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CORRELATE ADMISSION NLR RATIO WITH THE EARLY STROKE SEVERITY IN PATIENTS WITH ACUTE ISCHAEMIC STROKE IN TERTIARY CARE CENTRE

Dr Harshit Pawan Sharma,[1] Dr Anil Kumar Panwar,[2] Dr Shrikant Chaudhary,[3] Dr Puneet Rijhwani,[4] Dr Ram Kishan Jat[5]

[1]Resident, Department of Medicine, Mahatama Gandhi Medical College and Hospital, Jaipur, Rajasthan, India
[2,4,5] Professor, Department of Medicine, Mahatama Gandhi Medical College and Hospital, Jaipur, Rajasthan, India
[3]Associate Professor, Department of Medicine, Mahatama Gandhi Medical College and Hospital, Jaipur, Rajasthan, India

Corresponding Author: Dr Shrikant Chaudhary, Associate Professor, Department of Medicine, Mahatama Gandhi Medical College and Hospital, Jaipur, Rajasthan, India Email: Shrikantchoudhary2009@gmail.com

ABSTRACT

Introduction- Acute ischemic stroke is characterized by the sudden loss of neurological function due to infarction of brain tissue caused by arterial occlusion. The inflammatory response following a stroke involves various immune cells, including neutrophils and lymphocytes. The neutrophil to lymphocyte ratio (NLR) is a readily measurable marker from peripheral blood samples that reflects systemic inflammation. Elevated NLR levels have been associated with poor outcomes in various medical conditions, including ischemic stroke.

Aim and Objective- This study investigates the correlation between the neutrophil to lymphocyte ratio (NLR) upon admission and the early stroke severity in patients with acute ischemic stroke. Inflammation plays a crucial role in the pathophysiology of brain injury following ischemic stroke, with elevated NLR levels indicating a higher inflammatory response. This research aims to provide insights about the association on NLR with early stroke severity

Methods- A cohort of patients diagnosed with acute ischemic stroke was enrolled in this study. NLR was calculated from blood samples taken upon admission. Stroke severity was assessed using the National Institutes of Health Stroke Scale (NIHSS).

Results- The study demonstrates a clear association between Neutrophil-to-Lymphocyte Ratio (NLR) within the first 24 hours of admission and both stroke severity and functional outcomes in ischemic stroke patients. Higher NLR values correlate with more severe strokes, as indicated by NIHSS scores. This trend shows a significant increase in stroke severity across NLR quartiles, with the most pronounced differences observed between the lowest (Q1) and highest (Q4) quartiles.The Spearman correlation coefficient (ρ) of 0.176 with a p-value of 0.013 indicates a significant positive correlation between NLR and stroke severity assessed by NIHSS. NLR within the first 24 hours of admission serves as a robust predictor of both stroke severity and functional outcome. The study population predominantly comprised individuals over 45 years old, consistent with age being a significant risk factor for stroke. There was a male preponderance in the study, and other risk factors such as hypertension, diabetes mellitus (DM), and high cholesterol were prevalent among the participants, aligning with established stroke risk profiles. Differences in medical histories (e.g., diabetes, hypertension, smoking, alcohol use) across NLR quartiles further underscore the varying risk profiles associated with different NLR levels.

Conclusion- NLR is a promising biomarker for predicting early stroke severity and short-term functional outcomes in patients with acute ischemic stroke. Incorporating NLR measurement into routine clinical practice could enhance the prognostic assessment and management of stroke patients.

Keywords: NLR, stroke, biomarker.

INTRODUCTION

Cerebrovascular Accidents impose a significant burden, accounting for 6 million deaths and over 10% of all mortality annually, making stroke one of the primary threats to human health(1). Stroke can be categorized as Ischemic Stroke, which constitutes 85% of all acute strokes, and Haemorrhagic Stroke. Previous reports indicate that around 40% of all stroke deaths are linked to hemorrhagic stroke(2). Currently, the primary treatment for acute ischemic stroke involves reperfusion therapy, such as intravenous tissue plasminogen and endovascular therapy (EVT)(3). It is essential for clinicians to factors that impact the prognosis of stroke patients in order to develop appropriate teatment identify the key treatments aimed at improving clinical efficacy and patient prognosis.

The study of stroke prognosis has focused extensively on various biological markers, particularly in acute ischemic stroke (AIS), where early assessment can significantly impact clinical outcomes. Key markers such as fibrinogen and interleukin-6 (IL-6) have been identified as predictors of stroke severity and functional recovery over time [4, 5]. Central to the pathophysiology of AIS is inflammation, which attracts inflammatory cells like monocytes, lymphocytes, and neutrophils to the ischemic brain regions, contributing to tissue damage through the release of inflammatory mediators [6, 7, 8].

The neutrophil-to-lymphocyte ratio (NLR), a well-established marker in internal medicine, serves as a measure of systemic inflammation. Calculated by dividing neutrophil counts by lymphocyte counts, it has been extensively studied in stroke contexts, indicating an imbalance between pro-inflammatory neutrophils and anti-inflammatory lymphocytes. Elevated NLR has shown predictive value for outcomes such as stroke severity, functional impairments, and complications like secondary intracranial hemorrhage [12, 13, 14–17]. This suggests a potential link between NLR and neuroinflammation in AIS, influencing both short-term prognosis and long-term recovery [15, 18].

Neutrophils typically peak in the blood within hours of AIS onset, with infiltration into the brain peaking between 24 to 48 hours thereafter. Concurrently, pro-inflammatory cytokines released by neutrophils, akin to tumor necrosis factor-alpha, show a similar temporal pattern, peaking post-stroke and declining thereafter [9–11]. This delayed peak in neuroinflammation raises questions about the direct role of neutrophil elevation in brain inflammation and its potential as a prognostic indicator within the critical first 24 hours of stroke onset.

In contrast, lymphocytes accumulate in the brain post-stroke but at a slower rate than neutrophils. Various lymphocyte subsets, such as pro-inflammatory T Helper type 1 (TH1) and TH17 cells, exacerbate stroke complications, while regulatory T cells (Tregs) suppress immune responses and promote recovery [8, 12, 28–32]. Experimental models have demonstrated that decreased Treg presence correlates with increased brain damage and behavioral deficits following AIS, underscoring the complex roles of lymphocytes in stroke pathophysiology [11, 13].

The NLR, encompassing both neutrophil and lymphocyte dynamics, provides a simplified yet comprehensive assessment of post-stroke immune response compared to traditional leukocyte counts. High NLR at admission has been associated with large artery blockages and heart-related issues, highlighting its potential as an early indicator of stroke severity irrespective of etiology [9, 10]. Moreover, elevated NLR predicts adverse short-term and long-term health outcomes in AIS patients, suggesting its utility in guiding early treatment decisions and prognosis assessment [12, 13, 15, 18].

In conclusion, the interplay between neutrophils and lymphocytes in AIS reflects a nuanced relationship in stroke pathology, where NLR serves as a valuable prognostic tool. Its simplicity in measurement and predictive power for stroke severity and functional outcomes make it a promising biomarker in clinical practice. This study aims to explore the correlation between admission NLR and early stroke severity, as well as short-term functional prognosis, in AIS patients at a tertiary care center. By elucidating these associations, the study seeks to contribute to improved management strategies and outcomes in acute ischemic stroke.

Aim and Objective

This study investigates the correlation between the neutrophil to lymphocyte ratio (NLR) upon admission and the early stroke severity in patients with acute ischemic stroke. Inflammation plays a crucial role in the pathophysiology of brain injury following ischemic stroke, with elevated NLR levels indicating a higher inflammatory response. This research aims to provide insights about the association on NLR with early stroke severity.

MATERIALANDMETHODS:

A Hospital based Observational study, conducted on 100 patients (outpatient & inpatient) suspect with acute stroke, and evaluated under the department of General Medicine, Mahatma Gandhi Hospital from Aug 2022 to October 2023 were included in the study. Detailed history and necessary investigations will be undertaken. The purpose of the study was explained to the patient/guardians and informed consent obtained. Patients are selected for studies that satisfy all inclusion and exclusion criteria. Institute Ethics Committee approval will be taken before undertaking the study. Written and inform consent was taken from all participants before enrolment into the study.

Inclusion criteria*:*

(1)age ≥18 years

(2)time interval from symptom onset to admission ≤72 hr

(3)blood sampling performed within 24 hr after hospital admission

Exclusion criteria*:*
(1)Age<18 yrs
(2)Malignant tumors,
(3)Severe renal or hepatic diseases,
(4) Hematological diseases,
(5)Inflammatory or infectious diseases,
(6) History of immunosuppressant medications ,within the past 3 months
(7) Hemorrhagic stroke

Sample size calculation- Sample size was calculated using Epi Info Software at 5 % Confidence Interval using article of Kamalakannan S et al [209], where the total population was 78 and prevalence of sepsis was 44.29%. Hence the calculated size was 95 at 5% error. To drop out the failure we rounded of the sample size to 100.

Statisticalanalysis
Continuous variables were presented as mean with standard deviation (SD) or median with interquartile range (IQR) for data with normal and non-normal distributions, respectively, whereas categorical variables were described as number and percentage. For continuous variables spearman test was used to assess the intergroup difference. Multivariate binary logistic regression analysis was conducted to evaluate associations between NLR with early severity and short-term prognosis after adjustment for age, sex, and other possible confounders, involving all variates with a $P < 0.05$ in initial univariate analysis, with results exhibited as odds ratios (OR) and 95% confidence interval (CI). All statistical analyses were conducted with SPSS 16.0 software . $P < 0.05$ was considered statistically significant, $P < 0.01$ is considered high significant and $P < 0.01$ is considered highly significant.

OBSERVATIONS-

RESULTS-
TABLE NO 1- AGE DISTRIBUTION OF PATIENTS

AGE GROUP	NUMBER
18-30	13
30-45	17
45-60	36
>60	34
SEX	
MALE	70
FEMALE	30

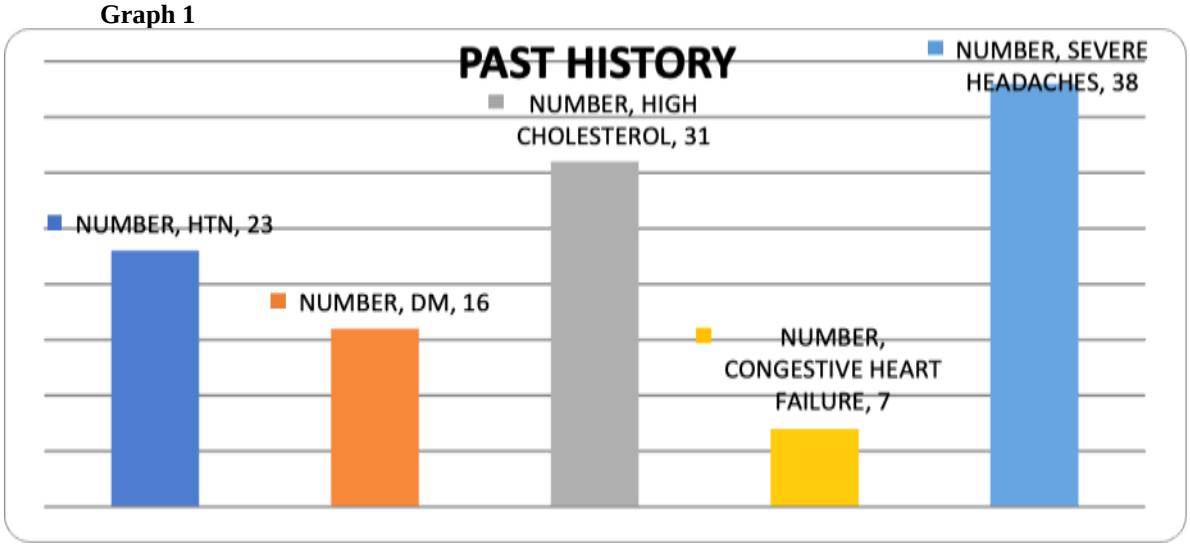
Age distribution of patients stated that majority i.e. 70% belonged to >45 year age group. Minimum pts were in 18-30 yrs. Sex distribution in above table states that majority of them were males i.e. 70% and 30% were females

TABLE NO 2 - PERSONAL HISTORY

	NUMBER	PERCENTAGE
ALCOHOL CONSUMPTION	10	9.8%
TOBACCO	12	11.8%

Above table stated that 9.8% were taking alcohol and 11.8% were consuming tobacco.

Graph 1



Among 100 patients, only 23 patients had HTN, 16 had DM, 31 had high cholesterol, 7 had CHF.38 pts had severe headaches.

TABLE 3- FAMILY HISTORY

FAMILY HISTORY	NUMBER
YES	12
NO	88
TOTAL	100

In our study 12% pts had family history of stroke

TABLE 4- NLR (NEUTROPHIL TO LYMPHOCYTE RATIO)

NLR RATIO	NUMBER
<1.84	25
1.848≤ NLR <2.548	25
2.548≤ NLR <3.728	25
NLR ≥3.728	25
TOTAL	100

TABLE 5- Baseline characteristics of the patients stratified by NLR

Characteristics	Overall (n=100)	Q1 (NLR <1.84) (n=25)	Q2 (1.848≤ NLR <2.548) (n=25)	Q3 (2.548≤ NLR <3.728) (n=25)	Q4 (NLR ≥3.728) (n=25)	P value
DEMOGRAPHY						
MEAN AGE (YRS) (RANGE)	63 [54–70]	61 [54–68]	62 [54–69]	63 [55–70]	64 [56–72]	<0.0001
Males	70	12	9	23	26	<0.0001
Females	30	10	7	6	7	0.97
BMI, kg/m^2, (RANGE)	24.49 (22.58–26.56)	24.21 (22.86–26.67)	24.49 (22.66–26.67)	24.61 (22.68–26.57)	24.62 (22.05–26.12)	<0.0001
ALCOHOLICS	10	1	3	1	5	<0.0001

Characteristics	Overall (n=100)	Q1 (NLR <1.84) (n=25)	Q2 (1.848≤ NLR <2.548) (n=25)	Q3 (2.548≤ NLR <3.728) (n=25)	Q4 (NLR ≥3.728) (n=25)	P value
SMOKERS	12	2	5	3	2	0.0051
PAST HISTORY						
Previous stroke	12	1	1	4	6	0.0004
Diabetes	16	4	3	4	5	0.0001
Coronary heart disease	7	1	2	2	2	0.4825
Hypertension	23	2	6	7	8	0.0007

NLR, neutrophil to lymphocyte ratio; BMI, body mass index; NIHSS, National Institutes of Health Stroke Scale; IQR, interquartile range.

Above table stated the baseline characteristics of the participants categorized based on NLR. In contrast to individuals in lower NLR quartile groups, those in higher NLR quartile groups were more likely to be male, older, have a higher BMI, have experienced a more severe stroke. Additionally, there were variations in the history of diabetes, hypertension, smoking, and drinking among individuals in the NLR quartile groups. Patients with higher NLR were more likely to have had a prior stroke and the other medical histories were similar across NLR quartile groups.

TABLE 6 - COMPARISON OF STROKE SEVERITY AND FUNCTIONAL OUTCOMES IN PATIENTS CATEGORIZED BY NLR QUARTILES.

	Q1 (NLR <1.84) (n=25)	Q2 (1.848≤ NLR <2.548) (n=25)	Q3 (2.548≤ NLR <3.728) (n=25)	Q4 (NLR ≥3.728) (n=25)	P1	P2	P3	P4
NIHSS	4.73 ± 3.47	5.75 ± 3.71	6.46 ± 3.06	8.78± 3.21	0.321	0.06	0.0001	0.0033

Results are presented as mean ± standard deviation (SD). P1, comparison between s 1 and 2; P2, comparison between quartiles 1 and 3; P3, comparison between quartiles 1 and 4; P4, comparison between quartile 2 and 4;

Abbreviations: NIHSS, National Institutes of Health Stroke Scale; p <0.05, ** p < 0.01. Above table stated that there is significant effect of increase in NLR ratio on severity of stroke assessed by NIHSS. Mean value of NIHSS increased with increase in NLR.

TABLE 7- CORRELATIONS OF NLR WITH STROKE SEVERITY

Variables	Spearman Correlation Coefficient (ρ)	*p*-Value
NIHSS	0.176	0.013 *

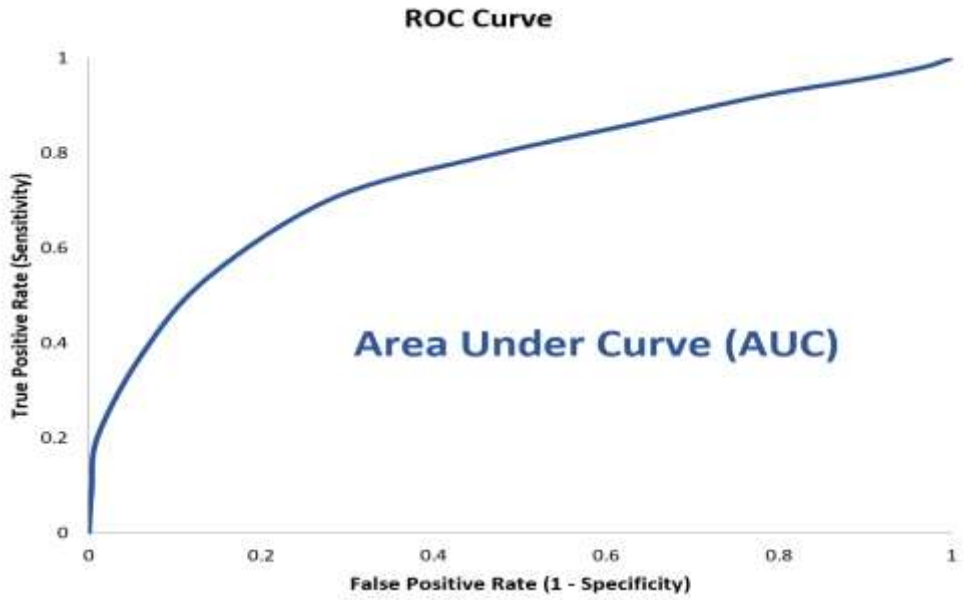
Abbreviations: NIHSS, National Institutes of Health Stroke Scale; * p < 0.05,
There was positive correlation of NLR ratio and NIHSS score. Thus we can use NLR ratio as a predictor of stroke severity .

TABLE 8- Logistic Regression Analysis Of The Associations Between The Optimal Nlr Cut-Offs And The Indicators Of Stroke Severity And Functional Outcomes.

Variables	AUC (95% CI)	Cut-Off Value	Sensitivity	Specificity
NIHSS	0.73 (0.52–0.69, p = 0.0321) *	2.09	0.70	0.52

Abbreviations: NIHSS, National Institutes of Health Stroke Scale;; AUC, area under the curve; OR, odds ratio; CI, confidence interval.
* p < 0.05,.

GRAPH 7-ROC FOR NLR AND NIHSS



In general, an AUC of 0.7 to 0.8 is considered acceptable. Hence we can use NLR as a acceptable method of screening for stroke severity

DISCUSSION

Our study focused on evaluating the Neutrophil-to-Lymphocyte Ratio (NLR) within the first 24 hours of admission as a prognostic indicator in patients suffering from ischemic stroke. We found that elevated NLR levels were consistently associated with poorer functional outcomes and increased mortality risk, regardless of the stroke's cause. This highlights NLR as a potentially valuable tool for predicting unfavorable clinical outcomes in both short- and long-term scenarios following ischemic stroke.

Demographically, our study showed a predominant age group of over 45 years, consistent with known stroke risk factors where advanced age significantly increases vulnerability. This finding aligns with broader stroke survivor statistics indicating that the majority are aged over 65 years, with mean ages reported between 60 to 70 years across various studies. Additionally, our study exhibited a male preponderance, a trend corroborated by similar findings in other research by Yoneda et al., Reganon et al., and Williams et al.

Among our study participants, 9.8% reported alcohol consumption, and 11.8% used tobacco, while hypertension, diabetes, and high cholesterol were identified as the most common comorbidities. These risk factors are well-documented in stroke literature, with hypertension being globally recognized as the foremost risk factor. Our findings regarding the prevalence of these factors generally aligned with global statistics, although rates of smoking and alcohol use were notably lower than reported in some literature.

NLR was stratified into quartiles in our study: q1 (<1.84), q2 (1.848 - 2.547), q3 (2.548 - 3.727), and q4 (≥3.728). Analysis revealed that higher NLR quartile groups correlated with male gender, older age, lower BMI, and more severe stroke . Moreover, there were variations in the prevalence of diabetes, hypertension, smoking, and drinking across NLR quartile groups. Higher NLR was also associated with a history of prior stroke or heart failure, suggesting its potential utility in predicting stroke severity.

Research suggests that NLR levels measured within 48-72 hours after stroke onset may provide the strongest predictive value for patient outcomes. However, our study focused on NLR within the first 24 hours of admission, which still proved effective in predicting short-term mortality and long-term functional impairment. Specifically, NLR levels above 3.872 were associated with increased risk of death, while levels above 2.846 predicted poor functional outcomes. These findings were consistent across different follow-up periods, including at the 12-month mark, highlighting NLR's sustained predictive capability.

The underlying immunological mechanisms linking NLR to stroke outcomes involve the immediate migration of neutrophils to damaged brain tissue post-stroke, exacerbating injury through inflammation and thrombus formation. Conversely, lymphocytes, particularly regulatory T cells, may exert protective effects by modulating inflammatory responses and promoting immune homeostasis.

In conclusion, NLR serves as a valuable biomarker in ischemic stroke prognosis, reflecting the intricate balance of post-stroke immunological responses involving neutrophils and lymphocytes. Its simplicity of measurement makes it an accessible tool for early risk stratification and treatment planning, potentially improving clinical outcomes through targeted interventions. Further research is needed to elucidate the precise immunological mechanisms and validate NLR's predictive utility across diverse patient populations and clinical settings.

1. Age distribution of patients stated that majority i.e. 70% belonged to >45 year age group. Minimum pts were in 18-30 yrs.
2. Sex distribution in above table states that majority of them were males i.e. 70% and 30% were females.
3. 9.8% were taking alcohol and 11.8% were consuming tobacco.
4. Among 100 patients, only 23 patients had HTN, 16 had DM, 31 had high cholesterol, 7 had CHF.38 pts had severe headaches.
5. In our study 12% pts had family history of stroke

In our study we stratified NLR in four quartiles. Which are-

1. <1.84
2. 1.848≤ NLR <2.548
3. 2.548≤ NLR <3.728
4. NLR ≥3.728
6. The baseline characteristics of the participants categorized based on NLR. In contrast to individuals in lower NLR quartile groups, those in higher NLR quartile groups were more likely to be male, older, have a lower BMI, , have experienced a more severe stroke, and be receiving intravenous thrombolysis or endovascular therapy. Additionally, there were variations in the history of diabetes, hypertension, smoking, and drinking among individuals in the NLR quartile groups. Patients with higher NLR were more likely to have had a prior stroke or heart failure, and the other medical histories were similar across NLR quartile groups.
7. There was positive correlation of NLR ratio and NIHSS score.Thus we can use NLR ratio as a predictor of stroke severity.

CONCLUSION-

Following an ischemic stroke, neutrophils and lymphocytes mediate distinct inflammatory responses and have varying effects on the clinical outcomes of patients. Patients with cardiogenic embolism and large artery atherosclerosis had significantly higher NLRs within the first 24 hours of admission. In patients with ischemic stroke, a high level of NLR was linked to an increased risk of both short- term adverse clinical outcomes, regardless of the underlying cause.

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