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Role of some inflammatory biomarkers in prediction of short-term outcome in acute ischemic stroke

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Abstract

Background: Several factors affect acute ischemic stroke (AIS) outcomes.

Objective: This study aimed to assess the role of the leukocyte count, neutrophil/lymphocyte ratio (NLR), and c reactive protein (CRP) as early predictors of outcome in AIS patients.

Methods: This study was conducted on 60 AIS patients. They were subjected to detailed history taking, clinical examination, brain imaging, and laboratory assessment including the CRP, white blood cell (WBC) count, absolute neutrophil count (ANC), absolute lymphocyte count (ALC), and NLR which is calculated by dividing ANC by ALC. Neurological scales were used to assess the level of consciousness by the Glasgow Coma Scale (GCS) and stroke severity by the National Institute of Health Stroke Scale (NIHSS) at the first 48 h of stroke onset as well as 1 week and 2 weeks later for the assessment of short-term functional neurological outcome.

Results: Sixty percent of the patients had unfavorable outcomes assessed by the Modified Rankin Scale (mRS). Patients with unfavorable outcomes had higher NIHSS scores. NLR was positively correlated with WBC count, ANC, and CRP. The higher WBC, NLR, and NIHSS, the unfavorable the outcome was.

Conclusion: The higher WBC, the NLR, and the level of CRP at the onset of AIS, the more severe stroke and the poorer the short-term outcome are expected.

Keywords: Stroke, Biomarkers, Neutrophil/lymphocyte ratio, C-reactive protein, Outcome

Introduction

Acute ischemic stroke is one of the major causes of death worldwide, and due to the high mortality and morbidity rates associated with stroke, it is becoming a major community health problem worldwide as the third of these cases are fatal and survivors usually have prolonged or irreversible disabilities [1].

Several factors affect stroke prognosis including age, stroke severity, lesion location, comorbid conditions, clinical findings, and related complications. Knowledge of the factors contributing to early neurologic deterioration after AIS can guide the early management strategies and lead to more favorable outcomes [2].

Aim

This study was designed to determine the role of the leukocyte count, NLR, and CRP in the prediction of short-term outcomes in acute ischemic stroke patients.

Methods

This is a prospective cohort study conducted on 60 AIS patients: 26 males and 34 females, with ages ranging from 45 to 95 years with a mean age of 64.8 ± 10.2 years. This study was done in intensive care and stroke units and neurology department during the period from February 2019 to February 2020.

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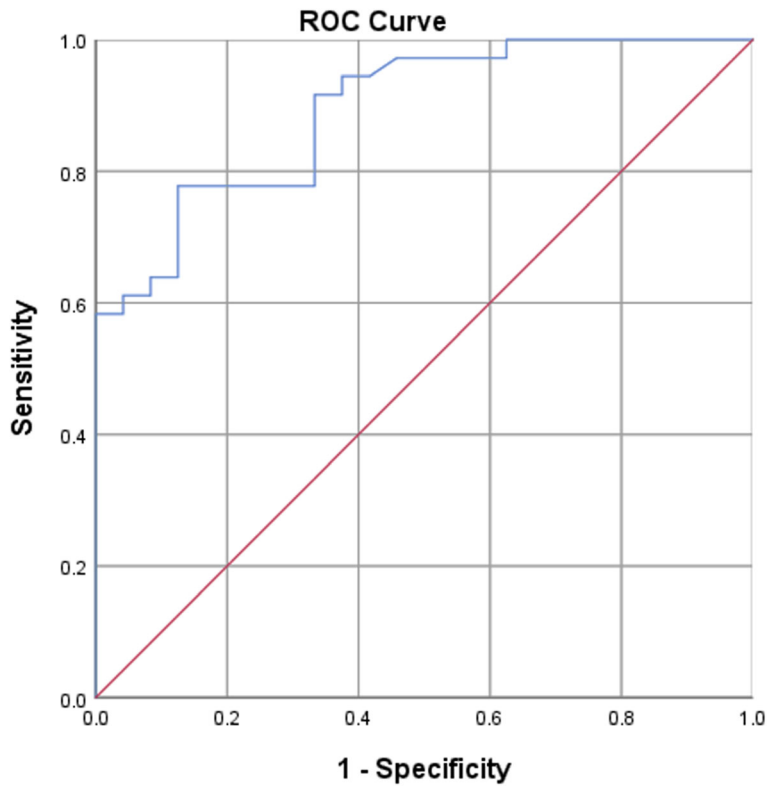

Fig. 1 Receiver operating characteristics curve (ROC) of neutrophil/lymphocyte ratio in the prediction of unfavorable outcomes

Ethical consideration

Written informed consent was obtained from each participant or written assent from their relatives, and the ethics of research was put by the Institutional Research Board (IRB) of faculty of medicine which was followed up thoroughly.

Inclusion criteria

Patients within the first 48 h of stroke onset were diagnosed clinically and confirmed by brain imaging (computed tomography (CT) and/or magnetic resonance imaging (MRI)).

Exclusion criteria

The following were excluded: hemorrhagic stroke and other neurological causes of acute focal cerebral dysfunction such as cerebral venous sinus thrombosis, head trauma, and infection. Also, respiratory failure, liver failure, and chronic renal diseases were excluded. Patients with a history of usage of steroids or immunosuppressant drugs, cancer, autoimmune disease, myeloproliferative disorders, hematological disorders, pregnancy, and postpartum stroke were excluded.

All participants were subjected to detailed neurological history taking (with stressing on the vascular, cardiac risk factors) and full general and neurological examination. The Glasgow Coma Scale (GCS) was used to detect the depth of coma [3], and stroke severity was assessed using the National Institutes of Health Stroke Scale (NIHSS) [4], and the Modified Rankin Scale (mRS) [5] assessed the outcome.

Routine laboratory investigations were done within 48 h of stroke onset including complete blood picture (total and differential WBC, ANC, ALC, NLR), CRP, liver function test, kidney function test, erythrocyte sedimentation rate, coagulation profile, and lipid profile.

NLR is calculated by dividing ANC by ALC [6].

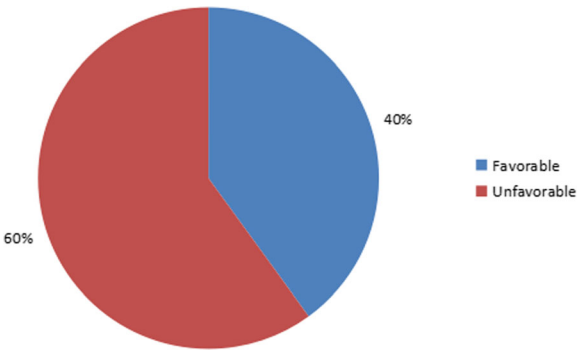

Fig. 2 Outcome of the studied patients

Table 1 Comparison between patients with favorable and unfavorable outcomes regarding inflammatory biomarkers, stroke severity, and short-term outcome

Variables	Favorable outcome patients	Unfavorable outcome patients	Test of sig.	*P* value
Age (years), mean ± SD	63.3 ± 10.2	65.8 ± 10.2	*T* 0.9	0.3
Sex				
Male	12 (50%)	14 (38.9%)	χ^2 0.724	0.395
Female	12 (50%)	22 (61.1%)		
Smoking				
Yes	3 (12.5%)	5 (13.9%)	Fisher 0.02	0.877
No	21 (87.5%)	31 (86.1%)		
Hypertension				
Yes	20 (83.3%)	31 (86.1%)	Fisher 0.087	0.768
No	4 (16.7%)	5 (13.9%)		
Diabetes				
Yes	13 (54.2%)	21 (58.3%)	χ^2 0.102	0.750
No	11 (45.8%)	15 (41.7%)		
Obesity				
Yes	1 (4.2%)	4 (11.1%)	Fisher 0.909	0.340
No	23 (95.8%)	32 (85.9%)		
Ischemic heart				
Yes	6 (25%)	10 (27.8%)	χ^2 0.057	0.812
No	18 (75%)	26 (27.8%)		
Transient ischemic attack				
Yes	9 (37.5%)	11 (30.6%)	χ^2 0.313	0.576
No	15 (62.5%)	25 (69.4%)		
Atrial fibrillation				
Yes	3 (12.5%)	12 (33.3%)	χ^2 3.33	0.068
No	21 (87.5%)	24 (66.7%)		
Dyslipidemia				
Yes	7 (29.2%)	11 (30.6%)	χ^2 0.013	0.908
No	17 (70.8%)	25 (69.4%)		
Glasgow Coma Scale				
Mild (>13)	14 (58.3%)	1 (2.8%)	χ^2 23.7	**<0.001****
Moderate (9–13)	10 (41.7%)	32 (88.9%)	15.3	**<0.001****
Severe (3–8)	0 (0.0%)	3 (8.3%)	Fisher	0.2
NIHSS, median (range)	6 (5–16)	15 (8–21)	MW 5.9	**<0.001****
White blood cell count (× 10^3/μL), median (IQ range)	9.9 (6.4–11.1)	10.8 (7.5–13.1)	MW 3.6	**0.04***
Neutrophil/lymphocyte ratio, median (IQ range)	2.5 (1.8–4.1)	5.2 (2.9–7.7)	MW 3.6	**0.04***
C-reactive protein (mg/L), median (IQ range)	16.7 (5.2–46.7)	35.0 (19.2–83.0)	MW 2.2	**0.02***
Erythrocyte sedimentation rate (mm), median (IQ range)	30.0 (20.0–55.8)	37.5 (23.5–57.5)	MW 1.0	0.3
Surrounding edema				
Yes	0 (0.0%)	10 (27.8%)	χ^2 8.0	**0.005***

Table 1 Comparison between patients with favorable and unfavorable outcomes regarding inflammatory biomarkers, stroke severity, and short-term outcome *(Continued)*

Variables	Favorable outcome patients	Unfavorable outcome patients	Test of sig.	*P* value
No	24 (100%)	26 (72.2%)		
Size of infarction				
Small	16 (66.7%)	4 (11.1%)	*20*	**<0.001****
Medium	7 (29.2%)	14 (38.9%)	0.6	0.4
Large	1 (4.2%)	18 (50.0%)	14	**<0.001****

IQ interquartile, *MW* Mann-Whitney, χ^2 chi-square test, *T T* test, *NIHSS* National Institute of Health Stroke Scale
**Highly significant
*Significant

Brain imaging was done via CT brain (Philips) and or MRI brain (Philips) to confirm the diagnosis of recent brain infarcts.

Each participant underwent electrocardiogram, echocardiography, and carotid Doppler ultrasonography.

All patients were followed up 1 week and 2 weeks post-stroke onset using NIHSS [4] and mRs [5]. The outcome was defined as favorable if mRS equals 0–2 and unfavorable outcome if mRS >2.

Statistical analysis

All data were collected, tabulated, and statistically analyzed using the Statistical Package for the Social Science (SPSS) software version 25 [7]. Quantitative data was presented as mean, median, and interquartile range. Qualitative data was presented as frequencies and proportions. The Kolmogorov-Smirnov and Levene tests were used to determine the distribution characteristics of variables and variance homogeneity. Pearson's chi-square (χ^2) test and Fisher's exact test were used to analyze qualitative data as appropriate. The Freidman test (F) was used to analyze dependent continuous data. The Student t test (T) and Mann-Whitney test (MW) were used to analyze continuous data between two groups as appropriate. The Kruskal-Wallis H (KW) tests were used to analyze continuous data between more than two groups. Spearman's correlation coefficient (r) was used to test the correlation between neutrophil/lymphocyte ratio and continuous variables. The sensitivity and specificity of NLR in the prediction of unfavorable outcomes in AIS patients were also assessed by a receiver operating characteristic (ROC) curve (Fig. 1). We found a significant cutoff > 3.7 with a sensitivity of 77.85 % and a specificity of 87.5% for NLR. P value of ≤ 0.05 was accepted as statistically significant, and P value ≤ 0.001 was considered highly significant [8].

Results

The number of AIS patients who fulfilled the criteria for inclusion in the current study was sixty patients (26 male patients and 34 female patients). Their ages ranged from 45 to 95 years with a mean age of 64.8 ± 10.2 years.

The percentage of the studied patients who had unfavorable outcomes (mRS was >2) was 60% as shown in Fig. 2.

There were statistically significant differences between patients with favorable and unfavorable outcomes. Favorable outcome patients had lower WBC count, lower NLR, lower CRP, and smaller size of infarction, and patients with unfavorable outcome had moderate GCS, higher NIHSS, and presence of surrounding edema (Table 1).

Table 2 Association between neutrophil/lymphocyte ratio, National Institute of Health Stroke Scale (NIHSS), and Modified Rankin Scale (mRS) among the studied patients

		Neutrophil/lymphocyte ratio			Test of sig.	*P* value
		<2 (*n* = 13)	**2-3 (*n* = 8)**	**>3 (*n* = 39)**		
NIHSS, median (range)	At admission	10 (6–17)	14.5 (7–19)	13 (5–21)	KW 4.3	0.1
	1 week post-stroke	9 (4–16)	11.5 (5–19)	11 (3–22)	KW 4.2	0.1
	2 weeks post-stroke	6 (4–13)	10 (5–22)	9 (3–22)	KW 4.9	0.08
mRS, *N* (%)	Favorable (0–2)	10 (76.9)	4 (50.0)	10 (25.6)	χ^2 10.9	**<0.001****
	Unfavorable (>2)	10 (23.1)	4 (50.0)	10 (74.4)		

KW Kruskal-Wallis, χ^2 chi-square test
**Highly significant

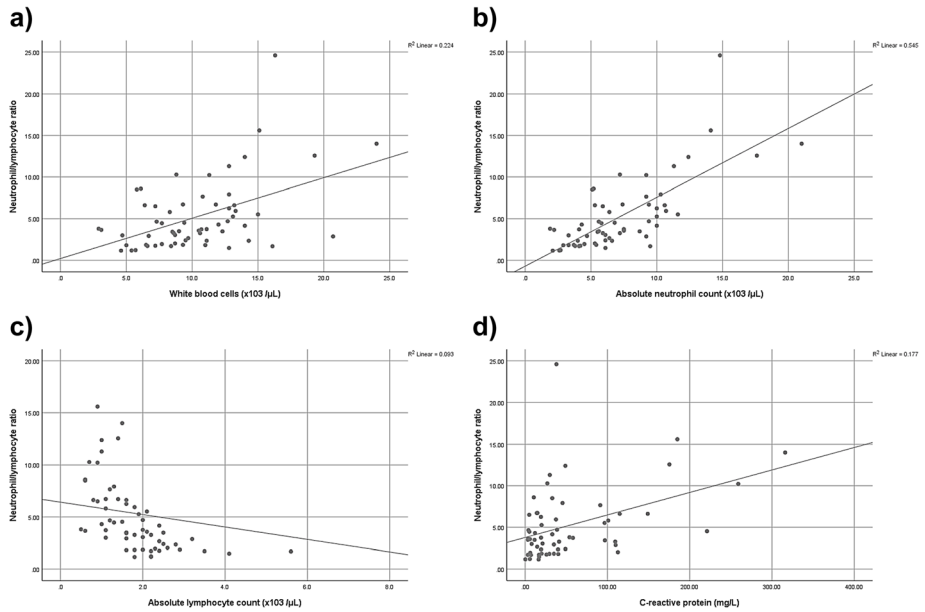

Fig. 3 Correlation coefficient of variables with neutrophil/lymphocyte ratio in acute ischemic stroke patients. *Significant. NLR, neutrophil/lymphocyte ratio; WBC, white blood cells

There was a high statistically significant association between high NLR and unfavorable mRS (Table 2).

NLR was positively correlated with WBC count, ANC, and CRP. On other hand, NLR was negatively correlated with ALC (Fig. 3).

The significant risk factors for unfavorable outcomes as expressed by mRS in the studied patients were higher WBC count, higher NLR, and higher NIHSS (Table 3).

Discussion

Accurate identification of stroke outcome predictors might help ideal beginning time for immediate intervention and management. So, it is important to detect the new prognostic factors besides the already known to control them at an early stage and help in improving outcomes in ischemic stroke patients [9] (Table 4).

Identification of the relationship between short-term outcomes of ischemic stroke and inflammatory biomarkers such as WBC, NLR, and CRP might aid in supporting that anti-inflammatory therapy might be a potential treatment for AIS. So, a better understanding of immunomodulation therapy might be the balance of anti-inflammatory and proinflammatory therapies to improve outcomes in ischemic stroke patients [6].

Regarding the short-term outcomes of AIS in our study, it was found that 24 patients (40%) had favorable outcomes while 36 patients (60%) had unfavorable outcomes.

This short-term outcome was not significantly related to the mean age. And this was in agreement with the results of Castellanos et al. [10].

This contradicted the findings of Bill et al. [11], who confirmed both functional dependence and death as an independent prognostic role of increasing age. This difference might be due to the different sample size and different ages.

According to the sex of our patients, there was no statistically significant relation with short-term outcomes. This was in agreement with the results of Geng et al. [12] who showed that there was no significant difference in sex between good and poor outcomes.

We found that the outcome of the studied patients was highly significantly related to the level of consciousness assessed by GCS. Similar results were obtained by another study that showed a strong correlation between lower GCS score and patient unfavorable outcomes [13].

Higher NIHSS showed a high significant association with the patient unfavorable outcomes (P value<0.001). This finding met with the finding of another study that found that high NIHSS was an independent predictor of the short-term outcomes in patients with AIS [14].

Concerning NLR as a good predictor of short-term outcomes in the AIS patients, our study showed that 74.4% of the AIS patients with high (>3) NLR was found to have unfavorable outcomes. The median Modified Rankin Scale (mRS) of those patients was 3. There was a highly significant association between patient outcomes assessed by mRS and NLR values (P value <0.001).

These results were consistent with the findings of Tokgoz et al. [9]; also, Xue et al. [6] found that a higher NLR was associated with stroke severity at admission and short-term unfavorable outcomes.

Table 3 Binary logistic regression analysis of the predictors of the unfavorable outcomes of acute ischemic stroke

Variables	Odds ratio	95% confidence interval	*P* value
White blood cell count	2.1	1.1–3.6	**0.02***
Neutrophil/lymphocyte ratio	2.5	1.2–4.8	**0.005***
C-reactive protein	2.6	1.0–4.6	**0.01***
NIHSS	1.8	1.1–2.9	**0.01***

NIHSS National Institute of Health Stroke Scale
*Significant

There was a significant association between patient unfavorable outcomes and elevation of admission CRP (*P* value = 0.02) in our study. This finding agreed with the results of Mitchell et al. [15] who found that the levels of CRP, an acute-phase reactant, were strongly associated with stroke severity and showed that elevation in CRP levels at the time of first ischemic stroke was associated with unfavorable outcomes.

Our study showed a statistically significant positive correlation between NLR and higher admission CRP, and these results were matched with the finding of Lee et al. [16].

We found that there was a statistically significant correlation between elevated WBC count and patients' outcomes, and this finding matched with the results of Geng et al. [12]. In our study, the elevated WBC count was statistically positively correlated with NLR values (*P* = 0.002). This was consistent with the results of Xue et al. [6].

Also, we found a highly significant positive association between NLR and ANC (*P* value <0.001), and this matched with the results of Xue et al. [6].

In our study, we found a highly significant negative association between NLR and ALC (*P* value <0.001), and this was consistent with the results of Kim et al. [17]. This result did not match with Kim et al. [18] who stated that lymphocytes were the sources of proinflammatory cytokines and cytotoxic substances and had a main negative contribution to ischemic brain.

Table 4 Diagnostic performance of neutrophil/lymphocyte ratio in the prediction of unfavorable outcomes

Variables	NLR
Cutoff point	More than 3.7
Sensitivity	77.8%
Specificity	87.5%
Accuracy	81.7%
Positive predictive value	90.3%
Negative predictive value	72.4%
Likelihood ratio positive	6.2
Likelihood ratio negative	0.25
Area under curve	0.89 (0.82–1.0)
***P* value**	**<0.001****

NLR neutrophil/lymphocyte ratio
**Highly significant

The most independent factors of unfavorable outcomes of ischemic stroke in our study were higher NIHSS, higher WBC count, higher NLR, and higher CRP.

Conclusion

The higher the biomarkers (total WBCs, NLR, and the level of CRP) at the onset of AIS, the poorer the short-term outcomes are expected.

Recommendations

We recommend using inflammatory blood biomarkers such as total WBC count, NLR values, and CRP values in predicting the short-term outcomes of acute ischemic stroke patients. These are easy methods in the prediction of short-term outcomes of AIS. Further studies should be done to evaluate the impact of these biomarkers on predicting the long-term outcomes in patients with acute ischemic stroke; also, other inflammatory biomarkers can be included in future studies such as several pro-inflammatory cytokines, especially interleukin-6, D-dimer, B-natriuretic peptide, matrix metallopeptidase-9 caspase-3, sRAGE, chimerin II, and secretagogin.

Abbreviations

AIS: Acute ischemic stroke; NLR: Neutrophil/lymphocyte ratio; CRP: C-reactive protein; WBC: White blood cell count; ANC: Absolute neutrophil count; ALC: Absolute lymphocyte count; GCS: Glasgow Coma Scale; NIHSS: National Institute of Health Stroke Scale; mRS: Modified Rankin Scale; IRB: Institutional Research Board; CT: Computed tomography; MRI: Magnetic resonance imaging; SPSS: Statistical Package for the Social Science; MW: Mann-Whitney test; KW: Kruskal-Wallis *H*; ROC: Receiver operating characteristic; sRAGE: Soluble receptor for advanced glycation end products

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Authors' contributions

YA, RN, PM, and AB carried out the work. YA designed the study, coordinated with the research team, and wrote the manuscript. YA and PM recruited the patients and gathered the clinical data. AB statistically analyzed and reviewed the manuscript. All authors were involved in writing the article or critically revising it for relevant intellectual material, and the final version to be published was accepted by all authors.

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Availability of data and materials
The data supporting the results of this article are included within the article.

Declarations

Ethics approval and consent to participate
The study was approved by the institutional ethics committee of the Faculty of Medicine, Zagazig University (number 4973, November 2018). Written consent was taken from all of the participants after explaining the details, benefits, and risks to them.

Consent for publication
Consent for publication has been obtained from the participants involved in the study to report their individual patient data.

Competing interests
The authors declare that they have no competing interests.

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