Journal of Crohn's and Colitis, 2023, **17**, 221–230
https://doi.org/10.1093/ecco-jcc/jjac128
Advance access publication 12 September 2022
Original Article

Prophylactic Medication for the Prevention of Endoscopic Recurrence in Crohn's Disease: a Prospective Study Based on Clinical Risk Stratification

Jeanine H. C. Arkenbosch[a,*], Evelien M. J. Beelen[a,*], Gerard Dijkstra[b], Mariëlle Romberg-Camps[c], Marjolijn Duijvestein[d,e], Frank Hoentjen[e,f], Sander van der Marel[g], P.W. Jeroen Maljaars[h], Sita Jansen[i], Nanne K. H. de Boer[j], Rachel L. West[k], Carmen S. Horjus[l], Laurents P. S. Stassen[m], Fiona D. M. van Schaik[n], Oddeke van Ruler[o], Bindia J. H. Jharap[p], Marijn Visschedijk[b], Alfred Janssen[q], Nicole S. Erler[r,s], Michail Doukas[t], Ariadne H. A. G. Ooms[u], Gursah Kats-Ugurlu[v], Christien Janneke van der Woude[a], Annemarie C. de Vries[a]; On behalf of the Dutch Initiative on Crohn's and Colitis (ICC)

[a]Department of Gastroenterology and Hepatology, Erasmus University Medical Center, Rotterdam, the Netherlands
[b]Department of Gastroenterology and Hepatology, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands
[c]Department of Gastroenterology and Hepatology, Zuyderland Medical Center, Sittard-Geleen, the Netherlands
[d]Department of Gastroenterology and Hepatology, Amsterdam University Medical Centers, University of Amsterdam, AGEM Research Institute, Amsterdam, the Netherlands
[e]Department of Gastroenterology and Hepatology, Radboud University Medical Center, Nijmegen, the Netherlands
[f]Division of Gastroenterology, Department of Medicine, University of Alberta, Edmonton, Canada
[g]Department of Gastroenterology and Hepatology, Haaglanden Medical Center, The Hague, the Netherlands
[h]Department of Gastroenterology and Hepatology, Leiden University Medical Center, Leiden, the Netherlands
[i]Department of Gastroenterology and Hepatology, Reinier de Graaf Groep, Delft, the Netherlands
[j]Department of Gastroenterology and Hepatology, Amsterdam University Medical Centers, Vrije Universiteit Amsterdam, AGEM Research Institute, Amsterdam, the Netherlands
[k]Department of Gastroenterology and Hepatology, Franciscus Gasthuis & Vlietland, Rotterdam, the Netherlands
[l]Department of Gastroenterology and Hepatology, Rijnstate Hospital, Arnhem, the Netherlands
[m]Department of Surgery, Maastricht University Medical Center, Maastricht, the Netherlands
[n]Department of Gastroenterology and Hepatology, University Medical Center Utrecht, Utrecht, the Netherlands
[o]Department of Surgery, IJsselland Hospital, Capelle aan den IJssel, the Netherlands
[p]Department of Gastroenterology and Hepatology, Meander Medical Center, Amersfoort, the Netherlands
[q]Department of Surgery, Zuyderland Medical Center, Sittard-Geleen, the Netherlands
[r]Department of Biostatistics, Erasmus University Medical Center, Rotterdam, the Netherlands
[s]Department of Epidemiology, Erasmus University Medical Center, Rotterdam, the Netherlands
[t]Department of Pathology, Erasmus University Medical Center, Rotterdam, the Netherlands
[u]Department of Pathology, Pathan BV, Rotterdam, the Netherlands
[v]Department of Pathology, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands

Corresponding author: A. C. De Vries, MD, PhD, Department of Gastroenterology and Hepatology Erasmus University Medical Center, PO Box 2040, 3000 CA, Rotterdam, the Netherlands. Tel: 0031 107 030 792; Email: a.c.devries@erasmusmc.nl
*These authors share first authorship

Abstract

Background: To prevent recurrence after ileocolonic resection [ICR] in Crohn's disease [CD], postoperative prophylaxis based on risk stratification is recommended in international guidelines. This study aimed to evaluate postoperative CD recurrence after implementation of a clinical management algorithm and to determine the predictive value of clinical and histological risk factors [RFs].

Methods: In this multicentre, prospective cohort study, CD patients [≥16 years] scheduled for ICR were included. The algorithm advised no postoperative medication for low-risk patients, and treatment with prophylaxis [immunosuppressant/biological] for high-risk patients [≥1 RF: active smoking, penetrating disease, prior ICR]. Clinical and histological RFs [active inflammation, granulomas, plexitis in resection margins] for endoscopic recurrence [Rutgeerts' score ≥i2b at 6 months] were assessed using logistic regression and ROC curves based on predicted probabilities.

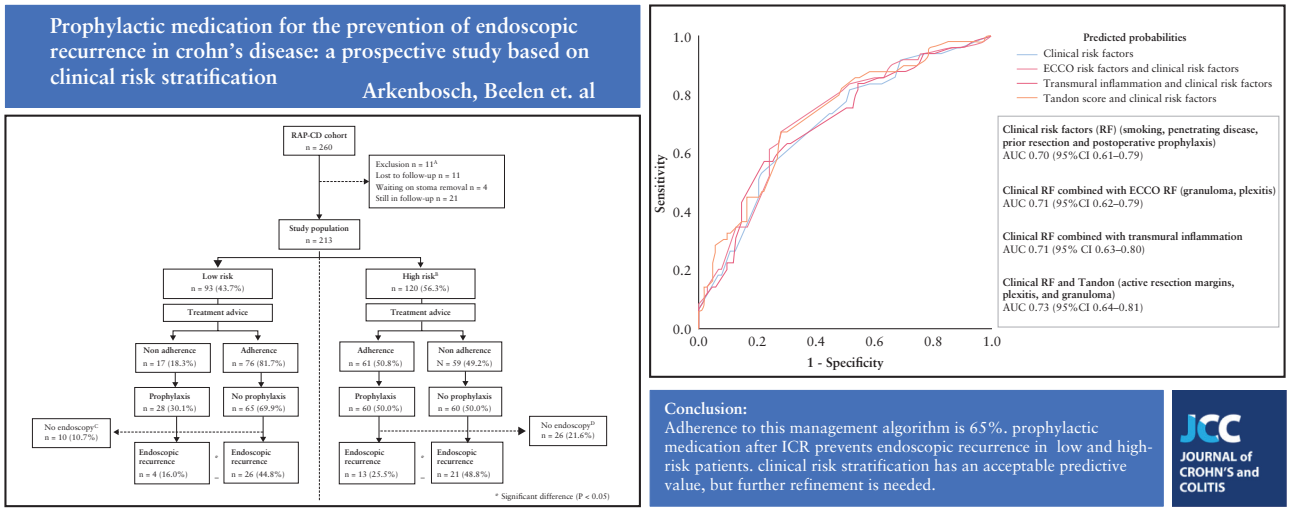
Results: In total, 213 CD patients after ICR were included [age 34.5 years; 65% women] (93 [44%] low-risk; 120 [56%] high-risk: 45 [38%] smoking; 51 [43%] penetrating disease; 51 [43%] prior ICR). Adherence to the algorithm was 82% in low-risk [no prophylaxis] and 51% in

high-risk patients [prophylaxis]. Endoscopic recurrence was higher in patients treated without prophylaxis than with prophylaxis in both low [45% vs 16%, $p = 0.012$] and high-risk patients [49% vs 26%, $p = 0.019$]. Clinical risk stratification including the prescription of prophylaxis corresponded to an area under the curve [AUC] of 0.70 (95% confidence interval [CI] 0.61–0.79). Clinical RFs combined with histological RFs increased the AUC to 0.73 [95% CI 0.64–0.81].

Conclusion: Adherence to this management algorithm is 65%. Prophylactic medication after ICR prevents endoscopic recurrence in low- and high-risk patients. Clinical risk stratification has an acceptable predictive value, but further refinement is needed.

Key Words: Ileocecal resection; postoperative recurrence; Crohn's disease

Graphical Abstract



1. Introduction

Although ileocolonic resection [ICR] rates in Crohn's disease [CD] patients have decreased over the past decades, ICR remains an important treatment of ileal or ileocolonic CD.[1,2] Postoperative recurrence after ICR is common. Historically, endoscopic recurrence rates are estimated at 65–80% within 1 year of surgery.[3] Currently, postoperative ileocolonoscopy within 6–12 months after ICR is considered the gold standard to timely diagnose postoperative endoscopic recurrence. Both neo-terminal ileum and ileocolonic anastomosis are assessed to identify the presence and severity of lesions, preceding clinical symptoms.[4,5]

To prevent postoperative endoscopic recurrence, current ECCO and AGA guidelines advise to start prophylactic medication after ICR in patients at high risk of recurrence.[4,6,7] However, identification of these high-risk patients remains a challenge as strong, consistent predictors are scarce. Commonly used clinical risk factors for postoperative recurrence include active smoking, penetrating disease behaviour and previous ileocolonic resection.[4] Nevertheless, the efficacy of prophylactic treatment, according to postoperative clinical risk stratification to prevent postoperative recurrence, is unknown. In the recent literature, it has been proposed to include histological features of the ICR specimens to enhance risk stratification. The ECCO evidence-based consensus on the surgical management of CD describes granulomas and myenteric plexitis as histological predictors.[4] A recent meta-analysis identified granulomas, myenteric and/or submucosal plexitis, and active inflammation of the resection margins as individual predictors of postoperative recurrence.[8] In addition, transmural lesions have been described as an important prognostic feature.[9] The predictive value and congruity of these histological findings for the postoperative course of CD remain uncertain.

In this study, we aimed to prospectively evaluate postoperative recurrence of CD after implementation of a management algorithm incorporating clinical risk stratification. Furthermore, we estimated the predictive value of known clinical and histological risk factors for endoscopic recurrence after ICR.

2. Methods

2.1 Study design

In this prospective, multicentre cohort study, patients with CD aged ≥16 years undergoing ICR in eight university and six non-academic hospitals were included from March 2017 until March 2021. Exclusion criteria were indication for ICR other than CD, absence of preoperative ileal disease activity, presence of active CD elsewhere in the gastrointestinal tract and/or permanent ileostomy.

A standardized postoperative management algorithm for the start of prophylactic medication was proposed. In this algorithm, all active smokers were strongly advised to quit smoking preoperatively. At ICR, patients were divided into two groups: group 1 [low risk of postoperative recurrence] and group 2 [high risk of postoperative recurrence]. Low risk was defined as the absence of risk factors for postoperative recurrence. High risk was defined as the presence of one or more of the following risk factors: active smoking, penetrating disease and/or previous ileocolonic resection. No prophylactic treatment was recommended in group 1, and start of prophylactic therapy after ICR was recommended in group 2. The choice of prophylactic therapy [immunomodulator and/or biological] was left to the discretion of the treating physician. Start or continuation of postoperative immunomodulators or biologicals before endoscopy for other indications, including but not limited to perianal fistula and extra-intestinal

manifestations, was recorded and not considered to be a protocol deviation. Postoperatively, an ileocolonoscopy was performed 6 months after ileocolonic anastomosis, with an accepted window of 3–9 months. To enhance risk stratification, histological risk factors were centrally assessed.

2.2 Clinical data collection

Data were collected at a preoperative visit, at ICR and at a postoperative visit at 6 months after ICR. The collected data consisted of patient-related characteristics [e.g. age, smoking status and body mass index], disease-related characteristics [e.g. disease duration, medication exposure prior to ICR and Montreal classification] and surgical characteristics [e.g. surgical technique and postoperative complications].

2.3 Endoscopic assessment

Ileocolonoscopy was recorded on high-resolution video. Two trained blinded central readers [J.A., E.B.] reviewed video-recordings of ileocolonoscopy in random order. The ileocolonic anastomosis was assessed according to the modified Rutgeerts' score (differentiating the i2 score in: ulcerations at the anastomosis [i2a] and more than five ulcerations in the neoterminal ileum [i2b]).[3,10] Endoscopic outcomes were subsequently compared with the primary assessment of the local endoscopist who performed the ileocolonoscopy. In the case of discrepancy between the central and local Rutgeerts' score, a conclusion was made based upon consensus between the two central readers. If no consensus was obtained, a third experienced endoscopist was consulted [A.C.V.]. If video recordings of the ileocolonoscopy were unavailable, endoscopic images were used for central reading.

2.4 Pathology assessment

All haematoxylin-eosin [H&E]-stained histology slides of the surgical resection specimen were centrally collected. Three experienced gastrointestinal pathologists [M.D., A.O. and G.K.] analysed samples in a blinded and random manner according to a standardized assessment schedule. Regular consensus meetings between all pathologists were organized to define the histopathological features assessed, to discuss ambiguous cases and to form a consensus opinion. The pathologists evaluated the following items at the proximal ileal and distal colonic margins in all available H&E-slides: presence of active inflammation, transmural inflammation, myenteric and/or submucosal plexitis, and granulomas. The most affected region was used to determine the score. Active inflammation in the resection margins was defined as presence of cryptitis in combination with crypt abscess[es], crypt destruction, ulceration[s] and/or erosion[s]. Transmural inflammation was defined as extension of inflammatory cells into the adipose tissue, including lymphoplasmacytic infiltrate of the subserosa. Plexitis was defined as the presence of four or more inflammatory cells [eosinophils, lymphocytes, mast cells and/or plasma cells] adjacent to or present in ganglia or nerve bundles in the myenteric and/or submucosal plexus. Granulomas were considered present if they were *de novo* identified, irrespective of their localization in the intestinal wall. Cryptolytic granulomas were excluded.

2.5 Endpoint

The primary endpoint was endoscopic recurrence defined as a Rutgeerts' score ≥i2b at ileocolonoscopy 6 months postoperatively.

2.6 Data analyses

Continuous variables were described as medians and interquartile ranges [IQR] and were compared using Mann–Whitney U test. Categorical variables, including the absolute risk of endoscopic recurrence in the different risk categories, were expressed as frequencies and percentages and compared using a chi-square test.

2.7 Regression models and ROC curves from predicted probabilities

A binary logistic regression model was fitted to assess associations between clinical risk factors and postoperative endoscopic recurrence. Clinical risk factors, identified in the current literature,[4,6,7] were included in this model and comprised: smoking, previous ileocolonic resection, young age at diagnosis, disease localization [Montreal L] at time of surgery, penetrating disease behaviour [Montreal B3] at time of surgery, and start of postoperative prophylaxis. Results from the logistic regression model were presented as odds ratios [OR] and 95% confidence intervals [CIs].

Predicted probabilities were estimated based on logistic regression models for endoscopic recurrence using the clinical and/or histological risk factors listed below. Receiver operating characteristic [ROC] curves from the predicted probabilities for endoscopic recurrence were plotted to assess the predictive value of clinical and histological predictors in patients with available ileocolonoscopy. First, an ROC curve was plotted including the predicted probabilities from the clinical risk factors used in our standardized management algorithm: active smoking, previous ileocolonic resection, penetrating disease behaviour and postoperative prophylactic medication. Second, ROC curves were plotted using predicted probabilities from the above-mentioned clinical risk factors combined with three histological risk profiles. The following three histological profiles in the resection margins were analysed: (a) adapted from the ECCO guideline[4] [presence of granulomas and/or myenteric plexitis], (b) based on the meta-analysis from Tandon *et al.*,[8] further referred to as Tandon risk factors [presence of active inflammation, granulomas and/or (myenteric and/or submucosal) plexitis], and (c) transmural inflammation.[9]

A *p*-value of 0.05 was accepted as statistically significant. All analyses were performed with IBM Statistical Packages for Social Sciences [SPSS] version 15.0 for Windows [IBM Corp.].

2.8 Ethical statement

This study was conducted in accordance with the ethical principles of the *Declaration of Helsinki*. All patients provided written informed consent prior to study inclusion. The research protocol was approved by the medical ethical committee of the Erasmus Medical Center Rotterdam [METC-2017-482] and by the local board of directors and/or research committee of all participating hospitals.

3. Results

3.1 Baseline characteristics

A total of 260 patients were included after ICR for CD in this ongoing cohort study, of whom 213 were included in the analysis [Figure 1]. The median age at ICR was 34.5 [IQR 25.7–51.1] years and 139 [65.3%] patients were women [Table 1]. Median

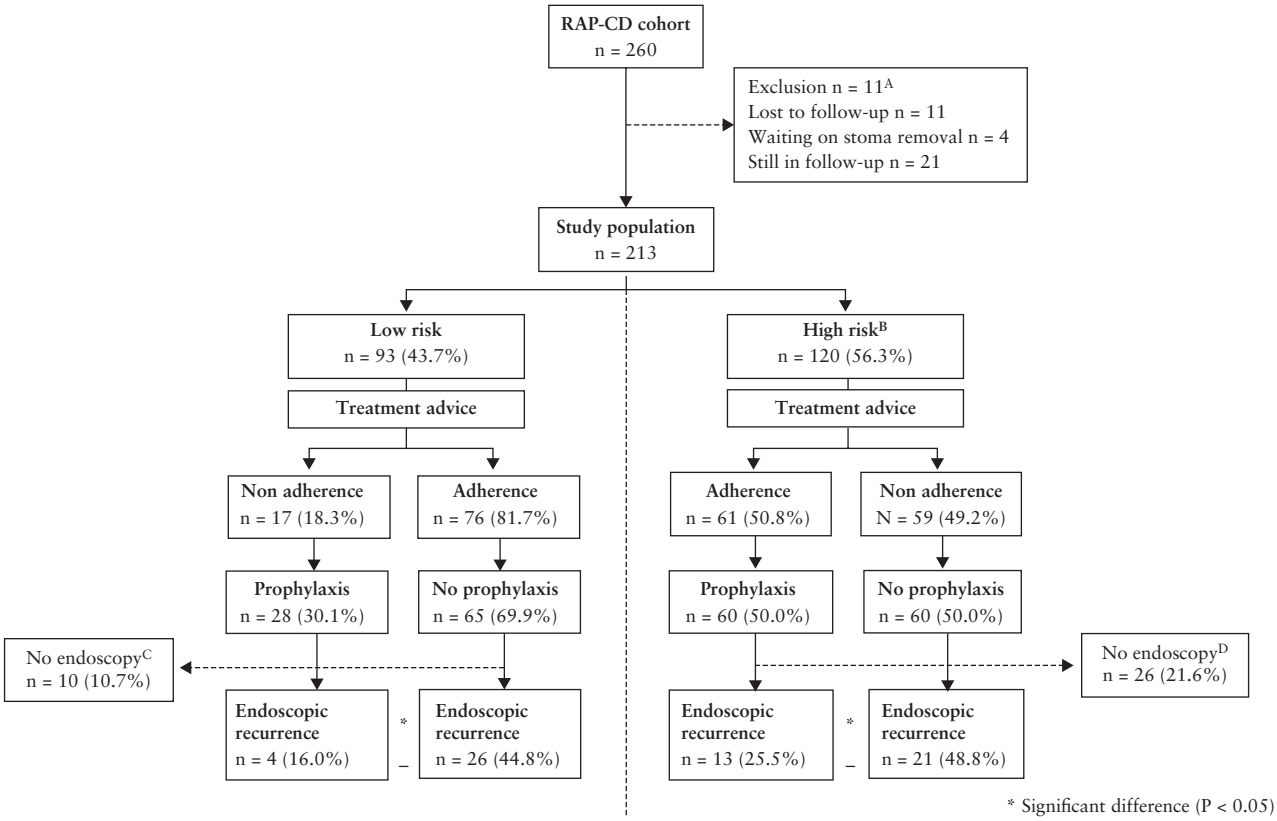


Figure 1. Study flow chart comparing endoscopic recurrence in low-risk and high-risk Crohn's disease patients after ileocolonic resection. [A]Reasons for exclusion were as follows: no ileocecal resection performed [*n* = 8], no histological ileal disease at time of surgery [*n* = 1], presence of malignancy in resection specimen leading to differences in postoperative follow-up [*n* = 1] and withdrawn informed consent [*n* = 1]. [B]Risk factors present: active smoking *n* = 45, previous resections *n* = 51, penetrating disease *n* = 51. [C,D]Including *n* = 2 with colonoscopy, but no available images for central read.

disease duration was 6.6 [IQR 1.6–13.0] years. Forty-five [21.3%] patients were active smokers of whom seven [15.6%] stopped smoking after ICR. A total of 51 [23.9%] patients had undergone a previous intestinal resection for CD, including 17 [8.0%] patients with more than one intestinal resection.

3.2 Surgical data

Indications for ICR included non-complicated CD disease in 41 [19.2%] patients [B1 according to the Montreal classification], stricturing disease [Montreal B2] in 121 [56.8%] patients and penetrating disease [Montreal B3] in 51 [23.9%] patients, based on preoperative imaging and operative findings [Table 1]. Disease localization at ICR was restricted to the ileum in 127 [59.6%] patients, and 86 [40.4%] patients had ileocolonic disease. Fifteen [7.0%] patients underwent a two-stage procedure with temporary stoma, after a median delay of 16 [IQR 12.0–40.0] weeks following primary surgery. Postoperative complications included anastomotic leakage in 11 [5.2%] patients and haemorrhage in six [2.8%] patients. Ten [4.7%] patients underwent repeat surgery, for an indication of anastomotic leakage in six patients, bleeding in two patients, ileus in one patient and abdominal infection in one patient. Postoperative mortality did not occur during follow-up.

3.3 Risk categories and prophylactic treatment

According to the standardized postoperative management algorithm, 93 [43.7%] patients were considered at low risk of postoperative CD recurrence. A total of 120 [56.3%] patients were considered at high risk of recurrence based on the presence of the above-mentioned risk factors. Overall, a total of 88 [43.1%] patients received postoperative prophylactic treatment to prevent postoperative recurrence (28 [30.1%] patients in the low-risk group vs 60 [50.0%] patients in the high-risk group). Prophylactic treatment was started after a median of 3.7 [IQR 0.6–8.6] weeks following ileocolonic anastomosis. Of the patients who received prophylactic treatment, 26 [29.6%] received immunomodulator monotherapy (24 [92.3%] thiopurine, two [7.7%] methotrexate), 46 [52.3%] biological monotherapy (of which 18 [39.1%] adalimumab, eight [17.4%] infliximab, four [8.7%] vedolizumab, 16 [34.7%] ustekinumab), and 16 [18.1%] combination therapy of an immunomodulator and biological. In the high-risk group, 20 [16.7%], 33 [27.5%] and seven [5.8%] patients received an immunomodulator, biological or a combination of both. In the low-risk group, six [6.5%], 13 [14.0%] and nine [9.7%] received an immunomodulator, biological or combination of both [Supplementary Table 1]. Of the patients who received postoperative prophylaxis in the low-risk group, three [10.7%] were newly started on prophylactic medication vs 25 [89.3%] who continued pre-operative treatment postoperatively. In the high-risk group, 25 [41.7%] patients vs 60 [58.3%] were newly started vs continued treatment postoperatively. See Supplementary Table 2 for specification of the different preoperative and postoperative treatment agents.

3.4 Adherence to protocol for postoperative prophylactic medication

Adherence to the proposed management algorithm was 65%; 76 out of 93 [81.7%] in the low-risk [no prophylaxis] group

Table 1. Baseline and surgical data of the study population who underwent ileocolonic resection for Crohn's disease. Low-risk was defined as no risk factors present and high-risk as one or more of the risk factors: smoking, penetrating disease and previous resection

		Total population [*n* = 213]		Low-risk group [*n* = 93]		High-risk group [*n*=120]	
Age at ICR, years		34.5 [25.8–51.1]		28.9 [23.2–43.2]		38 [28.1–53.4]	
Female		139	65.3	66	71.0	73	60.8
Smoking status at time of ICR	Never	105	49.8	61	66.3	44	37.0
	Previous	61	28.9	31	33.7	30	25.2
	Active	47	21.3	0	—	47	37.8
BMI at time of ICR		23.8 [21.3–25.9]		24.3 [21.1–26.9]		23.5 [21.3–25.8]	
Age at diagnosis [Montreal]	<17 years [A1]	37	17.5	19	20.4	18	15.1
	17–40 years [A2]	124	58.5	55	59.1	69	58.0
	>40 years [A3]	51	24.1	19	20.4	32	26.9
Location at ICR [Montreal]	Ileum [L1]	127	59.6	58	62.4	69	57.5
	Ileocolonic [L3]	86	40.4	35	37.6	51	42.5
Behaviour at ICR [Montreal]	Luminal [B1]	41	19.2	31	33.3	10	8.3
	Stricturing [B2]	121	56.8	62	66.7	59	49.2
	Penetrating [B3]	51	23.9	0	—	51	42.5
Prior upper GI localization [Montreal L4]		11	5.2	5	5.4	6	5.0
Perianal fistula at ICR		14	6.6	9	9.7	5	4.2
Positive family history		43	26.2	25	35.2	18	19.4
Prior intestinal resections	None	162	76.1	93	100.0	69	57.5
	1 resection	34	16.0	0	—	34	28.3
	>1 resection	17	8.0	0	—	17	14.2
Immunomodulator use prior to ICR		155	74.5	67	73.6	88	75.2
Anti-TNF use prior to ICR		145	69.0	62	68.1	83	69.7
Surgical approach	Laparoscopy	178	84.0	87	93.5	91	76.5
	Laparotomy	34	16.0	6	6.5	28	23.5
Length resected segment, cm		24 [23–26]		22 [20–25]		25 [24–27]	
Type of anastomosis	Side-to-side	181	95.3	79	94.0	102	96.2
	End-to-end	3	1.6	1	1.2	2	1.9
	End-to-side	6	3.2	4	4.8	2	1.9
	Unknown	23	10.8	9	9.7	14	11.7
Postoperative anastomotic leakage		11	5.2	4	4.8	7	5.8
Postoperative bleeding		6	2.8	4	4.8	2	1.9
Re-intervention for postoperative complicationa		10	4.8	4	4.8	6	5.0

Values are *n* [%] or median [interquartile range]. In the case of missing data, valid percentages are presented.
Abbreviations: ICR, ileocolonic resection; BMI, body mass index; GI, gastrointestinal; TNF, tumour necrosis factor.
[a]Re-intervention included laparotomy and/or laparoscopic procedures for postoperative complication.

and 61 of 120 [50.8%] in the high-risk group [prophylactic medication]. Factors disregarded in the high-risk group were smoking in 45.8% [27/59] of patients, penetrating disease in 42.4% [25/59] and/or previous resection in 33.9% [20/59]. The most common reasons for deviation from the proposed algorithm were physician's preference in 26 patients [11 low-risk and 15 high-risk patients] and patient's wish in 17 patients [one low-risk patient and 16 high-risk patients]. In the low-risk cases, protocol deviation was mostly due to weighing additional factors as risk factors, such as length of resected specimen, age at CD diagnosis and upper gastrointestinal localization [Montreal L4] at diagnosis. In 31 patients the reason for algorithm deviation was unknown [five low-risk and 26 high-risk patients]. In total, 7/45 [15.6%] smokers quit smoking between surgery and the 6-month visit, after they had already been divided into the high-risk category, and five of these patients had already received prophylactic medication.

3.5 Postoperative endoscopic recurrence

A total of 181 patients [84.9%] underwent ileocolonoscopy 6 months after ICR. Endoscopic images were available for central assessment of the Rutgeerts' score in 177 patients [83 low-risk and 94 high-risk patients]. Eighty [45.2%] of the central read endoscopies were video recorded and 97 [54.8%] were assessed on photographs.

Postoperative endoscopic recurrence [Rutgeerts' score ≥i2b] was diagnosed in 64/177 patients [36.2%], and at a similar rate in the low- (30 [36.1%]) and high-risk (34 [36.2%]) groups [p = 0.997]. In the low-risk group, endoscopic recurrence was diagnosed in 26 [44.8%] of the patients without postoperative prophylaxis compared to four [16.0%] patients with prophylaxis [p = 0.012]. In the high-risk group, endoscopic recurrence was also diagnosed more often in patients without prophylaxis (21 [48.8%]) compared to patients with prophylaxis (13 [25.5%], p = 0.019).

Endoscopic recurrence rates in the high-risk population were 6/19 [31.6%] for immunomodulator, 7/27 [25.9%] for biological and 0/5 [0%] for combination therapy; and respectively 0/5 [0%], 3/11 [27.3%] and 1/9 [11.1%] in the low-risk population. Due to the relatively low number of patients within subgroups no statistical analysis was performed.

The Rutgeerts' scores at postoperative endoscopy in the low- and high-risk groups are displayed in Figure 2. In the total cohort, 24 patients had endoscopic disease activity in the colon of whom 11 [45.8%] also had disease activity at the anastomosis or terminal ileum.

3.6 Predicted probability of clinical and histological risk factors for endoscopic recurrence

Multivariable logistic regression analysis of clinical risk factors for the risk of endoscopic recurrence showed an association with the start of postoperative prophylaxis (OR 0.34 [95% CI, 0.16–0.72]) and ileocolonic disease localization (OR 3.39 [95% CI 1.59–7.26], Table 2). No significant association could be demonstrated for active smoking (OR 1.84 [95% CI 0.75–4.45]), penetrating disease (OR 1.81 [95% CI 0.82–3.99]) and prior ICR (OR 1.38 [95% CI 0.59–3.22]).

For clinical risk factors incorporated in the management algorithm of this study [smoking, penetrating disease, prior ICR and prophylactic medication], the area under the curve [AUC] for endoscopic recurrence was 0.70 [95% CI 0.61–0.79]. Histological assessment of H&E-stained slides was performed in 196 [92.0%] patients. All histological items are listed in Table 3. The addition of histological factors to the clinical risk factors resulted in an AUC of 0.71 [95% CI 0.62–0.79] according to the ECCO guideline, an AUC of 0.73 [95% CI 0.64–0.81] for Tandon risk factors and an AUC of 0.71 [95% CI 0.63–0.80] for transmural inflammation [Figure 3].

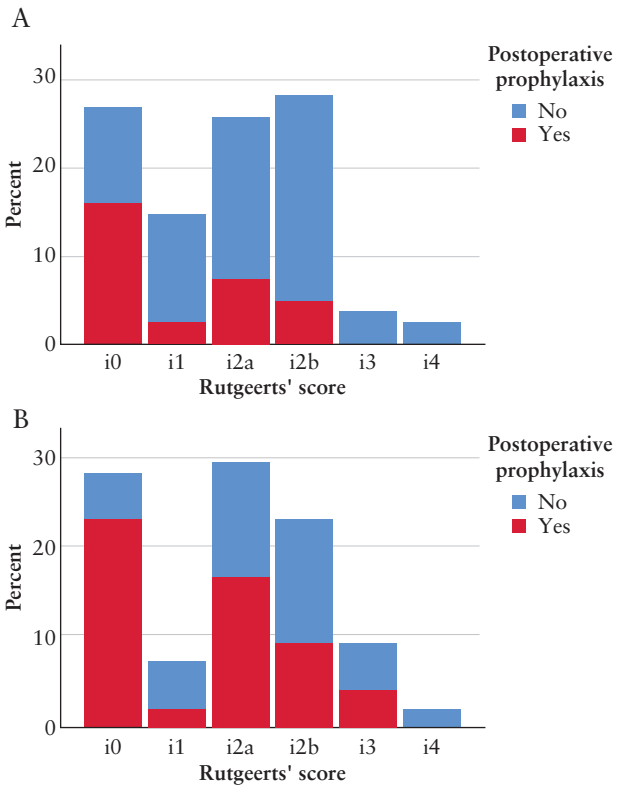


Figure 2. [A] Rutgeerts' score at colonoscopy 6 months after ileocolonic resection in 83 low-risk CD patients. [B] Rutgeerts' score at colonoscopy 6 months after ileocolonic resection in 94 high-risk CD patients.

4. Discussion

This prospective multicentre cohort study demonstrates that adherence to a standardized postoperative management algorithm incorporating clinical risk stratification is 65% after ICR in CD patients. Both physician and patient preferences caused deviations from the proposed management strategy. Prophylactic medication is associated with a risk reduction of endoscopic recurrence of 29% in low-risk and 23% in high-risk patients. Furthermore, the predictive value of current clinical risk factors including the prescription of postoperative prophylaxis for endoscopic recurrence [Rutgeerts' score >i2b] is acceptable. The addition of histological factors to the clinical risk factors has limited added predictive value.

Our data underline the importance of prophylaxis in high-risk patients. However, as the adherence to the proposed algorithm was only 65%, the reluctance of physicians and patients to the postoperative prescription of prophylactic medication requires exploration and, possibly, improved education. In particular, the high rate of active smokers [57%], which were not treated with prophylactic medication, requires

Table 2. Results from the binary logistic regression analyses of clinical risk factors for endoscopic recurrence [Rutgeerts' score ≥i2b] in 175 Crohn's disease patients who had an ileocolonoscopy at 6 months after ICR

	OR	95% CI		*p*-value
		Lower	Upper	
Active smoking	1.84	0.75	4.47	1.181
Previous ileocolonic resection	1.38	0.59	3.22	0.461
Young age at diagnosisb	0.62	0.29	1.32	0.218
Disease localization at ICRc	3.39a	1.59a	7.26a	0.002a
Penetrating disease behaviour at ICRd	1.81	0.82	3.99	0.144
Postoperative prophylactic medication	0.34a	0.16a	0.72a	0.005a

Abbreviations: OR, odds ratio; CI, confidence interval; ICR, ileocolonic resection.
[a]Statistically significant
[b]Young age defined as <30 years of age at ICR.
[c]Disease localization according to Montreal classification: ileocolonic vs ileal.
[d]Disease behaviour according to Montreal B3 classification.

Table 3. Histopathological assessment in Crohn's disease patients who underwent ileocolonic resection with available resection specimens

		Total population [*n* = 196]	
Median length of the resection specimen, centimetre		24	17.0-33.0
Proximal resection margin			
Active inflammation		41	21.8
Transmural inflammation		16	8.2
Plexitis		43	22.9
	Myenteric plexitis	28	15.1
	Submucosal plexitis	28	14.9
Granuloma		10	5.3
Distal resection margin			
Active inflammation		8	4.4
Transmural inflammation		2	1.0
Plexitis		32	16.2
	Myenteric plexitis	22	12.6
	Submucosal plexitis	16	8.7
Granuloma		6	3.2
Mesentery (*n* = 191 [97.0%])			
Chronic inflammatory cells		163	84.0
Absceding inflammation		35	18.3
Fibrosis		130	67.0
Granuloma		32	16.5
Lymph nodes (*n* = 132 [67.0%])			
Presence of giant cells		29	21.2
Presence of granuloma		34	24.8

Values are *n* [%] or median [interquartile range]. In the case of missing data, valid percentages are presented.

attention. Pre-operative counselling of patients to stop smoking could significantly reduce the risk of postoperative recurrence, and averting the need to take postoperative medication may serve as an extra motivation for patients to stop smoking.[11–13] Educating physicians on risk factors and the necessity of starting postoperative prophylaxis in high-risk patients might reduce postoperative recurrence rates. Current guidelines and the increasing number of publications on this topic contribute to this.

The balance between under- and overtreatment is a challenge in the low-risk group. This population seems insufficiently characterized by current guidelines,[4,6,7] because the risk of endoscopic recurrence without prophylaxis is still as high as 45%. In addition, a significant reduction in endoscopic recurrence is achieved after prescription of prophylactic medication. Although the overall risk of endoscopic recurrence is lower in the low-risk population without prophylaxis as compared to the high-risk population, the number needed to treat [NNT] to prevent one case of endoscopic recurrence was even lower in the low-risk population as compared to the high-risk population [NNT 3.5 vs 4.5]. Therefore, better identification of patients who would

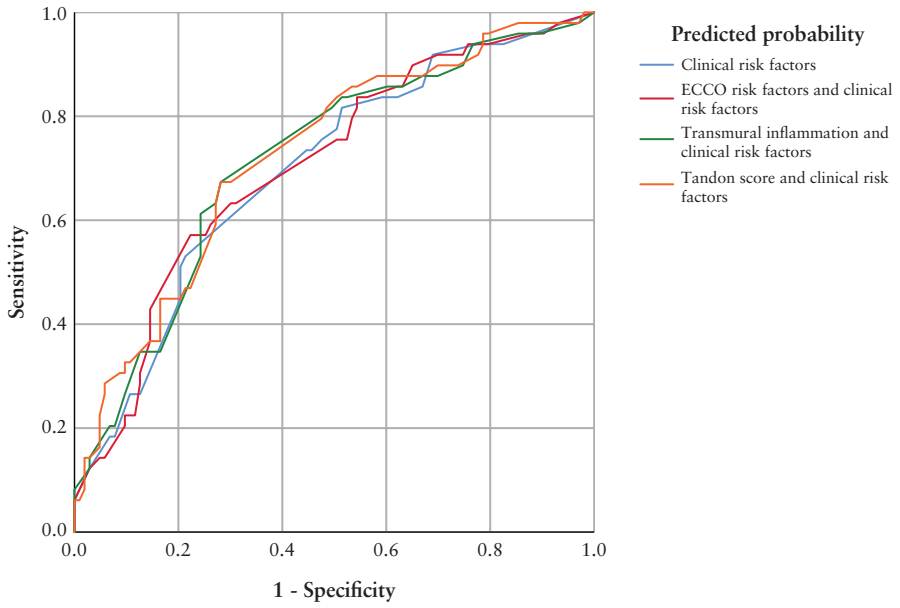


Figure 3. Receiver operating characteristic [ROC] curve depicting endoscopic recurrence after ileocolonic resection [ICR] in 129 Crohn's disease patients with endoscopy performed within 6 months after ICR and available histopathological examination. To assess the performance of different guidelines, combining clinical and histological risk factors, the predicted probabilities of endoscopic recurrence [Rutgeerts'score ≥i2b] were plotted against observed endoscopic recurrence rates. Abbreviations: AUC, area under the curve; CI, confidence interval, ECCO, European Crohn's and Colitis Organisation. Clinical risk factors: smoking, penetrating disease, prior resection and start of postoperative prophylaxis. ECCO risk factors: presence of granulomas and/or myenteric plexitis. Transmural inflammation: all layers of the intestinal wall affected and inflamed, with extension of the inflammatory cells down to the subserosal fat tissue. Tandon score: presence of active inflammation, granulomas and/or myenteric and/or submucosal plexitis.

benefit from postoperative prophylactic medication is warranted, whereas unnecessary exposure to immunomodulators or biologicals should be avoided. Taking disease localization into account may enhance risk stratification, since ileocolonic localization was associated with postoperative endoscopic recurrence in multivariable analysis. In our study, the AUC of the clinical and histological risk model improved from 0.73 to 0.76 after addition of ileocolonic disease localization. Confirmation of our finding in other datasets is necessary. Of note, an additional 13 patients had isolated colonic disease activity without ileal recurrence at postoperative endoscopy. Further assessment of a combined endpoint of endoscopic recurrence at the ileocolonic anastomosis as well as colonic inflammation would be of interest.

Incorporation of histological factors in the prediction model improved the predictive value for endoscopic recurrence up to 3%, as compared to the model with only clinical risk factors. Previous studies showed inconsistent results and failed to determine one specific histological factor as a clear predictor.[14,15] In our study, the predictive value was similar for the assessed histological risk factors proposed in the literature,[4,8,9] which mostly consists of a combination of several histological items. In the absence of more accurate predictors, histological assessment with one of these methods may be added to the clinical management algorithm, to identify a larger patient population with an indication for postoperative prophylaxis.

Prediction of postoperative recurrence of CD based on clinical and or histological risk factors remains a challenge; however, recent promising findings may translate to future biomarkers First, diversity of the T-cell population in the ICR specimen, defined as a larger number of clonal T-cell expansions, was significantly associated with active smoking and postoperative recurrence.[16] Second, Paneth cells are involved in CD susceptibility and pathogenesis,[17,18] and impaired Paneth cell phenotypes in the ileal resection specimen were found to be associated with postoperative recurrence.[19,20] Third, the composition of ileal mucosa-associated microbiota at the time of ICR could predict postoperative recurrence.[21,22] Finally, an altered body composition, characterized by sarcopenia and increased visceral fat, was previously shown to be associated with disease severity and adverse outcomes in CD.[23–25] Further improvement of the current risk stratification might also be achieved by refinement of known clinical risk factors. For example, the effect on postoperative prognosis of one prior ICR vs multiple prior ICRs or a short interval between two ICRs vs a long interval with quiescent disease between two ICRs could be further explored in future studies.

In this study, we have evaluated endoscopic recurrence as a primary endpoint. The definition of endoscopic recurrence according to the Rutgeerts' score is still a matter of debate. Although commonly applied in clinical practice and research, the Rutgeerts' score and modified Rutgeerts' score have not been validated in prospective cohorts.[3,26] In our study, the predictive value of clinical and histological markers was slightly higher for endoscopic recurrence defined as Rutgeerts' ≥i2b [AUC 0.73], as compared to Rutgeerts' ≥i2a [AUC 0.69]. This may indicate that the clinical algorithm has a higher predictive value for more severe recurrent lesions and poor prognosis. However, a worse prognosis of i2b vs i2a lesions has not been reported consistently.[27–29] Further investigation of the definition of endoscopic recurrence is required to obtain an accurate marker of long-term CD prognosis.

The long-term postoperative prognosis of treatment with prophylactic medication vs endoscopy-guided therapy is unknown. One randomized clinical trial concluded that prophylactic azathioprine was not superior to endoscopy-guided

azathioprine in achieving endoscopic remission.[30] However, that study was prematurely ended due to inadequate enrolment. A Cochrane review, including that trial and two cohort studies, concluded that the level of evidence is uncertain and larger trials are needed.[31]

In this cohort study, we limited potential bias by prospective inclusion and by central and blinded evaluation of endoscopies and resection specimens. Nevertheless, some limitations need to be taken into consideration. First, due to the observational design of the study, the prescription of prophylactic medication is weighed in the clinical risk models. This limits the applicability of the clinical risk stratification to decide on which patients need prophylaxis. In addition, we cannot exclude that interaction between different factors in the multivariable logistic regression model might have influenced the outcome. Nevertheless, this study serves as a validation of current guidelines. Second, the decision to start medication was left to the discretion of the treating physician. We cannot exclude the presence of predictors that were weighed to prescribe or omit prophylactic medication outside the proposed management algorithm, which may have caused confounding of the results. For instance, we observed that the vast majority of patients in the low-risk group receiving prophylaxis continued the preoperative agents. Further exploration of the motivation to continue medication in this subgroup seems warranted. In this study, we have tried to minimize this bias by collecting data on non-adherence. It is important to note that this drawback will also occur in randomized studies, as the decision to participate will also be influenced by these factors. Second, the type of medication was left to the discretion of the treating physician. The prescribed medication was in alignment with current guidelines. Unfortunately, our study was not powered to perform further analysis on recurrence rates per type of postoperative prophylaxis. Furthermore, 21% of patients started prophylactic medication with a delay up to 12 weeks postoperatively. Since all patients started medication for the indication of prevention of recurrence, they were included in the analysis. Finally, resection specimens were only reviewed by one of the three pathologists. The distinction between insignificant minimal and low-grade inflammation is difficult and has a high inter- and intra-observer variability.[32] However, we have tried to overcome this issue by using a uniform scoring format and organizing regular consensus meetings.

In conclusion, this study shows that prophylactic medication reduces the risk of endoscopic recurrence after ICR in both low- and high-risk patients with CD. Clinical risk stratification including the prescription of prophylaxis has an acceptable predictive value with a limited improvement after incorporation of histological assessment. Further refinement of risk stratification is required for patients considered at low risk to optimize individualized treatment.

Funding

None.

Conflict of Interest

Jeanine H. C. Arkenbosch, Evelien M. J. Beelen, Mariëlle Romberg-Camps, Sander van der Marel, P. W. Jeroen Maljaars, Sita Jansen, Carmen S. Horjus, Laurents P. S. Stassen, Bindia J. H. Jharap, Alfred Janssen, Nicole S. Erler, Michail Doukas, Ariadne H. A. G. Ooms, Gursah Kats-Ugurlu: none. Gerard Dijkstra has received a grant from Royal DSM and speaker fees from Abbvie, Janssen-Cilag, Takeda and Pfizer, all outside the submitted work. Marjolijn Duijvestein has received advisory fees from Echo Pharma, Alimentiv [formerly Robarts Clinical Trials]; unrestricted grants from Pfizer; speaker fees from Janssen, Merck & Co., Inc., Pfizer, Takeda, Tillotts Pharma, Galapagos, and BMS; and received nonfinancial support from Dr. Falk Pharma, all outside the submitted work. Frank Hoentjen has served on advisory boards or as a speaker for Abbvie, Janssen-Cilag, MSD, Takeda, Celltrion, Teva, Sandoz, and Dr Falk; received funding [Grants/Honoraria] from Dr Falk, Janssen-Cilag, Abbvie, and Takeda; and received consulting fees from Celgene, Janssen-Cilag, all outside the submitted work. Nanne K. H. de Boer has served as a speaker for AbbVie and MSD; served as a consultant and principal investigator for TEVA Pharma BV and Takeda; and received [unrestricted] research grant support from Dr. Falk, TEVA Pharma BV, MLDS and Takeda, all outside the submitted work. Rachel West has served on the advisory board and as invited speaker for Janssen, Pfizer, Takeda, and Galapagos, outside the submitted work. Fiona D. M. van Schaik has served on the advisory board for Falk, Takeda, and Galapagos, outside the submitted work. Oddeke van Ruler has served as an invited speaker for Janssen-Cilag; and has received non-financial support from Takeda, outside the submitted work. Marijn Visschedijk has served on the advisory board for Janssen-Cilag; and received speaker fees from Takeda, outside the submitted work. C. Janneke van der Woude received grants and/or fees for advisory boards and presentations from Pfizer, Abbvie, Celltrion, Falk Benelux, Takeda, Janssen, and Ferring, outside the submitted work. Annemarie C. de Vries has served on the advisory boards for Takeda, Janssen, Bristol Myers Squibb, Abbvie, Pfizer, and Galapagos; and received unrestricted research grants from Takeda, Janssen, and Pfizer, outside the submitted work.

Acknowledgements

The authors thank the surgical departments of the University Medical Center Groningen, Zuyderland Medical Center, Amsterdam University Medical Centers, Radboud University Medical Center, Haaglanden Medical Center, Leiden University Medical Center, Reinier de Graaf Groep, Amsterdam University Medical Centers Vrije Universiteit Amsterdam, Franciscus Gasthuis & Vlietland, Rijnstate Hospital, Maastricht University Medical Center, University Medical Center Utrecht, IJsselland Hospital and Meander Medical Center for assisting in patient inclusion and performing the ileocolonic resection to acquire the study population.

Author Contributions

All authors contributed to the acquisition and/or interpretation of the data, and critical revision of the manuscript for intellectual content. J.A., E.B., C.J.W. and A.C.V. contributed to the study design. J.A., E.B., N.S. and A.C.V. contributed to the statistical analysis. J.A., E.B. and A.C.V. contributed to drafting of the manuscript. All authors gave their final approval of the current version.

Data Availability Statement

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

Supplementary Data

Supplementary data are available online at *ECCO-JCC* online.

References

1. Beelen EMJ, van der Woude CJ, Pierik MJ, *et al*. Decreasing trends in intestinal resection and re-resection in Crohn's disease: a nationwide cohort study. *Ann Surg* 2021;**273**:557–63.
2. Tsai L, Ma C, Dulai PS, *et al*. Contemporary risk of surgery in patients with ulcerative colitis and Crohn's disease: a meta-analysis of population-based cohorts. *Clin Gastroenterol Hepatol* 2021;**19**:2031–2045.e11.
3. Rutgeerts P, Geboes K, Vantrappen G, Beyls J, Kerremans R, Hiele M. Predictability of the postoperative course of Crohn's disease. *Gastroenterology.* 1990;**99**:956–63.
4. Gionchetti P, Dignass A, Danese S, *et al*. 3rd European Evidence-based Consensus on the Diagnosis and Management of Crohn's Disease 2016: Part 2: Surgical Management and Special Situations. *Journal of Crohn's and Colitis* 2017;**11**:135–49.
5. De Cruz P, Kamm MA, Hamilton AL, *et al*. Crohn's disease management after intestinal resection: a randomised trial. *Lancet* 2015;**385**:1406–17.
6. American Gastroenterological A. American Gastroenterological Institute Guideline on the Management of Crohn's Disease After Surgical Resection: Clinical Decision Support Tool. *Gastroenterology.* 2017;**152**:276.
7. Nguyen GC, LoftusHirano EVI, Falck–Ytter Y, Singh S, Sultan S, *et al*. American Gastroenterological Association Institute Guideline on the Management of Crohn's Disease After Surgical Resection. *Gastroenterology* 2017;**152**:271–5.
8. Tandon P, Malhi G, Abdali D, Pogue E, Marshall JK, de Buck van Overstraeten A, *et al*. Active margins, plexitis, and granulomas increase postoperative Crohn's recurrence: systematic review and meta-analysis. *Clin Gastroenterol Hepatol* 2020.
9. Hammoudi N, Cazals-Hatem D, Auzolle C, *et al*. Association between microscopic lesions at ileal resection margin and recurrence after surgery in patients with Crohn's disease. *Clin Gastroenterol Hepatol* 2020;**18**:141–149.e2.
10. Domenech E, Manosa M, Bernal I, *et al*. Impact of azathioprine on the prevention of postoperative Crohn's disease recurrence: results of a prospective, observational, long-term follow-up study. *Inflamm Bowel Dis* 2008;**14**:508–13.
11. Reese GE, Nanidis T, Borysiewicz C, Yamamoto T, Orchard T, Tekkis PP. The effect of smoking after surgery for Crohn's disease: a meta-analysis of observational studies. *Int J Colorectal Dis* 2008;**23**:1213–21.
12. Ryan WR, Allan RN, Yamamoto T, Keighley MR. Crohn's disease patients who quit smoking have a reduced risk of reoperation for recurrence. *Am J Surg* 2004;**187**:219–25.
13. Cosnes J, Beaugerie L, Carbonnel F, Gendre JP. Smoking cessation and the course of Crohn's disease: an intervention study. *Gastroenterology* 2001;**120**:1093–9.
14. Bressenot A, Peyrin-Biroulet L. Histologic features predicting postoperative Crohn's disease recurrence. *Inflamm Bowel Dis* 2015;**21**:468–75.
15. Tandon P, Malhi G, Abdali D, Pogue E, Marshall JK, de Buck van Overstraeten A, *et al*. Active Margins, plexitis, and granulomas increase postoperative crohn's recurrence: systematic review and meta-analysis. *Clin Gastroenterol Hepatol* 2021;**19**:451–462.
16. Allez M, Auzolle C, Ngollo M, Bottois H, Chardiny V, Corraliza AM, *et al*. T cell clonal expansions in ileal Crohn's disease are associated with smoking behaviour and postoperative recurrence. *Gut* 2019;**68**:1961–1970.
17. Stappenbeck TS, McGovern DP. Paneth cell alterations in the development and phenotype of Crohn's disease. *Gastroenterology* 2016.
18. Cadwell K, Liu JY, Brown SL, *et al*. A key role for autophagy and the autophagy gene *Atg16l1* in mouse and human intestinal Paneth cells. *Nature* 2008;**456**:259–63.
19. VanDussen KL, Liu TC, Li D, *et al*. Genetic variants synthesize to produce paneth cell phenotypes that define subtypes of Crohn's disease. *Gastroenterology.* 2014;**146**:200–9.
20. Khaloian S, Rath E, Hammoudi N, *et al*. Mitochondrial impairment drives intestinal stem cell transition into dysfunctional Paneth cells predicting Crohn's disease recurrence. *Gut*. 2020;**69**:1939–51.
21. Sokol H, Brot L, Stefanescu C, *et al*. Prominence of ileal mucosa-associated microbiota to predict postoperative endoscopic recurrence in Crohn's disease. *Gut* 2020;**69**:462–72.
22. Machiels K, Pozuelo Del Río M, Martinez-De la Torre A, Xie Z, Pascal Andreu V, Sabino J, *et al*. Early postoperative endoscopic recurrence in Crohn's disease is characterized by distinct microbiota recolonization. *J Crohns Colitis* 2020;**14**:1535–46.
23. Cravo ML, Velho S, Torres J, Costa Santos MP, Palmela C, Cruz R, *et al*. Lower skeletal muscle attenuation and high visceral fat index are associated with complicated disease in patients with Crohn's disease: An exploratory study. *Clin Nutr ESPEN* 2017;**21**:79–85.
24. Gu P, Chhabra A, Chittajallu P, Chang C, Mendez D, Gilman A, *et al*. Visceral adipose tissue volumetrics inform odds of treatment response and risk of subsequent surgery in IBD patients starting antitumor necrosis factor therapy. *Inflamm Bowel Dis* 2021.
25. Grillot J, D'Engremont C, Parmentier AL, *et al*. Sarcopenia and visceral obesity assessed by computed tomography are associated with adverse outcomes in patients with Crohn's disease. *Clin Nutr* 2020;**39**:3024–30.
26. Ma C, Gecse KB, Duijvestein M, *et al*. Reliability of endoscopic evaluation of postoperative recurrent Crohn's disease. *Clin Gastroenterol Hepatol* 2020;**18**:2139–2141.e2.
27. Rivière P, Vermeire S, Irles-Depe M, Van Assche G, Rutgeerts P, de Buck van Overstraeten A, *et al*. No change in determining Crohn's disease recurrence or need for endoscopic or surgical intervention with modification of the Rutgeerts' scoring system. *Clin Gastroenterol Hepatol* 2019;**17**:1643–5.
28. Hammoudi N, Auzolle C, Tran Minh ML, *et al*. Postoperative endoscopic recurrence on the neoterminal ileum but not on the anastomosis is mainly driving long-term outcomes in Crohn's disease. *Am J Gastroenterol* 2020;**115**:1084–93.
29. De Cruz P, Hamilton AL, Burrell KJ, Gorelik A, Liew D, Kamm MA. Endoscopic Prediction of Crohn's disease postoperative recurrence. *Inflamm Bowel Dis* 2021.
30. Ferrante M, Papamichael K, Duricova D, *et al*. Systematic versus endoscopy-driven treatment with azathioprine to prevent postoperative ileal Crohn's disease recurrence. *J Crohns Colitis*. 2015;**9**:617–24.
31. Candia R, Bravo-Soto GA, Monrroy H, Hernandez C, Nguyen GC. Colonoscopy-guided therapy for the prevention of post-operative recurrence of Crohn's disease. *Cochrane Database Syst Rev* 2020;**8**:CD012328.
32. Geboes K, Riddell R, Ost A, Jensfelt B, Persson T, Lofberg R. A reproducible grading scale for histological assessment of inflammation in ulcerative colitis. *Gut*. 2000;**47**:404–9.