Fecal calprotectin in predicting small bowel capsule endoscopy findings in pediatric patients with known Crohn's disease

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Abstract

Fecal calprotectin (FC) has been proposed as a noninvasive surrogate marker of intestinal inflammation in inflammatory bowel disease. This study aimed to assess the capability of FC in predicting small bowel capsule endoscopy (SBCE) findings in pediatric patients with known Crohn's disease (CD). We retrieved data of consecutive patients aged 2 to 17 years old with established CD who underwent SBCE from Janurary 2017 to April 2020 and had endoscopic remission on ileocolonoscopy. Sixty-eight patients were included in the analysis. There were 13 patients with a weighted pediatric CD activity index ≥ 12.5, 47 patients with FC ≥ 200 µg/g, and 45 patients with significant small bowel (SB) inflammation [Lewis score (LS) ≥ 135]. The LS correlated weakly with FC ($R = 0.30$, $P < .05$). The area under the curve of FC as a surrogate diagnostic test for LS ≥ 135 was 0.691, and the optimal FC cutoff values were 242 µg/g with the corresponding sensitivity and specificity of 78% and 65%, respectively. The area under the curve of FC for moderate-to-severe inflammatory activity in the SB was 0.718. In patients with FC level ≥ 670 µg/g, LS ≥ 790 was found in 33% (9/27) of patients, with the sensitivity and specificity of 69% and 67%, respectively. FC may be used to predict SB mucosal inflammation in pediatric patients with confirmed CD having endoscopic remission on ileocolonoscopy.

Abbreviations: AUC = area under the curve, CD = Crohn's disease, CRP = C-reactive protein level, ESR = erythrocyte sedimentation rate, FC = fecal calprotectin, IBD = inflammatory bowel disease, LS = Lewis score, SB = small bowel, SBCE = small bowel capsule endoscopy, wPCDAI = weighted pediatric Crohn's Disease activity index.

Keywords: capsule endoscopy, Crohn's disease, disease activity, fecal calprotectin, pediatrics

1. Introduction

Crohn's disease (CD) is a chronic relapsing inflammatory bowel disease (IBD), affecting multiple sites of the gastrointestinal tract.[1] More than 60% of CD patients have small bowel (SB) lesions.[2] In order to improve the long-term outcomes, the concept of treat to target (T2T) has been adopted. Time-dependent objective treatment targets have been set out in the updated Selecting Therapeutic Targets in IBD recommendations, with the goal of treatment being mucosal healing and holistic remission.[3] Endoscopy plays a crucial role in defining the site and extent of a disease in order to plan an optimal therapy.[4] Small bowel capsule endoscopy (SBCE) is widely utilized because of its noninvasive and patient-friendly nature. It can visualize entire small-intestinal mucosa and facilitate detection of small intestinal abnormalities.[5] However, SBCE is accompanied with a number of limitations and complications. Thus, there is an urgent need for developing sensitive and inexpensive biomarkers to employ SBCE for identifying IBD with the highest diagnostic efficacy.[6]

Fecal calprotectin (FC) is a 36-kDa calcium and zinc-binding protein, secreted extracellularly by stimulated neutrophils or released by cell disruption or death.[7] It has been proposed as a noninvasive surrogate marker of intestinal inflammation in IBD and has a satisfactory diagnostic precision for the differentiation of organic and functional intestinal diseases[8] and for optimizing the use of endoscopic procedures.[9] To date, the role of FC in predicting SBCE findings in pediatric patients with CD has remained elusive. Therefore, the present study aims to retrospectively assess the capability of FC to predict SBCE findings in pediatric patients with known CD.

2. Methods

2.1. Study design

This is a retrospective single-center observational study, approved by the Ethics Committee in Children's Hospital of Fudan University. The inclusion criteria were as follows: CD patients aged 2 to 17 years old who underwent SBCE from Janurary 2017 to April 2020, had a FC measurement within 1 week before SBCE, and the observation of endoscopic remission on ileocolonoscopy. The CD was diagnosed using clinical, endoscopic, histological, and imaging findings according to the

second European evidence-based Consensus on the diagnosis and management of CD.[4] Endoscopic remission was defined by a Simple Endoscopic Score for CD of < 4.[10]

2.2. SBCE

Eligible patients underwent SBCE with OMOM capsule (Jinshan Science & Technology Group, Chongqing, China). All videos were analyzed by experienced gastroenterologists who were blinded to FC results. The diagnosis of CD was carried out based on the mucosal findings on SBCE as described previously.[11] Lewis score (LS) was employed to measure the activity of SB inflammation in accordance with descriptions provided previously.[12] A LS < 135 indicated normal or insignificant mucosal inflammation, LS in the range of 135 to 790 represented mild mucosal inflammation, and LS ≥ 790 signified moderate-to-severe inflammation.[13]

2.3. FC testing

Stool samples of patients who were suspected of having pediatric CD were collected and kept in a specific FC collection container before undergoing SBCE. Samples were stored at 4°C and processed in batches by an external laboratory (Suzhou Herui Biotech Co, Ltd, Suzhou, China). FC levels were detected using enzyme-linked immunosorbent assay (BUHLMANN Laboratories AG, Schönenbuch, Switzerland). Measurement range was 30 to 1800 µg/g. According to the laboratory guidelines, FC levels > 200 µg/g indicated active CD.

2.4. Clinical data

Demographic and phenotypic data were collected, including weighted pediatric CD activity index (wPCDAI) and routine laboratory parameters. The wPCDAI is an overall score that classifies patients into 4 disease activity categories: none, <12.5; mild, 12.5 to 40; moderate, >40 to 57.5; and severe, >57.5.[14] Routine laboratory parameters included: C-reactive protein (CRP) level, erythrocyte sedimentation rate (ESR), and albumin level within 2 weeks of SBCE. In addition, an elevated CRP level was defined as > 8 mg/L; elevated ESR was defined as > 21 mm/hour in males and > 26 mm/hour in females; a serum albumin level less than 39 g/L was defined as abnormal.

2.5. Statistical analysis

The levels of FC, LS, and wPCDAI were statistically analyzed. The correlation between LS and FC was assessed by the Pearson's correlation analysis. The strength of correlation was defined according to correlation coefficient as follows: 0 to 0.19, very weak; 0.2 to 0.39, weak; 0.4 to 0.59, moderate; 0.6 to 0.79, strong; 0.8 to 1.0, very strong, with positive coefficients indicating positive correlation and negative coefficients indicating negative correlation.[15] $P < .05$ was considered statistically significant.

The sensitivity and specificity of FC in predicting SBCE findings was calculated at different cutoff values, as analyzed by receiver operating characteristic curve. Test characteristics were determined by using a 2 × 2 contingency table. Pearson's chi-square test was used to analyze categorical variables. The data were statistically analyzed by using IBM SPSS statistic (version 20.0; Armonk, NY).

3. Results

3.1. Patients' baseline characteristics

A total of 68 patients were enrolled in this study, including 42 males and 26 females with a median age of 11.73 years (range, 4–16 years).

Among the 68 patients, there were 13 patients with wPC-DAI ≥ 12.5. Although all of the 68 patients had endoscopic remission (Simple Endoscopic Score for CD < 4), 50 (74%) patients still had inflammatory lesions on SBCE (Fig. 1), and 45 (66%) had significant inflammatory activity (LS ≥ 135) on SBCE (Table 1). Of the 45 patients with significant inflammatory activity, there were 10 patients with wPCDAI ≥ 12.5.

3.2. FC testing and SBCE findings

Among the 68 patients, there were 64, 52 and 47 patients with FC ≥ 50 µg/g, FC ≥ 100 µg/g, and FC ≥ 200 µg/g, respectively. The mean FC value was 723.5 µg/g (± 700.7). The proportions of patients with LS ≥ 135 in FC ≥ 50 µg/g and FC < 50 µg/g groups (67% vs 50%, $P = .481$), and in FC ≥ 100 µg/g and < 100 µg/g groups (71% vs 50%, $P = .118$) were similar. In the FC ≥ 200 µg/g group, there were significantly more patients with LS ≥ 135 than in FC < 200 µg/g group (74% vs 48%, $P = .031$); however, the mean of LS and wPCDAI had no significant difference between these 2 groups (Table 2).

Figure 1. SB ulcers as seen on capsule endoscopy in pediatric CD patients. CD = Crohn's disease, SB = Small bowel.

Table 1

Patients' demographic and clinical characteristics.

Character	Value
Gender, male/female	42/26
Age, years, median (range)	11.73 (4-16)
wPCDAI	
< 12.5	56
≥ 12.5	12
Positive SBCE findings	50
Minor lesions without LS	5
LS 135-790	32
LS > 790	13
FC (µg/g)	
<200	21
≥200	47
CRP elevated	5
ESR elevated	19
ALB abnormal	1

ALB = albumin, CD = Crohn's disease, CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, FC = fecal calprotectin, LS = Lewis score, SBCE = small bowel capsule endoscopy, wPCDAI = weighted pediatric Crohn's Disease activity index.

Table 2

SBCE findings and weighted pediatric CD activity index according to fecal calprotectin levels.

	FC < 200 µg/g	FC ≥ 200 µg/g	P value
LS ≥ 135, n (%)	10 (47.6)	35 (74.4)	.031
LS mean (±SD)	339.2 (± 848.6)	552.1 (± 669.5)	.575
wPCDAI ≥ 12.5	2 (9.5)	11 (23.4)	.179
wPCDAI mean (± SD)	3.6 (± 5.4)	8.0 (± 9.2)	.094

The values are expressed in %.
CD = Crohn's disease, FC = fecal calprotectin, LS = Lewis score, SD = standard deviation, SBCE = small bowel capsule endoscopy, wPCDAI = weighted pediatric Crohn's Disease activity index.

The mean LS was 486.4 (±729.7, range: 0–3933). There was a weak correlation between final LS and FC values ($rs = 0.30$; $P = .015$), and no correlation between LS and ESR, albumin or wPCDAI. FC values showed statistically significant but weak correlation with ESR ($rs = 0.31$; $P = .011$) and albumin ($rs = -0.31$; $P = .011$).

3.3. Predicting mild inflammatory activity in small bowel

The area under the cure (AUC) of FC as a surrogate diagnostic test for LS ≥ 135 on SBCE was 0.691 (95% confidence interval, 0.555–0.828, $P = .010$) (Fig. 2). The optimal FC cutoff values were 242 µg/g with a corresponding sensitivity and specificity of 78% and 65%, respectively. The sensitivity and specificity for significant inflammatory activity (LS ≥ 135), according to the FC cutoff values, is shown in Table 3.

3.4. Predicting moderate-to-severe inflammatory activity in small bowel

The AUC of FC for moderate-to-severe inflammatory activity in the SB was 0.718 (95% confidence interval, 0.581–0.856, $P = .015$) (Fig. 3). The optimal FC cutoff values were 670 µg/g with a corresponding sensitivity and specificity of 69% and 67%, respectively. The sensitivity and specificity for significant inflammatory activity (LS ≥ 790), according to the FC cutoff values, is shown in Table 4.

4. Discussion

To the best of our knowledge, although there were studies showing that FC could be used as a screening tool before undergoing SBCE,[16] this is the first study that evaluated the role of FC in predicting SBCE findings in pediatric patients with known CD.

Endoscopic remission is an important treatment goal in CD that is associated with improved clinical outcomes, including reduced hospitalization and surgery rates.[17] Change in the treatment should be considered if endoscopic remission has not been achieved.[3] Studies have shown that more than 60% of CD patients have small-bowel lesions,[2] and approximately 30% of patients have isolated SB involvement.[18] SBCE is extensively utilized in clinical practice to assess mucosal healing in confirmed CD patients during follow-up. In our analysis, we found that 66% pediatric CD patients had significant SB inflammation on SBCE despite endoscopic remission on ileocolonoscopy. Additionally, most of them had clinically inactive disease with wPCDAI < 12.5. Thus, SBCE examination is critical in achieving the therapeutic goal of treat to target regimens.

FC and CRP are the 2 most widely used biomarkers in IBD.[3] Compared with FC, serum CRP has higher specificity but low sensitivity.[19,20] In the present study, we also found FC to have significantly higher diagnostic accuracy for detecting SB
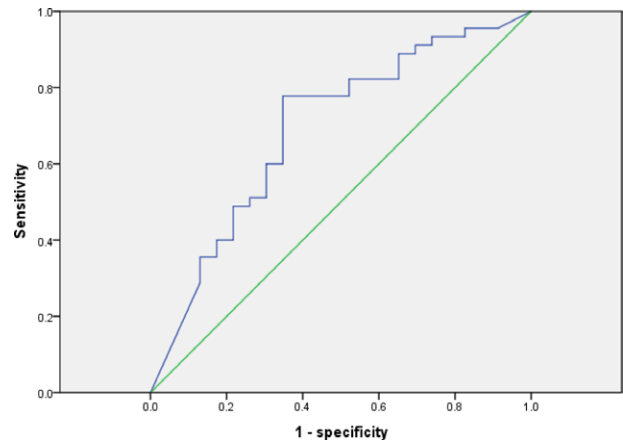

Figure 2. Receiver operator curve analysis for fecal calprotectin as a predictive marker for mild SB inflammation on SBCE (AUV = 0.691). A 242 µg/g cutoff of FC yielded the optimal compromise between sensitivity (78%) and specificity (65%). AUC = area under the curve, FC =fecal calprotectin, SB = Small bowel, SBCE = Small bowel capsule endoscopy.

Table 3

Diagnostic accuracy of fecal calprotectin, C-reactive protein, and wPCDAI for significant inflammatory activity (LS ≥ 135).

	Significant inflammatory activity			
	Sn	Sp	PPV	NPV
FC ≥ 50 µg/g	96	9	67	50
FC ≥ 100 µg/g	82	35	71	50
FC ≥ 200 µg/g	78	48	74	52
CRP ≥ 8 mg/L	11	100	100	37
ESR abnormal	33	83	79	39
FC ≥ 200 µg/g with another parameter abnormal*	33	91	88	41
wPCDAI ≥ 12.5	24	91	85	38
FC ≥ 200 µg/g with wPCDAI ≥ 12.5	20	96	82	38

* Another parameter abnormal means plus any conditions such as CRP ≥ 8mg/L, or ESR ≥ 21(male)/26(female) mm/h, or albumin ≤ 39g/L.
CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, FC = fecal calprotectin, LS = Lewis score, NPV = negative predictive value, PPV = positive predictive value, Sn = sensitivity, Sp = specificity, wPCDAI = weighted pediatric Crohn's Disease activity index.
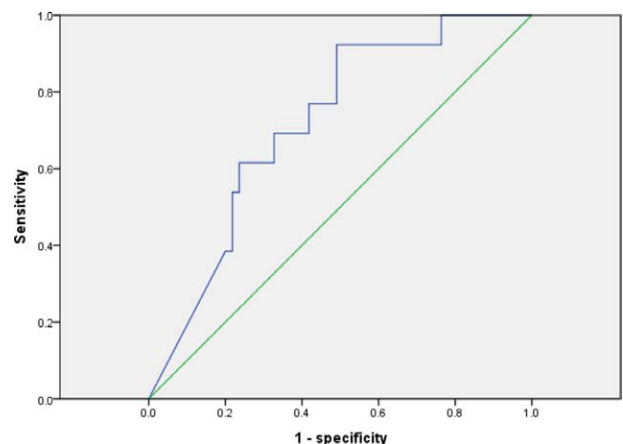

Figure 3. Receiver operator curve analysis for FC as a predictive marker for moderate to severe SB inflammation on SBCE (AUC = 0.718). A 670 µg/g cutoff of FC yielded the optimal compromise between sensitivity (69%) and specificity (67%). AUC = area under the curve, FC =fecal calprotectin, SB = Small bowel, SBCE = Small bowel capsule endoscopy.

Table 4

Diagnostic accuracy of fecal calprotectin for significant inflammatory activity (LS ≥ 790).

Cutoff values	Sn	Sp	PPV	NPV
FC ≥ 280 µg/g	92	49	30	97
FC ≥ 670 µg/g	69	67	33	90
FC ≥ 1018 µg/g	62	76	38	89

FC = fecal calprotectin, LS = Lewis score, NPV = negative predictive value, PPV = positive predictive value, Sn = sensitivity, Sp = specificity.

inflammation on SBCE compared to either CRP or ESR. The AUC of FC for presence of significant inflammatory activity in the SB was 0.691, which is similar to the results of previous studies,[21] or even higher than reported in other studies.[8,22,23]

We studied the diagnostic accuracy of different cutoff values of FC in predicting SBCE findings and found the optimal cutoff value to be 242 µg/g, which is higher than reported by previous studies.[24,25] Our cutoff value is similar with that in the post hoc analysis of effect of tight control management on CD, which demonstrated that achieving FC < 250 µg/g was strongly associated with mucosal healing as defined by a CD Endoscopic Index of Severity < 4 and no deep ulcers.[26] A meta-analysis of 14 studies found that the sensitivity of FC with cutoff values of 50, 100, and 200 µg/g was 83%, 73%, and 50%, respectively, while the specificity was 50%, 73% and 88%, respectively. The meta-analysis recommended the FC cutoff of 100 µg/g to be used for screening SB CD; however, the studies included in this meta-analysis had patients with suspected CD and those being reevaluated for CD which can affect the cutoff value. A recent report on magnetic resonance imaging enterography-based follow-up of pediatric patients with CD reported a FC cutoff value of < 300 µg/g to identify children with mucosal healing (assessed by endoscopy).[27] The European Society for Pediatric Gastroenterology and Nutrition Gastroenterology Committee has suggested that endoscopic evaluation should be considered in pediatric IBD patients in clinical remission with a FC > 300 µg/g as this cut off level accurately predicts mucosal inflammation.[28]

Several studies have shown that FC level correlates with significant SB inflammation, and the correlation coefficient varies from 0.232 to 0.663.[6,8,29,30] Additionally, a number of studies have found no correlation between FC level and LS.[31,32] In our study, we found that there was correlation between FC and LS, but it was weak ($rs = 0.30$; $P < .05$), a finding that is similar to that reported by previous studies.[29,33]

There are very few studies on the role of FC in predicting moderate–severe inflammation on SBCE. A study by Kopylov et al had found that FC can be used as a predictor of significant SB inflammation (define significant inflammation as LS ≥ 790) with the AUC of 0.63.[21] The current study also had similar findings, and the cutoff value associated with the optimal combination of sensitivity and specificity in Kopylov et al was 275 µg/g, compared to 670 µg/g in our study.

There are a number of limitations in the current study, including its retrospective nature and small sample size; however, in this study, the stool collection for FC testing was carried out within 1 week before SBCE in order to avoid appearance of a long interval between FC level and SBCE. In addition, capsule readers were blinded to the FC results at the time of SBCE reporting.

In conclusion, measurement of FC is significant for predicting inflammatory activity in the SB and selecting eligible pediatric patients with known CD for SBCE.

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Author contributions

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