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Original Article

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Lewis Score – Prognostic Value in Patients with Isolated Small Bowel Crohn's Disease

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Abstract

Background and aims: Small bowel capsule endoscopy (SBCE) allows mapping of small bowel inflammation in Crohn's disease (CD). We aimed to assess the prognostic value of the severity of inflammatory lesions, quantified by the Lewis score (LS), in patients with isolated small bowel CD.
Methods: A retrospective study was performed in which 53 patients with isolated small bowel CD were submitted to SBCE at the time of diagnosis. The Lewis score was calculated and patients had at least 12 months of follow-up after diagnosis. As adverse events we defined disease flare requiring systemic corticosteroid therapy, hospitalization and/or surgery during follow-up. We compared the incidence of adverse events in 2 patient subgroups, i.e. those with moderate or severe inflammatory activity (LS ≥790) and those with mild inflammatory activity (135 ≤ LS < 790).
Results: The LS was ≥790 in 22 patients (41.5%), while 58.5% presented with LS between 135 and 790. Patients with a higher LS were more frequently smokers ($p = 0.01$), males ($p = 0017$) and under immunosuppressive therapy ($p = 0.004$). In multivariate analysis, moderate to severe disease at SBCE was independently associated with corticosteroid therapy during follow-up, with a relative risk (RR) of 5 ($p = 0.011$; 95% confidence interval [CI] 1.5–17.8), and for hospitalization, with an RR of 13.7 ($p = 0 .028$; 95% CI 1.3–141.9).
Conclusion: In patients with moderate to severe inflammatory activity there were higher prevalences of corticosteroid therapy demand and hospitalization during follow-up. Thus, stratifying the degree of small bowel inflammatory activity with SBCE and LS calculation at the time of diagnosis provided relevant prognostic value in patients with isolated small bowel CD.

Keywords: Crohn's disease; small bowel capsule endoscopy; Lewis score; prognosis

1. Introduction

Crohn's disease (CD) is a heterogeneous entity that can affect the entire gastrointestinal tract. In up to 60% of patients the disease has small bowel involvement.[1–3] In patients with CD diagnosed by ileocolonoscopy, an investigation to determine the extent of CD in the small bowel is advisable.[2] This evaluation can be achieved by cross-sectional imaging by magnetic resonance enterography (MRE), computed tomography enterography (CTE) or small bowel capsule endoscopy (SBCE).[4] Although SBCE can only be used in patients with inflammatory phenotype (non-stricturing, non-penetrating) CD, with respect to mild lesions or those located in the proximal small bowel it has been clearly demonstrated that this method is more sensitive than MRE and CTE.[3,5] Recent studies have shown an association between jejunal lesions and worse clinical outcomes;[6]

moreover, the location and particularly the severity of small bowel lesions in patients with CD may influence therapeutic management,[7] reinforcing the importance of SBCE in patients with CD.

Several endoscopic scores (Rutgeerts score[8], the CD endoscopic index of severity [CDEIS][9] and the simple endoscopic score for CD [SES-CD][10]) have been developed to assess luminal CD endoscopic activity. Recent guidelines[4] for endoscopy in CD suggest the use of these scores in clinical practice since they have prognostic value.

A semi-quantitative scoring index, the Lewis score (LS),[11] has been proposed to quantify the inflammatory activity of the small bowel in CD. This score is based on the number and distribution of intestinal segments with villous oedema, ulceration and stenosis. To calculate the LS, the small bowel is first divided into equal thirds (tertiles) according to the transit time of the capsule. For each tertile, a numeric subscore is calculated, considering the extent and distribution of oedema and the number, size and distribution of ulcers. The final score is the sum of the worst-affected tertile plus the stenosis score (single/multiple, ulcerated/not ulcerated, traversed/not traversed by the capsule). The LS allows small bowel inflammatory activity to be classified into three grades: (1) normal or clinically insignificant mucosal inflammatory change (LS <135); (2) mild disease (135 ≤ LS < 790); and (3) moderate to severe disease (LS ≥790).[11] The LS has shown better performance than other SBCE scores in describing small bowel inflammation, with a good correlation with biochemical parameters of inflammation, such as C-reactive protein (CRP) and faecal calprotectin.[12,13] This score was recently validated with strong interobserver agreement,[14] reinforcing its utility in reporting small bowel inflammatory activity in clinical practice.

Even though SBCE has an important role in the management of patients with CD,[7,15] the prognostic value of inflammatory activity in the follow-up of these patients has not been assessed yet. If such inflammatory activity negatively impacts clinical outcome, it may influence therapeutic strategy and the management of patients with CD. In this setting we aimed to evaluate the prognostic value of the severity of inflammatory lesions at the time of diagnosis, quantified by the LS, in patients with isolated small bowel CD.

2. Methods

We performed a retrospective, single-centre study from January 2008 to December 2013, including all consecutive patients undergoing SBCE for suspected CD or with known isolated non-stricturing and non-penetrating small bowel CD, to assess the entire small bowel at the time of diagnosis. In patients with established CD (diagnosed by ileocolonoscopy), SBCE was performed within 1 month after its diagnosis, and no immunosuppressive therapy (anti-tumour necrosis factor [anti-TNF] and/or thiopurines) was initiated in the period between diagnosis and SBCE. All patients had had an ileocolonoscopy as the first endoscopic diagnostic procedure. Patients with obstructive symptoms and/or those with evidence of ileal stenoses at ileocolonoscopy and/or radiological or cross-sectional features of stricturing or penetrating disease were not eligible for SBCE and thus did not enter this study. Patients taking aspirin or non-steroidal anti-inflammatory drugs discontinued the medication at least 4 weeks before the SBCE examination, based on recommendations.[16] Patients followed a clear liquid diet for 24 h and then fasted for 12 h prior to SBCE (PillCam® SB2, Medtronic®). The SBCE videos were reviewed and the LS was calculated using the software application in the RAPID Reader® v.6, v.7 or v.8 workstation. Using the software application to calculate the LS, the small bowel was automatically divided into equal thirds (tertiles) according to the transit time of the capsule; in those cases where the capsule did not reach the caecum, small bowel tertiles were determined based on the last small bowel image. Based on another study in this field,[7] small bowel lesions were considered to have a proximal location if they were located in the upper two-thirds of the small bowel (first two tertiles of the SBCE) and had an LS ≥135. Small bowel inflammatory activity was classified into two grades: mild disease (135 ≤ LS < 790) and moderate to severe disease (LS ≥790).

All patients had at least 12 months of follow-up after diagnosis (mean 42 ± 17 months, range 12–77 months). The clinical variables evaluated at diagnosis were smoking status, family history of inflammatory bowel disease, extraintestinal manifestations, perianal disease, history of appendicectomy, treatment initiated after SBCE, and laboratory variables including serum haemoglobin, CRP, erythrocyte sedimentation rate (ESR) and ferritin.

The variables defined as adverse events,[2] indicating a worse outcome, were disease flare requiring systemic corticosteroid therapy, hospitalization and surgery during follow-up (excluding the presentation episode). The incidence of adverse events was analysed and compared between patients with higher LS (LS ≥790), corresponding to moderate or severe inflammatory activity, and patients with mild inflammatory activity (LS between 135 and 790).

Statistical analysis was performed with Statistical Package for the Social Sciences (SPSS) software version 20.0 (IBM, Armonk, New York, USA). The baseline quantitative data are presented as mean ± SD. For nominal variables, the χ^2 test or Fisher's exact test was used as appropriate, and Student's *t*-test was used for quantitative variables with normal distribution. Binary logistic regressions were adjusted considering as independent variables smoking status, family history of inflammatory bowel disease, extraintestinal manifestations, perianal disease, history of appendicectomy, small bowel inflammatory activity, and laboratory variables (serum haemoglobin, CRP, ESR and ferritin). Laboratory variables were used as quantitative variables. The variables measured at diagnosis were included as predictors if they were selected from bivariate analysis ($p < 0.1$). Predictive performance of the model was tested by assessing its discrimination (correct classification) and calibration (whether probabilities predicted by the model matched observed probabilities). Discrimination was measured using the area under the receiver operating characteristic curve (AUROC), and 95% confidence intervals (CIs) were reported.[17] A p value of less than 0.05 was considered statistically significant. All patients provided written informed consent for SBCE. The study was performed according to the Declaration of Helsinki and approved by the local ethics board of Centro Hospitalar do Alto Ave, Guimarães, Portugal.

3. Results

3.1. Patients' characteristics

Fifty-three consecutive patients were included (mean age 33 ± 13 years, 64% females), 57% underwent SBCE for suspected CD and 43% to assess disease extent and activity, at the time of diagnosis, in patients with known non-stricturing and non-penetrating ileal CD. Baseline characteristics are summarized in Table 1.

Small bowel imaging was performed in 24 patients (45%) prior to SBCE, revealing features of ileitis or unremarkable findings. Upper endoscopy was performed in 21 patients (40%), revealing no features of CD in any of the patients.

There were no statistical differences between the 2 groups (mild disease [135 ≤ LS < 790] vs moderate to severe disease [LS ≥790]), considering most of the clinical or laboratory variables studied (Table 1).

Table 1. Demographic and clinical data of all patients included in relation to the severity of small bowel lesions.

	Suspected CD (n = 30)	Established CD (n = 23)	Mild disease (135 ≤ LS <790)	Moderate to severe disease (LS ≥790)	p value
Gender					**0.017**
Male	7 (23%)	12 (52%)	7 (23%)	12 (55%)	
Female	23 (77%)	11 (48%)	24 (77%)	10 (45%)	
Age at SBCE, mean (SD), y	36 ± 15	29 ± 11	34 ± 11	32 ± 16	0.579
Follow-up after SBCE, mean (SD), mo	45 ± 17	39 ± 18	42 ± 18	43 ± 18	0.825
Smoker					**0.036**
Yes	5 (17%)	6 (26%)	3 (10%)	8 (36%)	
No	25 (83%)	17 (74%)	28 (90%)	14 (64%)	
Family history of IBD					1.000
Yes	4 (13%)	2 (9%)	4 (13%)	2 (9%)	
No	26 (87%)	21 (91%)	27 (87%)	20 (91%)	
Perianal disease					0.720
Yes	4 (13%)	5 (22%)	6 (19%)	3 (14%)	
No	26 (87%)	18 (78%)	25 (81%)	19 (86%)	
Extraintestinal manifestations					0.382
Yes	5 (17%)	1 (4%)	5 (16%)	1 (5%)	
No	25 (83%)	22 (96%)	26 (84%)	21 (95%)	
History of appendectomy					0.295
Yes	4 (13%)	0 (0%)	1 (3%)	3 (14%)	
No	26 (87%)	23 (100%)	30 (97%)	19 (86%)	
Haemoglobin, mean (SD), g/dL	13.5 ± 1.9	13.5 ± 1.1	13.7 ± 1.4	13.2 ± 1.8	0.349
CRP, mean (SD), mg/dL	11.7 ± 25.1	22.5 ± 31.2	10.8 ± 24.7	24.0 ± 31.4	0.086
ESR, mean (SD), mm/h	19.0 ± 15.4	20.1 ± 16.6	18.4 ± 15.2	21,1 ± 16.9	0.554
Ferritin, mean (SD), mg/dL	74.7 ± 61.6	78.0 ± 88.6	70.8 ± 55.1	83.9 ± 95.4	0.535
Lewis score, mean (SD)	1 077 ± 1 519	1 796 ± 1 589	338 ± 169	2 871 ± 1 476	
Proximal small bowel lesions	18 (60%)	18 (78%)	19 (61%)	17 (77%)	0.219
Thiopurines and/or anti-TNF					**0.004**
Yes	11 (37%)	15 (65%)	10 (32%)	16 (73%)	
No	19 (63%)	8 (35%)	21 (68%)	6 (27%)	

CD, Crohn's disease; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; LS, Lewis score; SBCE, small bowel capsule endoscopy; TNF, tumour necrosis factor.

However, in the group of patients with moderate to severe disease the frequencies of smokers (36 vs 10%, p = 0.036) and male sex (55 vs 23%, p = 0.017) were higher. The mean follow-up after SBCE was 42 months (range 12–77 months), with no difference between the two groups.

3.2. SBCE findings

Overall, SBCE detected mild lesions (135 ≤ LS < 790) in 31 patients (58.5%) and moderate to severe (LS ≥ 790) in 22 patients (41.5%). Among the 53 patients included in the study, 36 (68%) had significant inflammatory activity in the proximal small bowel; 10 of them had moderate to severe disease (LS ≥ 790). In 8 patients (15%) a stenosis was detected in SBCE, but capsule retention only occurred in 3 patients (6%). This occurred in 2 patients with suspected CD and in 1 patient with established CD who had no previous history of obstructive symptoms and had been submitted to small bowel cross-sectional imaging that did not identify any stenosis. The first 2 patients with suspected CD underwent surgery to retrieve the capsule and to confirm the diagnosis after an unsuccessful attempt at endoscopic removal. The patient with established CD was managed medically. The frequency of complete examinations, with the capsule reaching the caecum within the battery life, was 77% (n = 41).

3.3. Follow-up after SBCE

During the follow-up period, 25 patients (47%) experienced at least one disease flare, leading to surgery, hospitalization or corticosteroid therapy. In general, several risk factors for a disease flare were identified as relevant by univariate analysis: the presence of moderate to severe inflammatory activity (p < 0.001), the presence of perianal disease (p = 0.067) and higher levels of ESR and CRP (p = 0.095 and p = 0.019, respectively) Table 2. However in a binary logistic regression analysis considering these variables, only the presence of moderate to severe inflammation and perianal disease remained independent risk factors for disease flare, with a relative risk (RR) of 12.7 (p = 0.002; 95% CI 2.6–61.8) and 10.6 (p = 0.024; 95% CI 1.4–82.1), respectively (Table 3). The predictive performance of these variables for a disease flare was excellent, with an AUROC of 0.86 (95% CI 0.746–0.975).

Binary logistic regression models were also adjusted for each adverse event separately (surgery, hospitalization and corticosteroid therapy). None of the variables were associated with a higher risk for surgery. By univariate analysis smoking (p = 0 .09) and moderate to severe disease at SBCE (p = 0 .003) were statistically associated with a higher risk of corticosteroid therapy. However, in multivariate analysis only moderate to severe disease at SBCE was independently associated with corticosteroid therapy during follow-up, with an RR of 5 (p = 0.011; 95% CI 1.5–17.8). Moderate to severe disease at SBCE (p = 0 .006) and mean haemoglobin levels (11.9 vs 13.8 g/dL; p = 0.001) at diagnosis were associated with hospitalization in univariate analysis and were also independent risk factors for hospitalization in multivariate analysis, with an RR of 13.7 (p = 0.028; 95% CI 1.3–141.9) and 0.3/unit (p = 0.028; 95% CI 0.1–0.9), respectively.

Table 2. Univariate analysis of characteristics predictors of relapses.

	Relapse	No relapse	*p* value
Gender			0.983
Male	9 (36%)	10 (36%)	
Female	16 (64%)	18 (64%)	
Age at SBCE, mean (SD), y	32 ± 15	33 ± 11	0.745
Smoker			0.219
Yes	7 (28%)	4 (14%)	
No	18 (72%)	24 (86%)	
Family history of inflammatory bowel disease			0.196
Yes	1 (4%)	5 (18%)	
No	24 (96%)	23 (82%)	
Perianal disease			**0.067**
Yes	7 (28%)	2 (7%)	
No	18 (72%)	26 (93%)	
Extraintestinal manifestations			0.404
Yes	4 (16%)	2 (7%)	
No	21 (84%)	26 (93%)	
History of appendectomy			0.333
Yes	3 (12%)	1 (4%)	
No	22 (88%)	27 (96%)	
Lewis score ≥790	17 (68%)	5 (18%)	**0.001**
Lewis score	2191 ± 1801	674 ± 880	**0.001**
Proximal small bowel lesions	18 (72%)	18 (64%)	0.548
Haemoglobin, mean (SD), g/dL	13.2 ± 1.9	13.7 ± 1.3	0.254
C-reactive protein, mean (SD), mg/dL	26.5 ± 37.8	7.2 ± 8.6	**0.019**
Erythrocyte sedimentation rate, mean (SD), mm/h	23.5 ± 15.9	16.1 ± 15.2	**0.095**
Ferritin, mean (SD), mg/dL	65.3 ± 56.1	85.3 ± 85.5	0.333

SBCE, small bowel capsule endoscopy.

Table 3. Binary logistic regression for disease flare.

Predictor	RR	95% CI	*p* value	R^2 (Nagelkerke)
Lewis score ≥790	12.7	2.6 – 61.8	**0.002**	0.51
Perianal disease	10.6	1.4 – 82.1	**0.024**	
C-reactive protein	1.0	0.9 – 1.1	0.205	
Erythrocyte sedimentation rate	1.0	0.9 – 1.1	0.747	
AUROC	***p* value**		**95% CI**	
0.86	**<0.001**		0.746–0.975	

RR, relative risk; CI, confidence interval.

After SBCE, 16 patients in the moderate to severe group started immunosuppressive therapy (azathioprine or azathioprine and/or anti-TNF therapy) vs 10 patients in the mild group (73 vs 32%, $p = 0.004$). However, even with more effective therapy the group of patients with moderate to severe disease at SBCE presented with higher frequencies of surgery ($p = 0.071$), hospitalizations ($p = 0.006$) and new flares requiring corticosteroid therapy ($p = 0.003$) during follow-up (Table 2).

The proportion of patients that started treatment with thiopurines and/or biologics after SBCE was higher among patients with proximal small bowel lesions ($p = 0.011$). However, the numbers of surgeries, hospitalizations and corticosteroid therapies during follow-up were not different between patients with and without proximal small bowel lesions.

4. Discussion

The impact of the severity of endoscopic inflammation, quantified by the LS, in defining an aggressive course in patients with isolated small bowel CD has been scarcely reported in the literature thus far. In this study we assessed the prognostic value of the severity of inflammatory lesions, quantified by the LS, in patients with isolated small bowel CD, concluding that in patients with moderate to severe inflammatory activity (LS ≥790) at SBCE the prevalence of disease flares leading to corticosteroid therapy demand and hospitalizations during follow-up was higher when compared with patients with mild inflammatory activity (135 ≤ LS < 790).

The ECCO guidelines are clear about the importance of assessing the location and extent of CD in the small bowel at diagnosis, in order to establish the prognosis and to better define the therapeutic strategy.[2] Rosa et al.[18] demonstrated the importance of the LS to characterize and grade the inflammatory activity on SBCE in providing an earlier and more accurate diagnosis of CD in patients with suspected inflammatory bowel disease (IBD). A meta-analysis[19] compared the diagnostic yield of SBCE with other imaging modalities in patients with CD, including push enteroscopy, small bowel follow-through and CTE showed an overall superiority of SBCE over other imaging techniques. Although cross-sectional imaging has the advantage of evaluating the deep layers of the bowel wall and enabling the assessment of extra-luminal involvement, they have several limitations when compared with SBCE, such as lower sensitivity, heterogeneous availability and feasibility among different medical centres, variable observer expertise, claustrophobia for MRE, radiation exposure and contrast sensitivity for CTE.

Several studies[20–23] have tried to define clinical predictors of disabling and/or severe CD at diagnosis to clarify which patients should be considered for early treatment with thiopurines and/or biologics. The study of Beaugerie *et al.*[20] showed that perianal lesions, younger age and ileocolonic disease were associated with a poor prognosis in CD. In association with clinical factors, endoscopic scoring systems have shown prognostic relevance in patients with ileocolonic disease and the ability to predict postoperative recurrence.[4]

In recent studies[6,7] the prevalence of jejunal lesions in patients with CD was up to 50%. In concordance, in our study proximal significant inflammatory activity was detected in 68% of patients, which is indeed a very high prevalence of lesions out of reach of the colonoscope, often missed by other conventional imaging modalities. As in the study by Flamant *et al.*,[6] we found an association between proximal lesions and the start of therapy that included immunosuppressant and/or biologic agents shortly after SBCE; however, in our cohort this subset of patients did not have a higher prevalence of disease flares during follow-up.

In our study, the LS was determined to objectively quantify inflammatory activity and was associated with the likelihood of starting immunomodulators, as shown in a recent study.[7] In addition to these findings, on multivariate analysis only moderate to severe inflammatory activity at SBCE could predict independently any type of disease flare and, when analysed separately, the need for corticosteroid therapy and hospitalization, which is in concordance with previous studies performed in patients with ileocolonic CD.[24]

An LS ≥790 at presentation was associated with a trend to intestinal resection during follow-up, but this association was not statistically significant in either univariate or multivariate analysis. This may be related to the fact that only 6 patients underwent surgery (3 for occlusive symptoms and 3 for penetrating disease developed during follow-up), and for that reason we cannot exclude the possibility

of a type II error. The lower incidence of surgery during follow-up in our study probably resulted from selection bias of patients with non-stricturing and non-penetrating small-bowel CD.

According to the current trend, the treatment goal for CD is to achieve mucosal healing, which has been shown to increase corticosteroid-free remission and decrease surgery rates.[25,26] A recent prospective study tried to assess small bowel mucosal healing in CD patients 52 weeks after initiating immunomodulators and biologic therapy.[27] The authors demonstrated a rate of complete mucosal healing that was similar (up to 50%) to that seen in previous studies of ileocolonic CD.[28] However, in patients with a stricture identified on SBCE the outcome was poor, these patients having a higher chance of requiring surgery during follow-up. Importantly, this study has shown that SBCE is capable of safely and accurately monitoring the treatment response in patients with small bowel CD; we believe that the application of an index score is the only way to assess mucosal healing and treatment response in CD.

To our knowledge, this is the first study to assess the importance of SBCE and the LS in the definition of CD patients' outcomes. Our results support the idea that the grade of inflammatory activity (LS ≥790) is a more powerful predictor of worse prognosis than the lesion location itself. However, prospective studies are needed to confirm these data. In future it will be fundamental to identify patients with poor prognosis and risk of disabling disease at diagnosis, as they may benefit from more intensive treatments.

Our study has some limitations related to the heterogeneity of the patients and the retrospective design of the study. This is important since clinical decisions regarding the outcomes evaluated in this study (surgery, hospitalization and corticosteroid therapy) are often complex, multifactorial and multidisciplinary, and certainly do not rely on a single feature. However, in our centre we attempted to lessen this limitation, consolidating these decisions in 1 gastroenterologist, together with 1 surgeon (in case of surgery) fully dedicated to IBD. Additionally, patients with higher LS had worse prognosis even though they had received immunosuppressive therapy (anti-TNF and/or thiopurines) more frequently. In fact, there is a potential bias of higher LS indirectly reducing the incidence of negative outcomes by leading to a more aggressive therapeutic management, and in our study this may have resulted in underestimation of an even more pronounced effect of the LS regarding worse prognosis.

Another limitation is the relatively low SBCE completion rate (77%), with the potential to underestimate the LS. The completion rate in our study was similar to others reported for patients with established CD;[29] this prolonged transit time might be explained by delay in capsule progression in segments with inflammatory activity such as oedema and strictures, and possibly by alteration in the gut's motility.[7,30]

Regarding capsule retention, even though the rate of retention was low (4% in patients with established CD) compared with data reported in the literature,[25] in patients with established CD the contribution of disease extent evaluation may be a matter of discussion, whereas capsule retention can lead to invasive procedures or to surgery. In our study, only 1 patient with established CD presented with obstructive symptoms but was managed successfully with medical treatment. As a matter of fact, a recent study presented at Digestive Disease Week 2015[31] concluded that capsule retention is a rare event in patients with established CD, and the risk of capsule retention was not decreased by routine use of a patency capsule in all CD patients. However, SBCE in CD patients after positive capsule patency is associated with a high risk of capsule retention, and thus it may be useful in selected at-risk populations.

To conclude, the role of SBCE in the management and outcome of patients with small bowel CD is still evolving. Although further prospective studies are required, our study reinforces the importance of the LS in the management and prognosis of patients with small bowel CD, proving that higher inflammatory activity at diagnosis is associated with worse prognosis and disease outcomes.

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None.

Conflicts of Interest

None of the authors have conflicts of interest to declare.

Author Contributions

F. Dias de Castro performed the study, data analysis and literature search and drafted the manuscript; P. Boal Carvalho participated in the design of the study, reviewed the capsule endoscopies and performed statistical analysis; S. Monteiro participated in the design of the study and reviewed the capsule endoscopies; B. Rosa participated in the design of the study, reviewed the capsule endoscopies and revised the manuscript; J. Firmino Machado performed statistical analysis; M. J. Moreira revised the manuscript and reviewed the capsule endoscopies; J. Cotter participated in the design of the study, critically revised the manuscript and approved the final version to be submitted.

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