

Predictive value of systemic immune inflammation index for the inflammatory status and prognosis in patients with anti-neutrophil cytoplasmic antibody associated vasculitis

Valor predictivo del índice de inflamación inmunitaria sistémica para el estado inflamatorio y el pronóstico en pacientes con vasculitis asociada a anticuerpos anticitoplasma de neutrófilos

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RESUMEN

Introducción: El índice de inflamación inmunitaria sistémica (IIS) se ha explorado en algunos estudios de pacientes con vasculitis asociada a anticuerpos anticitoplasma de neutrófilos (VAA), con resultados contradictorios. **Objetivos:** Nuestro objetivo fue evaluar el papel del IIS en la diferenciación y predicción del estado inflamatorio y el pronóstico de los pacientes con VAA. **Materiales y métodos:** Este estudio incluyó a 39 pacientes con VAA diagnosticados mediante biopsia renal y a 39 controles sanos emparejados por edad y sexo. Los pacientes se dividieron en subgrupos según la positividad de ANCA y la tasa de filtración glomerular (TFG) al momento del diagnóstico y se les realizó seguimiento hasta su fallecimiento, la progresión a enfermedad renal terminal (ERCT) y el pronóstico final. Se calcularon el IIS, el índice plaquetario-linfocitos (IPL) y el índice neutrófilo-linfocito (INL). Se utilizó el análisis de la curva ROC para evaluar el valor diagnóstico del SII. Se utilizó el análisis de correlación de Spearman para analizar la correlación entre el INL, el PLR, el SII y el estado inflamatorio. **Resultados:** Todos los índices fueron significativamente

mayores en el grupo de pacientes ($p < 0,05$). En cuanto a los valores del área bajo la curva (AUC): el SII fue de 0,904 ($p = 0,001$); el INL fue de 0,940 ($p = 0,001$) y el PLR fue de 0,757 ($p = 0,001$). Si bien los pacientes ANCA positivos presentaron niveles más altos de SII en comparación con los pacientes ANCA negativos, no se encontraron diferencias entre los pacientes con diferentes niveles de eGFR ni entre los grupos de resultados. Además, el análisis de Spearman no mostró correlación entre el SII y la proteína C reactiva (PCR), la PCR/albúmina ni el porcentaje de la semiluna. **Conclusión:** El SII y el INL parecen ser marcadores valiosos para predecir la VAA. Lamentablemente, la IIS no demostró correlación alguna con el estado inflamatorio ni el pronóstico. Estudios prospectivos adicionales sobre este tema contribuirán a este trabajo.

Palabras Clave: índice de inmunoinflamación sistémica; vasculitis asociada a anticuerpos anticitoplasma de neutrófilos; pronóstico.

ABSTRACT

Introduction: The systemic immune-inflammation index (SII)

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has been explored in a few studies involving patients with antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV), yielding conflicting results. **Objectives:** We aimed to evaluate the role of SII in differentiating and predicting the inflammatory status and prognosis of AAV patients. **Materials and methods:** This study included 39 AAV patients diagnosed through renal biopsy and 39 age- and sex-matched healthy controls. Patients were divided into subgroups based on ANCA positivity and glomerular filtration rate (GFR) at the time of diagnosis. They were followed up until death, progression to end-stage renal disease (ESRD), or outcome. SII, platelet lymphocyte ratio (PLR), and neutrophil-lymphocyte ratio (NLR) were calculated. Receiver operating characteristic curve (ROC) analysis was used to evaluate the diagnostic value of SII. Spearman's correlation analysis was used to examine the relationship between NLR, PLR, SII, and inflammatory status. **Results:** All indices were significantly higher in the patient group ($p < 0.05$). Regarding the area under the curve (AUC) values: SII was 0.904 ($p = 0.001$); NLR was 0.940 ($p = 0.001$), and PLR was 0.757 ($p = 0.001$). While ANCA-positive patients had higher levels of SII compared to ANCA-negative patients, we found no difference between the patients with different eGFR levels and among outcome groups. Moreover, Spearman's analysis showed no correlation between SII and C-reactive protein (CRP), CRP/albumin, and the percentage of the crescent. **Conclusion:** SII and NLR appear to be valuable markers for predicting AAV. Unfortunately, SII failed to demonstrate any correlation with inflammatory status or prognosis. Further prospective studies on this subject will contribute to this area of research.

Keywords: systemic immune-inflammation index; antineutrophil cytoplasmic antibody-associated vasculitis; prognosis.

INTRODUCTION

Antineutrophil cytoplasmic antibody-associated vasculitis (AAV) is a life-threatening, multisystem autoimmune disease characterized by small-vessel vasculitis and necrotizing inflammation with few or no immune deposits. It

is associated with antineutrophil cytoplasmic antibodies (ANCA), which are classified into two types: myeloperoxidase (MPO-ANCA) and proteinase 3 (PR3-ANCA)^(1,2). AAV affects the ear, nose, throat, lungs, and kidneys⁽²⁾. Renal involvement is observed in approximately 25% of AAV patients. AAV can lead to microscopic hematuria, subnephrotic proteinuria, rapidly progressive glomerulonephritis, and progress to end-stage renal disease (ESRD)⁽¹⁾. Therefore, early diagnosis and rapid treatment are critical for survival.

ANCA plays a pivotal role in the pathogenesis of vascular damage in patients with AAV. To indicate ANCA reactivity (e.g., PR3-ANCA, MPO-ANCA, or ANCA-negative), a prefix should be added, as ANCA specificity identifies distinct disease categories^(2, 3, 4, 5).

Although the pathogenesis of AAV remains incompletely understood, accumulating evidence suggests that chronic inflammation plays an essential role⁽⁶⁻⁸⁾. Numerous inflammatory markers, including C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), have been utilized to assess disease activity in AAV^(6, 7). Because CRP and ESR may also be elevated in infections and malignancies, they are insufficient as specific biomarkers of disease activity. Therefore, new biomarkers have been investigated in vasculitis. The neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and systemic immune inflammation index (SII), calculated from neutrophil, platelet, and lymphocyte counts, have been used as inflammatory and prognostic markers in various diseases⁽⁹⁻¹²⁾. Currently, limited data exist regarding the clinical utility of SII in patients with AAV (11). Therefore, we aimed to evaluate SII levels, along with NLR and PLR, in patients with AAV and to investigate their clinical significance. Additionally, we aimed to evaluate the prognostic value of SII in this patient population.

MATERIALS AND METHODS

Study population

Thirty-nine patients diagnosed with pauci-immune glomerulonephritis by renal biopsy at the Nephrology Department of Bakirkoy Dr. Sadi Konuk Education and Research Hospital between June 2012 and June 2021 were included in the study. All AAV patients met the 2012

revised Chapel Hill Consensus Conference criteria^(1,4,5). The control group consisted of age- and sex-matched normotensive individuals who presented to the same clinic during the same period with non-inflammatory conditions and no evidence of kidney disease. Patients requiring hemodialysis at baseline were included in the study.

The exclusion criteria were as follows:

1) secondary infection, 2) hematologic disease, 3) human immunodeficiency virus, 4) chronic liver diseases and other autoimmune diseases, 5) history of blood transfusion within the last three months, 6) malignancy 7) use of medications that influence complete blood count parameters, 8) other types of vasculitis as classified by the 2012 Chapel Hill Consensus Conference, 9) AAV cases without renal involvement.

This study was approved by the Clinical Research Ethics Committee of Bakirkoy Dr. Sadi Konuk Research Hospital (approval number: 2021-04-17). The study was conducted in accordance with the principles outlined in the Declaration of Helsinki. We did not obtain informed consent due to the retrospective design of the study.

Clinical and laboratory data

Demographic data (age, sex) and laboratory findings at diagnosis and the last follow-up visit were collected from the hospital's electronic medical records. The patients' age at the time of diagnosis was recorded. Laboratory parameters included leukocyte count, platelet count, neutrophil count, lymphocyte count, CRP, CRP/albumin, serum creatinine, serum albumin, PR3-ANCA, MPO-ANCA, and estimated glomerular filtration rate (eGFR). The eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI)⁽¹³⁾. Serum ANCA levels were measured using antigen-specific enzyme-linked immunosorbent assays (ELISAs) for PR3-ANCA and MPO-ANCA. PR3-ANCA and MPO-ANCA levels above 4.5 U/mL were considered positive.

NLR, PLR, and SII values were calculated prior to the initiation of immunosuppressive therapy. SII was defined as (platelet count × neutrophil count) / lymphocyte count. NLR was calculated as the neutrophil count divided by the lymphocyte count, and PLR as the platelet count

divided by the lymphocyte count. NLR, PLR, and SII values of the control group were calculated and compared with those of AAV patients. The percentage of crescents was calculated as the number of glomeruli with crescents divided by the total number of glomeruli.

Patients with positive ANCA [ANCA (+)] and negative ANCA [ANCA (–)] status were compared in terms of inflammatory markers (SII, NLR, and PLR). Patients were also divided into two subgroups based on eGFR levels: those with eGFR levels of < 15 mL/min/1.73 m² and those with eGFR levels of > 15 mL/min/1.73 m². The latter are considered candidates for hemodialysis. We compared the SII, NLR, and PLR levels between these two groups.

Patients were followed until progression to end-stage renal disease (ESRD), death, or the final follow-up date (June 2021). ESRD was defined as dialysis dependence lasting more than three months. All follow-up data were obtained from the hospital's electronic medical records.

Statistical analysis

Statistical analyses were performed using the NCSS (Number Cruncher Statistical System) 2007 software (Kaysville, Utah, USA). Numerical variables were expressed as mean ± standard deviation and median (minimum–maximum), while categorical variables were presented as frequencies and percentages. The normality of quantitative data was assessed using the Shapiro–Wilk test. The Student's t-test was used for comparing two groups of normally distributed quantitative variables. When data were not normally distributed, we applied the Mann–Whitney U test for comparisons between two groups.

The Pearson Chi-square test and the Fisher–Freeman–Halton test were used to compare categorical variables. Pearson and Spearman correlation analyses were performed to evaluate relationships between variables. Receiver operating characteristic (ROC) curve analysis was used to determine the cut-off values for NLR, PLR, and SII. The Kaplan–Meier analysis was used to evaluate overall survival. A p-value of <0.05 was considered statistically significant.

RESULTS

The demographic characteristics and

laboratory findings of the study population are presented in **Table 1**.

A total of 39 patients with ANCA-associated vasculitis (AAV) were included, of whom 41% (n=16) were male, with a mean age of 55.62 ± 14.27 years at diagnosis. Twenty-six patients (66.7%) had at least one comorbid condition, most commonly hypertension (80.8%). The mean follow-up duration was 27.13± 21.49 months. Twenty-two patients (56.4%) were MPO-ANCA positive, five (12.8%) were PR3-ANCA positive, and twelve (30.8%) had undetectable circulating ANCA.

As presented in **Table 1**, the patient group had significantly higher values of leukocytes,

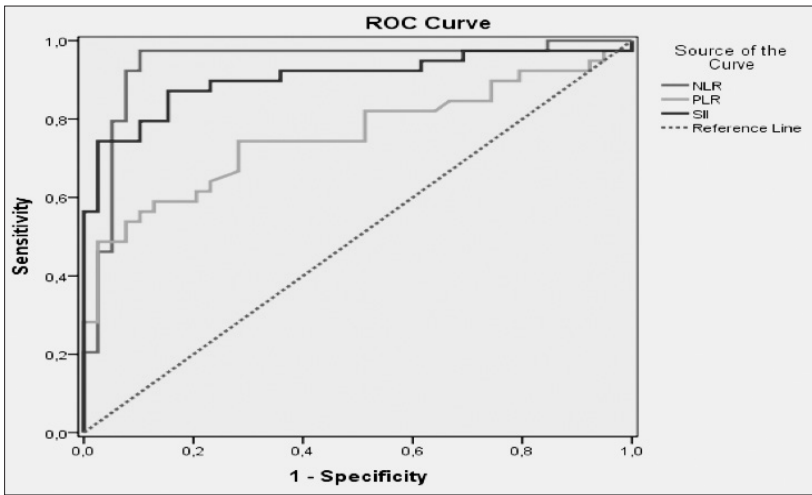
neutrophils, lymphocytes, NLR, PLR, and SII compared to the control group ($p < 0.05$ for all parameters). Given the statistically significant differences in hematological indices between the groups, the optimal cut-off values for NLR, PLR, and SII were determined using ROC analysis. The cut-off values were 2.41 for NLR (area under the curve [AUC] = 0.940; $p = 0.001$; 95% confidence interval [CI]: 0.877–1.000), 142.9 for PLR (AUC = 0.757; $p = 0.001$; CI: 0.646–0.868), and 680 for SII (AUC = 0.904; $p = 0.001$; CI: 0.831–0.977). Among the indices, the ROC curves for NLR and SII demonstrated the highest predictive performance in distinguishing patients with AAV (**Figure 1**).

Table 1: Demographic, clinical, and laboratory characteristics of ANCA-associated vasculitis patients and healthy controls

		Patient group (n=39)	Healthy control group (n=39)	p
Age (years)		55.62±14.27	55,36±15,06	
Gender	Male	16 (41.0)	16 (41.0)	
	Female	23 (59.0)	23 (59.0)	
Leucocytes(10 ³ /mL)		9.5(5.14-33.90)	6.6 (4.18-11.00)	0.001
Neutrophil(10 ³ /mL)		6.7 (2.92-32.20)	3.58 (1.73-7.03)	0.001
Platelet(10 ³ /mL)		282 (125-572)	267 (107-474)	0.166
Lymphocyte(10 ³ /mL)		1.32 (0.64-3.15)	2.01 (0.80-3.59)	0.001
NLR		4.8 (1.2-37.4)	1.9 (0.8-7.3)	0.001
PLR		177.9 (56.5-854.7)	125.1 (60.5-271.6)	0.001
SII		1401 (165.1-11232.6)	529.5 (187-1238.6)	0.001

Data were expressed as mean and median (interquartile range) for quantitative variables and n (%) for nominal variables. ANCA: Antineutrophil cytoplasmic antibody associated; WBC: White blood cell; NLR: Neutrophil-lymphocyte ratio; PLR: Platelet-lymphocyte ratio; SII: Systemic immune inflammation index

Figure 1: Receiver operating characteristic curves of the NLR, PLR, and SII for differentiating AAV patients



ROC for NLR was represented by the blue line with an AUC = 0.940 (95% CI 0.877–1.000, $p = 0.001$) with a sensitivity of 97.44% and a specificity of 89.74%, the ROC for PLR was represented by the green line with an AUC = 0.757 (95% CI 0.646–0.868, $p = 0.001$) with a sensitivity of 74.36% and a specificity of 71.79%, and the ROC for SII was represented by the purple line with an AUC = 0.904 (95% CI 0.831–0.977, $p = 0.01$) with a sensitivity of 87.18% and a specificity of 84.62%.

Compared to subjects in the ANCA-negative AAV group, those in the ANCA-positive group had significantly higher levels of PLR and SII ($p = 0.012$ and $p = 0.028$, respectively). While 66.7% ($n = 8$) of ANCA-negative cases had an SII value ≥ 680 , 96.3% ($n = 26$) of ANCA-positive cases

exceeded this threshold. Additionally, a higher proportion of ANCA-positive cases had elevated PLR values (>142.9) compared to ANCA-negative cases (81.5% vs. 58.3%, $p = 0.012$) (**Table 2**).

Table 2: NLR, PLR and SII Evaluation based on ANCA Status of the patient group

Patient group (n=39)	ANCA (-) (n=12)	ANCA (+) (n=27)	p
NLR <2.41 ≥2.41	0 (0.0) 12 (100)	1 (3.7) 26 (96.3)	0.484
PLR <142.9 ≥142.9	5 (41.7) 7 (58.3)	5 (18.5) 22 (81.5)	0.012
SII <680 ≥680	4 (33.3) 8 (66.7)	1 (3.7) 26 (96.3)	0.028

Data were expressed as n (%) for nominal parameters. **NLR:** Neutrophil-lymphocyte ratio; **PLR:** Platelet-lymphocyte ratio; **SII:** Systemic immune inflammation index; **ANCA:** Antineutrophil cytoplasmic antibody

Seventeen patients had an eGFR <15 mL/min/1.73 m², while twenty-two had an eGFR ≥ 15 mL/min/1.73 m². No significant differences in NLR, PLR, or SII levels were observed between the two groups ($p > 0.05$ for all

comparisons) (**Table 3**).

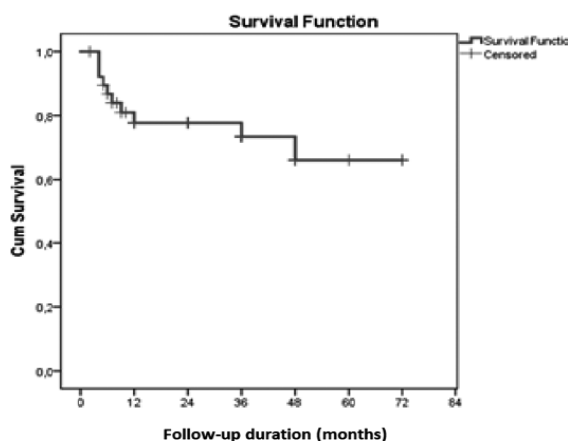
By the end of follow-up, nine patients (23.1%) had developed ESRD, and 10 (25.6%) had died. The mean overall survival time was 54.11 ± 4.79 months (**Figure 2**).

Table 3: NLR, PLR, and SII evaluation based on eGFR levels of the patient group

Patient group (n=39)	eGFR<15mL/min/1.73m ² (n=17)	eGFR≥15mL/min/1.73m ² (n=22)	p
NLR <2.41 ≥2.41	0 (0.0) 17 (100)	1 (4.5) 21 (95.5)	0.497
PLR <142.9 ≥142.9	7 (41.2) 10 (58.8)	3 (13.6) 19 (86.4)	0.126
SII <680 ≥680	2 (11.8) 15 (88.2)	3 (13.6) 19 (86.4)	0.910

Data were expressed as n (%) for nominal parameters **NLR:** Neutrophil-lymphocyte ratio; **PLR:** Platelet-lymphocyte ratio; **SII:** Systemic immune inflammation index; **eGFR:** Estimated glomerular filtration rate.

Figure 2: Survival analysis



The mean survival time was 54.111 ± 4.796 months. The last death was observed at the 30th month; the cumulative survival rate in this month is 66.1% and the standard error is 9.9%.

NLR, PLR, and SII levels did not significantly differ among the three outcome groups (survival, ESRD, and death) (**Table 4**).

Spearman’s correlation analysis revealed no

significant correlation between SII and CRP, CRP/albumin ratio, or percentage of crescents (**Table 5**).

Table 4: NLR, PLR, and SII evaluation according to the prognosis of the patient group

Patient group (n=39)	Survival (n=20)	ESRD (n=9)	Death (n=10)	p
NLR	4.9 (2.4-37.4)	5.6 (3.2-12.7)	4.2 (1.2-16.8)	0.655
PLR	223.2 (116.3-854.7)	142.9 (72.9-417.3)	140.4 (56.5-476.7)	0.058
SII	1616.8 (596.9-11232.6)	1313.8 (464.1-2279.9)	1040.3 (165.1-5481.7)	0.369
SII <680	2(10.0)	1 (11.1)	2 (20.0)	0.731
SII >680	18(90.0)	8 (88.9)	8 (80.0)	

Data were expressed as median and mean $\pm$ standard deviation for quantitative variables and n (%) for nominal variables. **NLR:** Neutrophil-lymphocyte ratio; **PLR:** Platelet-lymphocyte ratio; **SII:** Systemic immune inflammation index; **ESRD:** End-stage renal disease

Table 5: Relationship between CRP, NLR, PLR, Crescent (%), and SII measurements

	SII	
	r	p
CRP	0.160	0.330
NLR	0.918	0.001
PLR	0.739	0.001
Crescent (%)	0.158	0.338

NLR: Neutrophil-lymphocyte ratio; **PLR:** Platelet-lymphocyte ratio; **CRP:** C reactive protein; **SII:** Systemic immune inflammation index

DISCUSSION

The identification of non-invasive biomarkers capable of predicting diagnosis, disease activity, and prognosis remains a highly sought objective in AAV-related research. In the present study, we evaluated the clinical significance of SII, NLR, and PLR in 39 patients with AAV. Our findings demonstrated that SII, NLR, and PLR levels were significantly higher in patients with AAV compared to the control group, with SII and NLR showing the strongest predictive performance for disease. However, neither SII, NLR, nor PLR was significantly correlated with ESR or CRP, both of which are commonly used as markers of inflammation. In addition, none of the indices differed significantly among the outcome groups (survival, ESRD, and death). Further research is warranted to determine whether these markers are predictive of disease activity and prognosis.

The pathogenesis of AAV involves necrotizing inflammation of small- to medium-sized blood vessels, constituting a complex

process of immune dysregulation influenced by both genetic and environmental factors. Neutrophil priming, a crucial step in AAV pathogenesis, leads to the expression of ANCA antigens on the cell membrane, resulting in excessive neutrophil activation. This scenario, in turn, promotes cytokine production and the release of reactive oxygen species and lytic enzymes, thereby amplifying the inflammatory response⁽¹⁴⁾. Regardless of the initial trigger, acute inflammatory responses are typically associated with several alterations in hematological parameters. In recent years, numerous studies have investigated peripheral blood-derived platelet, neutrophil, and lymphocyte counts, confirming that PLR, NLR, and SII are associated with inflammatory activity and prognosis in various diseases^(8–12,15–17).

Although ANCA positivity and ANCA titers have long been used in clinical practice as indicators of disease activity, their primary utility lies in diagnosis, and they are not considered reliable markers of disease activity

during follow-up. ANCA positivity may persist for many years, even in patients who are in remission⁽¹⁶⁾. In our study, no significant differences were observed between ANCA-positive and ANCA-negative patients, suggesting that ANCA positivity is not a predictor of poor prognosis.

Huang et al. investigated the relationship between NLR at diagnosis and inflammatory status and disease activity among 188 patients with MPO-AAV and found that NLR was positively correlated with CRP. Moreover, a higher NLR was a predictor of increased mortality in MPO-AAV⁽¹⁸⁾. Similarly, in the study by Ahn et al., NLR at diagnosis was shown to correlate with vasculitis activity and to predict relapse, but not mortality, in patients with AAV⁽¹²⁾. In another study, 163 patients with AAV were enrolled to investigate whether PLR was associated with disease severity. The study confirmed that patients with severe AAV had significantly higher PLR values than those without severe disease⁽¹⁹⁾. The study conducted by Gunduz et al. showed that NLR, PLR, and the monocyte–lymphocyte ratio at diagnosis were associated with increased disease severity and poorer prognosis in AAV⁽²⁰⁾.

In contrast to previous studies, we did not find any clinical significance of NLR or PLR at diagnosis in estimating the prognosis of patients with AAV. Unfortunately, because data on extrarenal manifestations were not available for all patients, the relationship between complete blood count–derived cell ratios and the Birmingham Vasculitis Activity Score (BVAS) could not be assessed. We aim to conduct a large-scale, prospective study in the future to establish more definitive optimal cut-off values for SII, PLR, and NLR in predicting disease activity in patients with AAV, thereby facilitating their application in clinical practice. Moreover, the systemic immune-inflammation index (SII), a novel index that extends NLR and PLR, has recently been described in the literature as a significant marker of inflammation and prognosis in various clinical settings^(21,22).

The clinical utility of this easily calculated index has been explored in patients with AAV, with early studies suggesting a positive association between NLR, the Birmingham Vasculitis Activity Score (BVAS), and acute-

phase reactants, as well as poor renal outcomes. However, other studies have reported conflicting findings regarding the association between these indices and disease activity. Specifically, Chen et al. demonstrated that SII was positively correlated with CRP and ESR in patients with MPO-AAV, and that higher SII was associated with a reduced risk of ESRD⁽¹¹⁾. In contrast, Kim et al. found that patients with higher SII at diagnosis exhibited significantly more severe AAV activity and reduced relapse-free renal survival compared to those with lower SII levels⁽²²⁾. In the present study, we found that patients with AAV had higher levels of SII, NLR, and PLR compared to the control group. Furthermore, ROC curve analysis demonstrated that SII and NLR had the highest predictive capacity for distinguishing AAV patients from controls. However, Spearman's correlation analysis revealed that SII in patients with AAV was not correlated with CRP or CRP/albumin, which is inconsistent with previous findings⁽¹¹⁾. Previous studies have shown that the number of crescents is indicative of inflammatory burden and plays a critical role in determining renal prognosis⁽²³⁾. However, no correlation was observed between the percentage of crescents and the SII in our study. These findings suggest that SII is not associated with the inflammatory state or disease activity in patients with AAV. Moreover, our data showed that SII levels were similar between patients with severe renal impairment (GFR < 15 mL/min/1.73 m²) and those with moderate impairment (GFR ≥ 15 mL/min/1.73 m²), suggesting that SII is not associated with the degree of glomerular damage. Additionally, no significant differences were observed among the three outcome groups (survival, ESRD, and death). Further large-scale studies are warranted to determine whether SII can predict disease activity and prognosis.

Our study had several limitations. First, it is a retrospective design. Second, the relatively small sample size may limit the generalizability of our findings. Finally, the BVAS could not be assessed due to missing data.

CONCLUSION

This study is one of the few that have investigated the clinical significance of the systemic immune-inflammation index (SII) in

patients with AAV. The present study demonstrated that both the neutrophil-to-lymphocyte ratio (NLR) and SII were superior markers for predicting AAV. However, NLR, PLR, and SII failed to demonstrate any correlation with inflammatory status or prognosis. As these indices are derived from routine complete blood count analyses, future studies should be designed to explore further the diagnostic, discriminatory, and prognostic value of SII in AAV.

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Conflict of interest

No third party supported this study and did not receive any financial funding. All authors have read the manuscript and approved its submission. The authors declare that they have no conflicts of interest related to the publication of this manuscript. This manuscript has not been previously published.

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