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Male gender, active smoking and previous intestinal resection are risk factors of post-operative endoscopic recurrence in Crohn's disease: results from a prospective cohort study

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Summary

Background: After ileocaecal resection for Crohn's disease (CD), inflammatory lesions frequently recur on the anastomosis and/or on the neo-terminal ileum.

Aim: To identify predictors of early post-operative endoscopic recurrence.

Methods: From September 2010 to September 2017, the REMIND group conducted a prospective nationwide study in nine French academic centres. Data were collected at the time of surgery and endoscopy, performed 6-12 months after surgery. Endoscopic recurrence was defined as a Rutgeerts score ≥i2. Baseline factors associated with endoscopic recurrence were searched by univariate and multivariate regression analysis.

Results: Two hundred and eighty-nine CD patients were included. Endoscopy within 1 year following surgery was performed in 225 (78%) patients (104M/121F). Mean age and disease duration were 35 (12.2) and 8.8 (8.9) years respectively. Seventy (32%) patients were active smokers at surgery. One hundred and forty-two (63%) patients received at least one anti-TNF therapy before surgery. After surgery, 40 (18%) patients received thiopurines and 66 (29%) received an anti-TNF agent. Endoscopic recurrence occurred in 107 (47%) patients. In multivariate analysis, male gender (OR = 2.48 [IC 95% 1.40-4.46]), active smoking at surgery (OR = 2.65 [IC 95% 1.44-4.97]) and previous resection (OR = 3.03 [IC 95% 1.36-7.12]) were associated with a higher risk of endoscopic recurrence. Inversely, post-operative anti-TNF treatment decreased the risk of endoscopic recurrence (OR = 0.50 [IC 95% 0.25-0.96]).

Conclusions: Male gender, active smoking at surgery and previous intestinal resection are associated with a higher risk of endoscopic post-operative recurrence, while post-operative anti-TNF treatment is associated with a lower risk.

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List of REMIND study group investigators is provided in Appendix 1.

1 | INTRODUCTION

Despite improvements in the medical management of Crohn's disease (CD), more than two-thirds of patients need intestinal resection.[1-3] Post-operative recurrence is frequently observed and a preventive therapy is discussed in patients considered at risk. In a recent retrospective cohort study in two referral centres, clinical recurrence occurred in 45% by 5 years and 55% by 10 years and surgical recurrence in 7% by 5 years and 19% by 10 years.[4] Post-operative endoscopic recurrence features are mainly observed on the anastomosis and/or in the neo-terminal ileum, occurring in 70%-90% within 3 year following the resection.[5,6]

Rutgeerts et al demonstrated that the course of the disease was best predicted by the severity of the early post-operative lesions, as observed at ileocolonoscopy.[7] Indeed, patients with no or mild endoscopic lesions had a lower risk of clinical recurrence than patients with more severe endoscopic recurrence. Ileocolonoscopy is currently the gold standard to assess post-operative recurrence and to predict the risk of clinical recurrence.[8,9] The POCER study demonstrated that treatment according to clinical risk of recurrence, with early colonoscopy at 6 months post-operatively and treatment step up for recurrence, is superior to conventional drug therapy alone, in preventing disease recurrence.[10]

The main factors identified as increasing post-operative recurrence are active smoking, penetrating behaviour, history of perianal disease, prior intestinal resection, extent of small bowel resection and absence of prophylaxis treatment.[9,11-14] These risk factors were recently used in prospective clinical trials to select patients at high risk.[10,15]

Several therapies have been evaluated in the prevention of post-operative recurrence. A meta-analysis concluded that thiopurines and mercaptopurine are more effective than placebo in the prevention of clinical and endoscopic post-operative recurrence.[16] A recent randomised clinical trial demonstrated that mercaptopurine was effective in preventing post-operative clinical recurrence, but only in patients who were smokers.[17] Infliximab have a demonstrated efficacy in the prevention of post-operative endoscopic recurrence.[15,18,19] A sub-analysis performed in the POCER study suggested that adalimumab may be superior to thiopurines in preventing early endoscopic post-operative recurrence in high-risk patients.[20] In a recent randomised controlled trial, adalimumab was not superior to azathioprine to prevent post-operative endoscopic recurrence at 1 year, but the population was not selected for high risk for recurrence.[21]

The aim of our study was to identify predictors of post-operative endoscopic recurrence in a large prospective multicentric cohort of CD patients who underwent ileocolonic resection.

2 | METHODS

This is a prospective study performed in nine centres of the REMIND group. Inclusion criteria were: age >18 years, ileal or ileocolonic CD and indication of CD-related intestinal surgery (ileocolonic resection). A post-operative treatment was proposed according to a pre-established algorithm, based on the following risk factors: current smoking, previous bowel resection, penetrating phenotype and active perianal disease. No treatment or 5-aminosalycilic acid was proposed to patients with no risk factor; thiopurines, or anti-TNF agents in case of previous thiopurine failure, were prescribed in patients with one risk factor; anti-TNF therapy (alone or in combination with azathioprine) was prescribed in patients with two or more risk factors. About 6-12 months after surgery a colonoscopy was performed to assess the endoscopic recurrence according to the Rutgeerts score. The study was approved by the local ethic committee: Comité de protection des personnes Ile-de-France IV—CPP 2009/17.

2.1 | Data collection

Clinical and biological parameters were prospectively collected at two time points: at the time of surgery and at the post-operative endoscopy. Variables including demographical data (gender, age at diagnosis, age at surgery, smoking status at surgery), clinical data (disease phenotype and behaviour at surgery, according to the Montréal classification,[22] previous history of intestinal resection, Harvey-Bradshaw index at surgery and at time of post-operative endoscopy, surgery indication), treatment history including previous exposure to immunosuppressants (azathioprine, mercaptopurine or methotrexate) and anti-TNF agents, exposure to antibiotics within 4 weeks before surgery, exposure to 5ASA within 3 months before surgery, exposure to corticosteroids within 3 months before surgery, exposure to immunosuppressants within 3 months before surgery, exposure to anti-TNF agents within 3 months before surgery and date of the last anti-TNF administration, type of anti-TNF treatment (infliximab, adalimumab or others), nutritional data (weight, height, body mass index, oral or parenteral preoperative support) and surgical techniques (length of resection margin, length of small bowel resection and anastomotic technique) were analysed. Biological data were systematically collected on the day of surgery including haemoglobin, leucocytes, lymphocytes, neutrophils, platelets, albumin and C-reactive protein. Trough serum infliximab and adalimumab levels and anti-drugs antibodies were determined for all patients using the Lisa-Tracker Duo Infliximab enzyme-linked immunoassay (ELISA) kit (Theradiag, Marne La Vallée, France). Limits of detection were 10 ng/mL for both antibodies-to-adalimumab (ATA) and antibodies-to-infliximab (ATI). Trough levels of detection of anti-TNF drugs were 0.3 μg/mL.

2.2 | Endoscopic data

All endoscopic lesions were reported in all segments, including the anastomotic region and the neo-terminal ileum. The Rutgeerts score was evaluated for each patient by the physician who performed colonoscopy. Two physicians (MA and CA) checked the colonoscopy's report blinded of treatment. Endoscopic recurrence was defined as a Rutgeerts score ≥i2. We also used the modified Rutgeerts score published in a form of an abstract by Gesce et al to take into account the situation with ulcers confined to ileocolonic

anastomosis (as a nonrecurrence) and lesions of the neo-terminal ileum with or without anastomotic lesions (as recurrence).[23]

2.3 | Statistical analysis

Quantitative variables were expressed as median and interquartile ranges [Q1-Q3] or mean and SD according to their distribution; qualitative variables were expressed by frequency and percentage. The comparison of qualitative variables was realised by chi-squared or Fisher's exact tests (for variables with small sample sizes). For quantitative variables, we used the Student's *t* test (for variables with normal distribution and homogeneity of their variance). If these conditions were not valid we used the Mann-Whitney's test.

The identification of factors associated with the endoscopic recurrence was performed by logistic regression model. Results are expressed as odds ratio (OR) with 95% confidence intervals. In a sensitivity analysis, to address the possibility of treatment selection bias, we used propensity score for post-operative treatment statistically associated with endoscopic recurrence. The propensity score was estimated with the logistic regression analysis with the dichotomous exposure variable, for instance 1 = exposed to treatment (anti-TNF therapy) and 0 = unexposed to treatment (anti-TNF therapy). All variables that may influence the decision to prescribe a post-operative treatment were included in a multivariate logistic regression analysis (gender, stoma, age at surgery, smoking status at surgery, previous resection, penetrating phenotype, anoperineal lesion, Harvey-Bradshaw index at surgery, pre-operative treatment: anti-TNF, steroids, immunosuppressant therapy, antibiotics). We used the matching method with the technique of the nearest available matching on the estimated propensity score to construct a matched sample.[24]

P value <0.05 was considered significant. All statistical tests were two-sided. All analyses were performed using R software (R Foundation for Statistical Computing, Vienna, Austria), version 3.2.2.

3 | RESULTS

3.1 | Characteristics of patients at baseline

Two hundred and eighty-nine patients were included between 1 September 2010 and 30 September 2017. Fifty-six (19%) had no colonoscopy, for the following reasons: lost to follow up (n = 37), patient refusal (n = 16), need of a second surgery within 6 months (n = 2), pregnancy (n = 1). Two hundred and thirty-three patients underwent a post-operative endoscopy. Eight patients were excluded from the analysis for colonoscopy delayed of more than 12 months. Finally, 225 patients were analysed. The mean time between resection and colonoscopy was 7.3 (1.9) months. The flow chart is presented in Figure 1. Rutgeerts score was available in all patients except one due to a nonpassable colonic stricture. Demographic and clinical characteristics at the time of surgery are detailed in Table 1. Thirty-two (14%) patients had a two-stage surgery with temporary stoma. Seven patients had another small bowel resection and one patient had strictureplasty associated to ileocolonic resection. Four patients had also a colonic resection (three of the sigmoid for ileo-sigmoid fistulas, and one because of a stricture on the left angle.

3.2 | Post-operative prevention

After surgery, 88 patients received no treatment and 24 received 5ASA. Forty patients (18%) received an immunosuppressant alone (azathioprine, n = 38; methotrexate, n = 2). Sixty-six patients (29%)

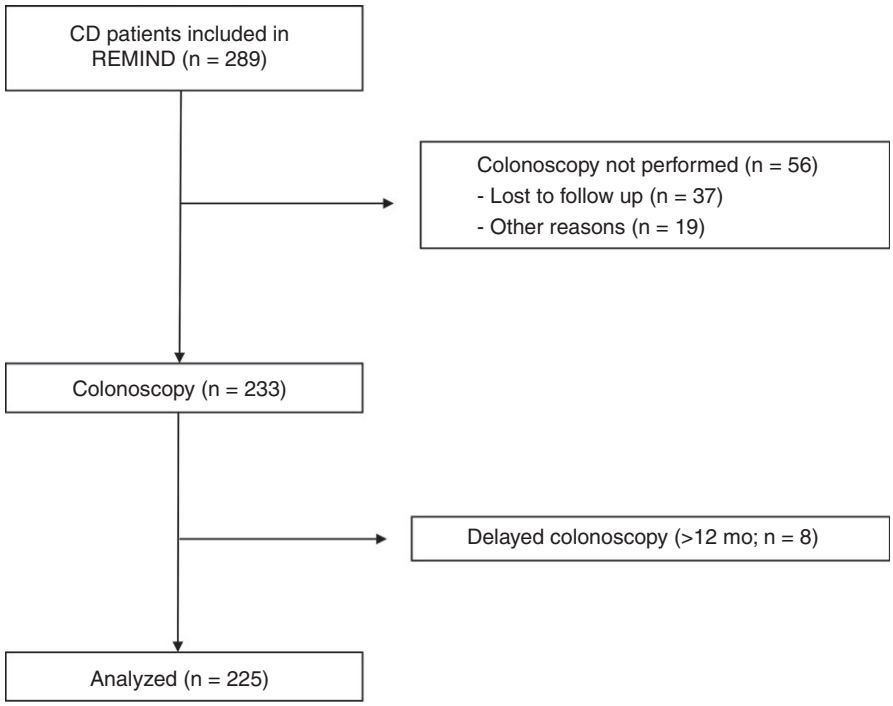

FIGURE 1 Flow chart

TABLE 1 Patient characteristics at time of surgery

	N = 225 (%)
Men	104 (47)
Mean age (y, SD)	34.6 (12)
Age at diagnosis	
≤16 y (A1)	26 (12)
17-40 y (A2)	176 (78)
>40 y (A3)	23 (10)
Mean disease duration (y, SD)	8.8 (9)
Mean time between resection and colonoscopy (mo, SD)	7.3 (1.9)
Active smoker at surgery	73 (32)
Smoking cessation	14 (19)
Previous intestinal resection	42 (19)
<10 y	14 (6)
Number of previous resection(s)	
0	183 (81)
1	29 (13)
2	9 (4)
3	4 (2)
Surgical indication	
Stricturing complication	126 (56)
Penetrating complication	85 (38)
Failure of drug therapy	14 (6)
Disease phenotype (Montreal classification)	
Inflammatory phenotype (B1)	9 (4)
Stricturing phenotype (B2)	117 (52)
Penetrating phenotype (B3)	99 (44)
Disease location (Montreal classification)	
Ileal (L1)	139 (62)
Ileocolonic (L3)	83 (37)
Anoperineal lesion	51 (23)
Extra-digestive symptoms	
Joint manifestations	41 (18)
Skin manifestations	12 (5)
Eye manifestations	4 (2)
Median Harvey-Bradshaw index (Q1-Q3)	5 (2-7)
Mean body mass index (kg/m^2, min-max)	21.8 (14-39)
Pre-operative enteral nutrition	37 (16)
Pre-operative parenteral nutrition	33 (15)
Previous exposure to anti-TNF therapy	142 (63)
Anti-TNF therapy <3 mo before surgery	112 (50)
Adalimumab	70 (62)
Infliximab	42 (38)
Previous exposure to thiopurines	163 (72)
Thiopurines <3 mo before surgery	71 (32)

received an anti-TNF therapy (adalimumab, n = 49 [74%]; infliximab, n = 15 [23%]; certolizumab, n = 1; golimumab, n = 1), as monotherapy in 55 patients or in combination with an immunosuppressant in 11 patients. Seven patients, who previously failed with or did not tolerate infliximab and adalimumab, received another biotherapy (ustekinumab, n = 4; vedolizumab, n = 3).

3.3 | Description of post-operative endoscopy

According to the Rutgeerts classification, 73 patients (32%) were i0 and 44 patients (20%) were i1, while 60 patients (27%), 20 patients (9%) and 27 patients (12%) were i2, i3 and i4 respectively.

Because the period of follow-up was 7 years with a median interval of 5 years we split the cohort in two groups: the first 5 years (cohort 1) and the 5 last years (cohort 2). When we compared these two populations (respectively n = 114 and n = 111) we did not observe statistical differences in the characteristics of patients. The rate of post-operative anti-TNF was 24% for cohort 1 versus 35% for cohort 2 (P = 0.082). The rate of recurrence was also similar in the two groups (50% vs 46%; P = 0.68).

3.4 | Predictors of post-operative endoscopic recurrence

In bivariate analysis, three factors were associated with an increased risk of post-operative endoscopic recurrence (Rutgeerts ≥i2): male gender, active smoking at surgery and previous intestinal resection (Table 2).

A multivariate analysis was performed after adjustment for gender, age, pre-operative anti-TNF, post-operative immunosuppressants, post-operative anti-TNF, previous intestinal resection, penetrating behaviour, perianal disease and active smoking at surgery. Male gender (OR = 2.48 [CI 95% 1.40-4.46]), active smoking at surgery (OR = 2.65 [CI 95% 1.44-4.97]) and previous intestinal resection (OR = 3.03 [CI 95% 1.36-7.12]) were associated with a higher risk of endoscopic recurrence, while post-operative anti-TNF treatment was associated with a lower risk (OR = 0.50 [CI 95% 0.25-0.96]) (Table 3). There were no interactions between the gender and other variables. The description of the cohort according to the gender is described in Table S1.

3.5 | Sensitivity analysis

A sensitivity analysis with propensity score method for bias reduction in the comparison of post-operative anti-TNF treatment was conducted (198 patients were matched 2:1). The characteristics of patients before and after matching is described in Tables S2 and S3. In this analysis, post-operative anti-TNF treatment was still associated with a decrease risk of endoscopic recurrence (OR = 0.52 [CI 95% 0.28-0.96]; P = 0.036).

Another sensitivity analysis was performed among the 112 patients who had no post-operative treatment (no anti-TNF, no immunosuppressive therapy) after surgery. In this analysis, male gender (OR = 3.92 [CI 95% 1.66-9.89]), previous intestinal resection (OR = 4.61 [CI 95% 1.15-23.22]) and active smoking at surgery (OR=2.78 [CI 95% 1.14-7.11]) were still associated with endoscopic recurrence i0-i1 versus i2-i4.

TABLE 2 Bivariate analysis: predictors of early endoscopic recurrence

	No endoscopic recurrence (i0-i1), n = 117 (%)	Endoscopic recurrence (i2-i4), n = 107 (%)	*P*-value
Gender (male)	43 (37)	60 (56)	0.006
Mean age (y, SD)	33.8 (11.8)	35.6 (12.4)	0.30
BMI (kg/m^2, SD)	21.5 (4.8)	22.0 (3.5)	0.40
Mean time between diagnosis and surgery (y, SD)	8.2 (8.4)	8.5 (9.6)	0.70
Previous intestinal resection	15 (13)	27 (25)	0.03
Indication for surgery			
Stricturing disease	63 (54)	63 (59)	0.30
Penetrating disease	49 (42)	36 (34)	
Other reasons	5 (5)	8 (7)	
Active smokers at surgery	26 (22)	46 (43)	0.001
Smoking cessation	4 (4)	10 (9)	0.80
Perianal disease	28 (24)	23 (22)	0.80
Penetrating phenotype	58 (50)	41 (38)	0.10
Anastomosis technique			
Side-to-side anastomosis	99 (85)	81 (76)	0.20
End-to-end anastomosis	16 (14)	24 (22)	
Side-to-end anastomosis	2 (1)	2 (2)	
Length of small bowel resection (cm)	22.6 (19.3)	23.5 (17.3)	0.70
Healthy resection margin (>5 cm)	64 (55)	48 (44)	0.10
Pre-operative antibiotics	41 (35)	35 (33)	0.80
Pre-operative steroids	39 (33)	38 (36)	0.80
Preoperative IS[a]	40 (34)	31 (29)	0.50
Pre-operative anti-TNFα[a]	59 (50)	53 (50)	1
Post-operative antibiotics	8 (7)	7 (6)	1
Post-operative IS	18 (15)	22 (21)	0.20
Post-operative anti-TNFα	40 (34)	26 (24)	0.09

[a]Received within the last 3 mo before surgery.

Considering that there is a risk of misclassification between i1 and i2, we conducted another sensitivity analysis with a strict definition of endoscopic remission corresponding to no lesions at all (i0) versus any lesions (i1-i4), using the same model of logistic regression. Seventy-three patients (32%) were graded i0 and 151 patients (68%) had a score ≥i1. Three clinical variables were associated with endoscopic recurrence: male gender (OR = 2.07 [CI 95% 1.12-3.92]; *P* = 0.02), active smoking at surgery (OR = 2.26 [CI 95% 1.15-4.63]; *P* = 0.02) and post-operative anti-TNF treatment (OR = 0.29 [CI 95% 0.15-0.57]; *P* < 0.001).

By using the modified Rutgeerts score, only one-third of patients (n = 84) had a post-operative endoscopic recurrence (i2b-i3-i4). In the same multivariable model, we identified the same risk factors: male gender (OR = 2.40 [1.36-4.30]; *P* = 0.003), active smoking at surgery (OR = 2.72 [1.11-3.82] *P* = 0.001), previous intestinal resection (OR = 3.11 [1.40-7.27]; *P* = 0.007) and post-operative anti-TNF treatment (OR = 0.49 [0.25-0.95]; *P* = 0.038). We also performed an analysis to identify risk factors of severe endoscopic recurrence (≥i3): only previous intestinal resection associated with post-operative endoscopic recurrence (OR = 3.54 [CI 95% 1.48-9.41]).

TABLE 3 Multivariable analysis: predictors of early endoscopic recurrence

	Odds ratio	95% confidence interval	*P*-value
Gender (male)	2.48	1.40-4.46	0.002
Age	0.99	0.96-1.02	0.51
Previous intestinal resection	3.03	1.36-7.12	0.008
Active smokers at surgery	2.65	1.44-4.97	0.002
Perianal disease	0.97	0.49-1.90	0.92
Penetrating complication	0.74	0.41-1.35	0.33
Pre-operative anti-TNFα	0.99	0.56-1.79	0.98
Post-operative IS[a]	0.93	0.46-1.86	0.83
Post-operative anti-TNFα[a]	0.50	0.25-0.96	0.04

[a]Received within the last 3 months before surgery.

3.6 | Adherence to the predefined algorithm

We looked whether post-operative therapies had been prescribed according to the predefined algorithm and presence of pre-established risk factors. Forty-four patients (20%) had no risk factor, 111 patients (49%) had one risk factor and 70 patients (31%) had two or more than two risk factors. In the patient's group with ≥two risk factors, only 40% of patients received post-operative anti-TNF therapy while it was suggested. Compared to patients with optimal treatment, being under-treated was associated with a higher rate of endoscopic recurrence (OR = 1.90 [CI 95% 1.06-3.44]).

3.7 | Rate of post-operative endoscopic recurrence according to the number of risk factors

According to our results, we selected active smoking at surgery, male gender and previous intestinal resection as clinical risk factors. We observed a rate of 29% of recurrence (Rutgeerts ≥i2) in patients with no risk factors, 46% in patients with one risk factor and 74% in patients with two or three risk factors. The rate of recurrence increased with the number of risk factors, with an OR of 2.08 [CI 95% 1.09-4.06; *P* = 0.03] for one risk factor and an OR of 6.86 [CI 95% 3.19-15.5; *P* < 0.001] for two or three risk factors. The rate of severe recurrence (i3-i4) increased with the number of risk factor (Figure 2). Severe endoscopic recurrence was associated with smoking but not with male gender. The recurrence rate of recurrence according to gender and smoking status are described in Figure S1.

Among patients who did not receive a post-operative anti-TNF therapy (n = 159), the rate of recurrence according to number of risk factors was higher as compared to the whole cohort. Indeed,

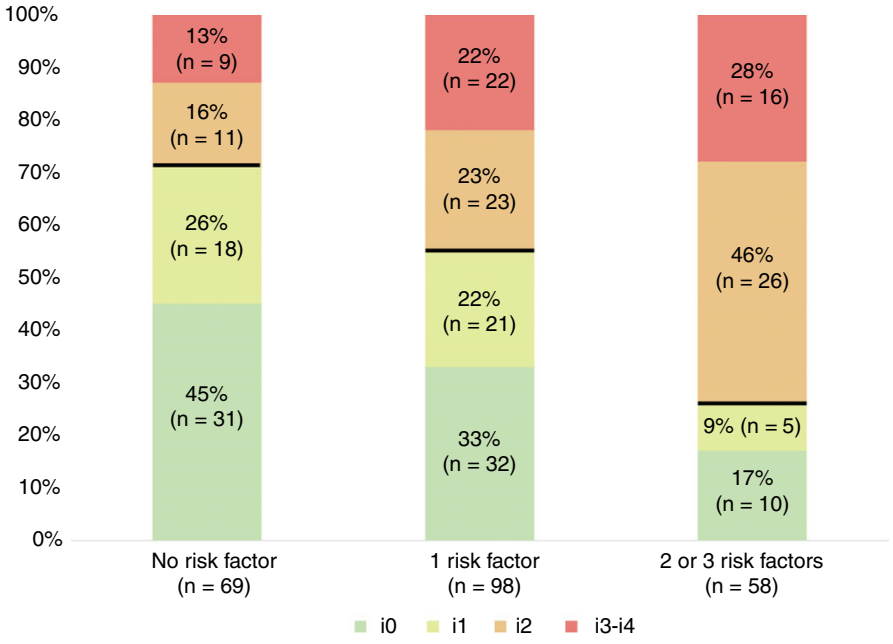

FIGURE 2 Rates of post-operative endoscopic recurrence (≥i2) according to number of risk factors

endoscopic recurrence was more frequent in patients with two or three risk factors (OR = 10.92 [CI 95% 4.14-32.2]; $P < 0.001$).

3.8 | Pharmacokinetics and immunogenicity

We analysed the efficacy of post-operative anti-TNF therapy (infliximab or adalimumab) according to the presence of anti-drug antibodies at time of surgery. Sixty-four patients received adalimumab (n = 49) or infliximab (n = 15), combined with an immunosuppressant in 11 patients (five with adalimumab and six with infliximab). Seventeen of those patients (26%) were naïve of anti-TNF therapy before surgery. Thirty-five patients had previously received adalimumab and 12 patients received infliximab. Thirty-six patients received the same anti-TNF treatment before and after surgery. At time of surgery, 10 patients had detectable anti-drug antibodies (five ATA and five ATI) and 43 had no anti-drug antibodies (11 missing data). Among the 10 patients who had anti-drug antibodies at time of surgery, eight (80%) presented an endoscopic recurrence (i2-i4). In contrast, the rate of endoscopic recurrence was 30% among the 43 patients who had no anti-drug antibodies at time of surgery ($P = 0.01$). Six of the eight patients having anti-drug antibodies at time of endoscopy had an endoscopic recurrence.

3.9 | Safety

There were no deaths. Post-operative complications have been reported in a previous study including 209 patients of the present cohort.[25] The rate of early post-operative complication (within 1 month after surgery) was 21%. No infusion reaction related to anti-TNF therapy was reported. No complication related to the colonoscopy was reported. One patient developed pulmonary tuberculosis after three injections of adalimumab.

4 | DISCUSSION

In this prospective multicentre cohort study, almost half of patients had an early post-operative endoscopic recurrence defined by a Rutgeerts score ≥i2. This cohort population is representative of patients followed in tertiary centres with almost two-third of patients already treated with anti-TNF monoclonal antibodies. We identified four factors associated with an increased risk of post-operative endoscopic recurrence: active smoking at surgery, previous intestinal resection, male gender and absence of post-operative anti-TNF therapy. The impact of active smoking behaviour has been previously demonstrated in retrospective studies to be associated with an increased risk of clinical, endoscopic and surgical recurrence.[26-28] In the prospective strategy trial POCER, smoking was also associated with an increased risk of endoscopic recurrence at 18 months (OR = 2.4 [CI 95: 1.2-4.8]).[10] In our study, smokers at time of surgery had an approximately threefold increased risk of endoscopic recurrence compared with nonsmokers. Only 19% of smokers at surgery stopped tobacco consumption after surgery. We did not observe a benefit among those patients, probably because of the short interval between surgery and endoscopy and a lack of power.

Importantly, we found that male gender was a risk factor for post-operative endoscopic recurrence. To the best of our knowledge, it is the first time that male gender is identified as a risk factor for post-operative recurrence in the literature. In our cohort, clinical characteristics were similar between men and women, including smoking behaviour. Interestingly, a previous GETAID study identified male gender as a risk factor for relapse after stopping infliximab.[29] Also, a retrospective study has reported an association between male gender and early colectomy in ulcerative colitis.[30] A recent study performed in early onset inflammatory bowel disease

(diagnosed before 10 years of age) found that males with CD had more upper gastrointestinal disease, more extensive disease and more severe disease activity at presentation than females.[31] Recently, Severs et al reported sex-related differences in two independent cohorts of inflammatory bowel disease patients. Male patients had more frequently an early onset CD (>16 years). They were more often diagnosed with ileal disease and they underwent more often small bowel and ileocaecal resection.[32] In our cohort, rates of previous resection between men and women were similar. Also, in our study, even if male gender was associated with post-operative endoscopic recurrence, it was not with severe endoscopic recurrence. Long-term follow-up will clarify if male gender is associated with a severe clinical outcome. These differences in disease outcome according to gender could be potentially related to hormonal, immunological, genetic, epigenetic or behaviour factors (such as diet and smoking behaviour).

Previous intestinal resection is considered as a common risk factor for post-operative recurrence. In our cohort, previous intestinal resection was associated with an increased risk of endoscopic recurrence. Interestingly the rate of previous intestinal resection was low in our cohort (17%) as compared to the POCER study where one-third of patients had a previous intestinal resection or to the PREVENT study where 43% of patients had a previous resection within 10 years. Similarly, to a recent prospective cohort or to two recent controlled randomised studies, we did not identify penetrating disease as a risk factor for endoscopic recurrence.[4,15,21] In a recent meta-analysis B3 phenotype was identified as a risk factor, however, there was a high heterogeneity.[33]

In our cohort, post-operative anti-TNF therapy was the only therapeutic drug associated with a reduction risk of endoscopic recurrence. Twenty-six patients (39%) treated with anti-TNF after surgery had an endoscopic recurrence (Rutgeerts ≥ i2). This rate was superior to the rates of post-operative recurrence found in the prospective randomised studies PREVENT and POCER, respectively 22.4% and 21%.[15,20] This lower efficacy of anti-TNF in our cohort could be related to the fact that almost two-third of our patients had been exposed to anti-TNF before surgery, while only a minority had been previously exposed to anti-TNF in these studies. The detection of anti-drug antibodies at time of surgery might be useful in the post-operative therapeutic decision. Indeed, patients with positive ATI or ATA had a higher rate of post-operative recurrence.

We found that the recommendations of the defined algorithm were not strictly followed in our cohort. This may reflect the difficulty to strictly follow the algorithm in clinical practice, which can be influenced by the patient choice.

There are several limitations to our study. First, there was no endoscopic central reading. We recognise that there is a risk of misclassification between i1 and i2, even if the agreement between the Rutgeerts score evaluated by the physician who performed the colonoscopy and the physicians who checked the colonoscopy's report was excellent (κ = 0.94 [IC 95% 0.11-1]). For this reason, we also performed an analysis with a definition of endoscopic recurrence by a Rutgeerts score ≥i1 (i0 vs i1-i4), and found the same risk factors. Second, we did not identify a protective effect of post-operative immunosuppressive therapy (mainly thiopurines). This could be explained by the low number of patients (n = 40) treated with immunosuppressants after surgery in our cohort. Nevertheless, studies are heterogeneous on efficacy of thiopurines.[34] Third, our period of observation was limited to the first year and the outcome was mainly based on endoscopic recurrence. We need to evaluate the impact of these risk factors on long-term clinical and surgical recurrence.

In this prospective multicentre nationwide cohort study, we identify active smoking at surgery, previous intestinal resection and male gender as risk factors of post-operative endoscopic recurrence. We also find a protective effect of anti-TNF therapy. These data provide an important insight for clinical practice and may modify current algorithms of post-operative management. A long-term follow-up of our cohort is needed to reinforce our findings.

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Author contributions: CA: statistical analysis, analysis and interpretation of data and drafting of the manuscript; SN: data collection and critical review of the manuscript; MLTM: data collection and critical review of the manuscript; AB: data collection and critical review of the manuscript; BP: data collection and critical review of the manuscript; CS: data collection; MF: data collection and critical review of the manuscript; PM: data collection and critical review of the manuscript; XT: data collection and critical review of the manuscript; XJ: interpretation of data and critical review of the manuscript; NH: data collection,PS: data collection, interpretation of

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SUPPORTING INFORMATION

Additional supporting information will be found online in the Supporting Information section at the end of the article.

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APPENDIX 1

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