

## The diagnostic utility of systemic immune inflammation index in differentiating crescentic glomerulonephritis subtypes

*La utilidad diagnóstica del índice de inflamación inmune sistémica para diferenciar los subtipos de glomerulonefritis con semilunas*

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### RESUMEN

**Introducción:** Los índices hematológicos se han utilizado como marcador de diagnóstico diferencial o predicción pronóstica de diversas enfermedades. Dado que, no existen estudios que hayan evaluado la relación entre el índice de inflamación inmune sistémica (SII) y la glomerulonefritis con semilunas (GN), nuestro objetivo fue investigar la utilidad diagnóstica del SII en los subtipos de GN con semilunas. **Métodos:** En estudio retrospectivo; los pacientes con GN con semilunas se dividieron en tres grupos: GN con semilunas tipo 1 (n = 1), GN con semilunas tipo 2 (n = 44) y GN con semilunas tipo 3 (n = 44). Como solo había 1 paciente en el grupo de GN con semilunas tipo 1, fue excluido. Los grupos se compararon en términos de SII, proporción de neutrófilos a linfocitos (NLR) y proporción de plaquetas a linfocitos (PLR). El SII se calculó mediante el recuento de plaquetas × recuento de neutrófilos/recuento de linfocitos. La capacidad predictiva de estos índices se determinó mediante el análisis de la curva de características operativas del receptor (ROC). Además, se analizó la correlación de los índices con marcadores inflamatorios y pruebas de función renal. **Resultados:** Los pacientes con GN con semilunas tipo 3 tenían niveles más altos de urea, creatinina, velocidad de sedimentación globular (ESR), SII, NLR y PLR; niveles más

bajos de tasa de excreción de proteínas de 24 horas y tasa de filtración glomerular estimada (eGFR) en comparación con el grupo de GN con semilunas tipo 2. Según la curva ROC, SII tuvo el nivel más alto de discriminación de subtipo de GN con semilunas y NLR fue el más bajo. Además, hubo una correlación positiva significativa entre el SII y el porcentaje de glomerulos con semilunas, urea y creatinina y, una correlación negativa entre el SII y la TFGe. **Conclusiones:** Este estudio reveló que un SII elevado podría reflejar la gravedad de la lesión renal en pacientes con GN con semilunas. Se necesitan más estudios con series grandes para confirmar los resultados anteriores.

**Palabras Clave:** Índice de inmunoinflamación sistémica; glomerulonefritis con semilunas

### ABSTRACT

**Introduction:** Hematological indices have been used as a marker for differential diagnosis or prognostic prediction of diverse diseases. Since no study has been conducted to search for the relationship between the systemic immune inflammation index (SII) and crescentic glomerulonephritis (GN), we aim to investigate the diagnostic utility of SII in crescentic GN subtypes. **Methods:** In this retrospective study, patients with crescentic GN were divided into

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three groups: type 1 crescentic GN (n=1), type 2 crescentic GN (n=44), and type 3 crescentic GN (n=44). There was only one patient in the type 1 crescentic GN group, so he was excluded. The groups were compared regarding SII, neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR). The SII was calculated by platelet count  $\times$  neutrophil count/lymphocyte count. The predictive ability of these indices was determined by using the receiver operating characteristic (ROC) curve analysis. Also, the correlation of the indices with inflammatory markers and renal function tests was analyzed. **Results:** Patients with crescentic GN type 3 had higher levels of urea, creatinine, erythrocyte sedimentation rate (ESR), SII, NLR, and PLR levels; they showed lower levels of 24-hour protein excretion rate and estimated glomerular filtration rate (eGFR) compared to crescentic GN type 2 group. According to the ROC curve, SII had the highest level of discriminating crescentic GN subtypes, and NLR was the lowest. Also, there was a significant positive correlation between SII and the percentage of crescentic glomeruli, urea, and creatinine, as well as a negative correlation between SII and eGFR. **Conclusions:** This study revealed that a high SII might reflect the severity of kidney injury in patients with crescentic GN. Further studies with large series are needed to confirm the above results.

**Keywords:** Systemic immune-inflammation index; crescentic glomerulonephritis

## INTRODUCTION

Crescentic glomerulonephritis (GN) is a life-threatening syndrome defined by the rapid loss of renal function, accompanied by features of the nephritic syndrome with proteinuria, glomerular hematuria, and oliguria<sup>(1)</sup>. Despite aggressive treatment, crescentic GN has a risk of kidney failure, requiring dialysis for up to 30% of patients<sup>(2)</sup>. It is characterized morphologically by extensive crescent formation (extra capillary proliferation in Bowman's space), and the crescent appears to represent a nonspecific response to severe injury to the glomerular capillary wall<sup>(3,4)</sup>.

Based on the immunofluorescence staining pattern, crescentic GN is classified into three types: type 1 crescentic GN (anti-glomerular basement

membrane antibody disease), which exhibits linear deposits of immunoglobulins along the glomerular basement membrane; type 2 crescentic GN (immune complex GN) is described as granular immune-complex deposits on the glomerular tuft, and type 3 crescentic GN (pauci-immune GN) is characterized by absent or little immune deposits with immunofluorescence staining of the glomeruli<sup>(3)</sup>.

In recent years, hematological indices have been used as biomarkers of inflammation due to their easy availability and cost-effectiveness<sup>(5,6,7,8)</sup>. Neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) are used as a marker for differential diagnosis or prognostic prediction of diverse diseases such as malignancies and inflammatory diseases<sup>(6,7,9,10)</sup>. The systemic immune-inflammation index (SII), based on lymphocyte, neutrophil, and platelet counts, has been developed recently. Studies have reported the use of SII as an indicator for autoimmune diseases or to predict the poor prognosis of malignancies and antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV)<sup>(5-10,11,12,13,14)</sup>.

However, to our knowledge, no study has investigated the relationship between SII and crescentic GN. We aimed to investigate the diagnostic utility of SII, NLR, and PLR in crescentic GN subtypes.

## MATERIALS AND METHODS

### Study population

All patients diagnosed with crescentic glomerulonephritis by biopsy between January 2014 and December 2021 at Bakirkoy Dr. Sadi Konuk Education and Research Hospital Nephrology Department were retrospectively analyzed. Patients who had the following conditions were excluded: <18 years old, blood transfusion history within the last three months, infections, autoimmune systemic diseases including rheumatoid arthritis, autoimmune liver diseases, and multiple sclerosis, malignancies, hematologic diseases, usage of drugs that can influence blood count parameters, and lack of data about laboratory results. This study was approved by the institutional clinical research local ethics committee (approval no: 2022-01-12). The informed consent was waived owing to the retrospective nature of the study.

### Clinical and laboratory data

Data on age, sex, laboratory results at the time of diagnosis with kidney biopsy (glucose, uric acid, total protein, albumin, urea, creatinine, neutrophil, leukocyte, thrombocyte, hemoglobin, estimated glomerular filtration rate [eGFR], erythrocyte sedimentation rate [ESR], C reactive protein [CRP], routine urine analysis, 24-hour urinary protein excretion rate) were collected from the hospital's electronic medical records. The eGFR was calculated using the CKD-EPI equation<sup>(15)</sup>. SII, NLR, and PLR were calculated. The SII was calculated by platelet count  $\times$  neutrophil count/lymphocyte count. The NLR was calculated by neutrophil/ lymphocyte count and PLR by platelet/lymphocyte count.

The renal biopsy reports noted the number of glomeruli, crescents, sclerotic glomeruli, crescent type, crescent percent, endocapillary cellularity, interstitial inflammation, interstitial fibrosis, tubular atrophy, and immunofluorescence staining findings. Patients were divided into three groups based on immunofluorescence microscopy: type 1 crescentic GN, type 2 crescentic GN, and type 3 crescentic GN. There were 44 patients in the type 2 crescentic GN group and 44 in the type 3 crescentic GN group. Since one patient was in the type 1 crescentic GN group, this patient was not included in the study. Out of 44 patients with type II crescentic GN subtypes, the distribution between causes showed 65.9 % had IgA nephropathy, 18.2% had Lupus Nephritis, 13.7% had Membranoproliferative GN (MPGN), and 2.3% had Membranous GN. All 44 patients with AAV were also classified under subtype III crescentic GN. SII, NLR, and PLR levels of types 2 and 3 crescentic GN groups were compared. Also, the correlation of the indices with inflammatory markers and renal function tests was analyzed.

### Statistical analysis

The NCSS (Number Cruncher Statistical System) 2020 program was used for statistical analysis. Descriptive statistical methods (mean, standard deviation, median, frequency, percentage, Q1 and Q3 percentage) were used to evaluate the study data. The suitability of quantitative data for normal distribution was tested using the Shapiro-Wilk test and graphical analysis. Student-t test was used to compare normally distributed quantitative variables between type 2 crescentic GN and type 3 crescentic GN. The Mann-Whitney U test was used to compare non-normally distributed quantitative variables between the two groups.

The Pearson chi-square test was used to compare qualitative data on the percentage distribution of glomerulonephritis subtypes. Spearman correlation analysis evaluated the relationships between quantitative variables and hematological indices.

As a multivariate analysis, the effects of other risk factors on SII were evaluated using linear regression (backward) analysis. Statistical significance was accepted as  $p < 0.05$ .

Diagnostic screening tests (sensitivity, specificity, positive predictive value, negative predictive value) and Receiver Operating Characteristic (ROC) analysis were used to determine the predictive value for the parameters.

### RESULTS

Demographic data and histopathological diagnosis of 88 crescentic GN patients are given in **Table 1**.

It was observed that 50% (n=44) of the cases

**Table 1:** Demographic data and Histopathological Diagnosis of crescentic GN patients

		Type II crescenticGN (n=44)	Type III crescenticGN (n=44)	P
Age		38 (18-80)	56 (31-82)	<b>*0.001</b>
Gender	Female	13 (29.5)	19 (43.2)	<b>**0.184</b>
	Male	31 (70.5)	25 (56.8)	
GN subtypes	AAV	0 (0.0)	44 (100.0)	
	IgA nephropathy	29 (65.9)	0 (0.0)	
	Lupus Nephritis	8 (18.2)	0 (0.0)	
	MPGN	6 (13.7)	0 (0.0)	
	Membranous GN	1 (2.3)	0 (0.0)	

Data were expressed as median (interquartile range) for quantitative variables and n (%) for categorical variables. The suitability of quantitative data for normal distribution was tested using the Shapiro-Wilk test. \*Student t test (mean+ SD (standard deviation) is given in the table.) \*\*Pearson ki kare test (n (%)) is given in the table. GN: Glomerulonephritis AAV: Antineutrophil cytoplasmic antibody associated vasculitis, GN: glomerulonephritis, IgA: Immunoglobulin A, MPGN: membranoproliferative glomerulonephritis

were crescentic GN type 2 and 50% type 3 crescentic GN. The age of patients with crescentic GN type 3 was statistically significantly higher than that of crescentic GN type 2 patients ( $p=0.01$ ). GN subtypes are presented in **Table 1**.

Laboratory characteristics according to crescentic GN subtypes are compared in **Table 2**.

Urea, creatinine, neutrophil, leukocyte, thrombocyte, ESR, SII, NLR, PLR levels, and the mean hospital stay of the patients were significantly higher in patients with crescentic GN type 3 in comparison to crescentic GN

type 2 ( $p=0.001$ ,  $p=0.001$ ,  $p=0.001$ ,  $p=0.005$ ,  $p=0.001$ ,  $p=0.001$ ,  $p=0.001$ ,  $p=0.001$ ,  $p=0.001$ , and  $p=0.001$  respectively). However, eGFR and 24 hr protein excretion rate was found to be lower in patients with crescentic GN type 3 ( $p=0.001$ ,  $p=0.022$ ). The pathological characteristics of the patients are given in **Table 2**. The percentage of crescentic glomeruli, fibrocellular, and fibrous crescents were significantly higher in type 3 crescentic GN than in type 2 crescentic GN ( $p=0.001$ ,  $0.002$ , and  $0.001$  respectively).

As a statistically significant difference was

**Table 2:** Comparison of Laboratory Findings between Crescentic GN type II and III

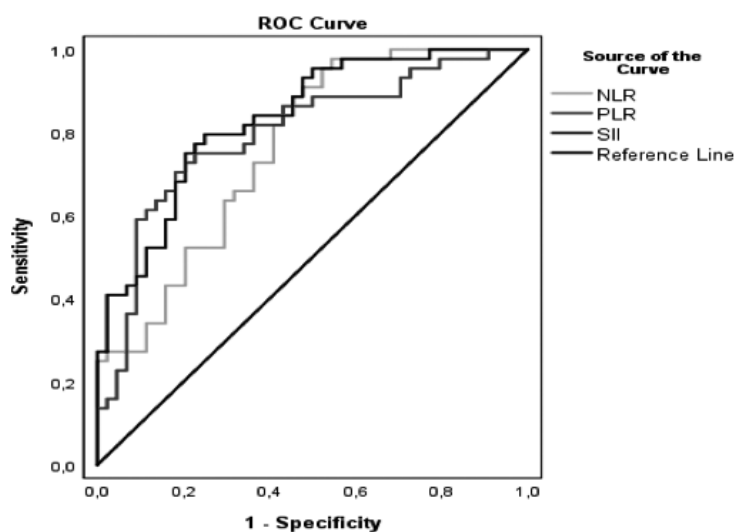
	Type II crescenticGN	Type III crescenticGN	p
Hemoglobin (g/dL)	11.51±2.28	9.61±1.73	<b>*0.001</b>
Neutrophil ( $10^3/uL$ )	5.61±2.32	8.49±4.48	<b>*0.001</b>
Leukocyte ( $10^3/uL$ )	8.41±2.65	11.06±4.63	<b>*0.005</b>
Trombocyte ( $10^3/uL$ )	238.07±90.69	330.77±117.41	<b>*0.001</b>
Lymphocyte ( $10^3/uL$ )	2±0.8	1.65±0.77	<b>*0.036</b>
NLR	2.5 (1.1-8.5)	4.4 (2.1-36.7)	<b>**0.001</b>
PLR	127.5 (45.4-326.2)	212.4 (61.6-824.3)	<b>**0.001</b>
SII	595.5 (186.5-2322.4)	1369.1 (338.7-13974.4)	<b>**0.001</b>
ESR (mm/h)	37.67±26.12	62.61±33	<b>**0.001</b>
CRP (mg/L)	8.81±15.59	22.18±35.51	<b>**0.042</b>
Urea (mg/dL)	70.3±44.8	109.16±63.64	<b>**0.001</b>
Creatinine (mg/dL)	2.15±2.21	3.4±2,6	<b>**0.001</b>
eGFR (ml/min/1.73m <sup>2</sup> )	65.24±42.72	32.85±30.3	<b>**0.001</b>
24-h urinary protein (g/dl)	3.997±3.635	2.202±1.566	<b>**0.022</b>
Duration of hospital stay(day)	21 (3-55)	22 (1-96)	<b>**0.001</b>
Percentage of crescentic glomerulus (n=88)	15.8 (2.9-77.8)	17.2 (7.4-84.6)	<b>**0.001</b>
Number of cellular crescents	1 (0-2,3)	2 (1-4)	<b>**0.078</b>
Number of fibrocellular crescents	0 (0-2)	3 (1-5)	<b>**0.001</b>
Number of fibrosis crescents	0 (0-0)	1 (0-2)	<b>**0.002</b>

Data was collected at the time of kidney biopsy.\*Student t test (mean±SD(standart deviation) is given in the table.) \*\*Mann Whitney U test (median (Q1-Q3 percentage) is shown in the table. GN: Glomerulonephritis, NLR: neutrophil-lymphocyte ratio, PLR: platelet-lymphocyte ratio, SII: systemic immune inflammation index, eGFR: estimated glomerular filtration rate, CRP C: reactive protein, ESR: erythrocyte sedimentation rate

observed between the patients with type 2 and 3 crescentic GN in terms of hematological indices (NLR, PLR, and SII), the optimal cut-off values were identified by ROC analysis (**Figure 1**).

The cut-off point was 2.36 (AUC=0.763;

**Figure 1:** ROC Analysis of NLR, PLR, and SII for Glomerulonephritis Subtypes Differentiation



**Fig 1.** Receiver operating characteristic curves of the **NLR** (neutrophil-lymphocyte ratio), **PLR** (platelet-lymphocyte ratio), and **SII** (systemic immune inflammation index) for differentiating **GN** (glomerulonephritis) subtypes. **ROC** for **NLR** was represented by the blue line with an **AUC**= 0.763 ( CI: 3,761-81.438 p =0.001) with a sensitivity of 95.45 % and a specificity of 47.73 %, the **ROC** for **PLR** was represented by the red line with an **AUC**= 0.796 (CI: 3.935-29.261 p =0.001) with a sensitivity of 70.45 % and a specificity of 81.82, and the **ROC** for **SII** was represented by the green line with an **AUC**=0.833 (CI: 4.287-31,748 p =0.001) with a sensitivity of 79.55 % and a specificity of 76.10 %.

p=0.001; CI: 3,761-81.438), 172.36 (AUC=0.796; p=0.001; CI: 3.935- 29.261), and 966.18 (AUC=0.833; p=0.001; CI: 4.287-31,748) for **NLR**, **PLR**, and **SII**, respectively. According to the ROC curve, **SII** had the highest level of discriminating

crencentic **GN** subtypes, and **NLR** was the lowest (**Figure 1**). The correlation of **SII**, **NLR**, and **PLR** with laboratory and histopathological findings is shown in **Table 3**.

There was a significant positive correlation

**Table 3:** Comparison of Hematological Indices with Laboratory and Histopathological Findings

	<b>NLR</b>		<b>PLR</b>		<b>SII</b>	
	<b>r</b>	<b>p</b>	<b>r</b>	<b>p</b>	<b>r</b>	<b>p</b>
<b>PLR</b>	0.666	<b>0.001</b>	-	-	-	-
<b>SII</b>	0.850	<b>0.001</b>	0.843	<b>0.001</b>	-	-
<b>ESR (mm/h)</b>	0.184	0.096	0.375	<b>0.001</b>	0.375	<b>0.001</b>
<b>CRP (mg/L)</b>	0.256	<b>0.016</b>	0.287	<b>0.007</b>	0.311	<b>0.001</b>
<b>Percentage of crescentic glomeruli (%)</b>	0.426	<b>0.001</b>	0.298	<b>0.008</b>	0.355	<b>0.001</b>
<b>Protein excretion rate (mg/24 h)</b>	-0.065	0.548	-0.053	0.625	-0.096	0.374
<b>Urea (mg/dL)</b>	0.409	<b>0.001</b>	0.263	<b>0.013</b>	0.324	<b>0.002</b>
<b>Creatinine (mg/dL)</b>	0.367	<b>0.001</b>	0.208	0.051	0.267	<b>0.012</b>
<b>e-GFR (mL/min/ 1.73 m2)</b>	-0.383	<b>0.001</b>	-0.254	<b>0.017</b>	-0.306	<b>0.004</b>

**r**: Spearman correlation coefficient analysis was used. **NLR**: neutrophil-lymphocyte ratio, **PLR**: platelet-lymphocyte ratio, **SII**: systemic immune inflammation index, **eGFR**: estimated glomerular filtration rate, **CRP**: reactive protein, **ESR**: erythrocyte sedimentation rate.

between **NLR** and the percentage of crescentic glomeruli, urea, and creatinine ( $r=0.426$ ;  $p=0.001$ ,  $r=0.409$ ;  $p=0.001$  and  $r=0.367$ ,  $p=0.001$ ,

respectively). Also, a negative correlation between **NLR** and **eGFR** ( $r=-0.383$ ;  $p=0.001$ ) was observed. **PLR** of the cases were positively correlated with

ESR, the percentage of crescentic glomeruli, and urea ( $r=0.375$ ;  $p=0.001$ ,  $r=0.298$ ;  $p=0.008$ , and  $r=0.263$ ;  $p=0.013$ , respectively) and negatively correlated with eGFR ( $r=-0.254$ ;  $p=0.017$ ). In addition, SII level was positively correlated with ESR, the percentage of crescentic glomeruli, urea, and creatinine ( $r=0.375$ ;  $p=0.001$ ,  $r=0.355$ ;  $p=0.001$ ,  $r=0.324$ ;  $p=0.002$ ), and  $r=0.267$ ;  $p=0.012$ , respectively), and negatively correlated with eGFR

( $r=-0.306$ ;  $p=0.004$ ).

A backward regression analysis was performed to determine the relationships between age, gender, creatinine, e-GFR, CRP, percentage of crescentic glomeruli, and SII. SII and CRP had an independent relationship ( $\beta=20.070$ ,  $p=0.011$ ). The rate of SII disclosure by CRP was 8.2% and was considered poor (Table 4).

## DISCUSSION

**Table 4:** Effects of Age, Gender, Creatinine, e-GFR, CRP and Crescentic Glomerular Percentage on SII

Dependent Variable	Independent Variable	$\beta$	t	p	F	Model (p)	R <sup>2</sup>
SII	Intercept	1206.94	5.246	0.001**	6.860	0.011*	0.082
	CRP (mg/L)	20.070	2.619	0.011*			
	Gender	387.378	0.904	0.369			
	Age	4.315	0.281	0.780			
	Percentage of crescentic glomeruli (%)	16.474	1.787	0.078			
	Creatinine (mg/dL)	-25.046	-0.210	0.834			
	e-GFR (mL/min/ 1.73 m <sup>2</sup> )	-4.341	-0.762	0.448			

Backward regression analysis was used. CRP C reactive protein, SII systemic immune inflammation index, eGFR estimated glomerular filtration rate.

The current study is the first report investigating NLR, PLR, and SII levels in patients with different crescentic GN types. Our results showed that NLR, PLR, and SII values were higher in patients with crescentic GN type 3 and that SII was superior to NLR and PLR in distinguishing crescentic GN subgroups. Further, all indices were positively correlated with CRP, and the percentage of crescentic glomeruli and urea was negatively correlated with eGFR. Additionally, creatinine and NLR/SII were found to be positively correlated. These results showed that a high NLR and SII might reflect the degree of glomerular injury.

Crescentic GN is a rare but severe form of GN. It has a glomerular and systemic inflammatory process characterized by activating systemic inflammatory markers and inflammatory findings in renal biopsy specimens<sup>(4-16)</sup>. Immune complexes, anti-glomerular basement membrane (anti-GBM) antibodies, and ANCA can initiate inflammatory glomerular injury that culminates in crescent formation. Innate and adaptive immune system

activation also plays a role in the pathogenesis of crescentic GN. Proinflammatory cytokines and chemokines increase the number and function of neutrophils and cause lymphocyte apoptosis. Therefore, neutrophils and lymphocytes play a role in type 2 crescentic GN and type 3 GN. Lupus nephritis is associated with subendothelial immune complex deposition that supports neutrophil infiltration leading to glomerular damage; in IgA vasculitis, the predominant cells in the inflammatory infiltrates are neutrophils and, ANCA are antibodies formed against granules of neutrophils and lysosomes of monocytes, mostly in IgG structure. Also, platelets play an active role in inflammation by regulating immune system cells<sup>(17)</sup>.

Therefore, components of complete blood cell parameters have emerged as valuable and cost-effective indices in diagnosis, estimating current disease activity, and predicting prognosis in many inflammatory diseases. In recent years, several

studies have evaluated the role of NLR and PLR in patients with GN. In a Korean study involving 160 AAV patients, it was reported that NLR could estimate the current activity and predict relapse during follow-up of AAV patients. However, this study had limitations, such as the small number of patients and the inability to conduct subgroup analyses of AAV<sup>(18)</sup>. Also, PLR, which has reciprocal patterns in response to the inflammatory burden of AAV, was found to be associated with the current activity of AAV<sup>(19,20)</sup>. In the article published in *Modern Rheumatology* in 2015, NLR and PLR were higher in patients with SLE than in the healthy population and higher in patients with renal involvement than without renal involvement<sup>(21)</sup>. This study did not investigate whether treating renal involvement of SLE leads to a decrease in NLR and PLR values.

Further investigations may provide more substantial evidence. As a novel inflammatory index, SII, calculated by three blood lineages (neutrophil, platelet, and lymphocytes), has gained importance in recent years since its relationships with the prognosis of malignant diseases and coronary artery disease have been demonstrated<sup>(10,11,12)</sup>. However, there have not been many studies searching for SII in GN, and more data must be collected from studies with multiple inflammation-based scores. Our study was the first to investigate SII's utility in patients with different crescentic GN types. Recently, Kim et al. analyzed 160 AAV patients and showed that SII is directly proportional to disease severity in patients with AAV and is also a predictor of poor outcomes<sup>(13)</sup>.

In contrast, Chen et al suggested that the risk of developing ESRD was lower in AAV patients with high SII values. This suggestion may be due to the following reasons: the follow-up period in the study was relatively short, and due to the study being retrospective, the immunosuppressive treatments given to the patients were not standardized<sup>(22)</sup>. Unfortunately, there are conflicting results between the ratio and renal outcome in AAV patients, and prospective studies with more patients are needed. Another retrospective study, which included 76 patients with SLE and 76 age- and sex-matched healthy controls, showed that SII, NLR, and PLR levels were higher in patients with SLE than in healthy controls. Also, it was reported that NLR was a better marker than SII in predicting SLE, and NLR, but not SII, could be helpful as an

indicator of lupus nephritis. As in our study, SII was positively correlated with CRP in this study<sup>(23)</sup>. A cross-sectional study, published in 2022, was conducted among adults with complete data about SII and urinary albumin-to-creatinine ratio in the 2005–2018 National Health and Nutrition Examination Survey. A positive correlation between proteinuria and SII was found. This study suggested that inflammation was associated with proteinuria, a kidney damage marker<sup>(24)</sup>. On the other hand, we found no correlation between SII and proteinuria. It is important to note that our study was limited to patients with crescentic glomerulonephritis, and therefore, our study population was smaller than the general population included in this one.

The current study studied the diagnostic utility of SII, NLR, and PLR in patients with different crescentic GN types. Neutrophils, leukocytes, thrombocytes, NLR, PLR, and SII values were lower in patients with immune complex GN. ROC analysis showed that SII was superior to NLR and PLR in discriminating crescentic GN subtypes. This result may be explained as follows. SII is based on lymphocyte, neutrophil, and platelet counts and is more comprehensive in reflecting the balance of host inflammatory and immune status than NLR and PLR. In our study, the patients with immune complex GN tended to have lower levels of urea, creatinine and higher levels of eGFR. The severity of kidney damage depends on the nature and type of immunologic process causing the disease and the degree of crescent formation. Patients with circumferential crescents in more than 80 percent of the glomeruli tend to present with advanced kidney failure that may not respond well to therapy. By comparison, patients with crescents in less than 50 percent of the glomeruli, mainly if the crescents are non-circumferential, typically follow a more indolent course and may even undergo remission<sup>(25)</sup>. Pathologic severity, activity, and chronicity of glomerular and tubulointerstitial disease can help refine the prognosis. In immune-complex GN, immune complexes are usually detected in subendothelial locations, where they are in close proximity to attract and activate neutrophils and monocytes, which are then in a prime location to cause maximal glomerular capillary wall injury. On the other hand, glomerular immune-complex localization appears to be less effective at inducing

crescent formation than ANCA or anti-GBM antibodies<sup>(25)</sup>. Similarly, our results revealed that the patients with crescentic GN type 2 had lower inflammatory burden and degrees of glomerular injury.

In our analysis, Spearman correlation demonstrated that all indices were positively correlated with CRP, the percentage of crescentic glomeruli, and urea, and negatively correlated with eGFR. Also, NLR and SII were positively correlated with creatinine. The positive correlation between the indices and the percentage of glomeruli with crescent shows that glomerular inflammation in crescentic GN is so severe that it can cause systemic inflammation and activate acute phase reactants. Also, higher values of SII and NLR reflect more severe inflammatory disease and glomerular damage. Indeed, prospective studies with more patients and subgroups are needed to assess the significance of SII in patients with crescentic GN.

Limitations of this study include the fact that we performed a retrospective analysis in a single center. The reasons for these limitations were that we could not access the data of some patients, and the number of samples was low. The other limitation is that there was no mention of systemic involvement in these diseases. Whether it is ANCA vasculitis, Lupus nephritis, or crescentic IgA, all these diseases can present with systemic manifestations that affect inflammatory markers, NLR, PLR, and SII. Thus far, as no published study in the literature aims to evaluate NLR, PLR, and SII in patients with different types of crescentic GN, we believe this study adds information about the clinical utility of hematological indices in clinical practice.

## CONCLUSIONS

This study is the first to investigate the diagnostic utility of NLR, PLR, and SII in patients with different crescentic GN types. SII was higher in type 3 crescentic GN than in type 2; this result may indicate that the inflammatory burden is more significant in type 3 crescentic GN than in type 2. Particularly, a high SII might reflect the severity of kidney injury in crescentic GN patients. Since SII is a readily available method characterized by a non-invasive approach and low cost, it has promising prospects for application. Further studies with large series are needed to confirm the

above results.

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## Conflict of interest

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