Turkish Journal of Neurology

Turk J Neurol 2025;31(1):16-24
Doi: 10.55697/tnd.2025.216

ORIGINAL ARTICLE

The potential of biomarkers to predict futile recanalization in stroke patients receiving endovascular treatment

Firat Karaaslan[1], Reşit Yilmaz[1], Fidel Demir[2], Müttalip Özbek[3], İbrahim Kaplan[4], Eşref Akil[5]

[1]Department of Neurology, Gazi Yaşargil Training and Research Hospital, Diyarbakır, Türkiye
[2]Department of Neurology, Selahaddin Eyyubi State Hospital, Diyarbakır, Türkiye
[3]Department of Neurology, Kızıltepe State Hospital, Mardin, Türkiye
[4]Department of Biochemistry, Dicle University Faculty of Medicine, Diyarbakır, Türkiye
[5]Department of Neurology, Dicle University Faculty of Medicine, Diyarbakır, Türkiye

ABSTRACT

Objectives: This study aimed to investigate the relationships between serum S100 calcium binding protein, neuron-specific enolase, matrix metalloproteinase-9, interleukin-6, N-terminal probrain natriuretic peptide, and N-methyl-D-aspartate receptor subunit NR2 biomarkers and futile recanalization in patients with acute ischemic stroke who were successfully recanalized with endovascular treatment.

Patients and methods: In this study, 44 patients (25 males, 19 females; mean age: 62.2±14.1 years; range, 26 to 81 years) with acute ischemic stroke due to acute anterior circulation large-vessel occlusion were prospectively analyzed between May 15, 2020 and October 15, 2020. Blood samples were taken at admission, as well as 6 and 24 h after endovascular treatment. A modified Rankin Scale (mRS) was used on the 90th day to identify futile reperfusion. Patients with mRS scores ≤2 were included in the favorable reperfusion group (n=20), while patients with mRS scores ≥3 were considered to exhibit futile reperfusion (n=24).

Results: There were no significant differences between the biomarker levels of the groups (p>0.05). There was no statistically significant correlation between biomarkers and 90-day mRS scores (p>0.05). Higher National Institute of Health Stroke Scale (NIHSS) scores (p=0.004), higher number of retriever passes (p=0.032), and higher diastolic blood pressure (p=0.037) were associated with futile recanalization. Multivariate logistic regression analysis showed that a higher NIHSS score at admission was an independent predictor of futile recanalization (odds ratio=1.216, 95% confidence interval 1.01-1.46, p=0.038).

Conclusion: A higher NIHSS score at admission was an independent predictor for futile recanalization. However, we concluded that biomarker levels were not associated with futile recanalization.

Keywords: Acute ischemic stroke, biomarkers, clinical outcome, endovascular treatment, futile recanalization.

The high rates of death and disability due to stroke increase the need for detailed investigations regarding stroke diagnosis, treatment, and follow-up. The early treatment of stroke can minimize the risk of death and disability. Endovascular treatment (EVT) and intravenous tissue-type plasminogen activator (IV-tPA) provide arterial reperfusion for the ischemic area and improve outcomes.[1] Endovascular treatment is a safe and efficient treatment modality for acute ischemic stroke due to intracranial large-vessel occlusion.[2] The number of patients who do not improve clinically despite successful recanalization of the occluded intracranial arteries is substantial. Worse clinical outcomes after EVT were found in almost more than half of patients.[3,4] The rapid recognition of patients who are at an increased risk of adverse outcomes can help target patients who deserve close attention and timely treatment. Therefore, in addition to clinical and neuroimaging parameters, plasma biomarkers may also help achieve these goals.[5,6] A panel of several markers derived from various pathophysiological

Correspondence: Firat Karaaslan, MD. Diyarbakır Dağkapı Devlet Hastanesi Nöroloji Kliniği, 21100 Yenişehir, Diyarbakır, Türkiye.
E-mail: drfrt1321@gmail.com
Received: June 03, 2024 **Accepted:** October 14, 2024 **Published online:** March 05, 2025
Cite this article as: Karaaslan F, Yilmaz R, Demir F, Özbek M, Kaplan İ, Akil E. The potential of biomarkers to predict futile recanalization in stroke patients receiving endovascular treatment. Turk J Neurol 2025;31(1):16-24. doi: 10.55697/tnd.2025.216

pathways after reperfusion therapy may be more conclusive than an isolated biomarker.

Studies demonstrated that S100 calcium-binding protein B (S100B) and neuron-specific enolase (NSE), which are released from neurons and astroglial cells damaged by acute ischemic stroke, are associated with clinical outcomes.[7,8] Matrix metalloproteinases (MMPs) are matrix-degrading enzymes with multifactorial effects in central nervous system physiology and pathology. A meta-analysis of 22 studies of MMP-9 revealed that high MMP-9 values were significantly related to larger infarct volume, increased stroke severity, and worse clinical outcomes.[9] N-terminal probrain natriuretic peptide (NT-proBN) is a cardiac hormone primarily released from the ventricles. Some, but not all, studies demonstrated meaningful associations between NT-proBNP and stroke severity, short-term clinical outcomes, and mortality.[10,11] Inflammation plays a significant role in the pathogenesis of acute ischemic stroke. Studies demonstrated that interleukin (IL)-6 contributed to poor clinical outcomes and stroke severity.[12,13] Excitotoxicity mediated by N-methyl-D-aspartate receptors (NMDAR) has been accepted as one of the main pathogenic mechanisms of ischemic stroke.[14]

Based on the studies mentioned above, this study aimed to reveal the potential of serum biomarkers identified to be associated with stroke to predict futile recanalization in patients who were successfully recanalized with EVT.

PATIENTS AND METHODS

In this study, 44 patients (25 males, 19 females; mean age: 62.2±14.1 years; range, 26 to 81 years) with acute ischemic stroke who were admitted to the Dicle University Faculty of Medicine between May 15, 2020 and October 15, 2020 were prospectively analyzed. The inclusion criteria were as follows: *(i)* patients diagnosed with acute ischemic stroke by clinical and imaging findings; *(ii)* presenting within the first 10 h of symptom onset; *(iii)* having a prestroke modified Rankin Scale (mRS) score of 0 to 1; *(iv)* being over 18 years old; *(v)* successful recanalization after EVT; *(vi)* having an Alberta Stroke Program Early Computed Tomography Score (ASPECTS) ≥6. The exclusion criteria were as follows: *(i)* presenting after the 10th h of the onset of acute ischemic stroke symptoms; *(ii)* being diagnosed with advanced dementia; *(iii)* the presence of severe mental retardation, *(iv)* a finding of bleeding in the brain images (intracerebral, subarachnoid, or subdural); *(v)* having advanced-stage cancer. The study protocol was approved by the Dicle University Faculty of Medicine Non-Interventional Clinical Research Ethics Committee (date 07.05.2020, no: 143). Written informed consent was obtained from all participants. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Blood samples were collected from the patients at three different timepoints both before and after EVT treatment. In this way, serum protein levels of the markers were determined before treatment. Consequently, how the marker levels progressed with the treatment was investigated.

The mRS was used on the 90th day to identify futile recanalization. Patients with mRS scores ≤2 were included in the favorable recanalization group, while patients with mRS scores ≥3 were considered to exhibit futile recanalization. Successful recanalization was defined as thrombolysis in cerebral infarction (TICI) scale of grade ≥2b.

All patients were operated on under sedoanalgesia. An 8F guide catheter was inserted into the carotid artery through the femoral sheath. While thrombectomy for the occluded artery was performed in patients with tandem occlusion, stent placement was performed in ipsilateral cervical carotid occlusion when required. In some cases, balloon angioplasty and stent placement were accomplished as required at the discretion of the operator.

In all patients, 20 mL blood samples were taken from the femoral artery or forearm veins into gel tubes at the time of admission and 6 and 24 h after EVT. After the samples were allowed to clot for 20 to 30 min, they were centrifuged at 800 rpm for 10 min, and the sera were separated and stored in six separate Eppendorf tubes for each patient at −80 °C until the study day. Frozen serum samples were thawed at room temperature on the day of analysis. Repeated freezing and thawing was avoided. Analyses were carried out at the biochemistry laboratory of Dicle University Faculty of Medicine. Blood samples were quantitatively measured with an enzyme-linked immunosorbent assay.

Demographic characteristics, such as age and sex, chronic disease history, laboratory findings, admission fever, and systolic/diastolic blood values of all patients, including those who received IV-tPA, were recorded. The time from the onset of symptoms to EVT puncture (symptom to puncture time), the time from arrival at the hospital to

TABLE 1
Comparison of patients' basis features grouped by 90-day mRS scores

	Favorable recanalization (n=20)					Futile recanalization (n=24)					
	n	%	Mean±SD	Median	IQR	n	%	Mean±SD	Median	IQR	*p*
Age (year)				65	44-81				61	30-78	0.539
Sex											0.259
Male	13	52				12	48				
Female	7	37				12	63				
Admission NIHSS			12.6±3.5					16.3±4.526			0.004
24th-hour NIHSS				1	0-7				22	12-30	0.001
Admission laboratory results											
Systolic blood pressure				130	118-175				62	112-192	0.071
Diastolic blood pressure			83.4±22.9					192.5±27.4			**0.037**
Blood glucose level				119	79-171				132	100-246	0.052
Total cholesterol			176.8±35.4					198.9±48			0.111
LDL			113.1±31					126±32.6			0.155
Creatinine				0.85	0.63-1.6				0.79	0.5-3.2	0.142
GFR			78.3±23.3					81±27.4			0.601
PTT			23.2±2.3					24±3.1			0.608
INR				1.12	0.98-2.01				1.14	0.88-2.5	0.829
Fever				36.6	36.5-36.9				36.6	36.1-37	0.186
Imaging aspect											
Admission MRI				7	6-9				8	8-8	0.661
Admission CT				8.2	7-10				7.2	5-9	0.276
Control MRI				6.5	5-9				5	1-6	**0.038**
Control CT				7	7-8				1	1-5	**0.001**
Door-imaging time (min)			23.3±11.6					23.1±12.6			0.926
Symptom-puncture time (min)			267.1±84.8					270.2±91.6			0.715
Door-puncture time (min)			46.9±17.9					44.1±14.7			0.757
Risk factors											
Hypertension	9	42.8				17	70				0.058
Hyperlipidemia	2	10				1	4				0.472
Diabetes	3	15				8	33				0.138
Cigarettes	5	25				3	14				0.322
Coronary artery disease	3	15				9	37				0.079
Atrial fibrillation	7	35				7	29				0.293
Congestive heart failure	1	5				1	4				0.923
IV-tPA	11	58				8	42				0.197
Vascular occlusions (anterior circulation)											0.360
Right hemisphere	12	53				11	47				
Left hemisphere	8	38				13	62				
OCSP classification											**0.007**
TACS	10	38				16	62				
PACS	10	56				8	44				
Number of retriever passes				1	1-3				3	1-9	**0.032**
Tandem occlusion	3	30				7	70				0.231
Aortic arcus bovine	2	25				6	75				0.176
Aortic arcus type											0.052
1	13	52							12	42	
2	6	38							10	62	
3	2	66							1	34	
TICI status											0.141
2b	2	20							8	80	
2c	9	60							6	40	
3	9	47							10	53	

mRS: Modified Rankin Scale; SD: Standard deviation; IQR: Interquartile range; NIHSS: National Institute of Health Stroke Scale; LDL: Low-density lipoprotein; GFR: Glomerular filtration rate; PTT: Partial thromboplastin time; INR: International normalized ratio; MRI: Magnetic resonance imaging; CT: Computed tomography; IV-tPA: Intravenous tissue-type plasminogen activator; OCSP: Oxfordshire community stroke project; TACS: Total anterior circulation syndrome; PACS: Partial anterior circulation syndrome; TICI: Thrombolysis in cerebral infarction.

EVT puncture (door to puncture time), and the time from arrival at the hospital until the end of imaging (door to imaging time) were calculated. Vascular occlusions of the cases occurred in the anterior circulation. Stroke subtypes in the case groups were categorized using the Bamford

classification system. Recanalization after EVT was calculated according to TICI scores. Vascular pathology localization and the presence of tandem lesions were noted. The aortic arch type and the presence of a bovine aortic arch were recorded. The number of retriever passes was specified in the transaction. The brain imaging ASPECTS score was obtained at admission and for the first 36 h after EVT.

Statistical analyses

Statistical analysis was performed using the IBM SPSS version 22.0 software (IBM Corp., Armonk, NY, USA). Continuous variables were defined as mean ± standard deviation (SD) for normally distributed variables and medians (interquartile range) for nonnormally distributed variables. Categorical variables were expressed as percentages and frequencies. Continuous variables' distributions were assessed with the Shapiro-Wilk test. The chi-square test was applied to categorical variables, and Fisher exact test was used if at least one of the groups included five or fewer patients. Spearman's rho correlation analysis was applied for variables. A t-test or the Wilcoxon test was used for comparisons in dependent groups, and a t-test or the Mann-Whitney U test was applied to compare continuous variables between two independent groups. Linear complex models were performed to measure changes in biomarker levels across the three timepoints, and the data were stratified according to the futile recanalization. The associations of radiological and clinical parameters with futile recanalization were analyzed with a multivariable binary logistic regression model. Variables put in the model were those that differed significantly in the univariate comparisons. A p-value <0.05 was considered statistically significant. Variables were assayed within a 95% confidence interval.

RESULTS

Twenty-four patients underwent futile recanalization, and 20 underwent favorable recanalization. The mean age was lower in the futile recanalization group, but there was no statistically significant difference between the groups. Intravenous thrombolysis was administered to 19 patients prior to EVT. Regarding demographic, clinical, and imaging results of the recanalization groups, National Institute of Health Stroke Scale (NIHSS) scores at admission (p=0.001), 24-h NIHSS scores (p=0.004), diastolic blood pressure at admission (p=0.037), number of retriever passes (p=0.032), and total anterior circulation stroke (p=0.007) were statistically higher in the futile recanalization group. The mean time from the onset of symptoms to EVT puncture in the futile recanalization group was 270.2 min. There was no significant difference between the risk factors of the patient groups. Control brain computed tomography (p=0.001) and magnetic resonance imaging ASPECT scores (p=0.038) were found to be significantly lower in the futile recanalization group. A comparison of the demographic, clinical, and radiological data between the futile and favorable recanalization groups is provided in Table 1.

The binary logistic regression analysis of variables is reported in Table 2. Multivariate logistic regression analysis showed that high NIHSS scores at admission were independent predictors of futile recanalization (odds ratio=1.216, 95% confidence interval 1.01-1.46, p=0.038). The comparison of six biomarkers taken from the serum at different times from the two groups with 90-day mRS scores is provided in Table 3. There was no remarkable distinction between the biomarkers used in the comparison. No correlation was found between 90-day mRS scores and the values of each biomarker taken at different times (p>0.05; Table 4).

The time courses for each biomarker for the favorable and futile recanalization groups according to 90-day mRS scores are shown in Figure 1. The levels of each biomarker at different times

TABLE 2
Multivariate logistic regression model of predictors to futile recanalization

Variables	*Adjusted OR	*Adjusted (95% CI)	*p*
Admission NIHSS	1.216	1.01-1.46	0.038
Diastolic blood pressure	1.034	0.98-1.08	0.156
Number of retriever passes	1.490	0.88-2.50	0.132

* Adjusted for Admission NIHSS, Admission Diastolic Blood Pressure, and Number of Retriever Passes; NIHSS: National Institute of Health Stroke Scale; OR: Odds ratio; CI: Confidence interval.

TABLe 3
Comparison of biomarkers

		Favorable recanalization (n=20)		Futile recanalization (n=24)		
	Time	Median	IQR	Median	IQR	*p*
S100B	Pre-EVT	218.4	120.4-1035.0	290.1	158.1-1673	0.195
	Post-EVT 6 h	243.7	140.2-959.1	239.7	108.6-1770	0.925
	Post-EVT 24 h	197.6	117.5-872.1	224.3	119.5-1586	0.316
NSE	Pre-EVT	4.9	2.89-101.2	4.9	3.7-30.0	0.953
	Post-EVT 6 h	4.8	3.66-15.5	5.6	3.5-116.2	0.396
	Post-EVT 24 h	4.8	3.76-9.3	5.0	3.5-184.5	0.540
NR2	Pre-EVT	29.5	21.07-65.1	28.2	21.4-1243.6	0.724
	Post-EVT 6 h	28.8	22.91-68.6	28.7	19.7-223.6	0.916
	Post-EVT 24 h	28.7	23.64-142.1	26.6	19.8-205.5	0.540
IL-6	Pre-EVT	24.6	19.24-117.2	26.4	18.0-262.1	0.596
	Post-EVT 6 h	26.0	18.28-388.7	25.4	18.9-342.0	1.000
	Post-EVT 24 h	25.8	18.62-94.2	30.0	20.5-285.9	0.451
MMP-9	Pre-EVT	25.7	17.28-141.0	26.5	17.1-769.9	0.465
	Post-EVT 6 h	33.2	16.94-134.4	25.7	19.7-299.4	0.897
	Post-EVT 24 h	26.4	18.49-132.6	2.2	18.9-441.4	0.759
NT-proBNP	Pre-EVT	2.0	1.43-12.0	2.0	1.5-14.5	0.596
	Post-EVT 6 h	1.9	1.53-10.3	1.8	1.5-27.1	0.981
	Post-EVT 24 h	1.9	1.59-18.5	290.1	1.5-23.6	0.869

IQR: Interquartile range; S100B: S100 calcium binding protein; EVT: Endovascular treatment; NSE: Neuron specific enolase; NR2: Subunit; IL-6: Interleukin; MMP-9: Matrix metallo proteinase-9; NT-proBNP: N-terminal prohormone of brain natriuretic peptide.

were higher in the favorable recanalization group. However, this difference was not statistically significant (p>0.05).

DISCUSSION

In this study, we investigated the utility of a panel of six biomarkers, each representing different pathological pathways, in predicting futile recanalization following EVT. Contrary to our expectations, none of these biomarkers were significantly associated with futile recanalization. Higher NIHSS scores at admission, a higher number of retriever passes, and a higher diastolic blood pressure at admission were shown to be associated with futile recanalization. These results aligned with the conclusions of other research on EVT.[15,16]

The S100B is a calcium-binding protein produced by astrocytes that exerts differential effects on neurons and glia. It was stated that S100B was an acceptable biomarker for ischemic stroke.[17] In a study investigating the use of S100B for brain damage in EVT, which had results similar to those

TABLE 4
Correlation between biomarkers and mRS scores

	Time	r	*p*
S100B	Pre-EVT	0.117	0.448
NSE		−0.049	0.753
MMP-9		−0.022	0.889
IL-6		0.015	0.925
NT-proBNP		0.044	0.776
NR2		−0.009	0.953
S100B	Post-EVT 6 h	−0.086	0.578
NSE		0.134	0.384
MMP-9		−0.092	0.551
IL-6		−0.064	0.680
NT-proBNP		0.007	0.967
NR2		−0.079	0.610
S100B	Post-EVT 24 h	0.013	0.933
NSE		0.048	0.756
MMP-9		−0.071	0.650
IL-6		0.028	0.855
NT-proBNP		−0.050	0.746
NR2		−0.149	0.339

mRS: Modified Rankin Scale; S100: Calcium binding protein B; NSE: Neuron specific enolase; MMP-9: Matrix Metallo Proteinase-9; IL-6: Interleukin-6; NT-proBNP: N-terminal prohormone of brain natriuretic peptide; NR2: Subunit; EVT: Endovascular treatment.

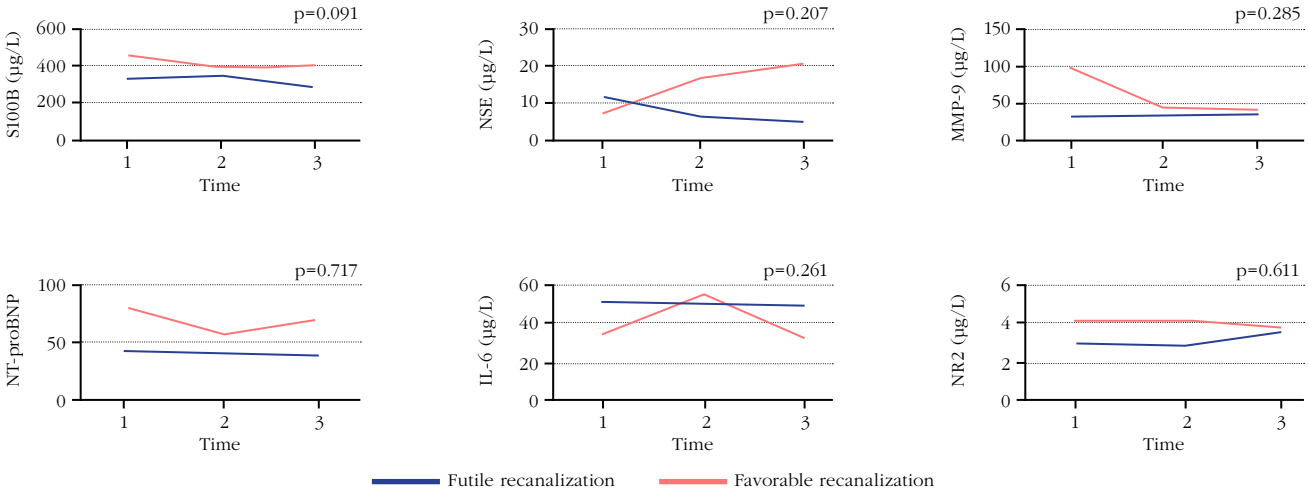

Figure 1. Temporal profiles of S100B, NSE, MMP-9, IL-6, NT-proBNP, NMDAR subunit NR2 according to recanalization groups. Time 1: Pre-EVT, Time 2: Post-EVT 6 h, Time 3: Post-EVT 24 h.

S100B: S100 calcium binding protein; NSE: Neuron specific enolase; MMP-9: Matrix metallo proteinase-9; NT-proBNP: N-terminal prohormone of brain natriuretic peptide; IL-6: Interleukin; NR2: Subunit; NMDAR: N-methyl-D-aspartate receptors; EVT: Endovascular treatment.

of our study, it was not found to be correlated with clinical results.[18] In another study, S100B was found to be correlated with the degree of ischemic tissue damage after EVT.[19] This difference with our study can be explained, at least in part, by differences in sampling times. Previous studies demonstrated that after vascular occlusion, maximum S100B levels were reached 48 to 72 h after the onset of symptoms.[20,21] Therefore, the longer the sampling delay, the more significant the association with stroke damage.

Neuron-specific enolase is a dimeric isoenzyme of enolase, a cytoplasmic glycolytic enzyme involved in the glucose metabolism of the central nervous system. It was observed to be increased in stroke.[22] In a meta-analysis that included twelve studies, NSE levels were found to increase with increasing stroke size, but there was no such correlation in two of the studies.[23] In two studies, high NSE levels were generally related to worse outcomes, while low NSE levels were ambiguous. In seven studies, prognosis at discharge and follow-up were compared with NSE levels; there was no association in four studies. In a study investigating the use of NSE after EVT, results similar to those of our study were obtained,[18] indicating that the power of NSE in predicting futile recanalization or short-term clinical outcomes may be weak.

Matrix metalloproteinase-9 is an important member of the extracellular proteinase family that is involved in the degradation of the extracellular matrix. In a study examining the relationship between the clinical outcomes of acute ischemic stroke and serum MMP-9, MMP-9 levels were related to increased mortality and worse clinical outcomes.[24] In a study investigating the biomarkers of unfavorable outcomes in patients with acute ischemic stroke with successful recanalization, increased MMP-9 levels were independent predictors of unsuccessful recanalization.[25] However, in two studies examining stroke patients who underwent successful recanalization with EVT, which had results similar to those of this study, MMP-9 was not related to clinical outcomes at three months.[26,27]

Interleukin-6 is a factor that plays a part in the pathogenesis, clinical course, and prognosis of ischemic stroke.[28] A meta-analysis was conducted that included 24 studies investigating the relationship between IL-6 and poor prognosis after stroke, and IL-6 was found to be associated with poststroke infection.[29] However, the detection of isolated IL-6 in stroke did not appear to be beneficial in terms of prognosis. In addition, in a study similar to our study, no relationship was found between futile reperfusion and IL-6.[30] This was consistent with our study. Larger and multicenter studies are needed to evaluate the relationship between IL-6 and clinical outcomes, particularly in stroke patients undergoing EVT.

The NMDAR is an ionotropic glutamate receptor subtype, and NR2 is one of its seven subunits.

The NR2 peptide is cleaved from the NMDAR in ischemia and is measurably released into the blood across the blood-brain barrier. One study showed that NR2 could potentially be useful in assisting diagnosis of acute ischemic stroke.[31] In a study investigating the relationship between serum NR2 levels and the severity of and prognosis after acute ischemic stroke, which found results similar to those of our study, serum NR2 antibody levels were found to be insufficient as a biomarker for determining the early diagnosis and clinical outcome of ischemic stroke.[32] The present study is the first to investigate the relationship between NR2 peptide levels and futile recanalization.

The main source of NT-proBNP is the ventricles, and it is synthesized from the ventricular muscle due to an increase in end-diastolic pressure and volume. It is thought to play an important role in hemodynamic regulation in the acute phase of stroke.[33] In a study aimed at investigating the relationship between early NT-proBNP and mortality in patients receiving reperfusion treatment, NT-proBNP was found to be associated with malignant edema and mortality.[34] A large-scale meta-analysis showed a significant correlation between higher NT-proBNP levels and poor prognosis in ischemic stroke patients.[35] In our study, there was no relationship between NT-proBNP and ineffective recanalization. The difference from previous studies may be due to differences in the methods and plasma sampling times.

Certain methodological limitations must be considered when describing the findings of this research. First, a relatively small number of patients were included due to strict inclusion criteria. For example, patients with failed recanalization (TICI <2b) were not included in this study. Second, patients were recruited from a single center and were limited in number; therefore, further studies with larger numbers of patients are needed. Third, since the treatments each patient received, such as endovascular interventions and supportive treatment, were not standardized, differences in treatments may have affected the observed results.

In conclusion, the findings of this study indicated that higher NIHSS score at admission was an independent predictor for futile recanalization. However, we concluded that biomarker levels were not associated with futile recanalization. Additional studies are required to confirm the predictive performance of these biomarkers regarding stroke outcomes. Biomarkers in patients who were completely recanalized with EVT did not show any prognostic ability. Additional studies are needed to include patients who did not receive EVT or were not completely recanalized with EVT.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Idea/concept, design, data collection and/or processing, literature review, writing the article, references and fundings, materials: F.K.; Idea/concept, design, control/supervision, critical review, materials, data collection and/or processing, literature review: R.Y.; Idea/concept, design, control/supervision, critical review, literature review: F.D.; Control/supervision, critical review, materials, data collection and/or processing: M.Ö.; Design, critical review, references and fundings, materials: İ.K.; Idea/concept, design, control/supervision, analysis and/or, interpretation, literature review, critical review, references and fundings, materials: E.A.

Conflict of Interest: The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding: The authors received no financial support for the research and/or authorship of this article.

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