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ORIGINAL RESEARCH

Systemic Immune-Inflammation Index: A Promising, Non-Invasive Biomarker for Crohn's Disease Activity and Severity Assessment

Yu'en Deng[1,2], Ting Fu[1], Dian Gao[3], Jianming Zhou[1], Xinhua Nie[1], Fenfen Wang[1], Qiongfang Yu[1]

[1]Department of Gastroenterology and Hepatology, The Second Affiliated Hospital, Jiangxi Medical College, Nanchang University, Nanchang, 330006, People's Republic of China; [2]Huankui Academy, Jiangxi Medical College, Nanchang University, Nanchang, 330031, People's Republic of China; [3]Department of Pathogen Biology and Immunology, Jiangxi Medical College, Nanchang University, Nanchang, 330006, People's Republic of China

Correspondence: Qiongfang Yu, Department of Gastroenterology and Hepatology, The Second Affiliated Hospital, Jiangxi Medical College, Nanchang University, Minde Road 1, Nanchang, 330006, People's Republic of China, Email qiongfangyu@yeah.net

Purpose: Crohn's disease (CD) is a chronic inflammatory disorder with periods of exacerbation and remission. We aim to evaluate the systemic immune-inflammation index (SII) as a prognostic biomarker in CD and its utility in predicting disease activity and severity.

Patients and Methods: This retrospective study analyzed CD patients using the Harvey-Bradshaw index (HBI) for disease stratification and the Simple Endoscopic Score for Crohn's Disease (SES-CD) for post-treatment evaluation. Data analysis was conducted using R software. Serological indices underwent predictive analysis through the receiver operating characteristic (ROC) curve. The least absolute shrinkage and selection operator (LASSO) regression and multivariate logistic regression identified independent prognostic factors to construct nomograms. Model validation was performed using the Concordance index (C-index), calibration analysis and decision curve analysis (DCA).

Results: In this study, 254 patients with Crohn's disease (CD) were enrolled, including 171 males and 83 females, with ages ranging from 13 to 74. SII was significantly elevated in active CD ($p<0.001$), correlating with disease severity ($p<0.001$). Although SII decreased in patients with mucosal healing ($p<0.001$), its prognostic accuracy (AUC=0.719) was lower than other biomarkers. However, SII emerged as an independent predictor for CD activity and severity with higher efficacy (AUC=0.774 and 0.807). The CD activity and severity prediction nomograms showed high C-indices (0.8038 and 0.8208), indicating strong predictive performance.

Conclusion: SII is a valuable biomarker for assessing CD severity and monitoring mucosal healing post-treatment. The SII-based nomograms offer a reliable model for evaluating CD progression, aiding in personalized treatment approaches and enhancing clinical decision-making. We recommend randomized controlled trials (RCTs) or studies with larger sample sizes to improve the model.

Keywords: Crohn's disease, biomarkers, inflammation, nomograms, disease progression

Introduction

Crohn's disease (CD) is a chronic intestinal disorder of multifactorial etiology, characterized by a relapsing-remitting condition but currently lacking a definitive cure.[1] This global disease has progressively increased incidence and prevalence.[2] The clinical spectrum of CD is heterogeneous, with patients often cycling through phases of symptom exacerbation and remission.[3] In periods of active disease, individuals may present with a constellation of gastrointestinal symptoms, including abdominal pain and diarrhea, alongside systemic and extraintestinal manifestations.[4] The pathological hallmarks of CD encompass chronic inflammation, mesenteric thickening, fistulas, and abscesses. Mucosal healing (MH), defined as the resolution of intestinal inflammation and ulceration, represents a critical therapeutic objective in CD patients.[5] In clinical practice, the assessment of MH post-treatment is predominantly conducted through invasive procedures such as endoscopy and tissue biopsy.[6] Given the invasive nature of these methods and the impracticality of frequent re-evaluations, there is a compelling desire for safer, more accessible, and non-invasive diagnostic means.[7] Such advancements would enable more precise evaluation of disease activity, facilitate timely intervention to control inflammation, and ultimately enhance

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patient outcomes. The emerging focus on comprehensive bowel assessment in CD, utilizing imaging and blood-based biomarkers, holds promise for significant advancements in the non-invasive evaluation of disease status.[8]

Serological markers have been extensively utilized in the evaluation of CD activity due to their objective nature and minimally invasive characteristics.[9] However, conventional markers like C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are not without limitations, as they can be elevated in a variety of conditions, including both infectious and non-infectious inflammations.[10,11] Pan et al proposed neutrophil-to-pre-albumin ratio (NPAR), a novel blood serum ratio, and demonstrated its value in predicting IBD patients' disease activity.[12] This has enlightened us to search for more specific and convenient biomarkers that can accurately reflect the disease activity in CD. The C-reactive protein to albumin ratio (CAR), a novel biomarker that integrates CRP and albumin levels, has emerged as a potentially useful indicator of CD disease activity.[13] Moreover, additional parameters within blood-based markers, such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR), and lymphocyte-to-CRP ratio (LCR), are increasingly recognized for their potential in assessing the activity of inflammatory conditions and prognostication in various clinical scenarios, including oncology.[14–16]

In recent years, the systemic immune-inflammation index (SII) has gained recognition as an innovative serological marker that quantifies the intensity of systemic inflammatory responses by integrating neutrophil, platelet, and lymphocyte counts. SII has demonstrated clinical utility in prognostically assessing autoimmune inflammatory conditions and tumor outcomes.[17,18] Specifically, the study by Wu et al revealed a significant positive correlation between SII levels and the inflammatory status and disease activity in patients with ankylosing spondylitis.[19] In this study, SII offers superior discriminative capabilities for disease activity compared to conventional markers such as CRP and ESR. Further research by Lin et al has shown that SII outperforms other novel markers, including PLR and NLR, in predicting active ulcerative colitis (UC), while the CRP-to-lymphocyte ratio (CLR) was found to have the highest predictive accuracy for severe UC.[20] These findings suggest that SII may provide a valuable adjunct in the prognostic evaluation of CD, potentially offering a more precise assessment of disease prognosis.

The present investigation conducted a comprehensive analysis to evaluate and compare the efficacy of the aforementioned inflammatory markers in the assessment of CD activity, severity, and the prediction of MH following therapeutic intervention. Additionally, a binary logistic regression model was developed and validated to forecast the disease progression in CD patients.

Materials and Methods

Study Design and Patients

A retrospective case-control study was conducted to assess the prognostic utility of various inflammatory markers in CD. The study population comprised patients diagnosed with CD from April 2012 to December 2023, with data extracted from the medical records of the Second Affiliated Hospital of Nanchang University. Inclusion criteria were based on diagnoses that met the criteria set forth in the Chinese Consensus on the Diagnosis and Treatment of Inflammatory Bowel Disease (Beijing, 2018) and the World Gastroenterology Organization Global Guidelines: Inflammatory Bowel Disease Update (August 2015).[21] Patients with other inflammatory bowel disease (IBD), active infections during treatment, or incomplete blood test data were excluded from the analysis. Disease progression was evaluated at the time of initial admission using the simplified Crohn's disease activity index (CDAI), also known as the Harvey-Bradshaw index (HBI). Patients were stratified into three groups based on their HBI scores: remission (HBI $\leq$ 4), mild activity (HBI=5–7), or moderate-severe activity (HBI $\geq$ 8).[22] HBI has a good correlation with CDAI in assessing the activity of Crohn's disease patients, and now it serves as a common alternative in clinical practice.[23]

MH was assessed for patients who received 1 to 6 months' treatment and achieved clinical remission (HBI $\leq$ 4). Patients who achieved clinical remission received various treatments. The major types of medications include aminosalicylate therapy, steroid therapy, immunosuppressive therapy, and biologics. Then, patients were re-estimated with endoscopic examinations and classified into either the mucosal healing (SES-CD =0–2) or non-mucosal healing groups (SES-CD $\geq$ 3) according to the Simple Endoscopic Score for Crohn's Disease (SES-CD).[24] Two assessors independently scored the patients, and any inter-rater discrepancies were adjudicated through consensus with a third assessor. The study

adhered to the principles of the Declaration of Helsinki and was approved by the Ethics Committee of the Second Affiliated Hospital of Nanchang University. Due to the study's retrospective nature, informed consent from individual participants was exempted by the ethics committee.

Data Collection

Clinical and serological data were meticulously collected at the time of initial hospital admission and from patients who subsequently achieved clinical remission following treatment. Extracted from the medical records were results from standard blood tests, including the complete white blood cell count, differential counts of neutrophils, lymphocytes, monocytes, and the total platelet count. Furthermore, levels of CRP, ESR, and serum albumin were documented. Series of inflammatory indices were calculated based on these parameters: NLR, PLR, LMR, SII, CAR, and LCR. These ratios were determined using the following formulae: NLR (neutrophil count/lymphocyte count), PLR (platelet count/lymphocyte count), LMR (lymphocyte count/monocyte count), SII (platelet count×NLR), CAR (CRP/albumin), and LCR (lymphocyte count/CRP). These calculated ratios serve as valuable markers for assessing inflammation and may provide insights into disease activity and prognosis in patients with CD.

Statistical Analysis

All statistical analyses were conducted using R software version 4.2.2. For the analysis of between-group differences, the "CBCgrps" package was employed.[25] Numerical variables adhering to a normal distribution were described using mean values ± standard deviation (SD). Conversely, variables that did not conform to a normal distribution were reported using medians and interquartile ranges (IQR). Continuous and categorical variables were represented as median (IQR) and number (proportion), respectively. Receiver operating characteristic (ROC) curve analysis was conducted using the "rms" and "pROC" to evaluate the predictive performance of the biomarkers, with the area under the curve (AUC) serving as the primary metric for predictive accuracy.

Inflammatory markers were identified using the least absolute shrinkage and selection operator (LASSO) regression, which effectively selects the most relevant predictors. Multivariate logistic regression analysis was applied to ascertain independent predictors and construct nomograms to predict disease progression in CD. The internal validity of the models was assessed through bootstrap resampling with 1000 repetitions. The Concordance index (C-index) was utilized to quantify the model's predictive accuracy, and calibration plots were generated to visualize the agreement between predicted and observed outcomes. The clinical utility of the predictive models was further appraised using decision curve analysis (DCA), which evaluates the net benefit of a test across different threshold probabilities. A p-value of less than 0.05 was considered indicative of statistical significance.

Results

Patient Enrollment

During the study period, 259 patients were diagnosed with CD. Due to incomplete data collection, the data from 5 patients were excluded from the analysis, resulting in a study population of 254 patients who fulfilled the inclusion criteria. Within this population, 96 patients were identified to be in remission at the time of the study, and 158 patients were classified as being in the activity group. Upon further categorization of the active disease group, it was found that 94 patients exhibited mild disease activity, whereas 64 patients presented with moderate-to-severe disease activity (as depicted in Figure 1). Following the intervention, 107 patients achieved clinical remission. An additional patient's data was omitted from the analysis due to the absence of pertinent data. Endoscopic assessments were performed, and it was noted that 53 patients demonstrated complete mucosal healing.

Clinical Characteristics of Patients

Table 1 displays the demographic and clinical characteristics of the study participants enrolled in the study. A comparison between the activity group and the remission group revealed that patients in the activity group had significantly elevated levels of CRP, ESR, SII, NLR, PLR, and CAR (all p-values < 0.001). In contrast, the levels of LMR and LCR were significantly lower in

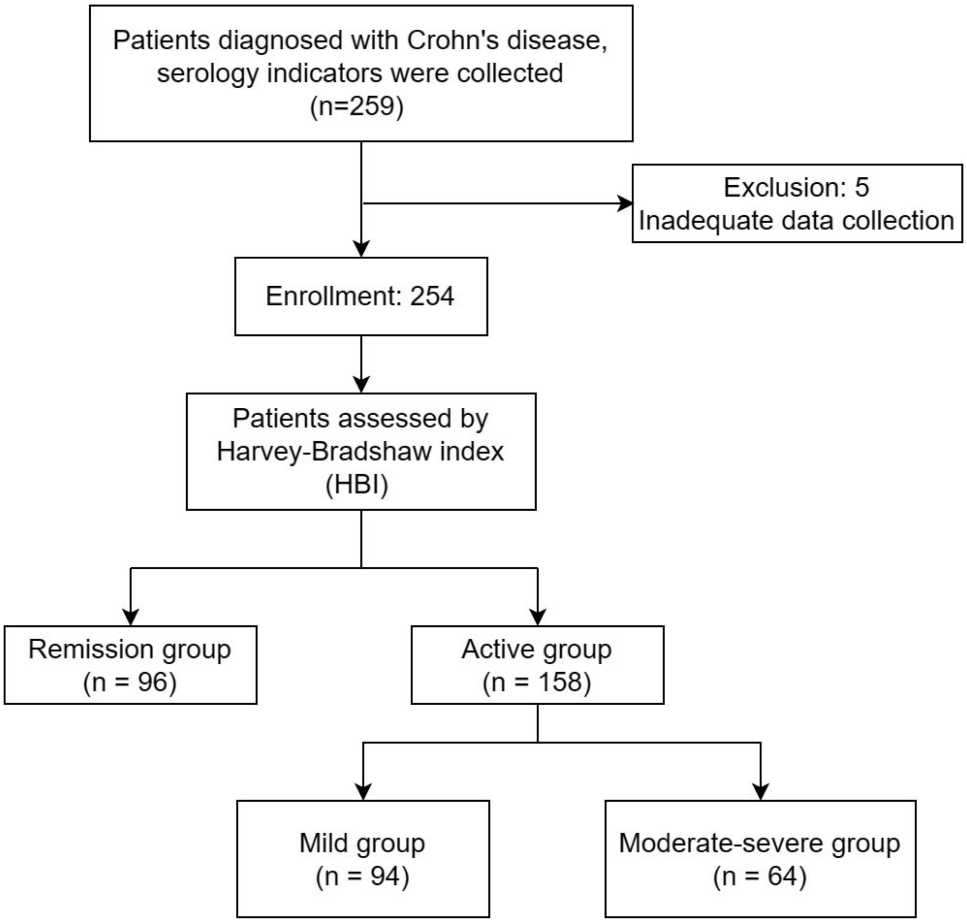

Figure 1 Flow diagram of patient enrollment and grouping.

the activity group compared to the remission group. Consistent with these findings, a comparison of the moderate-to-severe group with the mild group (as shown in Table 2) yielded similar trends, with the former exhibiting higher inflammatory markers and lower LMR and LCR values. Post-treatment analysis indicated that the non-mucosal healing group had significantly increased levels of SII, NLR, PLR, CAR, CRP, and ESR, and conversely, decreased LMR and LCR values compared to the mucosal healing group (as detailed in Table 3).

Evaluation of Inflammatory Biomarkers for Predicting CD Activity and Severity

ROC curve analysis was conducted to determine the predictive efficacy of inflammatory biomarkers for CD activity and severity, as depicted in Figure 2A and B. The results, detailed in Table 4, highlight the optimal cut-off points, along with the corresponding specificity and sensitivity values for each biomarker. SII demonstrated the greatest AUC of 0.774 for activity prediction, surpassing the AUC values of LCR, CAR, NLR, PLR, ESR and LMR, which were 0.763, 0.751, 0.720, 0.719, 0.716, and 0.710, respectively. Notably, SII's predictive power was marginally superior to that of CRP, which had an AUC of 0.774. In terms of predicting disease severity, SII again exhibited the most significant AUC at 0.807, leading the pack of biomarkers. The subsequent biomarkers in terms of predictive power were PLR, NLR, LMR, LCR, CAR, CRP, and ESR, with AUC values of 0.749, 0.734, 0.689, 0.662, 0.658, 0.642, and 0.620, respectively.

Predictive Performance of Inflammatory Markers for MH

ROC curve analysis was utilized to evaluate the prognostic accuracy of inflammatory markers in predicting MH among patients who achieved clinical remission following a single treatment course. The findings indicated that LCR, with an

Table 1 Baseline Characteristics of the 254 Patients With Crohn's Disease (CD)

Variables	Total (n=254)	Remission Group (n=96)	Active Group (n=158)	p-value
Age (year)	27 (21, 44)	32 (22, 48)	25 (20, 35.75)	0.002
Sex, n (%)				0.179
Female	83 (33)	26 (27)	57 (36)	
Male	171 (67)	70 (73)	101 (64)	
WBC ($\times10^9$/L)	6.92 (5.28, 9.23)	5.8 (4.58, 7.62)	8.14 (5.87, 10.25)	< 0.001
Neutrophil Count ($\times10^9$/L)	4.88 (3.28, 6.94)	3.6 (2.84, 5.17)	5.97 (3.73, 7.5)	< 0.001
Lymphocyte Count ($\times10^9$/L)	1.31 (1.02, 1.67)	1.38 (1.09, 1.74)	1.26 (1.01, 1.62)	0.102
Monocyte Count ($\times10^9$/L)	0.53 (0.37, 0.74)	0.41 (0.31, 0.57)	0.6 (0.41, 0.82)	< 0.001
Platelet Count ($\times10^9$/L)	328.5 (242.25, 406.5)	260.5 (212.25, 323.25)	366.5 (290.75, 455)	< 0.001
Albumin (g/L)	36.9 (31.82, 42.26)	40.19 (35.29, 44.06)	35.41 (31.03, 40.52)	< 0.001
CRP (mg/L)	33.55 (10.1, 71.77)	9.88 (2.47, 33.5)	48.41 (24.44, 90.18)	< 0.001
ESR (mm/h)	38 (17.25, 63.75)	20.5 (8.83, 47.25)	49 (27.25, 67.75)	< 0.001
SII	1204.42 (680.47, 2078.09)	706.08 (445.23, 1274.54)	1643.36 (981.65, 2738.35)	< 0.001
NLR	3.64 (2.55, 5.95)	2.8 (1.93, 3.79)	4.62 (3.04, 6.64)	< 0.001
PLR	243.78 (171.67, 359.28)	187.64 (136.06, 260.37)	288.06 (209.27, 399.78)	< 0.001
LMR	2.41 (1.65, 3.54)	2.99 (2.22, 4.87)	1.97 (1.53, 2.96)	< 0.001
CAR	0.88 (0.27, 2.18)	0.31 (0.06, 0.97)	1.41 (0.61, 2.86)	< 0.001
LCR	0.04 (0.02, 0.13)	0.11 (0.04, 0.57)	0.03 (0.01, 0.06)	< 0.001

Abbreviations: WBC, white blood cell; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; SII, systemic immune-inflammation index; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; LMR, lymphocyte-monocyte ratio; CAR, C-reactive protein to albumin ratio; LCR, lymphocyte-CRP ratio.

Table 2 Baseline Characteristics of the 158 Crohn's Disease (CD) Patients Who Were in the Active Group

Variables	Total (n=158)	Mild Group (n=94)	Moderate-Severe Group (n=64)	p-value
Age (year)	25 (20, 35.75)	26 (20, 35.75)	23.5 (20, 35.75)	0.559
Sex, n (%)				0.843
Female	57 (36)	35 (37)	22 (34)	
Male	101 (64)	59 (63)	42 (66)	
WBC ($\times10^9$/L)	8.14 (5.87, 10.25)	6.92 (5.5, 9.63)	8.86 (7.38, 11.4)	< 0.001
Neutrophil Count ($\times10^9$/L)	5.97 (3.73, 7.5)	4.96 (3.52, 6.96)	6.7 (5.49, 9.49)	< 0.001
Lymphocyte Count ($\times10^9$/L)	1.26 (1.01, 1.62)	1.33 (1.04, 1.71)	1.23 (0.93, 1.47)	0.018
Monocyte Count ($\times10^9$/L)	0.6 (0.41, 0.82)	0.54 (0.4, 0.76)	0.69 (0.48, 0.97)	0.020
Platelet Count ($\times10^9$/L)	374.07 ± 125.36	338.66 ± 118.45	426.08 ± 117.62	< 0.001
Albumin (g/L)	35.41 (31.03, 40.52)	36.77 (32.41, 41.07)	32.74 (30.38, 36.91)	0.003
CRP (mg/L)	48.41 (24.44, 90.18)	39.59 (17, 79.66)	56.62 (35.57, 105.34)	0.002
ESR (mm/h)	49 (27.25, 67.75)	39.5 (23, 64.75)	58.5 (33, 77.25)	0.010
SII	1643.36 (981.65, 2738.35)	1257.47 (751.93, 1760.74)	2745.41 (1744.9, 3810.89)	< 0.001
NLR	4.62 (3.04, 6.64)	3.84 (2.77, 5.44)	6.11 (4.03, 8.38)	< 0.001
PLR	288.06 (209.27, 399.78)	231.65 (185.06, 335.48)	358.94 (276.38, 503.21)	< 0.001
LMR	1.97 (1.53, 2.96)	2.34 (1.67, 3.38)	1.7 (1.23, 2.2)	< 0.001
CAR	1.41 (0.61, 2.86)	1.02 (0.42, 2.2)	1.66 (1.03, 3.36)	< 0.001
LCR	0.03 (0.01, 0.06)	0.03 (0.01, 0.09)	0.02 (0.01, 0.03)	< 0.001

Abbreviations: WBC, white blood cell; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; SII, systemic immune-inflammation index; NLR,neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; LMR, lymphocyte-monocyte ratio; CAR, C-reactive protein to albumin ratio; LCR, lymphocyte-CRP ratio.

AUC of 0.794, provided superior predictive accuracy for MH compared to other commonly used blood markers, as illustrated in Figure 2C. The predictive efficacy of LCR was notably higher than that of the CAR, CRP, ESR, PLR, SII, NLR, and LMR, with respective AUC values of 0.790, 0.789, 0.741, 0.720, 0.719, 0.696, and 0.690.

Table 3 Baseline Characteristics of the 106 Crohn's Disease (CD) Patients Who Achieved Clinical Remission

Variables	Total (n=106)	Mucosal Healing Group (n=53)	Non-Mucosal Healing Group (n=53)	p-value
Age (year)	25 (21, 37.5)	26 (20, 40)	25 (22, 31)	0.4
Sex, n (%)				1
Female	31 (29)	15 (28)	16 (30)	
Male	75 (71)	38 (72)	37 (70)	
WBC ($\times 10^9$/L)	5.8 (4.92, 7.13)	5.92 (4.93, 6.85)	5.58 (4.92, 7.67)	0.952
Neutrophil Count ($\times 10^9$/L)	3.79 (2.98, 4.73)	3.67 (2.77, 4.65)	4.02 (3.22, 4.92)	0.150
Lymphocyte Count ($\times 10^9$/L)	1.44 (1.06, 1.9)	1.66 (1.32, 2.06)	1.25 (0.83, 1.65)	< 0.001
Monocyte Count ($\times 10^9$/L)	0.4 (0.31, 0.51)	0.38 (0.32, 0.46)	0.41 (0.31, 0.57)	0.525
Platelet Count ($\times 10^9$/L)	247.5 (215, 299)	237 (199, 276)	269 (231, 333)	0.011
Albumin (g/L)	43.42 (40.45, 46.17)	45 (40.62, 47.83)	42.52 (40.07, 44.87)	0.017
CRP (mg/L)	5.02 (1.64, 16.5)	2.17 (0.5, 5.03)	10.44 (5, 33.44)	< 0.001
ESR (mm/h)	17.5 (5.5, 36.75)	10 (4, 22)	27 (12, 49)	< 0.001
SII	616.82 (426.65, 1122.75)	493.95 (350.11, 778.08)	729.3 (548.07, 1448.45)	< 0.001
NLR	2.64 (1.79, 3.9)	2.13 (1.64, 3.37)	3.21 (2.15, 5.3)	< 0.001
PLR	172.68 (123.62, 267.82)	148 (106.74, 198.95)	222.4 (144.85, 324.1)	< 0.001
LMR	3.6 (2.76, 4.97)	4.28 (3.28, 5.22)	3.18 (2.32, 4.18)	< 0.001
CAR	0.11 (0.03, 0.41)	0.04 (0.01, 0.11)	0.25 (0.11, 0.8)	< 0.001
LCR	0.28 (0.06, 1.15)	0.84 (0.34, 3.3)	0.14 (0.03, 0.28)	< 0.001

Abbreviations: WBC, white blood cell; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; SII, systemic immune-inflammation index; NLR,neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; LMR, lymphocyte-monocyte ratio; CAR, C-reactive protein to albumin ratio; LCR, lymphocyte-CRP ratio.

Establishment and Verification of a Predictive Nomogram for CD

The construction of the nomogram was predicated on prognostic variables derived from the LASSO and multivariate logistic regression. For the prediction of patients in the active phase of CD, LASSO regression incorporated five key variables: CRP, ESR, SII, PLR, and LMR, as depicted in Figure 3A and B. Simultaneously, when evaluating disease severity, only three variables were selected: ESR, SII, and PLR, shown in Figure 3C and D. In the subset of patients who attained clinical remission following a single treatment course, four variables were chosen, including ESR, SII, PLR, and LCR, as illustrated in Figure 3E and F.

A multivariate logistic regression analysis was performed to develop predictive models for the progression of CD, incorporating variables identified by the LASSO regression (refer to Table 5). The analysis revealed that CRP and SII were

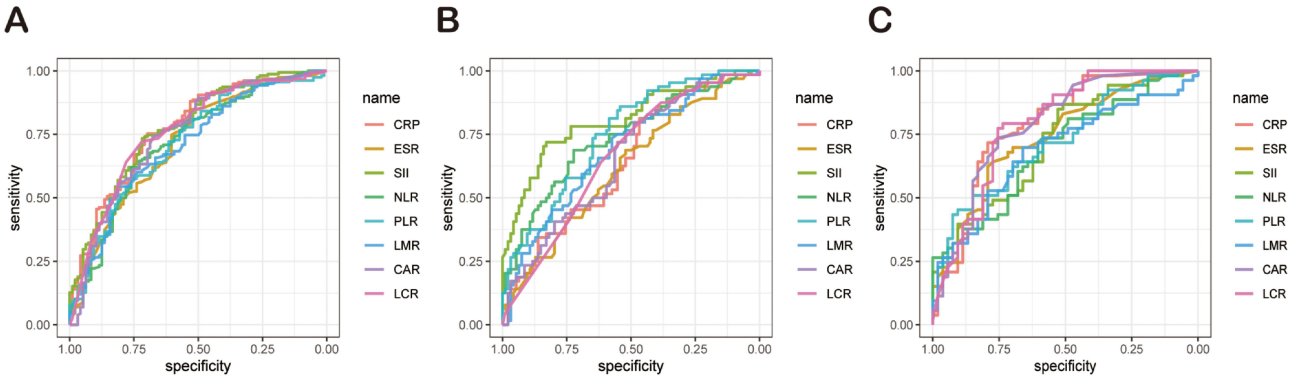

Figure 2 Receiver operating characteristic (ROC) curves of inflammation indices for predicting Crohn's disease (CD) activity (**A**), severity (**B**), and mucosal healing (**C**). **Abbreviations**: ROC, receiver operating characteristic; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; SII, systemic immune-inflammation index; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; CAR, C-reactive protein to albumin ratio; LCR, lymphocyte-CRP ratio; CD, Crohn's disease.

Table 4 AUC (Area Under Curve) in Predicting Crohn's Disease (CD) Activity, CD Severity and Mucosal Healing

AUC (95% CI)		Cutoff Point	Specificity	Sensitivity
AUC in predicting CD activity				
CRP	0.774 (0.714–0.833)	23.395	0.698	0.753
ESR	0.716 (0.650–0.782)	21.500	0.531	0.848
SII	0.774 (0.715–0.833)	1092.440	0.719	0.734
NLR	0.720 (0.654–0.786)	3.855	0.760	0.620
PLR	0.719 (0.653–0.784)	261.655	0.760	0.576
LMR	0.710 (0.644–0.776)	2.095	0.812	0.544
CAR	0.751 (0.688–0.815)	0.630	0.677	0.741
LCR	0.763 (0.702–0.825)	0.045	0.719	0.722
AUC in predicting CD severity				
CRP	0.642 (0.556–0.729)	34.295	0.468	0.812
ESR	0.620 (0.532–0.709)	41.500	0.512	0.688
SII	0.807 (0.736–0.879)	1907.115	0.830	0.719
NLR	0.734 (0.654–0.815)	5.045	0.723	0.688
PLR	0.749 (0.674–0.824)	238.480	0.543	0.859
LMR	0.689 (0.606–0.773)	2.160	0.574	0.734
CAR	0.658 (0.573–0.743)	0.905	0.489	0.797
LCR	0.662 (0.580–0.745)	0.035	0.468	0.797
AUC in predicting mucosal healing				
CRP	0.789 (0.701–0.877)	5.495	0.792	0.717
ESR	0.741 (0.648–0.835)	22.500	0.774	0.642
SII	0.719 (0.623–0.816)	494.665	0.509	0.868
NLR	0.696 (0.596–0.795)	2.335	0.585	0.736
PLR	0.720 (0.624–0.817)	221.290	0.849	0.509
LMR	0.690 (0.588–0.792)	3.660	0.660	0.698
CAR	0.790 (0.703–0.877)	0.115	0.755	0.736
LCR	0.794 (0.707–0.880)	0.310	0.755	0.774

Notes: The best cut-off point was defined when the Youden index was maximized. When the Youden index corresponds to multiple cut-off values, the cut-off value with higher sensitivity was chosen to select out the patients with high disease activity as much as possible.

Abbreviations: AUC, area under receiver operating characteristic; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; SII, systemic immune-inflammation index; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; LMR, lymphocyte-monocyte ratio; CAR, C-reactive protein to albumin ratio; LCR, lymphocyte-CRP ratio, CD, Crohn's disease.

significant independent predictors for CD activity ($p < 0.05$). In the context of disease severity, SII and ESR emerged as independent predictors ($p < 0.05$). Based on these independent predictors, nomograms were crafted to facilitate CD activity and severity prediction. The nomogram, which integrates SII and CRP, effectively predicted CD activity, while the combination of SII and ESR could estimate disease severity (as shown in Figure 4A and B). These nomograms provided a graphical and quantitative model for predicting the disease progression in individuals with CD, offering a valuable tool for clinical decision-making. Significantly, the LCR was identified as the sole prognostic indicator for predicting mucosal healing ($p < 0.05$), underscoring its clinical relevance in the management and prognosis of CD.

For internal validation, we utilized the bootstrap method, which was performed 1000 times. This methodology yielded C-index values of 0.8038 and 0.8208 for the respective nomograms, indicating their predictive accuracy. To further evaluate the fit of the nomograms, we employed calibration curves (as depicted in Figure 5A and B). Moreover, we conducted DCA to illustrate the clinical utility of the nomograms (refer to Figure 6A and B). The overall net benefit of grading clinical progression in CD guided by our nomograms was higher than relying solely on a single risk factor, which contributes positively to clinical decision-making.

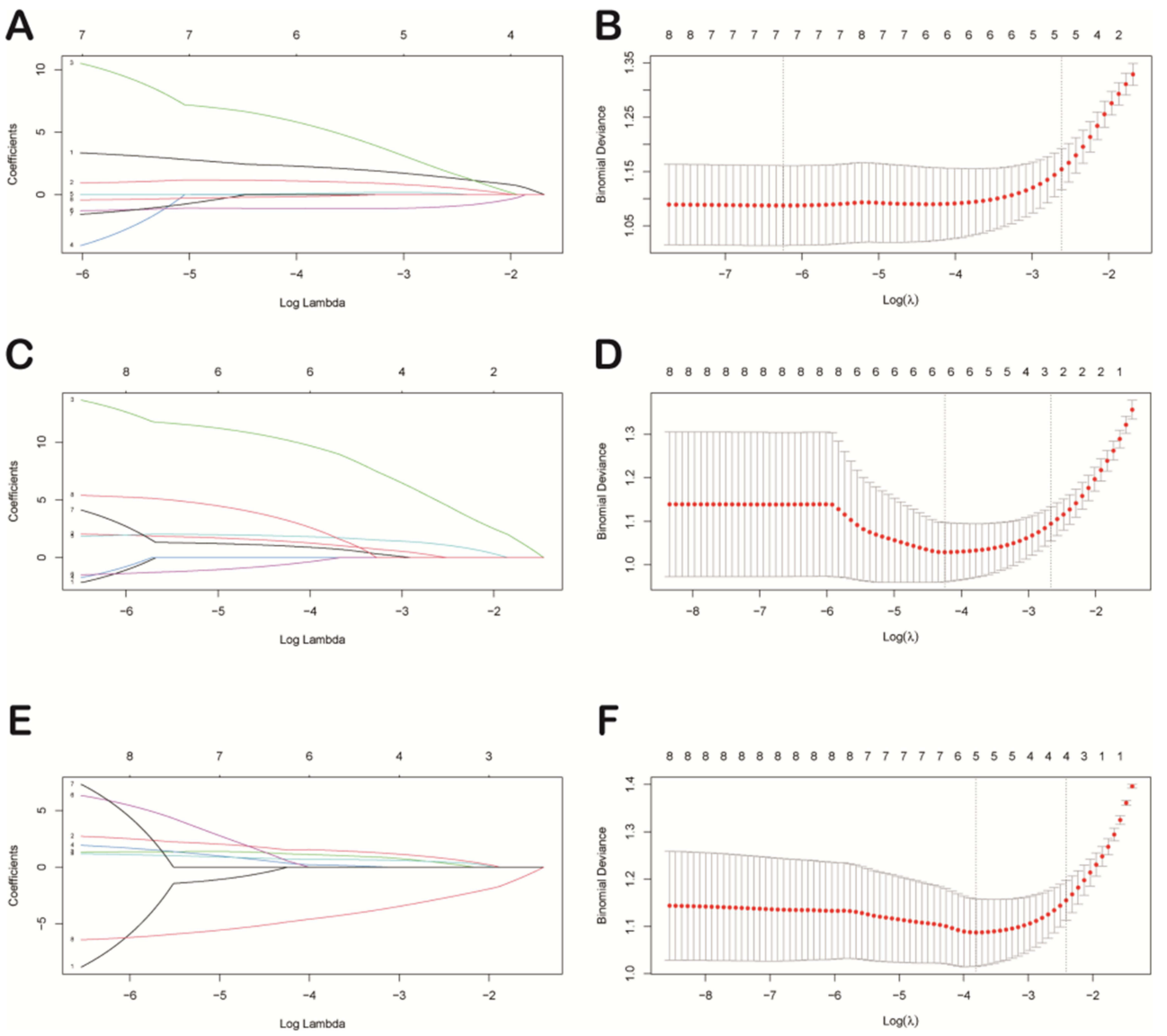

Figure 3 The least absolute shrinkage and selection operator (LASSO) regression analysis with tenfold cross-validation was used for predictor selection. (**A**) LASSO coefficient profiles of the eight risk factors to predict Crohn's disease (CD) activity. (**B**) Five risk factors (CRP, ESR, SII, PLR, and LMR) selected using LASSO regression analysis, based on the 1-SE criteria (right dotted line). (**C**) LASSO coefficient profiles of the eight risk factors to predict CD severity. (**D**) Three risk factors (ESR, SII, and PLR) selected using LASSO regression analysis. (**E**) LASSO coefficient profiles of the eight risk factors to predict mucosal healing. (**F**) Four risk factors (ESR, SII, PLR, and LCR) selected using LASSO regression analysis.

Abbreviations: CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; SII, systemic immune-inflammation index; PLR, platelet-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; LCR, lymphocyte-CRP ratio; LASSO, least absolute shrinkage and selection operator; SE, standard error.

Discussion

CD is a chronic and progressive form of IBD, characterized by an abnormal immune response to intestinal microorganisms in the intestinal mucosa.[26] The principal therapeutic objective in managing CD is to alleviate symptoms and induce clinical remission. Recently, there has been a growing focus on MH as a new treatment target due to advancements in our understanding of the disease and the use of immunosuppressants and biologics.[27] In clinical diagnostics, a spectrum of assessment techniques, including patient symptomatology review, radiologic imaging, endoscopic procedures, and histopathological analysis, are employed to gauge disease activity and patient status. These assessments are typically guided by a variety of scoring systems.[1] Nonetheless, these methodologies are not impervious to limitations. Subjectivity can influence scoring systems, and the invasive nature of endoscopic and biopsy procedures can lead to patient discomfort. These challenges underscore the need for a more efficient and less invasive disease monitoring and follow-

Table 5 Multivariate Logistic Regression Analysis in Predicting Crohn's Disease (CD) Activity, CD Severity and Mucosal Healing

Variables	OR (95% CI)	p-value
CD activity		
CRP	1.013 (1.004, 1.024)	0.009*
SII	1.001 (1.000, 1.001)	0.007*
ESR	1.011 (0.998, 1.025)	0.102
PLR	1.000 (0.997, 1.003)	0.968
LMR	0.924 (0.765, 1.100)	0.390
CD severity		
SII	1.001 (1.001, 1.002)	<0.001*
ESR	1.016 (1.002, 1.032)	0.035*
PLR	1.002 (0.999, 1.005)	0.266
CD mucosal healing		
SII	1.000 (1.000, 1.002)	0.474
ESR	1.014 (0.994, 1.039)	0.208
PLR	1.001 (0.994, 1.008)	0.721
LCR	0.394 (0.169, 0.699)	0.008*

Notes: Variables* with P-values less than 0.05 were selected.
Abbreviations: OR, odds ratio; 95% CI: 95% confidence interval; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; SII, systemic immune-inflammation index; PLR, platelet-to-lymphocyte ratio; LMR, lymphocyte-monocyte ratio; LCR, lymphocyte-CRP ratio, CD, Crohn's disease.

up approach. To overcome these limitations, a predictive model based on imaging characteristics to forecast MH in patients with CD has been devised.[28] Nowadays, there are a range of serological biomarkers that play a crucial role in detecting inflammation flare-ups in CD.[29] The prospect of disease progression monitoring through outpatient blood sampling presents a significant opportunity to enhance patient adherence to follow-up schedules and augment the efficacy of medical interventions.

This study has identified the SII as a significant independent prognostic factor associated with CD activity and severity. SII emerges as a pivotal biomarker for the stratification and grading of Crohn's disease severity. The integration of SII with established clinical markers, such as CRP and ESR, has culminated in the development of a nomogram model with heightened accuracy in the prediction of CD activity and severity. The predictive model demonstrated accurate calibration and robust clinical utility confirmed by calibration analysis and DCA. In cases where CD is diagnosed without concomitant autoimmune or inflammatory diseases, or infections, routine blood tests supplemented by SII-based nomograms can be employed for an initial disease progression assessment. This methodology presents substantial advantages for clinicians and patients, facilitating enhanced disease surveillance and the formulation of more effective management strategies.

An increasing body of evidence underscores the prognostic relevance of inflammatory biomarkers in the context of autoimmune diseases. These biomarkers provide insights into the equilibrium of inflammatory mediators and the dynamic state of the immune response.[30] While CRP and ESR are conventionally employed to gauge disease activity in IBD, their diagnostic sensitivity and specificity are not optimal.[31,32] Recent investigations have shed light on novel biomarkers, such as the CAR, NLR, PLR, and LMR, which have demonstrated considerable clinical utility in the assessment of IBD activity.[33] Notably, Xie et al's research suggested that SII levels could be pivotal in evaluating disease activity in UC as scored by the Mayo score.[34] Elgenidy et al's meta-analysis affirms the utility of SII as a diagnostic and monitoring biomarker for UC.[35]

In the present study, we conducted a comparative analysis of eight inflammatory biomarkers, including the aforementioned indicators, to assess their efficacy in determining CD activity, severity, and MH. Utilizing the ROC curve as a metric, we identified that SII was preeminent in predicting disease activity and was particularly effective in prognosing severe CD. However, the prognostic accuracy of SII for MH was less robust. Despite this, other serological markers

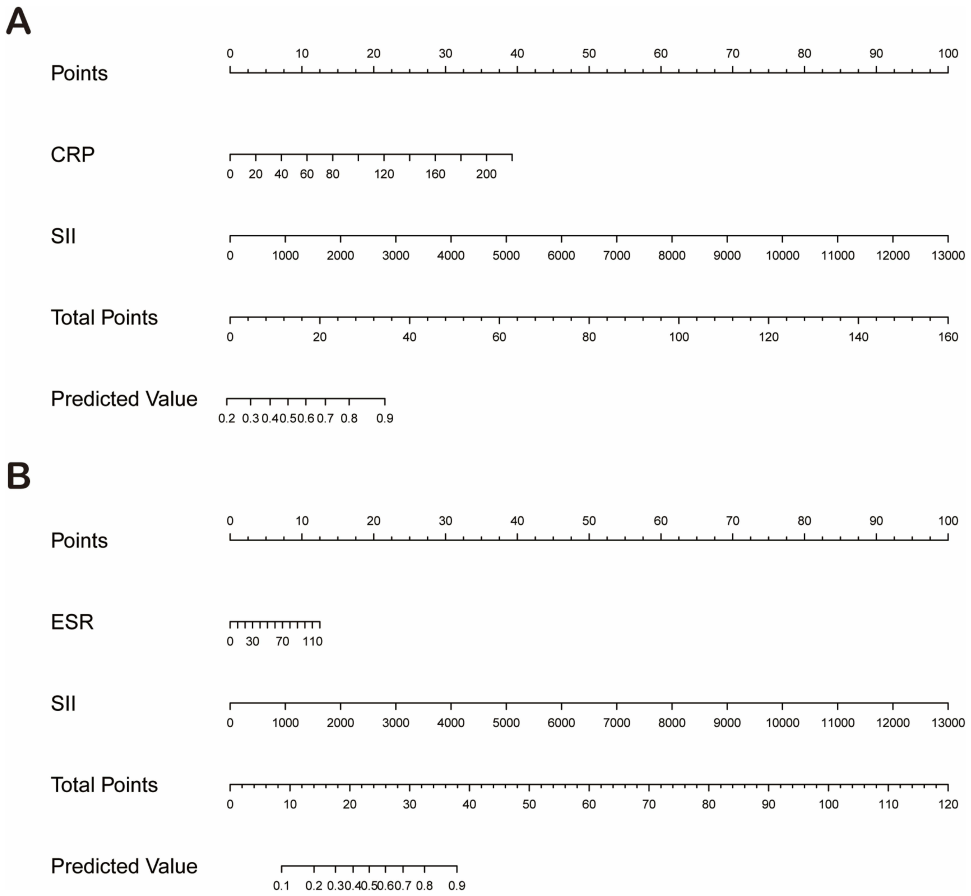

Figure 4 Nomograms to estimate the progression of patients with Crohn's disease (CD). (**A**) Nomogram to estimate CD activity. (**B**) Nomogram to estimate CD severity. To use the nomogram, a line is drawn from each indicator value to the points line, and the corresponding score is given using the indicator values. The scores for all indicators are then summed up. A line is then drawn from the total points line to the lowest line of the nomogram to determine the predicted value.

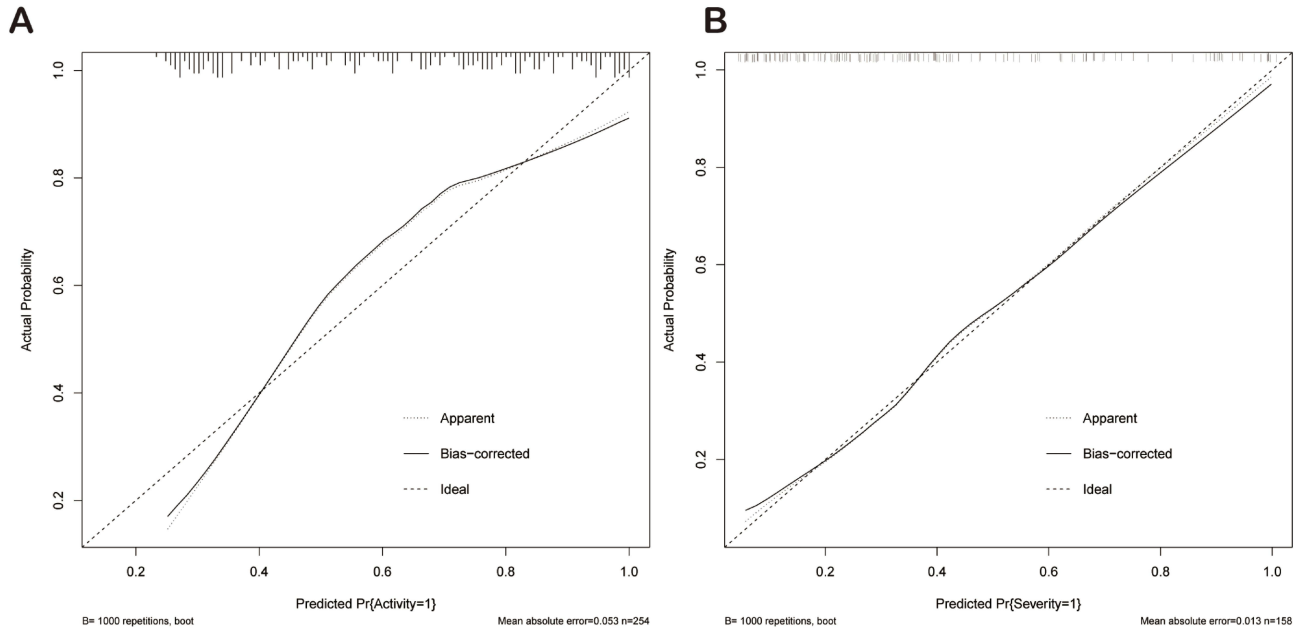

Figure 5 Calibration curves of the predictive model. (**A**) Calibration curve of the model to predict Crohn's disease (CD) activity. (**B**) Calibration curve of the model to predict CD severity. The X-axis represents the predicted probability of the nomogram, while the Y-axis represents the actual probability of progression grade in CD. Well-calibrated nomograms should have scatter points closely aligned along the diagonal. Bootstrapping with 1000 repetitions was employed for reliable results.

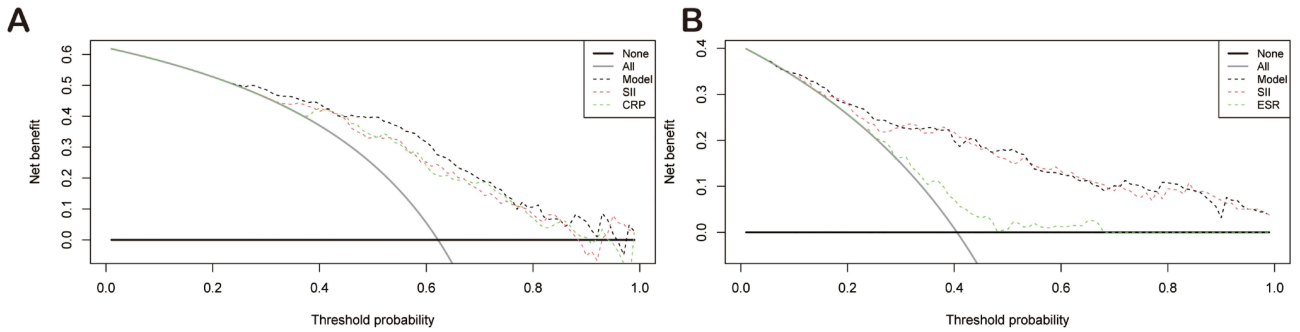

Figure 6 Decision curve analysis (DCA) of the predictive model. (**A**) DCA for predicting Crohn's disease (CD) activity. (**B**) DCA for predicting CD severity. The horizontal coordinate represents the threshold probability, while the vertical coordinate represents the net benefit rate after subtracting the drawbacks from the benefits. The nomograms provide more benefit when the threshold probability is between 24% and 96% for activity prediction and > 5% for severity prediction.
Abbreviation: DCA, Decision curve analysis.

within our analysis showed potential as post-treatment predictors of MH. Of particular interest, LCR stood out as an independent prognostic factor, exhibiting commendable sensitivity and specificity.

SII is derived from the calculation, which involves multiplying the platelet count by the neutrophil count and subsequently dividing it by the lymphocyte count. These three components—platelets, lymphocytes, and neutrophils—are integral to the inflammatory response and are closely associated with the progression of CD. In individuals with IBD, the peripheral blood platelets are in a state of heightened activity. An intense inflammatory response modifies the extracellular environment, which in turn leads to platelet activation and aggregation.[36] Studies have suggested that the reactive oxygen species (ROS)-NLRP3 inflammasome-interleukin-1β axis may be responsible for inducing platelet activation in patients with active CD.[37] Furthermore, lymphocytes from patients with active IBD are known to migrate from the peripheral blood to the site of bowel inflammation, resulting in a decreased peripheral lymphocyte count.[38] The identification of several specific T-cell subpopulations in the terminal ileum tissue of patients with severe CD indicates a shift in the number and activity of T-cell subsets.[39] Neutrophils play a significant role in the exacerbation of inflammation by contributing to the production and release of various inflammatory mediators that can damage the gut's mucosal barrier. This is achieved through increased ROS,[40] extracellular traps,[41] and engagement of other various pathways. Collectively, these processes culminate in leukocyte activation and the release of inflammatory mediators,[42] leading to subsequent alterations in inflammatory markers. Combined with the counts of three types of blood cells related to inflammation, an elevated SII value is indicative of a more pronounced in patients. This study has demonstrated that individuals in relatively active groups exhibit increased platelet and neutrophil counts alongside a reduced lymphocyte count. The increase in SII levels is statistically significant, underscoring its potential utility as a robust indicator of inflammatory status in patients with CD.

The present study recognizes the need for several enhancements in future research. Firstly, the incomplete serological data for a portion of the participants and the limited overall sample size may have compromised the representativeness of the findings. This issue was particularly evident in the analysis of the post-treatment CD subgroup, where the small sample may have limited the ability to draw robust conclusions about the association between SII and MH. Secondly, the use of subjective scoring indices for evaluating clinical remission in CD introduces potential bias and variability. To address these limitations, it is recommended that future multicenter prospective studies employ a larger and more diverse patient sample. Additionally, future studies should incorporate more objective, quantifiable measures to assess clinical outcomes, thereby improving the reliability and validity of the findings. Integrating immunobiological markers with advanced imaging modalities may provide a more comprehensive and objective assessment of disease progression. Furthermore, the dynamic changes in SII levels in patients with recurrent CD, in relation to treatment interventions, will be systematically monitored in future research. This approach will facilitate a better understanding of the prognostic implications of SII and inform the development of targeted therapeutic strategies.

Conclusion

SII is recognized as a pivotal biomarker for evaluating the inflammatory activity and severity in CD. A prognostic nomogram incorporating SII has been established as a dependable tool for CD trajectory evaluation. Serological markers, including SII, offer a non-invasive means to anticipate MH following treatment in CD, with the LCR demonstrating superior predictive capabilities.

Data Sharing Statement

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

Ethical Statement

Patient data is utilized solely for scientific research purposes. Without explicit patient consent, we will not disclose any information in any published materials that could potentially identify individual patients.

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Author Contributions

Y.D., T.F., and Q.Y. were instrumental in conceptualizing and designing the study. Y.D., T.F., J.Z., X.N., F.W., and Q.Y conducted the data curation and formal analysis. Y.D. and Q.Y. prepared the initial draft of the manuscript, while Y.D., D. G., and Q.Y handled the revisions and editing. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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