

**IMMUNE MECHANISMS OF REPERFUSION SYNDROME IN ISCHEMIC STROKE
FOLLOWING SYSTEMIC INTRAVENOUS THROMBOLYTIC THERAPY**

Yarashev A.R.¹

1. Bukhara Branch of the Republican Scientific Center for Emergency Medical Care,
Bukhara, Uzbekistan.

Eshonov O.Sh.²

2. Abu Ali ibn Sino Bukhara State Medical Institute, Bukhara, Uzbekistan.

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Research objective: *To investigate the immunopathogenetic features of reperfusion syndrome in patients with ischemic stroke following systemic intravenous thrombolytic therapy.*

Materials and Methods: *The study included 68 patients with ischemic stroke. Following systemic thrombolytic therapy, patients were divided into two groups based on the development of reperfusion syndrome: Group 1 consisted of 47 patients (69.1%) without reperfusion syndrome, and Group 2 consisted of 21 patients (30.9%) with reperfusion syndrome.*

Results: *The development of reperfusion syndrome following systemic thrombolytic therapy was associated with a progressive immunoinflammatory imbalance, manifested by a sequential increase in IL-6, IL-10, and the neutrophil-to-lymphocyte ratio (NLR). The findings suggest that the combination of a dynamic rise in IL-6 and NLR may serve as a potential laboratory marker for an adverse post-reperfusion course and outcome. Longitudinal monitoring of IL-6, IL-10, and NLR holds greater diagnostic and prognostic value than a single measurement taken at admission.*

Keywords: *ischemic stroke, thrombolytic therapy, alteplase, reperfusion syndrome.*

Relevance. Ischemic stroke (IS) remains a leading cause of disability and the second leading cause of death worldwide, claiming approximately 5.5 million lives annually. This figure is projected to rise to 10 million by 2050. Furthermore, 50% of stroke survivors suffer from chronic disability, placing a burden on the healthcare system and significantly reducing patients' quality of life. Regarding economic consequences, the World Stroke Organization estimates that global costs associated with stroke treatment exceed 721 billion US dollars per year [6,7,20,26].

Systemic thrombolytic therapy and endovascular thrombectomy are currently the primary treatments for acute ischemic stroke; however, their clinical efficacy is often compromised by ischemia-reperfusion injury (IRI), which can cause secondary brain damage—primarily through disruption of the blood-brain barrier (BBB) [8, 19].

Despite high recanalization rates (>90%) following endovascular thrombectomy, clinical outcomes remain unsatisfactory in approximately 50% of patients with acute ischemic stroke, and the significance of ischemia-reperfusion injury in this condition has recently been officially established [15, 18, 19].

Unfortunately, the restoration of blood flow to previously ischemic tissue exacerbates oxidative stress and leads to an increased release of pro-inflammatory cytokines; these trigger a series of pathological cascades that directly or indirectly cause apoptosis, BBB disruption, cerebral edema, and hemorrhagic transformation. Studies have shown that neuroinflammatory mechanisms, which are closely linked to oxidative stress, contribute significantly to neuronal

damage during the acute phase of cerebral ischemia, ultimately increasing the extent of brain injury and neurological deficits resulting from ischemia-reperfusion injury [12].

Ischemia-reperfusion injury, or reperfusion syndrome (RPS), involves a multitude of mechanisms—including the generation of reactive oxygen species (ROS), acidosis, calcium dysregulation, and the activation of inflammatory and regulated cell death pathways—that collectively worsen outcomes. The interplay of these mechanisms can ultimately lead to extensive neuronal death and neurological dysfunction, further exacerbating brain injury. A limited understanding of the pathogenetic mechanisms underlying RPS hinders the development of effective therapeutic interventions [1, 9, 16, 21, 22, 25, 26].

Microglial activation is an equally important component of secondary injury. Following the restoration of blood flow, microglial cells rapidly shift to a pro-inflammatory phenotype and begin to produce high levels of IL-1 β , IL-6, TNF- α , chemokines, and reactive oxygen species [6]. These mediators exacerbate neuronal damage, increase BBB permeability, and facilitate the recruitment of peripheral immune cells into the brain tissue. As the inflammatory response progresses, infiltration by neutrophils, monocytes, and T lymphocytes occurs, thereby sustaining persistent neuroinflammation. [6,11].

Upon activation and polarization toward the M1 phenotype, microglia release tumor necrosis factor-alpha (TNF- α), inflammatory interleukins such as IL-1 β and IL-6, other inflammatory cytokines, and reactive oxygen species into the bloodstream [12,17,24].

Modern understanding of reperfusion injury differs significantly from the traditional concept, which attributed the primary role exclusively to oxidative stress. It has now been established that the restoration of blood flow triggers a complex cascade of immune-inflammatory reactions, including innate immune activation, endothelial dysfunction, thrombo-inflammation, microcirculatory impairment, and blood-brain barrier damage. These processes unfold within the first few minutes following reperfusion and largely determine the subsequent course of the disease [2,3,4,7, 13,14].

To date, there are no generally accepted diagnostic criteria for RPS, its immunological predictors are insufficiently defined, and approaches to early risk stratification have not been developed [3–7,10].

The insufficient understanding of the immunological predictors of this syndrome underscores the importance of research aimed at identifying early markers of neuroinflammation and developing personalized approaches to preventing secondary brain injury—specifically, reperfusion-associated injury—in patients with ischemic stroke following systemic thrombolytic therapy.

The aim of the study was to investigate the immunopathogenetic features of reperfusion syndrome in patients with ischemic stroke following systemic intravenous thrombolytic therapy.

Materials and Methods. The study was conducted in the neuro-intensive care unit of the Bukhara branch of the Republican Research Center for Emergency Medicine (RRCEM) between 2025 and 2026. A total of 68 patients meeting the inclusion and exclusion criteria were enrolled.

General inclusion criteria were the acute phase of ischemic stroke and an age of 18–75 years. Exclusion criteria included atonic coma and decompensation of concomitant chronic diseases. Neurological status was assessed using the Glasgow Coma Scale (GCS) and the NIH Stroke Scale (NIHSS) upon hospital admission and during subsequent follow-up.

To assess the condition of the brain, all patients underwent multispiral computed tomography (MSCT) using a General Electric Revolution scanner (USA) upon admission to the hospital. The study analyzed the state of the brain parenchyma surrounding the established ischemic lesion and evaluated the patency of cerebrospinal fluid pathways, neuroimaging signs of cerebral edema, and the presence of hemorrhagic transformation.

All patients underwent a complete blood count with a detailed leukocyte differential.

Particular attention was paid to the neutrophil and lymphocyte counts, which were used to calculate the neutrophil-to-lymphocyte ratio (NLR).

Immunological studies for this work were conducted at the Bukhara Branch of the Institute of Immunology and Human Genomics of the Academy of Sciences of the Republic of Uzbekistan. Peripheral venous blood samples were collected at strictly defined time points: on the first day of hospitalization (baseline) and on days 3 and 5 of the post-reperfusion period.

All 68 patients received systemic thrombolytic therapy with Actilyse—in addition to standard treatment—within the therapeutic window (i.e., the first 4.5 hours after symptom onset), provided they exhibited neurological deficits and no visible ischemic zone on MSCT, and had no contraindications. Recombinant tissue plasminogen activator (r-tPA)—alteplase—was used for systemic intravenous thrombolysis at a dose of 0.9 mg/kg. Of the total dose, the first 10% was administered as an intravenous bolus, while the remaining 90% was infused slowly over one hour using an infusion pump. The maximum total dose was 90 mg.

Following systemic thrombolytic therapy, patients were divided into two groups based on the development of reperfusion syndrome (RPS): the first group consisted of 47 patients (69.1%) without RPS, and the second group comprised 21 patients (30.9%) with RPS. RPS manifested as hemorrhagic transformation in 8 patients (38.1%), worsening signs of cerebral edema on MSCT in 7 (33.4%), seizures followed by an exacerbation of neurological deficits in 4 (19.0%), and hyperthermia ($>39^{\circ}\text{C}$) in 2 (2.1%). It should be noted that these manifestations of RPS rarely occurred in isolation; typically, two or more symptoms were observed simultaneously.

In the first group ($n=47$), impaired consciousness of the type of stunning (11–12 points on the Glasgow Coma Scale, GCS) in combination with neurological disorders of moderate severity (5–15 points on the NIHSS scale) was registered in 43 people (91.5%). A stuporous state (9–10 points according to GCS) and moderately severe deficiency (16–20 points according to NIHSS) were noted in 3 patients (6.4%). Comatose state (7–8 points according to GCS) along with severe manifestations of stroke (21–42 points according to NIHSS) was verified in 1 subject (2.1%).

In the second group ($n=21$), the corresponding indicators were distributed as follows: moderate disturbances of consciousness and mild-to-moderate neurological deficits (GCS score of 11–12 and NIHSS score of 5–15) were observed in 3 patients (14.3%); moderately severe status according to both scales (GCS score of 9–10 and NIHSS score of 16–20) was found in 6 individuals (28.6%); and severe depression of central nervous system function (GCS score of 7–8 and NIHSS score of 21–42) was noted in 12 subjects (57.1%).

In the second group ($n=21$), the structure of the comorbid background had statistically significant differences: excess body weight was verified in the vast majority of subjects - in 16 cases (76.2%), while the proportion of people with concomitant diabetes mellitus was 71.4% (15 patients), and the frequency of arterial hypertension was 66.6% (14 patients), (Table 1).

Distribution of patients by number of comorbidities

Table 1

Comorbid conditions	TLT without RPS, n=47	TLT with RPS, n=21	p
Arterial hypertension	7 (14,8%)	14 (66,6%)	< 0,001
Obesity	9 (19,1%)	16 (76,2%)	< 0,001
Diabetes mellitus	2 (4,2%)	15 (71,4%)	< 0,001

The obtained data indicate the important role of metabolic syndrome and cerebral diabetic angiopathy in the development of reperfusion syndrome following thrombolytic therapy in patients with ischemic stroke.

Study results. In patients with ischemic stroke who underwent systemic intravenous thrombolytic therapy without developing reperfusion syndrome (RPS, n=47), the dynamics of immunoinflammatory markers were characterized by a moderate and transient increase in the concentration of the pro-inflammatory cytokine IL-6 during the early post-reperfusion period, followed by a decline; meanwhile, the level of the anti-inflammatory cytokine IL-10 showed a similar trend, followed by stabilization.

Upon admission, the IL-6 concentration was 117.85 ± 7.18 pg/mL, and the IL-10 concentration was 99.62 ± 8.93 pg/mL. On day 3 following thrombolytic therapy, a moderate increase in IL-6 levels to 123.88 ± 9.31 pg/mL was observed, which may reflect a transient activation of the pro-inflammatory response during the early reperfusion phase. Concurrently, the IL-10 concentration rose to 105.80 ± 6.62 pg/mL, indicating a simultaneous enhancement of anti-inflammatory regulation.

By day 5, IL-6 levels had decreased to 118.92 ± 10.05 pg/mL—returning virtually to baseline—while the IL-10 concentration remained relatively stable (102.83 ± 9.52 pg/mL). Thus, the dynamics of IL-6 and IL-10 in patients without RPS reflected a balanced immuno-inflammatory response, devoid of any progressive increase in pro-inflammatory activity.

The dynamics of the systemic neutrophil-to-lymphocyte ratio (SNLR) paralleled changes in the cytokine profile. Upon admission, the SNLR was 3.1; it rose to 3.4 on day 3 and decreased to 3.0 by day 5. Thus, following a brief increase in systemic inflammatory activity during the early post-reperfusion period, a subsequent normalization was observed.

Overall, in patients without reperfusion syndrome following systemic thrombolytic therapy, a transient activation of the immuno-inflammatory response was observed on day 3, followed by a decrease in IL-6 and SNLR levels by day 5, while IL-10 levels remained stable.

The absence of a progressive rise in IL-6 and SNLR over time may be considered a laboratory indicator of a controlled post-reperfusion course and a relatively preserved balance between pro-inflammatory and anti-inflammatory mechanisms (Table 2).

Dynamics of IL-6 and IL-10 levels ($M \pm m$) and the SNLR in patients with ischemic stroke following systemic thrombolytic therapy without RPS (n=47). Table 2.

Duration of the study	IL-6 (pg/mL), $M \pm m$	IL-10 (pg/mL), $M \pm m$	SNLR
Upon admission	$117,85 \pm 7,18$	$99,62 \pm 8,93$	3,1
Day 3	$123,88 \pm 9,31$	$105,80 \pm 6,62$	3,4
Day 5	$118,92 \pm 10,05$	$102,83 \pm 9,52$	3,0

In patients with ischemic stroke who developed reperfusion syndrome (RPS, n=21) following systemic intravenous thrombolytic therapy, marked progressive activation of the immuno-inflammatory response was observed during the early post-reperfusion period.

Upon admission, the IL-6 concentration was 118.85 ± 7.56 pg/mL, IL-10 was 103.62 ± 8.64 pg/mL, and the SNLR was 3.2. On day 3 after thrombolytic therapy, a significant increase in IL-6 levels to 152.88 ± 9.44 pg/mL was observed, accompanied by a rise in IL-10 to 125.40 ± 9.31 pg/mL and the SNLR to 4.3.

By day 5, a further intensification of immuno-inflammatory changes was observed: the IL-6 concentration reached 176.86 ± 8.47 pg/mL and IL-10 reached 156.85 ± 13.18 pg/mL, while the SNLR increased to 6.2. Thus, over the observation period, the levels of IL-6, IL-10, and SNLR increased by approximately 48.8%, 51.4%, and 93.8%, respectively, compared to baseline values.

The simultaneous rise in both the pro-inflammatory cytokine IL-6 and the anti-inflammatory cytokine IL-10 warrants particular attention. Such dynamics may indicate not only intensified pro-inflammatory activity but also the activation of a compensatory anti-inflammatory response aimed at limiting inflammatory damage. However, a marked increase in IL-6, combined with a progressive rise in the SNLR, points to persistent systemic inflammatory activation characteristic of a complicated post-reperfusion course.

Thus, the development of reperfusion syndrome following systemic thrombolytic therapy was associated with a progressive immuno-inflammatory imbalance, manifested by a sequential rise in IL-6, IL-10, and the IL-6/IL-10 ratio. These findings suggest that the combination of a dynamic increase in IL-6 and the IL-6/IL-10 ratio may serve as a potential laboratory marker for an adverse post-reperfusion course and the development of reperfusion syndrome (Table 3).

Динамика уровней IL-6 и IL-10 у пациентов с ишемическим инсультом после системной тромболитической терапии с РПС n=21. Таблица 3.

Duration of the study	IL-6 (pg/mL), M ± m	IL-10 (pg/mL), M ± m	SNLR
Upon admission	118,85 ± 7,56	103,62 ± 8,64	3,2
Day 3	152,88 ± 9,44	125,40 ± 9,31	4,3
Day 5	176,86 ± 8,47	156,85 ± 13,18	6,2

Discussion of results. A comparison of the dynamics of immunoinflammatory markers in patients with ischemic stroke following systemic intravenous thrombolytic therapy revealed significant differences between patients with an uncomplicated reperfusion course and those who developed reperfusion syndrome. Upon admission, the values of the studied markers were similar in both groups: IL-6 concentrations were 117.85 pg/mL in patients without reperfusion syndrome and 118.85 pg/mL in those with the syndrome; IL-10 levels were 99.62 and 103.62 pg/mL, respectively; and the SNLR was 3.1 and 3.2. These virtually comparable baseline values indicate that the marked difference in the immunoinflammatory profile between the groups developed primarily during the post-reperfusion therapy period.

On the third day following thrombolytic therapy (TLT), the group without reperfusion syndrome (RPS) showed only a moderate increase in IL-6—from 117.85 to 123.88 pg/mL—after which the concentration dropped to 118.92 pg/mL by the fifth day, effectively returning to baseline. In contrast, the group with RPS exhibited a consistent and more pronounced activation of the pro-inflammatory response: IL-6 levels rose from 118.85 pg/mL at admission to 152.88 pg/mL on day 3 and further to 176.86 pg/mL on day 5. Thus, by the fifth day, the IL-6 concentration in the RPS group was approximately 49% higher than baseline, whereas patients without RPS showed no significant cumulative increase in this marker. This indicates a difference in the nature of the post-reperfusion inflammatory response: in uncomplicated cases, it was predominantly transient, whereas in RPS, it followed a progressive course.

A similar trend was observed in the analysis of the anti-inflammatory cytokine IL-10. In the group without RPS, its concentration rose from 99.62 to 105.80 pg/mL by day 3, then decreased to 102.83 pg/mL by day 5. In contrast, in the group with RPS, IL-10 levels increased progressively from 103.62 to 125.40 pg/mL by day 3 and to 156.85 pg/mL by day 5. Thus, the marked increase in IL-10 in patients with RPS should be viewed as a manifestation of a compensatory anti-inflammatory response activated amidst an ongoing inflammatory reaction.

However, the concurrent significant rise in IL-6 indicates that the intensification of anti-inflammatory regulation was not accompanied by sufficient containment of the pro-inflammatory process.

The changes in the ISNL proved particularly revealing. At baseline, the values were virtually identical: 3.1 in patients without RPS and 3.2 in patients with RPS. By day 3, the ISNL had risen to 3.4 and 4.3, respectively; however, by day 5, the trends diverged significantly. In patients without RPS, the SNLR decreased to 3.0—slightly below the baseline value—whereas in the RPS group, it continued to rise, reaching 6.2. Thus, by day 5, the SNLR in patients with RPS was more than double that of the group without RPS and nearly twice its own baseline value.

Taken together, the results demonstrate two distinct patterns of the immuno-inflammatory response following systemic thrombolytic therapy. In the absence of reperfusion syndrome, a transient activation of the immuno-inflammatory system was observed on day 3, followed by a decrease in IL-6 and the neutrophil-to-lymphocyte ratio by day 5, alongside relative stabilization of IL-10. In contrast, the development of reperfusion syndrome was accompanied by a progressive increase in both IL-6 and IL-10, as well as a marked, progressive rise in the NLR.

Consequently, the defining difference in patients with reperfusion syndrome was not so much the magnitude of the initial immuno-inflammatory activation, but rather the lack of its timely resolution and its continued progression during the post-reperfusion period.

From a pathogenetic perspective, this suggests that following the restoration of blood flow, a subset of patients develops an excessive and poorly controlled inflammatory response, characterized by neutrophil activation, increased production of pro-inflammatory mediators, and a compensatory rise in anti-inflammatory cytokines. Such a state can contribute to blood-brain barrier disruption, exacerbate the vasogenic and cytotoxic components of cerebral edema, impair microcirculation, and—depending on the severity of the injury—lead to hemorrhagic transformation and other clinical manifestations of reperfusion syndrome.

Thus, the dynamic assessment of IL-6, IL-10, and the SNLR holds potentially greater diagnostic and prognostic value than a single measurement upon admission. In the study cohort, the direction of changes observed on days 3–5 was the key factor distinguishing an uncomplicated reperfusion course from post-reperfusion syndrome. A combination of persistently elevated IL-6 and a progressive rise in SNLR, accompanied by elevated IL-10, can be regarded as a characteristic immuno-inflammatory profile of a complicated post-reperfusion course.

The findings support the concept that reperfusion injury following systemic thrombolytic therapy represents not only a direct consequence of blood flow restoration but also a dynamic process of secondary immuno-inflammatory damage, the intensity of which may determine the severity of the subsequent clinical course of ischemic stroke.

The significant increase in IL-6 concentration observed in patients with reperfusion syndrome aligns with findings from recent studies identifying IL-6 as one of the most sensitive biomarkers for the severity of neuroinflammation and adverse outcomes in ischemic stroke. IL-6 enhances the expression of cell adhesion molecules, facilitates neutrophil migration across the vessel wall, increases blood-brain barrier permeability, and promotes the development of vasogenic cerebral edema. Elevated IL-6 levels are also associated with an increased risk of hemorrhagic transformation following reperfusion therapy.

No less important is the detected increase in SNLR in patients with reperfusion syndrome. The growth of this indicator reflects the predominance of the innate immune response over the adaptive one and indicates systemic activation of the inflammatory process.

Thus, the obtained results confirm that not only the intensification of the pro-inflammatory response but also the impairment of immune regulation mechanisms constitutes an important component of the pathogenesis of RPS.

Our results allow the immune-inflammatory response to be viewed as a key component of the pathogenesis of this complication and confirm the advisability of including immunological biomarkers in early risk stratification algorithms.

This study is the first to investigate the relationship of SNLR, IL-6, and IL-10 with early functional deterioration in patients with acute ischemic stroke receiving intravenous thrombolytic therapy.

Conclusions. Systemic intravenous thrombolytic therapy for ischemic stroke is accompanied by activation of the immune-inflammatory response, which is more pronounced in patients who develop reperfusion syndrome.

Reperfusion syndrome is characterized by elevated levels of IL-6 and SNLR, as well as an imbalance between pro- and anti-inflammatory mediators, compared to patients without reperfusion syndrome.

The combined assessment of IL-6, IL-10, and the IL-6/IL-10 ratio provides more informative value for evaluating the severity of neuroinflammation and the early risk of developing postoperative cognitive dysfunction than individual markers alone.

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