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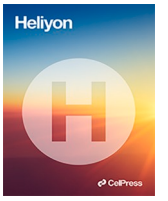

Research article

Systemic immune-inflammation index predicts first stroke and affects the efficacy of folic acid in stroke prevention

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ABSTRACT

Background: Systemic immune-inflammation index (SII) is a novel biomarker of growing interest in predicting stroke. The aim of this study was to investigate its predictive value and explore its effect modification on folic acid supplement for stroke primary prevention in a Chinese population with hypertension.

Methods: A total of 10,013 participants from the China Stroke Primary Prevention Trial with available neutrophil, platelet and lymphocyte count were included, including 5,019 subjects in the enalapril group and 4,994 in the enalapril-folic acid group. SII was calculated as (platelet × neutrophil)/lymphocyte. The primary endpoint was first stroke. Cox proportional hazards models were used to evaluate the association between SII and first stroke.

Results: A U-shape association between SII and first stroke risk was observed in enalapril group. Compared with the reference group (Quartile 2: 335.1 to $<443.9 \times 10^9$ cell/L), the adjusted HRs were 1.68 (95 % CI: 1.06–2.66, $P = 0.027$) in Quartile 1 ($<335.1 \times 10^9$ cell/L), 1.43 (95 % CI: 0.90–2.27, $P = 0.126$) in Quartile 3 (443.9 to $<602.6 \times 10^9$ cell/L), and 1.61 (95 % CI: 1.03–2.51, $P = 0.035$) in Quartile 4 ($\geq 602.6 \times 10^9$ cell/L). There was no significant association between SII and first stroke in the enalapril-folic acid group, with adjusted HR of 0.92 (95%CI: 0.54–1.56, $P = 0.749$) in Quartile 1($<334.7 \times 10^9$ cell/L), 1.36 (95%CI: 0.84–2.21, $P = 0.208$) in Quartile 3 (446.2 to $<595.2 \times 10^9$ cell/L), and 1.41 (95%CI: 0.87–2.27, $P = 0.163$) in Quartile 4 ($\geq 595.2 \times 10^9$ cell/L). A remarkable interaction between baseline SII and folic acid supplement for stroke prevention was observed, with particularly reduced risk by 44 % (HR: 0.56; 95 % CI: 0.34–0.90; $P = 0.018$) in the lowest SII group (P for interaction = 0.041).

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Conclusions: Among Chinese adults with hypertension, both low and high SII at baseline predicted increased first stroke risk. And compensatory folic acid particularly reduced first stroke risk in the lowest SII subgroup.

1. Introduction

Stroke remains the leading cause of death and disability worldwide [1]. Despite currently available knowledge of evidence-based interventions, the growing burden of stroke strongly suggests the deficiency of prevention strategy [2]. Thus, there is still an unmet need for a concise and reliable marker enable to optimize the risk stratification [3].

Increasing evidence has elucidated the importance of immune [4] and inflammation [5,6] in stroke pathophysiology. Particularly, neutrophil [7], lymphocyte [8,9] and platelet [10] are thought to play imperative roles. In addition, several inflammation and immune indices based on the complete blood count, such as platelet-lymphocyte ratio and neutrophil-lymphocyte ratio, have been created as potential predictors for stroke [10,11].

Systemic immune-inflammation index (SII), the ratio of platelet and neutrophil product to lymphocytes, is a novel biomarker that is thought to reflect the overall immune and inflammatory status. It was initially developed and proved to be of great prognostic value in malignancy [12], of which systemic inflammation and immune is a prominent hallmark [13]. Given a similar role of immune and inflammation, SII was recently introduced in the condition of stroke. Emerging evidence has documented the association between SII and stroke occurrence, severity and prognosis [14–16]. However, consistent conclusions were not reached in other studies [17,18]. For individuals with hypertension, the top risk factor of stroke [19], the predictive value of SII remains ambiguous.

Compensatory folic acid was a valid strategy for primary stroke prevention, especially in regions without mandatory fortification of grain products [20]. Furthermore, platelet count was thought to modify the efficiency of folic acid supplement [21], which suggested the potential modification effect of systemic inflammation. Whereas, if SII affects the efficacy of folic acid for primary stroke prevention remains unclear.

Therefore, this study sought to evaluate the predictive value of SII for the first-onset stroke, and assess the modification effect of SII on the pathway of stroke prevention by folic acid in a Chinese population with hypertension.

2. Methods

2.1. Study design and participants

This study is a post-hoc analysis of the China Stroke Primary Prevention Trial (CSPPT) (ClinicalTrials.gov Identifier:

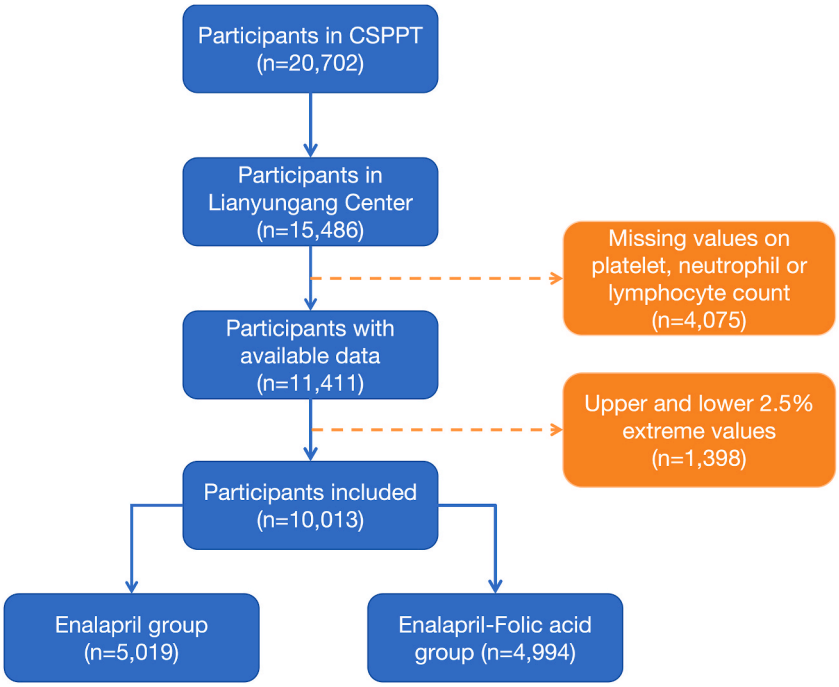

Fig. 1. Flowchart of the study participants. Abbreviation: CSPPT, China stroke primary prevention trial.

NCT00794885). The details of this project have been previously reported [20]. In brief, the CSPPT was a multicenter, randomized, double-blind, controlled clinical trial conducted from May 2008 to August 2013 in 32 communities in China. A total of 20,702 adults aged from 45 to 75 years, who were diagnosed with hypertension, were recruited. Hypertension was defined as seated, resting systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg at both the recruitment and the screening visit, or those who were exposed to antihypertensive medication at the time of enrollment. Patients with a history of physician-diagnosed stroke, myocardial infarction, heart failure, coronary revascularization, congenital heart disease or any other severe somatic diseases were excluded. Eligible participants were stratified by the methylenetetrahydrofolate reductase (MTHFR) C677T (rs1801133) genotypes (CC, CT, or TT) and randomly assigned in a 1:1 ratio to receive one of two treatments: a daily dose of 10 mg enalapril and 0.8 mg folic acid (the enalapril-folic acid group), or a daily dose of 10 mg enalapril alone (the enalapril group).

Of the 20,702 participants in the CSPPT, our analyses were limited to 15,486 individuals from one study center (Lianyungang). We excluded 4,075 individuals due to missing data on baseline platelet, neutrophil or lymphocyte counts. Anyone with upper and lower 2.5 % extreme values on any of the three hemocytes were further excluded empirically. Finally, 10,013 individuals were included in the final analysis. Of those, 5019 individuals were in the enalapril group, and 4,994 individuals were in the enalapril-folic acid group (Fig. 1).

2.2. Data collection

Baseline data were collected by trained staff using a standardized questionnaire. Demographic status, medical history, drug use and lifestyle (smoking and drinking status) were recorded. Height and weight were measured according to standard procedures. Body mass index (BMI) was calculated as weight (kg) divided by height (m) squared. Seated blood pressures were measured by following the standard method after at least 10 min of rest. Triplicate measurements were taken on the same arm, with at least 2 min breaks between readings. The mean systolic blood pressure (SBP) was used in the analysis. On-treatment SBP was calculated as the average of all follow-up SBP records. Smoking and drinking status were recorded as never, former or current smoker/drinker.

Overnight fasting venous blood samples were collected at baseline, and were used for laboratory test. Platelet, neutrophil and lymphocyte counts were obtained by a BC-3200 hematology analyzer (Mindray Medical, Shenzhen, China). SII was calculated according to the following formula [12]:

$$(\text{platelet} \times \text{neutrophil}) / \text{lymphocyte}$$

Serum folate, total homocysteine (tHcy), fasting plasma glucose (FPG) and lipids were measured using an automated clinical analyzer (Beckman Coulter). The estimated glomerular filtration rate (eGFR) was calculated using the formula of the Chronic Kidney Disease Epidemiology Collaborative (CKD-EPI) [22]. MTHFR C677T polymorphisms were detected on an ABI Prism 7900HT sequence detection system (Life Technologies, Carlsbad, California) using the TaqMan assay.

2.3. Follow-up and outcomes

Participants were scheduled for follow-up every three months. The primary outcome was the first nonfatal or fatal stroke (either ischemic or hemorrhagic stroke), excluding subarachnoid hemorrhage and silent stroke. All the study outcomes were reviewed and adjudicated according to standard criteria by an independent Endpoint Adjudication Committee.

2.4. Statistical analysis

Continuous variables were summarized as means ± SD or medians (25th percentile, 75th percentile) according to the normality, and were compared by Kruskal-Wallis test. Categorical variables were summarized as frequency (proportion) and were compared by Chi-squared test or Fisher's exact test as appropriate. SII was addressed as a categorical variable grouped by quartiles. Cox proportional hazards models were administered to estimate the hazard ratio (HR) and 95% confidence interval (CI). Non-stroke deaths were censored. The multivariate model adjusted for sex, age, BMI, baseline SBP, on-treatment SBP, FPG, total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), folate, tHcy, MTHFR C677T, eGFR, smoking status and drinking status. Subgroup analysis was performed to examine interaction and modification effect was assessed by Cox regression.

A 2-tailed $P < 0.05$ was considered to be statistically significant in all analyses. EmpowerStats (http://www.empowerstats.com) and R software, version 4.0.0 (http://www.R-project.org/), were used for all statistical analyses.

3. Results

3.1. Baseline characteristics of study participants

A total of 10,013 individuals were included in the final analysis. Of those, 5,019 individuals were in the enalapril group, and 4,994 individuals were in the enalapril-folic acid group. The baseline characteristics presented by quartiles of the overall population were comparable between the enalapril–folic acid group and the enalapril group except SII and its components (Table 1). During the 4.5-year follow-up period, a total of 345 first stroke incidents were recorded. Of those, 191 were in the enalapril group and 154 were in the enalapril-folic acid group.

3.2. Association between SII and first stroke in enalapril group

We firstly assessed the association between SII and first stroke in enalapril group. As summarized in Table 2, after adjusting for corresponding covariates, both the lowest (Quartile 1: $<335.1 \times 10^9$ cell/L) (HR: 1.68, 95%CI: 1.06–2.66, $P = 0.027$) and highest SII groups (Quartile 4: $\geq 602.6 \times 10^9$ cell/L) (HR: 1.61, 95%CI: 1.03–2.51, $P = 0.035$) showed significant higher risk of first stroke. The restricted cubic spline (RCS) curve displayed a U-shape relationship between SII and first stroke risk (Fig. 2A).

3.3. Association between SII and first stroke in enalapril-folic acid group

We further assessed whether folic acid supplement altered the association between SII and first stroke. As summarized in Table 3, compared with the reference group (Quartile 2: 334.7 to $<446.2 \times 10^9$ cell/L), multivariate regression illustrated comparable risks in other SII groups, with adjusted HR of 0.92 (95%CI: 0.54–1.56, $P = 0.749$) in Quartile 1, 1.36 (95%CI: 0.84–2.21, $P = 0.208$) in Quartile 3, and 1.41 (95%CI: 0.87–2.27, $P = 0.163$) in Quartile 4. In accord, the RCS curve did not display a remarkable U-shape relationship between SII and adjusted HR (Fig. 2B). These results suggested that mandatory folic acid eliminated the extra risk of first stroke in both low and high SII groups.

3.4. Subgroup analysis

To test the robustness of the association we observed in enalapril group and explore potential interaction, subgroup analysis was conducted. Participants were stratified by sex, age, BMI, baseline SBP, on-treatment SBP, MTHFR C677T, FPG, TC, folate, tHcy, eGFR, smoking status and drinking status. Continuous variables were dichotomized by median. As summarized in Table 4, there was no interaction between SII and any of the covariates (*P*-interaction >0.05 for all subgroups). We also stratified individuals by common clinical limits of the continuous variables, the results did not alter (Supplementary Table 1).

Table 1
Baseline characteristics of individuals in enalapril and enalapril-folic acid groups presented by quartiles of SII.

Subgroups	Q1 ($<334.9 \times 10^9$ cells/L)		Q2 (334.9 to $<444.6 \times 10^9$ cells/L)		Q3 (444.6 to $<598.5 \times 10^9$ cells/L)		Q4 ($\geq 598.5 \times 10^9$ cells/L)	
	Enalapril Group	Enalapril-Folic Acid Group	Enalapril Group	Enalapril-Folic Acid Group	Enalapril Group	Enalapril-Folic Acid Group	Enalapril Group	Enalapril-Folic Acid Group
N	1,252	1,251	1,269	1,234	1,215	1,288	1,283	1,221
Female, N (%)	777 (62.1)	771 (61.6)	767 (60.4)	804 (65.2)	735 (60.5)	758 (58.9)	760 (59.2)	704 (57.7)
Age, year	59.1 ± 7.3	59.1 ± 7.2	59.1 ± 7.5	58.9 ± 7.2	59.8 ± 7.8	59.5 ± 7.6	60.1 ± 7.8	60.2 ± 7.8
BMI, kg/m^2	25.9 ± 3.5	25.7 ± 3.6	25.8 ± 3.7	25.8 ± 3.5	25.7 ± 3.6	25.7 ± 3.5	25.2 ± 3.6	25.4 ± 3.8
SBP, mmHg	165.9 ± 20.3	166.9 ± 21.1	167.5 ± 21.1	166.8 ± 20.7	168.8 ± 21.7	168.4 ± 21.0	170.2 ± 20.8	168.5 ± 20.4
On-treatment SBP, mmHg	139.7 ± 11.6	139.6 ± 11.6	140.5 ± 11.9	139.9 ± 11.4	140.5 ± 12.1	140.3 ± 11.5	140.9 ± 11.5	140.8 ± 12.0
FPG, mmol/L	5.7 (5.2, 6.2)	5.6 (5.2, 6.2)	5.7 (5.2, 6.3)	5.6 (5.2, 6.3)	5.7 (5.2, 6.3)	5.6 (5.1, 6.2)	5.7 (5.2, 6.4)	5.6 (5.1, 6.4)
TC, mmol/L	5.5 (4.8, 6.2)	5.5 (4.8, 6.2)	5.5 (4.9, 6.3)	5.6 (4.9, 6.3)	5.5 (4.9, 6.3)	5.6 (4.9, 6.4)	5.7 (5.0, 6.5)	5.7 (5.0, 6.4)
TG, mmol/L	1.5 (1.1, 2.1)	1.4 (1.0, 2.0)	1.5 (1.1, 2.1)	1.5 (1.1, 2.1)	1.5 (1.1, 2.1)	1.5 (1.1, 2.1)	1.4 (1.1, 2.0)	1.4 (1.1, 2.0)
HDL-C, mmol/L	1.2 (1.0, 1.5)	1.3 (1.1, 1.5)	1.3 (1.0, 1.5)	1.2 (1.1, 1.5)	1.2 (1.1, 1.5)	1.3 (1.0, 1.6)	1.3 (1.1, 1.5)	1.3 (1.1, 1.5)
Folate, ng/mL	7.6 (5.4, 9.8)	7.7 (5.6, 9.8)	7.6 (5.5, 9.5)	7.6 (5.4, 9.7)	7.5 (5.3, 9.7)	7.2 (5.2, 9.4)	7.5 (5.2, 9.7)	7.3 (5.2, 9.4)
tHcy, umol/L	12.0 (10.0, 14.8)	12.0 (10.0, 14.9)	12.3 (10.1, 15.5)	12.2 (10.0, 15.3)	12.6 (10.6, 15.6)	12.8 (10.5, 16.0)	13.0 (10.7, 16.4)	13.2 (10.8, 16.9)
eGFR, mL/min/1.73m^2	97.0 (89.5, 102.8)	96.8 (88.5, 102.7)	96.8 (89.4, 102.7)	97.1 (89.6, 103.0)	96.2 (88.4, 103.1)	96.3 (87.8, 102.3)	95.8 (87.5, 102.0)	95.9 (87.7, 102.8)
SII, $\times 10^9$/L	278.1 (238.0, 308.1)	278.9 (243.0, 307.7)	388.8 (361.5, 416.7)	389.0 (361.6, 415.5)	513.0 (476.0, 550.1)	515.4 (475.6, 554.8)	513.0 (476.0, 550.1)	515.4 (475.6, 554.8)
Platelet, $\times 10^9$/L	211.0 (186.0, 240.2)	214.0 (186.0, 242.0)	238.0 (209.0, 273.0)	241.0 (211.2, 274.0)	259.0 (228.0, 293.0)	257.0 (228.0, 291.0)	259.0 (228.0, 293.0)	257.0 (228.0, 291.0)
Neutrophil, $\times 10^9$/L	2.8 (2.4, 3.2)	2.7 (2.4, 3.2)	3.4 (2.9, 3.9)	3.4 (2.9, 3.9)	4.0 (3.4, 4.6)	3.9 (3.5, 4.5)	4.0 (3.4, 4.6)	3.9 (3.5, 4.5)
Lymphocyte, $\times 10^9$/L	2.2 (1.9, 2.6)	2.2 (1.9, 2.6)	2.1 (1.8, 2.5)	2.1 (1.8, 2.5)	2.0 (1.7, 2.4)	2.0 (1.7, 2.3)	2.0 (1.7, 2.4)	2.0 (1.7, 2.3)
MTHFR genotype, N (%)								
CC	287 (22.9)	329 (26.3)	300 (23.6)	292 (23.7)	280 (23.0)	290 (22.5)	301 (23.5)	262 (21.5)
CT	638 (51.0)	604 (48.3)	623 (49.1)	617 (50.0)	606 (49.9)	637 (49.5)	639 (49.8)	626 (51.3)
TT	327 (26.1)	318 (25.4)	346 (27.3)	325 (26.3)	329 (27.1)	361 (28.0)	343 (26.7)	333 (27.3)

Abbreviation: BMI, body mass index; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; MTHFR, methylenetetrahydrofolate reductase; SBP, systolic blood pressure; SII, systemic immune-inflammation index; TC, total cholesterol; TG, triglyceride; tHcy, total homocysteine.

Table 2
The Association between baseline SII and first stroke in enalapril group.

SII × 10^9 cells/L	N	Cases (%)	Crude model		Adjusted model[a]	
			HR (95%CI)	*P* Value	HR (95%CI)	*P* Value
Q1 (<335.1)	1,255	50 (4.0)	1.44 (0.93, 2.21)	0.100	1.68 (1.06, 2.66)	0.027
Q2 (335.1 to <443.9)	1,252	35 (2.8)	ref	-	ref	-
Q3 (443.9 to <602.6)	1,257	47 (3.7)	1.34 (0.86, 2.07)	0.194	1.43 (0.90, 2.27)	0.126
Q4 (≥602.6)	1,255	59 (4.7)	1.69 (1.11, 2.57)	0.014	1.61 (1.03, 2.51)	0.035

Abbreviation: BMI, body mass index; CI, confidence interval; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; MTHFR, methylenetetrahydrofolate reductase; SBP, systolic blood pressure; SII, systemic immune-inflammation index; TC, total cholesterol; TG, triglyceride; tHcy, total homocysteine.

[a] Model adjusted for sex, age, BMI, baseline SBP, on-treatment SBP, FPG, TC, HDL-C, TG, folate, tHcy, MTHFR C677T, eGFR, smoking status and drinking status.

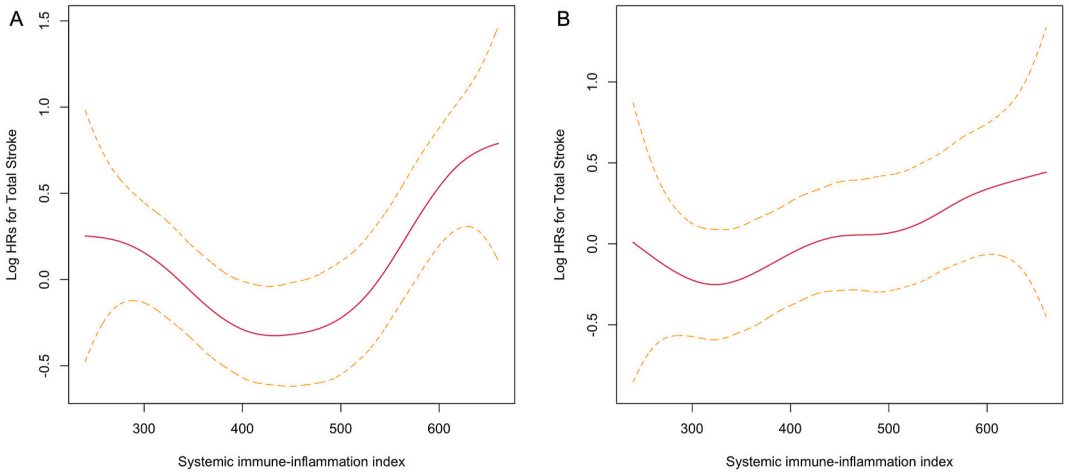

Fig. 2. Restricted cubic spline curve between baseline SII and first stroke risk. Curves for enalapril group (A) and enalapril-folic acid group (B) were plotted. X-axis indicates the baseline SII and Y-axis indicates the adjusted HR in logarithm scale.
Sex, age, BMI, baseline SBP, on-treatment SBP, FPG, TC, HDL-C, TG, folate, tHcy, MTHFR C677T, eGFR, smoking status and drinking status were adjusted. The solid line plotted the estimated HR value and the dotted line illustrated the 95%CI. Abbreviation: BMI, body mass index; CI, confidence interval; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; MTHFR, methylenetetrahydrofolate reductase; SBP, systolic blood pressure; SII, systemic immune-inflammation index; TC, total cholesterol; TG, triglyceride; tHcy, total homocysetine.

Table 3
The association between baseline SII and stroke in enalapril-folic acid group.

SII, × 10^9 cells/L	N	Cases (%)	Crude model		Adjusted model[a]	
			HR (95%CI)	*P* Value	HR (95%CI)	*P* Value
Q1 (<334.7)	1,248	29 (2.3)	0.85 (0.52, 1.40)	0.525	0.92 (0.54, 1.56)	0.749
Q2 (334.7 to < 446.2)	1,249	34 (2.7)	ref	-	ref	-
Q3 (446.2 to < 595.2)	1,248	43 (3.4)	1.26 (0.80, 1.97)	0.322	1.36 (0.84, 2.21)	0.208
Q4 (≥595.2)	1,249	48 (3.8)	1.40 (0.90, 2.17)	0.133	1.41 (0.87, 2.27)	0.163

Abbreviation: BMI, body mass index; CI, confidence interval; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; MTHFR, methylenetetrahydrofolate reductase; SBP, systolic blood pressure; SII, systemic immune-inflammation index; TC, total cholesterol; TG, triglyceride; tHcy, total homocysteine.

[a] Model adjusted for sex, age, BMI, baseline SBP, on-treatment SBP, FPG, TC, HDL-C, TG, folate, tHcy, MTHFR C677T, eGFR, smoking status and drinking status.

3.5. Effect modification of SII on folic acid supplement for stroke primary prevention

We further quantified the effect modification of SII on folic acid in stroke primary prevention. Compared with individuals in enalapril group, the stroke incidence of those receiving daily folic acid was reduced from 4.0 % to 2.3 % in the lowest SII group (Quartile 1: <334.9 × 10^9 cell/L), representing a relative risk reduction of 44 % (HR: 0.56, 95 % CI: 0.34–0.90, $P = 0.018$). In contrast,

Table 4
Subgroup analyses between SII and first stroke in enalapril group.

Subgroups	Q1 (<335.1 × 10^9 cells/L)			Q2 (335.1 to <443.9 × 10^9 cells/L)		Q3 (443.9 to <602.6 × 10^9 cells/L)			Q4 (≥602.6 × 10^9 cells/L)			*P* for interaction
	N	Cases (%)	HR (95%CI)	N	Cases (%)	N	Cases (%)	HR (95%CI)	N	Cases (%)	HR (95%CI)	
Sex												0.449
Male	476	24 (5.0)	1.58 (0.85, 2.94)	492	23 (4.7)	500	22 (4.4)	1.16 (0.61, 2.18)	512	26 (5.1)	1.14 (0.62, 2.10)	
Female	779	26 (3.3)	1.90 (0.94, 3.84)	760	12 (1.6)	757	25 (3.3)	1.94 (0.97, 3.88)	743	33 (4.4)	2.31 (1.17, 4.55)	
Age, year												0.824
<59.1 (median)	669	20 (3.0)	2.31 (1.07, 4.99)	653	12 (1.8)	601	16 (2.7)	1.51 (0.67, 3.40)	585	21 (3.6)	1.95 (0.90, 4.26)	
≥59.1	586	30 (5.1)	1.48 (0.83, 2.65)	599	23 (3.8)	656	31 (4.7)	1.43 (0.81, 2.51)	670	38 (5.7)	1.49 (0.87, 2.56)	
BMI, kg/m^2												0.464
<25.5 (median)	586	17 (2.9)	1.60 (0.79, 3.24)	621	17 (2.7)	608	24 (3.9)	1.62 (0.83, 3.14)	692	35 (5.1)	2.08 (1.12, 3.87)	
≥25.5	669	33 (4.9)	1.78 (0.97, 3.28)	631	18 (2.9)	648	23 (3.5)	1.30 (0.68, 2.50)	563	24 (4.3)	1.30 (0.68, 2.51)	
Baseline SBP, mmHg												0.727
<165.3 (median)	685	16 (2.3)	2.60 (1.00, 6.75)	648	7 (1.1)	620	13 (2.1)	2.26 (0.84, 6.07)	555	14 (2.5)	2.18 (0.82, 5.83)	
≥165.3	570	34 (6.0)	1.47 (0.86, 2.50)	604	28 (4.6)	637	34 (5.3)	1.26 (0.74, 2.13)	700	45 (6.4)	1.44 (0.87, 2.38)	
On-treatment SBP, mmHg												0.229
<139.1 (median)	649	14 (2.2)	1.63 (0.70, 3.80)	640	9 (1.4)	629	9 (1.4)	0.87 (0.33, 2.28)	591	19 (3.2)	1.99 (0.89, 4.47)	
≥139.1	606	36 (5.9)	1.57 (0.91, 2.72)	612	26 (4.2)	628	38 (6.1)	1.57 (0.92, 2.68)	664	40 (6.0)	1.40 (0.82, 2.39)	
MTHFR C677T												0.422
CC	287	14 (4.9)	1.83 (0.80, 4.19)	298	11 (3.7)	286	9 (3.1)	0.98 (0.39, 2.45)	297	12 (4.0)	1.07 (0.45, 2.51)	
CT	641	21 (3.3)	1.25 (0.63, 2.51)	612	18 (2.9)	634	22 (3.5)	1.27 (0.65, 2.48)	619	32 (5.2)	1.70 (0.90, 3.21)	
TT	327	15 (4.6)	2.55 (0.97, 6.71)	342	6 (1.8)	337	16 (4.7)	2.60 (1.00, 6.78)	339	15 (4.4)	2.09 (0.79, 5.52)	
FPG, mmol/L												0.138
<5.7 (median)	610	26 (4.3)	1.67 (0.88, 3.15)	613	16 (2.6)	610	15 (2.5)	0.81 (0.39, 1.65)	594	27 (4.5)	1.29 (0.68, 2.44)	
≥5.7	608	22 (3.6)	1.64 (0.84, 3.18)	604	17 (2.8)	616	31 (5.0)	2.00 (1.07, 3.73)	619	28 (4.5)	1.85 (0.98, 3.48)	
TC, mmol/L												0.126
<5.6 (median)	648	24 (3.7)	1.23 (0.65, 2.30)	614	20 (3.3)	633	21 (3.3)	0.98 (0.51, 1.87)	535	16 (3.0)	0.89 (0.45, 1.79)	
≥5.6	570	24 (4.2)	2.21 (1.12, 4.36)	603	13 (2.2)	593	25 (4.2)	2.08 (1.06, 4.09)	678	39 (5.8)	2.55 (1.35, 4.79)	
Folate, ng/mL												0.656
<7.6 (median)	608	28 (4.6)	2.04 (1.09, 3.84)	606	16 (2.6)	628	23 (3.7)	1.49 (0.78, 2.87)	630	29 (4.6)	1.54 (0.82, 2.87)	
≥7.6	626	21 (3.4)	1.28 (0.65, 2.52)	623	17 (2.7)	614	23 (3.7)	1.31 (0.68, 2.53)	612	29 (4.7)	1.62 (0.86, 3.07)	
tHcy, μmol/L												0.724
<12.5 (median)	678	19 (2.8)	1.59 (0.74, 3.43)	627	13 (2.1)	607	17 (2.8)	1.45 (0.67, 3.11)	544	19 (3.5)	1.98 (0.93, 4.20)	
≥12.5	553	30 (5.4)	1.77 (1.00, 3.15)	595	20 (3.4)	628	29 (4.6)	1.41 (0.79, 2.52)	685	37 (5.4)	1.42 (0.81, 2.47)	
eGFR, mL/min per 1.73 m^2												0.652
<96.5 (median)	574	29 (5.1)	1.91 (1.05, 3.46)	593	19 (3.2)	621	30 (4.8)	1.60 (0.88, 2.90)	649	33 (5.1)	1.52 (0.85, 2.72)	
≥96.5	644	19 (3.0)	1.31 (0.64, 2.70)	624	14 (2.2)	605	16 (2.6)	1.22 (0.58, 2.54)	564	22 (3.9)	1.72 (0.87, 3.44)	
Smoking status												0.462
Never Smoker	893	31 (3.5)	1.43 (0.81, 2.54)	892	24 (2.7)	867	27 (3.1)	1.21 (0.68, 2.17)	843	35 (4.2)	1.42 (0.81, 2.50)	
Former Smoker	105	3 (2.9)	0.74 (0.14, 3.95)	90	4 (4.4)	117	7 (6.0)	1.10 (0.26, 4.58)	92	7 (7.6)	1.29 (0.30, 5.62)	
Current Smoker	257	16 (6.2)	3.71 (1.43, 9.62)	270	7 (2.6)	272	13 (4.8)	2.37 (0.87, 6.40)	320	17 (5.3)	2.37 (0.93, 6.06)	

(*continued on next page*)

Table 4 (*continued*)

Subgroups	Q1 (<335.1 × 10^9 cells/L)			Q2 (335.1 to <443.9 × 10^9 cells/L)		Q3 (443.9 to <602.6 × 10^9 cells/L)			Q4 (≥602.6 × 10^9 cells/L)			*P* for interaction
	N	Cases (%)	HR (95%CI)	N	Cases (%)	N	Cases (%)	HR (95%CI)	N	Cases (%)	HR (95%CI)	
Drinking status												0.371
Never Drinker	877	33 (3.8)	1.72 (0.99, 2.98)	887	23 (2.6)	896	28 (3.1)	1.25 (0.71, 2.20)	883	40 (4.5)	1.47 (0.85, 2.53)	
Former Drinker	88	2 (2.3)	0.21 (0.02, 2.37)	81	4 (4.9)	89	3 (3.4)	0.39 (0.05, 2.99)	88	5 (5.7)	1.19 (0.25, 5.77)	
Current Drinker	290	15 (5.2)	2.92 (1.09, 7.84)	284	8 (2.8)	272	16 (5.9)	2.81 (1.07, 7.36)	284	14 (4.9)	2.18 (0.83, 5.71)	

Model adjusted, if not stratified, for sex, age, BMI, baseline SBP, on-treatment SBP, FPG, TC, HDL-C, TG, folate, tHcy, MTHFR C677T, eGFR, smoking status and drinking status.

Abbreviation: BMI, body mass index; CI, confidence interval; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; MTHFR, methylenetetrahydrofolate reductase; SBP, systolic blood pressure; SII, systemic immune-inflammation index; TC, total cholesterol; TG, triglyceride; tHcy, total homocysteine.

the stroke risk reduction in the other groups were modest, with adjusted HR of 0.95 (95%CI: 0.57–1.59) in Quartile 2 (334.9 to <444.6 × 10^9 cell/L), 1.00 (95%CI: 0.65–1.54, $P = 0.997$) in Quartile 3 (444.6–598.5 × 10^9 cell/L), and 0.88 (95%CI: 0.59–1.33, $P = 0.552$) in Quartile 4 (≥598.5 × 10^9 cell/L). The interaction test between SII and folic acid treatment for stroke primary prevention was statistically significant ($P = 0.041$) **(Table 5)**. These results suggested that folic acid supplement particularly reduced first stroke risk in individuals with the lowest baseline SII level.

4. Discussion

This study investigated the association between SII and first stroke risk in a Chinese population with hypertension. We observed a unique U-shape relationship between baseline SII levels and first stroke risk. Both low and high SII were associated with increased risk of first stroke independent of traditional risk factors. And folic acid supplement remarkably eliminated the additional risk, particularly in those at the lower tail of SII distribution.

SII was a novel indicator that was thought to comprehensively evaluate the overall immunity and inflammation status. It was initially introduced in hepatocellular carcinoma [12] and was recently investigated in the field of stroke. A study based on 85,154 general population showed that increment of SII was associated with increased 10-year risk of both ischemic and hemorrhage stroke [23]. Similarly, in coronary artery disease patients who underwent percutaneous coronary intervention, individuals in high SII group (≥694.3 × 10^9 cell/L) were prone to 96 % additional risk of incident stroke [24]. A recent meta-analysis involving 152,996 patients suggested that higher SII was associated with an increased risk for nearly all cardiovascular diseases including both ischemic and hemorrhagic stroke [25]. Consistent with previous documents, this study also demonstrated an unfavorable effect of elevated SII for higher stroke risk in hypertension population.

A plethora of evidence highlighted the crucial roles of immune and inflammatory mechanisms in hypertension and its complications [26]. Firstly, as regulators of cardiovascular inflammation and the first responders of innate immune, neutrophils were elevated in hypertensive patients [27,28]. They could contribute to ischemic damage by releasing elastase, metalloproteases, cathepsin G, reactive oxygen and nitrogen species, inflammatory cytokines, and forming neutrophil extracellular traps [29–31]. High baseline neutrophils were associated with an increased risk of first ischemic stroke among hypertensive patients [32]. Secondly, a bi-directional mendelian randomization study revealed the causal effect of platelets on hypertension [33]. Apart from well-known prothrombotic response, platelets are essential participants in the immune response that was thought to balance its pathogenic and regular thrombotic

Table 5
Effect modification of SII on folic acid Supplement for first stroke prevention.

SII, × 10^9 cells/L	Enalapril Group		Enalapril-Folic Acid Group		Crude Model		Adjusted Model		P for interaction
	N	Cases (%)	N	Cases (%)	HR (95 % CI)	*P* value	HR (95%CI)	*P* value	
Q1 (<334.9)	1,252	50 (4.0)	1251	29 (2.3)	0.57 (0.36, 0.90)	0.017	0.56 (0.34, 0.90)	0.018	0.041
Q2 (334.9 to <444.6)	1,269	37 (2.9)	1234	33 (2.7)	0.92 (0.57, 1.47)	0.719	0.95 (0.57, 1.59)	0.851	
Q3 (444.6 to <598.5)	1,215	45 (3.7)	1288	46 (3.6)	0.96 (0.64, 1.45)	0.856	1.00 (0.65, 1.54)	0.997	
Q4 (≥598.5)	1,283	59 (4.6)	1221	46 (3.8)	0.82 (0.56, 1.20)	0.308	0.88 (0.59, 1.33)	0.552	

Model adjusted for sex, age, BMI, baseline SBP, on-treatment SBP, FPG, TC, HDL-C, TG, folate, tHcy, MTHFR C677T, eGFR, smoking status and drinking status.

Abbreviation: BMI, body mass index; CI, confidence interval; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; MTHFR, methylenetetrahydrofolate reductase; SBP, systolic blood pressure; SII, systemic immune-inflammation index; TC, total cholesterol; TG, triglyceride; tHcy, total homocysteine.

and hemostatic functions [34]. On the other hand, certain types of lymphocytes, such as the Treg cells, could conferred neuroprotection by downregulating ischemic inflammation [35]. Taken together, increased SII could reflect overactive inflammation and immune disturbance, which mediate higher stroke risk.

Prior reports often illustrated a linear relationship between SII and incident stroke [23,25,36]. Yet a unique U-shape relationship was observed in this study, where low SII also appeared to impose additional stroke risk in the condition of hypertension. In accord, a prior study including 8524 adults with hypertension also reported a U-shape relationship between SII and all-cause mortality [37]. Actually, hemocytes involved in SII confer double-edged effects in stroke. For example, neutrophils that show signs of alternative activation, associated with the expression of Arg1 and YM1, might be beneficial in cerebral ischemia. It was proposed that neuroprotection observed after myeloid-selective Toll-like receptor 4 deletion was due to cytoprotective neutrophils [38,39]. Furthermore, it was documented that low platelet counts independently predicted stroke risk in the condition of hypertension [21]. One rational interpretation was massive platelet consumption caused by persistent pro-thrombosis inflammation. On the other hand, T cells could also be detrimental early in ischemia [8]. It was reported that T lymphocytes stimulated by hypertension can infiltrate into target organs, leading to vascular dysfunction and blood pressure elevation [40,41]. And low SII was also shown to align with reduced IL-10, a strong anti-inflammatory and immunosuppressive cytokine that promoted the survival of gliocytes and neurons [42,43]. Taken together, decreased SII could to some extent reflect the activation of pro-thrombosis inflammation and immune, as well as some defect of neuroprotective mechanism. Further studies are needed to uncover the underlying mechanism and validate this hypothesis.

An apparent bias that folic acid particularly reduced stroke incidence in individuals with low SII was observed in this study. In accord, previous analysis also showed that folic acid treatment may be specifically effective for preventing stroke in subgroup of low platelet counts [21]. The underlying mechanism remained ambiguous. Elevated homocysteine has long been known as a risk factor of stroke [44]. It could promote endothelial damage, augment leukocyte adhesion to the endothelium and enhance the platelet activity of aggregation [45,46]. As low SII to some extent implicated certain deficiency of neuroprotection, detrimental impact of high homocysteine on stroke appeared to be much more remarkable, which make patients with lowest SII benefit more from compensatory folic acid. Yet further studies are needed to validate this hypothesis.

Our study is of significant clinical and public health value. Firstly, as most clinical evidence on SII was derived from cross-section studies, this analysis examined the predictive value of SII for first stroke risk in a Chinese population with hypertension, expanding the prospective evidence of its clinical application in the cardiovascular field. Furthermore, our findings, if confirmed, may help to quickly identify individuals who are at high risk of first stroke and who would particularly benefit from folic acid supplement by conducting routine blood test, which is easily available, widely used and economical.

However, there are still some limitations needed to be stated. Firstly, the one-spot routine blood test conducted at baseline may not represent long-term immune-inflammation status across the follow-up duration. Secondly, interferences of certain types of inflammatory or immune disorders, as well as medication usage that potentially affects the hemocyte counts were not excluded due to incompleteness of relevant data. Thirdly, risks for different stroke subtypes were not estimated since the limited cases of hemorrhage stroke during the follow-up (25 in the enalapril group and 16 in enalapril-folic acid group). Finally, since a large portion (4075/15,486) of population were excluded due to unavailable data of hemocyte counts needed for SII calculation, there could possibly be a selection bias.

5. Conclusions

Among Chinese adults with hypertension, a U-shape association between SII and first stroke risk was observed. Both low and high SII at baseline predicted increased risk of first stroke. And compensatory folic acid particularly reduced stroke risk in the lowest SII subgroup. Further *in vivo* and *in vitro* studies are warranted to validate the findings and also provide potential mechanisms.

9. Ethic declaration

This study was reviewed and approved by the ethics committee of the Institute of Biomedicine, Anhui Medical University, Hefei, China, with FWA assurance number: FWA00001263. All participants provided informed consent to participate in the study.

10. Data availability

Data will be made available on request.

CRediT authorship contribution statement

Xiying Chi: Writing – review & editing, Writing – original draft. **Nan Zhang:** Writing – review & editing, Writing – original draft, Formal analysis, Data curation. **Fangfang Fan:** Methodology. **Jia Jia:** Project administration. **Jianhang Zheng:** Formal analysis, Data curation. **Lishun Liu:** Resources, Project administration, Methodology, Investigation. **Yun Song:** Resources, Project administration, Methodology, Investigation. **Binyan Wang:** Resources, Project administration, Methodology, Investigation. **Genfu Tang:** Resources, Project administration, Methodology, Investigation. **Xianhui Qin:** Resources, Project administration, Methodology, Investigation. **Yong Huo:** Resources, Project administration, Methodology, Investigation. **Jianping Li:** Visualization, Validation, Supervision, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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