A Study on the 'Neutrophil Lymphocyte Ratio (NLR)' As Prognostic Marker in Adult Patients with Acute Ischaemic Stroke (AIS)

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Abstract:

A cost-effective and reliable marker in prognostication of Acute Ischaemic Stroke (AIS) may be helpful in predicting the clinical outcome of stroke patients in low income and resource-limited countries like India. Of late, NLR(Neutrophil Lymphocyte Ratio) has been found as an indicator for prognosis in acute stroke, but data on its relation with length of hospitalisation, and functional outcome in ischaemic stroke are very limited. This study is aimed at determining the association between NLR and functional outcome among AIS patients.

Materials and Methods: The study was a prospective cross sectional cohort study conducted among cases of acute ischaemic stroke (AIS) admitted in the medical ward in Tripura Medical College and Dr. BRAM Teaching Hospital during the study period. A total of 101 eligible AIS cases were selected between June 2021 to June 2022. The NLR was calculated at admission and after 30 days of ischaemic stroke during follow-up. The functional outcome was assessed by MRS (Modified Rankin Scale) at admission and at discharge.

Results: The mean age of the study population was 60.28±10.72 years with two third cases were male (70.29%, n=71) and 29.70 %(n=30) cases were female. The mean NLR on day 1 and day 30 were 2.91±0.90 and 1.83±0.58, respectively. There was a positive correlation between NLR and length of hospital stay (r=0.96 ;).

Conclusion: NLR is a helpful marker in predicting duration of hospital stay and follow-up functional outcome after one month among patients hospitalized with acute ischemic stroke.

Keywords: AIS, NLR, Prognosis.

Introduction

There are more than 13.7 million new strokes occur globally every year and one in four above age 25 yrs. will suffer from a stroke in their lifetime. Ischemic stroke is considered as a major cause of disability as well as mortality in World.[1]

In India, the incidence of stroke ranged from 105 to 152/100,000 persons per year, of which, around 80% constitute acute Ischaemic Stroke.[2] During the past four decades, it has been observed that in high-income countries (HICs), there was 42 per cent decrease in stroke incidence and during the same period, a more than double increase in stroke incidence was observed in low and middle-income countries (LMICs).[3] India has been witnessing significant demographic, economic and

epidemiological transition over the past two decades. Consequently, it has resulted in an increase in life expectancy, and an increase in incidence of strokes as well.[4]

Affordable as well as reliable morbidity and mortality prognostic markers for stroke in low-income countries like India are very limited. In AIS, inflammation is considered as an important pathological process after cerebral Ischemia.[5,6,7] As part of inflammation, out of different white cells in peripheral circulation, neutrophils are known to mediate in ischaemic brain damage, and certain subtypes of lymphocytes play important roles in inflammation and brain protection.[8,9] Therefore, measurements of the ratio of Neutrophil to Lymphocyte (N/L) a better reflection of the balance between the levels of these cells and their respective immune activities than their individual counts. NLR is a cheap and basic haematological parameter that is readily available from the complete blood count, even in districts and peripheral hospitals across the country.

Given the paucity of data, variability of risk factors, outcome, and no well validated tool for prognostication in AIS, it forms an integral part of the management of stroke like counselling and physiotherapy. There is also a smaller number of studies on prognostic marker on Acute Ischaemic stroke in India including North-Eastern states, defining a cost-effective prognostic marker very much needed in developing countries like India. Therefore, this study had focussed on NLR as a prognostic marker of morbidity and mortality outcome in Acute Ischaemic stroke with the aim of assessing the relationship between NLR and stroke severity score in acute ischemic stroke and to find out functional outcome after 30 days of stroke in relation to NLR.

Methodology:

This study was a hospital-based cross sectional study conducted between June 2021 to June 2022. Data were collected from 101 cases of acute Ischaemic stroke admitted to the medical ward at Tripura Medical College and Dr. BRAM Teaching Hospital during the study period. All patients above 18yrs having clinical and CT confirmed diagnosis of Ischemic stroke less than 7 days and also those who presented with features of TIA were included in the study. Ischaemic Strokes due to trauma, neoplasm, active infection, Haematological disease, previous history of stroke or recurrent strokes and TIA > 7 Days, patients with incomplete or lacking medical, demographic, clinical laboratory and radiological data were excluded from the study.

Methods of Data Collection:

A total of 101 eligible diagnosed cases of Acute Ischemic stroke (AIS) admitted in "Tripura Medical College & Dr BRAM Teaching Hospital" between 1st June 2021 to 31st June 2022 fulfilling inclusion criteria were included in the study by adopting a nonprobability convenience sampling method.

The demographic profile of each patient was recorded. A detailed clinical examination was done for all the subjects of Ischaemic stroke to assess the severity of the scoring system.

Severity and outcome assessment of Ischaemic Stroke:

This functional outcome was assessed by the modified Rankin grade (MRS grade) based on the criteria (Dromerick, Edwards, & Diringer, 2003) as described on a case record sheet.

MRS grade criteria (Dromerick, Edwards, & Diringer, 2003):[10, 11]

Rankin Grade	Description
0	No symptoms
1	No significant disability despite symptoms; able to carry out all usual duties and activities
2	Slight disability: unable to carry out all previous activities but able to look after own affairs without assistance
3	Moderate disability: requiring some help, but able to walk without assistance
4	Moderately severe disability: unable to walk without assistance, and unable to attend to own bodily needs without assistance
5	Severe disability: bedridden, incontinent, and requiring constant nursing care and attention
6	Dead

Disability Score: Normal: 0-1, Mild: 2, Moderate: 3-4, Severe: 5, Dead: 6

NLR value Calculation Method:

NLR is derived by dividing absolute number of neutrophils to the absolute numbers of lymphocytes (NLR=Absolute Neutrophil Count/Absolute Leukocyte count). Interpretation of NLR depends on clinical context.

NLR was calculated at admission and the follow up at day 30. These two readings of NLR value was correlated with the severity Score (MRS Scale) after follow up clinical Examination to assess the prognosis as described in the aims of the study.

Statistical analysis:

Statistical analysis of the collected data was be done using IBM Statistics SPSS 25 Software. Continuous variables was denoted in the form of mean, median (minimum-maximum) or standard deviation (SD) and number (percentage) for categorical variables. Chi-square test or Fischer's test will be used where applicable and P value less than 0.05 will be considered as statically significance.

Ethical Clearance: Ethical Clearance was taken from the competent authority of Tripura Medical College and Dr. BRAM Teaching Hospital, Hapania.

Results:

Two thirds of the cases were males (70.29%, n=71) and the females being 29.70 %(n=30) with the mean age of the study population being 60.28±10.72 years. The most common comorbidities among the study population was HTN (79.2%, n=80) followed by Diabetes (29.7%, n= 3) [Table-1/Fig-1].

Table 1: Baseline Characteristics of the Study Population:

Variables		Number	Perrcent
Gender	Male	71	70.29
	Female	30	29.70
Hospital Stay	0-3	18	17.82
	4-6	56	55.44
	≥7	25	24.75
HTN		80	79.20
Diabetes		30	29.70
Dyslipidaemia		25	24.75
Anaemia		23	22.77
Smoking		14	13.86
CAD		12	11.86
Hypothyroidism		3	2.97

The mean NLR on admission and on follow up (day 30) were 2.91±0.90 and 1.83±0.58, respectively, which showed a significantly decreasing trend and statically significant.
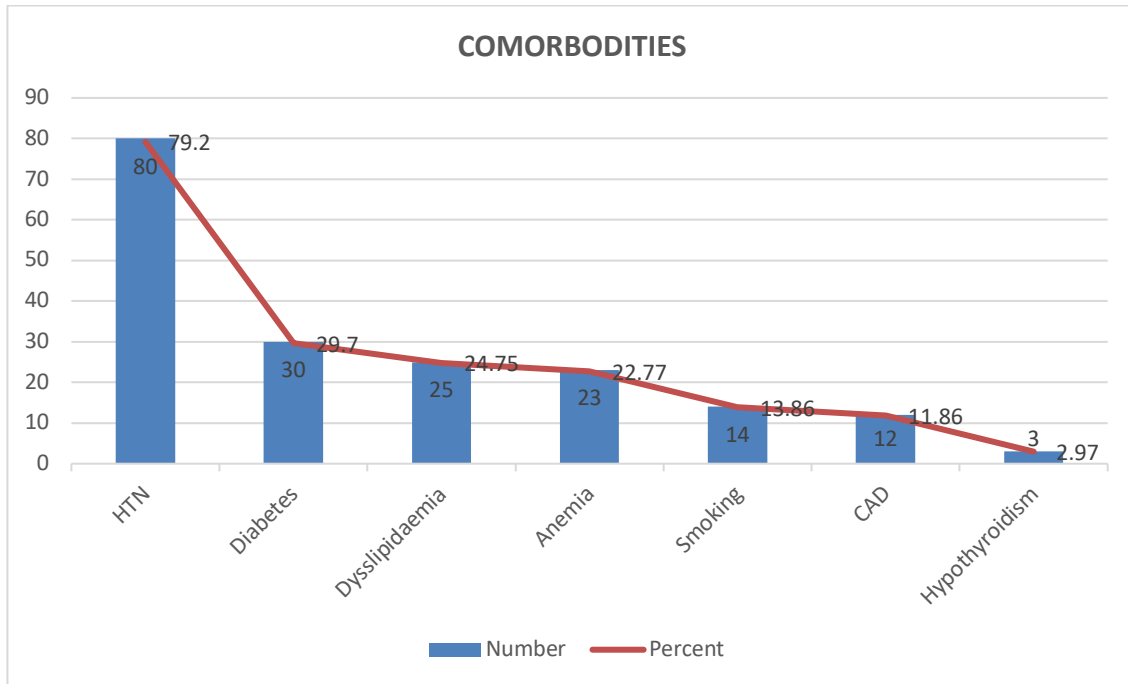

Figure 1: Comorbidities among the study Population

On the basis of length of stay at hospital, the NLR values on admission and on follow-up were categorised into three groups and were compared between the two values on follow-up visits. The three groups of NLR against length of hospital stay on admission were categorised as 2.76±0.64 (03 days), 2.90±1.08 (4-6 DAYS), and 3.07±0.99 (>7 days). At the same time, the NLR values on follow-up visits are also categorised into three groups by the length of hospital stay. (Table-2)

Table 2: Association between Hospital Say and NLR values

Hospital Stay (Duration)	NLR (Admission)	NLR (Discharge)	P-Value	Pearson's correlation coefficient(r)
0-3	2.76±0.64	1.58±0.49	0.03	
4-6	2.90±1.08	1.89±0.69	0.04	0.96
≥7	3.07±0.99	2.03±0.56	0.04	

From table 2, the NLR values in all 3 groups were observed and they found that the higher the NLR values, the length of hospital stay also increased and they were found to be statically significant as well (Table-2) with r factor 0.96. (Table-2). Among the subjects, there were no complications observed, like haemorrhagic transformation, aspirations, recurrent stroke, deep vein thrombosis, death etc. The functional outcome was measured using the MRS scale against the NLR values on admission. The MRS scale was also grouped into three against NLR values on admission and length of hospital stay. The MRS scale was applied after a clinical examination on follow-up and compared with NLR values on admission and length of stay in the hospital.

It was observed that the functional outcome of the stroke patients were better with lower NLR values on admission as well as the length of the hospital stay (Table-3).

Table 3: Association between NRL values and clinical Outcome

Hospital Stay	NLR(Admission)	MRS Grade (Discharge)	P Value
0-3	2.76±0.64	2.29±0.89	0.02
4-6	2.9±1.08	2.30±0.75	0.001
≥7	3.07±0.99	2.6±0.67	0.004

Discussion:

Of late, it has been observed that inflammation has an important role to play in events like stroke. After a stroke, the inflammation has a negative impact on brain tissues but, at the same time, may have beneficial effects by helping tissue restoration and regeneration over a time period. [13]

It's known that the subtypes of white blood cells have varied effects as inflammatory markers for injured tissues. Among them, neutrophils are the predominant inflammatory marker that respond and accumulate in the cerebral blood vessels shortly after the event of ischemic stroke.[14]

Decrease in leucocyte adherence by targeting various adhesion molecules prevents entry of leucocytes into the ischemic brain and this results in decreased neurological damage.

Neutrophils are the initial cells to respond after ischemic stroke, contributing to disruption of the blood brain barrier, cerebral oedema and brain injury. These effects are mediated by release of reactive oxygen species, proteases and cytokines like IL-1/IL-6, IL-8, TNF-alpha and chemokines. Neutrophils may contribute to her with platelet activation. [15,16]

A rise in the number of circulating neutrophils is observed in patients of ischemic stroke within the first few hours of stroke onset1 brain injury by obstructing microvasculature, damaging endothelial cells and extracellular matrix togetand is associated with stroke severity, infarct volume and worse functional outcome. [17,18]

Many factors may be attributed to the pathogenesis of acute ischemic stroke and finding reliable non-invasive biomarkers is the purpose of this study. In our prospective study, it was observed that higher NRL values at admission were associated with longer hospital stay and worse functional outcome at the end of day 30 on follow up, which were significant statically as well. [19]

Song et al., observed that NLR values at admission were found to be a better predictor of 3-month MRS functional outcomes than delayed measured NLR. [20]

Some studies have reported racial and ethnic differences in NLR, but in our study subjects, it was found that lower mean NLR values at admission and discharge were observed as compared to previous studies, which may indicate regional and ethnic variation. [21]

Our study showed that NLR values both at admission and follow up(30 days) were significantly related as it had been observed that fewer hospitals were observed with lower NLR values at admission with better functional outcome among the study population(MRS scale 1-2).

A comparative study conducted by Celikbilek A et al., observed that higher NLR values in patients with ischaemic stroke subjects than the control population(P value=0.001).[22, 23] In another study by Günes M et al., it was found that the length of hospital stay and morbidity had a positive correlation with having an NLR cut off value of 4.[43.24]

Each of these three groups of mean NLR values was compared with the duration of hospital stay among the study population,

and it was revealed that subjects with higher NLR values were associated with longer duration of hospital stay.

In a similar study by Zhao L et al., found that the NLR cut-off NLR value of 2.9 was associated with lengthier hospital stay.[24,25] Some clinical factors which may affect the clinical outcome of acute ischemic stroke are its severity at admission, geriatric age group, comorbidities, aspiration pneumonitis and infection. These factors may lengthen hospital stay, poor neurological outcome, complications, and even death.

In their study, He L et al, where post-stroke infections and NLR values were studied, showed that subjects with NLR values >5.79 were associated with more post-stroke infections.[26]

In our study, there were no cases of complications like haemorrhagic transformation, aspiration pneumonitis, infections like UTI, deep vein thrombosis, and death were observed among the study population.

In this present study, the mean NLR values had a positive correlation with functional outcome on the MRS scale at follow up (day 30). The higher the NLR values, the worse was the functional outcome as assessed by the MRS scale as seen in the three groups of mean NLR values (Table 2).

Cai W et al., also observed that higher NLR positively associated with higher NIHSS and infarct sizes, and determined that NLR >12.1±4.5 had a poor prognosis but there was no mention regarding complication and mortality.[27]

In another study, Brooks SD et al, demonstrated that NLR value >5.9 was associated with unfavourable clinical outcome and mortality at 90 day follow up.[28]

Limitation:

This was a hospital-based study with limited data. A further study with larger

samples may be conducted addressing the issues of standardization of the time points, as the timing of NLR values varies from study to study and so also the site of venous collection of blood samples.

Conclusion

This study have showed that NLR has a positive correlation among patients with AIS. NLR can be calculated easily at bedside and may be helpful predicting the prognosis and so also by early intervention in time, may influence better clinical outcome.

Finally Inflammation plays an important role in the pathogenesis of ischemic stroke and recruitment of inflammatory cells appear to exacerbate brain injury. Immnoblockade or genetic deletion of adhesion molecules like ICAM-1, P-selectin, B2 integrin have shown to reduce infarct volume in animal models. Anti-adhesion agents also appear to widen therapeutic window for thrombolytic therapy in experimental models. In future, further studies using those novel targets remains a potential area of research to improve the outcome.

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