

# Systemic Immune-Inflammation Index Was Significantly Associated with All-Cause and Cardiovascular-Specific Mortalities in Patients Receiving Peritoneal Dialysis

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**Purpose:** The prognosis of patients receiving peritoneal dialysis (PD) is associated with inflammation. Systemic immune-inflammation index (SII) is one of inflammatory markers, and the role in predicting clinical outcomes in PD patients is unclear. We aimed to investigate the relationship between the SII and all-cause and cardiovascular-specific mortalities in patients undergoing PD.

**Patients and Methods:** A total of 1419 PD patients from the First Affiliated Hospital of Sun Yat-sen University between January 1, 2007 and December 31, 2019 were retrospectively included at baseline, and the patients were followed up until November 31, 2021. SII was calculated as platelet count $\times$ neutrophil count/lymphocyte count. Kaplan–Meier curves and Cox proportional hazards regression models were used to determine the relationship between SII levels and all-cause and cardiovascular-specific mortalities.

**Results:** During follow-up (median period was 42 months), 321 patients died (171 died of cardiovascular disease). With adjustment for the potential confounding factors, each 1-SD increase in the SII was associated with 20.2% increase in all-cause mortality (hazard ratio [HR]: 1.202, 95% confidence interval [CI]: 1.088–1.327,  $P < 0.001$ ) and 28.0% increase in cardiovascular-specific mortality (HR: 1.280, 95% CI: 1.126–1.456,  $P < 0.001$ ). High SII (vs low SII) was significantly associated with increased risks of all-cause mortality (HR: 1.391, 95% CI: 1.066–1.815,  $P$ -value: 0.015) and cardiovascular-specific mortality (HR: 1.637, 95% CI: 1.185–2.261,  $P$ -value: 0.003). Subgroups analyses showed similar results for those younger than 65-year-old only.

**Conclusion:** Elevated SII level was independently associated with increased risks of all-cause and cardiovascular-specific mortalities in PD patients, especially for those younger than 65-year-old.

**Keywords:** all-cause mortality, cardiovascular mortality, peritoneal dialysis, systemic immune-inflammation index

## Introduction

Chronic kidney disease (CKD) is a global health problem, and peritoneal dialysis (PD) is an established treatment for patients with end-stage renal disease (ESRD).<sup>1</sup> The number of patients receiving PD has increased, and the quality of PD has been greatly improved in recent years. However, the mortality among PD patients remains high, and cardiovascular disease (CVD) is considered to be the main cause of death.<sup>2</sup>

Chronic inflammation is one of the important features of ESRD, and the inflammatory process is an important factor that increases the risk for cardiovascular events.<sup>3</sup> The systemic immune-inflammation index (SII) is an integrated and innovative inflammatory marker, calculated as platelet count $\times$ neutrophil count/lymphocyte count. The SII was initially used to predict the prognosis of most types of tumors. Now, the SII is thought to precisely assess inflammation status.<sup>4</sup>

Several studies have indicated that the SII may be a potential biomarker for CVD development, and elevated SII has been associated with an increased risk of CVD.<sup>5–7</sup> Moreover, Lai et al found that elevated SII increases the risk of all-cause and cardiovascular-specific mortalities among patients with CKD who are not receiving dialysis.<sup>8</sup>

To date, no studies have revealed an association between SII and all-cause and cardiovascular-specific mortalities in PD patients. The purpose of the present study was to assess whether SII is correlated with all-cause and cardiovascular-specific mortalities in patients undergoing PD.

## Patients and Methods

### Patients

This was a retrospective cohort study. All enrolled participants were patients in the First Affiliated Hospital of Sun Yat-sen University between January 1, 2007 and November 31, 2019. The exclusion criteria were as follows: (1) age <18 years old; (2) patients with a kidney transplant history; (3) patients with malignancy history; (4) patients with hematological disease; (5) patients who had catheter insertion in other PD centers; (6) hemodialysis (HD) >3 months; (7) duration of PD treatment <3 months; (8) patients with acute infection  $\leq 4$  weeks; (9) laboratory data obtained more than 3 months after PD initiation; and (10) missing data at baseline. This study was approved by the Research Ethics Committee of The First Affiliated Hospital of Sun Yat-sen University and was in accordance with the Declaration of Helsinki. All participants provided written informed consent.

### Systemic Immune-Inflammation Index (SII)

The Sysmex XE2100 and XE5000 (Sysmex Corporation, Kobe, Japan) were used to measure complete blood cell count. Data on patient complete blood cell count were also collected from the electronic medical records. The following formula was used to calculate the SII:  $\text{SII} = \text{neutrophil count (10}^9/\text{L)} \times \text{platelet count (10}^9/\text{L)} / \text{lymphocyte count (10}^9/\text{L)}$ . We performed receiver operating curve (ROC) analysis using the end point event as the status variable to determine the optimal cutoff value of the SII. According to the optimal cutoff value of the SII, patients were divided into two groups: low-SII and high-SII groups.

### Covariates

The clinical data of patients during the first 3 months of PD were retrospectively collected, including age, sex, renal diagnosis, history of diabetes mellitus (DM), history of CVD, white blood cell (WBC) counts, neutrophils, lymphocytes, platelets, hemoglobin, serum albumin, high-sensitivity C-reactive protein (hs-CRP), serum creatinine, blood urea nitrogen, estimated glomerular filtration rate (eGFR), neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), and medications including platelet inhibitors and beta-blockers.

### Follow-Up and Outcome

For health assessment, all participants were followed up in quarterly visits to our PD center or by telephone monthly until one of the following occurred: death, transfer for kidney transplantation, transfer to HD, transfer to another center, loss of contact, or the end of follow-up on December 31, 2021. Accurate death records and the exact causes of death were available for all deaths during the follow-up period.

The outcomes of our study were all-cause and cardiovascular-specific mortalities. CVD mortality was defined as death from myocardial ischemic events, heart failure, arrhythmia, sudden cardiac death, cerebrovascular accident, or peripheral vascular accident.

### Statistical Analysis

Statistical analyses were performed using IBM SPSS 25.0 software (IBM Corp., Armonk, NY, USA). Skewed distributions of continuous variables are presented as median and interquartile range (IQR), and the Mann–Whitney *U*-test was used for comparisons between groups. Categorical variables are presented as number and percentage, and the  $\chi^2$  test was used to compare differences between groups.

Kaplan–Meier survival analysis was used to generate survival curves and the Log rank test was applied to test for differences between survival curves. Multivariable Cox proportional hazards regression models were used to analyze the association between the SII and all-cause and CVD mortalities by calculating the hazard ratio (HR) and 95% confidence interval (CI) with adjustment for the potential confounding factors. When the end point was all-cause mortality, censoring could occur if a person was alive. When the end point was CVD mortality, censoring could occur if a person was alive or died owing to other causes. Incremental models were constructed as follows: model 1, unadjusted; model 2, adjusted for age and sex; model 3, adjusted for age, sex, diabetes, cardiovascular disease, hemoglobin, serum albumin, hs-CRP, serum creatinine, blood urea nitrogen, eGFR, platelet inhibitors, and  $\beta$ -blockers. Interactions between the SII and age and sex were tested separately.

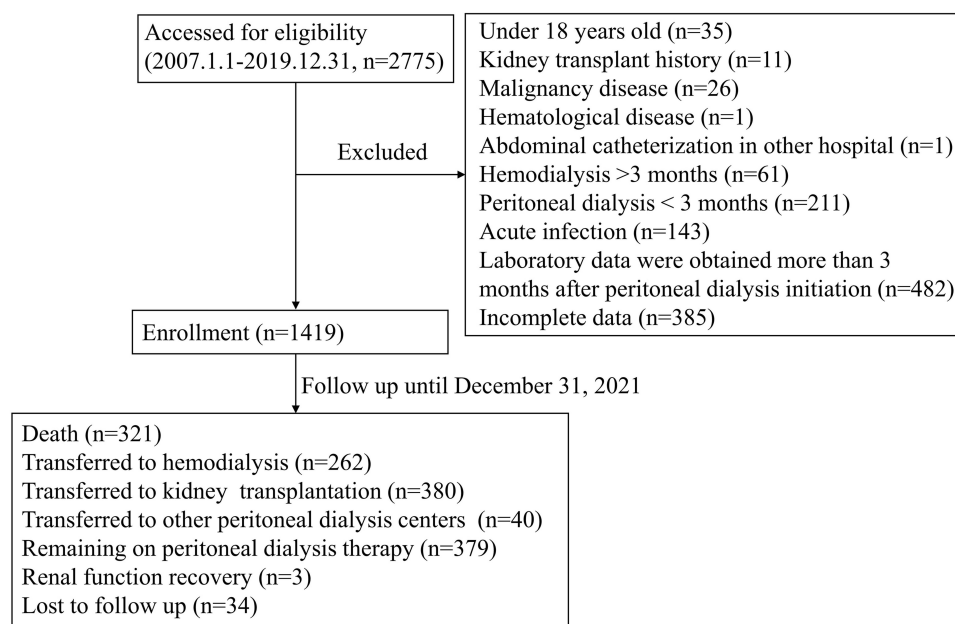
## Results

### Patient Characteristics

A total of 1419 patients undergoing PD were ultimately involved in our study. The median follow-up was 42 months (interquartile range: 22–71 months). During the period of follow-up, 262 (18.5%) patients were transferred to HD, 380 (26.8%) patients received renal transplantation, 40 (2.8%) patients were referred to other centers, 3 (0.2%) patients had recovery of renal function, and 34 (2.4%) patients were lost to follow-up. A total of 321 (22.6%) deaths occurred; among these, 171 patients died from cardiovascular diseases (Figure 1). Table 1 shows baseline characteristics of the study population according to all cause and CVD mortality. Compared with survivors, patients died from all-cause or CVD death were older, had a higher proportion with a history of diabetes or CVD, and had higher levels of WBCs, neutrophils, and hs-CRP. SII level was significantly higher in patients who died due to all-cause or CVD death compared with survivors (both  $P$ -values  $<0.05$ ), but either NLR or PLR was not statistically different between non-survivors and survivors.

### SII and All-Cause and CVD Mortality

ROC curve analysis was performed to determine the optimal cutoff value of the SII; and patients were divided into the low SII group and high SII group accordingly. The optimal cutoff values of the SII were 1168.13 for all-cause mortality and 625.19 for CVD mortality. In all-cause mortality analysis, there were 219 patients in the high-SII group and 1200



**Figure 1** Study flow chart.

**Table 1** Baseline Characteristics of Patients Receiving Peritoneal Dialysis According to All-Cause and CVD-Specific Mortalities

Variable	All-Cause Mortality		P value <sup>a</sup>	CVD Mortality		P value <sup>b</sup>
	No (n=1098)	Yes (n=321)		No (n=1248)	Yes (n=171)	
Demographics						
Age, years	41.0 (33.0, 51.0)	60.0 (50.0, 69.0)	<0.001	43.5 (34.0, 54.0)	61.0 (50.0, 71.0)	<0.001
Gender, n (%)			0.023			0.544
Female	415 (37.8)	144 (44.9)		488 (39.1)	71 (41.5)	
Male	683 (62.2)	177 (55.1)		760 (60.9)	100 (58.5)	
Renal diagnosis, n (%)			<0.001			<0.001
Primary glomerular disease	776 (70.7)	118 (36.8) <sup>c</sup>		883 (66.7)	61 (35.7) <sup>d</sup>	
Diabetic nephropathy	129 (11.7)	143 (44.5) <sup>c</sup>		194 (15.5)	78 (45.6) <sup>d</sup>	
Hypertensive nephrosclerosis	80 (7.3)	28 (8.7)		91 (7.3)	17 (9.9)	
Others	113 (10.3)	32 (10.0)		130 (10.4)	15 (8.8)	
Complication						
Diabetes, n (%)	157 (14.3)	153 (47.7)	<0.001	225 (18.0)	85 (49.7)	<0.001
CVD, n (%)	536 (48.8)	199 (62.0)	<0.001	625 (50.1)	110 (64.3)	<0.001
Medication						
Platelet inhibitor, n (%)	100 (9.1)	53 (16.5)	<0.001	121 (9.7)	32 (18.7)	<0.001
β-Blockers, n (%)	450 (41.0)	95 (29.6)	<0.001	499 (40.0)	46 (26.9)	0.001
Laboratory tests						
White blood cell, 10 <sup>9</sup> /L	6.3 (5.3, 7.5)	6.8 (5.7, 8.0)	<0.001	6.4 (5.3, 7.5)	6.8 (5.9, 8.0)	0.001
Neutrophil, 10 <sup>9</sup> /L	4.1 (3.3, 5.1)	4.5 (3.5, 5.4)	<0.001	4.2 (3.3, 5.1)	4.7 (3.8, 5.5)	<0.001
Lymphocyte, 10 <sup>9</sup> /L	1.4 (1.1, 1.7)	1.5 (1.2, 1.8)	0.114	1.4 (1.1, 1.7)	1.4 (1.1, 1.8)	0.949
Platelet, 10 <sup>9</sup> /L	235.5 (190.0, 286.0)	241.0 (200.0, 294.0)	0.027	237.0 (190.0, 288.0)	241.0 (200.5, 292.5)	0.092
Hemoglobin, g/L	107.5 (94.0, 120.0)	103.0 (90.0, 115.0)	<0.001	106.0 (94.0, 119.0)	104.0 (91.0, 116.0)	0.055
Serum albumin, g/L	38.0 (34.7, 40.6)	35.6 (32.0, 39.0)	<0.001	37.8 (34.2, 40.4)	36.1 (33.0, 39.0)	0.001
Hs-CRP, mg/L	1.3 (0.5, 3.6)	2.7 (0.9, 9.2)	<0.001	1.4 (0.6, 4.1)	3.1 (1.0, 10.4)	<0.001
SCr, μmol/L	718.0 (604.0, 899.0)	604.0 (495.0, 789.0)	<0.001	702.0 (586.5, 886.5)	629.0 (488.5, 833.5)	<0.001
BUN, mmol/L	15.8 (12.8, 19.3)	14.6 (11.7, 17.9)	<0.001	15.6 (12.6, 19.0)	14.6 (11.3, 18.3)	0.030
eGFR, mL/min/1.73m <sup>2</sup>	6.7 (5.4, 8.4)	7.5 (5.9, 9.6)	<0.001	6.8 (5.5, 8.5)	7.4 (5.7, 9.5)	0.009
NLR	2.9 (2.3, 3.8)	3.0 (2.2, 4.2)	0.369	2.9 (2.2, 3.9)	3.1 (2.4, 4.3)	0.014
PLR	167.3 (129.1, 214.3)	166.4 (125.3, 235.4)	0.703	166.2 (127.6, 215.2)	173.7 (127.4, 240.0)	0.129
SII, 10 <sup>9</sup> /L	692.7 (485.6, 961.4)	707.6 (497.4, 1075.4)	0.042	686.5 (482.7, 961.0)	757.8 (525.9, 1169.2)	0.002

**Notes:** <sup>a</sup>P value for difference of all-cause mortality (yes vs no); <sup>b</sup>P value for difference of CVD mortality (yes vs no).

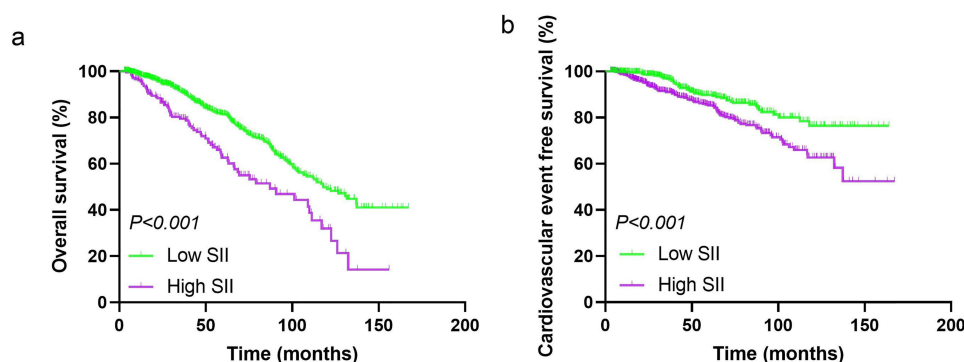
**Abbreviations:** CVD, cardiovascular disease; hs-CRP, high-sensitivity C-reactive protein; eGFR, estimated glomerular filtration rate; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammation index; SCr, serum creatinine; BUN, blood urea nitrogen.

patients in the low-SII group. In CVD mortality analysis, there were 815 patients in the high-SII group and 604 patients in the low-SII group.

In Kaplan–Meier analyses, we observed worse total survival (log-rank 28.75,  $P<0.001$ ) and cardiovascular event-free survival (log rank 14.13,  $P<0.001$ ) in patients with higher SII levels when compared with patients who had lower SII levels (Figure 2). In the multivariable Cox regression model with adjustment for age, sex, history of DM, history of CVD, hemoglobin, serum albumin, hs-CRP, serum creatinine, blood urea nitrogen, eGFR, platelet inhibitors, and β-blockers, each 1-SD increase in SII was significantly associated with 20.2% increased risk for all-cause mortality (HR: 1.202, 95% confidence interval (CI): 1.088–1.327,  $P<0.001$ ) and 28.0% increased risk for CVD mortality (HR: 1.280, 95% CI: 1.126–1.456,  $P<0.001$ ). Higher (vs lower) SII was significantly associated with 39.1% increased risk of all-cause mortality (HR: 1.391, 95% CI: 1.066–1.815,  $P<0.015$ ) and 63.7% increased risk of CVD mortality (HR: 1.637, 95% CI: 1.185–2.261,  $P=0.003$ ) (Table 2).

## Subgroup Analysis

The interaction tests showed that the interaction between the SII and sex was not significant, but the interaction between the SII and age was significant. Subgroup analysis indicated that after adjusting for confounding factors, higher SII was



**Figure 2** Kaplan–Meier estimates of overall survival (a) and cardiovascular event-free survival (b) in patients according to SII levels.

**Abbreviation:** SII, systemic immune-inflammation index.

independently associated with increased risks for all-cause mortality (HR: 1.944, 95% CI: 1.380–2.740,  $P < 0.001$ ) and CVD mortality (HR: 2.052, 95% CI: 1.337–3.149,  $P = 0.001$ ) in patients younger than 65-year-old but not in those older than 65-year-old (Table 3). Additionally, Kaplan–Meier survival curve analysis showed consistent results (Figure 3).

## Discussion

The SII is an integrated inflammatory biomarker that can reflect local immune responses and systemic inflammation in the whole human body.<sup>9</sup> Inflammation is highly prevalent in patients with CKD and is consistently related to CVD mortality.<sup>10</sup> Previous studies have shown that patients with CKD have higher SII values. The SII could predict in-hospital mortality in patients with COVID-19 infection who had CKD, including patients with moderate and advanced CKD (stage 3–5) and those undergoing maintenance HD.<sup>11</sup> Additionally, Lai et al found that a high SII on admission was an independent risk factor for all-cause and cardiovascular-specific mortalities in patients with CKD who were not receiving dialysis.<sup>8</sup> However, the relationship between the SII and prognosis in patients with CKD undergoing PD is unclear. For the first time, we revealed the association of the SII with all-cause and cardiovascular-specific mortalities in PD patients.

Traditional inflammatory markers such as hs-CRP, interleukin (IL)-6, and WBCs are elevated in PD patients<sup>12</sup> and contribute to CVD mortality.<sup>13–16</sup> Serum albumin associated with the inflammatory state also predicts CVD mortality.<sup>17</sup> However, compared with CRP and IL-6, the SII is inexpensive and is routinely tested, so there is no additional cost. Recently, new inflammatory markers based on routine blood tests, such as the NLR and PLR, have been widely used in clinical practice. The NLR and PLR are associated with all-cause and CVD mortality in patients undergoing PD.<sup>18–20</sup> However, these indicators include only one or two types of immune inflammatory cells, so they may not adequately reflect the state of inflammation. The SII, which is calculated using three types of immune cells (neutrophils, platelets, and lymphocytes) has significant predictive power.<sup>4</sup> In our study, we found that a high SII was associated with the risk of all-cause and cardiovascular-specific mortalities.

**Table 2** Associations of SII with All-Cause and CVD Mortality in Cox Regression Models

Group	Model 1 <sup>a</sup>		Model 2 <sup>b</sup>		Model 3 <sup>c</sup>	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
All-cause mortality						
SII (per 1-SD increase)	1.282 (1.166–1.409)	<0.001	1.172 (1.062–1.294)	0.002	1.202 (1.088–1.327)	<0.001
SII (high SII vs low SII)	2.016 (1.552–2.619)	<0.001	1.323 (1.013–1.727)	0.040	1.391 (1.066–1.815)	0.015
CVD mortality						
SII (per 1-SD increase)	1.370 (1.212–1.547)	<0.001	1.263 (1.112–1.433)	<0.001	1.280 (1.126–1.456)	<0.001
SII (high SII vs low SII)	1.839 (1.332–2.540)	<0.001	1.632 (1.182–2.255)	0.003	1.637 (1.185–2.261)	0.003

**Notes:** <sup>a</sup>Model 1: Unadjusted. <sup>b</sup>Model 2: Adjusted for age, sex. <sup>c</sup>Model 3: Adjusted for age, sex, diabetes, cardiovascular disease, hemoglobin, serum albumin, high-sensitivity C-reactive protein, serum creatinine, blood urea nitrogen, estimated glomerular filtration rate, platelet inhibitor, and  $\beta$ -blockers.

**Abbreviations:** SII, systemic immune-inflammation index; CVD, cardiovascular disease; HR, hazard ratio; CI, confidence interval.

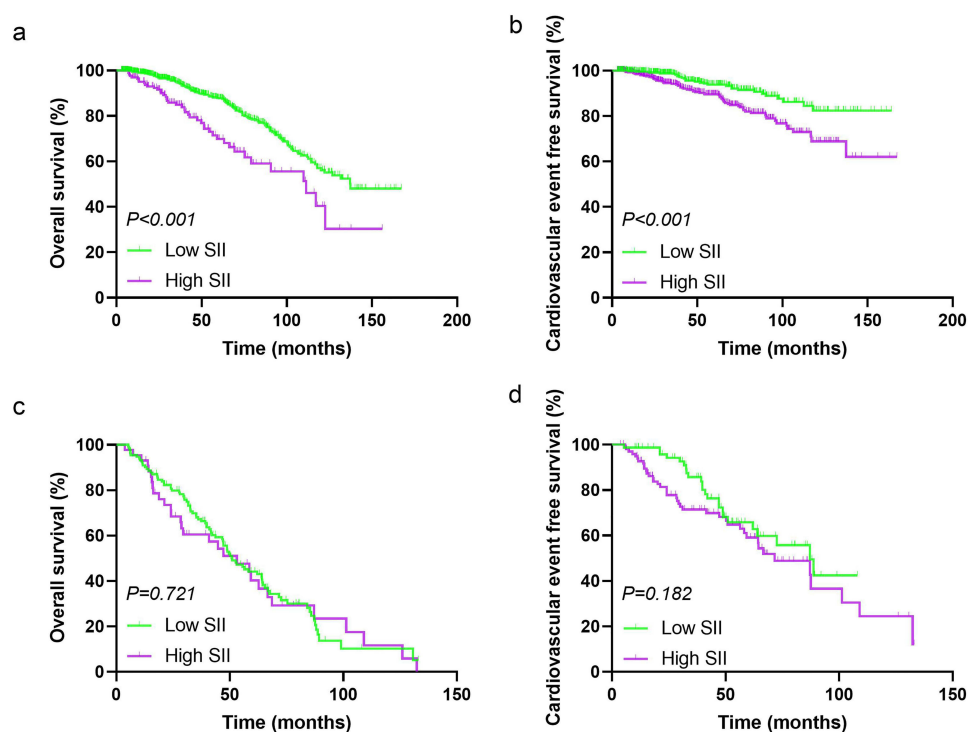
**Table 3** Subgroup Analysis of the Associations Between Higher (vs Lower) SII and All-Cause and Cardiovascular-Specific Mortalities

Subgroup	All-Cause Mortality			Cardiovascular Mortality		
	HR (95% CI)	P value	P for Interaction	HR (95% CI)	P value	P for Interaction
Age			<0.001			<0.001
<65	1.944 (1.380–2.740)	<0.001		2.052 (1.337–3.149)	0.001	
≥65	1.031 (0.656–1.621)	0.895	0.132	1.378 (0.815–2.330)	0.231	0.063
Gender						
Male	1.509 (1.031–2.209)	0.034		1.464 (0.976–2.196)	0.065	
Female	1.170 (0.793–1.726)	0.428		1.984 (1.134–3.473)	0.016	

**Notes:** Adjusted for diabetes, cardiovascular disease, hemoglobin, serum albumin, high-sensitivity C-reactive protein, serum creatinine, blood urea nitrogen, estimated glomerular filtration rate, platelet inhibitor,  $\beta$ -blockers, age, and sex.

**Abbreviations:** SII, systemic immune-inflammation index; HR, hazard ratio; CI, confidence interval.

Subgroup analysis showed that a high SII was related to the risk of all-cause and cardiovascular-specific mortalities in patients younger than 65-year-old, but not in patients older than age 65 years. One reason may be that the immune response is significantly reduced in older people.<sup>21</sup> Metcalf et al undertook transcriptional profiling using a heterogeneous population of peripheral blood mononuclear cells (PBMCs), and found that PBMCs isolated from older individuals ( $\geq 65$  years) exhibited a delayed and altered response to stimulation with toll-like receptor (TLR) 4 and TLR7/8 agonists compared with cells obtained from younger adults ( $\leq 40$  years).<sup>22</sup> Another reason may be that older patients show an absolute or relative reduction in inflammatory response. One study on community-acquired pneumonia found that cytokine levels were positively correlated with pneumonia severity index scores in younger but not in older patients.<sup>23</sup> Zeng et al found that the inflammatory marker NLR is an independent risk factor for adverse cardiovascular outcomes in



**Figure 3** Kaplan–Meier estimates of overall survival and cardiovascular event-free survival by category of SII in different subgroups (a) Kaplan–Meier estimates of overall survival by category of SII in the group younger than 65-year-old; (b) Kaplan–Meier estimates of cardiovascular event-free survival by category of SII in the group younger than 65-year-old; (c) Kaplan–Meier estimates of overall survival by category of SII in the group older than 65-year-old; (d) Kaplan–Meier estimates of cardiovascular event-free survival by category of SII in the group older than 65-year-old.

**Abbreviation:** SII, systemic immune-inflammation index.



patients undergoing PD who were younger than 65-year-old but not older than 60 years old.<sup>18</sup> This may also be owing to the small number of people older than age 65 years in our study (177 cases). Further studies are needed for validation.

Our study has certain limitations. First, this was a single-center retrospective study; therefore, selection bias is inevitable, and external validity is limited. Second, despite adjustment for potential confounders, we cannot completely rule out the possibility that uncontrolled confounders may explain the association. Third, we assessed SII levels only at baseline and did not record changes during follow-up.

## Conclusion

Elevated SII level was independently associated with increased risks of all-cause and CVD mortalities in patients undergoing PD, especially for those younger than 65-year-old. Application of the SII in clinical practice in predicting mortality for patients undergoing PD requires further multicenter prospective studies.

## Abbreviations

SII, systemic immune-inflammation index; PD, peritoneal dialysis; HR, hazard ratio; CI, confidence interval; CKD, chronic kidney disease; ESRD, end-stage renal disease; CVD, cardiovascular disease; HD, hemodialysis; ROC, receiver operating curve; DM, diabetes mellitus; WBC, white blood cell; hs-CRP, high-sensitivity C-reactive protein; eGFR, estimated glomerular filtration rate; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio.

## Data Sharing Statement

The datasets generated and analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

## Ethics Approval and Informed Consent

This study was approved by the Research Ethics Committee of The First Affiliated Hospital of Sun Yat-sen University and was in accordance with the Declaration of Helsinki. Informed consent was obtained from all individual participants included in the study.

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## Disclosure

The authors report no conflicts of interest in this work.

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