Association between systemic immune-inflammation index and risk of lower extremity deep venous thrombosis in hospitalized patients: a 10-year retrospective analysis

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Background: The systemic immune-inflammation index (SII), as a novel inflammatory biomarker, has recently attracted attention in cardiovascular disease research. However, the relationship between SII and risk of lower extremity deep venous thrombosis (LEDVT) remains unclear to date. Thus, this study aimed to explore the association in a large sample over a 10-year period (2012−2022).

Methods: All hospitalized patients undergoing lower extremity compression ultrasonography (CUS) examination were consecutively screened by searching our hospital information system database. The receiver operating characteristic (ROC) curve analysis was used to identify the optimal cut-off value for high and low SII group. Multivariate logistic regression analyses were performed to investigate the relationship between SII and LEDVT risk. Propensity score matching (PSM), subgroup and sensitivity analyses were also conducted. Moreover, restricted cubic spline (RCS) regression and two-piecewise linear regression models were used to assess the dose-response relationship between natural log transformed SII [ln(SII)] and risk of LEDVT.

Results: A total of 16,725 consecutive hospitalized patients were included, and 1,962 LEDVT events occurred. After adjusting for confounding factors, patients in the high SII group ($\geq 574.2 \times 10^9$/L) showed a 1.740-fold risk of LEDVT (95% CI: 1.546−1.959, $P < 0.001$), and elevated ln(SII) was associated with a 36.1% increased risk of LEDVT (95% CI: 1.278−1.449, $P < 0.001$). PSM, subgroup and sensitivity analyses confirmed the robustness of the association. A non-linear relationship was observed ($P_{non-linear} < 0.001$), with a threshold value of 5.6×10^9/L for all LEDVT events. Above the threshold, each unit increase in ln(SII) had a 1.369-fold higher risk of LEDVT (95% CI: 1.271−1.475, $P < 0.001$). The association also existed in both distal and proximal LEDVT.

Conclusion: Elevated SII is significantly associated with an increased risk of LEDVT in hospitalized patients. Additionally, the association is non-linear and exhibit a threshold effect.

1. Introduction

Lower extremity deep venous thrombosis (LEDVT), which refers to thrombus formation in the deep venous system of the legs, is a global medical problem that affects approximately 1 per 1,000 individuals annually (1). As is well known, LEDVT is a major cause of post-thrombotic syndrome (PTS), fatal pulmonary embolism (PE) and even sudden death in hospitalized patients (2, 3). Until now, early diagnosis and timely treatment remain an effective strategy to reduce the risk of these complications (4, 5). However, the accurate diagnosis of LEDVT is challenging due to its unspecific symptoms and signs, potentially leading to misdiagnosis and incorrect treatment decisions (5). On the other hand, thrombotic events cannot be completely prevented even with effective antithrombotic drugs, implying that other underlying mechanisms may contribute to the therapeutic gap (6).

Recently, immune inflammatory system has been found to play a key role in DVT initiation and resolution (7–9). The systemic immune-inflammation index (SII), as an integrated indicator of local immune response and systemic inflammation, was significantly associated with cerebral venous thrombosis (10), portal venous thrombosis (11), PE (12), and other cardiovascular diseases (e.g., ischemic stroke, myocardial infarction, peripheral arterial disease) (13). Although SII was also considered to be a promising potential marker for DVT (14), existing evidences on the association between SII and LEDVT risk were particularly limited and conflicting (15–18). In these studies, most of the study populations were orthopedic patients [e.g., total knee arthroplasty (TKA), hip fracture, tibial plateau fracture], thus leaving a relative lack of evidence for generalization to other hospitalized patients (15, 16, 18). Furthermore, these studies were limited by their relatively small sample size, ranging from 273 to 1,179 patients (15–18). More importantly, a recent meta-analysis has systematically assessed the quality of current studies, and the certainty of the evidence was rated as very low using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system (13). As a result, it is difficult to reach a consensus on the relationship between SII and LEDVT risk, thereby limiting its use in clinical practice (13, 14).

In the present study, we aimed to explore the association between SII and risk of LEDVT in a large sample, using our hospital information system (HIS) database over a 10-year period. To our knowledge, no previous study has evaluated the dose-response relationship between SII and LEDVT risk, in other words, whether this association is threshold or linear remains unclear. Therefore, we further examined the potential non-linear relationship for the association.

2. Method

2.1. Patients

This single-center, retrospective observational study was performed at a tertiary teaching hospital in China. The study protocol was reviewed and approved by the Institutional Ethics Committee of People's Hospital of Deyang City (No. 2021-04-019-K01), and the need for informed consent was waived owing to the retrospective nature of the study and anonymous data collection. In this study, all hospitalized patients between January 1, 2012 and July 31, 2022 were screened by searching the HIS database ($n = 671,456$), as described in our previous work (19). At the initial screening, 20,730 patients with lower extremity compression ultrasonography (CUS) were considered. After that, patients were excluded if they met any of the following criteria: (1) no neutrophil, platelet or lymphocyte data; (2) CUS examination earlier than routine blood test; (3) DVT or PE diagnosed on admission; (4) chronic DVT; (5) upper extremity DVT; (6) arterial thrombosis; (7) superficial venous thrombosis; (8) incomplete medical record; (9) age younger than 18 years. Finally, a total of 16,725 consecutive hospitalized patients were included in this study (Figure 1).
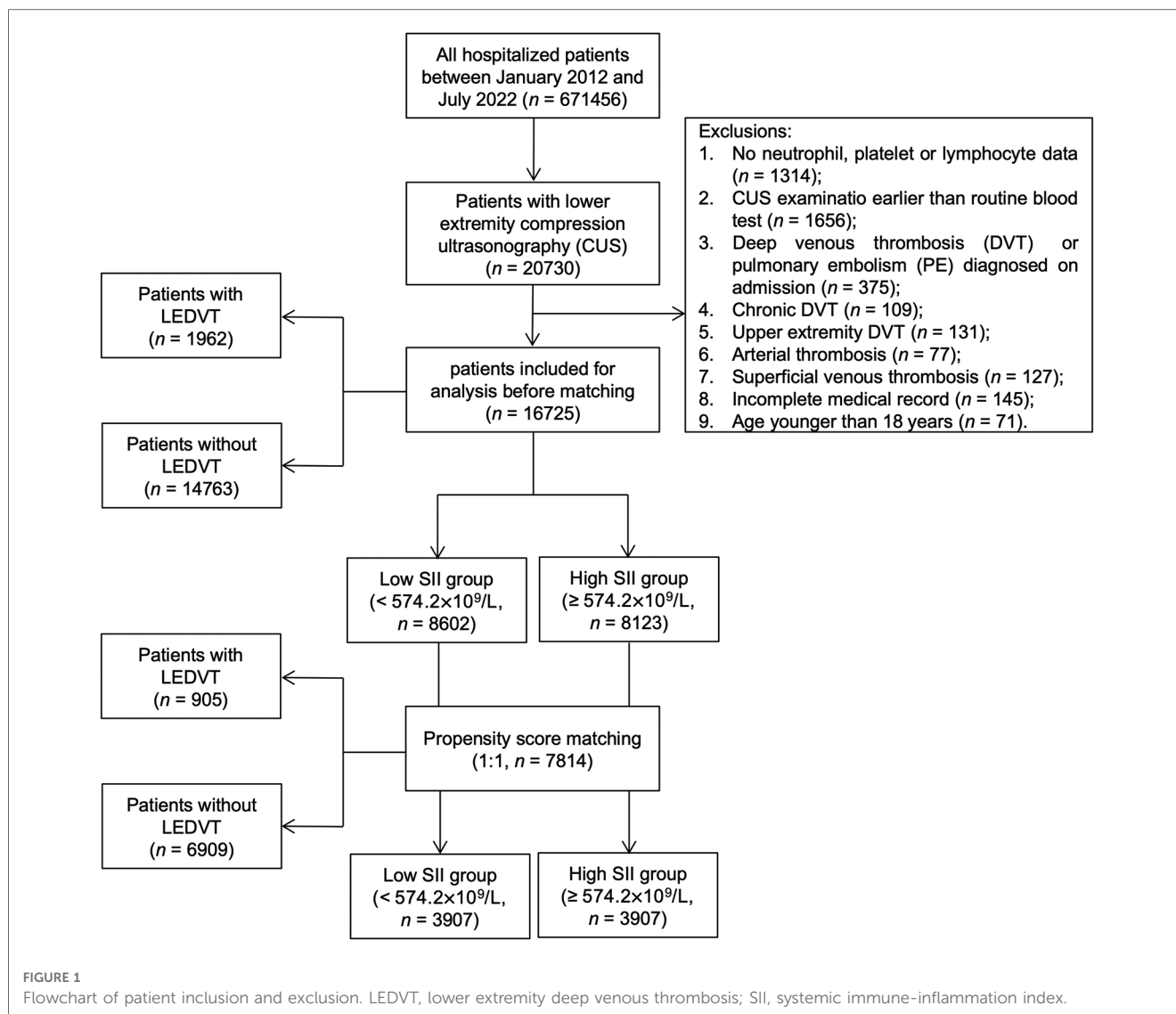
2.2. Data collection

The following patient characteristics were extracted from the electronic medical records: age, sex, body mass index (BMI), smoking and drinking history. According to the Working Group on Obesity in China, obesity was defined as BMI ≥ 28.0 kg/m^2 (20). Smoking and drinking status were categorized into never, former or current. In accordance with a previous study (21), the International Classification of Diseases-10 (ICD-10) of discharge diagnoses were used to identify comorbidities: hypertension (codes: I10-I13, I15), diabetes mellitus (codes: E11-E14), chronic obstructive pulmonary disease (COPD, codes: J42-J44), atrial fibrillation (code: I48), heart failure (code: I50), stroke (codes: I60-I64), hepatic insufficiency (codes: K72.0-K72.1, K72.9), renal insufficiency (codes: N17-N19) and cancer (codes: C00-C97, D00-D09).

At our institute, blood samples were routinely drawn on the day of admission or the second day after admission. After blood drawing, routine blood tests were performed immediately using automatic hematology analyzers (Sysmex XN2000, Kobe, Japan). In this study, several hematological indicators closely related to DVT were collected, including white blood cell (WBC, reference range: 3.5–9.5×10^9/L) (22), red blood cell (RBC, reference range: 3.8–5.1×10^9/L) (23), and hemoglobin (reference range: 115.0–150.0 g/L) (24).

The SII was calculated as described in our previous study (25), using the following formula: SII = neutrophil count (reference range: 1.8–6.3×10^9/L) × platelet count (reference range: 101.0–320.0×10^9/L)/lymphocyte count (reference range: 1.1–3.2×10^9/L). The unit of SII was expressed as 10^9/L.

2.3. Study outcomes

As we described previously (26), lower extremity CUS was performed by an experienced radiologist, and the results were reviewed by another senior radiologist, using a color-coded ultrasound system with a 3–9 MHz linear-array transducer (iU 22, Philips Healthcare, Netherlands). The scanning was routinely

FIGURE 1
Flowchart of patient inclusion and exclusion. LEDVT, lower extremity deep venous thrombosis; SII, systemic immune-inflammation index.

performed at iliac vein, common femoral vein, superficial femoral vein, deep femoral vein, popliteal vein, anterior tibial vein, posterior tibial vein, fibular vein and calf muscle vein. DVT was diagnosed according to Robinov group's criteria (27). The primary outcome was the occurrence of all LEDVT events during the hospitalization, which was double confirmed by ultrasound reports and ICD-10 diagnoses of LEDVT (codes: I80.1, I80.2, I80.3, I80.8, I80.9, I82.8 and I82.9). Based on the thrombus location recorded in the ultrasound reports, proximal LEDVT was defined as thrombus occurring in the popliteal vein and/or above, whereas below the popliteal vein as distal LEDVT. Patients with both proximal and distal thrombus were regarded as proximal LEDVT (28). The secondary outcomes were the occurrence of distal and proximal LEDVT.

2.4. Statistical analyses

Prior to analysis, missing values were detected in all variables, with 30.45% missing in obesity ($n = 5,093$), 4.25% missing in smoking status ($n = 710$), and 25.72% missing in drinking status ($n = 2,629$). Given the large number of missing values, missing indicator method was used to handle these missing data, and coded as a separate category (unknown) (29).

Normality of continuous variables (SII, age, WBC, RBC, hemoglobin) were first checked by the Shapiro-Wilk test, showing that none of these variables conformed to the normal distribution. Continuous variables were described as median [interquartile range (IQR)], whereas the other categorical variables were reported as numbers (percentages). The receiver operating characteristic (ROC) curve analysis was used to determine the optimal cut-off value for high and low SII group. Differences between the two groups were compared using Wilcoxon rank-sum test or Pearson's chi-square test. Furthermore, SII data was natural log transformed [ln(SII)], and the differences between patients with and without LEDVT were visualized by box and whisker plots (Tukey method).

Before multivariate analyses, the linearity assumption for continuous variables was checked by the Box-Tidwell test (30), it was found to be violated for age, WBC, RBC and hemoglobin.
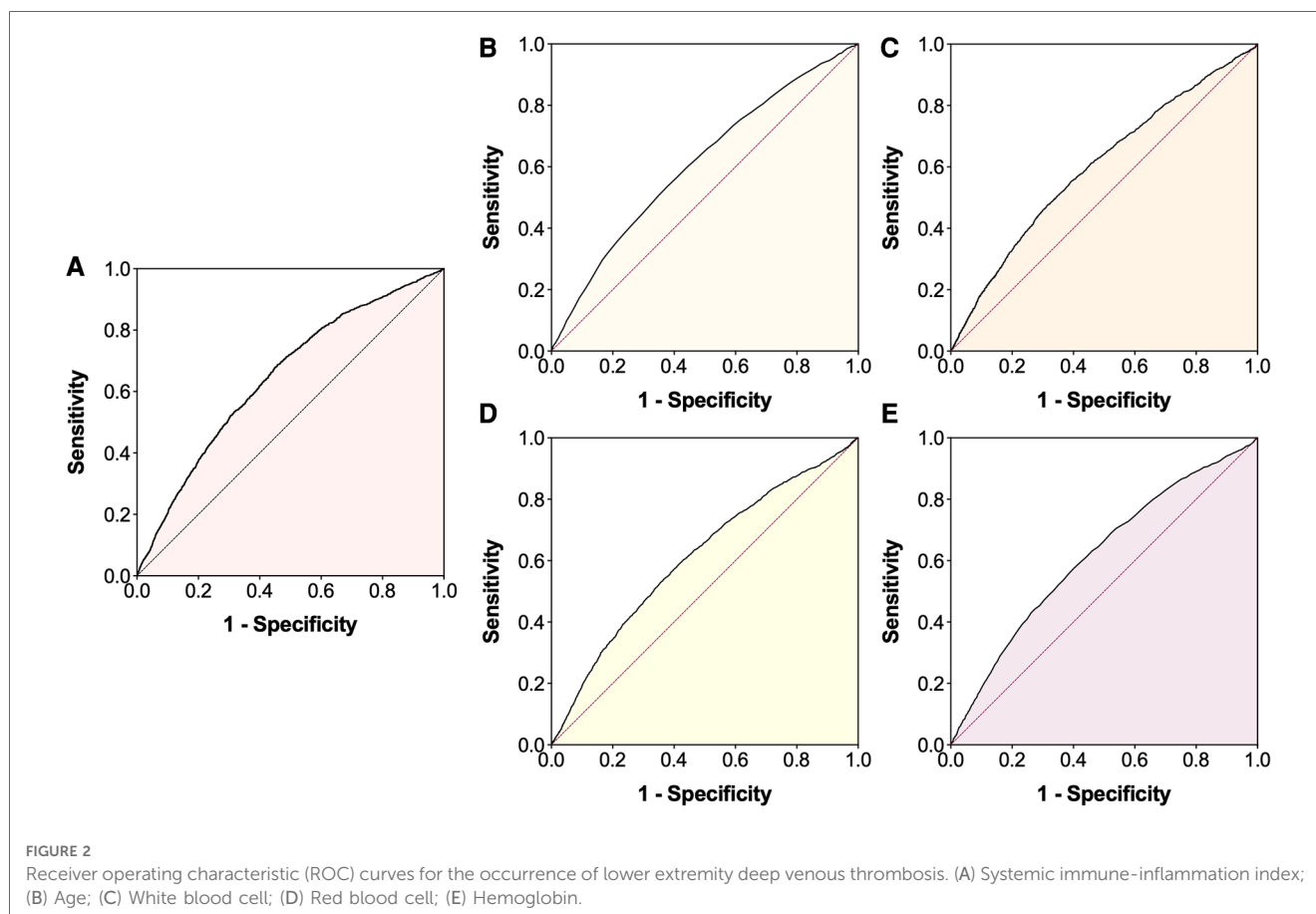
For this reason, these continuous variables were converted to categorical variables based on the cut-off values by ROC curves (**Supplementary Table S1**, **Figures 2B–E**). Multicollinearity was assessed by the variance inflation factor (VIF), with a VIF ≥ 5 indicating multicollinearity (31). No significant multicollinearity was found between variables (**Supplementary Table S2**). Subsequently, multivariate logistic regression analyses were performed to evaluate the association between SII and LEDVT risk in different models. Model 1: SII data was entered as a categorical variable (high vs. low SII). Model 2: SII data was entered as a continuous variable [per ln(SII) increase]. Confounders variables that influences both the independent variable (**Table 1**) and dependent variable (**Supplementary Table S3**) were included into the multivariate logistic analyses, including age, sex, obesity, diabetes mellitus, COPD, atrial fibrillation, heart failure, stroke, hepatic insufficiency, renal insufficiency, WBC, RBC, and hemoglobin. Adjusted odds ratios (*OR*) with 95% confidence intervals (*CI*) were calculated.

To further minimize the effect of potential confounders, a 1:1 propensity score matching (PSM) was performed between patients with high and low SII. Propensity scores for each patient were calculated using a multivariate logistic regression with the following variables: age, sex, obesity, smoking, drinking, hypertension, diabetes mellitus, COPD, atrial fibrillation, heart failure, stroke, hepatic insufficiency, renal insufficiency, cancer, WBC, RBC and hemoglobin. The greedy,

nearest-neighbor method without replacement was used for matching, with a caliper width of 0.20 standard deviation (SD) of the logit of the propensity score (32). Standardized mean difference (SMD) was used to evaluate the balance of baseline characteristics before and after matching, with a SMD < 0.1 indicating adequate balance (33). As mentioned above, multivariate logistic regression analyses were also conducted in these matched samples.

Moreover, we examined the association in subgroups stratified by age, sex, obesity, smoking, drinking, diabetes mellitus, COPD, atrial fibrillation, heart failure, stroke, hepatic insufficiency, renal insufficiency, cancer, WBC, RBC and hemoglobin, because these factors were found to be associated with LEDVT (**Supplementary Table S3**). Considering the sample size of each subgroup, subgroup analyses were limited to the primary outcome only before matching, and adjusted for confounders variables except for the one defining the subgroup. To determine the effect of missing data, sensitivity analyses based on complete cases were also performed.

Finally, we applied restricted cubic spline (RCS) regressions with 5 knots to explore the dose-response relationship between ln(SII) and risk of LEDVT. Nonlinearity was tested with a likelihood ratio test comparing the spline model to a linear model. If the non-linear association was observed, a two-piecewise linear regression model was used to estimate the threshold effect of ln(SII) on LEDVT risk.

FIGURE 2
Receiver operating characteristic (ROC) curves for the occurrence of lower extremity deep venous thrombosis. (A) Systemic immune-inflammation index; (B) Age; (C) White blood cell; (D) Red blood cell; (E) Hemoglobin.

All reported *P* values are two-sided, and *P* < 0.05 was considered statistically significant. All analyses were conducted using JMP Pro software (version 16.0.0; SAS Institute Inc., Cary, NC, USA) and GraphPad Prism (version 9.1.1; GraphPad Software, San Diego, California, USA).

3. Results

3.1. Baseline characteristics

The baseline characteristics are presented in **Table 1**. Overall, the median age was 66.0 years, 52.3% were men, 7.1% were obesity, 22.5% were current smoking and 27.5% were current drinking. The most common comorbidities were diabetes mellitus (38.9%) and hypertension (38.4%). The median SII and ln(SII) values were 555.0 (318.6, 1,098.4) × 10^9/L and 6.3 (5.8, 7.0) × 10^9/L, respectively. Using the ROC curve analysis (**Figure 2A**), the optimal cut-off value was 574.2 × 10^9/L for SII [sensitivity: 68.8%, specificity: 54.1%, area under curve (AUC): 0.647, 95% *CI*: 0.634–0.660]. The patients were then divided into low SII group (<574.2 × 10^9/L, *n* = 8,602, 51.4%) and high SII group (≥574.2 × 10^9/L, *n* = 8,123, 48.6%). Significant differences in most variables were observed between the two groups, except for smoking, drinking and cancer (**Table 1**).

3.2. LEDVT events

Of these patients, 1,962 (11.7%) were diagnosed with LEDVT and confirmed by CUS examinations. According to the thrombus location, 1,440 (73.4%) were distal LEDVT and 522 (26.6%) were proximal LEDVT. As shown in **Figure 3A**, patients with LEDVT had significant higher ln(SII) levels than those without (6.8 [6.2, 7.5] vs. 6.3 [5.7, 6.9] × 10^9/L, *P* < 0.001). This trend was also seen in distal and proximal LEDVT (*P* < 0.001).

3.3. Association between SII and LEDVT before matching

After adjusting for confounding factors (**Table 2**, Model 1), patients in the high SII group showed a 1.740-fold risk of LEDVT (95% *CI*: 1.546–1.959, *P* < 0.001). When SII was entered into the multivariate analysis as a continuous variable (Model 2), elevated ln(SII) still remained a significant risk factor (OR = 1.361, 95% *CI*: 1.278–1.449, *P* < 0.001). Also, this positive relationship existed in both distal and proximal LEDVT (**Figure 4A**). At the same time, age, sex, obesity, diabetes mellitus, atrial fibrillation, heart failure, stroke, hepatic insufficiency, WBC, RBC and hemoglobin were independently associated with a higher risk of LEDVT (**Table 2**, all *P* < 0.05).

TABLE 1 Baseline characteristics before and after propensity score matching.

Variables	All patients (*n* = 16,725)	Before matching (*n* = 16,725)				After matching (*n* = 7,814)			
		Low SII group (*n* = 8,602)	High SII group (*n* = 8,123)	SMD	*P* value	Low SII group (*n* = 3,907)	High SII group (*n* = 3,907)	SMD	*P* value
Age, year (median [IQR])	66.0 (55.0, 75.0)	65.0 (55.0, 73.0)	68.0 (56.0, 77.0)	0.118	<0.001	67.0 (57.0, 75.0)	67.0 (56.0, 76.0)	0.036	0.563
Men, *n* (%)	8,754 (52.3)	4,432 (51.5)	4,322 (53.2)	0.037	0.029	2,105 (53.9)	2,037 (52.1)	0.039	0.123
Obesity, *n* (%)	1,186 (7.1)	649 (7.5)	537 (6.6)	0.245	<0.001	280 (7.2)	279 (7.1)	0.033	0.341
Current smoking, *n* (%)	3,763 (22.5)	1,932 (22.5)	1,831 (22.5)	0.006	0.923	921 (23.6)	884 (22.6)	0.018	0.124
Current drinking, *n* (%)	4,597 (27.5)	2,398 (27.9)	2,199 (27.1)	0.012	0.473	1,105 (28.3)	1,074 (27.5)	0.005	0.681
Comorbidities, *n* (%)									
Hypertension	6,416 (38.4)	3,149 (36.6)	3,267 (40.2)	0.084	<0.001	1,671 (42.8)	1,603 (41.0)	0.039	0.119
Diabetes mellitus	6,510 (38.9)	3,777 (43.9)	2,733 (33.6)	0.239	<0.001	1,490 (38.1)	1,511 (38.7)	0.013	0.625
COPD	2,143 (12.8)	857 (10.0)	1,286 (15.8)	0.293	<0.001	535 (13.7)	518 (13.3)	0.021	0.573
Atrial fibrillation	806 (4.8)	336 (3.9)	470 (5.8)	0.228	<0.001	208 (5.3)	189 (4.8)	0.056	0.328
Heart failure	417 (2.5)	178 (2.1)	239 (2.9)	0.199	<0.001	115 (2.9)	97 (2.5)	0.097	0.21
Stroke	2,381 (14.2)	1,042 (12.1)	1,339 (16.5)	0.198	<0.001	656 (16.8)	638 (16.3)	0.018	0.584
Hepatic insufficiency	592 (3.5)	87 (6.86)	383 (3.75)	0.114	<0.001	127 (3.3)	137 (3.5)	0.043	0.531
Renal insufficiency	1,186 (7.1)	425 (4.9)	761 (9.4)	0.379	<0.001	307 (7.9)	299 (7.7)	0.016	0.735
Cancer	2,217 (13.3)	1,175 (13.7)	1,042 (12.8)	0.04	0.113	578 (14.8)	561 (14.4)	0.019	0.586
Laboratory data, median (IQR)									
WBC, 10^9/L	6.61 (5.20, 8.72)	5.56 (4.58, 6.73)	8.35 (6.55, 10.87)	1.013	<0.001	6.58 (5.51, 7.73)	6.63 (5.54, 7.84)	0.003	0.153
RBC, 10^9/L	4.20 (3.71, 4.63)	4.29 (3.86, 4.69)	4.08 (3.55, 4.56)	0.254	<0.001	4.23 (3.74, 4.65)	4.19 (3.69, 4.63)	0.014	0.359
Hemoglobin, g/L	127.0 (111.0, 140.0)	130.0 (117.0, 142.0)	122.0 (105.0, 136.0)	0.367	<0.001	126.0 (111.0, 139.0)	126.0 (110.0, 139.0)	0.022	0.614

SII, systemic immune-inflammation index; SMD, standardized mean difference; IQR, interquartile range; COPD, chronic obstructive pulmonary disease; WBC, white blood cell; RBC, red blood cell.
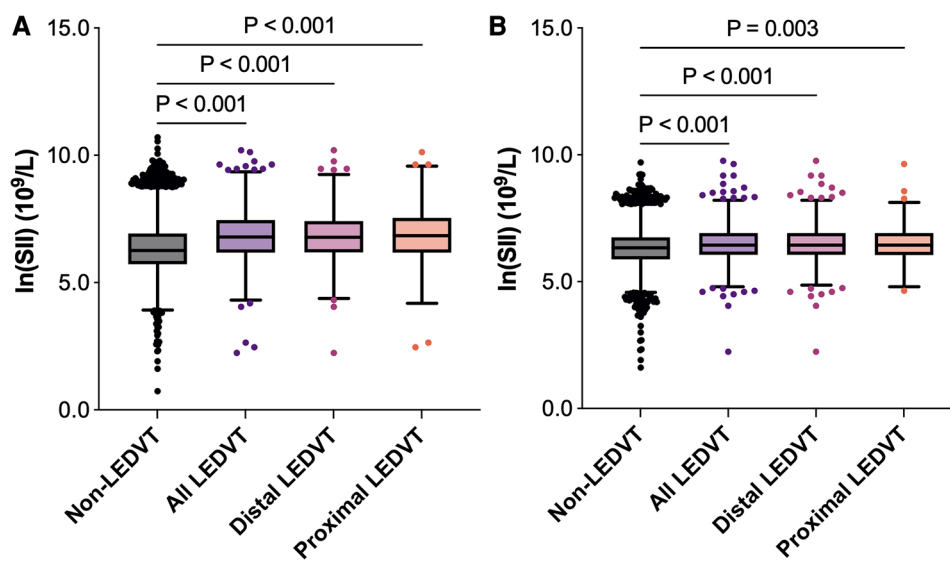
FIGURE 3
Box and whisker plots of ln(SII) in different groups. The box depicts the interquartile range (IQR), the horizontal line inside the box is the median, the whiskers extend to data points up to 1.5 × IQR, and dots are data points outside the whisker range. (A) Before matching. (B) After matching. SII, systemic immune-inflammation index; LEDVT, lower extremity deep venous thrombosis.

3.4. Association between SII and LEDVT after matching

After PSM, 7,814 patients were identified (3,907 in each group), and the baseline characteristics were well balanced between the two groups, with SMDs less than 0.1 for all variables (**Table 1**, **Supplementary Figure S1**). Among these patients, 905 (11.6%) had LEDVT, including 670 (74.0%) with distal LEDVT and 235 (26.0%) with proximal LEDVT. Similarly to the results before matching, patients with LEDVT

exhibited higher ln(SII) levels than those without, and this difference remained significant in patients with distal and proximal LEDVT (**Figure 3B**). The results of multivariate analyses indicated that both high SII group (OR = 1.422, 95% CI: 1.232–1.641, P < 0.001; **Table 3**, Model 1) and elevated ln (SII) (OR = 1.326, 95% CI: 1.200–1.465, P < 0.001; **Table 3**, Model 2) were significantly associated with an increased risk of LEDVT. Moreover, the forest plot showed that high SII was an independent risk factor for both distal and proximal LEDVT (**Figure 4B**, P < 0.05).

TABLE 2 Multivariate logistic regression analyses of factors associated with lower extremity deep venous thrombosis before matching (n = 16,725).

Variables	Model 1		Model 2	
	OR (95% *CI*)	*P* value	OR (95% *CI*)	*P* value
SII	1.740 (1.546–1.959)	<0.001	1.361 (1.278–1.449)	<0.001
Age	1.635 (1.473–1.815)	<0.001	1.627 (1.466–1.807)	<0.001
Sex	1.169 (1.056–1.294)	0.003	1.172 (1.059–1.297)	0.003
Obesity	1.592 (1.293–1.959)	<0.001	1.622 (1.318–1.997)	<0.001
Diabetes mellitus	2.406 (2.137–2.708)	<0.001	2.392 (2.124–2.692)	<0.001
COPD	1.163 (1.016–1.331)	0.028	1.132 (0.988–1.296)	0.074
Atrial fibrillation	1.363 (1.124–1.653)	0.002	1.371 (1.130–1.662)	0.001
Heart failure	1.379 (1.055–1.801)	0.019	1.382 (1.057–1.805)	0.018
Stroke	1.202 (1.051–1.375)	0.007	1.219 (1.066–1.394)	0.004
Hepatic insufficiency	1.621 (1.299–2.021)	<0.001	1.576 (1.262–1.967)	<0.001
Renal insufficiency	1.005 (0.840–1.201)	0.959	1.005 (0.840–1.202)	0.959
White blood cell	1.413 (1.265–1.579)	<0.001	1.314 (1.167–1.480)	<0.001
Red blood cell	1.392 (1.206–1.608)	<0.001	1.387 (1.200–1.602)	<0.001
Hemoglobin	1.327 (1.147–1.536)	<0.001	1.318 (1.138–1.526)	<0.001

OR, odds ratio; CI, confidence interval; SII, systemic immune-inflammation index; COPD, chronic obstructive pulmonary disease.
Model 1: adjust for SII (categorical variable, ≥574.2 vs. <574.2 × 10^9/L) and confounders variables, including age, sex, obesity, diabetes mellitus, chronic obstructive pulmonary disease, atrial fibrillation, heart failure, stroke, hepatic insufficiency, renal insufficiency, white blood cell, red blood cell, and hemoglobin.
Model 2: adjust for SII [continuous variable, per ln(SII) increase] and confounders variables mentioned above.

FIGURE 4
Forest plots for the association between SII and secondary outcome before matching (**A**) and after matching (**B**). Dots and horizontal lines represent adjusted odds ratio (OR) and 95% confidence interval (*CI*), respectively. Model 1: adjust for SII (categorical variable, ≥574.2 vs. <574.2 × 10⁹/L) and confounders variables, including age, sex, obesity, diabetes mellitus, chronic obstructive pulmonary disease, atrial fibrillation, heart failure, stroke, hepatic insufficiency, renal insufficiency, white blood cell, red blood cell, and hemoglobin. Model 2: adjust for SII [continuous variable, per ln (SII) increase] and confounders variables mentioned above. LEDVT, lower extremity deep venous thrombosis.
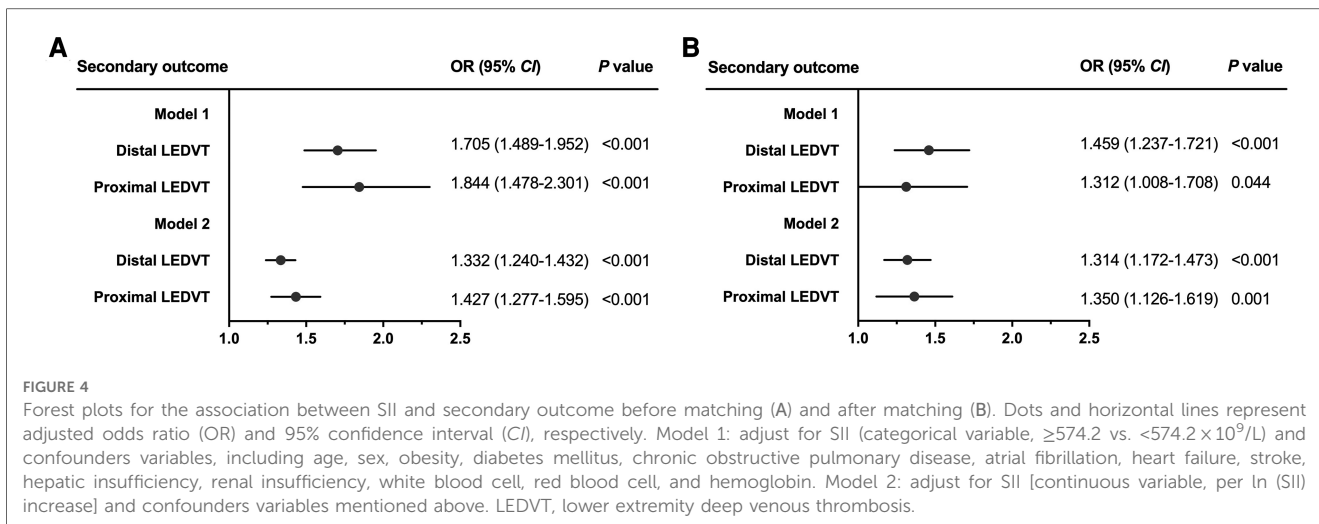
3.5. Subgroup analyses and sensitivity analyses

To further verify the robustness of this association, a series of subgroup analyses were conducted, and the results are graphically presented using a forest plot (**Figure 5**). Consistent with the main findings, patients with elevated ln(SII) had significantly higher adjusted ORs for LEDVT in nearly all subgroups (OR range: 1.257–1.483, all $P < 0.05$), except for patients with heart failure ($P = 0.908$), and renal insufficiency ($P = 0.216$).

After excluding 7,040 patients with any missing data, a total of 9,685 patients (1,015 with distal LEDVT, 309 with proximal LEDVT) before matching, and 4,642 patients (475 with distal LEDVT, 138 with proximal LEDVT) after matching were available for further analyses. All sensitivity analyses yielded similar findings to the main analyses (**Table 4**).

3.6. Dose-response relationship between SII and LEDVT risk

As shown in **Figure 6**, significant non-linear relationships were observed between ln(SII) and risk of all, distal and proximal LEDVT events ($P < 0.001$). As ln(SII) increased, the risk of LEDVT first decreased, reached a minimum and then increased rapidly. Using two-piecewise linear regressions, the threshold values of ln(SII) were 5.6×10^9/L for all LEDVT (SII = 270.4×10^9/L), 5.5×10^9/L for distal LEDVT (SII = 244.7×10^9/L), and 5.7×10^9/L for proximal LEDVT (SII = 298.9×10^9/L). Below the threshold, increased ln(SII) was not associated with risk of LEDVT (**Table 5**, all $P > 0.05$). Nevertheless, above the threshold, each unit increase in ln(SII) had a 1.369-fold, 1.338-fold and 1.390-fold increased risk of all, distal and proximal LEDVT, respectively ($P < 0.001$).

TABLE 3 Multivariate logistic regression analyses of factors associated with lower extremity deep venous thrombosis after matching ($n = 7,814$).

Variables	Model 1		Model 2	
	OR (95% *CI*)	*P* value	OR (95% *CI*)	*P* value
SII	1.422 (1.232–1.641)	<0.001	1.326 (1.200–1.465)	<0.001
Age	1.740 (1.495–2.025)	<0.001	1.729 (1.485–2.013)	<0.001
Sex	1.209 (1.042–1.402)	0.012	1.211 (1.045–1.405)	0.011
Obesity	1.491 (1.096–2.028)	0.011	1.496 (1.099–2.034)	0.010
Diabetes mellitus	2.318 (1.956–2.747)	<0.001	2.290 (1.932–2.714)	<0.001
COPD	1.105 (0.905–1.349)	0.328	1.073 (0.878–1.310)	0.492
Atrial fibrillation	1.296 (0.977–1.719)	0.072	1.302 (0.982–1.728)	0.067
Heart failure	1.785 (1.245–2.559)	0.002	1.799 (1.254–2.581)	0.001
Stroke	1.108 (0.915–1.343)	0.292	1.102 (0.910–1.335)	0.319
Hepatic insufficiency	1.879 (1.368–2.580)	<0.001	1.833 (1.333–2,521)	<0.001
Renal insufficiency	1.023 (0.791–1.324)	0.860	1.005 (0.777–1.301)	0.968
White blood cell	1.252 (1.074–1.459)	0.004	1.169 (1.001–1.366)	0.048
Red blood cell	1.435 (1.166–1.766)	0.001	1.429 (1.161–1.760)	0.001
Hemoglobin	1.341 (1.087–1.653)	0.006	1.316 (1.067–1.623)	0.010

OR, odds ratio; CI, confidence interval; SII, systemic immune-inflammation index; COPD, chronic obstructive pulmonary disease.
Model 1: adjust for SII (categorical variable, ≥574.2 vs. <574.2 × 10⁹/L) and confounders variables, including age, sex, obesity, diabetes mellitus, chronic obstructive pulmonary disease, atrial fibrillation, heart failure, stroke, hepatic insufficiency, renal insufficiency, white blood cell, red blood cell, and hemoglobin.
Model 2: adjust for SII [continuous variable, per ln(SII) increase] and confounders variables mentioned above.

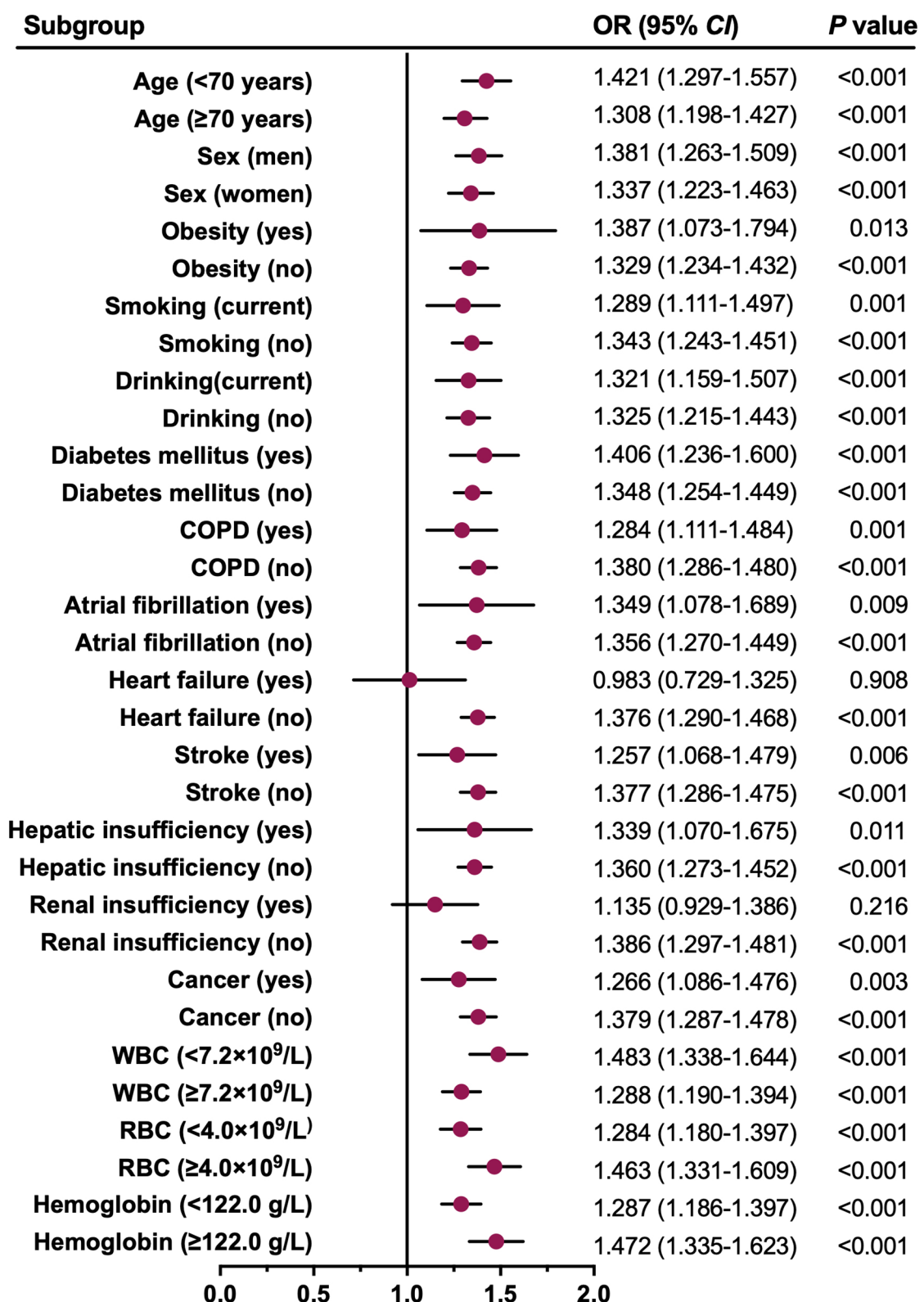| Subgroup		OR (95% CI)	P value
Age (<70 years)		1.421 (1.297-1.557)	<0.001
Age (≥70 years)		1.308 (1.198-1.427)	<0.001
Sex (men)		1.381 (1.263-1.509)	<0.001
Sex (women)		1.337 (1.223-1.463)	<0.001
Obesity (yes)		1.387 (1.073-1.794)	0.013
Obesity (no)		1.329 (1.234-1.432)	<0.001
Smoking (current)		1.289 (1.111-1.497)	0.001
Smoking (no)		1.343 (1.243-1.451)	<0.001
Drinking(current)		1.321 (1.159-1.507)	<0.001
Drinking (no)		1.325 (1.215-1.443)	<0.001
Diabetes mellitus (yes)		1.406 (1.236-1.600)	<0.001
Diabetes mellitus (no)		1.348 (1.254-1.449)	<0.001
COPD (yes)		1.284 (1.111-1.484)	0.001
COPD (no)		1.380 (1.286-1.480)	<0.001
Atrial fibrillation (yes)		1.349 (1.078-1.689)	0.009
Atrial fibrillation (no)		1.356 (1.270-1.449)	<0.001
Heart failure (yes)		0.983 (0.729-1.325)	0.908
Heart failure (no)		1.376 (1.290-1.468)	<0.001
Stroke (yes)		1.257 (1.068-1.479)	0.006
Stroke (no)		1.377 (1.286-1.475)	<0.001
Hepatic insufficiency (yes)		1.339 (1.070-1.675)	0.011
Hepatic insufficiency (no)		1.360 (1.273-1.452)	<0.001
Renal insufficiency (yes)		1.135 (0.929-1.386)	0.216
Renal insufficiency (no)		1.386 (1.297-1.481)	<0.001
Cancer (yes)		1.266 (1.086-1.476)	0.003
Cancer (no)		1.379 (1.287-1.478)	<0.001
WBC (<7.2×10^9/L)		1.483 (1.338-1.644)	<0.001
WBC (≥7.2×10^9/L)		1.288 (1.190-1.394)	<0.001
RBC (<4.0×10^9/L)		1.284 (1.180-1.397)	<0.001
RBC (≥4.0×10^9/L)		1.463 (1.331-1.609)	<0.001
Hemoglobin (<122.0 g/L)		1.287 (1.186-1.397)	<0.001
Hemoglobin (≥122.0 g/L)		1.472 (1.335-1.623)	<0.001
	0.0 0.5 1.0 1.5 2.0		

FIGURE 5

Forest plot for the association between ln(SII) and all LEDVT events in different subgroups. Dots and horizontal lines represent adjusted odds ratio (OR) and 95% confidence interval (CI), respectively. The associations (ORs) were adjusted for confounders variables except for the one defining the subgroup. COPD, chronic obstructive pulmonary disease; WBC, white blood cell; RBC, red blood cell.

TABLE 4 Sensitivity analyses of the association between ln(SII) and lower extremity deep venous thrombosis before and after matching.

Outcomes	Before matching (n = 9,685)		After matching (n = 4,642)	
	OR (95% CI)	P value	OR (95% CI)	P value
Primary outcome				
All LEDVT	1.315 (1.216–1.422)	<0.001	1.257 (1.110–1.423)	<0.001
Secondary outcome				
Distal LEDVT	1.289 (1.181–1.408)	<0.001	1.233 (1.073–1.417)	0.003
Proximal LEDVT	1.401 (1.208–1.624)	<0.001	1.344 (1.051–1.720)	0.019

OR, odds ratio; CI, confidence interval; SII, systemic immune-inflammation index; LEDVT, lower extremity deep venous thrombosis.
The associations (ORs) were adjusted for age, sex, obesity, diabetes mellitus, chronic obstructive pulmonary disease, atrial fibrillation, heart failure, stroke, hepatic insufficiency, renal insufficiency, white blood cell, red blood cell and hemoglobin.

4. Discussion

Thrombus formation is a complex process, which involves the interaction of a variety of blood cells, including neutrophils, platelets and lymphocytes (7, 8). Based on these blood cells, various immune-inflammation biomarkers were used as diagnostic and prognostic tools for DVT, such as neutrophil/lymphocyte ratio (NLR), and platelet/lymphocyte ratio (PLR) (14). The SII, which is a combination of neutrophils, platelets and lymphocytes, has emerged as a novel inflammation and

immune marker. As expected, we found that increased SII (either as categorical or continuous variable) was significantly associated with a higher risk of LEDVT. This finding was consistent with studies from Melinte et al. (15), Zhang et al. (16), and Mureşan et al. (17), as described in **Supplementary Table S4**. However, Liu et al. (18) evaluated the relationship between SII and DVT risk in 1,179 patients with tibial plateau fracture, and SII was not independently associated with the occurrence of preoperative DVT, although univariate analysis reached statistical significance. The possible reason for this might be that multivariate analysis included the collinear variables (e.g., neutrophils, platelets, NLR, PLR), thereby affecting the result. To address this issue, we calculated the VIFs for each regression models, and VIFs between all variables were less than 2.3 (**Supplementary Table S2**), indicating that our results were not affected by the multicollinearity.

Distal and proximal LEDVT often differ substantially in terms of patient characteristics, risk factors and clinical management (34). For this reason, we further explored whether this relationship existed in both distal and proximal LEDVT. Fortunately, the results persisted even after full adjustment, further supporting the association between SII and LEDVT risk. Moreover, a series of PSM analyses, subgroup analyses and sensitivity analyses were performed to assess the robustness of this association. These analyses yielded similar findings, suggesting that our results were robust and reliable. As such, our study provided strong evidence for a positive link between systemic inflammation and thrombosis, implying that targeting this interface might be a promising strategy to prevent
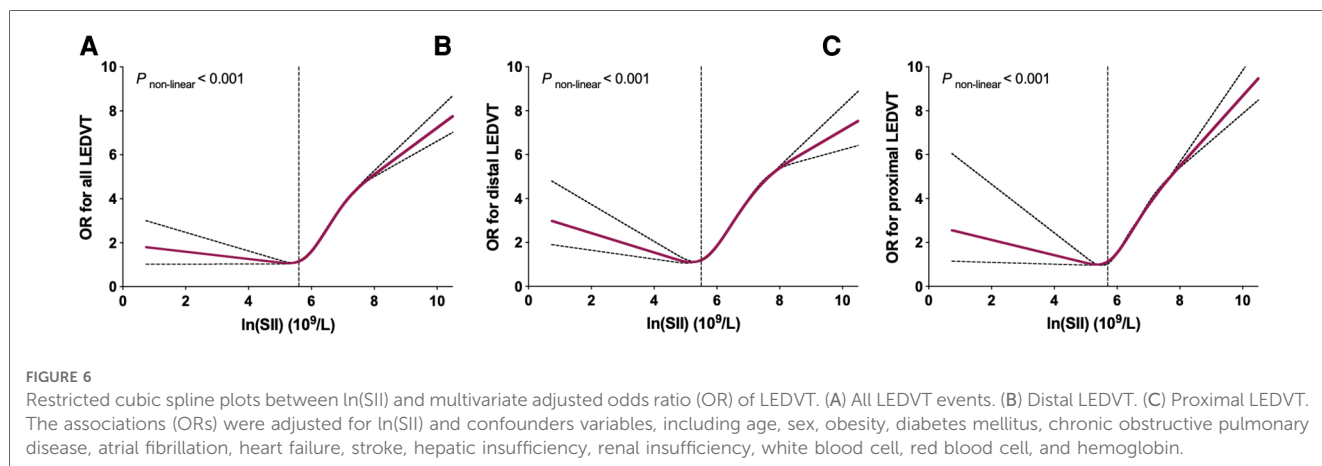

FIGURE 6
Restricted cubic spline plots between ln(SII) and multivariate adjusted odds ratio (OR) of LEDVT. (A) All LEDVT events. (B) Distal LEDVT. (C) Proximal LEDVT. The associations (ORs) were adjusted for ln(SII) and confounders variables, including age, sex, obesity, diabetes mellitus, chronic obstructive pulmonary disease, atrial fibrillation, heart failure, stroke, hepatic insufficiency, renal insufficiency, white blood cell, red blood cell, and hemoglobin.

TABLE 5 Threshold analyses for the association between ln (SII) and risk of LEDVT.

	All LEDVT		Distal LEDVT		Proximal LEDVT	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Threshold value	5.6 × 10⁹/L		5.5 × 10⁹/L		5.7 × 10⁹/L	
<Threshold value	0.933 (0.661–1.317)	0.693	0.859 (0.523–1.411)	0.549	0.730 (0.449–1.187)	0.205
≥Threshold value	1.369 (1.271–1.475)	<0.001	1.338 (1.231–1.455)	<0.001	1.390 (1.220–1.584)	<0.001

SII, systemic immune-inflammation index; LEDVT, lower extremity deep venous thrombosis; OR, odds ratio; CI, confidence interval.
The associations (ORs) were adjusted for age, sex, obesity, diabetes mellitus, chronic obstructive pulmonary disease, atrial fibrillation, heart failure, stroke, hepatic insufficiency, renal insufficiency, white blood cell, red blood cell and hemoglobin.

thrombosis and enhance the efficacy of anticoagulant therapy alone (6).

Furthermore, we observed a significant non-linear association between ln(SII) and LEDVT risk. As clearly shown in Figure 6, the risk of LEDVT first decreased and then increased rapidly with the rise of ln(SII). Although no previous study has investigated the dose-response relationship, similar non-linear associations were found between SII and risk of all-cause mortality (35, 36), arrhythmias (37), and rheumatoid arthritis (38). In these studies, the threshold values of ln(SII) were 5.97×10^9/L (35), 6.57×10^9/L (36), and 6.36×10^9/L (38), respectively. Using two-piecewise linear regressions, the threshold values in this study were 5.6×10^9/L for all LEDVT, 5.5×10^9/L for distal LEDVT, and 5.7×10^9/L for proximal LEDVT. Importantly, the risk of LEDVT increased rapidly after reaching the threshold value. For instance, each unit increase in ln(SII) above the threshold value was associated with a 1.369-fold increased risk of LEDVT. The SII is easily accessible, inexpensive, and feasible in routine clinical practice. Therefore, the threshold value of SII may be useful to identify hospitalized patients at high risk of LEDVT.

Notably, the diagnostic accuracy of SII for DVT was not high. In this study, the AUC was 0.647, with a sensitivity of 68.8% and specificity of 54.1%. Similarly, another two studies reported an AUC of 0.663 in elderly patients with hip fracture (16), and 0.605 in patients with tibial plateau fracture (18). In addition to its diagnostic role, a recent meta-analysis also showed that the pooled AUC, sensitivity and specificity were 0.63, 0.68 and 0.55, concluding that SII had a certain prognostic value for overall survival in patients with nasopharyngeal carcinoma (39). Due to its insufficient accuracy and complexity of thrombus formation, SII alone is not sufficient to diagnose LEDVT, and other clinical indicators need to be combined to improve the diagnostic ability. Future studies are thus required to explore whether the combination of SII with other biomarkers may provide additional diagnostic value in predicting DVT.

However, certain limitations should also be considered. First, this is an observational study and can only demonstrate association and not causation. At the same time, due to the retrospective nature of the study design, some important risk factors related to DVT could not be accessed, such as pregnancy status, hormone replacement therapy, prior history of venous thromboembolism (VTE), and antithrombotic therapy before admission. Additionally, antithrombotic drugs after LEDVT diagnosis were not obtained due to lack of detailed medication regimen in the database (19). Further prospective studies are still needed to confirm our findings. Second, the study population was restricted to hospitalized patients, and derived from a single academic medical center. This may limit generalization of these results. Third, the SII value is dynamic, and its dynamic status has been found to be associated with risk of cardiovascular diseases (40). In this study, we only used the SII data on admission, which may lead to underestimate this association (35). Fourth, all LEDVT events in this study were diagnosed by ultrasonography, which may lead to a lower accuracy than venography (26). Finally, although we carefully adjusted for potential confounders, biases resulting from unknown and unmeasured confounders may still exist (37).

In conclusion, elevated SII is significantly associated with an increased risk of LEDVT in hospitalized patients. Additionally, the association is non-linear and exhibit a threshold effect.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the Institutional Ethics Committee of People's Hospital of Deyang City (2021-04-019-K01). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

ZW: conceived and designed the study. HL, YL, and ML: collected the data. XC and YO: performed the statistical analysis. XC and YO: wrote the manuscript. ZW: supervised the study and approved the manuscript. All authors contributed to the article and approved the submitted version.

Funding

Acknowledgments

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2023.1211294/full#supplementary-material.

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