multicentre, observational study comparing short-term outcomes of surgical treatment of patients with inflammatory ileocaecal CD (inflammatory Crohn's disease, ICD) and patients undergoing surgery for complicated disease, with either fibrotic strictures or fistulas (complicated Crohn's disease, CCD).

The inflammatory phenotype was defined according to Maruyama et al. [14], namely resection performed for predominantly inflammatory disease, without previous resections (not related to postoperative recurrence, with no fibrotic stenosis or internal or external fistulas or blocked perforation).

Further, an algorithm for the management of patients with the inflammatory phenotype in those centres that offer surgery as an alternative to biological drugs as second-line treatment has already been published [9]. In this previous work specific clinical and radiological features of the inflammatory phenotype were established to differentiate these patients from those presenting with structural bowel damage.

Study design and setting

The present study was designed by four colorectal surgeons working in inflammatory bowel disease (IBD) tertiary referral centres located in Europe, with the assistance of a group of specialists in gastroenterology and statistics.

International centres were invited to participate in the study, all IBD tertiary referral and academic hospitals, which were the main criteria for selection. All participating hospitals have a multidisciplinary team (MDT) composed of surgeons, gastroenterologists, radiologists and other specialists related to the treatment of IBD patients. Twelve centres agreed to participate, located in Canada (one centre), the United States (three centres), Brazil (one centre), Europe (six centres) and China (one centre).

The number of patients included per centre can be found in Appendix 1.

Inclusion criteria

Patients operated on for primary isolated ileocaecal CD (the last 50 cm of the terminal ileum and caecum), either for the predominantly inflammatory phenotype or for complications of the disease (stricturing or fistulizing pattern), between January 2012 and December 2021 were considered eligible to participate in this study.

Patients with previous abdominal procedures for CD, and patients who had activity of the disease in other intestinal segments other than the ileocaecal region at the time of surgery, were excluded from the study (Figure 1).

Data collection and management

A retrospective review of eligible patients' clinical registries was performed by each centre. The information related to patients' clinical characteristics, operative procedures and short-/long-term outcomes was collected in an electronic database (RedCap, Research Electronic Data Capture, Vanderbilt University®) specifically designed for this purpose. Variables were chosen based on relevance to the study's objective and were further assessed by two IBD gastroenterologists and an expert in biostatistics. All eligible patients operated on consecutively from each centre were included in the database.

Variables analysed for this study

Preoperative variables

The analysed preoperative variables were gender, age, Charlson comorbidity score, smoking status (at the time of surgery), body mass index (BMI), preoperative anaemia, preoperative albumin levels, weight loss (defined as having lost at least 10% of normal weight within the last 6 months) and previous abdominal procedures.

Disease-related variables

The analysed disease-related variables were time from diagnosis of CD to surgery, Montreal classification [15], previous exposure to biological agents, time from the start of the first biological to surgery, perioperative exposure to biologicals (within 12 weeks of surgery), concomitant perianal disease, chronic exposure to corticosteroids (defined as having received more than 20 mg/day of prednisolone or equivalent for up to 6 weeks before surgery) [16] and requirement for preoperative nutritional optimization before the procedure (defined as patients who needed to be hospitalized to receive enteral or parenteral nutrition before undergoing surgery). The American Society of Anesthesiologists (ASA) score was also considered.

Intraoperative variables

The following intraoperative variables were analysed: operative time and requirement for prolonged surgery (using an arbitrary cut-off value of >150 min), character of surgery, minimally invasive (MIS) approach and the need for conversion, type of primary surgery (ileocaecal resection or right hemicolectomy), intraoperative complications (stratified according to the CLASSIC classification into minor or major depending on whether the event required a deviation from the ideal operative course or not) [17], associated procedures (defined as an additional CD-related procedure other than the resection of the compromised bowel at the ileocaecal region) and anastomosis type (manual or stapled).

Postoperative variables

The analysed postoperative variables were length of hospital stay and requirement for prolonged hospitalization (using an arbitrary cut-off value of >7 days), requirement for admission to the intensive care unit (ICU) after surgery, postoperative complications (defined as minor for Clavien–Dindo I or II or major for Clavien–Dindo >II) [18], anastomotic leak (defined as per the International Study Group of Rectal Cancer, and stratified into minor or major leak depending on the need or not for reoperation) [19], 30-day readmission and reoperation rate and 30-day mortality. The total length of the resected bowel was recorded according to the histopathology report.

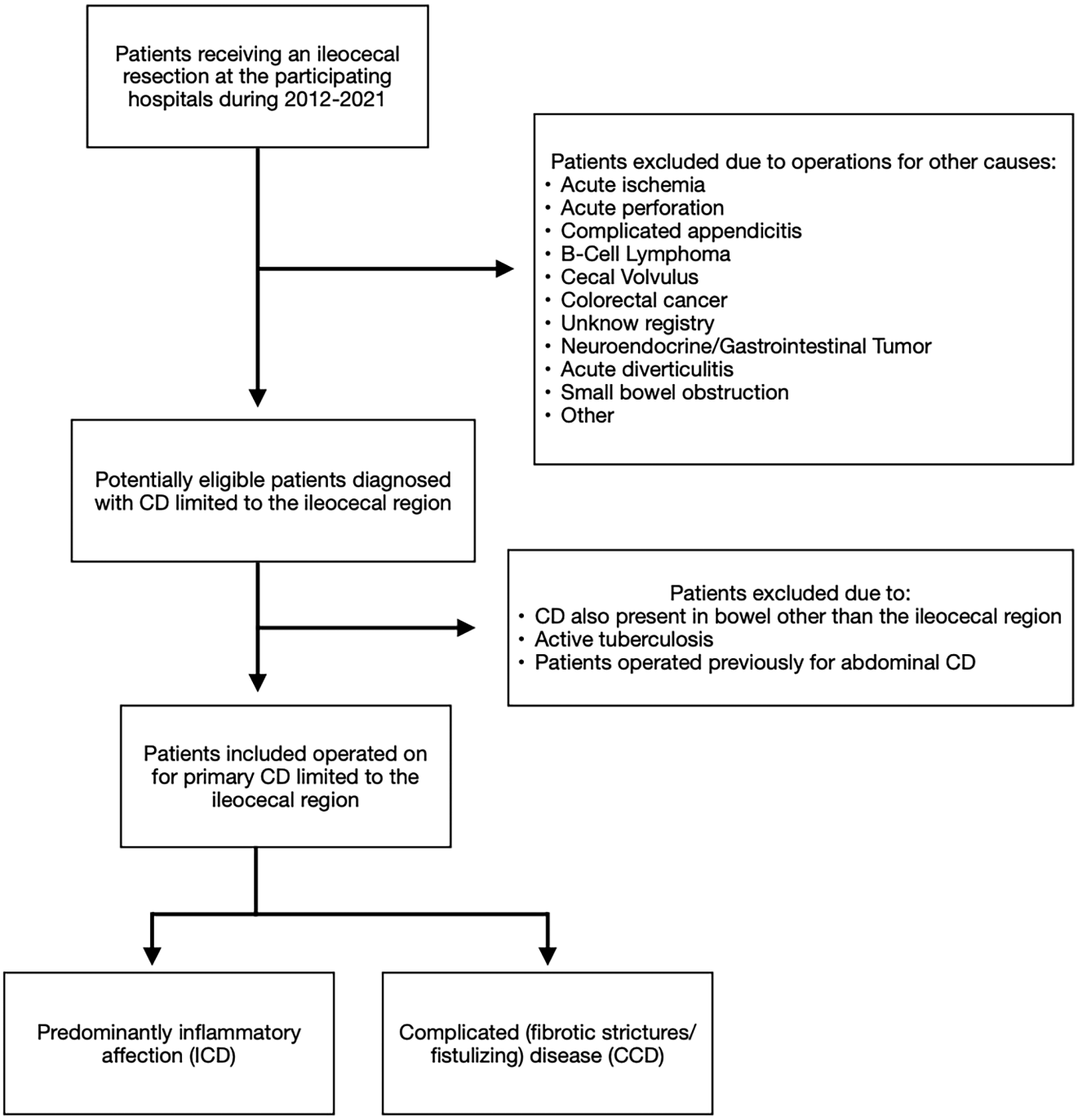

FIGURE 1 Flowchart showing the patient selection process.

Statistical analysis

Categorical data are described as percentages. Descriptive data were tested for normal distribution by the Kolmogorov–Smirnov test. For parametric data, mean and standard deviation are reported. For nonparametric data, median and interquartile range are presented. The chi-square test and Fisher's exact test (when appropriate) were used for the comparison of categorical variables, and Student's *t*-test or the Mann–Whitney *U*-test for quantitative variables. Odds ratio (OR) with 95% CI was calculated for all intraoperative and postoperative variables.

Logistic regression was used for multivariable analysis including all the preoperative variables considered clinically relevant by the authors and using different postoperative outcomes as dependent variables. A p-value of <0.05 was considered significant. The software Stata (statistical data analysis) was used for the analyses (v17, StataCorp, College Station, Texas, USA).

Ethical considerations

The study was registered in the Central Denmark Region's register of research projects (journal no. 1–16–02-200-22) and complies with the General Data Protection Regulation (EU GDPR) within the European Union. Data-sharing agreements were produced and signed between each participating centre and Aarhus University Hospital, Denmark (the host of the study). The study was approved by institutional review boards from all included centres according to good clinical practice standards as well as the local and national regulations of each centre's country.

RESULTS

Preoperative variables

Overall, 2013 patients were included, 1031 (51.2%) were female and the mean age was 37.56 years (SD 15.24 years). One thousand and twenty-two patients (85.5%) underwent surgery for CCD and 291 (14.5%) for ICD. Most ICD patients were operated on at four centres (based in Denmark, Italy the Netherlands and Brazil). There were no statistical differences between groups for age, sex and smoking status at the time of surgery, nor in comorbidities stratified by the Charlson score. The preoperative and disease-related characteristics of patients are summarized in Table 1.

In the CCD group, more patients had a low BMI (<20 kg/m^2) (19.4% vs. 14.4%, $p=0.045$), and there were more patients with preoperative anaemia in this group than in the ICD group (40.9% vs. 27%, $p<0.001$). In the CCD group, albumin levels were lower (3.8 vs. 3.9 g/dL, $p=0.033$) and more patients had albumin below 3 g/dL at the time of surgery (11.3% vs. 2.6%, $p<0.001$). Additionally, patients in the CCD group had significantly higher requirements for preoperative nutritional optimization (16.7% vs. 6.7%, $p<0.001$).

Disease-related variables

No significant differences were identified between groups regarding timing from diagnosis of CD to surgery, with the percentage of patients operated on more than 5 years after diagnosis being 49.8% in the CCD group and 42% in the ICD group. In the CCD group, 834 (48.4%) patients had a stricturing phenotype and 882 (51.22) had a penetrating phenotype. The CCD group had more patients with previous perianal CD (21.67% vs. 11.46%, $p<0.001$) and a significantly higher proportion of chronic exposure to steroids at the time of surgery (19.16% vs. 13.94%, $p=0.035$).

No differences were observed regarding perioperative exposure to biological drugs before surgery. Similarly, there was no difference in the number of different biologicals to which each patient was exposed, nor in the time since starting biological drugs to surgery. Both groups were similarly exposed to these drugs in the perioperative period (within 12 weeks from surgery).

Operative variables

Operative characteristics of patients are summarized in Table 2. Operative time was significantly longer in the CCD group, with 50.8% of patients requiring more than 150 min compared with only 20.4% in the ICD group ($p<0.001$, OR 4.03).

The number of patients operated on using MIS was significantly higher in the ICD group (93.1% vs. 84.3%, $p<0.001$, OR 2.51) and CCD patients had a higher rate of conversion to open surgery (9.3% vs. 1.9%, $p<0.001$, OR 5.44). Right hemicolectomy, rather than ileocaecal resection, was required more often in the CCD group compared with ICD (20.5% vs. 13.4%, $p=0.005$, OR 1.66).

Patients in the CCD group had higher requirements for additional CD-related surgical procedures (24.61% vs. 3.81%, $p<0.001$, OR 8.25). The most frequent associated procedures in this group were sigmoidectomy (26%), strictureplasty (20%) and enterectomy (19%), respectively.

The CCD group presented a higher incidence of intraoperative complications (2.67% vs. 0.35%, $p=0.017$, OR: 7.78). Further, as per the CLASSIC classification, in the CCD group 9.3% of complications were major whereas all complications in the ICD group were minor. A higher number of patients required a stoma in the CCD group (11.4% vs. 5.9%, $p<0.001$, OR: 0.40).

Postoperative results

Postoperative outcomes are shown in Table 3. Length of stay was longer for patients in the CCD group (6.8 vs. 4.9 days, $p=0.0003$), which had a higher incidence of prolonged hospitalization (more than 7 days) (23.9% vs. 12.2%, $p<0.001$, OR 2.27). Further, this group also had more requirement for postoperative stay in the ICU (4.9% vs. 2.9%, $p=0.031$, OR 2.44).

The rate of postoperative complications in the CCD group was higher than in the ICD group (26.1% vs. 21.3%, $p=0.083$, OR 1.30). When stratified according to severity, the number of patients with major postoperative complications was also higher in the CCD group (33% vs. 21.3%, $p=0.062$, OR 1.83). The most frequent complications were postoperative ileus (32%), abdominal abscess (14%) and gastrointestinal bleeding (11%).

The anastomotic leak rate for the whole cohort was 4.6%, and this event was more frequent in the CCD group (5% vs. 2.2%, $p=0.044$, OR 2.31). Furthermore, most leaks were classified as major in the CCD group, whereas in the ICD group half of the leaks were classified as minor.

Reoperation rates in the perioperative period were higher in the CCD group (6.2% vs. 2.8%, $p=0.018$, OR 2.35). No differences were observed between groups regarding readmission. The 30-day

TABLE 1 Preoperative variables.

Variable	All patients (*N* = 2013; 100%)	ICD (*N* = 291; 14.46%)	CCD (*N* = 1722; 85.54%)	*p*-value	Missing
Gender (Female)	1031 (51.22%)	167 (57.39%)	864 (50.17%)	0.023	0
Age (years), mean (SD)	37.56 (15.24)	39 (18.83)	37.31 (14.94)	0.081	2
Smoking	452 (22.68)	70 (24.39)	382 (22.39)	0.454	17
BMI (kg/m^2), mean (SD)	23.67 (4.95)	24.12 (4.63)	23.58 (5.01)	0.108	343
Low BMI (<20 kg/m^2)	376 (18.67%)	42 (14.43%)	334 (19.40%)	0.045	
Charlson comorbidity score					0
<2	1682 (83.56%)	233 (80.07%)	1449 (84.15%)	0.083	
2–3	253 (12.57%)	41 (14.09%)	212 (12.31%)	0.397	
>3	78 (3.87%)	17 (5.84%)	61 (3.54%)	0.060	
Anaemia	775 (38.91%)	78 (27%)	697 (40.93%)	<0.001	21
Albumin level (g/dL), mean (SD)	3.82 (0.59)	3.90 (0.46)	3.80 (0.62)	0.033	676
Low albumin (<3 g/dL)	131 (9.80%)	6 (2.63%)	125 (11.27%)	<0.001	
Previous surgery	454 (22.69%)	53 (18.21%)	401 (23.45%)	0.049	12
Time from diagnosis to surgery (months), Intrecuartile Range (IQR)				0.083	31
Less than 2 years	621 (31.33)	105 (36.46)	516 (30.46)		
2–5 years	397 (20.03)	62 (21.53)	335 (19.78)		
More than 5 years	964 (48.64)	121 (42.01)	843 (49.76)		
Urgent surgical procedure	319 (15.90%)	17 (5.86%)	302 (17.60%)	<0.001	7
Montreal classification A				0.001	29
1	218 (10.99%)	34 (11.85%)	184 (10.84%)		
2	1346 (67.84%)	170 (59.23%)	1176 (69.30%)		
3	420 (21.17%)	83 (28.92%)	337 (19.86%)		
Montreal classification l B					6
1	291 (14.46%)	291 (100%)	0		
2	834 (41.43%)	0	834 (48.43%)		
3	882 (43.82%)	0	882 (51.22%)		
Perianal disease	402 (20.19%)	33 (11.46%)	369 (21.67%)	<0.001	22
Chronic use of steroids (at the time of surgery)	365 (18.41%)	40 (13.94%)	325 (19.16%)	0.035	30
Previous exposure to biological drugs	1029 (51.50%)	152 (52.60%)	877 (51.32%)	0.688	15
Number of different biologicals received before surgery				0.419	18
1	659 (65.28%)	93 (63.27%)	566 (65.51%)		
2	235 (23.24%)	39 (26.53%)	196 (22.69%)		
3	94 (9.30%)	14 (9.52%)	80 (9.26%)		
4	23 (2.27%)	1 (0.68%)	22 (2.55%)		
Time with biologicals before surgery (months), median (IQR)	37.32 (47)	34.47 (42.5)	37.86 (49)	0.275	1124
Exposure to biologicals within 12 weeks before surgery	693 (70.36%)	102 (68.92%)	591 (70.61%)	0.678	44
Perioperative biological used				0.325	1
Infliximab	239 (34.54%)	42 (41.58%)	197 (33.33%)		
Adalimumab	266 (38.44%)	37 (36.63%)	229 (38.75%)		
Vedolizumab	82 (11.85%)	8 (7.92%)	74 (12.52%)		
Ustekinumab	77 (11.13%)	12 (11.88%)	65 (11%)		
Other	28 (4.05%)	2 (1.98%)	26 (4.40%)		
Nutritional optimization before surgery	291 (15.37%)	17 (6.69%)	274 (16.72%)	<0.001	120

TABLE 1 (Continued)

Variable	All patients (*N* = 2013; 100%)	ICD (*N* = 291; 14.46%)	CCD (*N* = 1722; 85.54%)	*p*-value	Missing
ASA Grade				<0.001	8
I	275 (13.72%)	65 (22.49%)	210 (12.24%)		
II	1264 (63.04%)	196 (67.82%)	1068 (62.24%)		
III	460 (22.94%)	26 (9%)	434 (25.29%)		
IV	6 (0.3%)	2 (0.69%)	4 (0.23%)		

Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index; CCD, complicated Crohn's disease; ICD, inflammatory Crohn's disease; IQR, interquartile range.

TABLE 2 Operative results.

Variable	All patients (*N* = 2013; 100%)	ICD (*N* = 291; 14.46%)	CCD (*N* = 1722; 85.54%)	*p*-value	OR (95% CI)	Missing
Operating time (min), mean (SD)	156 (58.56)	130 (41.21)	161 (60.22)	<0.001		741
Prolonged surgery (>150 min)	577 (45.36%)	46 (20.35%)	531 (50.76%)	<0.001	4.03 (2.8–5.8)	
Surgical approach				<0.001	2.51 (1.6–4)	1
Open	289 (14.36%)	20 (6.87%)	269 (15.63%)			
Minimally invasive	1723 (85.64%)	271 (93.13%)	1452 (84.37%)			
Conversion rate	140 (8.14%)	5 (1.85%)	135 (9.31%)	<0.001	5.44 (2.2–13.5)	3
Type of surgery				0.005	1.66 (1.2–2.4)	3
Ileocaecal resection	1619 (80.55%)	252 (86.60%)	1367 (79.52%)			
Right colectomy	391 (19.45%)	39 (13.40%)	352 (20.48%)			
Requirement for associated procedure	434 (21.61%)	11 (3.81%)	423 (24.61%)	<0.001	8.25 (4.4–15.4)	5
Intraoperative complications	44 (2.32%)	1 (0.35%)	43 (2.67%)	0.017	7.78 (1.1–56.9)	116
CLASSIC minor	40 (90.91%)	1 (100%)	39 (90.70%)			
CLASSIC major	4 (9.09%)	0	4 (9.30%)			
Primary anastomosis without stoma	1757 (87.54%)	272 (94.12%)	1485 (86.44%)	<0.001	0.40 (0.2–0.7)	6
Type of suture				0.139	0.70 (0.4–1.1)	6
Hand-sewn	187 (9.87%)	21 (7.45%)	166 (10.30%)			
Stapled	1707 (90.13%)	261 (92.55%)	1446 (89.70%)			

Abbreviations: CCD, complicated Crohn's disease; ICD, inflammatory Crohn's disease.

mortality rate for the whole cohort was 0.1%, with no difference between the groups.

The median length of the resected bowel was higher in the CCD group (28 vs. 23 cm, $p = 0.0001$). More patients in the ICD group required a short resection, defined as less than 20 cm (39.2 vs. 25.6 cm, $p < 0.001$, OR 0.53). The CCD group also had more extended bowel resections, defined as more than 50 cm (14.1% vs. 8.3%, $p = 0.017$, OR 1.80). Figure 2 summarizes the postoperative outcomes between groups.

Multivariate analysis

Surgery for complications of CD was an independent predictor for prolonged surgery (OR 3.44, $p = 0.001$) and the requirement for multiple intraoperative procedures (OR 8.39, $p = 0.030$). Additionally, several factors associated with CCD in the univariate analysis (such as anaemia, penetrating phenotype, weight loss, low albumin and requirement for preoperative nutritional optimization) were independent predictors of worse postoperative outcomes. Table 4 summarizes results of the multivariate analysis.

Sensitivity analysis

Since there was a significant heterogeneity in the number of patients included by each centre a separate analysis was performed excluding data from those centres which recruited fewer than 100 patients for the study. In this second analysis, the main results were similar, including higher requirements for prolonged

TABLE 3 Postoperative outcomes.

Variable	All patients (*N* = 2013; 100%)	ICD (*N* = 291; 14.46%)	CCD (*N* = 1722; 85.54%)	*p*-value	OR (95% CI)	Missing
Length of hospitalization (days), median (IQR)	6.53 (4)	4.91 (3)	6.81 (3)	0.0003		14
Prolonged hospitalization (>7 days)	444 (22.21%)	35 (12.15%)	409 (23.90%)	<0.001	2.27 (1.56–3.30)	
ICU after surgery	88 (4.54%)	6 (2.09%)	82 (4.96%)	0.031	2.44 (1.1–5.7)	73
Postoperative complications	510 (25.40%)	62 (21.31%)	448 (26.09%)	0.083	1.30 (0.9–1.8)	5
Minor complications (Clavien–Dindo < IIIa)	346 (68.24%)	48 (78.69%)	298 (66.82%)	0.062	0.54 (0.3–1.04)	3
Major complications (Clavien–Dindo > IIIa)	161 (31.76%)	13 (21.31%)	148 (33.18%)	0.062	1.83 (0.96–3.5)	3
Anastomotic leakage	84 (4.59%)	6 (2.22%)	78 (5%)	0.044	2.31 (1–5.4)	69
Minor fistula	26 (31.33%)	3 (50%)	23 (29.87%)			
Major fistula	77 (68.67%)	3 (50%)	54 (70.13%)			
Rehospitalization	140 (6.96%)	19 (6.53%)	121 (7.03%)	0.754	1.08 (0.7–1.8)	2
Reoperation	115 (5.72%)	8 (2.75%)	107 (6.22%)	0.018	2.35 (1.13–4.88)	3
Mortality	2 (0.10%)	0	2 (0.12%)	0.561	N/A	2
Length of resected bowel (cm), median (IQR)	27 (20.5)	23 (17)	28 (20)	0.0001		737
Short resection (<20 cm)	359 (28.13%)	94 (39.17%)	265 (25.58%)	<0.001	0.53 (0.4–0.7)	
Extended resection (>50 cm)	166 (13.01%)	20 (8.33%)	146 (14.09%)	0.017	1.80 (1.1–2.9)	

Abbreviations: CCD, complicated Crohn's disease; ICD, inflammatory Crohn's disease; ICU, intensive care unit; IQR, interquartile range.

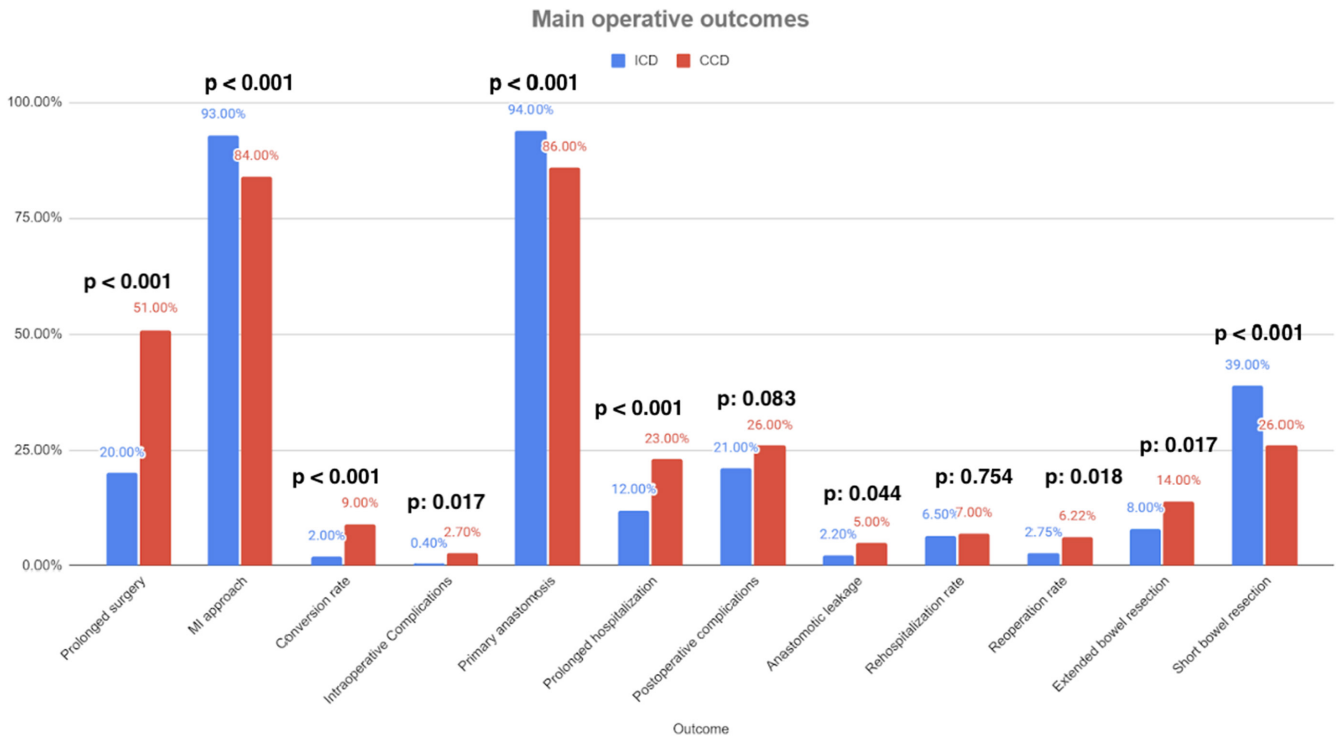

FIGURE 2 Main operative results (MI, minimally invasive).

surgery (OR 4.58, *p*:<0.001), need for conversion from MIS to conventional surgery (OR 4.45, *p*:<0.001) and higher incidence of intraoperative complications (OR 6.56, $p = 0.033$) in the CCD group. The ICD group was associated with higher rates of primary anastomosis without stoma (OR 0.36, $p < 0.001$) and short bowel resections (OR 0.52, $p < 0.001$).

TABLE 4 Multivariate analysis.

Variable	OR	Standard error	*p*-value	95% CI
Prolonged surgery				
Anaemia	1.86	0.46	0.012	1.15–3.02
Previous abdominal surgery	1.86	0.52	0.025	1.08–3.21
Complicated disease	**3.44**	**1.32**	**0.001**	**1.62–7.31**
Fistulizing phenotype	2.01	0.50	0.005	1.24–3.27
Conventional surgery				
Smoking	2.77	1.22	0.020	1.17–6.55
Weight loss	2.25	0.61	0.003	1.32–3.81
Fistulizing phenotype	4.98	2.57	0.002	1.81–13.071
Conversion to open surgery				
Fistulizing disease	4.25	1.72	<0.001	1.92–9.40
Associated surgery				
Complicated disease	**8.39**	**9.70**	**0.030**	**1.24–71.14**
Fistulizing phenotype	6.15	1.73	<0.001	3.53–10.69
Intraoperative complication				
Smoking	42.75	59.20	0.007	2.83–45.15
Primary anastomosis without stoma				
Smoking	0.51	0.17	0.049	0.26–0.99
Anaemia	0.48	0.16	0.024	0.25–0.90
Chronic steroids	0.46	0.17	0.032	0.23–0.94
Low albumin	0.37	0.17	0.035	0.15–0.93
Postoperative complications	1.50	0.39	0.124	0.90–2.50
Smoking	1.69	0.40	0.026	1.06–2.67
Charlson score>3	2.74	1.41	0.050	–7.52
ASA III/IV	1.77	0.44	0.021	1.09–2.90
Anastomotic leakage	1.60	0.93	0.421	0.51–4.98
Smoking	2.76	1.20	0.018	1.19–6.49
Rehospitalization				
Anaemia	0.43	0.18	0.042	0.19–0.97
Reoperation				
Urgent procedure	2.72	1.30	0.037	1.06–6.96
Mortality				
Urgent procedure	2.72	1.30	0.037	1.06–6.96
Extensive resection				
Smoking	2.29	0.89	0.033	1.07–4.90
Requirements of preoperative nutritional optimization	3.17	1.48	0.013	1.30–9.29
Low albumin	3.48	1.74	0.013	1.30–9.29
Short resection				
Anaemia	0.59	0.15	0.035	0.36–0.96
Weight loss	0.60	0.13	0.018	0.39–0.91
Fistulizing phenotype	0.44	0.13	0.005	0.25–0.78
Low albumin	0.23	0.15	0.025	0.64–0.83

Abbreviation: ASA, American Society of Anesthesiologists. Bold indicates the main variables of Complicated disease.

Anastomotic leakage (OR 1.86, $p=0.142$), postoperative complications (OR 1.23, $p=0.219$) and requirement for a reoperation (OR 1.93, $p=0.074$) were numerically more frequent in the CCD group, but these differences were not statistically significant.

The multivariate regression model was also repeated using these criteria, and surgery for complications of CD was still independently related to requirement for prolonged surgery (OR 3.62, $p=0.001$) and requirement for associated surgery (OR 6.34, $p=0.04$). Furthermore, we conducted an analysis to assess the effect of time from diagnosis of CD to surgery in the evaluated postoperative outcomes, dividing the cohort in two groups (those operated on within 2 years of diagnosis and those undergoing surgery after that period). When this variable was included in the multivariate regression model, timing per se was not independently related to any worse postoperative result.

DISCUSSION

The present study includes many patients operated on for ileocaecal CD and compares the outcomes of surgery between patients operated on earlier in the disease course (inflammatory phenotype) with those operated on for complicated disease. Patients who had an intervention earlier in the disease course had more favourable outcomes than those who underwent surgical procedures for complicated disease.

Patients in the CCD group had significantly higher proportions of preoperative anaemia and weight loss, as well as lower albumin levels and more requirements for preoperative nutritional optimization. Operative results favoured the group of patients operated on in an early fashion, who had fewer complications, a shorter hospital stay, higher rates of minimally invasive procedures, lower conversion rates and lower stoma rates. These results emphasize that patients who undergo surgery without CD-related complications such as malnutrition and anaemia have more favourable postoperative outcomes. A previous reasonable hypothesis for our findings is that performing earlier surgery during the disease course avoids the progression to structural bowel damage and improves the short-term outcomes for CD patients who require surgical resection.

Some other findings from this study are worth mentioning. Firstly, the fact that there were no differences between groups in the timing from diagnosis of CD to surgery. This contrasts with the idea that the definition of early surgery should be based on time from diagnosis per se, meaning that outcomes will necessarily be better the sooner after diagnosis the patient undergoes surgery, independent of the phenotype [12, 13]. A plausible explanation for this finding is that CD might have a different biological behaviour in different patients, with some being diagnosed with complications of the disease that lead to more expeditious surgery and others spending years without progression of the disease.

Secondly, exposure to biological agents before surgery was also similar between the two groups, and previous exposure to this class of medication before surgery was not associated with worse operative outcomes. This is a significant finding in the current era where there is a constant debate regarding offering surgery or biologicals as a second-line treatment after failure of conventional therapy, mainly based on the LIR!C trial [5]. This might mean that there is a need for a more dynamic concept of early surgery, where the fact that the patient did or did not receive one, two or more biological drugs does not necessarily imply that surgery will be indicated in a delayed fashion.

Perhaps the most important finding of our study is that the current international guidelines [20, 21], which suggest that surgery is only indicated when patients already present structural bowel damage, might have a negative impact on postoperative outcomes. While it may feel 'safer' to promote as many lines of medical therapy as possible prior to consideration of surgery this can result in a high cost for patients who need surgery at a later stage. As a consequence, patients might face surgery in a compromised biochemical and physical condition, with a higher risk of surgical complications and worse short-term outcomes.

The results of our study question the current accepted practice in most centres that mainly offer surgery for CCD, proven by the fact that 85% of the patients included in this cohort were operated on following this indication.

A possible transitory solution to this problem, while the international IBD community moves towards an accepted concept of what early surgery is and how it is defined, would be to present patients with short ileocaecal inflammatory CD in a MDT meeting after the diagnosis, or after they have failed one line of medical therapy. With that, physicians from different specialities, including gastroenterologists and surgeons, might be keener to identify a more adequate timing for surgery, preventing patients from suffering the adverse results shown in the present analysis. Evidence about the benefits of this strategy has been published recently [9].

One last finding of this study that is worth mentioning is the fact that patients operated on for uncomplicated disease had a significantly higher chance of avoiding a stoma. This consideration is very important, not only because the presence of a stoma can have a negative impact on the patient's quality of life, but also because closing the stoma afterward implies further possible morbidity. This should be taken into account when discussing individual patients at MDT meetings and when counselling patients on the potential treatment options.

This study has limitations that need to be disclosed. It is limited by its retrospective and multicentric nature, which might be associated with different surgical practices, especially between countries. The relative proportion of patients operated on in the ICD group compared with the CCD group is low, reflecting current practice. This, however, is a consequence of international standards that do not unequivocally advocate a 'truly' earlier indication of surgery. We chose a subjective definition for early CD, due to the already mentioned absence of an accepted consensus of what early means in CD, as well as the definition of ileocaecal disease as that affecting only the last 50 cm of the terminal ileum in these patients, which is also

subjective. We also used some arbitrary cut-off values to categorize continuous variables (i.e. to define prolonged surgery and prolonged hospitalization), and these values were defined by the study group's clinical experience rather than prior published data. Lastly, selection bias could not be excluded, since some of these hospitals only receive referrals of patients who are too sick to be treated elsewhere—this could possibly limit the extrapolation of these results to other settings.

However, this study has strengths, the main one being the size of the patient population. The study was only open to tertiary referral, highly specialized IBD centres, ensuring the quality of data as well as multidisciplinary care of patients in a supported environment. Furthermore, it provides real-life, global data, which are likely to be representative of this patient population and might have practical implications that can be more easily implemented.

CONCLUSION

Early surgery in patients who present an inflammatory phenotype of CD was associated with better outcomes when compared with patients operated on for complications of the disease who already had established bowel damage.

In an era when surgery can be seen as a last resort for patients who already have established bowel damage, these data will hopefully raise awareness that the current strategy may be associated with a high cost for patients. Even though further studies will focus on long-term differences between ICD and CCD patients, our results call for general reflection, looking for a change of practice that improves outcomes of surgery in patients that are currently being operated on later in the disease course.

AUTHOR CONTRIBUTIONS

Nicolas Avellaneda: Conceptualization; data curation; formal analysis; visualization; writing – original draft; writing – review and editing; project administration; supervision; investigation; methodology; software; validation. **Gianluca Pellino:** Conceptualization; writing – original draft; visualization; formal analysis; methodology; investigation; supervision; writing – review and editing. **Annalisa Maroli:** Conceptualization; data curation; formal analysis; visualization; writing – original draft; methodology; investigation; supervision; project administration; writing – review and editing. **Anders Tottrup:** Conceptualization; data curation; formal analysis; visualization; writing – original draft; writing – review and editing; project administration; supervision; methodology; investigation. **Gabriele Bislenghi:** Writing – review and editing; investigation; methodology; writing – original draft. **Jan Colpaert:** Writing – original draft; methodology; writing – review and editing; project administration; investigation. **Andre D'Hoore:** Conceptualization; writing – original draft; project administration; writing – review and editing. **Michele Carvello:** Conceptualization; data curation; formal analysis; visualization; writing – original draft; writing – review and editing; project administration; supervision; investigation; methodology. **Lorenzo Giorgi:** Writing – review and editing; project administration; supervision; investigation. **Patrizia Juachon:** Writing – review and editing; supervision; investigation; methodology. **Sanne Harsløf:** Conceptualization; writing – original draft; visualization; supervision; writing – review and editing. **Anthony de Buck Van Overstraeten:** Conceptualization; investigation; writing – original draft; writing – review and editing; methodology. **Pablo A. Olivera:** Methodology; supervision; writing – review and editing. **Javier Gomez:** Supervision; writing – review and editing; investigation. **Stefan D. Holubar:** Conceptualization; methodology; investigation; validation; supervision; writing – review and editing. **Eddy Lincango Naranjo:** Writing – review and editing; project administration; investigation; methodology. **Scott R. Steele:** Writing – review and editing; project administration; investigation; methodology. **Amit Merchea:** Writing – review and editing; project administration; supervision; investigation. **Andrew Shaker:** Methodology; project administration; writing – review and editing. **Marc Marti Gallostra:** Writing – review and editing; project administration; investigation; methodology. **Miquel Kraft:** Project administration; writing – review and editing; investigation; methodology. **Paulo Gustavo Kotze:** Methodology; writing – original draft; formal analysis; conceptualization; writing – review and editing; supervision; investigation; project administration. **Beatriz Yuki Maruyama:** Conceptualization; data curation; investigation; formal analysis; writing – review and editing. **Steven D. Wexner:** Writing – original draft; writing – review and editing; investigation. **Zoe Garoufalia:** Writing – review and editing; project administration; investigation; methodology. **Zhihui Chen:** Writing – review and editing; project administration; supervision; methodology. **Dieter Hahnloser:** Writing – review and editing; project administration; supervision; investigation; methodology. **Djana Rrupa:** Writing – review and editing; project administration; investigation; supervision; methodology. **Christianne Buskens:** Writing – review and editing; project administration; supervision; investigation; methodology. **Anouck Haanappel:** Methodology; investigation; supervision; writing – review and editing. **Janindra Warusavitarne:** Writing – review and editing; project administration; supervision; investigation; methodology. **Katherine J. Williams:** Conceptualization; investigation; validation; visualization; writing – original draft; writing – review and editing. **Peter Christensen:** Conceptualization; data curation; formal analysis; visualization; writing – original draft; writing – review and editing; validation; resources; investigation. **Albert Wolthuis:** Writing – review and editing; investigation. **Analia Potolicchio:** Writing – review and editing; investigation; supervision. **Antonino Spinelli:** Conceptualization; data curation; formal analysis; visualization; writing – original draft; writing – review and editing; project administration; supervision; investigation; methodology; resources.

AFFILIATIONS

[1]Department of Surgery, Aarhus University Hospital, Aarhus, Denmark
[2]General Surgery Department, CEMIC, Buenos Aires, Argentina
[3]Department of Advanced Medical and Surgical Sciences, Università Degli Studi Della Campania "Luigi Vanvitelli", Naples, Italy
[4]Colorectal Surgery, Vall d'Hebron University Hospital, Universitat Autonoma de Barcelona UAB, Barcelona, Spain

[5]Division of Colon and Rectal Surgery, IRCCS – Humanitas Research Hospital, Milan, Italy
[6]Department of Biomedical Sciences, Humanitas University, Milan, Italy
[7]Colorectal Surgery Department, Leuven University Hospital, Leuven, Belgium
[8]Colorectal Surgery Department, Sinai Health Hospital, Toronto, Ontario, Canada
[9]Inflammatory Bowel Disease Unit, Gastroenterology Section, Department of Internal Medicine, Centro de Educación Médica e Investigaciones Clínicas, Buenos Aires, Argentina
[10]Zane Cohen Centre for Digestive Diseases, Lunenfeld-Tanenbaum Research Institute, Sinai Health System, Toronto, Ontario, Canada
[11]Division of Gastroenterology, Mount Sinai Hospital, University of Toronto, Toronto, Ontario, Canada
[12]Colorectal Surgery Department, Cleveland Clinic, Cleveland, Ohio, USA
[13]Division of Colon and Rectal Surgery, Mayo Clinic, Jacksonville, Florida, USA
[14]Colorectal Surgery Unit, Pontifícia Universidade Católica Do Paraná (PUCPR), Curitiba, Brazil
[15]Ellen Leifer Shulman and Steven Shulman Digestive Disease Center, Cleveland Clinic, Weston, Florida, USA
[16]Gastrointestinal Surgery, First Affiliated Hospital, Sun Yat-Sen University, Guangzhou, China
[17]Colorectal Surgery Department, Lausanne University Hospital, Lausanne, Switzerland
[18]Colorectal Surgery Department, Amsterdam UMC, Location AMC, Amsterdam, The Netherlands
[19]Colorectal Surgery Department, St Marks Hospital, Harrow, UK
[20]Colorectal Surgery Department, Bordeaux Cancer Institute, Bordeaux, France

FUNDING INFORMATION

This study was not funded.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest while presenting this manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

COLLABORATORS

Patient recruitment: Sarah Driesch, University Hospital of Giessen and Marburg, Germany.

ORCID

Nicolas Avellaneda https://orcid.org/0000-0002-6802-7125
Gianluca Pellino https://orcid.org/0000-0002-8322-6421
Gabriele Bislenghi https://orcid.org/0000-0002-9212-9287
Jan Colpaert https://orcid.org/0000-0003-1738-2802
Sanne Harsløf https://orcid.org/0000-0002-6809-0909
Stefan D. Holubar https://orcid.org/0000-0002-2549-9042
Amit Merchea https://orcid.org/0000-0001-7880-7080
Steven D. Wexner https://orcid.org/0000-0001-8046-5753

REFERENCES

1. Thoreson R, Cullen JJ. Pathophysiology of inflammatory bowel disease: an overview. Surg Clin North Am. 2007;87(3):575–85. https://doi.org/10.1016/j.suc.2007.03.001
2. Peyrin-Biroulet L, Fiorino G, Danese S. First-line therapy in adult Crohn's disease: who should receive anti-TNF agents? Nat Rev Gastroenterol Hepatol. 2013;10(6):345–51. https://doi.org/10.1038/nrgastro.2013.31
3. Iesaelniks I, Kilger A, Glass H, Obermeier F, Agha A, Schlitt HJ. Perforating Crohn's ileitis: delay of surgery is associated with inferior postoperative outcome. Inflamm Bowel Dis. 2010;16(12):2125–30. https://doi.org/10.1002/ibd.21303
4. Lavorini E, Allaix ME, Ammirati CA, Astegiano M, Morino M, Resegotti A. Late is too late? Surgical timing and postoperative complications after primary ileocolic resection for Crohn's disease. Int J Colorectal Dis. 2022;37(4):843–8. https://doi.org/10.1007/s00384-022-04125-7
5. Ponsioen CY, de Groof EJ, Eshuis EJ, Gardenbroek TJ, Bossuyt PMM, Hart A, et al. Laparoscopic ileocaecal resection versus infliximab for terminal ileitis in Crohn's disease: a randomized controlled, open-label, multicentre trial. Lancet. 2017;2(11):785–92. https://doi.org/10.1016/S2468-1253(17)30248-0
6. de Groof EJ, Stevens TW, Eshuis EJ, Gardenbroek TJ, Bosmans JE, van Dongen J, et al. Cost-effectiveness of laparoscopic ileocaecal resection versus infliximab treatment of terminal ileitis in Crohn's disease: the LIR!C trial. Gut. 2019;68(10):1774–80. https://doi.org/10.1136/gutjnl-2018-317539
7. Stevens TW, Haasnoot SL, D'Haens GR, Buskens CJ, de Groof EJ, Eshuis EJ, et al. Laparoscopic ileocaecal resection versus infliximab for terminal ileitis in Crohn's disease: retrospective long-term follow-up of the LIR!C trial. Lancet. Gastroenterol Hepatol. 2020;5(10):900–7. https://doi.org/10.1016/S2468-1253(20)30117-5
8. Surgical IBD Latam Consortium, Avellaneda N, Rodrigues Coy CS, Fillmann HS, Saad-Hossne R, Muñoz JP, et al. Earlier surgery is associated to reduced postoperative morbidity in ileocaecal Crohn's disease: results from SURGICROHN – LATAM Study. Dig Liver Dis. 2022;55:589–94. https://doi.org/10.1016/j.dld.2022.09.011
9. Avellaneda N, Haug T, Worm Ørntoft MB, Harsløf S, Skovgaard Larsen LP, Tøttrup A. Short-term results of operative treatment of primary ileocaecal Crohn's disease. A retrospective, comparative analysis between early (luminal) and complicated disease. J Clin Med. 2023;12:2644.
10. Gomollon F. Surgery in ileocaecal Crohn's disease: one more option, sometimes the best? Lancet Gastroenterol Hepatol. 2017;2(11):768–9. https://doi.org/10.1016/S2468-1253(17)30294-7
11. Pellino G, Sampietro GM. Defining the role of abdominal surgery and its impact on the disease course in patients with Crohn's disease: unsolved issues and novel insights. Dig Liver Dis. 2023;55(5):587–8. https://doi.org/10.1016/j.dld.2023.01.159
12. Kotze PG, Oliveira Magro D, Real Martinez CA, Spinelli A, Yamamoto T, Warusavitarne J, et al. Long time from diagnosis to surgery may increase postoperative complication rates in elective CD intestinal resections: an observational study. Gastroenterol Res Pract. 2018;2018:4703281. https://doi.org/10.1155/2018/4703281
13. Agrawal M, Ebert AC, Poulsen G, Ungaro RC, Faye AS, Jess T, et al. Early ileocecal resection for Crohn's disease is associated with improved long-term outcomes compared to anti-tumor necrosis factor therapy: a population-based cohort study. Gastroenterology. 2023;165(4):976–985.e3. https://doi.org/10.1053/j.gastro.2023.05.051
14. Maruyama BY, Ma C, Panaccione R, Kotze PG. Early laparoscopic ileal resection for localized ileocaecal Crohn's disease: hard sell or a revolutionary new norm? Inflamm Intest Dis. 2022;7:13–20. https://doi.org/10.1159/000515959
15. Silverberg MS, Satsangi J, Ahmad T, Arnott ID, Bernstein CN, Brant SR, 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;19:5–36.
16. Bemelman WA, Warusavitarne J, Sampietro GM, Serclova Z, Zmora O, Luglio G, et al. ECCO-ESCP consensus on surgery for Crohn's disease. J Crohns Colitis. 2018;12:1–16. https://doi.org/10.1093/ecco-jcc/jjx061
17. Rosenthal R, Hoffmann H, Clavien PA, Bucher HC, Dell-Kuster S. Definition and classification of intraoperative complications (CLASSIC): Delphi study and pilot evaluation. World J Surg. 2015;39(7):1663–71. https://doi.org/10.1007/s00268-015-3003-y
18. 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(2):205–13.
19. Rahbari NN, Weitz J, Hohenberger W, Heald RJ, Moran B, Ulrich A, et al. Definition and grading of anastomotic leakage following anterior resection of the rectum: a proposal by the International Study Group of Rectal Cancer. Surgery. 2010;147(3):339–51. https://doi.org/10.1016/j.surg.2009.10.012
20. Lichtenstein G, Loftus E, Isaacs K, Regueiro MD, Gerson LB, Sands BE. ACG clinical guideline: management of Crohn's disease in adults. Am J Gastroenterol. 2018;113(4):481–517. https://doi.org/10.1038/ajg.2018.27
21. Gionchetti P, Dignass A, Danese S, Magro Dias FJ, Rogler G, Lakatos PL, et al. 3rd European evidence-based consensus on the diagnosis and management of Crohn's disease 2016: part 2: surgical management and special situations. J Crohns Colitis. 2017;11(2):135–49. https://doi.org/10.1093/ecco-jcc/jjw169

How to cite this article: Avellaneda N, Pellino G, Maroli A, Tottrup A, Bislenghi G, Colpaert J, et al. Short-term outcomes of surgical treatment for primary ileocaecal Crohn's disease: Results of the Crohn's(urg) study, a multicentre, retrospective, comparative analysis between inflammatory and complicated phenotypes. Colorectal Dis. 2024;26:1415–1427. https://doi.org/10.1111/codi.17056

APPENDIX 1

Number of patients included per centre