

Dynamic Change of Eosinophil and Acute Ischemic Stroke

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Research

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Abstract

Background: Eosinopenia has been shown to be a predicative factor for the infection and mortality in ischemic stroke patients which mainly focused on static eosinophil count. This study aimed to explore the relationship between dynamic change of eosinophil count and short-term prognosis of acute ischemic stroke (AIS).

Methods: A total of 174 patients with AIS were respectively enrolled. Blood samples for blood routine examination were obtained at admission before any treatments and the next day. Eosinopenia was defined as the continuous decrease of the count of eosinophil from the first day to the second. Infarct volume was measured by diffusion-weighted MR imaging volume. 90-day modified Rankin Scale scores were collected to assess the prognosis of patients with AIS.

Results: Patients were divided into two groups according to whether they have eosinopenia. Patients with eosinopenia were more likely to have large infarct volume ($3.2 [0.6-39.9] \text{ cm}^3$ vs $1.1 [0.3-6.0] \text{ cm}^3$, $P = .004$). Receiver operating characteristic analysis demonstrated that the eosinophil count on the second day was more accurate than the time of admission to identify the large cerebral infarction (LCI) (0.866 vs 0.603 , $P \leq .001$). Logistic regression analysis revealed that eosinopenia was independently associated with LCI ($P = .015$) and poor outcome ($P = .011$), and patients with eosinopenia had a 4.05-fold greater risk for LCI (95% CI 1.31-12.51) and a 4.29-fold greater risk for worse clinical outcomes (95% CI 1.27-14.51) than patients without.

Conclusion Eosinophil is a dynamic variable, and its variation is associated with poor outcome in acute ischemic stroke patients.

Introduction

Although recent advances in the treatment of cerebral vascular disease, patients with acute ischemic stroke still have a higher incidence, death and mutilation rate. In a follow-up to a 5-year study involving patients who had a transient ischemic attacks (TIA) or minor stroke and adopted aggressive risk-reduction measures, the rate of cardiovascular events including stroke was as high as 6.4%¹. It has initiated pondering that there probably have some other mechanisms we not completely understood are highly likely to play a key role in the pathogenesis of ischemic stroke and may provide novel therapeutic strategies to treat and prevent this disease.

Inflammatory and immune mechanisms which plays an important part in cerebral ischemic injury has already become present research focuses. Inflammatory responses lead to brain injury by aggravating the blood-brain barrier damage, microvascular failure, brain edema, oxidative stress, and neuronal cell death and affect the patients' long-term clinical prognosis². The interest in targeting inflammation was sprang up again following the inspiring results of improving clinical outcomes in stroke patients treated by

fingolimod and alteplase^{3,4}, providing another pathway alongside thrombolysis and lipid reduction to target for a decrease in the development of cerebral vascular diseases.

Many studies suggested an association of a poor prognosis, larger infarct size and hemorrhage transformation after intravenous thrombolysis or mechanical thrombectomy with initial neutrophil to lymphocyte⁵⁻⁸. Few studies showed that eosinophil is associated with mortality and severity in acute ischemic stroke (AIS) patients^{9,10}. However, all of these studies mostly focused on static cell counts at baseline, which probably not reflect the complicated dynamic changes of the patients' conditions. Therefore, we aimed to explore the temporal variation of the eosinophil in patients with acute ischemic stroke (AIS).

Participants And Methods

Participants

We performed a retrospective analysis of a prospectively collected database of consecutive AIS patients in Suzhou Municipal Hospital from January 2018 to March 2019.

Criterion for inclusion in this study was a first onset of AIS within 72 hours. The exclusion criterion were (1) infection; (2) any diseases and drugs can interfere with the measurement of eosinophil counts (for example, asthma, eosinophilic esophagitis, hypereosinophilic syndrome, tumor, glucocorticoid).

This study was approved by Ethics Committee of Suzhou Municipal Hospital.

Methods

Clinical protocol and laboratory measurements

The medical history of patients, including stroke risk factors, physical exam, blood routine and biochemistry, coagulation function were obtained at admission. Eosinopenia was defined as the continuous decrease of the count of eosinophil from admission to the next day. The neutrophil to lymphocyte ratio (NLR) was calculated by dividing the absolute neutrophil count over the absolute lymphocyte count from the same sample. NLR-increase was defined as the continuous increase of the NLR from admission to the following day. The severity of AIS was assessed by the National Institutes of Health Stroke Scale (NIHSS) at admission and discharge. At 90 days after stroke onset, patient disability was evaluated using the modified Rankin Scale. A poor outcome was defined as a modified Rankin Scale score > 3. Blood samples collected from patients at the admission before any treatment and in early morning of the second day, were analyzed using XN-10 (Sysmex, Kobe, Japan), which was calibrated daily.

Ct/mri And Infarct Volume

CT and MRI images were acquired by a multislice CT-scanner (Hispeed NX, GE, USA) and a 3.0 T Philips Ingenia scanner, respectively. All patients underwent a CT scan on admission, CT or MRI was repeated at 48 to 96 hours. The infarct area was manually delineated on each Diffusion-weighted MR imaging (6 mm width), and the infarct volume is a product of the measured area times the corresponding slice thickness. Large infarct volume was defined as a large hemisphere infarction with a diameter more than 3 cm and that involved more than two large, main arteries supply areas ¹¹.

Statistical analysis

Normal distribution variables are presented as the mean \pm SD and were compared using t tests. Non-normally distributed variables are presented as the interquartile range and were compared using Mann-Whitney U test. Pearson's χ^2 test was used to compare the differences in categorical variables. The receiver operating characteristic curves were used to test ability of the eosinophil and NLR for large cerebral infarction. Youden's index was used to test the eosinophil cut-off value. Backward stepwise logistic regression was applied to analyze predictor variables for large cerebral infarction and poor outcome. Two-tailed significance values were applied, a value of $P < 0.05$ was considered statistically significant. SPSS-statistical package 21.0 software (IBM, Armonk, NY, USA) was used for statistical analysis.

Results

Baseline characteristics of patients

Table 1 shows the baseline characteristics of participants. Three hundred and six consecutive patients were included in the study, after excluding patients with missing data of blood routine tests at admission, 174 patients were enrolled for the final analysis. There were 110 men (63.2%) and 64 women (36.8%) and the average age was 69.8 ± 12.7 years old. Patients with eosinopenia were identified in 63.2% and were more likely to have large infarct volume ($P = .004$), higher score of admission NIHSS ($P = .005$) and poor outcome ($P = .014$) compared with the patients with no eosinopenia. The distribution of TOAST stroke subtypes in these two groups are also shown in Table 1. Only the percentage of patients with cardioembolic exhibited significantly different ($P = .046$).

Table 1
Baseline characteristics of patients based on whether have eosinophil decline

	No eosinopenia (n = 64)	Eosinopenia (n = 110)	P-value
Age, years	71.1 ± 12.1	69.0 ± 13.0	0.302
Males	43 (67.2)	67 (60.9)	0.506
Hypertension	48 (75.0)	78 (70.9)	0.685
Diabetes	23 (35.9)	21 (19.1)	0.022*
Coronary artery disease	3 (4.7)	5 (4.5)	0.966
Atrial fibrillation	15 (23.4)	38 (34.5)	0.172
SBP, mmHg	156.1 ± 21.0	150.1 ± 21.5	0.113
DBP, mmHg	85.3 ± 18.1	85.0 ± 12.4	0.860
FPG, mmol/L	5.8 (5.2–8.1)	5.9 (5.0–7.6)	0.937
LDL-c, mmol/L	2.9 ± 1.0	2.8 ± 1.0	0.451
CRP, mg/L	5.4 (5.2–5.7)	5.9 (5.0–6.0)	0.162
Infarct volume (cm ³)	1.1 (0.3–6.0)	3.2 (0.6–39.9)	0.004*
Thrombolytic therapy	12 (18.8)	33 (30.0)	0.146
Admission NIHSS	5.0 (2.2–7.0)	7.0 (3.0–17.0)	0.005*
Discharge NIHSS	3.0 (1.0–8.0)	4.0 (1.0–13.0)	0.167
mRS	0.5 (0–2.0)	1 (0–4.0)	0.014*
Large vessel atherosclerosis	28 (43.8)	43 (39.1)	0.547
Cardioembolic	11 (17.2)	34 (30.9)	0.046*
Small vessel disease	22 (34.4)	18 (16.4)	0.219
Other	3 (2.7)	1 (1.6)	0.621
Unknown	2 (3.1)	12 (10.9)	0.069
<i>FPG</i> fasting plasma glucose, <i>SBP</i> systolic blood pressure, <i>DBP</i> diastolic blood pressure, <i>LDL-c</i> low density lipoprotein-cholesterol, <i>CRP</i> C-reactive protein, <i>NIHSS</i> National Institutes of Health Scale Score, <i>mRS</i> modified Rankin Scale. *P<0.05.			

Table 2
Associations of the dynamic change of NLR and eosinophil with large infarct volume

	Univariate analysis		Multivariate analysis	
	OR (95%CI)	P-value	OR (95%CI)	P-value
Eosinopenia	3.50 (1.56–7.80)	0.002	4.05 (1.31–12.51)	0.015
NLR-increase	6.52 (2.82–15.05)	0.000	3.72 (1.35–10.23)	0.011
Bivariate logistic regression analyses with adjustment for age, sex, hypertension, diabetes mellitus, coronary artery disease, fasting plasma glucose, admission NIHSS, discharge NIHSS, stroke subtype, and thrombolytic therapy. <i>OR</i> : odds ratio; <i>CI</i> : confidence interval.				

Table 3
Diagnostic values of different predictors for large infarct volume

	AUC (95% CI)	P	Cutoff value	Sensitivity (%)	Specificity (%)
1st NLR	0.564 (0.459–0.668)	0.190	3.972	57.1	64.8
2ed NLR	0.897 (0.848–0.953)	0.000	4.588	89.8	76.0
1st Eos	0.603 (0.501–0.705)	0.034	0.045	53.1	69.6
2ed Eos	0.866 (0.798–0.935)	0.000	0.025	87.8	81.6
2ed Eos%	0.898 (0.847–0.949)	0.000	0.250	85.7	88.0
2ed NLR + Eos%	0.926 (0.882–0.969)	0.000	3.717	89.8	86.4
<i>AUC</i> area under curve, <i>CI</i> confidence interval, <i>NLR</i> neutrophil to lymphocyte ratio, <i>Eos</i> eosinophil.					

Association Between Eosinopenia And Large Cerebral Infarction

Patients with eosinopenia had larger infarct volume (3.2 [0.6–39.9] cm³ vs 1.1 [0.3-6.0] cm³, $P = .004$). There was a prolonged decrease in the number of eosinophils in patients with large cerebral infarction (LCI) (Fig. 1, A). LCI were also associated with an increase in NLR (Fig. 1, B). The admission and the second day of eosinophil count both difference between patients with and without LCI ($P = .035$, $P < .001$ respectively), but the differ was more apparent in latter.

To investigate the diagnostic value of eosinophils at different times in predicting large cerebral infarction, receiver operating characteristic curves were used. It was obviously shown that the absolute eosinophil count on the second day had larger area under curve (AUC) (0.866 vs 0.603, $P < .001$), the result for the

NLR were similar to that of the eosinopenia (0.897 vs 0.564, $P < .001$), and the eosinophil percentage on the second day's AUC was largest. The absolute eosinophil count combined with the NLR on the second day was better in diagnosis of LCI, with a sensitivity of 89.8% and a specificity of 86.4% (area under curve = 0.926; 95% CI: 0.882–0.969).

Finally, multivariate analysis estimated effect sizes of eosinopenia and elevated NLR on larger lesion volumes and showed a similar pattern to the univariate analysis. Patients with eosinopenia or elevated NLR had significantly odds of LCI compared with patients without (OR = 4.05; 95% CI: 1.31–12.51; $P = .015$; OR = 3.72; 95% CI: 1.35–10.23; $P = .011$).

Association Between Eosinopenia And Poor Outcome

As shown in Table 1, patients with eosinopenia showed a higher score of NIHSS at admission (7.0 [3.0–17.0] vs 5.0 [2.2–7.0], $P = .005$), which might be translated into higher score of mRS (1 [0–4.0] vs 0.5 [0–2.0], $P = .014$) (Table 1). Both eosinopenia and NLR-increase were significantly associated with worse outcome in the univariate analysis. After adjusting for potential confounders, the association merely between eosinopenia and poor outcome was significant (OR = 4.29; 95% CI: 1.27–14.51; $P = .011$) (Table 4).

Table 4
Associations of the dynamic change of NLR and eosinophil with poor outcomes

	Univariate analysis		Multivariate analysis	
	OR (95%CI)	P-value	OR (95%CI)	P-value
Eosinopenia	3.09 (1.41–6.72)	0.005	4.29 (1.27–14.51)	0.011
NLR-increase	3.14 (1.52–6.47)	0.002	1.06 (0.39–2.89)	0.913
Bivariate logistic regression analyses with adjustment for age, sex, hypertension, diabetes mellitus, coronary artery disease, fasting plasma glucose, admission NIHSS, discharge NIHSS, stroke subtype, and thrombolytic therapy. <i>OR</i> : odds ratio; <i>CI</i> : confidence interval.				

Discussion

The present study is the first to suggest the eosinophil is a dynamic variable, and its variation is associate with large infarct volume and poor outcome.

A growing body of evidence suggests that inflammatory responses after a stroke might continuously shape the evolving pathology and affect the patients' long-term clinical outcome. In previous studies, a high NLR¹², high-sensitive C-reactive protein¹³ and lipoprotein-associated phospholipase A₂¹⁴ and a low

eosinophil count¹⁰ were found to be associated with poor prognosis in ischemic stroke patients. In addition, the NLR and eosinophil were associated with infarct volume^{5,6} and higher infection rate after a stroke occur¹⁰. However, all of these studies mostly focused on static value at baseline, which probably not reflect the complicated dynamic changes of the patients' conditions. Recent studies showed that NLR measured at admission before any treatment was not predictive of poor functional outcome after endovascular treatment^{8,15}, but NLR obtained at day 1 was independently associated with a worse outcome at 3 months. Our results were consistent with previous studies that have demonstrated this correlation between NLR at day 1 and a poor prognosis in patients with AIS. We first studied the relationship between dynamic change of eosinophil and acute ischemic stroke. Conclusion similar with the NLR, the eosinophil obtained at day 1 not at admission was independently associated with a worse outcome. We also found that compared with NLR and eosinophil measured at day 1, increased NLR and decreased eosinophils from admission to the next day were more meaningful after adjustment for potential confounders. By reading lots of literatures, there might be some interesting conclusions we observed. In two prospective cohort studies showed that increased eosinophils were independent predictors of cardiovascular and cerebrovascular events^{16,17}. However, in most retrospective studies demonstrated that eosinopenia was associated with worse clinical outcomes in patients with cardiac-cerebral vascular events^{9,10,18,19}. These different results may be due to differences in the timing of blood sample obtained and in the distribution of eosinophil in different stages of diseases. We may conjecture that healthy people with elevated eosinophil counts increase the risk of stroke as eosinophil can promote thrombosis and induce unstable plaque^{20,21}, once those people suffer a stroke a large number of eosinophils sharply declined and lead to poor prognosis through a number of mechanisms.

The mechanisms underlying these observations remain unclear. Acute stress can lead to eosinopenia by stimulating the release of adrenal glucocorticosteroids and epinephrine^{22,23}. Patients with large infarct volume may be more likely to activate the stress responses which may partly explained why those people were often accompanied by eosinopenia. Nevertheless, a sharply reduction in peripheral blood eosinophils does not only seem to be a result of adrenal mediation, because this was also observed in adrenalectomized rabbits²². Many researches proved that chemotactic factors such as complement 5a and fibrin fragments can mediate eosinophils migration to target organs or tissues, which may be one of the reason to drop the peripheral eosinophil count^{24,25}. Ping J et al. showed that eosinophil accumulation in the thrombus and decrease in peripheral blood in patients with acute coronary syndrome (ACS)²⁶. Another research reported that eosinophils were increasingly detectable within the injured myocardium and eosinophil-deficient patients with acute myocardial infarction demonstrated worse cardiac function^{18,27}. In our study, we found that 31% of stroke patients with eosinopenia were classified as the cardioembolic subtype. This implied that eosinophils promote thrombus formation and growth and lead to massive cerebral infarction. There was a research had already proved that the more eosinophils infiltrated the greater thrombi size in patients with acute coronary syndrome²⁸. Eosinopenia also be the result of degranulation which made eosinophils no longer be recognized in the circulation²⁹. Eosinophil granule proteins, including eosinophil cationic protein, eosinophil peroxidase, and major basic protein can

cause cytotoxic protein-mediated thrombosis and endothelial injury³⁰. ECP also stimulates fibroblast migration and fibrosis, which could play an important role in the development of atherosclerosis^{31–34}. It could be speculated that increased ECP and activated eosinophils were associated with increased incidence of AIS through effects on unstable plaque.

The main strength of our study is that we compared the variation of eosinophil in same patients at different time and found patients with eosinopenia were significantly associated with poor outcome, which may provide another pathway alongside thrombosis and lipid reduction to target for a decrease in the development of cerebral vascular diseases.

However, our findings also have some limitations. First, the sample size was small which could detract from the validity of the findings. Second, the kind and amount of inflammation factors changed over time. So as a dynamic index, the value of the eosinophil trajectory over time to predict AIS prognosis should be further explored. Future efforts should be directed to collect blood samples at more points to investigate the relationship between eosinophil and AIS. Finally, there was no researches reported eosinophils in thrombosis in AIS patients.

Conclusion

Patients with eosinopenia may have larger volume of cerebral infarction and poor outcome in AIS.

Declarations

Author contributions: QZC and ZMW conceived and designed the study. XFH and QRX collected the data. HMZ and XXH analyzed the data. ZMW and HMZ wrote the paper. All authors approved the final version of the paper.

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Ethics approval and consent to participate: The study protocol was approved by the Institutional Human Research Ethics Committees of Suzhou Municipal Hospital, and all patients or their relatives gave informed consent.

Conflicts of interest: The authors have no conflicts of interest to declare.

Availability of data and materials: The datasets analyzed during this study are available from the corresponding author on reasonable request.

Consent for publication: Not applicable.

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Figures

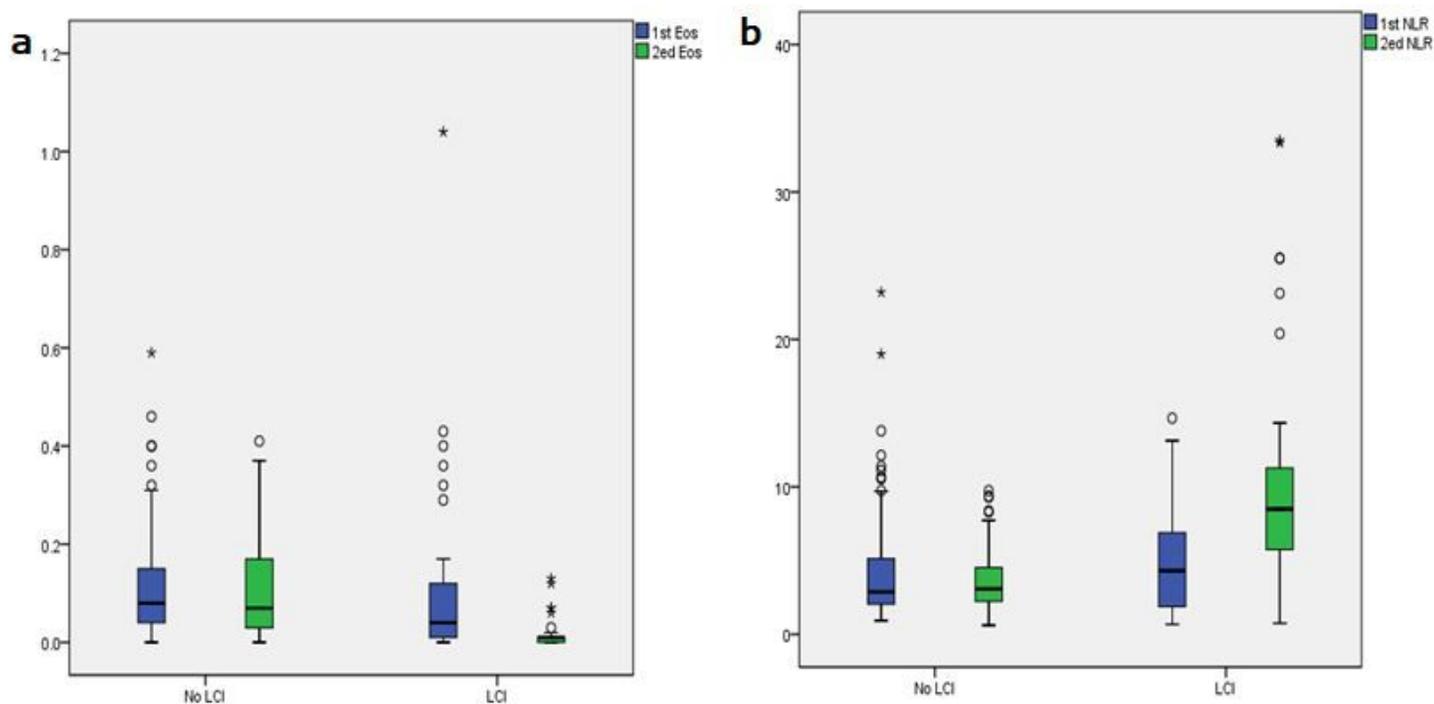


Figure 1

a Temporal profile of plasma absolute eosinophil count and b neutrophil to lymphocyte ratio (NLR) in stroke patients according to the presence of large cerebral infarction (LCI). Blue boxes mean the blood sample obtained at admission, green boxes in the second day.

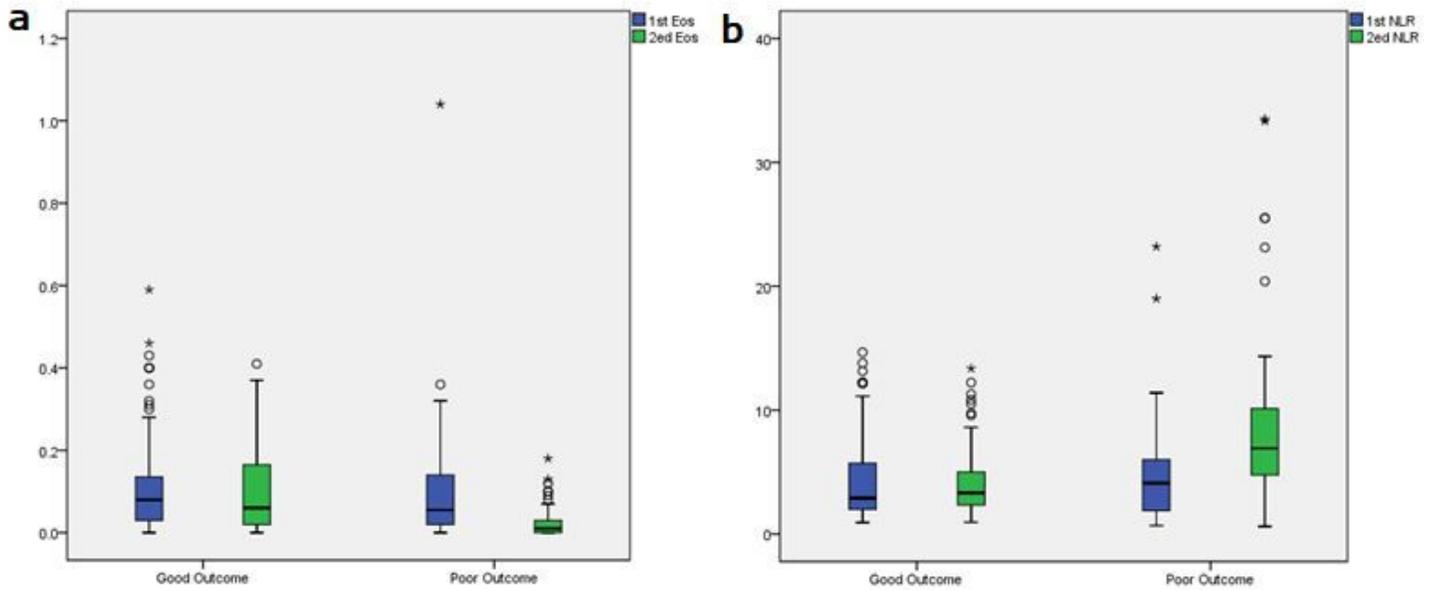


Figure 2

Temporal profile of plasma absolute eosinophil count and neutrophil to lymphocyte ratio (NLR) in stroke patients according to the clinical outcome. Blue boxes mean the blood sample obtained at admission, green boxes in the second day.

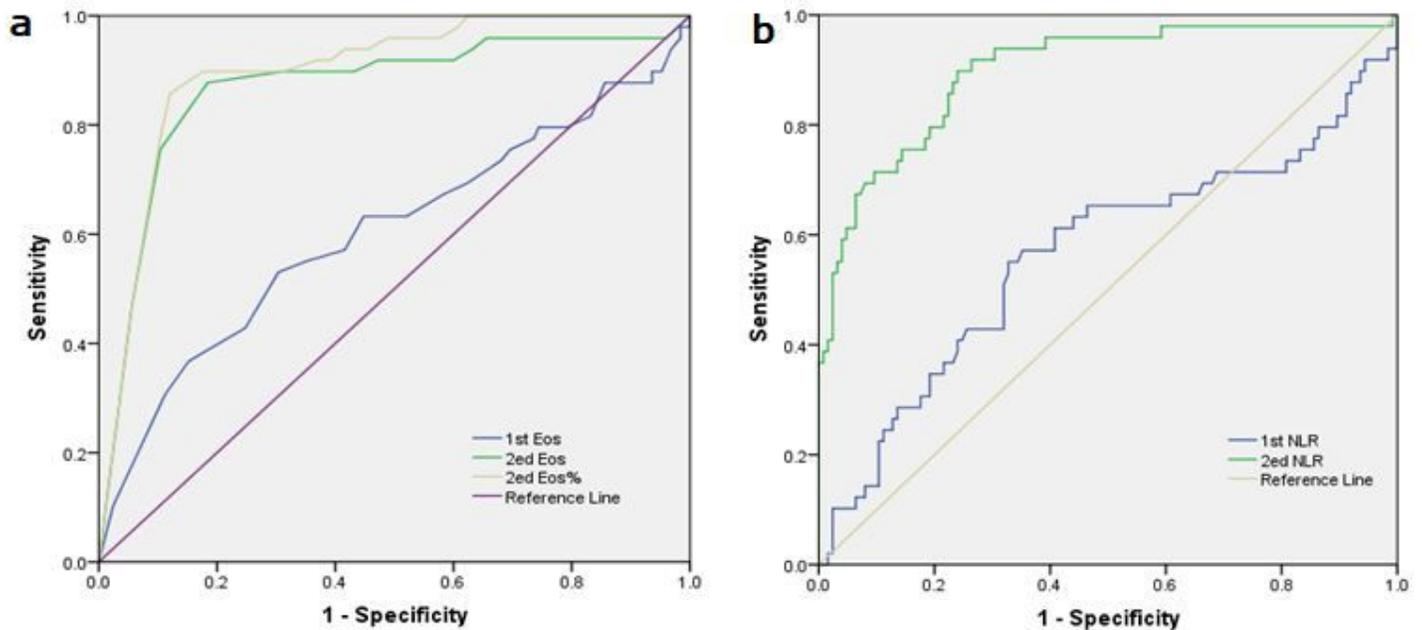


Figure 3

Discriminative ability in different times of the absolute eosinophil count and the neutrophil to lymphocyte ratio (NLR) for large cerebral infarction (LCI). a Receiver operator characteristic (ROC) curve for absolute eosinophil count or eosinophil percentage in predicting LCI and b ROC curve for NLR in predicting of LCI.