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Systemic inflammatory index as a predictive marker for the severity of coronary artery disease in individuals with chronic kidney disease

Meng-Qi ZHAO, Yang ZHANG, Xin HUANG, Jian-Jun PENG✉

Department of Cardiology, Beijing Shijitan Hospital, Capital Medical University, Beijing, China
✉ Correspondence to: pengjianjunmedical@163.com
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ABSTRACT

Objective To evaluate the correlation between the inflammatory intensity, as indicated by the systemic inflammatory index (SII), and the severity of coronary artery disease (CAD) in patients with chronic kidney disease (CKD).

Methods A total of 280 CKD patients who underwent coronary angiography were enrolled. CAD was evaluated using the Gensini score (GS). Patients were divided into the low, medium and high SII groups according to the tertiles of the SII values. Logistic regression analysis was conducted to analyze the relationship between SII and GS. The cutoff points for the sensitivity and specificity of SII in predicting GS were estimated by performing the receiver operating characteristic curve analysis.

Results Patients in the higher SII group had a higher prevalence of CAD ($P = 0.013$). In addition, the high SII group had more patients with complex CAD (triple-vessel disease and/or left main coronary artery stenosis) and chronic total occlusion lesions, and more patients required revascularization ($P < 0.05$). Correlation analysis suggested a positive relationship between SII and GS, and in comparison to neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio, SII displayed a stronger correlation with GS ($r = 0.332$, $P < 0.001$). Multifactorial logistic regression analysis revealed that SII is independently associated with the severity of CAD (adjusted OR = 1.14, 95% CI: 1.08–1.21, $P < 0.01$), particularly among elderly patients (age ≥ 65 years). Receiver operating characteristic curve analysis indicated that the optimal cutoff value for SII in predicting severe coronary artery stenosis (GS > 60) was 6.01 (sensitivity: 76.30%, specificity: 53.50%), with an area under the curve (AUC) of 0.705 (95% CI: 0.642–0.768, $P < 0.001$), which was statistically significantly better than platelet-to-lymphocyte ratio (AUC = 0.646, 95% CI: 0.579–0.713, $P < 0.001$) and neutrophil-to-lymphocyte ratio (AUC = 0.643, 95% CI: 0.574–0.712, $P < 0.001$).

Conclusions In patients with CKD, SII is independently associated with the severity of CAD, especially in individuals aged 65 years or older. Furthermore, SII functions as a predictive marker for the severity of coronary lesions.

Coronary artery disease (CAD) is a leading cause of worldwide morbidity and mortality, with the mortality rate for CAD currently standing at 27% and continuing to rise.[1] CAD is one of the most common complications and the leading cause of death in chronic kidney disease (CKD) patients.[2] In CKD patients, the risk of cardiovascular disease death is a staggering 30 times higher than that observed in the general population.[3] Therefore, early assessment of the severity of CAD in CKD patients and the identification of modifiable risk factor are crucial for improving patient outcomes.

CAD is an inflammatory condition of the arterial wall characterized by the development of atherosclerotic plaques in the epicardial arteries.[4] Nowadays, it is well established that CAD and CKD share similar epidemiological risk factors and common underlying molecular pathways. Chronic low-grade systemic inflammation has been proposed as the major unifying pathophysiological process in the development of both diseases.[5,6] Various inflammatory reaction markers have shown their independent predictive value for CAD and are strongly associated with CAD prognosis.[7–10] The correlation between monocyte-lymphocyte ratio,[11] neutrophil-to-lymphocyte ratio (NLR)[7] and platelet-to-lymphocyte ratio (PLR) and the severity of CAD has been confirmed in previous

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research.[12] It has also been shown that NLR was an predictor of short- and long-term mortality after revascularization for ST-segment elevation myocardial infarction.[13] Recently, the systemic inflammatory index (SII), which combines neutrophil count, lymphocyte count and platelet count, has been proposed as a comprehensive indicator reflecting a patient's inflammatory and immune status, initially applied to predict cancer prognosis.[14–16] More recently, its association with cardiovascular diseases has garnered significant attention. Studies have found that SII can predict adverse cardiovascular events in CAD patients.[17,18] Furthermore, inflammation has been shown to be associated with adverse cardiovascular outcomes in the CKD population.[19,20] Elevated SII levels are an independent risk factor for increased mortality in CKD patients, which improves risk prediction for long-term prognosis over traditional risk factors.[21]

However, the adverse effects of contrast agents on the kidneys have limited the assessment of CAD. In recent years, there has been a growing number of recent studies dedicated to finding non-invasive indicators for evaluating CAD in patients with CKD. This study aimed to explore the potential correlation between the SII and severity of coronary artery stenosis, with the goal of offering new predictors for high-risk CAD patients in clinical practice. To assess the severity of CAD in this study in a more relevant manner, the Gensini score (GS) was used to accurately reflect the degree of total coronary atherosclerosis burden.

METHODS

Study Population

Our population is represented by CKD patients undergoing nonurgent coronary angiography who did not undergo dialysis at Beijing Shijitan Hospital, Capital Medical University, Beijing, China from January 2021 to January 2023. CKD was considered to have a history of renal failure (requiring specialist follow-up and/or specific treatment) or an estimated glomerular filtration rate (eGFR) of less than 60 mL/min per 1.73 m^2 at admission, as defined by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula.[22] The following exclusion criteria were applied: (1) acute myocardial infarction; (2) prior coronary artery bypass grafting or percutaneous coronary intervention; (3) presence of heart diseases beyond CAD, such as myocarditis, valvular diseases, and severe heart failure (left ventricular ejection fraction < 30%); (4) severe hepatic dysfunction; (5) in the infectious phase or recovery phase of various acute and chronic infections; (6) thyroid disorders, tuberculosis, inflammatory bowel disease, autoimmune diseases, and hematological disorders; and (7) incomplete clinical data. Medical histories were obtained by reviewing the patients' electronic medical records and included age, sex, ethnicity, history of smoking, alcohol consumption, hypertension, diabetes mellitus (DM), dyslipidemia, history of renal insufficiency and history of dialysis, systolic blood pressure and diastolic blood pressure within 1 h of admission, and diagnosis and treatment during hospitalization. Hypertension was defined as systolic blood pressure > 140 mmHg and/or diastolic blood pressure > 90 mmHg or the need for antihypertensive medication. The diagnosis of DM was based on a previous history of DM treated with or without drug therapies, fasting glycemia > 126 mg/dL, random glycemia > 200 mg/dL or glycated hemoglobin (HbA1c) > 48 mmol/mol (6.5%). Dyslipidemia was defined as total cholesterol > 240 mg/dL, serum triglycerides > 150 mg/dL, high-density lipoprotein cholesterol (HDL-C) < 40 mg/dL, low-density lipoprotein cholesterol (LDL-C) ≥ 160 mg/dL, or diagnosis/treatment of dyslipidemia.

In this study, a total of 280 patients were screened. The study protocol was approved by the Institutional Review Board of Beijing Shijitan Hospital (No.sjtky11-1x-2023 (019)), Capital Medical University, Beijing, China, and written informed consent was obtained from all patients.

Laboratory Measurements

Before coronary angiography, we collected and verified patients' baseline characteristics from medical records. Under fasting conditions (usually on the second morning after admission), blood samples for biochemical tests were routinely collected from the antecubital vein within the same time window. The levels of white blood cells, neutrophils, hemoglobin, platelets, albumin, blood urea nitrogen, serum creatinine (SCr), eGFR, uric acid, total cholesterol, triglycerides, HDL-C, LDL-C, corrected calcium, HbA1c, thyroid-stimulating hormone, free triiodothyronine, and free thyroxine were measured using a fully automated biochemical analyzer. The SII was calculated as platelets count × neutrophil/lymphocyte ratio. NLR was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count. PLR was calcu-

lated by dividing the absolute platelet count by the absolute lymphocyte count.

Coronary Angiography

Coronary angiography was performed using an X-ray system according to the standard Judkins technique by at least two experienced clinicians, and all patients signed the informed consent form. CAD was defined as at least 50% stenosis of the vessel lumen diameter in one of the main coronary arteries (the right coronary artery, the left circumflex coronary artery, or left anterior descending coronary artery). The severity of CAD was evaluated by the GS.[23] The GS[24] of CAD is the product of the stenosis score of each coronary artery and the coronary segment score.

Diseased coronary vessels were categorized as single, double, and triple-vessel stenosis based on the number of stenotic vessels among the left anterior descending artery, left circumflex artery, and right coronary artery. Patients with stenosis ≥ 50% in diameter in the left main coronary artery (LMCA) were diagnosed with LMCA stenosis. Complex CAD was defined as triple-vessel disease and/or LMCA. Chronic total occlusion (CTO) was defined as arteries with atherosclerotic luminal narrowing resulting in TIMI grade 0 flow for over 3 months based on angiographic findings or the duration of patient symptoms and clinical presentation.[25]

Statistical Analysis

The data were analyzed using SPSS 26.0 (SPSS Inc., IBM, Armonk, NY, USA). Continuous variables were reported as mean ± SD, non-normally distributed variables as medians (interquartile range), and categorical variables as counts (percentages). Group comparisons for normally distributed continuous variables were performed using one-way analysis of variance, while for non-normally distributed continuous variables, the Kruskal-Wallis *H* test was applied. The Pearson's chi-squared test was utilized for comparing categorical variables across groups. Spearman's correlation test assessed correlation. Univariate and multivariate logistic regression analyses were executed to assess factors influencing the severity of CAD. The sensitivity and specificity cutoff points for predicting a high GS level by SII were determined through receiver operating characteristic (ROC) curve analysis. Statistical significance was defined as a *P*-value < 0.05.

RESULTS

Clinical Characteristics of the Participants

Among the 280 CKD patients, the mean age was 74.02 ± 10.65 years, 133 patients (47.50%) were male, and the mean eGFR value was 46.01 mL/min per 1.73 m^2. They were classified into three groups according to the tertiles of SII: patients with SII ≤ 5.252 were included in the low SII group (n = 93), patients with 5.252 < SII ≤ 8.226 were included in the medium SII group (n = 94) and patients with SII > 8.226 were included in the high SII group (n = 93). The baseline characteristics of patients are summarized in Table 1.

Patients with elevated SII levels had higher blood urea nitrogen, SCr, and lower eGFR (all P < 0.05). Patients with higher SII levels had higher proportion of CAD (P = 0.013). The mean GS levels for the three groups were 37.11 ± 38.52, 41.71 ± 38.67 and 57.99 ± 37.53, respectively; and the correlation between the SII level and GS was significant (P = 0.001). In addition, the high SII group had more patients with triple-vessel disease and CTO lesions (P < 0.05), and more patients required revascularization (P = 0.031). LMCA lesions were not significantly different in the three groups of patients. There were no significant differences of other variables among these groups (P > 0.05).

Factors Related to CAD

In this study, the severity of coronary artery stenosis was assessed based on the GS and the coronary angiography results. According to Table 1, as the levels of SII increased, the GS increased (P = 0.001). Spearman correlation analysis showed that HbA1c (r = 0.141, P = 0.018), platelet (r = 0.165, P = 0.006), PLR (r = 0.244, P < 0.001), NLR (r = 0.276, P < 0.001) and SII (r = 0.332, P < 0.001) were positively related to GS, while eGFR (r = -0.185, P = 0.002) exhibited a negative correlation with GS (Table 2). Notably, SII demonstrated the strongest correlation. Higher SII levels were associated with a greater incidence of complex CAD, as illustrated in Figure 1. As shown in Figure 2, higher SII levels were observed in the CAD group compared to the non-CAD group (P = 0.025). It's worth noting that the SII levels in the acute coronary syndrome (ACS) group were higher than those in the stable CAD group, although the difference was not statistically significant (P > 0.05).

Table 1 Baseline clinical characteristics.

Variables	Low SII group (n = 93)	Medium SII group (n = 94)	High SII group (n = 93)	P-value
Age, yrs	73.48 ± 10.20	73.99 ± 10.37	74.58 ± 11.42	0.782
Male	42 (37.63%)	42 (50.00%)	49 (54.84%)	0.471
Han nationality	90 (98.92%)	91 (94.68%)	89 (95.70%)	0.898
Systolic blood pressure, mmHg	137.68 ± 21.19	140.18 ± 21.39	136.98 ± 27.03	0.615
Diastolic blood pressure, mmHg	79.40 ± 12.39	78.22 ± 11.92	76.37 ± 16.14	0.311
Comorbidities and medical history				
Smoking	27 (22.58%)	26 (31.91%)	34 (38.71%)	0.368
Alcohol intake	9 (22.58%)	16 (31.91%)	19 (38.71%)	0.120
Hypertension	77 (84.95%)	86 (89.36%)	80 (86.02%)	0.207
Diabetes mellitus	40 (47.31%)	49 (45.74%)	55 (61.29%)	0.088
Dyslipidemia	84 (93.55%)	90 (92.55%)	87 (93.55%)	0.333
Laboratory parameters				
SII, %	3.80 ± 0.95	6.65 ± 0.09	14.47 ± 10.46	< 0.001
Hemoglobin, g/dL	128.05 ± 16.37	122.07 ± 22.31	122.85 ± 18.88	0.074
Albumin, g/dL	38.74 ± 3.91	38.74 ± 4.60	38.12 ± 4.32	0.522
Blood urea nitrogen, mmol/L	8.27 ± 2.34	9.68 ± 3.06	10.30 ± 3.47	< 0.001
Serum creatinine, μmol/L	110.91 ± 28.24	130.09 ± 48.20	127.71 ± 41.05	0.002
eGFR*, mL/min per 1.73 m^2	49.80 ± 8.94	43.95 ± 11.57	44.32 ± 11.12	< 0.001
Uric acid, μmol/L	408.01 ± 123.09	430.31 ± 121.38	447.16 ± 107.06	0.076
Total cholesterol, mmol/L	4.09 ± 0.91	4.45 ± 1.38	4.23 ± 1.23	0.123
Triglyceride, mmol/L	1.67 ± 0.88	1.93 ± 1.29	1.82 ± 1.01	0.250
High-density lipoprotein cholesterol, mmol/L	1.02 ± 0.23	1.07 ± 0.24	0.99 ± 0.25	0.059
Low-density lipoprotein cholesterol, mg/dL	2.67 ± 0.82	2.83 ± 1.05	2.78 ± 0.98	0.495
Corrected calcium, mmol/L	2.33 ± 0.12	2.34 ± 0.08	2.33 ± 0.11	0.771
HbA1c, %	6.70 ± 1.30	7.00 ± 1.45	6.99 ± 1.25	0.227
Thyroid-stimulating hormone, uIU/mL	3.25 ± 3.10	5.19 ± 15.22	2.58 ± 2.49	0.129
Free triiodothyronine, pg/mL	2.52 ± 0.51	2.43 ± 0.49	2.39 ± 0.38	0.175
Free thyroxine, ng/dL	1.24 ± 0.25	1.24 ± 0.28	1.32 ± 0.25	0.062
Coronary procedural information				
Coronary artery disease	74 (79.57%)	84 (89.36%)	87 (93.55%)	0.013
Gensini score	37.11 ± 38.52	41.71 ± 38.67	57.99 ± 37.53	0.001
Single vessel disease	20 (21.51%)	22 (23.40%)	18 (19.35%)	0.796
Double vessel disease	24 (25.81%)	17 (18.09%)	24 (25.81%)	0.352
Triple-vessel disease	30 (32.26%)	45 (47.87%)	45 (48.39%)	0.041
Left main coronary artery	4 (4.30%)	5 (5.32%)	11 (11.83%)	0.096
Chronic total occlusion	6 (6.45%)	18 (19.15%)	24 (25.81%)	0.002
Revascularization	56 (60.22%)	68 (72.34%)	72 (77.42%)	0.031

Data are presented as means ± SD or n (%). *Refer to calculate using the CKD-EPI formula. eGFR: estimated glomerular filtration rate; SII: systemic inflammatory index.

Ordered Logistic Regression Analysis of Coronary Artery Stenosis

Univariate and multivariate logistic regression analysis of the association between SII and the severity of coronary artery in patient with CKD are shown in Table 3. In univariate regression analysis, SII was associated with the severity of CAD [odds ratio (OR) = 1.17, 95% CI: 1.11–

Table 2 Correlation between continuous variables and the severity of coronary artery lesions.

Parameter	*r*	*P*-value
Age	-0.039	0.514
eGFR	-0.185	0.002
High-density lipoprotein cholesterol	-0.112	0.062
Low-density lipoprotein cholesterol	-0.019	0.756
HbA1c	0.141	0.018
Platelet	0.165	0.006
Neutrophil-to-lymphocyte ratio	0.276	< 0.001
Platelet-to-lymphocyte ratio	0.244	< 0.001
SII	0.332	< 0.001

eGFR: estimated glomerular filtration rate; SII: systemic inflammatory index.

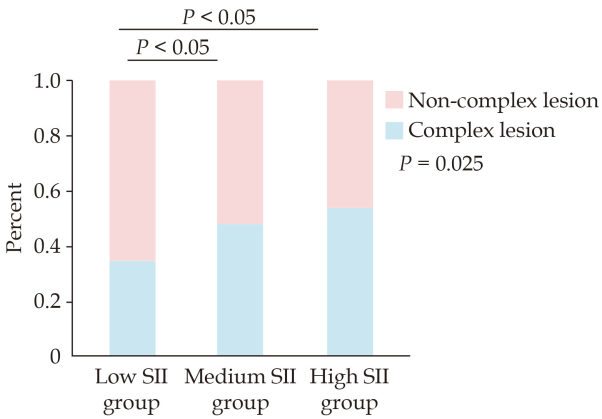

Figure 1 Bar graph showing the relationship between SII and the proportion of complex coronary artery disease (triple-vessel disease and/or left main coronary artery) among patient with chronic kidney disease. Comparison of the proportions of complex coronary artery lesions across the low, medium, and high SII groups using one-way analysis of variance. SII: systemic inflammatory index.

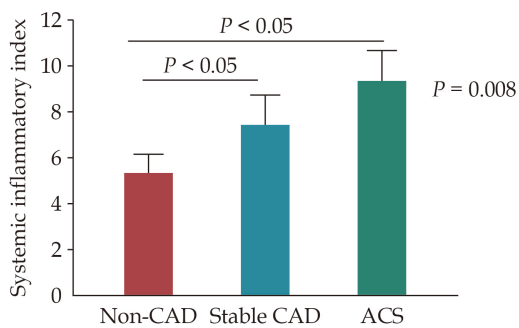

Figure 2 Comparison of systemic inflammatory index levels across the chronic kidney disease groups in non-CAD patients (*n* = 35), patients with stable CAD (*n* = 75), and patients with ACS (*n* = 170). ACS: acute coronary syndrome; CAD: coronary artery disease.

1.24, $P < 0.001$]. Moreover, even after adjustment for confounders in the multiple regression analysis, such as gender, age, hypertension, DM, dyslipidemia, blood urea nitrogen, SCr, eGFR, uric acid, HDL-C and HbA1c, SII levels remained to be independently associated with the severity of CAD (OR = 1.14, 95% CI: 1.08–1.21, $P < 0.001$).

Patients were further categorized based on age (< 65 years or ≥ 65 years), gender (female or male) and eGFR (< 45 mL/min per 1.73 m^2 or ≥ 45 mL/min per 1.73 m^2). As shown in Table 4, univariate logistic regression analysis revealed a significant and positive correlation between SII and GS in the older patient subgroup (OR = 1.18, 95% CI: 1.11–1.26, $P < 0.001$). This association retained its statistical significance even after adjusting for potential confounding factors (OR = 1.17, 95% CI: 1.10–1.25, $P < 0.001$). However, in the younger patient subgroup, this association did not reach statistical significance. It is worth noting that these correlations persisted across both eGFR and gender subgroups, and they remained significant even after controlling for confounding variables.

The Diagnostic Value of SII in CAD and Coronary Stenosis Severity

Using ROC curves, we compared the ability of the SII to predict severe coronary artery stenosis (GS > 60) in different patient groups. As depicted in Figure 3A, the SII demonstrated predictive value in both male and female patients. But the SII exhibited a stronger predictive value in female patients than in male patients. The area under the curve (AUC) for SII in female patients was 0.736 (95% CI: 0.650–0.872, $P < 0.001$), while in male patients, it was 0.670 (95% CI: 0.577–0.763, $P < 0.001$). As shown in Figure 3B, for patients aged ≥ 65 years, the AUC was 0.722 (95% CI: 0.651–0.792, $P = 0.036$). Conversely, for patients aged < 65 years, the SII had no predictive value with the AUC of 0.644 (95% CI: 0.487–0.800, $P = 0.072$). As shown in Figure 3C, the AUC was 0.685 (95% CI: 0.600–

Table 3 Univariate logistic regression analysis for variables associated with Gensini score.

Factor	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Male	1.54 (1.00–2.38)	0.051	1.72 (0.94–3.14)	0.081
Age	1.00 (0.98–1.02)	0.845	1.00 (0.98–1.03)	0.792
Hypertension	1.94 (1.01–3.71)	0.046	1.55 (0.77–3.13)	0.220
Diabetes mellitus	2.55 (1.64–3.97)	< 0.001	1.61 (0.91–2.83)	0.101
Dyslipidemia	1.65 (0.69–3.94)	0.256	1.38 (0.54–3.56)	0.501
SII	1.17 (1.11–1.24)	< 0.001	1.14 (1.08–1.21)	< 0.001
Hemoglobin	0.99 (0.98–1.00)	0.135	–	–
Blood urea nitrogen	1.16 (1.07–1.25)	< 0.001	1.05 (0.94–1.16)	0.395
Serum creatinine	1.01 (1.00–1.01)	0.007	0.99 (0.98–1.01)	0.481
eGFR	0.97 (0.95–0.99)	0.006	0.98 (0.93–1.02)	0.336
Uric acid	1.00 (1.00–1.00)	0.028	1.00 (1.00–1.00)	0.595
High-density lipoprotein cholesterol	0.40 (0.16–0.99)	0.046	0.75 (0.28–2.03)	0.572
Low-density lipoprotein cholesterol	1.04 (0.83–1.31)	0.705	–	–
HbA1c	1.30 (1.09–1.53)	0.003	1.13 (0.92–1.39)	0.248

Adjusted for gender, age, hypertension, diabetes mellitus, dyslipidemia, platelet, blood urea nitrogen, serum creatinine, eGFR, uric acid, high-density lipoprotein cholesterol and HbA1c. eGFR: estimated glomerular filtration rate; SII: systemic inflammatory index.

Table 4 Logistic regression analysis to assess the correlation between systemic inflammatory index and Gensini score in different populations.

Factor	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Age				
< 65	1.11 (0.96–1.28)	0.153	1.11 (0.95–1.30)	0.175
≥ 65	1.18 (1.11–1.26)	< 0.001	1.17 (1.10–1.25)	< 0.001
Gender				
Male	1.14 (1.06–1.23)	0.001	1.13 (1.05–1.22)	0.001
Female	7.21 (2.74–18.99)	< 0.001	1.19 (1.08–1.30)	< 0.001
eGFR				
< 45	1.21 (1.09–1.33)	< 0.001	1.21 (1.09–1.35)	0.001
≥ 45	1.13 (1.06–1.21)	< 0.001	1.11 (1.03–1.19)	0.004

Adjusted for age, sex, diabetes mellitus, hypertension, and dyslipidemia. eGFR: estimated glomerular filtration rate.

0.769, $P < 0.001$) in severe CKD patients (eGFR ≥ 45 mL/min per 1.73 m^2). And for patients with eGFR < 45 mL/min per 1.73 m^2, the AUC was 0.692 (95% CI: 0.589–0.794, $P < 0.001$). In Figure 3D, among all included patients, SII had an AUC of 0.705 (95% CI: 0.642–0.768, $P < 0.001$) to predict high GS in patients with CKD, which was statistically significantly better than PLR (AUC = 0.646, 95% CI: 0.579–0.713, $P < 0.001$) and NLR (AUC = 0.643, 95% CI: 0.574–0.712, $P < 0.001$). The optimal cutoff value for diagnosis based on the SII was 6.01, with sensitivity of 76.30% and specificity of 53.50%.

DISCUSSION

This study revealed that within the population of individuals with CKD, the SII is independently linked to the severity of CAD. This association is especially pronounced among elderly patients (aged 65 years or older). Furthermore, SII exhibited predictive capabilities for the severity of coronary stenosis.

Atherosclerosis is now considered not just a disorder of cholesterol accumulating within the vessel walls, but also a persistent, dynamic and inflammatory process in the vasculature.[4] Similarly, persistent low-grade infla-

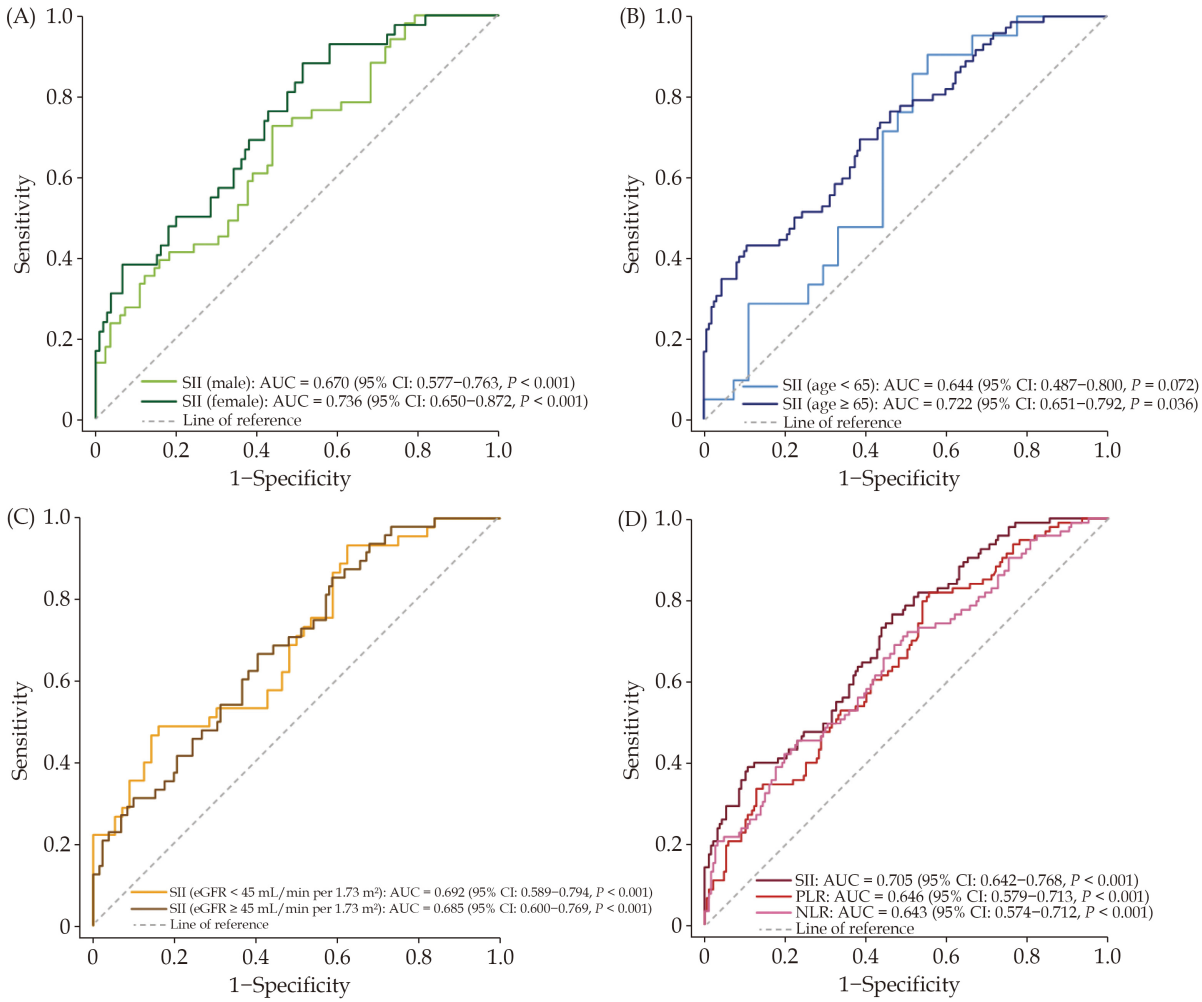

Figure 3 Comparison of receiver operating characteristic curves across gender (A), age (B), eGFR (C), and various variables (D) illustrates the predictive ability of SII for severe coronary stenosis. AUC: area under the curve; eGFR: estimated glomerular filtration rate; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; SII: systemic inflammatory index.

mmation and immune dysfunction are now considered hallmark features of CKD and are associated with mortality in these patients.[26] Many novel inflammation markers, such as the NLR and PLR, have been demonstrated to reflect the extent of systemic inflammation.[27] These markers are correlated with the severity, prognosis, and presence of CAD. Kaya, *et al*.[28] showed that NLR is a predictor of severe atherosclerosis and may aid in risk stratification for CAD. Similarly, Kurtul, *et al*.[29] confirmed a significant association between PLR and the severity and complexity of atherosclerosis in ACS patients. Furthermore, these markers have recently been studied as simple and feasible new prognostic inflammation markers associated with adverse cardiovascular outcomes.[30–33] However, Tamaki, *et al*.[34] suggested that a combination of NLR and PLR is more valuable than the single marker. Based on the evidence presented, the SII, which combines lymphocyte, neutrophil and platelet counts, may provide a relatively comprehensive reflection of the balance between the body's inflammation and immune status.[27] Previous research has confirmed that SII is a more accurate predictor of adverse outcomes in cervical and colorectal cancer patients compared to NLR and PLR.[35,36] Recently, Candemir, *et al*.[37] demonstrated that, compared to NLR and PLR, SII has higher predictive value in assessing the severity of CAD, and SII can also predict major cardiovascular events after coronary intervention treatment.[4] Based on the evidence presented, we hypothesized and demonstrated a higher prevalence of coronary heart disease in CKD patients with elevated SII levels. More importantly, a higher SII level was identified as an independent risk factor for the se-

verity of CAD (adjusted OR = 1.14, 95% CI: 1.08–1.21, P< 0.001). High SII levels were associated with complex CAD and the occurrence of CTO, and a greater likelihood of needing revascularization therapy. Correlation analysis indicated that SII has a stronger correlation with GS compared to PLR and NLR, and ROC curve analysis revealed that SII has a stronger predictive ability for the degree of coronary artery stenosis compared to PLR and NLR.

The mechanism underlying this phenomenon may be an increase in neutrophils and platelets caused by systemic inflammation, as well as a reduction in lymphocytes induced by elevated cytokines. Neutrophils can facilitate plaque disruption by releasing superoxide radicals, proteolytic enzymes, and arachidonic acid metabolites. In addition, they can aggregate with platelets when stimulated, leading to microvessel plugging and contributing to myocardial ischemia/infarction.[32] Besides their role in thrombosis, platelets play a crucial connecting role in inflammation, thrombosis, and atherosclerosis development.[38] Lymphocytes are another subtype of white blood cells, and the progression of inflammation in atherosclerotic lesions can trigger lymphocyte apoptosis. Subsequently, atherosclerotic plaques enlarge, leading to plaque rupture and subsequent thrombus formation.[39] Our study also confirmed that SII levels were higher in CAD patients than in non-CAD patients, whether they had ACS or stable CAD.[40] Furthermore, CKD is also characterized by a chronic inflammatory state.[41] Neutrophils can mediate inflammation in renal injury through various biochemical mechanisms, leading to further tissue damage and impairment of renal function.[42] Elevated neutrophil levels have been identified as a contributing risk factor for CKD.[43] In adult CKD patients, inflammation is associated with procoagulant and platelet activation factors, which contribute to cardiovascular disease mortality by promoting vascular calcification and the development of endothelial dysfunction.[44] Previous research has confirmed a direct correlation between inflammation and eGFR levels, with greater inflammation intensity in patients with lower kidney function, reaching a peak in dialysis patients.[45,46] Similarly, our study also indicated a statistically significant decrease in eGFR in patients with high SII levels.

Our study unveiled a stronger association between SII and GS in CKD patients aged 65 years or older. Furthermore, for elderly patients, SII exhibits a greater capacity to predict severe stenosis compared to younger patients. Accumulating evidence indicates that chronic low-grade inflammation is one of the mechanisms underlying the aging process, with inflammation being implicated in most typical age-related chronic diseases.[47] It is well established that age is a primary risk factor for CAD occurrence.[48] Current research has confirmed the age-dependent inflammatory characteristics of coronary artery plaques. Plaques in elderly coronary heart disease patients demonstrate increased $CD3^+$ T cell infiltration and greater myeloperoxidase production, indicating a plaque phenotype that leans toward atherogenesis and pro-inflammation.[49] A growing body of epidemiological studies shows that the presence of aging significantly increases the risk of CKD, with chronic inflammation increasingly recognized as a key determinant of this progression.[50] Notably, even in a state of health, older individuals display low-grade systemic chronic inflammation in the absence of overt infections. This suggests that as individuals age, their ability to control inflammation is limited, which may serve as the foundation for impaired kidney repair in the elderly. Microarray analysis of the human kidney has also confirmed that with increasing age, the renal microenvironment undergoes inflammation.[51]

Given the inherent risks associated with coronary angiography in patients presenting with CKD, the exploration of noninvasive approaches for assessing CAD in this patient population has emerged as a prominent focal point in contemporary research endeavors. Inflammatory markers, as noninvasive indicators, have the potential to predict the severity of coronary artery lesions, thereby offering novel opportunities for early identification and treatment of coronary heart disease in patients with concurrent CKD. Reducing inflammation has been shown to be efficacious in treating atherosclerosis and reducing cardiovascular events.[17] Consequently, SII emerges as a novel inflammation-related biomarker that is both straightforward to calculate and holds significant promise. We have compelling reasons to believe that SII possesses inherent practical and clinical significance.

LIMITATIONS

There are a few limitations of this study. Firstly, this is a retrospective study, which cannot determine the causal relationship between SII and the extent of CAD. Secondly, our study did not consider treatment modalities, which may affect SII levels and the severity of coronary stenosis. Last but not least, this was a cross-sectional, ob-

servational and single-center study, and we did not have long-term follow-up records to evaluate the effect of SII levels on the prognosis of patients.

CONCLUSIONS

In conclusion, our study reveals that the SII is independently associated with the severity of CAD, quantified by the GS, in CKD patients, especially among the elderly. Furthermore, elevated SII levels are correlated with a higher incidence of complex CAD and CTO, increasing the likelihood of requiring revascularization therapy. SII can serve as a valuable laboratory marker for predicting the severity of CAD in patients with CKD, and it exhibits its superior predictive value compared to NLR and PLR.

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