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Original Article

Predictive value of serum markers for mucosal healing in patients with inflammatory bowel disease

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Abstract: Objective: To investigate the value of serum markers in assessing mucosal healing (MH) and inflammatory activity in patients with inflammatory bowel disease (IBD). Methods: In this retrospective analysis, we examined data from 320 IBD patients, including 176 with ulcerative colitis (UC) and 144 with Crohn's disease (CD), alongside 100 healthy controls during the same period. Serum levels of various markers, including white blood cell (WBC), platelet count (PLT), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), platelet/lymphocyte ratio (PLR) and neutrophil/lymphocyte ratio (NLR) were evaluated. These indices were analyzed for their diagnostic value in endoscopic MH in IBD patients. The independent influencing factors affecting MH in IBD patients were identified by univariate and multivariate analyses. Results: The levels of WBC, PLT, ESR, CRP, PLR, and NLR were significantly higher in IBD patients, UC patients, and CD patients than in healthy controls (all $P < 0.05$). For those achieving MH, their WBC, PLT, ESR, CRP, PLR, and NLR levels were significantly lower than patients who did not achieve MH (all $P < 0.05$). The AUCs of WBC, PLT, ESR, CRP, PLR, and NLR for the diagnosis of MH were 0.729, 0.756, 0.673, 0.707, 0791, and 0.724, respectively. A multifactorial analysis found that the presence of abdominal pain (OR: 2.155, 95% CI: 1.081-4.297, $P < 0.05$), higher WBC (OR: 3.927, 95% CI: 2.008-7.681, $P < 0.001$), higher PLT (OR: 4.181, 95% CI: 2.078-8.412, $P < 0.001$), higher ESR (OR: 2.221, 95% CI: 1.082-4.562, $P < 0.05$), higher CRP (OR: 3.874, 95% CI: 1.861-8.065, $P < 0.001$), higher PLR (OR: 4.087, 95% CI: 1.586-10.534, $P < 0.01$), and higher NLR (OR: 2.688, 95% CI: 1.292-5.592, $P < 0.01$) were independent risk factors for failure in achieving MH. Conclusion: WBC, PLT, ESR, CRP, PLR, and NLR can be used as noninvasive markers for predicting MH in patients with IBD, and they hold promise for clinical application.

Keywords: Serum markers, prediction, inflammatory bowel disease, mucosal healing, retrospective study

Introduction

Inflammatory bowel disease (IBD) is a prevalent gastroenterological condition affecting the ileum, rectum, and colon [1, 2]. It is a chronic, progressive, and disabling inflammatory disorder of the intestinal tract, primarily encompassing ulcerative colitis (UC) and Crohn's disease (CD) [3, 4]. IBD presents with a wide range of clinical features. Intestinal symptoms include abdominal pain, diarrhea, and mucopurulent and bloody stools, while extraintestinal manifestations can involve oral ulcers and arthritis. These symptoms significantly impair the quality of life for patients, especially during the active and progressive stages of the disease [5, 6]. Historically, IBD was more prevalent in high-income Western countries. However, its prevalence is on the rise in South America, Eastern Europe, Asia, and Africa, attributed to economic development and lifestyle changes [7, 8]. Statistics indicate that the prevalence in North Africa and the Middle East is expected to increase by 2.3-fold from 2020 to 2035. In the high-income regions of the Asia-Pacific and South-East Asia, the prevalence is projected to increase by approximately 1.7-fold by 2035 [9].

The integrity of the intestinal mucosal barrier is pivotal in the pathogenesis of inflammatory bowel disease (IBD) [10, 11]. A compromised barrier results in increased mucosal permeability, allowing antigens, bacteria, and their lysis products to penetrate the submucosa. This penetration triggers the release of inflammatory cytokines and results in damage to epithelial

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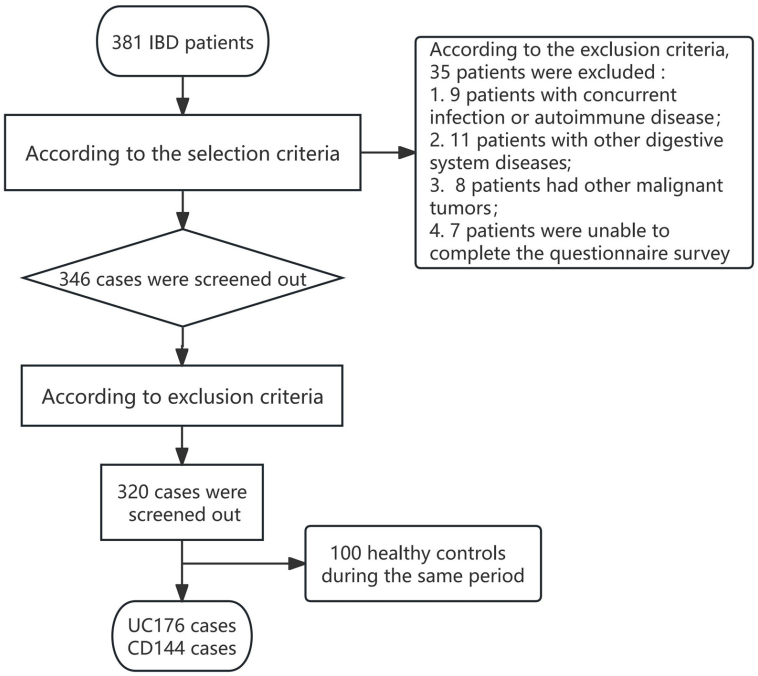

Figure 1. Flowchart of enrollment. IBD: inflammatory bowel disease.

cells [12, 13]. The damage to epithelial cells exacerbates the inflammatory process, creating a vicious cycle that contributes to the onset, progression, and chronicity of IBD [14]. Intestinal mucosal healing (MH) was originally defined by histological changes in the mucosa. Currently, with the advent of endoscopy, endoscopic MH has emerged as a crucial prognostic indicator in the treatment of patients with IBD. Research has shown that endoscopic MH is instrumental in predicting clinical remission and resection-free survival, highlighting the importance of observing intestinal mucosal changes and integrating histological assessments into the evaluation of IBD [15-17].

Invasive procedures like endoscopic evaluation and biopsy play a vital role in screening and assessing IBD activity. However, these methods come with several drawbacks, including invasiveness, associated anesthesia risks, discomfort and pain, high cost, and time constraints [18, 19]. Thus, the noninvasive examinations for assessing IBD activity are increasingly vital. Noninvasive tests and biomarkers serve as complementary tools to evaluate disease activity and monitor treatment efficacy [20].

This study aims to analyze commonly used biomarkers to identify methods that are accurate, safe, easily accessible, and timely for reflecting the extent of intestinal MH and inflammation. These methods are intended to supplement the diagnosis and management of patients with IBD.

Methods and materials

Research subjects

With ethics approval obtained from No. 215 Hospital of Shaanxi Nuclear Industry (approval number: 2024-013), this retrospective study analyzed data from 320 patients with IBD, including 176 cases of ulcerative colitis (UC) and 144 cases of Crohn's disease (CD), alongside 100 healthy controls during the same period. The study procedure is shown in **Figure 1**.

Inclusion criteria

(1) Patients aged 18 years or above. (2) Patients with IBD confirmed by the 2018 edition of the Consensus on the Diagnosis and Treatment of IBD [21], incorporating clinical assessment, laboratory examination, imaging examination, endoscopy, and histopathological findings. Healthy subjects were confirmed to be free of the disease. (3) Patients with comprehensive and complete clinical data, including medical records, laboratory tests, and endoscopic findings. (4) Patients with no recent history of taking aspirin or anticoagulant drugs.

Exclusion criteria

(1) Coexisting infection or autoimmune disease. (2) Concurrent other digestive system diseases. (3) Presence of malignant tumors. (4) Inability to understand the informed consent form or research procedures.

Criteria for mucosal healing

Endoscopic activity was assessed for UC patients using the modified Mayo scoring system [22]. A score of ≤ 1 was indicative of MH, a score of 1-2 (including 2) was indicative of remission, and a score of > 3 was indicative of active disease. Patients with CD were scored

Table 1. Clinical characteristics

	IBD Group (N=320)	UC Group (N=176)	CD Group (N=144)	Healthy control group (N=100)	t/χ^2	P
Age (years)	38.63±9.38	41.2±9.40	34.9±7.08	39.80±8.85	1.103	0.271
Gender (Male/Female)	209/111	101/75	108/36	69/31	0.463	0.496
BMI (kg/m^2)	21.89±2.97	21.32±3.29	20.67±3.67	22.01±3.11	0.349	0.728
Clinical manifestations, n (%)						
Fever	154 (48.13)	87 (49.43)	67 (46.53)			
Diarrhea	189 (59.06)	114 (64.77)	75 (52.08)			
Abdominal pain	220 (68.75)	124 (70.45)	96 (66.67)			
Bloody stool	179 (55.94)	142 (80.68)	27 (18.75)			
History of intestinal surgery (Yes/No)	35/285	11/165	24/120			
Site of lesion, n (%)						
Rectum (anatomy)		24 (13.64)				
Left half of the colon		40 (22.73)				
Whole colon		112 (63.64)				
Terminal ileum (anatomy)			17 (11.81)			
Colon (large intestine)			9 (6.25)			
Ileum (anatomy)			114 (79.17)			
Upper gastrointestinal tract			4 (2.78)			
Endoscopical activity, n (%)						
Mucosal healing period	97 (30.31)	52 (29.55)	45 (31.25)			
Remission period	82 (25.63)	44 (25.00)	38 (26.39)			
Active period	141 (44.06)	80 (45.45)	61 (42.36)			

BMI: Body Mass Index.

for activity severity using the (Crohn's disease activity index, CDAI) index. A CDAI ≤ 2 was classified as MH, a CDAI of 2-4 (including 4) was classified as remission, and a CDAI > 4 was classified as active disease [23].

Observation outcomes

By retrieving the hospital medical record system, gender, age, BMI, clinical manifestations, medical and surgical history, and lesion sites of the patients were collected and compared between the IBD cohort and control cohort. The routine blood results including absolute white blood cell (WBC), platelet count (PLT), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), platelet/lymphocyte ratio (PLR), and neutrophil/lymphocyte ratio (NLR) were also collected and compared between the two cohorts.

The IBD patients were then categorized into a MH group and a non-MH group based on these assessments. Subsequent comparisons of the routine blood indicators were made between MH and non-MH patients. To evaluate the diagnostic efficacy of routine indicators for identifying MH, Receiver Operating Characteristic (ROC) curve analysis was performed. Additionally, both univariate and multivariate analyses were conducted to identify independent factors that impede the achievement of MH.

Statistical methods

Statistical analyses were performed using SPSS version 26.0. Continuous data were expressed as mean ± standard deviation (Means ± SD) if the variables obeyed normal distribution, an independent t-test was used for comparison between groups. Count data were expressed as numbers and percentage, and χ^2 test was used for comparison between groups. The diagnostic value of each serological marker in relation to MH was evaluated using the ROC curve analysis. Significant indicators in one-way tests were included in binary logistic regression for identifying independent predictors of MH failure. A *p*-value of less than 0.05 was considered statistically significant.

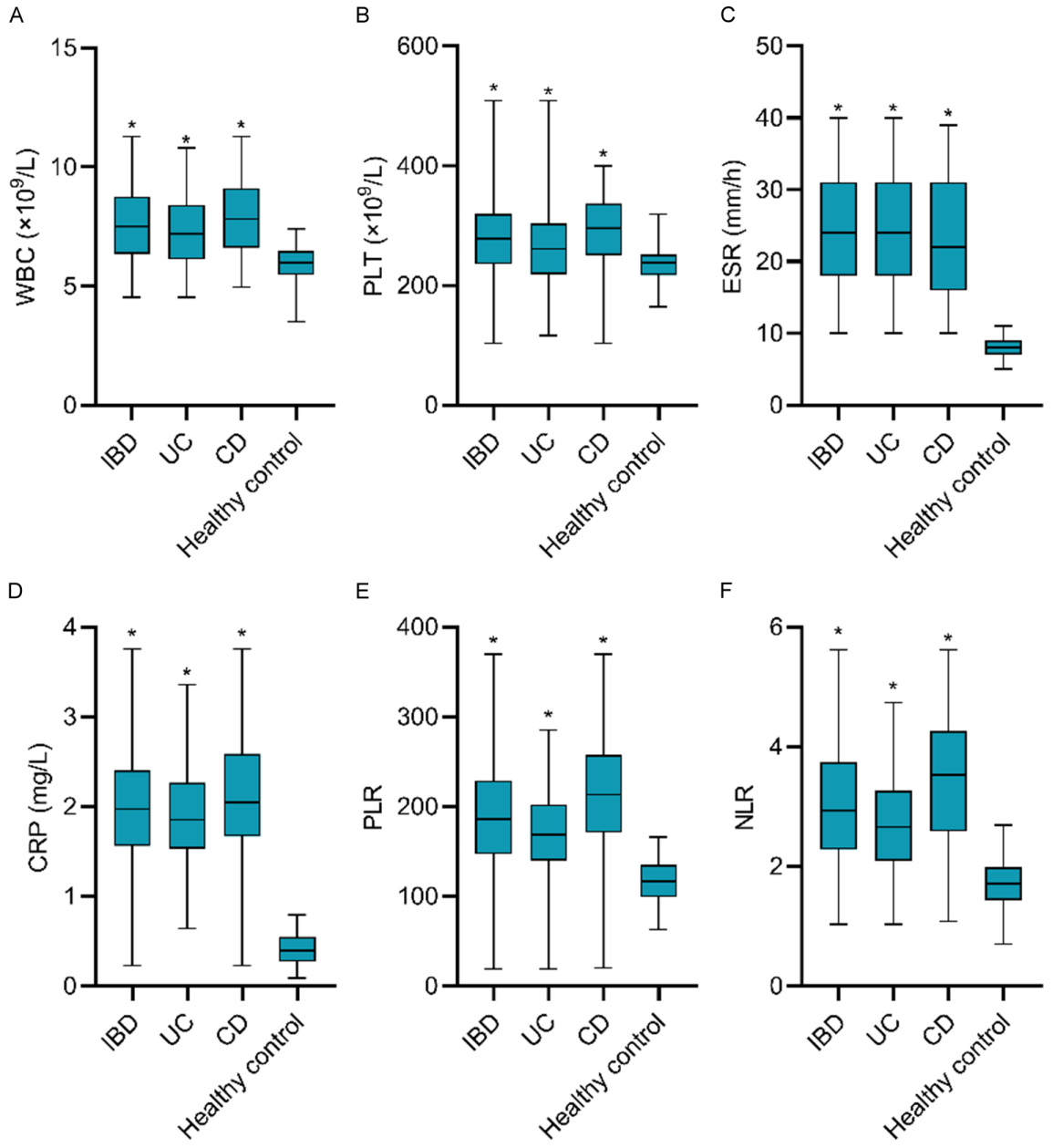

Figure 2. Serum marker levels in each group of subjects. WBC: white blood cell; PLT: platelet count; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; PLR: platelet/lymphocyte ratio; NLR: neutrophil/lymphocyte ratio. *, $P < 0.05$, compared with the healthy control group.

Results

Comparison of clinical characteristics between the two groups

A total of 320 patients with IBD were included in the study, including 176 patients with UC and 144 patients with CD, alongside 100 healthy subjects as control. There was no statistical difference in age, gender and BMI between the IBD group and the control group ($P > 0.05$). The clinical characteristics of all subjects are shown in **Table 1**.

Comparison of serum markers between the IBD groups and control group

Comparing the levels of serum markers WBC, PLT, ESR, CRP, PLR, and NLR in each group of subjects, it was found that the levels of WBC,

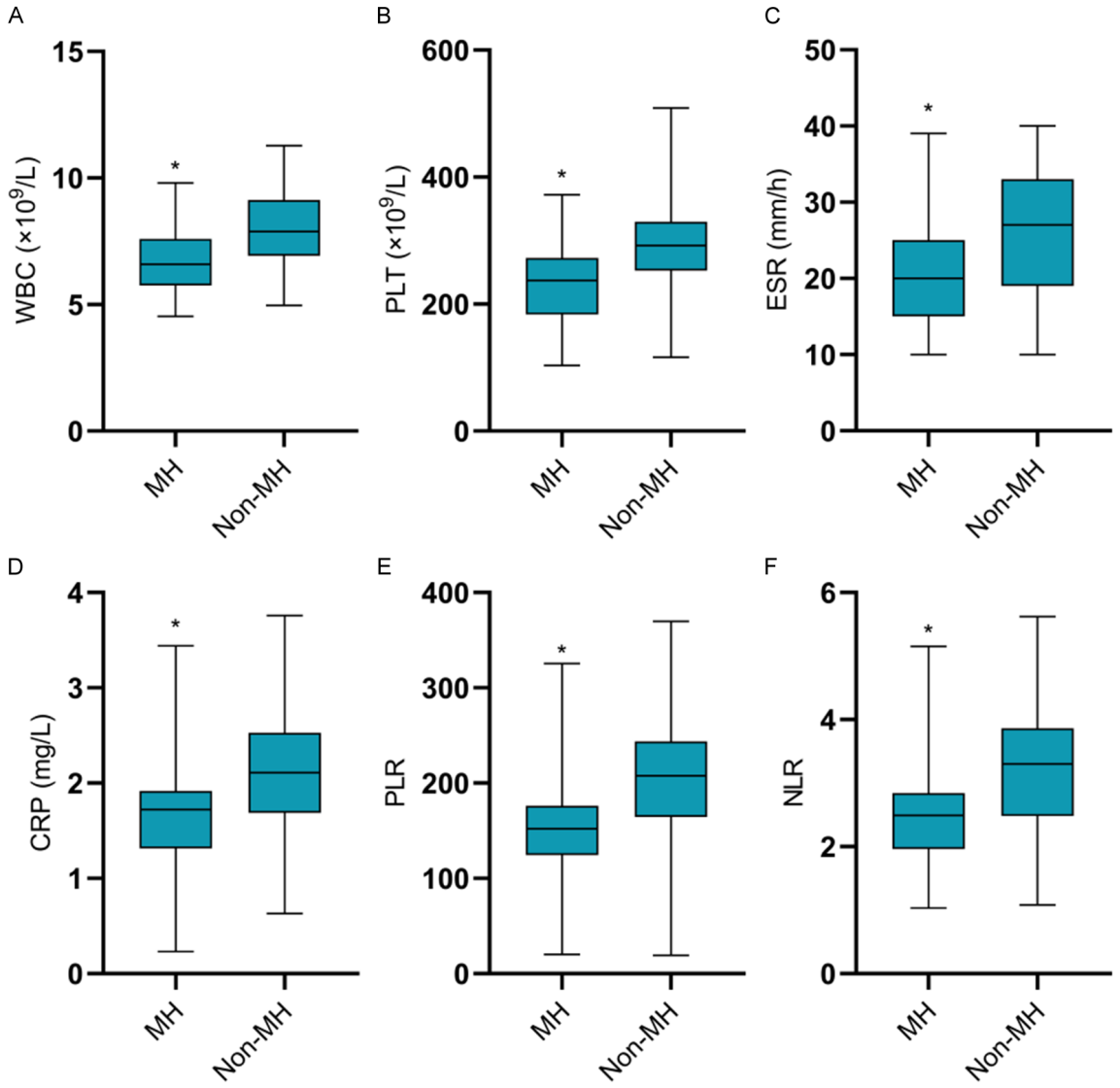

Figure 3. Serum marker levels in MH and non-MH patients. WBC: white blood cell; PLT: platelet count; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; PLR: platelet/lymphocyte ratio; NLR: neutrophil/lymphocyte ratio; MH: mucosal healing. *, $P < 0.05$, compared with the healthy control group.

PLT, ESR, CRP, PLR, and NLR in patients with IBD, patients with UC, and patients with CD were significantly higher than those in the healthy control group (all $P < 0.05$), see **Figure 2**.

Comparison of serum marker levels between patients with and without MH

A total of 97 out of 320 IBD patients achieved MH. Comparing the levels of each serum marker between MH and non-MH groups, it was found that WBC, PLT, ESR, CRP, PLR, and NLR were significantly lower in patients achieving MH than in those not (all $P < 0.05$), see **Figure 3**.

Diagnostic value of serum markers for MH

By plotting the ROC curves of serum marker indicators (WBC, PLT, ESR, CRP, PLR, and NLR) for diagnosis of MH, it was found that the AUCs of WBC, PLT, ESR, CRP, PLR, and NLR were 0.729, 0.756, 0.673, 0.707, 0791, and 0.724, respectively, demonstrating good diagnostic efficacy (**Table 2**; **Figure 4**).

Table 2. Diagnostic value of various serum marker for MH analyzed by ROC curve

	AUC	Sensitivity (%)	Specificity (%)	Cut-off value
WBC	0.729	76.23	60.82	> 6.920
PLT	0.756	63.68	80.41	> 277.595
ESR	0.673	53.81	78.35	> 25.500
CRP	0.707	61.88	81.44	> 1.995
PLR	0.791	56.50	92.78	> 199.800
NLR	0.724	63.23	82.47	> 2.980

WBC: white blood cell; PLT: platelet count; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; PLR: platelet/lymphocyte ratio; NLR: neutrophil/lymphocyte ratio; AUC: area under curve.

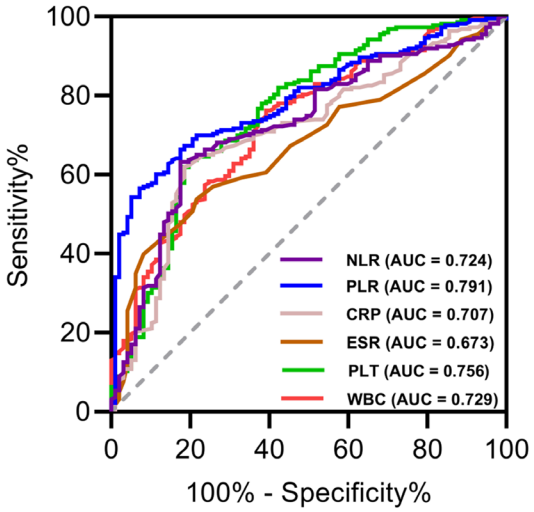

Figure 4. ROC curves of each serum marker in the diagnosis of MH. WBC: white blood cell; PLT: platelet count; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; PLR: platelet/lymphocyte ratio; NLR: neutrophil/lymphocyte ratio; MH: mucosal healing.

Univariate analysis of factors influencing MH

By univariate analysis of the indicators between MH and non-MH patients, it was found that there were statistical differences between the two groups in terms of fever, abdominal pain, WBC, PLT, ESR, CRP, PLR, and NLR (all $P < 0.05$), as shown in **Table 3**.

Multivariate analysis of factors affecting MH

The eight significant indicators in univariate analysis, fever, abdominal pain, WBC, PLT, ESR, CRP, PLR, and NLR were entered into the multivariate logistic regression analysis. The results revealed that abdominal pain (OR: 2.155, 95% CI: 1.081-4.297, $P < 0.05$), higher WBC (OR: 3.927, 95% CI: 2.008-7.681, $P < 0.001$), higher PLT (OR: 4.181, 95% CI: 2.078-8.412, $P < 0.001$), higher ESR (OR: 2.221, 95% CI: 1.082-4.562, $P < 0.05$), higher CRP (OR: 3.874, 95% CI: 1.861-8.065, $P < 0.001$), higher PLR (OR: 4.087, 95% CI: 1.586-10.534, $P < 0.01$), and higher NLR (OR: 2.688, 95% CI: 1.292-5.592, $P < 0.01$) were independent risk factors for patients' inability to achieve MH, while the presence of fever was not ($P > 0.05$), and the results are shown in **Table 4**.

Discussion

Numerous studies have established achieving clinical remission as the primary treatment goal for inflammatory bowel disease (IBD) [24]. However, achieving short-term clinical remission does not necessarily improve the long-term natural progression of IBD and long-term prognostic indicators, such as surgery and hospitalization rates [25]. A fundamental issue of IBD is the damage to the intestinal mucosal barrier, which facilitates the entry of microbes and other antigens into the internal environment, leading to uncontrolled immune activation [26]. Mucosal healing (MH) aims to restore this compromised barrier, reducing bacterial infiltration and subsequent immune reactions. As such, MH is anticipated to be a novel therapeutic target and endpoint [27, 28].

This study initially compared the levels of WBC, PLT, ESR, CRP, PLR, and NLR across different groups. It was found that IBD patients, including ulcerative colitis (UC) patients and Crohn's disease (CD) patients, exhibited significantly higher levels of WBC, PLT, ESR, CRP, PLR, and NLR compared to healthy subjects, indicating a heightened inflammatory response in IBD patients. Among the 320 IBD patients in this study, 97 achieved MH. A comparison revealed that the levels of WBC, PLT, ESR, CRP, PLR, and NLR in the MH group were significantly lower than those in the non-MH group, suggesting that reducing the inflammatory response, inflammatory mediator release, and achieving immune homeostasis may be beneficial for IBD patients to attain MH. Yang et al. [29] mentioned that 25(OH)D levels in CD patients were inversely related to disease activity and affected intestinal inflammation by affecting the Treg/Th17 balance. As patients' disease activity increases, ESR and PLT also

Table 3. Univariate analysis

	MH (n=97)	Non-MH (n=223)	t/χ^2	P
Age (years)	38.02±8.43	38.90±9.77	0.771	0.441
Gender (Male/Female)	68/29	141/82	1.410	0.235
BMI	21.73±3.05	21.95±2.93	0.616	0.538
Clinical manifestations, n (%)				
Fever	36 (38.14)	118 (52.47)	5.554	0.018
Diarrhea	49 (52.58)	140 (61.88)	2.421	0.120
Abdominal pain	58 (59.79)	162 (72.65)	5.197	0.023
Bloody stool	48 (49.48)	121 (54.26)	0.619	0.432
History of intestinal surgery (Yes/No)	9/88	26/197	1.978	0160
WBC			40.804	< 0.001
> 6.920×10^9/L	38 (39.18)	170 (76.23)		
≤ 6.920×10^9/L	59 (60.82)	53 (23.77)		
PLT			52.562	< 0.001
> 277.595×10^9/L	19 (19.59)	142 (63.68)		
≤ 277.595×10^9/L	78 (80.41)	81 (36.32)		
ESR			28.369	< 0.001
> 25.500 mm/h	21 (21.65)	120 (53.81)		
≤ 25.500 mm/h	76 (78.35)	103 (46.19)		
CRP			47.522	< 0.001
> 1.995 mg/L	22 (22.68)	144 (64.57)		
≤ 1.995 mg/L	75 (77.32)	79 (35.43)		
PLR			67.605	< 0.001
> 199.800	7 (7.22)	126 (56.50)		
≤ 199.800	90 (92.78)	97 (43.50)		
NLR			56.49	< 0.001
> 2.980	17 (17.53)	141 (63.23)		
≤ 2.980	80 (82.47)	82 (36.77)		

BMI: Body Mass Index; WBC: white blood cell; PLT: platelet count; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; PLR: platelet/lymphocyte ratio; NLR: neutrophil/lymphocyte ratio.

Table 4. Multivariate analysis

	β	OR (95% CI)	P
Fever	0.234	1.264 (0.651-2.453)	0.488
Abdominal pain	0.768	2.155 (1.081-4.297)	0.029
WBC	1.368	3.927 (2.008-7.681)	< 0.001
PLT	1.430	4.181 (2.078-8.412)	< 0.001
ESR	0.798	2.221 (1.082-4.562)	0.030
CRP	1.354	3.874 (1.861-8.065)	< 0.001
PLR	1.408	4.087 (1.586-10.534)	0.004
NLR	0.989	2.688 (1.292-5.592)	0.008

WBC: white blood cell; PLT: platelet count; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; PLR: platelet/lymphocyte ratio; NLR: neutrophil/lymphocyte ratio.

rise. Receiver operating characteristic (ROC) analysis revealed that the area under the curves (AUCs) for WBC, PLT, ESR, CRP, PLR, and NLR in diagnosing MH were 0.729, 0.756, 0.673, 0.707, 0.791 and 0.724, respectively, with good diagnostic performance. Another study by Soufli et al. [30] mentioned that NLR and PLR served as useful biomarkers for Crohn's disease and could predict the treatment response. Şimşek-Onat et al. [31] mentioned that the NLR value of children with IBD in the active phase was significantly higher than that in the remission phase, and the NLR value of children with CD was significantly higher than that of UC.

This study focused on identifying the independent factors that impede MH in patients with IBD. The univariate analysis identified fever, abdominal pain, WBC, PLT, ESR, CRP, PLR, and NLR as potential influencers that

correlated with failure to achieve MH. Further, multivariate logistic regression analysis confirmed that severe abdominal pain, elevated levels of WBC, PLT, ESR, CRP, PLR, and NLR independently increased the risk of not achieving MH. Significant abdominal pain could lead to profound mucosal injury, potentially disrupting the mucosal healing process. Additionally, such pain could negatively impact treatment outcomes [32, 33], as patients suffering from it often exhibit increased healthcare resource utilization and a higher propensity to develop depression, thus complicating and increasing the costs associated with managing IBD [34, 35]. Abdominal discomfort in IBD is usually monitored through common metrics like WBC, ESR, and C-reactive muscle score (CMS). Inflammatory markers such as WBC, ESR, CRP, PLR, and NLR reflect the underlying inflammatory nature of IBD's. Elevated levels of these markers typically denote active disease and mucosal damage, complicating the process of mucosal healing [36]. Moreover, an increase in PLT is also recognized as an inflammation indicator, as platelets accumulate at inflammation sites to enhance the inflammatory response and participate in vascular regeneration and wound healing. Consequently, high PLT counts in IBD may amplify the inflammatory response, posing challenges to mucosal healing [37]. The study by Schellenberg et al. [38] highlighted significant platelet aggregation in IBD mice, where an increased PLR correlated with a severely worsened colitis condition. PLR and NLR mirror a complex interaction between inflammation and immune response. Their elevated levels suggest an intensified inflammatory and immune response, indicating ongoing mucosal damage and destruction, which could hinder the mucosal healing process.

The innovation of this study lies in comprehensive evaluation of the diagnostic value of multiple serological markers, including PA, ALB, CRP, ESR, WBC, PLR, and NLR, for MH in IBD patients, introducing a possibility for non-invasive diagnosis of IBD and reducing the reliance on invasive examinations. At the same time, this study also identified independent factors that affect mucosal healing in IBD patients. It facilitates physicians in monitoring the therapeutic effects and adjusting treatment plans in a timely manner. Moreover, using these serum biomarkers as diagnostic tools may be cost-effective, as they are easily accessible, making them suitable for medical environments with limited resources.

While this study contributes valuable insights into the non-invasive diagnosis of MH in IBD using serological markers, its retrospective design introduces potential biases, marking a significant limitation. Another drawback is the lack of statistical analysis on the relationship between the patients' treatment regimen, including immunomodulators, glucocorticoids, and biologics, and serological markers, which could influence these markers. Nonetheless, the serological markers discussed in this study are advantageous for their accessibility, cost-effectiveness, simplicity, and ease of measurement in clinical settings, allowing for evaluation across different institutions.

In conclusion, WBC, PLT, ESR, CRP, PLR, and NLR are proven to be noninvasive markers for MH in IBD patients, offering valuable clinical application insight.

Disclosure of conflict of interest

None.

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