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Original Article

# Fecal Calprotectin at Postinduction Is Capable of Predicting Persistent Remission and Endoscopic Healing after 1 Year of Treatment with Infliximab in Pediatric Patients with Crohn's Disease

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**Background/Aims:** The recent update on Selecting Therapeutic Targets in Inflammatory Bowel Disease initiative has added a decrease in fecal calprotectin (FC) to an acceptable range as an intermediate target for Crohn's disease (CD). We aimed to investigate whether postinduction FC could predict future persistent remission (PR) and endoscopic healing (EH) after 1 year of treatment with infliximab (IFX) in pediatric patients with CD.

**Methods:** This multicenter retrospective observational study included pediatric patients with CD who were followed up for at least 1 year after starting IFX. The association of postinduction FC with PR and EH was investigated.

**Results:** A total of 132 patients were included in this study. PR and EH were observed in 71.2% (94/132) and 73.9% (82/111) of the patients, respectively. In multivariate logistic regression analysis, only the postinduction FC level was associated with PR (odds ratio [OR], 0.26; 95% confidence interval [CI], 0.08 to 0.66; p=0.009). The FC levels at initiation of IFX and postinduction were significantly associated with EH (OR, 0.73; 95% CI, 0.53 to 0.99; p=0.044 and OR, 0.20; 95% CI, 0.06 to 0.49; p=0.002, respectively). According to the receiver operating characteristic curve analysis, the optimal cutoff level for postinduction FC associated with PR was 122 mg/kg, and that associated with EH was 377 mg/kg.

**Conclusions:** Postinduction FC was associated with PR and EH after 1 year of treatment with IFX in pediatric patients with CD. Our findings emphasize the importance of FC as an intermediate target in the treat-to-target era. **(Gut Liver 2024;18:498-508)**

**Key Words:** Crohn disease; Calprotectin; Infliximab; Prognosis

## INTRODUCTION

Crohn's disease (CD) is a chronic inflammatory disease of any segment of the gastrointestinal tract characterized by recurrent relapses and remission.[1,2] The prevalence of CD has increased rapidly worldwide and is emerging as an important concern for clinicians.[3] Particularly, pediatric CD is more extensive and aggressive than adult-onset CD; therefore, it requires earlier introduction of biologics and intensive therapy.[4-6]

The conventional treatment goal for CD is to improve clinical symptoms. However, the severity of symptoms does not necessarily indicate endoscopic inflammation and might not be a reliable criterion for guiding therapeutic

adjustments to control persistent mucosal inflammation.[7] Additionally, it is common to find significant mucosal inflammation during complete clinical remission.[8] Therefore, according to the 2015 Selecting Therapeutic Targets in Inflammatory Bowel Disease, the currently accepted treat-to-target includes not only clinical remission but also endoscopic healing (EH).[9] The importance of EH stems from previous large-scale studies that evaluated anti-tumor necrosis factor (TNF) agents, which demonstrated that EH was associated with lower relapses.[10,11]

The CALM trial is the first study to demonstrate that decisions regarding the initiation of anti-TNF therapy based on biomarkers, such as fecal calprotectin (FC) and C-reactive protein (CRP), as well as clinical symptoms in early CD have better clinical and endoscopic outcomes than those based on clinical symptoms alone.[12] Consequently, the Selecting Therapeutic Targets in Inflammatory Bowel Disease-II initiative has added a decrease in FC to an acceptable range (<250 μg/g) as an intermediate target in CD.

Several studies have demonstrated the validity of FC as an alternative to ileocolonoscopy as well as the association between FC and endoscopic activity in CD.[13,14] However, there have been relatively few studies on the importance of FC as a predictor of disease outcomes, especially in pediatric CD. Therefore, we aimed to investigate whether postinduction FC could predict future persistent remission (PR) and EH after 1 year of treatment with infliximab (IFX) in pediatric patients with CD.

## MATERIALS AND METHODS

### 1. Ethics statement

This study was approved by the Institutional Review Board of Kyungpook National University Chilgok Hospital, and informed consent was waived owing to the retrospective nature of this study (IRB number: 2022-01-001).

### 2. Patients and data collection

This multicenter, retrospective observational study was conducted between January 2017 and December 2021 in the Department of Pediatrics of the following five tertiary medical centers in the Republic of Korea: Kyungpook National University Children's Hospital affiliated with Kyungpook National University Chilgok Hospital, Keimyung University Dongsan Medical Center, Ajou University Medical Center, Kosin University Gospel Hospital, and Soonchunhyang University Bucheon Hospital.

Pediatric patients with luminal CD who were diagnosed before 19 years of age and were followed up for at least 1 year after initiating treatment with IFX were included. Patients with missing postinduction FC data and primary non-responders were excluded. Primary nonresponse was defined as the necessity for a treatment change, such as undergoing bowel surgery or switching to an alternate anti-TNF therapy, or undergoing corticosteroid therapy until week 14, due to uncontrolled disease activity. CD was diagnosed according to the revised Porto criteria of the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition.[15] Disease classification and behavior, including perianal disease modifier, were based on the Paris classification.[16]

Baseline demographic and clinical data, including sex, age, disease phenotype, growth indicators, previous bowel or perianal surgery, and family history of inflammatory bowel disease (IBD) were obtained from the electronic medical records. At the initiation of IFX treatment, postinduction, and at 1-year follow-up, the following data were collected from the electronic medical records: age, disease duration, Pediatric Crohn's Disease Activity Index (PCDAI) score, white blood cell count, hematocrit, platelet count, serum albumin, erythrocyte sedimentation rate (ESR), CRP and FC levels, and Simple Endoscopic Score for Crohn's Disease. FC levels were measured using a fluorometric enzyme immunoassay at the Soonchunhyang University Bucheon Hospital and Kyungpook National University Children's Hospital, while an enzyme-linked immunosorbent assay was used at the other three centers.

### 3. Study design and definition

We evaluated factors including postinduction laboratory markers that were associated with PR and EH at 1 year of follow-up following IFX treatment. Postinduction was defined as 14 weeks after starting IFX treatment and before the fourth dose of IFX. PR was defined as corticosteroid-free sustained clinical remission without further dose intensification at 1 year of treatment with IFX in primary responders. EH was defined as Simple Endoscopic Score for Crohn's Disease ≤2, which corresponds to the absence of ulcers on ileocolonoscopy.[17] Clinical remission was defined as PCDAI <10 points,[18] while laboratory remission was defined as serum CRP <0.3 mg/dL. PCDAI scores and laboratory parameters were monitored before every IFX infusion. Dose intensification of IFX in the form of interval shortening was allowed in cases of suspected secondary loss of response, which was defined as worsening of clinical symptoms and a significant increase in serum CRP or FC levels at two consecutive visits plus a status that required dose intensification or switching the therapy.

### 4. Statistical analysis

For statistical comparisons between groups, the Student t-test or the Wilcoxon rank-sum test was used for continuous variables, and the chi-square or the Fisher exact test was used for categorical variables. Comparative data for continuous variables are reported as medians and interquartile ranges or means and standard deviations. Univariate and multivariate logistic regression analyses were performed to examine the associations between PR/EH and other variables. Univariate logistic regression analysis was performed to investigate the crude odds ratio (OR) for each factor; factors with p-value <0.1 in the univariate analysis were included in the multivariate analysis. The results are expressed as adjusted OR and 95% confidence interval (CI). Receiver operating characteristic curve analysis was performed to determine the optimal cutoff value of postinduction FC that could best predict clinical outcomes, and the Youden index was also calculated to obtain postinduction FC cutoff levels for achieving PR and EH with a specificity of ≥80%. Statistical significance was defined as p-value ≤0.05. All statistical analyses were performed using R, version 3.2.3 (R Foundation for Statistical Computing, Vienna, Austria).

## RESULTS

### 1. Baseline characteristics

Of the 162 eligible patients, 30 were excluded and 132 were included (Fig. 1). The median age at diagnosis was 13.5±2.8 years, and 64.4% (85/132) of the patients were male. B1 disease was observed in 84.8% (112/132) of patients, and 74.2% (98/132) of patients had perianal disease modifiers. The median disease duration at initiation of anti-TNF treatment was 0.19 years (interquartile range, 0.08 to 0.27 years), and 70.5% (93/132) were started on anti-TNF treatment within 3 months of diagnosis. Concomitant azathioprine was administered to 81.1% (107/132) of the patients. FC at IFX initiation was 1,721 μg/g (interquartile range, 918 to 3,029 μg/g). Detailed baseline characteristics at diagnosis and IFX initiation are summarized in Table 1.

### 2. Outcomes after 1 year of IFX treatment

Secondary loss of response was observed in 28.8% (38/132) of patients in whom interval shortening of IFX was performed. Of them, the response was recaptured in 81.6% (31/38) of patients, whereas 15.8% (6/38) were switched to adalimumab and 2.6% (1/38) required bowel resection. PR was observed in 71.2% (94/132) of the patients.

A total of 111 patients (84.1%) were followed up with ileocolonoscopy after 1 year of treatment. The reasons for a lack of follow-up ileocolonoscopy included the lack of ileocolonoscopy (n=14), switching to adalimumab (n=6), and bowel resection (n=1) (Fig. 1). Of those who underwent ileocolonoscopy after 1 year of treatment, clinical and laboratory remission was observed in 91.9% (102/111) and 91.0% (101/111) of patients, respectively, and EH was noted in 73.9% (82/111) of the patients.

Among the 31 patients with recaptured response following interval shortening, 30 underwent follow-up ileocolonoscopy at 1 year. Of these, 46.7% (14/30) had EH.

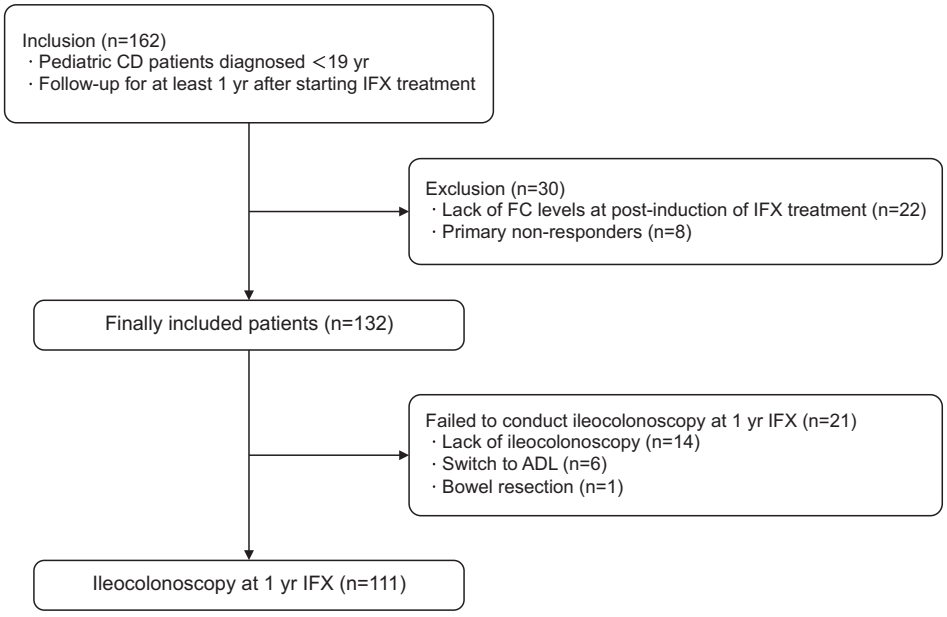


**Fig. 1.** Flowchart depicting study design. CD, Crohn's disease; IFX, infliximab; FC, fecal calprotectin; ADL, adalimumab.

**Table 1.** Baseline Characteristics (n=132)

| Characteristic | Category | Value |
|---|---|---|
| At diagnosis | | |
| Male sex | | 85 (64.4) |
| Age at diagnosis, yr | | 13.5±2.8 |
| Paris classification | | |
| Age | A1a | 17 (12.9) |
| | A1b | 103 (78.0) |
| | A2 | 12 (9.1) |
| Lower GI tract involvement | L1 | 18 (13.7) |
| | L2 | 4 (3.0) |
| | L3 | 110 (83.3) |
| Upper GI tract involvement | None | 15 (11.4) |
| | L4a | 34 (25.7) |
| | L4b | 15 (11.4) |
| | L4a+b | 68 (51.5) |
| Disease behavior | B1 | 112 (84.8) |
| | B2 | 17 (12.9) |
| | B3 | 3 (2.3) |
| Perianal disease modifier | No | 34 (25.8) |
| | Yes | 98 (74.2) |
| Growth | G0 | 104 (78.8) |
| | G1 | 28 (21.2) |
| 1st degree family history of IBD | | 6 (4.6) |
| At IFX initiation | | |
| Age at initiation of IFX, yr | | 13.8±2.8 |
| Duration from diagnosis to IFX, yr | | 0.19 (0.08–0.27) |
| IFX initiation within 3 mo of diagnosis | | 93 (70.5) |
| Prior bowel surgery | | 1 (0.8) |
| Prior perianal surgery | | 93 (70.5) |
| Prior biologics | | 1 (0.8) |
| Concomitant immunomodulator | | 107 (81.1) |
| PCDAI | | 35.0 (32.5–40.0) |
| WBC, /μL | | 8,690 (7,085–10,875) |
| Hematocrit, % | | 36.3±4.3 |
| Platelet count, $\times 10^3/\mu L$ | | 414 (333–513) |
| Albumin, g/dL | | 4.1 (3.6–4.4) |
| ESR, mm/hr | | 49 (30–79) |
| CRP, mg/dL | | 1.95 (0.69–4.84) |
| FC, mg/dL | | 1,721 (918–3,029) |

Data are presented as the number (%), mean±SD, or median (interquartile range).
A1a, 0–9 years; A1b, 10–16 years; A2, ≥17 years; GI, gastrointestinal; L1, distal 1/3 ileum±limited cecal disease; L2, colonic disease; L3, ileocolonic disease; L4a, upper disease proximal to ligament of Treitz; L4b, upper disease distal to the ligament of Treitz and proximal to the distal 1/3 ileum; L4a+b, upper disease involvement in both L4a and L4b; B1, nonstricturing nonpenetrating behavior; B2, stricturing behavior; B3, penetrating behavior; G0, no evidence of growth delay; G1, growth delay; IBD, inflammatory bowel disease; IFX, infliximab; PCDAI, Pediatric Crohn's Disease Activity Index; WBC, white blood cell count; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; FC, fecal calprotectin.

### 3. Comparison between patients with and without PR

PCDAI and serum albumin levels at initiation of IFX and postinduction PCDAI, platelet count, serum ESR and CRP levels, and FC levels were significantly different between those with PR and those without PR (Table 2). Postinduction FC level was significantly lower in patients with PR than in those without PR (median 70 mg/kg vs 471 mg/kg, p<0.001).

### 4. Comparison between patients with and without EH

Statistically significant differences were noted in white blood cell counts and FC levels at initiation of IFX and postinduction serum CRP and FC levels between patients with EH and those without EH (Table 3). FC levels at initiation of IFX and postinduction were significantly lower in those with EH than in those without EH (FC at initiation of IFX: 1,327 mg/kg vs 2,000 mg/kg, p=0.001 and FC at postinduction: 83 mg/kg vs 452 mg/kg, p<0.001).

### 5. Factors associated with PR and EH

According to the univariate logistic regression analysis, PCDAI and serum albumin levels at IFX initiation and postinduction PCDAI, platelet count, serum ESR and CRP levels, and FC levels were significantly associated with PR (Table 4). However, in the multivariate logistic regression analysis, only postinduction FC levels were associated with PR (OR, 0.26; 95% CI, 0.08 to 0.66; p=0.009).

Factors associated with EH at 1 year were also analyzed (Table 5). According to univariate and multivariate logistic regression analyses, FC levels at initiation of IFX and postinduction were significantly associated with EH (FC at initiation of IFX: OR, 0.73; 95% CI, 0.53 to 0.99; p=0.044 and FC at postinduction: OR, 0.20; 95% CI, 0.06 to 0.49; p=0.002).

### 6. Cutoff level of postinduction FC for predicting PR and EH

According to the receiver operating characteristic curve analysis, the optimal cutoff for postinduction FC associated with PR was 122 mg/kg (area under the curve 0.776, 95% CI 0.683 to 0.870, sensitivity 66.0%, specificity 81.6%, positive predictive value [PPV] 89.9%, negative predictive value [NPV] 49.2%; p<0.001) and that for EH was 377 mg/kg (area under the curve 0.749, 95% CI 0.629 to 0.869, sensitivity 87.8%, specificity 58.6%, PPV 85.7%, NPV 63.0%; p<0.001) (Fig. 2).

According to Youden's index, the postinduction FC cutoff levels for achieving PR and EH with specificity ≥80% were ≤122 mg/kg (sensitivity 66.0%, specificity 81.6%, PPV 89.9%, NPV 49.2%) and ≤50 mg/kg (sensitivity 31.7%, specificity 82.8%, PPV 83.9%, NPV 30.0%), respectively. The cutoff levels of postinduction FC required to achieve PR and EH are summarized in Tables 6 and 7, respectively.

**Table 2.** Comparisons between Patients with and without Persistent Remission at 1 Year (n=132)

| Variable | No (n=38) | Yes (*n*=94) | p-value |
|---|---|---|---|
| Male sex | 22 (57.9) | 63 (67.0) | 0.429 |
| Age at diagnosis, yr | 13.1±2.9 | 13.6±2.7 | 0.352 |
| Any colonic involvement at diagnosis | 35 (92.1) | 79 (84.0) | 0.346 |
| B1 behavior at diagnosis | 30 (79.0) | 84 (89.4) | 0.194 |
| Perianal modifier at diagnosis | 27 (71.1) | 71 (75.5) | 0.754 |
| Disease duration <3 mo to IFX initiation | 27 (71.1) | 66 (70.2) | 1.000 |
| Concomitant immunomodulator | 31 (81.6) | 76 (80.9) | 1.000 |
| Baseline PCDAI | 40.0 (35.0–45.0) | 35.0 (32.5–37.5) | 0.001 |
| Baseline WBC, /μL | 8,975 (7,440–10,930) | 8,600 (7,070–10,800) | 0.633 |
| Baseline hematocrit, % | 35.9±5.0 | 36.4±4.0 | 0.516 |
| Baseline platelet count, $\times10^3$/μL | 445 (355–583) | 408 (323–494) | 0.066 |
| Baseline albumin, g/dL | 3.8 (3.5–4.2) | 4.1 (3.8–4.4) | 0.009 |
| Baseline ESR, mm/hr | 54 (33–84) | 48 (29–78) | 0.629 |
| Baseline CRP, mg/dL | 1.98 (0.80–4.84) | 2.18 (1.02–3.22) | 0.732 |
| Baseline FC, mg/kg | 2,000 (1,326–3,995) | 1,432 (918–2,529) | 0.124 |
| Postinduction PCDAI | 5.0 (0.0–5.0) | 0.0 (0.0–5.0) | 0.002 |
| Postinduction WBC, /μL | 5,860 (5,080–7,340) | 5,485 (4,490–6,570) | 0.072 |
| Postinduction hematocrit, % | 38.9±3.7 | 39.0±3.3 | 0.763 |
| Postinduction platelet count, $\times10^3$/μL | 307±70 | 277±53 | 0.022 |
| Postinduction albumin, g/dL | 4.4 (4.3–4.6) | 4.5 (4.3–4.7) | 0.101 |
| Postinduction ESR, mm/hr | 10 (4–19) | 5 (2–10) | 0.009 |
| Postinduction CRP, mg/dL | 0.05 (0.04–0.27) | 0.05 (0.03–0.05) | 0.036 |
| Postinduction FC, mg/kg | 471 (151–1,000) | 70 (23–188) | <0.001 |

Data are presented as the number (%), mean±SD, or median (interquartile range).
B1, nonstricturing nonpenetrating behavior; IFX, infliximab; PCDAI, Pediatric Crohn's Disease Activity Index; WBC, white blood cell count; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; FC, fecal calprotectin.

**Table 3.** Comparison between Patients with and without Endoscopic Healing at 1 Year (n=111)

| Variable | No (n=29) | Yes (n=82) | p-value |
|---|---|---|---|
| Male sex | 18 (62.1) | 55 (67.1) | 0.794 |
| Age at diagnosis, yr | 13.3±2.5 | 13.7±2.8 | 0.557 |
| Any colonic involvement at diagnosis | 27 (93.1) | 71 (86.6) | 0.508 |
| B1 behavior at diagnosis | 25 (86.2) | 71 (86.6) | 1.000 |
| Perianal modifier at diagnosis | 19 (65.5) | 62 (75.6) | 0.419 |
| Disease duration <3 mo to IFX initiation | 22 (75.9) | 56 (68.3) | 0.596 |
| Concomitant immunomodulator | 25 (86.2) | 66 (80.5) | 0.684 |
| Baseline PCDAI | 35.0 (35.0–45.0) | 35.0 (30.0–37.5) | 0.183 |
| Baseline WBC, /μL | 9,730 (7,830–10,930) | 8,295 (6,680–10,220) | 0.038 |
| Baseline hematocrit, % | 36.1±5.2 | 36.4±4.2 | 0.767 |
| Baseline platelet count, $\times10^3$/μL | 441 (337–518) | 392 (332–507) | 0.513 |
| Baseline albumin, g/dL | 4.2 (3.5–4.3) | 4.0 (3.6–4.4) | 0.936 |
| Baseline ESR, mm/hr | 46 (31–66) | 48 (29–79) | 0.838 |
| Baseline CRP, mg/dL | 1.61 (0.81–5.21) | 1.80 (0.63–4.35) | 0.827 |
| Baseline FC, mg/kg | 2,000 (1,733–4074) | 1,327 (757–2,275) | 0.001 |
| Postinduction PCDAI | 0.0 (0.0–5.0) | 0.0 (0.0–5.0) | 0.483 |
| Postinduction WBC, /μL | 6,350 (5,490–8,000) | 5,700 (4,940–6,700) | 0.074 |
| Postinduction hematocrit, % | 39.2±3.7 | 39.1±3.4 | 0.858 |
| Postinduction platelet count, $\times10^3$/μL | 295±75 | 280±55 | 0.334 |
| Postinduction albumin, g/dL | 4.4±0.3 | 4.4±0.3 | 0.825 |
| Postinduction ESR, mm/hr | 6 (3–13) | 6 (2–12) | 0.401 |
| Postinduction CRP, mg/dL | 0.05 (0.04–0.12) | 0.05 (0.03–0.05) | 0.017 |
| Postinduction FC, mg/kg | 452 (125–1,172) | 83 (27–202) | <0.001 |

Data are presented as the number (%), mean±SD, or median (interquartile range).
B1, nonstricturing nonpenetrating behavior; IFX, infliximab; PCDAI, Pediatric Crohn's Disease Activity Index; WBC, white blood cell count; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; FC, fecal calprotectin.

**Table 4.** Logistic Regression Analyses of Factors Associated with Persistent Remission at 1 Year (n=132)

| Factor | Univariate logistic regression analysis | | Multivariate analysis with stepwise selection | |
|---|---|---|---|---|
| | OR (95% CI) | p-value | OR (95% CI) | p-value |
| Male sex | 1.48 (0.68–3.20) | 0.323 | | |
| Age at diagnosis | 1.07 (0.93–1.23) | 0.350 | | |
| Any colonic involvement at diagnosis | 0.45 (0.10–1.48) | 0.231 | | |
| B1 behavior at diagnosis | 2.24 (0.79–6.22) | 0.121 | | |
| Perianal modifier at diagnosis | 1.26 (0.53–2.89) | 0.595 | | |
| Disease duration <3 mo to IFX initiation | 0.96 (0.41–2.17) | 0.924 | | |
| Concomitant immunomodulator | 0.95 (0.34–2.43) | 0.923 | | |
| Baseline PCDAI | 0.96 (0.92–0.99) | 0.019 | 0.97 (0.92–1.02) | 0.217 |
| Baseline WBC | 1.00 (1.00–1.00) | 0.476 | | |
| Baseline hematocrit | 1.03 (0.94–1.13) | 0.513 | | |
| Baseline platelet count | 1.00 (0.99–1.00) | 0.053 | 1.00 (1.00–1.01) | 0.406 |
| Baseline albumin | 3.09 (1.40–7.25) | 0.007 | 2.29 (0.71–7.53) | 0.163 |
| Baseline ESR | 1.00 (0.99–1.01) | 0.601 | | |
| Baseline CRP | 0.95 (0.86–1.06) | 0.383 | | |
| Baseline FC | 0.85 (0.68–1.06) | 0.146 | | |
| Postinduction PCDAI | 0.94 (0.87–0.99) | 0.041 | 0.99 (0.92–1.07) | 0.854 |
| Postinduction WBC | 1.00 (1.00–1.00) | 0.079 | 1.00 (1.00–1.00) | 0.946 |
| Postinduction hematocrit | 1.02 (0.91–1.14) | 0.761 | | |
| Postinduction platelet count | 0.99 (0.98–1.00) | 0.012 | 1.00 (0.99–1.01) | 0.499 |
| Postinduction albumin | 3.25 (0.96–11.67) | 0.062 | 1.21 (0.23–6.42) | 0.823 |
| Postinduction ESR | 0.94 (0.90–0.98) | 0.006 | 0.99 (0.93–1.07) | 0.865 |
| Postinduction CRP | 0.01 (0.00–0.35) | 0.005 | 0.02 (0.00–0.64) | 0.052 |
| Postinduction FC | 0.15 (0.05–0.35) | <0.001 | 0.26 (0.08–0.66) | 0.009 |

OR, odds ratio; CI, confidence interval; B1, nonstricturing nonpenetrating behavior; IFX, infliximab; PCDAI, Pediatric Crohn's Disease Activity Index; WBC, white blood cell count; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; FC, fecal calprotectin.

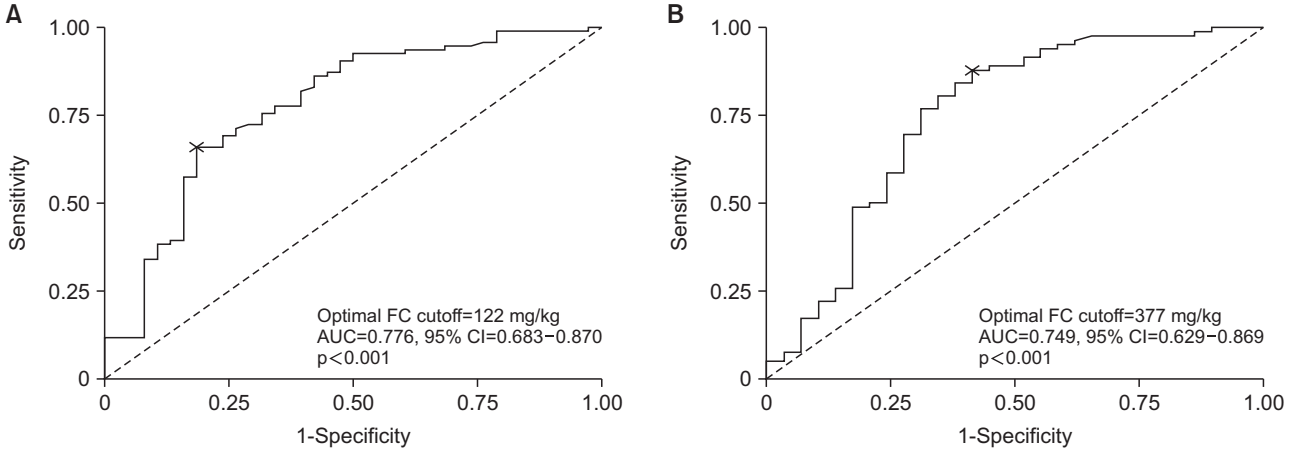


**Fig. 2.** Receiver operating characteristic curve of postinduction fecal calprotectin (FC) with infliximab in predicting (A) persistent remission and (B) endoscopic healing. The x marks indicate the optimal cutoff point for each graph. AUC, area under the curve; CI, confidence interval.

## DISCUSSION

In the era of precision medicine, there is increasing interest in predicting disease course through posttreatment response along with designing personalized treatment strategies through risk stratification. In this retrospective study, we demonstrated the utility of postinduction FC as a prognostic factor potentially associated with PR and EH, in pediatric patients with CD who had been receiving treatment with IFX and provided postinduction FC cutoff values calculated as 122 mg/kg and 377 mg/kg, respectively. In addition, it was calculated that FC cutoff levels of ≤122 mg/kg and ≤50 mg/kg were required to achieve PR and EH in 80% of pediatric CD patients during IFX therapy. To

**Table 5.** Logistic Regression Analyses of Factors Associated with Endoscopic Healing at 1 Year (n=111)

| Factor | Univariate logistic regression analysis | | Multivariate analysis with stepwise selection | |
|---|---|---|---|---|
| | OR (95% CI) | p-value | OR (95% CI) | p-value |
| Male sex | 1.24 (0.51–2.98) | 0.626 | | |
| Age at diagnosis | 1.05 (0.90–1.23) | 0.554 | | |
| Any colonic involvement at diagnosis | 0.48 (0.07–1.93) | 0.357 | | |
| B1 behavior at diagnosis | 1.03 (0.27–3.33) | 0.959 | | |
| Perianal modifier at diagnosis | 1.63 (0.64–4.05) | 0.295 | | |
| Disease duration <3 mo to IFX initiation | 0.69 (0.25–1.75) | 0.445 | | |
| Concomitant immunomodulator | 0.66 (0.18–2.01) | 0.493 | | |
| Baseline PCDAI | 0.98 (0.93–1.02) | 0.288 | | |
| Baseline WBC | 1.00 (1.00–1.00) | 0.053 | 1.00 (1.00–1.00) | 0.123 |
| Baseline hematocrit | 1.01 (0.92–1.12) | 0.764 | | |
| Baseline platelet count | 1.00 (1.00–1.00) | 0.444 | | |
| Baseline albumin | 1.23 (0.52–2.86) | 0.627 | | |
| Baseline ESR | 1.00 (0.99–1.02) | 0.636 | | |
| Baseline CRP | 0.99 (0.88–1.14) | 0.910 | | |
| Baseline FC | 0.66 (0.49–0.86) | 0.003 | 0.73 (0.53–0.99) | 0.044 |
| Postinduction PCDAI | 0.95 (0.87–1.05) | 0.315 | | |
| Postinduction WBC | 1.00 (1.00–1.00) | 0.103 | | |
| Postinduction hematocrit | 0.99 (0.87–1.12) | 0.856 | | |
| Postinduction platelet count | 1.00 (0.99–1.00) | 0.258 | | |
| Postinduction albumin | 1.18 (0.27–5.09) | 0.823 | | |
| Postinduction ESR | 0.99 (0.95–1.03) | 0.556 | | |
| Postinduction CRP | 0.56 (0.18–1.25) | 0.181 | | |
| Postinduction FC | 0.15 (0.05–0.38) | <0.001 | 0.20 (0.06–0.49) | 0.002 |

OR, odds ratio; CI, confidence interval; B1, nonstricturing nonpenetrating behavior; IFX, infliximab; PCDAI, Pediatric Crohn's Disease Activity Index; WBC, white blood cell count; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; FC, fecal calprotectin.

**Table 6.** Cutoff Levels of Postinduction FC in Predicting Persistent Remission after 1 Year of Treatment with Infliximab

| FC cutoff | Sensitivity, % | Specificity, % | PPV, % | NPV, % |
|---|---|---|---|---|
| ≤50 mg/kg | 39.4 | 84.2 | 86.0 | 36.0 |
| ≤100 mg/kg | 61.7 | 81.6 | 89.2 | 46.3 |
| ≤122 mg/kg | 66.0 | 81.6 | 89.9 | 49.2 |
| ≤200 mg/kg | 75.5 | 65.8 | 84.5 | 52.1 |
| ≤300 mg/kg | 85.1 | 57.9 | 83.3 | 61.1 |
| ≤400 mg/kg | 89.4 | 52.6 | 82.4 | 66.7 |
| ≤500 mg/kg | 91.5 | 50.0 | 81.9 | 70.4 |
| ≤600 mg/kg | 92.6 | 44.7 | 80.6 | 70.8 |

FC, fecal calprotectin; PPV, positive predictive value; NPV, negative predictive value.

**Table 7.** Cutoff Levels of Postinduction FC in Predicting Endoscopic Healing after 1 Year of Treatment with Infliximab

| FC cutoff | Sensitivity, % | Specificity, % | PPV, % | NPV, % |
|---|---|---|---|---|
| ≤50 mg/kg | 31.7 | 82.8 | 83.9 | 30.0 |
| ≤100 mg/kg | 53.7 | 75.9 | 86.3 | 36.7 |
| ≤200 mg/kg | 74.4 | 69.0 | 87.1 | 48.8 |
| ≤300 mg/kg | 82.9 | 62.1 | 86.1 | 56.3 |
| ≤377 mg/kg | 87.8 | 58.6 | 85.7 | 63.0 |
| ≤400 mg/kg | 87.8 | 55.2 | 84.7 | 61.5 |
| ≤500 mg/kg | 89.0 | 48.3 | 83.0 | 60.9 |
| ≤600 mg/kg | 91.5 | 44.8 | 82.4 | 65.0 |

FC, fecal calprotectin; PPV, positive predictive value; NPV, negative predictive value.

the best of our knowledge, this is the first pediatric study to demonstrate the usefulness of postinduction FC and suggest cutoff values in predicting anti-TNF treatment responses in pediatric CD patients.

Several study groups have proposed prediction models for the disease course in pediatric CD using postinduction clinical and biochemical markers.[19-23] For example, the GROWTH model suggested serum CRP level at 3 months for predicting steroid-free remission at 1 year and PCDAI, serum CRP level, and FC after induction therapy for predicting relapse.[20,21] Most of these models use clinical indices based on the subjective symptoms of patients. However, the limitations of patient-reported subjective symptoms and clinical indices, such as PCDAI, in predicting the disease course and mucosal inflammation are well-known.[24,25] Similarly, in adult studies, the Crohn's Disease Activity Index has been criticized for its poor reproducibility and inadequate correlation with objective indicators of disease activity, such as endoscopic findings and FC.[26] Likewise, our study revealed that there was no associa-

tion between postinduction PCDAI and 1-year clinical outcomes including PR and EH. In addition, biochemical markers, such as serum CRP and ESR levels are useful in identifying ongoing mucosal inflammation but not in predicting relapse since these markers do not elevate before an apparent clinical flare-up.[27] In our study, both postinduction serum ESR and CRP levels were not associated with 1-year PR and EH.

FC accounts for nearly 60% of the cytosolic protein content in neutrophils and is released following the activation and decomposition of neutrophils.[28] Therefore, elevated FC level is an indicator of mucosal neutrophilic infiltration and increased outflow to the intestinal lumen. Several studies have reported the advantages of FC over serum CRP in detecting endoscopic activity.[28-30] The associations between FC levels and mucosal inflammation as well as disease activity in patients with CD suggest that FC might be a useful biomarker in predicting relapse and clinical remission.[31-33]

We propose a postinduction cutoff level of FC of 122 mg/kg in predicting PR at 1 year because this value provided the best combination of sensitivity and specificity (area under the curve, 0.776; p<0.001). Our data are consistent with those of previous studies. Guidi *et al.*[34] reported that postinduction FC <168 mg/kg demonstrated 83% sensitivity and 74% specificity in predicting PR at 1 year in patients with IBD. Another study on anti-TNF agents found that postinduction FC <139 mg/kg predicted sustained clinical remission at 1 year although the enrolled patients were not on maintenance therapy with biologics (bridge therapy).[35]

As we mentioned, EH is the currently accepted long-term treatment target in CD, according to Selecting Therapeutic Targets in Inflammatory Bowel Disease in 2015.[9] "Treat-to-target approach" requires frequent assessment and evaluation of patients and modification of therapeutic strategy until the therapeutic goal is achieved. Bouguen *et al.*[36] revealed that adjustment of therapeutic strategy on the basis of frequent endoscopic evaluations to achieve EH was feasible in clinical practice. However, bowel preparation and frequent ileocolonoscopy procedures are limited in pediatric patients. The CALM study showed that establishing therapeutic strategies based on FC and CRP is more favorable for EH than based on clinical symptoms alone.[12] In this regard, our study provides further evidence that FC can be used to predict which patients will achieve long-term EH, and provides rationale for integrating FC into a biomarker-guided treat-to-target strategy.

We found that FC levels at initiation of IFX and postinduction were associated with EH. Additionally, the postinduction FC cutoff level in predicting EH after 1 year of treatment was 377 mg/kg. Furthermore, the cutoff FC level in predicting EH with a specificity of ≥80% was ≤50 mg/kg. Compared with other studies in adults with IBD, the cutoff value of postinduction FC in predicting EH after 1 year of IFX appears high. Guidi *et al.*[34] reported that postinduction FC ≤121 mg/kg had 79% sensitivity and 57% specificity in predicting EH in adults with IBD. According to another post-hoc analysis of two randomized controlled trials, 250 mg/kg was used as the cutoff point for postinduction FC in predicting EH in adult patients with ulcerative colitis.[37]

There are several possible explanations for these discrepancies. Unlike previous studies, our study included only patients with CD. Differences in the utility of FC between patients with CD and those with ulcerative colitis might be due to the differences in the inflammatory burden between isolated small bowel inflammation and colonic disease, and studies have demonstrated that the predictability of EH in FC is higher in ulcerative colitis patients than in CD.[38,39] In our study, 13.7% of patients with isolated small bowel (L1) CD were identified. However, PR and EH between L1 CD and the other sites were not compared. Therefore, it is difficult to directly compare our results with the results of other studies. Additionally, EH was defined as Simple Endoscopic Score for Crohn's Disease ≤2 only for the bowel segments accessible using ileocolonoscopy, and small bowels were excluded from the analyses. Furthermore, Korean pediatric patients with CD are more likely to have perianal modifiers when compared with their European counterparts.[40] In the present study, 74.2% (98/132) of patients had perianal disease modifiers. FC does not correlate well with mucosal inflammation in active perianal CD.[41] Therefore, caution is warranted when interpreting the postinduction FC cutoff values for EH in patients with perianal modifier.

Our study has some limitations. First, this was a retrospective study with inherent design limitations in comparison with prospective studies. However, all patients visited the outpatient clinics at regular intervals for IFX infusion, which permitted consistent clinical assessments for PR and monitoring for relapse. Second, we did not analyze IFX trough levels and anti-drug antibodies. The correlation between IFX trough levels and EH has been reported previously;[42] therefore, the present study is important in terms of costeffectiveness by elucidating the utility of a noninvasive and easily-accessible biomarker that can be used in real-world practice. Third, a majority of patients (74.2%) in this study had perianal disease. Therefore, the results should be interpreted carefully when predicting the disease course in European patients with a relatively lower prevalence of perianal disease.

In conclusion, postinduction FC was associated with PR and EH after 1 year of treatment with IFX in pediatric

patients with CD and was more informative than improvements in clinical symptoms. Postinduction FC cutoff values for PR and EH at 1 year were 122 and 377 mg/kg, respectively. Our findings emphasize the importance of FC as an intermediate target in the treat-to-target era.

## CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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Study concept and design: B.K. Data acquisition: Y.M.L., E.S.K., S.C., H.J.J., Y.B.K., S.Y.C., B.H.C., B.K. Data analysis and interpretation: Y.M.L., E.S.K., B.K. Statistical analysis: B.K. Funding acquisition: Y.M.L., B.K. Supervision: B.K. Drafting of the manuscript: Y.M.L., E.S.K., S.C., B.K. Critical revision of the manuscript for important intellectual content: H.J.J., Y.B.K., S.Y.C., B.H.C., B.K. Approval of final manuscript: all authors.

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