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ORIGINAL RESEARCH

# Fecal Calprotectin Combined with Blood Inflammatory Biomarkers Enhances Diagnostic Evaluation and Supports Mucosal Healing Assessment in Pediatric Crohn's Disease

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**Purpose:** Previous small-sample study suggested that fecal calprotectin (FC) combined with blood inflammatory biomarkers may aid in Crohn's disease (CD) diagnosis. This study aimed to validate the FC's diagnostic and mucosal healing assessment value of FC and a noninvasive composite index in pediatric CD.

**Patients and Methods:** Patients aged 2–17 years who underwent ileocolonoscopy for suspected or established CD were enrolled. Based on endoscopy, participants were classified into three groups: controls (functional gastrointestinal disorders), MH (mucosal healing, SES-CD <3, indicating minimal or absent visible inflammation), and ML (mucosal lesions, SES-CD ≥3). Fecal and blood samples were collected before endoscopy. Group differences were assessed using Kruskal–Wallis/Dunn's tests; correlations were evaluated via Spearman coefficients; ROC analysis was used to assess diagnostic performance. A composite index was constructed by weighting CRP, ESR, and IL-6 based on their correlations with FC.

**Results:** Among 123 participants, FC levels significantly differed across groups ($P < 0.001$), highest in patients with mucosal lesions. For distinguishing CD from controls, FC showed limited accuracy (AUC = 0.651), while the composite index improved performance (AUC = 0.754). In established CD, FC alone showed strong ability to differentiate mucosal healing from active disease (AUC = 0.888), with a slight improvement using the composite index (AUC = 0.921).

**Conclusion:** The composite index integrating FC with inflammatory markers improves diagnostic performance over FC alone for distinguishing CD from controls and slightly enhances mucosal healing assessment, supporting its potential utility as a practical noninvasive tool for clinical monitoring in pediatric CD.

**Keywords:** fecal calprotectin, pediatric Crohn's disease, biomarker, noninvasive monitoring

## Introduction

Crohn's disease (CD), a chronic inflammatory bowel disorder, is pathologically defined by discontinuous transmural inflammation that necessitates endoscopic verification for definitive diagnosis, given its nonspecific clinical manifestations (eg, abdominal pain, chronic diarrhea).[1,2] Although endoscopic mucosal healing (MH) has been established as a key therapeutic endpoint associated with sustained remission, the inherent risks of repeated endoscopic procedures (eg, perforation, sedation complications) and suboptimal patient adherence significantly limit their utility for long-term monitoring.[3,4]

Pediatric CD exhibits distinct clinical trajectories compared to adult-onset disease, characterized by more extensive intestinal involvement and accelerated progression.[5] This aggressive phenotype predisposes pediatric patients to unique

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complications including linear growth impairment, pubertal delay, and substantial quality-of-life deterioration—clinical manifestations rarely observed in adult populations.[5] Current surveillance strategies, predominantly reliant on symptom recognition and endoscopic confirmation, inherently detect relapse only after established inflammatory damage. However, the critical therapeutic window between subclinical immune activation and overt symptom manifestation[6] underscores the urgent need for predictive biomarkers enabling preemptive intervention. Recent advances in transcriptomic profiling have identified platelet-associated genes as potential diagnostic candidates through their dysregulated expression patterns in pediatric CD,[7,8] though their clinical utility requires rigorous validation in prospective cohorts.

Pediatric Crohn's disease has exhibited a rising incidence in China over the past decade. A systematic review reported that the incidence of inflammatory bowel disease (IBD) in mainland China has increased substantially in recent years, with the average incidence of pediatric Crohn's disease estimated at approximately 0.4 per 100,000 children during 2010–2013, followed by a marked upward trend thereafter.[9] However, despite this increasing disease burden, biomarker validation in Chinese pediatric populations remains limited. Most existing evidence has been derived from Western cohorts, and few studies have evaluated the diagnostic performance of noninvasive disease monitoring biomarkers specifically in Chinese children. This geographic and demographic underrepresentation underscores the urgent need for population-specific validation and adaptation of diagnostic tools.

Calprotectin, a neutrophil-derived protein reflecting intestinal inflammation,[10] is a calcium and zinc-binding protein, formed by a hetero complex of S100A8 and S100A9 proteins.[11] Calprotectin is found in various bodily fluids at concentrations proportional to the degree of inflammation, including in feces at levels roughly six times higher than in the blood.[11,12] It usually be measured by enzyme-linked immunosorbent assay methods (ELISA) in both feces and in various body fluids.[13] FC has been proven largely useful for determining the inflammatory origin of gastrointestinal symptoms differentiating between organic and non-organic diseases.[10] Also, FC is found an elevated intestinal inflammation marker in some disease like glaucoma,[14] systemic sclerosis[15] et al, also a potential marker of graft versus host disease after stem cell transplantation.[16]

FC has been extensively studied for diagnosing and monitoring CD in adults, yet consensus on optimal thresholds for correlating FC levels with clinical or endoscopic activity remains unresolved.[17] A 2019 meta-analysis of 65 studies demonstrated that FC at a 70 μg/g cutoff strongly correlated with the Simple Endoscopic Score for CD (SES-CD; $r = 0.75$), exhibiting 89% sensitivity, 72% specificity, and 87% overall accuracy for detecting endoscopic lesions.[17] Pediatric data are more limited but suggest FC's utility in detecting small intestinal inflammation, even in endoscopically quiescent CD. A Japanese cohort study ($n = 74$) reported that FC outperformed fecal immunochemical testing in specificity for predicting MH.[18] Further, combining FC with blood inflammatory biomarkers may enhance diagnostic precision in pediatric CD. A Polish study ($n = 26$) found that elevated FC, Erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) alongside decreased albumin significantly improved diagnostic accuracy (AUC = 0.917, $p = 0.038$).[19] These preliminary findings necessitate further validation across diverse populations to establish generalizability and clinical applicability, including underrepresented cohorts such as Chinese pediatric patients where comparable data remain scarce.

Therefore, the present study aims to evaluate the diagnostic and mucosal healing assessment value of FC and a composite biomarker index incorporating systemic inflammatory markers in Chinese children with CD. We hypothesize that the composite index will improve noninvasive assessment of endoscopic disease activity compared to FC alone.

# Materials and Methods

## Participants Recruitment

The diagnostic criteria for pediatric CD were established in accordance with the Expert Consensus on Diagnosis and Treatment of Inflammatory Bowel Disease in Children.[20] Inclusion criteria comprised: (1) age <18 years; (2) completion of colonoscopy; (3) absence of concurrent acute or chronic inflammatory conditions (excluding CD); (4) no history of autoimmune diseases. Disease activity was assessed using the Simplified Endoscopic Score for CD (SES-CD), which evaluates ulcer size, ulcerated surface area, affected mucosal area per segment, and presence of strictures, with each parameter scored from 0 to 3 points. Patients were classified as MH group (SES-CD < 3) or mucosal lesion (ML) group

(SES-CD ≥ 3), with total scores ranging from 0 to 56 indicating increasing severity.[21] This study was approved by the Institutional Review Board of Shanghai Ruijin Hospital (Agreement Number: 2020–26-3). For all participants under 18, parental / guardian consent and patient assent (where applicable) were obtained. This study was performed in accordance with the Declaration of Helsinki.

## Sample Collection

Clinical data including age and gender were retrieved from the hospital's electronic medical records system of Ruijin Hospital. Biological samples were collected prior to any therapeutic interventions to ensure baseline measurements. For fecal sample collection, approximately 0.25–0.30 g of fresh stool was aseptically transferred into sterile containers using disposable wooden applicators, with careful attention to avoid contamination from urine, vaginal secretions and extraneous secretions. Peripheral blood samples were drawn into EDTA tubes for complete blood counts, while serum samples were collected in gel-clot activator tubes and centrifuged at 3,000 g for 10 minutes within 2 hours of collection. For optimal preservation of analyte integrity, specimens requiring delayed processing were immediately stored at 2–8 °C. The collection, procession and preservation of samples followed the corresponding biological safety rules. Colonoscopy assessors and laboratory technicians analyzing stool and blood samples were blinded to each other's results to minimize bias.

## Laboratory Analysis

FC levels were quantified using the FA280 automated system (Sichuan Orienter Bioengineering Co., Ltd.) with a colloidal gold immunoassay method. CRP concentrations were measured by turbidimetric immunoassay on a BC-7500 analyzer (Mindray, Shenzhen, China), while interleukin-6 and tumor necrosis factor-alpha (TNF-α) levels were determined using the BD FACS Calibur flow cellometer (United States BD Company) and corresponding reagents (Qingdao Rescale Biotech Co., Ltd). ESR was assessed using the SD-1000 hemodialysis meter (Beijing Saikochid Technology Co., Ltd). All assays included daily calibration with manufacturer-provided standards and demonstrated inter-assay coefficients of variation below 10%, ensuring analytical reliability.

## Statistical Analysis Methods

Continuous variables were assessed for normality using Shapiro–Wilk tests, with $P < 0.05$ indicating non-normal distributions. Non-normally distributed data were presented as median (IQR), while normally distributed data were expressed as mean ± SD. Categorical variables were summarized as counts (%). For multi-group comparisons, the Kruskal–Wallis test was applied, followed by Dunn's post hoc tests with Bonferroni-adjusted P-values if significant differences were detected. Two-group comparisons were performed using Mann–Whitney *U*-tests (non-normal data) or independent t-tests (normal data with homogeneity of variance). Correlations between continuous variables were evaluated using Spearman's rank correlation (ρ), while Fisher's exact test or chi-square tests were used for categorical associations, as appropriate. Composite Index Construction: A composite index was developed to enhance predictive performance. CRP, ESR, and IL-6 were selected for inclusion based on significant Spearman correlations with FC and their biological plausibility. The respective correlation coefficients were applied as weights to construct the composite Index. This correlation-based weighting approach offers interpretability and practicality in an exploratory context. The index was subsequently evaluated for its association with SES-CD and diagnostic performance using ROC analysis. All analyses were conducted in R version 4.3.2, with statistical significance set at $P < 0.05$ (two-tailed).

# Results

## Participant Characteristics

A total of 123 patients who underwent diagnostic ileocolonoscopy for suspected CD at Ruijin Hospital between August 2023 and February 2025 were included in this study. The cohort comprised 32 patients (26.0%) with normal colonoscopy findings diagnosed with functional gastrointestinal disorders (FGIDs, Control group) and 91 patients (74.0%) diagnosed with CD (CD group) according to the pediatric inflammatory bowel disease diagnostic criteria.

The NC group (mean age 10.3 ± 3.3 years; 65.6% male) and CD group (mean age 11.7 ± 3.3 years; 65.9% male) showed comparable gender distributions (Chi-squared test, P = 0.976). Among CD patients, 40 (44.0%) achieved MH (SES-CD < 3) while 51 (56.0%) had active ML (SES-CD ≥ 3).

## Comparison of FC in Patients with CD to Controls

Statistical analysis revealed non-normally distributed FC levels across all groups (Shapiro–Wilk, all P ≤ 0.05), with median concentrations of 15.5 μg/g (IQR 10.6–54.5) in controls, 12.8 μg/g (IQR 10.3–31.6) in MH patients, and 316.1 μg/g (IQR 95.8–728.0) in ML patients. Initial comparison demonstrated significantly elevated FC levels in CD patients versus controls (Mann–Whitney *U*-test, P = 0.011; Figure 1A). Kruskal–Wallis testing confirmed substantial heterogeneity among the three groups ($\chi^2$ = 46.84, P < 0.001). Post-hoc analysis using Dunn's test with Bonferroni adjustment showed comparable FC levels between controls and MH patients (Z = 0.97, P = 0.166), while ML patients exhibited markedly higher concentrations than both controls (Z = −4.93, P < 0.001) and MH patients (Z = −6.36, P < 0.001), as illustrated in Figure 1B.

## Correlation Between FC Level and Endoscopic Severity

Among 91 CD patients, Spearman correlation analysis demonstrated a strong positive association between FC levels and SES-CD scores (Spearman's rho = 0.69, P < 0.05). Log-transformed FC values maintained this correlation (Figure 2A).

## Composite Index Including FC Level and Blood Inflammatory Parameters Associated with the SES-CD Score

To evaluate potential confounding effects and enhance predictive capacity, we systematically analyzed the relationships between FC level and systemic inflammatory markers in our cohort of 91 pediatric CD patients. Initial correlation analysis revealed significant positive associations between FC and all measured biomarkers: ESR (r = 0.68, P < 0.001), Interleukin 6 (IL-6) (r = 0.63, P < 0.001), CRP (r = 0.47, P < 0.001), and TNF-α (r = 0.29, P = 0.012) (Supplementary Figure 1).

Based on these findings, we developed composite indices incorporating FC with markers demonstrating significantly correlations. The optimal combination, comprising FC, CRP, ESR and IL-6, showed superior correlation with endoscopic disease severity (Spearman's ρ = 0.733, P < 0.001; Figure 2B). This composite index demonstrated enhanced predictive

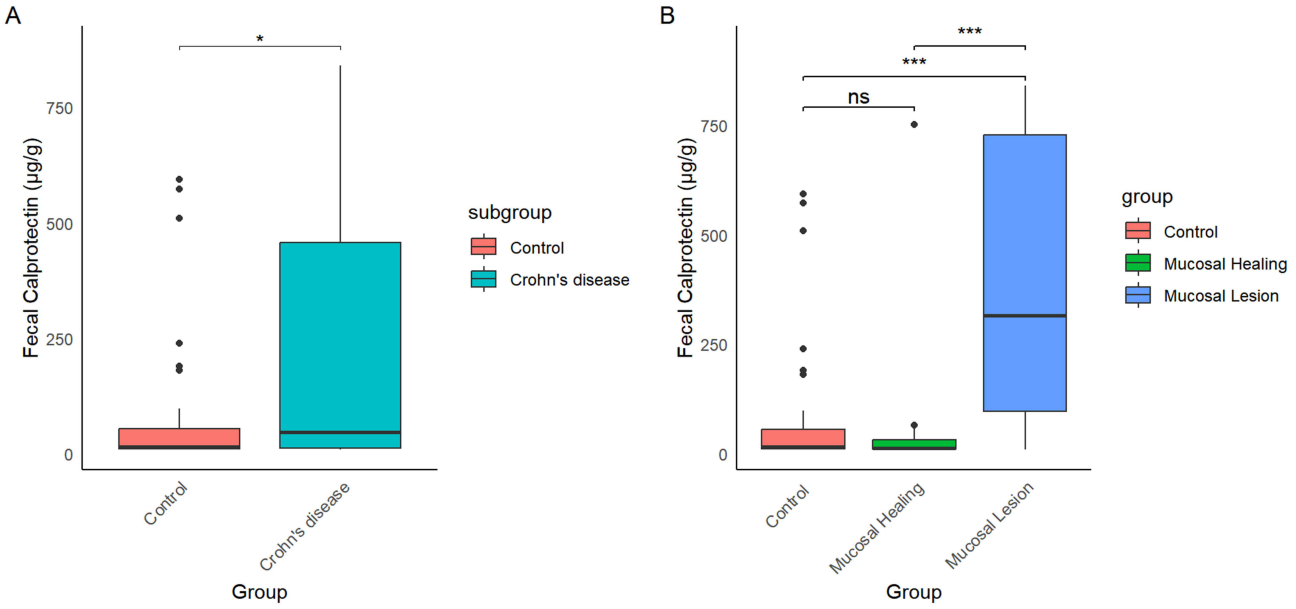


**Figure 1** Boxplot of FC levels in different groups. (**A**) Comparison between control group and CD group. (**B**) The boxplot demonstrates the distribution of FC concentrations among three study groups: control subjects with functional gastrointestinal disorders and normal colonoscopy findings (red), CD patients with MH (SES-CD score < 3, green), and CD patients with ML (SES-CD score ≥ 3, blue) (***P<0.001, *P<0.05).

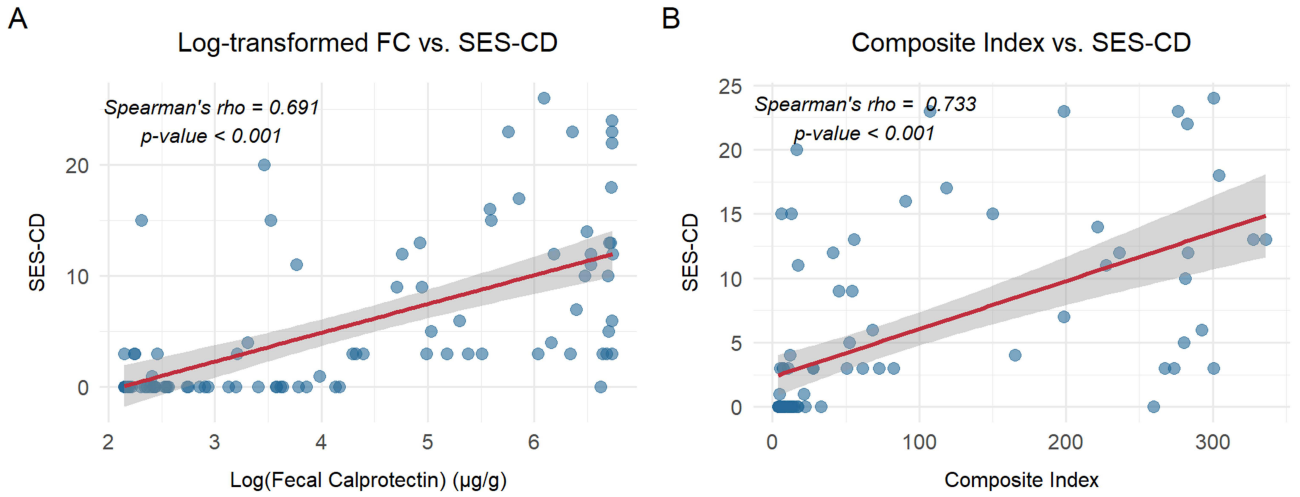


**Figure 2** FC level and composite index are both significantly correlated with the SES-CD score among 91 pediatric CD patients. (**A**) Correlation between FC level and SES-CD among 91 pediatric CD patients. Scatter plot illustrating the relationship between log10-transformed FC levels (x-axis) and SES-CD (y-axis) in 91 pediatric CD patients. (**B**) Scatter plot evaluating the association between a composite index (incorporating FC, CRP and ESR; x-axis) and SES-CD (y-axis). Red circles indicate MH status (SES-CD < 3), while blue triangles represent active mucosal inflammation (SES-CD ≥ 3).

value for SES-CD scores compared to individual biomarkers alone, suggesting its potential utility as a non-invasive tool for monitoring disease severity and prognostic assessment in pediatric CD.

Receiver operating characteristic (ROC) analysis revealed differential diagnostic performance of FC across clinical scenarios (Figure 3). The biomarker FC demonstrated limited discriminative capacity for distinguishing CD from FGIDs (AUC = 0.651, 95% CI= 54.7% - 75.6%, p = 0.011, Figure 3A), with sensitivity of 64.8% and specificity of 62.5% at the 22.8 µg/g cutoff threshold. Improved diagnostic accuracy was observed for composite index (AUC = 0.754, 95% CI = 65.4% - 85.4%, p<0.001, Figure 3B), where a 7.58 cutoff provided 66.3% sensitivity and 78.3% specificity. FC showed better performance in discriminating MH from ML among established CD patients (AUC = 0.888, 95% CI = 82.1% - 95.6%, p < 0.001, Figure 3C), achieving 80.4% sensitivity and 97.5% specificity at 73.3 µg/g. The composite inflammatory index incorporating FC, CRP, ESR and IL-6 showed slightly improved discrimination for discriminating MH from ML among established CD patients (AUC = 0.921, 95% CI = 86.0% - 98.1%, p < 0.001, Figure 3D), demonstrating diagnostic characteristics with 79.6% sensitivity, 94.9% specificity at the optimal cutoff 27.6, as detailed in Table 1.

## Discussion

This study provides comprehensive evidence supporting the utility of FC as a non-invasive biomarker for disease stratification and endoscopic severity assessment in pediatric CD patients. Our findings demonstrate three key clinical implications: (1) FC levels effectively discriminate active ML from both MH and FGIDs, (2) FC shows strong correlation with endoscopic disease severity as measured by SES-CD, and (3) a composite index incorporating FC with systemic inflammatory markers CRP, ESR and IL-6 offers enhanced predictive value for disease monitoring.

Emerging evidence positions FC as superior to conventional biomarkers in correlating with endoscopic activity. Grover et al's prospective cohort study revealed that FC outperforms both CRP and pediatric CD activity index in assessing mucosal inflammation, with a composite biomarker panel achieving 89% concordance with endoscopic outcomes — a finding that underscores its potential as a non-invasive treatment response endpoint.[22] Our data revealed striking FC concentration gradients across groups: ML (316.1 µg/g) > FGIDs (15.5 µg/g) ≈ MH (12.8 µg/g) (P < 0.001). This pattern aligns with the evolving paradigm that FC reflects subclinical inflammation even in endoscopically quiescent CD.[19] The robust FC-SES-CD correlation (ρ = 0.69) suggested heightened mucosal permeability in pediatric CD.

CD features recurrent flares and remissions driven by imbalanced cytokine production, Th1/Th17-derived pro-inflammatory versus regulatory T cell-derived anti-inflammatory.[23] Considering that, some blood inflammatory markers including CRP, ESR, IL-6, TNF-α were also collected to evaluate the potential correlation. CRP and ESR, as classical


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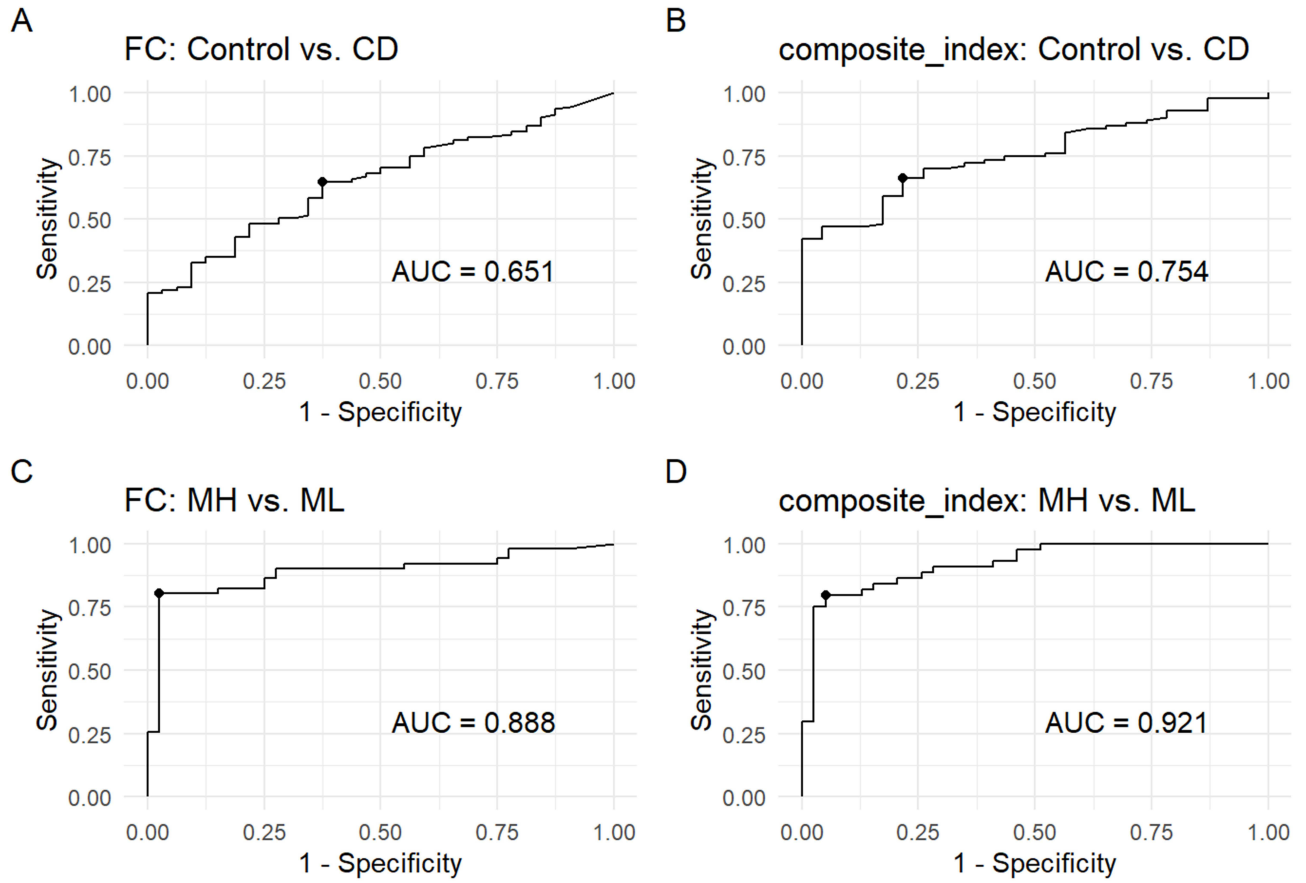


**Figure 3** Diagnostic performance of FC and FC-CRP-ESR-IL-6 composite index in CD assessment. (**A**) FC for discriminating CD from FGIDs. (**B**) Composite index for discriminating CD from FGIDs. (**C**) FC for discriminating MH from active lesions in CD. (**D**) Composite index for discriminating MH from active lesions in CD.

inflammatory biomarkers, play pivotal roles in early disease detection and dynamic activity monitoring of CD. Retrospective analyses demonstrate that elevated ESR levels in adult CD patients compared to healthy controls ($P < 0.01$) effectively stratify disease risk, forming the basis of novel predictive algorithms.[24] This diagnostic potential extends to pediatric populations, where Daniluk et al reported that integrating CRP, ESR, and hypoalbuminemia with FC significantly improves CD identification in symptomatic children (AUC = 0.917, P = 0.038).[19] Clinically, it has been

**Table 1** Correlations Between Laboratory and Clinical Markers and Endoscopic Disease Activities and the Area Under the Receiver Operating Characteristic Curve for Predicting Mucosal Healing in Patients with Established Crohn's Disease

| **Distinguish CD from FGIDs** | | | | | |
|---|---|---|---|---|---|
| | **Cutoff** | **Sensitivity** | **Specificity** | **AUROC** | **95% CI** |
| FC | 22.80 μg/g | 0.648 | 0.625 | 0.651 | 0.547–0.756 |
| Composite index* | 7.58 | 0.663 | 0.783 | 0.754 | 0.654–0.854 |
| **Predicting MH in established CD** | | | | | |
| | **Cutoff** | **Sensitivity** | **Specificity** | **AUROC** | **95% CI** |
| FC | 73.30 μg/g | 0.804 | 0.975 | 0.888 | 0.821–0.956 |
| Composite index* | 27.65 | 0.795 | 0.949 | 0.921 | 0.860–0.981 |

**Notes**: *The optimal composite index = FC + 0.47*CRP + 0.68*ESR + 0.63*IL-6.

confirmed that the normalization of CRP levels within three months after initiating adalimumab treatment serves as a reliable predictor for therapeutic efficacy, MH, and the need for dose escalation. This finding can guide the adjustment of treatment intensity and is applicable to patients with CD.[25] IL-6 contributes to CD inflammation through elevated mucosal and systemic levels.[26,27] Its complex signaling network provides both mechanistic insight and therapeutic potential.[23] TNF-α is a key pro-inflammatory cytokine in inflammatory bowel disease and significantly elevated in the serum of children with inflammatory bowel disease.[28] It binds to the TNF receptor and induces transcription of inflammatory factors, leading to fibroblast proliferation and intestinal fibrosis and contributing to intestinal narrowing.[29] We found that in CD patient, FC levels are significantly correlated with the level of these blood inflammatory markers, especially CRP, ESR and IL-6, which is similar to a previous study.[19] The composite index (FC + CRP + ESR + IL-6) demonstrated strong predictive accuracy ($\rho = 0.733$), offering a more structured and interpretable tool for noninvasive assessment.

Importantly, composite evaluation approaches combining FC with CRP have also demonstrated added diagnostic value in adult Crohn's disease. For example, A prospective study reported that sequential use of FC and CRP, structured into an algorithmic format, improved specificity and sensitivity in detecting endoscopic inflammation compared with either marker alone.[30] Although those adult studies did not construct formal statistical models, our structured, correlation-weighted composite index builds upon this evidence, providing a quantitative and reproducible tool tailored to pediatric patients. Our results are further supported by the ESPGHAN 2023 position paper, which endorses FC as a first-line monitoring tool for pediatric CD, while encouraging development of composite noninvasive indicators.[31]

In contrast to some previous studies that reported combinations of FC and blood inflammatory markers without a formalized model, we developed a structured composite index using correlation-based weighting. This approach enhances interpretability and clinical applicability, particularly in pediatric settings where noninvasive tools are in high demand. While *Daniluk* et al[19] highlighted the diagnostic value of combining FC with CRP and albumin, no formal composite was proposed. Our model provides a reproducible, data-driven framework for noninvasive disease monitoring. However, we acknowledge that this correlation-based method is exploratory in nature and not equivalent to regression-based modeling. Future refinements will include prospective validation, the application of multivariable or machine learning approaches, and the potential incorporation of additional markers such as albumin.

Despite these promising findings, several limitations warrant consideration. First, the single-center, cross-sectional design limits generalizability, causal inference and precludes assessment of longitudinal outcomes such as relapse or mucosal healing sustainability. Longitudinal studies with follow-up are necessary to further validate these observations. Second, although we excluded patients with overt infections or recent immunosuppressive therapy, unmeasured confounders—eg, recent antibiotics, diet, or subclinical infections—may have influenced FC levels. Third, we did not stratify by Paris classification (L1–L4), though disease location may affect FC concentrations. Lastly, assay variability across centers could influence threshold applicability, highlighting the need for standardization.

Nonetheless, these limitations do not compromise the strong diagnostic performance observed. A multicenter prospective study is currently planning to validate and refine our composite index, explore inclusion of additional markers such as albumin, and assess its cost-effectiveness compared with endoscopy. Based on current evidence, we advocate incorporating FC-based tools into routine pediatric CD management.

## Conclusion

In conclusion, our findings support FC as a valuable noninvasive biomarker for diagnosing pediatric Crohn's disease and monitoring mucosal healing. While the composite index combining FC with CRP, ESR, and IL-6 demonstrated only a modest improvement in discriminative performance over FC alone for mucosal healing assessment, it offers added clinical value by integrating systemic inflammatory signals. This integrative approach may enhance interpretability and decision-making in clinical settings, particularly in cases with ambiguous symptoms or borderline endoscopic findings.

Importantly, FC and related biomarkers are not diagnostic in isolation and should be interpreted within the broader clinical framework, including symptoms, imaging, and patient history. The composite index, due to its noninvasive nature and compatibility with routine tests, could be integrated into clinical monitoring algorithms to help guide treatment decisions and reduce reliance on repeat endoscopy, especially in pediatric populations. Future multicenter

prospective studies are warranted to validate the model, assess its longitudinal performance, and explore its cost-effectiveness for routine clinical application in pediatric CD management. These steps are essential to support broader implementation and optimize its role in clinical practice.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

The authors report no conflicts of interest in this work.

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