Original Article

OPEN ACCESS

Role of Neutrophil to Lymphocyte Ratio to Predict the Prognosis of Acute Ischemic Stroke

Masood Uz Zaman[1], Sunil Dat Maheshwari[2], Asfahan Akhtar Memon[3], Faraz Ahmed Channa[4], Safian Ahmed Memon[5], Areeba Khanzada[6]

[1]Assistant Professor of Neurology, [2]Assistant Professor of Medicine, [3,5]Senior Registrar Medicine,
[4]Assistant Professor of Neurology,
(Isra University Hyderabad)
[6]House officer, Isra University hospital Hyderabad

Author`s Contribution

[1,2]Substantial contributions to the conception or design of the work; or the acquisition, [3,4,6]Active participation in active methodology, [2,3,5]analysis, or interpretation of data for the work, [6]Drafting the work or revising it critically for important intellectual content

Funding Source: None
Conflict of Interest: None

Received: Nov 15, 2023
Accepted: May 23, 2024

Address of Correspondent
Dr. Sunil Dat Maheshwari
Assistant professor of Medicine,
Isra University Hyderabad
sgmaheshwari86@gmail.com

ABSTRACT

Objective: To determine the predictive value of the Neutrophil-to-Lymphocyte Ratio (NLR) in assessing the prognosis of acute ischemic stroke (AIS).

Methodology: This prospective cross-sectional study was done at Medicine and neurology departments of Isra University Hospital Hyderabad from March 2021 to February 2022. Patients aged 18 years or old, both genders who were presented at the neurology department with stroke (based on clinical features and confirmed on CT or MRI scan) within 24 hours of symptom onset were included. A 5ml blood sample was obtained from each patient for CBC. NLR was calculated by dividing the absolute neutrophil count by the absolute lymphocyte counts. The National Institutes of Health Stroke Scale (NIHSS) score was assessed upon admission and at the time of discharge.

Results: Mean age of the patients was 59.85±13.89 years. Females were in majority 52.9% and males were 47.1%. The overall mean NLR is 10.80, and the differences across stroke severity are statistically significant ($p = 0.049$). Regression analysis indicated that the NLR is a significant predictor of AIS severity at both admission and discharge. At admission, NLR explains 9.5% of the variance in NIHSS scores ($R^2 = 0.095$) with an F-value of 6.536 and a p-value of 0.013, showing statistical significance. Each unit increase in NLR is associated with a 0.268 increase in NIHSS score. At discharge, NLR explains 23.8% of the variance in NIHSS scores ($R^2 = 0.238$), with each unit increase in NLR corresponding to a 0.826 increase in NIHSS score ($p = 0.000$), indicating a stronger relationship between NLR and stroke severity.

Conclusion: The NLR has been identified as a strong predictor of acute ischemic stroke severity, accounting for a significant portion of the variance in NIHSS scores at admission. Given its ease of measurement and its significant association with stroke severity, further large-scale studies are recommended to explore the underlying mechanisms of this relationship.

Keywords: Stroke, Ischemia, NLR, NIHSS scores.

Cite this article as: Zaman MU, Maheshwari SD, Memon AK, Channa FA, Memon SA, khanzada A. Role of Neutrophil and Lymphocyte Ratio to Predict the Prognosis of Acute ischemic stroke. Ann Pak Inst Med Sci. SUPPL-1 (2024); 20(3):521-525. doi. 10.48036/apims.v20i2.1219.

Introduction

Acute ischemic stroke (AIS) represents an important contributor of mortality and morbidity globally,[1] defined by the fast onset of neurological impairments due to an impairment in blood supply to the brain. It is a third leading cause of death globally and is the most prevalent neurological disorder in adults. It also stands as the third largest contributor to disability-adjusted life-years (DALYs) worldwide. While stroke-related mortality has decreased in recent years, its incidence has risen in middle- and low-income countries, driven by health and demographic transitions. The pathophysiology of AIS involves a complex interplay encompasses immune cell activation, inflammation, and programmed cell death, with immune responses being particularly critical due to their dual role in causing tissue damage as well as promoting repair.[2,3] In the acute phase, the ischemia-triggered immune response harms the brain, while during the sub-acute phase, T cells and macrophages contribute to brain protection and repair.[2,4] The inflammatory response following ischemia is a complex process that triggers the activation of various inflammatory cells and during this process, ischemic tissues release chemokines and cytokines, attracting circulating peripheral leukocyte.[5] Of the leukocytes that infiltrate the affected brain regions, neutrophils are believed to play a key role in contributing to brain injury.[5,6]

On the other hand, Lymphocytes can also penetrate ischemic areas during the inflammatory response, although this occurs several days after an acute ischemic stroke, later than the arrival of neutrophils (4,8). The exact role of lymphocytes in ischemic brain injury remains a topic of debate. Lymphocytes, a subtype of leukocytes, are key mediators and may serve as predictors of neurological outcomes and it has been recently observed that among patients with leukocytosis, lymphocyte depletion has been identified as an indicator of a poor NIHSS (National Institutes of Health Stroke Scale) score.[8] Although further latest studies have highlighted the potential value of inflammatory biomarkers in predicting prognosis for patients with stroke. The neutrophil-to-lymphocyte ratio (NLR) emerged as a strong prognostic factor.[9-11] It represents a basically easy, cost-effective measurement derived from routine complete blood counts that reflects the body's neutrophil-lymphocyte balance. Neutrophils are often raised in response to acute inflammation, but lymphocytes are frequently reduced under stress or immunological activation. This imbalance may provide crucial insights into the underlying inflammatory mechanisms related to AIS. Few studies show that individuals with increased NLR at the time of admission are more likely to have poor outcomes three months later and may have an increased chance of developing symptomatic intra-cerebral hemorrhage (sICH).[12,13] These results show that the NLR may function as an indicator for the degree of severity of an inflammatory response and the level of neuronal injury. Usage of NLR into clinical practice may improve risk assessment and guide therapeutic approaches. As our understanding of stroke pathophysiology advances, the significance of inflammatory indicators such as NLR may become more important in establishing customized treatment methods. This gives clinicians the option to use NLR as part of a full assessment to better predict outcomes and identify patients at higher risk for problems. However this study has been done to evaluate the predictive role of neutrophil to lymphocyte ratio to predict the prognosis of acute ischemic stroke.

Methodology

This prospective cross-sectional study was done at Medicine and Neurology departments of Isra University Hospital Hyderabad. Study was done during one year of period from March 2021 to February 2022. Patients aged 18 years or old, both genders who were presented at the neurology department with stroke (based on clinical features and confirmed on CT or MRI scan) within 24 hours of symptom onset were included. All the patients presented with hemorrhagic stroke or other neurological conditions, patients with history of recent infection, autoimmune diseases, malignancies, or any ongoing chronic inflammatory condition, patients with history of any surgery or trauma within the past 30 days and those who were not agreed to take a part in study were excluded. Study was conducted after approved by the university ethical committee. Written informed consent was obtained from all patients or their legal representatives before participation in the study and all patients were counseled that their all information will kept confidential. Blood samples were collected from all patients within 24 hours of hospital admission. A 5ml blood sample was obtained each patients and a complete blood count (CBC) was performed by Hospital laboratory using an automated hematology analyzer to obtain absolute neutrophil and lymphocyte count. Neutrophil-to-lymphocyte ratio (NLR) was calculated by dividing the absolute neutrophil count by the absolute lymphocyte counts. The National Institutes of Health Stroke Scale (NIHSS) score was assessed upon admission and at the time of discharge. A score of ≤8 was categorized as indicative of a mild stroke, while a score greater than 8 was classified as a severe stroke. SPSS version 26 was used to enter and analyzed the data of study

Results

Mean age of the patients was 59.85±13.89 years. Females were in majority 52.9% and males were 47.1%. Overall mean of neutrophils, lymphocytes and NLR at admission and at discharge presented in Table I.

According to the mean NLR at admission, minor strokes (NIHSS 1-4) have a mean NLR of 3.50, moderate strokes (NIHSS 5-20) have a mean NLR of 8.67, and severe strokes (NIHSS 21-41) show the highest mean NLR of

14.70. The overall mean NLR is 10.80, and the differences across stroke severity are statistically significant (p = 0.049), indicating that NLR is higher in more severe strokes. (Table II)

Table I: Mean age, neutrophils, lymphocytes and NLR at admission and at discharge.

Age years	Mean±SD	59.85 ±13.89
Neutrophils at admission	Mean±SD	70.77±10.68
Neutrophils at discharge	Mean±SD	58.44±11.52
Lymphocytes at admission	Mean±SD	12.35±8.80
Lymphocytes at discharge	Mean±SD	15.14±15.21
NRL at admission	Mean±SD	10.80±10.57
NRL at discharge	Mean±SD	7.43±4.87
NIHSS score at admission	Mean±SD	18.17±9.22
NIHSS score at discharge	Mean±SD	12.08±8.37

Table II: Comparison of mean NLR according to NIHSS (severity of stroke) at the time of admission.

NIHSS severity of stroke) at admission	Mean NLR at admission			95% CI for Mean		p-value
	n	Mean	SD	Lower Bound	Upper Bound	
1-4 (Minor)	4	3.50	0.70	-2.85	9.85	0.049
5-20 Moderate)	39	8.67	7.40	6.27	11.07	
21-41 (Severe)	25	14.70	13.73	9.03	20.37	
Total	68	10.80	10.57	8.20	13.40	

CI= Confidence interval

At discharge based on stroke severity, patients with minor strokes (NIHSS 1-4) have a mean NLR of 5.86, moderate strokes (NIHSS 5-20) have a mean NLR of 7.35, and severe strokes (NIHSS 21-41) show a mean NLR of 9.50. The overall mean NLR at discharge is 7.45, but the differences across stroke severity are not statistically significant (p = 0.248). (Table III)

Table III: Comparison of mean NLR according to NIHSS (severity of stroke) at the time of discharge.

NIHSS (severity of stroke) at discharge	Mean NLR at discharge		95% CI for Mean		p-value
	N	Mean±SD	Lower Bound	Upper Bound	
1-4 (Minor)	10	5.86±3.13	3.62	8.09	0.248
5-20 (Moderate)	46	7.35±5.02	5.86	8.85	
21-41 (Severe)	12	9.50±5.51	5.55	13.44	
Total	68	7.45±4.90	6.25	8.66	

CI= Confidence interval

According to regression analysis to evaluates the NLR as a predictor of severity of AIS at admission. Results indicate a correlation coefficient (R) of 0.309, with an R^2 value of 0.095, meaning that the NLR explains approximately 9.5% of the variance in NIHSS scores. The adjusted R^2 is 0.081, suggesting a slight adjustment for the number of predictors in the model. The standard error of the estimate is 8.800. The F-value of 6.536 and the significant p-value of 0.013 indicate that the model is statistically significant. The coefficients show that the constant is 15.430, and for every unit increase in NLR, the NIHSS score increases by 0.268, which is statistically significant (p = 0.013). (Table IV)

Table IV: Regression Analysis of NLR as a Predictor of NIHSS Score in Acute Ischemic Stroke Severity at admission.

Model Summary and ANOVA					
R				0.309	
R Square				0.095	
Adjusted R Square				0.081	
Std. Error of Estimate				8.800	
F-value				6.536	
Sig. (p-value)				0.013	
Coefficients	**B**	**Std. Error**	**Beta**	**t**	**Sig.**
(Constant)	15.430	1.615	-	9.553	0.000
NLR	0.268	0.105	0.309	2.557	0.013

Furthermore regression analysis shows that the NLR is a significant predictor of NIHSS score at discharge also in acute ischemic stroke patients (p = 0.000). With an R^2 of 0.238, the model explains 23.8% of the variance in NIHSS scores. For every unit increase in NLR, the NIHSS score increases by 0.826, indicating a moderate positive relationship between NLR and stroke severity at discharge. (Table V)

Table V: Regression Analysis of NLR as a Predictor of NIHSS Score in Acute Ischemic Stroke Severity at discharge.

Model Summary and ANOVA					
R				0.488	
R Square				0.238	
Adjusted R Square				0.226	
Std. Error of Estimate				7.321	
F-value				20.268	
Sig. (p-value)				0.000	
Coefficients	**B**	**Std. Error**	**Beta**	**t**	**Sig.**
(Constant)	5.976	1.657	-	3.607	0.001
NLR	0.826	0.184	0.488	4.502	0.000

Discussion

Stroke is an increasing public health issue and continues to be one of the leading causes of death and disability globally. Neutrophil-to-Lymphocyte Ratio (NLR) has emerged as a potential predictor of stroke severity in patients with acute ischemic stroke. This study has been done on 68 acute ischemic stroke patients to evaluate the NLR as a prognostic predictor; with overall mean age of the patients was 59.85±13.89 years and almost equal gender distribution as 52.9% females and 47.1% males. In aligns to this study Abdu H et al[14] reported that the among the study participants, 150 (48.1%) were male and

162 (51.9%) were female with majority of patients were aged 45 years or older and overall average age was 60.8 ± 12.3 years and 69.6 ± 11.7 years for both genders male and female respectively. In the study by Arslan E et al[15] also reported that the average age was 51.12 ± 16.43 years, with a higher prevalence of males, comprising 65.7% of the participants. In the comparison of this study Iyigundogdu I et al[16] reported that the median age of the patients was 76 ± 12.5 years with male predominance 61.2%. Variations in average age and gender frequency across stroke studies can be due to a several factors including demographic, behavioral, sample selection criteria of the studies and geographical variations.

In this study basis on regression analysis to evaluate the NLR as a predictor of severity of AIS at admission, the adjusted R^2 was 0.081, suggesting a slight adjustment for the number of predictors in the model. The standard error of the estimate was 8.800 and The coefficients show that the constant was 15.430, and for every unit increase in NLR, the NIHSS score increases by 0.268, which is statistically significant ($p = 0.013$). Furthermore the NLR was also observed as significant predictor of NIHSS score at discharge in acute ischemic stroke patients ($p = 0.000$). With an R^2 of 0.238, the model explains 23.8% of the variance in NIHSS scores. For every unit increase in NLR, the NIHSS score increases by 0.826, indicating a moderate positive relationship between NLR and stroke severity at discharge. In aligns to this study Iyigundogdu I et al[16] reported that the neutrophil-to-lymphocyte ratio (NLR) and NIHSS scores at admission, length of hospital stay, mRS scores at discharge, and in-hospital mortality were all found to have a positive correlation. A meta-analysis indicated that raised NLR strongly linked to higher risk of (sICH), poor functional outcomes at 3 months, and raised 90 mortality in patients with AIS receiving reperfusion therapies.[17] Kim JY et al[7] also concluded that the an elevated Neutrophil-to-Lymphocyte Ratio (NLR) was significantly linked to increased NIHSS scores ($p = 0.011$), indicating greater stroke severity, and was also associated with unfavorable outcomes on the K-MBI ($p = 0.002$), reflecting poorer functional recovery.

Moreover, Ertugrul et al[18] found that increased NLR is related with a higher incidence of hemorrhagic transformation (HT) and 3-month mortality following stroke. Our findings are supported by Khan IA et al[19] who reported that the high NLR group exhibited significantly higher in-hospital mortality rates, indicating that NLR is a sensitive and specific predictor of in-hospital mortality. This suggests that elevated NLR levels may be useful for identifying patients at greater risk of adverse outcomes during hospitalization.[19]

Similarly, a study by Majid S et al[20] also reported that patients with acute ischemic stroke who present with an elevated NLR at the time of thrombolysis administration tend to have poor functional outcomes at 3 months, indicating that higher NLR levels may predict long-term recovery challenges following stroke.[20] Additionally, Hammam et al[21] found that NLR was significantly associated with stroke severity in adult patients with AIS when measured within 24 hours of symptom onset. Few other studies also found correlated findings regarding NLR predictor of stoke severity and its short term and long term outcomes.[22-24] However, this study has several limitations, including a small sample size, the absence of a control group, and the lack of follow-up on patient mortality and functional outcomes at three months. Therefore, further large-scale studies are recommended to validate our findings, addressing these limitations to strengthen the evidence for NLR as a predictor of stroke severity and outcomes.

Conclusion

As per the study conclusion the NLR is identified as a strong predictor of acute ischemic stroke severity, accounting for a considerable amount of the variance in NIHSS scores upon admission. Given its ease of measurement and significant association with stroke severity, it is recommended that NLR be included in routine clinical evaluations of stroke patients. However, further large-scale studies are needed to investigate the underlying mechanisms of this relationship, as well as the potential for combining NLR with other biomarkers to enhance predictive accuracy. Overall, utilizing NLR may improve early intervention strategies and patient outcomes in acute ischemic stroke care.

References

1. Saini V, Guada L, Yavagal DR. Global epidemiology of stroke and access to acute ischemic stroke interventions. *Neurology*. 2021 Nov 16;97(20_Supplement_2) https://doi.org/10.1212/WNL.0000000000012781
2. Zhang H, Guan J, Lee H, Wu C, Dong K, Liu Z, Cui L, Song H, Ding Y, Meng R. Immunocytes rapid responses post-ischemic stroke in peripheral blood in patients with different ages. *Frontiers in Neurology*. 2022 May 13;13:887526. https://doi.org/10.3389/fneur.2022.887526
3. Iadecola C, Buckwalter MS, Anrather J. Immune responses to stroke: mechanisms, modulation, and therapeutic potential. *J Clin Invest*. 2020;130:2777-88.

https://doi.org/10.1172/JCI135530

4. Rayasam A, Hsu M, Kijak JA, Kissel L, Hernandez G, Sandor M, et al. Immune responses in stroke: how the immune system contributes to damage and healing after stroke and how this knowledge could be translated to better cures? *Immunology*. 2018;154:363-76. https://doi.org/10.1111/imm.12918
5. Quan K, Wang A, Zhang X, Meng X, Chen P, Li H, Wang Y. Neutrophil to lymphocyte ratio and adverse clinical outcomes in patients with ischemic stroke. Ann Transl Med. 2021 Jul;9(13): 1047. https://doi.org/10.21037/atm-21-710
6. Herz J, Sabellek P, Lane TE, Gunzer M, Hermann DM, Doeppner TR. Role of neutrophils in exacerbation of brain injury after focal cerebral ischemia in hyperlipidemic mice. *Stroke*.2015;46:2916-25. https://doi.org/10.1161/STROKEAHA.115.010620
7. Kim JY, Park J, Chang JY, et al. Inflammation after ischemic stroke: the role of leukocytes and glial cells. *Exp Neurobiol*.2016;25:241-51. https://doi.org/10.5607/en.2016.25.5.241
8. Juli C, Heryaman H, Nazir A, Ang ET, Defi IR, Gamayani U. The lymphocyte depletion in patients with acute ischemic stroke associated with poor neurologic outcome. *Int J Gen Med*.2021;14:1843-51. https://doi.org/10.2147/IJGM.S308325
9. Xu C, Cai L, Yi T, Yi X, Hu Y. Neutrophil-to-lymphocyte ratio is associated with stroke progression and functional outcome in patients with ischemic stroke. *Brain and Behavior*. 2023 Nov;13(11) https://doi.org/10.1002/brb3.3261
10. Sharma D, Spring KJ, Bhaskar SM. Neutrophil-lymphocyte ratio in acute ischemic stroke: immunopathology, management, and prognosis. *Acta Neurologica Scandinavica*. 2021 Nov;144(5):486-99. https://doi.org/10.1111/ane.13493
11. Wijeratne T, Sales C, Karimi L, Jakovljevic M. Elevated neutrophil to lymphocyte ratio predicts in-hospital mortality among stroke patients in a metropolitan hospital in Australia, universal value-added measure in stroke care. *medRxiv*. 2021 Mar 3:2021-03. https://doi.org/10.1101/2021.03.01.21252317
12. Zhang J, Ren Q, Song Y, He M, Zeng Y, Liu Z, Xu J. Prognostic role of neutrophil-lymphocyte ratio in patients with acute ischemic stroke. *Medicine*. 2017 Nov 1;96(45) https://doi.org/10.1097/MD.0000000000008624
13. Guo Z, Yu S, Xiao L, Chen X, Ye R, Zheng P, et al. Dynamic change of neutrophil to lymphocyte ratio and hemorrhagic transformation after thrombolysis in stroke. *J Neuroinflammation*. 2016 Dec;13:1-8. https://doi.org/10.1186/s12974-016-0680-x
14. Abdu H, Seyoum G. Sex differences in stroke risk factors, clinical profiles, and in-hospital outcomes among stroke patients admitted to the medical ward of Dessie comprehensive specialized hospital, Northeast Ethiopia. *Degenerative Neurological and Neuromuscular Disease*. 2022 Jan 1:133-44. https://doi.org/10.2147/DNND.S383564
15. Arslan E, Cetinkaya O. Analysis of the demographic characteristics and clinical profile of acute ischemic strokes admitted to the emergency centre in the Somalia population. Afr J Emerg Med. 2022 ;12(3):216-24. https://doi.org/10.1016/j.afjem.2022.04.010
16. Iyigundogdu I, Derle E, Kibaroglu S, Can U. Neutrophil to lymphocyte ratio, stroke severity and short term clinical outcomes in acute ischemic stroke. *Neurology Asia*. 2021 Sep 1;26(3):479-84. https://doi.org/10.54029/2021cmz
17. Bi Y, Shen J, Chen SC, Chen JX, Xia YP. Prognostic value of neutrophil to lymphocyte ratio in acute ischemic stroke after reperfusion therapy. *Scientific Reports*. 2021 Mar 17;11(1):6177. https://doi.org/10.1038/s41598-021-85373-5
18. Wang L, Song Q, Wang C, Wu S, Deng L, Li Y, Zheng L, Liu M. Neutrophil to lymphocyte ratio predicts poor outcomes after acute ischemic stroke: a cohort study and systematic review. .J Neurol. Sci. 2019 Nov 15;406:116445. https://doi.org/10.1016/j.jns.2019.116445
19. Khan IA, Shahzad SK, Chaudhry AA, Khan SA, Aziz Z, Kiani SS, Toru FK. Correlation of neutrophil to lymphocyte ratio with in-hospital mortality in patients of acute coronary syndrome. *PAFMJ*. 2024 May 30;74(SUPPL-1) https://doi.org/10.51253/pafmj.v74iSUPPL-1.10495
20. Majid S, Lodhi OU, Niazi AK, Lodhi SU, Siddiqui M. Usefulness of neutrophil-to-lymphocyte ratio as a predictor of functional outcome in patients with acute ischemic stroke after thrombolysis therapy. *Baylor University Medical Center Proceedings*. 2021 Nov 2;34(6):664-667. https://doi.org/10.1080/08998280.2021.1938471
21. Shah D, Rajan R, Batra A, Anand I, Saraf A, Sethi P. Evaluation of neutrophil-to-lymphocyte ratio among ischemic stroke subtypes and stroke severity. *Journal of Stroke Medicine*. 2022 Jun;5(1):40-7. https://doi.org/10.1177/25166085221095183
22. Chen L, Zhang L, Li Y, Zhang Q, Fang Q, Tang X. Association of the neutrophil-to-lymphocyte ratio with 90-day functional outcomes in patients with acute ischemic stroke. *Brain Sciences*. 2024 Mar 4;14(3):250. https://doi.org/10.3390/brainsci14030250
23. Ying Y, Yu F, Luo Y, Feng X, Liao D, Wei M, et al. Neutrophil-to-lymphocyte ratio as a predictive biomarker for stroke severity and short-term prognosis in acute ischemic stroke with intracranial atherosclerotic stenosis. *Frontiers in Neurology*. 2021 Jul 29;12:705949. https://doi.org/10.3389/fneur.2021.705949
24. Liu Y, Li G, Jia J, Liu X, Guo J, Zhao X. Clinical significance of neutrophil to lymphocyte ratio in ischemic stroke and transient ischemic attack in young adults. *BMC Neurology*. 2022 Dec 14;22(1):481. https://doi.org/10.1186/s12883-022-03011-7