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ORIGINAL ARTICLE

Apex Score: Predicting Flares in Small-Bowel Crohn's Disease After Mucosal Healing

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Abstract

Background Optimal strategies for using small-bowel capsule endoscopy (SBCE) in established small-bowel Crohn's disease (CD) remain uncertain. Mucosal healing (MH) has emerged as a valuable predictor of a flare-free disease. We aimed to evaluate the occurrence of disease flare on patients with small-bowel CD and MH, as well as to create a score identifying patients in higher risk for this outcome.

Methods We analyzed consecutive patients submitted to SBCE for assessment of MH and included those where MH was confirmed. The incidence of disease flare was assessed during follow-up (minimum 12 months). A score predicting disease flare was created from several analyzed variables.

Results From 47 patients with MH, 12 (25.5%) had a flare (versus 48.3% in excluded patients without MH; $p = 0.01$). Age ≤ 30 years (OR = 70; p = 0.048), platelet count $\geq 280 \times 10^3$/L (OR = 12.24; p = 0.045) and extra-intestinal manifestations (OR = 11.76; p = 0.033) were associated with increased risk of CD flare during the first year after SBCE with MH. These variables were used to compute a risk-predicting score—the APEX score—which assigned the patients to having low (0–3 points) or high-risk (4–7 points) of disease flare and had excellent accuracy toward predicting disease relapse (AUC = 0.82; 95%CI 0.64–0.99).

Conclusion Patients with small-bowel CD and MH were not free of disease flares on the subsequent year, despite presenting lower rates when compared to those without MH. The APEX score demonstrated excellent accuracy at stratifying patients relapse risk and guiding further therapeutic options for patients achieving MH.

Keywords Crohn's disease · Mucosal healing · Capsule endoscopy · Small-bowel

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Introduction

Crohn's disease (CD) is a chronic and debilitating inflammatory disease characterized by a relapsing and remitting course. It can affect any portion of the gastrointestinal tract, including the small-bowel[1].

Classically, CD treatment has been guided by patients' symptoms and biomarkers of inflammatory activity [2]. However, mucosal healing (MH) has recently emerged as a potential therapeutic target [3]. According to recent European Crohn's and Colitis Organization guidelines, endoscopic response to therapy in CD should be evaluated within 6 months following initiation of treatment [4]. As stated by Peyrin-Biroulet et al. [5], controlling the inflammatory activity with simultaneous achievement of MH in CD is a crucial point in preventing flares and avoiding long-term complications such as small-bowel surgery. Nonetheless, optimal strategies for monitoring CD activity are still being defined [6].

Isolated small-bowel involvement (L1 with or without L4 disease, according to the Montreal classification) occurs in approximately 30% of patients with CD [7]. In this set of patients, small-bowel capsule endoscopy (SBCE) fulfills a pivotal role, since it is the only diagnostic tool able to directly assess MH throughout the entire small-bowel. This procedure is progressively becoming easier and faster to read for the physicians, as different detection methods are being developed in SBCE imaging, as is the case for ulcer detection [8].

Current recommendations support the use of SBCE for the evaluation of patients with established CD, if deemed to influence patients' management, as shown in previous reports [9, 10]. For that purpose, endoscopic Lewis score or capsule endoscopy CD activity index (CECDAI) score has been validated for standardized evaluation of CD inflammatory activity during SBCE [11, 12]. Lewis score (LS) classifies the small-bowel endoscopic inflammatory activity as absent or clinically insignificant ($LS < 135$), mild ($135 \leq LS < 790$) or moderate-to-severe ($LS \geq 790$), by taking into account the presence of edema, ulcerations and stenosis [12]. With this, LS provides an accessible way of quantitatively evaluate inflammatory activity evolution through disease progression or response to treatment.

Recent studies have been proposing the incorporation of SBCE to assess MH in treat-to-target algorithms for small-bowel CD, as was the case of the investigation by Ben-Horin and associates, where findings on SBCE predicted both short- and long-term risk of disease exacerbation [13, 14].

The primary aim of our study was to evaluate the occurrence of disease flares in patients with isolated small-bowel CD during the first year following a SBCE confirming MH. A secondary outcome was to test possible features identifying patients with a higher risk of having such a disease course and creating a score that would predict the risk of relapse in this set of patients.

Materials and Methods

Study Design and Patients Selection

We conducted a retrospective case–control study comprising adult patients with diagnosed CD, based on clinical, radiologic, endoscopic and histological criteria, who underwent SBCE for assessment of mucosal healing between January 2011 and March 2019 [1]. Only patients with L1 (with or without L4) disease, according to the Montreal classification, were included, since these patients are expected to benefit the most from a SBCE-based surveillance [15]. Patients with L3 (ileocolic) disease were excluded since colonic inflammatory activity could result in clinical flares despite small-bowel MH.

The sample consisted only of patients in clinical remission, defined as: asymptomatic, with no treatment changes in the previous 6 months and corticosteroid-free for at least 6 months. In order to consider patients with MH, all cases with a $LS \geq 135$ were excluded from our final sample. Incomplete examinations, when SBCE did not reach the cecum within the full time of the procedure, were also not considered. A minimum follow-up of 12 months was required after SBCE.

Disease flare was defined as the need for treatment escalation or intensification, hospitalization or bowel resection. Therapeutic changes were based on clinical, analytical and endoscopic findings. Demographical, clinical, endoscopic and laboratorial data were collected by medical records' review.

A diagram summarizing the study sample selection is presented in Fig. 1.

SBCE Procedure

Either PillCam® SB2 (January of 2011 to December of 2013) or SB3 (January of 2014 to March 2019) (Given Imaging—Medtronic) were used.

Patients with increased risk of capsule retention, such as patients with obstructive symptoms, with history of small-bowel resection or previously known strictures, were excluded.

Enrolled patients were instructed to start a clear liquid diet 24 h before the procedure, followed by fasting for 12 h prior to the SBCE ingestion [16]. Patients taking oral iron supplements were requested to suspend it 7 days before the SBCE. Patients were allowed to ingest clear liquids 2 h after

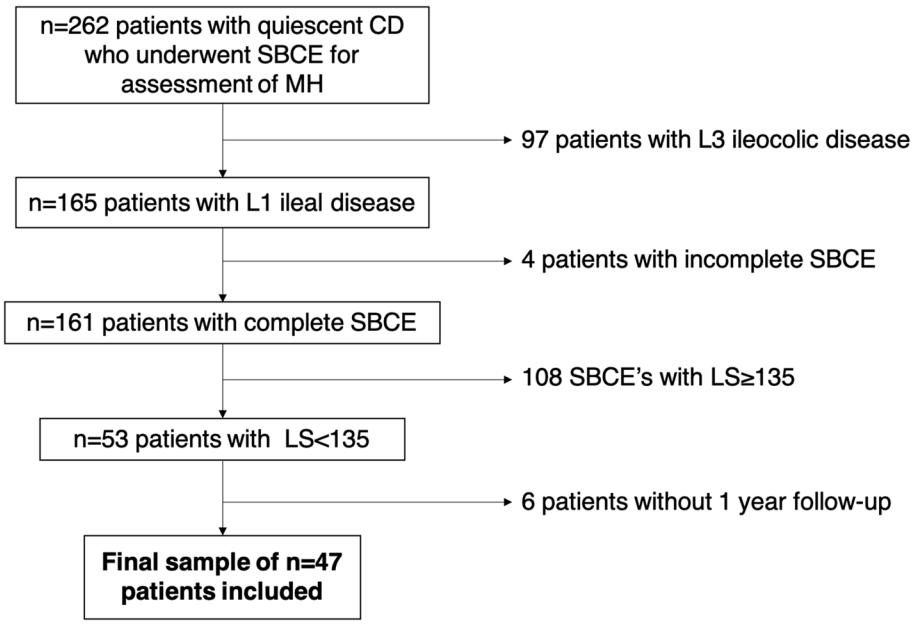

Fig. 1 Diagram displaying patients' selection process. CD—Crohn's disease; SBCE—small-bowel capsule endoscopy; MH—mucosal healing; LS—Lewis score

SBCE ingestion and to eat a light meal 4 h later, after SBCE passage into the small-bowel which was confirmed using the Real Time Viewer® (Given Imaging—Medtronic).

Inflammatory Biomarkers

All blood and fecal samples were collected within 4 weeks of the SBCE procedure.

Statistical Analysis

Statistical analysis was performed using SPSS® software, version 23 (IBM, Armonk, NY). Categorical variables are presented as frequencies and percentages and continuous variables as means and standard deviations (SD). Reported p values are two-tailed, with statistical significance being considered when p value < 0.05.

Univariate analysis was conducted with either Chi-square or Fisher's exact test for categorical variables and Student t test for continuous variables. For continuous variables with significant or near-significant differences on univariate analysis, a receiver operating characteristic (ROC) curve was performed in order to assess the optimal cut-off that would predict a higher risk of disease flare.

Multivariate analysis consisted of a binary logistic regression including significant ($p < 0.05$) and near-significant variables ($p < 0.10$) on univariate analysis. Possible cofactors were also included.

Variables with significant association with the dependent outcome ($p < 0.05$) on multivariate analysis were selected to be included in a predictive score for that outcome. The number of points associated with each variable was obtained by rounding adjusted regression coefficients to the nearest unit. The disease flare score performance was then assessed by testing the number of points in the score against the outcome variable (disease flare on the subsequent year) by means of a ROC curve, with determination of the area under the curve and the respective 95% confidence interval. Finally, a possible cut-off for the disease flare score was assessed based on flare occurrence in each of the possible score values.

Results

Sample Characterization

From patients with known small-bowel CD submitted to SBCE for MH assessment, 47 were eligible to be part of our study according to inclusion criteria. The sample consisted of 32 (68.1%) women, with a mean age of 36.2 ± 11.1 years. Maintenance treatment was most commonly kept with immunomodulators such as thiopurines (n = 36; 76.6%). A total of 16 (34%) of the patients had a history of extra-intestinal manifestations, with axial arthritis (n = 8) and uveitis (n = 5) being the most common. Perianal disease was reported in six (12.8%) of the cases. There were no reported capsule retention cases during SBCE. Table 1 summarizes the global characteristics of our sample.

Disease Flare During the Follow-up Period

In the 12-month follow-up, a total of 12 (25.5%) of the patients had a reported disease flare. The median time to flare onset was 6 (± 3.6) months. From those, 11 needed

Table 1 Patients' baseline characteristics. Results are presented in n (%) for categorical variables and mean (SD) for continuous variables

Variable	All patients (n = 47)
Demographics	
Female gender	32 (68.1%)
Age, in years	36.2 (±11.1)
Medical records	
Smoking habits	14 (29.8%)
BMI, in kg/m^2	27.1 (±5.2)
Crohn's disease characteristics	
Age at diagnosis, in years	33.1 (±11.3)
Time since diagnosis, in years	3.17 (±2.88)
Thiopurines treatment	36 (76.6%)
Biologics treatment	8 (17%)
Previous need for corticosteroid therapy	4 (8.5%)
Extra-intestinal manifestations	16 (34%)
Perianal disease	6 (12.8%)
Inflammatory biomarkers	
ESR, in mm	12.5 (±9.6)
C-reactive protein, in g/dL	4.0 (±9.8)
Serum albumin, in mg/dL	3.9 (±0.4)
Platelet count, in UIx10^3 per liter	255.3 (±65.4)
Fecal calprotectin, in µg/g	214.2(±306.3)
SBCE findings	
LS = 0	18 (38.3%)
0 < LS < 135	29 (61.7%)
Outcome	
Disease flare	12 (25.5%)
Treatment change or intensification	11 (23.4%)
Hospitalization	1 (2.1%)
Bowel resection	0 (0%)

BMI—body mass index; ESR—erythrocyte sedimentation rate; LS—Lewis score

treatment step-up, namely increased doses of thiopurines (n = 6), initiation of biologic treatment (n = 4) and adjustment of biologic administration dose (n = 1). One of the patients was hospitalized due to bowel obstruction, which was conservatively treated with bowel rest and parenteral nutrition with a successful response.

We also assessed the one-year flare rates among 89 patients not included in our sample with no MH (LS > 135), which, as expected, revealed to be significantly higher when compared to patients presenting with MH on SBCE (48.3% vs 25.5%; $p = 0.01$) (Fig. 2).

Predictors of Disease Flare During the Follow-up Period

In Table 2, a summary of the results obtained in univariate analysis of factors associated with disease flare in patients with MH is presented. Those with extra-intestinal manifestations (EIMs) (43.8% vs 16.1%; $p = 0.04$) and with previous need for systemic corticosteroid therapy (25.0% vs 2.9%; $p = 0.018$) had a higher rate of disease flare on the first year after index SBCE. Additionally, those having shorter-duration CD were also at a higher risk (2.0 ± 2.5 vs 3.6 ± 2.9 years; $p = 0.024$), with an optimal cut-off under or equal to 3 years (AUC = 0.77; sensitivity = 83.3%; specificity = 54.3%). Regarding inflammatory biomarkers, higher platelet counts (293.1 ± 77.0 vs 241.96 ± 56.3 × 10^9UI per liter; $p = 0.022$) and erythrocyte sedimentation rate (ESR) (14.8 ± 12.3 vs 11.6 ± 8.4 mm; $p = 0.025$) reflected higher incidences of disease flare as well. Optimal cut-offs for these markers were > 280 × 10^3 per liter (AUC = 0.69; sensitivity = 54.5%; specificity = 81.3%) and > 26 mm (AUC = 0.57; sensitivity = 27.3%; specificity = 96.6%), respectively. We also found nearly significant differences when comparing both groups regarding age at the time of the SBCE (33.7 ± 12.1 vs 37.1 ± 10.9 years; $p = 0.098$). Optimal cut-off for this variable consisted of an age under

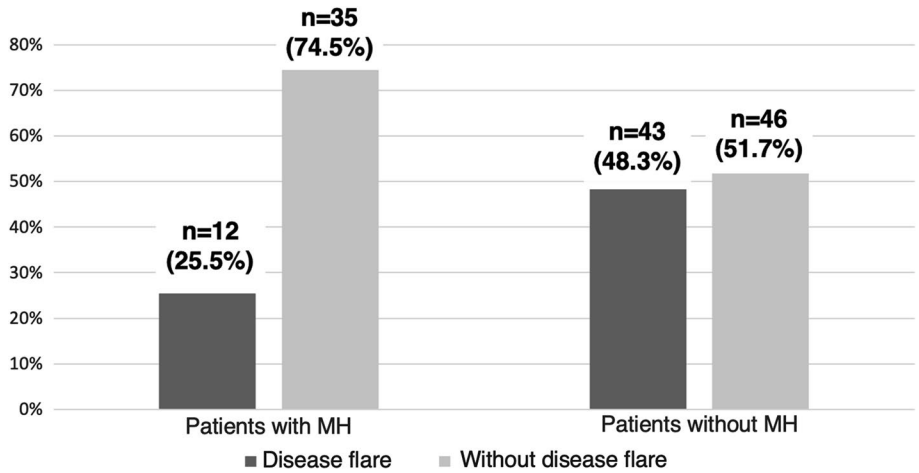

Fig. 2 Comparison of one-year disease flares on patients with and without mucosal healing. MH—mucosal healing

Table 2 Factors associated with disease flare—univariate analysis. Categorical variables are presented as n (%) and continuous variables as mean (± SD)

Variable	Disease flare (n = 12)	No disease flare (n = 35)	*p* value
Female gender	9 (75%)	23 (65.7%)	0.552
Age, in years	33.7 (± 12.1)	37.1 (± 10.9)	0.098
Smoking habits	5 (41.7%)	9 (25.7%)	0.297
BMI, in kg/m^2	25.1 (± 8.0)	27.8 (± 4.8)	0.559
Age at diagnosis, in years	31.7 (± 12.1)	33.6 (± 11.2)	0.615
Time since diagnosis, in years	2.0 (± 2.5)	3.6 (± 2.9)	**0.024**
Thiopurines treatment	10 (83.3%)	26 (74.3%)	0.523
Biologics treatment	1 (8.3%)	7 (20%)	0.353
Previous need for systemic corticoid therapy	3 (25.0%)	1 (2.9%)	**0.018**
Extra-intestinal manifestations	7 (58.3%)	9 (25.7%)	**0.040**
Perianal disease	0 (0%)	6 (17.1%)	0.125
ESR, in mm	14.8 (± 12.3)	11.6 (± 8.4)	**0.025**
C-reactive protein, in g/dL	5.0 (± 12.5)	3.6 (± 8.8)	0.682
Serum albumin, in mg/dL	3.8 (± 0.5)	4.0 (± 0.3)	0.364
Platelets count, in UIx10^3 per liter	293.1 (± 77.0)	241.9 (± 56.3)	**0.022**
Fecal calprotectin, in µg/g	90.5 (± 116.3)	255.5 (± 341.8)	0.369
LS = 0	4 (33.3%)	14 (40%)	0.682

Bold values represent *p* values < 0.05

BMI—body mass index; ESR—erythrocyte sedimentation rate; LS—Lewis score

or equal to 30 years (AUC = 0.61; sensitivity = 58.3%; specificity = 68.6%).

Gender was not proven to result in significant differences in flare rates (75.0% vs 65.7%; $p = 0.552$). Other variables that have also shown no differences between groups were smoking habits (41.7% vs 25.7%; $p = 0.297$); body mass index (25.1 ± 8.0 vs 27.8 ± 4.8 kg/m^2; $p = 0.559$); age at diagnosis (31.7 ± 12.1 vs 33.6 ± 11.2 years; $p = 0.615$); type of treatment—either with thiopurines (83.3% vs 74.3%; $p = 0.523$) or biologics (8.3% vs 20.0%; $p = 0.353$); perianal disease(0.0% vs 17.1%; $p = 0.125$); C-reactive protein (CRP) (5.0 ± 12.5 vs 3.6 ± 8.8 g/dL; $p = 0.682$); serum albumin levels (3.8 ± 0.5 vs 4.0 ± 0.3 mg/dL; $p = 0.364$) and fecal calprotectin levels (90.5 ± 116.3 vs 255.5 ± 341.8 µg/g; $p = 0.369$). It should also be noted that the frequency of patients having a LS equal to zero was similar between groups (33.3%vs40.0%; $p = 0.682$).

After performance of multivariate analysis, age under or equal to 30 years (OR 12.24; CI95% = 1.03–146.22; $p = 0.048$), EIMs (OR 11.76; CI95% = 1.22–111.11; $p = 0.033$) and platelets count over 280×10^9 per liter (OR 8.70; CI95% = 1.05–71.43; $p = 0.045$) were found to be independent predictive factors for the occurrence of disease flare on the first year after having a SBCE showing MH. The results of the multivariate analysis are shown in Table 3.

Table 3 - Final predictive variables for occurrence of disease flare—multivariate analysis

Variable	Odds ratio	Wald CI 95%	*p* value
Time since diagnosis less than 3 years	4.19	0.54–32.64	0.172
Extra-intestinal manifestations	11.76	1.22–111.11	**0.033**
Platelets count > 280×10^3 per liter	8.70	1.05–71.43	**0.045**
Age under 30 years	12.24	1.03–146.22	**0.048**
Biologics Treatment	0.05	0.01–1.24	0.068

Bold values represent *p* values < 0.05

APEX Score Development

Based on rounded regression coefficients, we determined the number of points for each variable within the final predictive model (Table 4). According to that, we developed the APEX score that can range from 0 to 7 points: Age under 30 years—3 points; Platelets over 280×10^9 per liter—2 points and extra-intestinal manifestations—2 points. The score revealed a suitable discriminative power and excellent accuracy when tested against the outcome (AUC = 0.82; IC95% = 0.64–0.99) (Fig. 3). By opposing the score to the outcome variable, we stratified our sample in two groups with different disease flare risks in the subsequent 12 months (Table 4): low-risk group (0 to 3 points)—overall flare risk of 10.8%; and high-risk group (4 to 7 points)—overall flare risk of 80%.

Table 4 The APEX score for disease flare prediction and the corresponding stratification of groups by different risks

Variable	Regression coefficient	Score points
Age under 30 years (A)	2.51	+3 points
Platelets count > 280×10^3 per liter (P)	2.16	+2 points
Extra-intestinal manifestations (EX)	2.47	+2 points
Risk group	Possible points	Flare risk
Low risk	0–3	10.8%
High risk	4–7	80.0%

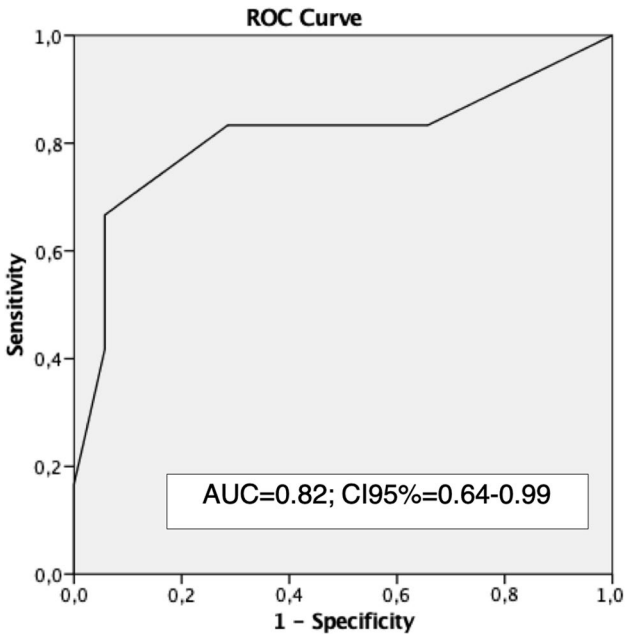

Fig. 3 ROC curve testing the accuracy of APEX score in identifying patients in which disease flare has occurred. AUC—area under the curve; ROC—receiver operating characteristic

Discussion

Optimal strategies for monitoring disease activity and avoiding long-term complications in CD are still being debated, especially in the case of small-bowel disease. Currently, SBCE has an unquestionable role on the diagnosis of ileal CD according to clinical practice guidelines [9, 17]. However, the same is not true for established CD. A major concern that may have been causing apprehension for this indication is the possible higher risk of capsule retention in the later set of patients [18]. Nonetheless, it is now becoming clear that SBCE is a safe method to assess endoscopic activity in established small-bowel CD. In 2015, Nemeth et al. have already shown that capsule retention is a rare event in patients with known CD [19]. In their series of 343 patients with established CD, only 8 (2.3%) capsule retentions were reported. Moreover, a recently published meta-analysis by Pasha and associates supports these findings [20], by concluding that even if retention rates could be slightly higher in established than in suspected CD, they still are reported in less than 5% of the cases. Our sample confirmed these results as no capsule retention case was reported, reinforcing the positive safety profile of SBCE for small-bowel CD follow-up. SBCE has also been reported to have superior diagnostic yield when compared to other modalities such as small-bowel radiography, computed tomography enterography and colonoscopy with ileoscopy in patients with established CD, as proven by a meta-analysis by Dionisio et al.[21].

Treatment escalation in CD, classically guided by clinical symptoms, is being replaced by wider and more demanding treat-to-target approaches, which pursuit not only clinical but also endoscopic endpoints [22]. These new approaches were developed as several studies reported weak correlations between patients' symptoms and endoscopic activity in CD [23, 24]. For that reason, MH has become one of the main therapeutic goals in CD management, since it has been shown to associate with increased rates of corticosteroid-free clinical remission and fewer relapse episodes [25]. In the case of isolated small-bowel CD, this led to an expanding use of SBCE in order to assess endoscopic activity in response to treatment.

Few studies have been conducted in the last two decades for evaluation of SBCE use in the assessment of CD MH [14]. The investigation published by Hall et al.[26] was the first to prospectively assess MH in a cohort of symptomatic patients with small-bowel CD after institution of immunomodulator or biologic therapy. This study showed that in 28 patients with baseline small-bowel activity, 12 (42%) had symptoms and biochemical responses accompanied by endoscopic remission in SBCE. In 2018, Nakamura et al.[27] reported that from 29 patients with LS over 135 who received additional treatment, improvement of LS was seen in 23 (79.3%). However, most of these series comprised both patients with and without significant inflammatory activity on SBCE. To our knowledge, our study is the first

to specifically evaluate the follow-up of patients with clinical remission and already proven MH on SBCE.

Our series showed that among patients with quiescent small-bowel CD who underwent SBCE showing MH, nearly three-quarters remained relapse-free during the subsequent year, with only 25.5% of the patients needing treatment change or intensification or even hospitalization due to CD exacerbation. Most of the patients who relapsed (83.3%) were under therapy with thiopurines within therapeutic ranges. It should be noticed that these treatment step-ups were decided upon flares of gastrointestinal symptoms, supported by endoscopic and biochemical findings.

The flare incidence in our study was similar to a previous investigation by Dias de Castro et al.[28], which included patients with newly diagnosed small-bowel CD, and therefore not having MH. These results may be explained as disease flare was differently defined in our investigation, with treatment changes and intensifications, which occur more frequently, also being included as a flare criterion.

Regarding potential predictors of increased risk of disease relapse, the infliximab discontinuation in Crohn's disease patients in stable remission on combined therapy with immunosuppressors (STORI) trial was one of the first prospective studies that carried a follow-up of patients with CD remission [29]. The authors projected to identify possible risk factors to have a disease relapse during the follow-up period, what would be useful upon selecting those patients having a low risk of relapsing when stepping-down treatment. In a similar way, we proposed to construct a model that could work as decision-making assistant, by recognizing patients with MH who had higher chances of relapsing on the year following SBCE. As shown, age under 30 years old (A), a platelet count over 280×10^3 units per liter (P) and the presence of EIMs (EX) were the independent predictive factors of such event. With these results, we constructed the APEX score, a scoring system that classifies the patient as having low or high risk of small-bowel CD flare after having a SBCE showing MH.

Our study agreed with previous reports on predictors of CD outcomes in which a younger age, especially under 40 years old, has been consistently associated with a more difficult-to-control disease and a higher risk of long-term complications [30, 31]. The EPIC (Early Predictive parameters of Immunosuppressive therapy in Crohn's disease) study prospectively developed a risk model in order to predict a complicated disease course, whose final version included age at diagnosis under 40 years [32]. However, it must be stressed that these studies all included CD patients regardless of disease location. In our investigation directed toward patients with small-bowel CD, a lower cut-off was rather seen, as patients under 30 years at the time of SBCE presented a significant risk of relapse, with a 12-fold increased risk comparing to older patients.

Regarding systemic inflammatory biomarkers, only increased platelet count independently predicted the occurrence of a disease flare. The optimal cut-off for forecasting the flare outcome was a platelet count over 280×10^3 units per liter. This value does not represent the presence of thrombocytosis according to its definition, but these findings may indicate that higher platelet counts, even within normal range values, could work as an early marker of small-bowel CD flare within the subsequent months, possibly reflecting subclinical inflammatory system changes before progression into overt clinical flares.

Regarding other serum inflammatory markers, our series showed no significant differences between groups when adjusting them in multivariate analysis. Previously, a meta-analysis by Mosli et al.[33] concluded that CRP levels equal or greater to 5 mg/L, despite being highly specific for detection of endoscopic disease activity, have a very poor sensitivity and a negative test would not exclude significant gastrointestinal inflammatory activity. In fact, it has already been shown that indirect inflammatory biomarkers are inconsistently correlated with inflammatory activity in CD, as none of them is specific for the disease nor does have a sufficiently long half-life in order to predict long-term outcomes [5, 34, 35]. It must be stated that most of these studies were directed toward patients with both ileal and colonic CD, differently from our study population, which may partially explain the differences between our results and what is already been described. A prime example is the case of fecal calprotectin that has been shown to have a good correlation with endoscopic or imaging disease activity on colonic CD, but not on isolated ileal disease, as was the case of our patients [36].

Another factor observed as a significant predictor of disease flare was the presence of EIMs. EIMs occur in up to 50% of the patients with CD [37], as was seen in our group. This constitutes a major aspect, as EIMs have been proven to adversely impact patients' quality of life [38]. The most common reported EIMs in our series of patients with MH were axial arthropathy and uveitis, which was not surprising since these do not parallel intestinal disease activity [39]. However, they should not be regarded as completely unrelated features as patients with EIMs ended up presenting a higher risk of needing treatment step-up after an intestinal inflammatory activity flare, when adjusted for other possible predictors. These findings match previous reports describing that inflammatory bowel disease patients with EIMs are more likely to present with disease activity during their clinical course [40].

Currently, the definition of endoscopic remission in SBCE remains uncertain, as there is no consensus on the therapeutic goal to reach in luminal small-bowel CD, with both complete luminal healing (LS = 0) and the absence of deep or superficial ulcerations (LS < 135) being described

as the desirable target depending on the series [14]. For that reason, our group compared the occurrence of disease flare rates between patients with a LS equal to zero and patients with all other LS bellow 135, in order to assess if complete healing of small-bowel mucosa would lead to better outcomes, with no significant differences (40.0% vs 33.3%; $p = 0.682$), thus this variable was not included in the final predictive score.

Facing our results, SBCE has been shown to be a safe and effective method of assessing small-bowel CD activity. Furthermore, it seems reasonable to conclude that MH as shown by this endoscopic technique remains a desirable therapeutic goal on patients with isolated small-bowel CD, since nearly 75% of the patients presenting such reduced endoscopic activity remain with a stable disease on the subsequent year.

Regarding the 25% of patients who relapse, some factors such as younger age, EIMs and higher platelet counts, may be helpful for clinicians when identifying higher-risk patients, and whether deciding to perform earlier clinical, analytical and/or endoscopic reevaluation. Furthermore, the presence of these risk factors could be of great interest when a treatment intensification or step-down is considered. The APEX score may become a crucial tool on that decision, as it demonstrated an impressive discriminative power (AUC = 0.82; IC95% = 0.64–0.99) in identifying patients' risk of relapse after having a SBCE with MH. For example, patients scoring in the high-risk group (4 to 7 points) could be considered for earlier treatment intensification, and earlier follow-up intervals, as the relapse rate in this setting is around 80%.

APEX score constitutes a simple score to apply, being easily assessable to every gastroenterologist in everyday clinical practice. If further validated, which is already in progress at our department, it may become an extremely valuable tool following SBCE for assessment of MH. Further prospective investigations with larger samples are required in order to confirm and support our findings and to shed light on remaining questions such as possible advantages in having a LS of zero or the optimal timings of SBCE procedure.

Author's contribution All authors contributed to and agreed on the content of the manuscript. MSilvaV designed the study, carried out data analysis and drafted the manuscript. FM carried out data collection and analysis. BCP. and DCF. contributed to the design of the study and critically revised the manuscript. CGT, RB and MMJ critically revised the manuscript. CJ critically revised and approved the final version of the manuscript.

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Declarations

Conflicts of interest The authors declare that they have no conflicts of interest.

Ethical approval This study conforms to the ethical guidelines of the 1975 Helsinki Declaration (6th revision, 2008) as reflected in a priori approval by the institution's ethics committee. This investigation was retrospectively conducted, being descriptive, without prospective interventions or control group. Patients received current standard of care, without randomization or experimental intervention. All data collected were anonymized. For this type of study formal consent is not required, even though all patients signed a written informed consent before the procedure. This article does not contain any studies with animals performed by any of the authors.

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