

# Neutrophil-to-Lymphocyte Ratio Better Than High-Sensitivity C-Reactive Protein in Predicting Stroke-Associated Pneumonia in Afebrile Patients

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**Purpose:** To evaluate the association between neutrophil-to-lymphocyte ratio (NLR) and stroke-associated pneumonia (SAP) in patients with acute ischemic stroke (AIS) without fever and to clarify whether NLR has an advantage over high-sensitivity C-reactive protein (hs-CRP) in predicting SAP.

**Patients and Methods:** A total of 434 patients with AIS without fever were assessed in this study. Multivariable analysis was used to evaluate the relationship between NLR and SAP, and the receiver operating characteristic (ROC) curve was used to compare the predictive value of NLR and hs-CRP.

**Results:** Among the total patients, 18 (4.1%) developed SAP. After adjusting for confounders, NLR (adjusted odds ratio [aOR] = 1.60; 95% confidence interval [CI], 1.30–1.96;  $p < 0.001$ ) remained independently associated with an increased risk of SAP. In addition, the area under the curve (AUC) of NLR (0.862 [0.826–0.893]) was higher than that of hs-CRP (0.738 [0.694–0.779]).

**Conclusion:** We found that compared with hs-CRP, NLR was significantly associated with the occurrence of SAP in patients with AIS without fever and showed a more effective predictive value for SAP.

**Keywords:** stroke, pneumonia, neutrophil, lymphocyte, high-sensitivity C-reactive protein, inflammation

## Introduction

Stroke-associated pneumonia (SAP), defined as new onset pneumonia within 7 days after stroke, is a common complication in patients with acute ischemic stroke (AIS).<sup>1</sup> It has been reported that 7–38% of patients with stroke experience SAP.<sup>2–6</sup> For these patients, not only do the length of hospital stay and cost of hospitalization increase significantly, but the risks of disability and death also greatly increase.<sup>7,8</sup> It is well known that pyrexia is key in the diagnosis of pneumonia; however, studies have shown that 25–66% of patients with SAP may not have pyrexia.<sup>9,10</sup> This may make clinicians ignore the infection. Therefore, a simple and effective biomarker is needed to quickly identify SAP in afebrile patients.

Neutrophil-to-lymphocyte ratio (NLR), calculated by dividing the absolute neutrophil count by the absolute lymphocyte count, is a novel marker of systemic inflammation and infection.<sup>11,12</sup> C-reactive protein (CRP), one of the most accessible and widely used biomarkers, also plays a key role in the identification and evaluation of infections.<sup>13,14</sup> High-sensitivity C-reactive protein (hs-CRP) is

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a sensitive marker of inflammation, it detects low concentrations of CRP using a high-sensitivity assay technique.<sup>15</sup> Several studies have demonstrated that high NLR and CRP levels could predict SAP in patients with AIS.<sup>16,17</sup> At the same time, elevated CRP has also been shown to improve the diagnostic accuracy of the current SAP algorithms, independent of pyrexia.<sup>18</sup> However, the predictive value of hs-CRP and NLR in patients with AIS without fever remains unknown. In this study, we aimed to evaluate the association between NLR and SAP in AIS patients without fever and to clarify whether NLR has an advantage over hs-CRP in predicting SAP.

## Patients and Methods

### Study Population

This study was approved by the Ethics Committee of The Second Hospital of Tianjin Medical University. We retrospectively studied all patients with AIS who were admitted to the neurology ward of The Second Hospital of Tianjin Medical University from November 2018 to October 2020. Computed tomography (CT) or magnetic resonance imaging (MRI) was used to confirm the diagnosis of AIS. Patients were eligible for inclusion if they were  $\geq 18$  years of age and had onset of symptoms  $\leq 72$  h at recruitment. The exclusion criteria were (1) patients with severe hepatic or renal diseases; (2) having recently undergone major trauma or surgery; (3) a history of a malignant tumor, hematologic disease, or immunosuppressive treatment; (4) temperature  $\geq 38^{\circ}\text{C}$  at any one time within 7 days of stroke onset; (5) active infection at admission or incomplete medical records.

### Data Collection

The demographic and clinical characteristics, such as age, sex, previous history of diabetes, hypertension, atrial fibrillation, stroke, smoking, stroke severity at admission, occurrence of SAP, and relevant laboratory data (blood cell counts and hs-CRP), were recorded within 24 h of admission. Stroke severity was assessed using the National Institutes of Health Stroke Scale (NIHSS). The diagnostic criteria for SAP were based on the Chinese expert consensus on the diagnosis and treatment of SAP (Supplementary Table 1).

### Statistical Analyses

For continuous variables with non-normal distributions, the data are presented as median + interquartile range

(IQR), while normal distributions are expressed as mean  $\pm$  standard deviation (SD). Univariate analyses were conducted using the Mann–Whitney *U*-test and the independent-samples *t*-test. For categorical variables, frequency and percentage were used to express the data and were evaluated using the chi-squared test. To assess the basic characteristics of the subjects in the high NLR group, we also conducted another comparison between the high and low NLR groups by dichotomizing the cohort with the median NLR (2.56). The predictive values of NLR and hs-CRP were compared using the area under the curve (AUC) of the receiver operating characteristic (ROC) curve. All statistical analyses were performed using SPSS 19.0 and MedCalc 15.2.2, and statistical significance was set at  $P < 0.05$ .

## Results

A total of 434 patients with AIS (mean age, 68 years; men, 66%) were included in our study, and the majority (60%) were admitted within 24 h of symptom onset. The median initial NIHSS and NLR were 2 (1–5) and 2.56 (1.95–3.60), respectively. Of the patients, 18 (4.1%) developed SAP, and none of them had a fever of  $> 38^{\circ}\text{C}$  at any one time within 7 days of stroke onset.

Compared with the patients in the non-SAP group, patients in the SAP group were older and nonsmokers, had a higher proportion of females, atrial fibrillation, and had higher levels of initial NIHSS, hs-CRP, and white blood cell (WBC) counts. In addition, the level of NLR in the SAP group was also significantly higher than that in the non-SAP group (6.43 [4.39–8.00] vs 2.51 [1.91–3.45],  $P < 0.001$ ) (Table 1). After adjusting for confounders, NLR (1.60 [1.30–1.96],  $P < 0.001$ ) and initial NIHSS (1.16 [1.04–1.28],  $P = 0.006$ ) remained independent predictors of SAP (Table 2).

We also conducted another comparison between the high and low NLR groups. The incidence of SAP was significantly higher in the high NLR group than in the low NLR group (8.3% vs 0,  $P < 0.001$ ). In addition, patients in the high NLR group were older and presented a higher proportion of hypertension and atrial fibrillation, and they had higher levels of initial NIHSS, hs-CRP and WBC counts than those in the low NLR group (Table 3).

ROC analysis revealed that the optimal value for NLR to predict SAP was 4.64, with a sensitivity and specificity of 77.8% and 88.5%, respectively. NLR (0.862 [0.826–0.893]) showed a higher AUC value than that of WBC

**Table 1** Baseline Characteristics of Afebrile Patients with SAP and Non-SAP with AIS

	Non-SAP (n = 416)	SAP (n = 18)	P
Age (years), median (IQR)	67(60–76)	81(71–83)	< 0.001
Male, n (%)	278(67%)	7(39%)	0.015
Smoke, n (%)	181(44%)	2(11%)	0.006
Hypertension, n (%)	348(84%)	13(72%)	0.343
Diabetes, n (%)	153(37%)	4(22%)	0.208
Previous stroke, n (%)	170(41%)	5(28%)	0.268
Atrial fibrillation, n (%)	41(10%)	6(33%)	0.006
Initial NIHSS, median (IQR)	2(1–5)	8(5–12)	< 0.001
Hs-CRP (mg/L), median (IQR)	3.04(1.52–7.18)	14.06(3.21–96.47)	0.001
WBC ( $\times 10^9/L$ ), median (IQR)	7.02(5.91–8.39)	8.95(7.53–10.28)	0.001
Neutrophil ( $\times 10^9/L$ ), median (IQR)	4.55(3.61–5.60)	6.99(4.98–8.41)	< 0.001
Lymphocyte ( $\times 10^9/L$ ), median (IQR)	1.76(1.33–2.20)	1.20(0.84–1.51)	< 0.001
NLR, median (IQR)	2.51(1.91–3.45)	6.43(4.39–8.00)	< 0.001

**Abbreviations:** AIS, acute ischemic stroke; SAP, stroke-associated pneumonia; NIHSS, National Institute of Health Stroke Scale; hs-CRP, high-sensitivity C-reactive protein; WBC, white blood cell; NLR, neutrophil-to-lymphocyte ratio; IQR, interquartile range.

**Table 2** Multivariable Analysis of Possible Predictors of SAP

	OR (95% CI)	P
Male	0.66(0.17–2.48)	0.536
Age	1.06(0.99–1.13)	0.111
Smoke	0.35(0.06–2.03)	0.240
Atrial fibrillation	1.53(0.40–5.81)	0.535
hs-CRP	1.00(1.00–1.01)	0.716
Initial NIHSS	1.16(1.04–1.28)	0.006
NLR	1.60(1.30–1.96)	< 0.001

**Abbreviations:** SAP, stroke-associated pneumonia; hs-CRP, high-sensitivity C-reactive protein; NIHSS, National Institute of Health Stroke Scale; NLR, neutrophil-to-lymphocyte ratio.

(0.729 [0.685–0.771]), neutrophils (0.800 [0.759–0.837]), lymphocytes (0.773 [0.731–0.812]), and hs-CRP (0.738 [0.694–0.779]) (Table 4).

## Discussion

To the best of our knowledge, our study was the first to investigate the relationship between NLR, hs-CRP, and SAP in afebrile patients. We found that compared with hs-CRP, NLR was significantly associated with the occurrence of SAP in AIS patients without fever and showed a more effective predictive value for SAP.

At present, the diagnosis of SAP is difficult. This is not only because the diagnostic criteria for SAP are inconsistent, but also because there is a lack of prospective studies for validation.<sup>19</sup> It is also due to the fact that the clinical presentation of patients is often atypical and vague, and the sensitivity of laboratory and radiological tests, such as chest radiography and sputum cultures, is low.<sup>8,10,19,20</sup>

CRP, an acute-phase inflammatory protein, promotes the aggregation or deposition of damaged cells or exogenous microorganisms, leading to the activation of the classical complement pathway that promotes phagocytosis by macrophages.<sup>21</sup> Currently, CRP is widely used as a biomarker for patients with cancer, stroke, infections and cardiovascular diseases.<sup>22–25</sup> It has also been proven to be highly sensitive for the diagnosis of bacterial infections, even in patients without fever.<sup>26</sup> In AIS, elevated CRP has been shown to be strongly associated with the occurrence of stroke-associated infection (SAI) and SAP.<sup>16,17,27</sup>

NLR is an economical, simple and timely blood biomarker that is well known as a predictor of infection and inflammation. It has shown a higher predictive value than the traditional inflammatory markers in various diseases, such as stroke, cancer, and multiple sclerosis.<sup>28–30</sup> In patients with AIS, damage-associated molecular patterns (DAMPs) released from injured neurons exacerbate focal inflammation, causing the infiltration of neutrophils and other peripheral inflammatory cells, secretion of large amounts of inflammatory mediators, and a disseminated inflammatory response throughout the brain, leading to further damage to the brain tissue and neurons.<sup>31</sup> After that, there is immunosuppression, as the injured brain initiates an adaptive response that reduces the inflammatory response as well as the autoimmune response to neuronal antigens.<sup>32</sup> Meanwhile, the sympathetic and hypothalamic-pituitary-adrenal (HPA) axis is activated and secretes catecholamines and cortisol, leading to increased apoptosis and dysfunction of lymphocytes, as

**Table 3** Baseline Characteristics of Afebrile Patients with Low and High NLRs with AIS

	Low NLR (NLR ≤ 2.56)	High NLR (NLR > 2.56)	P
No. of patients	217	217	
SAP, n (%)	0	18(8%)	< 0.001
Age (years), median (IQR)	67(58–76)	69(62–79)	0.001
Male, n (%)	138(64%)	147(68%)	0.363
Smoke, n (%)	96(44%)	87(40%)	0.382
Hypertension, n (%)	171(79%)	190(88%)	0.015
Diabetes, n (%)	83(38%)	74(34%)	0.369
Previous stroke, n (%)	89(41%)	86(40%)	0.769
Atrial fibrillation, n (%)	16(7%)	31(14%)	0.021
Initial NIHSS, median (IQR)	2(1–4)	3(1–6)	< 0.001
hs-CRP (mg/L), median (IQR)	2.73(1.41–5.80)	3.94(1.78–12.42)	0.001
WBC (×10 <sup>9</sup> /L), median (IQR)	6.74(5.58–8.02)	7.60(6.22–8.81)	0.001
Neutrophil (×10 <sup>9</sup> /L), median (IQR)	3.92(3.13–4.88)	5.41(4.35–6.68)	< 0.001
Lymphocyte (×10 <sup>9</sup> /L), median (IQR)	2.11(1.76–2.55)	1.41(1.09–1.68)	< 0.001

**Abbreviations:** AIS, acute ischemic stroke; SAP, stroke-associated pneumonia; NIHSS, National Institute of Health Stroke Scale; hs-CRP, high-sensitivity C-reactive protein; WBC, white blood cell; NLR, neutrophil-to-lymphocyte ratio; IQR, interquartile range.

**Table 4** Predictive Values of Different Indicators in the Prediction of Stroke-Associated Pneumonia in Afebrile Patients

	AUC	95% CI	Optimal Cutoff Value	Sensitivity	Specificity	P
WBC	0.729	0.685–0.771	8.67	61.11%	80.29%	0.0013
Neutrophil	0.800	0.759–0.837	6.58	72.22%	88.46%	< 0.0001
Lymphocyte	0.773	0.731–0.812	1.47	77.78%	69.71%	< 0.0001
hs-CRP	0.738	0.694–0.779	2.66	94.44%	44.95%	< 0.0001
NLR	0.862	0.826–0.893	4.64	77.78%	88.46%	< 0.0001

**Abbreviations:** AUC, area under the curve; CI, confidence interval; WBC, white blood cell; hs-CRP, high-sensitivity C-reactive protein; NLR, neutrophil-to-lymphocyte ratio.

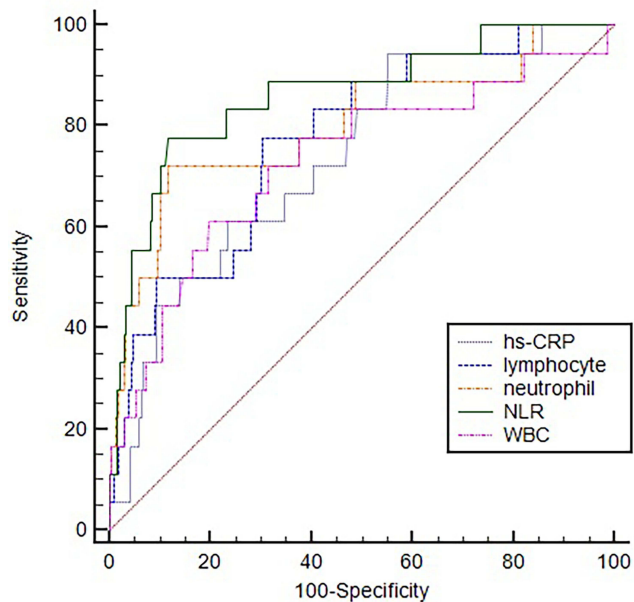
well as decreased secretion of immunoglobulins.<sup>33–37</sup> The activation of the sympathetic nervous system after stroke also mobilizes neutrophils in peripheral reservoirs, leading to an increase in the number of circulating neutrophils.<sup>38</sup> In addition, as shown in Table 3, patients in the high NLR group had more risk factors for developing SAP, such as advanced age, higher rates of hypertension and atrial fibrillation, and higher stroke severity. This may also be the reason that a high NLR could predict the occurrence of SAP in patients with AIS without fever.

In this study, we found that patients with a high initial NIHSS were more likely to develop SAP, which is consistent with the findings of the previous studies.<sup>16,17</sup> Moreover, compared to hs-CRP, NLR may be a more valuable marker to help distinguish the SAP group from the non-SAP group. There are several possible explanations for this phenomenon. First, SAP, unlike simple bacterial infections, is a respiratory syndrome caused by a complex interaction between bacterial, chemical, and immunocompromising factors.<sup>35</sup> This is the reason why prophylactic antibiotics neither reduce the

incidence of SAP nor improve its prognosis.<sup>39,40</sup> Immunosuppression is one of the main mechanisms leading to the development of SAP, and immunosuppression is highly correlated with NLR, which makes NLR a more effective predictor of the development of SAP. Second, the exact role of CRP in the diagnosis of SAP remains unclear. For example, in the studies of STROKE-INF and MAPS, elevated CRP was found in 44% and 91% of patients with AIS, while only 12% and 73% of these patients developed SAP, respectively.<sup>10,40</sup> In the present study, hs-CRP levels were not independently associated with the occurrence of SAP. This was consistent with the study by Emsley et al, where it was found that an elevated CRP level is common in acute stroke patients due to inflammation caused by infarction or hemorrhage, even in the absence of infection.<sup>41</sup> Therefore, as shown in Figure 1, the area under the curve (AUC) of NLR (0.862 [0.826–0.893]) was higher than that of hs-CRP (0.738 [0.694–0.779]).

Our study had several limitations. First, this study was a single-center retrospective design and was thus subject to

## ROC curve for indicators



**Figure 1** Comparison of predictive value between NLR and other indicators in the prediction of stroke-associated pneumonia in afebrile patients.

selection bias. Second, the time of admission may have resulted in bias. SAP events have been reported to occur mainly during the first 2 to 3 days. Therefore, although 60% of our patients were admitted within 24 h of symptom onset, it was still possible to miss some of them. Third, due to incomplete data, we could not evaluate the relationship between the NLR and SAP dynamically. Fourth, there are still many other unknown factors influencing our results, despite our best efforts to control the bias with multivariate models. Fifth, although we reviewed 2 years of data, the sample size was small, especially for the patients in the SAP group. Therefore, a multicenter prospective study with more sample data is needed to confirm our findings.

## Conclusion

Compared with hs-CRP, NLR was significantly associated with the occurrence of SAP in AIS patients without fever, and showed a more effective predictive value in predicting SAP. Moreover,  $NLR > 4.64$  could be applied to screen for SAP, even in AIS patients without fever.

## Ethics Statement

This study adheres to the principles of the Declaration of Helsinki. The study involving human participants were reviewed and approved by the Ethics Committee of The

Second Hospital of Tianjin Medical University (No. KL2021K003). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

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## Disclosure

Dr Xiangkun Wu reports personal fees from Hebei Yanda Hospital, during the conduct of the study. The authors report no other conflicts of interest in this work.

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