

## ORIGINAL ARTICLE

# Post-Operative Recurrence of Colonic Crohn's Disease After Colectomy: The RESECOL Study by the Young Group of GETECCU

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## ABSTRACT

**Background and Aims:** Post-operative recurrence (POR) of colonic Crohn's Disease (CD) after segmental (SC) or subtotal colectomy (STC) is scarcely described. Therefore, we aimed to report the rates and predictors of POR in this setting.

**Methods:** Multicentre, nationwide, retrospective study including colonic CD patients undergoing SC or STC. Clinical, endoscopic, radiologic and surgical POR were assessed and POR-free survival was compared between procedures. Cox regression determined predictors of post-colectomy POR. Inverse probability of treatment weighting (IPTW) was carried out for sensitivity analyses.

**Results:** A total of 224 patients were included (157 SC, 67 STC). Clinical POR occurred less frequently after SC than after STC (38% vs 63%,  $p=0.001$ ), as did endoscopic POR (50% vs 71%,  $p=0.012$ ); whereas radiologic and surgical POR rates were similar ( $p=0.1$  and  $p=0.992$ , respectively). Clinical POR-free survival at 1 and 5 years was higher after SC than after STC (82% and 64.8% vs 67.6% and 39%, log-rank  $p=0.001$ ). Endoscopic POR-free survival followed a similar pattern (log-rank  $p<0.001$ ). In multivariable Cox regression, SC remained protective against clinical (HR 0.54 [0.36–0.81]) and early endoscopic POR (HR 0.54 [0.35–0.82]). After IPTW, SC was still associated with a significantly lower risk of clinical and endoscopic POR.

**Conclusion:** Clinical and endoscopic POR rates are significantly lower following SC compared with STC in colonic CD, while radiologic and surgical recurrence rates were similar. SC shows a protective effect regarding clinical and early endoscopic POR. These data support segmental resection of colonic CD when feasible.

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## 1 | Introduction

Colonic Crohn's Disease (CD) represents the third most frequent disease location, following ileocecal and isolated ileal disease [1]. Despite significant advances in medical therapy, the cumulative risk of surgery in CD remains substantial, with estimates of approximately 22%–30% within 10 years of diagnosis for colonic CD, and 75%–90% for ileocecal CD [2].

Recent cohort studies report endoscopic post-operative recurrence (POR) of CD in approximately 37%–59% of patients within 6–12 months after ileocecal resection, whereas clinical POR during the same period occurs in 9%–17% [3]; therefore, several guidelines address both the natural history and medical management of POR at this site [4, 5]. However, the rates, predictors and optimal management of POR after colonic resection remain undefined. Previous evidence suggests that segmental colectomy (SC) is associated with lower stoma rates and improved surgical recurrence compared with subtotal colectomy (STC) [6]. Moreover, the absence of postoperative biologic therapy has also been independently associated with an increased risk of surgical recurrence after colectomy in CD [7]. However, a broader and updated description of POR in this setting is lacking.

Therefore, the aim of this study was to describe rates of clinical, endoscopic, biologic, radiologic and surgical POR after colonic resection and to explore demographic, clinical and therapy-related factors associated with POR in this setting.

## 2 | Methods

### 2.1 | Study Design

The RESECOL project was a retrospective, nationwide cohort study promoted by the Young Group of the Spanish Working Group on Crohn's Disease and Ulcerative Colitis (GETECCU). We included adult patients ( $\geq 18$  years) from 44 Spanish hospitals and 1 Latin American Center with a diagnosis of CD according to the European Crohn's and Colitis Organisation (ECCO) criteria [8], who underwent segmental colectomy (any colonic resection with colocolonic anastomosis) or subtotal colectomy (colonic resection with ileorectal anastomosis) between 2006 and 2023. Only colonic resections indicated for medically refractory disease, stenosing or fistulizing disease, or inability to perform adequate dysplasia surveillance (e.g., due to extensive pseudopolypoidosis) were included. Exclusion criteria were right hemicolectomy with ileocolonic anastomosis, any colonic resection resulting in definitive stoma, advanced colorectal neoplasia as an indication for surgery, colectomies for reasons different than CD (e.g., diverticulitis) and insufficient follow-up data to assess the primary endpoint.

The following demographic and clinical baseline characteristics were collected from digital hospital records: Age, sex, smoking status, duration of disease (years from diagnosis), location and behaviour of CD according to Montreal classification, presence of perianal disease, extraintestinal manifestations, previous CD-related surgery, number of previously failed advanced therapies (biologics and/or Janus Kinase inhibitors), previous immunomodulator failure (IMM: azathioprine, mercaptopurine,

methotrexate), histopathology of the surgical specimen (presence of granulomas, myenteric plexitis or positive resection margins—i.e. histological inflammation in the proximal margin), most recent faecal calprotectin (fCal) determination at the time of POR and POR prevention regime. We considered POR prevention any IMM or advanced agent prescribed within 3 months from surgery.

The primary endpoints were the rates of clinical and surgical POR according to the subtype of colectomy. Clinical POR was defined as the first symptomatic flare during follow-up requiring salvage therapy. Salvage therapy was defined as the initiation of any immunosuppressive (including corticosteroids) or advanced agent in untreated patients, or any switch or escalation from previously prescribed POR prevention. Surgical POR was defined as any CD-related surgical reintervention at the previous anastomotic site.

Secondary endpoints included differences in endoscopic POR, radiologic POR, fCal values and POR-free survival according to the subtype of colectomy, and identification of factors associated with post-colectomy POR. Endoscopic POR was defined as anastomotic and/or perianastomotic CD-associated lesions at the first endoscopy after surgery. Radiologic POR was defined as radiologic changes at the anastomotic site attributable to CD, such as bowel wall hyperenhancement or thickening, detected by magnetic resonance imaging (MRI) or intestinal ultrasound (US).

Study data were collected and managed using REDCap (Research Electronic Data Capture) electronic data capture tools hosted at La Paz University Hospital [9, 10].

### 2.2 | Statistical Analysis

Quantitative variables were summarised as means (standard deviations [SD]) or medians (interquartile ranges [IQR]), according to distribution, and categorical variables as frequencies and percentages. Comparisons were performed using Student's *t*-test or the Wilcoxon rank-sum test for continuous data, and the chi-squared test or Fisher's exact test for categorical data, as appropriate.

Receiver operating characteristic (ROC) curve analysis was performed to evaluate the performance of fCal to predict POR according to the subtype of colectomy. The area under the curve (AUC) with 95% confidence intervals (CIs) was calculated using the DeLong method. The optimal cutoff value for fCal to discriminate patients with and without POR was determined by the Youden Index.

For survival analysis, time-to-event was calculated from the date of surgery until the first occurrence of the event (clinical, endoscopic or radiologic POR) or last follow-up. Median follow-up time to POR was determined by reverse Kaplan–Meier estimates. Patients without the event at last follow-up were censored. Time-to-event analyses included only patients with valid dates for surgery and for the event or censoring; cases with missing or non-interpretable dates were excluded from the survival models. Recurrence-free survival was estimated using

the Kaplan–Meier method, and groups were compared using the log-rank test.

Univariable Cox proportional hazards regression was first performed to identify covariates associated with POR. Variables with  $p < 0.10$  in univariable analysis, along with clinically relevant factors for POR in CD according to previous literature (sex, B3 phenotype, perianal disease, previous resection, myenteric plexitis, granulomas, positive histopathological margins, type of POR prevention—IMM, anti-TNF-) [11] were subsequently entered into multivariable Cox regression models. To reduce the risk of overfitting, we additionally performed penalised Cox regression with least absolute shrinkage and selection operator (LASSO), using 10-fold cross-validation. Predictors retained by LASSO were re-entered into a standard Cox model to obtain unbiased hazard ratio (HR) estimates with 95% CIs. The proportional hazards assumption was evaluated using scaled Schoenfeld residuals, and for covariates violating this assumption, time-dependent Cox models were fitted.

For sensitivity analyses, inverse probability of treatment weighting (IPTW) based on a propensity score was applied to balance baseline characteristics between surgical strategies. The propensity score was estimated using multivariable logistic regression including all clinically relevant baseline covariates. Stabilised IPTW weights were used to create a balanced pseudo-population, as assessed by standardised mean differences (SMD, threshold  $\leq 0.10$  considered acceptable). Group comparisons after weighting were performed using IPTW-weighted statistical tests (Rao-Scott adjusted chi-square) and IPTW-adjusted Cox models with robust variance estimation.

Statistical significance was set at  $p < 0.05$ . All analyses were conducted using R version 4.3.1 (R Core Team, 2023) [12].

The reporting of this study conforms to the STROBE (Strengthening The Reporting Of Observational studies in Epidemiology) guidelines [13].

### 2.3 | Ethical Considerations

The study was conducted according to the ethical standards of the Declaration of Helsinki (2013 version), and the study protocol was approved by the ethical committee of the promoting center (La Paz University Hospital, local code PI-6361). Given the retrospective nature of the study and the utilisation of deidentified data, consent to participate was not required or sought.

## 3 | Results

A total of 224 patients were included: 157 (70.1%) underwent SC and 67 (29.9%) STC. Compared with STC, SC patients were significantly older, had a higher prevalence of B3 phenotype, and more frequently underwent surgery for this indication. POR prevention was prescribed in most patients, with no differences between groups. Baseline characteristics are detailed in Table 1.

Histopathology of the surgical specimen was available in 124 (79%) patients undergoing SC and in 47 (70.1%) undergoing STC.

Granulomas were observed in 33 (26.8%) patients after SC and in 12 (25.5%) after STC ( $p = 1$ ). Positive resection margins were reported in 26 (20.8%) SC and 15 (31.9%) STC specimens ( $p = 0.16$ ). Myenteric plexitis was identified in 26 (20.5%) SC patients and in 10 (21.3%) STC resections ( $p = 1$ ).

### 3.1 | Rates of Post-Operative Recurrence Among Subtypes of Colectomy

Overall, clinical POR developed in 102 patients (45.5%): 60 (38.2%) in the SC group and 42 (62.7%) in the STC group ( $p = 0.001$ ). Surgical recurrence occurred in 17 (10.8%) patients in the SC group and in 8 (11.9%) in the STC group ( $p = 0.992$ ).

Endoscopic evaluation was available in 190 patients (84.8%): 131 (83.4%) in the SC group and 59 (88.1%) in the STC group. The median time from surgery to the first endoscopic assessment was 24.4 months (IQR 7.5–101.3). Endoscopic POR was detected in 66 (50.4%) SC patients and in 42 (71.2%) STC patients ( $p = 0.012$ ).

MRI or IUS for the assessment of radiologic POR were performed in 132 patients (58.9%): 102 (65%) in the SC group and 30 (44.8%) in the STC group. The median time to the first radiologic evaluation was 38.2 months (IQR 10.4–94.1). Radiologic POR was observed in 44 (43.1%) and 18 (60%) patients, respectively ( $p = 0.1$ ).

### 3.2 | Calprotectin Values According to POR Status Between Subtypes of Colectomy

The median time from surgery to fCal determination was 67.7 (IQR 18.4–141.3), 53.4 (IQR 9.5–121.8) and 62.1 months (IQR 19.7–107.2) for clinical, endoscopic and radiologic recurrence assessments, respectively. fCal levels were significantly higher in patients with POR compared with those without recurrence, both after SC and STC, for clinical, endoscopic and radiologic definitions of recurrence (Figure 1).

The optimal fCal cutoff value to predict clinical POR was 202  $\mu\text{g/g}$  after SC and 152  $\mu\text{g/g}$  after STC. At these thresholds, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were 71%, 85%, 65% and 88% for SC and 77%, 79%, 77% and 79% for STC, respectively. For endoscopic POR, the optimal cutoff values were 113  $\mu\text{g/g}$  after SC and 387  $\mu\text{g/g}$  after STC. The corresponding sensitivity, specificity, PPV and NPV were 72%, 77%, 72% and 77% for SC and 60%, 100%, 100% and 54% for STC. Corresponding AUC and ROC curves are represented in Figure 2.

### 3.3 | Survival Analyses

For time-to-event analyses, 3 patients were excluded from the clinical recurrence model (2 SC and 1 STC), 1 patient from the endoscopic model (1 SC), and 1 patient from the radiologic model (1 SC) due to missing or non-interpretable dates. Median follow-up exceeded 6 years for all outcomes (Table S1). Clinical and endoscopic POR-free survival were significantly higher after SC than after STC ( $p = 0.001$  and  $p = 0.00096$ , respectively;

**TABLE 1** | Baseline characteristics of the study population.

| Characteristics                           | Segmental colectomy <i>N</i> = 157 <sup>a</sup> | Subtotal colectomy <i>N</i> = 67 <sup>a</sup> | <i>p</i> <sup>b</sup> |
|---|---|---|-----------------------|
| Age in years                              | 44.1 (15.2)                                     | 39.2 (14.2)                                   | <b>0.010</b>          |
| Sex                                       |   |   | 0.2                   |
| Female                                    | 86 (55%)  | 30 (45%)                                      |                       |
| Male                                      | 71 (45%)  | 37 (55%)                                      |                       |
| Smoking                                   |   |   | 0.2                   |
| No  | 74 (47%)  | 33 (50%)                                      |                       |
| Yes                                       | 27 (17%)  | 17 (26%)                                      |                       |
| Ex-smoker                                 | 56 (36%)  | 16 (24%)                                      |                       |
| Unknown                                   | 0   | 1   |                       |
| Disease duration in years                 | 9.7 (18.3)                                      | 9.5 (10.3)                                    | 0.4                   |
| CD location according to Montreal         |   |   | 0.4                   |
| L2  | 66 (42%)  | 33 (49%)                                      |                       |
| L3  | 91 (58%)  | 34 (51%)                                      |                       |
| CD phenotype according to Montreal        |   |   | <b>0.003</b>          |
| B1  | 26 (17%)  | 20 (30%)                                      |                       |
| B2  | 63 (40%)  | 33 (49%)                                      |                       |
| B3  | 68 (43%)  | 14 (21%)                                      |                       |
| Perianal disease                          | 48 (31%)  | 26 (39%)                                      | 0.2                   |
| Number of previous CD-related surgery     |   |   | > 0.9                 |
| None                                      | 135 (86%)                                       | 56 (84%)                                      |                       |
| 1   | 11 (7%)   | 5 (7.5%)                                      |                       |
| 2   | 5 (3.2%)  | 2 (3%)  |                       |
| 3   | 6 (3.8%)  | 4 (6%)  |                       |
| Number of prior advanced therapy failures |   |   | 0.12                  |
| 1   | 113 (72%)                                       | 44 (66%)                                      |                       |
| 2   | 22 (14%)  | 13 (19%)                                      |                       |
| 3   | 14 (8.9%)                                       | 2 (3%)  |                       |
| 4   | 4 (2.5%)  | 5 (7.5%)                                      |                       |
| 5   | 3 (1.9%)  | 2 (3%)  |                       |
| 6   | 1 (0.6%)  | 0 (0%)  |                       |
| 7   | 0 (0%)  | 1 (1.5%)                                      |                       |
| Prior immunomodulator failure             | 56 (36%)  | 23 (34%)                                      | 0.8                   |
| Indication for surgery                    |   |   | <b>&lt; 0.001</b>     |
| Medically refractory disease              | 13 (8.3%)                                       | 17 (25%)                                      |                       |
| Stenosing disease                         | 83 (53%)  | 34 (51%)                                      |                       |
| Impossibility for CRC screening           | 3 (1.9%)  | 1 (1.5%)                                      |                       |
| Fistulizing disease                       | 51 (32%)  | 8 (12%)                                       |                       |
| Other                                     | 7 (4.5%)  | 7 (10%)                                       |                       |

(Continues)

TABLE 1 | (Continued)

| Characteristics | Segmental colectomy <i>N</i> = 157 <sup>a</sup> | Subtotal colectomy <i>N</i> = 67 <sup>a</sup> | <i>p</i> <sup>b</sup> |
|-----------------|---|---|-----------------------|
| POR prophylaxis |   |   | 0.4                   |
| Mesalamine      | 19 (12.1%)                                      | 14 (20.8%)                                    |                       |
| Metronidazol    | 16 (10.2%)                                      | 8 (11.9%)                                     |                       |
| Azathioprine    | 57 (36.3%)                                      | 22 (32.8%)                                    |                       |
| Methotrexate    | 4 (2.5%)  | 1 (1.5%)                                      |                       |
| Infliximab      | 21 (13.3%)                                      | 12 (17.9%)                                    |                       |
| Adalimumab      | 27 (16.9%)                                      | 6 (8.9%)                                      |                       |
| Certolizumab    | 2 (12.7%)                                       | 0 (0%)  |                       |
| Ustekinumab     | 7 (4.4%)  | 5 (7.4%)                                      |                       |
| Vedolizumab     | 4 (4.1%)  | 2 (2.9%)                                      |                       |
| ≥ 2 therapies   | 35 (22.2%)                                      | 14 (20.8%)                                    |                       |

<sup>a</sup>Mean (SD); *n* (%).

<sup>b</sup>Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test. Note: Bold values represent statistically significant results.

Figure 3), whereas radiologic recurrence-free survival did not differ between groups (Figure S1).

### 3.4 | Predictors of POR

Several predictors of POR were detected in univariable Cox regression (Tables S2 and S3). Hereon, we report on the multivariable regression. Multivariable Cox proportional hazards models identified the type of colectomy (SC vs STC) and myenteric plexitis as independent predictors of clinical POR (HR 0.54, 95% CI 0.35–0.84 and HR 2.27, 95% CI 1.32–3.92, respectively). Regarding endoscopic POR, myenteric plexitis (HR 1.96, 95% CI 1.05–3.67), female sex (HR 0.66, 95% CI 0.44–0.98), B3 phenotype (HR 0.61, 95% CI 0.38–0.98) and POR prevention with IMM (HR 0.64, 95% CI 0.42–0.99) were independently associated in the multivariable model (Table 2).

To reduce the risk of overfitting, a penalised Cox regression using LASSO was also performed. Predictors retained after LASSO were then re-entered into a standard Cox model. In this refitted model, SC (vs STC) remained protective against clinical POR, whereas smoking and myenteric plexitis were associated with an increased risk (Table 3). For endoscopic POR, only myenteric plexitis and positive histopathology margins were retained as significant predictors (Table 4).

Schoenfeld residuals indicated violation of the proportional hazards assumption for type of colectomy and IMM prophylaxis in the model for endoscopic POR (Supporting Information). Consequently, a Cox model with a log-time interaction was fitted. The HR for both variables showed significant association with endoscopic POR at 12 months but not thereafter (Table 5).

### 3.5 | Sensitivity Analyses in the Overall Cohort

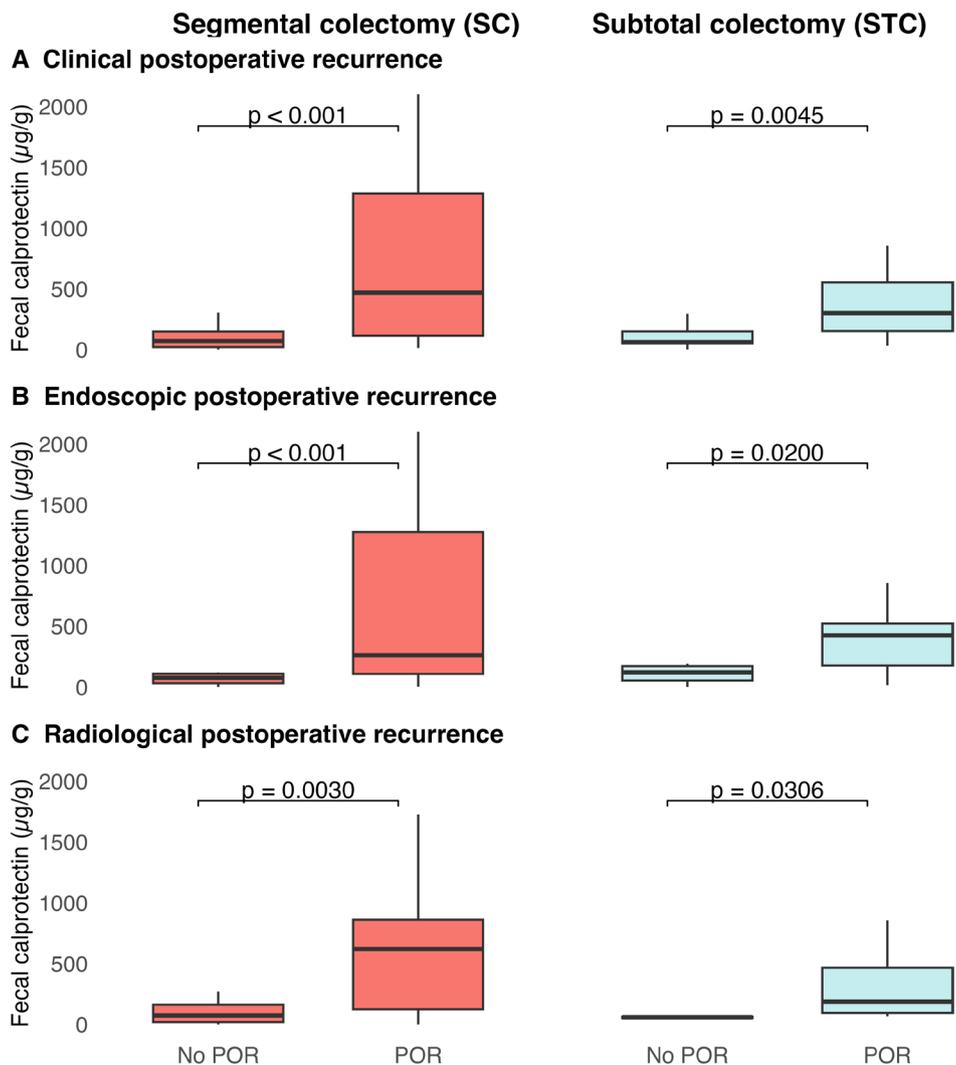
Given the variability in post-operative assessment timing, sensitivity analyses were performed restricting evaluations within

12 and 24 months after surgery. Within 12 months, endoscopy was available in 42 SC and 25 STC patients, with endoscopic POR in 59.5% vs 84.0%, respectively ( $p=0.069$ ), while radiologic assessment was too limited for formal comparison. In this time-restricted analysis, fCal remained significantly higher in patients with POR than in those without, particularly in the SC group, whereas analyses in STC were limited by small sample size (Table S4). Extending the window to 24 months increased the number of evaluable patients (58 SC vs 35 STC for endoscopy; 44 vs 11 for imaging) and confirmed higher POR rates after STC (endoscopic: 58.6% vs 80.0%,  $p=0.042$ ; radiologic: 43.2% vs 72.7%,  $p=0.10$ ). In this extended timeframe, fCal was also significantly higher in STC patients with endoscopic POR (424.3 [176.2–521.5] vs 120.0 [52.4–171.5]  $\mu\text{g/g}$ ;  $p=0.017$ ) and radiologic POR (187.0 [93.2–465.0] vs 58.0 [51.5–63.0]  $\mu\text{g/g}$ ;  $p=0.026$ ).

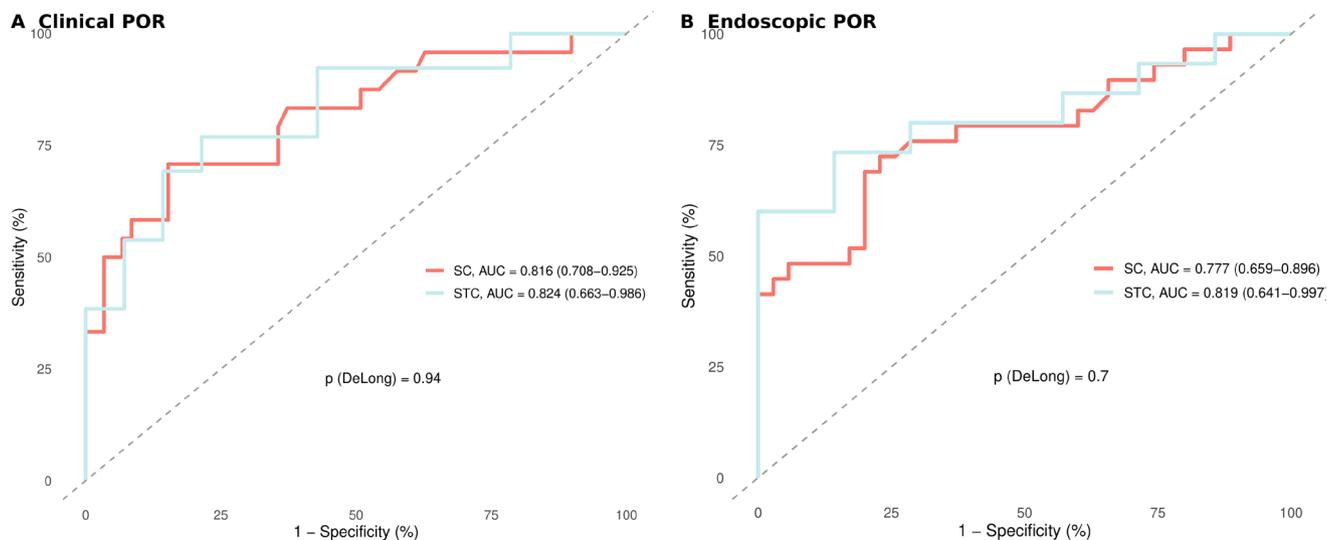
Additionally, we performed another sensitivity analysis excluding patients with affected surgical margins. Clinical POR remained significantly more frequent after STC compared with SC (53.4% vs 34.8%,  $p=0.017$ ). Endoscopic POR was also numerically higher in the STC group, although this difference did not reach statistical significance (56.9% vs 45.0%,  $p=0.12$ ). In survival analyses for the same subgroup, SC was associated with significantly higher clinical recurrence-free survival at both 1 and 5 years compared with STC (1 year: 79.2% vs 64.2%, 5 years: 58.5% vs 27.8%, log-rank  $p=0.004$ ). Similarly, endoscopic recurrence-free survival remained significantly higher after SC (1 year: 77.5% vs 58.5%, 5 years: 57.6% vs 24.9%, log-rank  $p=0.017$ ).

### 3.6 | Sensitivity Analyses in the IPTW-Weighted Cohort

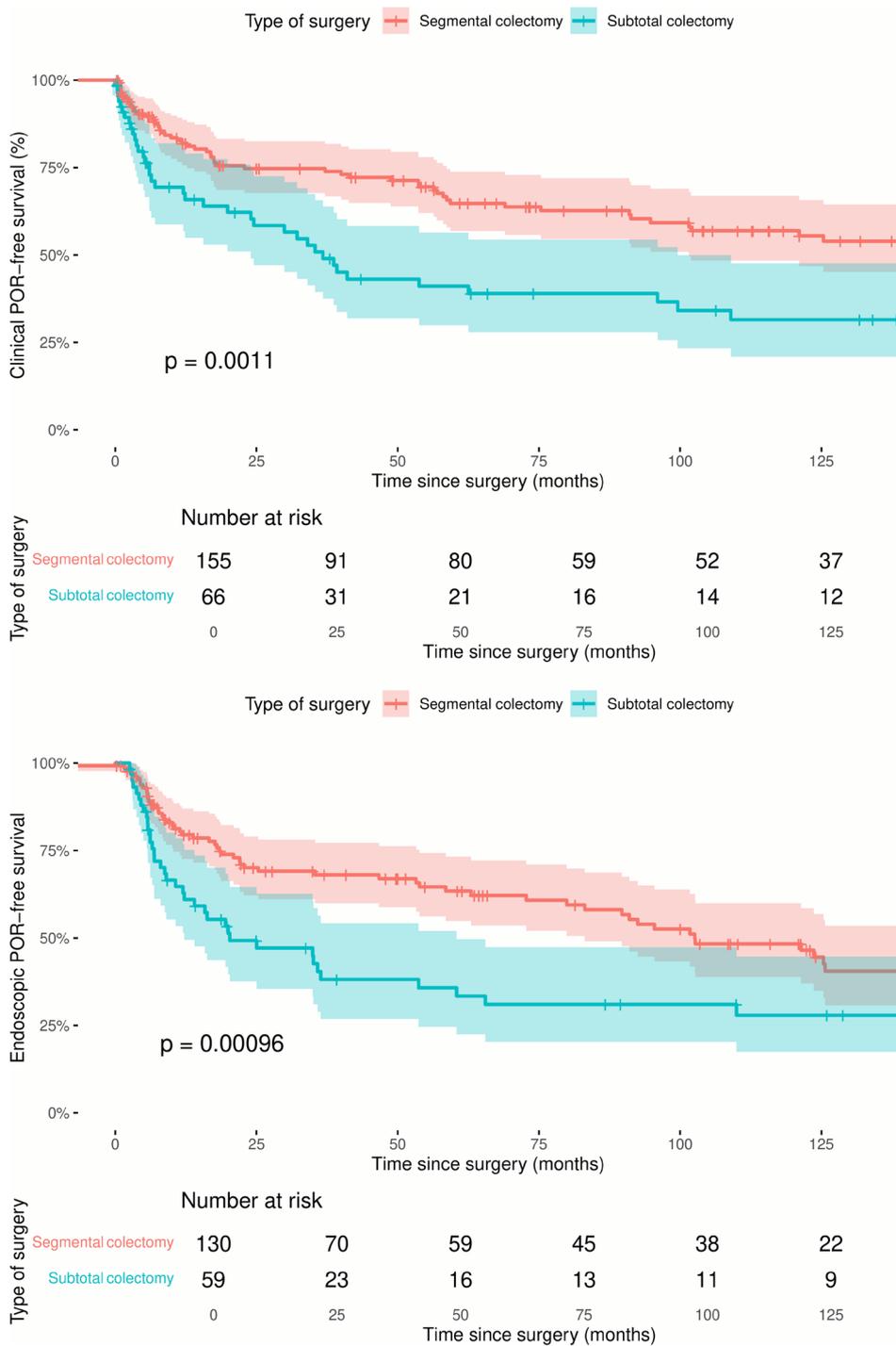
After applying IPTW, baseline covariates were well balanced between groups, with all SMD  $\leq 0.10$  (Table S5). In the IPTW-weighted population, clinical POR developed in 39.8% of patients undergoing SC and 70.8% of those undergoing STC ( $p<0.001$ ) while surgical POR occurred in 13.0% vs 14.1%,



**FIGURE 1** | Boxplots for fCal values between segmental and subtotal colectomy according to POR status. fCal, faecal calprotectin; POR, post-operative recurrence.



**FIGURE 2** | ROC curves for fCal and Clinical POR (left) and endoscopic POR (right), with corresponding AUC. AUC, area under the curve; fCal, faecal calprotectin; POR, post-operative recurrence; ROC, receiver operating characteristic.



**FIGURE 3** | Kaplan–Meier curves with 95% CIs for clinical and endoscopic POR-free survival. CIs, confidence intervals; POR, post-operative recurrence.

respectively ( $p=0.85$ ). Endoscopic POR occurred in 52.7% of SC patients vs 72.7% of STC patients ( $p=0.023$ ), while radiologic POR was observed in 46.5% vs 63.2%, respectively ( $p=0.19$ ). Among patients in the IPTW-weighted cohort who underwent endoscopy within the first postoperative year, endoscopic POR remained more frequent after STC vs SC (90.7% vs 63.2%;  $p=0.001$ ). After IPTW-weighted Cox models, SC was associated with a significantly lower risk of clinical (HR 0.50, 95% CI 0.32–0.78) and endoscopic (HR 0.58, 95% CI 0.36–0.94) POR.

#### 4 | Discussion

In this nationwide, retrospective study, patients with CD undergoing SC had significantly lower rates of both clinical and endoscopic POR compared with those undergoing STC. Clinical and endoscopic POR-free survival were higher after SC, while radiological and surgical recurrence rates did not differ significantly between groups. SC remained an independent protective factor after multivariable analysis, time-dependent

**TABLE 2** | Complete results from the multivariate Cox proportional hazards regression for clinical and endoscopic POR.

| Characteristics             | Clinical POR |            |              | Endoscopic POR |            |              |
|-----------------------------|--------------|------------|--------------|----------------|------------|--------------|
|                             | HR           | 95% CI     | <i>p</i>     | HR             | 95% CI     | <i>p</i>     |
| Sex                         |              |            |              |                |            |              |
| Female                      | 1.01         | 0.67, 1.53 | > 0.9        | 0.66           | 0.44, 0.98 | <b>0.037</b> |
| B3 phenotype                | 0.92         | 0.57, 1.49 | 0.7          | 0.61           | 0.38, 0.98 | <b>0.039</b> |
| Perianal disease            | 1.06         | 0.68, 1.64 | 0.8          | 1.08           | 0.71, 1.64 | 0.7          |
| Previous surgery            | 1.16         | 0.64, 2.11 | 0.6          | 1.13           | 0.61, 2.10 | 0.7          |
| Smoking                     | 1.57         | 0.94, 2.61 | 0.083        | 1.50           | 0.92, 2.45 | 0.11         |
| Type of colectomy           |              |            |              |                |            |              |
| SC                          | 0.54         | 0.35, 0.84 | <b>0.006</b> | 0.79           | 0.51, 1.22 | 0.3          |
| Myenteric plexitis          | 2.27         | 1.32, 3.92 | <b>0.003</b> | 1.96           | 1.05, 3.67 | <b>0.035</b> |
| Granulomas                  | 1.02         | 0.59, 1.79 | > 0.9        | 1.00           | 0.60, 1.67 | > 0.9        |
| Positive margins            | 0.87         | 0.49, 1.55 | 0.6          | 1.66           | 0.99, 2.80 | 0.054        |
| POR prevention with IMM     | 1.01         | 0.67, 1.53 | > 0.9        | 0.64           | 0.42, 0.99 | <b>0.046</b> |
| POR prevention with antiTNF | 0.82         | 0.50, 1.34 | 0.4          | 1.04           | 0.64, 1.70 | 0.9          |

Abbreviations: POR, post-operative recurrence; HR, hazard ratio; CI, confidence interval; SC, segmental colectomy; IMM, immunomodulator. Note: Bold values represent statistically significant results.

**TABLE 3** | Results of the multivariable Cox regression for clinical POR fitted with predictors retained after penalised LASSO variable selection.

| Characteristic     | HR   | 95% CI     | <i>p</i>     |
|--------------------|------|------------|--------------|
| Smoking            | 1.65 | 1.00, 2.70 | <b>0.049</b> |
| Type of colectomy  |      |            |              |
| STC                | —    | —          |              |
| SC                 | 0.54 | 0.36, 0.81 | <b>0.003</b> |
| Myenteric plexitis | 2.17 | 1.30, 3.61 | <b>0.003</b> |

Note: Bold values represent statistically significant results. Abbreviations: CI, confidence interval; HR, hazard ratio; SC, segmental colectomy; STC, subtotal colectomy.

modelling and IPTW-weighted sensitivity analyses; and we confirmed the association of previously recognised POR risk factors after ICR with POR after colonic resection. These findings suggest that segmental resections may be preferable in colonic CD and underscore the importance of incorporating established POR risk factors into clinical decision-making in this setting.

Previous retrospective cohorts have shown that SC is associated with lower stoma rates and improved surgical recurrence when compared with STC in colonic CD [14–16]. However, these studies do not reflect current strategies for POR prophylaxis, nor contemporary medical and endoscopic assessment and management. Recently, the SCOTCH project reported lower long-term rates of surgical recurrence after SC compared with STC and identified the absence of POR prophylaxis as an independent risk factor for surgical recurrence in CD

**TABLE 4** | Results of the multivariable Cox regression for endoscopic POR refitted with predictors retained after penalised LASSO variable selection.

| Characteristic           | HR   | 95% CI     | <i>p</i>     |
|--------------------------|------|------------|--------------|
| Sex                      |      |            |              |
| Male                     | —    | —          |              |
| Female                   | 0.67 | 0.45, 1.00 | 0.051        |
| B3 Montreal phenotype    | 0.65 | 0.42, 1.02 | 0.061        |
| Smoking                  | 1.54 | 0.96, 2.49 | 0.075        |
| Type of colectomy        |      |            |              |
| STC                      | —    | —          |              |
| SC                       | 0.76 | 0.50, 1.16 | 0.2          |
| Myenteric plexitis       | 1.97 | 1.10, 3.54 | <b>0.023</b> |
| Positive margins         | 1.70 | 1.02, 2.83 | <b>0.042</b> |
| POR Prophylaxis with IMM | 0.67 | 0.44, 1.02 | 0.060        |

Abbreviations: CI, confidence interval; HR, hazard ratio; POR, postoperative recurrence; SC, segmental colectomy; STC, subtotal colectomy; IMM: immunomodulator. Note: Bold values represent statistically significant results.

[7]. While SCOTCH mainly addressed surgical recurrence, the RESECOL cohort evaluates clinical, endoscopic and radiological outcomes, which have not previously been explored. The present data confirm a lower rate of clinical POR in CD patients undergoing SC compared with STC and, for the first time in the literature, also a lower rate of endoscopic recurrence, both in univariable and multivariable analysis, as well

**TABLE 5** | Hazard ratios for segmental colectomy (SC) and prophylaxis with immunomodulator (IMM) in the time-dependent Cox model for endoscopic POR. POR, post-operative recurrence.

| Time (months) from surgery | SC versus STC, HR (95% CI) | IMM prophylaxis versus No prophylaxis, HR (95% CI) |
|----------------------------|----------------------------|--|
| 12                         | <b>0.54 (0.35–0.82)</b>    | <b>0.48 (0.25–0.93)</b>                            |
| 24                         | 0.68 (0.44–1.03)           | 0.90 (0.45–1.80)                                   |
| 36                         | 0.77 (0.49–1.22)           | 0.96 (0.48–1.92)                                   |
| 48                         | 0.85 (0.52–1.41)           | 1.02 (0.50–2.09)                                   |
| 60                         | 0.92 (0.54–1.58)           | 1.06 (0.49–2.28)                                   |

Note: Bold values represent statistically significant results.

as after IPTW. Regarding radiologic POR, rates were numerically higher for STC, but differences did not reach statistical significance, probably due to the low number of patients in the STC group with available imaging. Surgical recurrence rates were similar among subgroups in the study, opposite to what has previously been reported. However, the overall rates of re-intervention were low in the study for both groups, likely related to advances in IBD medical therapy in recent years [17].

fCal is widely used in patients undergoing ICR, as it has prognostic value for the development of POR at the first endoscopy [18], and is also useful for subsequent follow-up of these patients [19]. In this study, patients with POR after colectomy exhibited significantly higher fCal values compared with those without POR; therefore, faecal biomarkers may provide valuable information in this scenario. This is also the first study reporting fCal cutoffs for the monitoring of CD patients after colectomy.

Moreover, our cohort adds to the identification of risk factors for POR in this setting. Smoking, positive proximal histopathological margin of the surgical specimen and myenteric plexitis are associated with an increased risk of POR after ICR [20, 21]. A consistent link of these factors with POR after colonic resection was confirmed in our data, as all variables remained significant after LASSO-guided refitting of the Cox regression. However, such association was not established for granulomas, which are also associated with POR after ICR [21]. Male sex and previous intestinal resection have also been proposed as risk factors for post-ICR POR [20, 22], while female sex has previously been linked to POR after colectomy [23]. Nonetheless, sex did not retain a significant association in the final multivariable model of our study.

To our knowledge, this is the largest cohort of patients with CD undergoing colonic resection that comprehensively describes clinical, endoscopic, biological and radiologic outcomes, while also exploring possible risk and protective factors for POR in this setting. Nevertheless, several limitations of the study should be acknowledged. First, given its retrospective design, the study carries an inherent risk of selection bias and unmeasured confounding. Current definitions of clinical POR

require demonstration of concomitant endoscopic POR [11], as patients in the post-operative period could also present with alternative causes for symptoms, such as bile acid diarrhoea or small intestinal bacterial overgrowth [24]. In the study, not all patients meeting the definition of clinical POR underwent endoscopic evaluation; however, since the definition of clinical POR in the study required initiation of immunosuppressive therapy, we consider alternative explanations for symptoms to be less likely than true clinical recurrence. Also, our definition of endoscopic POR is unconventional, as no established indices exist to define POR at the colocolonic or ileorectal anastomosis. The Rutgeerts score was developed for termino-terminal ileocolonic anastomoses [25], thus was not considered for patients in our cohort. Regarding risk factors for POR, we didn't compile the number of affected colonic segments, which has previously been associated with poorer outcomes [7, 26]. This limitation is particularly relevant, as the choice of surgical strategy is influenced by disease extent, anatomical considerations and surgeon preference; consequently, some degree of confounding by indication cannot be excluded. To mitigate this limitation, we performed a sensitivity analysis with IPTW based on a comprehensive set of baseline variables to achieve balanced comparison groups, which yielded results consistent with those in the overall cohort. Furthermore, the timing of postoperative assessments—including endoscopy, radiology and fCal measurements—was heterogeneous across patients, which may have introduced variability in outcome ascertainment. This was addressed through another sensitivity analysis restricted to evaluations performed within the first and two postoperative years, with an overall direction and magnitude of the results consistent with the primary analysis. Regarding radiologic POR, MRI and IUS in the study were assessed without standardised scoring systems, which may have introduced inter-center variability. Additionally, while undergoing SC may have a protective effect for endoscopic POR in the present study, this was found to be time-dependent and lost statistical significance beyond 12 months of follow-up. We believe this aligns with the time-dependent protective effect of POR prophylaxis with IMM, also reported in our regression analysis. Loss of response to prophylactic IMM has been described in the prevention of POR at the ileocecal region [27]; consequently, it could also be expected after colonic resection. Although anti-TNF agents show greater efficacy than IMM for the prevention of POR [28], our study was likely underpowered to detect an association between anti-TNF prophylaxis and reduced POR due to the small number of patients receiving anti-TNFs after surgery. Finally, regarding histopathological data, they were not available for all patients and were neither centrally reviewed nor analysed using validated scores, which may have affected the assessment of plexitis and margin involvement.

In conclusion, in this cohort, POR remains common after colectomy—both SC and STC—in CD. However, SC was associated with significantly lower rates of both clinical and endoscopic POR compared with STC. fCal serves as a non-invasive marker of POR in this setting. Previously established POR risk factors (such as smoking, positive margins and myenteric plexitis), as well as protective factors (such as POR prevention with an IMM) were confirmed to be relevant also after colectomy in CD and may guide prophylactic strategies

in these patients. Furthermore, SC remained protective for POR after multivariable regression and IPTW-weighted sensitivity analyses. Although prospective research is still warranted, these data support segmental resection of colonic CD when feasible.

### Author Contributions

**J. L. Rueda García:** conceptualization, methodology, data curation, formal analysis, writing – original draft, writing – review and editing. **C. Suárez Ferrer:** conceptualization, methodology, data curation, formal analysis, writing – review and editing, supervision. **I. García de la Filia Molina:** data curation, writing – review and editing. **C. Rivas:** data curation, writing – review and editing. **A. Fernández-Clotet:** data curation, writing – review and editing. **E. Céspedes Martínez:** data curation, writing – review and editing. **C. Martínez Cuevas:** data curation, writing – review and editing. **D. C. Balderramo:** data curation, writing – review and editing. **L. Arias:** data curation, writing – review and editing. **H. Martínez Lozano:** data curation, writing – review and editing. **M. Vaamonde Lorenzo:** data curation, writing – review and editing. **M. Calafat:** conceptualization, data curation, writing – review and editing. **D. Martín Rodríguez:** data curation, writing – review and editing. **J. X. Segarra Ortega:** data curation, writing – review and editing. **J. P. Gisbert:** data curation, writing – review and editing. **E. Brunet-Mas:** data curation, writing – review and editing. **I. González-Partida:** data curation, writing – review and editing. **E. Cerrillo Bataller:** data curation, writing – review and editing. **P. Varela Trastoy:** data curation, writing – review and editing. **K. Auquilla Pauta:** data curation, writing – review and editing. **L. Igualada Escribano:** data curation, writing – review and editing. **M. Marquès-Camí:** data curation, writing – review and editing. **C. Muñoz Villafranca:** data curation, writing – review and editing. **R. M. de Francisco García:** data curation, writing – review and editing. **A. Elosua González:** data curation, writing – review and editing. **I. Bastón-Rey:** conceptualization, data curation, writing – review and editing. **J. Martínez-Cadilla:** data curation, writing – review and editing. **L. Pardeiro Mariño:** data curation, writing – review and editing. **O. Belén-Galipienso:** data curation, writing – review and editing. **P. Vázquez García:** data curation, writing – review and editing. **M. Latre:** data curation, writing – review and editing. **P. Sendra Rumbou:** data curation, writing – review and editing. **A. Altadill Mauri:** data curation, writing – review and editing. **M. C. López-Martín:** data curation, writing – review and editing. **Á. Ponferrada-Díaz:** data curation, writing – review and editing. **M. R. Arribas López:** data curation, writing – review and editing. **S. Rodríguez-Sánchez:** data curation, writing – review and editing. **P. M. Wolfe García:** data curation, writing – review and editing. **M. A. Ruiz-Ramírez:** data curation, writing – review and editing. **O. Moralejo Lozano:** data curation, writing – review and editing. **P. Sanz Segura:** data curation, writing – review and editing. **L. Madrigal Bayonas:** data curation, writing – review and editing. **J. M. Huguet:** data curation, writing – review and editing. **G. Torres:** data curation, writing – review and editing. **I. Alonso Abreu:** data curation, writing – review and editing. **M. D. Martín-Arranz:** data curation, writing – review and editing. **M. Mañosa Ciria:** conceptualization, data curation, writing – review and editing. **Y. Zabana:** supervision, data curation, writing – review and editing. All authors read and approved the final manuscript.

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## Data Availability Statement

The data underlying this article will be shared on reasonable request to the corresponding author.

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### Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Data S1:** apt70608-sup-0001-Supinfo.docx.