

Retrospective Cohort Study

Effective immune-inflammation index for ulcerative colitis and activity assessments

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Abstract**BACKGROUND**

The inverse association between systemic immune-inflammation index (SII) and overall survival in tumors has been studied.

AIM

To evaluate the hematological indexes for assessing the activity of ulcerative colitis (UC).

METHODS

In this case-control study, 172 UC patients and healthy participants were included. Comparisons were made among groups of white blood cells, hemoglobin, platelets, neutrophils, lymphocytes, monocytes, SII, neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR). The relationship with hematological inflammation was verified by Spearman correlation analyses. The efficiency of SII, NLR, and PLR for distinguishing between UC and severe disease status was assessed by the receiver operator curve and logistic regression analyses.

RESULTS

The values of SII, NLR, and PLR were higher in UC patients than in controls ($P < 0.001$) and were positively correlated with the Mayo endoscopic score, extent, Degree of Ulcerative Colitis Burden of Luminal Inflammation (DUBLIN) score, and Ulcerative Colitis Endoscopic Index of Severity (UCEIS). The cut-off NLR value of 562.22 predicted UC with a sensitivity of 79.65% and a specificity of 76.16%. Logistic regression analysis revealed that patients with SII and NLR levels above the median had a significantly higher risk of UC ($P < 0.05$). Risk factors independently associated with DUBLIN ≥ 3 included SII ≥ 1776.80 [odds ratio (OR) = 11.53, $P = 0.027$] and NLR value of 2.67-4.23 (OR = 2.96, $P = 0.047$) on

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multivariate analysis. Compared with the first quartile, SII ≥ 1776.80 was an independent predictor of UCEIS ≥ 5 (OR = 18.46, $P = 0.012$).

CONCLUSION

SII has a certain value in confirming UC and identifying its activity.

Key Words: Ulcerative colitis; Systemic immune-inflammation index; Endoscopic score; Neutrophil-to-lymphocyte ratio; Platelet-to-lymphocyte ratio; Disease activity

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Core Tip: Although endoscopy examination is the standard for assessing ulcerative colitis (UC) relapse, it is invasive, intolerable, and weakly repeatable. Non-invasive parameters can be used to assess the disease activity of UC. However, the value of routine blood testing for predicting UC severity has not been studied in depth. This study evaluated the differential leucocytic ratio, such as systemic immune-inflammation index, neutrophil-to-lymphocyte ratio, and platelet-to-lymphocyte ratio, to provide easy and reliable methods for disease activity.

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INTRODUCTION

Ulcerative colitis (UC) is a chronic, non-specific inflammatory condition in the colon, which has recently increased in Asia. Etiology may be associated with genetic susceptibility, intestinal flora disorders, multiple environmental factors, and abnormal immune disorders^[1]. The overall prevalence exceeds 0.3% in North America, Oceania, and most European countries^[2]. Inflammatory bowel disease (IBD) is the third highest risk factor for colorectal cancer (CRC), and 18% of IBD-related CRC cases occur in patients with a history of less than 8 years^[3]. Cross-sectional imaging under endoscopy may accurately reflect current inflammation of the intestines. Endoscopy biopsy plays a dominant role in determining a diagnosis, disease severity, treatment response, recurrence, and CRC. However, it is expensive, invasive, and weakly repeatable, and the disease may be aggravated by surgery. Hence, we continued to explore non-invasive measures to determine the severity of UC and the level of inflammatory burden.

Blood, urine, and fecal indicators may prevent these limitations and have been studied to indicate the inflammatory state. Urine markers are rarely studied and have no clinical application^[4]. The most important acute phase serological markers are C-reactive protein (CRP) and the erythrocyte sedimentation rate (ESR), which are useful for predicting relapse, severity, and response to treatment^[5-8]. Fecal calprotectin (FC) can be derived from neutrophils and may reflect the destruction of the epithelial barrier and the inflammatory process of the intestine. Compared to blood markers and symptomatic flare, FC is the best to trace relapse, particularly after colectomy, with values ≤ 100 $\mu\text{g}/\text{mg}$, indicating remission without a need for colonoscopy^[9,10]. However, due to the variation in testing methodologies and cut-off values, non-specific markers including ESR, CRP, and FC are vulnerable to various pathological conditions and not generally accepted criteria for disease monitoring^[11]. Thus, there is a need to identify new indicators to improve diagnostic efficiency, cost performance, safety, and convenience.

Recent studies have shown that the platelet-to-lymphocyte ratio (PLR) and neutrophil-to-lymphocyte ratio (NLR) may help to diagnose UC and its activity^[12-14]. However, the potential role of PLR and NLR in patients with UC remains controversial. Compared PLR and NLR only consists of two circulating immune cells, the systemic immune-inflammation index (SII) integrates platelets (PLTs), neutrophils, and lymphocytes. SII is a useful biomarker of the inflammatory status and immune response. A higher SII value indicates a relatively low lymphocyte count and high

neutrophil and PLT counts, demonstrating a stronger inflammatory response and weaker cell-mediated immunity. Elevated SII is a weak prognostic predictor of various malignant solid tumors including digestive system tumor, renal cancer, germ-cell tumors, metastatic castration-resistant prostate cancers, non-small cell lung cancer, and small cell lung cancer^[15-17]. Infiltration and metastasis of malignant tumors are inflammatory-mediated processes. However, there is no study in the literature regarding SII in UC.

In this study, we evaluated the diagnostic value of SII and determined if SII is more advantageous for assessing disease severity than NLR or PLR in patients with UC.

MATERIALS AND METHODS

Participants

The data analyzed in this study were from January 2017 to December 2019, and included 172 patients with UC and 172 healthy controls from Huaian No. 1 People's Hospital. Data on sex, age, duration of illness, frequency of defecation, stool consistency, pulse, and body temperature were extracted from the medical record. The diagnosis of UC was based on consensus for the diagnosis and treatment of IBD as the UC group. Participants with hematological disease, liver, and kidney damage, tumors, certain forms of autoimmune diseases, and infections were excluded. The study was approved by the medical ethics committee of The Affiliated Huai'an No. 1 People's Hospital of Nanjing Medical University Institutional. Informed consent was waived in this retrospective study.

Laboratory investigation

Venous blood was taken from the fasting state in the morning and then analyzed by the automatic analyzer certified by our hospital. A blood test can yield measurements of white blood cells (WBCs), hemoglobin (HB), PLTs, neutrophils, lymphocytes, and monocytes. Based on the above parameters, SII, PLR, and NLR were determined.

Colonoscopy score

The patient underwent colonoscopy in the endoscopic center of our hospital after intestinal preparation. The endoscopic outputs were documented in detail by professional experts, and then rated based on previous literature. Extent is classified as follows^[18]: E1 = proctosigmoiditis, E2 = left-sided colitis (distal to splenic flexure), E3 = pancolitis (proximal to splenic flexure). The Mayo endoscopic score (MES)^[19] is considered to be 0 points for normal or inactive lesions, 1 point for mild (redness, the reduced texture of blood vessel, and mildly brittle mucosa), 2 points for moderate (significant erythema, disappeared texture of blood vessel, brittle or eroded mucosa), and 3 points (spontaneous mucosal bleeding or ulceration). The score for Degree of Ulcerative Colitis Burden Luminal Inflammation (DUBLIN) is the MES multiplied by the maximal extent score^[20]. The Ulcerative Colitis Endoscopic Index of Severity (UCEIS) includes three parts: Vascular pattern, bleeding, erosions, and ulcer of the mucosa, with each component graded between 0 and 3 (normal to severe)^[21].

Statistical analysis

Statistical analysis was performed using SPSS 26.0 software (SPSS Inc., Chicago, IL, United States). The data were stratified according to age and gender. Matching of the propensity score between patients and controls was precise and fuzzy with 1:1.02 age and sex matching. The Kolmogorov-Smirnov test was done to detect normality. Data between groups were compared using the Mann-Whitney U test for continuous variables and the chi-squared test for categorical variables. The relationship between inflammatory markers in blood and extent, MES, DUBLIN score, and UCEIS was verified by Spearman correlation analyses. Receiver operating characteristic (ROC) curves were constructed to evaluate the diagnostic efficiency of SII, NLR, and PLR. Multivariate logistic regression was performed to identify the risk factor of UC and the severe UC status (DUBLIN score ≥ 3 and UCEIS ≥ 5). The first quartile was set as a reference, and $P < 0.05$ was considered statistically significant.

RESULTS

Participants' clinical characteristics

The median ages of the UC and control groups were 48.00 and 47.50 years, respectively ($P = 0.545$). No statistically significant differences in age and gender between UC patients and controls were observed. The median SII values of active UC patients and controls were 1063.23 and 384.86, respectively ($P < 0.001$). UC patients had lower levels of HB and lymphocytes and higher values of WBC, PLT, neutrophils, NLR, PLR, and SII compared to the healthy subjects ($P < 0.05$) (Table 1).

Correlation of inflammation markers and endoscopic score

SII, NLR, and PLR showed a positive correlation with endoscopic severity scores (extent, MES, DUBLIN score, and UCEIS), whereas SII was the most reliable indicator of inflammation markers (Table 2). The relationship among NLR, PLR, extent, MES, DUBLIN score and UCEIS was weak (all $P > 0.05$). Although Spearman correlation analysis of active UC indicated a significant correlation of SII with extent, DUBLIN score and UCEIS, no correlation was found with MES ($r = 0.124$, $P = 0.106$).

ROC curves of inflammation markers

Analysis of the ROC curve showed that the optimum SII cut-off point for UC was 562.22, with an area under the curve (AUC), sensitivity, and specificity of 0.856, 79.65%, and 76.16%, respectively (Table 3). The AUC value of the NLR was 0.858, and there was no statistical difference relative to SII ($P = 0.86$). The cut-off value of NLR was 2.66, with 75% sensitivity and 82.56% specificity. The AUC of SII and NLR was statistically different from that of PLR ($P < 0.01$).

Inflammation markers for UC and disease severity

Multivariate logistic regression showed that SII and NLR were associated with UC and higher endoscopic scores. Compared to the lowest quartile, SII and NLR levels in the third and highest quartile levels were independent risk factors for UC ($P < 0.05$) (Table 4), but were not the values in other levels. The odds ratio (OR) for DUBLIN 3 was 11.53 and 2.96 at SII 1776.80 and NLR of 2.67-4.23, respectively ($P < 0.05$) (Table 5). Table 6 shows that the OR was 18.46 at SII 1776.80 for UCEIS 5 ($P < 0.05$).

DISCUSSION

Routine blood testing is the most commonly used detection index, but additional studies are required for its use as an indicator of IBD activity. This study determined if SII could diagnose and predict the severity of the UC. The preliminary findings of our study showed elevated levels of neutrophils and PLTs, and reduced levels of leukocytes in patients with UC. Various pathogenic factors may disrupt the balance of the intestinal mucosal immune system, either directly or indirectly. Polymorphonuclear neutrophils are first recruited into the intestine when the body is suffering from an infection or mucosal injury. Activated neutrophils also develop overproduced proteases, including elastase, proteinase, and matrix metalloproteinases, which may reduce the levels of junctional proteins, leading to epithelial barrier defects^[22,23]. Lymphocyte subsets are considered to cause IBD ulcers. Abnormal gut-homing lymphocyte has identified endothelial ligands by expressing specific surface receptors, causing an overactive immune response and damage to the intestine^[24]. The development and clinical trials of the anti-leukocyte adhesion agent are underway, and the United States Food and Drug Administration approved the powder injection of vedolizumab in 2014 for patients with moderate to severe UC and Crohn's disease with reduced efficacy of conventional drugs and anti-tumor necrosis factor (anti-TNF) antibodies^[25]. Our results confirmed the lower levels of active UC in peripheral blood lymphocytes. Histopathological examination of UC showed diffuse and chronic infiltration of the inflammatory cells^[26]. Neutrophils, lymphocytes, plasma cells, monocytes, and eosinophils were seen in the lamina propria, and neutrophils were found in the glandular epithelial cells. Active IBD is characterized by cryptitis and a formation of the crypt abscess. PLTs serve as a bridge between coagulation and inflammation^[27,28]. Previous studies have indicated that PLT count, PLT-PLT, and PLT-leukocyte aggregates are increased in blood circulation, and colonic veins are associated with disease activity^[29]. Upon activation, PLTs secrete inflammatory molecules derived from PLTs, synthesize a series of mediators, and generate

Table 1 Clinical and laboratory characteristics of patients with ulcerative colitis and healthy controls

	Control, n = 172	Ulcerative colitis, n = 172	P value
Male, n (%)	96 (55.81%)	91 (52.90%)	0.588
Age (yr)	47.50 (37.00-56.00)	48.00 (35.00-57.00)	0.545
WBC ($\times 10^9/L$)	5.37 (4.47-6.29)	7.26 (5.85-9.23)	< 0.001
HB (g/L)	138.00 (125.00-152.50)	131.00 (122.00-143.00)	0.001
PLT ($\times 10^9/L$)	213.00 (179.50-251.00)	245.00 (197.00-312.00)	< 0.001
N ($\times 10^9/L$)	3.11 (2.55-3.86)	5.48 (4.07-7.25)	< 0.001
L ($\times 10^9/L$)	1.67 (1.35-2.08)	1.25 (0.97-1.70)	< 0.001
M ($\times 10^9/L$)	0.30 (0.24-0.37)	0.33 (0.18-0.49)	0.295
SII ($\times 10^9/L$)	384.86 (282.31-557.42)	1063.23 (587.24-1787.87)	< 0.001
NLR, %	1.83 (1.45-2.47)	4.31 (2.73-6.47)	< 0.001
PLR, %	127.49 (98.71-156.21)	191.87 (130.97-263.89)	< 0.001

HB: Hemoglobin; L: Lymphocytes; M: Monocytes; N: Neutrophils; NLR: Neutrophil-lymphocyte ratio; PLR: Platelet-lymphocyte ratio; PLT: Platelet; SII: Systemic immune-inflammation index; WBC: White blood cell.

Table 2 Correlation analysis between systemic immune-inflammation index and endoscopic score

	MES		Extent		DUBLIN		UCEIS	
	r	P value	r	P value	r	P value	r	P value
SII	0.124	0.106	0.174	0.023	0.193	0.011	0.227	0.003
NLR	0.068	0.375	0.146	0.056	0.139	0.068	0.130	0.088
PLR	0.043	0.577	0.060	0.432	0.074	0.336	0.108	0.158

DUBLIN: Degree of Ulcerative Colitis Burden of Luminal Inflammation; MES: Mayo endoscopic score; NLR: Neutrophil-lymphocyte ratio; PLR: Platelet-lymphocyte ratio; SII: Systemic immune-inflammation index; UCEIS: Ulcerative Colitis Endoscopic Index of Severity.

Table 3 Receiver operating characteristic analyses of systemic immune-inflammation index, neutrophil-lymphocyte ratio and platelet-lymphocyte ratio in diagnosing ulcerative colitis

Variable	Cut-off	AUC (95%CI)	Sensitivity, %	Specificity, %	P value
SII	> 562.22	0.856 (0.814-0.891)	79.65	76.16	< 0.001
NLR	> 2.66	0.858 (0.817-0.893)	75.00	82.56	< 0.001
PLR	> 156.54	0.754 (0.705-0.799)	65.70	76.16	< 0.001

AUC: Area under the receiver operating characteristic curve; CI: Confidence interval; NLR: Neutrophil-lymphocyte ratio; PLR: Platelet-lymphocyte ratio; SII: Systemic immune-inflammation index.

extracellular vesicles in IBD inflammatory cascades^[30]. PLTs that express P-selectin, glycoprotein IIb/IIIa, CD-40 ligand, and glycoprotein 53 may interact with inflammatory cells that cause tissue injury. Meanwhile, inflammatory mediators such as interleukin-6 (IL-6) stimulate bone marrow thrombopoiesis and accelerate the metabolism of PLT, forming a vicious circle^[29,31,32]. Drugs that inhibit PLT inflammatory makers may alleviate the course of disease in IBD models despite the risk of aggravating ulcer bleeding. For patients with UC, higher SII values result from elevated peripheral blood neutrophils and PLTs, and lower lymphocyte levels.

NLR and PLR levels can predict activation of UC and endoscopic mucosal injury^[12,33]. Similar results were found in our study showing that NLR, PLR, and SII levels were higher in UC patients and correlated with the endoscopic score. In distinguishing UC, the AUC of SII and NLR was higher than that of PLR, and the SII

Table 4 Multivariate logistic regression analyses of the relationship between inflammatory indicators and ulcerative colitis

	B	P value	Odds ratio	95%CI
SII				
346.44	Reference			
346.45-574.88	0.56	0.241	1.76	0.69-4.52
574.89-1084.51	1.24	0.031	3.45	1.12-10.63
1084.52	3.03	0.001	20.64	3.57-119.18
NLR				
1.69	Reference			
1.70-2.53	0.64	0.163	1.91	0.77-4.71
2.54-4.60	1.32	0.010	3.73	1.37-10.18
4.61	2.53	0.001	12.52	2.77-56.60
PLR				
111.93	Reference			
111.94-149.11	-0.15	0.718	0.87	0.40-1.90
149.11-203.33	-0.26	0.560	0.77	0.32-1.84
203.34	-0.38	0.517	0.68	0.21-2.18

NLR: Neutrophil-lymphocyte ratio; PLR: Platelet-lymphocyte ratio; SII: Systemic immune-inflammation index.

Table 5 Multivariate logistic regression analyses of the relationship between inflammatory indicators and degree of ulcerative colitis burden of luminal inflammation 3

	B	P value	Odds ratio	95%CI
SII				
589.63	Reference			
589.64-1047.18	0.51	0.372	1.66	0.55-5.04
1047.19-1776.79	0.86	0.299	2.36	0.47-11.98
1776.80	2.45	0.027	11.53	1.33-100.15
NLR				
2.66	Reference			
2.67-4.23	1.09	0.047	2.96	1.01-8.65
4.24-6.46	0.85	0.237	2.33	0.57-9.49
6.47	-0.20	0.820	0.82	0.15-4.49
PLR				
132.35	Reference			
132.36-190.31	-0.59	0.286	0.56	0.19-1.63
190.32-263.47	-0.33	0.620	0.72	0.20-2.65
263.48	-1.06	0.201	0.35	0.07-1.76

NLR: Neutrophil-lymphocyte ratio; PLR: Platelet-lymphocyte ratio; SII: Systemic immune-inflammation index.

was an independent indicator of UC and for the status of severe disease. SII is a novel inflammatory marker based on neutrophils, lymphocytes, and PLTs. Chronic intestinal inflammation in patients with UC has been associated with the risk of hospitalization, colectomy, thrombosis, cardiovascular problems, and malignant tumors^[34]. Monitoring the burden of intestinal inflammation is, therefore, critical for evaluating the progress of the disease activity and recognizing patients who need to upgrade their treatment regimens. The differential leucocytic ratio is an easily applicable and cost effective test, which could be more helpful for monitoring the inflammatory burden when they are used together with the serum laboratory inflammation index. Other studies have suggested that higher levels of SII predict shorter overall survival or progression-free survival in various malignancies, because the inflammatory reaction is crucial for the tumor progression^[15,16].

The current goal of UC treatment is mucosal healing. While not all endoscopic scores have been thoroughly validated to date, MES and UCEIS are frequently used indicators to measure endoscopic inflammation activity. The DUBLIN score is determined based on the MES. We found that the NLR, PLR, and SII levels were correlated with endoscopic scores. In this context, Akpınar *et al.*^[12] demonstrated that NLR and PLR could identify and predict active diseases under endoscopy, as described by the Rachmilewitz endoscopic activity index. Another study showed that lower levels of both baseline NLR and PLR were associated with mucosal healing in UC patients after 54 wk of anti-TNF therapy^[35]. In this study, logistic regression analysis showed that the higher levels of SII were independently associated with UC, DUBLIN ≥ 3 , and UCEIS ≥ 5 . The risks of treatment failure, colectomy, drug improvement, and enhancement of treatment plan are related to DUBLIN ≥ 3 ^[20]. Four grades of UCEIS scores were stratified: remission (0-1), mild (2-4), moderate (5-6), and severe (7-8)^[36]. When UCEIS was ≥ 5 , 27/54 (50%) needed rescue therapy, and 18/54 (33%) came to colectomy during the follow-up compared to UCEIS ≤ 4 ^[37]. The results of this study show that SII could be used as brief information on activity and degree of mucosal damage prior to the endoscopic examination, in particular for patients with high responsiveness to invasive investigations or unable to obtain equipment during the active period. Although the promising efficacy needs further study, non-invasive indicators have a supporting role in predicting active lesions.

This study had some limitations. First, this retrospective analysis was not able to remove the possible bias. Second, the cases studied were from a single institution, and it is unknown in their region or country. Third, it is rudimentary to investigate the SII value in the blood, and subsequent studies should be conducted on the relationship between SII and histological injury-related indicators. To conclude, this is the first study to provide evidence that SII can assist with UC diagnosis. Defining a known cut-off value will help determine the diagnosis and severity of UC if the results of this study are further verified.

CONCLUSION

Our analysis showed that the SII, NLR, and PLR were significantly elevated and were related to endoscopic severity in UC patients, which can help in diagnosing UC and determining the endoscopic severity of this disease. Moreover, because elevated levels of SII are an independent risk factor for patients with active UC, paying attention to this factor may lead to the early identification of UC and prevent disease progression. In addition, the SII values can be used to track disease severity and provide physicians with information to adjust treatment protocols when colonoscopy is not available. Further research is needed on the correlation between differential leucocytic ratio and histological severity of mucosal injury. This first application of SII was based on evidence to determine the importance of diagnosing UC, and the severity of the disease.

Table 6 Multivariate logistic regression analyses of the relationship between inflammatory indicators and ulcerative colitis endoscopic index of severity 5

	B	P value	Odds ratio	95%CI
SII				
589.63	Reference			
589.64-1047.18	1.09	0.146	2.98	0.69-12.94
1047.19-1776.79	1.57	0.129	4.81	0.63-36.56
1776.80	2.92	0.012	18.46	1.89-180.30
NLR				
2.66	Reference			
2.67-4.23	0.06	0.934	1.06	0.27-4.23
4.24-6.46	0.05	0.954	1.05	0.20-5.41
6.47	-0.61	0.534	0.54	0.08-3.71
PLR				
132.35	Reference			
132.36-190.31	-1.06	0.139	0.35	0.09-1.41
190.32-263.47	-0.96	0.212	0.38	0.09-1.73
263.48	-1.20	0.174	0.30	0.05-1.70

NLR: Neutrophil-lymphocyte ratio; PLR: Platelet-lymphocyte ratio; SII: Systemic immune-inflammation index.

ARTICLE HIGHLIGHTS

Research background

Peripheral blood-derived inflammation-based scores have limited clinical value in ulcerative colitis (UC).

Research motivation

Assess the clinical disease activity.

Research objectives

Explore a simple and readily available predictor.

Research methods

Mann-Whitney *U* test, spearman correlation analyses, receiver operator curve, and logistic regression analyses.

Research results

Systemic immune-inflammation index (SII), neutrophil-to-lymphocyte ratio, and platelet-to-lymphocyte ratio values were correlated with endoscopic score.

Research conclusions

SII could help confirm UC and identify the activity.

Research perspectives

Track the activity of disease and guide adjustment of treatment protocols.

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