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Prognostic Value of Neutrophil /Lymphocyte Ratio in Acute Ischemic Stroke patients Either Received Reperfusion Therapy or Not

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ABSTRACT

Background: Very few studies have investigated the specific relationship between neutrophil-lymphocyte ratio (NLR) and the short-term prognosis of patients with acute ischemic stroke (AIS) and after receiving intravenous thrombolysis.

Objectives: To discuss if there is a relationship between neutrophil-lymphocyte ratio and stroke severity in the emergency department and short-term prognosis whether the patient is treated by reperfusion therapy or not to use it as a rapid prognostic marker in acute ischemic stroke patients.

Patients and Method: A prospective comparative interventional study was done on 56 patients with acute ischemic stroke at Menoufia University Hospitals. They were selected according to certain inclusion and exclusion criteria. NLR was assessed from the patients' blood samples. Initial stroke severity was evaluated by Glasgow Coma Score (GCS), National Institutes of Health Stroke Scale (NIHSS) score and modified ranking scale (mRS), then was re-evaluated later after 24 hours of admission and after one month.

Results: NLR among ischemic stroke patients with a bad prognosis was significantly higher than that of the patients who had a good prognosis. The optimal cutoff value of NLR for the prediction of unfavorable outcomes was 4.15 with a sensitivity of 100% and a specificity of 88.5%.

Conclusion: Elevated NLR on the hospital admission is an easy and strong predictor of poor outcomes in AIS patients either receiving reperfusion therapy or not.

Keywords: Acute ischemic stroke, Intravenous thrombolysis, Neutrophil-to-lymphocyte ratio, outcome.

INTRODUCTION

Cerebrovascular stroke is the second most common cause of death after ischemic heart disease and the third most common cause of disability in adults [(1)]. The overall crude prevalence rate of stroke in Egypt is 963/100,000 population [(2)]. Using intravenous reperfusion therapy is the most important in treating patients suffering from acute ischemic stroke.

This treatment should be given as fast as possible, perfectly within 4:5 hours after the onset of the symptoms and within 60 minutes from the arrival of the patient to the emergency room [(3)]. Acute ischemic stroke is an inflammatory process in which the diseased tissues releases chemokines and cytokines, and recruits peripheral circulating leukocytes. Among the leucocytes, neutrophils were known to be an important mediator and early neutrophilia was demonstrated to be accompanied by larger stroke volumes and bad outcome. Lymphocytes also infiltrate the ischemic tissues and cause inflammatory responses [(4)].

Admission Neutrophil-to-Lymphocyte Ratio (NLR) is supposed to be a readily available and inexpensive predictor for short-term prognosis in acute ischemic stroke (AIS) patients [(5)]. In recent studies, NLR was shown to correlate with mortality in patients with AIS [(6)]. However, the problem is that the effects of NLR on functional outcome in AIS are still uncertain. This study aimed to discuss if there is a relationship between neutrophil-lymphocyte ratio and stroke severity in the emergency department and short-term prognosis either the patient is treated by iv reperfusion therapy (r-tPA) or not. Using this ratio as a fast marker on arrival at the hospital can help in predicting the prognosis of the patients of acute ischemic stroke in an easy manner.

Therefore, a higher NLR should be taken into consideration in patients with AIS and these patients should be followed more closely in terms of poor outcomes. This study aimed to investigate whether a high NLR is associated with a poor outcome in patients with AIS and after receiving r-tPA.

PATIENTS AND METHODS

This study included 56 ischemic stroke patients who were admitted with history of neurologic symptoms, signs, and neuroimaging of acute ischemic stroke into the Emergency Department at Menoufia University Hospitals. Sample size was calculated using Epi-Info program.

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Inclusion Criteria: Adult Patients (18 years old or more**),** patients with stroke proven by clinical picture and CT and within 24 hours from onset of symptoms.

Exclusion Criteria:

Patients younger than 18 year**s,** patients with an infection history within 2 weeks before stroke onset, patients with hematologic disorders, immunosuppressant drug users (steroids), patients with hepatic and renal failure, patients with trauma, surgery, neoplasm, and intoxication and patients who refused to participate**.**

Clinical data for all patients were recorded, complete blood count test using the peripheral venous blood samples was taken on admission to the emergency department. NLR was calculated, using Beckman Coulter LH 750 hematology analyzers (Beckman Coulter, Miami, Florida, USA). Neuroimaging like C.T brain was done using Toshiba Alexion (CanonMedical, Tokyo, Japan), 16-channel computed tomography (WDC, USA).

Initial stroke severity was evaluated by Glasgow Coma Score (GCS), National Institutes of Health Stroke Scale (NIHSS) score, and modified ranking scale (mRS) then was re-evaluated later after 24 hours of admission and after one month from the onset of symptoms.

Ethical approval:

An approval of the study was obtained from Menoufia University academic and ethical committee. Every patient signed an informed written consent for acceptance of the operation.

Statistical analysis

Data were collected, tabulated, and statistically analyzed using an IBM-compatible personal computer with Statistical Package for the Social Sciences (SPSS) version 23 (IBM SPSS statistics for windows, version 23.0, Armnok, NY: IBM Corp.).

Two types of statistical analysis were performed:

(a) Descriptive statistics e.g. qualitative data were expressed in Number (N), percentage (%), while quantitative data were expressed as mean (X^2) ± standard deviation (SD), and range (minimum-maximum).

(b) Analytic statistics e.g. Student's t-test is a test of significance used for comparison of quantitative variables between two groups of normally distributed data, while Mann Whitney's test was used for comparison of quantitative variables between two groups of not normally distributed data. Wilcoxon test was used to compare two consecutive readings of not-normally distributed data in the same group. Spearman correlation was used to show a correlation between two continuous not normally distributed variables.

Significant test results were quoted as two-tailed probabilities. The significance of the obtained results was judged at the 5% level ($P \geq 0.05$). A p-value ≤ 0.05 was set to be significant.

RESULTS

A total of 56 patients were enrolled in this study and followed up for one month. The mean age of the study population was 62 (35–90) years old, and 48% of the study populations were males. Baseline characteristics of the study groups and Biochemical and laboratory parameters including neutrophil, lymphocyte, NLR, and lipid profile had no significant differences between the two groups ($P > 0.05$ for all) as shown in table (1).

Then, a comparison about the prognosis between the two study groups was done (Table 2). 68.8% of the patients who had r-tPA had a good prognosis, and only 31.3% of them had a bad prognosis.

While in patients who did not receiver-tPA, 55% of them had a bad prognosis, and 37.5% had a good prognosis. There was a highly significant strong negative correlation between NLR and GCS post, while there was a highly significant strong positive correlation between NLR and NIHSS post and MRS post (Table 3).

Among the enrolled 56 patients, 40 patients did not receive rt-PA, 37.5% of them (15 patients) had a good prognosis, and their NLR on admission was 2.9 ± 0.7. And 55% of these patients (22 patients) had a bad prognosis, and their NLR on admission was 10.1 ± 2.7. On the other side, the 16 patients who received r-tPA, 68.7% of them (11 patient) had a good prognosis, and their NLR on admission was 3.3 ± 1.7 while 31% of these patients (5 patients) had a bad prognosis and their NLR on admission was7.04 ± 1.1 (Table 4).

So, NLR can be used as a prognostic marker in AIS patients and NLR ≥ 4.15 predicted a bad prognosis with a specificity of 88.5%% and sensitivity of 100% (Table 5).

Table (1): Socio-demographic characteristics and Biochemical parameters of studied groups.

	With r-tPA (N=16)		Without r-tPA (N=40)		Test of significance	P-value
	N	%	N	%		
Age (years) Mean ± SD Range	67.9 ± 8.05 50-81		66.6 ± 11.5 35-90		t= 0.44	0.7
Sex: Female Male	8 8	50 50	20 20	50 50	-	-
Comorbidity: Yes No	15 1	93.7 6.3	37 3	92.5 7.5	FE= 0.03	1
	With r-tPA (N=16)		**Without r-tPA (N=40)**		**Test of significance**	**P-value**
	Mean ± SD Range		**Mean ± SD Range**			
N/L ratio	4.5 ± 2.3		6.9 ± 4.2		U= 1.9	0.06
Cholesterol (mg/dl)	155 ± 22.6		169.2 ± 29.5		t= 1.7	0.09
TGS (mg/dl)	135.3 ± 33.3		141.3 ± 24.1		t= 0.7	0.5
HDL (mg/dl)	41.9 ± 4.8		37.4 ± 5.6		t= 1.4	0.2
LDL (mg/dl)	117.8 ± 24.9		116.6 ± 1.3		t= 0.1	0.9

U: Mann-whitney test N: Number, Range: Minimum-maximum, t: student t test, FE: Fischer's Exact test

Table (2): Prognosis of studied groups.

Prognosis	With r-tPA (N=16)		Without r-tPA (N=40)		Test of significance	P-value
	N	%	N	%		
Good	11	68.8	15	37.5	X^2= 4.9	0.085
Bad	5	31.3	22	55		
No change	0	0	3	7.5		

Table (3): Correlation between NLR and GCS post, NIHSS post, MRS post.

	NLR	
	r_s	P-value
GCS post	-0.7	**0.001*<**
NIHSS post	0.8	**0.001*<**
MRS post	0.7	**0.001*<**

r_s: Spearman correlation coefficient, * significant

Table (4): Relation between NLR and disease prognosis in the studied groups.

	With r-tPA (N=16)		Test of sig.	P-value	Without r-tPA (N=40)			Test of sig.	P-value	Post-Hoc test (Tamhan)
	Good Prognosis (N=11)	Bad Prognosis (N=5)			Good Prognosis (N=15)	Bad Prognosis (N=22)	No change (N=3)			
NLR: Mean ± SD Range	3.3 ± 1.7 1.7-6.1	7.04 ± 1.1 5.5-8.2	**U**= 2.9	**0.004***	2.9 ± 0.7 1.6-3.8	10.1 ± 2.7 4.5-13.9	2.6 ± 1.5 1.7-4.3	**K-W**= 2.9	**<0.001***	**P1: < 0.001** **P2:** 0.98 **P3: 0.005***

K-W: Kruskal-wallis test, P: p-value, P1: between good & bad, P2: between good & no-change, P3: between bad & no-change, * significant

Table (5): ROC curve for NLR as a predictor for bad disease prognosis in all patients against good prognosis**.**

AUC	Accuracy	Cut-off point	Significance	Sensitivity	Specificity
1	100%	4.15≥	0.001<	100%	88.5%

AUC: area under curve

DISCUSSION

A prospective study was done on 56 patients with acute ischemic stroke at Menoufia University Hospitals. The mean age of the study population was 62 years old. In this study a comparison between the prognosis of the two study groups revealed that 68.8% of the patients who had reperfusion therapy (which is the majority) had a good prognosis. Patients who did not receive reperfusion therapy, 55% of them had a bad prognosis. This comes in agreement with **Tork *et al.*** [7].

The study also revealed that there was a highly significant strong negative correlation between neutrophil lymphocytic ratio and GCS post, while there was highly significant strong positive correlation between neutrophil lymphocytic ratio and NIHSS post and MRS post that comes in agreement with **Xue and colleagues** [8]**.** Also in this study, 37.5% of the patients who didn't receive reperfusion therapy had a good prognosis and their NLR on admission was 2.9 ± 0.7. And 55% of these patients had a bad prognosis and their NLR on admission was 10.1 ± 2.7.

On the other side, 68.7% of the patients who received reperfusion therapy had a good prognosis and their NLR on admission was 3.3 ± 1.7, while 31% of these patients had a bad prognosis and their NLR on admission was7.04 ± 1.1. So NLR can be used as a prognostic marker in AIS patients and NLR ≥ 4.15 predicted a bad prognosis with a specificity of 88.5%% and sensitivity of 100%. This result is in accordance with **Brooks *et al.*** [9] but with higher cutoff point (5.9) to predict poor outcome. On the other hand, very few studies have investigated the specific relationship between neutrophil-to-lymphocyte ratio (NLR) and the short term outcomes of patients suffering from acute ischemic stroke (AIS) and receiving intravenous thrombolysis. According to these patients this study results come in agreement with **Liu *et al.*** [10]**.**

The possible underlying mechanism of the relationship between higher NLR and bad prognosis in patients may be explained by that NLR may increase as a result of inflammatory response in AIS to be a marker indicating the severity and extent of necrotic tissue and its associated biochemical pathways. Previous studies have shown that increased neutrophils release cytokines, chemokines, free oxygen radicals, and other inflammatory mediators, which result in blood-brain barrier disruption, neuronal cell death, and hemorrhagic transformation after AIS. All these occurred changes are associated with poor outcome and may contribute to the mortality of AIS [11]**.**

So NLR can be used as a prognostic marker in AIS patients and NLR ≥ 4.15 predicted a bad prognosis with a specificity of 88.5% and sensitivity of 100%.

The differences between the results of this study and others could be explained by that the study was conducted with limited time and the sample size was relatively small. It could be interesting to evaluate the long-term prognostic value of NLR with a larger sample size in AIS patients. In addition, although we excluded patients with active infection, many diseases and factors that might affect inflammatory markers may not be taken into consideration.

Neutrophil/lymphocytic ratio is a simple, non-expensive, fast and easy marker for predicting stroke severity on admission. Using this ratio as a fast marker on arrival at the hospital can help in predicting the prognosis of the patients of acute ischemic stroke in an easy manner. Therefore, a higher NLR should be taken into consideration in patients with AIS and these patients should be followed more closely in terms of poor outcomes.

CONCLUSION

Elevated NLR at the hospital admission is an easy and strong predictor of poor outcomes in AIS patients. Also, NLR was also found to be associated with prognosis in AIS patients who take reperfusion therapy where higher NLR can predict poor outcome.

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