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Research Paper

Systemic Inflammation Biomarkers Ratio as Predictors of Clinical Outcomes in Ischemic Stroke

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ABSTRACT

Background: Strokes are among the major causes of disabilities worldwide. In recent years, there has been considerable interest in evaluating stroke prognoses.

Objectives: In this investigation, we studied the association of lymphocyte-monocyte ratio (LMR), neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and ESR-CRP ratio (ECR) with 3 months outcomes among those with acute ischemic stroke (AIS).

Materials & Methods: We carried out the present cross-sectional investigation among AIS patients at an academic hospital in northern Iran (from 2019 to 2021). Within 24 hours after the onset of symptoms, laboratory and clinical data of the patients were obtained. We assessed the results using the modified rankin scale (mRS) 90 days after the initial assessment. Statistical significance for comparing descriptive data was determined as $P<0.05$.

Results: We entered 341 participants (Mean±SD age: 69.10±13.55 years, 53.1% female) into this investigation. Based on univariate analysis, there were poor correlations between NLR ($r=0.361$, $P<0.001$), PLR ($r=0.215$, $P<0.05$), CRP ($r=0.234$, $P<0.001$), LMR ($r=-0.184$, $P<0.05$), and ECR ($r=-0.191$, $P<0.05$) and a 3-month mRS. Also, after three months, the NLR, PLR, and CRP values were higher in the patients who died, but the LMR ($P<0.001$) and ECR ($P<0.05$) were lower. In multivariate comparison, only ECR was independently higher among the participants who died within 3 months ($P<0.05$).

Conclusion: In this study, ECR within 24 hours of symptoms onset was related to functional outcomes and mortality at 3-month follow-up. Thus, ECR might provide valuable prognostic information at a relatively low cost.

Keywords: Ischemic stroke, Patient outcomes assessment, Leukocyte counts, C-reactive protein, Blood sedimentation

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Highlights

• Early prediction of stroke outcomes is beneficial and can assist clinicians in ensuring effective stroke treatment and functional recovery when stroke patients are admitted to the hospital.

• Laboratory findings determine the prognosis of acute ischemic stroke.

• Neutrophil-lymphocyte ratio, platelet-lymphocyte ratio, C-reactive protein (CRP), lower lymphocyte-monocyte ratio, and erythrocyte sedimentation rate (ESR)-CRP ratio indicate poorer outcomes based on a 3-month modified rankin scale.

• Neutrophil-lymphocyte ratio, platelet-lymphocyte ratio, and C-reactive protein were higher among those who died within 3 months compared to survivors, but lymphocyte-monocyte ratio and ESR-CRP ratio were lower in those who died.

Introduction

Strokes are the world's second most common mortality cause and the third most common disability-causing condition [1]. Early prediction of stroke outcomes could benefit patients and can assist clinicians in ensuring effective stroke treatment and functional recovery when individuals with stroke receive hospitalization. In this regard, researchers have studied biomarkers that can predict stroke treatment response and outcome. They can vary significantly from patient to patient. Several factors affect the prognosis of stroke, including stroke type, patient age, and stroke severity [2–4]. Some studies suggest laboratory findings are prognostic factors in acute ischemic stroke (AIS) [5, 6].

An important pathophysiologic feature of AIS is inflammation [7]. A wealth of evidence suggests that immune system components play a crucial role by initiating and propagating ischemic neurological damage to the brain. The development of the immunosuppressive response to brain ischemia could lead to concurrent infectious diseases [8]. Lymphocyte-monocyte ratio (LMR) and neutrophil-lymphocyte ratio (NLR) have been reported as potential biomarkers of baseline inflammation and AIS morbidity and mortality [9–11]. However, the platelet-lymphocyte ratio (PLR) offers significantly better prognostic value than single platelet counts in stroke. It is an inexpensive, readily accessible, and comprehensive marker of inflammatory processes. PLR offers primarily two main potential benefits: 1) An integrated measure that provides supplementary data in addition to current measures and 2) More consistency compared to individual blood parameters, which are susceptible to variation due to dehydration, excessive hydration, and the condition of the blood samples [12]. The C-reactive protein (CRP), an acute-phase protein, is the most widely used marker of inflammation in peripheral blood [13]. A higher level of CRP in the blood is also independently associated with a greater risk of future vascular events or mortality [14]. We found that few studies examined the association of AIS prognosis and mortality with NLR, PLR, LMR, erythrocyte sedimentation rate (ESR), CRP, and ESR-CRP ratio (ECR) variables. Accordingly, this investigation aimed to determine the potential associations of NLR, PLR, LMR, and ECR levels with the AIS prognosis (defined as mRS score) and mortality within 3 months after stroke.

Materials and Methods

We conducted the present cross-sectional investigation at an academic hospital in northern Iran. This study included 614 AIS patients admitted between September 2019 and June 2021 for analysis. This study was conducted using subjects who met with all (2) these conditions: 1) Adults (over the age of 18), 2) Documented clinical diagnosis of AIS. The exclusion criteria constituted 1) Those with terminal cancers, hematological disorders, recently undergoing major injuries or surgeries, and severe liver, other neurological, or renal diseases based on clinical history and laboratory findings; 2) Those taking immunosuppressive medications; 3) History of active infectious diseases within two weeks before admission, myocardial infarction within 4 weeks before admission; 4) Usage of steroid, anti-platelet or anti-coagulant; 5) Patients suspected of having COVID-19 based on the findings of blood sample tests (leukocytosis, lymphopenia and elevated CRP or chest CT scans; 6) Individuals who reported symptoms of COVID-19 subjectively at any stage of the study.

Information obtained from clinical documentation included age, gender, predisposing diseases, duration of hospitalization, smoking, and rehabilitation after stroke (10 sessions or more). After applying the inclusion-exclusion criteria, 241 individuals were not eligible for inclusion. Moreover, 32 participants did not follow up with the research team 3 months after their acute ischemic stroke.

Demographic characteristics such as age, sex, duration of hospitalization, and baseline vascular risk factors (smoking, diabetes mellitus, dyslipidemia, hypertension, previous strokes, atrial fibrillation, and coronary artery diseases) were obtained using the institution's databases. Laboratory testing of the blood samples was performed no later than 24 hours from the onset of symptoms. Laboratory and imaging data were collected using an automated testing method. Laboratory findings included a total blood count with white blood cell differentials, urea and electrolytes, hepatic function assessments, and ESR and CRP checked on admission.

A neurology specialist and 3 medical students assessed the outcomes with the modified rankin scale (mRS) [15] following 90 days after the initial assessment.

Statistical analysis

Data analysis was conducted using descriptive statistics such as percentage, frequency, and Mean±SD. We performed the Kolmogorov-Smirnov test to assess the normality of the results and applied Levene's test for variance homogeneity. We utilized the Spearman's rank correlation coefficient for determining the associations of NLR, LMR, PLR, ESR, CRP, and ECR with 3-month clinical outcomes. The Mann-Whitney U test was used to compare means between alive and dead patients. Linear or ordinal regression analyses were conducted to examine the interplay among multiple independent factors on outcomes. We ran the analysis using statistics of IBM SPSS software, version 26 at a significance level of $P<0.05$.

Results

Three hundred and forty-one subjects were included in the study, and their information was analyzed. As shown in Table 1, the sample population consists of the following general characteristics and laboratory results.

The correlation of NLR, LMR, PLR, ESR, CRP, and ECR levels with 3-month mRS

The univariate analysis shows that higher NLR, RLR, and CRP and lower LMR and ECR indicate poorer outcomes based on the 3-month mRS (Table 2).

Although a significant correlation exists between NLR, RLR, CRP, LMR, and ECR with 3-month mRS, the fact that r values are less than 0.4 suggests the study variables lack a strong correlation. After adjusting for age, gender, mRS upon hospital discharge, smoking, duration of hospitalization, stroke rehabilitation, and underlying diseases, no significant relationship was found between NLR, LMR PLR, CPR, ECR, and 3-month mRS (Table 3).

The correlations of NLR, LMR, PLR, ESR, CRP, and ECR levels with 3 months mortality in AIS patients

The three-month follow-up showed that 128 stroke patients (46.2%) had died, while 149 patients (53.8%) survived (Table 4).

Patients who died had a higher age compared to those who survived. There were no significant differences in other variables among participants. The univariate analysis showed that NLR, PLR, and CRP were higher among those who lost their lives within three months than the survivors. However, LMR and ECR were lower in those who died. In multivariate analysis, ECR remained independently associated with 3 months mortality ($P<0.05$), but NLR, LMR, PLR, ESR, and CRP were not associated with 3 months mortality (Table 5).

Discussion

Our investigation evaluated the clinical significance of LMR, PLR, NLR, ESR, CRP, and ECR in predicting 3-month functional outcomes and mortality after acute ischemic stroke. Based on the univariate analysis, NLR, PLR, and CRP were higher among those who lost their lives within 3 months than the survivors, but LMR and ECR were lower in those who died. In multivariate analysis, ECR remained independently associated with the 3-month mortality rate, but the relationship between other variables and mortality was not significant. The present research findings show a weak relationship exists between NLR, PLR, CRP, LMR, and ECR with the 3-month mRS. Monocytes, lymphocytes, platelets, and neutrophils may have distinct roles in inflammatory processes and the development of different diseases. When

Table 1. General characteristics of the study population (n=341)

Classification of Variables	Characteristic	Mean±SD/No. (%)
Demographic characteristics	Age (y)	69.10±13.55
	Female sex	181(53.3)
	Duration of hospitalization (d)	5.69±4.99
Underlying disease	Hypertension	178(52.1)
	Atrial fibrillation	6(1.7)
	Diabetic mellitus	53(15.5)
	Dyslipidemia	15(4.3)
	Cardiovascular disease	4(1.1)
Rehabilitation after stroke	Yes	96(28.2)
Current smoker	Yes	99(29.6)
Laboratory data	White blood cell (n/mmc)	9658.1±3543.8
	Neutrophil (n/mmc)	73.13±11.173
	Lymphocyte (n/mmc)	23.1±11.41
	Monocyte (n/mmc)	1.82±0.8
	Eosinophil (n/mmc)	2.02±2.004
	Platelet (n/mmc)	215254.8±76520.331
	ESR (mg/dL)	41.33±28.98
	CRP (mg/dL)	25.03±33.52
	AST (U/L)	32.64±32.09
	ALT (U/L)	64.52±28.02
	ALP (U/L)	219.48±100.72
	BUN (mg/dL)	12.3±2.7
	Cr (mg/dL)	1.03±0.62

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Abbreviations: ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; AST: Aspartate transaminase; ALT: Alanine transaminase; ALP: Alkaline phosphatase; BUN: Blood urea nitrogen; Cr: Creatinine.

AIS occurs, platelets do not function normally [16], leading to overactivation and accumulation of platelets and causing clots and blockage of blood vessels [17]. It has been shown that high neutrophil counts confer an adverse prognosis on cardiovascular patients, whereas high lymphocyte counts confer a protective effect [18, 19]. In acute ischemic events, stress activates the hypothalamic-pituitary-adrenal system.

Consequently, a greater level of cortisol release results in a decreased level of lymphocytes [20]. Considering these factors separately may miss their interactions and associations with different medical conditions, yet exploring them together may not shed any light on the opposing roles they seem to have. Therefore, dynamic measurements of NLR, MLR, and PLR may serve as a more accurate outcome measurement than single measurements.

Table 2. Simple correlation of the NLR, LMR, PLR, ESR, CRP, and ECR levels with the 3-month clinical outcome

Variables	r	Sig.
NLR	0.361	<0.001
LMR	-0.184	<0.001
PLR	0.215	<0.05
ESR	0.044	0.468
CRP	0.234	<0.001
ECR	-0.191	<0.05

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Abbreviations: ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; NLR: Neutrophil-lymphocyte ratio; LMR: Lymphocyte-monocyte ratio; PLR: Platelet-lymphocyte ratio.

Firstly, our data indicated high NLR was associated with unfavorable 3-month functional outcomes and death. In previous studies, higher NLR was associated with poor functional outcomes at discharge from the hospital during the first 3 days of the stroke occurrence [21]. Also, studies have shown that increased NLR among those with acute myocardial infarction reliably predicted death and morbidity during hospitalization [22], along with inefficient heart perfusion following percutaneous coronary angioplasty [23]. In another study, a high admission NLR is associated with independent prediction of func-

Table 3. Multivariate analysis of the correlation between the NLR, LMR, PLR, ESR, CRP, and ECR levels and 3-month clinical outcome

Variables	Std. Error	Sig.	Odds Ratio	95% Confidence Interval	
				Lower Bound	Upper Bound
Age (y)	0.013	<0.05	1.036	0.005	0.050
Sex	0.304	0.524	1.850	-0.385	0.762
Duration of hospitalization	0.035	0.425	0.981	-0.024	0.110
Underlying disease	0.295	0.294	1.526	-0.339	0.767
Rehabilitation after stroke	0.290	<0.001	0.592	-2.102	-0.932
Current smoking	0.386	0.640	0.982	-0.634	0.819
mRS of discharge time from the hospital	0.143	<0.001	5.454	1.409	1.954
NLR	0.055	0.791	0.697	-0.339	0.056
LMR	0.015	0.451	0.999	-0.048	0.015
PLR	$2.066E^{-5}$	0.582	1.000	$-2.540E^{-5}$	0.000
ESR	0.006	0.849	0.993	-0.018	0.007
CRP	0.006	0.926	1.001	-0.010	0.012
ECR	0.033	0.147	0.957	-0.073	0.046

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Abbreviations: ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; NLR: Neutrophil-lymphocyte ratio; LMR: Lymphocyte-monocyte ratio; PLR: Platelet-lymphocyte ratio; mRS: Modified rankin scale.

Table 4. Comparing the means of the NLR, LMR, PLR, ESR, CRP, and ECR between dead and survived patients with AIS

Variables	Mean±SD		Sig.
	Dead Patients	Survived Patients	
NLR	5.68±4.4	3.3±2.2	<0.001
LMR	11.9±4.4	17.1±10.6	<0.001
PLR	15182.2±13869.7	10007.1±6473.6	<0.001
ESR	42.71±28.439	40.16±29.482	0.286
CRP	35.48±30.34	31.10±20.41	<0.001
ECR	4.17±3.55	6.80±5.67	<0.05

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Abbreviations: ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; NLR: Neutrophil-lymphocyte ratio; LMR: Lymphocyte-monocyte ratio; PLR: Platelet-lymphocyte ratio.

tion, recanalization, and treatment with IV rtPA (recombinant tissue plasminogen activator) after AIS [11].

In addition, our data indicated that elevated levels of PLR significantly predicted poor outcomes in terms of function and mortality within 3 months. PLR might play a role in determining the outcome of acute ischemic strokes. It has been shown that platelets and lymphocytes determine the outcome of ischemic vascular diseases, such as myocardial infarction and cerebral infarction [24–27]. PLR data may offer useful information about ischemic events. There have been several studies examining this perspective. In individuals with acute myocardial infarction, PLR was an independent

Table 5. Multivariate analysis of correlations of 3 months mortality in AIS patients

Variables	Std. Error	Sig.	Odds Ratio	Lower Bound	Upper Bound
Age (y)	0.001	0.004	0.923	-0.007	-0.001
Sex	0.037	0.595	0.723	-0.093	0.053
Duration of hospitalization	0.004	0.220	0.929	-0.012	0.003
Underlying disease	0.036	0.158	0.877	-0.120	0.020
Rehabilitation after stroke	0.041	0.000	0.165	0.316	0.480
Current smoking	0.042	0.031	0.318	-0.173	-0.008
mRS of discharge time from the hospital	0.012	0.000	0.195	-0.185	-0.136
NLR	0.011	0.488	1.243	-0.014	0.029
LMR	0.002	0.060	1.100	0.000	0.008
PLR	0.000	0.321	1.000	0.000	0.000
ECR	0.007	0.010	1.015	-0.007	0.009
ESR	0.001	0.387	1.008	-0.001	0.002
CRP	0.001	0.793	0.999	-0.001	0.002

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Abbreviations: ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; NLR: Neutrophil-lymphocyte ratio; LMR: Lymphocyte-monocyte ratio; PLR: Platelet-lymphocyte ratio; mRS: Modified rankin scale.

predictor of mortality and incidence of major adverse cardiovascular events in [28] hospital and long-term [29, 30]. A high PLR level was observed in unstable angina pectoris sufferers having impaired coronary collateral circulation [31]. Gary et al. [32] also identified a significant association between elevated PLR and increased chances of severe limb ischemia in critically ill patients. This association may be useful in identifying patients with an increased risk of vascular complications. Studies of cerebrovascular diseases have shown that a higher PLR is associated with stroke [33]. Another study used A high PLR value as an indirect measure of stroke patients' infarcted area and a relatively low recanalization rate following thrombectomy treatment [34].

Our data indicated low LMR levels were associated with unfavorable 3-month functional outcomes and death. According to the reports, LMR is linked to poor outcomes in various cancers [35, 36] and coronary artery disease [37, 38]. Similarly, in a study, lymphocyte and monocyte counts were measured before and 24 hours following mechanical thrombectomy in AIS patients. In that study, a lower LMR 24 hours after mechanical thrombectomy significantly predicted impaired functional prognosis. However, admission LMR was not significant as a predictor of 3-month mRS [8].

Two possible explanations support the association between plasma CRP after an ischemic stroke and clinical outcomes. The first scenario involves worsening clinical outcomes after cerebral infarction caused by CRP. However, if CRP serves a beneficial rather than a harmful function by eliminating necrotic and apoptotic cells [39], plasma CRP may increase to counteract an exacerbating factor. For example, a recent study showed that the administration of pure human CRP to healthy adult volunteers showed no proinflammatory effects [40]. Further, CRP-deficient mice do not offer a reduced risk of atherosclerosis, debunking the concept that CRP might contribute to atherosclerosis [41]. There is a need for further studies to investigate plasma CRP's pathophysiological role in acute ischemic stroke. As a result of this investigation, those with acute ischemic stroke who died or had an unfavorable outcome had higher CRP levels and lower ECR. A published prospective case-control investigation demonstrated that increased CRP upon hospitalization independently predicted functional prognosis one month after an acute ischemic stroke [42]. Similarly, in a study, higher serum CRP levels were significantly associated with unfavorable outcomes after AIS [14].

Conclusion

In this study, ECR within 24 hours of symptoms onset was related to functional outcomes and mortality at 3-month follow-up, suggesting ECR as a cost-effective and useful prognostic indicator.

Study limitations

The current study's main limitation was the COVID-19 outbreak, which eliminated many patients suspected of being infected. At the same time, it was impossible to state whether they were infected. Also, in our study, one limitation was that we did not know exactly when the blood samples were collected, even if they were collected within 24 hours. Thus, the time elapsed from stroke onset could not be adjusted. It is also necessary to further investigate the effect of other inflammatory cytokines, such as interleukin (IL)-8, IL-6, IL-4, and IL-1 on long-term outcomes in AIS.

Stroke severity is one of the main determinants of mortality and poor prognosis, which should have been included as a confounding variable, or the study was conducted in patients with a more limited range of stroke severity. However, it was not possible because of the limited number of samples.

Ethical Considerations

Compliance with ethical guidelines

All study procedures were in compliance with the ethical guidelines of the Declaration of Helsinki 2013. The study protocol was approved by the Ethics Committee of Guilan University of Medical Sciences (Code: IR.GUMS.REC.1398.506).

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Authors contributions

Conceptualization and study design: Arman Keymoradzadeh and Alia Saberi; Data acquisition: Parastoo Mohammadi, Amirhossein Roshan, and Alia Saberi; Statistical analysis: Arman Keymoradzadeh; Data interpretation: Alia Saberi, Arman Keymoradzadeh, Amirhossein Roshan, and Parastoo Mohammadi; Writing–original draft: Alia Saberi, Arash Bakhshi, and Arman Keymoradzadeh; Data analysis, writing the original draft, review, editing, and final approval: All authors.

Conflict of interest

The authors declared no conflict of interest.

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