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Correlation between severity of neurological impairment and left ventricular function in patients with acute ischemic stroke

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Abstract
Acute Ischemic Stroke (AIS) is a leading cause of disability, morbidity and mortality saddling the overburdened Global Health System. LV dysfunction is a well established risk factor for AIS, however its significance as a prognostic marker for in-hospital morbidity after AIS was hardly ever studied.
Aim: To evaluate the Left Ventricular function and determine its correlation with the severity of neurological impairment. To appraise whether LV dysfunction is a prognostic marker for in-hospital morbidity.
Materials & Methods: Between November 2019 and October 2021, a prospective study was conducted at Rajah Muthiah Medical College and Hospital. 75 study participants with AIS were enrolled and clustered into two groups on the basis of NIHSS. Study population with NIHSS < 6 were designated as Group-1 and those with NIHSS ≥ 6 as Group-2. Left ventricular function was assessed using routine 2D Echocardiography. In addition, the two inflammatory biomarkers, Neutrophil-Lymphocyte Ratio (NLR) and Platelet-Lymphocyte Ratio (PLR) were computed from Complete Blood Count (CBC).
Results: The study showed that the patients in Group-2 had higher values of NLR and PLR but lower LVEF than those in Group-1. The threshold values of NLR, PLR and LVEF obtained from the ROC curve were 4.1, 195 and 64% respectively. The values of NLR & PLR greater than 4.1 & 195 along with LVEF <64% were associated with severe neurological impairment and higher in-hospital morbidity.
Conclusion: NLR and PLR have a significant positive correlation with NIHSS, whereas LVEF has significant negative association with NIHSS. Hence, NLR, PLR and LVEF, subsequent to AIS, can be used as a prognostic marker for in-hospital morbidity.

Keywords: acute ischemic stroke**,** national institute of health stroke scale, neutrophil lymphocyte ratio, platelet lymphocyte ratio, left ventricular ejection fraction.

Introduction
Acute Ischemic Stroke (AIS) ranks next to ischemic heart disease as an overwhelming cause of mortality worldwide, estimated at 5.5 million per annum [1]. Apart from mortality, the increasing morbidity and chronic disability of the survivors further encumbers the health system. With 12.2 million incidences of stroke, 101 million prevalent cases and 143 million DALYs, AIS is a disease of massive public health importance with serious socio-economic impact [2].
Although, AIS can be prevented by controlling the risk factors [3] and treated effectively through advancements in thrombolysis and endovascular therapy, [4] the incidence and prevalence is on the increase due to rising atherosclerotic process with age and scarce therapeutic golden window period for reperfusion. Eventually, multiple organ dysfunction syndrome pursues leading to unfavorable outcomes.
Previous studies have shown that, subsequent to acute severe brain injury, there is an overwhelming inflammatory response, cytokine storm and profound immune perturbation due to the activation of damage-associated molecular patterns (DAMPs) signal pathway.[5] In addition, the association between DAMP signalling pathway and deterioration of LV function after brain death has also been established in the earlier research work.[6] Putting together the aforementioned facts, following acute brain injury, there is severe immune dysregulation ultimately leading to worsening of LV function. Hence, NLR and PLR (the two novel indices representative of systemic inflammation) along with LVEF

(the prime indicator of Left Ventricular function) are being analyzed extensively in this study.

It is crucial to identify the prognostic indicators for AIS to segregate the potentially high risk patients for focused treatment modalities. In our study, the prognostic potential of LVEF is analyzed so that the integrity of LV systolic function can be evaluated and preserved as early as possible, to improve the neurological prognosis after AIS.

Materials & Methods

Study design

This is a prospective Cross-Sectional study conducted amongst patients presenting in the medicine ward of Rajah Muthiah Medical College & Hospital, Chidambaram with acute ischemic stroke. The study period is between November 2019 and October 2021. The study protocol was approved by the Institutional Research and Ethical Committee and written informed consents were received from the study population.

Inclusion and exclusion criteria

All patients presenting in the medicine ward of Rajah Muthiah Medical College & Hospital, Chidambaram with acute ischemic stroke, regardless of age were included in the study. Patients with existing heart disease, transient ischemic attack, ECG changes suggestive of coronary heart disease and acute hemorrhagic stroke were excluded from the study.

Patients enrolment and allocation

At the time of admission, the functional neurological impairment was assessed using NIHSS. The patients were segregated into two separate groups – Group-1 with NIHSS < 6 and Group-2 with NIHSS ≥ 6. The entire study population included 75 subjects amongst which 38 fall under Group-1 and the remaining 37 in Group-2.

Study protocol

The information of patients including baseline profile and co-morbidities were collected from patients and their family members, earlier medical records and relevant clinical evidence. Routine blood investigations were carried out and NLR & PLR were derived from the values of Absolute Neutrophil Count, Absolute Lymphocyte Count and Platelet Count. 2D echocardiographic analysis was performed within 5 days of admission. Treatment was initiated as per the recommended guidelines for stroke.

Statistical Analysis

For discrete and categorical variables, Chi-square tests were applied and for continuous variables, independent t-tests were carried out. Pearson's correlation methodology was used to assess the relationship of NIHSS to NLR, PLR and LVEF. Receiver Operating Characteristic Curve (ROC) was plotted and using the same, the optimal cut-off values of NLR, PLR and LVEF for moderate to severe AIS were identified. Statistical analysis was performed using Microsoft Excel and SPSS statistical tool for Windows OS version 10 and a p-Value < 0.05 was considered statistically significant.

Results

Baseline Clinical Characteristics Analysis

Table 1: Baseline clinical characteristics of the study population of Group-1 and Group-2

Variables	Total (n=75)	Group-1 (n=38)	Group-2 (n=37)	p-Value
Age	62.99±9.42	63.34±9.48	62.62±9.34	0.372
Male sex	46 (61.3%)	22 (57.9%)	24 (64.7%)	0.768
Smoker	23 (30.7%)	11 (28.9%)	12 (32.4%)	0.835
Alcoholic	13 (17.3%)	6 (15.8%)	7 (18.9%)	0.782
Diabetes	27 (36.0%)	13 (34.2%)	14 (37.8%)	0.847
Hypertension	45 (60.0%)	21 (55.3%)	24 (64.9%)	0.655
Dyslipidemia	38 (50.7%)	18 (47.4%)	20 (54.1%)	0.746

Data are expressed as Mean ± standard deviation or No. (%). Chi-square test was used for analysis of qualitative variables and unpaired t-test for quantitative variables.

The above detailed table demonstrates that there were no significant statistical differences between Group-1 and Group-2 in terms of clinical characteristics like age, male sex, smoking, alcoholism, diabetes, hypertension and dyslipidemia.

An analysis of the data also leads to an inference that the older age (Mean age 63 years), male sex (61.3%), hypertension (60%) and dyslipidemia (50.7%) are the major contributing significant risk factors and co-morbidities associated with AIS in both the study groups.

Baseline Laboratory Characteristics Analysis

Table 2: Baseline laboratory characteristics of the study population of Group-1 and Group-2

Variables	Total (n=75)	Group-1 (n=38)	Group-2 (n=37)	p-Value
Neutrophil (cells / cu.mm)	6310 (3670-7570)	5950 (3670-7350)	6460 (4320-7570)	0.043
Lymphocyte (cells / cu.mm)	1460 (1010-2440)	1585 (1280-2070)	1340 (1010-1890)	< 0.001
Platelet count (lakhs / cu.mm)	3.03±0.52	2.86±0.47	3.21±0.50	0.001
NLR	3.98 (2.35-7.03)	3.52 (2.35-4.81)	4.22 (3.41-7.03)	< 0.001
PLR	188.44 (143.95-306.60)	174.11 (148.95-202.74)	242.62 (175.68-306.60)	< 0.001

Data are expressed as Mean ± std. deviation or Median (Range). Statistical results were obtained using unpaired t-test. Abbreviations: NLR-Neutrophil Lymphocyte Ratio, PLR-Platelet Lymphocyte Ratio.

The following findings are demonstrated on analyzing the laboratory arithmetic values of Group-1 and Group-2:

a. Higher values of Neutrophils, lower levels of Lymphocytes and high Platelet count are present in Group-2 compared to Group-1 and their respective p-values demonstrate a significant correlation with the severity of neurological impairment
b. The two derived inflammatory markers, Neutrophil-Lymphocyte Ratio (NLR) and Platelet-Lymphocyte Ratio (PLR), also statistically confirm that their higher levels are associated with higher NIHSS scores.
c. Hence, subsequent to acute severe brain injury, there is an overwhelming inflammatory response, cytokine storm and profound immune perturbation (as evidenced by increase in NLR and PLR), which strongly correlate to morbidity in patients with AIS.

Baseline Stroke Severity (Using NIHSS)

Table 3: Baseline NIHSS score of the study population of Group-1 and Group-2

Variables	Total (n=75)	Group-1 (n=38)	Group-2 (n=37)	p-Value
Average NIHSS	8.87±6.18	3.92±1.00	13.95±5.01	< 0.001

Data are expressed as Mean ± std. deviation. Statistical results were obtained using unpaired t-test.

The average NIHSS value is significantly higher in Group-2 compared to Group-1. Hence, Group-1 patients got affected with mild stroke while Group-2 patients suffer from moderate to severe stroke.

Echocardiographic Outcomes

Table 4: Echocardiographic outcomes between Group-1 and Group-2

Variables	Total (n=75)	Group-1 (n=38)	Group-2 (n=37)	p-Value
LVIDd	4.95±0.64	4.75±0.38	5.15±0.78	0.002
LVIDs	3.01±0.58	2.84±0.56	3.19±0.56	0.004
LVEF	63.03±6.94	67.16±4.90	53.57±6.16	< 0.001
Mild to Severe MR	19 (25.3%)	6 (15.8%)	13 (35.1%)	0.109
Mild to Severe TR	9 (12%)	3 (7.9%)	6 (16.2%)	0.317

Data are expressed as Mean ± standard deviation or No. (%).Chi-square test was used for analysis of qualitative variables and unpaired t-test for quantitative variables. Abbreviations: LVIDd- Left Ventricular Internal Diameter end diastole, LVIDs- Left Ventricular Internal Diameter end systole, LVEF- Left Ventricular Ejection Fraction, MR-Mitral Regurgitation, TR-Tricuspid Regurgitation.

The following inferences are evident in this study, based on the statistical values obtained from 2D ECHO findings:

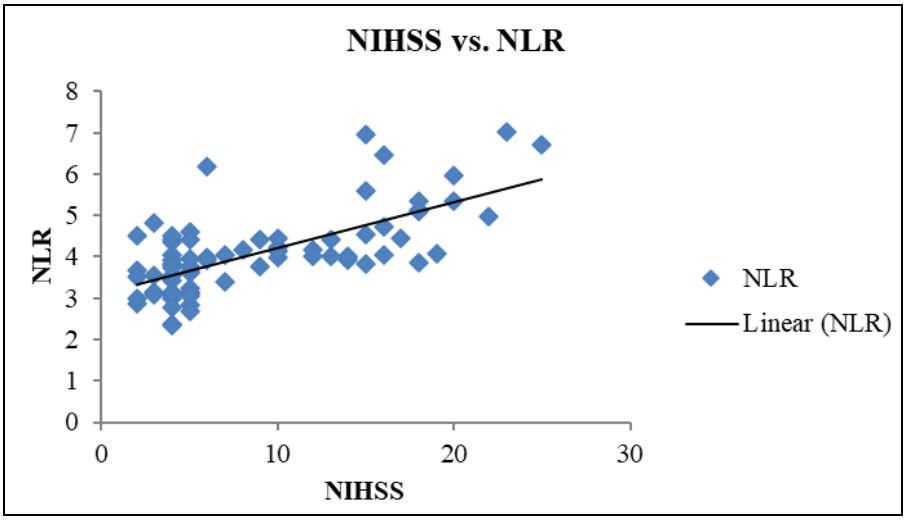
a. The mean value of LVEF for Group-2 is significantly low at 53.57, compared to 67.16 for Group-1. So, in patients with NIHSS ≥ 6, the LVEF is lower suggesting a higher systolic dysfunction.
b. Both LVIDd (p=0.002) and LVIDs (p=0.004) are statistically significant. It is also obvious that Left Ventricular Internal Diameter end systole (LVIDs) exhibited an inverse relationship with LVEF.
c. There is apparent MR and TR in Group-2 than in Group-1 but did not show any statistical significance.
d. It is statistically evident that the more severe the AIS, the more obvious are the LV systolic dysfunction.

Relationship of Stroke Severity (NIHSS) To Inflammatory Markers (NLR and PLR) and LV Systolic Function

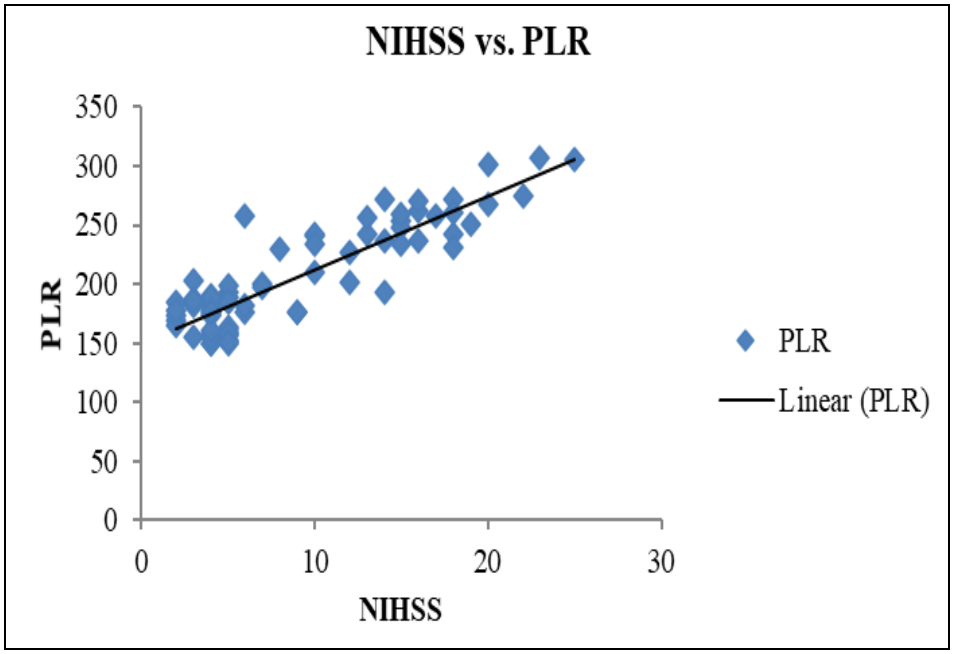
The statistical data were derived using regression analytic tools and ANOVA test.

Table 5: Correlation of NLR, PLR and LVEF to NIHSS

Variables	Correlation Coefficient (R)	p-Value
NIHSS vs. NLR	0.683	< 0.001
NIHSS vs. PLR	0.884	< 0.001
NIHSS vs. LVEF	- 0.780	< 0.001



(A)



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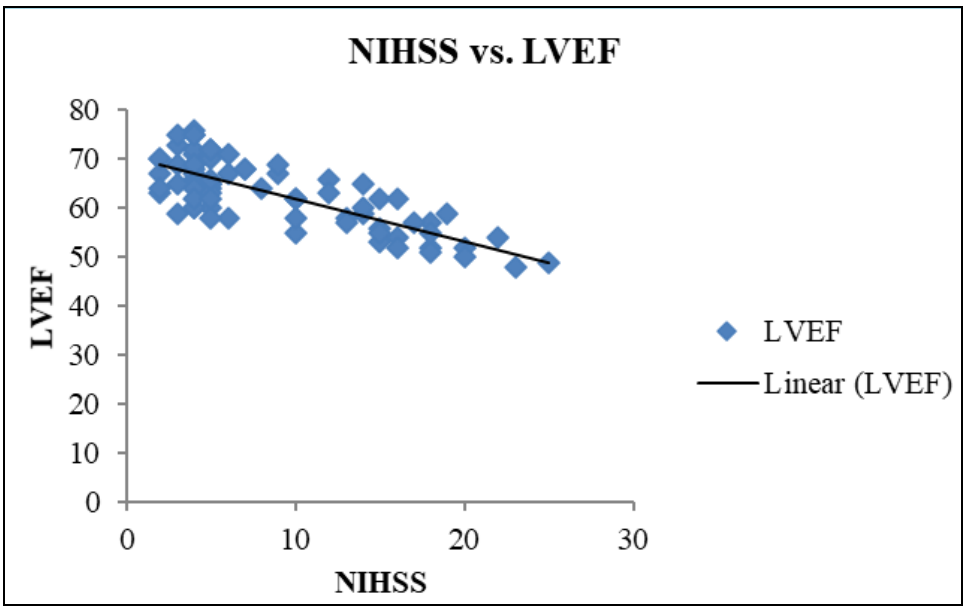

(C)

Fig 1: Correlation of NIHSS to NLR, PLR and LVEF using scatter line graph. **(A)** Scatter line graph between NIHSS and NLR showing positive correlation with Pearson's coefficient (R) = 0.683. **(B)** scatter line graph between NIHSS and PLR showing positive correlation with Pearson's coefficient (R) = 0.884. **(C)** scatter line graph between NIHSS and LVEF showing negative correlation with Pearson's coefficient (R) = - 0.78.

The correlation analysis shows that NIHSS has significant positive correlation with NLR and PLR as evidenced by correlation coefficient of 0.683 and 0.884 respectively. Furthermore, the NIHSS has substantial negative correlation with LVEF as evidenced by Pearson's coefficient of - 0.78.

Receiver Operating Characteristic Curve (ROC) and Cut-Off Value Determination for NIHSS ≥ 6:

Table 6: AUC and Youdens's Index for determination of cut-off value

Variable	AUC	Youden's Index	Cut-Off Value	Sensitivity	Specificity
NLR	0.864	0.566	4.1	0.595	0.816
PLR	0.950	0.433	195.4	0.865	0.947
LVEF (%)	0.849	0.560	63.5	0.757	0.763

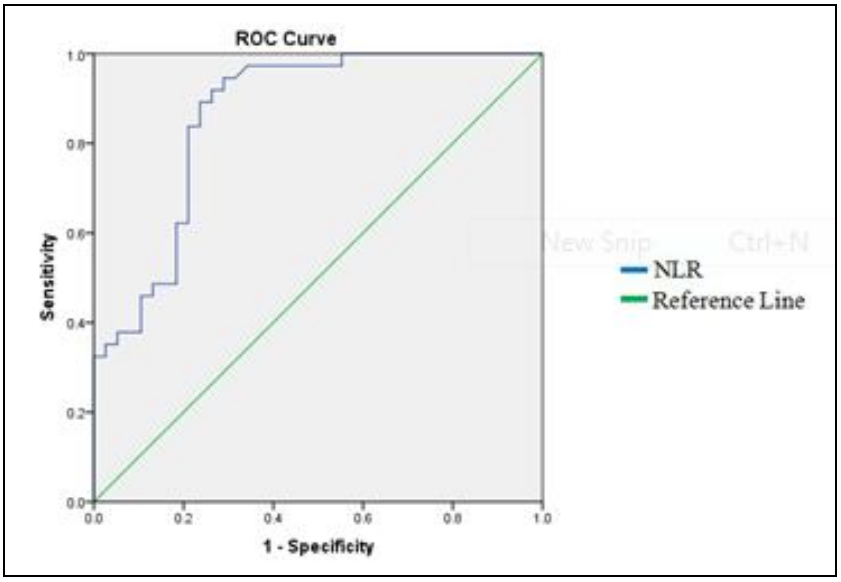

Fig (A): ROC curve for NLR vs. NIHSS

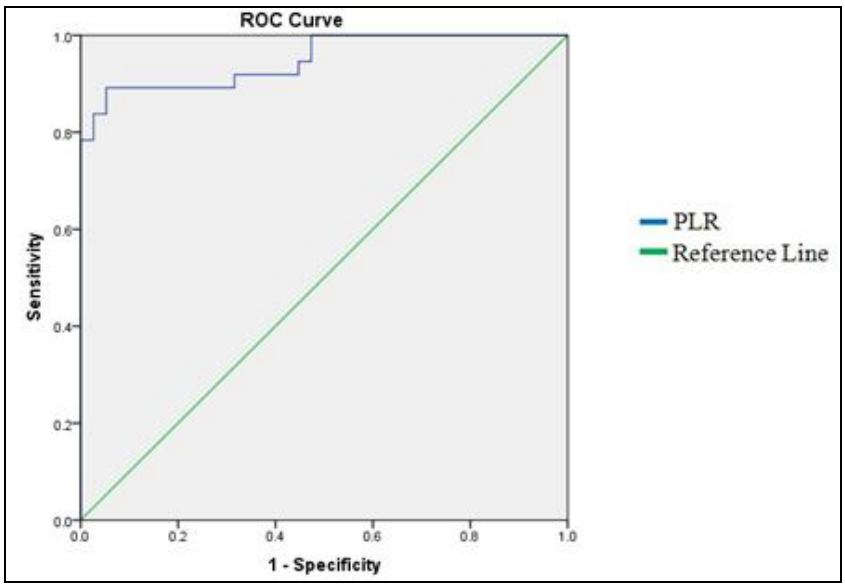

Fig (B): ROC curve for PLR vs. NIHSS

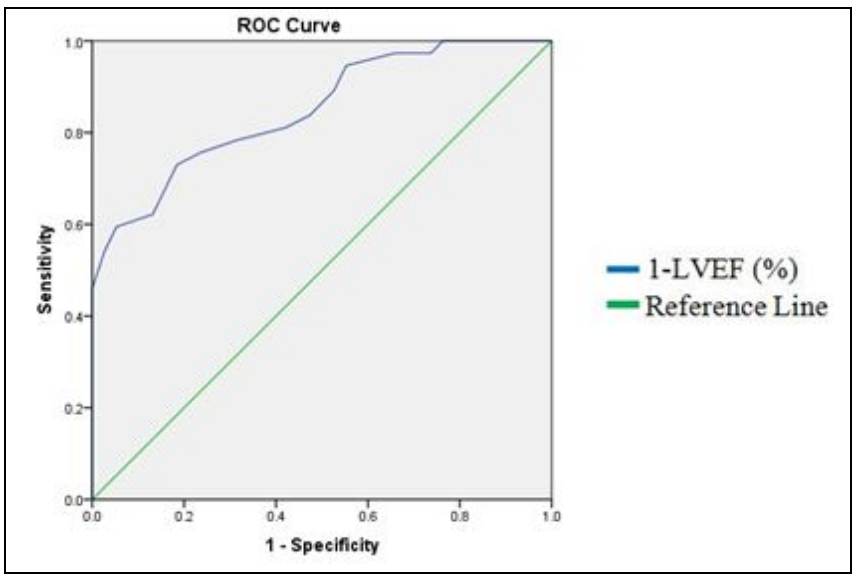

Fig (C): ROC curve for 1-LVEF vs. NIHSS

Fig 2: ROC curve for the determination of cut-off value using AUC and Youden's index for NLR, PLR and LVEF in Group-2 patients. **(A)** ROC curve for NLR vs. NIHSS. **(B)** ROC curve for PLR vs. NIHSS. **(C)** ROC curve for 1-LVEF vs. NIHSS

ROC curve of NLR and LVEF has a good probability of detection whereas PLR has an excellent probability of detection. The cut-off values of NLR, PLR and LVEF for NIHSS ≥ 6 were 4.1, 195 and 64% respectively. Hence, it can be construed that values greater than the cut-off for NLR and PLR along with LVEF less than 64% suffer severe stroke and have predictable poorer neurological outcomes.

Discussion

75 patients were enrolled in this prospective study designed to investigate the correlation between LV systolic function and stroke severity. Previously, in the year 2006, Allison G. Hays et al [7] published a study on "Left Ventricular Systolic Dysfunction and the risk of Ischemic Stroke" in a subset of subjects from the Northern Manhattan study (NOMAS) to prove that LV Dysfunction is independently associated with increased risk of ischemic stroke. Further, in the year 2014, Tomar et al. [8] published a study on "ECG and Echocardiographic abnormalities in stroke and its prognostic significance" focusing mainly on the mortality aspect. Subsequently, in the year 2019, Pei-Hsun Sung[9] studied "The correlation between Left Ventricular Function and neurological impairment" amongst the East Asian ethnicities and demonstrated a positive correlation between the two. This present study is the first clinical observational study carried out on the Indian population of South East Asian continent and it revealed several striking findings.

Among the patients studied, 38.7% belong to the age group of 51 to 60 years, followed by 30.7% between 61 to 70 years. There are fewer incidences of stroke noted in the younger group (< 50 years) and as well in the older population (> 70 years). The mean age of the study population is 63. In Hays et al study (year 2006) [7], the mean age of the study population was 70. The higher incidence of stroke in the present study at a lower mean age of 63 is due to the co-morbidities associated with sedentary life style and changing dietary habits over the last decade.

The male-to-female ratio is 61.3: 38.7 in our study. This contrasts with the NOMAS study[7] where the similar ratio was 44: 56, which may be attributed to the prevalence of smoking and alcohol intake by women in western countries.

50% of patients in the current study are smokers and 28.3% alcoholic. In the NOMAS study [7], 23% were smokers while 40% alcoholic. It may be observed that the prevalence of smoking habit is high with Indians while alcoholism is dominant among westerners.

The incidence of co-morbidities are in the descending order of Hypertension, Dyslipidemia and Diabetes, each accounting for 60%, 51% and 36% respectively in our study. Whereas in the Pei-Hsun Sung et al [9] and NOMAS study[7], the hypertensives were 80% and 78% respectively, due to differences in the ethnic habits, lifestyle variations and excessive salt intake of their study population.

Neutrophil-Lymphocyte Ratio (NLR) and Platelet-Lymphocyte Ratio (PLR) are derivatives of CBC, which is a simple, economical and extensively used test. In the recent days, NLR and PLR have gained enormous importance as novel markers and prognostic indicators in many ailments such as inflammatory diseases[10], cardio-vascular diseases[11] and cancer [12]. In this present study, an essential finding is that NLR and PLR strongly correlates to the neurological severity assessed by NIHSS. This makes it evident that following acute ischemic stroke, depending on the brain infarct area / volume, there is systemic inflammatory reaction and immune dysregulation leading to upward trend in NLR and PLR [13].

Numerous studies conducted previously have demonstrated a cause-effect relationship of chronic LV dysfunction (heart failure) leading to AIS owing to atherosclerosis as a common risk factor [7, 14, 15]. Interestingly, our study is one of the pioneers to establish the existence of a converse relationship as well, that is, AIS leads to LV dysfunction in non-CAD population. Based on the extent of decrease in the LV function, the severity of neurological impairment increases. Hence, our study highlights that lower LVEF can be used as a parameter for prediction of poor prognostic outcome in acute ischemic stroke.

By performing focussed neurological examination, NLR / PLR value analysis and LVEF assessment, the physician can objectively recognize and segregate "potentially high risk" AIS patients necessitating ICU care and extend focussed therapeutic strategy in parallel to restore the maximum possible integrity of LV systolic function at the earliest.

Limitations

This study has limitations. Firstly, it was conducted on a small population at a single centre. Further studies with larger number of patients across multiple locations are required to support the present observation. Secondly, owing to lack of long term follow-up, the prognostic value of LVEF on a long term could not be arrived at. Thirdly, the exact underlying mechanism between acute ischemic stroke and lower LVEF remains ambiguous. Finally, as Coronary Angiogram was not performed on this study population, the percentage of the patients with lower LVEF due to obstructive CAD remains undetermined.

Conclusion

The present study demonstrates that AIS patients with severe neurological dysfunctions exhibit higher NLR / PLR and lower LVEF. LVEF can be used as a novel prognostic marker to identify potentially high risk AIS patients.

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