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Alimentary Tract

Long-term comparative outcomes after ileocecal resection for inflammatory versus complicated Crohn's disease. A multicenter, retrospective study (Crohn's-Urg)☆

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ABSTRACT

Background: Surgical intervention in Crohn's disease (CD) is often reserved for complications or failure of medical therapy. However, the benefits of early ileocecal resection for inflammatory phenotype (ICR) in patients with uncomplicated disease remain debated, particularly regarding long-term outcomes compared with complicated cases.

Methods: This international, multicenter, retrospective cohort study evaluated long-term outcomes of ICR in patients with inflammatory (uncomplicated) and complicated CD phenotypes. Data from 2013 patients (291 with uncomplicated CD) who underwent surgery between 2012 and 2022 were analyzed. The primary endpoint was endoscopic disease recurrence, with secondary outcomes including clinical and surgical recurrence, fecal calprotectin levels, and risk factors for recurrence. Statistical analyses included Kaplan-Meier survival estimates, Cox regression, and multivariable modeling.

☆ The data from this study will be available within reasonable request.

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Results: Complicated CD patients had higher rates of preoperative anemia, emergent surgery, and open procedures. Despite these differences, long-term endoscopic (HR: 1.03; $p = 0.748$), clinical (HR: 1.35; $p = 0.073$), and surgical recurrence rates (HR: 0.77; $p = 0.419$) were comparable between groups. Protective factors for recurrence included laparoscopic surgery (HR: 0.74; $p = 0.009$) and postoperative prophylaxis (HR: 0.63; $p < 0.0001$), while preoperative anemia (HR: 1.52; $p < 0.0001$) and positive margins (HR: 1.36; $p = 0.001$) increased recurrence risk.
Conclusion: Long-term outcomes of ICR are similar in inflammatory and complicated CD when appropriate surgical and medical management is applied. Optimizing perioperative care and mitigating modifiable risk factors may improve outcomes, supporting the role of surgery even in less complicated CD cases.

1. Introduction

Crohn's disease (CD) is a chronic inflammatory condition often affecting the ileocecal region [1]. In cases where the inflammation is limited to this area without complications, initial treatment typically involves first- and second-line medical therapies, with surgery reserved as a last resort for patients who do not respond to medication or develop disease-related complications such as fibrotic stenosis or internal or external fistulas [2].

However, surgery performed later in the disease progression or due to complications can result in significant morbidity, adversely impacting patients' quality of life [3]. Consequently, recent research has increasingly explored the potential benefits of earlier ileocecal resection, suggesting that a proactive approach may lead to better outcomes before complications arise [4,5].

While it seems logical that complications associated with ileocecal resection would be lower when performed before complications from CD develop, there has been limited reporting on the long-term outcomes for patients undergoing surgery for uncomplicated versus complicated disease.

A previous publication on the short-term outcomes of this multicenter study comparing ileocecal resections in patients with uncomplicated versus complicated CD [6] reported that the latter was associated with worse results. This manuscript now presents the long-term results of this comparison between the two groups, hypothesizing that these outcomes could be similar to those previously presented.

2. Material and methods

2.1. Study design and eligibility criteria

This study was an international, multicentric, retrospective, cohort investigation, conducted in twelve tertiary referral centers known for the surgical treatment of Inflammatory Bowel Disease (IBD) (Figure S1). The study was approved by the ethical committees of all participating centers. The final report was prepared according to the Strengthening the Reports of Observational Studies in Epidemiology (STROBE) guidelines.

A first analysis based on this cohort, focused on short-term comparative results has been previously published [6].

2.2. Inclusion and exclusion criteria

Consecutive patients with histologically proven CD who had isolated ileocecal (distal 50 cm of the terminal ileum and cecum) disease, either predominantly inflammatory phenotype or complicated disease (stricturing or penetrating phenotypes), and did not have previous abdominal procedures due to CD, were eligible for this study. Patients who underwent surgery between January 2012 and December 2021 were included; patients with disease activity other than the ileocecal region were excluded.

Patients were allocated to the study cohorts according to the disease phenotype: patients with inflammatory phenotype (Montreal B1) were sorted into the Inflammatory Crohn's disease (ICD) cohort. In contrast, patients with complicated disease were sorted in the Complicated Crohn's disease (CCD) group.

2.3. Endpoints and data collection

The study's primary endpoint was the incidence rate ratio of endoscopic disease recurrence between the study cohorts. Endoscopic disease recurrence was defined as a Rutgeert's score equal to or higher than i2a at any endoscopic examination performed during the postoperative follow-up. The secondary endpoints of the study included: the incidence rate ratio of clinical disease recurrence (defined as a reported CD Activity Index higher than 150), the incidence rate ratio of surgical recurrence, and the median difference of six, 12, and 24-month Fecal Calprotectin (µg/mg) between the study cohorts. Additionally, the study aimed to explore the risk and protective factors of endoscopic and clinical disease recurrence in the study population.

Data and variables were retrospectively retrieved from prospectively maintained databases at each participating center. A detailed list of the study variables, and related definitions, is reported in Table S1. Data were collected in an electronic Case Report Form (eCRF) hosted by the RedCap Electronic Data Capture (EDC) (RedCap, Research Electronic Data Capture, Vanderbilt University ®).

2.4. Statistical analysis

Categorical and dichotomous variables are presented as number over the total and percentages, while continuous variables were tested for normal distribution using the Shapiro-Wilks test (with $p < 0.05$ indicating non-normal distribution) and are presented as mean ± standard deviation if normally distributed or median and interquartile range [IQR] if skewed. Missing data were analyzed for pattern distribution and imputed using a regression-based multiple imputation model. Continuous variables were analyzed using an unpaired T-test or Mann-Whitney test, according to their distribution. Categorical and dichotomous variables were analyzed with a Pearson's χ^2 test or Fisher's exact test, as appropriate. Multiple comparison of Fecal Calprotectin was performed with a Kruskal-Wallis test and Dunn's correction. Survival curves-including endoscopic, clinical, and surgical disease-free survival-were estimated by the Kaplan-Meier method and survival comparisons were performed with a Log-rank (Mantel-Cox) test, reporting the Hazard Ratios (HR) with related 95 % Confidence Intervals (95 % CI). For patients who had died or lost to follow-up, data were censored at the time of death, according to the cause, or last documented follow-up. A multivariable Cox proportional hazards regression analysis was performed to ascertain the effect of clinical and surgical variables in influencing the risk of recurrence. The model was tested for fitting using the Omnibus statistics. For each

Table 1
Baseline characteristics, mean ± standard deviation, median [IQR], n (%).

	ICD	CCD	*p*-value
Number of patients	291	1722	
Age, years	39.02 ± 0.98	37.31 ± 0.36	0.078
Gender, females	124 (43 %)	458 (50 %)	0.026
Smokers	70 (24 %)	382 (22 %)	0.494
BMI, Kg/m^2	24.12 ± 0.27	23.58 ± 0.13	0.074
CCI	0 [0–0]	0 [0–0]	0.400
Preoperative anemia	78 (27 %)	697 (40 %)	<0.0001
Preoperative albumin, mg/dL	3.90 ± 0.02	3.80 ± 0.01	0.076
Preoperative weight loss (> 10 % of previous weight)	39 (13 %)	251 (15 %)	0.652
Previous abdominal surgeries	53 (18 %)	401 (23 %)	0.058
Time from diagnosis to surgery, months	48 [15–120]	76 [27–134]	<0.0001
Fistulizing disease	–	882 (51 %)	<0.0001
Previous steroids treatment	40 (14 %)	325 (19 %)	0.039
Previous biologic treatment	152 (52 %)	877 (51 %)	0.704
Previous biologic treatment duration, months	26 [12–49]	29 [12–48]	0.352
Preoperative nutrition optimization	17 (6 %)	274 (16 %)	<0.0001
ASA classification			<0.0001
ASA I	65 (22 %)	210 (12 %)	
ASA II	198 (68 %)	1074 (62 %)	
ASA III	26 (9 %)	434 (25 %)	
ASA IV	2 (1 %)	4 (1 %)	

Abbreviations: IQR, Interquartile Range; ICD, Inflammatory Crohn's Disease; CCD, Complicated Crohn's Disease; BMI; Body Mass Index; CCI, Charlson Comorbidity Index; ASA, American Society of Anesthesiologists.
Categorical and dichotomous variables were analyzed with a Pearson's χ^2 test or Fisher's exact test. Continuous variables were tested for normality with the Shapiro-Wilks test and analyzed with an unpaired *t*-test if normally distributed or Mann-Whitney test if skewed.

variable in the model, the HR and 95 % CI were reported. All the analyses were unpaired and two-sided; *p*-value<0.05 were considered statistically significant. Analyses were performed using IBM SPSS Statistics for Windows, Version 24.0 (Armonk, NY: IBM Corp). Graphics were made with GraphPad Prism 5 Software (GraphPad Software, Inc., San Diego, California, USA) and Microsoft® Excel (Microsoft Corporation, Redmond, WA, USA).

3. Results

3.1. Baseline and operative characteristics

Between January 2012 and December 2022, 2013 patients who met the eligibility criteria were identified, 291 were allocated in the ICD cohort and 1722 were allocated to the CCD cohort (Figure S2). Among CCD patients, 51 % presented with penetrating phenotype. The CCD group had a higher proportion of female patients (50 % vs 43 %; $p = 0.026$). The median time from diagnosis to surgery was longer in the CCD group compared with ICD (76 [27–134] months vs 48 [15–120] months; $p < 0.0001$).

While CCD patients received preoperative chronic steroids treatment more frequently (19 % vs 14 %; $p = 0.039$), no difference was found in the proportion of patients receiving preoperative biologics (52 % vs 51 %; $p = 0.404$).

Patients in the CCD group had more preoperative anemia (40 % vs 27 %; $p < 0.0001$), lower BMI (23.87 ± 0.13 vs 24.47 ± 0.27; $p = 0.074$), and lower levels of preoperative albumin (3.82 ± 0.01 vs 3.89 ± 0.02; $p = 0.076$). Further, CCD patients were more frequently indicated to preoperative nutrition optimization (16 % vs 6 %; $p < 0.0001$). Even though the study cohorts displayed a similar Charlson Comorbidity Index ($p = 0.400$), a higher proportion of CCD patients was classified in a high ASA grade (25 % vs 9 %; $p < 0.0001$) (Table 1). Compared with ICD, a higher proportion of CCD patients was operated in emergent settings (17 % vs 6 %; $p < 0.0001$), and, accordingly, a higher proportion of CCD patients received open surgery (16 % vs 7 %; $p < 0.0001$), with longer operative time (158.00 ± 1.39 vs 134.50 ± 2.57; $p < 0.0001$). CCD patients had a higher risk of undergoing surgical conversion to open surgery (8 % vs 3 %; $p < 0.0001$) and intraoperative complications (3 % vs 1 %; $p = 0.015$) compared with ICD patients (Table 2).

Table 2
Operative characteristics, mean ± standard deviation, median [IQR], n (%).

	ICD	CCD	*p*-value
Number of patients	291	1722	
Urgent procedure	17 (6 %)	302 (17 %)	<0.0001
Surgical approach			<0.0001
Minimally invasive	271 (93 %)	1452 (84 %)	
Open	20 (7 %)	269 (16 %)	
Conversion to open surgery	5 (2 %)	135 (8 %)	<0.0001
Operative time, minutes	134.50 ± 2.57	158.00 ± 1.39	<0.0001
Anastomotic suture			0.229
Stapled	270 (93 %)	1556 (90 %)	
Handsewn	21 (7 %)	166 (10 %)	
Anastomosis configuration			0.007
End-to-end	4 (1 %)	57 (3 %)	
End-to-side	11 (4 %)	149 (9 %)	
Side-to-side	267 (92 %)	1474 (86 %)	
KONO-S	9 (3 %)	42 (2 %)	0.543
Anastomosis orientation			<0.0001
Isoperistaltic	67 (23 %)	651 (38 %)	
Anisoperistaltic	224 (77 %)	1071 (62 %)	
Mesenteric resection	44 (15 %)	265 (15 %)	1.000
Intraoperative complications	1 (1 %)	43 (3 %)	0.015

Abbreviations: IQR, Interquartile Range; ICD, Inflammatory Crohn's Disease; CCD, Complicated Crohn's Disease.
Categorical and dichotomous variables were analyzed with a Pearson's χ^2 test or Fisher's exact test. Continuous variables were tested for normality with the Shapiro-Wilks test and analyzed with an unpaired *t*-test if normally distributed or Mann-Whitney test if skewed.

After surgery, CCD patients had a higher reoperation rate (6 % vs 3 %; $p = 0.019$) and longer length of hospital stay (5 [4–7] vs 4 [3–6]; $p < 0.0001$) compared with ICD patients. CCD patients underwent more extensive intestinal resections (28 [19–43] cm vs 24 [17–37] cm; $p < 0.0001$) but had a lower risk of positive resection margins (14 % vs 20 %; $p = 0.010$). Postoperative antibiotic use was higher in the CCD patients (32 % vs 17 %; $p < 0.0001$) (Table 3).

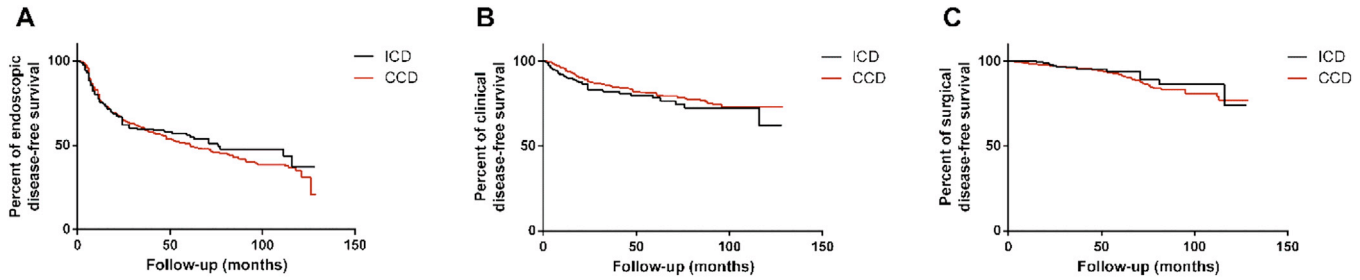

Fig. 1. A) Endoscopic disease-free survival of Inflammatory Crohn's disease patients (ICD, black line) and Complicated Crohn's disease patients (CCD, red line). No difference was found between the study cohorts (HR: 1.03; 95 % CI: 0.24 to 1.37; $p = 0.748$). The proportion of endoscopic disease-free survival (number of subjects at risk) at 12, 90, and 120 months of ICD vs CCD patients was 76 % vs 76 % (179/291 vs 1122/1722), 48 % vs 48 % (19/291 vs 79/1722), and 37 % vs 31 % (2/291 vs 9/1722) respectively. The median endoscopic disease-free survival was 76 and 61 months. B) Clinical disease-free survival of ICD patients (black line) and CCD patients (red line). No difference was found between the study cohorts (HR: 1.35; 95 % CI: 0.97 to 2.02; $p = 0.073$). The proportion of clinical disease-free survival (number of subjects at risk) at 12, 90, and 120 months of ICD vs CCD patients was 91 % vs 94 % (179/291 vs 1122/1722), 72 % vs 74 % (19/291 vs 79/1722), and 62 % vs 73 % (2/291 vs 9/1722) respectively. C) Surgical disease-free survival of ICD patients (black line) and CCD patients (red line). No difference was found between the study cohorts (HR: 0.77; 95 % CI: 0.44 to 1.19; $p = 0.419$). The proportion of surgical disease-free survival (number of subjects at risk) at 12, 90, and 120 months of ICD vs CCD patients was 100 % vs 98 % (182/291 vs 1144/1722), 86 % vs 83 % (31/291 vs 152/1722), and 74 % vs 77 % (2/291 vs 9/1722) respectively.

Table 3
Postoperative outcomes, median [IQR], n (%).

	ICD	CCD	*p*-value
Number of patients	291	1722	
Length of hospital stay, days	4 [3–6]	5 [4–7]	<0.0001
Postoperative complications	62 (21 %)	448 (26 %)	0.094
Anastomotic leak	6 (2 %)	78 (4 %)	0.056
SSI	11 (4 %)	72 (4 %)	0.874
Postoperative reoperation	8 (3 %)	107 (6 %)	0.019
Hospital readmission	19 (6 %)	121 (7 %)	0.901
Mortality	–	2 (1 %)	1.000
Positive resection margins	59 (20 %)	245 (14 %)	0.010
Extend of bowel resection, cm	24 [17–37]	28 [19–43]	<0.0001
Postoperative antibiotic treatment	54 (17 %)	549 (32 %)	<0.0001

Abbreviations: IQR, Interquartile Range; ICD, Inflammatory Crohn's Disease; CCD, Complicated Crohn's Disease; SSI, Surgical Site Infection.
Categorical and dichotomous variables were analyzed with a Pearson's χ^2 test with Fisher's exact test. Continuous variables were analyzed with a Mann-Whitney test.

3.2. Long-term outcomes

After surgery, a higher proportion of CCD patients received postoperative prophylactic medication, and the prophylaxis treatment was longer compared with ICD patients (46 % vs 37 %; $p = 0.011$; 74 [40–74] days vs 60 [20–74] days; $p < 0.0001$). The most frequent treatment in both cohorts comprised biological agents (Table 4).

The incidence rate of endoscopic (HR: 1.03; 95 % CI: 0.24 to 1.37; $p = 0.748$), clinical (HR: 1.35; 95 % CI: 0.97 to 2.02; $p = 0.073$), and surgical (HR: 0.77; 95 % CI: 0.44 to 1.19; $p = 0.419$) disease recurrence was comparable between ICD and CCD patients (Fig. 1).

No difference was found in the levels of Fecal Calprotectin at six (116 [47–265] µg/mg vs 98 [43–224] µg/mg; $p = 0.491$), 12 (80 [41–260] µg/mg vs 81 [30–214] µg/mg; $p = 0.442$), and 24 months (75 [36–242] µg/mg vs 71 [31–296] µg/mg; $p = 0.573$) after surgery. The multiple comparison revealed no significant improvements over time in the Fecal Calprotectin levels within the cohorts ($p = 0.308$) (Fig. 2).

3.3. Risk factors of disease recurrence

Univariable and multivariable analyses were performed to ascertain the impact of preoperative and surgical variables on the risk of developing endoscopic and clinical recurrence.

At univariable analysis, preoperative anemia (HR: 1.50; 95 % CI: 1.30 to 1.73; $p < 0.0001$), previous biologics treatment (HR: 1.28; 95 % CI: 1.11 to 1.48; $p = 0.001$), postoperative complications (HR: 1.18; 95 % CI: 1.00 to 1.39; $p = 0.046$), and positive resection margins (HR: 1.34; 95 % CI: 1.11 to 1.62; $p = 0.002$) resulted as risk factors of endoscopic recurrence, while increased BMI (HR: 0.98; 95 % CI: 0.97 to 1.00; $p = 0.049$), fistulizing disease (HR: 0.84; 95 % CI: 0.73 to 0.98; $p = 0.024$), previous steroids treatment (HR: 0.75; 95 % CI: 0.62 to 0.91; $p = 0.004$), laparoscopic surgery (HR: 0.69; 95 % CI: 0.55 to 0.86; $p = 0.001$), anisoperistaltic anasto-

Table 4
Postoperative medications and surveillance, median [IQR], n (%).

	ICD	CCD	*p*-value
Number of patients	291	1722	
Postoperative prophylaxis	109 (37 %)	786 (46 %)	0.011
Biologics	63 (22 %)	498 (29 %)	
Thiopurines	27 (9 %)	158 (9 %)	
Mesalamine	1 (1 %)	20 (1 %)	
Metronidazole	9 (3 %)	29 (2 %)	
Other			
Combined therapies	9 (3 %)	81 (5 %)	
Prophylaxis duration, days	60 [20–74]	74 [40–74]	<0.0001
Documented surveillance during the first year after surgery	179 (61 %)	1046 (61 %)	0.846
Time from surgery to first endoscopy, months	7 [6–9]	6 [6–9]	0.252

Abbreviations: IQR, Interquartile Range; ICD, Inflammatory Crohn's Disease; CCD, Complicated Crohn's Disease.
Categorical and dichotomous variables were analyzed with a Pearson's χ^2 test or Fisher's exact test. Continuous variables were analyzed with a Mann-Whitney test.

Table 5
Univariable and multivariable analysis of the variables influencing the incidence rate of endoscopic disease recurrence.

	Univariable analysis			Multivariable analysis		
	HR	95 % CI	*p*-value	HR	95 % CI	*p*-value
Age, years	0.99	0.99 to 1.00	0.122			
Gender (vs males)	1.13	0.98 to 1.31	0.075			
Smokers	1.08	0.92 to 1.28	0.308			
BMI, Kg/m^2	0.98	0.97 to 1.00	0.049	0.99	0.97 to 1.01	0.221
Preoperative anemia	1.50	1.30 to 1.73	<0.0001	1.52	1.31 to 1.76	<0.0001
Preoperative albumin, mg/dL	1.07	0.96 to 1.21	0.190			
Preoperative weight loss	1.16	0.96 to 1.40	0.113			
Time from diagnosis to surgery, months	1.00	0.99 to 1.00	0.549			
Fistulizing disease	0.84	0.73 to 0.98	0.024	0.86	0.74 to 1.00	0.050
Perianal disease	0.68	0.19 to 3.15	0.736			
Previous steroids treatment	0.75	0.62 to 0.91	0.004	0.81	0.67 to 0.98	0.038
Previous biologic treatment	1.28	1.11 to 1.48	0.001	1.35	1.16 to 1.56	<0.0001
Preoperative nutrition optimization	0.98	0.81 to1.21	0.901			
Surgical approach (vs open)	0.69	0.55 to 0.86	0.001	0.74	0.59 to 0.92	0.009
Anastomotic suture (vs handsewn)	1.06	0.83 to 1.36	0.612			
Anastomosis configuration (vs End-to-end)			0.007			
End-to-side	0.61	0.34 to 1.06	0.079			
Side-to-side	0.94	0.59 to 1.48	0.792			
KONO-S	1.52	0.82 to 2.81	0.180			
Anastomotic orientation (vs isoperistaltic)	0.78	0.67 to 0.90	0.001	0.75	0.65 to 0.87	<0.0001
Mesenteric resection	1.38	1.15 to 1.66	<0.0001			
Postoperative complications	1.18	1.00 to 1.39	0.046	0.91	0.97 to 1.07	0.254
Positive resection margins	1.34	1.11 to 1.62	0.002	1.36	1.12 to 1.66	0.002
Extend of bowel resection, cm	1.00	0.99 to 1.01	0.422			
Postoperative antibiotics treatment	1.11	0.95 to 1.29	0.189			
Postoperative prophylaxis	0.68	0.59 to 0.79	<0.0001	0.63	0.54 to 0.73	<0.0001

The Cox proportional hazard regression model resulted statistically significant (Omnibus test: χ [10]= 126.97; $p < 0.0001$).

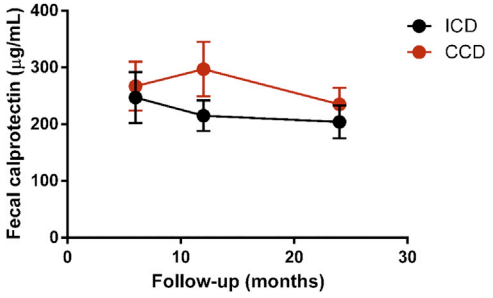

Fig. 2. Fecal calprotectin values (µg/mg, mean ± standard error) of Inflammatory Crohn's disease (ICD) patients (black dots and line) and Complicated Crohn's disease (CDD) patients (red dots and line) at six (247 ± 45 n = 109 vs 266 ± 43 n = 205), 12 (215 ± 27 n = 121 vs 297 ± 48 n = 250), and 24 months (204 ± 29 n = 102 vs 235 ± 29 n = 248) after surgery. Multiple comparison test (Kruskal-Wallis) found no difference was found in fecal calprotectin levels at each timepoint between the study cohorts ($p = 0.308$).

mosis orientation (HR: 0.78; 95 % CI: 0.67 to 0.90; $p = 0.001$), and postoperative prophylactic medications (HR: 0.68; 95 % CI: 0.59 to 0.79; $p < 0.0001$) resulted protective factors. At multivariable analysis, preoperative anemia (HR: 1.52; 95 % CI: 1.31 to 1.76; $p < 0.0001$), previous biologics treatment (HR: 1.35; 95 % CI: 1.16 to 1.56; $p < 0.0001$), and positive margins (HR: 1.36; 95 % CI: 1.12 to 1.66; $p = 0.001$) were confirmed as risk factors, while previous steroids treatment (HR: 0.81; 95 % CI: 0.67 to 0.98; $p = 0.038$), laparoscopic approach (HR: 0.74; 95 % CI: 0.59 to 0.92; $p = 0.009$), and prophylactic medications (HR: 0.63; 95 % CI: 0.54 to 0.73; $p < 0.0001$) resulted as independent protective factors (Table 5).

In addition, at univariable analysis, clinical recurrence was negatively influenced by preoperative anemia (HR: 1.59; 95 % CI: 1.23 to 2.06; $p < 0.0001$), preoperative weight loss (HR: 1.54; 95 % CI: 1.13 to 2.10; $p = 0.006$), previous biologics treatments (HR: 1.36; 95 % CI: 1.05 to 1.76; $p = 0.019$), preoperative nutritional optimization (HR: 1.61; 95 % CI: 1.18 to 2.21; $p = 0.003$), stapled anastomosis (HR: 2.52; 95 % CI: 1.34 to 4.76; $p = 0.004$), anti-peristaltic anastomosis orientation (HR: 1.88; 95 % CI: 1.37 to 2.57; $p < 0.0001$), and positive resection margins (HR: 1.76; 95 % CI: 1.26 to 2.37; $p = 0.001$). Increased age at surgery (HR: 0.98; 95 % CI: 0.98 to 0.99; $p = 0.032$) and time from diagnosis to surgery (HR: 0.99; 95 % CI: 0.99 to 1.00; $p = 0.018$), and penetrating phenotype (HR: 0.73; 95 % CI: 0.56 to 0.95; $p = 0.023$) were instead protective factors. The multivariable analysis confirmed preoperative anemia (HR: 1.47; 95 % CI: 1.12 to 1.93; $p = 0.005$), previous biologics treatment (HR: 1.32; 95 % CI: 1.01 to 1.72; $p = 0.040$), anti-peristaltic anastomosis orientation (HR: 1.46; 95 % CI: 1.04 to 2.05; $p = 0.027$), and positive margins (HR: 1.47; 95 % CI: 1.06 to 2.05; $p = 0.019$) as risk factors, while the only protective factors was fistulizing disease phenotype (HR: 0.67; 95 % CI: 0.51 to 0.88; $p = 0.004$) (Table 6).

4. Discussion

This study presents a thorough comparison of long-term outcomes and recurrence risk factors in patients with inflammatory Crohn's disease (ICD) and complicated Crohn's disease (CCD), following ileocecal resection. Our findings suggest that, despite the more severe nature of CCD, long-term outcomes—including endoscopic, clinical, and surgical recurrence rates— are similar between ICD and CCD patients when appropriate surgical and medical strategies are employed, rejecting our prior hypothesis.

The comparable recurrence rates between ICD and CCD groups are particularly noteworthy. These findings align with previous research, such as the study by Kotze et al. [7], which showed that rigorous postoperative management can result in similar long-term outcomes for patients with aggressive Crohn's phenotypes and those with less severe disease. Furthermore, the absence of significant differences in Fecal Calprotectin levels at six, twelve, and twenty-four months postoperatively between the groups underscores the critical role of effective postoperative management in controlling disease activity, regardless of initial disease severity.

One factor contributing to the similar recurrence rates is the higher proportion of CCD patients in our study who received ex-

Table 6
Univariable and multivariable analysis of the variables influencing the incidence rate of clinical disease recurrence.

	Univariable analysis			Multivariable analysis		
	HR	95 % CI	*p*-value	HR	95 % CI	*p*-value
Age, years	0.98	0.98 to 0.99	0.032	0.99	0.98 to 1.00	0.167
Gender (vs males)	0.97	0.75 to 1.25	0.842			
Smokers	1.14	0.85 to 1.52	0.369			
BMI, Kg/m^2	1.01	0.98 to 1.03	0.460			
Preoperative anemia	1.59	1.23 to 2.06	<0.0001	1.47	1.12 to 1.93	0.005
Preoperative albumin, mg/dL	0.82	0.67 to 1.01	0.059			
Preoperative weight loss	1.54	1.13 to 2.10	0.006	1.26	0.90 to 1.77	0.175
Time from diagnosis to surgery, months	0.99	0.99 to 1.00	0.018	0.99	0.99 to 1.00	0.096
Fistulizing disease	0.73	0.56 to 0.95	0.023	0.67	0.51 to 0.88	0.004
Perianal disease	1.32	0.18 to 9.47	0.778			
Previous steroids treatment	0.81	0.57 to 1.13	0.214			
Previous biologic treatment	1.36	1.05 to 1.76	0.019	1.32	1.01 to 1.72	0.040
Preoperative nutrition optimization	1.61	1.18 to 2.21	0.003	1.35	0.95 to 1.91	0.091
Surgical approach (vs open)	0.89	0.55 to 0.86	0.561			
Anastomotic suture (vs handsewn)	2.52	1.34 to 4.76	0.004	1.76	0.90 to 3.44	0.099
Anastomosis configuration (vs End-to-end)			0.566			
End-to-side	0.95	0.38 to 2.40	0.918			
Side-to-side	0.88	0.39 to 1.99	0.773			
KONO-S	0.23	0.03 to 1.88	0.170			
Anastomotic orientation (vs isoperistaltic)	1.88	1.37 to 2.57	<0.0001	1.46	1.04 to 2.05	0.027
Mesenteric resection	0.57	1.15 to 1.66	0.025			
Postoperative complications	0.82	0.61 to 1.06	0.194			
Positive resection margins	1.73	1.26 to 2.37	0.001	1.47	1.06 to 2.05	0.019
Extend of bowel resection, cm	0.99	0.99 to 1.01	0.443			
Postoperative antibiotics treatment	1.21	0.91 to 1.59	0.177			
Postoperative prophylaxis	0.94	0.63 to 1.20	0.665			

Abbreviations: HR, Hazard Ratio; 95 % CI, 95 % Confidence Intervals; BMI, Body Mass Index.
The Cox proportional hazard regression model resulted statistically significant (Omnibus test: χ [10]= 62.85; $p < 0.0001$).

tended prophylactic medication. This approach may have mitigated the more severe initial disease course in the CCD group, emphasizing the importance of individualized treatment strategies.

Ileocecal resection is increasingly regarded as a potential first-line treatment for limited CD, especially after studies like the LIR!C trial demonstrated its efficacy comparable to that of biologic therapy as a second-line treatment [8]. Additionally, Agrawal et al. [9] found that early ileocecal resection in newly diagnosed ileocecal Crohn's disease reduced long-term adverse outcomes—such as hospitalizations, systemic corticosteroid use, major surgeries, or perianal disease—by 33 % compared to initial treatment with anti-TNF agents. These findings highlight the need for further research on surgery's role in CD. Our study adds to this growing body of evidence, suggesting that with proper perioperative care, even patients with a complicated disease profile can achieve similar long-term outcomes in clinical and endoscopic activity.

Our analysis identified several key risk factors for endoscopic and clinical recurrence. Preoperative anemia (HR: 1.52, $p < 0.0001$) was strongly associated with an increased recurrence risk, a noteworthy finding given that anemia is a common extraintestinal manifestation of inflammatory bowel disease (IBD) [10] and has been linked to poorer postoperative outcomes [11]. Prior biological treatment (HR: 1.35, $p < 0.0001$) and positive resection margins (HR: 1.36, $p = 0.001$) were also significant predictors of recurrence. The association between positive resection margins and increased recurrence risk remains debated. Kelm et al. [12] reported that positive margins correlated with higher rates of severe endoscopic recurrence at six months and beyond, while Fazio et al. [13] found a negative association between affected margins and recurrence. Our findings would seem to favor achieving clear margins during surgery to reduce the risk of recurrence.

Another interesting finding is the protective role of laparoscopic surgery (HR: 0.74, $p = 0.009$). Previous studies on this topic have been mixed, with some randomized controlled trials [14,15] and observational studies [16] reporting no significant differences in recurrence rates based on the surgical approach. However, those studies often had smaller sample sizes, whereas our study's larger patient population and extended follow-up provide a more robust evaluation of the potential benefits of laparoscopic surgery.

Receiving postoperative prophylactic medication also emerged as a protective factor against recurrence (HR: 0.63, $p < 0.0001$). Notably, many patients who underwent surgery for luminal disease alone received postoperative prophylaxis, raising the question of potential overtreatment. Future studies should focus on identifying which patients in this group could benefit from a more tailored approach, potentially avoiding unnecessary medication.

Lastly, this study identified anti-peristaltic anastomosis (HR: 1.46, $p = 0.027$) to be a risk factor for clinical recurrence. A meta analysis comparing end-to-end anastomosis vs. other anastomotic techniques [17] including 661 patients found that side-to-side anastomosis had less complications but no differences in the long-term. On the other hand, a randomized controlled trial [18] comparing stapled side-to-side anastomosis versus Kono-S anastomosis (end-to-end) reported that the latter was associated with fewer endoscopic and clinical recurrences. Nevertheless, these findings were challenged by a more recent and larger randomized controlled trial which reported no differences between these 2 groups [19]. It is therefore difficult to define which anastomotic configuration should be preferred after an ileocaecal resection.

It is important to acknowledge the limitations of our study. First, the retrospective design introduces potential biases that may affect our findings. Additionally, since most patients received care at IBD referral centers, the results may not fully represent outcomes in community or non-specialized settings. Longer follow-up periods could offer further insights into disease progression and relapse risk over time. Lastly, the expertise of the physician performing postoperative control endoscopies was not assessed, carrying along a possible bias con these studies.

Despite these limitations, our study has notable strengths, including its large sample size and multicenter design. Few studies have directly compared the surgical outcomes of ICD and CCD, and our findings shed light on potentially modifiable factors influencing disease relapse after surgery, opening avenues for future research.

5. Conclusion

In summary, while ileocecal resection in patients with luminal Crohn's disease is associated with better short-term outcomes than surgery for CCD, long-term results between the groups are ultimately similar. This study also highlights several key risk factors for relapse, suggesting areas where modifying these factors could improve outcomes following ileocecal resection in Crohn's disease patients.

Author contribution

Conceptualization, methodology, formal analysis, data curation, writing original draft: NA, AM, GP, MC, AT, AS. Investigation, recruitment, writing (review and editing): GB, JC, AD, LG, PJ, SH, ABVO, PO, JG, SH, ELN, SRS, AM, AS, MMG, MK, PGK, RMMA, SDW, ZG, ZC, DH, DR, CB, AH, JW, KJW PC, AW, JL, AA.

Declaration of competing interest

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

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.dld.2025.07.009.

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