ORIGINAL ARTICLE

CONTENTS

Prognostic significance of interleukin-6 in patients with acute ischemic stroke undergoing thrombectomy

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ABSTRACT

Aim: To evaluate the prognostic significance of plasma interleukin-6 levels as a predictor of functional outcomes and motor recovery in the acute phase of ischemic stroke.

Materials and Methods: In 2023, 70 patients with acute cerebral vessel occlusion undergoing mechanical thrombectomy were examined. The cohort included 44 (63%) men and 26 (37%) women, aged 38 to 80 years (65.3±9.4). Stroke severity was assessed using the NIHSS (8–23 points), and functional status at discharge was evaluated using the mRS (mRS 0–3: favorable outcome, mRS 4–6: unfavorable outcome). Plasma interleukin-6 concentrations were measured by enzyme-linked immunosorbent assay on days 1 and 7 of the disease.

Results: A statistically significant correlation was found between interleukin-6 levels and the severity of neurological deficits in patients with NIHSS ≤15 and >15 points during the acute phase of ischemic stroke. Interleukin-6 levels were 8.5±0.7 vs. 13.1±0.9 pg/mL on day 1 and 9.8±1.2 vs. 26.4±3.2 pg/mL on day 7 ($p<0.01$). Patients with a negative functional outcome had higher interleukin-6 levels both at admission (9.0±0.7 vs. 13.6±1.0 pg/mL) and over time (9.2±0.6 vs. 31.3±3.6 pg/mL; $p<0.01$). Additionally, higher interleukin-6 levels were observed in patients with hemorrhagic transformation after thrombectomy compared to those without transformation: 15.0±2.1 vs. 27.5±4.4 pg/mL on day 7 ($p<0.01$).

Conclusions: Plasma interleukin-6 levels correlate with the severity of neurological deficits, functional status, and the presence of hemorrhagic transformation, making it a prognostic biomarker for the course and outcome of acute ischemic stroke.

KEY WORDS: interleukin-6, thrombectomy, ischemic stroke, biomarkers, large vessel occlusion, intraoperative neuromonitorin

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INTRODUCTION

Acute ischemic stroke (AIS) is one of the leading causes of mortality and disability. Its occurrence is often due to insufficient cerebral blood supply caused by stenosis or occlusion of the large vessels in the anterior or posterior circulations [1]. Recent advancements in endovascular thrombectomy (TE) have significantly improved reperfusion rates in patients with AIS caused by large vessel occlusion [2]. However, data from five key TE studies indicate that over 50% of patients experience severe impairments, including loss of cognitive, speech, and motor functions, even after successful recanalization of occluded vessels [3]. This outcome may be linked to unsuccessful recanalization and reperfusion injury caused by an inflammatory response in which interleukin-6 (IL-6) — a multifunctional cytokine of immune cells — plays a key role. Elevated serum IL-6 levels are associated with larger infarct volumes and worse clinical outcomes in stroke patients [4].

In recent years, significant attention in the pathogenesis of ischemic stroke has been focused on pathobiochemical changes that play a key role in the processes of early and delayed brain tissue damage [5]. Numerous studies emphasize the critical role of inflammation in stroke pathophysiology, driven by the release of various cytokines and acute-phase proteins. However, the precise function of these cytokines, their impact during the acute and late phases, and their association with treatment outcomes remain subjects of ongoing debate [6]. Since inflammation contributes to edema formation and may trigger apoptosis, inflammatory biomarkers are promising indicators of prognosis and potential targets for neuroprotective therapy [7].

Ischemic damage triggers an inflammatory response in the brain, accompanied by the activation of various cytokines, including IL-6, which participates in numerous inflammatory processes. Experimental models of focal cerebral ischemia demonstrate a

rapid increase in interleukin-6 mRNA levels and its biological activity. However, the pro-inflammatory role of IL-6 in the central nervous system following experimental ischemia remains not fully understood [8]. The relationship between the levels of peripheral inflammatory markers and treatment outcomes in stroke patients is also insufficiently studied. In cases of AIS, some studies indicate a positive correlation between blood IL-6 concentration, infarct volume, stroke severity, or outcomes within six months [9], while others found no such association between serum IL-6 levels and infarct volume or stroke severity after three months [10].

AIM

The aim of our study was to measure the levels of the pro-inflammatory cytokine IL-6 in AIS patients upon admission and during the dynamic acute phase of the stroke, as well as to evaluate its relationship with stroke severity, the development of hemorrhagic transformation, and clinical outcomes.

MATERIALS AND METHODS

A total of 70 patients aged 18 and older with acute ischemic stroke were included in the prospective investigation. The stroke was first-time onset (confirmed by CT/MRI with symptom onset within the previous 24 hours), and mechanical thrombectomy was performed. Patients were included in the study group based on inclusion criteria. Among them, 44 (63%) were men and 26 (37%) were women, with ages ranging from 38 to 80 years (65.3 ± 9.4 years).

Exclusion criteria included: patients with hemorrhagic stroke confirmed by CT/MRI; transient ischemic attack (symptom regression within 24 hours); fever at onset or within a week prior to stroke; rheumatologic disease; autoimmune disease or any acute or chronic infection in history; immunosuppressive therapy (corticosteroids); severe renal or liver dysfunction. A detailed medical history and neurological examination were conducted. The severity of stroke at admission was assessed using the National Institutes of Health Stroke Scale (NIHSS), and patients were divided into groups with moderate (NIHSS ≤15) and severe (NIHSS >15) neurological deficits, comprising 30 and 40 patients, respectively. Functional capacity at discharge was evaluated using the modified Rankin Scale (mRS). Outcomes were classified as favorable (mRS group 0–3) or unfavorable (mRS group 4–6).

The quantitative determination of IL-6 concentration was performed using the enzyme-linked immunosorbent assay (ELISA) method with the DIA-IL-6 kit (DiaProph-Med, Ukraine). Blood samples for serum analysis were collected within the first 24 hours after hospitalization and again on days 7–10 of treatment. Five milliliters of venous blood were drawn into a sterile container and kept at room temperature for 45–60 minutes before centrifugation at 1400 rpm for 15 minutes. Serum was separated and stored at −20°C until further analysis. All samples were thawed only once for laboratory testing.

Symptomatic intracranial hemorrhage (sICH) was defined as any extravascular blood accumulation in the brain parenchyma or subarachnoid space accompanied by clinical deterioration, characterized by an increase of at least 4 points on the NIHSS scale. Hemorrhagic transformation was observed in 24 patients (34.3%) and classified according to the European Cooperative Acute Stroke Study II (ECASS II) scale as HI1 in 10 patients, HI2 in 4, PH1 in 4, and PH2 in 6 patients. Eight patients exhibited asymptomatic hemorrhagic transformation, while sICH was observed in 16 patients. Among the 6 deceased patients, 2 died due to malignant brain infarction, 3 from sICH, and 1 from myocardial infarction.

Statistical calculations were performed using Statistica 7.0 for Windows software (StatSoft Inc., USA). Data were analyzed using arithmetic mean (M) and standard deviation (SD), and the Student's t-test was applied to assess statistical significance between the compared groups. The coefficient of determination (R^2) was used to evaluate the quality of the regression model. Results were considered significant at $p<0.05$.

RESULTS

The serum IL-6 level within the first 24 hours after hospital admission in the group of patients with moderate neurological deficit (NIHSS ≤15) was significantly lower compared to patients with severe neurological deficit (NIHSS >15 at the admission), measuring 8.5 ± 0.7 pg/mL versus 13.1 ± 0.9 pg/mL, respectively ($p < 0.01$).

On day 7, the serum IL-6 level in the NIHSS ≤15 group was 9.8 ± 1.2 pg/mL, while in the NIHSS > 15 group, it reached 26.4 ± 3.2 pg/mL ($p < 0.01$). The differences between the compared groups on day 1 and day 7 were statistically significant. Within-group comparison (based on the paired Student's t-test) showed no statistically significant increase in IL-6 levels in the group with moderate neurological deficit ($p > 0.05$). However, in patients with severe neurological deficit, the IL-6 level significantly increased by day 7 to 26.4 ± 3.2 pg/mL ($p < 0.01$) (Fig. 1).

In the group of patients with a favorable functional outcome at discharge (mRS 0–3), the serum IL-6

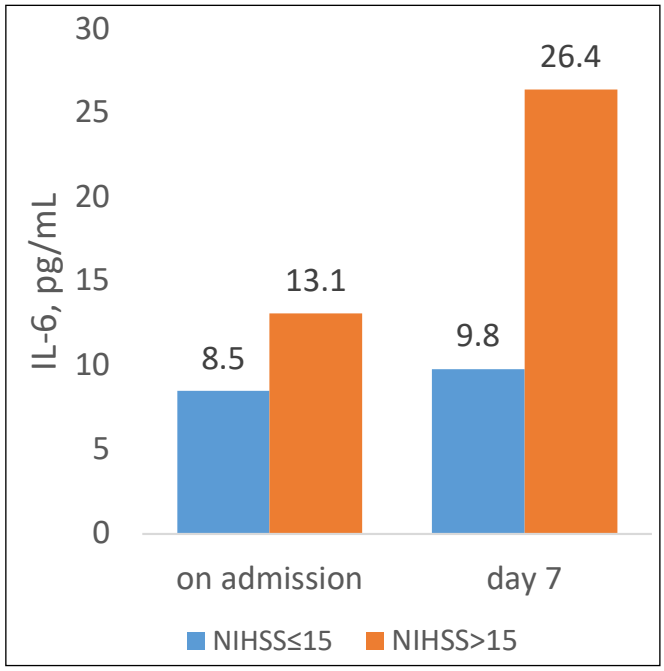

Fig. 1. Correlation between the severity of neurological deficit and IL-6 blood levels
Picture taken by the authors

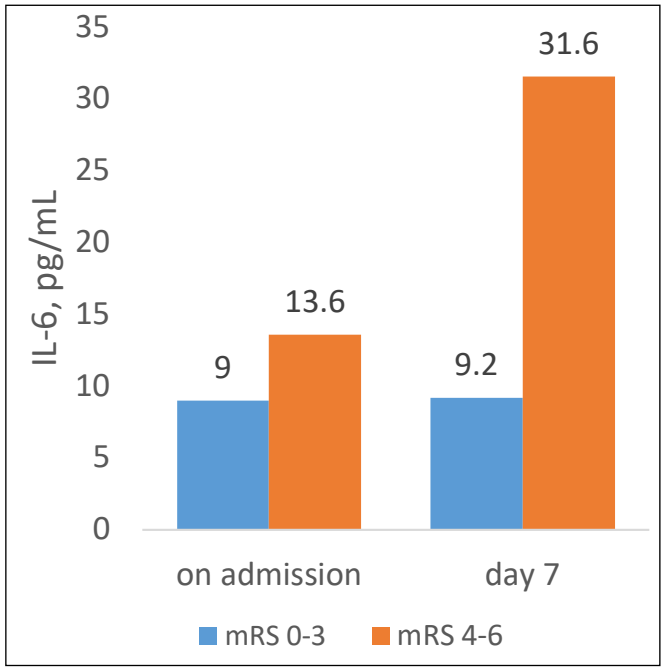

Fig. 2. Correlation between functional independence and IL-6 blood levels
Picture taken by the authors

level within the first 24 hours was significantly lower compared to patients with an unfavorable functional outcome (mRS 4–6), measuring 9.0 ± 0.7 pg/mL versus 13.6 ± 1.0 pg/mL, respectively ($p < 0.01$). A similar trend was observed dynamically: on day 7, IL-6 levels were 9.2 ± 0.6 pg/mL in the favorable outcome group

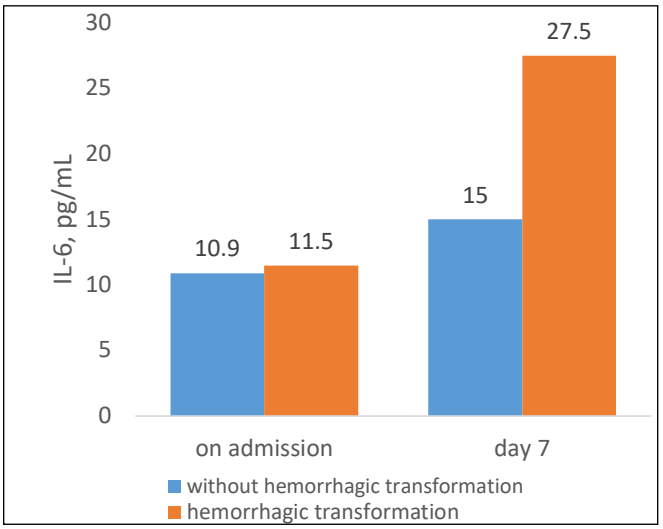

Fig. 3. Correlation between the presence of hemorrhagic transformation and IL-6 blood levels
Picture taken by the authors

versus 31.3 ± 3.6 pg/mL in the unfavorable outcome group ($p < 0.01$). Within-group analysis showed that IL-6 levels significantly increased by day 7 in the group with unfavorable functional outcomes, while no significant changes were observed in the group with favorable outcomes (Fig. 2).

Within the first 24 hours, no significant difference in serum IL-6 levels was observed between patients with hemorrhagic transformation and those without it (11.5 ± 1.0 pg/mL and 10.9 ± 0.8 pg/mL, respectively, $p > 0.05$). However, by day 7, a statistically significant difference was noted between the group with hemorrhagic transformation and the group without it after thrombectomy—15.0 ± 2.1 pg/mL versus 27.5 ± 4.4 pg/mL, respectively ($p < 0.01$). Within-group analysis showed that IL-6 levels increased by day 7 in both groups, but patients with hemorrhagic transformation exhibited a more pronounced rise (Fig. 3).

A weak correlation was identified between IL-6 levels and stroke severity, as assessed by the NIHSS scale. Patients with higher NIHSS scores tended to have elevated IL-6 levels, indicating a greater degree of neuronal damage associated with increased stroke severity. The coefficient of determination (NIHSS = 9,12 + 0,49 × IL-6, R = 0,42, $R^2 = 0,18$, $p < 0,01$) was 0.18, suggesting that 18% of the variation in stroke severity could be attributed to destructive processes accompanied by the release of IL-6 beyond neural cells. This indicates that while IL-6 is not the sole marker, it remains an important indicator of neural tissue damage that correlates with stroke severity (Fig. 4).

A weak correlation was also observed between IL-6 levels and the functional outcomes of patients at discharge, as assessed by the mRS scale. Patients with

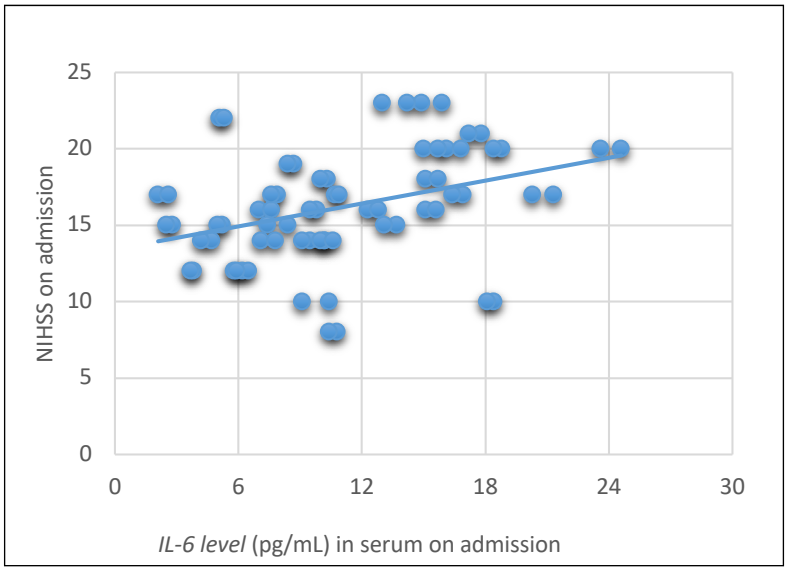

Fig. 4. Scatterplot of the correlation between IL-6 levels on the first day and NIHSS score
Picture taken by the authors

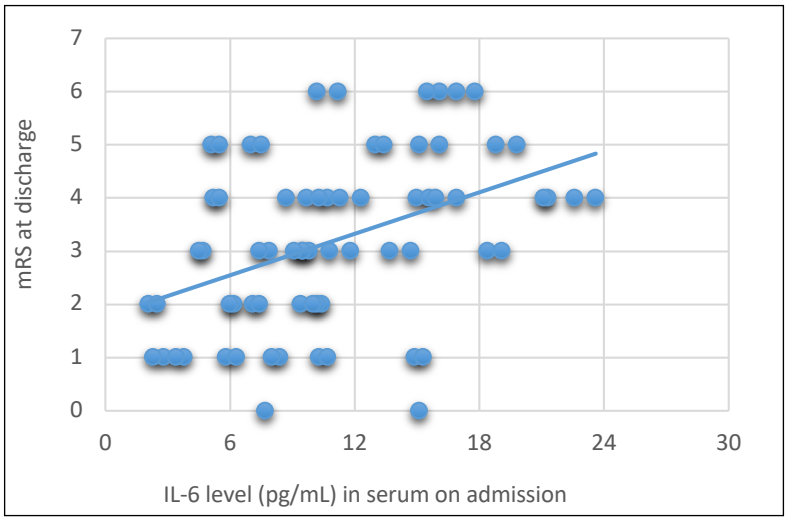

Fig. 5. Scatterplot of the correlation between IL-6 levels on the first day and mRS score
Picture taken by the authors

higher IL-6 levels generally had higher mRS scores, indicating poorer functional outcomes. The coefficient of determination for this correlation (mRS = 2,14 + 0,32 × IL-6, R = 0,46, R^2 = 0,21, p < 0,01) suggests that only 21% of the variation in functional outcomes can be explained by processes leading to increased IL-6 levels. This further highlights the limited role of IL-6 in predicting long-term functional recovery after a stroke (Fig. 5).

DISCUSSION

It has been established that the immuno-inflammatory response plays a key role in the pathogenesis of stroke, influencing its onset, progression, and prognosis. During immunological stress and inflammation, endothelial cells release numerous inflammatory factors, increasing endothelial cell adhesion and promoting the attachment and infiltration of inflammatory cells. This process, in turn, leads to the accumulation of lipids and foam cells, contributing to arterial occlusion and disruption of the blood-brain barrier (BBB), which negatively impacts clinical outcomes [7]. Elevated serum IL-6 levels are associated with more severe neurological deficits and are considered an unfavorable prognostic factor in AIS. IL-6 correlates with radiological indicators such as the mean lesion volume on DWI at admission, perfusion deficit, and final infarct size [11]. Recent studies have identified elevated peripheral blood IL-6 levels as a potential biomarker of ineffective reperfusion in patients undergoing thrombectomy. Low IL-6 levels at baseline have been associated with the «first-pass effect,» defined as achieving complete or near-complete reperfusion after a single thrombectomy attempt, which is a prognostic factor for favorable outcomes in AIS patients [12]. Notably, preclinical studies suggest a dual role of IL-6, demonstrating its ability to promote angiogenesis after stroke while simultaneously reducing ischemic damage [11].

As established in our study, severe neurological deficits are associated with an increased risk of hemorrhagic transformation and poorer treatment outcomes. These

deficits are often accompanied by elevated levels of inflammatory markers at the onset of the disease, consistent with the findings of Gan Y. et al. [13]. It is believed that IL-6 levels are closely linked to the pathogenesis of stroke. Inflammation is now regarded as a promising therapeutic target for reducing stroke risk, as IL-6 is a key mediator of inflammation that promotes leukocyte aggregation and thrombosis, leading to atherosclerosis and, consequently, stroke. Understanding the relationship between IL-6 levels and stroke progression could facilitate the development of novel approaches for stroke prevention and treatment based on the anti-inflammatory properties of cytokines [14].

During reperfusion, inflammation plays a crucial role in exacerbating brain damage. Activated peripheral leukocytes migrate into brain tissue, contributing to BBB disruption, brain edema, and microcirculatory disturbances, ultimately leading to further damage to brain structures [15]. Neutrophils and macrophages are the primary sources of matrix metalloproteinases, which degrade the vascular basement membrane, intensify BBB disruption, provoke hemorrhagic transformation, and exacerbate brain edema [16]. Clinical studies show that serum IL-6 levels increase within the first 24 hours of acute ischemic stroke, a finding consistent with our data, and have a significant association with infarct size and mortality rates [17].

During the inflammatory response, IL-6 not only accelerates lipid deposition and foam cell formation but also stimulates the phosphorylation of vascular endothelial cadherin, leading to vascular damage. IL-6 further activates cytotoxic T-lymphocytes and stimulates antibody production by B-cells, amplifying inflammation [18]. These immune and inflammatory responses directly contribute to the formation and progression of atherosclerotic plaques. The inflammatory process in cerebral vessels is a key mechanism underlying stroke development, highlighting the correlation between IL-6 levels at different stages post-stroke and functional outcomes following thrombectomy [19].

CONCLUSIONS

1. Patients with moderate deficits (NIHSS ≤15 points) at admission demonstrated a statistically significantly lower level of IL-6 compared to patients with severe deficits (NIHSS >15 points). This difference persisted on the 7th day of the acute phase.
2. Patients with favorable functional outcomes (mRS 0–3) had lower IL-6 levels compared to those with unfavorable outcomes (mRS 4–6), with this trend also remaining evident on the 7th day.
3. A significant increase in IL-6 levels in patients with hemorrhagic transformation on the 7th day highlights the prognostic value of this marker as an indicator of complications.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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