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Association between Systemic Immune-Inflammation Index and Mortality in Type 2 Diabetes Patients Complicated with Ischemic Stroke: A Retrospective Cohort Study

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Abstract: Background: When type 2 diabetes mellitus (T2DM) occurs concomitantly with ischemic stroke, it poses a major challenge to global public health and is related to poor prognosis. Inflammation is a crucial factor driving the progression of this condition. The systemic immune-inflammation index (SII), which was considered capable of comprehensively assessing the overall immunity and inflammation, has a relationship with the mortality of T2DM patients suffering from ischemic stroke that has not yet been fully clarified. This study seeks to investigate the relationship between SII and mortality at 28 days and one year in T2DM patients complicated with ischemic stroke. Methods: The research utilized data from the MIMIC-IV database, with participants categorized into three groups based on SII tertiles. The primary outcome focused on mortality at 28 days and one year. The association between SII and mortality was assessed through smoothed curve fitting methods and multivariate Cox regression analyses. To analyse cumulative survival rates across these time frames, Kaplan-Meier curves were employed. Additionally, receiver-operating characteristic (ROC) curves were generated to gauge the predictive capabilities of SII. To ensure the reliability of the findings, subgroup analyses were performed. Results: This study evaluated a total of 1,204 patients. The results indicated that an increase in SII correlated with an increased likelihood of mortality at both 28 days and one year among individuals with T2DM complicated by ischemic stroke. Higher levels of SII were significantly linked to an elevated hazard ratio for 28-day (HR: 1.43, $P < 0.01$) and 1-year (HR: 1.27, $P < 0.01$) mortality in this patient group. A nonlinear relationship between SII and mortality in this patient population was evident from the smoothed fitting curve ($P < 0.01$). The ROC analysis demonstrated that SII outperformed both the SOFA and GCS scores in predicting mortality in this patient population. The decision curve analysis reinforced that SII offered a superior net benefit compared to the SOFA and GCS scores. Subgroup analyses showed no significant interaction between SII and all subgroups (P value of interaction > 0.05). Conclusion: In T2DM patients with ischemic stroke, higher SII levels correlated with increased mortality at 28 days and one year.

Keywords: Type 2 Diabetes Mellitus (T2DM); Ischemic Stroke; Systemic Immune-Inflammation Index (SII); Mortality

1. Introduction

In recent decades, the incidence of ischemic stroke has continued to rise and is now the third leading cause of death worldwide, with a high rate of disability [1]. Diabetes mellitus is a major risk factor for ischemic stroke and has a negative impact on the prognosis of patients [2]. In particular, patients with diabetes and stroke have higher rates of mortality and disability than non-diabetic stroke patients, significantly reducing their quality of life [3, 4].

Stroke also carries a significant economic burden, with the annual direct and indirect economic burden of stroke in the United States estimated at $45.5 billion [5]. The identification of modifiable risk factors as a primary objective is imperative to reduce the disease's poor prognosis and financial burden.

It has been shown that inflammation is essential to the pathophysiology of both diabetes and stroke, contributing to the development and progress of both diseases [6, 7]. There is growing evidence that the breakdown of the blood-brain barrier (BBB) during an ischemic stroke allowed peripheral inflammatory cells to infiltrate, potentially worsening the outcome of the stroke [8, 9]. For example, increased neutrophil counts correlate with stroke severity and mortality [10]. The decrease in lymphocytes may be related to the immunosuppressive state and affect the body's ability to repair the ischemic injury [11]. After an ischemic stroke, monocytes secrete pro-inflammatory cytokines that affect infarct tissue and exacerbate ischemic injury [12]. Research has shown that in patients suffering from ischemic stroke, the neutrophil-to-lymphocyte ratio (NLR) can be utilized as an independent prognostic indicator [13, 14]. The clinical outcomes are generally poorer for those with higher NLR [15].

As an emerging marker of overall immunity and inflammation, the systemic immune-inflammation index (SII) has been proven to mirror the severity of the inflammatory response [16]. Research indicates a robust correlation between SII and the prognosis of various conditions, including rheumatoid arthritis [17], prostate cancer [18], diabetes mellitus [18], sepsis [19], hepatic steatosis [20], heart failure [21], and nasopharyngeal carcinoma [22]. Research indicates a strong correlation between SII and the prognosis of various conditions [23]. Higher levels of the SII have been tied to an augmented risk of stroke among patients with asthma [24]. As demonstrated by Wang et al., SII has been shown to have a significant association with all-cause, cardiovascular, and cardiovascular and cerebrovascular mortality in the general population [25]. Liang et al. conducted a meta-analysis of 25,626 patients in nine cohorts, which demonstrated that high SII at admission was significantly associated with an increased risk of all-cause short-term mortality in patients with sepsis [26]. Furthermore, Cao et al. observed that in people with hypertension, higher SII was significantly associated with a higher risk of cardiovascular mortality [27]. Cheng et al. observed similar results, demonstrating that high levels of SII in hypertensive patients are closely associated with a higher risk of all-cause mortality and cardiovascular mortality [28].

The association of SII with mortality in critically ill patients with T2DM complicated with ischemic stroke remains poorly studied. Therefore, this study aims to shed light on the connection between SII and mortality at 28 days and one year in T2DM patients who have suffered an ischemic stroke, utilizing the comprehensive MIMIC-IV database for analysis.

2. Materials and Methods

2.1. Data Source

The data utilized in this retrospective cohort study were sourced from the MIMIC-IV database, version 2.2 (accessible at). Maintained by the Massachusetts Institute of Technology's Laboratory for Computational Physiology, this comprehensive database houses anonymized medical records of patients admitted to Beth Israel Deaconess Medical Center from 2008 to 2019 [29]. These records contain demographics, clinical indicators, vital signs, disease names, treatment measures, and survival rates. This study does not require informed consent or ethical review because the database is open to the public and the identification is hidden to protect patient privacy. The data extraction of this study was completed by Zhu Hongwei, who participated in the training and examination of the Collaborative Institutional Training Initiative (CITI Program) as required and obtained the database access (record ID: 13158546).

2.2. Study Population

The MIMIC-IV database (version 2.2) included 73,180 patients admitted to the ICU, with 50,920 of these being first-time admissions [30]. Inclusion criteria Eligible patients were: (a) individuals who fulfilled the requirements for the diagnosis of T2DM complicated with ischemic stroke, as detailed in the ninth and tenth editions of the International Classification of Diseases; (b) those who had their first ICU admission; and (c) adults aged ≥18 years. Exclusion criteria: Patients were excluded if they had key variables missing such as platelet count, neutrophils, lymphocytes, main intervention, and treatment indicators. Finally, 1204 T2DM patients with ischemic stroke were included for analysis (**Figure 1**).

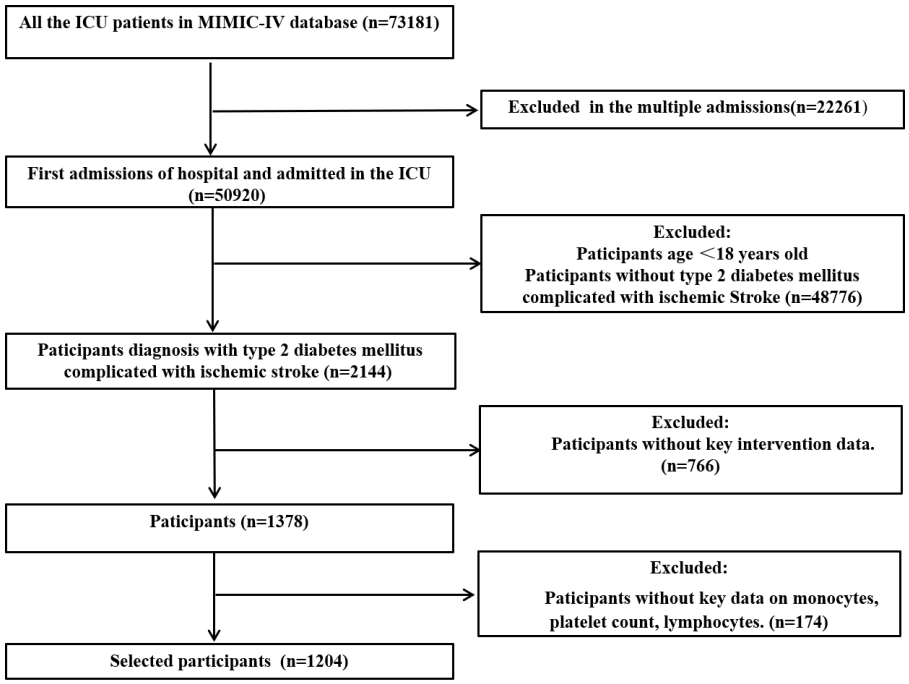

Figure 1. Flowchart of literature screening.

2.3. Data Extraction

Relevant data were extracted using PostgreSQL 16. The extracted data included: 1) General information of patients: age, gender, race, marriage, and BMI; 2) Laboratory data: white blood cell(WBC) count, lymphocyte percentage, red blood cell(RBC) count, neutrophil percentage, platelet (PLT) count, albumin(ALB), aspartate aminotransferase(AST), blood urea nitrogen(BUN), monocyte percentage, alanine aminotransferase(ALT), serum glucose, glycosylated hemoglobin(HBA1C), calcium, bicarbonate, prothrombin time (PT); 3) Disease complications: hypertension, cardiovascular disease(CVD); 4) Vital signs at first admission: heart rate(HR), respiratory rate(RR), oxygen saturation (SPO2); 5) Clinical score: Acute physiology score III (APSIII), Simplified acute physiological score II (SAPSII), sequential organ failure assessment (SOFA), Glasgow Coma scale score (GCS) GCS; 6) Medications: aspirin, statins; and 7) Invasive operation and examination: mechanical ventilation and dialysis. The SII was defined as platelet count×neutrophil percentage/lymphocyte percentage.

2.4. Handling of Outliers and Missing Values

The researchers first deleted variables with missing values above 20%. Variables with a missing value below 20%, were supplemented by multiple completions. This process was completed by the "mice" package in R software, and the random forest algorithm—which was trained using additional non-missing variables—was employed to analyze numerous substitutions. The cap method was adopted to deal with the variables with abnormal values, with a cutoff of 1 and 99%.

2.5. Outcome

The study outcome was all-cause mortality at 28 days and one year post-ICU admission.

2.6. Statistical Analysis

Normally distributed continuous variables were summarized using the mean±standard deviation, while non-normally distributed variables were described by the median and interquartile range. For data of normal distribution, analysis of variance (ANOVA) was employed, while for those deviating from normal distribution, the Kruskal-Wallis test was adopted. Categorical variables were expressed as counts and percentages, with comparisons made using the chi-square test.

To assess potential confounding factors, we examined the impact of all variables on mortality at 28 days and one year using a univariate Cox proportional hazards model. Subsequently, the multivariate analysis included all variables deemed clinically or statistically significant. Model 1 was an unadjusted model. In the context of mortality, the adjusted variables for Model 2 encompassed age, gender, race, and marital status. For Model 3 in relation to mortality, the adjusted variables included gender, race, age, albumin, ALT, glucose, calcium, bicarbonate, CVD, aspirin use, statin use, and APIII. In order to compare the predictive ability of SII with that of SOFA and GCS in relation to mortality among T2DM complicated with ischemic stroke, we analyzed the area under the curve (AUC) of the receiver operating characteristic (ROC) along with sensitivity and specificity. The disease-related survival of patients in various SII groups was evaluated and compared using Kaplan–Meier (KM) survival analysis. The influence of general data, complications, and main intervention measures on the research results was further analyzed by subgroup analysis, which aimed at evaluating the reliability and robustness of the research results. Meanwhile, the likelihood ratio test was used to evaluate the interaction between SIRI and subgroups. For the statistical analysis, R version 4.3.2 was employed. All statistical tests were conducted at a significance level of $P < 0.05$.

3. Results

3.1. Baseline Characteristics

This research comprised 1204 cases of T2DM complicated with ischemic stroke (**Table 1**). Patients were classified into three groups based on the SII tertile: T1 (≤667.06), T2 (667.06–1369.10), and T3 (⍰1369.10). The baseline features of each group are shown in Table 1. Older age was often linked to a greater SII. Patients with higher SII all had high APSIII and SAPSII scores. Those with greater SII levels had lower levels of albumin, lymphocytes, and bicarbonate than those with lower SII levels, but higher levels of BUN, creatinine, white blood cells, PT, glucose, and neutrophils. There were no observed variations in the groups' glycosylated hemoglobin, BUN, INR, and creatinine. The mortality of 28 days and one year for T2DM complicated with ischemic stroke increased in concert with an increase in SII.

Table 1. Patient outcomes and baseline characteristics by SII.

Parameters	Total (n = 1204)	T1 (N = 401)	T2 (N = 401)	T3 (N = 402)	P Value
Demographic Variables					
Age (years)	70.0 (62.0,80.0)	69.0 (60.0,79.0)	70.0 (61.0,79.0)	72.0 (64.0,81.0)	0.022
Gender:					0.797
Male	620 (51.5%)	204 (50.9%)	212 (52.9%)	204 (50.7%)	
Female	584 (48.5%)	197 (49.1%)	189 (47.1%)	198 (49.3%)	
Marital status:					0.163
Single	296 (24.6%)	106 (26.4%)	90 (22.4%)	100 (24.9%)	
Married	549 (45.6%)	191 (47.6%)	189 (47.1%)	169 (42.0%)	
Other	359 (29.8%)	104 (25.9%)	122 (30.4%)	133 (33.1%)	
Race:					0.009
White	694 (57.6%)	212 (52.9%)	227 (56.6%)	255 (63.4%)	
Other	510 (42.4%)	189 (47.1%)	174 (43.4%)	147 (36.6%)	
Vital Signs					
HR (bpm)	98.2 (97.7,98.7)	98.1 (97.7,98.7)	98.2 (97.7,98.8)	98.2 (97.7,98.7)	0.533
RR (bpm)	18.0 (15.0,22.0)	17.0 (15.0,21.0)	18.0 (14.0,21.0)	19.0 (16.0,23.0)	<0.001
SpO2 (%)	85.0 (85.0,88.0)	85.0 (85.0,88.0)	85.0 (85.0,88.0)	85.0 (85.0,88.0)	0.331
Laboratory Parameters					
ALB (g/dL)	3.90 (3.40,4.20)	3.90 (3.60,4.20)	3.90 (3.50,4.30)	3.70 (3.23,4.20)	<0.001
ALT (IU/L)	48.5±177	38.6±101	34.4±97.1	72.3 ±271	0.004
AST (IU/L)	63.5±258	49.3 ±156	44.2±162	96.8 ±384	0.006
BUN (mg/dL)	21.0 (15.0,30.0)	20.0 (15.0,28.0)	21.0 (15.0,28.0)	22.0 (15.2,31.8)	0.064
Calcium (mEq/L)	9.01 (0.77)	9.07 (0.70)	9.10 (0.77)	8.85 (0.81)	<0.001
Creatinine (mg/dL)	1.10 (0.80,1.40)	1.00 (0.80,1.30)	1.00 (0.80,1.40)	1.10 (0.80,1.40)	0.286
Glucose (mg/dL)	152 (115,220)	136 (105,192)	154 (115,220)	180 (128,239)	<0.001
HBA1C (%)	6.90 (6.20,8.10)	6.80 (6.10,8.20)	7.00 (6.30,8.20)	6.90 (6.10,8.00)	0.189
Bicarbonate (mEq/L)	24.9±4.08	25.5±3.84	25.2±3.78	24.1±4.46	<0.001
Lymphocyte (%)	19.7±10.6	30.6±8.76	18.9±5.17	9.74±4.00	<0.001
Monocyte (%)	5.91±2.55	6.61±2.57	5.99±2.44	5.12±2.44	<0.001
Neutrophil (%)	71.3±12.4	58.6±9.50	72.5±6.09	82.9±6.42	<0.001
Pt (seconds)	13.6±5.62	13.7±7.10	13.1±4.09	14.0±5.23	0.079

Table 1. *Cont.*

Parameters	Total (n = 1204)	T1 (N = 401)	T2 (N = 401)	T3 (N = 402)	P Value
INR	1.23±0.65	1.24±0.88	1.18±0.41	1.28±0.54	0.087
WBC (K/uL)	8.60 (6.80,10.9)	7.20 (5.90,8.70)	8.50 (6.90,10.5)	10.4 (8.50,14.0)	<0.001
Platelets (K/uL)	234 (186,288)	205 (161,252)	236 (196,289)	266 (206,310)	<0.001
SII (K/uL)	1339±1216	412±147	959±205	2642±1292	<0.001
Comorbidity Diseases, n (%)					
Hypertension:					0.002
No	322 (26.7%)	100 (24.9%)	90 (22.4%)	132 (32.8%)	
Yes	882 (73.3%)	301 (75.1%)	311 (77.6%)	270 (67.2%)	
CVD:					0.757
No	777 (64.5%)	253 (63.1%)	261 (65.1%)	263 (65.4%)	
Yes	427 (35.5%)	148 (36.9%)	140 (34.9%)	139 (34.6%)	
Interventions, n (%)					
Aspirin:					0.461
No	132 (11.0%)	39 (9.73%)	43 (10.7%)	50 (12.4%)	
Yes	1072 (89.0%)	362 (90.3%)	358 (89.3%)	352 (87.6%)	
Statins:					0.061
No	141 (11.7%)	35 (8.73%)	50 (12.5%)	56 (13.9%)	
Yes	1063 (88.3%)	366 (91.3%)	351 (87.5%)	346 (86.1%)	
MV:					0.413
No	565 (46.9%)	199 (49.6%)	182 (45.4%)	184 (45.8%)	
Yes	639 (53.1%)	202 (50.4%)	219 (54.6%)	218 (54.2%)	
Thrombolysis:					0.795
No	965 (80.1%)	317 (79.1%)	324 (80.8%)	324 (80.6%)	
Yes	239 (19.9%)	84 (20.9%)	77 (19.2%)	78 (19.4%)	
Clinical Severity					
APSIII	42.0 (31.8,54.0)	41.0 (30.0,53.0)	40.0 (31.0,53.0)	44.0 (33.0,57.0)	0.014
GCS	15.0 (14.0,15.0)	15.0 (14.0,15.0)	15.0 (14.0,15.0)	15.0 (14.0,15.0)	0.351
SAPSII	35.0 (27.0,43.0)	34.0 (27.0,42.0)	34.0 (27.0,42.0)	36.0 (28.0,44.0)	0.033
SOFA	1.00 (0.00,2.00)	1.00 (0.00,3.00)	1.00 (0.00,2.00)	1.00 (0.00,2.00)	0.045
Outcomes, n (%)					
28-day mortality:					<0.001
No	1124 (93.4%)	389 (97.0%)	381 (95.0%)	354 (88.1%)	
Yes	80 (6.64%)	12 (2.99%)	20 (4.99%)	48 (11.9%)	
1-year mortality:					<0.001
No	970 (80.6%)	350 (87.3%)	337 (84.0%)	283 (70.4%)	
Yes	234 (19.4%)	51 (12.7%)	64 (16.0%)	119 (29.6%)	

Normally distributed continuous variables are presented as mean ± standard deviation, nonnormally distributed continuous variables as medians with their median (interquartile ranges (IQR)), and categorical variables as total number and percentage.
SII group:T1: ≤667.06 ; T2: 667.06 -1369.10; T3:⍰1369.10; HR: Heart rate; RR: respiratory frequency; ALT: Alanine Aminotransferase; PT: prothrombin time; INR: international normalized ratio; BUN: blood urea nitrogen; AST: Asparate Aminotransferase; ALB: serum albumin; RBC: red blood cells count; WBC: white blood cells count; HBA1C: glycosylated hemoglobin; CVD: cardiovascular disease; SOFA : sequential organ failure assessment score; SAPSII: Simplified acute physiological score II;APSIII: acute physiological score III; GCS: Glasgow coma scale; MV: mechanical ventilation.

3.2. The Relationship between SII and Mortality in T2DM Complicated with Ischemic Stroke

In order to scrutinize the connection between SII and mortality at both 28 days and one year, multivariable covariate Cox hazard regression models were set up. When SII was regarded as a continuous variable, the unadjusted model revealed a notable association between SII and mortality (OR: 1.43; 95% CI 1.27-1.62; P < 0.001). The variables such as gender, age, race, respiratory frequency, albumin, glucose, alanine aminotransferase (ALT), calcium, bicarbonate, CVD, aspirin, statins, and APSIII all entered the adjusted multivariate Cox hazard regression models, SII was still significantly correlated with the 28-day mortality (HR:1.30; 95% CI: 1.11–1.52; P < 0.01). In T2DM complicated by ischemic stroke, we noted a similar relationship between SII and one-year mortality as well. Furthermore, when SII was considered as a categorical variable, in the unadjusted model, the mortality at both 28 days and one year for SII T3 was substantially higher than that for SII T1. In the fully adjusted model, this disparity remained statistically significant. **Table 2** presents the results of the Cox regression analysis.

The relationship between SII and the mortality at 28 days and one year in T2DM complicated with ischemic stroke was analyzed through smoothed curve fitting. The findings revealed a non-linear correlation, suggesting that increased levels of SII are linked to an elevated risk of mortality within both 28 days and one year (p < 0.001) (**Figure 2**).

Kaplan-Meier survival curves further demonstrated that the mortality of 28 days was significantly greater in

Table 2. The relationship between SII and mortality in T2DM patients with ischemic stroke.

	SII	T1	T2	T3	p for Trend
28-day mortality	Per 1000-unit increase				
Model 1	1.43(1.27–1.62)	1	1.60(0.78–3.30)	3.83(2.02–7.24)	<0.001
Model 2	1.43(1.26–1.61)	1	1.69(0.82–3.48)	3.98(2.10–7.57)	<0.001
Model 3	1.27(1.10–1.46)	1	1.48(0.71–3.12)	2.92(1.44–5.94)	<0.001
1-year mortality					
Model 1	1.27(1.18–1.38)	1	1.28(0.89–1.68)	2.62(1.89–3.63)	<0.001
Model 2	1.27(1.17–1.37)	1	1.31(0.91–1.91)	2.51(1.80–3.48)	<0.001
Model 3	1.13(1.03–1.24)	1	1.35(0.92–1.98)	2.06(1.42–3.00)	<0.001

Model 1: baseline (unadjusted).
Model 2: adjusted taking into account race, gender, age,and marital status.
Model 3: adjusted for multivariate variables: age, race, gender, albumin, ALT, glucose, calcium, bicarbonate, CVD,aspirin, statins, and APSIII.

the high SII cohort compared to those with low SII levels (log-rank test: p<0.001). A similar trend was evident for the 1-year mortality, with the high SII group again showing a markedly increased risk (log-rank test: p<0.001). These results highlight the consistent link between elevated levels of SII and poorer survival outcomes in T2DM patients with ischemic stroke.

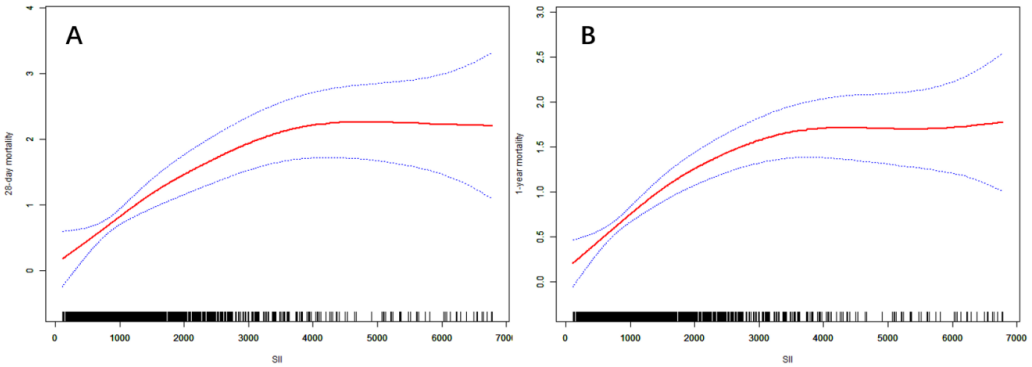

Figure 2. The association between the SII and mortality at both 28 days (**A**) and 1 year (**B**) in individuals with T2DM complicated with ischemic stroke was examined. The analysis revealed a nonlinear connection between SII levels and mortality outcomes. The solid red line illustrates the smoothed curve that correlates the variables, while the blue shaded areas indicate the 95% confidence interval derived from this fitting.

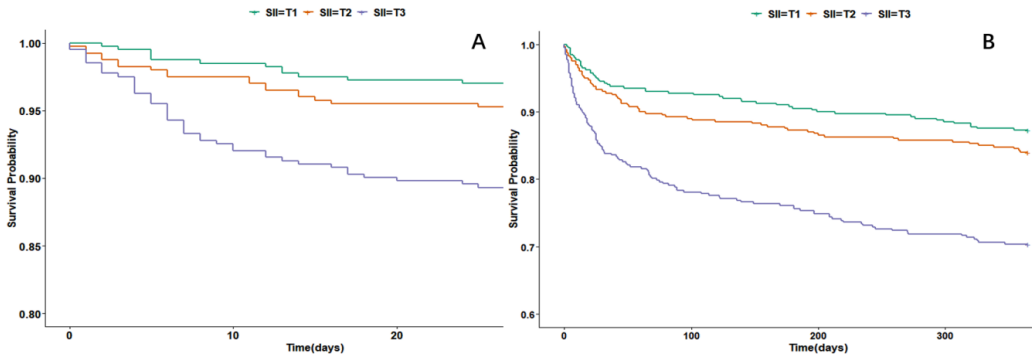

Figure 3. Kaplan-Meier curves for cumulative survival rates at 28-day (**A**) and 1-year (**B**).

The analysis demonstrated that T2DM patients with ischemic stroke in the high SII group had markedly reduced survival rates compared to their counterparts in the low SII group, both at the 28-day and 1-year group, as depicted in **Figure 3**.

3.3. Prognostic Value of SII in T2DM Patients with Ischemic Stroke

When it comes to predicting mortality at 28 days and one year in T2DM complicated with ischemic stroke, the predictive values of SII outshine those of SOFA and GCS. In the prediction of mortality at 28 days among T2DM complicated with ischemic stroke, the AUC value of SII (AUC: 0.69, 95% CI: 0.62 - 0.75) surpasses that of SOFA (0.57, 95% CI: 0.50 - 0.64). For predicting mortality at one year in T2DM complicated with ischemic stroke, the AUC of SII is 0.64 (95% CI: 0.60 - 0.68), which is greater than the AUC values of SOFA (AUC: 0.57, 95% CI: 0.53 - 0.61).

As demonstrated in **Figure 4**, the ROC curves for SII, APSIII and SOFA scores in predicting mortality at 28 days and one year in individuals with T2DM patients with ischemic stroke are displayed. **Table 3** shows a comparison of parameters related to the ROC curve.

Figure 5 shows the decision curve (AUC) for SII, APSIII and SOFA scores in predicting mortality at 28 days and one year in T2DM complicated with ischemic stroke. When the risk threshold possibility is within 0-100%, the larger area under the decision curve (AUC) indicates the greater net benefit of the corresponding model. As shown in the figure, the net benefit of SII was greater than that of SOFA scores, indicating that SII may have a good clinical effect.

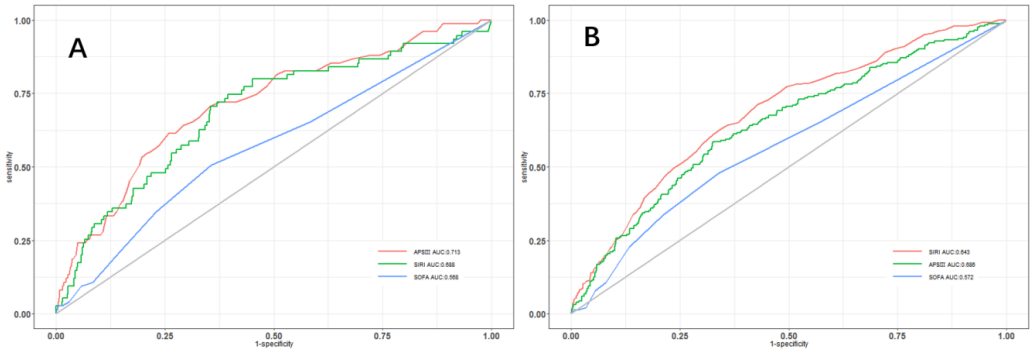

Figure 4. The ROC curves of SII, APSIII and SOFA scores for predicting mortality at 28 days (**A**) and one year (**B**) in T2DM complicated with ischemic stroke.

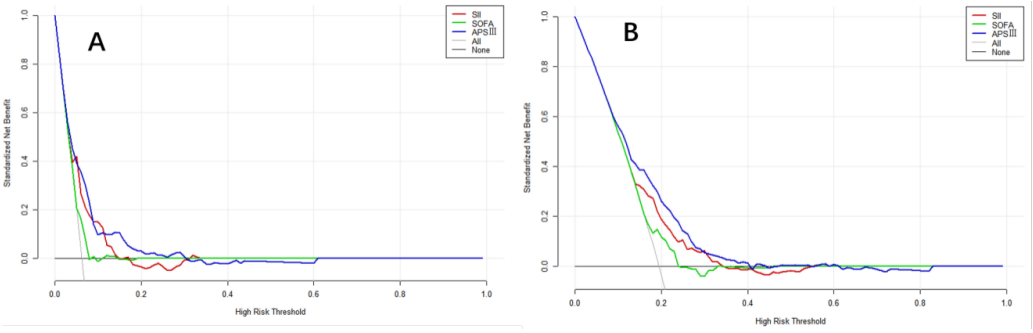

Figure 5. The calibration curves of SII, APSIII and SOFA scores in predict mortality at 28 days (**A**) and one year (**B**) in T2DM complicated with ischemic stroke.

3.4. Subgroup Analysis

The patient's marital status, gender, race, disease complications, and intervention strategies were taken into consideration while stratifying and analyzing interactions. SII and each subgroup had no interaction, according to interaction analysis ($P > 0.05$). A significant interaction was found between SII and hypertension (P for interaction < 0.05) in one year in critically ill patients with T2DM complicated with ischemic stroke. This indicates that SII is linked to mortality at 28 days and one year of the majority of subgroups of T2DM complicated with ischemic stroke and that its impact on these outcomes remained constant across all subgroups (**Figure 6**).

Table 3. Comparison of parameters related to the ROC curve.

	AUC	95% CI	Threshold	Specificity	Sensitivity	Youden's Index
28-day mortality						
SIIROC	0.69	0.62–0.75	1132.5	0.61	0.75	0.35
APSIIIROC	0.72	0.66–0.78	52.5	0.74	0.62	0.36
SOFAROC	0.57	0.50–0.64	1.5	0.64	0.51	0.15
1-year mortality						
SIIROC	0.64	0.60–0.68	1236.7	0.67	0.59	0.26
APSIIIROC	0.67	0.53–0.61	46.5	0.66	0.63	0.29
SOFAROC	0.57	0.53–0.61	1.5	0.66	0.48	0.14

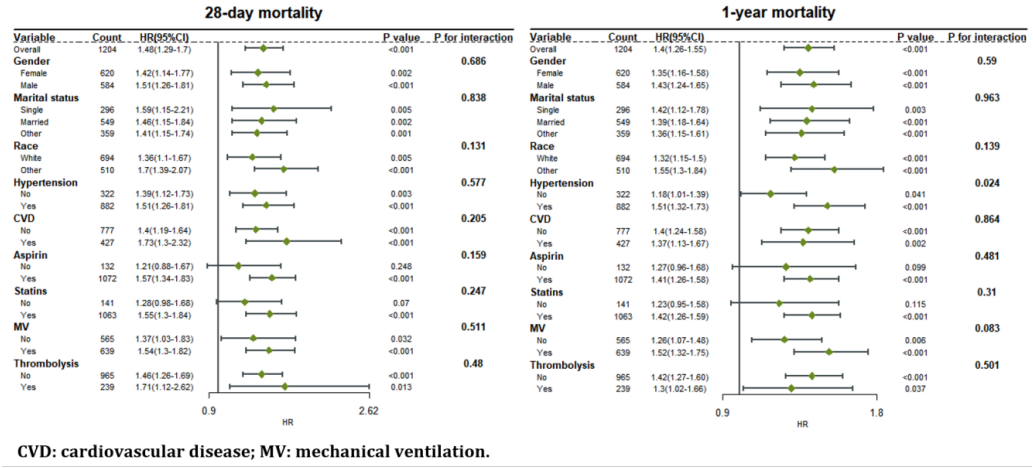

Figure 6. Subgroup analysis of the relationship between SII and mortality of T2DM patients with ischemic stroke.

4. Discussion

Ischaemic stroke is a major cause of disability and mortality, with a rising incidence and causing serious harm to human health [31]. Diabetes is strongly associated with ischaemic stroke, and about one-third of stroke patients have T2DM [32]. Compared with non-diabetic ischaemic stroke patients, those with diabetes have higher rates of disability, longer hospital stays, higher costs, higher rates of recurrence, and higher mortality [33, 34]. Therefore, early identification of high-mortality T2DM complicated with ischemic stroke in the intensive care unit (ICU) and selection of appropriate treatment may reduce risk and improve prognosis. Our study evaluated the relationship between SII and mortality at 28 days and one year in critically ill patients with T2DM complicated with ischemic stroke. The main findings are as follows: (1) Even after adjustment for potential confounders, elevated SII levels were significantly linked to higher mortality at 28 days and one year in critically ill patients with T2DM complicated with ischemic stroke. (2) Smoothed curve fitting showed that mortality at 28 days and one year in T2DM complicated with ischemic stroke increased with increasing SII. (3) When compared with the SOFA scores, SII exhibited a higher AUC for predicting mortality at 28 days and one year. (4) Subgroup analysis showed that this relationship was consistent across subgroups of sex, race, marital status, coexisting hypertension, CVD, aspirin use, and statin use, demonstrating the robustness of the findings.

Inflammation is a cornerstone of the immune response and holds a crucial position in the pathophysiology of both diabetes and cerebrovascular disease [35–37]. Chronic, low-grade inflammation in diabetic patients has been shown to lead to damage of vascular endothelial cells, activation of platelets, and thrombosis, thereby spurring the development of atherosclerosis and upping the risk of cerebrovascular events [38]. Neutrophils are pivotal in the inflammatory response linked to atherosclerosis [39, 40]. They cause endothelial cell damage and tissue ischemia by discharging a variety of inflammatory mediators, chemotactic agents, and reactive oxygen species [41]. Platelet activation also holds a crucial position in atherosclerotic thrombosis in diabetes [42]. It has been reported that

patients with impaired glucose metabolism, namely in the early phases of diabetes, display heightened platelet activation and thromboxane (TX) synthesis [42]. In contrast, lymphocytes play a regulatory role in inflammation and may help curb the progression of atherosclerosis [43]. There is also increasing evidence that inflammation plays an important role in the progression of acute ischemic stroke. Numerous investigations have underscored the pivotal role that neutrophils play in ischemic stroke [44, 45]. The function of neutrophils is therefore a significant factor in the prognosis of stroke [46]. The frequency of peripheral blood neutrophils has been identified as an early prognostic indicator of stroke [46]. Conversely, lower lymphocyte counts have been linked to poorer long-term outcomes in stroke patients [47].

SII, a novel biomarker for systemic inflammatory and immunological response based on the counts of neutrophils, platelets, and lymphocytes [48], has recently been attracting a great deal of attention owing to its potential in predicting the prognosis of various diseases, such as cancer [49], infectious diseases [50, 51] and cardiovascular disease [52]. Li et al. highlighted SII as a reliable predictor of mortality among patients undergoing peritoneal dialysis, revealing that higher SII levels correlate with an elevated risk of death [53]. Cheng et al. demonstrated that increased levels of SII were linked to a greater likelihood of stroke in individuals who had suffered asthmatics [24], while Lai et al. observed that elevated SII levels were tied to greater cardiovascular mortality in individuals with chronic kidney disease (CKD) [54]. Hu et al. revealed that elevated SII levels significantly raise the likelihood of post-stroke depression [55], while Li et al. further demonstrated that SII independently forecasts early progression/recurrence of stroke in individuals with acute atherosclerotic ischemic stroke [56]. Our study found that patients with hypertension had a higher 1- year mortality than those without hypertension, which is consistent with the findings of Yang et al. [27]. As far as the authors are aware, no research has evaluated SII's association with short-term and long-term mortality in critically ill patients with T2DM complicated with ischemic stroke. Consequently, there is considerable potential to utilize SII as a prognostic indicator for T2DM complicated with ischemic stroke.

The limitations of the current study are outlined below. Firstly, it is a retrospective analysis. Although the researchers conducted multivariate adjustment and subgroup analysis, the possibility of residual confounding factors still exists. Secondly, the SII was calculated using only the results of the first test after the patient entered the ICU. Exploration of additional time points and dynamic change level studies is recommended. Third, there is no detailed information on the location and volume of stroke in our study, so it is not able to explore whether the association between SII and prognosis differs in patients with different location and volume of stroke. Fourthly, there were no detailed functional prognostic indicators of stroke patients in our study, such as Rankin scores or Barthel indices, so it was not possible to investigate whether there were differences in the correlation between SII and functional prognosis in patients with type 2 diabetes complicated by ischaemic stroke. Finally, our research was conducted in the American population, and it remains unclear whether our findings can be generalized to other populations. Considering these factors, prospective, randomized controlled trials are needed for further validation.

5. Conclusions

Increased SII levels were observed to be linked to a higher risk of both short-term and long-term mortality in T2DM complicated with ischemic stroke. SII demonstrated satisfactory performance in predicting mortality in T2DM complicated with ischemic stroke. This finding suggests that SII could serve as a promising early predictor of mortality in T2DM complicated with ischemic stroke.

Author Contributions

Conceptualization, H.Z. and G.S.; methodology, H.Z.; software, H.Z.; validation, H.Z. and G.S.; formal analysis, H.Z.; investigation, H.Z.; resources, H.Z. and G.S.; data curation, H.Z.; writing—original draft preparation, H.Z.; writing—review and editing, G.S.; visualization, G.S.; supervision, G.S.; project administration, G.S.; funding acquisition, G.S.. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement

This study utilized the Medical Information Mart for Intensive Care (MIMIC) database, which is a publicly available.The MIMIC database is overseen by the Institutional Review Boards (IRB) of the Massachusetts Institute of Technology (MIT) and Beth Israel Deaconess Medical Center (BIDMC), and its use has been approved for research purposes.

Since the data are de-identified and do not contain protected health information, individual patient consent and additional ethical approval were waived. The study was conducted in accordance with the Declaration of Helsinki, and the principal investigator has completed the necessary ethics training and obtained certification for using the MIMIC database (record ID: 13158546).

Informed Consent Statement

Informed consent was obtained from all subjects involved in the study.

Data Availability Statement

Publicly available datasets were analyzed in this study. These data can be found here: https://mimic.mit.edu/. Further inquiries can be directed to the corresponding author.

Acknowledgments

The authors have no acknowledgments to declare.

Conflicts of Interest

The authors declare no conflict of interest.

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