

CLINICAL STUDY

The relationship between neutrophil/lymphocyte, monocyte/lymphocyte, platelet/lymphocyte ratios and clinical outcomes after ninety days in patients who were diagnosed as having acute ischemic stroke in the emergency room and underwent a mechanical thrombectomy

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ABSTRACT

AIM: To determine whether there was a relationship between the neutrophil/lymphocyte (NLR), monocyte/lymphocyte (MLR), and the platelet/lymphocyte ratios (PLR) measured in blood samples taken at admission and clinical outcomes (CO) on the 90th day in patients, who were diagnosed as acute ischemic stroke (AIS) in the emergency department (ED) and underwent a mechanical thrombectomy (MT).

METHOD: Patients aged ≥ 18 years, who were diagnosed as AIS in the ED and underwent MT were included in the study. Patients, who received diagnostic codes of "Cerebrovascular Diseases" (CVD) according to the ICD-10 diagnostic codes were identified. One hundred fifty patients were enrolled in the study. Modified Rankin Scale (mRS) score was used to determine neurologic status on the 90th day. The patients were divided into the two groups: good and poor CO (mRS 0–2 and mRS 3–6, respectively). The groups were compared in terms of age, sex, and NIHSS, ASPECT, and mRS scores.

RESULTS: The rates of successful recanalization and good CO were 81.3 % and 38.7 %, respectively. The mortality rate was 22 %. The recanalization rates in the good and poor CO groups were 100 % and 69.6 %, respectively. Recanalization was achieved in 73.6 % of those with hyperlipidaemia and 88.5 % of those without hyperlipidaemia, which was statistically significant ($p = 0.034$). We observed a statistically significant relationship between the clinical outcome and NLR, MLR, PLR ($p < 0.05$). As the result of multivariate analysis, we found only NLR as an independent risk factor for poor CO ($p = 0.043$). There was also a statistically significant difference between mortality and NLR, PLR ($p = 0.001$).

CONCLUSION: We found that NLR, MLR, PLR values were associated with CO after 90 days; high rates were associated with poor CO and low rates were associated with good CO (Tab. 7, Ref. 38). Text in PDF www.elis.sk

KEY WORDS: acute ischemic stroke; neutrophil/lymphocyte ratio, monocyte/lymphocyte ratio; platelet/lymphocyte ratio; thrombectomy.

Aim and introduction

Stroke is responsible for a significant portion of mortality and has been the third most common cause of mortality worldwide for the last 50 years (1). Acute ischemic stroke (AIS) occurs due to thrombotic mechanisms, embolic mechanisms or hypoperfusion and accounts

for 87 % of all the strokes (2). Standard treatment of AIS consists of the use of tissue plasminogen activator (tPA) and mechanical thrombectomy for the recanalization of occlusion in brain vessels. Many clinical studies showed the benefits of endovascular recanalization in occlusions of the anterior circulation (3–6). Studies published after the second half of the 1990s showed that intravenous (IV) tPA in AIS has been beneficial when given in the hours immediately after the onset of the symptoms (7). The European Stroke Organization (ESO) refers to mechanical thrombectomy as the first-line treatment in patients with AIS in whom there is large vessel occlusion and IV thrombolytic therapy is contraindicated. The guidelines suggest a mechanical thrombectomy in combination with IV thrombolytic therapy in the treatment of patients with proximal occlusion within the first 6 hours. Accordingly, IV thrombolytic therapy should be started within 4.5 hours in eligible cases and mechanical thrombectomy should be performed within 6 hours of symptom onset (8).

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In some previous studies, the ratios of neutrophils/lymphocytes (NLR), monocytes/lymphocytes (MLR), and platelets/lymphocytes (PLR) were shown to be indicative of systemic inflammation, to play an important role in venous thromboembolism, and to be effective in determining the tendency to thrombosis (9–11). NLR and PLR were reported to be better indicators of inflammation than leukocyte counts in the whole blood counts (12), and NLR was shown to be an indicator of prognosis in cancer, cardiac diseases, pulmonary embolism, and sepsis (13–21). As far as we know, there was no study that investigated the relationship between NLR, MLR, PLR and clinical outcomes in patients with AIS undergoing a mechanical thrombectomy.

Our aim in this study was to determine whether there was a relationship between NLR, MLR, PLR measured in blood samples taken at admission and clinical outcomes on the 90th day in patients, who were diagnosed with AIS in the emergency department and underwent a mechanical thrombectomy.

Materials and methods

This study was approved by Samsun Training and Research Hospital Ethics Committee on May 29, 2018 (Session No.: 2018/14, Decision No.: TUEK 112-2018 GOKAEK/1-2). Mechanical thrombectomy for AIS began to be performed on January 1, 2017; therefore, patients who were diagnosed with AIS in the emergency department and underwent a mechanical thrombectomy between January 1, 2017, and May 29, 2018, were enrolled in the study. For this purpose, patients, who received “Cerebrovascular Diseases” (SVH) diagnostic codes according to the International Statistical Classification of Diseases and Related Health Problems (ICD-10) diagnostic codes were identified through the hospital information system and their files were obtained. Those, who underwent a mechanical thrombectomy were included in the study. A data collection form was created to collect data in a standard manner. In the data collection form; age, sex, known diseases, laboratory findings (e.g. glucose, urea, creatinine, leukocytes, neutrophils, lymphocytes, monocytes, and platelets) were included. The National Institutes of Health Stroke Scale (NIHSS) score was used to determine the neurologic status at admission, and the Alberta Stroke Program Early Computed Tomography (ASPECT) and Modified Rankin Scale (mRS) scores were used to determine the neurologic status on the 90th day. The patients were divided into the two groups: patients with good clinical outcomes (mRS 0–2) and patients with poor clinical outcomes (mRS 3–6). The groups were compared in terms of age, sex, and NIHSS, ASPECT, and mRS scores. The relationship between NLR, MLR, PLR ratios and clinical outcome was investigated.

Inclusion and exclusion criteria

The study included patients aged over 18 years, who had AIS and underwent a mechanical thrombectomy.

Exclusion criteria: patients with hematologic malignancies, patients younger than 18 years, patients treated for infection for the last two weeks or patients having signs of active infection, patients with known collagen tissue diseases, patients with a history

of gastrointestinal bleeding or major trauma within the last one week, and patients using immunosuppressive drugs.

Statistical analysis

The data were analysed using the IBM SPSS V23 software package. Conformance to normal distribution was examined using the Shapiro-Wilk test. The Mann-Whitney U test was used to compare data without normal distribution with recanalization, clinical outcomes, and mortality. The Chi-square test was used to compare categorical data. Independent risk factors of mortality and good clinical outcomes were analysed using univariate and multivariate logistic regression analyses. The results of the analyses are presented as the median (min-max) for quantitative data, and categorical data are presented as frequency (percentage). The level of statistical significance was accepted as $p < 0.05$.

Results

Of the patients in the study, 44.7 % were female and 55.3 % were male. The rate of successful recanalization was 81.3 %, and the rate of good clinical outcome was 38.7 %. The distributions of patients according to categorical data are given in Table 1.

There was no statistically significant relationship between recanalization and sex, hypertension (HT), diabetes mellitus (DM), atrial fibrillation (AF), and coronary artery disease (CAD) ($p > 0.05$). There was a statistically significant relationship between

Tab. 1. The distributions of patients according to categorical data.

	Number (n)	Percent (%)
Sex		
Female	67	44.7
Male	83	55.3
Recanalization success		
Recanalization was achieved	122	81.3
Recanalization was not achieved	28	18.7
Clinical outcome		
Good clinical outcome	58	38.7
Poor clinical outcome	92	61.3
HT		
-	12	8.0
+	138	92.0
DM		
-	108	72.0
+	42	28.0
AF		
-	112	74.7
+	38	25.3
HL		
-	72	48.0
+	78	52.0
CAD		
-	96	64.0
+	54	36.0
Mortality		
Live	117	78.0
Dead	33	22.0

AF – Atrial Fibrillation, DM – Diabetes Mellitus, HT – hypertension, CAD – Coronary Artery Disease, HL – Hyperlipidemia

Tab. 2. Comparison of categorical data according to recanalization success.

	Recanalization		Test statistics	p
	achieved n (%)	Not achieved n (%)		
Sex				
Female	55 (82.1)	12 (17.9)	$\chi^2=0.046$	0.998
Male	67 (80.7)	16 (19.3)		
Clinical outcome				
Good clinical outcome	58 (100)	0 (0)	$\chi^2=19.745$	<0.001
Poor clinical outcome	64 (69.6)	28 (30.4)		
HT				
-	8 (66.7)	4 (33.3)	$\chi^2=1.848$	0.174
+	114 (82.6)	24 (17.4)		
DM				
-	91 (84.3)	17 (15.7)	$\chi^2=1.541$	0.214
+	31 (73.8)	11 (26.2)		
AF				
-	90 (80.4)	22 (19.6)	$\chi^2=0.082$	0.775
+	32 (84.2)	6 (15.8)		
HL				
-	53 (73.6)	19 (26.4)	$\chi^2=4.504$	0.034
+	69 (88.5)	9 (11.5)		
CAD				
-	79 (82.3)	17 (17.7)	$\chi^2=0.034$	0.855
+	43 (79.6)	11 (20.4)		
Mortality				
Live	99 (84.6)	18 (15.4)	$\chi^2=2.855$	0.091
Dead	23 (69.7)	10 (30.3)		

χ^2 – Chi-square test statistics, AF – Atrial Fibrillation, DM – Diabetes Mellitus, HT – hypertension, CAD – Coronary Artery Disease, HL – Hyperlipidemia

Tab. 4. Comparison of quantitative data according to clinical outcome.

	Clinical outcome		Test statistics	p
	Good	Poor		
Age (year)	64 (36–80)	68.5 (32–87)	U=2253.5	0.109
Time (minute)	245 (120–385)	250 (125–420)	U=2235	0.094
NIHSS	13.5 (6–20)	16 (4–24)	U=2045.5	0.016
ASPECT	9 (6–10)	8 (5–10)	U=2159.5	0.043
Systolic Blood Pressure (mmHg)	150 (80–190)	160 (110–220)	U=1763	<0.001
Diastolic Blood Pressure (mmHg)	87.5 (50–110)	90 (60–120)	U=2016.5	0.010
Pulse Rate / Min	74 (60–100)	77 (64–117)	U=1890.5	0.003
Fever (°C)	36.4 (36–37)	36.4 (36–37.8)	U=2554	0.655
BMI (kg/m ²)	27.7 (22–35.2)	27.5 (22–35.4)	U=2363.5	0.239
Sodium (mEq/L)	138 (128–158)	138 (117–148)	U=2136.5	0.039
Glucose (mg/dL)	121.5 (82–447)	157.5 (85–691)	U=1932.5	0.005
Leukocyte	9.5 (4.3–27.4)	10.2 (6.4–20.7)	U=2178	0.059
Hb (gr/dL)	12.7 (7.8–16.6)	12.8 (8.4–17.4)	U=2556.5	0.667
Htc	37.8 (27.1–47.7)	37.2 (25.8–50.4)	U=2635	0.899
RDW	14.4 (12.1–21)	14.1 (12.5–25.3)	U=2530.5	0.595
Plt	234 (47–428)	220.5 (104–379)	U=2558.5	0.673
Neutrophil	6.8 (1.8–23.7)	8.5 (3.2–17.3)	U=1902.5	0.003
Lymphocyte	1.9 (1–4.6)	1.3 (0.5–4.8)	U=1578.5	<0.001
Monocytes	0.5 (0.2–8.2)	0.5 (0.1–1.3)	U=2647	0.935
Urea	34 (20–116)	44 (19–137)	U=2103.5	0.029
Creatinine (mg/dL)	0.8 (0.5–1.7)	0.9 (0.5–5.4)	U=2165.5	0.050
Neutrophil/Lymphocyte	3.5 (0.4–21.6)	6.9 (0.7–24.7)	U=1438.5	<0.001
Monocyte/Lymphocyte	0.3 (0.1–2.2)	0.4 (0–1.1)	U=1788	0.001
Plt/Lymphocyte	124 (11.2–229.1)	161 (62.1–541.4)	U=1691	<0.001

U – Mann–Whitney U test statistics, BMI – Body mass index, Hb – Hemoglobin, Htc – Hematokrit, Plt – Platelet

Tab. 3. Comparison of categorical data by clinical outcome.

	Clinical outcome		Test statistics	p
	Good n (%)	Poor n (%)		
Sex				
Female	27 (40.3)	40 (59.7)	$\chi^2=0.136$	0.712
Male	31 (37.3)	52 (62.7)		
HT				
-	1 (8.3)	11 (91.7)	$\chi^2=5.061$	0.024
+	57 (41.3)	81 (58.7)		
DM				
-	47 (43.9)	60 (56.1)	$\chi^2=4.594$	0.032
+	10 (23.8)	32 (76.2)		
AF				
-	43 (38.4)	69 (61.6)	$\chi^2=0.000$	1.000
+	15 (39.5)	23 (60.5)		
HL				
-	19 (26.4)	53 (73.6)	$\chi^2=8.801$	0.003
+	39 (50)	39 (50)		
CAD				
-	32 (33.3)	64 (66.7)	$\chi^2=2.604$	0.107
+	26 (48.1)	28 (51.9)		
Mortality				
Live	58 (100)	59 (64.1)	$\chi^2=24.623$	<0.001
Dead	0 (0)	33 (35.9)		

χ^2 – Chi-square test statistics, AF – Atrial Fibrillation, DM – Diabetes Mellitus, HT – hypertension, CAD – Coronary Artery Disease, HL – Hyperlipidemia

good clinical outcome and recanalization ($p < 0.001$). Recanalization rate was 100 % in those with good clinical outcome and 69.6 % in those with poor clinical outcome. Recanalization was achieved in 73.6 % of those with hyperlipidemia (HL) and 88.5 % of those without HL, and this difference was statistically significant ($p = 0.034$) (Tab. 2).

Although there was no statistically significant relationship between the clinical outcome and sex, AF, and CAD ($p > 0.05$), there was a statistically significant relationship between the clinical outcome and HT, DM, HL ($p < 0.05$) (Tab. 3).

We observed no statistically significant relationship between the clinical outcome and age, duration, fever, body mass index (BMI), leukocyte, haemoglobin, haematocrit, RDW, platelet count, monocyte count, and creatinine ($p > 0.05$). There was a statistically significant relationship between the clinical outcome and NIHSS, ASPECT, blood pressure, pulse, sodium, glucose, neutrophil count, lymphocyte count, NLR, MLR, PLR, and PNR ($p < 0.05$) (Tab. 4).

There was no statistically significant relationship between mortality and sex, DM, and AF ($p > 0.05$), but there was a statistically significant relationship between mortality and HT, HL, and CAD ($p < 0.05$) (Tab. 5).

Tab. 5. Comparison of categorical data according to mortality.

	Mortality		Test statistics	p
	Live n (%)	Dead n (%)		
Sex				
Female	49 (73.1)	18 (26.9)	$\chi^2=1.197$	0.274
Male	68 (81.9)	15 (18.1)		
HT				
-	5 (41.7)	7 (58.3)	$\chi^2=7.865$	0.005
+	112 (81.2)	26 (18.8)		
DM				
-	88 (81.5)	20 (18.5)	$\chi^2=2.048$	0.152
+	29 (69)	13 (31)		
AF				
-	86 (76.8)	26 (23.2)	$\chi^2=0.152$	0.697
+	31 (81.6)	7 (18.4)		
HL				
-	48 (66.7)	24 (33.3)	$\chi^2=9.133$	0.003
+	69 (88.5)	9 (11.5)		
CAD				
-	82 (85.4)	14 (14.6)	$\chi^2=7.390$	0.007
+	35 (64.8)	19 (35.2)		

χ^2 – Chi-square test statistics, AF – Atrial Fibrillation, DM – Diabetes Mellitus, HT – hypertension, CAD – Coronary Artery Disease, HL – Hyperlipidemia

There was no statistically significant relationship between mortality and age, ASPECT score, blood pressure, fever, BMI, glucose, leukocyte count, haemoglobin, haematocrit, RDW, platelet, neutrophil, monocyte and lymphocyte counts, urea, creatinine

Tab. 6. Comparison of quantitative data according to mortality.

	Mortality		Test statistics	p
	Live	Dead		
Age (year)	66 (33–81)	72 (32–87)	U=1579	0.110
Time (minute)	245 (120–420)	265 (160–420)	U=1408	0.018
NIHSS	15 (6–24)	14 (4–24)	U=1477.5	0.039
ASPECT	8 (6–10)	9 (5–10)	U=1704.5	0.291
Systolic Blood Pressure (mmHg)	150 (80–220)	160 (110–220)	U=1707	0.307
Diastolic Blood Pressure (mmHg)	90 (50–120)	90 (60–110)	U=1878.5	0.809
Pulse Rate / Min	76 (60–110)	82 (64–117)	U=1277.5	0.003
Fever (°C)	36.4 (36–38)	36.4 (36–38)	U=1819.5	0.608
BMI (kg/m ²)	27.7 (22–35)	26.8 (23–33)	U=1697.5	0.290
Sodium (mEq/L)	138 (117–158)	137 (129–142)	U=1457	0.031
Glucose (mg/dL)	136 (82–691)	142 (95–321)	U=1584.5	0.116
Leukocyte	9.8 (4–27)	10.6 (6–15)	U=1654.5	0.210
Hb (gr/dL)	12.7 (8–17)	12.8 (8–16)	U=1898	0.883
Htc	37.4 (27–50)	37.1 (26–48)	U=1883.5	0.831
RDW	14.3 (12–25)	14.5 (13–21)	U=1821.5	0.621
Plt	223 (47–428)	230 (146–377)	U=1704	0.304
Neutrophil	7 (2–24)	8.8 (4–13)	U=1511.5	0.057
Lymphocyte	1.6 (1–5)	1.3 (1–4)	U=1555.5	0.089
Monocytes	0.5 (0–8)	0.5 (0–1)	U=1929	0.995
Urea	39 (19–137)	46 (19–71)	U=1750.5	0.414
Creatinine (mg/dL)	0.9 (1–5)	0.9 (1–2)	U=1889	0.849
Neutrophil/Lymphocyte	4.2 (0–25)	6.5 (2–15)	U=1469.5	0.036
Monocyte/Lymphocyte	0.3 (0–2)	0.4 (0–1)	U=1540.5	0.077
Plt/Lymphocyte	130 (11–541)	159.3 (80–411)	U=1447	0.028

U – Mann–Whitney U test statistics, BMI – Body mass index, Hb – Hemoglobin, Htc – Hemotokrit, Plt – Platelet

and MLR ratio ($p > 0.05$), but there was a statistically significant relationship between mortality and duration, NIHSS score, pulse, value of sodium, NLR, and PLR ratios ($p < 0.05$) (Tab. 6).

According to univariate test results, we found that recanalization success, BMI, and glucose were not risk factors, whereas NLR, MLR, and PLR ratios were risk factors for poor clinical outcome. The increase in NLR increased the risk of poor clinical outcome by 1.266 times. The increase in MLR increased the risk of poor clinical outcome by 4.178 times, and the increase in PLR increased risk by 1.012 times.

As the result of multivariate analysis, we found that only NLR was an independent risk factor ($p = 0.043$). The increase in NLR increased the risk of poor clinical outcome by 1.347 times (Tab. 7).

Discussion

To the best of our knowledge, no studies investigated the relationship between NLR, MLR, PLR and clinical outcomes in patients with AIS undergoing a mechanical thrombectomy. It is known that immune response is vital in pathogenesis of AIS and that ischemic and anoxic brain tissues trigger the migration of leukocytes in peripheral blood to the damaged area. Neutrophils are the first migrating blood cells to the ischemic area, secreting inflammatory mediators, causing an increased damage to the ischemic area. By different mechanisms, such as. interaction with platelet and coagulation factors and release of proteases, neutrophils promote ischemia by inducing thrombosis (22). The number of studies

on diagnostic value of blood cell ratios and their predictive values in diseases, has recently shown an increase. Although these ratios are easy to measure, it has been shown in many studies that there is a strong correlation between them and cerebral ischemia (23). Lim et al investigated the predictive value of PLR and NLR in demonstrating the severity of the disease in patients with AIS and transient ischemic attack (TIA), concluding that they were valuable predictive markers (24). Altintas et al showed a relationship between an increased PLR and increased infarction volume and the incidence of poor prognosis in patients with AIS (25). We found a statistically significant difference between the groups with good and poor clinical outcomes in terms of the ASPECT, similar to other studies. We found the ASPECT score was significantly lower in patients with poor clinical outcomes.

Platelet activation and aggregation are important in the pathogenesis of AIS. In pathologic conditions, over-activation and aggregation of platelets can cause thrombosis and vascular occlusion, which can result in ischemic stroke and ischemic heart disease (26). Many studies showed that platelet

Tab. 7. Identification of independent risk factors affecting good clinical outcome.

	Univariate		Multivariate	
	OR (%95 GA)	p	OR (%95 GA)	p
Recanalization success	1464024076 (0–0)	0.998	1471309743.837 (0–0)	0.998
BMI	0.943 (0.860–1.035)	0.217	0.962 (0.858–1.08)	0.515
Glucose	1.006 (1.000–1.012)	0.045	1.003 (0.997–1.01)	0.330
NLR	1.266 (1.133–1.414)	<0.001	1.347 (1.01–1.796)	0.043
MLR	4.178 (1.137–15.351)	0.031	1.361 (0.32–5.794)	0.676
PLR	1.012 (1.006–1.018)	<0.001	1.001 (0.99–1.013)	0.840

distribution width (PDW) and the mean platelet width (MPW) are increased, whereas platelet numbers are decreased in the circulatory systems of patients with AIS (27, 28). In their study, Soyulu et al reported that PLR correlated with carotid stenosis in patients with AIS (29). In our study, we observed that PLR differed according to the clinical outcome, but found no differences in platelet counts.

Treatment of AIS is limited to IV or intraarterial tPA and mechanical endovascular treatments. These strategies benefit eligible patients, but involve some risks. When performing recanalization treatments, the decision is made after profit/loss comparisons are made. The most commonly evaluated stroke risk factors are age, infarction volume, and the NIHSS score (30, 31). In our study, we found that the median values of NIHSS differed according to the clinical outcomes.

Measuring the degree of immune dysfunction immediately after stroke can offer prognostic information to determine which patients will respond most appropriately to endovascular intervention. Neutrophils play a critical role in atherosclerosis and are important in plaque rupture, reperfusion damage, and plaque remodelling (32). Massiot et al found that the ratios of NLR and PLR were significantly associated with the severity of symptomatic internal carotid artery stenosis (33). In their study, Pektezel et al investigated the NLR value and immune response to thrombolytic therapy in patients with AIS and reported that increased NLR was a marker of acute stress response associated with stroke during the first 24 hours and was associated with poor prognosis, but that the pre-treatment NLR value had no importance in predicting response to IV tPA (34). In our study, we determined that NLR, MLR, and PLR values were effective in determining the clinical outcomes.

NLR is a marker of systemic inflammation and has been reported in recent studies to be an important marker of post-AIS 60-day mortality (35). Petrone et al investigated patients' immune response to AIS and its effects on diagnosis, treatment, and prognosis, and reported that the ratio of NLR was predictive and was an important marker in AIS (36). Brooks et al investigated the relationship between NLR evaluated at the time of admission to the emergency room and the clinical outcome of patients with AIS on the 90th day after endovascular stroke treatment and reported that NLR was associated with the clinical outcome (37). In our study, MLR and PLR values along with NLR values were risk factors for poor clinical outcome on the 90th day after mechanical thrombectomy. As the result of multivariate analysis, we found that only NLR was an independent risk factor for a poor clinical outcome ($p = 0.043$).

Maier et al investigated the level of mortality and disability according to baseline blood pressure in patients with AIS, who

underwent a mechanical thrombectomy, and reported that systolic blood pressure above 180 mm Hg before thrombectomy had a detrimental effect on good clinical outcomes, and also increased mortality (38). In our study, we also found that there was a statistically significant relationship between systolic and diastolic blood pressures at the time of admission to the emergency room and clinical outcome in patients undergo-

ing a mechanical thrombectomy, but there was no significant relationship between blood pressure and mortality. We thought that this difference was due to the heterogeneous distribution of blood pressures in the patients in our study. In our study, we also found that NLR and PLR were related with mortality ($p < 0.001$), similar to other studies.

Our study had limitations specific to retrospective studies. It was difficult to access all the data because the data recording system and files were scanned retrospectively.

Conclusions

The NLR, MLR, and PLR were associated with the clinical outcome on 90th day in patients undergoing mechanical thrombectomy; high rates were associated with a poor clinical outcome and low rates were associated with a good clinical outcome. NLR and PLR are parameters that could be used to predict mortality in patients with AIS.

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