

# Increased Systemic Immune-Inflammation Index Was Associated with Type 2 Diabetic Peripheral Neuropathy: A Cross-Sectional Study in the Chinese Population

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**Background:** Systemic immune-inflammation index (SII), a novel inflammatory marker, has been demonstrated to be associated with type 2 diabetes mellitus (T2DM) and its vascular complications, however, the relation between SII and diabetic peripheral neuropathy (DPN) has been never reported. We aimed to explore whether SII is associated with DPN in Chinese population.

**Methods:** A cross-sectional study was conducted among 1460 hospitalized patients with T2DM. SII was calculated as the platelet count  $\times$  neutrophil count/lymphocyte count, and its possible association with DPN was investigated by correlation and multivariate logistic regression analysis, and subgroup analyses.

**Results:** Patients with higher SII quartiles had higher vibration perception threshold and prevalence of DPN (all  $P < 0.01$ ), and SII was independently positively associated with the prevalence of DPN ( $P < 0.01$ ). Multivariate logistic regression analysis showed that the risk of prevalence of DPN increased progressively across SII quartiles ( $P$  for trend  $< 0.01$ ), and participants in the highest quartile of SII was at a significantly increased risk of prevalent DPN compared to those in the lowest quartile after adjustment for potential confounding factors (odds rate: 1.211, 95% confidence intervals 1.045–1.404,  $P < 0.05$ ). Stratified analysis revealed positive associations of SII quartiles with risk of prevalent DPN only in men, people less than 65 years old, with body mass index  $< 24 \text{ kg/m}^2$ , duration of diabetes  $> 5$  years, hypertension, dyslipidaemia, poor glycaemic control, and estimated glomerular filtration rate  $< 90 \text{ mL/min/1.73 m}^2$  ( $P$  for trend  $< 0.01$  or  $P$  for trend  $< 0.05$ ). The receiver operating characteristic curve analysis revealed that the optimal cut-off point of SII for predicting DPN was 617.67 in patients with T2DM, with a sensitivity of 45.3% and a specificity of 73%.

**Conclusion:** The present study showed that higher SII is independently associated with increased risk of DPN, and SII might serve as a new risk biomarker for DPN in Chinese population.

**Keywords:** systemic immune-inflammation index, diabetic peripheral neuropathy, vibration perception threshold, type 2 diabetes mellitus, Chinese population

## Introduction

Diabetic peripheral neuropathy (DPN) is one of the most common long-term complications of diabetes that frequently presents with peripheral nerve dysfunction accompanied with typical characteristics of pain and numbness, which not only results in an increase in the risk of foot ulceration and subsequent amputation, but also leads to a considerable

disability and cardiovascular mortality.<sup>1–3</sup> Therefore, DPN has posed a great challenge for both medical professionals and the entire society. Despite a high lifetime prevalence of approximately 50%,<sup>4</sup> the symptoms are insidious in onset,<sup>1</sup> and there is no approved therapy to prevent or cure DPN apart from good glycemic therapy.<sup>3</sup> Therefore, emphasis should be laid on effective surveillance, early detection and diagnosis of DPN.

Although the pathogenesis is complex and not well established, chronic inflammation has been suggested to be involved in the occurrence and development of DPN.<sup>5,6</sup> Recently, close interaction of inflammation and immune system-related cells such as neutrophils, lymphocytes, and platelets, and their combinations such as neutrophil-to-lymphocyte (NLR) and platelet-to-lymphocyte (PLR) with the pathogenesis of DPN has attracted great attention.<sup>7–9</sup> However, these indicators that include just one or two kinds of immune-inflammatory cells may not adequately reflect the state of inflammation. The systemic immune-inflammation index (SII), an integrated and novel inflammatory biomarker integrating three different cells, could better and more objectively reflect the state of inflammation and immune balance in the body compared with neutrophil and lymphocyte counts as well as the NLR and PLR,<sup>10–12</sup> and has been developed to predict and evaluate the prognosis and clinical outcomes of various malignant tumors types, autoimmune disorders, atherosclerotic cardio-cerebrovascular diseases, and other diseases.<sup>10,11,13–16</sup> Moreover, emerging data have also shown that elevated levels of SII were found to be associated with diabetes mellitus, diabetic retinopathy (DR), diabetic kidney disease (DKD), and diabetic foot infections,<sup>17–21</sup> all of which are associated with high burden of inflammation.<sup>22–24</sup> Considering the role of chronic inflammation in the pathogenesis of DPN, and that DPN, DR, DKD, and diabetic foot infections share multiple common pathogenetic pathways and risk factors, such as inflammation, thus elevated levels of SII may be associated with the development of DPN. As far as we are aware, the relationship of the SII with DPN, however, has never been investigated.

Therefore, the objective of the present study was to investigate the relationship between SII and risk of presence of DPN in Chinese adults with type 2 diabetes mellitus (T2DM), which may help clinicians early recognize patients at high risk for DPN and initiate the prompt, appropriate treatment for prevention.

## Materials and Methods

### Study Population

This is a cross-sectional study, where T2DM inpatients aged 18–89 years were recruited from August 2012 to September 2015 in the department of Endocrinology and Metabolism at the Affiliated Hospital of Southwest Medical University. T2DM was defined according to the 1999 World Health Organization (WHO) diagnostic criteria.<sup>25</sup> Subjects with diabetic foot ulcers and amputation were excluded from the study. Diabetic subjects with stroke were not an exclusion criterion. The details of the other inclusion and exclusion criteria are described elsewhere.<sup>26</sup> Ultimately, 1460 eligible participants (716 men and 744 women) were included in the analysis.

The study was approved by the Ethics Committee of the Affiliated Hospital of Southwest Medical University in China, and informed consent was obtained from all patients before data collection. Study procedures were performed in accordance with the Declaration of Helsinki ethical principles for medical research involving human subjects.

### General Clinical and Biochemical Measurements

A face-to-face interview was carried out by trained interviewers to collect data, including demographic data, lifestyle (smoking and drinking status, etc.), personal medical history, duration of diabetes, and family history of diabetes. Body weight in light clothes and without shoes was measured with a digital scale to the nearest 0.1 kg, and height was measured without shoes to the nearest 0.1 cm. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. The patients' systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured three times using a mercury sphygmomanometer while the subject in a sitting position, and the mean value was recorded.<sup>26</sup>

After all subjects had fasted for at least 8 h, venous blood samples were collected. Fasting blood glucose (FBG), 2 hour postprandial blood glucose (PBG), total cholesterol (TC), triglyceride (TG), high density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and serum creatinine (Cr) were measured using a 7060 full-automatic biochemical analyzer (Hitachi) at the registered central laboratory located at the Affiliated Hospital of

Southwestern Medical University. Glycated hemoglobin A1C (HbA1c) was measured by the anion exchange high performance liquid chromatography (Arkray Eluent 80A). Neutrophil count, lymphocyte count, and platelet (PLT) count were determined using an automated blood cell counter (Mindray BC-6800). The NLR was calculated by dividing the neutrophil count by lymphocyte count. The SII was calculated as platelet  $\times$  neutrophil/lymphocyte counts.<sup>6</sup> The glycemic exposure (GE) index was calculated using the following equation: GE index = (HbA1c)<sup>1/2</sup>  $\times$  (duration of DM in years)<sup>1/8</sup>.<sup>27</sup> The estimated glomerular filtration rate (eGFR) was estimated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation that includes age, sex, and race.<sup>26,28</sup>

According to the manufacturer's instructions, urinary albumin and creatinine were measured from three fresh morning spot urine sample on three separate occasions within 6 months, and the urinary albumin-to-creatinine ratio (ACR) was computed and was reported in milligrams per gram (mg/g).<sup>29</sup>

## Assessment and Diagnostic Criteria of DPN

All T2DM patients were asked whether they had neuropathic symptoms, including numbness, pain (prickling or stabbing, shooting, electric shocks, burning or aching pain), and paresthesia (abnormal cold or heat sensation, allodynia and hyperalgesia) in the toes, feet, legs or upper-limb. Vibration perception threshold (VPT) was assessed at the metatarsophalangeal joint dig I using a neurothesiometer (Bio-Thesiometer; Bio-Medical Instrument Co., Newbury, OH, USA) according to previously published methods.<sup>29</sup> A VPT  $\geq 15$  V was defined as impaired vibration perception.<sup>30–32</sup> DPN was diagnosed clinically based on the presence of one or more neuropathic symptoms and impaired vibration perception in the feet,<sup>30,31</sup> and then participants were divided into DPN group and no DPN group.

## Other Classifications and Definitions

According to the Chinese Guidelines on Prevention and Treatment of obesity in Adults, participants with a BMI of 24–27.9 kg/m<sup>2</sup> were defined as overweight, and obesity was defined as BMI of  $\geq 28$  kg/m<sup>2</sup>.<sup>33</sup> Hypertension was defined as SBP  $\geq 140$  mmHg, DBP  $\geq 90$  mmHg, or use of antihypertensive medication.<sup>26,32,34</sup> Dyslipidaemia was defined as either incident abnormal lipid laboratory results (comprised of TC > 200 mg/dL, TG > 150 mg/dL, LDL-C > 130 mg/dL, or HDL-C < 40 mg/dL) or incident lipid-lowering medications prescriptions (consisting of prescription of statins, bile acid resins, and fibrates).<sup>35</sup> Glycaemic control was assessed in terms of the HbA1c level and poor glycaemic control was defined as HbA1c  $\geq 7\%$  and a level < 7% reflects good glycaemic control, according to the American Diabetes Association.<sup>36</sup> Coronary heart disease (CHD) was defined as a positive history of myocardial infarction, bypass operation, a diagnostic finding in angiography or positive exercise test.<sup>26,34</sup> Stroke was considered present if diagnosed according to previous medical records or if a pathological finding by CT and MRI of the brain.<sup>34</sup> Peripheral arterial disease (PAD) was considered present in all subjects with an ankle-brachial index (ABI) < 0.9 in one leg, and/or a history of prior treatment for PAD.<sup>26,29,34</sup> DR was determined by using fundus photography (Canon Inc., Kanagawa, Japan), which was performed by an ophthalmologist.<sup>26,29,34</sup> A participant with an eGFR < 90 mL/min/1.73 m<sup>2</sup> was considered to have impaired renal function, and mild and moderate impaired renal function were defined as 60  $\leq$  eGFR < 90 mL/min/1.73 m<sup>2</sup> and 30  $\leq$  eGFR < 60 mL/min/1.73 m<sup>2</sup> respectively.<sup>37,38</sup> Albuminuria was defined as urinary ACR  $\geq 30$  mg/g.<sup>29</sup> Albuminuria was then divided into microalbuminuria (30 mg/g  $\leq$  urinary ACR < 300 mg/g) and macroalbuminuria (urinary ACR  $\geq 300$  mg/g).<sup>39,40</sup> DKD was diagnosed with eGFR < 60 mL/min/1.73 m<sup>2</sup>, albuminuria, or both in T2DM patients.<sup>26,29,34</sup>

## Statistical Analysis

Statistical analyses were conducted using the Statistical Package for Social Sciences (SPSS) (version 20.0; IBM, Chicago, IL). For continuous variables, results were presented as mean  $\pm$  standard deviation (SD). Continuous variables were compared by Student's *t* test and one-way analysis of variance (ANOVA), whereas skewed distribution variables were compared by Mann-Whitney U and Kruskal–Wallis tests. For categorical variables, results were presented as n (%), and intergroup comparisons were analyzed using a  $\chi^2$  test. Correlations between variables were examined using Spearman correlation analysis and partial correlation analysis. The univariate and multivariable logistic regression analyses were conducted to investigate the association of SII and other variables with the risk of presence of DPN. We then categorized patients into four quartile groups by SII levels: quartile (Q)1 group, 71.16–328.44; Q2 group, 328.49–478.92; Q3 group, 479.89–735.59; and Q4 group, 741.09–7173.95. Binary logistic regression analyses were conducted to investigate the association between SII quartiles and DPN. The Q1 served as the

reference group. The odds ratios (ORs) and 95% confidence intervals (CI) were reported. Possible dose-response relationships between SII levels and DPN were examined by the trend test. We also conducted stratified analyses by sex (men and women), age ( $\geq 65$  and  $< 65$  years), BMI ( $\geq 24$  and  $< 24$  kg/m<sup>2</sup>), duration of diabetes ( $> 5$  and  $\leq 5$  years), hypertension (Yes and No), dyslipidaemia (Yes and No), poor glycaemic control (Yes and No), and eGFR ( $\geq 90$  and  $< 90$  mL/min/1.73 m<sup>2</sup>) to further validate the consistency of the above-mentioned findings. Last, the predictive validity of SII for the presence of DPN was determined using receiver operating characteristic (ROC) curves and area under the curve (AUC) in all subjects, male subjects, and female subjects. All tests were two-tailed, and *P*-value of  $< 0.05$  was considered statistically significant.

## Results

### Clinical and Laboratory Characteristics

Clinical and laboratory characteristics of participants are given in Table 1. Among the 1460 participants included in this study, 590 participants (40.41%) had DPN. The prevalence of DPN according to SII quartiles were 31.23%, 32.88%, 41.64% and 55.89% respectively. The subjects with higher SII were more likely to be older ( $P < 0.05$ ). Moving from the lowest to the highest SII quartile, we observed increased levels of FBG, PBG, HbA1c, GE index, neutrophil count, NLR, PLT count, serum Cr, urinary ACR, VPT, as well as increased percentages of participants with HbA1c  $\geq 9\%$  and VPT  $\geq 25$ V, prevalence of overweight, hypertension, microalbuminuria, macroalbuminuria, albuminuria, moderate impaired renal function, DKD, and PAD, and

**Table 1** Characteristics of Study Participants According to SII Quartiles

Variable	Total	Q1	Q2	Q3	Q4	<i>P</i>
	(n=1460)	(n=365)	(n=365)	(n=365)	(n=365)	
		71.16–328.44	328.49–478.92	479.89–735.59	741.09–7173.95	value
Male, n (%)	716 (49.04)	194 (53.15)	171 (46.85)	172 (47.12)	179 (49.04)	0.295
Age (years)	59.73 $\pm$ 11.31	58.78 $\pm$ 11.31	59.24 $\pm$ 10.74	59.58 $\pm$ 11.47	61.31 $\pm$ 11.59	0.013
Height (m)	1.60 $\pm$ 0.08	1.61 $\pm$ 0.08	1.60 $\pm$ 0.08	1.60 $\pm$ 0.08	1.60 $\pm$ 0.08	0.060
Weight (kg)	62.59 $\pm$ 11.43	64.37 $\pm$ 11.11	62.76 $\pm$ 11.25	62.89 $\pm$ 11.77	60.31 $\pm$ 11.27	0.000
BMI (kg/m <sup>2</sup> )	24.27 $\pm$ 3.68	24.66 $\pm$ 3.50	24.51 $\pm$ 3.78	24.44 $\pm$ 3.46	23.47 $\pm$ 3.84	0.000
$< 24$ kg/m <sup>2</sup> , n (%)	752 (51.51)	180 (49.32)	166 (45.48)	173 (47.40)	233 (63.84)	0.000
24–28 kg/m <sup>2</sup> , n (%)	502 (34.38)	131 (35.89)	139 (38.08)	142 (38.90)	90 (24.66)	0.000
$\geq 28$ kg/m <sup>2</sup> , n (%)	206 (14.11)	54 (14.79)	60 (16.44)	50 (13.70)	42 (11.51)	0.277
Duration of diabetes (years)	7.61 $\pm$ 6.37	7.41 $\pm$ 6.13	7.59 $\pm$ 6.25	7.23 $\pm$ 6.18	8.22 $\pm$ 6.88	0.284
$\leq 5$ years, n (%)	646 (44.25)	169 (46.30)	161 (44.11)	169 (46.30)	147 (40.27)	0.310
6–10 years, n (%)	486 (33.29)	114 (31.23)	122 (33.42)	121 (33.15)	129 (35.34)	0.707
$> 10$ years, n (%)	328 (22.47)	82 (22.47)	82 (22.47)	75 (20.55)	89 (24.38)	0.673
Smoking, n (%)	314 (21.51)	77 (21.10)	77 (21.10)	85 (23.29)	75 (20.55)	0.812
Drinking, n (%)	235 (16.10)	63 (17.26)	65 (17.81)	59 (16.16)	48 (13.15)	0.320
SBP (mmHg)	132.26 $\pm$ 20.70	130.18 $\pm$ 19.45	131.58 $\pm$ 19.98	133.99 $\pm$ 21.62	133.27 $\pm$ 21.53	0.094
DBP (mmHg)	72.04 $\pm$ 12.02	71.92 $\pm$ 11.31	72.27 $\pm$ 11.75	73.11 $\pm$ 12.42	70.86 $\pm$ 12.51	0.230
Hypertension, n (%)	760 (52.05)	161 (44.11)	183 (50.14)	201 (55.07)	215 (58.90)	0.000
TC (mmol/L)	4.86 $\pm$ 1.34	4.90 $\pm$ 1.35	4.86 $\pm$ 1.15	4.91 $\pm$ 1.28	4.78 $\pm$ 1.54	0.125
TG (mmol/L)	2.36 $\pm$ 2.64	2.74 $\pm$ 3.50	2.39 $\pm$ 2.11	2.26 $\pm$ 1.88	2.04 $\pm$ 2.70	0.000
HDL-C (mmol/L)	1.17 $\pm$ 0.36	1.16 $\pm$ 0.36	1.17 $\pm$ 0.37	1.18 $\pm$ 0.35	1.19 $\pm$ 0.36	0.713
LDL-C (mmol/L)	2.78 $\pm$ 0.99	2.70 $\pm$ 0.96	2.76 $\pm$ 0.93	2.85 $\pm$ 0.93	2.83 $\pm$ 1.12	0.149
Dyslipidaemia, n (%)	999 (68.42)	254 (69.59)	245 (67.12)	260 (71.23)	240 (65.75)	0.493
FBG (mmol/L)	10.89 $\pm$ 5.21	9.98 $\pm$ 4.43	10.29 $\pm$ 4.68	11.12 $\pm$ 5.27	12.17 $\pm$ 6.06	0.000
PBG (mmol/L)	16.09 $\pm$ 5.12	15.69 $\pm$ 5.20	15.67 $\pm$ 5.08	16.46 $\pm$ 5.25	16.53 $\pm$ 4.90	0.008
GE index	3.86 $\pm$ 0.60	3.76 $\pm$ 0.57	3.80 $\pm$ 0.59	3.88 $\pm$ 0.57	4.00 $\pm$ 0.63	0.000
HbA1c (mmol/mol)	80.85 $\pm$ 27.34	77.19 $\pm$ 27.28	77.67 $\pm$ 25.02	82.80 $\pm$ 27.32	85.76 $\pm$ 28.78	0.000
HbA1c (%)	9.55 $\pm$ 2.50	9.21 $\pm$ 2.50	9.26 $\pm$ 2.29	9.73 $\pm$ 2.50	10.00 $\pm$ 2.63	0.000
$< 7\%$ , n (%)	214 (14.66)	76 (20.82)	56 (15.34)	44 (12.05)	38 (10.41)	0.000

(Continued)

Table 1 (Continued).

Variable	Total	Q1	Q2	Q3	Q4	P
	(n=1460)	(n=365)	(n=365)	(n=365)	(n=365)	
		71.16–328.44	328.49–478.92	479.89–735.59	741.09–7173.95	
7–9%, n (%)	465 (31.85)	115 (31.51)	130 (35.62)	116 (31.78)	104 (28.49)	0.231
≥9%, n (%)	781 (53.49)	174 (47.67)	179 (49.04)	205 (56.16)	223 (61.10)	0.001
Neutrophil (*10 <sup>9</sup> /L)	4.58±2.18	3.14±1.30	3.91±0.99	4.58±1.19	6.68±2.84	0.000
Lymphocyte (*10 <sup>9</sup> /L)	1.66±0.63	1.97±0.70	1.80±0.56	1.59±0.52	1.26±0.46	0.000
NLR	3.31±2.82	1.73±1.08	2.29±0.68	3.06±0.95	6.14±4.20	0.000
PLT (×10 <sup>9</sup> /L)	197.60±68.58	148.75±45.08	188.85±48.12	208.02±57.23	244.78±80.10	0.000
SII	658.02±642.13	234.68±61.02	404.25±43.22	590.86±73.58	1402.30±915.11	0.000
Serum Cr (μmol/L)	68.08±26.00	65.41±21.42	65.37±23.54	68.81±27.86	72.74±29.73	0.006
eGFR (mL/min/1.73 m <sup>2</sup> )	93.72±23.48	96.91±20.71	95.92±22.03	93.01±23.80	89.03±26.31	0.000
≥90, n (%)	951 (65.14)	264 (72.33)	246 (67.40)	239 (65.48)	202 (55.34)	0.000
60–90, n (%)	354 (24.25)	76 (20.82)	93 (25.48)	81 (22.19)	104 (28.49)	0.070
30–60, n (%)	155 (10.62)	25 (6.85)	26 (7.12)	45 (12.33)	59 (16.16)	0.000
Urinary ACR (mg/g)	208.07±20.08	87.13±13.83	159.62±32.01	331.79±55.52	256.25±45.73	0.000
Microalbuminuria, n (%)	394 (26.99)	89 (24.38)	82 (22.47)	95 (26.03)	128 (35.07)	0.001
Macroalbuminuria, n (%)	128 (8.77)	20 (5.48)	31 (8.49)	42 (11.51)	35 (9.59)	0.034
Albuminuria, n (%)	522 (35.75)	109 (29.86)	113 (30.96)	137 (37.53)	163 (44.66)	0.000
ABI	1.02±0.15	1.03±0.14	1.03±0.12	1.02±0.15	1.00±0.19	0.307
VPT (V)	16.45±10.08	13.79±7.19	14.76±8.52	17.17±10.65	20.09±12.08	0.000
<15V, n (%)	870 (59.59)	251 (68.77)	245 (67.12)	213 (58.36)	161 (44.11)	0.000
15–25V, n (%)	368 (25.21)	92 (25.21)	81 (22.19)	89 (24.38)	106 (29.04)	0.192
≥25V, n (%)	222 (15.21)	22 (6.03)	39 (10.68)	63 (17.26)	98 (26.85)	0.000
Diabetic complications (%)						
DPN, n (%)	590 (40.41)	114 (31.23)	120 (32.88)	152 (41.64)	204 (55.89)	0.000
DKD, n (%)	591 (40.48)	125 (34.25)	123 (33.70)	153 (41.92)	190 (52.05)	0.000
DR, n (%)	183 (12.53)	41 (11.23)	50 (13.70)	40 (10.96)	49 (13.42)	0.690
CHD, n (%)	131 (8.97)	35 (9.59)	31 (8.49)	35 (9.59)	30 (8.22)	0.874
Stroke, n (%)	291 (19.93)	76 (20.82)	61 (16.71)	75 (20.55)	79 (21.64)	0.347
PAD, n (%)	153 (10.48)	28 (7.67)	27 (7.40)	42 (11.51)	56 (15.34)	0.001

**Note:** Data are mean ± SD.

**Abbreviations:** SD, standard deviation; Q, quartile; DPN, diabetic peripheral neuropathy; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; FBG, fasting blood glucose; PBG, 2 hour postprandial blood glucose; GE index, glycemic exposure index; HbA1c, glycated hemoglobin A1c; NLR, neutrophil-to-lymphocyte; PLT, platelet; SII, systemic immune-inflammation index; Cr, creatinine; eGFR, estimated glomerular filtration rate; ACR, albumin- to-creatinine ratio; ABI, ankle-brachial index; VPT, vibration perception threshold; DKD, diabetic kidney disease; DR, diabetic retinopathy; CHD, coronary heart disease; PAD, peripheral arterial disease.

decreased levels of weight, BMI, TG, lymphocyte count, and eGFR ( $P<0.01$  or  $P<0.05$ ). No significant difference was seen between SII quartiles for sex distribution, height, duration of diabetes, smoking, drinking, SBP, DBP, TC, HDL-C, LDL-C, ABI, percentages of participants with HbA1c 7–9% and VPT 15–25V, prevalence of obesity, dyslipidaemia, DR, mild impaired renal function, CHD, and Stroke ( $P>0.05$ ). [Supplementary Table 1](#) reported characteristics of all T2DM patients by DPN. In type 2 diabetic patients, participants with DPN showed significantly older age, longer duration of diabetes, less drinking, higher levels of SBP, GE index, HbA1c, neutrophil count, NLR, SII, serum Cr, urinary ACR, VPT, prevalence of hypertension, microalbuminuria, macroalbuminuria, albuminuria, DKD, DR, CHD, stroke, and PAD, and lower TC, TG, DBP, lymphocyte count, eGFR, ABI, and prevalence of overweight and dyslipidaemia ( $P<0.01$  or  $P<0.05$ ). [Supplementary Table 2](#) reported characteristics of all T2DM patients by sex. Compared with men, the women had significantly older age, longer duration of diabetes, less smoking and drinking, higher levels of lymphocyte count, PLT count, percentages of participants with HbA1c <7%, prevalence of hypertension, DR, and PAD, and lower FBG, PBG, HbA1c, NLR, ABI, percentages of participants with HbA1c ≥9%, and prevalence of overweight, dyslipidaemia, macroalbuminuria, albuminuria, DKD, and PAD ( $P<0.01$  or  $P<0.05$ ).

## The Relationships Between SII and DPN- Related Risk Factors

Spearman correlation analysis showed that SII was positively associated with age, SBP, FBG, PBG, GE index, HbA1c, neutrophil count, NLR, PLT count, serum Cr, urinary ACR and VPT and the prevalence of hypertension, microalbuminuria, macroalbuminuria, albuminuria, moderate impaired renal function, DKD, DPN, and PAD, and negatively with BMI, drinking, TC, TG, lymphocyte count, and eGFR ( $P<0.01$  or  $P<0.05$ ; Table 2). Partial correlation analysis controlling for sex, age, BMI, and duration of diabetes demonstrated that SII was positively associated with FBG, PBG, GE index, HbA1c, neutrophil count, PLT count, serum Cr, VPT, prevalence of obesity, hypertension,

**Table 2** The Relationships between SII and DPN-Related Risk Factors

Variables	<i>r</i>	<i>P</i> -value	Adjusted <i>r</i>	Adjusted <i>P</i> -value
Age	0.084	0.001	-	-
Sex	0.030	0.246	-	-
Duration of diabetes	0.025	0.344	-	-
BMI	-0.124	0.000	-	-
Obesity	-0.041	0.113	0.053	0.048
Smoking	-0.013	0.618	-0.005	0.855
Drinking	-0.053	0.044	-0.031	0.249
SBP	0.066	0.012	0.003	0.931
DBP	-0.031	0.238	-0.035	0.295
Hypertension	0.111	0.000	0.104	0.002
TC	-0.057	0.033	-0.080	0.016
TG	-0.125	0.000	-0.014	0.675
HDL-C	0.026	0.327	-0.058	0.079
LDL-C	0.038	0.153	0.009	0.794
Dyslipidaemia	-0.015	0.581	-0.015	0.650
FBG	0.158	0.000	0.193	0.000
PBG	0.097	0.000	0.102	0.002
GE index	0.152	0.000	0.111	0.001
HbA1c	0.134	0.000	0.111	0.001
Neutrophil	0.706	0.000	0.721	0.000
Lymphocyte	-0.453	0.000	-0.359	0.000
NLR	0.831	0.000	0.873	0.000
PLT	0.532	0.000	0.442	0.000
Serum Cr	0.074	0.005	0.100	0.003
eGFR	-0.124	0.000	-0.137	0.000
Moderate impaired renal function	0.130	0.000	0.115	0.000
Urinary ACR	0.152	0.000	0.052	0.119
Microalbuminuria	0.085	0.001	0.111	0.001
Macroalbuminuria	0.056	0.031	0.042	0.201
Albuminuria	0.112	0.000	0.135	0.000
ABI	-0.051	0.053	-0.103	0.000
VPT	0.219	0.000	0.198	0.000
DPN	0.193	0.000	0.149	0.000
DKD	0.138	0.000	0.121	0.000
DR	0.009	0.725	-0.031	0.251
CHD	-0.005	0.856	-0.035	0.289
Stroke	0.023	0.388	0.008	0.821
PAD	0.106	0.000	0.113	0.000

**Abbreviations:** SII, systemic immune-inflammation index; DPN, diabetic peripheral neuropathy; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; FBG, fasting blood glucose; PBG, 2 hour postprandial blood glucose; GE index, glycemic exposure index; HbA1c, glycated hemoglobin A1c; NLR, neutrophil-to-lymphocyte; PLT, platelet; Cr, creatinine; eGFR, estimated glomerular filtration rate; ACR, albumin- to-creatinine ratio; ABI, ankle-brachial index; VPT, vibration perception threshold; DKD, diabetic kidney disease; DR, diabetic retinopathy; CHD, coronary heart disease; PAD, peripheral arterial disease.



microalbuminuria, albuminuria, moderate impaired renal function, DKD, DPN, PAD, and inversely correlated with TC, lymphocyte count, eGFR, and ABI ( $P < 0.01$  or  $P < 0.05$ ; Table 2).

## Univariate and Multivariate Logistic Analysis of Factors Associated with DPN

Table 3 shows univariable and multivariable analyses of factors associated with DPN. On univariable analysis, age, duration of diabetes, GE index, HbA1c, NLR, SII, hypertension, dyslipidaemia, DKD, DR, CHD, stroke, and PAD were significantly associated with DPN ( $P < 0.01$  or  $P < 0.05$ ). SII remained independently significantly associated with an increased risk of DPN on multivariable analysis (OR = 1.001, 95% CI 1.000–1.001;  $P < 0.05$ ).

### Adjusted ORs and 95% CIs for DPN According to SII Quartiles

As presented in Table 4, there was a 35.7% increase in DPN risk per SD increase in SII (OR = 1.357, 95% CI 1.041–1.769) after adjusting for sex, age, BMI, duration of diabetes, smoking, drinking, hypertension, dyslipidaemia, HbA1c, NLR, DKD, DR, CHD, stroke, and PAD. A graded association with DPN and increase in SII quartiles was observed ( $P$  for trend  $< 0.01$ ). Participants in the highest quartile of SII had a significantly higher risk of DPN compared with those in Q1 (OR = 1.211, 95% CI 1.045–1.404). Moreover, there was a significant association of DPN in participants with the highest SII compared with those with lower SII levels (OR for Q4 versus Q1, 2, 3 = 1.517, 95% CI 1.069–2.154) after multivariate adjustment.

## Association of SII Quartiles with Increased Risk of DPN in Stratified Analysis

Stratified analyses were adopted in the different subgroups to further validate the above-mentioned results, shown in Table 5. After comprehensive adjustment of sex, age, BMI, duration of diabetes, smoking, drinking, hypertension, dyslipidaemia, HbA1c, NLR, DKD, DR, CHD, stroke, and PAD, except the strata variable, higher SII quartiles showed significant correlations with elevated risk of DPN prevalence only in men, people less than 65 years old, with BMI  $< 24 \text{ kg/m}^2$ , duration of diabetes  $> 5$  years, hypertension, dyslipidaemia, poor glycaemic control, and eGFR  $< 90 \text{ mL/min/1.73 m}^2$  ( $P$  for trend  $< 0.01$  or  $P$  for trend  $< 0.05$ ). Interactions of age, duration of diabetes, hypertension, dyslipidaemia, hypertension, dyslipidaemia and poor glycaemic control, and eGFR stratification with SII quartiles were significant ( $P$  for interaction  $< 0.01$  or  $P$  for interaction  $< 0.05$ ).

**Table 3** Univariate and Multivariate Logistic Analysis of Factors Associated with DPN

Variables	Univariate Analysis			Multivariate Analysis		
	B	OR (95%CI)	P-value	B	OR (95%CI)	P-value
Male sex	0.030	1.031 (0.836–1.270)	0.777	0.429	1.535 (1.166–2.022)	0.002
Age	0.072	1.075 (1.063–1.087)	0.000	0.063	1.066 (1.049–1.082)	0.000
BMI	−0.028	0.972 (0.944–1.001)	0.059			
Duration of diabetes	0.069	1.072 (1.054–1.091)	0.000			
Hypertension	0.586	1.796 (1.453–2.221)	0.000			
Dyslipidaemia	−0.231	0.794 (0.631–0.999)	0.049			
FBG	0.011	1.011 (0.991–1.031)	0.278			
PBG	0.016	1.106 (0.996–1.037)	0.122			
GE index	0.796	2.217 (1.812–2.713)	0.000			
HbA1c	0.073	1.075 (1.031–1.121)	0.001	0.206	1.229 (1.010–1.495)	0.040
NLR	0.134	1.143 (1.092–1.197)	0.000			
SII	0.001	1.001 (1.000–1.001)	0.000	0.001	1.001 (1.000–1.001)	0.014
DKD	0.758	2.133 (1.722–2.644)	0.000	0.377	1.458 (1.101–1.930)	0.009
DR	0.635	1.887 (1.381–2.577)	0.000	0.578	1.783 (1.222–2.601)	0.003
CHD	0.959	2.610 (1.804–3.776)	0.000	0.577	1.780 (1.117–2.838)	0.015
Stroke	0.602	1.825 (1.409–2.364)	0.000			
PAD	1.295	3.652 (2.549–5.233)	0.000			

**Note:** B is the standardized coefficient and measures the influence of each variables on DPN.

**Abbreviations:** OR, odds ratio; CI, confidence intervals; DPN, diabetic peripheral neuropathy; BMI, body mass index; FBG, fasting blood glucose; PBG, 2 hour postprandial blood glucose; GE index, glycemic exposure index; HbA1c, glycated hemoglobin A1c; NLR, neutrophil-to-lymphocyte; SII, systemic immune-inflammation index; DKD, diabetic kidney disease; DR, diabetic retinopathy; CHD, coronary heart disease; PAD, peripheral arterial disease.

**Table 4** Adjusted ORs and 95% CIs for DPN According to SII Quartiles

SII	DPN	
	OR (95% CI)	P
Per SD increase	1.357 (1.041–1.769)	0.024
Quartiles of SII		
Q1 (71.16–328.44)	1 (reference)	
Q2 (328.49–478.92)	1.039 (1.006–1.073)	0.019
Q3 (479.89–735.59)	1.076 (0.842–1.375)	0.557
Q4 (741.09–1713.95)	1.211 (1.045–1.404)	0.011
P for trend	0.008	
Q4 versus. Q1, Q2, Q3	1.517 (1.069–2.154)	0.020

**Notes:** Data are expressed as OR (95% CIs) +P value, unless stated otherwise. Adjusted OR is the odds ratio calculated using binary logistic regression analysis after adjustments for sex, age, BMI, duration of diabetes, smoking, drinking, hypertension, dyslipidaemia, HbA1c, NLR, DKD, DR, CHD, stroke, and PAD.

**Abbreviations:** OR, odds ratio; CI, confidence intervals; DPN, diabetic peripheral neuropathy; SII, systemic immune-inflammation index; SD, standard deviation; Q, quartile; BMI, body mass index; HbA1c, glycated hemoglobin A1c; NLR, neutrophil-to-lymphocyte; DKD, diabetic kidney disease; DR, diabetic retinopathy; CHD, coronary heart disease; PAD, peripheral arterial disease.

**Table 5** Stratified Analyses of SII and Risk of Prevalence of DPN by Sex, Age, BMI, Duration of Diabetes, Hypertension, Dyslipidaemia, Poor Glycaemic Control, and eGFR

Variable	SII Quartiles					
	Q1	Q2	Q3	Q4		
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	P <sub>trend</sub>	P <sub>interaction</sub>
	P-value	P-value	P-value	P-value		
Sex						0.067
Men (716)	1	0.800 (0.437–1.463)	1.658 (1.127–2.441)	1.065 (1.012–1.121)	0.003	
Women (744)	1	1.031 (0.989–1.074)	0.993 (0.951–1.037)	0.969 (0.930–1.010)	0.611	
Age, years						0.026
≥65 (523)	1	0.532 (0.276–1.023)	1.021 (0.973–1.072)	0.977 (0.937–1.018)	0.722	
<65 (937)	1	1.244 (0.733–2.112)	1.288 (0.932–1.780)	1.356 (1.114–1.650)	0.002	
BMI, kg/m <sup>2</sup>						0.122
≥24 (708)	1	0.736 (0.417–1.300)	0.963 (0.682–1.360)	1.088 (0.845–1.400)	0.287	
<24 (752)	1	1.119 (0.612–2.045)	1.269 (0.871–1.850)	1.297 (1.062–1.584)	0.014	
Duration of diabetes, years						0.024
>5 (813)	1	1.012 (0.598–1.714)	1.192 (0.868–1.638)	1.189 (0.984–1.437)	0.047	
≤5 (647)	1	0.708 (0.367–1.364)	0.878 (0.584–1.320)	1.161 (0.891–1.512)	0.323	
Hypertension						0.007
Yes (760)	1	0.846 (0.473–1.511)	1.071 (0.763–1.503)	1.229 (0.999–1.512)	0.039	
No (700)	1	0.844 (0.467–1.526)	1.117 (0.774–1.613)	1.154 (0.919–1.448)	0.164	
Dyslipidaemia						0.003
Yes (999)	1	0.884 (0.530–1.475)	1.087 (0.803–1.471)	1.280 (1.071–1.529)	0.005	
No (461)	1	0.739 (0.367–1.489)	0.952 (0.611–1.485)	1.012 (0.767–1.336)	0.934	
Poor glycaemic control						0.019
Yes (1246)	1	1.023 (0.658–1.592)	1.181 (0.900–1.548)	1.232 (1.051–1.445)	0.007	
No (214)	1	0.320 (0.092–1.113)	0.497 (0.239–1.032)	1.041 (0.633–1.712)	0.899	
eGFR, mL/min/1.73 m <sup>2</sup>						0.036
≥90 (951)	1	0.877 (0.530–1.451)	0.984 (0.724–1.336)	1.185 (0.971–1.448)	0.162	
<90 (509)	1	1.029 (0.499–2.121)	1.209 (0.783–1.866)	1.223 (0.964–1.551)	0.033	

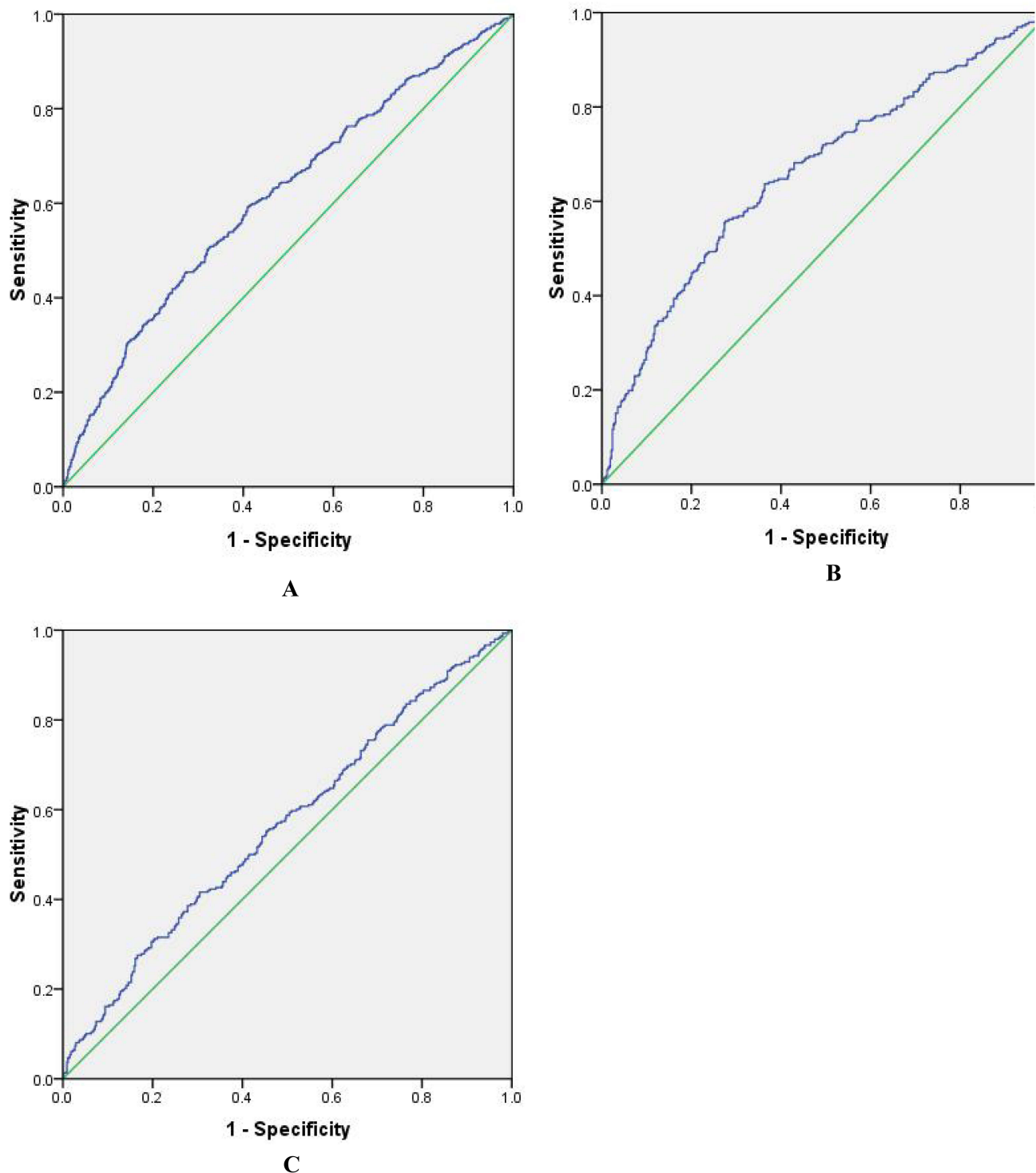
**Notes:** Data are expressed as OR (95% CI) +P value, unless stated otherwise. Model adjusted for sex, age, BMI, duration of diabetes, smoking, drinking, hypertension, dyslipidaemia, HbA1c, NLR, DKD, DR, CHD, stroke, and PAD. Stratification variables were excluded from the multivariable model.

**Abbreviations:** OR, odds ratio; CI, confidence intervals; P<sub>trend</sub>, P for trend; P<sub>interaction</sub>, P for interaction; Q, quartile; DPN, diabetic peripheral neuropathy; SII, systemic immune-inflammation index; BMI, body mass index; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin A1c; NLR, neutrophil-to-lymphocyte; DKD, diabetic kidney disease; DR, diabetic retinopathy; CHD, coronary heart disease; PAD, peripheral arterial disease.



## Predictive Value of SII in Screening for the Presence of DPN in T2DM Patients

To further explore the predictive value of SII for DPN, the ROC curve analysis was performed. As shown in Figure 1, the best cut-off value for SII to predict the presence of DPN was 617.67 (sensitivity: 45.3%; specificity: 73%; and AUC:



**Figure 1** (A) ROC analysis of SII to indicate DPN for all subjects. AUC = 0.614; 95% CI: 0.584–0.641;  $P < 0.05$ ; identified SII cutoff value = 617.67; Youden index = 0.183; sensitivity: 45.3%; specificity: 73%. (B) ROC analysis of SII to indicate DPN for male subjects. AUC = 0.662; 95% CI: 0.621–0.703;  $P < 0.05$ ; identified SII cutoff value = 557.25; Youden index = 0.282; sensitivity: 55.8%; specificity: 72.4%. (C) ROC analysis of SII to indicate DPN for female subjects. AUC = 0.564; 95% CI: 0.522–0.606;  $P < 0.05$ ; identified SII cutoff value = 617.67; Youden index = 0.111; sensitivity: 41.6%; specificity: 69.5%.

**Abbreviations:** ROC, receiver operating characteristic; SII, systemic immune-inflammation index; DPN, diabetic peripheral neuropathy; AUC, area under the curve.

0.614; **Figure 1A**), 557.25 (sensitivity: 55.8%; specificity: 72.4%; and AUC: 0.662; **Figure 1B**), and 617.67 (sensitivity: 41.6%; specificity: 69.5%; and AUC: 0.564; **Figure 1C**) in all diabetic subjects, male diabetic subjects, and female diabetic subjects, respectively.

## Discussion

To our knowledge, this is the first study to explore the potential association of SII with DPN in Chinese patients with T2DM. We revealed that T2DM patients with DPN had significantly elevated SII levels, and the risk of DPN progressively increased across SII quartiles. Additionally, stratified analysis showed that subjects with higher SII quartiles had an increased risk of DPN than those with lower quartiles, especially in men, people less than 65 years old, with BMI < 24 kg/m<sup>2</sup>, duration of diabetes > 5 years, hypertension, dyslipidaemia, poor glycaemic control, and eGFR < 90 mL/min/1.73 m<sup>2</sup>. Last, the ROC curve analysis revealed that the optimal cut-off point of SII for predicting DPN was 617.67 in patients with T2DM, with a sensitivity of 45.3% and a specificity of 73%. These findings suggest that high SII may be associated with the presence of DPN in Chinese patients with T2DM, and may be used as an additional indicator of risk of DPN.

There is substantial evidence showing that low-grade inflammation are also contributing factors in the development and progression of T2DM and its microvascular complications, such as DPN.<sup>5,6,18,21,26</sup> SII is a relatively novel inflammation biomarker based on peripheral lymphocyte, neutrophil, and platelet counts, which largely reflects three pathways of inflammatory response, thrombus formation and adaptive immune response in the host.<sup>41–43</sup> Studies have demonstrated that SII can predict the prognosis and clinical outcomes of certain inflammatory diseases, various atherosclerotic cardio-cerebrovascular diseases (eg myocardial infarction, heart failure, stroke, peripheral arterial disease), and other diseases,<sup>16,42–45</sup> and may be associated with a metabolic disorder and its components, such as diabetes mellitus, metabolic syndrome, dyslipidemia, central obesity, DR, DKD, diabetic foot infections<sup>16–18,37</sup> that are closely associated with low-grade inflammation,<sup>22–24</sup> suggesting that SII may be associated with the presence of DPN, and high SII may be an early signal for being at risk for DPN. In the present study, we found that patients in the highest quartile of SII levels had significantly higher prevalence of DPN, percentages of participants with VPT ≥ 25V, and levels of VPT, a widely recommended indicator of the presence and severity of confirmed clinical neuropathy,<sup>26</sup> than those in the lowest quartile. Likewise, increased levels of SII were observed in patients with DPN. Moreover, SII was found to be positively associated with VPT levels and prevalence of DPN, even after adjusting for sex, age, BMI, and duration of diabetes. These results together demonstrated that elevated SII seem to be closely associated with DPN. In addition, we observed that SII was independently associated with an increased risk of DPN even after multivariable adjustment, and the risk of DPN was progressively increased across SII quartiles. Of note, participants in the highest quartile of SII had a 51.7% increased risk of developing DPN compared to those in the lower quartiles. These results indicate that there may be a potential mechanistic association between elevated levels of SII and the prevalence of DPN. More importantly, SII could predict the presence of DPN, especially in the male patients, suggesting that elevated SII may be an early signal for being at risk for DPN, and SII could be considered to be a sensitive parameter in predicting the DPN. SII can be considered as a modified powerful combination of NLR and PLR, and has been proposed to be more valuable than either NLR or PLR alone in predicting inflammatory status and prognosis in various clinical settings.<sup>12,46,47</sup> Our findings are consistent with previous literature showing that inflammatory biomarkers, such as NLR and PLR were independently associated with DPN,<sup>7–9,48,49</sup> further suggesting that SII, another marker of inflammation, could be linked to an increased risk of the presence and severity of DPN, and SII might be a novel and reliable predictive marker of DPN in Chinese patients with T2DM.

A particularly novel finding in this study is the sex disparities in the relationship between SII and DPN, namely, higher SII quartiles were significantly associated with the risk of prevalence of DPN in men but not in women in stratified analyses, which further was supported by the results of the multivariable logistic regression analysis showing that male sex was independently significantly associated with the risk of prevalence of DPN. Such a sex discrepancy might be attributed to several factors. First, compared with female diabetic patients, male diabetic patients had significantly poorer glycaemic control (higher levels of FBG, PBG, and HbA1c), greater prevalence of overweight, dyslipidaemia and macroalbuminuria, and higher levels of inflammation (higher NLR and lower lymphocyte), all of

which have been reported to be related to DPN.<sup>26,50,51</sup> Second, men's lifestyle may be more hazardous than women's is. Specifically, compared with women, men might have more smokers and drinkers, more stressful jobs, less seeking of health consultation and services, and lower compliance with treatment,<sup>51,52</sup> which were risk factors for DPN.<sup>53–55</sup> Third, testosterone deficiency may be another plausible explanation for the sex disparity observed in the association of SII with DPN. Studies have demonstrated that 7% of men would develop testosterone deficiency after 50 years old,<sup>56</sup> and testosterone deficiency is more common in men with diabetes than those without,<sup>57</sup> while male diabetic patients in our study had a mean age of over 58, resulting in an increased risk of testosterone deficiency. Moreover, epidemiological surveys have shown that circulating total testosterone level is inversely related to obesity, and the prevalence of testosterone deficiency is up to 79% in obese individuals,<sup>56</sup> while our study population had an overweight/obesity prevalence of 51.54%. Therefore, many male diabetic patients in the present study are at risk for testosterone deficiency. It is reported that testosterone deficiency may lead to a more pronounced deficit of neurosteroids and further result in loss of function of neurosteroids's protection and regeneration of peripheral nerves affected by different forms of pathologic alterations, ultimately leading to the development and development of DPN.<sup>52,57</sup> Studies found that abnormal sex hormone levels may cause alterations in inflammatory state and immune response,<sup>16</sup> and increased risk of testosterone deficiency is associated with the SII in men.<sup>16,56</sup> These results together demonstrated that there might be a positive correlation between SII and testosterone deficiency and DPN, and testosterone deficiency might at least partially mediate the potential relationship between SII and DPN. Nevertheless, the current research cannot fully explain this phenomenon, more evidence is needed to illuminate the actual mechanisms of gender difference in the association of SII with DPN risk.

Compelling data indicate that advanced age and overweight/obesity play important roles in the development and progression of DPN.<sup>7,34</sup> The present study also revealed that T2DM patients with DPN had significantly older age than those without, and age was independently significantly associated with the risk of prevalence of DPN, further supporting the role of advanced age in DPN. However, the stratified analysis demonstrated a significant correlation of higher SII quartiles with an increased risk for DPN prevalence in subjects aged < 65 years old but not those aged ≥ 65 years old, which be due to several factors. First, a significant difference in sample size of two subgroups might lead to imprecise estimations. Second, there is an interaction of age with SII on DPN in T2DM patients, SII might impact the effect of the prevalence of DPN greater than the effect of age. Another surprising finding in our study is that a significantly association between SII and the risk of prevalence of DPN was only observed in non-overweight/obesity subjects in stratified analyses, which was consistent with previous literature from Yan et al and Tayama et al showing that visceral fat area and preperitoneal fat levels were positively correlated with nerve conduction velocity and amplitude potential,<sup>34,58</sup> suggesting that there might be a complex mechanism correlation between overweight/obesity or visceral fat and DPN. In the present study, insignificant decrease in BMI was observed in T2DM patients with DPN, and SII was negatively associated with BMI, which were inconsistent with previous studies showing that higher baseline levels of BMI was associated with DPN<sup>59</sup> and SII had a significant positive linear correlation with increased BMI.<sup>60</sup> These seemingly contradictory results might be interpreted as unintentional weight loss in individuals with longstanding inadequate diabetes control as well as multiple systemic insults or comorbidities.<sup>61</sup> In addition, although diabetic subjects with overweight/obesity are often accompanied by dyslipidemia, multiple macrovascular complications, such as CHD, hypertension, macrovascular arteriosclerosis, and microvascular complications than those without, they may become more concerned about their condition and adopt various measures, such as controlling blood glucose, blood pressure, and blood lipids, and making dietary and lifestyle changes that are beneficial for weight loss and improved neurological function,<sup>34</sup> which may be one of the causes for the difference in the relationship between SII and DPN in diabetic subjects with and without overweight/obesity, but further studies need to be designed for confirmation.

Emerging studies have suggested that longer diabetes duration, poor glycaemic control, hypertension, dyslipidaemia, and impaired renal function are important risk factors for DPN.<sup>55,62</sup> The present study also showed that T2DM subjects with DPN had significantly longer diabetes duration, higher GE index, HbA1c, proportions of poor glycaemic control, SBP, TG, urinary ACR, prevalence of hypertension, dyslipidaemia, impaired renal function, microalbuminuria, macroalbuminuria, albuminuria, and lower eGFR compared with those without. Moreover, the logistic regression analysis demonstrated that diabetes duration, GE index, hypertension, dyslipidaemia, especially HbA1c and DKD were

significantly associated with the risk of prevalence of DPN. These results further suggested that longer diabetes duration, poor glycaemic control, hypertension, dyslipidaemia, and DKD might be correlated with the prevalence of DPN. In addition, the stratified analysis demonstrated significant correlations of higher SII quartiles with an increased risk for DPN only in subjects with diabetes duration >5 years, hypertension, dyslipidaemia, poor glycaemic control, and eGFR <90 mL/min/1.73 m<sup>2</sup>. Besides, we observed interactions of diabetes duration, poor glycaemic control, hypertension, dyslipidaemia, and eGFR with SII on DPN in T2DM subjects. Moreover, the subjects in the higher SII quartiles exhibited higher FBG, PBG, GE index, HbA1c, proportions of HbA1c ≥ 9%, urinary ACR, microalbuminuria, macroalbuminuria, albuminuria, and prevalence of hypertension, moderate impaired renal function, and DKD, and lower eGFR, and partial correlation analysis controlling for sex, age, BMI, and duration of diabetes demonstrated that SII was positively associated with FBG, PBG, GE index, HbA1c, prevalence of hypertension, microalbuminuria, albuminuria, moderate impaired renal function, DKD, and inversely correlated with eGFR. These results together suggested that interplays between elevated SII and longer diabetes duration, poor glycaemic control, hypertension, dyslipidaemia, and DKD synergistically contribute to the development and progression of DPN. Thus, it is of great importance to monitor SII for early screening for DPN among specific populations in the inflammatory states to further prevent and delay the development and progression of DPN by incorporating changes in lifestyle and necessary medical treatments. We believe that considering SII as part of the management strategy is beneficial for DPN care.

There are some potential limitations to interpreting our results that need to be addressed. First, the retrospective cross-sectional nature of this study rendered our observations susceptible to inherent bias and causality could not be established, allowing for only an interpretation of an association between SII and DPN. Therefore, prospective studies with larger sample size are still required to clarify the causality. Second, the present regression models did not contain the jobs, compliance with treatment, dietary habits, lifestyle, consumption of various medicines, such as hypoglycemic agents, antihyperlipidemic drugs, anti-hypertension drugs, antiplatelet drugs, and dietary habits and lifestyle, and we did not consider the effects of above mentioned factors on inflammation, coagulation parameters, and metabolism levels. Third, participants in our study were mainly middle-age or elderly, and were inpatients who generally had poorer metabolic control and a more serious illness than those in outpatient, which may limit the generalization of our findings to other populations. Fourth, validated but not routinely used inflammatory markers, such as C-reactive protein, tumor necrosis factor- $\alpha$ , interleukin-6, and circulating testosterone were not used to reflect the inflammatory status and sex hormones levels because these markers are not routinely determined for all T2DM patients in our hospital. Despite these limitations, our analyses also have some noteworthy strengths. A key finding was that our study was the first study to reveal the association of SII with DPN in Chinese patients with T2DM and its different subgroups. Second, the study followed a relatively large sample of middle-aged and elderly people, a standardized method of data collection and measurement and evaluation of various cardiovascular metabolic diseases at a single center, and was controlled for most potential confounders, which can raise the reliability of our findings.

## Conclusion

SII levels were significantly higher in T2DM patients with DPN than in the subjects with non-DPN, and elevated levels of SII were independently associated with an increased risk of DPN in Chinese patients with T2DM, especially in men, people less than 65 years old, with BMI < 24 kg/m<sup>2</sup>, duration of diabetes >5 years, hypertension, dyslipidaemia, poor glycaemic control, and eGFR < 90 mL/min/1.73 m<sup>2</sup>. Moreover, SII could predict the presence of DPN. These data suggest that SII, potentially reflecting the balance of the inflammatory, immune, and thrombotic pathways, might be a novel and useful biomarker of DPN, and could further help identify T2DM patients at high-risk of developing DPN. We believe that by targeting these high-risk patients and implementing early intensive multiple metabolic and vascular risk factors control, we may help reduce their future risk of DPN and its associated adverse clinical outcomes, further providing an important guiding significance for early screening and management of DPN in Chinese patients with T2DM.

## Data Sharing Statement

The dataset used and/or analyzed during the present study are available from the corresponding author on reasonable request.

## Ethics Approval and Consent to Participate

Study procedures were performed in accordance with the Declaration of Helsinki ethical principles for medical research involving human subjects. The study was approved by the Ethics Committee of the Affiliated Hospital of Southwest Medical University in China, and informed consent was obtained from all patients before data collection.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

Jia Li, Xing Zhang and Yi Zhang are co-first authors for this study. All authors declare no conflicts of interest in this work.

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