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Inflammatory markers and functional outcome score in different subgroups of ischaemic stroke: a prospective cohort study

Mohammad Sadegh Fakhari ,[1] Leila Poorsaadat,[2] Amir Almasi-Hashiani,[3] Mohsen Ebrahimi-Monfared[2]

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[1]Student Research Committee, Arak University of Medical Sciences, Arak, Iran (the Islamic Republic of)
[2]Department of Neurology, Arak University of Medical Sciences, Arak, Iran (the Islamic Republic of)
[3]Department of Epidemiology, Arak University of Medical Sciences, Arak, Iran (the Islamic Republic of)

Correspondence to
Dr Leila Poorsaadat;
leilamd@yahoo.com

ABSTRACT

Background Acute ischaemic stroke (AIS) is a leading cause of disability and mortality worldwide. Determining subgroups and outcomes of AIS may lead to better treatment. We aimed to investigate the relationship between inflammatory markers and subgroups of AIS with further follow-up of patients in terms of functional outcome score.

Methods In this prospective cohort study, we examined white cell count (WCC), neutrophil count, lymphocyte count, neutrophil-to-lymphocyte ratio (NLR), erythrocyte sedimentation rate (ESR) and qualitative C reactive protein (CRP), in the first 24 hours of patients' admission. Patients were assigned to AIS subgroups as defined by the TOAST criteria. Then patients' disability score was followed up after 3 and 6 months, using the modified Rankin Scale.

Results We included 217 patients with AIS. The mean age of participants was 72.07 years, and we included 92 women (42.4%). For the AIS subgroup, 83 (38.25%) patients had large artery atherosclerosis (LAA), 41 (18.89%) had cardioembolism and 62 (28.57) had small vessel obstruction. Neutrophil count and NLR showed a statistically significant difference in the subgroups of AIS and were highest in the 'other' subgroup of AIS ($p<0.05$). Lymphocyte count, ESR and qualitative CRP showed no statistically significant difference between subgroups ($p>0.05$). WCC, neutrophil count and NLR showed a positive correlation with functional outcomes ($p<0.05$), other markers did not correlate with outcomes ($pp>0.05$).

Conclusion We can conclude that neutrophil count and NLR are available inflammatory biomarkers for predicting outcomes and these two biomarkers are associated with AIS subgroups. However, ESR, qualitative CRP and lymphocyte count do not appear to be correlated with outcomes or subgroup of AIS.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ There might be an association between neutrophil-to-lymphocyte ratio and poor neurological outcomes.

WHAT THIS STUDY ADDS

⇒ Neutrophil-to-lymphocyte ratio not only could predict the outcome of acute ischaemic stroke but also associates with the aetiology of the disease.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Neutrophil-to-lymphocyte ratio is a low-cost, readily available inflammatory marker to predict outcome of acute ischaemic stroke in practice, However, further studies are required to assure this association.

INTRODUCTION

Stroke is a leading cause of mortality and disability worldwide, with acute ischaemic stroke (AIS) accounting for 82% of all strokes.[1] AIS is the leading cause of long-term disability to date.

The prognosis and outcome of AIS depend on the particular subgroup, and clinical guidelines recommend specific treatments for each subgroup.[2] Several studies have identified specific characteristics according to AIS subgroup. For example, some studies have emphasised the role of specific inflammatory biomarkers.[3 4] These studies have found higher levels of these markers in specific subgroups.

While brain tissue was previously thought to be immune to systemic inflammatory responses, recent studies have highlighted inflammation as an important pathophysiological factor.[5] More recently, studies have focused on the effects of acute systemic inflammatory responses at AIS on the outcomes of thrombolytic therapy.[6] This highlights the importance of investigating the role of inflammatory markers at AIS. Previous studies have reported an association between poor neurological outcomes and higher white cell count (WCC) and neutrophil-to-lymphocyte ratios (NLR),[7 8] but there is little research in this regard.

Therefore, we aimed to investigate the association between specific inflammatory

markers and AIS subgroups with further follow-up of the functional outcome score.

METHODS AND MATERIALS

Study design and population

In this prospective cohort study, we followed patients enrolled in a population-based stroke registry at Arak University of Medical Sciences. This registry, established in 2019, collects various data on patients diagnosed with stroke in Arak, Iran. Given the high prevalence of stroke, nearly 400 patients diagnosed with stroke are fully enrolled in this registry programme each year. Because this is a prospective study, we collected data from patients who met our inclusion criteria from October 2020 to March 2022.

The inclusion criteria were as follows: (1) Patients were hospitalised with a confirmed diagnosis of AIS by a neurologist (LP or ME-M) and according to WHO criteria[9] and (2) Brain CT scan excluded new cerebral haemorrhage. Exclusion criteria were as follows: (1) any chronic disease related to inflammatory markers (severe renal or liver failure, autoimmune diseases, cancer, rheumatic diseases, haematological diseases, etc); (2) any acute disease related to inflammatory markers (severe trauma, surgery or any type of infection within 2 weeks before the onset of disease, especially COVID-19) and (3) congenital absence of middle cerebral artery (MCA) or internal carotid artery.

Clinical and biochemical assessments

Demographic data such as age and gender were obtained from medical records. All patients underwent a complete questionnaire designed by the authors regarding their previous illnesses, hospitalisations, trauma, medical history and allergic history, as well as complete examinations including complete blood count, erythrocyte sedimentation rate (ESR), qualitative C reactive protein (CRP), brain CT scan, brain MRI, 12-lead ECG, echocardiography and carotid Doppler ultrasound.

AIS subgroups were classified according to the Trial of Org 10172 in Acute Stroke Treatment(TOAST) classification, which was previously defined and divided AIS into five groups: (1) large artery disease, (2) cardioembolism (CE), (3) small vessel obstruction (SVO), (4) stroke of undetermined aetiology and (5) stroke of other determined aetiology.[10] Patients were categorised as having 'undetermined aetiology' if either more than one cause was associated with their condition or all evaluations failed or were incomplete. We also recorded data on the vascular territory of the ischaemic lesions, which were confirmed by a neurologist (LP or ME-M) after a review of the MRI results. The basis for determining the lesion territory in our study was provided by previous methods of Tatu *et al*,[11 12] which have been used recently in several studies.[13]

Blood biomarkers were only assessed within the first 8 hours after admission. Our laboratory variables were complete blood count, ESR and CRP. Blood counts included WCC, neutrophil count, lymphocyte count and NLR.

Follow-up of outcome

To evaluate the outcome of AIS, we used the modified Rankin Scale (mRS). Initially, patients' disability was assessed as an early outcome of AIS in the emergency department. Given that most AIS patients were older adults with potential comorbidities causing disability, we also recorded their mRS scores prior to admission. By comparing admission mRS scores to prehospital mRS scores, we were able to determine the early disability score of patients specifically caused by the acute event, that is, AIS. Subsequently, the late functional outcomes of patients were followed at 3 and 6 months. To obtain preadmission mRS scores, we interviewed either the patients or their roommates about their previous functional status. To assess the mRS score at 3 and 6 months, we used a simplified mRS questionnaire administered via telephone.[14]

Blinding

To prevent any bias, data collection was done as follows. The diagnosis of AIS subgroup was determined by a neurologist (LP or ME-M), inflammatory biomarkers were documented by the experienced staff of the registry of stroke in certain papers, and follow-up was done by a trained medical intern (MSF) either in-person or by telephone. In the end, our data analyst (AA-H) gathered the final data with patients' IDs and analysed them. In this way, data collection was blinded.

Statistical analysis

Shapiro-Wilk test was used to test normality. Descriptive indices (mean and SD) were used to describe quantitative variables and count and percent were used to describe qualitative variables. Likelihood ratio χ^2 test, one-way and repeated measure analysis of variance (ANOVA), and correlation analysis was utilised to analyse data. Data analysis was performed using Stata statistical software V.13 (StataCorp) at a significance level of 0.05.

RESULTS

Demographic and clinical data

A total number of 217 patients from our population met the inclusion criteria. The baseline characteristics of the patients are shown in table 1. The mean age of the patients with AIS was 72.07 years and most of the patients were men. Table 1 also demonstrates results from inflammatory markers, cardiac assessment (including ECG and echocardiography), carotid Doppler ultrasound, length of hospital stay, history of stroke, AIS subgroup and territory of infarction. The most common subgroup in our population was LAA, followed by SVO and CE, and the most frequent territory of infarct was the MCA which accounts for almost half of the patients in this population. AIS

Table 1 Baseline characteristics of all patients (n=217)

Demographic	
Age, years, mean±SD (95% CI)	72.07±12.67 (70.38 to 73.76)
Gender, female, n (%)	92 (42.4)
Echocardiography	
EF, mean±SD (95% CI)	45.41±0.56 (44.31 to 46.52)
CVD, n (%)	85 (39.17)
ECG rhythm	
Sinus	169 (77.87)
AF	40 (18.43)
Other arrhythmia	8 (3.7)
Carotid Doppler ultrasound	
Carotid plaque, n (%)	128 (58.99)
Carotid stenosis, n (%)	27 (12.44)
Lab data	
WCC, mean±SD, $x10^9$/L (95% CI)	8.023±2.088 (7.65 to 8.40)
Neutrophil count, mean±SD, $x10^9$/L (95% CI)	5.540±2.615 (5.19 to 5.89)
Lymphocyte count, mean±SD, $x10^9$/L (95% CI)	1.838±0.843 (1.73 to 1.95)
NLR, mean±SD (95% CI)	3.87±3.30 (0.22 to 3.43)
ESR, mean (SD) (95% CI)	21.73±16.60 (19.51 to 23.95)
CRP, n (%)	
0	108 (49.77)
1+	47 (21.66)
2+	40 (18.43)
3+	22 (10.14)
AIS characteristics	
History of AIS, n (%)	37 (17.05)
LOHS, mean±SD (95% CI)	5.11±0.24 (4.63 to 5.58)
AIS subgroup	
LAA, n (%)	83 (38.25)
CE, n (%)	41 (18.89)
SVO, n (%)	62 (28.57)
Other known aetiologies, n (%)	16 (7.37)
Undetermined, n (%)	15 (6.91)
Vascular territory	
ACA, n (%)	11 (5.07)
MCA, n (%)	99 (45.62)
PCA, n (%)	17 (7.83)
ICA, n (%)	7 (3.23)
VA, n (%)	7 (3.23)
BA, n (%)	8 (3.69)
SCA, n (%)	18 (8.29)
AICA, n (%)	18 (8.29)
PICA, n (%)	7 (3.23)
Border zone, n (%)	16 (7.37)
Multiple territories, n (%)	25 (11.52)
Outcome	
Admission mRS, mean±SD (95% CI)	2.66±0.92 (2.48 to 2.84)

Continued

Table 1 Continued

3 months mRS, mean±SD (95% CI)	2.46±0.13 (2.19 to 2.72)
6 months mRS, mean±SD (95% CI)	2.70±0.15 (2.41 to 2.99)
6 months mortality, n (%)	36 (16.59)

ACA, anterior cerebral artery; AF, atrial fibrillation; AICA, anterior inferior cerebellar artery; AIS, acute ischaemic stroke; BA, basilar artery; CE, cardioembolism; CRP, C reactive protein; CVD, cardiac valve dysfunction; EF, ejection fraction; ESR, erythrocyte sedimentation rate; ICA, internal carotid artery; LAA, large artery atherosclerosis; LOHS, length of hospital stay; MCA, middle cerebral artery; mRS, modified Rankin Scale; NLR, neutrophil-to-lymphocyte ratio; PCA, posterior cerebral artery; PICA, posterior inferior cerebellar artery; SCA, superior cerebellar artery; SVO, small vessel occlusion; VA, vertebral artery; WCC, white cell count.

territories were not distributed evenly in all subgroups. Most patients with multiple infarction territories were in the CE stroke subgroups. AIS in MCA territory was most common in LAA (47.4%), and SVO (25.25%) subgroups, respectively.

Inflammatory markers and AIS subgroups

We analysed levels of different inflammatory markers in different AIS subtypes and the results are demonstrated in table 2. Among all markers evaluated in this study, only neutrophil count and NLR measures in different subgroups were found to be statistically significant ($p<0.05$). Levels of both of these markers were highest in 'other aetiologies' and CE subgroups, respectively, and lowest in SVO. Levels of WCC count favour a statistically significant difference. Neither ESR nor CRP levels in different subgroups of AIS showed a statistically significant difference.

Inflammatory markers and outcome

Assessment of the correlation between inflammatory markers and outcome measures is demonstrated in table 3. These results show that the correlation between WCC, neutrophil count and NLR and all outcome measures in this study are statistically significantly correlated. However, neither lymphocyte count nor ESR showed a statistically significant correlation. The trend of the mean outcome measures in different results of qualitative CRP is shown in figure 1. The graph shows that with CRP levels of 2+ and 3+, mean outcome measures are worse, both at admission and after a 6-month follow-up.

AIS subgroups and outcome

The evaluation of outcome scores according to different AIS subgroups is shown in table 4. As it can be concluded from the table, only admission outcome scores are statistically significant differences between AIS subgroups. Outcome measures are highest in other aetiologies, and LAA subgroups and lowest in SVO. The trend of outcomes among different AIS subgroups is depicted in figure 2. Outcome results in SVO are lowest both at the beginning and after a 6-month follow-up. LAA and other aetiologies show the worst scores on admission, though they act the same in the follow-up and have a better recovery in the first 3 months after AIS.

Table 2 Levels of different inflammatory markers in AIS subgroups according to TOAST

	AIS subgroups					
Inflammatory marker	**LAA (n=83)**	**CE (n=41)**	**SVO (n=62)**	**Other (n=16)**	**Undetermined (n=15)**	**P value**
WCC, mean±SD, $x10^9$/L	8.11±2.67	8.83±2.70	7.75±2.42	9.84±4.33	7.23±2.93	0.067
Neutrophil count, mean±SD, $x10^9$/L	5.61±2.55	5.48±2.62	5.14±2.10	7.58±4.09	4.79±2.16	0.013
Lymphocyte count, mean±SD, $x10^9$/L	1.87±0.89	1.68±0.79	1.95±0.78	1.73±0.82	1.79±1.05	0.575
NLR, mean±SD	3.94±3.04	4.17±3.51	3.11±1.74	6.22±7.10	3.29±1.38	0.014
ESR, mean±SD	19.63±15.03	22.49±18.17	24.03±17.05	24.50±20.58	18.87±14.09	0.481
CRP, n (percentage in each subgroup)						
0	40 (48.19)	17 (41.46)	36 (58.06)	7 (43.75)	8 (53.33)	0.569
1+	16 (19.28)	10 (24.39)	14 (22.58)	3 (18.75)	4 (26.67)	
2+	17 (20.48)	9 (21.95)	10 (16.13)	2 (12.50)	2 (13.33)	
3+	10 (12.05)	5 (12.20)	2 (3.21)	4 (25.00)	1 (6.67)	

AIS, acute ischaemic stroke; CE, cardioembolism; CRP, C reactive protein; ESR, erythrocyte sedimentation rate; LAA, large artery atherosclerosis; NLR, neutrophil-to-lymphocyte ratio; SVO, small vessel occlusion; TOAST, the Trial of Org 10172 in Acute Stroke Treatment; WCC, white cell count.

Table 3 Correlation between different inflammatory markers and outcome measures

Outcome	WCC count	Neutrophil count	Lymphocyte count	NLR	ESR
Prehospital to admission mRS difference					
Correlation Coefficient	0.188	0.232	−0.068	0.267	0.676
P value	0.005	0.001	0.321	0.000	0.322
Admission mRS					
Correlation Coefficient	0.212	0.250	−0.074	0.277	0.046
P value	0.002	0.000	0.281	0.000	0.502
3 months mRS					
Correlation coefficient	0.207	0.275	−0.167	0.359	0.439
P value	0.002	0.00	0.012	0.000	0.520
6 months mRS					
Correlation coefficient	0.164	0.217	−0.148	0.305	0.044
P value	0.016	0.013	0.030	0.000	0.520

ESR, erythrocyte sedimentation rate; mRS, modified Rankin Scale; NLR, neutrophil-to-lymphocyte ratio; WCC, white cell count.

DISCUSSION

Main findings

We investigated the relationship between certain inflammatory markers and AIS subgroups and observed that only neutrophil count and NLR could be viable options. However, other markers could not keep pace. Also, we assessed inflammatory markers on admission, to see if they could predict functional outcome results, nonetheless, only WCC, neutrophil count and NLR could predict the outcome results. Furthermore, exploring the relationship between AIS subgroups and functional outcome scores, we noticed that AIS subgroups are only linked with outcome scores on admission.

Inflammatory markers versus outcome of AIS

The role of systemic inflammatory markers in the acute phase of ischaemic stroke has been investigated by several researchers so far. Most of which have focused on specific biomarkers such as interleukin-6 and tumour necrosis factor-α.[15] Molecular markers have been recently highlighted for AIS as they should be considered in the management and prediction of the disease.

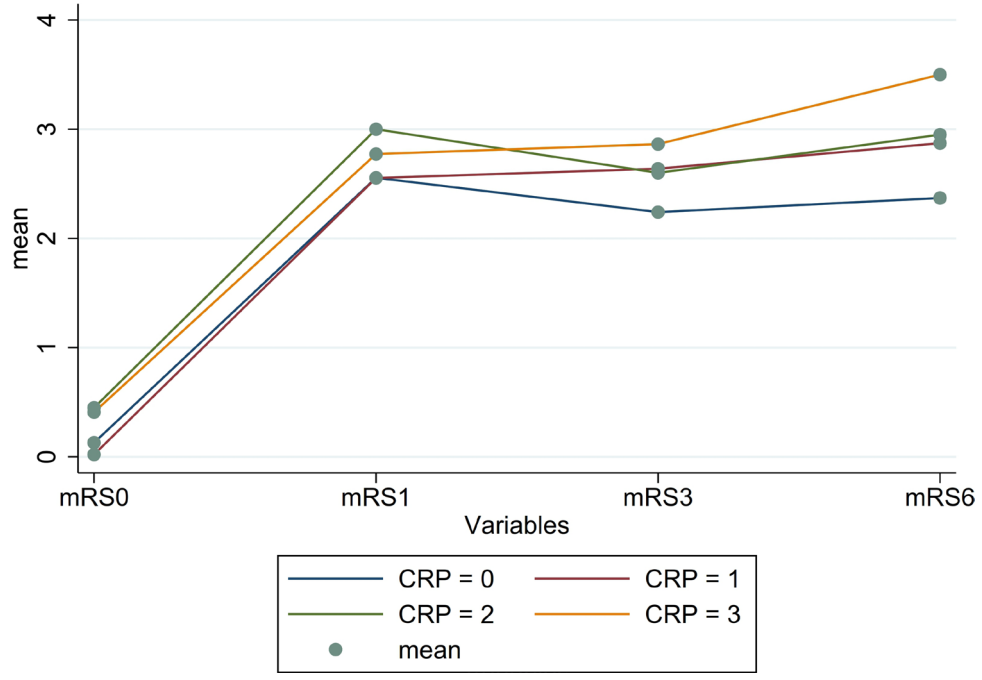

Figure 1 The trend of mean outcome measures in different qualitative CRP Scores. mRS0 refers to prehospital outcome scores, mRS1 refers to admission outcome scores, mRS3 refers to the 3-month outcome and mRS6 refers to 6-month outcome scores. CRP, C reactive protein; mRS, modified Rankin Scale.

Table 4 Outcome measures in different subgroups of AIS according to TOAST

Outcome	AIS subgroups					P value
	LAA (n=83)	CE (n=41)	SVO (n=62)	Other (n=16)	Undetermined (n=15)	
Prehospital to admission mRS difference, mean±SD	2.72±1.40	2.44±1.23	2.05±1.05	2.88±1.36	2.40±1.12	0.018
Admission mRS, mean±SD	3.06±1.43	2.61±1.36	2.13±1.11	2.88±1.36	2.53±1.30	0.001
3 months mRS, mean±SD	2.69±2.11	2.66±1.88	2.00±1.74	2.44±2.22	2.53±1.96	0.296
6 months mRS, mean±SD	2.98±2.21	3.10±2.18	2.11±1.87	2.50±2.42	2.73±2.09	0.106

AIS, acute ischaemic stroke; CE, cardioembolism; LAA, large artery atherosclerosis; SVO, small vessel occlusion; TOAST, the Trial of Org 10172 in Acute Stroke Treatment.

Studies in this field have mostly emphasised the effect of inflammatory markers on the outcome of stroke. Juli *et al* have found an association between lymphocyte depletion in the acute phase of AIS and poor neurological outcomes.[16] Recently, some articles have marked an association between NLR and poor neurological outcomes. Sarejloo *et al* reviewed the relationship between NLR and early neurological deterioration. It was concluded that elevated NLR was linked to poor neurological outcomes in AIS, and NLR was introduced as a unique inflammatory biomarker associated with immune system dysfunction.[17] Our results are consistent with the above-mentioned review. Moreover, we observed that neutrophil count is separately associated with poor neurological outcomes, but lymphocyte count does not have a statistically significant correlation with the outcome. New articles in this regard have investigated novel indices such as the Systemic Inflammatory Response Index and Inflammatory Prognostic Index and have found an association between these indices and the short-term prognosis of AIS.[18]

Inflammatory markers versus subgroups of AIS

There are limited data on the role of inflammatory markers in different stroke subtypes. However, certain conditions are linked to a higher inflammatory response. Internal carotid artery occlusion, as one of the conditions related to the LAA subtype of stroke, is associated with higher ESR and high-sensitive CRP.[19] On the other hand, some articles investigated the immuno-inflammatory markers such as interleukins in different subtypes of stroke.[4]

Subgroups of AIS versus outcome

On the other hand, the relationship between AIS subtypes and the functional outcome has been well investigated.

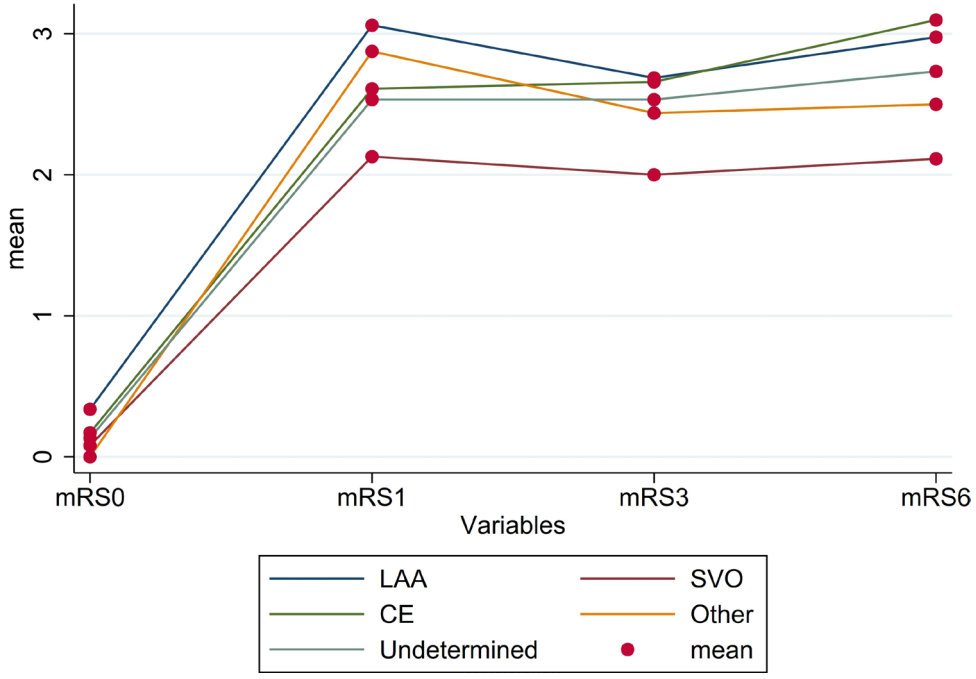

Figure 2 The trend of mean outcome measures in different subgroups of acute ischaemic stroke. mRS0 refers to prehospital outcome scores, mRS1 refers to admission outcome score, mRS3 refers to the 3-month outcome and mRS6 refers to 6-month outcome scores. CE, cardioembolism; LAA, large artery atherosclerosis; mRS, modified Rankin Scale; SVO, small vessel occlusion.

Lacunar infarcts or SAAs have been known to cause the least disability due to the small infarct size, and our study supports this hypothesis. On the contrary, LAA in our study has the worst functional outcome. Different studies have marked either LAA or CE as the worst AIS subtype in terms of functional outcome.[20 21] This could be due to differences in the evaluated populations, and the role of some of the confounding variables. Further studies can perform multivariate analysis in a larger sample size to determine the exact subgroup with the worst functional outcome. Nonetheless, this emphasises the importance of these two aetiologies—LAA and CE—for physicians and patients for secondary prevention and precise treatment.

In this study, the two aetiologies, LAA and other aetiologies, defined by the TOAST criteria were similar in functional outcome scores. This highlights the importance of determining the aetiology of AIS, so that specific management of a certain aetiology could lead to a better prognosis.

Strengths and limitations

The findings of this article should be interpreted in light of its strengths and limitations. We evaluated AIS patients in a prospective cohort and gathered broad information on their stroke subtypes and inflammatory markers, and followed them after 3 and 6 months in terms of functional outcome scores. However, our work has some limitations that should be acknowledged. First, our selection had bias in its nature, since the patients who come to hospital have more severe symptoms. Therefore, some patients with minor symptoms of AIS are excluded. Furthermore, as we excluded all inflammatory-related disease, AIS due to inflammatory disease—such as arthritis—is excluded. Also, we did not correct our results according to confounding variables. It is also noteworthy that we evaluated basic inflammatory markers. New studies mostly focus on immune-inflammatory markers such as interleukins. Also, we evaluated qualitative CRP, which is quite an old-fashioned inflammatory biomarker. Nonetheless, these biomarkers are low cost and easily available. Another limitation of our work is the small sample size. This was substantially due to the COVID-19 pandemic, as patients with concurrent infections or any other condition related to increased inflammatory markers have been excluded.

CONCLUSION

We can infer from the results of this study that neutrophil count and NLR can serve as low cost and readily available inflammatory biomarkers for predicting functional outcomes and they are also associated with subgroups of AIS. On the contrary, ESR, qualitative CRP and lymphocyte count did not correlate with outcome or subgroup of AIS.

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Competing interests None declared.

Patient consent for publication Consent obtained directly from patient(s).

Ethics approval This study involves human participants and this study was approved by the Ethical Committee of Arak University of Medical Sciences (ethical code: IR.ARAKMU.REC.1400.066) and written informed consent was obtained from the participants. Participants gave informed consent to participate in the study before taking part.

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ORCID iD

Mohammad Sadegh Fakhari http://orcid.org/0000-0002-0350-447X

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