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ORIGINAL ARTICLE

Endoscopy and Procedures

Clinical validation and accuracy assessment of the Capsule Endoscopy-Crohn's Disease index (CE-CD)

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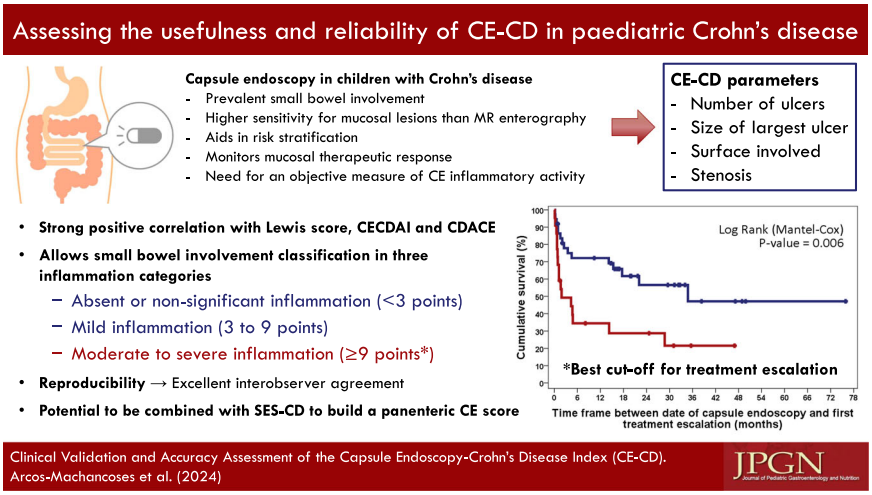
Abstract

Objectives: To compare the recently proposed Capsule Endoscopy-Crohn's Disease index (CE-CD) to pre-existing capsule endoscopy (CE) scores, to measure its precision and accuracy to predict adverse clinical outcomes in children with Crohn's disease (CD).

Methods: Children with CD who underwent CE at diagnosis and had, at least, 1-year follow-up postprocedure were selected. Capsule study was viewed and the different indices were independently scored by two trained paediatric gastroenterologists. The relationship between pre-existing scores and CE-CD was assessed by linear regression analysis. Clinical outcomes prediction assessment was based on receiver operating characteristics curves, survival analysis and Cox regression. Finally, interobserver agreement was measured.

Results: Fifty-nine patients were finally included. CE-CD showed a strong positive correlation with the Lewis score ($\rho = 0.947$) and the Capsule Endoscopy Crohn's Disease Activity Index (CECDAI) ($\rho = 0.982$). Both CE-CD and CECDAI were significant predictors of treatment escalation (hazard ratio 1.07 and 1.09, respectively, with both p-values < 0.01). However, no score predicted risk of hospital admission, surgery or clinical/endoscopic relapse. The presence of moderate-to-severe small bowel (SB) inflammation, defined as a score of ≥9 on CE-CD, provided a hazard ratio of treatment escalation of 2.6 (95% confidence interval: 1.3–5.3). This cut-off provided the optimal sensitivity/specificity pair: 48.4%/89.3%. No interobserver misclassification among inflammation categories given by CE-CD were observed (kappa 100%).

Conclusion: CE-CD is a useful tool to document SB inflammation in children with CD. It correlates strongly with classical scores, can better predict need for treatment escalation and shows good interobserver agreement.



KEYWORDS
CD, CE, paediatric, SES, ulcers

1 | INTRODUCTION

It is estimated that at least 40% of children with Crohn's disease (CD) show small bowel (SB) involvement.[1] Moreover, CD can be exclusively confined to the SB in about 30% of the patients, especially in younger patients.[2] Assessing the SB is a major indication for capsule endoscopy (CE) in children.[3,4] Actually, 50% of CE studies in the paediatric population are conducted to evaluate SB in CD,[5] followed by investigation of SB bleeding.[6] CE adds complementary information to that given by magnetic resonance enterography (MRE) when studying topographical extension. This helps in accurate phenotyping of the disease as per Paris classification.[7] Despite MRE being preferred over CE when stenosis is suspected, CE should be considered even after a negative MRE, due to the higher sensitivity and negative predictive value for mucosal lesions.[8] Mucosal healing (MH) is considered to be the foremost therapeutic goal when managing CD. Its achievement is associated with better long term outcomes, including reduced need for hospitalisation and surgery.[9] CE is an effective tool to monitor SB mucosal therapeutic response and ensure MH.[10,11] In fact, positive CE results lead to treatment modification in the majority of patients.[12]

For this purpose, several endoscopic scoring systems have been implemented to standardise the description of CE findings.[13] The Lewis score (LS) was the first score to be introduced and is most used, being embedded in CE reviewing softwares. LS has well-defined cut-off values for disease activity but is largely influenced by stenosis. It also includes villous oedema, which is a poorly reproducible parameter and is not considered an endoscopically relevant feature of CD.[14] To overcome this limitation, the Capsule Endoscopy Crohn's Disease Activity Index (CECDAI) was devised.

What is Known

- Capsule Endoscopy-Crohn's Disease index (CE-CD) has recently been proposed to describe small bowel involvement in paediatric Crohn's disease.
- CE-CD only considers ulcers and stenosis. However, beyond being simple, it has proven to be a reproducible and predictive score in the only study published so far.

What is New

- CE-CD correlates with previously described capsule endoscopy scores and has greater accuracy to predict further need to escalate treatment.
- The threshold between mild and moderate-to-severe inflammation categories has also proven to be the best cut-off to predict treatment escalation.
- CE-CD allows a highly reproducible classification in three inflammation categories.

The CECDAI evaluates only three variables in the proximal and distal SB segments.[15] It is, therefore, simpler, correlates strongly with LS,[16] and seems to better reflect active inflammation.[17] However, neither LS nor CECDAI highlight the extent of the disease or provide direct information about the presence of stenosis based on the score value. To address these shortcomings the Crohn's Disease Activity in Capsule Endoscopy (CDACE) has been developed.[18] Additionally, many endoscopists do not use currently

available CE scores as frequently as ileocolonoscopy scores.[19] Hence, the recent proposal of the Capsule Endoscopy-Crohn's Disease index (CE-CD). CE-CD, taking advantage of the familiarity effect, has the Simple Endoscopic Score for Crohn's Disease (SES-CD) as a model, and uses the same parameters to assess SB inflammation.[20]

Our aim was to compare CE-CD to pre-existing scores (LS, CECDAI and CDACE) with the main outcome measure of adverse clinical results prediction in children with CD.

2 | METHODS

2.1 | Design and study population

This was a single-centre retrospective study conducted at a major paediatric IBD tertiary referral centre. Patients aged 6–18 years old with a diagnosis of CD who underwent CE between 2015 and 2021, and having at least 1 year follow up, were identified through the institutional Inflammatory Bowel Disease database. Patients with a history of nonsteroidal anti-inflammatory drug intake in the 4 weeks leading up to the CE were excluded. Only the first exploration was considered when CE was repeated over time in the same patient. CE footage was assessed by two trained gastroenterologists and discrepancies were resolved by agreement. Additionally, relevant clinical information including demographics, disease duration, severity, laboratory values and data about concurrent medical treatment were collected. A representative subset of patients' CE records was independently evaluated by a third investigator to conduct the reproducibility analysis. The study was carried out under the 'Declaration of Helsinki's' principles, and approved by the Centre's Health Research Authority with the consideration of a retrospective audit work using data obtained as part of regular patient care.

2.2 | CaE procedure

CE was performed with the PillCam™ SB3 CE system (Medtronic) either ingested or endoscopically placed in duodenum, based on patient preference, age and concomitant indication for oesophagogastroduodenoscopy. Fasting before the procedure and bowel preparation with sodium picosulfate, senna and simethicone were in keeping with established centre specific protocol. Oral fluids were allowed 2 h after CE placement or ingestion, and meal 4 h after. When assessing the CE video sequences, investigators were initially blinded to laboratory results, background clinical information and the original CE report. All images were reviewed using the PillCam™ software version 9 (Medtronic).

2.3 | Capsule endoscopic scoring systems

Using the progress indicator function of the CE reviewing software, thumbnails were created at the first duodenal image and at the first caecal image. When the examination was completed without the CE reaching the colon, scores were calculated by dividing the SB into the appropriate number of sections with the last image considered the end recorded segment of the SB. Transit times provided by the CE reviewing software were used to divide SB into two (CECDAI), three (LS and CE-CD) or four parts (CDACE).

As previously reported, LS was computed based on the scores given by two parameters (villous oedema and ulcers) in each tertile, and a third parameter (stenosis) that was evaluated for the entire SB. Final LS corresponded to maximum tertile points plus the stenosis score. According to the primary study documenting the development of LS, <135 points is designated normal or clinically insignificant mucosal inflammation, a score between 135 and 790 is mild, and a score ≥790 is moderate to severe.[14] PillCam™ software aided in the automatically calculation of LS.

CE-CD, CECDAI and CDACE were all manually calculated. Tables included as Supporting Information: Digital Content 1 detail their specific features and outline their advantages and disadvantages.

2.4 | Laboratory tests measurements

When available, haemoglobin, c-reactive protein, serum albumin and faecal calprotectin (FC) results from samples obtained within 2 weeks before the CE procedure were registered. FC was analysed using a validated human calprotectin enzyme-linked immunosorbent assay kit (CALPRO).

2.5 | Statistical analysis

Spearman's rank coefficient (ρ), Pearson's linear correlation coefficient (r) and the coefficient of determination (R^2) were used to study the correlation between the CE-CD and the other previously described CE scores.

Furthermore, Cox proportional hazard regression analyses were performed between different CE scores (independent variables) and clinical outcomes (need for surgery or hospitalisation due to CD-related complications, clinical and endoscopic relapse, and need for treatment escalation), over for the follow-up period.

The abovementioned LS cut-offs have already been used to extrapolate by linear regression the corresponding values in the original study describing CE-CD (LS: 135 = CE-CD: 9, and LS: 790 = CE-CD: 13).[20] Our

linear regression equations were also applied to obtain the equivalent LS cut-offs for CE-CD, CECDAI and CDACE, rounding to the nearest integer. To validate CE-CD cut-offs, clinical and analytical differences between the resulting severity groups were studied. To this effect, the Kaplan–Meier model was used and differences in the occurrence of the clinical outcomes over time were assessed by means of the log rank (Mantel–Cox) test.

Additionally, the area under the receiver operating characteristics (ROC) curve for every score was calculated. Sensitivity and specificity were obtained for all possible cut-offs and the optimal one was chosen using a costs ratio of 1.[21]

The Kruskal–Wallis *H*-test was used to evaluate differences in continuous variables between groups and X^2 test for dichotomous variables. Fisher's exact test was used when appropriate.

We finally studied the interrater reliability of CE-CD and classical scores using the intraclass correlation coefficient (ICC) and the kappa statistic with quadratic weighting for LS and CE-CD categories.

Statistical analyses were performed on IBM SPSS® 21.0 (IBM) and Stata® 14.0 (StataCorp). *p* Values of <0.05 were considered statistically significant.

3 | RESULTS

Demographics are summarised in Table 1. Sixty-five patients were identified from the database, 6 cases were excluded due to lack of data and 59 cases were finally included in the analysis. Thirty-nine (66%) capsules were placed endoscopically with the aid of the specific delivery device (US Endoscopy). Children who swallowed the capsule were significantly older than those with endoscopic placement (median age 14.2 vs. 12.6 years old, *p*-value 0.013). CE results led to a reassignment of the disease phenotype based on the Paris classification in 44.1% of the cases. MRE was previously performed in 16/59 (27.1%). According to LS, absent or insignificant inflammation was found in 28 patients (47.5%) while 11 cases (18.6%) had mild inflammation and the remaining 20 cases (33.9%) had moderate-to-severe inflammation. CECDAI, CDACE and CE-CD score distribution had an average of 6.3 ± 7.1 (range 0–21), 206.1 ± 206.6 (range 0–543) and 7.4 ± 8.7 (range 0–28), respectively.

TABLE 1 Demographical and clinical characteristics of the study population.

Parameter	Value
Sex (male/female)	35/24 (59.3%/40.7%)
Age (years)	13.3 (11.7–15.0)
Disease duration (months)	13 (8–18)
Faecal calprotectin (μg/g)	939 (264–1685)
Haemoglobin (g/dL)	12.6 (11.4–13.5)
C-reactive protein (mg/L)	7.0 (7.0–19.0)
Serum albumin (g/dL)	4.2 (3.7–4.4)
Lewis score	225 (0–1368)
CECDAI	3 (0–12)
CDACE	165 (0–440)
CE-CD	5 (0–14)
Any positive finding in magnetic resonance enterography (inflammation or stenosis)	11 (68.6%)
Reassignment in Paris classification's location parameter after knowing capsule endoscopy findings	26 (44.1%)
Significant adverse clinical outcomes	
Hospitalisation due to worsening or complication or need to escalate	17 (28.8%)
Any treatment escalation	31 (52.5%)
Need for surgery due to Crohn's disease activity	2 (3.4%)
Any significant clinical relapse	23 (39.0%)
Any significant endoscopical relapse	13 (22.0%)
Any significant adverse clinical outcome	39 (66.1%)
Concurrent medication (single or in combination)	
5-aminosalicylates	3 (5.1%)
Methotrexate	3 (5.1%)
Azathioprine	24 (40.7%)
Steroids	8 (13.6%)
Anti-TNF-α	20 (33.9%)
Other biologic drugs	1 (1.7%)
Exclusive enteral nutrition	8 (13.6%)

Note: Data are expressed as number (percentage) or median (interquartile range).

Abbreviations: CDACE, Crohn's Disease Activity in Capsule Endoscopy; CE-CD, Capsule Endoscopy-Crohn's Disease index; CECDAI, Capsule Endoscopy Crohn's Disease Activity Index; TNF, tumour necrosis factor.

3.1 | Correlation between CE scores

All CE scores showed significant correlation between them (Supporting Information: Digital Content 2). The highest correlation between CE scores was that of the CECDAI and the CE-CD, with $\rho = 0.962$, $r = 0.982$ and an adjusted $R^2 = 0.924$ (Figure 1).

LS accepted cut-offs matched with <3 points (MH) and ≥9 points (moderate-to-severe inflammation) in CE-CD, resulting in three inflammation categories with 28, 9 and 22 patients, respectively, in order of increasing severity. Regarding CECDAI and CDACE,

their equivalent values were <3 and ≥6 points (28, 7 and 24 patients within each resulting inflammation category), and <118 and ≥209 points (30, 0 and 29 children within each resulting inflammation category), respectively.

3.2 | Clinical outcomes' prediction through CE scores and external validation of CE-CD cut-offs

High CE scores significantly increased the risk of treatment escalation but did not imply higher risk of hospitalisation or either clinical or endoscopic relapse (Table 2). Taking into account the need for treatment escalation, ROC curves were plotted for CE scores and for FC (Panel A, Figure 2). Their area under the curve were: 65.4% (95% confidence interval [CI]: 46.6%–84.3%) for LS, 71.1% (95% CI: 53.1%–89.2%) for CECDAI, 72.6% (95% CI: 55.0%–90.2%) for CDACE, 72.4% (95% CI: 54.7%–90.2%) for CE-CD and 65.1% (95% CI: 45.4%–84.7%) for FC. The optimal cut-off for anticipating treatment escalation using the CE-CD score was ≥9 points, the same as the moderate-to-severe SB inflammation outset point, showing a sensitivity of 48.4% (95% CI: 32.0%–65.2%) and a specificity of 89.3% (95% CI: 72.8%–96.3%). However, the best cut-off for the same purpose using CECDAI differed from both inflammation thresholds: ≥11 points, with a sensitivity of 51.6% (95% CI: 34.8%–68.0%) and a specificity of 85.7% (95% CI: 68.5%–94.3%). The widest gap between the MH cut-off and the best threshold to predict treatment escalation was that of the CDACE: ≥332 points, with a sensitivity of 51.6% (95% CI: 34.8%–68.0%) and a specificity of 81.5% (95% CI: 63.3%–91.8%). Patients with moderate-to-severe inflammation based on CE-CD had a shorter time to treatment escalation than those with mild SB inflammation in the short to midterm (Panel B, Figure 2). The hazard ratio for treatment escalation with a score of ≥9 points in CE-CD was 2.6 (95% CI: 1.3–5.3). A detailed clinical and laboratory comparison between the different CE-CD SB inflammation categories can be accessed in Supporting Information: Digital Content 3.

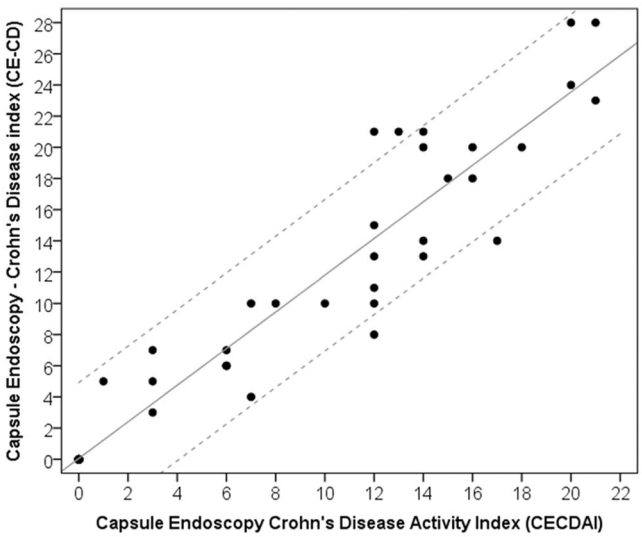


FIGURE 1 Scatter plot representing the approximately linear relationship between Capsule Endoscopy-Crohn's Disease Index (CE-CD) and Capsule Endoscopy Crohn's Disease Activity Index (CECDAI): $\rho = 0.982$, $r = 0.962$, adjusted $R^2 = 0.924$ ($p < 0.001$). The solid line represents the linear regression equation (95% confidence interval between dashed lines).

3.3 | Interrater reliability of CE scores

The global agreement ICCs were found to be 0.998 (95% CI: 0.996–0.999) for CE-CD, 0.954 (95% CI: 0.920–0.974) for CECDAI and 0.865 (95% CI: 0.843–0.895) for CDACE. Moreover, kappa statistic

TABLE 2 Cox regression analyses between capsule endoscopy scores and faecal calprotectin, and the emergence of adverse clinical outcomes (dependent variables).

Hazard ratio (95% CI)	Lewis score	CECDAI	CDACE	CE-CD	Faecal calprotectin
Surgery	1.001 (0.998–1.003)	1.232 (0.552–2.754)	1.009 (0.973–1.047)	1.161 (0.654–2.062)	Not applicable
Hospital admission	1.000 (0.999–1.000)	0.951 (0.879–1.029)	0.998 (0.996–1.001)	0.958 (0.898–1.023)	1.000 (0.999–1.000)
Clinical relapse	1.000 (0.999–1.001)	0.952 (0.890–1.019)	0.999 (0.996–1.001)	0.956 (0.902–1.012)	1.000 (0.999–1.000)
Endoscopic relapse	1.000 (1.000–1.000)	0.963 (0.883–1.051)	0.999 (0.996–1.002)	0.977 (0.911–1.049)	1.000 (0.999–1.001)
Treatment escalation	1.000 (0.999–1.001)	1.088 (1.033–1.145)[a]	1.002 (1.001–1.004)[a]	1.068 (1.027–1.111)[a]	1.000 (1.000–1.000)
Any adverse clinical outcome	1.000 (1.000–1.000)	1.053 (1.004–1.104)[a]	1.001 (0.999–1.003)	1.040 (1.001–1.079)[a]	1.000 (1.000–1.000)

Note: When stating 'not applicable' implies that analysis was not feasible due to lack of data.

Abbreviations: CDACE, Crohn's Disease Activity in Capsule Endoscopy; CE-CD, Capsule Endoscopy-Crohn's Disease index; CECDAI, Capsule Endoscopy Crohn's Disease Activity Index; CI, confidence interval; TNF, tumour necrosis factor.

[a]Statistically significant hazard ratio obtained through univariate Cox regression.

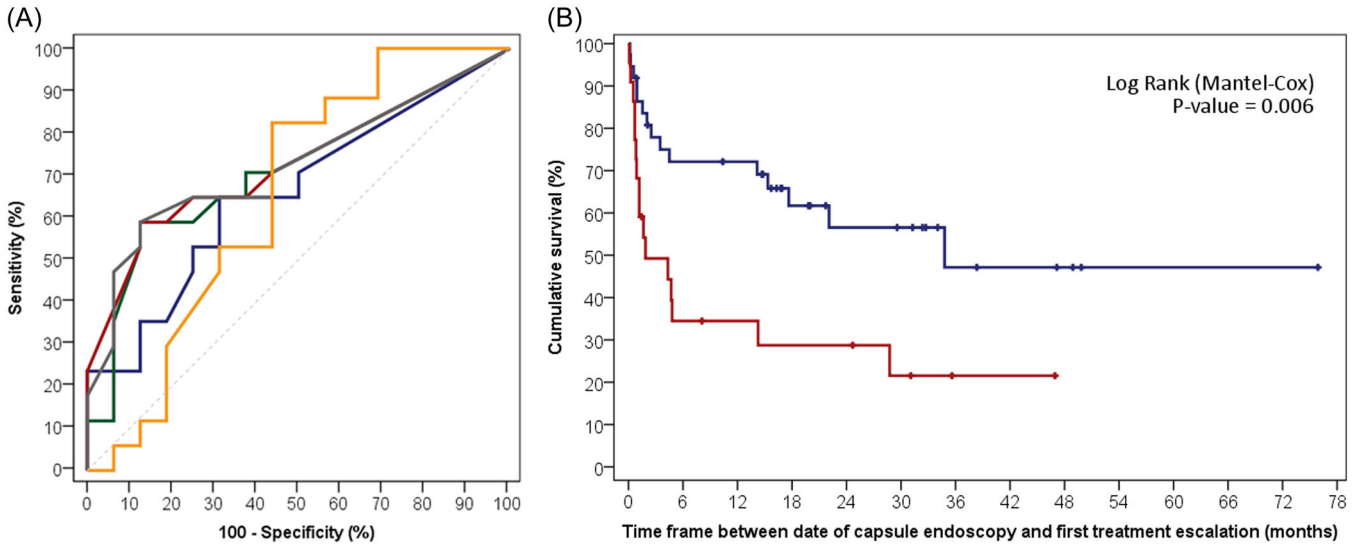


FIGURE 2 (A) Receiver operating characteristic curves illustrating the accuracy of capsule endoscopy scores and faecal calprotectin to predict treatment escalation in paediatric Crohn's disease. Blue: Lewis score (AUC 65%). Green: CECDAI (AUC 71%). Red: CDACE (AUC 73%). Grey: CE-CD (AUC 72%). Yellow: Calprotectin (AUC 65%). (B) Kaplan–Meier analysis depicting the emergence of first treatment escalation. Blue: Absent or mild small bowel inflammation (<9 points in CE-CD). Red: Moderate-to-severe small bowel inflammation (≥9 points in CE-CD). AUC, area under the curve; CDACE, Crohn's Disease Activity in Capsule Endoscopy; CE-CD, Capsule Endoscopy-Crohn's Disease index; CECDAI, Capsule Endoscopy Crohn's Disease Activity Index.

taking into account the SB inflammation categories with our LS-derived cut-offs, was 100% for CE-CD, 98.8% for CECDAI and 90.0% for CDACE.

4 | DISCUSSION

Among all the available scores for endoscopic assessment for nonresected Crohn's disease patients, the SES-CD is the most widely used in clinical trials, both in adults and children.[13,19,22] CD activity in ileocolonoscopy measured with this tool shows a trend to independently predict treatment escalation in paediatric patients with CD.[23] One barrier to day-to-day use by clinicians is the complex nature of scoring systems. The recently developed Simplified Endoscopic Mucosal Assessment for Crohn's Disease (SEMA-CD) is intended to counteract this when reporting ileocolonoscopies.[24] CE-CD is an SES-CD-based CE score for children with CD.[20] As with SEMA-CD, CE-CD is meant to be simpler than the most acknowledged CE reporting standard for CD: the LS. Additionally, CE-CD can potentially be combined with SES-CD since includes its same parameters. CE-CD applicability was therefore assessed in children with CD to evaluate its prognostic capability and reproducibility.

We have demonstrated that CE-CD predicts treatment escalation in a different population from that of the primary study.[20] Nevertheless, our cut-offs have been stablished at a lower level. Adult studies have shown that LS ≥ 264 has a negative predictive value of 96% for CD-related emergency hospitalisations within 1 year.[25] Patients with an LS > 270 have a higher risk of exacerbation without additional treatment.[26] In consequence, it has been suggested that those LS cut-off values should determine treatment strategies for CD. Those cut-offs correspond with 4 points in CE-CD according to our linear regression equation and shows consistency with our proposal for lowering the thresholds between inflammation categories given in the original experience.[20] Thus, it seems reasonable to direct clinical attention to patients with CE-CD ≥ 9 (this is, with a moderate-to-severe SB inflammation), since they are highly likely to need treatment escalation soon. However, children with mild SB inflammation on CE might also need close follow up. In fact, the sensitivity at 48.4% evidence that approximately half the patients with a CE-CD score <9 ends up needing treatment escalation too. This could also be related to possible disease extension or disease evolution in the paediatric age group.

Our sample shows some significant differences from the one used by Oliva et al.[20] The main one is that the group with mild SB inflammatory activity is underrepresented in comparison to moderate and severe categories, accounting for less than 20%. This may have an impact on the selection of cut-offs as our patient population may not be fully representative of the mild SB inflammation subgroup. However, despite the representative population being different, the cut-offs were essentially the same. CE-CD considers three parameters: number of ulcers, size of the largest ulcer and surface area involved. Thus, if points are given due to presence of ulcers, it is mandatory that additional

points will be added because of their size and surface area covered. Essentially, any segmental ulcer will thus guarantee 3 points in that tertile. Consequently, this may have contributed to better interobserver agreement with CE-CD. With reference to the moderate inflammation threshold, CE-CD has shown an interesting performance. Our patient cohort showed that CE-CD ≥ 9 was an optimal cut off to predict treatment escalation. This matches with the original study done by Oliva et al.[20] We see this finding as an external validation of the cut-off and as evidence in favour of its reliability/reproducibility. Descriptively speaking, a score of 9 can be achieved with ulceration seen in all SB segments. This ties in nicely with a well-known poor outcome predictor in paediatric CD, extensive or panenteric inflammation.[27] Indeed, even though the severity of lesions found in panenteric CE can predict therapeutic escalation, the only factor associated with endoscopic recurrence in children has proven to be the disease extension.[28] Additionally, the L4b phenotype (upper disease distal to ligament of Treitz and proximal to terminal ileum) was added to nearly half of the patients of our sample after CE. This is similar to a change in phenotype of 36% of children done by Oliva et al.[20] This result highlights the usefulness of CE in assessing the extension of CD at diagnosis, and also the importance of objectively identifying moderate-to-severe SB inflammation.

Regarding the performance of CECDAI, our cut-offs have been closed to those given in the external validation conducted by Yablecovitch et al.[16] In that experience, the LS-extrapolated nonsignificant inflammation threshold was set at 5.4, and 9.2 represented the beginning of the moderate-to-severe inflammation status. Taking into account that CECDAI does not provide decimal results, there is a close gap between their and our cut-offs. Concerning CDACE, it is notable that, despite higher scores corresponding to higher mucosal inflammation, it has not a continuous range of possible values. Indeed, possible scores can only finish in digits 0, 1, 2 or 3, that represent the stenosis parameter (see Supporting Information: Digital Content 1).[18] Thus, our cut-offs at 0118 (no inflammation) and 0209 (moderate-to-severe inflammation) has no possible interpretation.

There are some limitations to be pointed out. First, we have only considered LS as originally described, but we have not calculated the cumulative LS. Admittedly, cumulative LS shows a stronger correlation with CECDAI as compared to worst tertile LS.[16] It is not improbable that cumulative LS, despite needing manual calculation, could better reflect SB inflammation and provide higher clinical outcome prediction ability. Additionally, it has not been possible to describe the relationship between clinical scores (such as the Paediatric Crohn's Disease Activity Index or the Mucosal Inflammation Noninvasive Index[29,30]) and CE scores, as lack of clinical data has not made it feasible. Also, CE has not been systematically and cross-sectionally performed exactly at the same time of CD natural history in every patient. This may influence the representativity of our study population. As previously mentioned, since more severe patients may be more likely to undergo CE, it is possible that milder forms of SB inflammation were not properly represented. Finally, due to inconsistency in ileocolonoscopy reporting, we had not had the chance to add up SES-CD scores to CE-CD scores and to build some sort of combined panenteric score. This, in fact, would be a remarkable advantage of CE-CD and assessing its performance will need to be evaluated in further detail in subsequent studies. In line with this objective, comparison with alternative panenteric capsule scores, like the Eliakim score, is advisable.[31]

To conclude, CE-CD is a moderately accurate CE score to assess SB involvement in children with CD. It shows an excellent reproducibility, with very low risk of misclassification between categories. It correlates strongly with other validated CE scores, such as CECDAI, and has the advantage of being far simpler than LS and using the same parameters as SES-CD. Children with a score of 9 or more are at risk of treatment escalation in the short-medium term. However, a lower threshold (set at 3 points) may be considered to indicate mild SB inflammation.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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SUPPORTING INFORMATION

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

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