

Peer Review File

Article information: <http://dx.doi.org/10.21037/atm-20-1640>

Reviewer A

Comment 1: The background of this study is too simple, and do not reflect the important role of NRL supplied in the clinical settings. As we all know, AIS might be corrected if reperfusion occurred within several hours, the neurological sign, CT and the doctors' experiences may be more essential to confirm the AIS within a short time. However, NRL confirms the AIS over more ten hours, missing the time window, and the sensitivity only reaches 70%, specificity only 50%, so, why we still analyze the NRL, rather than conducting further imaging test. Most of the posterior circulation stroke is life-threatening, a ten-hour blood test is not worthy in the stroke diagnosis.

Reply 1: We are grateful for the reviewer's constructive comment. According to the reviewer's suggestion, we have added relevant background information about NLR. Furthermore, we totally agree with the reviewer's opinion that the neurological sign, CT and the doctors' experiences may be more essential to confirm the AIS within a short time. However, missed diagnosis of AIS ranges from 2-26% mostly with nonfocal symptoms like altered mental status, dizziness and headache (Curr Neurol Neurosci Rep 2017;17:15.). DW-MRI is proven to be sensitive in the detection of cerebral infarction. However, ordering head MRI for all suspected AIS patients will inevitably cause waste of limited medical resources. Although the diagnostic performance of NLR only reaches a sensitivity of 70%, and a specificity of 50%, combined with other information, the NLR could be helpful in identifying these atypical AIS. As for the timeliness, complete blood count analysis actually could be finished within half an hour, and it will not slow the diagnosis and treatment of these patients. We hope the reviewer is satisfied with our response. Thanks again for the reviewer's comments.

Changes in the text:

We have added relevant background information about NLR (See Introduction part, paragraph three, marked in yellow).

Comment 2: In the 'Background' section, the NIHSS, CT, ED introductions are redundant.

Reply 2: We are thankful for this valuable comment. According to the reviewer's suggestion, we have simplified the introductions of NIHSS, CT, and ED. And we added more background information about NLR. This could indeed make the background more logical. Thanks again for the reviewer's constructive suggestion.

Changes in the text:

We have simplified the introductions of NIHSS, CT, and ED (See Introduction part, paragraph one, marked in yellow).

Comment 3: HINTS test is more available to identify the central or peripheral dizziness or vertigo in AIS.

Reply 3: Thanks a lot for this constructive comment. We totally agree with the reviewer's opinion that HINTS test is an useful tool to discriminate central from peripheral dizziness or vertigo. However, there are also limitations in the use of HINTS. In most of patients with acute transient vestibular syndrome, the vestibular symptoms or signs had already resolved when the patients arrived at the hospital. HINTS could not be used in this kind of patients (Stroke. 2017 Mar;48(3):556-562.). Furthermore, the HINTS testing may be not well-performed in the ED department with a non neuro-opthomologist. We have added relevant discussion in our manuscript. We hope the reviewer is satisfied with our response. Thanks again for this valuable comments.

Changes in the text:

We have added relevant discussion about the HINTS in our manuscript (See Discussion part, paragraph two, marked in yellow).

Comment 4: As for multivariate analysis, how the author selected the risk factors, this should be detailed.

Reply 4: We thank the reviewer for this important comment. In our study, we included variables with $p < 0.05$ in the univariate analysis into the multivariate logistic regression analysis. We have added this important information in our manuscript. Thanks again for the reviewer's comment.

Changes in the text:

We have added the detailed description of multivariate analysis in our manuscript. (See Statistical Analysis part, paragraph two, marked in yellow).

Comment 5: How to combined several factors to calculate the AUC values, the weightings of each items should be presented and the calculating processes should be detailed.

Reply 5: We are sorry for our over simple expression of the statistical analysis. Combined diagnostic performance was investigated using a binary logistic regression with a value of 1 coding for cerebral infarction and 0 for non-cerebral infarction. This resulted in a constant of -4.19, a beta of 0.35 for NLR ($p < 0.001$), 0.57 for Male ($p = 0.046$), 0.81 for Smoking ($p = 0.023$), 0.99 for Diabetes ($p = 0.001$), and 1.06 for Hypertension ($p = 0.001$). Predicted logit is a single value representing the outcomes derived from NLR, smoking, diabetes and hypertension.

Predicted Logit = - 4.19 + (0.35 × NLR) + (0.57 × Male) + (0.81 × Smoking) + (0.99 × Diabetes) + (1.06 × Hypertension)

From this formula, a predicted probability was calculated using the following formula:

$$\text{Predicted probability} = \frac{e^{\text{Predicted Logit}}}{(1 + e^{\text{Predicted Logit}})}$$

e = Euler's number (2.71828)

The predicted probability is a number between 0 and 1. The patient has a high possibility of cerebral infarction when the predicted probability is closer to 1. A value close to 0 represents a low probability of cerebral infarction. Then, the predicted probability data was used to calculate the AUC value of the combined model. A predicted probability > 0.15173 was calculated as the best cutoff value of the combined model. We have added this information in our manuscript. Thanks again for the reviewer's comment.

Changes in the text:

We have added the detailed description of combined diagnostic performance in our manuscript. (See Supplementary material, marked in yellow).

Comment 6: What is the diagnosis of the patients with non-IS, please identify.

Reply 6: We are grateful for the reviewer's important comments. In our study, all the patients had a MRI within seven days after the head CT and were assessed in the neurology clinic or hospitalization. We carefully reviewed the medical records of the study patients. And we found the symptoms of non-IS patients were diagnosed as secondary symptom resulting hypertension (188, 52.22%), diabetes (36, 10%), peripheral vertigo (21, 5.83%) vertebrobasilar insufficiency (11, 3.06%), mild cognitive impairment (6, 1.67%), and no specific diagnosis (27.22%). There were no patients diagnosed as infection and inflammatory disease, brain hemorrhage, tumors, brain cancer, metabolic disease or psychiatric disorders which may have an effect on the value of NLR. We have added this information in our manuscript. We hope the reviewer is satisfied with our revision. Thanks again for the reviewer's suggestion.

Changes in the text:

We have added the diagnosis results of non-IS patients in our manuscript. (See Result part, paragraph two, marked in yellow).

Reviewer B

Comment 1: Authors should specialize the diagnosis of cerebral infarction in this article.

Reply 1: We are sorry for our over simple expression. In our study, the final diagnosis of cerebral infarction was diagnosed by neurologists based on the detailed medical history, neurological examination, clinical assessment (NIHSS score) and imaging results including brain CT and MR-DWI results. We have added this important information in our manuscript. Thanks again for the reviewer's suggestion.

Changes in the text:

We have further described the diagnosis process of cerebral infarction in our manuscript. (See Study Population part, paragraph two, marked in yellow).

Comment 2: The author did not collect the history of medications when collecting the data, which has been shown to have a particularly significant effect on patients with cerebral infarction. In addition, the state of coagulation function at admission also affects the occurrence of subsequent cerebral infarction.

Reply 2: We are grateful for the reviewer's valuable comments. We totally agree with the reviewer's opinion that both the medication and coagulation function play a role in the occurrence of cerebral infarction. According to the reviewer's suggestion, we have recollected the patients' medication information including antiplatelet agent, anticoagulation agent and lipid lowering agent, and coagulation function information including platelet count, PT, APTT, fibrinogen and TT. And we found no significant difference in the medications and coagulation function between cerebral infarction group and non-cerebral infarction group. We have added this important information in our manuscript. Thanks again for the reviewer's important comment.

Changes in the text:

We have added the results of the medication and coagulation function information in our manuscript. (See Result part, paragraph two, Table 1, marked in yellow).

Comment 3: The author through analysis demonstrated neutrophil to lymphocyte ratio may identify CT negative cerebral infarction with nonfocal symptoms. However, what is the mechanism of this discovery is worth explaining in the discussion.

Reply 3: We are sorry for our over simple expression. Neutrophils have been reported to increase within 15 min of ischemia and surround cerebral vessels; they infiltrate after 6-8 h, peaking at 24-48 h, while lymphocytes decrease after an ischemic stroke, peaking at 24-48 h (J Cereb Blood Flow Metab 2015;35:888-901.). Elevated NLR may represent a marker of severity of tissue inflammation due to ischemic injury (Expert Rev Cardiovasc Ther 2013;11:55-9.), while the injury may be too early to be seen in the CT. Thus, it was conceivable that NLR elevated in CT negative cerebral infarction. According to the reviewer's suggestion, we have added more discussion about the mechanism of the NLR value in CT negative cerebral infarction with nonfocal symptoms. We hope the reviewer is satisfied with our revision. Thanks again for the reviewer's valuable suggestion.

Changes in the text:

We have added more discussion about the mechanism of the NLR value in CT negative cerebral infarction with nonfocal symptoms. (See Discussion part, paragraph four, marked in yellow).

Comment 4: The author states in the article that the diagnosis of cerebral infarction is confirmed within 7 days. However, from the time of admission to the diagnosis of DWI-positive, the changes in the treatment and condition may affect the outcome.

Reply 4: We are grateful for the reviewer's important comment. We admit that the changes in the treatment and condition may affect the outcome from the time

of admission to the diagnosis of DWI-positive. However, there was no significant difference in the time interval from admission to MRI scanning between cerebral infarction group and non-cerebral infarction group. As the study patients had diverse symptoms, the treatment condition was diverse and was difficult to compare between the two groups. We have added this information in the limitation part. We hope the reviewer is satisfied with our revision. Thanks again for the reviewer's valuable comment.

Changes in the text:

We have added the influence of the treatment condition on the final diagnosis as a limitation. (See Discussion part, paragraph seven, marked in yellow).