Evaluation of Neutrophil to Lymphocyte Ratio with Neurological Severity and Short-Term Outcome in Acute Ischemic Stroke

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Abstract

Introduction: *Stroke represents a significant global health care challenge, ranking as the second most common cause of mortality and disability worldwide. Inflammatory process plays an important role in pathophysiology of acute ischemic stroke. These inflammatory responses increase the brain damage and cause neurological deterioration. Neutrophils and lymphocytes serve as pivotal mediators of inflammatory response.*

Aims and Objectives: *This study aims to evaluate the association between the Neutrophils to lymphocyte ratio (NLR) with the initial severity of stroke and the short-term functional outcome using the NIHSS and BARTHEL index respectively.*

Materials and Methods: *We conducted an observational cross-sectional study on 80 patients admitted at Father Muller Medical College Hospital, which is a tertiary care centre in Mangalore between May 2023 to April 2024. Diagnosis of stroke was based on clinical evaluation and Radiological imaging. Peripheral blood samples were collected for complete blood count within 24 hours of stroke onset. The NLR was determined by dividing the absolute neutrophil count (ANC) to the absolute lymphocyte count (ALC). This was then correlated with the NIHSS and the BARTHEL index.*

Results: *This study included 80 patients, with the mean age of 65.1 years. Majority of the patients were in the age group 51-70years (55%). The mean NLR was found to be 13.39. The mean NIHSS and BARTHEL index was 11.08 and 63.69 respectively. The NLR showed significant correlation with the initial stroke severity and the short-term functional outcomes. For the purpose of correlation NLR was divided into three groups i.e. >3, 3-5 and >5. Patients with higher NLR (>5) were more likely to have a severe stroke and greater dependency. Conversely, those with lower NLR (<3) had a minor stroke and slight dependency. 80% of the patients with severe stroke had a NLR above 5, while 82% of the patients with minor stroke had a NLR below 3 (p value <0.001). This study also found a strong correlation between NIHSS and the BARTHEL index - patients with lower NIHSS and NLR were found to have a better short term function outcome.*

Conclusion: *NLR was found to be significantly associated with the initial severity of stroke and the short-term functional outcome. Because of its high specificity, low cost, routine use NLR can be used for the prediction of severity of stroke and patients can be prioritised for specialised treatment thus reducing the mortality rates.*

Introduction

Stroke represents a significant global healthcare challenge, ranking as the second most common cause of both mortality and disability worldwide, trailing behind ischemic heart disease.[1] The financial burden associated with stroke treatment and post-stroke care is considerable. According to the World Health Organisation (WHO), defines stroke as "rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting 24 hours or longer or leading to death, with no apparent cause other than that of vascular origin.[2]

The early identification of individuals susceptible to stroke could play a pivotal role in the implementation of primary prevention strategies.[3]

It is a well-known fact that inflammatory process play an important role in pathophysiology of acute ischemic stroke.[4] Under normal conditions inflammatory mediators are at low level however during ischemic injury pro inflammatory markers such as cytokines, chemokines are markedly raised which results in progression of the brain lesion.[5] These inflammatory responses increase the brain damage and cause neurological deterioration.[4] Neutrophils and lymphocytes serve as pivotal mediators of the inflammatory response and are instrumental in the pathophysiology of cerebrovascular diseases. Studies have elucidated a correlation between the early elevation of white blood cell (WBC) and neutrophil counts in acute ischemic stroke (AIS) and both an increased infarct volume and heightened stroke severity.[6] Raised WBCs and neutrophils are also predictors of stroke and known to be responsible for stroke recurrences.[7] Studies have also shown association of poor prognosis in acute ischemic stroke with low lymphocyte count.[8]

The neutrophil-to-lymphocyte ratio (NLR) is an easily calculable marker from the routine differential WBC count, which is done as part of standard of care to nearly all stroke patients.

Recently, NLR has garnered attention as an index of systemic inflammatory status, notably within the Asian demographic.[9] Its prognostic utility has been substantiated in various malignancies and coronary artery diseases.[10,11] In one cardiovascular study, NLR was found to surpass WBC count in prognostic efficacy and disease severity stratification.[11] Emerging studies on cerebrovascular accidents have demonstrated a correlation between elevated NLR and heightened mortality in acute ischemic stroke (AIS) patients.[12,13]

Notwithstanding its cost-effectiveness and widespread availability in clinical settings, NLR remains under-researched in patients of acute ischemic stroke across different populations, including the Indians. This study aims to evaluate the association between NLR with the initial severity of stroke and the short-term outcome using NIHSS and BARTHEL index respectively.

Materials and Methods

An observational cross-sectional study was conducted at Dept of General Medicine, Father Muller Medical College Hospital a tertiary care centre in Mangalore, Karnataka over a period of one year from May 2023 to April 2024. 80 cases were included, who were diagnosed with first ever episode of acute ischemic stroke.

Inclusion Criteria

All patients of more than 18 years of age, who presented to the hospital within 24 hours, with new onset focal neurological deficits and were diagnosed as having first attack of Acute Ischemic stroke with clinical radiological evidence were included in the study.

Exclusion Criteria

- Patients who presented 24 hours after the onset of symptoms
- Acute haemorrhagic Stroke or transient ischemic attack
- Second or recurrent episode of stroke
- Patients with recent trauma, surgery, neoplasm, active infection, immunosuppressive agent use, haematological disease, inflammatory

disease, severe hepatic and renal disease, acute metabolic disease and intoxication.

This study was approved by the Ethics committee of the institution. A written informed consent was taken from the patients or their attenders willing to participate in the study. A detailed history was taken, and a thorough clinical examination was done. The diagnosis of stroke was determined by clinical examination and confirmed through computed tomography (CT) and magnetic resonance imaging (MRI). The specified comorbidities and risk factors included a history of hypertension, atrial fibrillation (AF), diabetes mellitus, smoking, coronary artery disease (CAD), and dyslipidemia.

Patients divided according to TOAST classification into large artery atherosclerosis, cardioembolic stroke or a lacunar stroke. Stroke severity at presentation was calculated by using NHISS Score. Short term functional outcome was measured at the 5th day or at discharge which ever was earlier using the BARTHEL index.

Peripheral blood samples were collected in EDTA tubes within 24 hours of stroke symptoms onset. These samples were analysed for complete blood count and differential leukocyte count (DLC) using a fully automated haematology analyser. The neutrophil-to-lymphocyte ratio (NLR) was determined by dividing the absolute neutrophil count (ANC) by the absolute lymphocyte count (ALC). This was then correlated to the NIHSS score and BARTHEL index.

Table 1: NIHSS Stroke scale

NIHSS STROKE SCALE	STROKE SEVERITY
0	No stroke symptoms
1-4	Minor stroke
5-15	Moderate stroke
16-20	Moderate to severe stroke
24-42	Severe stroke

Table 2: BARTHEL Index

| BARTHEL INDEX	DEPENDENCY
0-20	Total Dependency
21-60	Severe Dependency
61-90	Moderate Dependency
91-100	Slight Dependency

Statistical Tools

Data collected from the patients was tabulated using Microsoft Excel. The data was entered in tables as frequency, percentages, mean standard deviation, graphs and pie charts. The data was analysed using the Chi square test/Fishers exact test. Statistical analysis for the data collected was done using SPSS (Statistical Package for social Sciences) 23.0 version.

P value was tested at 5% level of significance.

Results

In this study, a total of 80 patients were included out of which 62 were males and 18 were females. Mean age was found to be 65.1 years with a standard deviation of 13.16 years. Majority of the patients were found to be in the age group 51-70 years, 44 patients (55%) followed by 27 patients above the age of 70 (33.8%) and 9 patients in the age group 30-50 years.
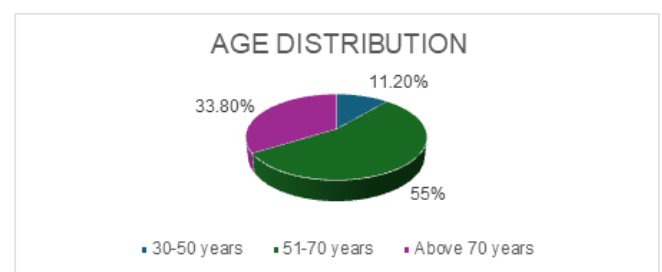
Figure 1: Age distribution of the subjects

Hypertension was found to be the most common associated comorbidity (75%) followed by type 2 diabetes mellitus (48.8%), ischemic heart disease (15%), dyslipidemia (8.8%) and 5% of the patients had COPD.
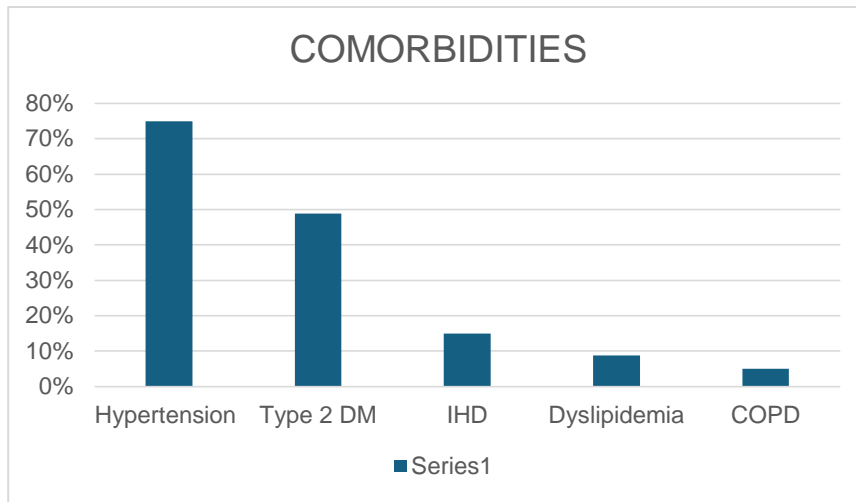
Figure 2: Comorbidites

16.3% of the patients (13 patients) were smokers and 17.5% of the patients (14 patients) were found to have significant history of alcohol.

Motor weakness was found to be the most common mode of presentation (71.3%) followed by dysarthria (26.3%), vertigo (13.8%), Dysphagia (7.5%), altered sensorium (7.5%), Aphasia (6.3%) and 2.5% of the people presented with headache and paraesthesia.
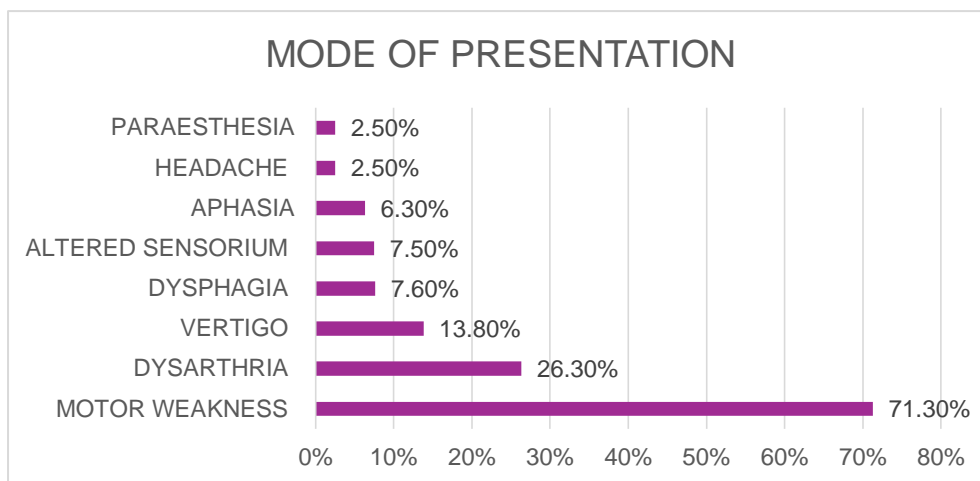

Figure 3: Mode of Presentation

As per the TOAST criteria, 70% of the people had a large artery atherosclerosis followed by 18.8% of the patients who had lacunar stroke and 12.5% of the people had a cardioembolic stoke.
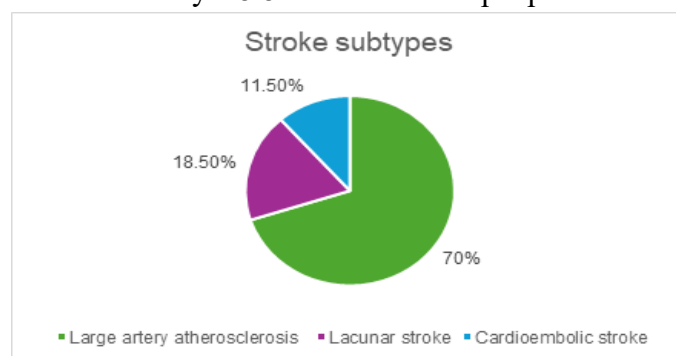

Figure 4: Stroke subtypes

The mean NIHSS score was found to be 11.08 with a standard deviation of 6.50, on the 5th day post admission the BARTHEL index was found to be 63.69 with a standard deviation of 39.82.

The mean N/L ratio was 13.39 with a standard deviation of 8.88.

Table 3: Table showing classification of patients as per NIHSS

NIHSS SCORE	CLASSIFICATION	PATIENTS	%
0-4	MINOR STROKE	33	42.5%
5-15	MODERATE STROKE	24	30.0%
16-20	MODERATE TO SEVERE STROKE	3	3.8%
21-42	SEVERE STROKE	19	23.8%

Table 4: Table showing classification of patients as per BARTHEL index

BARTHEL	CLASSIFICATION	PATIENTS	%
0-20	TOTAL DEPENDENCY	20	25.0%
21-60	SEVERE DEPENDENCY	11	13.8%
61-90	MODERATE DEPENDENCY	19	23.8%
91-99	SLIGHT DEPENDENCY	30	37.6%

Table 5: Classification of patients as per NLR

NLR	No of patients	Percentage
<3	41	51.3%
3-5	12	15%
>5	27	33.7%

Table 6: Correlation of NLR with subtypes of strokes

NLR	Large artery atherosclerosis	Cardioembolic Stroke	Lacunar stroke
<3	28	7	21
3-5	5	2	3
>5	9	3	2

1. Correlation of NLR with stroke subtypes
Correlation of NLR with the TOAST classification didn't show statistically significant correlation. P value for large artery atherosclerosis was 0.447. For cardioembolic stroke it was 0.886 and for lacunar stroke it was 0.445

Table 7: Correlation of NLR with the NIHSS Score

NLR	Minor stroke	Moderate Stroke	Mod-severe stroke	Severe stroke	P value
<3	28	12	0	1	<0.001
3-5	2	7	0	3	
>5	4	5	3	15	

2. Correlation of NLR with the NIHSS score

NLR and severity of stroke determined using NIHSS score showed significant correlation with a P valve of <0.001. 80% of the patients who had NIHSS score of more than 24 (severe stroke) had a NLR of greater than 5. Among patients who had a minor stroke 82% of the patients had a NLR of less than 3.

Table 8: Correlation of NLR with BARTHEL index

NLR RATIO	Total dependency	Severe dependency	Moderate dependency	Slight dependency	
<3	1	1	14	25	P value <0.001
3-5	2	5	4	1	
>5	17	5	1	4	

3. Correlation of NLR with the BARTHEL index

NLR and short-term functional outcome determined using the BARTHEL index showed a significant correlation with a P value <0.001. Around 85% of the patients who had total dependency at the 5th day post admission had NLR more than 5 at the time admission.83.33% of the patients who had slight dependency were found to have a NLR of less than 3.

4. Correlation of NIHSS with BARTHEL index

Patients with good short term functional outcome had lower NIHSS Score and lower NLR on Admission.Those with poor short term functional outcome showed high NIHSS Score and high NLR (r value-0.898 and p value <0.001).

Discussion

This study was conducted to evaluate the relationship between the NLR and the initial severity of the stroke and the short-term outcome of the stroke. Studies with similar objectives are sparse within the Indian subcontinent. Furthermore, studies done globally have employed different variables, which may not be entirely congruent with those of the present research yet remain sufficiently comparable for analytical purposes.

The most recognised classification is the trial of Org in acute stroke treatment (TOAST) classification, which divides ischemic stroke into large artery atherosclerosis, cardioembolic or artery to artery embolism, small vessel occlusion or penetrating artery disease, stroke of other determined etiology like nonatherosclerotic vasculopathies, hyper-coagulable disorders, and stroke of undetermined etiology subtypes. In India, large vessel atherosclerosis stands out as the predominant cause of acute ischemic stroke (AIS).[14] Numerous established factors, including stroke severity, type, advanced age, gender, vascular risk profiles, and impaired consciousness, serve as predictors of mortality and morbidity post-acute stroke.[15]

Brain ischemia and trauma precipitate profound inflammatory responses within cerebral tissues. Neuronal cells are capable of producing cytokines and chemokines and can express adhesion molecules that facilitate localised inflammatory processes. The up-regulated expression of adhesion molecules on both cerebral endothelial cells and circulating leukocytes leads to the accelerated recruitment of these cells to the ischemic region. Neutrophil infiltration into the damaged area represents the primary response to ischemic brain injury. Neutrophils are major sources of free oxygen radicals following a stroke, directly contributing to neuronal damage. It has been suggested that baseline neutrophil levels might be associated with the severity of tissue damage, the risk of re infarctions, and poor neurological outcomes.[16] Similarly, lymphocytes are integral to the inflammatory response. Their numbers begin to

increase on the first day following a stroke, peaking around the seventh day. T-cell lymphocytes are particularly implicated in the repair of inflamed tissues. This T-cell-mediated repair process is associated with the release of cytokines and growth factors by T cells, which modulate microglial activation and facilitate tissue recovery.[17]

In the present study, a notable male preponderance was noted among the patients diagnosed with acute ischemic stroke, attributable to the prevailing sociocultural biases within the Indian context.

Hypertension was found to be the most common comorbidity associated with acute ischemic stroke.

In our study the mean NLR was found to be 13.39 which significantly higher compared to a study done by Desai and Jadhav.[18] In a study conducted by Drumil shah et al.[19] high neutrophil-to-lymphocyte ratio (NLR) significantly correlated with stroke severity and subtype. An NLR above 6.07 predicted moderate-to-severe stroke with high specificity. NLR was notably higher in embolic strokes compared to other types, indicating its potential as a biomarker for stroke prognosis. However, in our study we found no significant correlation between the NLR and the stroke subtypes.

Similar to study done Lavanya d et.al [20] our study found a significant correlation between the NLR and stroke severity at presentation with a P value <0.001. Correlation of NLR with the BARTHEL index which was assessed at the 5th day post admission or at discharge was found to be statistically significant with a P value <0. 001. Hence, patients exhibiting more favourable prognostic indicators, characterised by lower NIHSS and higher BARTHEL index values, NLR was found to be low. Whereas those with poor prognosis, marked by higher NIHSS score and lower BARTHEL index showed elevated NLR.

Conclusion

NLR was found to be significantly associated with the initial severity of stroke and the short-term outcome in adult patients with acute ischemic stroke when evaluated within 24 hours of onset of symptoms.NLR when above 5, has high specificity in predicting the stroke severity. Because of its routine use, low cost, easy to measure and high specificity NLR can be used for prediction of initial severity and short term outcome in acute ischemic stroke. Patients with high NLR at admission can be prioritised for specialised treatments, potentially lowering mortality rates and reducing post-stroke complications. This approach also allows families of stroke patients to prepare for possible negative outcomes, thereby enhancing the quality of end-of-life care for these patients.

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