Original Article

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Role of Platelet to Lymphocyte Ratio, Neutrophil to Lymphocyte Ratio and Lymphocyte to Monocyte Ratio in Acute Ischaemic Stroke Severity: A Prospective Cohort Study

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ABSTRACT

Introduction: Stroke is one of the leading causes of mortality and morbidity worldwide, with ischaemic stroke being the most common . Inflammation plays a key role in the pathogenesis of ischaemic stroke and the tissue injury that occurs poststroke, leading to stroke severity.

Aim: To assess whether the Neutrophil to Lymphocyte Ratio (NLR), Lymphocyte to Monocyte Ratio (LMR), and Platelet to Lymphocyte Ratio (PLR) ratios correlate with the severity of ischaemic stroke in acute ischaemic stroke cases.

Materials and Methods: This was a prospective cohort study conducted at KR Hospital, Mysore, Karnataka, India from July 2021 to June 2022, wherein 106 ischaemic stroke cases presenting within 24 hours of symptom onset were assessed, and the outcomes at discharge or at the end of one week were noted. Routine investigations and Non Contrast Computed Tomography (NCCT) brain scans were performed at the time of admission. National Institute of Health Stroke Scale (NIHSS) scoring was conducted at admission, and patients were grouped into mild to moderate stroke (<16) and severe stroke (≥16) categories. The values of PLR, NLR, and LMR were calculated from the blood routine performed at admission. The data was entered into Microsoft Excel and analysed using Statistical Package for the Social Sciences (SPSS) 25.0 software. A p-value of <0.05 was considered statistically significant.

Results: The mean age in this study was 62.67±14.225 years, of which the majority 76 (71.7%) were males. Co-morbidities included hypertension 53 (50%), diabetes 26 (24%), previous history of stroke 13 (12.3%), chronic alcohol consumption 44 (41.5%), and smoking 47 (44.3%) within the study population, and no significant association was found with stroke severity. Approximately 17% presented with severe stroke, while 83% presented with mild to moderate stroke. The total count in the mild to moderate stroke (<16) group was 10.5345±3.91 $10^3/mm^3$ and in the severe stroke group (≥16), it was 15.445±10.27 $10^3/mm^3$. In the mild to moderate stroke group (<16), the mean NLR, PLR, and LMR were 5.93±5.16, 179.79±120.72, and 6.14±6.98, respectively. In the severe stroke group (≥16), the mean NLR, PLR, and LMR were 13.83±24.62, 175.1±89.20, and 3.96±3.89, respectively.

Conclusion: The PLR, NLR, and LMR ratios can be used to assess the severity of stroke cases, especially in resource-limited settings.

Keywords: Cerebrovascular accident, Inflammation, Leucocytes, Mortality, Neurologic deficit, Platelet count, White blood cell count

INTRODUCTION

A stroke or cerebrovascular accident is defined as an abrupt onset of a neurological deficit that is attributable to a focal vascular cause [1]. It is mainly classified into two main types-ischaemic and haemorrhagic, with ischaemic stroke being the most common (80%) [2]. Ischaemic stroke can further be classified based on its aetiology, mainly as cardioembolic, atherosclerotic, lacunar stroke, and others [3]. Stroke is the second leading cause of death worldwide, with around 6.2 million lives lost in 2015, an increase of 830,000 since the year 2000 [1]. It is also the second most common disabling condition in individuals aged 50 years or older worldwide. Most stroke-related deaths and disabilities occur in developing countries [4]. Additionally, many people in developing countries live in rural areas where access to healthcare is negligible, leading to a higher prevalence and mortality in these areas [5-8]. Stroke is a multifactorial disease regulated by modifiable and non modifiable risk factors. Modifiable factors include a history of hypertension, diabetes mellitus, coronary heart disease, obesity, socio-economic status, and alcoholism [1,9,10], while non modifiable risk factors include age and race. Almost 80% of these stroke cases could be reduced through lifestyle modifications [9,10].

White Blood Cell (WBC) count is a marker of inflammation and has been associated with the development of cardiovascular diseases such as acute myocardial infarction and cerebrovascular diseases [11,12]. In ischaemic stroke, once ischaemia occurs, the infarction core releases inflammatory mediators, such as proteases and reactive oxygen species, which increase endothelial dysfunction, tissue necrosis, and cerebral oedema. There is also an increase in WBCs in the peripheral blood, mainly neutrophils, in the initial 3-4 days [12]. Previous research has shown that in patients with acute ischaemic stroke, a higher WBC count was an independent predictor of stroke severity in the acute stage and was also associated with poor short-term and long-term clinical outcomes, as well as an increased risk of stroke recurrence [13].

Platelets have a role in the formation of thromboemboli, which may initiate stroke symptoms [14,15]. When endothelial cell damage occurs (plaque rupture), activated platelets aggregate and contribute to the development of thrombotic lesions [16]. Activated platelets initiate the formation of a haemostatic plug and provide a scaffolding for coagulation activation. Platelets can be activated by various stimuli, such as exposure of the vascular subendothelium, fibrin deposition, and abnormal surfaces like atheroma. The presence of platelet thrombi on atheroma in situ suggests the relevance of platelet physiology in stroke. Additionally, certain antiplatelet agents (e.g., aspirin) significantly reduce the incidence of ischaemic stroke after initial transient ischaemic attacks [14,16,17].

Several studies have shown that a lower platelet count in ischaemic stroke patients can lead to greater severity and worse prognosis [18,19]. Several scoring systems are available to grade the severity and prognosis in stroke cases, including the modified Rankin score, NIHSS, and the Scandinavian Stroke Scale [20]. The NIHSS is a quantitative measure of stroke-related neurological impairment, with scores ranging from 0 to 42 [21]. Based on the NIHSS, stroke can be classified as minor (1-4), moderate (5-15), severe (16-20), or very severe (21-42) [22]. According to Adams HP Jr et al., an NIHSS score of ≥16 is associated with severe stroke [23]. The stroke volume in ischaemic stroke patients also correlates with the NIHSS score [24].

Previous research has shown that a higher WBC count at admission [13] and an abnormal platelet count (<150,000 or >450,000 per µL) are predictors of stroke severity and also correlated with the 30-day mortality [25]. Another study demonstrated that a 25% increase in WBC and leukocyte count was associated with a higher risk of stroke, and also that a higher WBC count, higher neutrophil count, and lower lymphocyte count were associated with a higher incidence of fatal stroke [26].

While it is already known that inflammation plays a key role in the pathophysiology of stroke, and that a higher WBC count and abnormal platelet count are associated with cardiovascular diseases [27,28], their role in stroke severity and prognosis is still under investigation. In this study, the PLR, NLR, and LMR, are used as surrogate blood markers to assess severity in acute ischaemic stroke cases.

The aim of the present study was to assess whether the PLR, NLR, and LMR ratios correlate with the severity of ischaemic stroke in acute stroke cases.

MATERIALS AND METHODS

This was a prospective cohort study conducted at KR Hospital, Mysore (MMC&RI, Mysore) from July 2021 to June 2022. Ethical clearance was obtained from the Institutional Ethics Committee (IEC) (EC REG: ECR/134/Inst/KA/2013/RR-19).

Inclusion criteria: Patients aged over 18 years presenting with clinical features suggestive of acute ischaemic stroke within 24 hours, with radiologically confirmed NCCT brain, and who provided valid informed consent were included in the study.

Exclusion criteria: Patients with a history of leukaemia/lymphomas or lymphoproliferative disorders, chronic liver disease, immune thrombocytopenic purpura, anaemia, pancytopenia, chronic infections, and immunocompromised conditions like HIV were excluded from the study. Patients presenting with acute infections were also excluded.

Sample size: The sample size was calculated using the formula:

$$n=z^2 (PQ)^2/d^2$$

with a 95% confidence interval.

Z=(1.96) at a 95% confidence interval

P=proportion of prevalence=1%=0.01 [29]

Q=1-P=1.0-0.01=0.99

D=Margin of error or confidence interval=2%=0.02

N=95 samples ~ 106

The total sample size was 106.

After obtaining IEC for the study, cases that met the inclusion criteria and had clinical features suggestive of acute stroke (presenting within 24 hours of symptom onset) and were admitted to KR Hospital, Mysore, were enrolled in the study. Relevant history was obtained, and clinical examination and baseline NIHSS scoring [21,22] at admission were documented. Complete blood count was performed, and from this, the NLR, PLR, and LMR ratios were calculated. NCCT brain imaging was done to confirm the diagnosis and rule out haemorrhagic stroke or venous infarct. Preliminary data on patients' demographics, past illnesses, personal history, and addictive habits, as well as their co-morbidities, were collected. Other routine investigations, including lipid profile, random blood glucose levels, renal function tests, liver function tests, and serum electrolytes, were also conducted.

Using statistical methods, the correlation between NIHSS scoring PLR, NLR, and LMR ratios was analysed based on the available data. The cases were grouped as mild to moderate stroke (<16) and severe stroke (≥16) according to the NIHSS [21,23] scoring at admission. These cases were then followed-up until discharge or day 7, and the outcomes were noted as improved, completely recovered, deteriorated/death, or unchanged condition.

STATISTICAL ANALYSIS

The data obtained from the study was entered into Microsoft Excel sheets and double-checked for accuracy. The data was analysed using IBM SPSS software version 25.0 and presented as descriptive statistics in the form of tables. Before conducting correlational analysis, the normality of the data was assessed using the Shapiro-Wilk test. Pearson's chi-square test was used to determine the significance of the NLR, PLR, and LMR ratios with NIHSS in stroke severity. The significance of co-morbidities and risk factors with stroke severity was also examined. Continuous data were presented as mean±SD. The independent t-test was used to test the significance of mean differences between two quantitative variables. A p-value of <0.05 was considered statistically significant.

RESULTS

A total of 106 cases were studied. The mean age was 62.67±14.225 years, with ages ranging from 28 years to 100 years. The majority of cases were aged >61 years, and the highest number of cases fell within the 61-70 age group [Table/Fig-1]. This indicates that the incidence of stroke increases with age. There was a male preponderance, with 76 cases (71.7%) being male. Nearly all cases presented with hemiplegia/hemiparesis. Around 55 cases (51.9%) had presented with altered sensorium, 58 cases (54.7%) with speech disturbances, 15 cases (14.2%) with giddiness, and 12 cases (11.3%) with seizures.

The baseline NIHSS score was divided into two categories, as shown in [Table/Fig-2].

Age group (years)	n (%)
20-30	2 (1.9)
31-40	5 (4.7)
41-50	15 (14.2)
51-60	25 (23.6)
61-70	28 (26.4)
71-80	24 (22.6)
81-90	6 (5.7)
91-100	1 (0.9)

[Table/Fig-1]: Age distribution of study participants (n=106).

NIHSS score	Category	n (%)
0 <16	Mild to moderate stroke	88 (83)
≥16	Severe stroke	18 (17)

[Table/Fig-2]: NIHSS score categories.

The risk factors studied included a history of chronic smoking 47 (44.3%) and chronic alcohol consumption 44 (41.5%), as shown in [Table/Fig-3]. A history of diabetes was present in 26 cases (24.5%), and a previous history of stroke was seen in 13 cases (12.3%). Most cases did not have a previous history of stroke [Table/Fig-3].

Most cases in the mild to moderate severity did not have a significant history of alcohol consumption. Co-morbidities like hypertension

were present in 53 cases (50%), but the presence of hypertension was not statistically significant with the severity of stroke, as shown in [Table/Fig-3,4]. However, a few cases with non compliant/ uncontrolled hypertension did present with a higher NIHSS score and higher severity.

Risk factor			NIHSS		Total
			<16	≥16	
Smoking	Yes	Count	37	10	47
		(%)	42.0	55.6	44.3
	No	Count	51	8	59
		(%)	58.0	44.4	55.7
Alcohol	Yes	Count	35	9	44
		(%)	39.8	50.0	41.5
	No	Count	53	9	62
		(%)	60.2	50.0	58.5
Hypertension	Yes	Count	43	10	53
		(%)	48.9	55.6	50.0
	No	Count	45	8	53
		(%)	51.1	44.4	50.0
Diabetes	Yes	Count	22	4	26
		(%)	25.0	22.2	24.5
	No	Count	66	14	80
		(%)	75.0	77.8	75.5
Stroke History	Yes	Count	10	3	13
		(%)	11.4	16.7	12.3
	No	Count	78	15	93
		(%)	88.6	83.3	87.7

[Table/Fig-3]: Risk factors with comparison between the two NIHSS groups.

Risk factor	Test applied	Value	df	Asymptotic significance (2-sided)	Exact Sig. (2-sided)
Smoking	Pearson Chi-square	1.105	1	0.293	
	Fisher's-Exact test				0.311
Alcohol	Pearson Chi-square	0.644	1	0.422	
	Fisher's-Exact test				0.443
Hypertension	Pearson Chi-square	0.268	1	0.605	
	Fisher's-Exact test				0.797
Diabetes	Pearson Chi-square	0.062	1	0.803	
	Fisher's-Exact test				1.000
Stroke history	Pearson Chi-square	0.391	1	0.532	
	Fisher's-Exact test				0.460

[Table/Fig-4]: Association of risk factors with stroke severity.

Overall, no significant association was found between the studied risk factors and severity of stroke in this study, as shown in [Table/Fig-4].

The mean White Blood Cell (WBC) count was 11,000 cells/µL, with a mean of 10.53±3.91 10^3/mm^3 in mild to moderate severity cases and 15.45±10.27 10^3/mm^3 in severe stroke. The platelet count had a mean value of 2.62 ±0.752 lakh/cumm in the mild to moderate group and 2.52±1.49 lakh/cumm in the severe stroke group. In the mild to moderate stroke (<16), the mean NLR, PLR and LMR were 5.93±5.16, 179.79±120.72, and 6.14±6.98, respectively. In the severe stroke group (≥16), the mean NLR, PLR, and LMR were 13.8±24.62, 175.1±89.20, and 3.96±3.89, respectively, as shown in [Table/Fig-5]. [Table/Fig-6] shows that, other than the total WBC count and NLR ratio, there was no significant difference in the other ratios according to the severity of stroke.

It was noted that the NLR ratio showed a positive correlation with the NIHSS scoring at admission in acute ischaemic stroke cases and was significant (<0.05). It can be used to assess severity in acute ischaemic stroke cases. However, the PLR and LMR ratio showed a negative correlation with NIHSS scoring done at admission, which was not significant [Table/Fig-7].

Out of the 106 cases, 63.2% showed improvement, 34% remained in the same condition at discharge, and 2.8% resulted in death [Table/Fig-8].

Variables	NIHSS	N	Mean±Std. Deviation	Std. Error mean
Total count (cells×10^3/mm^3)	<16	88	10.53±3.91	0.41705
	≥16	18	15.45±10.27	2.42226
Platelet count (lakh/cumm)	<16	88	2.62±0.75	0.0802
	≥16	18	2.52 ±1.49	0.3527
NLR ratio	<16	88	5.93±5.16	0.55013
	≥16	18	13.83±24.62	5.80471
PLR ratio	<16	88	179.79±120.72	12.86898
	≥16	18	175.10±89.20	21.02639
LMR ratio	<16	88	6.14±6.98	0.74452
	≥16	18	3.96±3.89	0.91852

[Table/Fig-5]: NLR, PLR, LMR with NIHSS categories at admission.

Independent samples test				
t-test for equality of means				
H	t	df	Sig. (2-tailed)	Mean difference
Total count	-3.466	104	0.001**	-4.91684
Platelet count	0.406	104	0.686	0.0962
NLR ratio	-2.772	104	0.007*	-7.90138
PLR ratio	0.156	104	0.876	4.69277
LMR ratio	1.282	104	0.203	2.18143

[Table/Fig-6]: Independent samples t-test for NLR, PLR and LMR at admission.

NLR ratio	Pearson correlation	0.285
	Sig. (2-tailed)	0.003*
	N	106
PLR ratio	Pearson correlation	-0.020
	Sig. (2-tailed)	0.835
	N	106
LMR ratio	Pearson correlation	-0.120
	Sig. (2-tailed)	0.222
	N	106

[Table/Fig-7]: Correlation of NLR, PLR, LMR with NIHSS scoring at admission.

			NIHSS		Total
			<16	≥16	
Status at day 7	Improving	Count	59	8	67
		(%)	67.0%	44.4%	63.2%
	Unchanged	Count	29	7	36
		(%)	33.0%	38.9%	34.0%
	Death	Count	0	3	3
		(%)	0.0%	16.7%	2.8%
Total		Count	88	18	106
		(%)	100.0%	100.0%	100.0%

	Value	df	Asymptotic significance (2-sided)
Pearson Chi-square	16.029	2	<0.001

[Table/Fig-8]: Outcome (At day 7) association with NIHSS categories.

DISCUSSION

In the present study, 106 acute ischaemic stroke cases were included, and the outcomes were noted at day 7. It was observed that the NLR and PLR ratios were higher, while the LMR ratio was lower in cases with a higher severity.

A study done by Chen C et al., involving 448 acute ischaemic stroke cases showed that the NLR and PLR ratios were independent predictors of the functional outcome at three months and could be used to assess prognosis and also identify high risk cases in ischaemic stroke cases [30]. Bhaskar S et al., conducted a retrospective study on 608 acute ischaemic stroke cases at John Hunter Hospital between January 2006 and December 2013. They concluded that the initial stroke severity had a significant impact on the probability of death and overall stroke outcome at 90 days. Regression analysis showed that the initial stroke severity independently predicted 90-day mortality (odds ratio=1.16; p<0.001; 95% Confidence interval (CI)=(1.12, 1.2)) [31].

Sadeghi F et al., concluded in their study that a combination of high NLR ratio and low LMR ratio after thrombolysis in acute ischaemic stroke cases could predict a poor functional outcome [18]. In another study involving a total of 1005 patients, Song Q et al., concluded that a lower LMR ratio was associated with a higher risk of haemorrhagic transformation in a cases of acute ischaemic stroke [32].

Cao X et al., conducted a study from January 2017 to May 2018 on 633 acute ischaemic stroke cases and studied the peripheral blood cell ratios with 90-day mortality in these cases. They concluded that an NLR > 3.23 had a significant negative correlation (p-value <0.001) with 90-day mortality in acute ischaemic stroke cases [33].

In a study conducted by Park MG et al., which included 102 ischaemic stroke cases, the LMR ratio was calculated on day one and day seven post-stroke. It was noted that a lower LMR value on day one was associated with a higher incidence of infections such as pneumonia and urinary tract infections. Additionally, a lower LMR ratio at day seven was not only associated with a higher incidence of infections but also a poorer prognosis at three months poststroke. They concluded that LMR can be used for assessing stroke-induced immunosuppression [34].

A retrospective study conducted by Elsheik WM et al., on 60 ischaemic stroke cases showed that the NLR ratio was higher in ischaemic stroke cases than in the control group. It could be used as a marker to assess severity (NLR > 2.05 as a cut-off for unfavourable outcome) (p-value <0.05) in stroke cases [35]. Gong P et al., in their study involving 1060 cases conducted from April 2016 to September 2019, concluded that NLR, PLR, and LMR can predict post-thrombolysis early neurological deterioration [36].

In another study conducted by Sharma D and Gandhi N, which included 100 cases and 100 controls, it was concluded that the mean PLR was higher in the cases (235.98±93.92) than in the controls (115.60±27.87) with p-value=0.0001. They also found that PLR had a linear positive correlation with the NIHSS score [37].

In the present study, no significant statistical difference was found in the mild to moderate stroke and severe stroke cases with respect to age, gender, smoking, alcohol, diabetes, and hypertension. However, the incidence of stroke increased with age, with the majority of cases being over 61 years old. The youngest case was 28 years old. This reflects that the incidence of stroke is also increasing in the younger age group due to genetic factors and sedentary lifestyle changes such as dyslipidaemia, tobacco use, smoking, and physical inactivity, as seen in the study by George MG [38]. Other studies, such as the Greater Cincinnati Northern Kentucky Stroke Study and the Dijon Stroke Registry, have also shown an increase in stroke in the younger population, predominantly ischaemic stroke [38].

Out of the 106 cases, 63.2% showed improvement, 34% remained in the same condition at discharge, and 2.8% resulted in death Most of the cases showed improvement within the first few days in this study, while around one-third of the cases had no change in their disability. A very small number of cases completely recovered, which were included in the percentage showing improvement. This may reflect that while mortality has reduced with treatment in stroke cases, the morbidity has increased, leading to a decreased quality of life. In the Guangzhou Biobank Cohort Study, it was shown that the incidence of stroke was higher in individuals with higher inflammatory markers. However, this could not be assessed in the present study as only cases that had already presented with acute ischaemic stroke were included [26].

Dias RA et al., noted that while many inflammatory markers have been studied in cerebrovascular disorders, the NLR is the most widely studied biomarker. They may also serve as potential therapeutic targets to improve the outcome or decrease complications in these cases [39].

Limitation(s)

As a long-term follow-up of the cases could not be conducted, the prognostic value of PLR, NLR, and LMR in acute ischaemic stroke severity could not be assessed. A larger sample size would have also increased the validation of PLR, NLR, and LMR as new serological markers. Since only cases that presented with stroke symptoms were included in the study, it could not be determined whether the presence of chronic inflammation was the cause of stroke in these patients.

CONCLUSION(S)

The NLR and LMR ratios can be used to assess the severity of acute ischaemic stroke cases, particularly in resource-limited settings and rural populations. Utilising all three markers, PLR, NLR, and LMR together, can also enhance sensitivity. However, further studies are needed to confirm these findings.

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