#### ORIGINAL RESEARCH

# Association of Systemic Immune-Inflammation Index and Systemic Inflammation Response Index with Diabetic Kidney Disease in Patients with Type 2 Diabetes Mellitus

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**Purpose:** To evaluate the association of the systemic immune-inflammatory index (SII) and systemic inflammatory response index (SIRI) with the clinical and pathological features and progression of diabetic kidney disease (DKD).

**Patients and Methods:** We analyzed 303 patients with type 2 diabetes mellitus (T2DM), classifying them into distinct groups: T2DM, early DKD (EDKD), and clinical DKD (Cli-DKD). Variations in SII and SIRI levels across these groups and their association with renal function were assessed. Logistic regression analysis was used to identify independent risk factors for DKD. Additionally, in 43 patients with biopsy-confirmed DKD, we analyzed the relationship between SII, SIRI, and pathological changes. Kaplan–Meier survival analysis and the Cox proportional hazards model were used to assess the influence of SII and SIRI levels on outcomes in patients with DKD.

**Results:** SII and SIRI were significantly higher in the Cli-DKD group than in the T2DM and EDKD groups, and were positively correlated with the urinary albumin-creatinine ratio and negatively correlated with estimated glomerular filtration rate. Notably, SIRI was identified as an independent risk factor for DKD development. Additionally, a lower SII score was associated with a higher cumulative survival rate.

**Conclusion:** This study demonstrates an association between SII, SIRI, and renal function in patients with T2DM. A high SIRI was an independent risk factor for DKD, while an elevated SII was associated with an increased risk of kidney disease progression in biopsy-confirmed DKD cases. Our findings underscore the potential implications of utilizing SII and SIRI as cost-effective and readily available inflammatory indicators for monitoring DKD in primary care settings.

Keywords: diabetes, renal complications, inflammatory markers, prognosis, immune response, biomarkers

#### Introduction

Diabetic kidney disease (DKD) is a chronic kidney disease caused by diabetes mellitus and is the most common cause of end-stage renal disease(ESRD).<sup>1</sup> The development of DKD involves various factors, including altered hemodynamics, glycolipid metabolism disorders, stress, inflammation, and genetic susceptibility.<sup>2–4</sup> Despite aggressive treatments such as glucose lowering, blood pressure control, lipid management, and renal hemodynamic improvement, DKD still affects 58.6% of patients with diabetes.<sup>5</sup> As researchers have delved into the pathogenesis of DKD, evidence has emerged highlighting the pivotal role of inflammation in its progression.<sup>3,6,7</sup> Numerous studies have indicated that elevated levels of inflammatory markers, such as tumor necrosis factor receptors (TNFRs), intercellular adhesion molecule-1 (ICAM-1), monocyte chemotactic protein-1 (MCP-1), and interleukins, are valuable in the diagnosis and progression of DKD.<sup>7,8</sup>

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However, the clinical utility of these inflammatory markers is constrained by their relatively high cost and demanding operational requirements.

Routine blood tests are a standard feature of hospital examinations widely employed in population health assessments. From these blood cell counts, two important indices—the systemic immune-inflammatory index (SII) and systemic inflammatory response index (SIRI)—are derived. In contrast to the variability seen in a single blood cell count, these indices offer a more sensitive and comprehensive reflection of the balance between inflammation and immunity within the body. First proposed in 2014 and 2016, respectively,<sup>9,10</sup> The SII and SIRI have gained widespread use not only in predicting the prognosis of malignancies<sup>9,11–14</sup> but also in assessing the occurrence and severity of coronary artery disease.<sup>15–19</sup> However, despite their established roles in various medical contexts, there is limited research on the application of SII and SIRI in DKD, particularly regarding disease progression, pathology, and prognosis. The study aimed to analyze the correlation between the SII, SIRI, clinical progression, pathological changes, and prognosis of patients with DKD to further clarify the value of these indices in assessing the severity, disease progression, and prognosis of DKD. The findings from this study are anticipated to enhance clinical decision-making in DKD.

## **Materials and Methods**

#### Study Populations

This retrospective non-interventional study posed no unnecessary risks to participants, and all patient identifiers were either removed or anonymized. The study made every effort to protect the privacy and safety of the participants. The Ethics Committee of the First Affiliated Hospital of Chongqing Medical University reviewed the study and deemed it in accordance with the Declaration of Helsinki(Approval Number: K2023-119), thus informed consent was waived by the Ethics Committee.

Exclusion criteria were defined as follows: (1) Acute complications of diabetes mellitus, such as diabetic ketoacidosis; (2) various acute and chronic infections; (3) systemic diseases, such as hematologic diseases, rheumatism, malignant neoplasms, autoimmunity; (4) medications affecting lymphocytes, neutrophils, platelets, and mononuclear cells(such as melphalan, propylthiouracil, methimazole, etc.); (5) non-diabetic nephropathies; (6) receiving continuous renal replacement therapy; (7) pregnant women; and (8) patients with incomplete clinical data. Additionally, patients with DKD and fewer than five glomeruli were excluded.

#### Study Populations a

A total of 1373 patients with type 2 diabetes mellitus (T2DM) between the ages of 18–80 years who were admitted to the First Affiliated Hospital of Chongqing Medical University between January 2020 and December 2021 were reviewed retrospectively. Of these, 303 patients were enrolled in the study. A flowchart of the study selection methodology is shown in Figure 1. The diagnosis of T2DM was made in accordance with the World Health Organization diagnostic criteria.

#### Study Populations B

A total of 65 patients with biopsy-confirmed DKD, treated between January 2013 and September 2020 at the First Affiliated Hospital of Chongqing Medical University, were initially considered for inclusion. Ultimately, 43 patients with DKD were included in the validation cohort. A flowchart of the study selection methodology is shown in Figure 2. Renal biopsy was indicated based on the presence of abnormal, active urine sediment. Additionally, inclusion criteria encompassed a rapid increase in urinary albumin or the manifestation of nephrotic syndrome, along with a rapid decrease in the estimated glomerular filtration rate (eGFR) in the short term.

## **Clinical and Laboratory Parameters**

Various clinical and laboratory parameters, including age, sex, body mass index(BMI), systolic blood pressure(SBP), diastolic blood pressure(DBP), duration of diabetes, diabetic retinopathy, history of hypertension, treatment (e g hypoglycemic program and RAS inhibitor), fasting blood glucose, high-sensitivity C-reactive protein(hs-CRP), hemoglobin A1c(HbA1c), white blood cell count, serum creatinine (SCr), blood urea nitrogen(BUN), serum uric acid(UA), urinary albumin-to-creatinine ratio(UACR)/ 24 hours urinary protein quantitative, albumin, triglyceride(TG), and cholesterol levels were extracted from the patient's medical history. The SII was calculated as platelet count × neutrophil count/lymphocyte count, and the SIRI was calculated as monocyte



Figure I Flowchart of study population A.

count  $\times$  neutrophil count/lymphocyte count. The eGFR was determined using the Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI).

Renal tissue was obtained via percutaneous renal biopsy and sent to the Pathological Diagnosis Center of Fuzhou General Hospital of Nanjing Military Command for analysis. Pathological changes in the kidneys were assessed using light microscopy, immunofluorescence, and electron microscopy. Each specimen was evaluated by the same group of pathologists. Subsequently, the patients were classified based on the 2010 staging criteria for diabetic nephropathy established by the International Society for Renal Pathology.

#### Grouping

#### Study Populations A

Based on UACR and eGFR, patients with T2DM were categorized into the following groups: T2DM group: UACR <30 mg/g and eGFR  $\geq$ 90 mL/min/1.73 m<sup>2</sup>(157 cases); Early DKD (EDKD) group: UACR  $\geq$ 30 to <300 mg/g and



Figure 2 Flowchart of study population B.

eGFR $\geq$ 60 mL/min/1.73 m<sup>2</sup>(69 cases); and Clinical DKD (Cli-EDKD) group: UACR  $\geq$ 300 mg/g or eGFR<60 mL/min/ 1.73 m<sup>2</sup>(77 cases).

#### Study Populations B

Patients in study population B were categorized into low and high SII groups, as well as low and high SIRI groups, based on the median SII and SIRI of this population.

## Outcomes

Through a review of electronic medical records and conducting phone interviews, data regarding the outcomes for study population B were gathered. These outcomes were defined as instances of SCr levels elevating by 2-fold or more compared to baseline, progression to end-stage renal failure, hospital admission due to kidney disease, or mortality. The study was monitored until April 1, 2023.

## Statistical Analysis

Statistical analysis was conducted using SPSS software (version 26.0). Quantitative data with a normal distribution were presented as mean±SD, and group comparisons were performed via LSD-*t*–test or ANOVA. Quantitative data that did not follow a normal distribution were expressed as medians (upper and lower quartiles), and group comparisons were performed using nonparametric tests. Categorical variables were expressed as percentages (%), and chi-square tests were employed for group comparisons. Correlations between the SII and SIRI and clinical indicators were analyzed using Pearson's or Spearman correlation analysis. Logistic regression analysis was used to explore risk factors for DKD. To clarify the impact of the SII and SIRI on the prognosis of DKD, Kaplan-Meier (K-M) survival curves and Cox regression modeling were constructed.

## Results

## Study Population A

#### Comparison of Clinical Characteristics and Laboratory Findings of Patients with T2DM

The characteristics of the 303 patients with T2DM are presented in Table 1. The proportions of diabetic retinopathy and UACR were high, indicating a correlation with renal function deterioration (P<0.001). Compared to the T2DM and EDKD groups, the Cli-DKD group exhibited a higher BMI and increased proportions of oral hypoglycemic agents, SII, SIRI, SCr, uric acid, and BUN. However, lower levels of Hb, albumin, and eGFR were observed (P<0.05). Patients with DKD showed significantly higher rates of hypertension and usage of renin–angiotensin–aldosterone system (RAAS) inhibitors, along with elevated values for SBP, leukocyte count, neutrophil count, and TG compared to those without DKD (P<0.05). Nevertheless, there were no significant differences among the three groups regarding age, sex, duration of diabetes, DBP, proportions of hypoglycemic drugs + insulin and insulin, fasting blood glucose, platelets, lymphocytes, monocytes, toll protein, aspartate transaminase, alanine transaminase, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and hs-CRP levels.

#### Correlations Between SII and SIRI and Laboratory Parameters

As shown in Table 2, the SII was positively correlated with the duration of diabetes (Rs=0.147, P=0.01), SIRI (Rs=0.721, P<0.001), SCr (Rs=0.158, P=0.006), BUN (Rs=0.242, P<0.001), UACR (Rs=0.183, P<0.001), and hs-CRP (Rs=0.147, P=0.01), whereas it was negatively correlated with eGFR (Rs=-0.263, P<0.001) and TG (Rs=-0.127, P=0.027). Similarly, the SIRI was positively correlated with the duration of diabetes (Rs=0.219, P<0.001) SII (Rs=0.721, P<0.001), SCr (Rs=0.227, P<0.001), BUN (Rs=0.362, P<0.001), UACR (Rs=0.224, P<0.001) and hs-CRP levels (Rs=0.181, P=0.002), whereas it was negatively correlated with eGFR (Rs=-0.348, P<0.001).

#### Risk Factors for DKD in Patients with T2DM

Logistic regression analysis (Table 3) was used to determine independent risk factors. Univariate logistic analysis revealed that SII (OR=1.001, 95% CI=1.000~1.002, P=0.043) and SIRI (OR=2.067, 95% CI=1.415~3.018, P<0.001) were significantly associated with the development of DKD. After adjusting for age, sex, BMI, presence of diabetic retinopathy, glucose-lowering treatment, use of RAAS inhibitors, comorbid hypertension, SBP, DBP, fasting blood glucose, Hb, toll protein, albumin, alanine transaminase, aspartate transaminase, SCr, UA, BUN, total cholesterol, TG, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, HbA1c, hs-CRP, and SII, the multivariate logistic analysis revealed that SIRI remained an independent risk factor for DKD(OR=2.185, 95% CI=1.031~4.628, P=0.041).

## Study Population B

#### Baseline Characteristics of DKD

As shown in Table 4, a total of 43 patients with biopsy-confirmed DKD with T2DM were included in the study. Of these, 31 were male, and 12 were female, with an average age of 47.81±9.50 years. The average duration of diabetes mellitus among the participants was 4 years(IQR 1.25,8.00), and the mean BMI was 24.41±3.32(kg/m<sup>2</sup>). Notably, 60.47% of the patients had comorbid hypertension, and 65.12% had comorbid diabetic retinopathy. The median 24-hour urinary protein

Table	I Demogra	aphic and	Clinical	Characteristics	of Study	Participants
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Variable	T2DM	EDKD	Cli-DKD	Р
	(n=157)	(n=69)	(n=77)	
Gender(male/female)	108/49	45/24	49/28	0.704
Age (years)	58 (53,66)	62 (54,66)	62 (53,68)	0.420
BMI (kg/m <sup>2</sup> )	23.53 (21.91,25.75)	24.22 (22.39,25.33)	25.15 (23.24,28.04)*▲	<0.001
Duration of diabetes(years)	10.00 (5.00,15.00)	12.00 (6.00,16.00)	12.00(8.00,18.00)	0.145
Diabetic retinopathy (%)	31 (19.70%)	28 (40.60%) <sup>a</sup>	48 (63.20%) <sup>ab</sup>	<0.001
Hypertension (%)	58 (36.90%)	45 (65.20%) <sup>a</sup>	61 (79.20%) <sup>a</sup>	<0.001
SBP (mmHg)	131.66±17.88	140.65±17.87*	4 .8 ± 9.23*	<0.001
DBP (mmHg)	78.45±12.38	79.90±11.51	80.96±13.66	0.334
Oral hypoglycemic agent (%)	76 (48.40%)	32 (46.40%)	21 (27.30%) <sup>ab</sup>	0.007
Insulin (%)	19 (12.10%)	5 (7.20%)	13 (16.90%)	0.206
Hypoglycemic agent+ Insulin (%)	59(37.60%)	29 (42.00%)	41 (53.20%)	0.074
RAAS inhibitor (%)	29 (18.50%)	25 (36.20%) <sup>a</sup>	37 (48.10%) <sup>a</sup>	<0.001
FBG (mmol/L)	7.90 (6.60,10.30)	8.30(6.20,10.50)	8.70(6.80,10.70)	0.682
HbAIc (%)	8.60(7.40,10.20)	9.30(7.90,10.40)*	9.10(7.70,11.30)	0.035
Leukocyte (×10 <sup>9</sup> /L)	6.18(5.36,7.28)	6.26 (5.36,7.78)	7.01 (5.82,7.95)*	0.029
Hb (g/L)	143.63±14.22	144.13±16.88	33.36±21.65*▲	<0.001
Platelet (×10 <sup>9</sup> /L)	197.00(161.00,233.00)	202.00(162.00,226.00)	186.00(160.00,220.00)	0.698
Neutrophil (×10 <sup>9</sup> /L)	3.83(3.09,4.66)	4.12(3.33,5.37)*	4.45(3.63,5.44)*	<0.001
Lymphocyte (×10 <sup>9</sup> /L)	1.73(1.39,2.10)	1.56(1.35,2.21)	1.49(1.19,1.87)	0.06
Monocyte (×10 <sup>9</sup> /L)	0.42(0.34,0.54)	0.42 (0.35,0.53)	0.45(0.37,0.59)	0.124
SII(×10 <sup>9</sup> /L)	456.98(314.72,621.92)	465.20(321.44,620.67)	547.57(445.36,777.80)*▲	0.003
SIRI(×10 <sup>9</sup> /L)	0.96(0.64,1.39)	1.20(0.73,1.52)	.3 (0.97, .97)*▲	<0.001
Total protein (g/L)	67.00 (64.00,71.00)	66.00(63.00,71.00)	66.00(60.00,71.00)	0.387
Albumin (g/L)	42.92±3.46	42.96±3.75	39.35±5.86*▲	<0.001
ALT(u/L)	19.00(14.00,29.00)	20.00(13.00,29.00)	19.00 (15.00,25.00)	0.883
AST(u/L)	18.00(14.00,21.00)	18.00(15.00,22.00)	18.00(15.00,25.00)	0.541
SCr (umol/L)	66.00(59.00,76.00)	70.00(57.00,80.00)	04.00(76.00, 35.00) *▲	<0.001
Uric acid (umol/l)	299.00(248.00,365.00)	336.00(260.00,396.00)	395.00 (344.00,456.00)*▲	<0.001
BUN (mmol/l)	5.80(4.90,7.10)	6.40(4.90,7.50)	8.20(6.40,9.90)*▲	<0.001
eGFR (mL	96.68(88.90,105.41)	95.25(76.15,103.71)	56.57 (44.48,83.58)*▲	<0.001
/min ·1. 73 m²)				
UACR (mg/g)	10.70(6.40,15.40)	63.80(38.30,139.40)*	689.50(314.10,1347.90)* <sup>▲</sup>	<0.001
Total cholesterol (mmol/l)	4.38(3.47,5.00)	4.37(3.87,5.06)	4.60(3.47,5.76)	0.289
Triglyceride (mmol/l)	1.30(0.91,2.35)	1.68(1.15,2.50)*	2.02(1.22,3.08)*	0.002
HDL-C (mmol/l)	1.09(0.94,1.37)	1.04(0.91,1.32)	1.07(0.87,1.27)	0.594
LDL-C (mmol/l)	2.42(1.39,3.19)	2.57(1.72,2.96)	2.29(1.42,3.19)	0.909
hs-CRP (mg/l)	0.70(0.40,1.81)	0.88(0.52,1.92)	0.94(0.52,1.92)	0.373
	1	1	1	

Notes: \*Compared to the T2DM group, P < 0.05.  $\blacktriangle$ : Compared to the EDKD group, P < 0.05. a: Compared to the T2DM group, P < 0.017. b: Compared to the EDKD group, P < 0.017.

Abbreviations: BMI body mass index; SBP systolic blood pressure; DBP diastolic blood pressure; RAAS Renin-Angiotensin-Aldosterone System; FBG fasting blood glucose; HbA1c glycosylated hemoglobin; Hb hemoglobin; SII systemic immune-inflammation index; SIRI systemic inflammation response index; ALT alanine aminotransferase; AST glutamic oxaloacetic transaminase; Scr serum creatinine; BUN blood urea nitrogen; eGFR estimated glomerular filtration rate; UACR urinary microalbumin to creatinine ratio; HDL-C high-density lipoprotein cholesterol; LDL-C low-density lipoprotein cholesterol; hs-CRP high-sensitivity c-reactive protein.

excretion was 3.74 g/d (IQR 2.20,7.56), and the mean eGFR was  $56.27\pm27.82 \text{ mL/min/1.73 m}^2$ . The median follow-up duration was 32 months (IQR 4.36,59.61). Over the follow-up period, 26 patients (60.47%) experienced outcome events. Among them, 12(46.15%) progressed to ESRD, six(23.08%) experienced a doubling of serum creatinine, six (23.08%) were readmitted to the hospital due to renal disease, and two (7.69%) died.

Variable	SII		SIRI		
	rs	Ρ	rs	Р	
BMI (kg/m²)	0.032	0.584	0.061	0.291	
Duration of diabetes(years)	0.147	0.01	0.219	<0.001	
FBG (mmol/L)	-0.061	0.29	0.01	0.869	
HbAIc (%)	-0.025	0.664	-0.39	0.495	
SII(×10 <sup>9</sup> /L)	-	-	0.721	<0.001	
SIRI(×10 <sup>9</sup> /L)	0.721	<0.001	-	-	
Scr (umol/L)	0.158	0.006	0.227	<0.001	
Uric acid (umol/l)	-0.024	0.672	0.072	0.21	
BUN (mmol/l)	0.242	<0.001	0.362	<0.001	
eGFR (mL/min·l. 73 m <sup>2</sup> )	-0.263	<0.001	-0.348	<0.001	
UACR (mg/g)	0.183	<0.001	0.224	<0.001	
Total cholesterol (mmol/l)	-0.077	0.18	-0.075	0.193	
Triglyceride (mmol/l)	-0.127	0.027	-0.012	0.832	
HDL-C (mmol/l)	0.083	0.152	-0.015	0.799	
LDL-C (mmol/l)	-0.06	0.295	-0.04	0.485	
hs-CRP (mg/l)	0.146	0.011	0.181	0.002	

Table 2	2 Correlations	Between	SII,	SIRI	and	Clinical	Characteristics	in	T2DM
Patients									

Notes: rs: Spearman Correlation Analysis.

Abbreviations: BMI body mass index; FBG fasting blood glucose; HbA1c glycosylated hemoglobin; SII systemic immune-inflammation index; SIRI systemic inflammation response index; Scr serum creatinine; BUN blood urea nitrogen; eGFR estimated glomerular filtration rate; UACR urinary microalbumin to creatinine ratio; HDL-C high-density lipoprotein cholesterol; LDL-C low-density lipoprotein cholesterol; hs-CRP hig.

Variable	OR	95% CI	Р
Model I			
SII(×10 <sup>9</sup> /L)	1.001	1.000~1.002	0.043
SIRI(×10 <sup>9</sup> /L)	2.067	1.415~3.018	<0.001
Model 2			
Gender	2.769	1.161~6.600	0.022
Hypertension (%)	2.966	1.287~6.834	0.011
Diabetic retinopathy (%)	4.891	2.351~10.178	<0.001
SBP(mmHg)	1.028	1.006~1.051	0.012
SCr(umol/l)	1.042	1.021~1.064	<0.001
HbAIc(%)	1.356	1.124~1.636	0.001
SIRI(×10 <sup>9</sup> /L)	2.185	1.031~4.628	0.041

Table 3 Risk Factors for DKD in Patients with Type 2 Diabetes

Abbreviation: SBP systolic blood pressure; HbA1c glycosylated hemoglobin; SII systemic immuneinflam.

## Relationship Between Pathological Changes and SII, SIRI in Patients with DKD

Table 5 illustrates the association between pathological changes and SII as well as SIRI in patients with DKD. Glomerular lesions were categorized into non-progressive (RPS I and II) and advanced stages(RPS III and IV).<sup>20</sup> Notably, higher SII values were observed in patients with segmental sclerosis and glomerular immunoglobulin G (IgG) deposits. However, no statistically significant association was observed between SII and glomerular class, interstitial fibrosis and tubular atrophy score, interstitial inflammation, arteriosclerosis score, and deposits of IgA, IgM, C3d, and C1q(P>0.05). Similarly, SIRI did not show statistically significant correlations with these aforementioned pathological changes(P>0.05).

Variable	Values
Ν	43
Follow-up time (months)	32.00(4.39,59.61)
Gender(male/female)	31/12
BMI (kg/m <sup>2</sup> )	24.41±3.32
Age (years)	47.81±9.50
Duration of diabetes (years)	4.00(1.25,8.00)
Hypertension (%)	26 (60.47%)
Diabetic retinopathy (%)	28 (65.12%)
SBP (mmHg)	156.09±21.63
DBP (mmHg)	90.89±12.29
Oral hypoglycemic agent (%)	26 (60.47%)
Insulin (%)	II (25.58%)
Hypoglycemic agent+ Insulin (%)	6 (13.95%)
RAAS inhibitor (%)	20 (46.51%)
CKD stage(1/2/3a/3b/4/5)	(4/15/7/8/7/2)
SII(×10 <sup>9</sup> /L)	659.09(500.36,935.27)
SIRI(×10 <sup>9</sup> /L)	1.39(0.98,2.04)
SCr (umol/L)	122.00(101.00,178.50)
Uric acid (umol/l)	384.98±101.13
BUN (mmol/l)	8.85±3.42
eGFR (mL/min·l. 73 m <sup>2</sup> )	56.27±27.82
Ccr (mL/min)	97.75±64.20
24-hour urinary protein quantitative (g/24h)	3.74 (2.20,7.56)
Glomerular class(I/IIa/IIb/III/IV)	(0/4/7/26/6)
IFTA Score (0/1/2/3)	(0/16/13/13)
Interstitial inflammation (Yes/No)	32/11
Arteriosclerosis score (0/1/2/3/4/ unknown)	(0/3/5/15/10/10)
Segmental sclerosis (Yes/No)	(14/28)
IgG deposition (Yes/No)	(12/30)
IgM deposition (Yes/No)	(30/12)
IgA deposition (Yes/No)	(16/26)
C3d deposition (Yes/No)	(36/6)
Clq deposition (Yes/No)	(20/18)
Outcome (%)	26(60.47%)
ESRD (%)	12(46.15%)
Serum creatinine doubled (%)	6(23.08%)
Admission for kidney disease (%)	6(23.08%)
Death (%)	2(7.69%)

## $\label{eq:absolution} \textbf{Table 4} \ \textbf{Baseline Clinical and Laboratory Characteristics of Patients with DKD}$

Abbreviations: BMI body mass index; SBP systolic blood pressure; DBP diastolic blood pressure; RAAS Renin-Angiotensin-Aldosterone System; CKD chronic kidney disease; SII systemic immune-inflammation index; SIRI systemic inflammation response index; Scr serum creatinine; BUN blood urea nitrogen; eGFR estimated glomerular filtration rate; Ccr endo-genous creatinine clearance rate; IFTA interstitial fibrosis and tubular atrophy; IgA Immunoglobulin A; IgG Immunoglobulin G; IgM Immunoglobulin M, C3d complement 3d; C1q complement 1q; ESRD end-stage renal disease.

## Clinical Characteristics of DKD with Different SII and SIRI Levels

The median SII and SIRI were  $659.09 \times 10^{9}$ /L and  $1.39 \times 10^{9}$ /L, respectively, and patients were subsequently categorized into two groups based on these medians. The clinical features of patients with DKD with different SII and SIRI values are shown in Table 6. Patients with elevated SII demonstrated higher counts of leukocytes, platelets, and neutrophils and increased levels of SIRI, SCr, and 24-hour urinary protein. Conversely, they showed lower levels of UA, Ccr, and eGFR

Pathological Characteristics	SII (×10 <sup>9</sup> /L)	Р	SIRI (×10 <sup>9</sup> /L)	Р
Glomerular class		0.090		0.540
Non-progressive stage	500.56 (417.18,661.84)		1.22(0.96,1.83)	
Advanced phase	726.13 (542.06,978.93)		1.52(1.02,2.04)	
IFTA Score		0.265		0.407
I	552.43(494.23,805.73)		1.34(0.77,1.91)	
2–3	748.48(500.16, 1001.12)		1.52(1.19,2.05)	
Interstitial inflammation		0.404		0.290
no	569.40(456.25,832.86)		1.21(0.96,1.54)	
yes	707.28(511.26,935.27)		1.56(1.02,2.07)	
Arteriosclerosis score		0.119		0.063
I	617.20(579.99,765.50)		1.35 (0.98,1.51)	
2	487.91(469.41,541.33)		0.95 (0.74,1.26)	
3	1073.33(557.13,1320.49)		2.03 (1.21,2.51)	
4	739.26(659.09,855.09)		1.59 (1.51,2.10)	
Segmental sclerosis		0.040		0.191
no	532.37(417.87,735.35)		1.22(0.88,1.59)	
yes	739.26 (552.43,1084.81)		1.58(1.21,2.07)	
Immunofluorescence staining				
lgG		0.009		0.100
No	591.55(498.76,840.62)		1.34(0.95,1.60)	
Yes	967.50(666.94,1754.37)		2.06(1.14,2.51)	
IgM		0.231		0.419
No	554.27(456.25,868.96)		1.22(0.90,2.09)	
Yes	726.13(541.33,956.74)		1.53(1.21,2.03)	
IgA		0.437		0.917
No	638.14(487.91,956.74)		1.53(0.95,2.09)	
Yes	681.12(554.27,1005.05)		1.37(1.14,1.82)	
C3d		0.314		0.429
No	545.68(417.87,735.35)		1.22(1.00,1.59)	
Yes	681.12(519.85,978.93)		1.52(1.02,2.07)	
Clq		0.320		0.748
No	593.30(498.76,735.35)		1.34(1.00,1.68)	
Yes	729.63(519.65,1026.52)		1.41(0.90,2.16)	

Table	5 Relationshi	b Between	Pathological	Changes	and SII a	and SIRI in	Patients	with DKD

**Notes**: Denotes significance at a P value of <0.05.

Abbreviations: SII systemic immune-inflammation index; SIRI systemic inflammation response index; IFTA interstitial fibrosis and tubular atrophy; IgA Immunoglobulin A; IgG Immunoglobulin G; IgM Immunoglobulin M, C3d complement 3d; C1q complement 1q.

(P<0.05). Similarly, the high SIRI group exhibited elevated counts of leukocytes, neutrophils, and monocytes alongside higher levels of SII, SCr, and 24-hour urinary protein. Notably, this group displayed reduced counts of lymphocytes, as well as lower levels of UA, creatinine, and eGFR (P<0.05). Despite these differences in laboratory parameters, no significant differences were observed in terms of medical history (gender, age, BMI, duration of diabetes, diabetic retinopathy, hypertension, SBP, DBP) and medication use (RAAS inhibitor, oral hypoglycemic agent, insulin, hypoglycemic agent + insulin) between the subgroups categorized based on the median SII and SIRI. In addition, there were no statistically significant differences in Hb, lymphocyte count, monocyte count, and BUN levels between the groups categorized based on the median SII(P>0.05). The levels of Hb, UA, platelet count, and BUN were also found to be nonstatistically significant in the median SIRI group(P>0.05).

## Prognostic Impact of SII and SIRI in DKD

The Kaplan-Meier survival analysis revealed statistically significant differences within the SII subgroup (P=0.008) (Figure 3). However, no significant difference was observed in the SIRI subgroup (P=0.159) (Figure 4). Univariate

Variable	s	511	Ρ	SIRI		Р
	<659.09×10 <sup>9</sup> /L	≥659.09×10 <sup>9</sup> /L		<1.39×10 <sup>9</sup> /L	≥1.39×10 <sup>9</sup> /L	
Gender(male/female)	15/6	16/6	0.924	14/8	17/4	0.206
Age (years)	46.14±10.38	49.41±8.51	0.265	46.45±10.23	49.24±8.68	0.343
BMI (kg/m <sup>2</sup> )	24.30±3.61	24.51±3.09	0.834	24.19±3.63	24.65±3.02	0.661
Duration of diabetes(years)	4.00 (2.00,8.00)	3.50 (1.00,9.00)	0.609	3.50 (1.00,8.00)	4.00 (2.00,9.00)	0.272
Diabetic retinopathy (%)	12.00(57.10%)	16(72.70%)	0.284	14.00(63.60%)	14(66.70%)	0.835
Hypertension (%)	15.00(71.40%)	I I (50.00%)	0.151	16.00(72.70%)	10(47.60%)	0.092
SBP (mmHg)	153.48±28.29	158.59±23.03	0.445	152.14±20.40	160.24±22.59	0.224
DBP (mmHg)	89.67±13.31	92.23±11.41	0.501	89.14±12.47	92.90±12.10	0.321
Oral hypoglycemic agent (%)	15.00(71.40%)	11.00(50.00%)	0.151	15.00(68.20%)	11.00(52.40%)	0.289
Insulin (%)	4.00(19.00%)	7.00(31.80%)	0.337	3.00(13.60%)	8.00(38.10%)	0.066
Hypoglycemic agent+ Insulin (%)	3.00(14.30%)	2.00(9.10%)	0.956	3.00(13.60%)	2.00(9.50%)	0.674
RAAS inhibitor (%)	11.00(52.40%)	9.00(40.90%)	0.451	10.00(45.50%)	10.00(47.60%)	0.887
Leukocyte (×10 <sup>9</sup> /L)	6.40±1.30	7.90±1.79	0.003	6.01 (5.49,7.40)	7.65(6.84,9.26)	0.001
Hb(g/L)	123.95±31.06	112.73±19.27	0.160	121.32±27.62	114.95±24.49	0.429
Platelet (×10 <sup>9</sup> /L)	160.00(150.00,209.00)	241.50(186.00,279.00)	0.002	179.50(151.00,245.00)	201.00(161.00,247.00)	0.259
Neutrophil (×10 <sup>9</sup> /L)	4.21±0.99	5.89±1.69	<0.001	3.87(3.49,4.99)	5.93(4.79,6.93)	<0.001
Lymphocyte(×10 <sup>9</sup> /L)	1.58±0.40	1.34±0.43	0.073	1.58±0.43	1.32±0.39	0.045
Monocyte (×10 <sup>9</sup> /L)	0.40±0.12	0.45±0.10	0.222	0.38±0.10	0.48±0.10	0.002
SII(×10 <sup>9</sup> /L)	500.16(417.86,542.78)	935.27(761.60,1223.21)	<0.001	511.26 (417.87,636.23)	861.67 (664.59,1223.21)	<0.001
SIRI(×10 <sup>9</sup> /L)	1.00(0.79,1.28)	2.02(1.51,2.63)	<0.001	0.98(0.79,1.25)	2.05(1.59,2.63)	<0.001
SCr (umol/L)	107.00 (84.00, 129.00)	157.50 (114.00,209.00)	0.012	107.00 (79.00, 152.00)	156.50 (114.00,209.00)	0.0240
Uric acid (umol/l)	425.38±110.31	346.41±75.334	0.009	402.91±111.05	366.19±88.34	0.238
BUN (mmol/l)	8.83±3.75	8.87±3.17	0.974	8.52±3.42	9.20±3.48	0.521
eGFR (mL/min ·1. 73 m <sup>2</sup> )	66.88±21.19	46.14±24.97	0.013	64.81±27.85	47.32±25.42	0.038
Ccr (mL/min)	112.30 (88.00,145.80)	64.55 (32.90,88.80)	<0.001	110.40 (82.90,145.80)	66.60 (46.00,90.60)	0.014
24 hours urinary Protein-quantitative (g/24h)	2.77(0.67,4.16)	6.52(3.19,8.93)	<0.001	3.09(0.77,4.16)	6.49(2.92,8.93)	0.013
Outcome (%)	8(38.10%)	18(81.80%)	0.003	10(45.50%)	16(76.20%)	0.039

Table o Cillical Characteristics of DICD ratients with Different Sir and Sirt Leven
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Abbreviations: BMI body mass index; SBP systolic blood pressure; DBP diastolic blood pressure; RAAS Renin-Angiotensin-Aldosterone System; Hb hemoglobin; SII systemic immune-inflammation index; SIRI systemic inflammation response index; Scr serum creatinine; BUN blood urea nitrogen; eGFR estimated glomerular filtration rate; Ccr endogenous creatinine clearance rate.

Cox regression analysis (Table 7) identified a significant association between a high SII and DKD progression [HR 2.887, 95% CI (1.252–6.658), P=0.013]. After adjusting for age, sex, BMI, hypertension, duration of diabetes, and diabetic retinopathy, the multivariate Cox regression analysis revealed that high SII remained an independent risk factor for DKD progression [HR 3.240,95% CI (1.179–8.905), P = 0.023]. Further adjustment for baseline eGFR, 24-hour urinary protein quantification, segmental sclerosis, and IgG deposition yielded an HR >1; however, it was not statistically significant. Univariate COX regression analyses revealed no statistically significant effects of SIRI on renal outcomes in patients with DKD.

## Discussion

DKD is a prevalent microvascular complication of diabetes that significantly raises the risk of death.<sup>3</sup> In this study, we aimed to investigate the relationship between SII and SIRI and DKD progression. Our findings reveal noteworthy associations between these indices, clinical parameters, and renal outcomes. In the intricate pathophysiology of DKD, inflammation is believed to play a significant role, representing one of the many contributing factors.<sup>7</sup> Immune cells, including monocytes, are recognized as key players in the inflammatory processes.<sup>21</sup> When stimulated by hyperglycemia and advanced glycation end products (AGEs), intrinsic renal cells and resident renal macrophages express ICAM-1 and secrete MCP-1 and colony-stimulating factor-1 (CSF-1). MCP-1 stimulates the bone marrow to release monocytes into the blood, leading to an increase in the number of peripheral blood monocytes. Additionally, MCP-1, ICAM-1, and CSF-



Figure 3 Kaplan-Meier analysis in the different level of SII.



Figure 4 Kaplan-Meier analysis in the different level of SIRI.

1 collaborate to recruit monocytes to the kidneys, where they transform into macrophages. These macrophages then ingest oxidized lipids, forming foam cells that are deposited in the kidney, leading to glomerular atherosclerosis and ultimately accelerating renal fibrosis.<sup>22–24</sup>

Neutrophils are important components of the innate immune system. When activated, they release the anti-apoptotic proteins A1 and Bcl-xL, which delay neutrophil apoptosis and increase circulating neutrophil levels.<sup>25</sup> Additionally, they

Variables	HR	95% CI	Р
Model I			
<sup>a</sup> ≥659.09×10 <sup>9</sup> /L	2.887	1.252~6.658	0.013
<sup>b</sup> ≥1.39×10 <sup>9</sup> /L	1.746	0.787~33.872	0.170
Model 2			
<sup>a</sup> ≥659.09×10 <sup>9</sup> /L	3.24	1.179~8.905	0.023
<sup>b</sup> ≥1.39×10 <sup>9</sup> /L	1.657	0.532~5.162	0.384
Model 3			
<sup>a</sup> ≥659.09×10 <sup>9</sup> /L	2.237	0.788~6.351	0.130
<sup>b</sup> ≥1.39×10 <sup>9</sup> /L	I.477	0.437~4.996	0.532
Model 4			
<sup>a</sup> ≥659.09×10 <sup>9</sup> /L	2.583	0.851~7.844	0.094
<sup>b</sup> ≥1.39×10 <sup>9</sup> /L	1.946	0.540~7.014	0.309

 $\label{eq:stable_table$ 

**Notes:** a: Using SII<659.09×10<sup>9</sup>/L as a reference; b: Using SIRI<1.39×10<sup>9</sup>/L as a reference. Model I was not adjusted for any factors. Model 2 was adjusted for age, sex, BMI, hypertension, diabetic retinopathy, and duration of diabetes. Model 3 was adjusted for Model 2+eGFR, 24-hour urinary protein-quantitative. Model 4 was adjusted for Model 3+Segmental sclerosis, IgG deposit.

produce reactive oxygen species, cytotoxic proteases, and inflammatory cytokines, causing endothelial dysfunction and initiating renal inflammation, ultimately exacerbating kidney injury.<sup>4,26,27</sup> Lymphocytes, integral to acquired immunity, regulate inflammation. T cells recruited to the kidney release interferons and TNF, while B lymphocytes contribute to renal damage by producing immunoglobulins, forming immune complex deposits, or activating the complement system. Additionally, CD4+ T cells directly stimulate fibroblasts, causing renal fibrosis.<sup>4,27</sup> Notably, clinical studies have shown that patients with DKD exhibit lower lymphocyte counts.<sup>28</sup> The reason for abnormal lymphocyte recruitment in the kidney and reduced circulating lymphocytes is unclear. Some researchers have suggested a link to increased lymphocyte apoptosis in a high-sugar environment; however, further research is necessary to determine the precise mechanism.<sup>29</sup> Platelets also play a role in immune and inflammatory responses. Platelet counts increase in patients with diabetes due to elevated thrombopoietin expression, which is influenced by inflammatory agents such as interleukin-1 (IL-1) and IL-6.<sup>30</sup> Inflammation further activates platelets, which release cytokines and chemokines that exacerbate renal inflammation and fibrosis by promoting white blood cell aggregation at the site of inflammation.<sup>31</sup> DKD progresses insidiously to ESRD, with a considerably higher incidence than that of other forms of CKD. Renal biopsy remains the gold standard for diagnosis; however, it is invasive, technically demanding, renal, and not widely accepted. Therefore, identifying markers that can accurately assess DKD is crucial for improving patient outcomes.

The SII = platelet count × neutrophil count/lymphocyte count, while SIRI = monocyte count × neutrophil count/ lymphocyte count. As novel inflammatory markers, the SII and SIRI indices demonstrate robust sensitivity to the inflammatory status across a diverse range of diseases, making them readily detectable and cost-effective. Consequently, they have gained widespread utilization in the fields of oncology and cardiovascular medicine. Recent studies have indicated that low lymphocyte counts and high neutrophil, monocyte, and platelet counts are independent risk factors for DKD.<sup>32,33</sup> Therefore, we hypothesized a link between SII, SIRI, and DKD. Elbeyle et al<sup>34</sup> reported a strong association between high SII and diabetic retinopathy, indicating a potential relationship between SII and diabetic microvascular complications. A study involving 36,463 Americans showed an independent association between elevated SII levels and urinary albumin excretion.<sup>35</sup> In an NHANES-based study, patients with T2DM and DKD exhibited significantly higher SII levels than those without DKD.<sup>36</sup> Zhang et al<sup>37</sup> demonstrated that SIRI was a risk factor for DKD in patients with T2DM. Consistent with these findings, our study revealed higher SII and SIRI levels in the Cli-DKD group compared to the T2DM and EDKD groups, with positive correlations to UACR and negative correlations to eGFR. Moreover, logistic regression analysis identified SII and SIRI as significant risk factors for DKD in patients with T2DM. Notably, even after controlling for confounding factors, SIRI remained an independent risk factor, with the DKD odds ratio increasing by a factor of 2.185 for every unit increase in SIRI. Importantly, we verified the connection between the novel inflammatory markers SII and SIRI and the occurrence and progression of DKD. In a subset of 43 patients diagnosed with DKD via renal biopsy, elevated SII and SIRI levels were associated with increased 24-hour urinary protein quantification and SCr, along with lower CCr and eGFR. Dynamic monitoring of SII and SIRI assists clinicians in identifying DKD and evaluating its status.

Pathological alterations are valuable for assessing lesion severity and estimating patient prognosis in DKD. In a comprehensive follow-up study, the severity of glomerular lesions and IFTA were significantly correlated with renal outcomes.<sup>38</sup> Emphasizing the importance of altering renal pathology, numerous studies have confirmed the significance of immunofluorescence. Poor renal outcomes have been observed in patients with glomerular IgG, IgM, C1q, and C3 deposits,<sup>39,40</sup> along with segmental sclerosis and extracapillary cell proliferation, indicating DKD progression to ESRD.<sup>41</sup> These findings are critical considerations in the management of patients with DKD. However, there have been no reports on the pathological characteristics and prognoses of SII and SIRI in patients with DKD. Our study revealed higher SII in patients with segmental sclerosis and IgG deposition, suggesting a potential relationship between SII and DKD prognosis. Kaplan-Meier survival analysis revealed that patients with a higher SII had poorer DKD outcomes. Cox regression analysis indicated that an increased SII is a potential risk factor for renal prognosis in patients with DKD. Even after controlling for essential conditions, renal function, and related pathological factors, the HR of SII remained >1, indicating its significance as a risk factor for a poor prognosis. However, no association was found between SIRI and renal prognosis. The study's identification of 74.4% of patients with grade III or IV glomerular lesions may not fully capture the potential utility of SII and SIRI in DKD. Further analyses that include patients with grade I and II lesions are necessary.

In addition, our results suggest that independent risk factors for DKD include female sex, combined diabetic retinopathy, hypertension, elevated systolic blood pressure, and high HbA1c levels. This implies that maintaining optimal blood pressure and blood glucose control may reduce the risk of developing DKD. This study explored the relationship between DKD and hs-CRP, a well-known indicator of inflammation, and sequentially higher hs-CRP levels in the T2DM, EDKD, and Cli-DKD groups, although the difference was not statistically significant. The reduced T2DM sample size and anti-inflammatory properties of glucose-lowering medications may account for this result. While the study did not distinguish between specific types of glucose-lowering medications, evidence suggests that these medications, including metformin, SGLT-2 inhibitors, DPP4 inhibitors, and GLP-1 agonists, have anti-inflammatory properties.<sup>41,42</sup> Therefore, the potential impact of medication on the study findings cannot be disregarded, and additional research is necessary to examine the correlation between glucose-lowering medications and SII and SIRI.

This study has certain limitations, including a small sample size and a lack of data for patients who refused renal puncture or had contraindications. Given the retrospective nature of the study, it was impossible to avoid selection bias and unclear causal relationships. Therefore, multicenter and large-sample prospective studies must be conducted in the future to fully investigate the interactions between SII and SIRI, the onset and progression of DKD, and to understand the impacts of SII and SIRI on renal prognosis in DKD.

## Conclusion

Our study underscores the significance of SIRI as an independent risk factor for DKD. Furthermore, both SII and SIRI exhibit practical implications for the accurate diagnosis and classification of DKD. Notably, our findings reveal a robust association between elevated SII levels and an unfavorable prognosis in DKD. Given their cost-effectiveness, ready accessibility, and reproducibility, SII and SIRI emerge as valuable tools for effectively monitoring patients with DKD patients, particularly in primary care settings.

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## Disclosure

The authors report no conflicts of interest in this work.

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