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Original Research Article

Assessing Diagnostic Utility of NLR to Predict Poor Functional Outcomes in Patients with Hemorrhagic Stroke and To Compare it with the Intracranial Hemorrhage (ICH) Score: A Comparative Study

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Abstract

Aim: The aim of this study was to evaluate the diagnostic utility of NLR to predict poor functional outcomes in patients with hemorrhagic stroke and to compare it with the intracranial hemorrhage (ICH) score.

Material & Methods: Patients who presented to the emergency department with clinical features suggestive of stroke were evaluated with computed tomography (CT) brain to identify ICH. The ICH scores and NLR were estimated at the time of admission. Modified Rankin Scale (mRS) score equal to or greater than 3 at 90 days was used to define poor functional outcomes (major disability or death). Receiver operating characteristic (ROC) curve was plotted with NLR and the ICH score to analyze and compare their discriminative ability to predict poor functional outcomes.

Results: A total of 100 patients were included in this study, 65 males and 35 females. The mean age of the study group was 64.6 years (SD = 12.6). 32% had ICH score 2 followed by 21% had ICH score 1. Of the total 100 patients, 65 subjects (65%) had mRS score greater than or equal to 3 at 90 days. These patients were categorized as the poor functional outcome group. 35 patients (35%) had mRS score less than 3 at 90 days and were categorized as the good outcome group. The all-cause mortality at 90 days was 16 (16%) in the study. The difference of Laboratory variables and the ICH score according to 90 days of outcomes were found to be statistically significant. At their cutoff values, NLR compared to the ICH score was found to be more sensitive but less specific. There was no significant difference in accuracy between NLR and the ICH score.

Conclusion: In patients with hemorrhagic stroke, NLR at admission is a good predictor of functional outcomes at 90 days. When compared to the ICH score, NLR is more sensitive but less specific in predicting poor functional outcomes.

Keywords: Functional outcomes, Hemorrhagic stroke, Intracranial hemorrhage, Modified Rankin scale, Neutrophil-to-lymphocyte ratio, The ICH score.

Introduction

Stroke is a leading cause of death and acquired disability in adults. [1] With almost 6 million deaths and more than 10% of all mortality every year, stroke has become one of the predominant threats to human health. [2] The major subtypes of stroke are ischemic stroke and hemorrhagic stroke, representing approximately 80% and 20% of types, respectively. [3] Hemorrhagic stroke accounts for 10–15% of all types of strokes. It carries higher mortality and morbidity in comparison to ischemic stroke. [4] Hemorrhagic strokes are caused by rupture of a blood vessel resulting in bleeding into the cerebral parenchyma with or without extension into the ventricles. They account for 10–20% of all strokes. [5] Intracranial hemorrhage (ICH) has high mortality and morbidity in spite of recent advances in medical intensive care and neurosurgical interventions. [6] According to previous reports, about 40% of all stroke deaths are attributable to hemorrhagic stroke. [7]

In recent years, inflammation has been shown to have a strong relationship with the occurrence of stroke, and negative effects in both experimental and clinical data. [8,9] After stroke, the inflammatory response is activated and plays a significant role in secondary brain injury. [10] The inflammatory process is mediated by numerous inflammatory mediators including adhesion molecule (e.g., Pselectin), cytokines (e.g., IL-1, IL-6), chemokine (e.g., CCL2), and protease (e.g., matrix metalloproteinase-9). It is a complex process that can induce the activation and immunosuppression of a variety of inflammatory cells. Furthermore, all brain cells (such as glial

cells, endothelial cells, and neurons) and peripheral immune cells (such as neutrophils and lymphocytes) are contributors to the post-stroke inflammation. [11,12] Previous studies have found the different roles of neutrophils and lymphocytes in the progression and prognosis after stroke. Neutrophils could re-infiltrate the ischemic site in the first few hours after stroke, and then release chemical mediators related to increased tissue damage and poor neurological prognosis. [13] At the same time, stroke could trigger a special immunosuppressive state, [10] such as the activation of neutrophils, which leads to a decrease in lymphocytes, [14] and certain types of lymphocytes are considered to be important brain protective immune regulators; the decrease of these lymphocytes may lead to deterioration of nerve function. [15]

The neutrophil-to-lymphocyte ratio (NLR) in the peripheral blood has recently emerged as a biomarker of inflammation. Neutrophil to lymphocyte ratio (NLR) as a reflection of innate (neutrophilic) and adaptive (lymphocytic) immune responses have been widely studied due to their convenience to obtain from peripheral blood. The increased NLR level with neutrophilic elevation and lymphocytic depletion indicates the imbalanced interaction between stroke-induced central inflammation and peripheral inflammation.

Increased NLR is a negative prognostic indicator in acute ischemic stroke (AIS) and spontaneous intra-cerebral hemorrhage (ICH). [16,17,18] Thus, the overall strength of evidence of NLR as an adverse prognostic factor in hemorrhagic stroke is inadequate and inconsistent. Additionally, there is limited evidence comparing NLR as a prognostic biomarker with existing clinico-radiological prognostic models in hemorrhagic stroke like the ICH score. [19] Hence the aim of the study was to explore the role of NLR as a prognostic biomarker in patients with hemorrhagic stroke and to compare it with the ICH score to predict functional outcomes.

Material & Methods

A prospective observational study was conducted at the Department of Anesthesiology and Critical care, AIIMS, Patna, Bihar, India. Patients were recruited for the study over the period of 8 months. Sample size was 100 cases.

Inclusion Criteria

Patients above 18 years who presented to the emergency department within 24 hours of onset of stroke symptoms and evidence of hemorrhagic stroke in CT brain were included in the study.

Exclusion Criteria

Patients with a history of trauma, fever, prior stroke, or current anticoagulant medications were excluded.

Methodology

Data regarding baseline demographics and the ICH score at presentation were collected and documented. The values of absolute neutrophil count (ANC) and absolute lymphocyte count (ALC) were obtained from the complete blood count results (Sysmex XN-1000 Hematology Analyzer) at admission, and NLR was calculated for each patient at presentation. The study endpoint was functional outcomes at 90 days. It was assessed by telephonic conversation using Modified Rankin Scale (mRS). Patients with mRS greater than or equal to 3 (major disability or death) were categorized as having poor functional outcomes.

Statistical Analysis

Categorical and quantitative variables were expressed as frequency (percentage) and mean ± standard deviation (SD), respectively. Descriptive statistics such as mean ± SD, median with interquartile range (IQR), minimum, and maximum were used to describe quantitative parameters. Receiver operating characteristic (ROC) graphs were plotted, and the area under the curve (AUC) was calculated to assess diagnostic accuracy of NLR and the ICH score in detecting poor outcomes and to assess the optimal cutoff scores. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy had been calculated. For all statistical interpretations, $p<0.05$ was considered as the threshold for statistical significance. Statistical analysis was performed using the statistical software package SPSS, version 20.0.

Results

Table 1: Baseline demographics and ICH score on admission

Demographics	
Age, mean ± SD	64.6 ± 12.6
Male sex, N (%)	65 (65%)
Female sex, N (%)	35 (35%)
ICH score, mean ± SD	2.44 (SD = 1.32)
ICH score, N (%)	
Score 0	7 (7%)

Score 1	21 (21%)
Score 2	32 (32%)
Score 3	18 (18%)
Score 4	18 (18%)
Score 5	4 (4%)

A total of 100 patients were included in this study, 65 males and 35 females. The mean age of the study group was 64.6 years (SD = 12.6). 32% had ICH score 2 followed by 21% had ICH score 1.

Table 2: Functional status at 90 days

Poor functional outcomes, mRS ≥3, N (%)	65 (65%)
Good functional outcomes, mRS <3, N (%)	35 (35%)
Fatal outcomes, mRS = 6, N (%)	16 (16%)

Of the total 100 patients, 65 subjects (65%) had mRS score greater than or equal to 3 at 90 days. These patients were categorized as the poor functional outcome group. 35 patients (35%) had mRS score less than 3 at 90 days and were categorized as the good outcome group. The all-cause mortality at 90 days was 16 (16%) in the study.

Table 3: Laboratory variables on admission

	Mean ± SD	Median (IQR)	Minimum	Maximum
ANC (cells/µL)	8565.3 ± 2652.2	8498.5 (6825.5–10262.75)	1200.0	16450.0
ALC (cells/µL)	2345.9 ± 1044.8	2348 (1506.75–3163.5)	285.0	5250.0
NLR	5.5 ± 4.7	3.77 (2.22–6.79)	0.7	31.7

The mean NLR of the study population was 5.34 (SD = 4.74). The mean NLR of the poor outcome group was 6.57 (SD = 5.24) and that of the good outcome group was 2.75 (SD = 1.56). The difference was statistically significant with a p-value of 0.001.

Table 4: Laboratory variables and the ICH score according to 90 days of outcomes

Variables	Outcome	Mean	SD	p
Age	0	62.06	12.36	0.018
	1	66.14	12.97	
ANC	0	6875.55	1985.65	0.001
	1	9332.04	2536.94	
ALC	0	2834.86	878.62	0.001
	1	2084.89	1084.469	
NLR	0	2.78	1.56	0.001
	1	6.54	5.24	
ICH score	0	1.48	0.94	0.001
	1	2.86	1.255	

The mean NLR of the poor outcome group was 6.54 (SD = 5.24) and that of the good outcome group was 2.78 (SD = 1.56). The difference was statistically significant with a p-value of 0.001. The mean ANC of the poor outcome group was higher when compared to the good outcome group and the difference was statistically different with a p-value of 0.001. The mean ICH score at admission was 2.40 (SD of 1.32). The poor functional outcome group had a higher mean ICH score of 2.86 (SD = 1.25) compared to the good outcome group that had a mean ICH score of 1.48 (SD = 0.94). The difference of Laboratory variables and the ICH score according to 90 days of outcomes were found to be statistically significant.

Table 5: Comparison of accuracy of outcome prediction at 90 days between NLR and the ICH score

	NLR	ICH score	Z	p
Sensitivity	82.0	67.3	3.537	0.000
Specificity	66.4	78.2	2.346	0.014
False positive	33.7	21.8	2.360	0.016
Positive predictive value	69.1	73.7	0.850	0.402
Negative predictive value	82.1	72.2	2.080	0.036
Positive likelihood ratio	2.5	3.1	0.316	0.752
Negative likelihood ratio	0.2	0.4	0.284	0.778
Accuracy	74.7	72.8	0.383	0.706

At their cutoff values, NLR compared to the ICH score was found to be more sensitive but less specific. There was no significant difference in accuracy between NLR and the ICH score.

Discussion

The neutrophil-to-lymphocyte ratio (NLR) in the peripheral blood has recently emerged as a biomarker of inflammation. It has been studied in multiple disease states including solid tumors, sepsis, connective tissue diseases, and stroke. [20-23] Majority of the research with NLR has been conducted in ischemic stroke. There are very few studies pertaining to NLR in hemorrhagic stroke and to the best of our knowledge, none so far in the Indian population. Previous studies by Lattanzi et al. and Geide-Jeppe et al. have shown that high NLR on admission is associated with poor functional outcomes and increased mortality in patients with spontaneous ICH. [24,25] However, the study by Sun et al. has failed to demonstrate any association between NLR and functional outcomes or mortality in ICH. [26] Thus, the overall strength of evidence of NLR as an adverse prognostic factor in hemorrhagic stroke is inadequate and inconsistent. Additionally, there is limited evidence comparing NLR as a prognostic biomarker with existing clinico-radiological prognostic models in hemorrhagic stroke like the ICH score. [27]

A total of 100 patients were included in this study, 65 males and 35 females. The mean age of the study group was 64.6 years (SD = 12.6). 32% had ICH score 2 followed by 21% had ICH score 1. Of the total 100 patients, 65 subjects (65%) had mRS score greater than or equal to 3 at 90 days. These patients were categorized as the poor functional outcome group. 35 patients (35%) had mRS score less than 3 at 90 days and were categorized as the good outcome group. The all-cause mortality at 90 days was 16 (16%) in the study. The mean NLR of the poor outcome group was 6.54 (SD = 5.24) and that of the good outcome group was 2.78 (SD = 1.56). The difference was statistically significant with a p-value of 0.001. The mean ANC of the poor outcome group was higher when compared to the good outcome group and the difference was statistically different with a p-value of 0.001. Neutrophil-to-lymphocyte ratio (NLR) is an emerging biomarker for assessing the systemic inflammatory status of an individual, including in patients with cardiovascular disease, peripheral vascular disease, and cancer. NLR has also been associated with the prognosis of patients with acute ischemic stroke. For example, a higher NLR has been associated with greater initial stroke severity and a higher short-term mortality rate [28,29], as well as with poorer short-term functional outcomes and an increased risk of recurrent ischemic stroke. [30,31] A higher NLR has also been associated with several post-stroke complications, including higher risks of symptomatic hemorrhagic transformation and symptomatic intracerebral hemorrhage. [32,33]

The mean ICH score at admission was 2.40 (SD of 1.32). The poor functional outcome group had a higher mean ICH score of 2.86 (SD = 1.25) compared to the good outcome group that had a mean ICH score of 1.48 (SD = 0.94). The difference of Laboratory variables and the ICH score according to 90 days of outcomes were found to be statistically significant. At their cutoff values, NLR compared to the ICH score was found to be more sensitive but less specific. There was no significant difference in accuracy between NLR and the ICH score. Apart from NLR, it is also observed in this study that statistically significant difference exists between good and poor outcome group with respect to age and ICH score also. The mean age of the group with poor outcomes is found to be higher when compared to the mean age of the good outcome group (68 vs 63 years). This finding was in contrast with the findings of Tekinarslan et al. where age more than 65 years was found to be an important poor prognostic factor in patients with hemorrhagic stroke. [34] NLR is a systemic inflammatory biomarker that reflects the balance between circulating neutrophils and lymphocytes. NLR at hospital admission has been shown to correlate positively with the NIHSS scores of acute ischemic stroke patients, with a higher NLR being associated with an increased risk of 60-day mortality. [29] An increased NLR was also shown to be associated with unfavorable outcomes on the modified Rankin Scale 3 months after stroke onset, as well as with unfavorable outcomes on the modified Barthel Index at discharge. [30,31]

Conclusion

In patients with hemorrhagic stroke, NLR at admission is a good predictor of functional outcomes at 90 days. When compared to the ICH score, NLR is more sensitive but less specific in predicting poor functional outcomes.

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