# Peer Review File

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Reviewer A

Comment 1: Introduction - Line 79-81: The authors write that: Several studies have used NLR as a prognostic indicator for ischemic stroke and found that increased NLR was associated with mortality or poor functional outcomes of patients with ischemic stroke". Please be more specific and name the "poor functional outcomes"(i.e. modified Rankin Scale). Moreover, please consider adding information regarding an association between NLR and post-stroke delirium as one of the unfavorable outcomes, ref. Kotfis K, Bott-Olejnik M, Szylińska A, Rotter I. Could Neutrophil-to-Lymphocyte Ratio (NLR) Serve as a Potential Marker for Delirium Prediction in Patients with Acute Ischemic Stroke? A Prospective Observational Study. J Clin Med. 2019 Jul 22;8(7):1075. doi: 10.3390/jcm8071075. PMID: 31336587; PMCID: PMC6679160.

Reply 1: We have read the above reference and modified our text as advised.

Changes in the text: Please see Page 4, lines 83-84.

Comment 2: Statistical analysis: Line 149-150 - information in the Statistical analysis section regarding NLR quartiles is not specific enough - the authors write that patients were classified into 4 groups by NLR quartiles, but this is too broad, please specify.

Reply 2: We have added some data and modified our text as advised.

Changes in the text: Please see Page 9, lines 182-184 and Table 1.

Comment 3: Conclusions: Line 335-337: The conclusions are not specific enough. The phrase "High level of NLR..." should be replaced by "Level of NLR above...

Reply 3: We have added some data and modified our text as advised.

Changes in the text: Please see Page 12-13, lines 263-265, 267-269; Page 15, lines 310-313 and Table 3.

Comment 4: Results: Please be more specific and give cut-off points when referring to "high NLR" both in the main text of the results section, and in the abstract.

Reply 4: We have added some data and modified our text as advised.

Changes in the text: Please see Page 12-13, lines 263-265, 267-269; Page 15, lines 310-313 and Table 3.

Comment 5: Figure 1: Study Flow-chart should include the exact number of participants at 3-months and 6-months of follow-up.

Reply 5: We have added some data and modified Figure 1 as advised.

Changes in the text: Please see Figure 1.

Reviewer B

Comment 1: In this study, 37 references are cited, where 7 are from 2001-2010, and the rest are from 2011 onwards. This supports the report of recent and relevant

findings. In addition, 18 references are cited in the introduction section, 1 in the methods section, and 18 in the discussion section.

Reply 1: Thanks for your comment.

Comment 2: The abstract background is actually the objectives of the study and not the background. Therefore, I would advise the authors to either rename it to objectives or to provide a background.

Reply 2: We have modified our text as advised.

Changes in the text: Please see Page 2, lines 28-31.

Comment 3: The introduction section is well explained and supported by evidence, in order to provide sufficient background information.

Reply 3: Thanks for your comment.

Comment 4: The methods section is well detailed, and clearly explains the methodology that is used in the study. The authors successfully described the database, ethics approval, inclusion and exclusion criteria, and analysis.

Reply 4: Thanks for your comment.

Comment 5: In the methods section in ‘Neutrophil, lymphocyte count testing, and NLR calculation’ in lines 120-127, the descriptions are written in a confusing aspect, it seems that the authors conducted the NLR measurement. However, if I understood

correctly, the data was taken directly from the CNSR-III database? If that is the case, I would advise the authors to revise this paragraph accordingly.

Reply 5: The data on neutrophil count and lymphocyte count were taken directly from the CNSR-III database. We then calculated the NLR by the below formula.

NLR = neutrophil count/lymphocyte count

Changes in the text: Please see Page 8, lines 132-133.

Comment 6: In the results section, I think it would be better to report the median NLR levels of each quartile in the top row in all the results tables 1, 2, and 3.

Reply 6: We have added some data and modified our text as advised.

Changes in the text: Please see Page 9, lines 182-184 and Table 1.

Comment 7: In the results section, I think it would be best to revise line 192: '420 (3.23%) patients ended up with death'. Maybe to '420 (3.23%) patients died'.

Reply 7: We have modified our text as advised.

Changes in the text: Please see Page 10, line 200.

Comment 8: In the results section, in line 198, I think it is better to remove the word 'obviously'.

Reply 8: We have modified our text as advised.

Changes in the text: Please see Page 10, line 206.

Comment 9: In the results section, I think lines 219-220 can be deleted: ‘And in patients with stroke of other determined cause, NLR had relationship with poor functional outcomes at 3-month follow-up and death at 12-month follow-up.’

Reply 9: Stroke of other determined cause is one of the etiologies in the TOAST classification. We think it would be better not to delete this sentence.

Comment 10: In the discussion section, I advise the authors to add the relevant NLR values when discussing the specific contributions in stroke prognosis.

Reply 10: We have added some data and modified our text as advised.

Changes in the text: Please see Page 12-13, lines 263-265, 267-269; Page 15, lines 310-313 and Table 3.

Comment 11: In the discussion section, I think the authors can delete the following in lines 301-302: ‘our result was different, and’.

Reply 11: We have modified our text as advised.

Changes in the text: Please see Page 15, line 321.

Comment 12: In the discussion section, in lines 307-319, when discussing the NLR values in different ischemic stroke etiologies, for example, you may consider referring to a recent review paper (Harpaz D. et al. Diagnostics 2020) to report some of the following details: “Moreover, neutrophil–lymphocyte ratio (NLR), which is calculated by dividing the concentration of neutrophils by the concentration of

lymphocytes, was reported to indicate ischemic stroke from atherosclerosis etiology, as well as in cardioembolic etiology [110–116]. The NLR is an inflammatory marker that has been recently introduced and examined in several coronary artery disease studies [136–140]. Elkind M. S. et al. [111] reported higher leukocyte counts in cardioembolic and atherosclerotic stroke etiologies. Moreover, Guven H. et al. [112] reported both higher leukocyte and neutrophil counts in great artery atherosclerosis, while the counts were lower in the lacunar group. Additionally, Gokhan S. et al. [110] reported that the NLR ratio level was significantly ($p < 0.001$) higher in the great artery atherosclerosis or atherothrombosis group (6.67 ± 3.74) compared to the other etiologies groups (cardioembolic: 1.74 ± 0.40; lacunar: 3.75 ± 1.74; unknown origin: 3.00 ± 1.49). Tokgoz S. et al. [113] also reported that the NLR was significantly higher ($p = 0.001$) in both the atherosclerotic (6.5 [IQR 7.2]) and cardioembolic (7.5 [IQR 8.9]) stroke subgroups than the lacunar infarct (3.20 [IQR 3.50]) subgroup. Lök U. and U. Gülaçti [115] reported that the NLR level did not vary significantly among the stroke subtypes ($p = 0.070$), while the neutrophil counts (103/μL) were significantly different ($p = 0.008$) (large-artery disease [5.3 ± 1.5]; cardioembolic [8.9 ± 4.01]; lacunar [6.1 ± 2.0] and undetermined [7.1 ± 3.6]). Domaç, F. et al. [114] reported that the NLR levels in atherothrombotic and cardioembolic groups were 3.26 ± 2.35 and 4.46 ± 5.6, respectively, and this was found to be statistically significant ($p = 0.03$)."

Reply 12: We have read the above reference and modified our text as advised.

Changes in the text: Please see Page 16, lines 335-337.

Comment 13: In the conclusions section, I would advise the authors to consider adding additional details to highlight the most important findings of the study.

Reply 13: We have modified our text as advised.

Changes in the text: Please see Page 17, lines 360-361.