



RESEARCH ARTICLE

Neutrophils and leukocytes in acute ischemic stroke: Traditional markers for predicting clinical outcomes

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ABSTRACT

Objective: Systemic inflammation, particularly involving leukocytes and neutrophils, plays a critical role in stroke pathophysiology and lesion evolution and may influence treatment safety and outcomes. This study aimed to evaluate the prognostic value of admission leukocyte and neutrophil counts in patients with acute ischemic stroke treated with intravenous thrombolysis and/or mechanical thrombectomy.

Method: A total of 101 patients with ischemic stroke in the middle cerebral artery (MCA) territory who were treated with intravenous tissue plasminogen activator (IV tPA), mechanical thrombectomy (MT), or bridging therapy were analyzed. Demographic, clinical, laboratory, and neuroimaging data were collected. Infarct and hemorrhage volumes were calculated using the ABC/2 method. Clinical outcomes were assessed using National Institutes of Health Stroke Scale (NIHSS) scores and the modified Rankin Scale (mRS). Associations between inflammatory markers, radiological findings, hemorrhagic transformation, and functional outcomes were analyzed.

Results: Higher admission leukocyte and neutrophil counts were significantly associated with large artery atherosclerosis and were observed in patients undergoing mechanical thrombectomy or bridging therapy. Elevated leukocyte and neutrophil levels were associated with larger infarct volumes, an increased risk of intracranial hemorrhage, and poorer functional outcomes. Patients with unfavorable outcomes and those who died within 90 days had significantly higher leukocyte and neutrophil counts. Higher glycated hemoglobin (HbA1c) and C-reactive protein (CRP) levels and lower high-density lipoprotein (HDL) levels were associated with hemorrhagic transformation and poor prognosis. Successful recanalization was associated with smaller infarct volumes and better functional outcomes.

Conclusion: Admission leukocyte and neutrophil counts are associated with stroke etiology, hemorrhagic complications, and functional outcomes following reperfusion therapy. These readily available inflammatory biomarkers may serve as useful prognostic indicators in the management of acute ischemic stroke.

Keywords: Acute ischemic stroke, mechanical thrombectomy, intravenous thrombolysis, leukocyte, neutrophil

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INTRODUCTION

Acute ischemic stroke is a leading cause of mortality and long-term disability worldwide despite significant advances in reperfusion therapies. A substantial proportion of patients experience unfavorable outcomes, highlighting the need for readily available biomarkers that may assist in prognostic assessment and clinical decision-making.

Ischemic stroke triggers an acute inflammatory response characterized by the recruitment of various immune cells, particularly neutrophils and leukocytes, which play pivotal roles in disease pathophysiology (1). Elucidating the dynamics and behavior of these cells may enhance our understanding of the mechanisms underlying ischemia-related brain injury.

Following ischemic stroke, an inflammatory cascade is initiated in the brain, encompassing both local and systemic immune responses. Neutrophils are among the first immune cells to migrate into ischemic tissue, with evidence demonstrating their accumulation within the first 12 hours. This early neutrophil infiltration contributes significantly to secondary brain injury by promoting oxidative stress, releasing proinflammatory mediators, and disrupting the blood-brain barrier, thereby adversely affecting recovery (1–3). Neutrophils contribute to the early inflammatory response and become further activated during reperfusion after stroke, potentially contributing to the no-reflow phenomenon (2). This increased activation can intensify cerebral edema and exacerbate neuronal injury, highlighting the importance of the inflammatory process (4, 5).

Inflammatory markers are closely associated with the severity of ischemic stroke and subsequent clinical outcomes. Elevated leukocyte and neutrophil levels, in particular, have been associated with larger infarct volume, more severe initial neurological impairment, a greater likelihood of hemorrhagic transformation, and unfavorable clinical outcomes (3–6).

This study aimed to assess the relationship between admission leukocyte and neutrophil counts and radiological and functional outcomes in patients with acute ischemic stroke treated with intravenous tissue plasminogen activator (IV tPA) and/or mechanical thrombectomy. We examined the associations of these inflammatory markers with stroke etiology, hemorrhagic transformation, infarct volume, and 90-day functional outcomes to clarify their prognostic value in patients with acute ischemic stroke.

METHODS

Patient Selection

Patients admitted to the hospital with a diagnosis of acute ischemic stroke and treated with IV tPA and/or mechanical thrombectomy were included in the study. Based on the type of reperfusion therapy received, patients were categorized into three groups: those treated with IV tPA alone, those who underwent mechanical thrombectomy alone, and those who received bridging therapy, defined as mechanical thrombectomy following IV tPA administration. Only patients with acute ischemic stroke involving the middle cerebral artery territory were included. Ethical approval for this study was obtained from the Yeditepe University Clinical Research Ethics Committee (approval number: 1212). Written informed consent was obtained from the patients and/or their relatives.

Clinical Information and Neuroimaging

Demographic characteristics, including age and sex, were recorded. Detailed clinical data were collected, including baseline National Institutes of Health Stroke Scale (NIHSS) scores and the presence of comorbidities such as diabetes mellitus, hypertension, atrial fibrillation, and previous stroke. Laboratory parameters obtained at admission included complete blood count parameters (leukocyte and neutrophil counts), serum lipid profiles (low-density lipoprotein [LDL] and high-density lipoprotein [HDL]), glycated hemoglobin (HbA1c), and C-reactive protein (CRP) levels. To evaluate treatment time intervals, symptom-to-door, door-to-needle, symptom-to-puncture, and puncture-to-recanalization times were recorded.

Procedural data, including the number of passes, the method employed, and recanalization status according to the modified Thrombolysis in Cerebral Infarction (mTICI) score, were recorded.

Clinical outcomes were evaluated using NIHSS scores at 24 hours and at discharge and the modified Rankin Scale score at 90 days.

Stroke etiology was determined after etiological investigations according to the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification.

The presence of intracranial hemorrhage after treatment was evaluated using cranial computed tomography (CT) according to the European Cooperative Acute Stroke Study (ECASS) criteria. Infarct volume was assessed using follow-up cranial magnetic resonance imaging (MRI) or CT obtained at least 24 hours after treatment. Infarct size was calculated

using the ABC/2 formula, where A represents the largest infarct diameter, B represents the diameter perpendicular to A, and C represents the number of imaging slices containing the infarct multiplied by the slice thickness. Infarct volume was then estimated as $A \times B \times C / 2$. Similarly, in patients with hemorrhagic transformation, intracranial hemorrhage volume was calculated using the same method on cranial CT images obtained at 24 hours.

Statistical Analysis

Statistical analyses were performed using appropriate parametric and nonparametric tests according to the distribution of the data. Nonparametric data were expressed as medians and interquartile ranges, whereas parametric data were expressed as means and standard deviations. Differences between groups were analyzed using Student's t-test or the Mann-Whitney U test, as appropriate, and correlation analyses were performed using Pearson's or Spearman's correlation tests. Fisher's exact test was used to evaluate categorical data. A p value <0.05 was considered statistically significant. Statistical analyses were performed using SPSS version 30.0.0 and GraphPad Prism version 9.1.2.

RESULTS

A total of 101 patients were enrolled in the study. Of these, 54 (53.5%) underwent mechanical thrombectomy, 31 (30.7%) were treated with IV tPA alone, and 16 (15.8%) received both IV tPA and mechanical thrombectomy (bridging therapy). Fifty-six (55.4%) patients were male and 45 (44.6%) were female. Twenty (19.8%) patients did not have a proximal occlusion, whereas 27 (26.7%) had an internal carotid artery (ICA) occlusion, 33 (32.7%) had a middle cerebral artery (MCA) M1 segment occlusion, and 21 (20.8%) had an MCA M2 segment occlusion (Table 1).

All patients underwent noncontrast cranial tomography on admission and at 24 hours. Baseline Alberta Stroke Program Early CT Scores (ASPECTS) ranged from 6 to 10. Overall, nine (8.9%) patients had an ASPECTS of 6, 27 (26.7%) had a score of 7, 25 (24.8%) had a score of 8, 32 (31.7%) had a score of 9, and eight (7.9%) had a score of 10.

The median leukocyte count was 8,355/ μ L (interquartile range [IQR]: 6,582.5–10,697.5) in the overall study population, 6,980/ μ L (IQR: 6,020–9,470) in the IV tPA group, 9,060/ μ L (IQR: 6,590–11,030) in

the mechanical thrombectomy group, and 9,125/ μ L (IQR: 7,067.5–10,847.5) in the bridging therapy group. The median neutrophil count and neutrophil percentage were 4,060/ μ L (IQR: 3,120–6,390) and 61.0%, respectively, in the IV tPA group; 6,270/ μ L (IQR: 4,060–8,455) and 68.3%, respectively, in the mechanical thrombectomy group; and 5,880/ μ L (IQR: 4,585–7,105) and 65.9%, respectively, in the bridging therapy group. Both neutrophil count and neutrophil percentage differed significantly among the treatment groups ($p=0.007$ and $p=0.003$, respectively) (Fig. 1a, b), with patients treated with mechanical thrombectomy having significantly higher neutrophil counts and percentages than those treated with IV tPA alone. To assess whether infection might account for the differences in neutrophil counts, CRP levels were compared among the groups; no significant difference was observed ($p=0.089$).

Successful recanalization was achieved in 55 (78.6%) patients who underwent mechanical thrombectomy (MT), including 42 (77.8%) in the MT-alone group and 13 (81.3%) in the bridging therapy group (Fig. 2a).

According to the TOAST classification, 23 (22.8%) patients had large artery atherosclerosis, 44 (43.6%) had cardioembolism, and 14 (13.9%) had small vessel disease. Four (4%) patients had other determined etiologies, such as vasculitis, and 16 (15.8%) were classified as having cryptogenic stroke. Analysis of the relationship between leukocyte and neutrophil counts and stroke etiology revealed that patients with large artery atherosclerosis had significantly higher leukocyte and neutrophil numbers than patients with other etiologies ($p=0.004$ and $p=0.006$, respectively).

The median lesion volume at 24 hours was 3,857.68 mm³ (IQR: 1,322.19–35,372.16) in the IV tPA group, 106,375.61 mm³ (IQR: 20,674.22–218,992.67) in the mechanical thrombectomy group, and 42,654.81 mm³ (IQR: 11,903.33–106,176.53) in the bridging therapy group. Seventy-five (74.3%) patients had no intracranial hemorrhage. Intracranial hemorrhage was observed in three (9.7%) patients in the IV tPA group, 18 (33.3%) in the MT group, and five (31.3%) in the bridging therapy group. Lesion volume differed significantly among the treatment groups ($p<0.001$), with patients undergoing mechanical thrombectomy having significantly larger lesion volumes than those treated with IV tPA alone. Hemorrhage volume also differed significantly among the groups ($p=0.044$), with greater hemorrhage volumes observed in the mechanical thrombectomy group than in the IV tPA group.

Table 1: Patient characteristics according to treatment group

	IV tPA (n=31)	MT (n=54)	Bridging therapy (n=16)	Total (n=101)	p
Demographic characteristics					
Age (mean±SD)	66.1±14.8	67.2±13.1	62.3±15.2	66.1±13.9	0.52
Female sex, n (%)	14 (45.2)	26 (48.1)	5 (31.3)	45 (44.6)	0.49
Medical history					
Diabetes mellitus, n (%)	15 (48.4)	19 (35.2)	7 (43.8)	41 (40.6)	0.47
Hypertension, n (%)	22 (71)	32 (59.3)	10 (62.5)	64 (63.4)	0.56
Hyperlipidemia, n (%)	22 (71)	30 (55.6)	10 (62.5)	62 (61.4)	0.37
Atrial fibrillation, n (%)	9 (29)	25 (46.3)	4 (25)	38 (37.6)	0.15
Previous stroke, n (%)	9 (29)	12 (22.2)	1 (6.3)	22 (21.8)	0.08
Smoking, n (%)	7 (22.6)	7 (13)	4 (25)	18 (17.8)	0.38
Clinical characteristics					
Baseline NIHSS score (median, IQR)	6 (4-9)	13 (11-15.25)	9.5 (7-12.75)	11 (7-14)	0.001
Occlusion site					
ICA	1 (3.2)	21 (38.9)	5 (31.3)	27 (26.7)	0.015
M1 segment	–	27 (50)	6 (37.5)	33 (32.7)	
M2 segment	10 (32.3)	6 (11.1)	5 (31.3)	21 (20.8)	
Symptom-to-door time (median, IQR)	70.5 (52.5-118)	137.5 (50-283.25)	61 (40-87)	90 (50-202)	0.015
Door-to-needle time (median, IQR)	79 (59-100)	–	72 (64.5-86)	73 (61-95)	0.47
Symptom-to-puncture time (median, IQR)	–	313.5 (195-420)	177 (146-235)	240 (177-363)	0.001
Puncture-to-recanalization time (median, IQR)	–	28 (20-51.5)	30 (14.25-62.75)	28.5 (19.5-59)	0.9
Interventional procedures					
Technique employed					0.42
Stent retriever, n (%)	–	25 (47.2)	9 (56.3)	34 (49.3)	0.97
Aspiration, n (%)	–	19 (35.8)	3 (18.8)	22 (31.9)	
Combined, n (%)	–	9 (17)	4 (25)	13 (18.8)	
Number of passes (median, IQR)	–	1 (1-3)	1.5 (1-2.75)	1 (1-3)	0.97
Recanalization score					
mTICI 0-2a	–	12 (22.3)	3 (18.8)	15 (21.4)	0.53
mTICI 2b-3	–	42 (77.7)	13 (81.2)	55 (78.6)	
Clinical outcomes					
NIHSS score at 24 hours (median, IQR)	4 (3-7)	10.5 (7.75-14)	7 (4-14)	8 (4-12.5)	<0.001
NIHSS score at discharge (median, IQR)	3 (0-5.25)	8 (4-13)	6 (3-9)	5 (2-11)	<0.001
mRS score at 90 days					0.003
mRS 0-2	24 (77.4)	22 (40.7)	5 (31.3)	51 (50.5)	0.003
mRS 3-5	5 (16.1)	16 (29.7)	8 (50)	29 (28.7)	
mRS 6	2 (6.5)	16 (29.6)	3 (18.8)	21 (20.8)	

SD: Standard deviation; IQR: Interquartile range; ICA: Internal carotid artery.

Leukocyte and neutrophil counts differed significantly between patients with and without intracranial hemorrhage ($p=0.022$ and $p=0.029$, respectively) (Fig. 1c, d). Higher leukocyte and neutrophil counts were associated with intracranial hemorrhage. HbA1c levels showed a similar

association ($p=0.04$). Patients with higher HDL levels had a lower frequency of intracranial hemorrhage at 24 hours ($p=0.021$), whereas LDL levels did not differ significantly ($p=0.27$). Similar findings were observed in the subgroup of patients who underwent mechanical thrombectomy and achieved successful

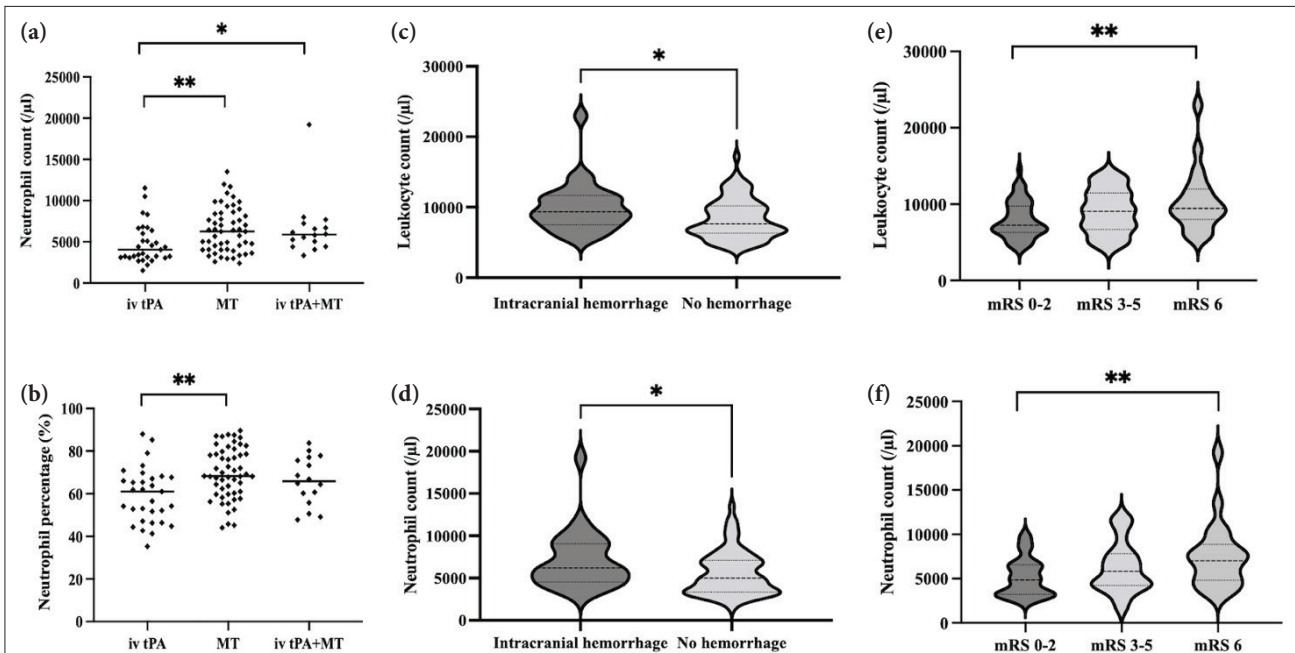


Figure 1. Neutrophil and leukocyte profiles according to treatment, hemorrhagic transformation, and functional outcome. Neutrophil count and ratio were higher in the mechanical thrombectomy and bridging therapy groups than in the intravenous tissue plasminogen activator (IV tPA) group ($p=0.007$ and $p=0.003$, respectively) (a, b). Leukocyte and neutrophil counts were higher in patients with intracranial hemorrhage at 24 hours ($p=0.022$ and $p=0.029$, respectively) (c, d) and in patients with poor functional outcomes at 90 days ($p=0.019$ and $p=0.008$, respectively) (e, f).

recanalization. In this subgroup, leukocyte and neutrophil counts, HDL cholesterol levels, and HbA1c levels differed significantly between patients with and without intracranial hemorrhage ($p=0.026$, $p=0.041$, $p=0.009$, and $p=0.046$, respectively).

The modified Rankin Scale (mRS) was used to assess functional outcomes during follow-up. Patients with mRS scores of 0–2 were considered functionally independent. At 90 days, 51 (50.5%) patients achieved functional independence (mRS 0–2), including 24 (77.4%) in the IV tPA group, 22 (40.7%) in the mechanical thrombectomy group, and five (31.3%) in the bridging therapy group. Twenty-one (20.8%) patients had died by 90 days (Fig. 2b).

Lesion and hemorrhage volumes at 24 hours differed significantly according to functional independence ($p<0.001$ and $p=0.003$, respectively). Hemorrhage volume was significantly greater in patients with an mRS score of 6. Functionally independent patients had smaller lesion volumes at 24 hours. Patients with a favorable functional outcome (mRS 0–2) demonstrated a significantly greater reduction in NIHSS score from baseline to 24 hours after treatment ($p=0.002$).

Leukocyte and neutrophil counts differed significantly among the 90-day functional outcome

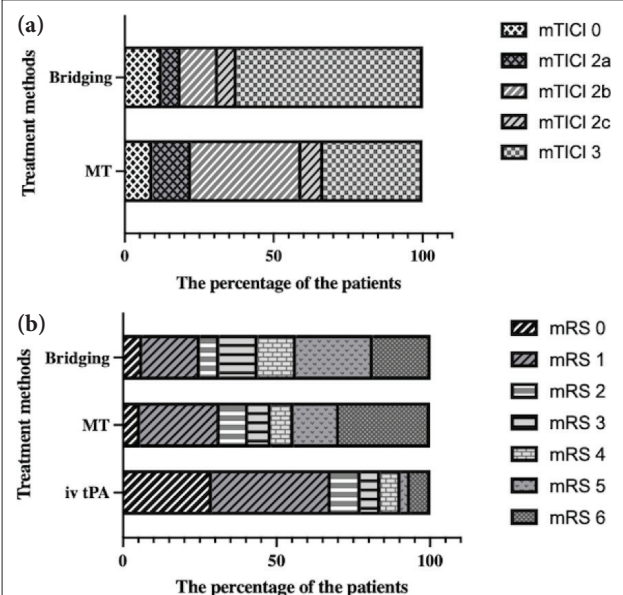


Figure 2. Recanalization scores and clinical outcomes. Modified Thrombolysis in Cerebral Infarction (mTICI) scores (a) and modified Rankin Scale (mRS) scores (b) of patients at 90 days according to treatment method.

groups ($p=0.019$ and $p=0.008$, respectively), with the highest values observed in patients with an mRS score of 6 at 90 days (Fig. 1e, f). In addition, CRP,

HDL cholesterol, and HbA1c levels were significantly associated with functional outcomes ($p=0.017$, $p=0.020$, and $p=0.020$, respectively). Higher CRP and HbA1c levels, together with lower HDL cholesterol levels, were associated with unfavorable functional outcomes.

Recanalization status, determined using the mTICI scoring system, was associated with lesion volume at 24 hours ($p=0.033$); patients with successful recanalization (mTICI 2b–3) had smaller lesions at 24 hours. Recanalization status was also significantly associated with the 90-day mRS score ($p=0.041$), with unsuccessful recanalization being associated with poorer functional outcomes.

DISCUSSION

This study examined the associations between inflammatory biomarkers and clinical outcomes in patients with acute ischemic stroke undergoing intravenous thrombolysis and/or mechanical thrombectomy. Our results demonstrated that admission leukocyte and neutrophil counts were associated with stroke etiology, hemorrhagic transformation, and functional outcomes, highlighting the role of systemic inflammation in stroke pathophysiology and prognosis following reperfusion therapy.

Patients undergoing mechanical thrombectomy or bridging therapy had significantly higher leukocyte and neutrophil counts than those treated with IV tPA alone. CRP levels did not differ significantly among the treatment groups, suggesting that infection was unlikely to account for the observed differences. In addition, none of the patients included in the study had a hematological disorder known to alter complete blood count parameters. These findings may reflect differences in underlying stroke severity, as patients treated with mechanical thrombectomy typically have large vessel occlusions and more extensive ischemic injury. Consistent with this interpretation, previous studies have demonstrated that elevated leukocyte and neutrophil counts at admission are strongly associated with the presence of large vessel occlusion (7). Moreover, lymphocyte counts and ratios have been shown to predict large vessel occlusion in acute ischemic stroke (8).

Patients with large artery atherosclerosis had higher leukocyte and neutrophil counts than those with other stroke etiologies. Large artery atherosclerosis is characterized by persistent

vascular inflammation and unstable atherosclerotic plaques, conditions that may predispose patients to an amplified inflammatory response during acute ischemia (4). Higher levels of systemic inflammatory markers, particularly leukocyte counts, have been associated with an increased risk of cerebrovascular disease, including acute ischemic stroke resulting from atherosclerosis (9). These findings underscore the important role of inflammation in the development of atherosclerosis and subsequent vascular occlusion. Our results further support existing evidence that the systemic inflammatory burden varies among stroke subtypes and may affect both therapeutic response and clinical outcomes.

Hemorrhagic transformation is one of the most feared complications of reperfusion therapy. In this study, higher leukocyte and neutrophil counts were significantly associated with intracranial hemorrhage at 24 hours. Considering the potential effect of recanalization on hemorrhagic transformation, subgroup analyses were performed in patients who underwent mechanical thrombectomy and achieved successful recanalization. The associations persisted in this subgroup, suggesting that inflammation may be associated with hemorrhagic risk independently of angiographic reperfusion. Both experimental and clinical studies have demonstrated that neutrophil-driven inflammatory processes, together with endothelial injury, proteolytic enzyme release, and oxidative stress, can increase vascular permeability and thereby promote hemorrhagic transformation (1, 4). Moreover, admission and postprocedural neutrophil-to-lymphocyte ratios have been identified as independent prognostic factors for intracranial hemorrhage and functional outcomes in patients with large vessel occlusion (6, 10–12).

Functional outcome at 90 days, assessed using the modified Rankin Scale, was significantly associated with leukocyte and neutrophil counts. Patients who died had the highest leukocyte and neutrophil levels, whereas those who achieved functional independence had lower counts and showed greater early neurological improvement, as reflected by a larger reduction in NIHSS scores. Consistent with these findings, previous clinical studies have reported that elevated leukocyte and neutrophil counts in acute ischemic stroke are associated with larger infarct volumes and poorer functional outcomes (13–16). Neutrophils are among the first immune cells recruited to ischemic brain tissue and are known to promote blood-brain

barrier disruption, microvascular impairment, and secondary neuronal injury, which may account for their association with poorer radiological and clinical outcomes (4).

Moreover, elevated HbA1c levels were associated with an increased risk of hemorrhage, suggesting that poor long-term glycemic control may compromise microvascular integrity. In contrast, higher HDL levels were associated with a lower risk of hemorrhagic complications, potentially because of their anti-inflammatory and endothelial-protective effects. Additionally, increased CRP and HbA1c levels, together with reduced HDL levels, were associated with poorer functional outcomes, underscoring the complex interplay among inflammation, metabolic status, and stroke recovery.

Recent evidence indicates that higher HbA1c levels are associated with an increased risk of poor functional recovery and higher mortality in patients with acute ischemic stroke (17, 18). HbA1c reflects chronic glycemic status and may therefore provide important information regarding long-term outcomes (19). Accordingly, patients with poor prestroke glycemic control may experience worse neurological outcomes. HDL modulates macrophage and adipocyte function through cholesterol transport mechanisms, thereby exerting anti-inflammatory and antiatherosclerotic effects (20, 21). In acute ischemic stroke, the neutrophil-to-HDL cholesterol ratio (NHR) has been identified as a potential prognostic marker, with an elevated NHR associated with poor functional outcomes in patients treated with either intravenous thrombolysis or mechanical thrombectomy (22, 23).

Successful recanalization was associated with smaller infarct volumes and better functional outcomes, emphasizing that timely and effective reperfusion remains a key prognostic factor (24). Lesion volume at 24 hours was closely associated with both hemorrhagic transformation and functional outcome. Larger lesion volumes were associated with an increased risk of hemorrhagic complications and poorer clinical outcomes, as previously reported in the literature (25).

Although neutrophil and leukocyte counts have been extensively investigated in acute ischemic stroke, the present study extends previous work in several important ways. Specifically, it examines acute reperfusion therapies across defined patient subgroups, provides a detailed analysis of radiological

parameters, including lesion volume, hemorrhage volume, and reperfusion scores, and simultaneously evaluates additional laboratory markers such as HbA1c and CRP.

This study has several limitations. First, as a single-center study, the findings may not be fully generalizable to broader patient populations. The relatively modest sample size, particularly within the treatment subgroups, may have limited the statistical power to detect smaller differences and conduct more detailed subgroup analyses. Finally, only admission leukocyte and neutrophil counts were evaluated; serial measurements and additional inflammatory biomarkers might have provided a more comprehensive assessment of the temporal inflammatory response.

Our results indicate that systemic inflammation, particularly neutrophil-mediated responses, is associated with the safety and functional outcomes of reperfusion treatment for acute ischemic stroke. These findings suggest that leukocyte and neutrophil counts, which are routinely available in clinical practice, may serve as useful prognostic indicators. A better understanding of inflammatory mechanisms, particularly those involving neutrophils, may contribute to the development of future therapeutic strategies aimed at modulating the immune response and potentially improving outcomes in patients with ischemic stroke.

Ethical Approval: This study was approved by The Yeditepe University Clinical Research Ethics Committee with approval number 1212, date: 07.05.2020.

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Contribution Categories		Author Initials
Category 1	Concept/Design	S.A., B.Y., Y.G.O.
	Data acquisition	S.A.
	Data analysis/Interpretation	S.A., B.Y.
Category 2	Drafting manuscript	S.A.
	Critical review or revision of manuscript	B.Y., Y.G.O.
Category 3	Final approval and accountability	S.A., B.Y., Y.G.O.
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