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ORIGINAL RESEARCH

Hemoglobin-to-Inflammation Marker Ratios Reflect Endoscopic Activity in Inflammatory Bowel Disease

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Aim: To investigate the diagnostic value of hemoglobin-to-inflammation marker ratios (Hb/WBC, Hb/Neu, Hb/PLT, Hb/CRP) in assessing endoscopic activity in inflammatory bowel disease (IBD), including ulcerative colitis (UC) and Crohn's disease (CD).

Methods: A single-center retrospective cross-sectional study was conducted. We screened patients diagnosed with UC or CD between January 2017 and July 2025. Patients were excluded if they had coexisting severe gastrointestinal/infectious diseases potentially affecting endoscopic or laboratory results, iron supplements intake, incomplete data, or a significant time discrepancy (>3 days) between endoscopy and laboratory testing. Ultimately, 270 IBD patients (175 UC, 95 CD) were included for the primary cross-sectional analysis. Clinical data, laboratory indicators, and endoscopic scores (Mayo Endoscopic Score, Ulcerative Colitis Endoscopic Index of Severity [UCEIS], Simplified Endoscopic Score for Crohn's Disease [SES-CD]) were collected. Receiver operating characteristic (ROC) curve analysis, correlation analysis, multivariate logistic regression, and sensitivity analyses were employed.

Results: The Hb/CRP ratio demonstrated the best performance in distinguishing endoscopic active phase from remission phase in IBD. In UC patients based on the Mayo Endoscopic Score, the area under the curve (AUC) of Hb/CRP was 0.924 (95% CI: 0.884–0.964); based on the UCEIS score, the AUC was 0.890 (95% CI: 0.842–0.938); in CD patients based on the SES-CD score, the AUC was 0.839 (95% CI: 0.749–0.929). Hb/CRP significantly outperformed hemoglobin alone across all subgroups (all $P<0.01$), while showing comparable diagnostic accuracy to CRP alone. It also served as an independent protective factor for disease remission phase in multivariate analysis (odds ratio [OR] range = 1.007 to 1.014, all $P<0.01$). Sensitivity analyses stratified by anemia status confirmed the robustness of Hb/CRP, particularly in UC patients. However, the absence of fecal calprotectin (FC) data is a key limitation of the study.

Conclusion: Hemoglobin-to-inflammation ratios, particularly Hb/CRP, show promising diagnostic performance for assessing endoscopic activity in IBD in this retrospective study. They may serve as non-invasive adjunctive tools for clinical disease activity monitoring, though their comparative value against established biomarkers like FC warrants further prospective validation.

Keywords: inflammatory bowel disease, hemoglobin, C-reactive protein, endoscopic activity, diagnosis

Introduction

Inflammatory bowel disease (IBD) is a chronic, relapsing intestinal inflammatory disorder characterized by immune dysregulation. It primarily comprises Ulcerative colitis (UC) and Crohn's disease (CD).[1] In recent years, studies have identified multiple methods to evaluate IBD activity, including endoscopic scoring and biomarker detection.[2–6] For UC, three common endoscopic scoring systems are primarily used: UCCIS, UCEIS, and the Mayo.[7] For Crohn's disease, The Simplified Endoscopic Score for Crohn's Disease (SES-CD), serving as a simplified version of Crohn's Disease Endoscopic Index of Severity (CDEIS), maintains high correlation while offering superior operability and reproducibility.[4,8] Although endoscopic scoring shows significant diagnostic value in assessing IBD activity, it requires

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an invasive colonoscopy procedure. Previous studies have identified multiple biomarkers that demonstrate strong discriminatory value for IBD activity.[9,10] However, these indicators are often influenced by factors such as infection. Therefore, there is a clinically urgent need for non-invasive serological markers that can reliably reflect endoscopic activity and assist in differentiating between infection and intrinsic disease activity.

Fecal calprotectin (FC) has been established as the current non-invasive gold standard for evaluating mucosal healing in IBD,[11] However, the inability of many hospitals to conduct this test limits its application. Its limitations in terms of convenience, rapid availability, and cost also constrain its utility for frequent and rapid clinical application.[12] Therefore, there remains a clinical need to explore more readily accessible, rapidly reportable, and cost-effective biomarkers to aid in the assessment of endoscopic activity in IBD. C-reactive protein (CRP) is a commonly used systemic inflammatory marker in inflammatory bowel disease. However, a significant proportion of patients with active mucosal inflammation, particularly those with disease confined to the mucosal layer or the distal colon, may exhibit normal or only mildly elevated CRP levels. Therefore, CRP alone cannot consistently reflect endoscopic activity. Notably, ratios such as CRP-to-hemoglobin ratio (CRP/Hb) and CRP/Albumin have demonstrated value in stratifying disease severity and predicting outcomes in conditions like sepsis and neurocritical care within emergency medicine and critical care settings.[13–15] This suggests that combining markers reflective of anemia with those indicative of acute-phase inflammation may provide more comprehensive pathophysiological information than either marker alone. However, the diagnostic performance of similar ratios for assessing endoscopic activity in IBD remains insufficiently explored.

Based on this rationale, our retrospective analysis investigates the diagnostic efficacy of several ratios: hemoglobin-to-white blood cell ratio (Hb/WBC), hemoglobin-to-neutrophil ratio (Hb/Neu), hemoglobin-to-platelet ratio (Hb/PLT), and hemoglobin-to-C-reactive protein ratio (Hb/CRP). These ratios are used to assess endoscopic activity in IBD, including UC and CD. The research analyzed correlations between these ratios and established endoscopic scoring systems. Moreover, it further evaluated their capability in distinguishing UC and CD patients with varying endoscopic activity levels. In addition, after adjusting for confounding factors, this study examined whether these ratios remained independent predictors of endoscopic activity. All in all, this is a hypothesis-generating, associative analysis aimed at evaluating the combined predictive value of these common tests, not at defining a new unified biological pathway.

Methods

Study Design and Patient Selection

This retrospective study investigated the clinical value of individual indicators (Hb, WBC, Neu, PLT, CRP) and ratio indicators (Hb/WBC, Hb/Neu, Hb/PLT, Hb/CRP) in assessing endoscopic activity of IBD. We enrolled patients diagnosed with UC or CD between January 2017 and July 2025. Inclusion criteria: (1) Endoscopic reports or clinical diagnosis of UC/CD; (2) Complete endoscopic documentation with clear images and definitive reports; (3) Complete laboratory results obtained within 3 days before or after endoscopy. Exclusion criteria: (1) Coexisting severe gastrointestinal/infectious diseases potentially affecting endoscopic scores or laboratory results; (2) Incomplete endoscopic or laboratory data, or significant time discrepancy (>3 days) between endoscopy and laboratory testing. (3) Patients who received blood transfusions or intravenous iron therapy within the 7 days prior to their blood draw were excluded from the analysis. After applying the exclusion criteria, 13 patients were excluded due to incomplete data, 89 due to a time interval >3 days between endoscopy and laboratory testing, and 2 due to receipt of blood transfusion or intravenous iron therapy within 7 days prior to blood draw. The study included 270 IBD patients (175 UC, 95 CD) for two independent statistical analyses. A flowchart illustrating the screening and enrollment process is presented in Figure 1.

Data Collection and Endoscopic Scoring

Patient data including gender, age, and disease classification were collected. Laboratory results (including Hb, WBC, Neu, PLT, CRP) and endoscopic findings were also recorded. Different scoring systems were employed depending on disease type. For UC patients, the Mayo endoscopic scores and UCEIS score was used. Mayo endoscopic scores of 0–1 were classified as the remission phase, while scores of 2–3 indicated the active phase.[2,16] For UCEIS, a total score of 0–1 denoted remission phase, while scores ≥2 denoted active phase. For endoscopic activity stratification: 0 points denoted

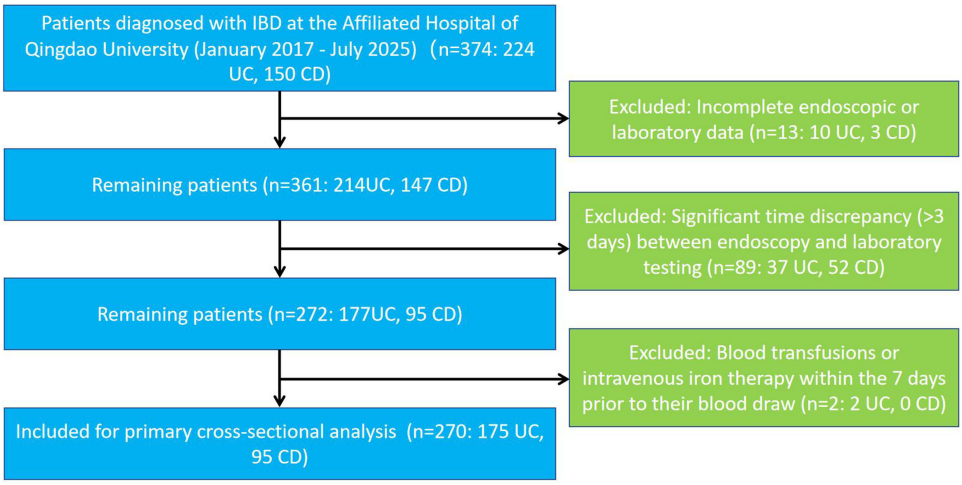

Figure 1 Flow diagram of inclusion and exclusion.

inactive disease, 1–3 points indicated mild activity, 4–6 points signified moderate activity, and 7–8 points represented severe activity.[3,16] CD patients were assessed using the SES-CD score across intestinal segments: terminal ileum, right colon, transverse colon, left colon (including sigmoid), and rectum. Scores 0–2 corresponded to remission phase, 3–6 indicated mild activity, 7–15 signified moderate activity, and scores ≥16 denoted severe activity.[4,17] All endoscopic images and videos were retrospectively and independently reviewed by two expert endoscopists who were blinded to the patients' laboratory results (including CRP and Hb levels) and final clinical diagnoses. Any discrepancies were resolved by consensus. Detailed scoring criteria are available in Supplementary Tables 1–3.

Data Analysis

ROC Curve Analysis and Optimal Cut-off Value Determination

Receiver operating characteristic (ROC) curves were plotted for each ratio (Hb/WBC, Hb/Neu, Hb/PLT, Hb/CRP) and individual parameter (Hb, WBC, Neu, PLT, CRP) to assess their diagnostic efficacy in distinguishing between the active phase and remission phase. The area under the curve (AUC) was calculated, and DeLong's test was employed to compare AUC differences between the ratios and individual parameters. The optimal cut-off values for each ratio were determined based on the Youden index. AUC values were reported with 95% confidence intervals (CIs). Subsequently, the corresponding sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (LR+), negative likelihood ratio (LR-), and accuracy rate were calculated for each optimal cut-off.

Correlation Analysis

Spearman's rank correlation coefficients were calculated between each ratio, individual indicators, and endoscopic scores including the Mayo endoscopic score, UCEIS, and SES-CD.

Discrimination of Endoscopic Activity Levels

Differences in ratios across endoscopic activity groups (remission, mild, moderate, severe) were compared using the Kruskal–Wallis *H*-test.

Multivariate Logistic Regression Analysis

To evaluate whether hemoglobin-to-inflammation ratios were independently associated with endoscopic activity, separate multivariable logistic regression models were constructed for each ratio (Hb/WBC, Hb/Neu, Hb/PLT, and Hb/CRP). Due to high collinearity among these ratios (all derived from hemoglobin), they were not included simultaneously in a single model. Each model was adjusted for potential confounders, including age, sex, disease type, and anemia status. The dependent variable was endoscopic activity. Results were reported as odds ratios (ORs) with 95% confidence intervals (CIs).

Sensitivity Analyses

To assess the robustness of our findings and address potential confounding, the following sensitivity analyses were performed:

Stratification by anemia severity: Based on baseline hemoglobin levels, patients were classified into two strata: no anemia (hemoglobin ≥130 g/L in males, ≥120 g/L in females) and anemia (hemoglobin <130 g/L in males, <120 g/L in females). The AUC of each ratio was calculated for each stratum to assess whether diagnostic performance varied across different hemoglobin levels.

Statistical Software

Data analysis was performed using SPSS (version 27.0).

Ethical Statement

This retrospective observational study was conducted in full compliance with the ethical principles outlined in the Declaration of Helsinki. The study protocol was reviewed and approved by the Ethics Committee of The Affiliated Hospital of Qingdao University (Approval No.: QYFY WZLL 30516).

Written informed consent was obtained from all individual participants included in the study prior to data collection. The consent covered the use of clinical data, laboratory results, and endoscopic findings for research purposes, as well as the publication of anonymized data. To ensure patient privacy and data confidentiality, all patient identifiers were removed prior to data analysis. Data were anonymized and accessed only by authorized research personnel for the purposes outlined in this study. All analyses were performed on this de-identified dataset. The consent process and timeline are documented, and de-identified copies of the consent form template and representative signed examples have been provided to the editors/reviewers for verification.

Results

Baseline Characteristics

A total of 270 IBD patients were enrolled, including 175 UC cases and 95 CD cases. Baseline data are shown in Table 1. Regarding disease classification, extensive colitis (E3) was the most prevalent subtype among UC patients (114 cases, 65.1%), while among CD patients, the three lesion locations had similar case numbers, with inflammatory behavior (B1, 61 cases, 64.2%) predominating. In laboratory indicators, the UC group and CD group exhibited similar median levels of Hb, WBC, Neu, and PLT; however, the CD group demonstrated higher median CRP levels (4.1 mg/L vs 2.5 mg/L). Further analysis of ratio indicators revealed no significant differences in Hb/WBC, Hb/Neu, or Hb/PLT ratios between groups. However, the Hb/CRP ratio was significantly higher in the UC group than in the CD group (49.3 vs 29.7). Endoscopic activity revealed that in the UC group, 99 patients were in the active phase and 76 in the remission phase according to the Mayo Endoscopic Score; based on the UCEIS score, 108 patients were in the active phase and 67 in the remission phase; in the CD group, according to the SES-CD score, 66 patients were in the active phase and 29 in the remission phase.

Hb/CRP Demonstrates Diagnostic Efficacy in Assisting the Evaluation of IBD Endoscopic Activity

In the UC group, results based on the Mayo Endoscopic Score showed that Hb/CRP had an AUC of 0.924 (95% CI: 0.884–0.964). Compared with its individual components, Hb/CRP significantly outperformed Hb (AUC=0.733, 95% CI: 0.661–0.806, P<0.001), while no significant difference was observed between Hb/CRP and CRP (AUC=0.920, 95% CI: 0.878–0.961, P=0.278) (Table 2, Figures 2A and 3A). Among other ratio indicators, Hb/WBC (AUC=0.777, 95% CI: 0.708–0.846), Hb/Neu (AUC=0.759, 95% CI: 0.688–0.829) and Hb/PLT (AUC=0.810, 95% CI: 0.747–0.873) also demonstrated good discriminatory capability, significantly superior to their corresponding single indicators WBC (AUC=0.705, 95% CI: 0.628–0.782, P<0.001) and Neu (AUC=0.697, 95% CI: 0.620–0.775, P<0.001), as well as to Hb (AUC=0.733, 95% CI: 0.661–0.806, P=0.016) for Hb/PLT, while no significant difference was observed between Hb/PLT and PLT (AUC=0.783, 95% CI: 0.717–0.850, P=0.075). Nevertheless, Hb/WBC and Hb/Neu showed no

Table 1 Baseline Characteristics of IBD Patients

Characteristic	UC (N=175)	CD (n=95)
Age (years)	52.0[38.0–62.0]	40.0[29.0–52.0]
Gender (Male/Female)	93/82	54/41
Classification	UC (extent): E1 (limited proctitis): 22 (12.6%) E2 (left-sided colitis): 39 (22.3%) E3 (extensive colitis): 114 (65.1%)	CD (location): L1 (ileum): 34 (35.8%) L2 (colon): 25 (26.3%) L3 (ileocolon): 36 (37.9%) CD (behavior): B1 (inflammatory): 61(64.2%) B2 (stricturing): 23(24.2%) B3 (fistulating): 11(11.6%)
Hb	123.0[106.0–137.0]	123.0[111.0–137.0]
WBC	6.2[5.0–8.0]	6.0[4.7–7.1]
Neu	3.6[2.6–5.1]	3.6[2.6–5.0]
PLT	251.0[208.0–333.0]	267.0[213.0–347.0]
CRP	2.5[0.8–10.5]	4.1[1.2–12.9]
Hb/WBC	20.0[14.0–25.9]	20.7[15.9–27.5]
Hb/Neu	34.2[22.9–49.5]	36.6[22.9–46.2]
Hb/PLT	0.49[0.32–0.64]	0.46[0.36–0.59]
Hb/CRP	49.3[10.6–173.5]	29.7[8.5–102.9]
Endoscopic active phase/ remission phase	By Mayo: 99/76; By UCEIS: 108/67	66/29
Endoscopic activity stratification	By Mayo: Active 99, Remission 76 By UCEIS: Inactive (0) 37, Mild (1–3) 45, Moderate (4–6) 46, Severe (7–8) 47	By SES-CD: Inactive (0–2) 29, Mild (3–6) 14, Moderate (7–15) 26, Severe (≥16) 26
Anemia	59 (33.7%)	26 (27.4%)

Abbreviations: UC, ulcerative colitis; CD, Crohn's disease; E1, proctitis; E2, left-sided colitis; E3, extensive colitis; L1, ileal disease; L2, colonic disease; L3, ileocolonic disease; B1, inflammatory behavior; B2, stricturing behavior; B3, fistulizing behavior; Hb, hemoglobin (g/L); WBC, white blood cell count ($\times 10^9$/L); Neu, neutrophil count ($\times 10^9$/L); PLT, platelet count ($\times 10^9$/L); CRP, C-reactive protein (mg/L); Mayo, Mayo Endoscopic Score; UCEIS, Ulcerative Colitis Endoscopic Index of Severity; SES-CD, Simplified Endoscopic Score for Crohn's Disease.

Table 2 DeLong Test Results of Single Indicators and Ratio Indicators

	AUC difference	P value
UC mayo		
Hb-Hb/WBC	−0.044(−0.119, 0.032)	0.257
WBC*-Hb/WBC	−0.072(−0.109, −0.035)	<0.001
Hb-Hb/Neu	−0.026(−0.109, 0.058)	0.549
Neu*-Hb/Neu	−0.061(−0.091, −0.032)	<0.001
Hb-Hb/PLT	−0.077(−0.139, −0.014)	0.016
PLT*-Hb/PLT	−0.026(−0.026, 0.003)	0.075
Hb-Hb/CRP	−0.190(−0.263, −0.118)	<0.001
CRP*-Hb/CRP	−0.012(−0.020, −0.004)	0.278
UC UCEIS		
Hb-Hb/WBC	−0.040(−0.118, 0.038)	0.315
WBC*-Hb/WBC	−0.059(−0.095, −0.024)	0.001
Hb-Hb/Neu	−0.028(−0.112, 0.058)	0.522
Neu*-Hb/Neu	−0.051(−0.080, −0.022)	0.001
Hb-Hb/PLT	−0.049(−0.114, 0.016)	0.138
PLT*-Hb/PLT	−0.025(−0.055, 0.005)	0.105

(*Continued*)

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Table 2 (Continued).

	AUC difference	P value
Hb-Hb/CRP	−0.183(−0.257, −0.109)	<0.001
CRP*-Hb/CRP	−0.001(−0.009, 0.008)	0.899
CD		
Hb-Hb/WBC	0.037(−0.109, 0.182)	0.622
WBC*-Hb/WBC	−0.069(−0.132, −0.006)	0.033
Hb-Hb/Neu	0.014(−0.143, 0.172)	0.861
Neu*-Hb/Neu	−0.046(−0.088, −0.003)	0.035
Hb-Hb/PLT	0.032(−0.091, 0.155)	0.608
PLT*-Hb/PLT	−0.064(−0.122, −0.005)	0.032
Hb-Hb/CRP	−0.192(−0.310, −0.073)	0.002
CRP*-Hb/CRP	−0.009(−0.023, 0.005)	0.206

Notes: * Since SPSS software requires aligned testing directions between single indicators and ratio indicators during ROC analysis, inverse values of WBC, Neu, PLT, and CRP were analyzed, producing AUC values matching previously reported results.
Abbreviations: Hb, hemoglobin; WBC, white blood cell count; Neu, neutrophil count; PLT, platelet count; CRP, C-reactive protein; Hb/WBC, hemoglobin-to-white blood cell ratio; Hb/Neu, hemoglobin-to-neutrophil ratio; Hb/PLT, hemoglobin-to-platelet ratio; Hb/CRP, hemoglobin-to-C-reactive protein ratio; UC, ulcerative colitis; Mayo, Mayo Endoscopic Score; UCEIS, Ulcerative Colitis Endoscopic Index of Severity; CD, Crohn's disease.

statistically significant difference in diagnostic efficacy compared to the single indicator Hb (both P>0.05). (Table 2, Supplementary Figure 1A–C and Supplementary Figure 2A–C).

Based on UCEIS Scores in the UC group, Hb/CRP achieved an AUC of 0.890 (95% CI: 0.842–0.938), which was significantly higher than Hb (AUC=0.707, 95% CI: 0.632–0.782, P<0.001) but showed no significant difference compared with CRP (AUC=0.889, 95% CI: 0.842–0.937, P=0.899) (Table 2, Figures 2B and 3B). Among the other three ratio indicators, Hb/WBC (AUC=0.747, 95% CI: 0.675–0.820) and Hb/Neu (AUC=0.735, 95% CI: 0.662–0.809) significantly surpassed their corresponding single indicators WBC (AUC=0.688, 95% CI: 0.609–0.767, P=0.001) and Neu (AUC=0.684, 95% CI: 0.605–0.763, P=0.001), while no significant difference was observed between Hb/PLT (AUC=0.756, 95% CI: 0.687–0.826) and PLT (AUC=0.731, 95% CI: 0.659–0.804, P=0.105). Compared with Hb (AUC=0.707, 95% CI: 0.632–0.782), Hb/WBC (P=0.315), Hb/Neu (P=0.522), and Hb/PLT (P=0.138) showed no statistically significant difference in diagnostic efficacy. (Table 2, Supplementary Figure 1D–F and Supplementary Figure 2D–F).

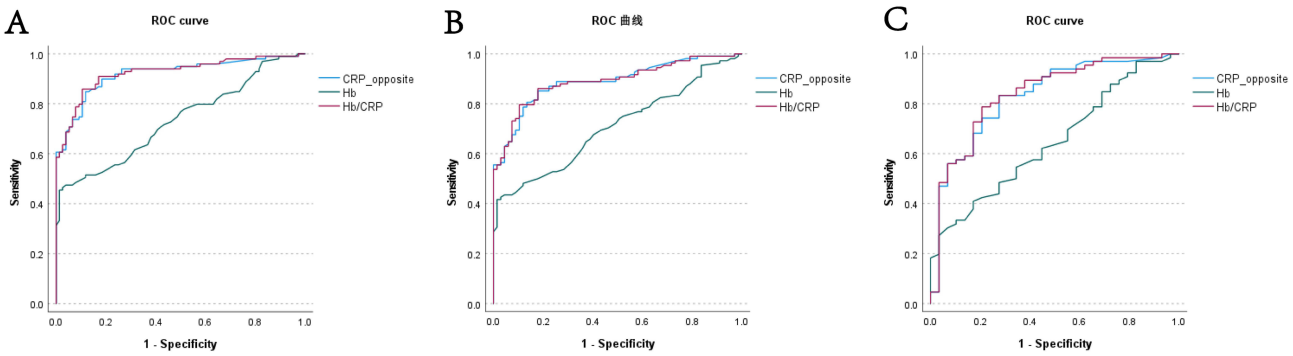

Figure 2 ROC curves of Hb/CRP for distinguishing endoscopic activity. (**A**) ROC curve of Hb/CRP in UC patients based on Mayo Endoscopic Score, with an AUC of 0.924 (95% CI: 0.884–0.964, P<0.001). (**B**) ROC curve of Hb/CRP in UC patients based on UCEIS score, with an AUC of 0.890 (95% CI: 0.842–0.938, P<0.001). (**C**) ROC curve of Hb/CRP in CD patients based on SES-CD score, with an AUC of 0.839 (95% CI: 0.749–0.929, P<0.001).

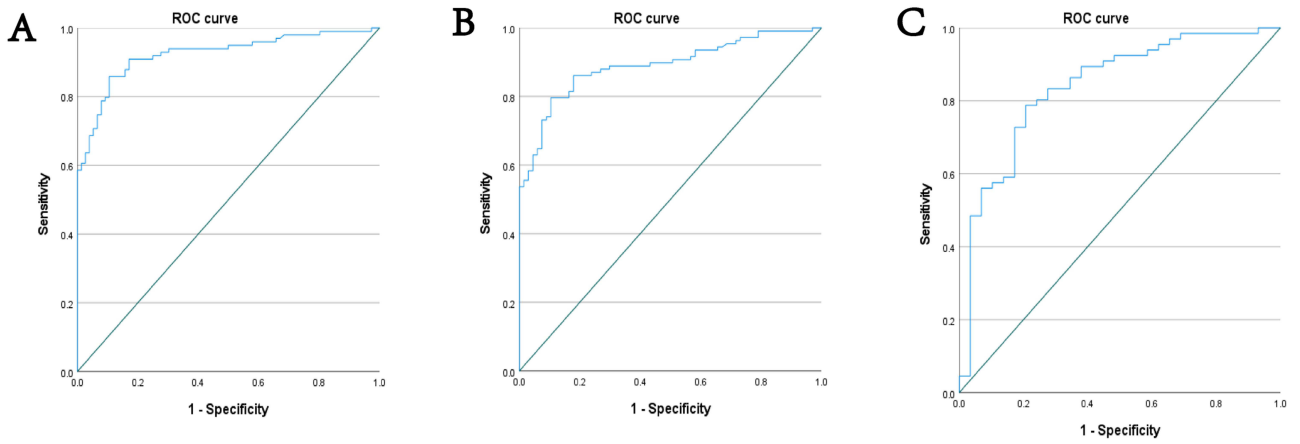

Figure 3 Delong test comparing the AUCs of Hb/CRP with its individual components. (**A**) Comparison of AUCs between Hb/CRP (AUC=0.924, 95% CI: 0.884–0.964), Hb (AUC=0.733, 95% CI: 0.661–0.806), and CRP (AUC=0.920, 95% CI: 0.878–0.961) in UC patients based on Mayo Endoscopic Score. Hb/CRP significantly outperformed Hb (P<0.001), while no significant difference was observed between Hb/CRP and CRP (P=0.278). (**B**) Comparison of AUCs between Hb/CRP (AUC=0.890, 95% CI: 0.842–0.938), Hb (AUC=0.707, 95% CI: 0.632–0.782), and CRP (AUC=0.889, 95% CI: 0.842–0.937) in UC patients based on UCEIS score. Hb/CRP significantly outperformed Hb (P<0.001), while no significant difference was observed between Hb/CRP and CRP (P=0.899). (**C**) Comparison of AUCs between Hb/CRP (AUC=0.839, 95% CI: 0.749–0.929), Hb (AUC=0.647, 95% CI: 0.533–0.762), and CRP (AUC=0.830, 95% CI: 0.739–0.922) in CD patients based on SES-CD score. Hb/CRP significantly outperformed Hb (P=0.002), while no significant difference was observed between Hb/CRP and CRP (P=0.206).

Results based on SES-CD scores in the CD Group were consistent with those in the UC Group. The AUC of Hb/CRP was 0.839 (95% CI: 0.749–0.929), which was significantly higher than Hb (AUC=0.647, 95% CI: 0.533–0.762, P=0.002) but showed no significant difference compared with CRP (AUC=0.830, 95% CI: 0.739–0.922, P=0.206) (Table 2, Figures 2C and 3C). Regarding other ratio indicators, Hb/WBC (AUC=0.611, 95% CI: 0.489–0.732), Hb/Neu (AUC=0.633, 95% CI: 0.512–0.755) and Hb/PLT (AUC=0.615, 95% CI: 0.501–0.730) significantly surpassed their corresponding single indicators WBC (AUC=0.542, 95% CI: 0.408–0.676, P=0.033), Neu (AUC=0.588, 95% CI: 0.459–0.716, P=0.035), and PLT (AUC=0.551, 95% CI: 0.435–0.668, P=0.032). Compared with Hb (AUC=0.647, 95% CI: 0.533–0.762), Hb/WBC (P=0.622), Hb/Neu (P=0.861), and Hb/PLT (P=0.608) showed no statistically significant difference in diagnostic efficacy. (Table 2, Supplementary Figure 1G–I and Supplementary Figure 2G–I).

When distinguishing between the active phase and remission phase of IBD using three scoring criteria, Hb/CRP consistently demonstrated the best comprehensive diagnostic efficacy (Table 3). In the UC group based on the Mayo Endoscopic Score criteria, Hb/CRP achieved a sensitivity of 85.9%, specificity of 89.5%. In the UC group based on the UCEIS criteria, Hb/CRP showed a sensitivity of 79.6%, specificity of 89.6%. In the CD group based on the SES-CD criteria, Hb/CRP exhibited a sensitivity of 78.8%, specificity of 79.3%. In conclusion, the Hb/CRP ratio represents a novel, readily available composite index that performs comparably to, and in some analyses shows a statistically significant improvement over, CRP alone for assessing endoscopic activity.

Hb/CRP Negatively Correlates with IBD Endoscopic Activity Scores and Effectively Differentiates IBD Endoscopic Activity Levels

The results of Spearman correlation analysis revealed that the Hb/CRP ratio exhibited the strongest significant negative correlations with all endoscopic scores, with the largest absolute correlation coefficients: Mayo Endoscopic Score (r=0.806, P<0.001), UCEIS (r=0.755, P<0.001), and SES-CD (r=0.635, P<0.001) (Table 4). The absolute values of correlation coefficients for all other ratio indicators were also greater than those of their corresponding single inflammatory markers, although some single markers, such as WBC and PLT in the CD group, did not reach statistical significance (P>0.05) (Table 4). To further confirm the value of Hb/inflammation marker ratios in differentiating IBD endoscopic activity, we performed Kruskal–Wallis tests to evaluate their diagnostic efficacy across multiple dimensions. In the UC group stratified by UCEIS, Hb/CRP demonstrated the optimal discriminative capability with the highest H-value (H=92.914, P<0.001), and the other three ratio indicators also showed statistically significant differences (all P<0.001). In the CD group stratified by SES-CD, Hb/CRP remained the most effective indicator (H=40.296, P<0.001),

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Table 3 Results Under the Cut-off Value

Indicators	Cut-off Value	Sensitivity	Specificity	Youden's Index	Positive Predictive Value	Negative Predictive Value	Positive Likelihood Ratio	Negative Likelihood Ratio	Accuracy Rate
UC Mayo									
Hb/WBC	18.91	67.7%	80.3%	0.48	0.90	0.47	3.44	0.40	71.0%
Hb/Neu	33.69	67.7%	77.6%	0.45	0.89	0.47	3.02	0.42	70.3%
Hb/PLT	0.46	66.7%	82.9%	0.50	0.92	0.47	3.90	0.40	71.0%
Hb/CRP	60.05	85.9%	89.5%	0.75	0.96	0.70	8.18	0.16	86.9%
UC UCEIS									
Hb/WBC	20.83	73.1%	70.1%	0.43	0.87	0.49	2.44	0.38	72.3%
Hb/Neu	33.69	63.9%	77.6%	0.42	0.89	0.44	2.85	0.47	67.5%
Hb/PLT	0.41	53.7%	89.6%	0.43	0.93	0.41	5.16	0.52	63.2%
Hb/CRP	60.05	79.6%	89.6%	0.69	0.95	0.61	7.65	0.23	82.3%
CD SESCD									
Hb/WBC	20.98	60.6%	69.0%	0.30	0.84	0.39	1.95	0.57	62.8%
Hb/Neu	29.05	43.9%	86.2%	0.30	0.90	0.36	3.18	0.65	55.1%
Hb/PLT	0.41	43.9%	82.8%	0.27	0.88	0.35	2.55	0.68	54.2%
Hb/CRP	52.17	78.8%	79.3%	0.58	0.91	0.58	3.81	0.27	78.9%

Abbreviations: UC, ulcerative colitis; Mayo, Mayo Endoscopic Score; UCEIS, Ulcerative Colitis Endoscopic Index of Severity; CD, Crohn's disease; SES-CD, Simplified Endoscopic Score for Crohn's Disease; Hb/WBC, hemoglobin-to-white blood cell ratio; Hb/Neu, hemoglobin-to-neutrophil ratio; Hb/PLT, hemoglobin-to-platelet ratio; Hb/CRP, hemoglobin-to-C-reactive protein ratio. Cut-off values were determined using the Youden index, which maximizes the sum of sensitivity and specificity.

Table 4 Spearman Correlation Coefficient Analysis Results

	Mayo Endoscopy Score	P	UCEIS score	P	SESCD score	P
Hb	−0.475	<0.001	−0.481	<0.001	−0.323	0.001
WBC	0.448	<0.001	0.442	<0.001	0.187	0.069
Hb/WBC	−0.588	<0.001	−0.580	<0.001	−0.333	<0.001
Neu	0.445	<0.001	0.457	<0.001	0.328	0.001
Hb/Neu	−0.562	<0.001	−0.573	<0.001	−0.419	<0.001
PLT	0.552	<0.001	0.512	<0.001	0.186	0.071
Hb/PLT	−0.608	<0.001	−0.580	<0.001	−0.302	0.003
CRP	0.795	<0.001	0.741	<0.001	0.618	<0.001
Hb/CRP	−0.806	<0.001	−0.755	<0.001	−0.635	<0.001

Abbreviations: Mayo, Mayo Endoscopic Score; UCEIS, Ulcerative Colitis Endoscopic Index of Severity; SES-CD, Simplified Endoscopic Score for Crohn's Disease; Hb, hemoglobin; WBC, white blood cell count; Neu, neutrophil count; PLT, platelet count; CRP, C-reactive protein; Hb/WBC, hemoglobin-to-white blood cell ratio; Hb/Neu, hemoglobin-to-neutrophil ratio; Hb/PLT, hemoglobin-to-platelet ratio; Hb/CRP, hemoglobin-to-C-reactive protein ratio.

while the remaining ratio indicators also reached statistical significance (all P<0.05) (Supplementary Table 4). These results further support Hb/CRP as a clinically practical indicator for assessing endoscopic activity in IBD.

Hb/PLT and Hb/CRP as Independent Protective Factors Toward Remission Phase

In UC patients, multivariate logistic regression analysis identified Hb/WBC, Hb/Neu, Hb/PLT, and Hb/CRP as independent protective factors for remission phase. When grouped by Mayo Endoscopic Score, each unit increase in Hb/WBC (OR=1.099, 95% CI: 1.042–1.158, P<0.001), Hb/Neu (OR=1.034, 95% CI: 1.012–1.056, P=0.002), Hb/PLT (OR=56.184, 95% CI: 5.107–618.059, P<0.001), and Hb/CRP (OR=1.009, 95% CI: 1.005–1.014, P<0.001) was significantly associated with transitioning from the active phase to remission phase. Similar results were observed when grouped by UCEIS, with Hb/WBC (OR=1.090, 95% CI: 1.034–1.148, P=0.001), Hb/Neu (OR=1.019, 95% CI: 1.003–1.034, P=0.017), Hb/PLT (OR=16.118, 95% CI: 1.752–148.258, P=0.014), and Hb/CRP (OR=1.007, 95% CI: 1.003–1.011, P<0.001) all remaining significant protective factors (Table 5). Among CD patients, Hb/CRP emerged as

Table 5 Multivariate Logistic Regression Results

	P	OR (95% CI)
UC Mayo		
Hb/WBC	<0.001	1.099(1.042–1.158)
Hb/Neu	0.002	1.034(1.012–1.056)
Hb/PLT	<0.001	56.184(5.107–618.059)
Hb/CRP	<0.001	1.009(1.005–1.014)
UC UCEIS		
Hb/WBC	0.001	1.090(1.034–1.148)
Hb/Neu	0.017	1.019(1.003–1.034)
Hb/PLT	0.014	16.118(1.752–148.258)
Hb/CRP	<0.001	1.007(1.003–1.011)
CD SESCD		
Hb/WBC	0.053	1.083(0.999–1.173)
Hb/Neu	0.021	1.0353(1.005–1.066)
Hb/PLT	0.071	29.333 (0.744–1155.872)
Hb/CRP	<0.001	1.014(1.006–1.023)

Abbreviations: UC, ulcerative colitis; Mayo, Mayo Endoscopic Score; UCEIS, Ulcerative Colitis Endoscopic Index of Severity; CD, Crohn's disease; SES-CD, Simplified Endoscopic Score for Crohn's Disease; Hb/WBC, hemoglobin-to-white blood cell ratio; Hb/Neu, hemoglobin-to-neutrophil ratio; Hb/PLT, hemoglobin-to-platelet ratio; Hb/CRP, hemoglobin-to-C-reactive protein ratio; OR, odds ratio; CI, confidence interval.

the most robust independent protective factor for remission phase, with each unit increase associated with an OR of 1.014 (95% CI: 1.006–1.023, P<0.001). Additionally, Hb/Neu also demonstrated a significant protective effect (OR=1.035, 95% CI: 1.005–1.066, P=0.021). However, Hb/WBC (OR=1.083, 95% CI: 0.999–1.173, P=0.053) and Hb/PLT (OR=29.333, 95% CI: 0.744–1155.872, P=0.071) did not reach statistical significance (Table 5).

Sensitivity Analyses Stratified by Anemia Status

When stratified by anemia status. In UC patients, Hb/CRP consistently showed the highest AUCs across all subgroups (Supplementary Table 5 and Supplementary Figure 3), based on the Mayo Endoscopic Score, Hb/CRP achieved AUCs of 0.978 (95% CI: 0.939–1.000, P<0.001) in anemic patients and 0.871 (95% CI: 0.802–0.940, P<0.001) in non-anemic patients. Hb/WBC demonstrated AUCs of 0.759 (95% CI: 0.604–0.915, P=0.010) and 0.695 (95% CI: 0.593–0.796, P<0.001), while Hb/Neu yielded AUCs of 0.724 (95% CI: 0.553–0.896, P=0.026) and 0.694 (95% CI: 0.593–0.795, P<0.001), and Hb/PLT showed AUCs of 0.892 (95% CI: 0.809–0.975, P<0.001) in anemic patients and 0.723 (95% CI: 0.629–0.817, P<0.001) in non-anemic patients, respectively. Consistent findings were observed using the UCEIS score. Hb/CRP again showed the highest AUCs, with values of 0.951 (95% CI: 0.891–1.000, P<0.001) in anemic patients and 0.829 (95% CI: 0.752–0.905, P<0.001) in non-anemic patients. Hb/WBC showed AUCs of 0.699 (95% CI: 0.521–0.876, P=0.073) and 0.674 (95% CI: 0.575–0.773, P=0.001) in anemic and non-anemic patients, Hb/Neu yielded AUCs of 0.684 (95% CI: 0.488–0.880, P=0.097) and 0.677 (95% CI: 0.578–0.775, P=0.001), while Hb/PLT demonstrated AUCs of 0.841 (95% CI: 0.741–0.941, P=0.002) and 0.661 (95% CI: 0.562–0.759, P=0.003). In CD patients, Hb/CRP demonstrated AUCs of 0.667 (95% CI: 0.196–1.000, P=0.356) in anemic patients and 0.821 (95% CI: 0.722–0.920, P<0.001) in non-anemic patients. Hb/WBC demonstrated AUCs of 0.870 (95% CI: 0.732–1.000, P=0.041) and 0.519 (95% CI: 0.375–0.662, P=0.795) in anemic and non-anemic patients. Hb/Neu yielded AUCs of 0.884 (95% CI: 0.744–1.000, P=0.033) and 0.538 (95% CI: 0.395–0.682, P=0.594), while Hb/PLT showed AUCs of 0.739 (95% CI: 0.494–0.984, P=0.185) and 0.524 (95% CI: 0.386–0.662, P=0.743).

Discussion

Patients with active phase IBD frequently present with anemia. Inflammatory markers such as WBC, CRP, and PLT increase during infection or endoscopic activity. However, CRP is not elevated in all patients with active phase, and therefore does not comprehensively reflect the activity of IBD. Can hemoglobin-to-inflammation ratios reduce the confounding effects of infection and help evaluate endoscopic activity more accurately? This study demonstrates that the Hb/CRP represents a promising composite biomarker for assessing endoscopic activity in IBD. Among the four evaluated ratios (Hb/WBC, Hb/Neu, Hb/PLT, Hb/CRP), Hb/CRP consistently exhibited the most favorable diagnostic performance across both UC and CD, effectively distinguishing active phase from remission phase, and achieved high sensitivity, specificity, PPV, NPV, and accuracy. Notably, while Hb/CRP significantly outperformed Hb alone across all subgroups, its diagnostic accuracy was comparable to CRP alone, with no statistically significant differences observed in Delong comparisons. The primary clinical value of Hb/CRP may therefore not rest solely on incremental diagnostic gain over CRP but on its ability to integrate two routine parameters (Hb and CRP) into a single index that reflects both inflammatory and anemic components, potentially offering a different clinical perspective. This conclusion may be explained by the interleukin-6 (IL-6)-hepcidin axis theory.[18] During active inflammation, elevated IL-6 serves a dual role: it directly stimulates hepatocytes to produce CRP,[19] while concurrently upregulating hepcidin synthesis.[20] Hepcidin, in turn, degrades the cellular iron exporter ferroportin, sequestering iron within macrophages and enterocytes, thereby inducing a functional iron deficiency that impairs erythropoiesis and reduces hemoglobin levels.[21] Consequently, the Hb/CRP ratio is not merely an arithmetic combination but a pathophysiologically integrated index that quantifies the relative dominance of systemic inflammation and its consequent anemia. The other ratios reflect distinct but related pathways. Hb/WBC and Hb/Neu capture the interplay between anemia and the innate immune response, as white blood cell and neutrophil counts typically rise during active inflammation; decreases in these ratios indicate inflammation-mediated leukocytosis relative to hemoglobin. Hb/PLT pairs hemoglobin with platelet count, given that platelets behave as acute-phase reactants in active phase; a low Hb/PLT thus suggests inflammation-driven thrombocytosis relative to hemoglobin. From a clinical perspective, decreases in any of these ratios suggest active inflammation with concomitant anemic consequences, supporting the presence of endoscopic activity. Conversely, increases in these ratios, especially following treatment, may signal endoscopic remission phase as they reflect resolution of both inflammation and its downstream effects. These ratios are intended as adjunctive indicators to aid in non-invasive disease monitoring when interpreted alongside clinical context.

Literature reports that single indicators like Hb, WBC, Neu, PLT, and CRP correlate with endoscopic activity levels; however, their diagnostic accuracy is generally limited.[10,22–24] A study stratified endoscopic activity levels using the Mayo Endoscopic Score and SES-CD Score. The results showed that Hb negatively correlated with endoscopic activity ($r = -0.47$ with Mayo Score; $r = -0.42$ with SES-CD Score), whereas PLT and CRP showed positive correlations ($r = 0.57$ and 0.51 with Mayo Score; $r = 0.57$ and 0.59 with SES-CD Score).[25] Moreover, its diagnostic performance could be further enhanced when combined with fecal biomarkers.[25] Furthermore, studies distinguishing IBD activity levels based on clinical scores (such as CDAI) rather than endoscopic scores also indicate that Hb, PLT, and CRP exhibit variations among patients with different disease activity levels. However, their diagnostic efficacy and correlation coefficients remain limited.[22–24] Our findings offer novel indicators for clinical assessment of IBD endoscopic activity.

In this study, we found that four ratio indicators—Hb/WBC, Hb/Neu, Hb/PLT, and Hb/CRP—had higher diagnostic efficacy for endoscopic activity in UC than in CD. We hypothesize that this phenomenon may be related to differences in clinical symptoms and pathogenesis between UC and CD. Regarding clinical manifestations, UC patients typically present with prominent bloody stools, mucopurulent bloody stools, and tenesmus.[26] This direct blood loss, coupled with the relatively uniform mucosal insult,[27] creates a predictable link between the degree of endoscopic inflammation, systemic inflammatory markers, and hemoglobin levels, allowing blood-based ratios to serve as reliable proxies. In contrast, CD Patients primarily present with abdominal pain, diarrhea, fistulas, and intestinal obstruction, while frank hematochezia is relatively uncommon.[28] Anemia is more closely associated with impaired absorption of iron and vitamin B12.[29] And the heterogeneity across intestinal segments and disease stages in CD reduces the consistency of Hb-based ratios in reflecting endoscopic activity.[30] The lower predictive accuracy in CD could indeed stem from unassessed small

bowel lesions, as our study did not utilize capsule endoscopy for comprehensive small bowel evaluation.[31,32] The complex pathophysiology of anemia in CD involves multiple mechanisms including chronic inflammation, iron malabsorption due to proximal small bowel disease or resection, and medication effects, making anemia prediction more challenging compared to ulcerative colitis. These factors potentially limit the discriminatory efficacy of Hb-related ratios in CD.

Sensitivity analyses stratified by anemia status confirmed the robustness of Hb/CRP. In UC patients, Hb/CRP maintained high diagnostic performance across both anemic and non-anemic subgroups, consistently achieving the highest AUCs among all ratio indicators. In contrast, Hb/WBC, Hb/Neu, and Hb/PLT exhibited only modest performance, particularly in non-anemic patients, with some failing to reach statistical significance in this subgroup. In CD patients, Hb/CRP demonstrated good diagnostic value in non-anemic patients ($P<0.001$), while its performance in anemic patients did not reach statistical significance ($P=0.356$). The other three ratio indicators showed significant diagnostic value only in anemic patients and lacked statistical significance in non-anemic patients. These findings suggest that Hb/CRP may integrate both inflammatory and anemic pathways more effectively than ratios based solely on hemoglobin and leukocyte or platelet counts, though its utility in anemic CD patients requires further investigation.

In clinical practice, FC remains the non-invasive gold standard for mucosal inflammation,[11] yet it faces challenges related to unable to test in hospital, sample collection stability, and cost.[12] In contrast, Hb and CRP are ubiquitous, inexpensive, rapidly available components of routine complete blood counts almost in every hospital. This integrated measure may prove useful in several practical scenarios: (1) as a rapid and low-cost adjunct tool for assessing endoscopic activity in outpatient or emergency settings, particularly when fecal testing is not immediately feasible; (2) for dynamic monitoring of treatment response, where it may more sensitively reflect the simultaneous resolution of inflammation and anemia; (3) to aid in the interpretation of borderline-elevated CRP levels—in the context of significant anemia, a low Hb/CRP ratio may raise suspicion for active phase rather than other inflammatory conditions. Therefore, even with modest diagnostic gains, the ratio's practical value is significant—its future integration into electronic health records for automatic calculation and display would make it a truly effortless and convenient clinical aid.

The interpretation of our findings must be tempered by an acknowledgment of the study's limitations. First and foremost, major limitation of this study is the lack of data on fecal calprotectin, which is currently the best-validated non-invasive biomarker for mucosal inflammation in IBD. Therefore, we could not benchmark the performance of the CRP/Hb and Hb/CRP ratios against this established standard. Future studies directly comparing these ratios to fecal calprotectin are needed to determine their relative utility and potential niche. Second, although Hb/CRP demonstrated superior diagnostic performance compared with Hb across all subgroups, Delong test comparisons between Hb/CRP and CRP revealed no statistically significant differences in either UC or CD. This suggests that the addition of hemoglobin to CRP does not significantly enhance diagnostic accuracy beyond CRP alone in this cohort. Third, although sensitivity analyses stratified by anemia status provided valuable insights, the number of anemic CD patients was limited (n=26), which may have reduced statistical power and contributed to the non-significant findings in this subgroup. Future studies with larger anemic cohorts are needed to validate the performance of Hb/CRP in this population. These findings highlight that while Hb/CRP offers a composite index that integrates both inflammatory and anemic pathways, its incremental diagnostic value over CRP alone may be limited. Further prospective studies are needed to determine whether this ratio provides meaningful clinical utility beyond established biomarkers such as CRP. Other limitations include the single-center nature, potential for selection bias, and the inherent inter-observer variability in endoscopic scoring.

In summary, this study introduces the Hb/CRP ratio as a novel, pathophysiologically grounded, and practical biomarker for the assessment of endoscopic activity in IBD. It is important to emphasize that these ratios should be considered exploratory or adjunctive indicators that may complement, rather than replace, established endoscopic assessment. They do not currently serve as reliable standalone markers of endoscopic activity. While not intended to replace established standards like FC, the current study emphasizes Hb/CRP as one component of a broader clinical assessment rather than a definitive surrogate for mucosal inflammation. Future rigorous prospective validation will be crucial to precisely delineate its role in the evolving landscape of non-invasive IBD monitoring.

Abbreviations

AUC, Area under the curve; CAR, C-reactive protein-to-albumin ratio; CD, Crohn's disease; CDEIS, Crohn's Disease Endoscopic Index of Severity; Cis, Confidence intervals; CRP, C-reactive protein; ESR, Erythrocyte sedimentation rate; FC, Fecal calprotectin; Hb, Hemoglobin; Hb/WBC, Hemoglobin-to-white blood cell; Hb/Neu, Hemoglobin-to-neutrophil; Hb/PLT, Hemoglobin-to-platelet; Hb/CRP, Hemoglobin-to-C-reactive protein; IBD, Inflammatory bowel disease; LMR, Lymphocyte-to-monocyte ratio; LR-, Negative likelihood ratio; LR+, Positive likelihood ratio; MH, Mucosal healing; Neu, Neutrophil; NLR, Neutrophil-to-lymphocyte ratio; NMR, Neutrophil-to-monocyte ratio; NPV, Negative predictive value; OR, Odds ratio; ORM, Orosomucoid; PLR, Platelet-to-lymphocyte ratio; PLT, Platelet; PPV, Positive predictive value; ROC, Receiver operating characteristic; SES-CD, Simplified Endoscopic Score for Crohn's Disease; UC, Ulcerative colitis; UCEIS, Ulcerative Colitis Endoscopic Index of Severity; WBC, White blood cell.

Data Sharing Statement

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

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Author Contributions

All authors meet the ICMJE (International Committee of Medical Journal Editors) criteria for authorship and have approved the final version of the manuscript for submission. Each author has agreed to be accountable for all aspects of the work. The specific contributions are detailed below using the CRediT taxonomy:

Zhaoyi Wu: Conceptualization, Data curation, Formal analysis, Investigation, Visualization, Writing – original draft.

Qian Zhang: Data curation, Formal analysis, Investigation.

Hui Li: Data curation, Formal analysis, Investigation.

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Bin Cao: Conceptualization, Funding acquisition, Project administration, Resources, Supervision, Writing – review & editing.

Hongyun Wei: Conceptualization, Funding acquisition, Project administration, Resources, Supervision, Writing – review & editing.

All authors 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 have no conflicts of interest.

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