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ORIGINAL ARTICLE

Effect of inflammatory response before mechanical thrombectomy on prognosis in stroke patients

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A mechanikus thrombectomia előtti gyulladási válasz hatása a stroke-betegek prognózisára

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Háttér és cél – A mechanikus thrombectomia az akut stroke legfontosabb kezelési módja; a sikeres thrombectomia ellenére a betegek jelentős részénél nem érhető el jó funkcionális eredmény. Ez a tanulmány a neutrophil-lymphocytá arány (neutrophil lymphocyte ratio, NLR) kórházi felvételnél mért értékeinek hatását vizsgálta a sikeresen rekanalizált betegek funkcionális kimenetelére.

Módszerek – Visszamenőlegesen elemeztük azokat a betegeket, akiknél mechanikus thrombectomiát végeztek elülső rendszerbeli nagyérelzáródás miatt, és összehasonlítottuk a sikeresen rekanalizált betegek felvételi NLR-értékeivel és a három hónapos klinikai módosított Rankin-skála (mRS) pontszámaival.

Eredmények – Az összesen 126 beteg közül, akiknél a megadott időszakon belül thrombectomiát végeztek, 97 sikeres rekanalizációval rendelkező beteget vontunk be a vizsgálatba. A teljes sikeres rekanalizációs arány 77% volt. Az mRS ≤ 2 (n = 65) betegek átlagos NLR-értéke szignifikánsan alacsonyabbnak bizonyult, mint az mRS ≥ 3 (n = 32) betegeké (p < 0,001). Gyenge és szignifikáns korrelációt találtunk a National Institutes of Health Stroke Scale (NIHSS) érték és az NLR között (r = 0,315, p = 0,002).

Következtetés – Az NLR-érték összefüggést mutat a mechanikus thrombectomiával kezelt betegek sikertelen rekanalizációjával. Ezért úgy gondoljuk, hogy a gyulladás thrombectomia előtti szuppressziója növeli a sikeres thrombectomia esélyét.

Kulcsszavak: stroke, mechanikus thrombectomia, gyulladás, neutrophil-lymphocytá arány, prognózis

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Background and purpose – Mechanical thrombectomy is the most important treatment modality in acute stroke; despite successful thrombectomy, good functional outcome is not achieved in a significant proportion of patients. This study examined the effect of neutrophil lymphocyte ratio (NLR) values at admission on functional outcomes in successfully recanalized patients.

Methods – Patients who underwent mechanical thrombectomy due to anterior system major vessel occlusion were retrospectively analyzed and compared with the admission NLR values and 3-month clinical modified Rankin Scale (mRS) scores of successfully recanalized patients.

Results – Of a total of 126 patients who underwent thrombectomy within the specified period, 97 patients with successful recanalization were included in the study. The overall successful recanalization rate was calculated as 77%. The mean NLR of patients with mRS ≤ 2 (n=65) was found to be significantly lower than patients with mRS ≥ 3 (n=32) (p<0.001). A weak and significant correlation was found between National Institutes of Health Stroke Scale (NIHSS) value and NLR (r= 0.315, p=.002).

Conclusion – NLR value has been found to be associated with futile recanalization in mechanical thrombectomy patients. Therefore, we think that suppression of inflammation before thrombectomy will increase the chance of successful thrombectomy.

Keywords: stroke, mechanical thrombectomy, inflammation, neutrophil to lymphocyte ratio, prognosis

Recanalization with mechanical thrombectomy is the most important treatment with proven efficacy in acute stroke patients. Randomized controlled studies have shown that endovascular therapy (EVT) is more effective than standard medical therapy in patients with acute ischemic stroke caused by large vessel occlusion¹⁻⁴.

The modified treatment in cerebral infarction (mTICI) is used to assess vessel recanalisation after endovascular treatment. A value indicating reperfusion of more than 50% of the affected area is called mTICI 2b and complete recanalisation is called mTICI 3. On the other hand, modified Rankin scale (mRS) (ranging from 0 [no symptoms] to 6 [death]) is generally used to evaluate disability status, and 0-2 indicates functional independence³. Despite successful endovascular treatment mTICI \geq 2b, 25-50% of patients do not have a good clinical outcome (mRS 3-6) and this is called futile recanalization (FR)^{5,6}.

Early identification of factors associated with poor clinical outcome despite successful recanalization may lead to the development of adjunctive therapeutic strategies to increase the benefit of EVT. Factors thought to be associated with FR include admission National Institutes of Health Stroke Scale (NIHSS) score, glucose levels, number of thrombectomy, and collateral conditions⁷⁻⁹.

Neutrophils are among the first cells to rise in the blood after ischemic stroke and contribute to the breakdown of the blood-brain barrier (BBB), brain edema, and increased brain damage. After ischemic stroke, the number of circulating neutrophils increases while the number of lymphocytes decreases, resulting in an increase in the neutrophil-to-lymphocyte ratio (NLR)¹⁰⁻¹².

Some studies have predicted that NLR at baseline may predict prognosis in patients with ischemic stroke treated with iv. thrombolytic (IVT) or EVT, finding that higher pre-treatment NLR is associated with symptomatic intracerebral haemorrhage (sICH) or worse 3-month functional outcomes. It was thought that this might be due to neuroinflammation induced by increased NLR¹²⁻¹⁵. In this study, we examined the effect of NLR and other prognostic factors in patients who did not achieve good clinical results despite successful recanalization with EVT.

Materials and methods

Patients who underwent mechanical thrombectomy at two different center from April 2021 to January 2023 were retrospectively analyzed. Patients with intracranial proximal artery occlusion in the anterior circulation (ie, intracranial carotid artery or M1/M2 segments of middle cerebral artery) indicated by Digital Subtraction Angiography (DSA) were included in the study. Patients in whom thrombectomy was initiated within 6 hours of the onset of stroke and who achieved nearly or complete recanalization (mTICI 2b or 3) were included. NIHSS score, demographic data, vascular risk factors, medical

history, and initial stroke severity were determined for all patients before the procedure. Collateral status, which may affect the prognosis, was determined by using the modified TAN score. Patients with an Alberta Stroke Program Early CT Score (ASPECTS) of 8 and above were included in the study in order not to affect the prognosis before the procedure. Patients who used any anti-inflammatory drugs before the procedure were excluded from the study.

Complete blood count taken at admission before thrombectomy and neutrophil and lymphocyte counts of the patients were analyzed as percentages of total white blood cells (WBC). NLR was calculated as the ratio of the percentage of neutrophils to the percentage of lymphocytes.

In the 3-month evaluation of the patients' good clinical outcome, face-to-face interviews or telephone evaluations were made with the patients, and the patients' good functional neurological status was defined as mRS \leq 2.

Statistical analysis

Data were evaluated using the Statistical Package for the Social Sciences (SPSS) version 21.0. Descriptive statistics are presented as frequency (n) and percentage (%) for categorical variables, Mean \pm Standard deviation (Mean \pm Ss) or Median and Minimum value (Min) - Maximum value (Max) for continuous variables. Chi-square test was used to compare categorical variables. The compatibility of continuous variables with the assumption of normal distribution was evaluated with the Kolmogorov-Smirnov test, and since the data were not normally distributed, the Mann-Whitney U test was used to compare continuous variables between two independent groups. In statistical analyses, $p < 0.05$ was accepted as significant.

Results

Of a total of 126 patients who underwent thrombectomy within the specified period, 97 patients with successful recanalization were included in the study. The overall successful recanalization rate was calculated as 77%. The mean age of the 97 patients included in the study was 65.3 years (24-86) and 50 were male (51.5%) and 47 were female. Baseline characteristics are shown in **Table 1**. Good clinical outcome (mRS \leq 2) was found in 67% (n: 65) of the patients who were successfully recanalized (mTICI 2b-3), and futile recanalization was found in 33% (n: 32) (**Table 2**). The mean NLR of patients with mRS \leq 2 (n=65) was found to be significantly lower than patients with mRS \geq 3 (n=32) ($p < 0.001$) (**Table 2** and **Figure 1**).

The TAN collateral value of 89.2% of patients with mRS \leq 2 (n=65) was found to be good (2-3). 62.5% of patients with mRS \geq 3 (n=32) had a poor (0-1) TAN collateral value.

Table 1. Baseline characteristics of patients

Characteristics (n: 97)	n (%)
Age (mean) (min-max)	65.3 (24-86)
Gender (Male)	50 (51.5)
CT ASPECT score, median (IQR)	9 (8-10)
NIHSS score on admission, median (IQR)	19 (14-24)
Vascular risk factors, n (%)	
Hypertension	74 (76.2)
Diabetes mellitus	48 (49.4)
Atrial fibrillation	40 (41.2)
Coronary artery disease	73 (75.2)
Hyperlipidemia	19 (19.5)
Stroke etiology, n (%)	
Cardioembolism	49 (50.5)
Large artery atherosclerotic disease	10 (10.3)
Unknown etiology	38 (39.1)

Values are mean (SD), median (IQR), or n (%) as appropriate. ASPECT: Alberta Stroke Program Early CT Score for MCA territory stroke; CT: computed tomography; IQR: interquartile range; NIHSS: National Institutes of Health Stroke Scale.

Good mRS value was found to be associated with good TAN collateral value ($p < 0.001$) (Table 3). A weak and significant correlation was found between NIHSS value and NLR ($r = 0.315$, $p = .002$). An increase in NLR values was observed in patients with high NIHSS (Figure 2).

Discussion

Ischemic stroke is a major health concern, accounting for a significant number of incident strokes. Reperfusion therapies, such as endovascular thrombectomy (EVT) have emerged as crucial interventions to improve clinical outcomes for patients with acute ischemic stroke (AIS) secondary to large vessel occlusion (16, 17). However, despite successful recanalization, a substantial proportion of patients experience unfavorable functional outcomes^{18, 19}.

The pathophysiology of ischemic stroke involves a complex interplay of various factors, including the inflammatory response. In the acute stage of stroke, the occlusion of distal cortical pial collateral vessels leads to the release of adhesion molecules, cytokines, and chemokines by the arterial endothelium. This in turn triggers the recruitment of leukocytes, primarily neutrophils to the

Table 2. Clinical outcome and mean NLR values

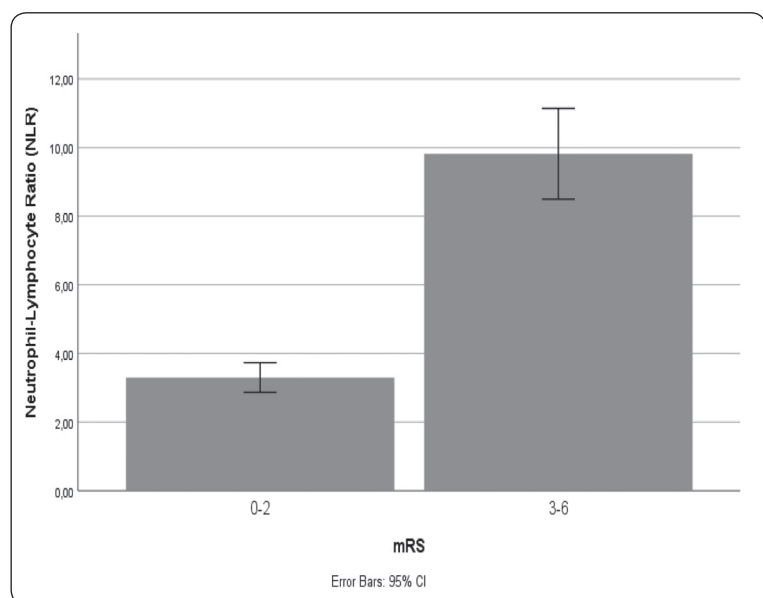
mRS (n, %)	NLR mean (min-max)	Statistics value
≤ 2 (n:65, 67.0%)	3,30 (1.1-10.0)	$p < 0.001$
≥ 3 (n:32, 33.0%)	9,82 (2.9-21.0)	U=103,00

mRS: Modified Rankin Scale; NLR: neutrophil lymphocyte ratio

ischemic cerebral vessels^{20, 21}. Neutrophils infiltrate the ischemic or infarcted tissue through the damaged blood-brain barrier exacerbating the inflammatory cascade²¹.

In recent years, there has been growing interest in using inflammation-related biomarkers to predict outcomes in AIS patients. Among these biomarkers, the neutrophil-to-lymphocyte ratio (NLR) has gained attention as a reliable and cost-effective measure of systemic inflammation²². Studies have demonstrated the potential of NLR as a prognostic indicator for mortality, functional status, angiographic outcomes, intracerebral hemorrhage, and stroke-associated infections or pneumonia in AIS patients, including those undergoing reperfusion therapies²⁰⁻²².

Several studies have investigated the association between NLR and outcomes in AIS patients undergoing EVT. In one study, Ma et al. found that higher NLR values were independently associated with unfavorable functional outcomes in AIS patients with successful recanalization after EVT¹⁷. Similarly, another study by Al-Mufti et al. demonstrated that elevated NLR was predictive of poor outcomes, including mortality and the need for prolonged invasive mechanical ventilation in COVID-19 patients with acute ischemic stroke due to large vessel

**Figure 1.** Clinical outcome and mean NLR values

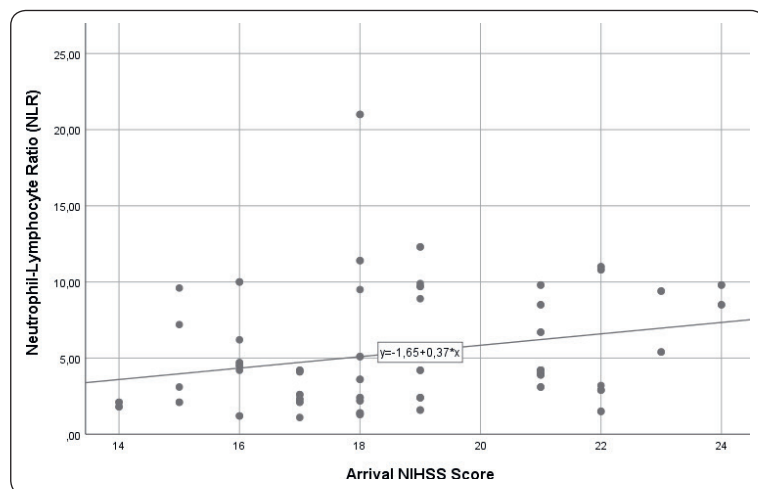


Figure 2. NIHSS and NLR correlation

Table 3. Clinical outcome and collateral status

mRS		Tan collateral		Total
		Good (2-3)	Poor (0-1)	
≤2	Frequency	58	7	65
	%	89.2%	10.8%	100.0%
≥3	Frequency	12	20	32
	%	37.5%	62.5%	100.0%
Total		70	27	97
P		<0.001		

mRS: Modified Rankin Scale

occlusion¹⁶. In our study, we found high NLR values in patients who were similarly recanalized to futile.

In addition to baseline NLR values, the dynamic changes in NLR over time have also been investigated. A study by Li et al. assessed dynamic NLR in patients who underwent EVT for ischemic stroke with acute large artery occlusion and found that increased NLR in the early stage within 3 days after treatment was associated with an increased risk of mortality at 1 month¹⁸. Interestingly, the NLR of survivors decreased more than that of nonsurvivors within 1 month after EVT, even after adjustments for confounders.

Increased NLR value, which is a marker of systemic inflammation in patients with successful recanalization, increases futile recanalization and therefore suggests that these patients should be given systemic anti-inflammatory agents such as corticosteroid before the procedure.

Experimental evidence has shown that blood flow is not restored in some randomly distributed brain areas after reopening of the cerebral circulation and platelets and leukocytes contribute to the futile recanalisation²³. The recanalization and reperfusion of the previously hypoxic brain areas increase the pro-inflammatory function of platelets and activate complex thrombo-inflammatory pathways that contribute to the ischemia-reperfusion injury. In our study, higher NLR values were found in patients with higher NIHSS values, suggesting more cerebral damage and more inflammatory response in these patients.

While the association between NLR and outcomes in AIS patients undergoing EVT is established, the underlying mechanisms are yet to be fully elucidated. The inflammatory response, characterized by the activation of leukocytes, platelets, and pro-inflammatory mediators, is believed to play a vital role in the pathophysiology of AIS¹⁹. It is possible that the elevated NLR reflects the extent of systemic inflammation and physiological stress, which may outweigh the potential benefit of mechanical thrombectomy in some patients.

Conclusion

The neutrophil lymphocyte ratio (NLR) has emerged as a promising biomarker for predicting outcomes in AIS patients undergoing mechanical thrombectomy. Higher NLR values have been associated with unfavorable functional outcomes and increased mortality. Additionally, the dynamic changes in NLR over time may provide further insights into the prognosis of patients post-EVT. However, more research is needed to fully understand the underlying mechanisms and validate the utility of NLR as a prognostic tool. The use of inflammation-related biomarkers, such as NLR, in clinical practice has the potential to enhance risk stratification and guide treatment decisions in AIS patients undergoing mechanical thrombectomy.

CONFLICT OF INTEREST – The authors declare no conflict of interest.

References

- Berkhemer OA, Fransen PSS, Beumer D, et al. A randomized trial of intraarterial treatment for acute ischemic stroke. *N Engl J Med* 2015;372(1):11-20.
<https://doi.org/10.1056/NEJMoa1411587>
- Goyal M, Demchuk AM, Menon BK, et al. Randomized assessment of rapid endovascular treatment of ischemic stroke. *N Engl J Med* 2015;372(1):1019-30.
<https://doi.org/10.1056/NEJMoa1414905>
- Jovin TG, Chamorro A, Cobo E, et al. Thrombectomy within 8 hours after symptom onset in ischemic stroke. *N Engl J Med* 2015;372(24):2296-306.
<https://doi.org/10.1056/NEJMoa1503780>
- Saver JL, Goyal M, Bonafeet A, et al. Stent-retriever thrombectomy or intravenous t-PA vs. t-PA alone in stroke. *N Engl J Med* 2015;372(24):2285-95.
<https://doi.org/10.1056/NEJMoa1415061>
- Hussein HM, Saleem MA, Qureshi AI. Rates and predictors of futile recanalization in patients undergoing endovascular treatment in a multicenter clinical trial. *Neuroradiology* 2018;60(5):557-63.
<https://doi.org/10.1007/s00234-018-2016-2>
- Molina CA. Editorial: Futile recanalization in mechanical embolectomy trials: a call to improve selection of patients for revascularization. *Stroke* 2010;41(5):842-3.
<https://doi.org/10.1161/STROKEAHA.110.580266>
- Gilberti N, Gamba M, Premi E, et al. Leukoaraiosis is a predictor of futile recanalization in acute ischemic stroke. *J Neurol* 2017;264(3):448-52.
<https://doi.org/10.1007/s00415-016-8366-y>
- Baek JH, Kim BM, Heo JH, et al. Number of stent retriever passes associated with futile recanalization in acute stroke. *Stroke* 2018;49(9):2088-95.
<https://doi.org/10.1161/STROKEAHA.118.021320>
- Horie N, Morofuji Y, Iki Y, et al. Impact of basal ganglia damage after successful endovascular recanalization for acute ischemic stroke involving lenticulostriate arteries. *J Neurosurg* 2019;132(6):1880-8.
<https://doi.org/10.3171/2019.3.JNS182909>
- Segel GB, Halterman MW, Lichtman MA. The paradox of the neutrophil's role in tissue injury. *J Leukocyte Biol* 2011;89(3):359-72.
<https://doi.org/10.1189/jlb.0910538>
- Jickling GC, Liu D, Ander BP, Stamova B, Zhan X, Sharp FR. Targeting neutrophils in ischemic stroke: translational insights from experimental studies. *J Cereb Blood Flow Metab* 2015;35(6):888-901.
<https://doi.org/10.1038/jcbfm.2015.45>
- Semerano A, Laredo C, Zhao Y, et al. Leukocytes, collateral circulation, and reperfusion in ischemic stroke patients treated with mechanical thrombectomy. *Stroke* 2019;50(12):3456-64.
<https://doi.org/10.1161/STROKEAHA.119.026743>
- Brooks SD, Spears C, Cummings C, VanGilder RL, Stinehart KR, Gutmann L, et al. Admission neutrophil-lymphocyte ratio predicts 90 day outcome after endovascular stroke therapy. *J Neurointerventional Surg* 2014;6:578-83.
<https://doi.org/10.1136/neurintsurg-2013-010780>
- Maestrini I, Strbian D, Gautier S, et al. Higher neutrophil counts before thrombolysis for cerebral ischemia predict worse outcomes. *Neurology* 2015;85(16):1408-16.
<https://doi.org/10.1212/WNL.0000000000002029>
- Zhu W, Guo Z, Yu S. Higher neutrophil counts before thrombolysis for cerebral ischemia predict worse outcomes. *Neurology* 2016;86(11):1077.
<https://doi.org/10.1212/01.wnl.0000481976.41273.a1>
- Al-Mufti F, Khandelwal P, Sursal T, et al. Neutrophil-Lymphocyte ratio is associated with poor clinical outcome after mechanical thrombectomy in stroke in patients with COVID-19. *Interv Neuro-radiol* 2023;29(4):386-92.
<https://doi.org/10.1177/15910199221093896>
- Ma J, Guo W, Xu J, et al. Platelet-to-lymphocyte ratio and neutrophil-to-lymphocyte ratio are independently associated with functional outcomes in acute ischemic stroke patients with successful recanalization after endovascular thrombectomy. *Front Neurol* 2022;13:1039060.
<https://doi.org/10.3389/fneur.2022.1039060>
- Li S, Hu L, Wang J, et al. Prolonged increased neutrophil-to-lymphocyte ratio is associated with mortality after successful revascularization for treatment of acute ischemic stroke. *BMC Neurol* 2022;22(1):326.
<https://doi.org/10.1186/s12883-022-02847-3>
- Kollikowski AM, Schuhmann MK, Nieswandt B, et al. Local leukocyte invasion during hyperacute human ischemic stroke. *Ann Neurol* 2020;87(3):466-79.
<https://doi.org/10.1002/ana.25665>
- Macrez R, Ali C, Toutirais O, et al. Stroke and the immune system: from pathophysiology to new therapeutic strategies. *Lancet Neurol* 2011;10(5):471-80.
[https://doi.org/10.1016/S1474-4422\(11\)70066-7](https://doi.org/10.1016/S1474-4422(11)70066-7)
- Weyland CS, Mokli Y, Vey JA, et al. Predictors for failure of early neurological improvement after successful thrombectomy in the anterior circulation. *Stroke* 2021;52:1291-8.
<https://doi.org/10.1161/STROKEAHA.120.030519>
- Švitoňska M, Slomka A, Korbal P, et al. Association of neutrophil-to-lymphocyte ratio and lymphocyte-to-monocyte ratio with treatment modalities of acute ischaemic stroke: a pilot study. *Medicina* 2019;55:342.
<https://doi.org/10.3390/medicina55070342>
- Stoll G, Nieswandt B. Thrombo-inflammation in acute ischaemic stroke-implications for treatment. *Nat Rev Neurol* 2019;15(8):473-81.
<https://doi.org/10.1038/s41582-019-0221-1>