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Research article

# Neutrophil to lymphocyte ratio and five-year mortality in patients with acute ischemic stroke

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ABSTRACT

*Background:* Previous studies linked neutrophil to lymphocyte ratio (NLR) with short-term mortality after acute ischemic stroke (AIS), but its relationship with long-term mortality remains unclear. This study investigates the association between NLR and five-year mortality in AIS patients.

*Method:* We analyzed 416 AIS patients from April 2012 to January 2016 at Zhangjiagang TCM Hospital. Admission NLR was divided into quartiles: Q1 (<2.00), Q2 (2.00–3.05), Q3 (3.06–5.46), and Q4 (≥5.46). We assessed 5-year all-cause and vascular mortality using Kaplan-Meier, Cox regression, and receiver operating characteristic (ROC) curve analyses.

*Results:* Over five years, 134 (32.2 %) all-cause deaths and 114 (27.4 %) vascular deaths occurred. Elevated NLR was significantly associated with increased risks of all-cause and vascular mortality. Multivariate Cox analysis identified stroke history (HR: 1.57, 95 % CI 1.08–2.30), baseline National Institutes of Health Stroke Scale (NIHSS) score (HR: 1.09, 95 % CI 1.05–1.12), and NLR (HR: 1.09, 95 % CI 1.05–1.12) as independent risk factors for all-cause mortality. These factors also predicted 5-year vascular mortality: stroke history (HR: 1.65, 95 % CI 1.10–2.49), NIHSS score (HR: 1.10, 95 % CI 1.06–1.13), and NLR (HR: 1.08, 95 % CI 1.05–1.10). NLR quartiles were significantly linked to both outcomes: all-cause mortality HRs were Q2 (1.87, 95 % CI 1.00–3.51), Q3 (2.40, 95 % CI 1.31–4.39), Q4 (2.77, 95 % CI 1.47–5.24), P for trend = 0.001; vascular mortality HRs were Q2 (1.76, 95 % CI 0.88–3.55), Q3 (2.34, 95 % CI 1.14–4.40), Q4 (2.57, 95 % CI 1.28–5.16), P for trend = 0.002. Kaplan-Meier survival analysis revealed significantly higher mortality rates in higher NLR quartiles (log-rank $p < 0.001$). ROC analysis identified optimal NLR cutoff values of 3.42 for predicting 5-year all-cause mortality (AUC 0.689) and 3.51 for vascular-cause mortality (AUC 0.700), with moderate sensitivity and specificity.

*Conclusions:* Higher NLR at admission was linked with five-year all-cause mortality and mortality attributed explicitly to vascular causes in AIS patients.

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## 1. Introduction

Stroke is a prominent contributor to mortality rates on a global scale [1]. In China, it is noteworthy that the prevalence of heart disease has been superseded by another health condition, resulting in a shift in the most common cause of mortality [2]. Although intravenous thrombolysis and endovascular thrombectomy have made significant advances in acute ischemic stroke (AIS) treatment, understanding key factors that influence patient mortality is crucial for clinicians aiming to improve clinical outcomes.

The inflammatory response plays a vital role in the physiological mechanisms of ischemic stroke, especially the response after acute stroke, and has an essential function in post-ischemic injury. The infiltration of neutrophils, lymphocytes, and platelets into damaged brain tissue and the liberation of neurotoxins and inflammatory cytokines lead to further deterioration of neurological function [3,4] and even lead to fatality. Previous investigations have consistently demonstrated that elevated neutrophils and reduced lymphocytes are closely linked to poor prognosis of ischemic stroke [5,6].Therefore, neutrophil to lymphocyte ratio (NLR) may be correlated to clinical prognosis, including death, in ischemic stroke patients.

Earlier investigations have shown that NLR has been used as a factor that can be used to anticipate mortality rates over an extended period in individuals diagnosed with acute ST-segment elevation myocardial infarction [7,8]. Nevertheless, there is a lack of consensus concerning the correlation between NLR and mortality in ischemic stroke patients. Yu [9]et al. showed that NLR failed to accurately predict the occurrence of in-hospital mortality among ischemic stroke patients. Recent research has indicated that elevated levels of NLR are associated with a poor prognosis and death three months after AIS [10–12]. Meanwhile, the association of NLR with long-term all-cause death from ischemic stroke, especially from vascular death, remains unclear. Therefore, our investigation aimed to establish a link between the NLR and the incidence of 5-year all-cause mortality and vascular mortality in individuals with AIS.

## 2. Materials and methods

### 2.1. Study design and population

We identified AIS patients from Zhangjiagang Traditional Chinese Medicine (TCM) Hospital between April 2012 to January 2016. According to World Health Organization (WHO) guidelines, AIS was identified and validated by computed tomography or magnetic resonance imaging. The following additional criteria were also excluded: (1) 72-h period from the time of onset to admission (n = 116); (2) clinical data missing (n = 6); (3) no neutrophil count or lymphocyte count (n = 5); and (4) follow-up at 5-year loss (n = 8); a total of 416 patients, for whom data was available, were ultimately included in the present study (a flowchart depicting the process of choosing participants; Fig. 1). The Ethics Committee of Zhangjiagang TCM Hospital approved the current investigation, with a waiver of informed consent from patients as a result of the retrospective nature of the investigation.

### 2.2. Data Collection

Herein, we gathered baseline demographic data encompassing stroke severity and vascular risk factors as determined by the National Institutes of Health Stroke Scale (NIHSS), medication usage, diagnosis-related information, and imaging data. The vascular risk factors encompassed in this study comprised hypertension, diabetes mellitus, a prior history of stroke, a prior atrial fibrillation history, a previous occurrence of coronary heart disease, alcohol consumption, and present or past smoking status.

Blood samples were obtained within a 24-h following the patient's admission to the hospital. The quantification of white blood cell and peripheral differential counts was conducted. The analysis of serum low-density lipoprotein cholesterol (LDL-C) and other biochemical parameters was performed by a commercially available Olympus AU5400 automatic biochemical analyzer (First Chemical CO, LTD, Japan) and commercial reagents. The NLR was determined by dividing the neutrophil count by the lymphocyte

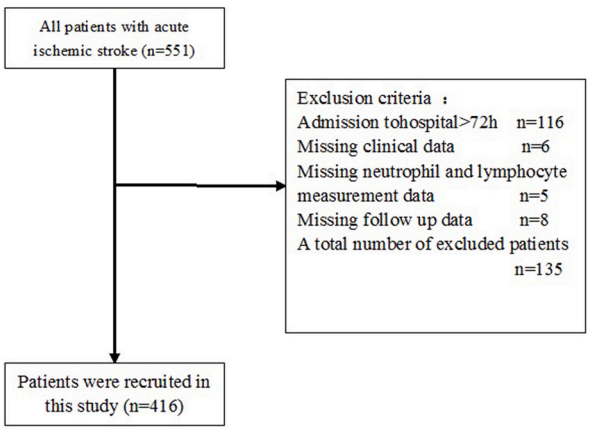


**Fig. 1.** Flowchart of participants selection.

count.

### 2.3. Outcome assessment and follow-up

In this study, the primary research outcome was 5-year mortality. Follow-up data were collected by examining hospital records or interviews conducted in person or via telephone with patients, their families, or their physicians. The determination of the cause of death was made based on an analysis of medical records and death certificates.

### 2.4. Statistical analysis

Normally distributed continuous variables were reported as mean ± standard deviation (SD), while non-normally distributed variables were presented as the median and interquartile range (IQR). Categorical variables were described with frequency and percentage (%). Statistical analyses included the *t*-test for continuous variables, the Chi-square or Fisher's exact test for categorical variables, and the Mann-Whitney *U* test for non-normally distributed variables. Patients were grouped into quartiles based on their admission NLR values. Differences in continuous variables among NLR quartile groups were assessed using one-way ANOVA or the Kruskal-Wallis test. Cox regression analysis evaluated the relationship between mortality outcome and clinical features, including variables with a $P < 0.1$ in the multivariate analysis. Additionally, Cox regression was used to examine the association between NLR and end-point event, with and without adjustment for relevant confounding factors. Receiver operating characteristic (ROC) curves determined cutoff values for mortality prediction, and Kaplan-Meier analysis evaluated prognostic value, with significance set at $P < 0.05$. Data were analyzed using SPSS version 22.0 and visualized with GraphPad Prism version 9.3.

## 3. Results

### 3.1. Baseline characteristics

A total of 134 (32.2 %) all-cause deaths and 114 (27.4 %) vascular-related deaths were documented over the five-year follow-up period. Table 1 summarizes the baseline characteristics of the study population. In the cohort stratified by 5-year all-cause mortality, there were no significant differences in gender, alcohol consumption, hypertension, diabetes mellitus, history of coronary heart disease (CHD), diastolic blood pressure (BP), total cholesterol (TC), LDL-C, and fasting plasma glucose (FPG) between survivors and non-survivors. However, significant differences were observed in age, smoking status, atrial fibrillation, systolic BP, heart rate, white blood cell (WBC) count, triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), and NLR. Notably, NLR levels were significantly higher in the non-survivor group compared to the survivor group. Similarly, in the cohort stratified by 5-year vascular mortality, no statistical differences were found in alcohol consumption, hypertension, diabetes mellitus, history of CHD, diastolic BP, TC, LDL-C, HDL-C, and FPG between the groups. However, age, gender, smoking status, atrial fibrillation, systolic BP, heart rate, WBC count, TG, and NLR showed substantial differences. Similarly, NLR levels were notably elevated in non-survivors compared to survivors (Fig. 2).

**Table 1**
Baseline characteristics of the study subjects.

| Characteristics | 5-year all-cause mortality cohort | | | | 5-year vascular-cause mortality cohort | | |
|---|---|---|---|---|---|---|---|
| | All subjects | Non-survivors | Survivors | *P*-value | Non-survivors | Survivors | *P*-value |
| | N = 416 | N = 134 | N = 282 | | N = 114 | N = 302 | |
| Age, y | 72.0 (16.0) | 80.0 (10.0) | 67.0 (16.0) | ***<0.001*** | 80.0 (9.0) | 68.0 (16.0) | ***<0.001*** |
| Male/female | 207/209 | 59/75 | 148/134 | 0.107 | 47/67 | 160/142 | ***0.032*** |
| Smoking (%) | 107 (25.7) | 24 (17.9) | 83 (29.4) | ***0.012*** | 19 (16.7) | 88 (29.1) | ***0.009*** |
| Drinking (%) | 81 (19.5) | 20 (14.9) | 61 (21.6) | 0.107 | 17 (14.9) | 64 (21.2) | 0.149 |
| Hypertension | 288 (69.2) | 98 (73.1) | 190 (67.4) | 0.234 | 84 (73.7) | 204 (67.5) | 0.227 |
| Diabetes mellitus | 90 (21.6) | 24 (17.9) | 66 (23.4) | 0.203 | 21 (18.4) | 69 (22.8) | 0.328 |
| History of CHD | 22 (5.3) | 12 (4.3) | 10 (7.5) | 0.172 | 9 (7.9) | 13 (4.3) | 0.144 |
| Atrial fibrillation | 63 (15.1) | 37 (27.6) | 26 (9.2) | ***<0.001*** | 34 (29.8) | 29 (9.6) | ***<0.001*** |
| Systolic BP, mmHg | 150.0 (25.0) | 160.0 (30.0) | 150.0 (33.0) | ***0.001*** | 160.0 (30.0) | 150.0 (28.0) | ***0.003*** |
| Diastolic BP, mmHg | 88.5 (15.0) | 89.5 (20.0) | 85.0 (13.0) | 0.218 | 90.0 (20.0) | 85.0 (13.0) | 0.126 |
| Heart rate (times/min) | 75.0 (10.0) | 78.0 (15.0) | 72.0 (10.0) | ***0.001*** | 80.0 (15.0) | 72.0 (10.0) | ***<0.001*** |
| WBC count ( $\times 10^9$/L) | 6.4 (2.9) | 6.9 (3.9) | 6.3 (2.6) | **0.041** | 7.0 (3.8) | 6.3 (2.6) | ***0.007*** |
| NLR | 3.1 (3.5) | 4.6 (5.0) | 2.7 (2.4) | ***<0.001*** | 4.8 (5.5) | 2.7 (2.4) | ***<0.001*** |
| TC, mmol/L | 4.5 (1.4) | 4.4 (1.5) | 4.6 (1.4) | 0.263 | 4.5 (1.5) | 4.6 (1.4) | 0.360 |
| TG, mmol/L | 1.3 (1.0) | 1.4 (1.1) | 1.1 (0.6) | ***<0.001*** | 1.0 (0.7) | 1.4 (1.1) | ***<0.001*** |
| LDL-C, mmol/L | 2.7 (1.2) | 2.5 (1.4) | 2.7 (1.2) | 0.277 | 2.5 (1.5) | 2.7 (1.2) | 0.307 |
| HDL-C, mmol/L | 1.3 (0.5) | 1.4 (0.6) | 1.3 (0.5) | **0.041** | 1.4 (0.5) | 1.3 (0.5) | 0.099 |
| FPG, mmol/L | 5.5 (1.7) | 5.5 (1.6) | 5.4 (1.8) | 0.491 | 5.7 (1.9) | 5.5 (1.5) | 0.835 |

Data are expressed as mean ± standard deviation, or median (interquartile range), or number of patients (%).
Abbreviation: CHD, coronary heart disease; BP, blood pressure; WBC, white blood cell; NLR, neutrophil to lymphocyte ratio; TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; FPG, fasting plasma glucose.

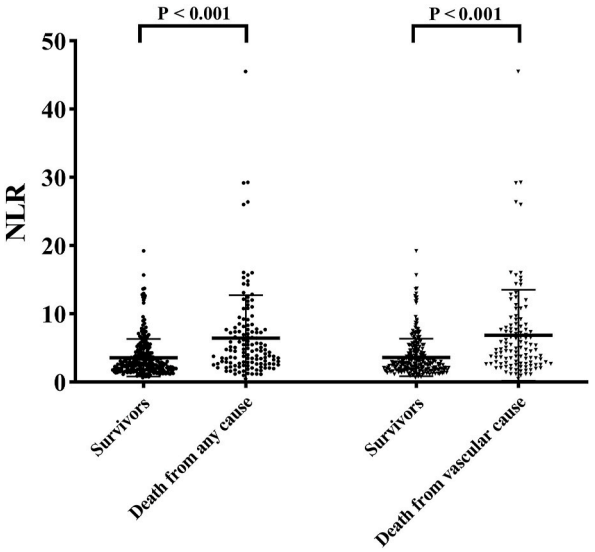


**Fig. 2.** Comparison of NLR levels between groups.

### 3.2. Clinical features and mortality outcomes

As shown in Table 2, univariate Cox regression analysis revealed that 5-year all-cause mortality was significantly associated with a history of stroke, time from onset to sample, baseline NIHSS score, and NLR. Specifically, the associations were as follows: history of stroke (HR: 1.48, 95 % CI 1.02–2.15, P = 0.037), time from onset to sample (HR: 0.99, 95 % CI 0.98–1.00, P = 0.050), baseline NIHSS score (HR: 1.11, 95 % CI 1.09–1.14, P < 0.001), and NLR (HR: 1.11, 95 % CI 1.08–1.14, P < 0.001). Additionally, the Oxfordshire Community Stroke Project (OCSP) subtype was linked to mortality outcomes. Multivariate analysis confirmed that a history of stroke (HR: 1.57, 95 % CI 1.08–2.30, P = 0.019), baseline NIHSS score (HR: 1.09, 95 % CI 1.05–1.12, P < 0.001), and NLR (HR: 1.09, 95 % CI 1.05–1.12, P < 0.001) remained significant predictors of all-cause mortality. Furthermore, these factors were also identified as independent prognostic indicators for 5-year vascular mortality: history of stroke (HR: 1.65, 95 % CI 1.10–2.49, P = 0.017), baseline NIHSS score (HR: 1.10, 95 % CI 1.06–1.13, P < 0.001), and NLR (HR: 1.08, 95 % CI 1.05–1.10, P < 0.001).

**Table 2**
Relationship between mortality outcome and clinical features.

| *Death from any cause* | Univariable | | Multivariable | | *Death from vascular cause* | Univariable | | Multivariable | |
|---|---|---|---|---|---|---|---|---|---|
| Variables | HR (95 % CI) | *P*-value | HR (95 % CI) | *P*-value | Variables | HR (95 % CI) | *P*-value | HR (95 % CI) | *P*-value |
| History of stroke | 1.48 (1.02–2.15) | ***0.037*** | 1.57 (1.08–2.30) | ***0.019*** | History of stroke | 1.53 (1.03–2.28) | ***0.035*** | 1.65 (1.10–2.49) | ***0.017*** |
| Thrombolytic therapy | 1.74 (0.77–3.95) | 0.184 | | | Thrombolytic therapy | 1.69 (0.69–4.14) | 0.252 | | |
| Time onset-to-sample | 0.99 (0.98–1.00) | ***0.050*** | 1.00 (0.99–1.01) | 0.787 | Time onset-to-sample | 0.98 (0.97–0.99) | ***0.013*** | 0.99 (0.98–1.01) | 0.383 |
| Length of stay | 1.00 (0.97–1.03) | 0.902 | | | Length of stay | 1.01 (0.98–1.04) | 0.610 | | |
| Baseline NIHSS score | 1.11 (1.09–1.14) | ***<0.001*** | 1.09 (1.05–1.12) | ***<0.001*** | Baseline NIHSS score | 1.13 (1.10–1.15) | ***<0.001*** | 1.10 (1.06–1.13) | ***<0.001*** |
| NLR | 1.11 (1.08–1.14) | ***<0.001*** | 1.09 (1.05–1.12) | ***<0.001*** | NLR | 1.11 (1.09–1.14) | ***<0.001*** | 1.08 (1.05–1.11) | ***<0.001*** |
| Subtype of OCSP | | | | | Subtype of OCSP | | | | |
| TACI | 1.00 (reference) | | 1.00 (reference) | | TACI | 1.00 (reference) | | 1.00 (reference) | |
| PACI | 0.21 (0.12–0.36) | ***<0.001*** | 0.75 (0.38–1.50) | 0.421 | PACI | 0.18 (0.11–0.32) | ***<0.001*** | 0.77 (0.38–1.59) | 0.483 |
| POCI | 0.19 (0.10–0.39) | ***<0.001*** | 0.70 (0.31–1.56) | 0.378 | POCI | 0.19 (0.09–0.38) | ***<0.001*** | 0.79 (0.35–1.79) | 0.567 |
| LACI | 0.12 (0.07–0.21) | ***<0.001*** | 0.64 (0.28–1.45) | 0.282 | LACI | 0.10 (0.05–0.17) | ***<0.001*** | 0.66 (0.28–1.58) | 0.352 |

Abbreviation: HR, hazard ratio; CI, confidence interval; NIHSS, National Institutes of Health Stroke Scale; NLR, neutrophil to lymphocyte ratio; OCSP, Oxfordshire Community Stroke Project; TACI, Total Anterior Circulation Infarct; PACI, Partial Anterior Circulation Infarct; POCI, Posterior Circulation Infarct; LACI, Lacunar Circulation Infarct.

### 3.3. Characteristics of study participants according to NLR quartiles

Admission NLR was categorized into quartiles: Q1 (<2.00), Q2 (2.00–3.05), Q3 (3.06–5.46), and Q4 (≥5.46). Table 3 lists the features of the investigation population-related NLR quartile. In comparison to patients with fewer NLR levels, those with higher NLR levels were more likely to be old and more likely to have atrial fibrillation. Other stroke risk factors were not different across NLR quartile groups. Patients exhibiting elevated NLR levels also displayed notable distinctions in their metabolic profile, characterized by heightened levels of white blood cells (WBCs). Patients who were in the greater quartiles of NLR exhibited a greater likelihood of presenting with severe neurologic deficits upon admission. Moreover, patients with higher NLR levels had more 5-year mortality.

### 3.4. Association of NLR quartiles with mortality outcomes

Table 4 illustrates the association between NLR quartiles and mortality outcomes. In the cohort stratified by 5-year all-cause mortality, Model 4, adjusted for age, smoking status, atrial fibrillation, systolic BP, heart rate, WBC count, HDL-C, TG, baseline NIHSS score, and history of stroke, revealed multivariate hazard ratios (HRs) for all-cause mortality as follows: Q2 (HR: 1.87, 95 % CI 1.00–3.51), Q3 (HR: 2.40, 95 % CI 1.31–4.39), and Q4 (HR: 2.77, 95 % CI 1.47–5.24), with a trend P-value of 0.001. For vascular-cause mortality, in the fully adjusted model, the multivariate HRs for Q2, Q3, and Q4 compared to Q1 (reference) were 1.76 (95 % CI 0.88–3.55), 2.34 (95 % CI 1.14–4.40), and 2.57 (95 % CI 1.28–5.16), respectively (P for trend = 0.002).

### 3.5. Kaplan-Meier survival analysis for 5-year mortality

The Kaplan-Meier curves in Figs. 3–4 illustrate the relationship between quartiles and 5-year all-cause mortality and death from vascular causes. The findings revealed significant gradients in both 5-year mortality rates for all causes and mortality rates attributed explicitly to vascular causes across the quartiles of NLR. Notably, the high NLR group exhibited a substantially elevated hazard of death. The observed difference was significant based on the log-rank test (P < 0.001).

**Table 3**
Characteristics of study participants according to NLR quartiles.

| Characteristics | NLR | | | | |
|---|---|---|---|---|---|
| | Q1<br><2.00<br>N = 104 | Q2<br>2.00–3.05<br>N = 105 | Q3<br>3.06–5.46<br>N = 104 | Q4<br>≥5.46<br>N = 103 | *P*-value |
| Age, y | 70.0 (14.0) | 71.0 (15.0) | 73.0 (17.0) | 77.0 (17.0) | ***0.016*** |
| Male/female | 45/59 | 60/45 | 58/46 | 44/59 | 0.055 |
| Smoking (%) | 28 (26.9) | 31 (29.5) | 35 (33.7) | 13 (12.6) | ***0.004*** |
| Drinking (%) | 23 (22.1) | 27 (25.7) | 22 (21.2) | 9 (8.7) | ***0.013*** |
| Hypertension | 74 (71.2) | 71 (67.6) | 69 (66.3) | 74 (71.8) | 0.790 |
| Diabetes mellitus | 21 (20.2) | 23 (21.9) | 26 (25.0) | 20 (19.4) | 0.771 |
| History of CHD | 2 (1.9) | 4 (3.8) | 7 (6.7) | 9 (8.7) | 0.128 |
| Atrial fibrillation | 8 (7.7) | 11 (10.5) | 13 (12.5) | 31 (30.1) | ***<0.001*** |
| Systolic BP, mmHg | 150.0 (34.0) | 150.0 (33.0) | 155.5 (25.0) | 160.0 (30.0) | ***0.007*** |
| Diastolic BP, mmHg | 85.0 (10.0) | 85.0 (10.0) | 85.5 (15.0) | 90.0 (20.0) | 0.193 |
| Heart rate (times/min) | 75.0 (10.0) | 72.0 (11.0) | 72.0 (10.0) | 80.0 (15.0) | ***0.008*** |
| WBC count ( $\times 10^9$/L) | 5.7 (2.1) | 5.8 (2.3) | 6.5 (2.5) | 8.6 (3.8) | ***<0.001*** |
| TC, mmol/L | 4.5 (1.3) | 4.8 (1.4) | 4.5 (1.4) | 4.5 (1.6) | 0.365 |
| TG, mmol/L | 1.5 (1.2) | 1.4 (1.0) | 1.3 (0.8) | 1.0 (0.7) | ***<0.001*** |
| LDL-C, mmol/L | 2.6 (1.1) | 2.8 (1.1) | 2.5 (1.3) | 2.7 (1.5) | 0.616 |
| HDL-C, mmol/L | 1.3 (0.5) | 1.3 (0.5) | 1.2 (0.5) | 1.3 (0.5) | 0.243 |
| FPG, mmol/L | 5.4 (1.2) | 5.3 (1.3) | 5.5 (1.9) | 6 (2.1) | ***0.033*** |
| History of stroke | 31 (29.8) | 25 (23.8) | 22 (21.2) | 23 (22.3) | 0.474 |
| Thrombolytic therapy | 3 (2.9) | 1 (1.0) | 3 (2.9) | 6 (5.8) | 0.245 |
| Time onset-to-sample, h | 12.0 (45.0) | 15.0 (28.0) | 10.5 (20.0) | 5.0 (12.0) | ***<0.001*** |
| Length of stay, day | 10.0 (6.0) | 11.0 (6.0) | 11.5 (5.0) | 11.0 (8.0) | 0.083 |
| Baseline NIHSS score | 4.0 (4.0) | 4.0 (4.0) | 4.0 (4.0) | 8.0 (10.0) | ***<0.001*** |
| Subtype of OCSP | | | | | ***<0.001*** |
| TACI | 3 (2.9) | 2 (1.9) | 4 (3.8) | 14 (13.6) | |
| PACI | 34 (32.7) | 43 (41.0) | 37 (35.6) | 45 (43.7) | |
| POCI | 5 (4.8) | 11 (10.5) | 12 (11.5) | 19 (18.4) | |
| LACI | 62 (59.6) | 49 (46.7) | 51 (49.0) | 25 (24.3) | |
| All-cause mortality (%) | 16 (15.4) | 27 (25.7) | 34 (32.7) | 57 (55.3) | ***<0.001*** |
| Vascular-cause mortality (%) | 13 (12.5) | 22 (21.0) | 27 (26.0) | 52 (50.5) | ***<0.001*** |

Data are expressed as mean ± standard deviation, or median (interquartile range), or number of patients (%).
Abbreviation: CHD, coronary heart disease; BP, blood pressure; WBC, white blood cell; NLR, neutrophil to lymphocyte ratio; TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; FPG, fasting plasma glucose; NIHSS, National Institutes of Health Stroke Scale; OCSP, Oxfordshire Community Stroke Project; TACI, Total Anterior Circulation Infarct; PACI, Partial Anterior Circulation Infarct; POCI, Posterior Circulation Infarct; LACI, Lacunar Circulation Infarct.

**Table 4**
Association of NLR quartiles with mortality outcome.

| Death from any cause | HR (95 % CI) | | | | | Death from vascular cause | HR (95 % CI) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Q1 <2.00 N = 104 | Q2 2.00–3.05 N = 105 | Q3 3.06–5.46 N = 104 | Q4 ≥5.46 N = 103 | *P*-trend | | Q1 <2.00 N = 104 | Q2 2.00–3.05 N = 105 | Q3 3.06–5.46 N = 104 | Q4 ≥5.46 N = 103 | *P*-trend |
| Model1: crude, no adjustment | 1.0 | 1.72 (0.93–3.19) | 2.39 (1.32–4.33) | 4.92 (2.83–8.59) | ***<0.001*** | Model1: crude, no adjustment | 1.0 | 1.72 (0.87–3.41) | 2.32 (1.20–4.50) | 5.42 (2.95–9.97) | ***<0.001*** |
| *P*-value | | 0.086 | ***0.004*** | ***<0.001*** | | *P*-value | | 0.121 | ***0.013*** | ***<0.001*** | |
| Model2: adjusting for age, smoking, AF | 1.0 | 1.71 (0.92–3.19) | 2.38 (1.31–4.35) | 4.19 (2.38–7.41) | ***<0.001*** | Model2: adjusting for age, smoking, gender, AF | 1.0 | 1.68 (0.84–3.38) | 2.30 (1.18–4.51) | 4.45 (2.38–8.31) | ***<0.001*** |
| *P*-value | | 0.089 | ***0.005*** | ***<0.001*** | | *P*-value | | 0.143 | ***0.015*** | ***<0.001*** | |
| Model3: adjusting for age, smoking, AF, systolic BP, heart rate, WBC, HDL-C, TG | 1.0 | 1.74 (0.93–3.24) | 2.27 (1.23–4.16) | 3.11 (1.65–5.86) | ***<0.001*** | Model3: adjusting for age, smoking, gender, AF, systolic BP, heart rate, WBC, TG | 1.0 | 1.66 (0.83–3.34) | 2.13 (1.08–4.22) | 2.98 (1.49–5.97) | ***<0.001*** |
| *P*-value | | 0.084 | ***0.008*** | ***<0.001*** | | *P*-value | | 0.155 | ***0.029*** | ***0.002*** | |
| Model4: adjusting for age, smoking, AF, systolic BP, heart rate,WBC, HDL-C, TG, baseline NIHSS score, history of stroke | 1.0 | 1.87 (1.00–3.51) | 2.40 (1.31–4.39) | 2.77 (1.47–5.24) | ***0.001*** | Model4: adjusting for age, smoking, gender, AF, systolic BP, heart rate, WBC, TG, baseline NIHSS score, history of stroke | 1.0 | 1.76 (0.88–3.55) | 2.34 (1.14–4.40) | 2.57 (1.28–5.16) | ***0.002*** |
| *P*-value | | ***0.050*** | ***0.005*** | ***0.002*** | | *P*-value | | 0.112 | ***0.020*** | ***0.008*** | |

Abbreviation: HR, hazard ratio; CI, confidence interval; AF, atrial fibrillation; BP, blood pressure; WBC, white blood cell; HDL-C, high-density lipoprotein cholesterol; TG, triglyceride; NIHSS, National Institutes of Health Stroke Scale; NLR, neutrophil to lymphocyte ratio.

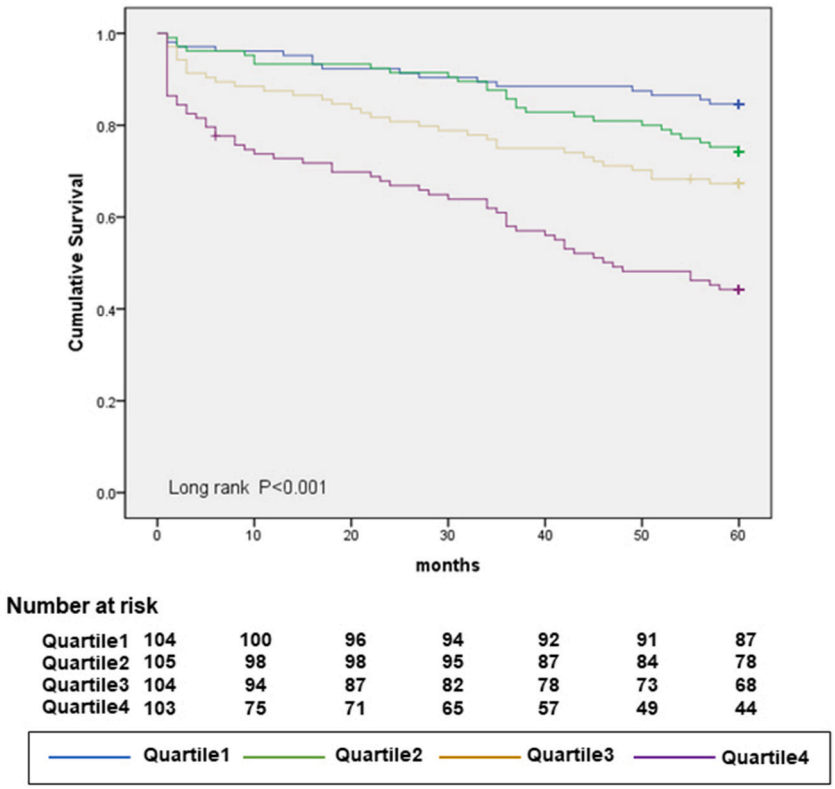


**Fig. 3.** NLR quartiles and 5-year all-cause mortality.

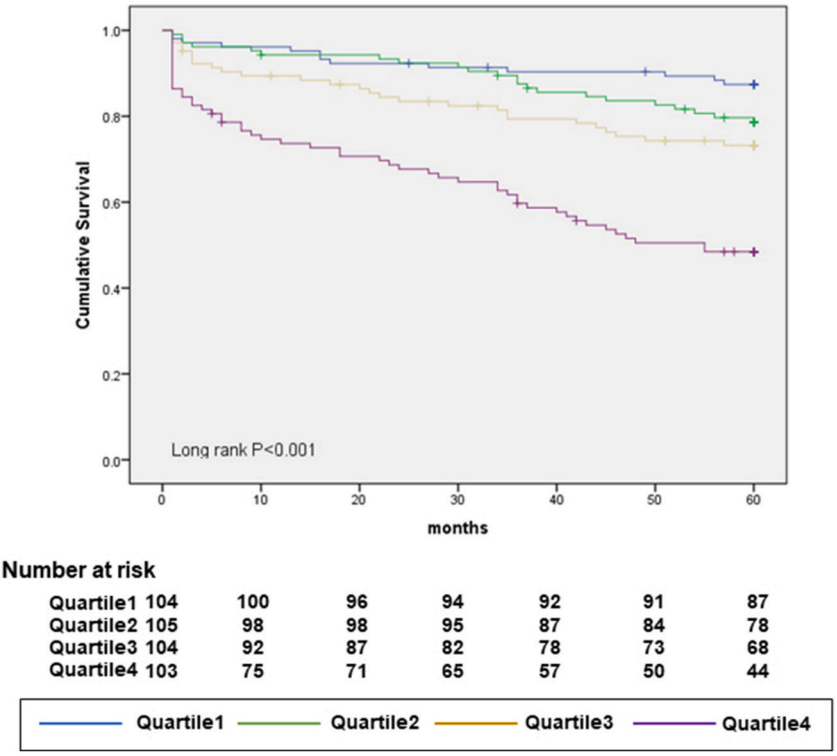


**Fig. 4.** NLR quartiles and 5-year vascular-cause mortality.

### 3.6. The value of NLR for predicting the mortality outcomes

ROC analysis of NLR to predict mortality outcomes revealed (Figs. 5–6) that NLR value 3.42 was the best cutoff level for predicting 5-year all-cause mortality, which gave 65.7 % sensitivity and 64.9 % specificity with an area under the curve (AUC) of 0.689 (95 % CI 0.63–0.75, $P < 0.001$). Moreover, 3.51 was the optimal cutoff level to predict 5-year vascular-cause mortality, presenting 66.7 % sensitivity and 66.2 % specificity with an AUC of 0.700 (95 % CI 0.64–0.76, $P < 0.001$).

## 4. Discussion

Herein, we aim to assess the prognostic validity of admission NLR in predicting both all-cause mortality and mortality attributed explicitly to vascular causes over five years in our study. This investigation utilized data from a cohort of 416 patients. The outcomes of our investigation indicate a significant association between elevated NLR upon admission and increased mortality rates over five years, encompassing both all-cause mortality and mortality attributed explicitly to vascular causes.

Recent studies have demonstrated that the NLR serves as a predictor for early neurological deterioration and mortality at the three-month mark in AIS patients [13–15]. Although patients with ischemic stroke can currently receive intravascular reperfusion therapy, the mortality in these patients is still high. NLR within 24 h before [16] or after [17,18] intravenous thrombolysis or intravascular thrombectomy can predict hemorrhagic transformation and 3-month mortality. Additionally, several investigations have investigated the strong association between the NLR and one-year mortality in AIS [19,20]. Quan [20] et al. discovered that an elevated NLR level within the initial 24 h following admission is linked to a heightened risk of adverse clinical outcomes, both in the short-term and long-term, among ischemic stroke patients, irrespective of the underlying cause. The NLR $\geq$3.180, with a sensitivity of 58.39 % and specificity of 66.69 %, can potentially be a predictive factor for one-year mortality. Additionally, we increased the duration of the follow-up period and observed that the aforementioned correlation remained statistically significant after a 5-year follow-up. NLR was determined to be a significant independent prognostic factor for all-cause mortality. Hence, the NLR may be regarded as a prognostic indicator for both short-term and long-term mortality outcomes among individuals afflicted with ischemic stroke. In our ROC analysis of NLR for predicting 5-year all-cause mortality, a cutoff value of 3.42 demonstrated 65.7 % sensitivity and 64.9 % specificity, with an AUC of 0.689. The optimal cutoff for predicting 5-year vascular-cause mortality was 3.51, yielding 66.7 % sensitivity and 66.2 % specificity, with an AUC of 0.700. Although these AUC values indicate moderate predictive ability, NLR could be a valuable marker for long-term mortality risk stratification in clinical practice.

In our study, stroke causes high 5-year mortality (32.2 %), and NLR was a better indicator of five-year vascular death, which may have several explanations. First, after ischemic stroke, the blood-brain barrier breakdown in the local region, caused by ischemia, facilitates the entry of inflammatory factors, such as neutrophils and lymphocytes. These inflammatory factors have long-term effects and may affect the prognosis of ischemic stroke patients, including death. Neutrophils possess the potential to instigate additional thrombus formation through the release of molecules or interactions with platelets. Consequently, they may obstruct microvessels, impede perfusion, and ultimately result in prolonged ischemia [21]. In contrast, lymphocytes exhibit a delayed accumulation in the post-ischemic brain, albeit slower than neutrophils. Lymphocyte response post-stroke has been shown to be increasingly complex, with diverse beneficial and detrimental roles at different time points after stroke for various subsets of lymphocytes. Even 30 days after stroke, lymphocytes were still high, indicating that lymphocytes mediated neuroplasticity and the potential beneficial effect of enhancing post-stroke recovery may last months and years after stroke [22,23].

Second, atherosclerosis is a chronic inflammatory process. AIS may be a more intense inflammatory response caused by chronic inflammation, which affects the prognosis of AIS and is closely linked to vascular death. Multiple studies have provided empirical evidence supporting a strong link between the NLR and plaque stability in the carotid artery [24,25], carotid artery stenosis [26], and intracranial artery stenosis [27]. Higher NLR leads to instability of carotid and intracranial artery plaques, leading to the occurrence or recurrence of ischemic stroke and, in severe cases, patient death. This is probably another reason why higher NLR in patients with AIS leads to more vascular death.

Our investigation encountered multiple constraints. First, this investigation consists of a retrospective analysis conducted at a single center. Although some possible relevant factors are eliminated by multi-factor analysis, other non-predicable or improper factors still cannot be eliminated completely. Therefore, correlations reflected by this study might be deflected. Second, this investigation is mainly based on a relatively small Chinese population. The research results shall be recommended carefully to populations with genetic backgrounds. Moreover, patients with missing neutrophil and lymphocyte counts are excluded, which may cause deflection in the research conclusions. Third, the selection process exclusively includes patients admitted to the hospital 72 h following a stroke, which cannot accurately evaluate neutrophil or lymphocyte count during the peak stage. The research conclusions shall be further proved by increasing coverage of occurrence time and cases and by dynamic observation of neutrophil and lymphocyte counts.

## 5. Conclusions

The presence of an elevated level of NLR upon admission was found to be significantly correlated with both overall mortality and mortality attributed explicitly to vascular causes within a five-year period among individuals diagnosed with AIS.

## Ethics and consent statement

This study was approved by the Ethics Committee of the Zhangjiagang TCM Hospital, approval number: No. KY2022-6-5-1。

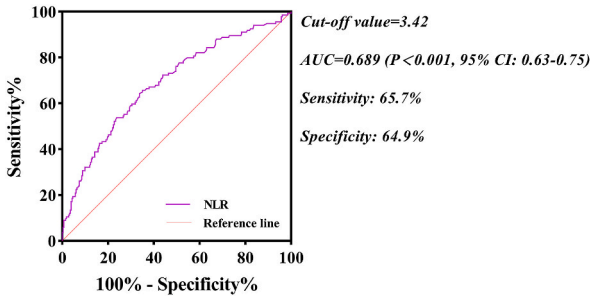


**Fig. 5.** ROC analysis of NLR to predict 5-year all-cause mortality outcome.

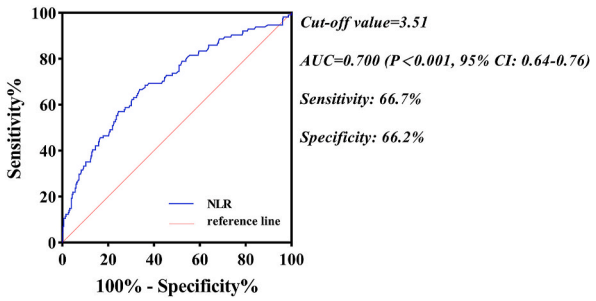


**Fig. 6.** Predictive Value of NLR for 5-year vascular-cause mortality.

*Competing interests*

The authors have declared that no competing interest exists.

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## Data availability statement

Data will be made available on reasonable request.

## CRediT authorship contribution statement

**Yisi Shan:** Writing – review & editing, Writing – original draft. **Rong Zhang:** Writing – original draft. **Juan Lu:** Data curation. **Lingling Huang:** Data curation. **Yadong Wang:** Methodology, Investigation. **Fengdan Long:** Methodology, Investigation. **Yaming Sun:** Writing – review & editing, Writing – original draft.

## 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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