RESEARCH PAPER

Acta Neurobiol Exp 2024, 84: 70–79
DOI: 10.55782/ane-2024-2540

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Time-dependent changes in blood cells, NIHSS and mRS according to reperfusion treatment type in stroke patients who developed hemorrhagic complication

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Hemorrhagic complications may be seen following reperfusion therapy with rtPA and/or thrombectomy after acute ischemic stroke (AIS). Neutrophils, lymphocytes, and platelets have important roles in the inflammatory and immune responses that develop in these patients. We investigated time-dependent changes in blood cells, NIHSS and mRS values according to type of reperfusion therapy in AIS patients who developed cerebral hemorrhage. In AIS patients who underwent rtPA and/or thrombectomy and developed cerebral hemorrhage within the first 24 hours after treatment, leukocyte, neutrophil, lymphocyte, platelet counts and their ratios were recorded on admission, 1st, 3rd, and 7th days. NIHSS values on admission, 3rd days and mRS values on admission, discharge, and the 3rd month were recorded. These values were compared according to the type of reperfusion therapy. Out of 436 AIS patients, rtPA was applied in 50.5%, thrombectomy in 28.2%, and rtPA+thrombectomy in 21.3%. Hemorrhage developed in 25.5% of the patients. Patients treated with thrombectomy had a greater rate of cerebral hemorrhage. Pre-stroke mRS values were lower in all therapy types than mRS scores at discharge and the 3rd month. The NIHSS scores did not differ significantly in 3 days. Depending on the type of reperfusion treatment, there are a few time-dependent significant changes observed in the blood cell counts and ratios. In conclusion, there is a relation between the type of reperfusion therapy and the time-dependent changes in blood cells and ratios as well as mRS scores among AIS patients who have undergone rtPA and/or thrombectomy and developed cerebral hemorrhage.

Key words: ischemic stroke, blood cells, mRS, NIHSS, reperfusion therapy, hemorrhage

INTRODUCTION

Reperfusion therapies applied with intravenous recombinant tissue plasminogen activator (rtPA) and endovascular thrombectomy (EVT) are the most effective treatment methods in patients with acute ischemic stroke (AIS) (Brooks et al., 2014). Providing cerebral reperfusion with the application of rtPA and/or EVT treatments in appropriate cases in AIS may significantly improve the clinical course of the patients. However, complications such as hemorrhage or development of reperfusion injury may occur after reperfusion therapies. It has been shown that intracerebral hemorrhage (ICH) and reperfusion injury with their resultant neurovascular effects are facilitated by immune responses that develop after stroke (Pikija et al., 2018). Inflammatory processes play a key role in thrombosis. Neutrophils, lymphocytes and platelets, which are involved in inflammatory and immune responses, have important roles in predicting the prognosis in post-reperfusion patients. The numbers, proportions, and time-dependent changes in these cells in the early post-stroke period are associated with clinical course and prognosis (Dentali et al., 2016).

Received 11 March 2023, accepted 14 December 2023

Platelets adhere to the damaged vessel wall at the vascular injury site and release their enzyme-containing granules (Gremmel et al., 2016). Afterwards, leukocytes gather in the thrombus region and initiate the thrombo-inflammatory response, which has also been found to be related to the degree of organ damage and severity of clinical course (Diacovo et al.,1996; Hagberg et al., 1998). Neutrophils are rapidly recruited in the ischemic region and release reactive oxygen species (ROS), proteases, and cytokines (Segel et al., 2011).

Along with this thrombo-inflammatory development, the blood-brain barrier (BBB) is also disrupted and brain damage may develop (Kolaczkowska and Kubes, 2013; Jickling et al., 2015). Acute stress can increase the neutrophil, but decrease the lymphocyte counts. Worse clinical outcome has been reported in patients with ischemic and hemorrhagic stroke with higher neutrophil and lower lymphocyte counts (Lattanzi et al., 2016; Zhang et al., 2019).

Development rates of hemorrhagic transformation (HT) and 3-month mortality rates were found to be higher in patients with AIS having higher neutrophil/lymphocyte ratio (NLR) (Zhang et al., 2019). In patients with AIS who underwent revascularization with rtPA and/or EVT, higher NLR on admission were found to be associated with the risk of HT within the first 24 hours and the deterioration in neurological findings (Świtońska et al., 2020).

Comparatively lower platelet/neutrophil ratios (PNR) have been defined as an independent risk factor for worsening in early- and late-term neurological findings after rtPA treatment, development of HT, and poor prognosis in the 3rd month after stroke (Wang et al., 2020). PNR is a better biomarker of thrombosis and severity of inflammation than only platelet or neutrophil counts (Jin et al.,2019).

In this study, we aimed to investigate time-dependent changes in lymphocyte, platelet, neutrophil counts and their ratios, the National Institutes of Health Stroke Scale (NIHSS) and the Modified Rankin Scale (mRS) values according to the type of reperfusion therapy performed in AIS patients who received rtPA and/or thrombectomy and developed ICH within the first 24 hours of treatment.

METHODS

Patients over the age of 18 who admitted to our stroke center between January 2018 and March 2020 with the diagnosis of AIS, underwent rtPA or rtPA+ thrombectomy within the first 4.5 hours or only thrombectomy within the first 24 hours of the onset of stroke symptoms, and developed symptomatic or non-symptomatic ICH complication detected on brain computed tomography taken within the first 24 hours after these reperfusion therapies were included into the study.

This study was conducted retrospectively from data obtained for clinical purposes. Clinical Trials ethics Committee of University of Health Sciences, Fatih Sultan Mehmet Training and Research Hospital. Approval Issue #: FSM EAH-KAEK 2020/133. Date: September 10, 2020. This study was evaluated by the scientific committee of Fatih Sultan Mehmet Training and Research Hospital, and it was decided that there is no objection in using the data of the patients in the files. (Issue #: E-17073117-050.06. Date: June 22, 2021).

NIHSS, which shows the severity of neurological deficit (Hage, 2011), and the Modified Rankin Scale (mRS), which shows the degree of disability (Banks and Marotta, 2007), values were used as clinical outcomes of stroke patients.

Patients who had malignancy, infection, hematological, rheumatological, or immunological diseases, pregnant women or patients who had a stroke previously were not included in the study. In this retrospective study, the leukocyte, neutrophil, lymphocyte, and platelet counts, and the ratios of platelet/lymphocyte, platelet/neutrophil, platelet/leukocyte, neutrophil/leukocyte, neutrophil/lymphocyte on day 0 (admission day, before reperfusion therapy) and on the 1st, 3rd and 7th days after reperfusion therapy were recorded. In addition, NIHSS values on days 0 and 3, and mRS values on day 0, at discharge and 3 months later were recorded.

Statistical analysis

The 2007 NCSS (Number Cruncher Statistical System; Kaysville, Utah, USA) program was used for statistical analysis. The study data were evaluated using descriptive statistical methods (mean, standard deviation, median, frequency, ratio, minimum, maximum), and fitness of the data to normal distribution pattern was assessed with the Shapiro-Wilk test. Friedman test was used in comparisons of the data of three or more periods while Wilcoxon test was used in comparisons of the data of two periods. Chi-square analysis was applied to determine the relationship between qualitative data. Level of statistical significance was set at $p<0.05$.

RESULTS

A total of 436 patients (218 women, and 218 men) were included in the study. rtPA was applied in 50.5% (n=220), thrombectomy in 28.2% (n=123) and both rtPA and thrombectomy in 21.3% (n=93) of the cases. In 25.5% (n=111) of the patients, hemorrhagic complications developed after reperfusion therapies. When the type of reperfusion therapy and the rate of hemorrhagic complication were compared, the rate of this complication was found to be significantly higher in those treated with thrombectomy (p=0.001) (Fig. 1).

Comparison of NIHHS scores according to the type of reperfusion therapy

There was no significant difference in NIHSS scores between admission day and 3rd day in patients who developed hemorrhagic complications after receiving rtPA, thrombectomy or rtPA + thrombectomy (Table 1).

Comparison of mRS scores according to the type of reperfusion therapy

The mRS scores showed statistically significant differences when pre-stroke, discharge and 3rd month values were compared according to the type of reperfusion therapy (p=0.001). In all treatment types pre-stroke mRS values were found to be lower compared to mRS scores at discharge and 3rd month (p=0.001, Fig. 2).

Comparison of time-dependent changes in blood cell counts according to the type of reperfusion therapy

In rtPA group, leukocyte and neutrophil values were significantly lower on admission compared to the measurements performed between the 1st, 3rd and 7th days. While lymphocyte and platelet values on admission were found to be higher than those recorded on other days (p<0.01, Fig. 3).

In thrombectomy group, leukocyte and neutrophil measurements on admission were found to be significantly lower than the measurements on days 1, and 3 (p<0.01, Fig. 3). There was no significant difference between these days in terms of lymphocyte counts (p>0.05). Platelet counts on admission were found to be significantly higher than those recorded on day 3

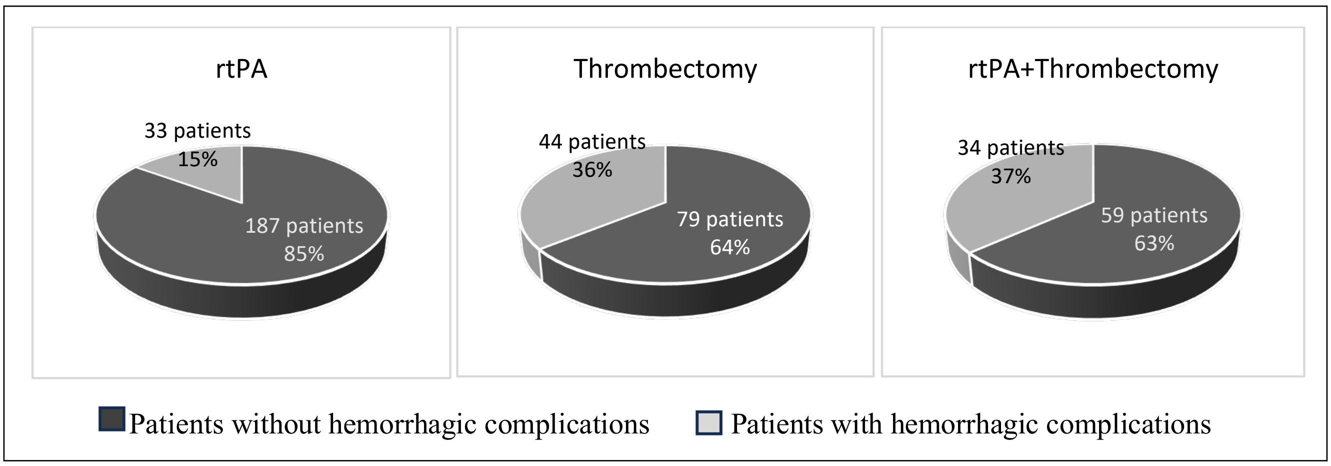
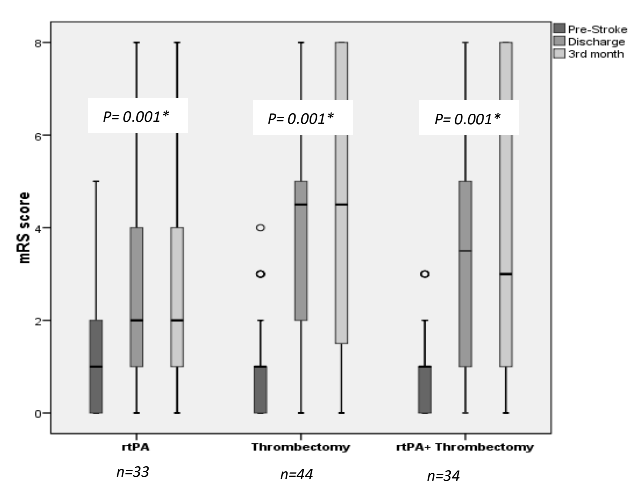


Fig. 1. Relationship between type of reperfusion therapy, and the development of hemorrhagic complications in patients with acute ischemic stroke. (p=0.001: Chi-square test). rtPA: recombinant tissue plasminogen activator.

Table 1. Comparison of NIHSS scores according to the type of reperfusion therapy.

Type of reperfusion therapy	Cases (n)	NIHHS on admision day Min–Max (Median)	NIHSS on 3rd day Min–Max (Median)	P value*
rtPA	33	3–22 (10)	0–28 (8)	0.219
Thrombectomy	44	4–28 (16)	2–25 (15)	0.477
rtPA+ Thrombectomy	34	5–20 (14.5)	0–25 (11)	0.059

*Wilcoxon Test. rtPA: recombinant tissue plasminogen activator NIHHS: National Institutes of Health Stroke Scale.



	Median (Q1-Q3)	Median (Q1-Q3)	Median (Q1-Q3)
Pre-Stroke	1,0 (0-2)	1,0 (0-1)	1,0 (0-1)
Discharge	2,0 (1-4)	4,0 (2-5)	3,5 (1-5)
3 rd month	2,0 (1-4)	4,5 (1,5-8)	3,0 (1-8)

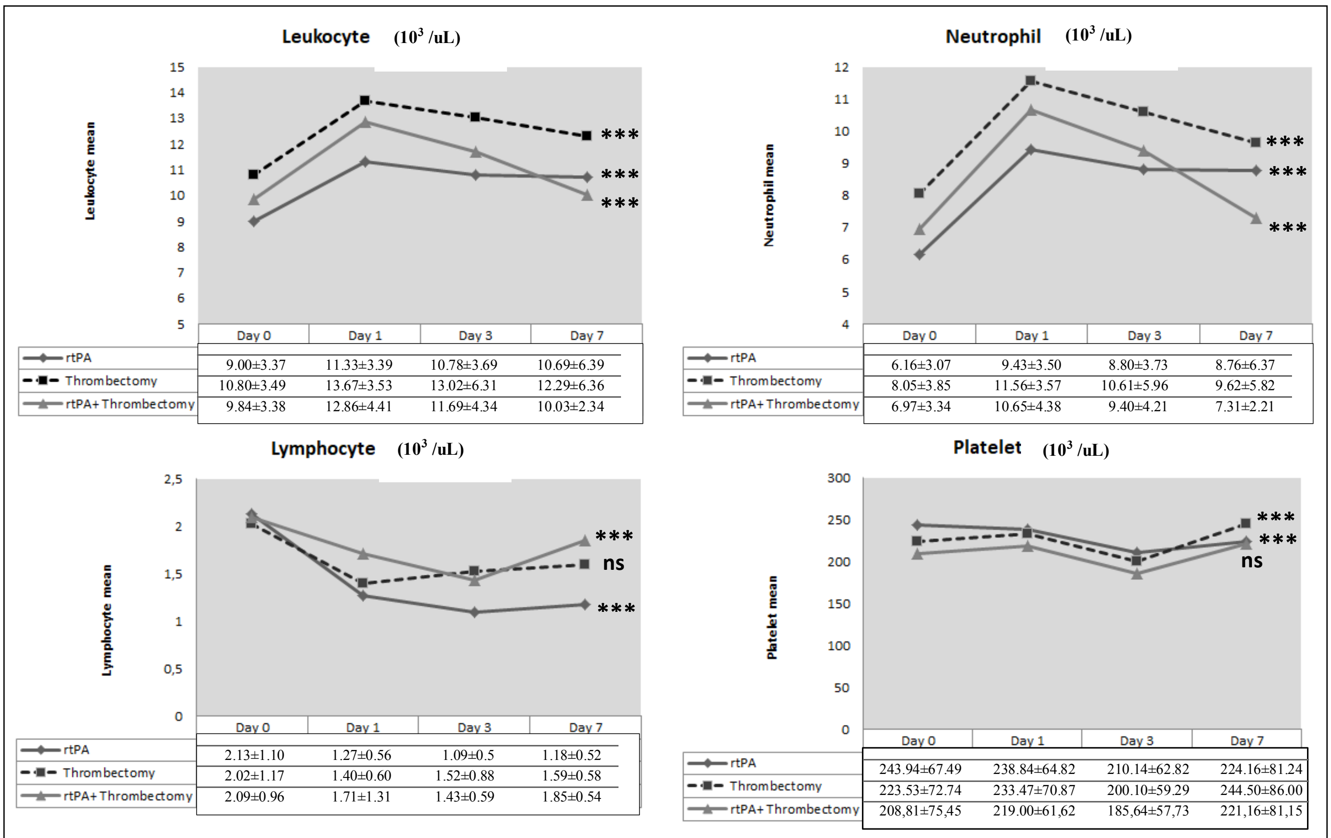
Fig. 2. Comparison of mRS scores according to the type of reperfusion therapy. *Friedman Test. rtPA: Recombinant tissue plasminogen activator mRS: Modified rankin scale. Q1-Q3: 25th-75th percentile.

(p<0.01). Platelet counts on day 3 were found to be lower than the 1st and 7th day measurements (p<0.01, Fig. 3).

In rtPA + thrombectomy group, leukocyte and neutrophil counts on admission were found to be significantly lower than the counts recorded on days 1, and 3 (p<0.01). In addition, 7th day-leukocyte counts were found to be lower than those on days 1, and 3 (p<0.01). The 1st day neutrophil counts were lower than those found on day 7 (p<0.01), and the 3rd day-neutrophil counts were higher than the 7th day counts (p<0.01, Fig. 3).

Lymphocyte counts on admission were found to be significantly higher than those on days 1, and 3 (p<0.01). The lymphocyte counts on day 1 were lower compared to day 7 (p<0.01), and the lymphocyte counts on day 3 were lower compared to day 7 (p<0.01, Fig. 3).

There was no significant difference between these days in terms of platelet counts (p>0.05, Fig. 3).



Leukocyte (10^3/uL)

	Day 0	Day 1	Day 3	Day 7
rtPA	9.00±3.37	11.33±3.39	10.78±3.69	10.69±6.39
Thrombectomy	10.80±3.49	13.67±3.53	13.02±6.31	12.29±6.36
rtPA+ Thrombectomy	9.84±3.38	12.86±4.41	11.69±4.34	10.03±2.34

Neutrophil (10^3/uL)

	Day 0	Day 1	Day 3	Day 7
rtPA	6.16±3.07	9.43±3.50	8.80±3.73	8.76±6.37
Thrombectomy	8.05±3.85	11.56±3.57	10.61±5.96	9.62±5.82
rtPA+ Thrombectomy	6.97±3.34	10.65±4.38	9.40±4.21	7.31±2.21

Lymphocyte (10^3/uL)

	Day 0	Day 1	Day 3	Day 7
rtPA	2.13±1.10	1.27±0.56	1.09±0.5	1.18±0.52
Thrombectomy	2.02±1.17	1.40±0.60	1.52±0.88	1.59±0.58
rtPA+ Thrombectomy	2.09±0.96	1.71±1.31	1.43±0.59	1.85±0.54

Platelet (10^3/uL)

	Day 0	Day 1	Day 3	Day 7
rtPA	243.94±67.49	238.84±64.82	210.14±62.82	224.16±81.24
Thrombectomy	223.53±72.74	233.47±70.87	200.10±59.29	244.50±86.00
rtPA+ Thrombectomy	208,81±75,45	219.00±61,62	185,64±57,73	221,16±81,15

Fig. 3. Comparison of time-dependent changes in blood cell counts according to the type of reperfusion therapy (mean ± SD). *** p=0.001 (Friedman Test). ns: not significant, p>0.05 (Friedman Test). rtPA: recombinant tissue plasminogen activator.

Comparison of time-dependent changes in blood cell ratios according to the type of reperfusion therapy

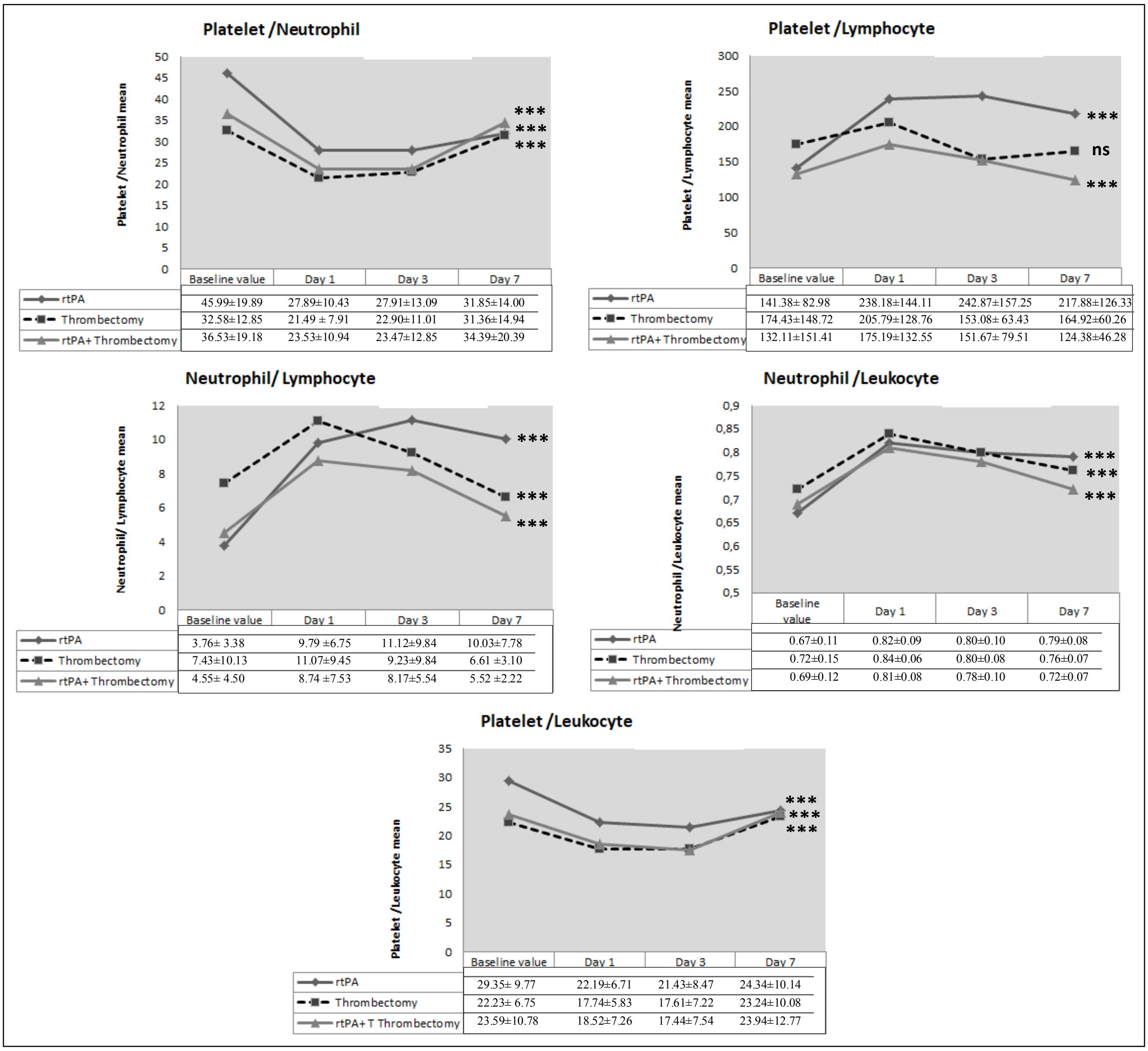
In rtPA group, PNR ratios on admission day were higher than those on the 1st, 3rd and 7th days ($p<0.01$, Fig. 4). platelet/lymphocyte ratios (PLRs) on admission were found to be lower compared to PLRs on 1st and 3rd days ($p<0.01$, Fig. 4).

The NLRs on admission were lower than the NLRs on 1st, 3rd, and 7th days ($p<0.01$, Fig. 4). The neutrophil/leukocyte ratios on admission were found to be lower than the those on the 1st, 3rd and 7th days ($p<0.01$). In addition, the lower neutrophil/leukocyte ratio on day 1 compared to day 7 is statistically significant ($p<0.01$, Fig. 4).

The platelet/leukocyte ratios on admission were found to be significantly higher than those on days 1, 3, and 7 ($p<0.01$, Fig. 4).

In thrombectomy group, the PNRs on admission were found to be significantly higher than those on the 1st and 3rd days ($p<0.01$, Fig. 4). The PNR on day 7, was found to be higher compared to days 1, and 3 ($p<0.01$, Fig. 4).

PLRs did not differ according to days ($p>0.05$).



Platelet /Neutrophil

	Baseline value	Day 1	Day 3	Day 7
rtPA	45.99±19.89	27.89±10.43	27.91±13.09	31.85±14.00
Thrombectomy	32.58±12.85	21.49 ± 7.91	22.90±11.01	31.36±14.94
rtPA+ Thrombectomy	36.53±19.18	23.53±10.94	23.47±12.85	34.39±20.39

Platelet /Lymphocyte

	Baseline value	Day 1	Day 3	Day 7
rtPA	141.38± 82.98	238.18±144.11	242.87±157.25	217.88±126.33
Thrombectomy	174.43±148.72	205.79±128.76	153.08± 63.43	164.92±60.26
rtPA+ Thrombectomy	132.11±151.41	175.19±132.55	151.67± 79.51	124.38±46.28

Neutrophil/ Lymphocyte

	Baseline value	Day 1	Day 3	Day 7
rtPA	3.76± 3.38	9.79 ±6.75	11.12±9.84	10.03±7.78
Thrombectomy	7.43±10.13	11.07±9.45	9.23±9.84	6.61 ±3.10
rtPA+ Thrombectomy	4.55± 4.50	8.74 ±7.53	8.17±5.54	5.52 ±2.22

Neutrophil /Leukocyte

	Baseline value	Day 1	Day 3	Day 7
rtPA	0.67±0.11	0.82±0.09	0.80±0.10	0.79±0.08
Thrombectomy	0.72±0.15	0.84±0.06	0.80±0.08	0.76±0.07
rtPA+ Thrombectomy	0.69±0.12	0.81±0.08	0.78±0.10	0.72±0.07

Platelet /Leukocyte

	Baseline value	Day 1	Day 3	Day 7
rtPA	29.35± 9.77	22.19±6.71	21.43±8.47	24.34±10.14
Thrombectomy	22.23± 6.75	17.74±5.83	17.61±7.22	23.24±10.08
rtPA+ T Thrombectomy	23.59±10.78	18.52±7.26	17.44±7.54	23.94±12.77

Fig. 4. Comparison of time-dependent changes in blood cell ratios according to the type of reperfusion therapy (mean ± SD). *** $p=0.001$ (Friedman Test). ns: not significant, $p>0.05$ (Friedman Test). rtPA: recombinant tissue plasminogen activator.

The NLRs was found to be significantly lower on admission compared to the day 1 ($p<0.01$, Fig. 4). The NLRs on day 1 was found to be higher than those on days 3, and 7 ($p<0.01$, Fig. 4).

The neutrophil/leukocyte ratio was found to be significantly lower on admission compared to the 1st and 3rd days ($p<0.01$, Fig. 4). Neutrophil/leukocyte ratios on day1 were found to be higher compared to days 3 and 7 ($p<0.01$, Fig. 4).

The platelet/leukocyte ratio was found to be higher on admission compared to the 1st and 3rd days ($p<0.01$, Fig. 4). The platelet/leukocyte ratios on day 7 were found to be significantly higher compared to days 1, and 3 ($p<0.01$, Fig. 4).

In rtPA + thrombectomy group, the PNRs on admission were higher than the values found on the 1st and 3rd days ($p<0.01$, Fig. 4). The PNRs on day 1 were lower significantly compared to those on day 7 ($p<0.01$, Fig. 4). PNRs on day 3 were found to be lower compared to PNR values on day 7 ($p<0.01$, Fig. 4).

The PLRs on admission was found to be significantly lower than PLRs on days 1, and 3 ($p<0.01$, Fig. 4).

The NLRs on admission were found to be significantly lower than those on days 1, and 3 ($p<0.01$, Fig. 4). NLRs on day 1 were higher compared to day 7 ($p<0.01$, Fig. 4). The NLRs on day 3 were higher compared to day 7 ($p<0.01$, Fig. 4).

The neutrophil/leukocyte ratios on admission were found to be significantly lower compared to days 1, and 3 ($p<0.01$, Fig. 4). The neutrophil/leukocyte ratios on day1 were higher compared to days 3, and 7 ($p<0.01$, Fig. 4). The neutrophil/leukocyte ratios on day 3 were higher compared to day 7 ($p<0.01$, Fig. 4).

The platelet/leukocyte ratios were significantly higher on admission compared to the 1st and 3rd days ($p<0.01$, Fig. 4). The platelet/leukocyte ratios on day 1were lower compared to day 7 ($p<0.01$, Fig. 4). The platelet/leukocyte ratios on day 3 were lower compared to day 7 ($p<0.01$, Fig. 4).

DISCUSSION

We assessed leukocyte, neutrophil, lymphocyte and platelet counts and their ratios in our patients who received reperfusion therapy with rtPA and/or thrombectomy and developed intracerebral hemorrhagic complications within the first 24 hours on the day of admission to the hospital and on days 1, 3 and 7, and demonstrated time-dependent changes in these parameters according to the subtypes of reperfusion therapy. In addition, we found that mRS values increased in patients in all three forms of reperfusion therapies at discharge and in the 3rd month, relative to the admission day. On the other hand, we did not find any significant difference in the NIHSS values between the day of admission and on day 3 in the treatment groups.

There is a complex interaction between the central nervous system (CNS) and the immune system in AIS. Acute stroke induces inflammatory processes in the artery wall and brain parenchyma (Kakhki et al., 2020). Platelets adhere to the damaged wall at the vascular injury site and release their enzyme-containing granules (Andrews et al., 2017; Holinstat, 2017). Inflammatory cells recruit to the ischemic area within the first few minutes to hours. In the stroke process, neutrophils are the first responder cells among inflammatory cells (Perez-de-Puig et al., 2015). Post-ischemia neutrophils pass through the cerebral endothelium during the migration process, releasing a variety of proteases and reactive oxygen products (ROS) that contribute to the disruption of the blood-brain barrier (BBB) (Segel et al., 2011). Neutrophils, lymphocytes, monocytes/macrophages from the blood, microglia in the CNS, and peripheral immune cells are recruited into the ischemic cerebral hemisphere, resulting in a strong inflammatory response (Anrather and Iadecola, 2016; Rayasam et al., 2018).

After the onset of AIS, the spleen is the main source of peripheral immune cells that recruited to the brain (Seifert et al., 2012). The cellular composition of the spleen changes dramatically after AIS. Specifically, significant changes in spleen function are observed that increase the production of circulating proinflammatory cytokines, induce activation of systemic T and B lymphocytes, and help peripheral immune cells and inflammatory mediators invade the brain (Hongchen et al., 2021). The bidirectional and dynamic crosstalk between inflammation and poststroke the BBB indicates that distinct time-dependent changes and immune cells play different roles in this pathological process (Huang et al., 2020).

NETosis, the release process of neutrophil extracellular traps (NETs), also develops in the pathogenic process of stroke. After ischemic injury, neutrophils and NETs play a role in the deterioration of neurological function, primarily by disrupting the BBB and facilitating thrombosis (Li et al., 2022). All these events develop after ischemic stroke and show a time-dependent change.

The increase of neutrophil counts may aggravate the deterioration of the BBB after thrombolysis and cause neural dysfunction (Guo et al., 2018). The increase in neutrophil counts on day 3 in all treatment groups of our stroke patients who developed cerebral hemorrhage within the first 24 hours after reperfusion therapy suggests that the thrombo- inflammatory effects of these cells are greater on 3rd day after the onset of treatment. In our patients who underwent thrombectomy, significant difference in leukocyte and neutrophil counts was not maintained on day 7 compared to the values on day of admission. The fact that leukocyte and neutrophil counts are closer to the baseline values in patients who underwent thrombectomy may indicate that inflammatory and immunological responses are normalized earlier than in other treatment groups.

Acute stress increases the neutrophil and decreases the lymphocyte counts. It has been reported that lymphocyte counts have a neuroprotective effect and contribute to the improvement of neurological function (Macrez et al., 2011). Lymphocytes also play an important role in the development of inflammation. Lymphocytes constantly accumulate on the damaged vascular endothelium and influence disease progression. Lymphocytes particularly play their anti-inflammatory role in the long-term after the onset of AIS (Kollikowski et al., 2020). However, among circulating T lymphocytes Th1 and Th17 exacerbate neuroinflammation and block the neuroprotective effects of other cytokines (Krämer et al., 2019). Among our patients who underwent reperfusion therapy after ischemic stroke and developed cerebral hemorrhage within the first 24 hours, those who received rtPA had higher lymphocyte levels on day of admission than the values on days 1, 3, and 7 after treatment. On the other hand, in patients who received both rtPA and thrombectomy treatments, lymphocyte counts were higher on the day of admission compared to the values detected on day 3, lower on the 1st day compared to the 7th day, and lower on the 3rd day compared to the 7th day. This shows that the number of neuroprotective lymphocytes decreased in the early days after the treatment in patients who received rtPA or rtPA+thrombectomy treatments and developed cerebral hemorrhage. These findings support the information that the number of lymphocytes decreases in the early stages with the acute stress caused by the development of ischemia and hemorrhage.

The increase in lymphocytes on day 7 may be related to the their late-term effects (Kollikowski et al., 2020). However, in our study, there were no significant changes in lymphocyte counts according to days in patients who underwent thrombectomy. With this finding, it can be interpreted that thrombectomy creates less stress and does not affect lymphocyte counts. This issue needs to be investigated in more detail.

Platelets are cells that actively contribute to the development of ischemia and hemorrhage. Activated platelets adhering to the vascular wall in atherosclerotic plaque rupture trigger arterial thrombosis, leading to ischemia or infarction (Kannan et al., 2019; Fuentes et al., 2019). AIS may cause abnormalities in platelet functions, and excessive activation and accumulation of platelets may inhibit ischemic recovery (Xu et al., 2016). Excessive platelet consumption due to thrombosis can lead to decreased platelet counts in peripheral blood (Chen et al., 2015; Maegerlein et al., 2018). Low platelet counts have been associated with poor prognosis in stroke patients treated with intravascular thrombectomy (Desai et al., 2019). In our patients with ischemic stroke who received reperfusion therapy and developed cerebral hemorrhage, platelet counts were found to be higher on admission day compared to the 3rd day counts in patients who had undergone only rtPA or only thrombectomy. Platelet counts were lower on day 3 compared to days 1 and 7 in patients who underwent thrombectomy. This suggests that in patients who underwent rtPA or thrombectomy, and then developed hemorrhagic complications, platelets with a life span of seven days were more predominantly depleted on the 3rd day, and then their number increased towards the 7th day with the addition of newly released platelets to the circulation. NLR is a parameter that can show the contribution of neutrophils to inflammation and their destructive effects, their anti-inflammatory protective effects, and contribution to immune regulation (Song et al., 2019; Wang et al., 2019). In this respect, NLR may show the inflammatory level and stress state of the body. Higher NLR values have been reported in hemorrhagic strokes in patients with a poor prognosis (Lattanzi et al., 2019; Wang et al., 2019). After thrombectomy in ischemic stroke, lower NLRs have been associated with good prognosis. Besides higher NLRs have been related to the risk of adverse treatment outcomes such as symptomatic intracranial hemorrhage (SICH) and mortality (Aly et al., 2021; Lux et al., 2020; Ozgen et al., 2020). Low pre-, and post-treatment NLR values in AIS patients treated with rtPA have been reported as independent factors associated with good clinical outcome in medium- and long-term follow-up (Chen et al., 2022). In addition, a high NLR value before rtPA treatment was found to be an independent risk factor for SICH (Maestrini et al., 2015). Świtońska et al. (2020) reported that high NLR at admission was associated with an increased risk of hemorrhagic transformation and neurological deterioration in the first 24 hours in AIS patients who underwent revascularization with rtPA and/or EVT. In our patients, NLR level was lower on day 0 compared to days 1, 3 and 7 in the rtPA treatment group, on day 0 compared to day 1 in the thrombectomy group, and on day 0 compared to days 1 and 3 the in rtPA+thrombectomy group. In addition, NLR was higher on day 1 than on days 3 and 7 in the thrombectomy group, on day 1 compared to day 7 in both the rtPA and the thrombectomy groups, on day 3 compared to day 7 in the rtPA+thrombectomy group.

This finding shows that NLR increased after treatment compared to pre-treatment NLR in patients who underwent reperfusion therapy and developed hemorrhagic complications which also indicates that not only the NLR value on admission, but also NLR values during post-reperfusion follow-ups are valuable. In our study, the increase in NLR on day 1 was significant in patients who underwent thrombectomy and rt-PA+thrombectomy and developed intracerebral hemorrhagic complications which may be related to the increased inflammatory and immunological response induced by hemorrhagic complications in these patients. In addition, the change in NLR values over time confirms the occurrence of time-dependent change in the counts and ratios of blood cells.

Increases in PLR values have been reported in ischemic conditions such as AIS, myocardial infarction and peripheral occlusive arterial diseases (Temiz et al., 2014; Gary et al., 2013; Azab et al., 2012). More successful recanalization results have been reported in AIS patients with low PLR levels (Altintas et al., 2016). In our study, which included patients who developed hemorrhagic complications after reperfusion therapy, PLRs were lower on day 0 compared to days 1 and 3 in patients who underwent rtPA and rtPA+thrombectomy, however there was no difference in PLR values after thrombectomy. This finding demonstrates that even if the PLR values on day 0 are low in patients receiving reperfusion therapy, when hemorrhagic complications develop there was no decrease in the mRS values at discharge and in the third month. It means that, in our study the low PLR value on day zero have not suggested that it is a positive indicator of the clinical outcome.

PNR is an index that reflects the balance between platelet and neutrophil counts in the process of thrombosis and inflammation. Previous studies have shown that the interaction between platelets and neutrophils aggravates the inflammatory response in thrombosis (Wang et al., 2020). The rtPA treatment causes changes in the numbers and ratios of blood cells. The rtPA treatment does not only convert plasminogen to plasmin, but also degrades fibrin in thrombus and produces soluble fibrin degradation products, exacerbates platelet activation and aggregation. As a result, the PNR changes (Wang et al., 2020). Both the decrease in platelet counts caused by thrombosis and the increase in neutrophil counts due to inflammation cause a decrease in PNR values. rtPA treatment also affects the PNR values with changes in platelets and neutrophils (Rubenstein et al., 2004; Matosevic et al., 2013). A low PNR value may predict a poor clinical outcome (Wang et al., 2020). In our study, PNR values on day 0 were higher than days 1, 3 and 7 in patients who received rtPA. In the thrombectomy group, the PNR was higher on day 0 compared to days 1 and 3, and the PNR values on days 1 and 3 were lower relative to day 7. In patients who underwent rt-PA+thrombectomy, PNR was higher on day 0 compared to days 1 and 3, but it was lower on day 1 compared to day 7, and on day 3 compared to day 7. The decrease in the PNR values of our patients in all three treatment groups on the days 1, and 3 may be related to the negative immunological and inflammatory effects of the developing cerebral hemorrhage. The increase in the PNRs again on day 7 in patients who underwent thrombectomy and rtPA+thrombectomy can be explained by the newly formed platelet population entering the circulation.

In eligible patients with AIS, rtPA treatment can be performed before mechanical thrombectomy (MTE). However, the value and safety of bridging therapy to direct MTE remains controversial (Kurminas al., 2020). In some studies, an increased tendency in the risk of cerebral hemorrhage in patients with MCA occlusion who received rtPA before MTE has been reported (Kurminas al., 2020). Among our patient groups, hemorrhagic complications developed most frequently in the group that received rtPA+thrombectomy treatment.

In our AIS patients who developed hemorrhagic complications within the first 24 hours after reperfusion therapy, mRS values at discharge and the 3rd month were higher than pre-stroke mRS values. This result indicates that the disability of patients who developed hemorrhagic complications after reperfusion therapies worsened.

In our previous study, peripheral blood cell counts and ratios and NIHSS values were studied in patients with AIS who underwent rtPA +/- thrombectomy and their time- dependent changes in above-mentioned parameters were shown (Kömürcü et al., 2020). In this current study, only AIS patients who developed hemorrhagic complications were evaluated and comparisons of time-dependent changes in these parameters and also mRS values were evaluated according to the types of reperfusion therapy. In our current study, the blood cell counts of ischemic stroke patients who received reperfusion therapy and experienced hemorrhage complication were comparable to those of stroke patients in the study published in 2020. However, when evaluated according to reperfusion treatment subtypes, we found time-dependent changes in blood cell numbers and rates in the current study.

As limitations of our study, it can be stated that monocytes, eosinophils, erythrocytes and subgroups of lymphocytes, which may have important roles in stroke, and also the blood cells and their ratios at the 3rd month after stroke were not included in the evaluation.

CONCLUSIONS

Blood cells play crucial roles in the inflammatory and immune responses in developing ischemic stroke and it's complications. There are time-dependent changes in mRS and NIHSS values, as well as in leukocyte, neutrophil, lymphocyte, thrombocyte counts and their ratios in patients with ischemic stroke who developed hemorrhagic complications after reperfusion therapy. In our study, hemorrhagic complication was substantially higher in patients treated with thrombectomy. Pre-stroke mRS values were found to be lower in all types of reperfusion treatment than mRS scores at discharge and the 3rd month. There was no significant difference in NIHSS scores in 3 days. According to these mRS and NIHSS values, patients who experience ICH during the first 24 hours following reperfusion treatments do not significantly benefit from the treatments; in fact, their functional levels worsen both early and late periods. Depending on the type of reperfusion treatment, there are a number of time-dependent significant changes observed in the blood cell counts and ratios. In conclusion, the time-dependent changes in blood cells and ratios, as well as mRS scores in acute ischemic stroke patients who underwent rtPA and/or thrombectomy and developed cerebral hemorrhage have been found to be related with the reperfusion therapy. The prospective studies will be crucial in the selection of rtPA and/or thrombectomy treatments in stroke patients, since there is a noteworthy relation between the type of reperfusion treatment and the development of hemorrhage complications.

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