Eosinophil-to-monocyte ratio is a potential biomarker in the prediction of functional outcome among patients with acute ischemic stroke

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Abstract

**Background and Purpose**

It has been showed that eosinophils are decreased and monocytes are elevated in patients with ischemic stroke, but the impact of eosinophil-to-monocyte ratio (EMR) on clinical outcomes among patients with acute ischemic stroke remains unclear. The aim of this study is to determine the relationship between EMR on admission and three-month poor functional outcome in patients with acute ischemic stroke.

**Methods**

A total of 521 consecutive patients admitted to our hospital within 24 hours after onset of acute ischemic stroke were prospectively enrolled and categorized in terms of quartiles of EMR on admission between August 2016 and September 2018. The endpoint was the poor outcome defined as modified Rankin Scale score of 3 to 6 at month 3 after admission.

**Results**

As EMR decreased, the risk of poor outcome increased \( (P<0.001) \). Logistic regression analysis revealed that EMR was independently associated with poor outcome after adjusting potential confounders (odds ratio, 0.10; 95% CI, 0.03–0.36; \( P=0.0004 \)), which is consistent with the result of EMR (quartile) as a categorical variable (odds ratio, 0.24; 95% CI, 0.10–0.53; \( P_{\text{trend}}<0.0001 \)). A non-linear relationship was detected between EMR and poor outcome, whose point was 0.28. Subgroup analyses further confirmed these associations. The area under the curve of EMR for the prediction of poor outcome in receiver operating characteristic analysis was 0.653 (95% CI, 0.603–0.703; \( P=0.003 \)). Furthermore, the addition of EMR to conventional risk factors improved the predictive power for poor outcome (net reclassification improvement: 3.54%, \( P=0.230 \); integrated discrimination improvement: 2.11%, \( P=0.001 \)).

**Conclusion**

EMR on admission was independently correlated with poor outcome in patients with acute ischemic stroke, suggesting that EMR may be a potential prognostic biomarker for ischemic stroke.

**Introduction**
Inflammatory and immunological responses play pivotal roles in the pathogenesis of acute ischemic stroke (AIS) which is still a main challenge to public health [1-3]. Leukocytes including neutrophils, lymphocytes and monocytes are indispensable inflammatory cells and are associated with endothelial dysfunction, thrombosis, blood-brain barrier disruption and tissue damage in AIS [1-4]. Moreover, eosinophils have also been shown to be inflammatory cells and were able to regulate the inflammatory responses by facilitating the resolution of inflammation [5]. Recent studies have discovered that stroke triggers an acute decrease in circulating eosinophil counts and an increase in circulating monocytes [6]. Furthermore, post-stroke low circulating eosinophil count was inversely associated with stroke severity and risk of mortality, and high peripheral blood monocyte level was associated with high risk of poor outcome after stroke [7, 8]. These studies, however, did not control for stroke severity and had other issues such as its retrospective nature or the small sample size that limit interpretation of the findings. In addition, all of these studies are mainly focused on a single subpopulation of leukocytes, which may not provide a comprehensive study for the eosinophils and monocytes [7, 8]. Thus, eosinophil-to-monocyte ratio (EMR), a novel biomarker reflecting the integrated application value of eosinophils and monocytes, is needed to identify patients at high risk of poor prognosis.

In this study, we aimed to determine the relationship between EMR on admission and three-month poor functional outcome, and to explore the predictive value of EMR in the poor functional outcome in patients with AIS.

**Methods**

**Study Population**

Consecutive patients with ischemic stroke admitted to the department of encephalopathy at our hospital from August 2016 to September 2018 were prospectively recruited. The inclusion criteria for enrollment were as follows: (1) diagnosis of AIS according to the World Health Organization criteria based on patient history, clinical data, and neuroimaging results (computed tomography or magnetic resonance imaging) [9]; (2) time from onset of stroke to hospitalization was <24 hours; and (3) the patient or their relatives provided informed consent. Study exclusion criteria were: 1) asthma,
eosinophilic esophagitis, hypereosinophilic syndrome, evidence of active infection, chronic inflammatory, autoimmune diseases, steroid therapy, cancer, blood system diseases, previous stroke with partial recovery, severe hepatic or renal dysfunction (90 patients); 2) unavailable complete blood cell count or medical records (48 patients); 3) lost to follow-up (n=29). At last, 521 consecutive ischemic stroke patients were included in the current study. (flowchart of participants selection: Fig. I in the Additional file 1). The study protocol was approved by the institutional Human Research Ethics Committees of Suzhou Integrated Traditional and Western Medicine Hospital, and all patients or their relatives gave informed consent.

**Clinical Protocol and Laboratory Tests**

Medical history including potential stroke risk factors, clinical examination, blood tests, 12-lead electrocardiogram and treatment administration were performed at admission. Stroke severity was assessed by a certified neurologist using the National Institutes of Health Stroke Scale (NIHSS) at admission. The etiologic subtypes of ischemic stroke were classified according to the TOAST (Trial of ORG 10172 in Acute Stroke Treatment) criteria [10]. Given the relatively small number of participants in the other determined etiology and unknown subtypes, we combined these two groups into one group (other etiology/unknown).

In all patients, peripheral venous blood samples were obtained for the measurement of leucocytes, the value of EMR and measuring serum lipid levels. EMR was calculated by dividing eosinophil count by monocyte count. The follow-up data were achieved by telephone. The endpoint was the poor outcome at month 3 after admission with a modified Rankin Scale (mRS) score of 3-6.

**Statistical Analysis**

The total procedure of statistical analysis was divided into five steps. First, baseline characteristics of study participants were presented according to the quartiles of EMR. The one-way ANOVA (normal distribution), Kruskal-Wallis H (skewed distribution) test and chi-square test (categorical variables) were used to determine any significant differences between groups according to the quartiles of EMR. Second, we used a univariate regression model to evaluate the associations between EMR and three-month poor outcome in patients with AIS. Moreover, according to the recommendation of the STROBE
statement, we simultaneously showed the results from unadjusted, minimally adjusted analyses (age and sex) and those from fully adjusted analyses (all potential covariates: age, sex, history of hypertension, history of diabetes mellitus, history of hyperlipidemia, history of previous stroke, history of coronary heart disease, history of atrial fibrillation, current cigarette smoking, ischemic stroke subtypes, triglyceride, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, NIHSS score at baseline and receiving treatment with intravenous recombinant tissue plasminogen activator) in multivariate logistic regression model [11]. Third, we used generalized additive models (GAM) to identify the non-linear relationships because EMR was a continuous variable. If a non-linear relationship was observed, a two-piecewise linear regression model was used to calculate the threshold effect of the EMR on poor outcome in terms of the smoothing plot. When the ratio between poor outcome and EMR appeared obvious in a smoothed curve, the recursive method automatically calculates the inflection point, where the maximum model likelihood will be used [11]. Fourth, we conducted subgroup analyses to assess the robustness of association between low EMR and poor outcome of AIS by using stratified linear regression models. The modifications and interactions between EMR and subgroup variables on the poor outcome were tested by likelihood ration tests [12]. Fifth, receiver operating characteristic (ROC) curves were used to test the overall discriminative ability of the EMR, eosinophils and monocytes for poor outcome. The differences in discriminative ability were tested using the DeLong method [13]. Moreover, we constructed a conventional model (only including conventional risk factors: aforementioned all potential covariates) and a new model (including conventional risk factors and EMR) by logistic regression model. To assess the improvement in risk prediction for poor prognosis of ischemic stroke by adding EMR to conventional risk factors, we calculated net reclassification improvement (NRI) and integrated discrimination improvement (IDI) through comparing these 2 models. All of the analyses were performed with the statistical software package R (http://www.R-project.org, The R Foundation) and EmpowerStats (http://www.empowerstats.com, X&Y Solutions, Inc., Boston, MA). A two-sided P value < 0.05 was considered to be statistically significant [11].

Results
Baseline Characteristics of Patients

Most of the baseline characteristics were balanced between patients included and patients excluded (Table I in the Additional file 1). A total of five hundred and twenty-one patients with ischemic stroke were included in the current study and the average age was 69 years. Main baseline characteristics of study participants according to quartiles of EMR are presented in Table 1. The participants with lower EMR values tended to be older, female and to have subtype of cardioembolism, and had higher NIHSS score, history of hyperlipidemia, higher high-density lipoprotein cholesterol levels, and lower levels of triglyceride. These patients also were more likely to have poor outcome (Table 1).

Univariate and multivariate analysis

The results of univariate analysis showed that age, female, history of previous stroke, history of coronary heart disease, history of atrial fibrillation, subtype of cardioembolism and NIHSS score were positively correlated with poor outcome, whereas history of hyperlipidemia, triglyceride, subtype of small-artery occlusion and EMR were negatively associated with poor outcome (Table 2).

Table 3 summarizes the results of multivariate logistic regression model. The EMR as a continuous variable was independently associated with a smaller risk of poor outcome with an adjusted odds ratio (OR) of 0.23 (95% confidence interval (CI), 0.09–0.56) after adjustment for age and sex (minimally adjusted model) and 0.10 (0.03–0.36) after adjustment for all potential covariates (fully adjusted model). For the purpose of sensitivity analysis, we converted the EMR into categorical variable by quartile and calculated P for trend, the OR (95% CI) of poor outcome for those in the highest quartile of EMR were 0.24 (0.10-0.53) compared with patients in the lowest quartile of EMR. The P for trend was <0.0001.

The analyses of non-linear relationship

In the present study, we analyzed the non-linear relationship between EMR and poor outcome (Fig. 1). The result of smooth curve showed that the relationship between EMR and poor outcome was non-linear after adjustment for all potential covariates (P=0.0008). We compared linear regression model (fitting the relationship between EMR and poor outcome by a linear) and two-piecewise linear regression model (fitting the relationship between EMR and poor outcome by a curve) (Table 4). The P
for log likelihood ratio test is 0.017 which is less than 0.05. This result indicates that the two-piecewise linear regression model should be used to fit the relationship between EMR and poor outcome. By using a two-piecewise linear regression model, we calculated the inflection point was 0.28. On the left of inflection point, the effect size was 0.00 (95% CI: 0.00–0.08, P=0.0003). However, on the right side of the inflection point, we did not observe a significant association between EMR and poor outcome (0.44, 95% CI:0.10-2.02, P=0.2897; Table 4).

The results of subgroup analyses

As is shown in Table 5, the test of interactions was significant for NIHSS (P for interaction=0.0015), while the tests of interactions were not statistically significant for age, sex, history of hypertension, history of diabetes mellitus, history of hyperlipidemia, history of previous stroke, history of coronary heart disease, history of atrial fibrillation, current cigarette smoking, ischemic stroke subtypes and receiving treatment with intravenous recombinant tissue plasminogen activator (P values for interaction were larger than 0.05). The effect sizes of EMR on poor outcome showed significant differences in different NIHSS score. EMR was negatively associated with poor outcome in participants with minor stroke (NIHSS score < 4) (0.00, 95 % CI:0.00- 0.04, P=0.0006). However, the effect sizes of EMR on poor outcome was statistically non-significant in participants with NIHSS score ≥ 4 (P=0.1026; P for interaction=.0015 in the fully adjusted model).

Incremental Prognostic Value of EMR in Patients With Ischemic Stroke

ROC curves comparing the discrimination performance of EMR, eosinophil and monocyte count on poor outcome are shown in Fig. 2. The area under the curve (AUC) of EMR (AUC: 0.6532; 95%CI:0.6032-0.7031) for poor outcome is greater than those of eosinophils (AUC:0.6257; 95%CI: 0.5746-0.6769; P=0.0007) and monocytes (AUC: 0.5831; 95%CI: 0.5317-0.6344;P= 0.0452). In addition, we examined whether adding serum EMR to the conventional risk factors improved the risk prediction of clinical outcomes after AIS. And we found adding EMR to conventional risk factors significantly improved predictive power for poor outcome (NRI: 3.54%, P=0.230; IDI: 2.11%, P=0.001).

Discussion

Our study demonstrated the lower EMR on admission was associated with higher risk of three-month
poor functional outcome in patients with AIS. This association was independent of established risk factors for stroke prognosis, and had a segmental and different population-specific trend. On the left side of the inflection point (EMR<0.28), the effect size was 0.00 (95% CI: 0.00-0.08, P=0.0003). On the right side of the inflection point (EMR≥ 0.28), the relationship between EMR and poor outcome cannot be observed (0.44, 95% CI:0.10-2.02, P=0.2897). And the stronger association between EMR and poor outcome was detected in minor stroke populations by subgroup analysis. Besides, EMR had a bigger AUC than eosinophil or monocyte count, and showed good calibration. Furthermore, adding EMR to conventional risk factors could improve risk prediction for poor outcome. These findings indicated that EMR may be a potential prognostic biomarker for ischemic stroke.

Previous studies have shown that stroke triggers an acute decrease in circulating eosinophil counts while monocytes are significantly increased after AIS [6]. Furthermore, post-stroke low circulating eosinophil count was inversely associated with stroke severity and risk of mortality, and high peripheral blood monocyte level was associated with high risk of poor outcome after stroke [7, 8]. These studies, however, did not control for stroke severity and have other issues such as its retrospective nature or the small sample size that limit interpretation of the findings. In addition, all of these studies are mainly focused on a single subpopulation of leukocytes, which may not provide a comprehensive study for the eosinophils and monocytes [7, 8]. Thus, eosinophil-to-monocyte ratio (EMR), a novel biomarker reflecting the integrated application value of eosinophils and monocytes, is needed to identify patients at high risk of poor prognosis. A recent study revealed that a lower EMR on admission was associated with higher 1-month and long-term mortality in patients with ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention [14]. To the best of our knowledge, this is the first study to study EMR in stroke. We found the lower EMR was associated with poor outcome, and also proved EMR was of certain value in predicting poor outcome in patients with AIS.

In the present study, we demonstrated that there was a saturating effect on the linear relationship between poor outcome and EMR. The inflection point we calculated by the recursive algorithm was 0.28. The result means the negatively linear association between poor outcome and EMR is only
present in participants with relatively low EMR level. For those with relatively high EMR level, this linear relationship cannot be found. There is no current study to explore the non-linear relationships between poor outcome and EMR, but the previous investigations might give us some clues. A recent study revealed that the adjusted odds ratio reflecting the effect sizes of eosinophils on cerebral infarct volume in the Q4 (the reference group), Q3, Q2 and Q1 group were 1.00, 2.416, 4.988 and 50.791, respectively. Similarly, on the effect sizes of eosinophils on poor outcome, the odds ratio in 4 quartiles of eosinophils (from high to low) were 1.00, 2.747, 4.804 and 30.2991, respectively [7]. Moreover, on the effect sizes of monocytes on novel plaque formation, the odds ratio in 4 quartiles of monocytes (from low to high) were 1.00, 1.17, 1.12 and 1.85, respectively [15]. This kind of non-equidistant changes in effect size suggested that there may be a nonlinear relationship between EMR and poor outcome. Given that GAM can handle non-parametric smoothing and has obvious advantages in dealing with non-linear relations, the use of GAM will help us to better discover the real relationships between EMR and poor outcome [11]. Therefore, we use the GAM to clarify their nonlinear relationship in the present study and a nonlinear relationship between EMR and poor outcome was detected after adjusting for all potential covariates.

Given that the percentage of eosinophils was negatively correlated with infarct volume and eosinopenia had the potential to predict the severity of AIS [7, 16, 17], we adjusted baseline NIHSS in the multivariable models and performed further subgroup analyses stratified by NIHSS score to eliminate the confounding effects of the severity of AIS. We found that the significant association of EMR with poor outcome was independent of the baseline NIHSS in stroke patients, especially in participants with minor stroke (NIHSS score < 4; P for interaction=0.0015 in the fully adjusted model). These results suggested that EMR had additional prognostic value when baseline NIHSS was considered, and the application conditions of EMR for the prediction of functional outcome among patients with AIS needed to arouse our attention; in other words, we should apply EMR for the prediction of poor outcome in participants with minor stroke. The reason why the effect sizes of EMR on poor outcome showed significant differences in different NIHSS score remains unclear. We hypothesized that the complicated complication of patients with severe stroke and higher NIHSS itself
might cause some disruptions to the relationship between EMR and poor outcome. Further studies are needed to investigate this hypothesis.

In the present study, we also explored whether EMR had greater and additional prognostic value for poor outcome by using of various statistical methods. First, the AUC of EMR for poor outcome is greater than that of eosinophil or monocyte count, suggesting that EMR is superior to only the eosinophil count or monocyte count for distinguishing the occurrence of poor outcome. The reasons for such a superiority of EMR may relate to what the EMR represents. The EMR reflects the balance between eosinophil and monocyte levels, which may be comprehensively summarize the overall systematic inflammation conditions [14]. Second, the NRI value is positive, though statistically it makes no difference. Moreover, the IDI value is not only positive, but also statistically significant. That, along with the guide advises that the visual representation of the relationship between predicted and observed (not the specific $P$ value) is the best way to evaluate calibration [17], suggest EMR could significantly improve the predictive power for primary outcome beyond established traditional risk factors (NRI: 3.54%; IDI: 2.11%). Therefore, we hypothesized that serum EMR might be useful in risk stratification of poor outcome among patients with ischemic stroke and could assist the selection of high-risk patients in future clinical practice. If patients have low EMR levels at admission, they may be at high risk of poor outcome and should receive aggressive monitoring and therapeutic interventions.

The mechanisms underlying these observations are not well established, but they seem to be related to the roles of eosinophils and monocytes in ischemic insult. Eosinophils are able to secrete over 35 cytokines, growth factors and chemokines, including IL-4, IL-13 and vascular endothelial growth factor (VEGF). IL-4 and IL-13 are capable of inducing the activation of the M2 phenotype microglia, which possess neuroprotective properties by facilitating the resolution of inflammation. And VEGF might be neuroprotective by the modulation of angiogenesis [5, 19, 20]. Monocytes are able to infiltrate into the central nervous system as early as 4 h following acute brain ischemia, which can contribute to inflammation and brain injury on one hand, but on the other hand, certain subpopulations of monocytes are beneficial with a phenotype that could promote the resolution of inflammation,
angiogenesis and tissue repair [21]. The reasons for such a difference may relate to monocytes being a heterogeneous population with proinflammatory or anti-inflammatory phenotypes. The phenotypes of monocytes include CD14$^{\text{high}}$CD16$^{-}$ (classical monocytes), CD14$^{\text{dim}}$CD16$^{+}$ and CD14$^{\text{high}}$CD16$^{+}$ [21]. It is worth noting that the classical monocytes account for nearly 90%, which have deleterious effects after stroke. Nevertheless, the other two phenotypes contribute about 10% of monocytes, which play a beneficial role in patients with stroke [21]. Therefore, the comprehensive effects of peripheral blood monocytes reflect the roles of classical monocytes during the study of monocytes as a whole. Given the deleterious effects of classical monocytes and the possible neuroprotective effect of eosinophils, our study found the lower EMR on admission was associated with higher risk of three-month poor functional outcome in patients with AIS.

The main strength of our study is that the clinical information and blood samples of all patients were collected in a prospective fashion with a relatively large sample size.

The great stroke severity is associated with increase in leukocyte levels and the risk of poor outcome [5, 19-22]. We limited these potential confounders by adjusting NIHSS score in multivariate logistic regression model and conducting subgroup analyses to assess the robustness of association between low EMR and poor outcome of AIS. In addition, we provided a comprehensive study for the eosinophils and monocytes by combining the two into a novel biomarker (EMR). Nonetheless, our current findings also have some limitations. First, the majority of acute critical patients were transferred to higher level hospitals due to the grass-roots hospitals nature of ours, which might result in the baseline NIHSS scores being relatively low and existing deviations of the enrolled patients. Thus, the findings might not generalize to other populations, particularly those with high NIHSS scores. Second, the predictive value of EMR for poor outcome is relatively low. The reasons for the low predictive value may relate to the complicated roles of eosinophils and monocytes in ischemic insult, which have proinflammatory or anti-inflammatory properties [5, 19, 21]. For example, we did not categorize the monocytes subpopulations which include CD14$^{\text{high}}$CD16$^{-}$, CD14$^{\text{dim}}$CD16$^{+}$ and CD14$^{\text{high}}$CD16$^{+}$ phenotypes [21]. Further studies are needed to investigate this hypothesis. Third, we neither explored
the mechanisms by which eosinophils and monocytes affected the neurovascular unit damage nor investigated what factors regulated the changes of eosinophils and monocytes after ischemic strokes in animal studies. These are going to be the focus of our next work, especially exploring the role of eosinophils in AIS and its mechanism.

Conclusion
In conclusion, we found that lower EMR on admission was associated with higher risk of three-month poor functional outcome, indicating that EMR may be a potential prognostic biomarker for AIS. Further studies from other samples of patients with AIS are needed to validate our results.

Abbreviations
AIS: acute ischemic stroke; AUC: area under the curve; CI: confidence interval; EMR: eosinophil-to-monocyte ratio; IDI: integrated discrimination improvement; IQR: interquartile range; mRS: modified Rankin Scale; NIHSS: National Institutes of Health Stroke Scale; NRI: net reclassification improvement; OR: odds ratio; ROC: receiver operating characteristic; TOAST: Trial of ORG 10172 in Acute Stroke Treatment; VEGF: vascular endothelial growth factor.

Declarations

Ethics approval and consent to participate
The study protocol was approved by the institutional Human Research Ethics Committees of Suzhou Integrated Traditional and Western Medicine Hospital, and all patients or their relatives gave informed consent.

Consent for publication
Not applicable.

Availability of data and material
The datasets during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests
The authors declare that they have no competing interests.

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Authors' contributions

SHY, YL, CYZ and ZLG contributed to the concept and rationale for the study. SHY and YL were responsible for the first draft. CYZ and ZLG contributed statistical analyses. TZ, CRH, YF, QZ, FYZ and HH performed the data collection. CYZ and ZLG contributed to the first revision. All authors read and approved the final manuscript.

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Table 1. Baseline characteristics of study participants according to quartiles of eosinophil-to-monocyte ratio (EMR)

| Characteristics                        | Q1     | Q2               | Q3               | Q4               | P value |
|----------------------------------------|--------|------------------|------------------|------------------|---------|
| No. of patients                        | 125    | 135              | 130              | 131              | 0.006   |
| Age, years, mean (SD)                  | 72.54 (13.50) | 70.09 (12.48) | 67.58 (12.64) | 67.59 (13.96) |         |
| Female, (%)                            | 64 (51.20%) | 69 (51.11%)     | 50 (38.46%)     | 49 (37.40%)     | 0.026   |
| Hypertension, (%)                      | 113 (90.40%) | 109 (80.74%)    | 113 (86.92%)    | 110 (83.97%)    | 0.150   |
| Diabetes, %                            | 34 (27.20%) | 31 (22.96%)     | 34 (26.15%)     | 28 (21.37%)     | 0.671   |
| Hyperlipidemia, %                      | 36 (28.80%) | 53 (39.26%)     | 55 (42.31%)     | 65 (49.62%)     | 0.008   |
| Previous stroke, %                     | 26 (20.80%) | 28 (20.74%)     | 21 (16.15%)     | 21 (16.03%)     | 0.594   |
| Coronary heart disease, %              | 16 (12.80%) | 10 (7.41%)      | 14 (10.77%)     | 11 (8.40%)      | 0.461   |
| Atrial fibrillation, %                 | 26 (20.80%) | 25 (18.52%)     | 19 (14.62%)     | 16 (12.21%)     | 0.245   |
| Current cigarette smoking, %           | 14 (11.20%) | 8 (5.93%)       | 19 (14.62%)     | 13 (9.92%)      | 0.138   |
| NIHSS, median (IQR)                    | 4 (2-8) | 4 (2-6)         | 3 (1-6)         | 2 (1-6)         | 0.005   |
| Stroke subtypes                         |        |                  |                  |                  | 0.006   |
| Large artery atherosclerosis           | 40 (32.00%) | 61 (45.19%)     | 48 (36.92%)     | 39 (29.77%)     |         |
| Cardioembolic stroke                   | 21 (16.80%) | 22 (16.30%)     | 17 (13.08%)     | 17 (12.98%)     |         |
| Small artery disease                   | 59 (47.20%) | 52 (38.52%)     | 64 (49.23%)     | 75 (57.25%)     |         |
| Other etiology/unknown                 | 5 (4.00%) | 0 (0.00%)       | 1 (0.77%)       | 0 (0.00%)       |         |
| IV rtPA, %                             | 7 (5.60%) | 13 (9.63%)      | 9 (6.92%)       | 16 (12.21%)     | 0.237   |
| Triglyceride, mmol/L, median (IQR)     | 1.20 (0.89-1.60) | 1.38 (1.00-1.82) | 1.40 (0.94-1.92) | 1.52 (1.06-2.38) | 0.005   |
| Total cholesterol, mmol/L, mean (SD)   | 4.77 (1.06) | 4.99 (1.18)     | 4.92 (1.37)     | 5.00 (1.04)     | 0.364   |
| High-density lipoprotein cholesterol, mmol/L, mean (SD) | 1.36 (0.35) | 1.34 (0.39)     | 1.28 (0.37)     | 1.24 (0.37)     | 0.035   |
| Low-density lipoprotein cholesterol, mmol/L, mean (SD) | 2.37 (0.70) | 2.52 (0.74)     | 2.48 (0.82)     | 2.53 (0.70)     | 0.290   |
| EMR, median (IQR)                      | 0.04 (0.01-0.05) | 0.12 (0.10-0.15) | 0.26 (0.21-0.30) | 0.49 (0.40-0.76) | <0.001  |
| Poor outcome                           | 65 (52.00%) | 53 (39.26%)     | 34 (26.15%)     | 29 (22.14%)     | <0.001  |

EMR, eosinophil-to-monocyte ratio; IQR, interquartile range; IV rtPA, intravenous recombinant tissue plasminogen activator; NIHSS, National Institutes of Health Stroke Scale.

Table 2. The results of univariate analysis
Characteristics | Statistics | Effect size | $P$ value
--- | --- | --- | ---
Age, years, mean (SD) | $69.42 \pm 13.27$ | $1.05 (1.03, 1.06)$ | $<0.000$ 1
Female, (%) | 232 (44.53%) | $1.48 (1.03, 2.12)$ | 0.0352 1
Hypertension, (%) | 445 (85.41%) | $1.47 (0.86, 2.52)$ | 0.1608
Diabetes, (%) | 127 (24.38%) | $1.30 (0.86, 1.97)$ | 0.2083
Hyperlipidemia, (%) | 209 (40.12%) | $0.68 (0.47, 0.99)$ | 0.0469
Previous stroke, (%) | 96 (18.43%) | $2.08 (1.33, 3.27)$ | 0.0014
Coronary heart disease, (%) | 51 (9.79%) | $3.31 (1.82, 5.99)$ | $<0.000$ 1
Atrial fibrillation, (%) | 86 (16.51%) | $4.93 (3.01, 8.07)$ | $<0.000$ 1
Current cigarette smoking, (%) | 54 (10.36%) | $1.22 (0.68, 2.18)$ | 0.4995
NIHSS, median (IQR) | 3 (1-6) | $1.49 (1.38, 1.60)$ | $<0.000$ 1

Stroke subtypes
- Large artery atherosclerosis | 188 (36.08%) | $1.0$ |
- Cardioembolic stroke | 77 (14.78%) | $2.81 (1.61, 4.91)$ | 0.0003
- Small artery disease | 250 (47.98%) | $0.33 (0.22, 0.50)$ | $<0.000$ 1

Other etiology/unknown | 6 (1.15%) | $0.00 (0.00, Inf)$ | 0.9795

IV rtPA, (%) | 45 (8.64%) | $1.04 (0.55, 1.97)$ | 0.9044
Triglyceride, mmol/L, median (IQR) | 1.36 (0.99-1.88) | $0.83 (0.69, 0.99)$ | 0.0426
Total cholesterol, mmol/L, mean (SD) | $4.92 \pm 1.17$ | $1.02 (0.88, 1.19)$ | 0.7649
High-density lipoprotein cholesterol, mmol/L, mean (SD) | $1.30 \pm 0.37$ | $1.30 (0.80, 2.10)$ | 0.2889
Low-density lipoprotein cholesterol, mmol/L, mean (SD) | $2.48 \pm 0.74$ | $1.07 (0.84, 1.37)$ | 0.5758
EMR, median (IQR) | $0.18 (0.07-0.37)$ | $0.19 (0.08, 0.46)$ | 0.0002

EMR, eosinophil-to-monocyte ratio; IQR, interquartile range; IV rtPA, intravenous recombinant tissue plasminogen activator; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio.

The model failed because of the small sample size.

Table 3. Relationship between eosinophil-to-monocyte ratio (EMR) and functional outcomes among patients with acute ischemic stroke in different models

| Variable | Non-adjusted model | Minimally adjusted model | Fully adjusted model |
| --- | --- | --- | --- |
| | OR (95%CI) | $P$ | OR (95%CI) | $P$ | OR (95%CI) | $P$ |
| EMR | $0.19 (0.08, 0.46)$ | 0.0002 | $0.23 (0.09, 0.56)$ | 0.0011 | $0.10 (0.03, 0.36)$ | 0.0004 |
| EMR (quartile) | | | | | | |
| Q1 | 1.0 | | 1.0 | | 1.0 | |
| Q2 | $0.60 (0.36, 0.98)$ | 0.0398 | $0.64 (0.38, 1.07)$ | 0.0869 | $0.56 (0.29, 1.01)$ | 0.0903 |
| Q3 | $0.33 (0.19, 0.55)$ | <0.0001 | $0.38 (0.22, 0.66)$ | 0.0005 | $0.29 (0.13, 0.62)$ | 0.0015 |
| Q4 | $0.26 (0.15, 0.45)$ | <0.0001 | $0.30 (0.17, 0.52)$ | <0.0001 | $0.24 (0.10, 0.53)$ | 0.0005 |
| $P$ for trend | <0.0001 | <0.0001 | <0.0001 | <0.0001 |

Non-adjusted model: we did not adjust other covariants
Minimally adjusted model: we adjusted age and sex
Fully adjusted model: we adjusted age, sex, history of hypertension, history of diabetes mellitus,
history of hyperlipidemia, history of previous stroke, history of coronary heart disease, history of atrial fibrillation, current cigarette smoking, ischemic stroke subtypes, triglyceride, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, NIHSS score at baseline and receiving treatment with intravenous recombinant tissue plasminogen activator

EMR, eosinophil-to-monocyte ratio; OR, odds ratio.

Figures
The non-linear relationship between eosinophil-to-monocyte ratio (EMR) and functional outcomes of ischemic stroke. A nonlinear relationship between them was detected after adjusting for age, sex, history of hypertension, history of diabetes mellitus, history of hyperlipidemia, history of previous stroke, history of coronary heart disease, history of atrial fibrillation, current cigarette smoking, ischemic stroke subtypes, triglyceride, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, NIHSS score at baseline and receiving treatment with intravenous recombinant tissue plasminogen activator.
The non-linear relationship between eosinophil-to-monocyte ratio (EMR) and functional outcomes of ischemic stroke. A nonlinear relationship between them was detected after adjusting for age, sex, history of hypertension, history of diabetes mellitus, history of hyperlipidemia, history of previous stroke, history of coronary heart disease, history of atrial fibrillation, current cigarette smoking, ischemic stroke subtypes, triglyceride, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, NIHSS score at baseline and receiving treatment with intravenous recombinant tissue plasminogen activator.
Figure 2

Prognostic value of eosinophil-to-monocyte ratio (EMR) in patients with ischemic stroke

Receiver operator characteristic (ROC) curves comparing the discrimination performance of EMR, eosinophils and monocytes on poor outcome.
Figure 2

Prognostic value of eosinophil-to-monocyte ratio (EMR) in patients with ischemic stroke

Receiver operator characteristic (ROC) curves comparing the discrimination performance of EMR, eosinophils and monocytes on poor outcome.

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