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ORIGINAL RESEARCH

Association of the Cumulative Inflammatory Index and Long-Term Mortality in Stroke-Associated Pneumonia

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Background: Stroke-associated pneumonia (SAP) represents a common complication that increases the mortality risk in individuals who have experienced a stroke. We aimed to explore the relationship between the cumulative inflammatory index (IIC) and long-term mortality in patients with SAP.

Methods: This study sourced participants with SAP from the Nanjing Stroke Registry Program. The IIC was computed using the formula: (mean corpuscular volume × red cell distribution width × neutrophils) divided by (lymphocytes × 1000). To gauge the diagnostic utility of inflammatory markers, time-dependent receiver operating characteristic curves were plotted. Furthermore, to elucidate the connection between IIC and long-term mortality, survival analysis was conducted via Cox proportional hazard regression models.

Results: The analysis enrolled a total of 557 SAP patients, with a median age of 66 years and 391 males accounting for 70.2% of the cohort. The predictive accuracy of the IIC for mortality was 0.697 (95% confidence interval [CI]: 0.637–0.757). In Cox proportional hazard regression models, the IIC was significantly related to mortality (continuous: hazard ratio [HR]: 1.04; 95% CI: 1.02–1.06; P <0.001; tertile 3 versus tertile 1: HR: 3.03; 95% CI: 1.75–5.25; P <0.001). Restricted cubic spline analysis demonstrated a progressively escalating association between IIC and mortality among SAP patients, with statistical significance (P = 0.003).

Conclusion: This research revealed that elevated IIC levels were linked to a heightened long-term mortality risk among individuals with SAP. IIC may emerge as a feasible and robust biomarker for mortality prediction in SAP patients.

Keywords: stroke, pneumonia, cumulative, mortality, red blood cell

Introduction

Globally, stroke ranks as the second most common cause of mortality, while in China, it stands as the primary contributor to both death and disability. This condition is defined by abrupt-onset neurological impairments.[1,2] Ischemic strokes account for roughly 75 to 80% of all stroke cases. Within 7 days following an ischemic stroke, stroke-associated pneumonia (SAP) emerges as a frequently encountered complication. Reported incidence rates for this condition have ranged from 7% to 38%.[3–5] Numerous investigations have demonstrated that among infections occurring after stroke, SAP exhibits the most robust link to elevated mortality and poor prognosis.[6,7] Systemic inflammation has the potential to compromise immune function and trigger localized inflammatory reactions. This process not only results in immunosuppression but also elevates the likelihood of infections occurring after a stroke.[8] Earlier investigations have indicated

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that inflammatory markers including the neutrophil-to-lymphocyte ratio (NLR), systemic immune-inflammation index (SII), and platelet count served as significant predictors for severe acute pancreatitis. These biomarkers were also found to be correlated with adverse outcomes following stroke.[9–11] However, the association between inflammatory markers and long-term mortality among SAP patients has been scarcely investigated.

The cumulative inflammatory index (IIC) functions as a novel hematological inflammatory parameter that mirrors erythrocyte modifications under inflammatory conditions. This marker underscores the potential interplay between blood cell counts and cellular traits in inflammatory states. The formula of this index incorporates the red cell distribution width (RDW) and mean corpuscular volume (MCV), and evidence has shown it can serve as a predictor for pancreatitis outcomes.[12] Ioan Sabin Poenariu et al observed that the IIC correlated strongly with the established inflammation indices in ulcerative colitis.[13] Another study revealed an association between the IIC and Tumor Node Metastasis staging, tumor pathological differentiation, patient age and gender, as well as overall survival rate in colorectal adenocarcinoma, highlighting the pivotal role of inflammation in cancer progression.[14] Our previous study showed that SII were related to mortality in SAP patients.[11] However, the correlation between IIC and stroke inflammation has been rarely reported. Thus, we broadened the study design to investigate the association between the IIC and SAP patients' long-term mortality, aiming to offer guidance for early identification of individuals at high mortality risk.

Materials and Methods

The data underlying the findings of this study can be obtained from the corresponding author upon reasonable request.

Study Population

This research adopted a retrospective analysis approach for a prospective registry—specifically, the Nanjing Stroke Registry Program—encompassing the period from January 1, 2013, to December 31, 2019. The specifics of the Nanjing Stroke Registry Program have been documented in prior scholarly works.[15] The Ethics Review Board of Jinling Hospital (approval number: 2010NLY018) provided ethical clearance for this study, which was executed in compliance with the Declaration of Helsinki. Informed consent was obtained from all participants.

Patients were selected based on the subsequent inclusion criteria: (1) aged 18 years or older; (2) diagnosis of acute ischemic stroke (AIS) made within 7 days of symptom onset; (3) AIS verification through brain Computed Tomography or Magnetic Resonance Imaging scans either before admission or during hospitalization; (4) identification of SAP within the initial seven days following the index stroke. Patients were excluded from the study if they met any of the following criteria: (1) lacked available measurements for inflammatory indicators; (2) presented with an active infection at admission, had an infection within two weeks prior to admission, or had active tuberculosis; (3) history of hematological tumor or autoimmune disease; (4) had insufficient follow-up data; or (5) passed away within one month during the follow-up period.

Clinical Information

Baseline patient characteristics were gathered by independent researchers, encompassing demographic traits, vital signs, medical history, laboratory results, antibiotic information, medications at discharge, and clinical scoring metrics. Laboratory assessments were systematically collected within the first 24 hours post-admission. Patients' smoking histories were classified into nonsmokers, former smokers, and current smokers. Former smokers were defined as individuals who had quit smoking for over 30 days before the index stroke, while all other smokers were categorized as current smokers.[16] An analogous definition was applied to drinking status. The National Institutes of Health Stroke Scale (NIHSS) was employed to assess the severity of stroke.[17] Stroke subtypes were classified using the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification system.[18]

Inflammatory Markers

We calculated the inflammatory markers using the following equations: IIC = MCV × RDW× neutrophils) / (lymphocytes × 1000);[13] NLR = neutrophils / lymphocytes; Platelet to lymphocytes ratio (PLR) = platelet / lymphocytes; C-reactive protein to albumin ratio (CAR) = C-reactive protein / albumin.

Sap

SAP was defined in accordance with the guidelines issued by the "Pneumonia in Stroke Consensus Group":[5] (1) The following criteria were considered, with at least one being met: a. Unexplained fever (body temperature >38°C);b. Leukopenia (white blood cell count <4000/mm^3) or leukocytosis (white blood cell count >12,000/mm^3);c. In adults aged ≥70 years, unexplained altered mental status. (2) The following criteria were applied, with at least two being satisfied: a. New-onset purulent sputum, 24-hour change in sputum characteristics, increased respiratory secretions, or heightened suctioning needs; b. New or aggravated cough, dyspnea, or tachypnea (respiratory rate >25/min); c. Rales, crackles, or bronchial breath sounds upon auscultation; d. Deterioration in gas exchange. (3) Additionally, at least two consecutive chest radiographs must demonstrate at least one of the following findings: a. New or progressive and persistent lung infiltrate; b. Pulmonary consolidation; c. Cavitation. The pneumonia severity index (PSI) was utilized to evaluate the severity of SAP (Table S1)[19].

Follow-up and Clinical Outcome

The clinical outcome was defined as all-cause mortality, confirmed via standardized telephone interviews administered by a qualified nurse or medical practitioner. Patients underwent follow-up assessments at the 3rd, 6th, and 12th months after discharge in the first year, with annual follow-ups thereafter.

Statistical Analysis

Continuous variables were described as mean ± standard deviation or median (interquartile range) based on normality assumptions, and were compared using Student's *t*-test or the Mann–Whitney *U*-test. Categorical variables were reported as counts (percentages) and analyzed with the chi-square test or Fisher's exact test. IIC was processed as a continuous variable and a categorical variable after being split into tertiles (4.72 and 9.21). For variables with missing values, Little's MCAR test (P = 0.976) confirmed they were missing at random, and 5-fold multiple imputation via chained equations was used for imputation.

We utilized Cox proportional hazards regression models to explore the relationship of IIC with long-term mortality among SAP patients. The Kaplan-Meier curves were compared across the IIC tertiles using the long-rank test. The proportional hazard assumptions were assessed using the Schoenfeld residuals test, and no violations were found. Model 1 represented the unadjusted model, while Model 2 was a multivariate model that incorporated adjustments for critical variables associated with mortality. These included demographic factors, medical history, and inflammatory markers, such as: age, gender, body mass index, NIHSS score, TOAST subtyping criteria, history of hypertension, diabetes, atrial fibrillation, leukocyte count, C-reactive protein (CRP), blood glucose levels, and interleukin-6. Model 3 included variables with univariable *P* values < 0.1, selected through backward variable elimination, excluding MCV, RDW, neutrophils, and lymphocytes (components of the IIC). The final variables included in the Model 3 were age, temperature, NIHSS, hypertension, atrial fibrillation, albumin antibiotics and PSI.

The diagnostic validity of inflammatory markers was evaluated by examining the curve area values (AUC) derived from time-dependent receiver operating characteristic (ROC) curve analyses, with variables incorporated from Model 3. The diagnostic utility of diverse inflammatory markers was contrasted via Delong tests. The restricted cubic spline incorporating three knots set at the 25th, 50th, and 75th percentile thresholds within the distribution was applied to further examine the form and trend of the correlation between IIC and long-term mortality, while accounting for confounders embedded in Model 3.

In sensitivity analysis, competing risk regression models using Fine and Grey's approaches were applied to examine the relationship between IIC and stroke-specific mortality, considering deaths from other causes as competing events. To assess the association between dynamic changes in IIC and mortality, patients were stratified into high and low groups at both admission and discharge based on the median IIC value at each time point. By combining these classifications, four distinct trajectories were defined: (1) Low to Low, (2) Low to High, (3) High to Low, and (4) High to High. Furthermore, subgroup analyses were performed to validate the stability of the associations between IIC and long-term mortality across different SAP patient groups.

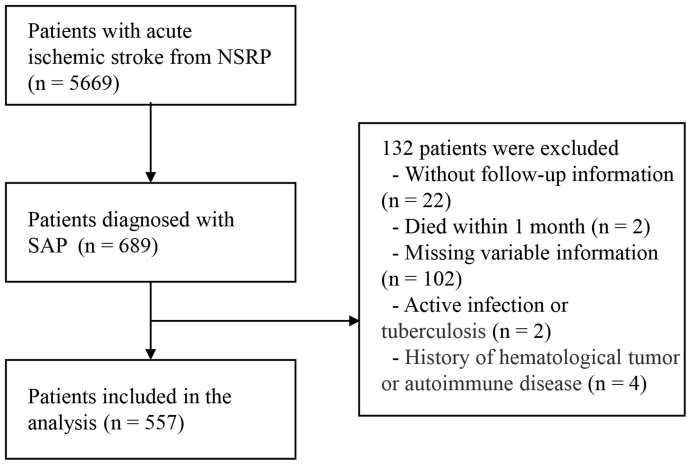

Figure 1 Flow Chart of the Study.
Abbreviations: The final analysis comprised 557 SAP patients, following the exclusion of 132 individuals due to missing follow-up information, death within one month, missing variable data, active infection or tuberculosis, or a history of hematological tumor or autoimmune disease. NSRP: Nanjing Stroke Registry Program; SAP, stroke-associated pneumonia.

All statistical analyses were performed using R version 4.2.1 (R Foundation, Vienna, Austria), and statistical significance was defined as a two-sided P value <0.05.

Results

As illustrated in Figure 1, the final analysis comprised 557 SAP patients, following the exclusion of 132 individuals from the Nanjing Stroke Registry Program. The median age was 66 [58–73] years, and 391 (70.2%) patients were male.138.9 (20.5) patients were current smokers and 138.9 (20.5) were current drinkers. During a median of 2.9 [1.1–4.4] years, 149 (26.8) patients died. Over a median follow-up period of 2.9 [1.1–4.4] years, 149 (26.8%) patients passed away. Deceased patients were generally older and showed elevated temperatures, pulse rates, NIHSS scores, and PSI values. They also had a higher incidence of atrial fibrillation and cardioembolic stroke, increased levels of RDW, glucose, and inflammatory biomarkers, while presenting with reduced triglyceride and albumin levels (all P <0.05; Table 1). After stratification

Table 1 The Baseline Characteristics of the Study Population

Characteristics	Total (n = 557)	With Mortality (n = 149)	Without Mortality (n = 408)	*P* value
Age, years	66.0 [58.0, 73.0]	70.0 [63.0, 78.0]	64.0 [56.0, 71.0]	<0.001
Male, n (%)	391 (70.2)	100 (67.1)	291 (71.3)	0.392
BMI, kg/m^2	24.5 (3.4)	24.4 (3.3)	24.5 (3.4)	0.728
Vital signs				
Systolic blood pressure, mmHg	138.9 (20.5)	138.0 (21.1)	139.2 (20.3)	0.546
Temperature, °C	37.6 [37.0, 38.3]	38.0 [37.5, 38.7]	37.5 [36.9, 38.2]	<0.001
Pulse, n/min	92.0 [81.0, 112.0]	102.0 [88.0, 119.0]	90.0 [80.0, 109.0]	<0.001
Smoking, n (%)				0.349
Nonsmokers	250 (44.9)	73 (49.0)	177 (43.4)	
Former smokers	47 (8.4)	14 (9.4)	33 (8.1)	
Current smokers	260 (46.7)	62 (41.6)	198 (48.5)	
Drinking, n (%)				0.166
Nondrinkers	341 (61.2)	100 (67.1)	241 (59.1)	
Former drinkers	86 (15.4)	22 (14.8)	64 (15.7)	
Current drinkers	130 (23.3)	27 (18.1)	103 (25.2)	

(*Continued*)

Table 1 (Continued).

Characteristics	Total	With Mortality	Without Mortality	*P* value
	(n = 557)	(n = 149)	(n = 408)	
Medical history, n (%)				
Hypertension	395 (70.9)	114 (76.5)	281 (68.9)	0.099
Diabetes mellitus	96 (17.2)	28 (18.8)	68 (16.7)	0.645
Coronary heart disease	166 (29.8)	39 (26.2)	127 (31.1)	0.305
Atrial fibrillation	116 (20.8)	54 (36.2)	62 (15.2)	<0.001
Dyslipidemia	96 (17.2)	29 (19.5)	67 (16.4)	0.475
NIHSS, score	13.0 [6.0, 19.0]	17.0 [11.0, 25.0]	11.0 [5.0, 17.0]	<0.001
Pneumonia severity index, score	81.0 [65.0, 102.0]	102.0 [81.0, 128.0]	76.0 [63.0, 93.0]	<0.001
TOAST, n (%)				<0.001
LAA	221 (39.7)	53 (35.6)	168 (41.2)	
CES	184 (33.0)	70 (47.0)	114 (27.9)	
SVS	27 (4.8)	5 (3.4)	22 (5.4)	
SOD	86 (15.4)	16 (10.7)	70 (17.2)	
SUD	39 (7.0)	5 (3.4)	34 (8.3)	
Blood examination				
White blood cells, $\times10^9$/L	9.1 [7.1, 11.7]	9.5 [7.6, 12.3]	8.9 [6.9, 11.2]	0.005
Lymphocyte, $\times10^9$/L	13.9 [9.4, 20.6]	10.6 [7.4, 14.5]	15.7 [10.6, 23.3]	<0.001
Neutrophils, $\times10^9$/L	78.9 [70.5, 84.7]	82.9 [78.2, 87.5]	76.1 [68.2, 83.2]	<0.001
C-reactive protein, mg/L	8.0 [2.5, 22.7]	11.8 [4.5, 32.7]	6.8 [2.3, 19.2]	<0.001
Platelet, $\times10^9$/L	13.4 [8.7, 21.4]	17.6 [12.5, 27.6]	11.8 [8.0, 18.2]	<0.001
Mean corpuscular volume, fL	91.0 (5.5)	91.7 (5.8)	90.7 (5.4)	0.082
Red cell distribution width, %	13.1 [12.7, 13.7]	13.3 [12.8, 13.9]	13.1 [12.6, 13.7]	0.008
Glucose, mmol/L	6.4 [5.2, 8.1]	6.8 [5.7, 9.0]	6.1 [5.0, 7.9]	<0.001
High-density lipoprotein, mmol/L	1.5 (7.0)	1.9 (9.6)	1.4 (5.8)	0.532
Low-density lipoprotein, mmol/L	2.5 [2.0, 3.1]	2.5 [1.9, 3.0]	2.6 [2.0, 3.2]	0.073
Triglyceride, mmol/L	1.1 [0.9, 1.6]	1.0 [0.8, 1.3]	1.2 [0.9, 1.6]	0.001
Total cholesterol, mmol/L	4.3 (1.3)	4.2 (1.1)	4.3 (1.3)	0.138
Interleukin-6, ng/L	18.9 [9.1, 45.3]	24.9 [11.8, 59.9]	16.6 [8.3, 44.3]	0.001
Albumin, g/L	38.3 [35.1, 41.3]	36.6 [33.3, 40.2]	39.0 [35.8, 41.5]	<0.001
Antibiotics, n (%)				0.125
Cephalosporins, carbapenems and monobactams	326 (58.5)	81 (54.4)	245 (60.0)	
Fluoroquinolones	49 (8.8)	9 (6.0)	40 (9.8)	
Penicillins	7 (1.3)	3 (2.0)	4 (1.0)	
None	175 (31.4)	56 (37.6)	119 (29.2)	
Medications at discharge, n (%)				
Antiplatelet drugs	434 (77.9)	104 (69.8)	330 (80.9)	0.138
Anticoagulants	101 (18.1)	28 (18.8)	73 (17.9)	0.905
Inflammatory markers				
NLR	5.6 [3.4, 9.0]	7.8 [5.5, 11.8]	4.8 [2.9, 7.9]	<0.001
PLR	13.4 [8.7, 21.4]	17.6 [12.5, 27.6]	11.8 [8.0, 18.2]	<0.001
CAR	0.2 [0.1, 0.6]	0.3 [0.1, 0.9]	0.2 [0.1, 0.5]	<0.001
IIC	6.7 [4.0, 10.9]	10.2 [6.5, 14.6]	5.7 [3.5, 9.3]	<0.001
IIC at discharge	5.0 [3.6, 8.0]	6.7 [4.9, 11.8]	4.6 [3.3, 7.1]	<0.001

Abbreviations: BMI, body mass index; CAR, C-reactive protein-albumin ratio; CES, cardio-embolism; IIC, cumulative inflammatory index; LAA, large-artery atherosclerosis; NIHSS, National Institute of Health Stroke Scale; NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; SOE, stroke of other determined etiology; SUE, stroke of undetermined etiology; SVS, small-vessel occlusion; TOAST, Trial of ORG 10172 in Acute Stroke Treatment.

into tertiles, patients with higher IIC levels were characterized by older age, elevated temperatures, pulse rates, NIHSS scores, and PSI. They also presented with a greater incidence of atrial fibrillation, cardioembolic stroke, dyslipidemia, and use of anticoagulants at discharge. Moreover, they demonstrated elevated glucose and inflammatory biomarker

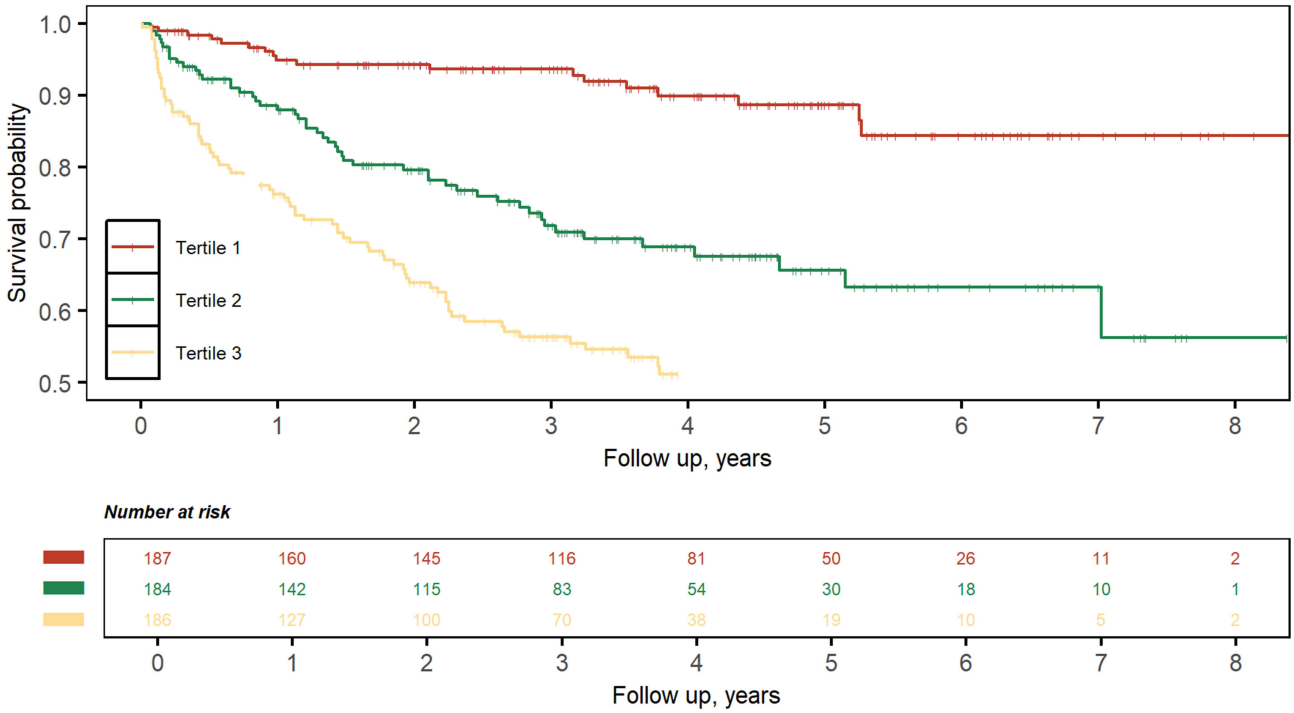

Figure 2 Kaplan-Meier Survival Curves of the Long-Term Mortality According to the Cumulative Inflammatory Index Tertiles.
Abbreviations: Patients with stroke-associated pneumonia in the third tertile (yellow line) of the cumulative inflammatory index exhibited the highest mortality risk, whereas those in the first tertile (red line) had the lowest ($P < 0.001$).

levels, reduced concentrations of low-density lipoprotein, triglycerides, and total cholesterol, along with decreased albumin levels (all P <0.05; Table S2). Survival analysis using the Kaplan-Meier method revealed that SAP patients in the upper tertiles of IIC faced a heightened mortality risk (P <0.001; Figure 2).

In Cox proportional hazard regression models, the IIC was significantly linked to long-term mortality in SAP patients across model 1 (continuous: hazard ratio [HR]: 1.06; 95% confidence interval [CI]: 1.04–1.08; P <0.001; tertile 3 versus tertile 1: HR: 5.94; 95% CI: 3.56–9.91; P <0.001), model 2 (continuous: HR: 1.04; 95% CI: 1.02–1.06; P <0.001; tertile 3 versus tertile 1: HR: 3.95; 95% CI: 2.22–7.05; P <0.001), and model 3 (continuous: HR: 1.04; 95% CI: 1.02–1.06; P <0.001; tertile 3 versus tertile 1: HR: 3.03; 95% CI: 1.75–5.25; P <0.001; Table 2). These models were adjusted for variables with P <0.1 in univariable analysis (Table S3) and via backward selection. ROC curve analyses showed that the

Table 2 Cox Hazard Proportional Models for the Cumulative Inflammatory Index and Mortality in Stroke-Associated Pneumonia

IIC	Model 1		Model 2		Model 3	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Continuous	1.06 (1.04–1.08)	<0.001	1.04 (1.02–1.06)	<0.001	1.04 (1.02–1.06)	<0.001
Tertile 1	Reference		Reference		Reference	
Tertile 2	3.38 (1.97–5.78)	<0.001	2.58 (1.47–4.54)	0.001	2.13 (1.22–3.73)	0.008
Tertile 3	5.94 (3.56–9.91)	<0.001	3.95 (2.22–7.05)	<0.001	3.03 (1.75–5.25)	<0.001
Competing risk regressions	1.05 (1.02–1.08)	0.004	1.05 (1.02–1.08)	0.004	1.05 (1.02–1.08)	0.004

Notes: Model 1 was unadjusted model.Model 2 was adjusted for demographic variables, medical history and inflammatory markers including: age, sex, BMI, NIHSS, TOAST, hypertension, diabetes mellitus, atrial fibrillation, white blood cells, C-reactive protein, glucose, and interleukin-6. Model 3 was adjusted for variables with P <0.1 in the univariable analysis and back-ward selection method. The variables included in the final model were age, temperature, NIHSS, hypertension, atrial fibrillation, albumin, antibiotics and pneumonia severity index. Competing risk regression models were conducted to assess stroke-related mortality, with deaths from other causes categorized as competing risks.
Abbreviations: BMI, body mass index; CI, confidence interval; HR, hazard ratio; IIC, cumulative inflammatory index; NIHSS, National Institute of Health Stroke Scale; TOAST, Trial of ORG 10172 in Acute Stroke Treatment.

IIC (AUC: 0.697; 95% CI: 0.637–0.757; Figure 3) exhibited comparable diagnostic accuracy to other inflammatory markers: NLR (AUC: 0.695; 95% CI: 0.687–0.828), PLR (AUC: 0.669; 95% CI: 0.607–0.732), and CAR (AUC: 0.644; 95% CI: 0.575–0.713; Figure S1).

Restricted cubic spline analysis indicated an upward trend in the association between IIC and mortality among SAP patients (P = 0.003; Figure 4). When performing sensitivity analyses, the link between IIC and mortality persisted in competing risk regression models designating stroke-related mortality as the primary outcome (HR: 1.05; 95% CI: 1.02–1.08, P = 0.004; Table 2). The dynamic changes of IIC were significantly associated with mortality in model 1 (HR for trajectory: Low to Low versus trajectory: High to High: 0.16; 95% CI: 0.09–0.30; P <0.001), model 2 (HR for trajectory: Low to Low versus trajectory: High to High: 0.21; 95% CI: 0.11–0.42; P <0.001), and model 3 (HR for trajectory: Low to Low versus trajectory: High to High: 0.29; 95% CI: 0.15–0.56; P <0.001; Table S4). Furthermore, no significant interactions were detected between subgroup factors and IIC in relation to prolonged mortality among SAP patients, except for atrial fibrillation and stroke severity. We classified stroke severity into minor (≤5), moderate (6–15), and severe (≥16) categories based on NIHSS scores and found that IIC was associated with mortality in SAP patients across all stroke severity groups (Figure S2).

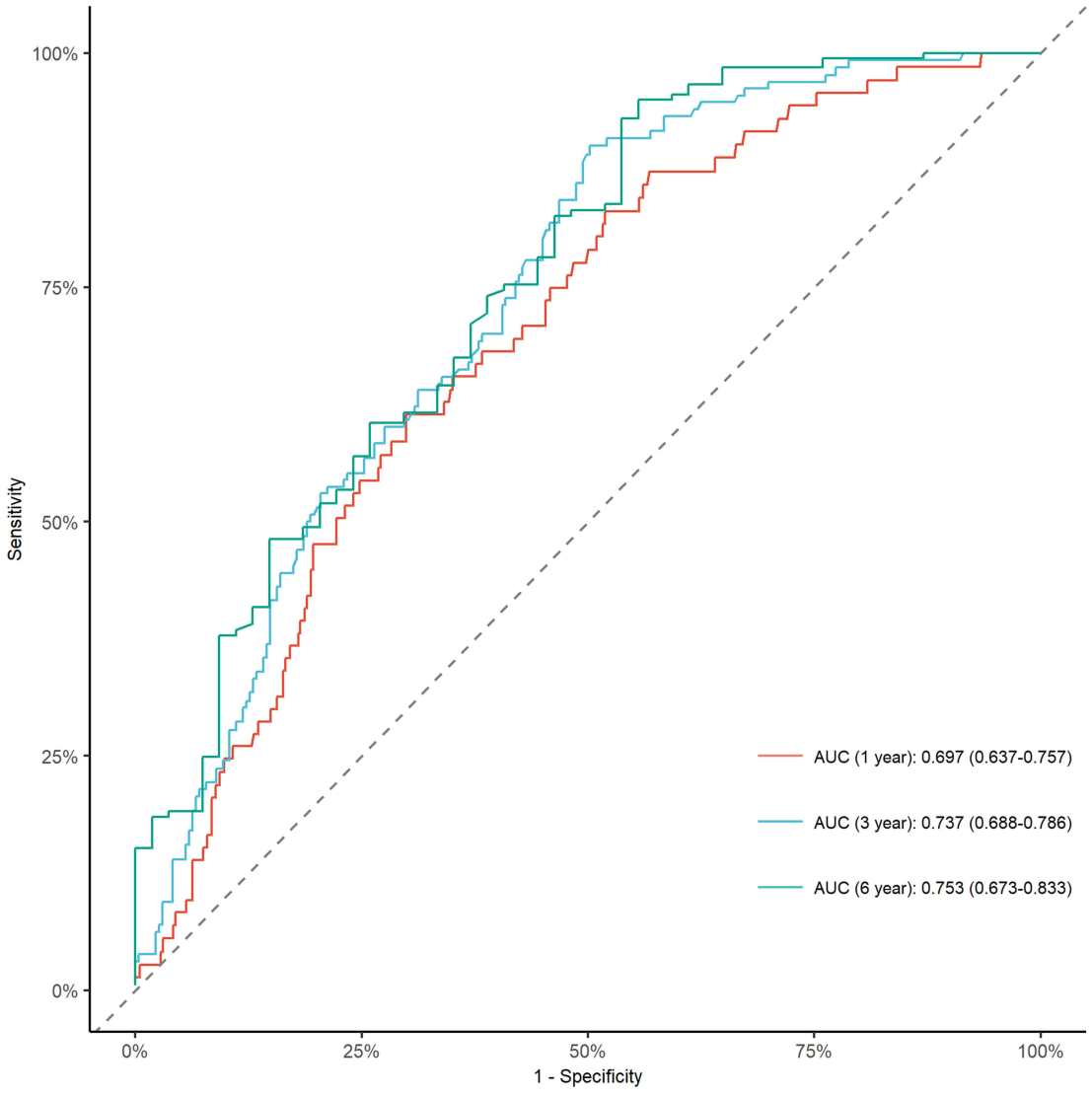

Figure 3 ROC Curve for the Cumulative Inflammatory Index.
Abbreviations: The AUCs (95% CI) of IIC were 0.697 (0.637–0.757) for 1-year, 0.737 (0.688–0.786) for 3-year, and 0.753 (0.673–0.833) for 6-year mortality. AUC, area under the curve; CI, confidence interval; ROC, receiver operating characteristic curve.

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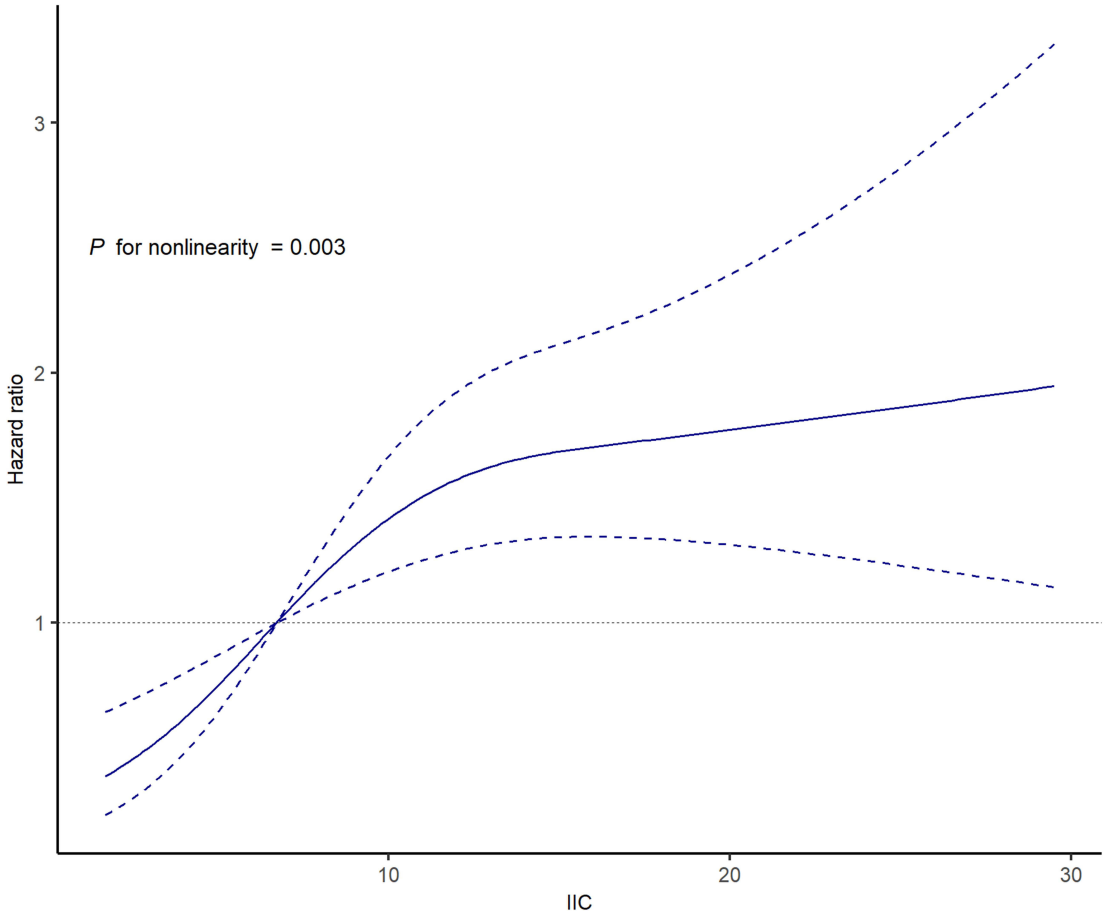

Figure 4 Analysis of Restricted Cubic Spline Regression between the Cumulative Inflammatory Index and the Mortality in Stroke-Associated Pneumonia.
Abbreviations: The restricted cubic spline was plotted with 3 knots positioned at the 25th, 50th, and 75th percentiles of the IIC values. The solid line denoted the hazard ratio, while the dashed lines illustrated the 95% confidence interval. The reference line at hazard ratio = 1 represented the point of no association between the IIC and the risk of the mortality. Hazard ratios above 1 indicated an increased risk, while those below 1 indicated a decreased risk. IIC, cumulative inflammatory index.

Discussion

The present research demonstrated that IIC could serve as a predictor for the long-term mortality of SAP patients. These results suggested that after accounting for potential confounding factors, higher IIC levels were significantly associated with elevated risks of mortality. IIC may confer a modest prognostic advantage over traditional inflammatory markers in SAP patients, potentially aiding in identifying those at high mortality risk, and guiding physicians in implementing protective treatments to improve patient outcomes.

SAP, a frequent complication among stroke patients, generally manifests within the initial week post-stroke. Previous investigations have indicated that SAP incidence spans between 1.4% and 46.8%,[19,20] and it serves as a critical indicator of adverse functional outcomes and heightened mortality risks in stroke patients.[20,21] Our research revealed that 12.2% of stroke patients developed SAP, and among SAP cases, 26.8% succumbed during the follow-up period. Previous studies showed that inflammatory biomarkers could accurately predict the risk of SAP. Adiguzel et al utilized general linear models to explore the correlation between peripheral inflammation markers and SAP. Their results suggested that NLR levels could predict the occurrence of pneumonia following acute ischemic stroke.[22] Zhao et al revealed that in critically ill patients with intracerebral hemorrhage, NLR was independently associated with SAP, demonstrating high predictive accuracy and clinical value in assessing the prognosis of intracerebral hemorrhage.[23]

Additionally, inflammatory biomarkers were also linked to mortality in ischemic stroke patients. Hm et al found that IL-6 and fibrinogen were associated with predicting all-cause mortality in ischemic stroke survivors. In contrast, high-sensitivity C-reactive protein showed predictive value for mortality in non-stroke populations.[24] Marta-Enguita et al

conducted a comprehensive analysis of the outcomes in 748 patients with acute ischemic stroke and investigated the association of plasma calprotectin levels with mortality. The findings demonstrated that heightened calprotectin levels were linked to not only elevated mortality but also poor functional outcomes.[25] However, few studies have directly evaluated inflammatory marker levels in relation to long-term mortality among SAP patients. Here, we built upon our prior research[26] and established a strong link between IIC and mortality in this patient population.

The IIC was initially employed to assess prognosis in acute pancreatitis patients with COVID-19, and it yielded significant results in mortality.[13] Consistent with prior studies, we observed a rising trend in IIC levels correlating with the risk of mortality, showing accurate prognostic predictive power. Among ulcerative colitis patients, notable disparities emerged when contrasting the severe, moderately affected, and mildly symptomatic groups. These distinctions were closely associated with established inflammatory markers.[12] Furthermore, studies have indicated that the IIC is associated with multiple obesity-related parameters in individuals with prediabetes and type 2 diabetes. It exhibits a sensitivity of 61.70% and a specificity of 60.00%, with an AUC of 0.572 for predicting inflammatory conditions in such populations.[26] Consequently, an increased IIC level might imply latent immunological and inflammatory modifications linked to undiagnosed SAP. In clinical practice, RDW and MCV are routinely calculated for nearly all patients undergoing a whole blood test, making the IIC calculation convenient and serving as an early biomarker for risk stratification, facilitating anti-inflammatory interventions, and improving personalized patient care. Additionally, we found that the AUC of IIC for predicting 6-year mortality was higher than for 1- and 3-year mortality. A possible explanation was that, biologically, IIC integrated acute inflammatory signals (neutrophils and lymphocytes) with chronic hematologic risk markers (RDW and MCV). The latter may have a relatively greater influence on long-term mortality—for example, elevated RDW and macrocytosis are associated with death years later.[27] Recent studies of IIC and related markers also supported these observations: elevated RDW predicted both early and late mortality in pneumonia;[27] lymphopenia was associated with increased long-term mortality in critically ill patients;[28] and higher MCV correlated with cardiovascular and cerebrovascular mortality over 5–9 years.[29]

The IIC's advantage over traditional inflammatory markers in pneumonia patients is primarily attributable to the inclusion of RDW and MCV in its formula. RDW serves as a quantitative indicator reflecting the variability in red blood cell dimensions, whereas MCV describes the mean size and volume of erythrocytes circulating in the blood. Earlier investigations have suggested that RDW is associated with prolonged mortality in individuals with community-acquired pneumonia and inpatient mortality in those with ventilator-associated pneumonia.[27,30] In the setting of ischemic stroke, a longitudinal analysis revealed that increased MCV values were linked to an elevated likelihood of stroke-related fatality.[29] A cross-sectional analysis demonstrated that MCV served as an independent predictor for short-term mortality.[31] Furthermore, elevated RDW values were linked to a higher stroke risk within a population-wide cohort analysis.[31] Additionally, pre-thrombolysis RDW values emerged as an independent risk factor for 12-month mortality among individuals with acute ischemic stroke.[32] Therefore, the potential mechanism linking the IIC to mortality in SAP patients can be elucidated as follows. Firstly, red blood cell markers can interact with inflammatory markers, thereby increasing their predictive value for inflammatory status. Elevated RDW has been shown to correlate with various inflammatory markers, including NLR, C-reactive protein, and IL-6, in individuals with acute ailments such as acute toxic exposure and heart failure.[33] Secondly, red blood cell markers may influence the pathogenesis and progression of atherosclerosis. A longer erythrocyte lifespan will reduce erythrocyte turnover, leading to impaired antioxidative function and altered cell shape.[34] These changes can disrupt hemostasis and promote atherosclerotic thrombosis.[35] Thirdly, inflammatory diseases can alter the erythropoiesis process through the inhibition of erythropoietin gene transcription.[36] Elevated red blood cell indices, reflecting inflammation-related and oxidative stress mechanisms, might contribute to a decline in erythrocyte count and impaired infiltration into the microvasculature. This can reduce oxygen delivery to peripheral organs, potentially aggravating cerebral ischemia-reperfusion injury and elevating the mortality risk after SAP.[37]

Based on existing literature, this research represents the initial investigation into the association between the IIC and prolonged mortality among individuals with SAP. However, several limitations existed. Firstly, this study adopted a retrospective approach based on a registry from a single medical institution, a circumstance that might give rise to prejudices because of incomplete variable data. Second, the IIC was computed solely according to the initial blood

sample measurement within the first day of hospitalization, without considering subsequent parameter fluctuations, which may introduce potential bias related to the timing of peak values. However, we incorporated the dynamic changes of IIC, which we hope may help mitigate bias related to blood sampling times. Third, as the research was carried out among Chinese participants, it might impede the applicability of the results to other demographic groups. Finally, data on anti-inflammatory medication treatment were not collected, potentially leading to unmeasured confounders with inherent biases.

Conclusion

In conclusion, this research revealed that a greater IIC was linked to a heightened likelihood of long-term death among SAP patients. The IIC can serve as a feasible and trustworthy biomarker for predicting mortality in SAP cases, enabling the detection of high-risk individuals who might derive advantages from early anti-inflammatory intervention.

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Disclosure

The authors report no conflicts of interest in this work.

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