Predicting Endoscopic Crohn's Disease Activity Before and After Induction Therapy in Children: A Comprehensive Assessment of PCDAI, CRP, and Fecal Calprotectin

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Background: Mucosal healing (MH) is a vital early endpoint in management of Crohn's disease (CD). MH depends on endoscopic assessment and there is increasing interest in non-invasive proxies, Pediatric Crohn's Disease activity Index (PDCAI), C-reactive protein (CRP) and fecal calprotectin (FC). These proxies must be validated against endoscopic disease activity (SES-CD) at diagnosis and after induction therapy in well characterized cohorts of children with CD.

Methods: A prospective cohort of 24 newly diagnosed children (<16 yr) with luminal CD quantifiable on complete ileo-colonoscopy had paired PCDAI, CRP, FC and SES-CD at diagnosis and after 8 weeks therapy with exclusive enteral nutrition or steroids.

Results: At diagnosis: PCDAI had poor correlation (r = 0.33); CRP (r = 0.54) and FC (r = 0.46) had moderate correlation with SES-CD. After induction therapy: 11/24 had inactive disease (SES-CD 0-2); PCDAI (r = 0.34) and CRP (0.28) had poor correlation with SES-CD, many children with SES-CD ≥3 having normalization of both PCDAI and CRP. FC had good correlation (r = 0.50) but many with SES-CD 0-2 had FC >200 μg/gm stool. FC<500 (positive likelihood ratio, 3.2) and FC drop >50% (positive likelihood ratio, 3.8) had greater predictive value for inactive disease. Composite PCDAI (<10), CRP (<5 mg/dl) & FC <500 μg had excellent Negative LR (0.2) predicting inactive disease.

Conclusions: PCDAI is unreliable for endoscopic disease severity assessment. Only FC correlates with endoscopic activity after therapy but cut off <200 μg is too high for defining endoscopic recovery in children. Composite normalized PCDAI, CRP and FC <500 μg should be considered the non-invasive endpoint for treatment response in pediatric CD.

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Key Words: Crohn's disease, endoscopy, C-reactive protein, calprotectin

Deep remission with mucosal healing early in the course of treatment is recognized as the best predictor of favorable long-term outcomes in adults with CD,[1–3] but pediatric evidence is scarce. Two small pediatric studies demonstrated improved relapse rates and hospitalizations at 1 year in those achieving good endoscopic outcomes after induction therapy.[4,5] The gold standard for assessing mucosal inflammation is endoscopy, but this is invasive and impractical for regular monitoring, which requires studies to use surrogate markers, proxies like clinical disease activity index (CDAI), Pediatric Crohn's Disease activity Index (PCDAI), C-reactive protein (CRP), and fecal calprotectin (FC), to assess therapeutic response. This is of particular concern when noninvasive proxies like CDAI and PCDAI are used to determine treatment escalation and as endpoints for research outcomes.

Poor concordance between CDAI and endoscopic disease activity is well established in adults with active CD with up to 70% of patients in clinical remission (CR) having significant mucosal lesions.[6,7] The PCDAI is a clinical tool like CDAI, which includes subjective variables and, unlike CDAI, PCDAI, has not been validated against established endoscopic disease activity scores.

Serum CRP and FC are in widespread use as proxies for endoscopic disease activity. In a prospective adult endoscopic study, CRP (r = 0.53) and FC (r = 0.75) had good correlation with simple endoscopic disease activity scores (simple endoscopic score for Crohn's disease [SES-CD]).[8] In a small pediatric study, good correlation of FC to SES-CD (r = 0.76) was demonstrated in 11 children with CD and quantifiable ileocolonic lesions on endoscopy.[9] A larger multicenter prospective study in children with CD demonstrated that CRP and FC had good correlation with each other but neither had good correlation with PCDAI. Endoscopic severity was not assessed in this study.[10] Studies using FC in children to measure CR demonstrate that many children do not normalize FC to <200 μg/g

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stool. A pediatric Finnish study treating children with IBD in CR with steroids and a Scottish study treating children with CD in CR with exclusive enteral nutrition (EEN) showed the majority of children in CR had elevated FC.[11,12]

Pediatric studies evaluating performance of PCDAI, CRP, and FC against a validated endoscopic disease activity tool to measure therapeutic response are warranted. The purpose of our study was to correlate these proxies with simple endoscopic score (SES-CD) at diagnosis and assess their performance in predicting endoscopic disease scores after primary induction therapy with EEN or steroids.

METHODS

Population and Study Design

This study cohort is an extension of our previously described prospective study (Australia New Zealand Clinical Trials Registry—ACTRN12612001032842) of 32 newly diagnosed children with CD (<16 yr) offered EEN or steroids as induction therapy and commenced on early thiopurines (<3 mo) conducted between November 2009 and December 2013 in a tertiary pediatric hospital.[5] Institutional ethics approval was granted, and written consent obtained from patients and parents. We analyzed 24 children who had luminal CD quantifiable on complete ileocolonoscopy and paired PCDAI, CRP, FC, and endoscopy at diagnosis and after 8-week induction therapy. Eight were excluded (6 without paired FC, 1 with isolated proximal small intestinal CD, and 1 with incomplete follow-up endoscopy). CR was defined as PCDAI ≤10; biochemical remission (BR) as CRP <5 mg/dL and PCDAI <10. A PCDAI greater than 30 signifies moderate-to-severe pediatric CD.[13] FC was measured by a quantitative enzyme immunoassay. FC <200 μg/g is the accepted adult cutoff for defining endoscopicaly inactive disease.[14] Endoscopic disease activity was determined by the endoscopist at time of procedure using the validated SES-CD.[15] Disease activity was defined as inactive (0–2), mild (3–6); moderate (7–15), or severe (>15).[16] We comprehensively evaluated the performance of paired PCDAI, CRP, FC, and SES-CD for assessing endoscopic disease activity at diagnosis and after treatment to measure therapeutic response.

STATISTICS

All statistical calculations were performed using GraphPad Prism version 6.00 for Windows, GraphPad Software, San Diego, CA. The correlation between endoscopic disease activity (SES-CD) with clinical, serologic, and fecal biomarkers was estimated using the nonparametric Spearman's rank correlation coefficient. Paired *t* test was used for analysis of proxies before and after induction therapies. Unpaired *t* test was used for calculating CR, BR, and FC between ileal and ileocolonic disease phenotype. Sensitivity, specificity, and likelihood ratio were compared between proxies to predict endoscopic disease inactivity.

RESULTS

Paired clinical (PCDAI), biochemical (CRP), fecal (FC), and endoscopic data (SES-CD) were available in 24 children treated with either EEN (n = 20) or steroids (n = 4). Baseline results and disease phenotype are given in Table 1. Paired data on each parameter at diagnosis and after induction therapy are given in Table 2.

At Diagnosis

The performance of PCDAI, CRP, and FC against SES-CD is given in Figures 1–3. Highlighted is the lack of correlation (r = 0.33, *P* = nonsignificant) for PCDAI against SES-CD. CRP (r = 0.54, *P* = 0.006) and FC (r = 0.46, *P* = 0.02) have moderate correlation against SES-CD.

TABLE 1. Demographics at Diagnosis

Included	24 (15 males)
Excluded	8
	6 paired FC not available
	2 endoscopic score not available
	1 isolated proximal SB CD
	1 incomplete colonoscopy
Age	13.5 (99% CI, 12.2–13.88)
Disease distribution	
A1a (0–<10)	1
A1b (10–17)	23 (92%)
Ileocolonic L3	18 (75%)
Ileal L1	5 (21%)
Colonic L2	1 (4%)
Disease modifier	Upper GI
Upper GI	58%
L4a	11 (45%)
L4a + L4b	3 (13%)
Perianal	3 (13%)
Disease behavior	
Inflammatory	20 (83%)
Stricturing	4 (17%)
Clinical disease severity PCDAI	
Mild <30	2 (8%)
Moderate to severe >30	22 (92%)
Endoscopic disease severity	
Mild (SES-CD, 3–6)	1 = 4%
Moderate (SES-CD, 7–15)	12 = 50%
Severe (SES-CD, >16)	11 = 46%

CI, confidence interval; GI, gastrointestinal.

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TABLE 2. Paired PCDAI, CRP, FC, and SES-CD at Diagnosis and After induction Therapy

	At Diagnosis				After Induction Therapy			
Patient	PCDAI	CRP	FC	SES-CD	PCDAI	CRP	FC	SES-CD
1	32.5	17	1300	4	20	5	620	0
2	40	42	1100	15	5	1	70	0
3	35	24	470	11	10	4	950	0
4	47.5	19	1300	25	5	1	280	0
5	35	20	510	8	0	1	170	0
6	35	14	1100	15	5	2	480	0
7	42.5	54	460	22	5	2.7	330	0
8	17.5	71	1200	18	0	1	420	0
9	32.5	23	1800	21	0	1	180	0
10	45	29	580	18	30	8	170	0
11	32.5	22	1300	13	0	2.7	380	2
12	47.5	100	240	15	10	28	450	3
13	37.5	34	240	12	5	7	1300	3
14	42.5	11	550	9	5	1	1000	3
15	32.5	43	800	12	5	1	220	4
16	47.5	13	410	12	5	1	220	4
17	32.5	10	580	12	10	5	100	6
18	32.5	59	500	23	10	30	300	7
19	37.5	17	1800	18	15	4.5	580	8
20	37.5	138	2200	32	15	4.5	900	8
21	57.5	19	600	18	5	6	930	9
22	60	78	1400	30	30	5	1400	12
23	55	72	1900	17	10	1	1500	13
24	22.5	15	130	11	5	3.4	1240	15

After Induction Therapy

Overall therapeutic response after therapy include CR (PCDAI <10) in 19 of 24 children (79%), BR/CR (PCDAI ≤10 and CRP <5 mg/dL) in 16 of 24 (65%), and endoscopic remission (inactive disease SES-CD, 0–2) in 11 of 24 (46%).

The performances of PCDAI, CRP, and FC against SES-CD are given in Figures 4–6. Highlighted is the poor correlation of PCDAI (r = 0.34, *P* = nonsignificant) and CRP (r = 0.28, *P* = nonsignificant) with SES-CD. Of the 13 children with active endoscopic disease postinduction, 10 (77%) were in CR (PCDAI ≤10), 5 (38%) were in clinical and BR. FC (r = 0.50, *P* = 0.01) had a moderate correlation with SES-CD, and only 1 child (8%) with active disease had a normal FC (<200 μg/g of stool). However, 7 of 11 children (63%) with inactive endoscopic disease postinduction had persistent FC >200 μg/g.

In children with active endoscopic disease after induction, mean FC levels did not drop significantly (Table 3). Greater FC values were observed after treatment in those with active

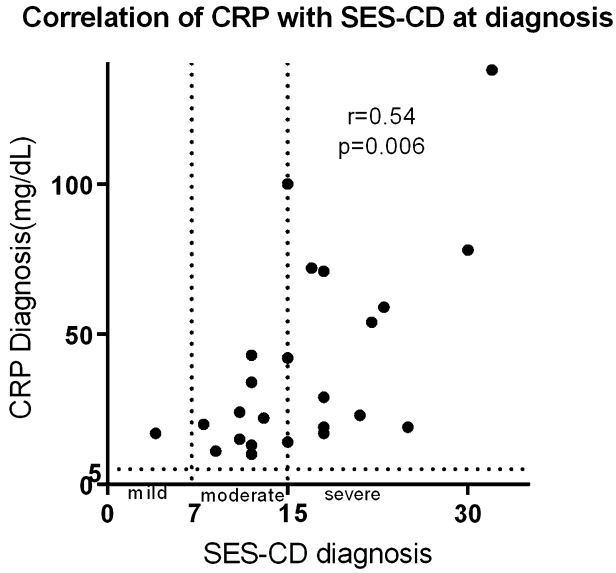

FIGURE 2. Correlation of CRP with SES-CD at diagnosis.

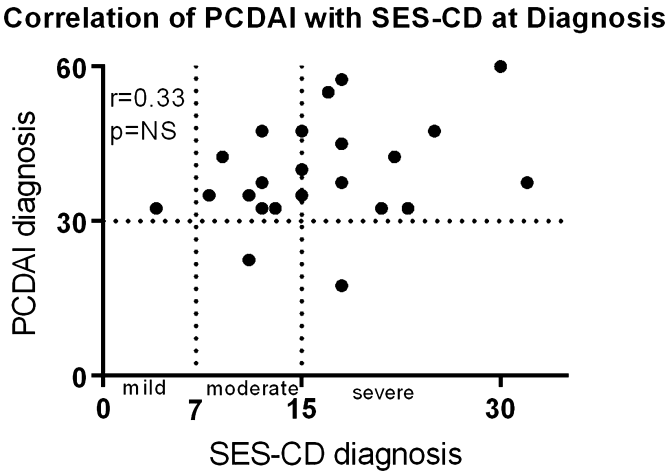

FIGURE 1. Correlation of PCDAI with SES-CD at diagnosis.

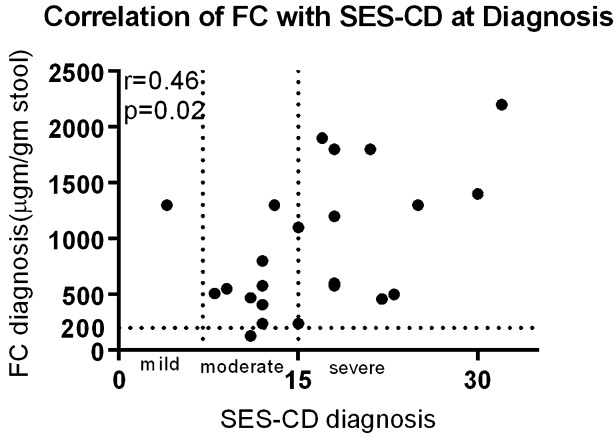

FIGURE 3. Correlation of FC with SES-CD at diagnosis.

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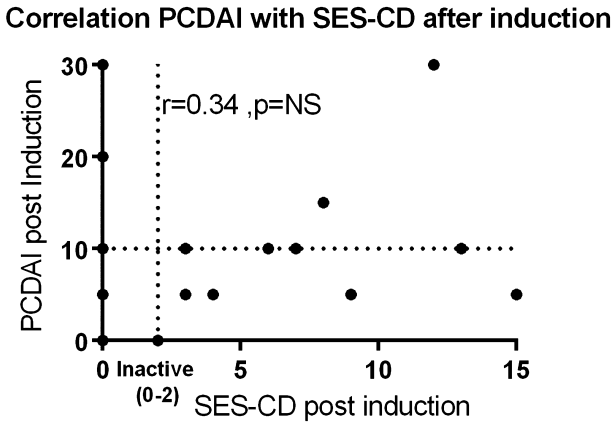

FIGURE 4. Correlation of PCDAI with SES-CD after induction.

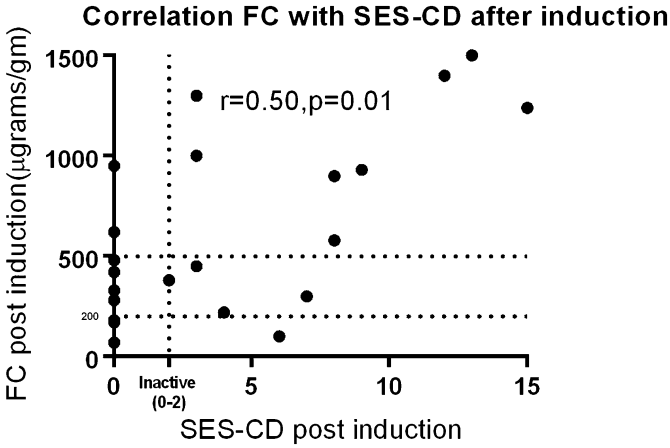

FIGURE 6. Correlation of FC with SES-CD after induction.

ileocolonic versus ileal disease alone (Table 4). Distribution of FC after treatment based on endoscopy outcomes are illustrated in Figure 7.

A drop in FC >50% from diagnosis to postinduction therapy has greater utility than FC <200 μg and FC <500 μg for inactive endoscopic disease with specificity 82% and PLR 3.8. Combining PCDAI ≤10, CRP <5 mg/L, and FC <500 μg/g provides much greater sensitivity, specificity, PLR of 5.3, and negative likelihood ratio 0.2 compared with other proxies (Table 5).

DISCUSSION

In this well-characterized prospective study of treatment naive children with moderate-to-severe CD, we demonstrate that PCDAI is a poor marker of endoscopic disease severity at diagnosis and a poor predictor of endoscopic treatment success. We confirm adult studies that demonstrate CRP and FC to be the current best noninvasive markers of endoscopic disease severity at presentation. We also confirm studies demonstrating FC to be the most reliable proxy for predicting good endoscopic outcomes after induction therapies and to inform follow-up. We confirm reports that a postinduction cutoff FC <200 μg/g is less reliable in children as many children with CR, BR, and endoscopic remission will have FC >200 μg/g. We report the novel findings that FC drop >50% after induction therapy provides much greater reliability for predicting inactive disease than FC <200 μg/g and that a composite of PCDAI ≤10, CRP <5 mg/dL, and FC <500 μg/g is an excellent proxy for accurately identifying inactive endoscopic disease after EEN or steroid induction in children with CD with specificity of 85% and positive likelihood ratio (PLR) of 5.3. The post hoc analysis of SONIC trial highlighted the inadequacy of CDAI as a measure of study entry criteria, and therapeutic outcome with almost 50% of patients treated with biologics in CR had active endoscopic or biochemical evidence of residual disease activity.[17,18] Clinical improvement is important for quality of life but is an unreliable marker of endoscopic disease severity and should not be used to assess endoscopic severity, treatment outcomes, or the performance of newer noninvasive proxies. We have now confirmed that the pediatric clinical tool, PCDAI, should also no longer be used as a determinant of disease severity, or not informing treatment escalation strategies, or not a major endpoint to determine treatment success, either for clinical or research purposes.

CRP is superior to PCDAI and CDAI as a noninvasive proxy of intestinal inflammation particularly at diagnosis and for monitoring progress. Normalization of the CRP is a common and important therapeutic outcome. However, in our cohort, almost 60% of children with normalized CRP and CR still had active endoscopic lesions, and so alone, a fall in CRP at 8 weeks is insufficient reassurance of endoscopic recovery.

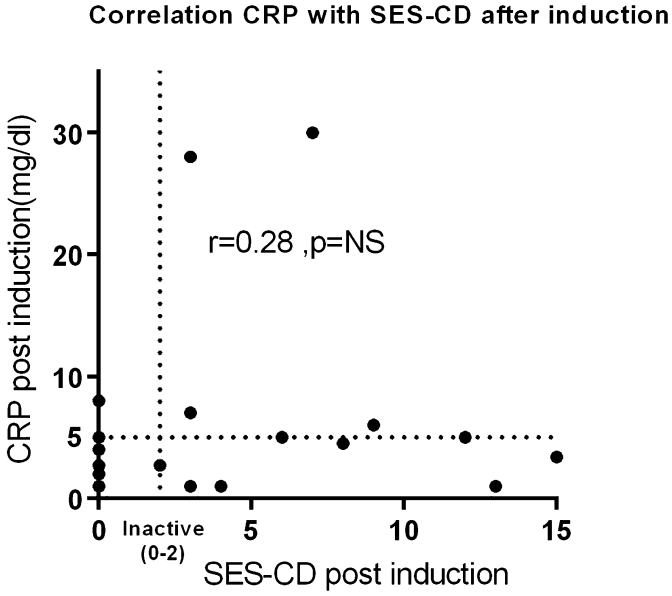

FIGURE 5. Correlation of CRP with SES-CD after induction.

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TABLE 3. PCDAI, CRP, FC, and SES-CD at Diagnosis and After Induction: Inactive Versus Active Disease

	Postinduction Inactive Endoscopic Disease (SES, 0–2)			Postinduction Active Endoscopic Disease (SES-CD ≥3)		
Mean (95% CI)	Diagnosis	Postinduction	*P*	Diagnosis	Postinduction	*P*
Mean PCDAI 95% CI	35.9 (30.4–41.3)	7.27 (0.84–13.7)	0.0001	42 (35–48.5)	10 (5.7–14.2)	0.0001
Mean CRP 95% CI	30.45 (18.4–42.5)	2.67 (1.1–4.1)	0.0005	47 (22.4–71.2)	7.5 (1.6–13.4)	0.002
Mean FC 95% CI	1010 (713–1308)	368 (199–536)	0.003	873 (448–1297)	780 (481–1079)	NS
Mean SES-CD 95% CI	15.45 (11.2–19.6)	0.18 (−0.22 to 0.5)	0.0001	17 (12.6–21.4)	7.3 (4.8–9.7)	0.003

CI, confidence interval; NS, nonsignificant.

TABLE 4. Mean FC Level Based on Disease Location After Induction Therapy

Mean (SD)	Ileal	Ileocolonic	*P*
FC active Disease (n = 13)	365 (286)	1018 (390)	0.006
FC Inactive disease (n = 11)	455 (288)	158 (81)	0.05

The correlation between endoscopic disease activity and FC has been well studied in adult populations and ranges from moderate to good, 0.35 to 0.72.[14,19,20] In a small pediatric study, good correlation of FC to SES-CD (r = 0.76) was observed; however, only 11 children had quantifiable ileocolonic lesions on endoscopy, and others with isolated ileal disease were scored on ultrasound alone.[9] Another multicenter prospective study in children with CD confirmed good correlation between CRP and FC, but neither correlated with PCDAI nor the vital correlation with endoscopic severity was assessed.[10] Studies using FC in children to measure CR, including a study using EEN which has a high rate of endoscopic remission, demonstrate that many children do not normalize FC to <200. A Finnish study treating children with IBD in CR with steroids and a Scottish study treating children with CD in CR with EEN showed that the majority of children in CR had elevated FC.[11,12] We have demonstrated that FC to be the most reliable marker of disease severity postinduction therapy but that adult cutoff values of FC <200 are not appropriate for the pediatric population. All 7 patients with persisting FC >200 with inactive endoscopic disease had CR and BR and no evidence on MR enterography at diagnosis of proximal small bowel disease. Two of these 7 had follow-up MR enterography that was also normal suggesting that the elevated FC values from these children were not from residual, undetected, proximal CD. MR enterography was not discussed in this article as there were insufficient pairs for meaningful analysis.

Although FC cutoff <200 is not appropriate in the pediatric population, an absolute cutoff of 500 provides greater specificity. Of greater interest is the finding that a dynamic change in FC, a drop >50% from diagnosis has an excellent reliability for predicting inactive disease. The combination of clinical and FC proxies to accurately predict endoscopic disease inactivity has been previously reported in adult studies with combined CDAI, CRP, and fecal biomarkers having sensitivity and specificity of 79% and 70%.[19] Another adult study combined FC and Harvey Bradshaw Index to give sensitivity

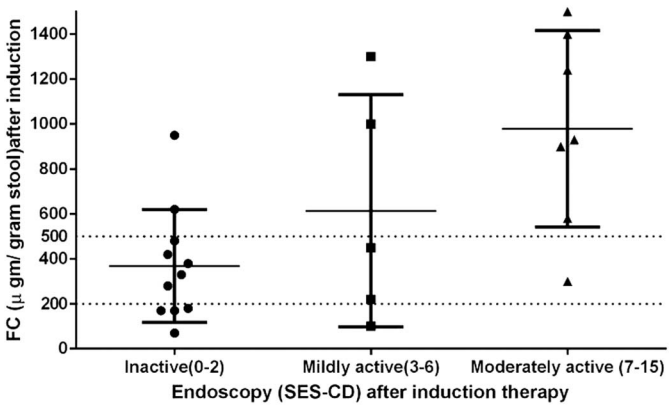

FIGURE 7. FC levels based on SES-CD scores after induction.

TABLE 5. Likelihood Ratio of Proxies Against Endoscopic Scores (SES-CD)

	Sensitivity, %	Specificity, %	Positive LR	Negative LR
CR (PCDAI ≤10)	47	60	1.1	0.8
BR (PCDAI ≤10, CRP <5)	64	80	3.2	0.4
FC <200 μg/g	80	63	2.3	0.3
FC <500 μg/g	64	80	3.2	0.4
FC >50% drop from diagnosis	69	82	3.8	0.38
BR and FC <500 μg/g	82	85	5.3	0.2

LR, likelihood ratio.

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86% and specificity of 86% and 82% for inactive mucosal disease.[20] Using PCDAI, CRP, and FC <500 μg/g, we confirmed a sensitivity of 82% and specificity of 85% with PLR 5.3 and negative likelihood ratio 0.2. Despite limitations of a small sample and lack of centralized endoscopic scoring, our results provide practical guide to reliably predict endoscopic healing using combination of clinical and objective markers.

CONCLUSIONS

Proxies of endoscopic mucosal healing after induction therapies are increasingly important for the management of patients with CD and for the assessment of new treatments. In a well-characterized cohort of children with CD, we have demonstrated that PCDAI is unreliable for this purpose, CRP has moderate utility, and FC has the best individual utility. FC drop >50% is more appropriate for use in children, and a composite of PCDAI, CRP, FC <500 μg has high positive and good negative likelihood ratios for inactive endoscopic mucosal disease and is an excellent proxy of mucosal healing and endpoint for deep remission.

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