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IMPACT OF HISTOLOGICAL REMISSION FOR PREDICTING CLINICAL RELAPSE IN CROHN'S DISEASE: A POST HOC ANALYSIS OF THE PROSPECTIVE STORI COHORT

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ABSTRACT

Background and aims: Achieving deep remission, encompassing clinical, endoscopic, and biological remission, is the goal in managing Crohn's disease (CD). The role of histological remission (HR) remains unclear. This study aimed to examine the impact of histological inflammation on clinical relapse risk in CD and explore the relationship between histology, endoscopic scores, and biomarkers.

Methods: Patients from the prospective STORI (Stable Remission on Combined Therapy with Immunosuppressors) cohort underwent ileocolonoscopy with Crohn's Disease Endoscopic Index of

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Severity calculation and 2 biopsies from the most inflamed or previously inflamed areas. Histological scores (Robarts, Geboes, modified Geboes, Nancy, and IBD-DCA) were determined by 2 independent pathologists in a central reading process. Histological remission was defined by specific score thresholds. Clinical relapse, defined by Crohn's Disease Activity Index (CDAI) > 250 or a CDAI increase of 70 points over 2 weeks, was monitored for at least 1 year.

Results: Out of 115 patients included in STORI, 160 biopsies (44 ileal and 116 colonic) from 76 patients were analyzed. Histological remission rates were 46% (Nancy), 55% (Robarts), 61% (Geboes), and 41% (IBD-DCA). During follow-up, 35 patients (46%) experienced a clinical relapse: 37% with HR and 56% without, based on the Nancy score. Among the mucosal healing subgroup (45 patients), 34% with HR, and 44% without relapsed (p = 0.18). Histological scores did not predict clinical relapse. Only fecal calprotectin was a significant predictor in multivariate analysis (p = 0.029).

Conclusions: Despite correlations with endoscopy and biomarkers, histological scores did not predict clinical relapse in CD patients in remission. Thus, these scores are not recommended for clinical practice to assess relapse risk in CD.

KEY WORDS

Histological inflammation; Crohn's disease; clinical relapse

Introduction

Crohn's disease (CD) is a chronic progressive disease leading to the accumulation of structural bowel damages over time.[1] The irreversible accumulation of tissue damages is associated with a poor quality of life and a high disabling index.[2]

With the emergence of new effective treatments able to induce mucosal healing (MH), the management of inflammatory bowel diseases (IBD) has critically evolved and the validated targets are the control of symptoms but also the achievement of MH, the normalization of biomarkers and the completion of a normal quality of life. In the recent revision of the Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE2) consensus, support is growing for the achievement of histological remission (HR) in ulcerative colitis (UC) as a potential goal.[3] In patients with UC, histological inflammation is a strong predictor of clinical relapse, surgery, hospitalizations, corticosteroids use and is associated with a higher risk of colorectal cancer.[4,5] Subsequently,

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histological assessment has become a major endpoint in the recent clinical trials and growing evidence support the achievement of new therapeutic targets, including histo-endoscopic remission or histo-endoscopic improvement. However, the difficulty to achieve histological healing can be a barrier for its use in daily clinical practice. Although histology is a potential outcome measure in CD, histological activity is not used in clinical trials, nor in clinical practice. In contrast to UC, the added value of histology in predicting CD outcome is less clear. Few studies assessed whether histologic activity predicts long-term prognosis in CD, and all of them had a retrospective design with heterogenous patient's population, no standardization of the biopsy's location, and also no central reading. The aim of our study was to ascertain whether persistent histological activity was associated with further clinical relapse in the population of CD patients included in the prospective STORI (Stable Remission on Combined Therapy with Immunosuppressors) cohort by using different histological scores. The secondary aims were to study the correlation of the different histological scores to predict HR, to study the correlation between the different histological scores to predict endoscopic remission and to study for correlation between HR according to the different score and the level of FC and hsCRP.

Patients and Methods

STUDY DESIGN AND PATIENTS

The study of infliximab diSconTinuation in CrOhn's disease patients in stable Remission on combined therapy with Immunosuppressors (STORI) was a prospective multicentre cohort study including 115 patients from 20 GETAID centers in France and Belgium between March 2006 and December 2009.[6] STORI aimed to assess clinical relapse after infliximab cessation in patients with CD in clinical remission treated with infliximab and antimetabolite agents (azathioprine, 6-mercaptopurine, or methotrexate). All the patients included in the STORI study were eligible for inclusion. The patients and disease characteristics were prospectively recorded. An ileocolonoscopy was performed between screening and last infliximab infusion, with Crohn's Disease Endoscopic Index of Severity (CDEIS) calculation. Two biopsies were taken according to the STORI protocol, in the most inflamed area in case of macroscopic signs of inflammation, or in a previously inflamed area in case of normal endoscopy. For patients with colonic and ileal involvement, biopsies were

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taken from both locations. Mucosal healing was defined by the absence of ulcers at the endoscopy. Normal endoscopy was defined by a CDEIS of 0. High-sensitivity C-reactive protein (hsCRP) and fecal calprotectin (FC) levels were measured at the inclusion in STORI. The thresholds identified in STORI for FC (<300 pg/L) and hsCRP (<5 mg/L) were used in this study. Clinical relapse was prospectively evaluated in the STORI trial and defined by a Crohn's Disease Activity Index (CDAI) > 250 or CDAI between 150 and 250 with an increase of 70 points during 2 successive weeks compared to the inclusion visit.

HISTOLOGICAL ASSESSMENT

Paraffin-embedded-tissue blocks and hematoxillin-eosin- stained slides from the patients included in STORI were sent for central reading to the pathological department of Saint- Antoine Hospital, Paris, France. When paraffin-embebbed- tissue blocks were available, new slides were prepared in Saint-Antoine for hematoxilin-eosin (HE) coloration. In case of unavailability, the HE-stained slides from STORI were used for analysis. Material of insufficient quality was excluded from the analysis. The histological assessment was performed by 2 pathologists, digestive-dedicated (MS and DE), and blinded for the results of the endoscopy and of CD outcomes. Two slides per patient were evaluated. The following histological scores/indexes were calculated: the Nancy index,[7] the Geboes score,[8] the simplified Geboes score,[9] the Robarts index,[10] and the IBD-Distribution, Chronicity, and Activity score (IBD-DCA).[11]

Histological remission was defined by a Nancy index = 0,[7] a Geboes score $\leq$ 2,[8] a simplified Geboes score grade = 0,[9] a Robarts index $\leq$ 3,[10] an IBD-DCA score C $\leq$ 1 and A = 0.[11] Histological response (HRSP) was defined by a Nancy index $\leq$ 1,[7] a score Geboes $\leq$ 3,[8] a simplified Geboes score grade $\leq$ 1,[9] a Robarts index $\leq$ 9,[10] an IBD-DCA score C $\leq$ 2 and A = 0.[11] In case of discrepancy for the histological evaluation of the 2 slides from the same location, the most severe score was considered for the analysis. The histological results of colonic and ileal biopsies were analyzed separately and together. In case of discordance for the histological evaluation between the ileum and the colon for patients with both locations available, the most severe score was considered for the analysis. Anastomotic biopsies were considered in the ileal biopsy group. A summary of the 4 histological scoring schemes used in the study are illustrated in Supplementary Table 1.

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STUDY OUTCOMES

The impact of HR and HRSP on the risk of clinical relapse according to the different scores and indexes was evaluated. Each histological item was individually analyzed as potential predictive factor of clinical relapse: architectural changes, chronic inflammation, lamina propria neutrophils, surface epithelium neutrophils, cryptitis, crypt abscess, lamina propria eosinophils, probably erosion/focally stripped epithelium, unequivocal erosion, ulceration/granulation tissue, regenerative epithelium, granuloma, basal plasmacytosis, and distribution. The analyses were performed in the entire cohort, in the subgroup of patients with MH, and in the subgroup of patients with normal endoscopy.

CORRELATIONS BETWEEN HISTOLOGICAL SCORES, BIOMARKERS AND ENDOSCOPY

The correlation between the different endoscopic scores/ indexes and between histology and biomarkers (FC and HS-CRP) was evaluated. In patients with MH, a predictive model of clinical relapse including HR, normal hsCRP, normal FC, and normal endoscopy was tested. Additional analyses were performed to identify the optimal cutoff of FC predictive of HR.

STATISTICAL ANALYSIS

Results are expressed as frequencies (%) for qualitative parameters and as medians and interquartile range (IQR) for quantitative parameters. Relapse-free survival was represented as a Kaplan-Meier curve. Univariate and multivariate

Cox regression models were used to study the relapse-free survival. Spearman correlation and Kruskal-Wallis test were used to study the associations between histological scores/ parameters and endoscopic score. The Youden method was used to obtain the best cutoff for HR on the basis of the FC.

Results were considered significant at the 5% significance level ($p < 0.05$). All statistical analyses were carried out by SAS (version 9.4; SAS Institute, Cary, NC, USA) and the figures with R version 4.3.1.

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Results

STUDY POPULATION

Among the 115 patients included in STORI,[6] biopsies were available in 76 patients from 15 GETAID centers in France and Belgium. The reason for the absence of inclusion of the last 39 patients was the lack of interest of 5 centers to participate in this study (Figure 1). One hundred and sixty biopsies were analyzed including 116 colonic biopsies in 58 patients and 44 ileal biopsies in 22 patients. Four patients had biopsies in both locations (Figure 1). Paraffin-embedded-tissue blocks were available in 69 patients and only HE-stained slides in 7 patients. No patient was excluded for insufficient quality of the material. The demographic, clinical, biological, and endoscopic characteristics of the patients are described in Table 1. Most patients had minimal symptoms with median CDAI of 36.8 (IQR: 19.7-62.8) and low endoscopic and biological activity with median CDEIS of 1.00 (IQR: 0.00-3.20), median FC of 51.0 µg/g (IQR: 31.5-286) and median hsCRP of 2.00 mg/L (1.00-4.80). Forty-five patients (59.2%) had MH and 23 (30.3%) patients had a normal endoscopy at the inclusion in STORI. Clinical relapse was observed in 35/76 patients (46%) during the STORI whole follow-up.

HISTOLOGICAL RESULTS

In the entire cohort (*n* = 76), HR was observed in 35 (46.1%), 42 (55%), 46 (60.5%), 37 (48.7%), 37 (48.7%), and 36 (47.4%) patients according to the Nancy index, Robarts index, Geboes score, simplified Geboes model 3, simplified Geboes model 9, and IBD-DCA score, respectively. The detailed histological scores are illustrated in Table 2. The median Robarts index was 3.0 (IQR: 0.0-14.5). Histological response was observed in 37 (48.7%), 53 (69.7%), 51 (67.1%), 46 (60.5%), 51 (67.1%), and 36 (47.4%) patients according to the Nancy index, Robarts index, Geboes score, simplified Geboes model 3, simplified Geboes model 9, and IBD-DCA score respectively. The detailed histological results are summarized in Tables 2 and 3.

In the subgroup of patients with MH (*n* = 45, 59.2%), Histological remission was observed in 29 (64.4%), 32 (71.1%), 35 (77.8%), 29 (64.4%), 29 (64.4%), and 28 (62.2%) patients according to the Nancy index, Robarts index, Geboes score, simplified Geboes model 3, simplified Geboes model 9, and IBD-DCA score, respectively. Histological response was observed in 29 (64.4%), 37 (82.2%), 37 (82.2%), 35 (77.8%), 37 (82.2%), and 28 (62.2%) patients according to the Nancy index, Robarts index,

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Geboes score, simplified Geboes model 3, simplified Geboes model 9, and IBD-DCA score, respectively. Histological remission in the different endoscopic subgroups is illustrated in Figure 2. Examples of HE histological biopsy samples are illustrated in Figure 3.

CLINICAL OUTCOME ACCORDING TO HISTOLOGICAL STATUS

ANALYSIS OF POOLED COLONIC AND ILEAL BIOPSIES

In the entire cohort (n = 76), 13/35 (37%) patients with HR according to the Nancy score experienced a clinical relapse during the STORI follow-up compared to 23/41 (56%) in patients without HR (p = 0.26) (Figure 4). In the subgroup of patients with MH, 10/29 (34%) patients with HR, according to the Nancy score experienced a clinical relapse during the STORI follow-up compared to 7/16 (44%) in patients without HR (p = 0.18). The survival without clinical relapse in patients with MH according to the achievement of HR is illustrated in Figure 5. In the subgroup of patients with a CDEIS of zero, 7/17 (41.2%) patients with HR according to the Nancy index experienced a clinical relapse during the STORI follow-up compared to 2/6 (43.8%) in patients without HR (p = 0.18). No specific histological item was predictive of clinical relapse in the different subgroups. In a multivariate model

Figure 1 *Patients' disposal.*

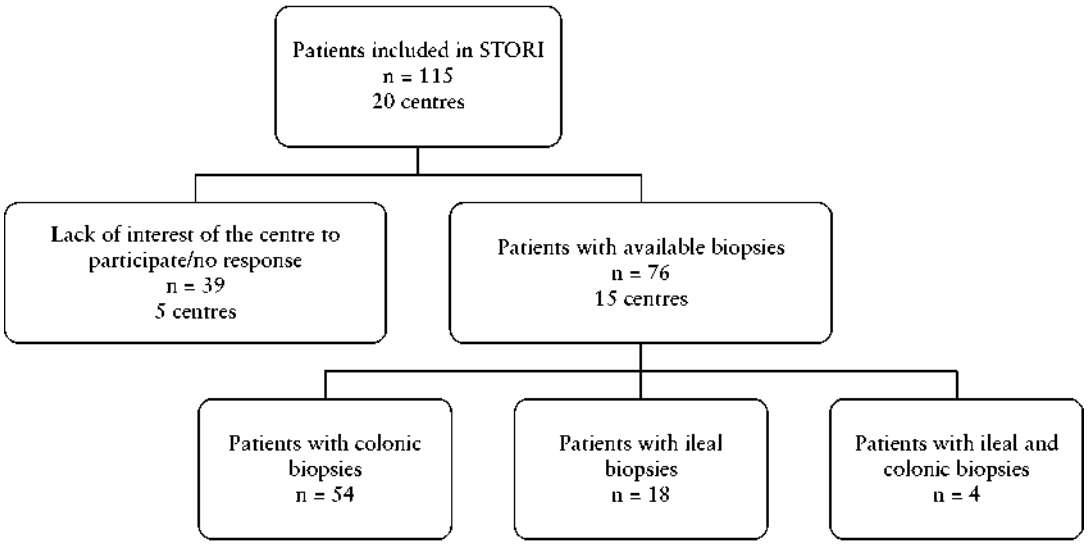

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Table 1 *Patients' characteristics.*

Patients' characteristics (*n* = 76)	***N* (%) or median (IQR)**
Female gender	45 (59.2)
Age (years)	31.6 (25.6-39.0)
Active smoking	28 (36.8)
Previous IBD resection	17 (22.4)
Disease duration (years)	7.75 [4.05-11.6]
Montreal classification	
L1	8 (10.5)
L2	23 (30.3)
L3	44 (57.9)
L4	6 (7.9)
P+	6 (7.9)
B1	68 (10.8)
B2	6 (7.9)
B3	1 (1.3)
Previous intestinal resection	17 (22.4)
CDAI	36.8 [19.7-62.8]
CRP US (mg/L) (*n* = 71)	2.00 [1.00-4.80]
Fecal calprotectin (µg/g) (*n* = 57)	51.0 [31.5-286]
Trough level IFX	4.66 [2.12-8.99]
CDEIS	1.00 [0.00-3.20]
Mucosal healing	45 (59.2)

Abbreviations: CDAI, Crohn's Disease Activity Index; CDEIS, Crohn's Disease Endoscopic Index of Severity; CRP, C-reactive protein; IBD, inflammatory bowel disease; IQR, interquartile range.

including CDEIS, FC, hsCRP, and the Nancy score, only FC was predictive of clinical relapse in the subgroup of patients without ulcers (FC > 300 pg/L: $p = 0.029$; CDEIS > 0: $p = 0.17$; hsCRP > 5 mg: $p = 0.14$; Nancy score > 0: $p = 0.14$).

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ANALYSIS OF ILEAL BIOPSIES

In the entire cohort (*n* = 76), around one third of the patients with ileal biopsies (*n* = 22) experienced a clinical relapse (7/22, 31.8%). The value of the different histological scores was not predictive of clinical relapse (Nancy index: *p* = 0.2, Robarts index: *p* = 0.43; Geboes score: *p* = 0.32; and IBD-DCA: *p* = 0.32) nor the HR regarding the different scores (Nancy index: *p* = 0.16; Robarts index: *p* = 016; Geboes score: *p* = 0.16, simplified Geboes model 3: *p* = 0.16, simplified Geboes model 9: *p* = 0.16, and IBD- DCA: *p* = 0.32). Similar results were obtained for the analysis of the subgroup of patients without ulcers (*n* = 15, 5/15 patients with clinical relapse, HR yes/no: Nancy index: *p* = 0.24; Robarts index: *p* = 0.24; Geboes score: *p* = 0.24, simplified Geboes model 3: *p* = 0.24, simplified Geboes model 9: *p* = 0.24, and IBD-DCA: *p* = 0.24). No specific histological item was predictive of clinical relapse in the different subgroups.

ANALYSIS OF COLONIC BIOPSIES

In the entire cohort (*n* = 76), around half of the patients with colonic biopsies (*n* = 58) experienced a clinical relapse (31/58, 53.4%). The value of the different histological scores was not predictive of clinical relapse (Nancy index: *p* = 0.69, Robarts index: *p* = 0.58; Geboes score: *p* = 0.32; and IBD-DCA: *p* = 0.23) nor the HR regarding the different scores (Nancy index: *p* = 0.97; Robarts index: *p* = 0.42; Geboes score: *p* = 0.49, simplified Geboes model 3: *p* = 0.72, simplified Geboes model 9: *p* = 0.72, and IBD-DCA: *p* = 0.73). Similar results were obtained for the analysis of the subgroup of patients without ulcers (*n* = 34, 14/34 patients with clinical relapse, HR yes/no: Nancy index: *p* = 0.90; Robarts index: *p* = 0.90; Geboes score: *p* = 0.98, simplified Geboes model 3: *p* = 0.90, simplified Geboes model 9: *p* = 0.90, and IBD-DCA: *p* = 0.90). No specific histological item was predictive of clinical relapse in the different subgroups.

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Table 2 *Histological scores in the entire population.*

Nancy index	***N* (%)**
0	35 (46.1)
1	2 (2.6)
2	11 (14.5)
3	16 (21.1)
Geboes score[#]	***N* (%)**
<2B.1 (Grade 0)	37 (48.7)
<2B.2 (Grade 1)	9 (11.8)
<5.3 (Grade2)	14 (18.4)
≥ 5.3 (Grade 3)	16 (21.1)
IBD-DCA	***N* (%)**
D0	19 (25.0)
D1	21 (27.6)
D2	36 (47.4)
C0	19 (23.8)
C1	45 (59.2)
C2	12 (15.0)
A0	36 (47.4)
A1	16 (21.1)
A2	24 (31.6)
Robarts index	**Median (IQ)**
	3.00 (0.00-14.5)

Abbreviations: IBD-DCA, IBD-Distribution, Chronicity, and Activity score; IQ, interquartile range.

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CORRELATION BETWEEN HISTOLOGY, ENDOSCOPY, AND BIOMARKERS

A very high correlation was found between the different histological scores (Table 4). A correlation was observed between the different histological scores and the results of the endoscopy according to the CDEIS (Nancy: $r = 0.42$, $p < 0.0001$; Geboes: $r = 0.46$, $p < 0.0001$; Robarts: $r = 0.45$, $p < 0.0001$, IBD-Distribution, Chronicity, and Activity score (IBD DCA): $p = 0.001$). The presence of architectural changes ($p = 0.028$), moderate chronic inflammation ($p = 0.003$), presence of lamina propria neutrophils ($p = 0.003$), the presence of surface epithelium neutrophils ($p = 0.0001$), presence of unequivocal erosion ($p = 0.039$), and the presence of regenerative epithelium ($p = 0.017$) were correlated with endoscopic scores. A correlation was observed between histological scores and FC (Nancy: $r = 0.48$, $p \leq 0.0002$; Geboes: $r = 0.45$, $p = 0.0004$; Robarts: $r = 0.48$, $p = 0.0003$, IBD DCA:

Table 3 *Detailed histological characteristics.*

Histological characteristics, *n* = 80	**Categories**	***N* (total observations)**	***N* (%)**
Architectural changes	Absent	78	41 (52.6)
	Mild		27 (34.6)
	Moderate		6 (7.7)
	Severe		4 (5.1)
Chronic inflammation	Absent	80	28 (35.0)
	Mild		29 (36.3)
	Moderate		14 (17.5)
	Severe		9 (11.3)
Lamina propria neutrophils	Absent	80	38 (47.5)
	Mild		25 (31.3)
	Moderate		9 (11.3)
	Severe		8 (10.0)
Surface epithelium neutrophils	Absent	79	57 (72.2)
	Present		22 (27.8)
Cryptitis	Absent	80	58 (72.5)
	5% of the crypts		13 (16.3)
	<50% of the crypts		6 (7.5)
	>50% of the crypts		3 (3.8)
Crypt abcess	Absent	80	71 (88.8)

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	Present		9 (11.3)
Lamina propria eosinophils	Absent	80	72 (90.0)
	Mild		6 (7.5)
	Moderate		2 (2.5)
Probably erosion/focally stripped epithelium	Absent	80	67 (83.8)
	Present		13 (16.3)
Unequivocal erosion	Absent	80	71 (88.8)
	Present		9 (11.3)
Ulceration/granulation tissue	Absent	80	66 (82.5)
	Present		14 (17.5)
Regenerative epithelium	Absent	80	70 (87.5)
	Present		10 (12.5)
Granuloma	Absent	80	75 (93.8)
	Present		5 (6.3)
Basal plasmacytosis	Absent	17	11 (64.7)
	Present		6 (35.3)
Distribution	Absent	80	18 (22.5)
	Mild		23 (28.8)
	Moderate		39 (48.8)

p = 0.0032). The correlation between histological scores and US CRP was significant but low (Nancy: r = 0.29, p < 0.012; Geboes: r = 0.31, p = 0.008; Robarts: r = 0.46, p = 0.00013, IBD DCA: p = 0.031). A cutoff of 153 pg/mL for FC was associated with HR according to the different histological scores/ indexes with a high sensitivity and specificity (Table 5).

Discussion

This post hoc analysis of the STORI cohort demonstrated that approximately 50% of patients in clinical remission have HR based on the various histological tools used. The proportion of patients with HR was higher in the subgroup of patients with MH, ranging from 61% to 78%, and even higher in case of normal endoscopy, ranging from 74% to 91%. Studies have shown that patients who achieved MH in UC experienced better clinical outcomes.[12-14] In the STORI cohort including patients in clinical remission only, MH was associated with lower relapse rate.[6] In this study, although numerically lower, the relapse rate did not differ significantly based on HR status in the total population (37% with HR vs 56% without HR) or in patients with MH (35% with HR vs 44% without HR).

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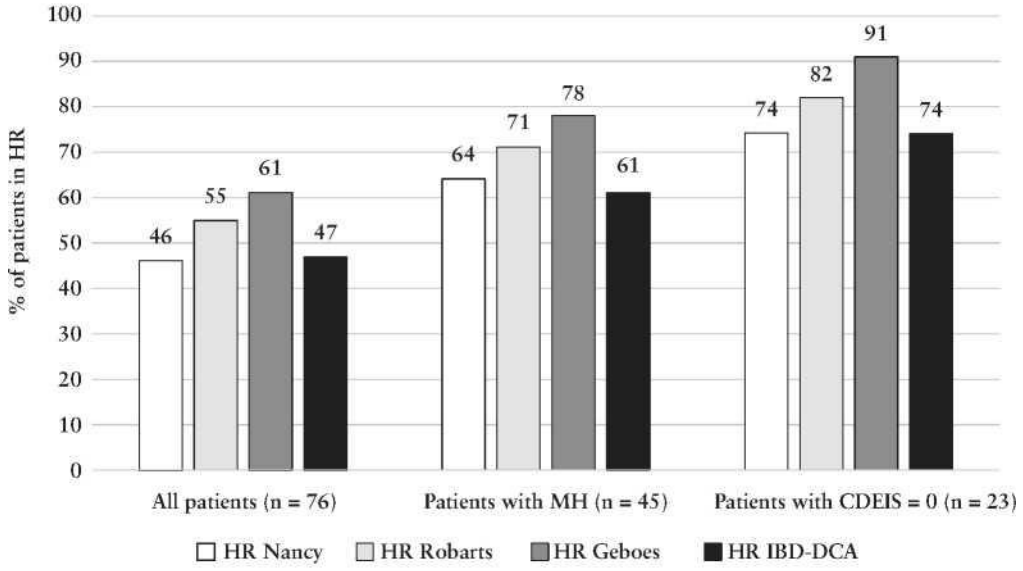
Conflicting results exist in the literature regarding the relationship between histological activity and clinical outcomes in CD.[15-20] In a retrospective study by Christensen involving 101 patients in clinical remission, 63% had MH and 55% had HR, similar to our findings.[15]

Figure 2 *Histological remission according to the different scores in the entire cohort, in the subgroup of patients with mucosal healing and in the subgroup of patients with Crohn's Disease Endoscopic Index of Severity = 0*



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However, 36% of patients with MH in this study exhibited persistent signs of histological activity, compared to less than 25% in our cohort. In contrast to our findings, histology was predictive of clinical relapse and corticosteroid use. Hun et al.[16] conducted a study involving 129 CD patients in endoscopic remission and found no correlation between histological activity and the future risk of relapse over the subsequent 2 years. Baars et al.[17] included 152 patients with IBD, with only 32 CD patients in endoscopic remission. Their study found no prognostic difference between patients with only endoscopic remission compared to those with both endoscopic and HR. A recent meta-analysis comprising 28 studies and 2806 patients (2677 UC; 129 CD) demonstrated that histologically active disease was associated with an overall increased risk of relapse in UC, but no association between histologic activity and relapse was found in CD.[18] These conflicting findings may be attributed to several factors including the complex heterogeneity of disease location, and the patchy nature of microscopic inflammation, which renders histological assessment susceptible to biopsy bias. Despite our efforts to prospectively collect biopsies from previously inflamed areas in cases MH or

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from the most inflamed area in the absence of MH, our study did not find a correlation between histology and clinical disease outcome. One possible explanation could be a lack of statistical power, as only 76 out of the 115 initial patients from the STORI cohort were included in this post hoc analysis. Another important point is the location of the biopsies. The major strength of our study is the standardization of the biopsy locations. Nevertheless, it is impossible to ensure that a biopsy taken from a previously inflamed area came precisely from the site where the disease was most severe. Finally, another challenge arises from the transmural nature of CD. Transmural inflammation can persist despite achieving MH. Several studies have demonstrated that achieving transmural healing is associated with better clinical outcomes compared to MH alone.[19-21] This suggests that transmural healing could serve as an additional target and may even be more relevant compared to histology alone.

Another limitation in validating the use of histology in CD is the lack of validated scoring system. ECCO suggests that histological scoring systems for UC can be applied to CD patients.[22] Recently, the International Organization of Inflammatory Bowel Disease (IO-IBD) recommended different objectives to assess HR in UC and CD, including the disappearance of neutrophil infiltration in the lamina pro- pria.[23] In our study, we used the validated UC scores of Nancy, Robarts, and Geboes, along with the newly recognized IBD- DCA score, a simple histological activity score for UC and CD, recently agreed and validated by a large group of IBD specialists.[11] Histological remission for all scores included the absence of polynuclear neutrophils in the epithelium and lamina propria. Signs of chronicity indicated by the presence of lymphocytes were permitted in all scoring systems except for the Nancy and the IBD-DCA. This may account for the lower frequency of remission observed with the Nancy score and the IBD-DCA compared to other scores. In UC, a direct comparison of the Nancy index, the Robarts index, and the Geboes score, demonstrated that each tool reliably produced valid scores, sensitive to changes in disease activity over time in UC.[23-27] To the best of our knowledge, no such comparison has been performed in CD. Our study revealed a very high correlation between the Nancy, Robarts, Geboes, and IBD- DCA scores in assessing histological inflammation in CD. These findings suggest that all these scores can be used interchangeably in both clinical practice and clinical trials.

In our multivariate model, including CDEIS, FC, hsCRP, and histology, only FC emerged as predictive of clinical relapse within the subgroup of patients with MH ($p = 0.029$). These findings underscore the capacity of FC to predict clinical relapse among CD patients in clinical remission despite the limited

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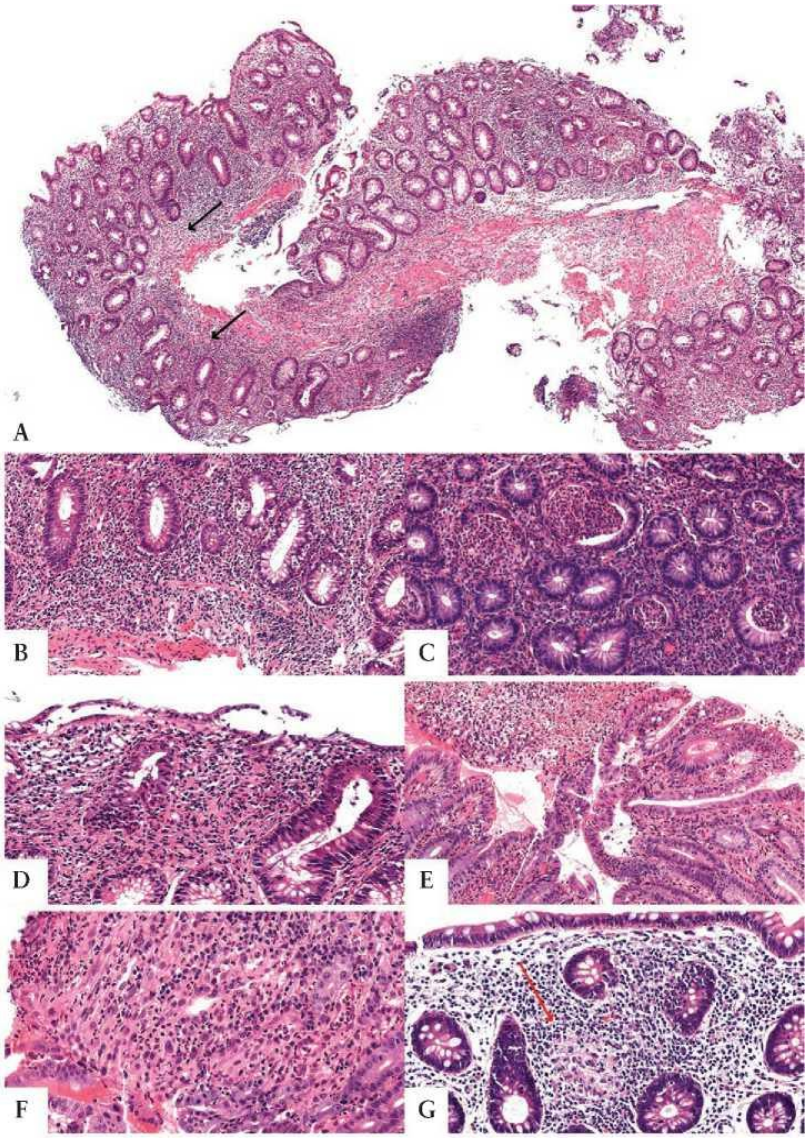
patient cohort. Given the patchy nature of CD, FC appears to offer a more precise assessment of overall residual inflammation, as it reflects the entire mucosal surface compared to random biopsies, even if appropriately located.

Figure 3 *Examples of hematoxylin and eosin-stained histological biopsy samples ((A) low-power view, 5x; (B-G) intermediate power view, 20x): (A) Colon biopsy showing diffusely inflamed mucosa with architectural modifications, band-like plasmacytosis (arrows); the surface epithelium is regenerative and focally stripped. (B) Detail on the basal plasmocytosis; multiple cryptitis lesions can also be seen. (C) Example of colonic mucosa with numerous crypt abscesses. (D) Inflamed colonic mucosa with cuboid/regenerative and focally striped surface epithelium. (E) Mucosal erosion with intraepithelial neutrophils and fibrin-leucocytic exudate. (F) Mucosal ulceration with granulation tissue (G) Small epithelioid granuloma (arrow) in a colonic mucosa.*



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We were able to propose a FC threshold of 153 pg/g, demonstrating high sensitivity (96%) in predicting HR. To the best of our knowledge, no established cutoff value exists for predicting HR in CD. In UC, Sipponen et al. proposed a FC threshold of 155 pg/g to predict HR, which closely aligns with our findings.[28] In CD, the same group demonstrated a correlation between FC and colonic histology but not with ileal histology.

Our study presents several strengths. A unique aspect of our study is the prospective and standardized collection of biopsies, the central reading design and the detailed histological description using 4 scores/indexes. Unlike some available retrospective studies, which not always provide accurate information on the location of included biopsies and which are based on the local pathological report with no central reading

process, our study documented the precise site of biopsies, which is crucial in CD due to its patchy nature. Our study has certain limitations. First, we encountered challenges due to the unavailability of some biopsy samples. Second, the presence of missing data regarding biomarkers potentially affects the reliability of our results. Finally, for some analysis including the correlation with biomarkers, the inability to conduct a separate analysis of ileal and colonic histological results is a limitation. Given the distinct pathophysiological characteristics of these 2 regions in CD, a separate analysis would have provided a more nuanced understanding of the disease process and its correlation with biomarkers.

Figure 4 *Clinical relapse according to histological remission assessed by the Nancy score in the whole population (n = 76). HR, histological remission.*

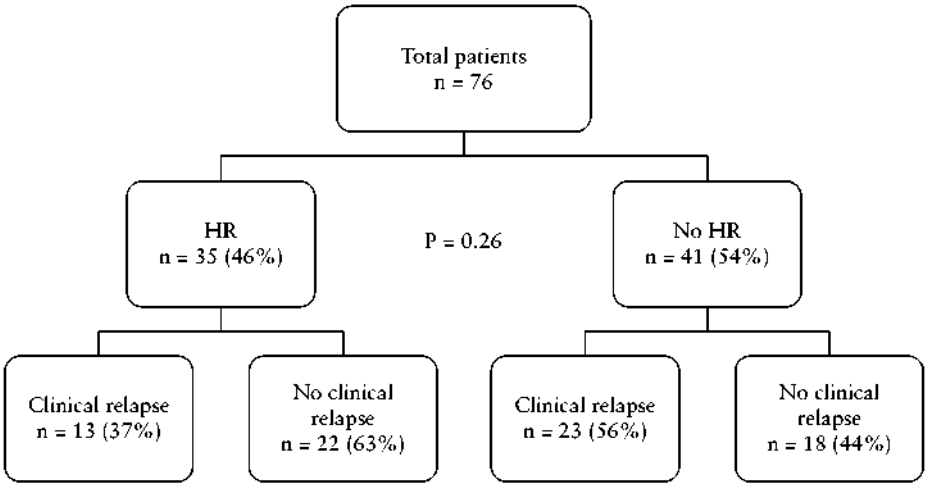

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Figure 5 *Relapse-free survival according to histological remission evaluated by the different histological scores/indexes in patients with mucosal healing.*

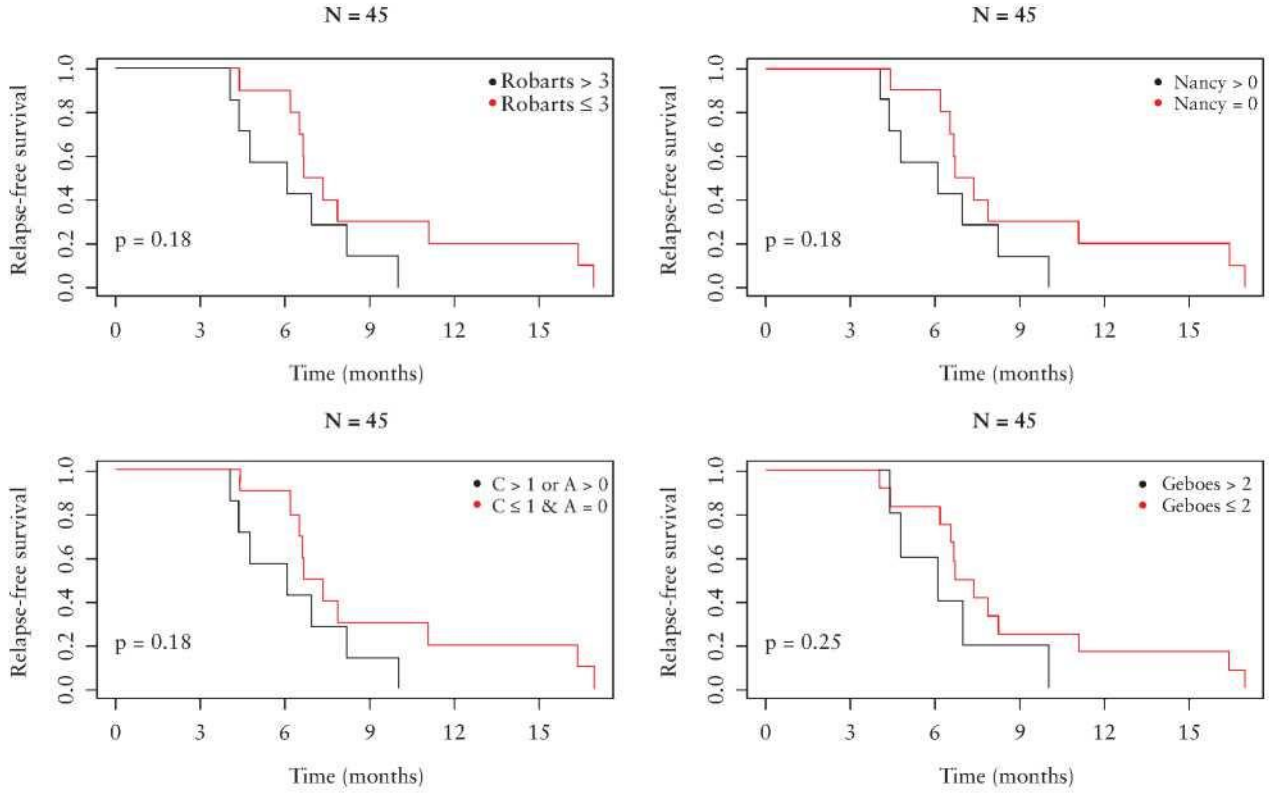

Table 4 *Correlation between the different histological scores/indexes.*

Spearman correlation coefficients, *N* = 80	**Nancy**	**Geboes**	**Robarts**
Nancy	1.00	0.93, $p < 0.0001$	0.94, $p < 0.0001$
Geboes	0.93, $p < 0.0001$	1.00	0.99
Robarts	0.94, $p < 0.0001$	0.99, $p < 0.0001$	1.00, $p < 0.0001$

In conclusion, in this post hoc analysis of the STORI cohort, HR was achieved in approximately 50% of the patients in the entire cohort, and in about two-thirds of the patients with MH. No histological parameters, including HR or HRSP assessed with 4 different scores/indexes by a central reading procedure, were predictive of clinical relapse in our population, regardless of the subgroup. An excellent correlation was observed between the different scores. Our findings do not support the routine use of these histological scores or parameters in their current form to predict the clinical outcome of CD, but they confirm FC as the best marker for predicting clinical relapse in CD. Future

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larger prospective cohorts, including additional histological factors and stricter biopsy's location are needed to confirm these findings, likely requiring a higher number of biopsies taken from multiple locations.

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None declared.

CONFLICT OF INTEREST

None declared.

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AUTHORS CONTRIBUTIONS

CR was involved in the design of the study, the collection of the slides samples, the acquisition and the analysis of the data and the conception of the manuscript. EL was involved in the design and the conception of the study and the reviewing of the manuscript. DA and MS centralized the hematoxillin- eosin-stained slides, reviewed all the slides and corrected the manuscript. MF, AA, RA, MN, YB, SN, PM, DL, SV, AB, MDV, and JMG collected and sent the hematoxillin-eosin- stained slides of the patients included in STORI in their center and reviewed the manuscript.

DATA AVAILABILITY

Data that support the findings of this study are available as individual anonymised data upon request to the corresponding author.

Supplementary Data

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

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