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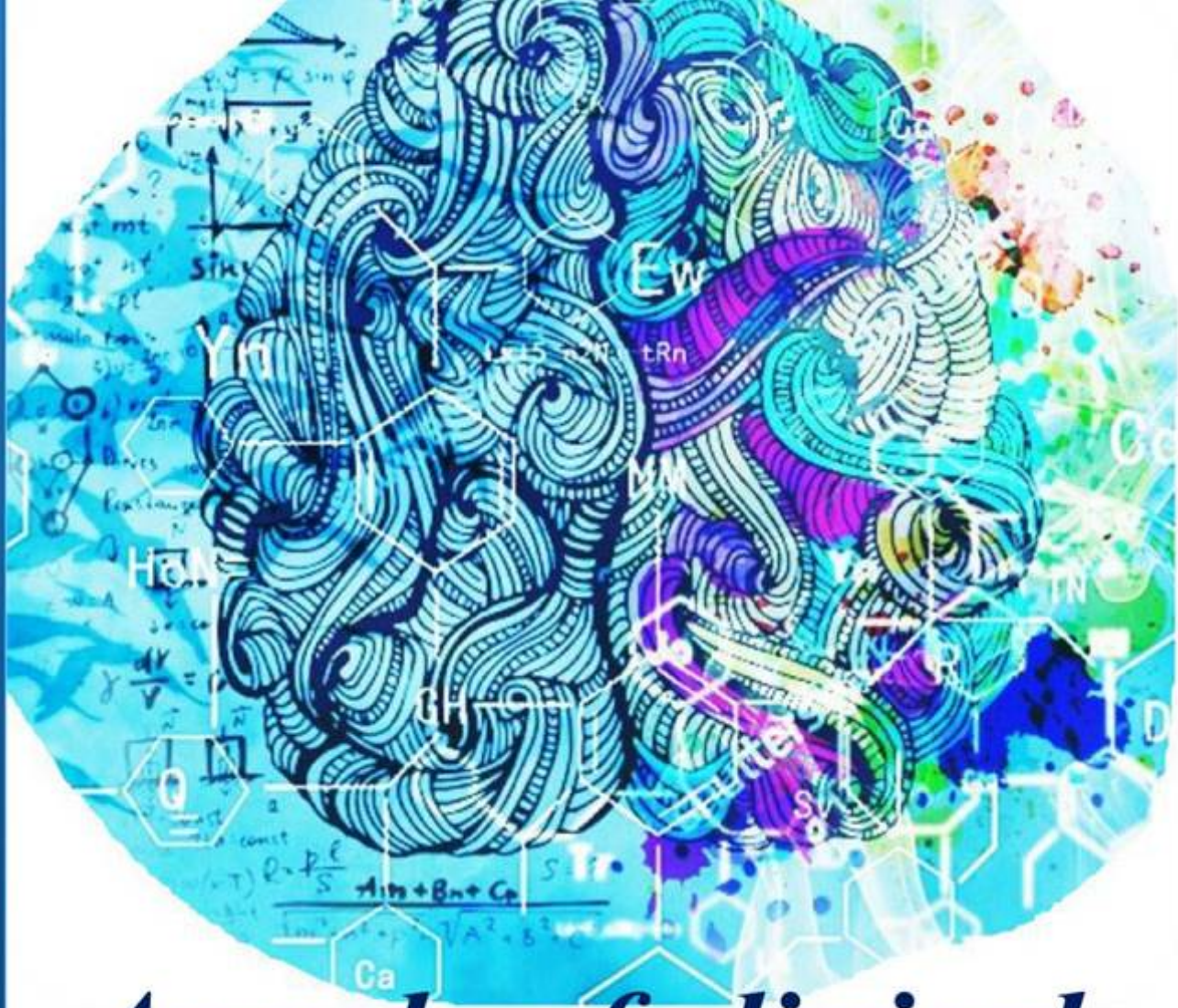

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INFLAMMATORY BIOMARKERS AND INSULIN RESISTANCE IN ACUTE ISCHEMIC STROKE OF DIFFERENT ETIOLOGIES

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ABSTRACT

This study explores differences in inflammatory biomarkers in the acute period of ischemic stroke according to different etiologies and emphasizes the role of insulin resistance (IR) as a contributing metabolic factor. Serum levels of ICAM-1, hs-CRP, SII, and NLR were compared between stroke subtypes, and associations with IR were analyzed. Findings suggest that cardioembolic strokes exhibit higher inflammatory activity, whereas lacunar subtypes show lower biomarker levels. Moreover, IR was frequent among patients and correlated with elevated inflammatory markers, suggesting a synergistic role in worsening vascular damage.

Key words: acute ischemic stroke, insulin resistance, inflammation biomarkers, TOAST, cardioembolic stroke.

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ВОСПАЛИТЕЛЬНЫЕ БИОМАРКЕРЫ И ИНСУЛИНОРЕЗИСТЕНТНОСТЬ ПРИ ОСТРОМ ИШЕМИЧЕСКОМ ИНСУЛЬТЕ РАЗНОЙ ЭТИОЛОГИИ

АННОТАЦИЯ

Это исследование посвящено изучению различий в уровнях воспалительных биомаркеров в остром периоде ишемического инсульта в зависимости от его различных этиологий и подчёркивает роль инсулинорезистентности (ИР) как значимого метаболического фактора. В работе сравнивались сывороточные уровни ICAM-1, hs-CRP, SII и NLR между подтипами инсульта, а также анализировались их ассоциации с ИР. Результаты показали, что при кардиоэмболическом инсульте наблюдается более выраженная воспалительная активность, тогда как при лакунарном подтипе уровни биомаркеров были ниже. Кроме того, у пациентов часто выявлялась ИР, которая коррелировала с повышенными воспалительными маркерами, что указывает на её синергическую роль в усугублении сосудистого повреждения.

Ключевые слова: острый ишемический инсульт, инсулинорезистентность, воспалительные биомаркеры, TOAST, кардиоэмболический инсульт.

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ТУРЛИ ЭТИОЛОГИЯЛИ ИШЕМИК ИНСУЛЬТДА ЯЛЛИҒЛАНИШ БИОМАРКЕРЛАРИ ВА ИНСУЛИН РЕЗИСТЕНТЛИГИ

АННОТАЦИЯ

Ушбу тадқиқот турли этиологияли ишемик инсультнинг ўткир даврида яллиғланиш биомаркерлари даражасидаги фарқларни ўрганади ҳамда инсулин резистентлигини (IR) муҳим метаболик омил сифатидаги ролини баҳолайди. Тадқиқотда ICAM-1, hs-CRP, SII ва NLR кўрсаткичлари инсультнинг турли типлари ўртасида таққосланди ва уларнинг IR билан боғлиқлиги таҳлил қилинди. Натижалар шуни кўрсатдики, кардиоэмболик инсультларда яллиғланиш фаоллиги юқорироқ бўлиб, лакунар инсультларда биомаркерлар даражаси пастроқ кузатилди. Бундан ташқари, беморларда IR тез-тез учраб, яллиғланиш маркерларининг ошиши билан боғлиқ экани аниқланди, бу эса унинг томир шикастланишини кучайтиришда синергетик роль ўйнашини кўрсатади.

Калит сўзлар: ўткир ишемик инсульт, инсулинга резистентлик, яллиғланиш биомаркерлари, TOAST, кардиоэмболик инсульт.

Background. In developed countries, stroke ranks as the third most common cause of death and is the leading contributor to long-term disability. Ischemic stroke, which constitutes about 87% of all strokes [5], is the predominant type. Acute stroke treatment, where feasible, involves reopening the blocked artery, typically through intravenous administration of recombinant tissue plasminogen activator (tPA). In cases of large intracranial vessel occlusion, this approach is supplemented with endovascular mechanical thrombectomy [17].

The TOAST (Trial of Org 10172 in Acute Stroke Treatment) classification system [1] is commonly used to categorize ischemic stroke causes. This system identifies large artery atherosclerosis (20%), cardioembolism (20%), small vessel occlusion (20%), other determined causes (5%, such as dissections or genetic disorders), and a cryptogenic category (30%) for strokes of unknown origin [3]. Identifying the cause of the stroke is crucial for initiating targeted secondary prevention strategies that effectively reduce the risk of recurrence. However, the presence of multiple potential causes in a single patient can create diagnostic uncertainty and complicate treatment prioritization. Biomarkers hold promise for assisting in determining the underlying cause.

Since the causes of stroke subtypes vary (e.g., atherosclerosis versus cardiac embolism), it is hypothesized that specific serum protein expression profiles could be associated with different stroke etiologies. While no biological marker has et been identified that can definitively determine stroke cause [16], blood-based biomarkers may help improve classification of ischemic stroke mechanisms, enabling more precise therapeutic interventions. A better understanding of ischemic stroke pathophysiology could lead to enhanced prevention strategies as well as advances in diagnosis and treatment. Therefore, this study aims to explore potential links between different etiological stroke subtypes.

Growing evidence indicates that systemic inflammation and metabolic dysfunction, particularly insulin resistance (IR), are central to the pathophysiology of ischemic stroke. IR contributes to endothelial dysfunction, accelerates atherosclerosis, promotes platelet activation, and enhances pro-inflammatory cytokine release. Clinical studies demonstrate that IR not only increases the risk of first-ever ischemic stroke but also worsens outcomes and elevates the likelihood of

recurrence. Despite this, IR is rarely considered in biomarker-based stratification of ischemic stroke patients.

Purpose of the study. To compare the concentration of inflammatory biomarkers (ICAM-1, hs-CRP, SII, NLR) between different ischemic stroke subtypes and to evaluate the contribution of insulin resistance to biomarker changes and stroke outcomes.

Materials and methods. This observational study included 68 consecutive patients admitted with acute ischemic stroke (AIS) to the Department of Neurology, Tashkent Medical Academy, between January and June 2022. In addition, 32 age- and sex-matched healthy volunteers served as the control group. Eligible patients were adults (≥18 ears) presenting within 24 hours of the first-ever ischemic stroke. AIS was confirmed by clinical evaluation and neuroimaging (CT or MRI). At admission, demographic and clinical data, vascular risk factors, and lifestyle habits were collected through structured questionnaires and chart reviews. Stroke severity was assessed using the National Institutes of Health Stroke Scale (NIHSS), and functional outcome during hospitalization was determined using the modified Rankin Scale (mRS). Stroke subtype classification followed the TOAST criteria, which divide ischemic strokes into large artery atherosclerosis (LAA), cardioembolism, small vessel occlusion, other determined etiology, and cryptogenic stroke. Peripheral venous blood was obtained within 24 hours of admission. Serum was separated by centrifugation within 30 minutes and stored at −20 °C until analysis. High-sensitivity C-reactive protein (hs-CRP) and intercellular adhesion molecule-1 (ICAM-1) concentrations were determined using commercial ELISA kits (AO “Vector-Best,” Russia; BioVendor R&D, Czech Republic). The systemic immune-inflammation index (SII) and neutrophil-to-lymphocyte ratio (NLR) were calculated from routine complete blood counts. Fasting blood glucose and insulin were measured in all AIS patients. Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) was calculated. HOMA-IR value >2.5 was considered evidence of insulin resistance.

Results. Overall, 68 patients suffering from acute ischemic stroke (AIS) with a mean age of 63.8 ears were included in the study. The mean systolic blood pressure (SBP) was 154.4 ± 28.6 mmHg, and the mean diastolic pressure was 91.8 ± 7.9 mmHg. Hypertension was present in all patients (100%), while diabetes mellitus was observed in 8 (11.8%) and atrial fibrillation in 6 (8.8%). Coronary heart disease was found in 14 patients (20.6%).

Insulin resistance (IR), assessed by the HOMA-IR index, was detected in **28 patients (41.2%)**. Importantly, a considerable proportion of patients with IR had no prior diagnosis of diabetes, confirming the presence of subclinical metabolic dysfunction. The mean HOMA-IR across the entire cohort was 2.8 ± 1.1, compared to 1.6 ± 0.5 in the control group ($p < 0.01$).

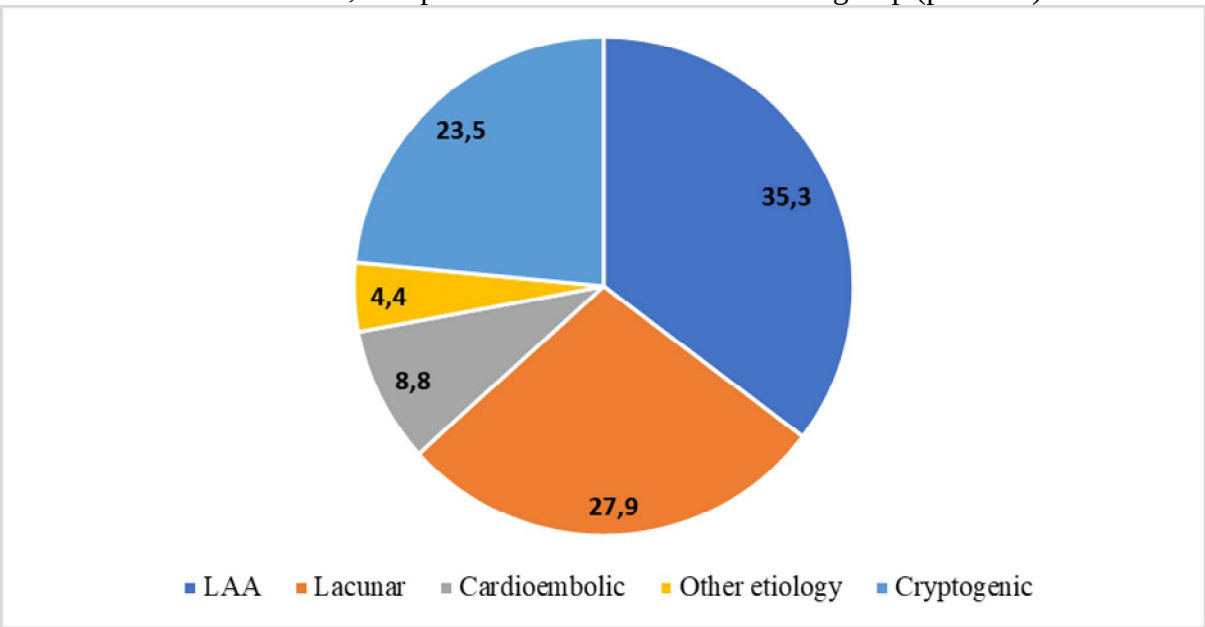

Figure 1. Frequency of stroke subtypes

When analyzed according to TOAST subtypes, **cardioembolic strokes** demonstrated the highest inflammatory activity, with elevated ICAM-1 (328.47 ± 196.83 ng/ml), hs-CRP (4.75 ± 2.26 mg/L), SII (2006.33 ± 1769.41), and NLR (9.03 ± 8.27). **Lacunar strokes** showed the lowest biomarker concentrations across all parameters. Large artery atherosclerosis (LAA) and cryptogenic strokes presented intermediate values (Table 1).

Insulin resistance was most frequent in **LAA (50%)** and **cardioembolic (50%)** subtypes, while only 23.7% of lacunar stroke patients demonstrated IR. The presence of IR was consistently associated with higher biomarker levels: patients with IR had significantly higher ICAM-1 ($p < 0.01$), hs-CRP ($p < 0.05$), and NLR ($p < 0.05$) compared to non-IR patients within the same subtype.

Table 1

Concentration of biomarkers and insulin resistance according to ischemic stroke subtypes

Biomarkers / HOMA-IR	**LAA**	**Cardioembolic**	**Lacunar**	**Other etiology**	**Cryptogenic**	**Control group**
ICAM-1 (ng/ml)	210.13 ± 167.8*	328.47 ± 196.83*	151.64 ± 47.94*	194.07 ± 100.5*	200.92 ± 94.75*	76.5 ± 17.55
hs-CRP (mg/L)	3.05 ± 1.68*	4.75 ± 2.26*	2.3 ± 1.17*	2.98 ± 1.37*	3.47 ± 2.04*	0.98 ± 0.23
SII	1134.99 ± 1333.89*	2006.33 ± 1769.41*	554.6 ± 470.6*	732.57 ± 695.3*	911.37 ± 815.9*	257.7 ± 45.66
NLR	4.98 ± 5.88*	9.03 ± 8.27*	3.03 ± 2.58*	3.55 ± 2.57*	4.03 ± 3.35*	1.72 ± 0.43
HOMA-IR (mean)	3.1 ± 1.2*	3.3 ± 1.1*	2.1 ± 0.8	2.5 ± 0.9	2.6 ± 1.0	1.6 ± 0.5
IR prevalence (%)	50%	50%	23.7%	33.3%	37.5%	9.3%

***p < 0.01 vs. control**

Functionally, IR was linked to worse short-term outcomes: 67.9% of patients with IR had an mRS ≥ 3 at discharge compared to 38.1% of those without IR ($p < 0.05$). This highlights the synergistic role of metabolic and inflammatory mechanisms in determining stroke severity.

Parameter	**IR (n=28)**	**Non-IR (n=40)**	**p-value**
Mean ICAM-1 (ng/ml)	298.6 ± 172.4	184.7 ± 95.2	<0.01
Mean hs-CRP (mg/L)	4.12 ± 1.87	2.71 ± 1.39	<0.05
Mean NLR	6.82 ± 4.44	3.95 ± 2.73	<0.05
HOMA-IR	3.3 ± 1.0	1.9 ± 0.6	<0.001
Poor outcome (mRS ≥ 3 at discharge)	67.9%	38.1%	<0.05

Explanation *-p<0.001

Point estimates presented in the following can be interpreted as the mean difference between a specific etiology. Inflammatory biomarker's levels were significantly higher in the cardioembolic stroke subjects compared with the large vessel atherosclerotic subtype. Furthermore, inflammatory biomarkers levels were significantly lower in the lacunar subtype.

Discussion. The present study demonstrated significant variations in inflammatory biomarker levels among ischemic stroke subtypes. Cardioembolic strokes were characterized by markedly elevated concentrations of ICAM-1, hs-CRP, SII, and NLR, whereas lacunar strokes displayed the lowest values. These findings support previous reports that immune activation and systemic inflammation differ according to stroke mechanisms, reflecting distinct underlying pathophysiological processes [6,10,12,18].

A key addition in this study was the evaluation of insulin resistance (IR). We observed IR in more than 40% of patients, including those without a history of diabetes mellitus. Importantly, IR was associated with significantly higher levels of ICAM-1, hs-CRP, and NLR, irrespective of the stroke subtype, and was linked to unfavorable functional outcomes at discharge. These observations are in agreement with earlier research indicating that IR accelerates atherosclerosis, promotes systemic inflammation, and contributes to plaque instability [7,21,23].

The biological plausibility of these findings is well supported. IR impairs endothelial insulin signaling, leading to increased expression of adhesion molecules such as ICAM-1 and VCAM-1 [19]. In addition, IR enhances the release of pro-inflammatory cytokines (IL-6, TNF-α), which elevate circulating CRP and promote leukocyte activation [8,22]. These mechanisms explain the synergistic relationship between IR and elevated inflammatory biomarkers in acute ischemic stroke.

Our findings are consistent with studies showing that biomarkers like hs-CRP, NLR, and ICAM-1 may differentiate between stroke etiologies [11,14,15]. Moreover, they extend prior work by demonstrating that metabolic dysfunction, specifically IR, amplifies these inflammatory processes and worsens short-term prognosis. Taken together, these results underscore the importance of integrating metabolic and inflammatory markers into stroke risk assessment and management.

Several limitations should be acknowledged. The sample size was relatively modest, and IR was assessed only once in the acute phase, which may not capture temporal fluctuations. Moreover, residual confounding by obesity, lipid abnormalities, or glycemic variability cannot be excluded. Further large-scale, prospective studies are needed to confirm these findings and to evaluate the role of therapeutic interventions targeting IR in ischemic stroke patients.

Conclusion. This study highlights that inflammatory biomarker profiles differ significantly between ischemic stroke subtypes and that the coexistence of insulin resistance amplifies systemic inflammation and worsens functional outcomes. Cardioembolic strokes exhibited the highest biomarker levels, while lacunar strokes had the lowest, et the presence of IR was consistently associated with increased inflammatory activity across all subtypes.

Our results suggest that routine assessment of IR (e.g., via HOMA-IR) in acute ischemic stroke could serve as a simple and cost-effective tool to identify high-risk patients. Combining inflammatory biomarkers with metabolic indicators may improve etiological classification, prognostic accuracy, and guide more personalized prevention and treatment strategies.

In conclusion, insulin resistance represents an important metabolic factor in the pathophysiology of ischemic stroke. Incorporating IR into biomarker-based models could enhance patient stratification, optimize secondary prevention, and open new therapeutic opportunities [7,19,21,23].

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