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Predictive accuracy of fecal calprotectin for histologic remission in ulcerative colitis

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Background/Aims: Accurate assessment of disease activity is crucial for effective management and treatment of ulcerative colitis (UC). This study evaluated the correlation between clinical, endoscopic, and histologic measures of disease activity in UC. **Methods:** Clinical, biochemical, endoscopic, and histologic disease activity was studied in 347 patients with UC. Agreements among various histologic classification systems, namely the Geboes Score (GS), Continuous GS, Nancy Index (NI), and Robarts Histopathology Index (RHI), were analyzed. The predictive accuracy of fecal calprotectin (FC) for endoscopic and histologic remission was assessed. **Results:** We demonstrate a fair to moderate correlation between clinical, endoscopic, and histologic measures of disease activity in UC. There was a robust concordance among GS, Continuous GS, NI, and RHI in distinguishing between patients in histologic remission or activity. The NI detected 75% of patients who met the remission criteria according to the RHI, whereas the RHI identified all patients in remission as defined by the NI. FC levels below 150 μg/g had >70% accuracy in predicting endoscopic remission. FC levels below 150 μg/g showed ≥80% accuracy, and FC levels below 100 μg/g demonstrated ≥85% accuracy in predicting histologic remission, regardless of the scoring index applied. Elevated FC levels were associated with both acute and chronic inflammatory infiltrates in biopsy samples. **Conclusions:** FC is a reliable predictor of histologic remission, with higher accuracy at lower thresholds. The GS, Continuous GS, NI, and RHI demonstrate comparable performance. FC could help stratify patients' need for colonoscopy for the assessment of endoscopic and histologic remission. **(Intest Res 2025;23:144-156)**

Key Words: Colitis, ulcerative; Biopsy; Endoscopy; Histology

INTRODUCTION

Therapeutic targets in ulcerative colitis (UC) have transitioned over time from mere symptom control to mucosal healing, which entails both endoscopic as well as histologic healing. The concept of remission in UC is a continuum of symptomatic and endoscopic remission, which is now evolving to histologic and molecular remission.[1-3] Persistent histologic activity is associated with increased relapse rates, corticosteroid usage, therapy escalation, need for surgery and long-term complications.[4-7] Therefore, histologic remission is now considered a suitable endpoint for clinical trials, though it is yet to be translated in clinical practice as a compulsory formal target.[3,8] Among the commonly utilized instruments for assessing histopathological disease activity in UC patients are the Geboes

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Score (GS), continuous GS, Robarts Histopathology Index (RHI), and Nancy Index (NI).[9-12] The hallmark of disease activity in all the histologic indices is the presence of neutrophils. However, there is lack of standardized reporting formats and comparative measurements of performance of the different histologic scores.[13] This gap complicates the decision-making process for clinicians aiming to identify the optimal index for both clinical trials and practical applications. Furthermore, while there is clinical trial data on correlation between clinical symptoms (stool frequency and blood in stools), fecal biomarkers such as calprotectin, endoscopic disease activity, and histologic inflammation; examining the performance of these disease outcome measures, in relation to each other, is crucial for understanding their practical utility in real-world situations.[14-17]

Fecal calprotectin (FC) is a noninvasive biomarker that plays a crucial role in assessing disease activity in UC. Elevated FC levels correspond with mucosal inflammation, making it a suitable candidate for prediction of histologic remission. Nonetheless, gaps persist in determining the optimal FC threshold for defining histologic remission across diverse patient populations. Investigating the predictive accuracy of FC is imperative to standardize outcome assessment and establish optimal disease activity thresholds. This approach is essential for enhancing consistency in evaluating specific outcomes and improving the management of UC.

In this study, we evaluated a large cohort of patients with UC for clinical symptoms (partial Mayo Score, PMS), FC, endoscopic severity (Mayo Endoscopic Score, MES), and histologic disease activity (GS, continuous GS, NI, and RHI). Our objectives were threefold: (1) to evaluate the association between these scoring systems for assessing disease activity; (2) to determine if FC can predict the endoscopic and histologic disease activity; (3) to evaluate and compare the performance of the different histologic indices in relation to each other.

METHODS

1. Study Population

Adult (>18 years of age) patients with an established diagnosis of UC (based on the European Crohn's and Colitis Organisation and European Society of Gastrointestinal and Abdominal Radiology guidelines) were included.[18] The demographic profile (age, sex), clinical history (disease duration and extent), and disease activity (including symptoms of stool frequency and rectal bleeding, FC, and endoscopic and histologic assessments, all performed with a week of each other) were noted for all the patients. Patients with missing/incomplete data were excluded from the analysis.

2. Study Design

This was a prospective observational cohort study conducted at Dayanand Medical College and Hospital, Ludhiana, India from January 2021 to December 2022. This study was approved by the Institutional Ethics Committee of Dayanand Medical College and Hospital (IEC number: DMCH/R&D/2020/23). All the included patients provided written informed consent.

3. Assessment of Disease Activity

1) Clinical Assessment

The clinical disease activity was evaluated using PMS. The PMS uses the 3 noninvasive components of the Mayo Score (stool frequency, rectal bleeding and physician's global assessment), score ≤1 was classified as clinical (symptomatic) remission. The MES evaluates for the macroscopic inflammation of the colonic mucosa, and score of 0 was taken as endoscopic remission. The total Mayo Score was calculated by adding PMS and MES, and a score of ≤2 was taken as remission. As an exploratory end point, the Ulcerative Colitis Endoscopic Index of Severity (UCEIS) was also calculated for each patient.

2) Measurement of FC

Patients were instructed to collect stool samples in dedicated clean containers at home, ensuring no contamination with water or urine. These samples were then brought to the hospital, typically within 4–6 hours of collection. Approximately 100 μg of each sample was used for the analysis of FC using the semi-quantitative point of care test, QuantOn Cal (Preventis, Bensheim, Germany; range, 25–2,000 μg/g), following the manufacturer's instructions.

3) Endoscopic Assessment

All the patients underwent high definition white light sigmoidoscopy/colonoscopy using EC-760ZP and EC-760R scope series (Fujifilm, Tokyo, Japan) within 1 week of clinical assessment and FC testing. Endoscopic remission was defined as MES of 0. A single skilled endoscopist (Ajit Sood), blinded to the clinical disease activity and FC values determined the MES based on the central reading of the video-colonoscopy images.

4) Histologic Assessment

During sigmoidoscopy/colonoscopy, rectal and sigmoid colon biopsies were obtained. Two biopsies were taken from each segment. The biopsies were taken from the endoscopically normal area in patients in endoscopic remission. However, in presence of active inflammation (defined as MES ≥1), the biopsies were taken from the most inflamed areas. These biopsy samples were then centrally analyzed by 2 independent gastrointestinal pathologists, each with over 5 years of experience in inflammatory bowel disease histology. The pathologists were blinded to the patients' clinical, FC, and endoscopic findings. For each patient, the biopsy with the highest histologic grade was selected for evaluation. Disagreements among the pathologists were resolved with the involvement of a third gastrointestinal pathologist using a multi-headed microscope to determine a final score. The cutoffs for disease remission/activity were calculated based on the standard criteria using GS, continuous GS, NI, and RHI. The GS and continuous GS include architecture of the crypts, chronic inflammatory infiltrate in the lamina propria, eosinophils in the lamina propria, neutrophils in the lamina propria and epithelium, crypt destruction and surface epithelial injury in the form of erosions and ulcers. The GS ≤2.0 and continuous GS ≤6 indicate histologic remission.[9,10] The NI follows a 4-level categorization where 0 indicates no or mild chronic inflammatory infiltrate, 1 indicates a moderate to severe chronic inflammatory infiltration without an acute inflammatory infiltrate, 2 includes mild increase in the acute inflammatory infiltrate, 3 indicates moderately active disease characterized by moderate to severe infiltration by neutrophils and 4 characterized by erosions and ulcers.[12] The NI of 0 was taken as histologic remission. The RHI score is based on evaluation of the chronic inflammatory infiltrate, lamina propria neutrophils and eosinophils, neutrophils in the epithelium and erosion and ulceration, and varies from 0 (no disease activity) to 33 (severe disease activity).[11] The histologic remission was defined by a RHI score of ≤3.[19]

4. Statistical Analysis

Quantitative data were presented as mean±standard deviation or median and interquartile range (IQR). Categorical data were summarized as the percentage of the group total. Categorical data were compared using either the chi-square test (for parametric data) or the Kruskal-Wallis one-way analysis of variance test or Mann Whitney test (for non-parametric data). The Fisher exact test was performed when the anticipated frequency was less than 5. A probability value (*P*-value) less than 0.05 was considered statistically significant. Receiver operating characteristics (ROC) curves were generated and the area under the curve (AUC) calculated to summarize the predictive ability of FC with regards to different outcomes that were assessed.

The performance of different parameters was evaluated for the estimation of sensitivity, specificity, accuracy, predictive values and kappa values. Sensitivity measured how well a "test" identified patients in remission compared to a reference standard. Specificity assessed the test's ability to identify patients with active disease in line with the reference standard. The positive predictive value indicated the proportion of patients identified as being in remission by the test who truly are in remission according to the reference standard. Negative predictive value indicated the proportion of patients identified as having active disease by the test who actually do have active disease according to the reference standard.

Spearman's rho (ρ) was used for assessment of correlation between disease activity indices. For interpretation of the correlation coefficient, the following parameters were used[20]: 1.00 (–1.00), perfect correlation; 0.80 to 0.99 (–0.80 to –0.99), very strong correlation; 0.60 to 0.79 (–0.60 to –0.80), moderate correlation; 0.30 to 0.59 (–0.30 to –0.60), fair correlation; 0.10 to 0.29 (–0.10 to –0.30), poor correlation; 0.00 to 0.09 (0.00 to –0.10), no correlation.

All statistical calculations were done using Statistical Package for the Social Science (SPSS) version 21 (IBM Corp., Armonk, NY, USA) statistical program for Microsoft Windows.

RESULTS

1. Disease Characteristics

The enrolled cohort comprised 347 patients (mean age 39 years, 52.4% males) with UC. Majority (n=238, 68.8%) of the patients had left-sided colitis followed by pancolitis (n=61, 17.6%) and proctitis (n=48, 13.8%). Peripheral arthritis was the most prevalent (6.9%) extraintestinal manifestation. Concomitant therapy with oral 5-aminosalicylates was administered to all patients; while 28.2% (n=98) and 13.5% (n=47) patients received tofacitinib and thiopurines, respectively. The use of biologics was infrequent.

A majority of the patients had active disease as defined by the Mayo Score. The median FC was 345 μg/g (IQR, 68–1,091 μg/g). Four different cutoffs were considered for FC: 100, 150, 200, and 250 μg/g. Of the patients assessed, 99 (28.5%), 115

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Table 1. Baseline Characteristics

Characteristic	Value (n = 347)
Age (yr)	39.3 ± 14.6
Sex	
Female	165 (47.6)
Male	182 (52.4)
Disease extent	
Proctitis	48 (13.8)
Left-sided colitis	238 (68.6)
Pancolitis	61 (17.6)
Extraintestinal manifestations	
Peripheral arthritis	24 (6.9)
Axial arthritis	3 (0.8)
Nephrolithiasis	4 (1.1)
Cholelithiasis	3 (0.8)
DVT	1 (0.3)
Concomitant therapy	
5-Aminosalicylates (oral)	347 (100)
5-Aminosalicylates (rectal)	196 (56.5)
Thiopurines	47 (13.5)
Corticosteroids	29 (8.4)
Hydrocortisone enema	75 (21.6)
Tofacitinib	98 (28.2)
Infliximab	4 (1.2)
Vedolizumab	1 (0.3)
Baseline disease activity indices	
Partial Mayo Score	4 (2–6)
Mayo Endoscopic Score	2 (1–3)
Total Mayo Score	6 (3–8)
Fecal calprotectin (μg/g)	345 (68–1,091)
Geboes Score	5.3 (3.1–5.4)
Continuous Geboes Score	12 (7–14)
Nancy Index	4 (3–4)
Robarts Histopathology Index	22 (9–27)
Partial Mayo Score	
≤ 1	75 (21.6)
> 1	272 (78.4)
Mayo Endoscopic Score	
0	82 (23.6)
≥ 1	265 (76.4)
Total Mayo Score	
≤ 2	71 (20.5)
> 2	276 (79.5)
Fecal calprotectin (μg/g)	
< 100	99 (28.5)
< 150	115 (33.1)
< 200	131 (37.8)
< 250	147 (42.4)
Geboes Score	
≤ 2.0	24 (6.9)
> 2.0	323 (93.1)
Continuous Geboes Score	
≤ 6	84 (24.2)
> 6	263 (75.8)
Nancy Index	
0	47 (13.5)
≥ 1	300 (86.5)
Robarts Histopathology Index	
≤ 3	62 (17.9)
> 3	285 (82.1)

Values are presented as mean ± SD, number (%), or median (IQR).
DVT, deep venous thrombosis; SD, standard deviation; IQR, interquartile range.

(33.1%), 131 (37.8%), and 147 (42.4%) recorded values falling below these respective cutoffs (Table 1).

2. Correlation between Clinical, Endoscopic, and Histologic Assessments

Correlation analysis was performed between the different disease activity measures. There was a fair correlation between PMS and MES, moderate correlation between MES and total Mayo Score, and very strong correlation between the PMS and total Mayo Score. All the histologic indices had poor to fair correlations with PMS, and fair correlations with MES and total Mayo Score. The GS correlated very strongly with NI and the RHI. Additionally, there was a moderate correlation between the NI and the RHI (Table 2). The correlations between different disease activity indices and UCEIS are presented in Supplementary Table 1.

3. Histologic Outcomes

At the time of assessment, majority of the patients had evidence of histologic activity. The histologic remission rates were as follows: 24 patients (6.91%) based on GS, 84 patients (24.20%) based on continuous GS, 47 patients (13.54%) based on NI, and 62 patients (17.86%) based on RHI. Overall, 22 pa-

Table 2. Correlation between Clinical, Endoscopic, and Histologic Assessments (n = 347)

Variable	Partial Mayo Score	Mayo Endoscopic Score	Total Mayo Score	Geboes Score	Continuous Geboes Score	Nancy Index	Robarts Histopathology Index
Partial Mayo Score	1.00	0.46	0.93	0.29	0.31	0.34	0.29
Mayo Endoscopic Score	0.46	1.00	0.73	0.40	0.43	0.43	0.42
Total Mayo Score	0.93	0.73	1.00	0.36	0.39	0.42	0.37
Geboes Score	0.29	0.40	0.36	1.00	0.77	0.80	0.90
Continuous Geboes Score	0.31	0.43	0.39	0.77	1.00	0.76	0.92
Nancy Index	0.34	0.43	0.42	0.80	0.76	1.00	0.77
Robarts Histopathology Index	0.29	0.42	0.37	0.90	0.92	0.77	1.00

The values depicted are Spearman's correlation coefficient (ρ). All the values are significant at $P < 0.001$.

Table 3. Performance of Histologic Indices in the Assessment of the Other Histologic Indices

Variable	Sensitivity	Specificity	PPV	NPV	Accuracy	Kappa	SE
NI (< 1)							
GS (≤ 2)	100 (92–100)	92 (89–95)	68 (58–76)	100 (98–100)	93 (90–96)	0.77	0.05
Continuous GS (≤ 6)	100 (92–100)	87 (83–91)	56 (48–63)	100 (98–100)	89 (85–92)	0.66	0.05
RHI (≤ 3)	100 (92–100)	95 (91–97)	75 (65–83)	100 (98–100)	95 (92–97)	0.84	0.04
GS (≤ 2)							
NI (< 1)	68 (55–78)	100 (98–100)	100 (92–100)	93 (90–95)	93 (91–95)	0.78	0.05
Continuous GS (≤ 6)	94 (86–99)	93 (90–96)	77(69–84)	98 (96–100)	93 (90–96)	0.81	0.04
RHI (≤ 3)	90 (80–95)	100 (98–100)	100 (94–100)	97 (95–99)	98 (96–99)	0.93	0.03
RHI (≤ 3)							
GS (≤ 2)	100 (94–100)	97 (95–99)	89 (80–95)	100 (98–100)	98 (95–99)	0.93	0.03
Continuous GS (≤ 6)	98 (91–100)	92 (88–94)	72 (64–79)	99 (97–100)	93 (89–95)	0.79	0.04
NI (< 1)	75 (63–85)	100 (98–100)	100 (92–100)	95 (92–96)	95 (93–97)	0.84	0.04
Continuous GS (≤ 6)							
RHI (≤ 3)	72 (61–82)	99 (97–100)	98 (89–100)	91 (88–94)	93 (89–96)	0.79	0.04
GS (≤ 2)	77 (67–86)	98 (96–99)	94 (85–97)	93 (90–95)	93 (90–96)	0.81	0.04
NI (< 1)	55 (44–67)	100 (98–100)	100 (92–100)	87 (84–90)	89 (85–93)	0.66	0.05

Values are presented as % (95% confidence interval).
PPV, positive predictive value; NPV, negative predictive value; SE, standard error; NI, Nancy Index; GS, Geboes Score; RHI, Robarts Histopathology Index.

tients (6.34%) were categorized as being in histologic remission, regardless of the histologic index used.

4. Comparative Performances of Histologic Indices

The histologic disease activity was compared across different histologic indices. Using the cutoff of zero for NI to define remission, the RHI, GS, and continuous GS identified all patients in remission, whereas 95%, 92%, and 87% of patients were classified as active disease, respectively. However, on comparing NI and RHI, NI detected 75% of patients who qualified to be in remission according to RHI whereas RHI identified all patients who were in remission as defined by NI. NI could nevertheless recognize all patients with active disease on RHI. With GS ≤2 as a remission reference, 68% and 90% of patients were classified as such by NI and RHI, respectively. Additionally, all patients who exhibited histologic activity as determined by the GS were similarly categorized as such by the NI and RHI (Table 3).

The NI exhibited a sensitivity of 55% and 61% to discern patients in clinical and endoscopic remission, respectively. Using

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Table 4. Accuracy between Histologic Indices and Clinical and Endoscopic Outcomes

Variable	Sensitivity	Specificity	PPV	NPV	Accuracy	Kappa	SE
Performance of histologic indices in relation to the clinical and endoscopic outcomes							
NI (< 1)							
Partial Mayo Score ≤ 1	55 (40–69)	83 (79–88)	34 (27–43)	92 (89–94)	79 (75–84)	0.31	0.06
Mayo Endoscopic Score 0	61 (46–75)	82 (77–86)	35 (28–43)	93 (90–95)	79 (74–83)	0.33	0.06
RHI (≤ 3)							
Partial Mayo Score ≤ 1	53 (40–66)	85 (80–89)	44 (35–53)	89 (86–91)	79 (74–83)	0.35	0.06
Mayo Endoscopic Score 0	53 (40–66)	82 (78–87)	40 (32–49)	89 (86–91)	77 (72–82)	0.32	0.06
GS (≤ 2)							
Partial Mayo Score ≤ 1	49 (37–62)	85 (80–89)	45 (36–55)	87 (84–90)	78 (73–83)	0.33	0.06
Mayo Endoscopic Score 0	53 (41–66)	83 (78–88)	45 (36–54)	87 (84–91)	77 (73–82)	0.35	0.06
Continuous GS (≤ 6)							
Partial Mayo Score ≤ 1	50 (38–61)	87 (82–91)	56 (46–65)	84 (81–87)	78 (73–83)	0.39	0.06
Mayo Endoscopic Score 0	51 (40–62)	85 (80–89)	52 (43–61)	84 (81–87)	77 (72–81)	0.37	0.06
Performance of endoscopic outcomes in relation to clinical and histologic outcomes							
Mayo Endoscopic Score 0							
Partial Mayo Score ≤ 1	40 (29–51)	84 (79–88)	44 (34–53)	82 (79–84)	73 (68–78)	0.25	0.06
NI (< 1)	35 (25–46)	93 (89–96)	61 (48–73)	82 (79–84)	79 (75–84)	0.33	0.06
RHI (≤ 3)	40 (29–51)	89 (84–92)	53 (42–63)	82 (80–85)	77 (72–81)	0.32	0.06
GS (≤ 2)	45 (34–56)	87 (83–91)	53 (43–63)	83 (80–86)	77 (73–82)	0.35	0.06
Continuous GS (≤ 6)	52 (41–63)	84 (79–88)	51 (42–59)	85 (82–88)	76 (72–81)	0.37	0.06

Values are presented as % (95% confidence interval).
PPV, positive predictive value; NPV, negative predictive value; SE, standard error; NI, Nancy Index; RHI, Robarts Histopathology Index; GS, Geboes Score.

RHI ≤3, 53% of patients each in clinical and endoscopic remission were classified accurately. Among patients in endoscopic remission, 35% showed histologic remission based on NI, 40% based on RHI, 45% based on GS, and 52% based on continuous GS. On the other hand, among patients with endoscopic activity, 93% had histologic activity according to NI, 89% according to RHI, 87% according to GS, and 84% according to continuous GS (Table 4).

5. Correlation between FC and Clinical, Endoscopic and Histologic Indices

A correlation analysis was used to determine the relationship between FC levels and the clinical, endoscopic and the histologic status of the patients. The FC had fair correlations with PMS ($\rho = 0.36$, $P < 0.001$), MES ($\rho = 0.48$, $P < 0.001$) and total Mayo Score ($\rho = 0.46$, $P < 0.001$). There was also a fair correlation between FC and GS ($\rho = 0.46$, $P < 0.001$), continuous GS ($\rho = 0.49$, $P < 0.001$), NI ($\rho = 0.56$, $P < 0.001$) and RHI ($\rho = 0.49$, $P < 0.001$) (Fig. 1). The strength of these correlations were independent of the disease extent (Supplementary Table 2, Supplementary Figs. 1-6).

The median FC values were lower in patients in clinical and endoscopic remission. Increasing endoscopic activity corresponded to a rise in FC levels (Fig. 2). Similarly, the patients in histologic remission had lower median FC values compared to those with histologic activity (median FC (μg/g): 25 [25–28.5] vs. 461 [198–1,678] for GS, 25 [25–78.75] vs. 476 [211–1,764] for continuous GS, 25 [25–25] vs. 422 [166.25–1,620] for NI, and 25 [25–25] vs. 456 [180.50–1,663] for RHI, $P < 0.001$ for all the indices) (Fig. 3).

Four cutoff values were evaluated for association of FC and clinical, endoscopic and histologic outcomes. The performance of FC in relation to assessment of clinical and endoscopic remission remained consistent irrespective of the cutoff values used. However, more stringent cutoffs (< 100 μg/g) increased the sensitivity of FC in identifying patients in histologic remission across all the histologic indices. The specificity of FC, which pertains to identifying histologic activity, remained consistent regardless of the cutoff values utilized, for all histologic indices (Table 5).

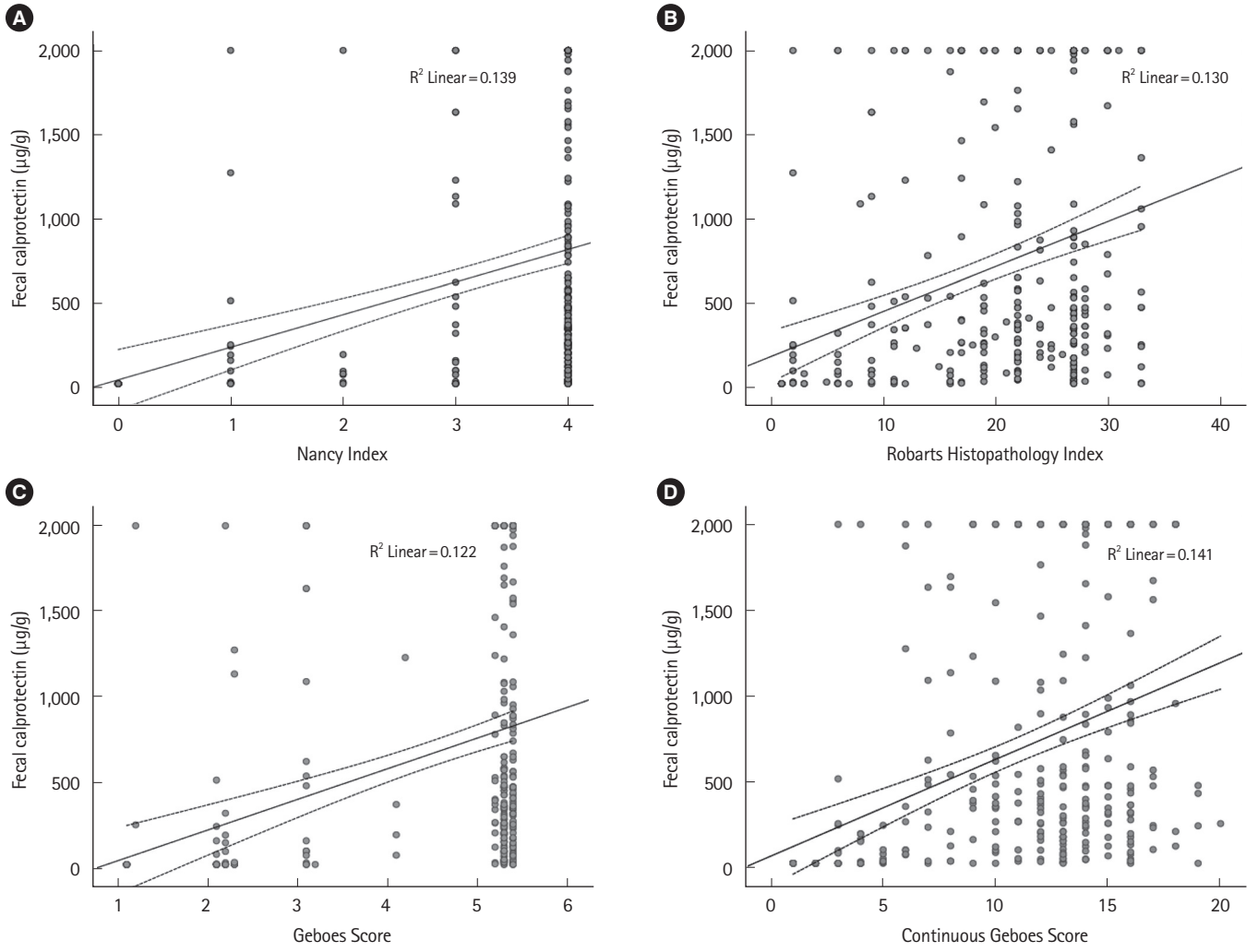

Fig. 1. Correlation plots for fecal calprotectin and different histologic indices. (A) Nancy Index. (B) Robarts Histopathology Index. (C) Geboes Score. (D) Continuous Geboes Score.

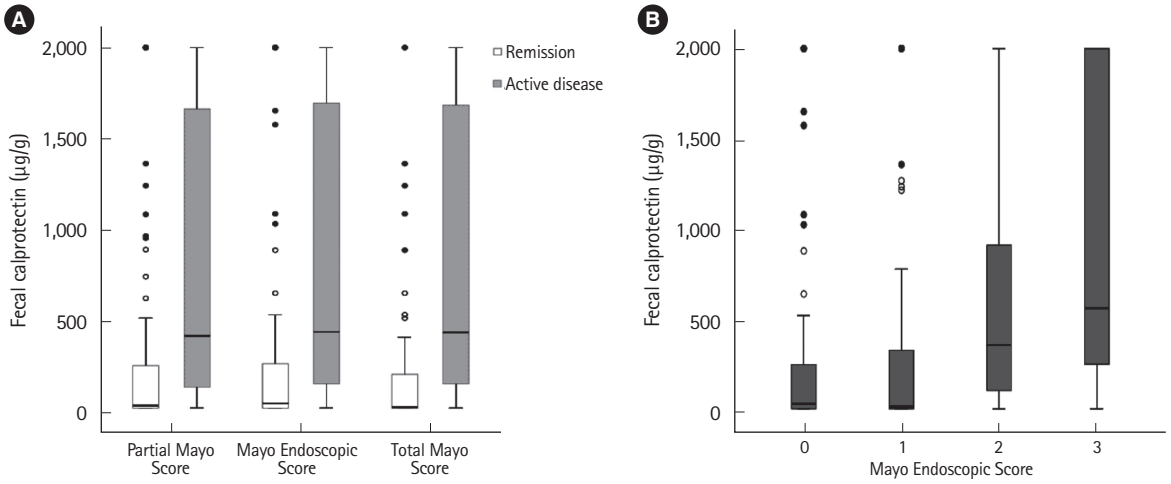

Fig. 2. Fecal calprotectin stratified according to the (A) clinical and endoscopic disease activity and (B) Mayo Endoscopic Score.

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Table 5. Performance of Different Cutoffs of FC in Assessment of Clinical, Endoscopic and Histologic Indices

Variable	Sensitivity	Specificity	PPV	NPV	Accuracy	Kappa	SE
FC (≤ 100 μg/g)							
Partial Mayo Score ≤ 1	43 (33–53)	87 (82–91)	57 (47–66)	79 (76–82)	74 (69–79)	0.33	0.06
Mayo Endoscopic Score 0	48 (38–58)	86 (81–90)	58 (49–67)	80 (77–83)	75 (70–80)	0.37	0.06
NI < 1	47 (37–57)	100 (98–100)	100 (92–100)	82 (79–85)	85 (80–88)	0.55	0.05
RHI ≤ 3	54 (44–64)	96 (93–98)	87 (77–93)	84 (81–86)	84 (80–88)	0.58	0.05
GS ≤ 2	57 (47–67)	95 (91–97)	82 (72–89)	84 (81–87)	84 (80–88)	0.58	0.05
Continuous GS ≤ 6	66 (56–75)	92 (88–95)	78 (69–85)	87 (84–90)	85 (81–88)	0.62	0.04
FC (≤ 150 μg/g)							
Partial Mayo Score ≤ 1	40 (31–49)	87 (82–91)	61 (51–70)	74 (71–77)	71 (66–76)	0.30	0.05
Mayo Endoscopic Score 0	43 (34–53)	86 (81–90)	69 (51–70)	75 (72–78)	72 (67–76)	0.32	0.05
NI < 1	40 (31–50)	100 (98–100)	100 (92–100)	77 (74–80)	80 (75–84)	0.48	0.05
RHI ≤ 3	47 (38–57)	97 (93–99)	88 (78–94)	79 (75–81)	80 (76–84)	0.51	0.05
GS ≤ 2	50 (40–60)	95 (91–97)	84 (74–90)	79 (76–82)	80 (75–84)	0.51	0.05
Continuous GS ≤ 6	60 (50–69)	93 (89–96)	82 (73–88)	82 (79–85)	82 (78–86)	0.57	0.05
FC (≤ 200 μg/g)							
Partial Mayo Score ≤ 1	37 (29–46)	87 (82–92)	65 (55–74)	69 (66–72)	68 (63–73)	0.27	0.05
Mayo Endoscopic Score 0	40 (32–49)	86 (81–91)	64 (55–73)	70 (67–73)	69 (64–74)	0.29	0.05
NI < 1	35 (27–44)	100 (98–100)	100 (92–100)	72 (69–74)	75 (70–80)	0.41	0.05
RHI ≤ 3	43 (34–52)	97 (94–99)	91 (82–96)	74 (71–76)	77 (72–81)	0.46	0.05
GS ≤ 2	46 (37–55)	96 (92–98)	88 (79–94)	74 (71–77)	77 (72–82)	0.47	0.05
Continuous GS ≤ 6	55 (46–64)	94 (91–97)	86 (78–92)	77 (74–81)	80 (75–84)	0.54	0.05
FC (≤ 250 μg/g)							
Partial Mayo Score ≤ 1	38 (30–46)	90 (85–94)	74 (64–82)	66 (63–69)	68 (63–73)	0.31	0.05
Mayo Endoscopic Score 0	40 (32–48)	88 (83–92)	71 (62–79)	66 (63–69)	68 (62–73)	0.30	0.05
NI < 1	32 (24–40)	100 (98–100)	100 (92–100)	66 (64–69)	71 (66–76)	0.35	0.04
RHI ≤ 3	39 (31–48)	98 (95–99)	93 (84–97)	68 (65–71)	73 (68–77)	0.41	0.04
GS ≤ 2	42 (34–50)	96 (92–98)	89 (80–95)	69 (66–72)	73 (68–78)	0.42	0.05
Continuous GS ≤ 6	51 (42–59)	95 (91–98)	89 (81–94)	72 (69–76)	76 (71–81)	0.49	0.05

Values are presented as % (95% confidence interval).
PPV, positive predictive value; NPV, negative predictive value; SE, standard error; FC, fecal calprotectin; NI, Nancy Index; RHI, Robarts Histopathology Index; GS, Geboes Score.

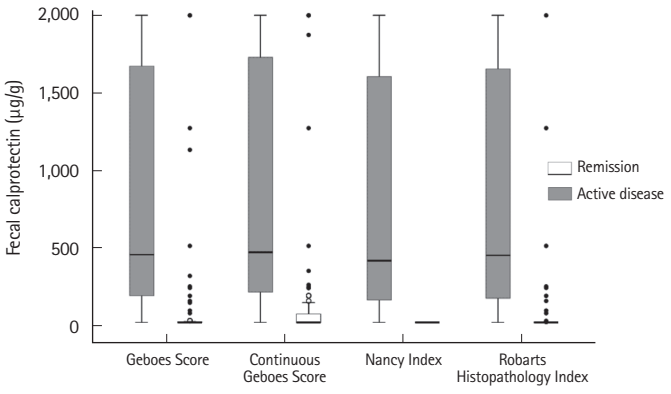

Fig. 3. The fecal calprotectin values stratified according to the histologic disease activity using different histologic indices.

The FC values were also analyzed in relation to specific histologic features. The FC levels associated with the presence of chronic inflammatory infiltrate, even when patients with neutrophilic infiltrate and erosions/ulcers were excluded. The FC levels were also higher in the presence of neutrophils in either lamina propria or epithelium, compared to those where neutrophils were absent (Fig. 4).

We also plotted the ROC curves and AUC to evaluate the predictability of FC regarding the clinical, endoscopic and histologic outcomes. The ROC curve had high AUC in the assessment of histologic activity irrespective of the index used (AUC: 0.90 [0.85–0.95] for GS, 0.89 [0.84–0.95] for continuous GS, 0.98 [0.96–0.99] for NI, and 0.92 [0.88–0.96] for RHI). For as-

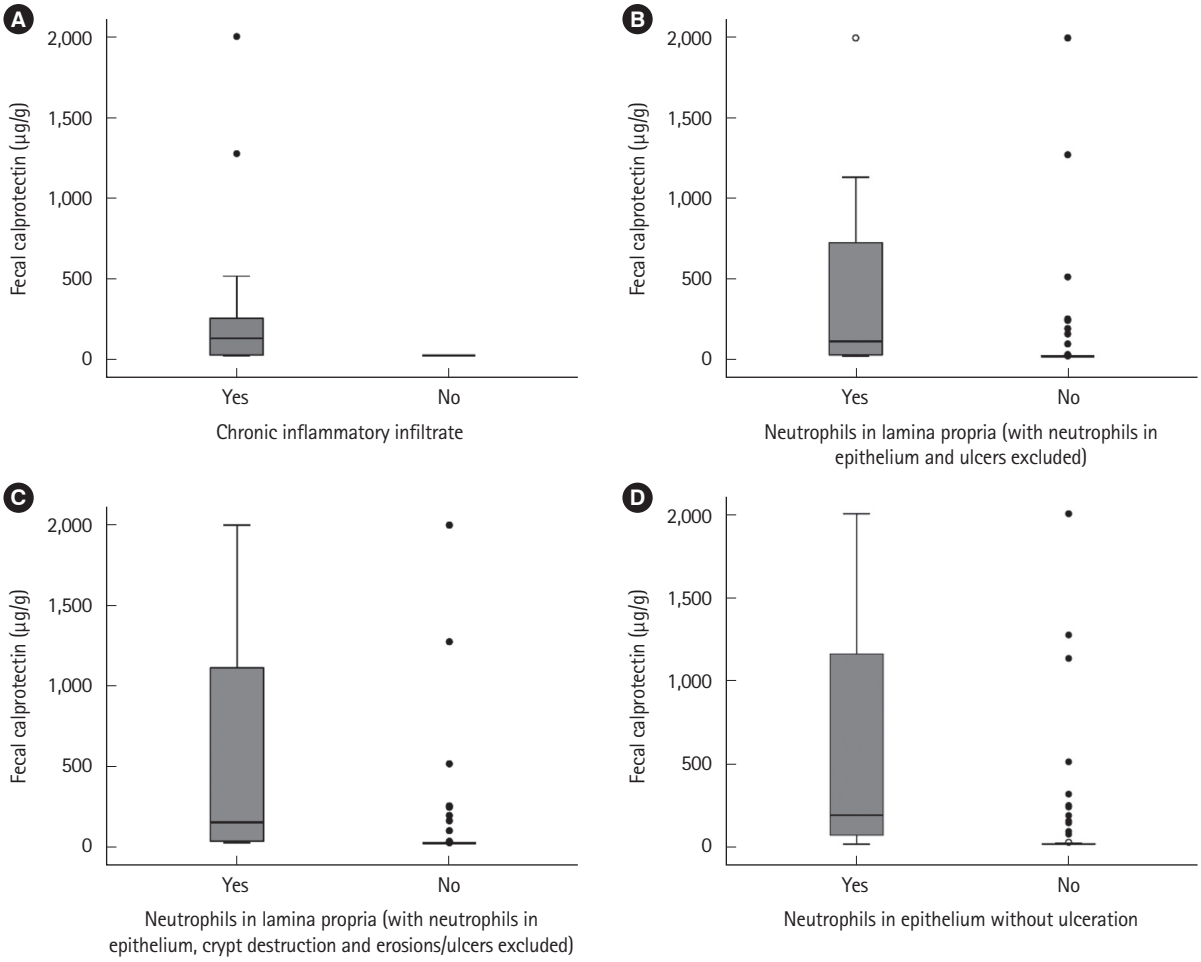

Fig. 4. Fecal calprotectin values stratified according to (A) presence of chronic inflammatory infiltrate (neutrophils in lamina propria, neutrophils in epithelium and erosions or ulcers, excluded) (B) neutrophils in lamina propria (with neutrophils in epithelium and ulcers excluded) (C) neutrophils in lamina propria (with neutrophils in epithelium, crypt destruction and erosions/ulcers excluded), and (D) neutrophils in epithelium without ulceration.

sessment of association between FC and Mayo Score, the AUC was 0.74 (0.68–80.00) for MES and 0.79 (0.73–0.85) for total Mayo Score (Fig. 5).

DISCUSSION

The therapeutic targets of UC have evolved over time from control of symptoms to mucosal healing. Disease assessment in UC involves sequential assessment of clinical symptoms, inflammatory biomarkers, endoscopic and histologic features. Achievement of normalization at each of these steps indicates the depth of remission. However, this does not occur concurrently, and discrepancies exist between clinical, biochemical, endoscopic, and histologic parameters.[16,17,21,22] We performed a comparative analysis between the different parameters used to assess disease activity and also collated the performance of GS, continuous GS, NI, and RHI in relation to each other.

The majority of the patients enrolled in the current study had active disease. There were fair to moderate correlations between clinical, biochemical, and endoscopic disease activity scores. The concordance between different histologic indices was high. Though each histologic index demonstrated acceptable measurement properties, RHI performed better than NI in identifying patients in histologic remission. The differences in these histologic indices can be attributed to the different parameters being assessed and the depth of mucosa (epithelium or lamina propria) at which the histologic activity is being assessed.

In accordance with previous literature, a proportion of patients in endoscopic remission demonstrated histologic activity.[9,23-26] Interestingly however, nearly 7% to 15% of the patients with evidence of endoscopic activity had histologic remission.

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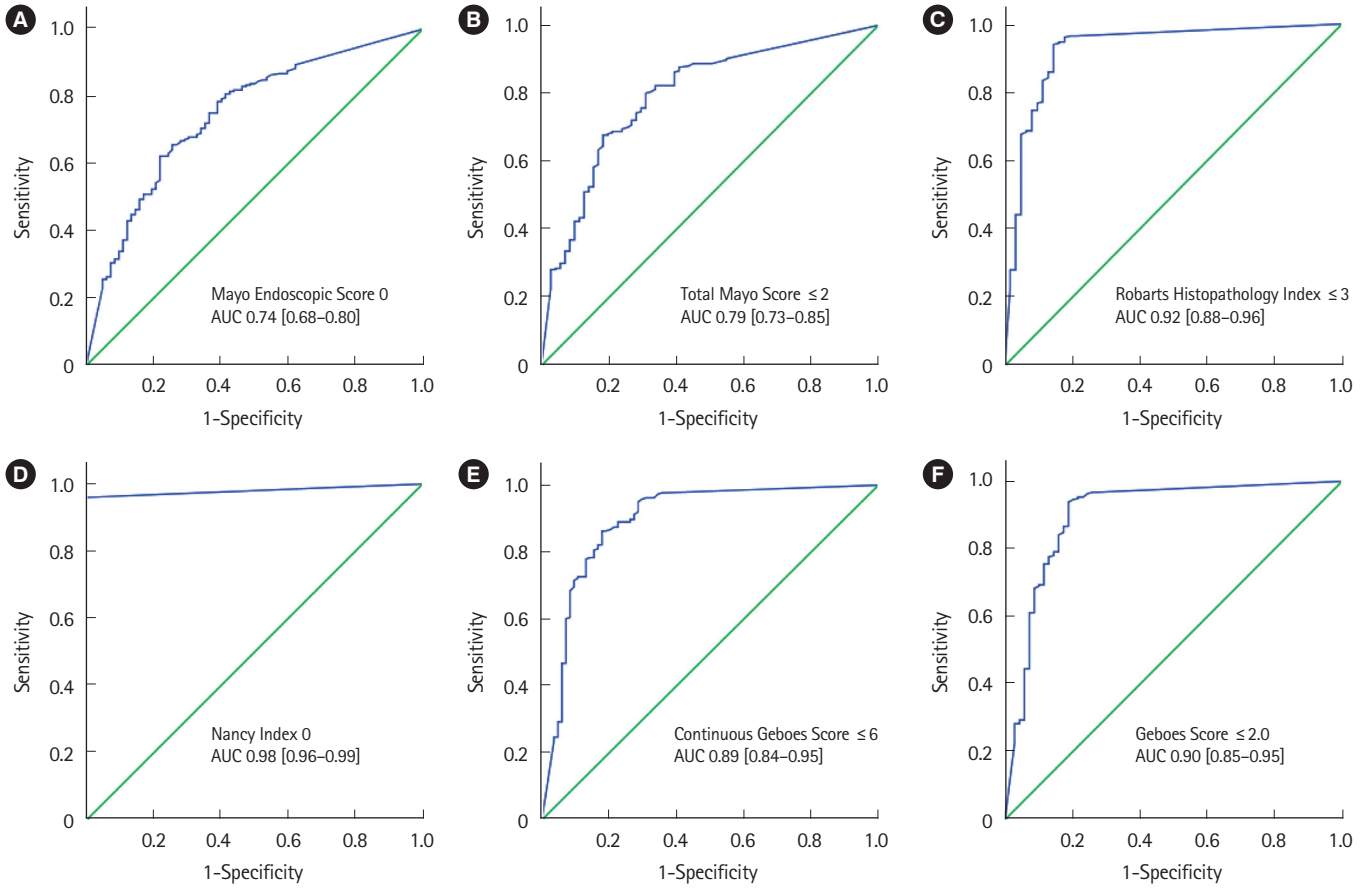

Fig. 5. The receiver operating characteristics curves for fecal calprotectin and its predictive value for clinical, endoscopic and Histologic outcomes. (A) Mayo Endoscopic Score. (B) Total Mayo Score. (C) Robarts Histopathology Index. (D) Nancy Index. (E) Continuous Geboes Score. (F) Geboes Score. AUC, area under the curve.

This is an intriguing observation indicating achievement of histologic remission before endoscopic remission. Mucosal healing in UC involves intrinsic molecular pathways in epithelial cells as well as interactions between epithelial cells and other cells in lamina propria.[27] We hypothesize that the intestinal wound healing pre-dates the endoscopic mucosal healing. The observation that histologic activity may be present in patients in endoscopic remission implies that histologic injury precedes observable endoscopic changes. Recovery of the disease is also likely to follow the same sequence.[28,29] We therefore propose that just as histologic healing is a reflection of the normalization of aberrant immune responses (though a differential gene expression may persist), endoscopic findings mirror the histologic activity and not vice versa. This however needs larger prospective studies for confirmation and validation.

The FC values had fair correlations with clinical, endoscopic, and histologic scores and were able to predict remission with good accuracy. A lower cutoff for FC (less than 100 μg/g) had >80% accuracy in identifying patients who were in histologic remission, regardless of the histologic indices used.[30] The FC values also had a better correlation with histologic indices suggesting a closer association between the two, compared to clinical and endoscopic disease activity parameters. A positive association between presence of acute inflammatory infiltrate on histology and high FC levels was also demonstrated. However, in contrast to previous reports, FC also demonstrated a positive association with chronic inflammatory infiltrate despite the absence of neutrophils, suggesting that FC can identify even lower grades of histologic activity.[13] These findings suggest that FC is a better surrogate marker for histologic activity than endoscopic healing.

The study presents a comprehensive analysis of disease characteristics and assessment methods in UC. The strengths of the study include a large cohort size providing robust data for analysis, and the focus on evaluating the disease activity indices in patients with active disease, a crucial area that often

remains underexplored. The similar performance of the histologic indices in both patients in remission and active disease underscores the reliability and validity of these indices across the spectrum of the disease. Additionally, we used stringent criteria to define both endoscopic (MES 0) and histologic remission (cutoffs for NI and RHI were 0 and ≤3, respectively). These cutoffs mandate the absence of neutrophils from the mucosa to depict histologic remission.[19] Despite these strict cutoffs, we could demonstrate the predictive value of FC in identifying histologic remission. This gives the confidence with which one can spare a patient from an endoscopic examination based solely on the noninvasive and cheaper FC test. However, the study's single-center design restricts the generalizability of findings to broader populations, and its cross-sectional nature precludes longitudinal follow-up, limiting the ability to assess the disease progression over time. Moreover, the expertise required by pathologists and endoscopists to apply these indices may hinder their widespread applicability in general clinical practice. Additionally, topical therapy may reduce inflammation or achieve endoscopic remission in the distal colon, while disease activity persists in the more proximal segments. Since only a sigmoidoscopy was performed in this study, this approach may have under-reported disease activity in the proximal colonic segments.

In summary, our study revealed fair correlations across various domains of disease assessment, including clinical, biochemical, endoscopic, and histologic indices. We found strong agreement between the GS, continuous GS, NI, and RHI. Additionally, FC levels below 150 μg/g showed >70% accuracy in predicting endoscopic remission. Specifically, FC levels below 150 μg/g demonstrated 80% or higher accuracy, and levels below 100 μg/g showed 85% accuracy in predicting histologic remission, regardless of the scoring index used. This information could help stratify patients' need for colonoscopy to assess both endoscopic and histologic remission. Our findings highlight the potential of both FC and histologic indices, when implemented in a standardized manner, to provide valuable insights into disease activity. This standardized approach holds promise in informing therapeutic decisions, thereby enhancing clinical management strategies.

ADDITIONAL INFORMATION

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Conflict of Interest

Sood A is on the advisory board of Janssen Pharmaceuticals (Asia-Pacific) and received honorarium for speaker events from Pfizer India and Takeda India. Sood A is an editorial board member of the journal but was not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflicts of interest relevant to this article were reported.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

Author Contributions

Conceptualization: Singh A (1st author), Midha V, Sood A. Data curation: Singh A (1st), Bhardwaj A, Kahlon BK, Dhaliwal AS, Sharma R, Singh D, Jain D, Kaur S, Singh A (12th author), Narang V, Kaur H. Formal analysis: Sood A (1st), Bansal N, Sharma R. Investigation: Sood A, Singh A, Midha V. Methodology: Singh A (1st), Midha V, Sood A. Project administration: Sood A, Midha V, Singh A (1st). Resources: Singh A, Midha V, Sood A. Supervision: Sood A, Midha V. Validation: Bhardwaj A, Sood A, Midha V. Visualization: Bhardwaj A, Sharma R, Singh A, Midha V, Sood A. Writing - original draft: Singh A (1st), Bhardwaj A, Sharma R, Sood A. Writing - review & editing: Singh A (1st), Bhardwaj A, Mahajan R, Kaur K, Midha V, Sood A. Approval of final manuscript: all authors.

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Supplementary Material

Supplementary materials are available at the Intestinal Research website (https://www.irjournal.org).

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