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Original Article NEUROLOGY

Retrospective analysis of the data of patients who were admitted to the secondary care hospital with the diagnosis of acute ischemic stroke and received intravenous thrombolytic therapy

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ABSTRACT

OBJECTIVE: Acute ischemic stroke is a cause of long-term disability in developing countries. Intravenous tissue plasminogen activator (iv-tPA) is the most effective medical treatment shown to provide clinical improvement. Our aim in this study is to investigate the relationship between the clinical data of our patients treated with iv-tPA and the changes in serum inflammatory parameters; and to help increase the prevalence of treatment in secondary hospitals.

METHODS: Forty-nine patients diagnosed as acute ischemic stroke and treated with iv-tPA at Siirt Research and Training Hospital between April 2019 and June 2020 were included in this study. Demographic and clinical findings, serum platelet/lymphocyte ratio (PLR), neutrophyle/ lymphocyte ratio (NLR) and CRP/albumin ratio (CAR), radiological data, symptom-door-needle times, trombectomy, complication and mortality rates, pre and post treatment 7th day of National Institutes of Health Stroke Scale Scores (NIHSS) and first and third-month of modified Rankin Scale (mRS) scores, and prognosis were evaluated.

RESULTS: The mean age was 71.2±13.7 years. Female-to-male ratio was almost 1. Decreases in the post-treatment NIHSS scores were statistically significant compared with the baseline ($p<0.001$). First month's mRS score was statistically decreased in the third month follow up significantly ($p=0.002$). There were significant differences between the baseline and post-treatment laboratory values. Significant increases in the values of NLR, and CAR were detected ($p=0.012$, $p=0.009$). Correlation analysis revealed significant positive correlations between post-treatment NIHSS and CAR, PLR, NLR. PLR and NLR were significantly correlated with the third month mRS score ($p<0.001$, $p=0.011$). Symptom-to-door time, door-to-needle time, and symptom-to-needle time were not correlated with the NIHSS and mRS scores.

CONCLUSION: It would be beneficial to treat the patients with iv-tPA in secondary-staged hospitals and should be widespread. Rapid treatment is sufficient and can reduce complications and poor outcomes. Elevated levels of NLR, PLR, and CAR predict modest consequences.

Keywords: Acute ischemic stroke; inflammation; prognosis; tissue plasminogen activator; trombolyhtic.

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Stroke is one of the most common causes of long-term disability in developing countries and mortality worldwide [1]. Intravenous tissue plasminogen activator (iv-tPA), which has been used since the early 1990s, is the most effective medical treatment shown to provide clinical improvement in acute ischemic stroke patients. After the physicians' awareness has risen, and the number of stroke units increased, the clinical use

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has enlarged nationwide [1–3]. Thrombolytic therapy is generally performed in the universities and tertiary hospitals, and not used widely enough in the secondary state hospitals due to the lack of physicians, equipment, and the difficulty of transporting the patients to stroke centers. In this study, we aimed to share our clinical findings since the day we started the practice in our hospital, demonstrate the alterations in serum inflammatory markers of platelet-to-lymphocyte (PLR), neutrophil-to-lymphocyte (NLR), and C-reactive protein-to-albumin (CAR) ratios before and after the 7th day of the treatment, and evaluate their interactions with baseline and post-treatment National Institute of Health Stroke Scale (NIHSS) scores, and first and third-month of modified Rankin Scale (mRS) scores.

Highlight key points

- Stroke is one of the most common causes of long-term disability in developing countries and mortality worldwide.
- Intravenous tissur plasminogen activator (tPA) treatment's initial administration is related to reduced mortality and better prognosis.
- Elevated levels of NLR, PLR, and CAR predict modest consequences.

MATERIALS AND METHODS

This retrospective cross-sectional study included 49 individuals with the diagnosis of acute ischemic stroke (AIS) who treated with iv-tPA between the dates of April 2019 and April 2020 at Siirt Research and Training Hospital Neurology Department in Siirt, Turkiye. Patients who applied after April 2020 were not included into the study due to the hospital's transformation from the secondary to the tertiary facility. After providing the patients' informed consent or from their first-degree relatives, alteplase was administrated according to the AHA/ASA guideline [4]. Computed tomography (CT) and CT-angiography were performed in the emergency department. The patients who obliged mechanic thrombectomy were transferred to a 2-hour-away stroke unit. The age, sex, the use of medication, comorbidities, etiology, carotid artery stenosis, total dose of iv-tPA treatment, pre and post-treatment 7th day of NIHSS scores, and serum inflammatory parameters of PLR, NLR, and CAR [5] were investigated. After the treatment, the development of hemorrhagic transformation, the intervention with endovascular recanalization or physical rehabilitation, the change in mRS [6] scores of the first and the third month, and mortality rates were inspected. Blood specimens were obtained from the medial cubital vein and stored in ethylenediaminetetraacetic acid (EDTA) covered tubes. Laboratory results were operated by ADVIA 1800 (Siemens Healthcare Diagnostics, Tokyo, Japan) for serum concentrations of C-reactive protein (CRP) and albumin, and Mindray BC6800 (Shenzen, Mindray Bio-Medical Electronics, Co., Ltd) for hematology parameters. Values of albumin concentrations were stated in grams per decilitre (g/dL), CRP was milligrams per decilitre (mg/dL), and platelet, neutrophile, lymphocyte were per microlitre (μl). The NLR, PLR, and CAR values were estimated by dividing neutrophil measures by lymphocyte measures, total platelet measures by the total lymphocyte measures, and total CRP measures by the total albumin measures.

Statistical Analysis

Descriptive statistics were given as mean±standard deviation and median with interquartile range (IQR) of 25% to 75% for continuous variables depending on their distribution. Numbers and percentages were used for categorical variables. The numerical variables' normal distribution was analyzed by the Kolmogorov-Smirnov test and checked by Q-Q plots and histograms. The Levene test checked the homogeneity of the variances. In evaluating the differences between the baseline and post-treatment laboratory parameters, a paired t-test was used when the variables showed normal distribution. The Wilcoxon test was used when the variables did not show normal distribution. For the analysis of changes in the NIHSS scores during the treatment, the Mann-Whitney U and Kruskal Wallis tests were used based on each parameter's number. Spearman Rho correlation coefficient was used to analyze the NIHSS and mRS scores' associations with other numerical variables. Whether the clinically significant variables affect the change between the baseline and post-treatment NIHSS scores was evaluated using the Nonparametric Analytical Method of Longitudinal Data in Factor Experiments (https://cran.r-project.org/web/packages/nparLD/nparLD.pdf). The error graph was used to visualize the results. For statistical analysis, "Jamovi project (2020), Jamovi (Version 1.6.3) [Computer Software] (Retrieved from https://www.jamovi.org), JASP (Version 0.14) (Retrieved from https://jasp-stats.org) and R-project (version 4.0.3) were used. The significance level (p-value) was set at 0.05 in all statistical analyses.

Table 1. Baseline characteristics and clinical risk factors of the patients

Variable		
Age (year)†, ‡	71.2±13.7	71.0 [62.0–81.0]
Age groups$^{\beta}$		
<65 years	15 (30.6)	
≥65 years	34 (69.4)	
Sex$^{\beta}$		
Female	24 (49.0)	
Male	25 (51.0)	
Etiology$^{\beta}$		
Atherosclerotic	21 (42.9)	
Cardiogenic	14 (28.6)	
Lacunar infarcts	10 (20.4)	
Others	4 (8.2)	
Smoking$^{\beta}$	21 (42.9)	
Comorbidity$^{\beta}$	44 (89.8)	
Hypertension	29 (59.2)	
Atrial fibrillation	14 (28.6)	
Previous myocardial infarction	11 (22.4)	
Diabetes mellitus	10 (20.4)	
Cerebrovascular disease	10 (20.4)	
Chronic heart failure	9 (18.4)	
Hyperlipidemia	8 (16.3)	
Carotid artery stenosis$^{\beta}$		
Present	25 (51.0)	
Absent	24 (49.0)	
Use of anti-coagulant medications$^{\beta}$	4 (8.2)	
Use of anti-platelet medications$^{\beta}$	13 (26.5)	

†: Mean±SD; ‡: Median [Q1–Q3]; β: n (%).

Table 2. Technical details of intravenous tissue plasminogen activator therapy

Variable		
Total dose for iv-tPA†, ‡	70.4±10.5	68.5 [63.0–76.0]
Baseline NIHSS†, ‡	9.6±4.7	10.0 [6.0–13.0]
Post-treatment NIHSS†, ‡	6.2±4.7	6.0 [2.0–10.0]
Area of infarct$^{\beta}$		
Anterior system	41 (83.7)	
Posterior system	8 (16.3)	
Symptom to door time (min)†, ‡	55.9±68.0	30.0 [2.0–90.0]
Door to needle time (min)†, ‡	19.8±28.7	15.0 [0.4–30.0]
Symptom to needle time (min)†, ‡	74.8±80.6	45.0 [2.3–125.0]
Development of hemorrhagic transformation$^{\beta}$	8 (16.3)	

†: Mean±SD; ‡: Median [Q1–Q3]; β: n (%).

Table 3. Treatment outcomes

Variable		
Intervention$^{\beta}$	6 (12.2)	
Physical rehabilitation$^{\beta}$	18 (36.7)	
mRs - 1. Month†, ‡	2.5±2.0	2.0 [1.0–4.5]
mRs - 3. Month†, ‡	2.0±2.2	1.0 [0.0–4.0]
Prognosis$^{\beta}$		
Survivor	38 (77.6)	
Non-survivor	11 (22.4)	

†: Mean±SD; ‡: Median [Q1–Q3]; β: n (%).

RESULTS

Baseline characteristics and clinical risk factors are given in Table 1. The study included 49 acute ischemic stroke patients with a mean age of 71.2±13.7 years. The majority of the patients (69.4%) were ≥65 years. The female-to-male ratio was almost 1. Atherosclerotic diseases were more frequent etiological risk factor seen in 21 patients (42.9%). Twenty-one patients (42.9%) were active smokers. In 44 patients (89.8%), we detected at least one comorbidity. Among them, hypertension (59.2%) and atrial fibrillation (28.6%) were the most common diseases. Carotid artery stenosis was detected in almost half of the patients (51.0%). The use of anti-coagulant and anti-platelet medications was seen in four (8.2%) and 13 patients (26.5%). The total dose for iv-tPA was 70.4±10.5 ml. The median baseline NIHSS score was 10.0, whereas the post-treatment score was calculated as 6.0. Decreases in the post-treatment NIHSS scores were statistically significant compared with the baseline NIHSS scores ($p<0.001$). Most of the infarcts were located in the anterior system (83.7%). The median values of symptom-to-door time, door-to-needle time, and symptom-to-needle time were found as 30.0 min, 15.0 min, and 45.0 min, respectively. Hemorrhag-

Table 4. Changes of laboratory variables according to the treatment

	Time		p
	Baseline	Post-treatment	
Hemoglobin (g/dL)†	13.8±1.8	13.2±1.9	**0.004**€
RBC (10^3/μL)†	5.0±0.8	4.7±0.8	**<0.001**€
Neutrophil count (10^3/μL)‡	5.2 [4.2–6.9]	6.2 [5.3–7.9]	0.109¥
Lymphocyte count (10^3/μL)	2.2±1.0	1.8±0.8	**0.002**€
Platelet count (10^3/μL)‡	232.0 [178.0–282.0]	255.0 [199.0–287.0]	0.198¥
MCV (fL)‡	88.0 [84.9–90.9]	89.1 [85.8–92.0]	0.128¥
RDW (%)‡	50.8 [48.3–53.2]	51.1 [45.8–55.3]	0.633¥
PLR‡	112.3 [75.2–135.4]	137.4 [106.0–213.7]	0.085¥
NLR‡	2.2 [1.7–4.3]	4.1 [2.4–8.5]	**0.012**¥
Albumin (g/dL)†	4.0±0.5	3.9±0.8	0.145€
CRP (mg/dL)‡	7.4 [3.7–15.1]	10.7 [6.2–19.9]	**0.006**¥
CAR‡	1.8 [0.9–3.7]	3.1 [1.4–5.3]	**0.009**¥

†: Mean±SD; ‡: Median [Q1–Q3]; β: n (%); ¥: Wilcoxon test; €: Paired t test.

ic transformation developed in eight patients (16.3%). The variables regarding the details of the treatment are summarized in Table 2. In six patients (12.2%), no intervention was needed. Post-treatment physical rehabilitation was applied in 18 patients (36.7%). Although the first month's median mRS score was calculated as 2.0, the value decreased to 1.0 in the third month follow-up. The change in mRS scores from the first month to the third month was significant (p=0.002). There were 11 deaths in the study group, with a mortality rate of 22.4% (Table 3). There were significant differences between the baseline and post-treatment laboratory values (Table 4). The mean hemoglobin, red blood cell (RBC), and lymphocyte count values were significantly decreased after the treatment (p=0.004, p<0.001, and p=0.002). Significant increases in the values of NLR, CRP, and CAR were detected (p=0.012, p=0.006, and p=0.009).

Correlation analysis revealed significant positive correlations between post-treatment NIHSS score and CAR, PLR, and NLR (Table 5). As the values of CAR, PLR, and NLR increased, post-treatment NIHSS score also increased. PLR and NLR were significantly correlated with the third-month mRS score (r=0.467, p<0.001 and r=0.364, p=0.011).

Analysis of ΔNIHSS score between demographic and clinical variables is given in Table 6. There was no significant difference in ΔNIHSS scores between the patients <65 and ≥65 (p=0.343). The ΔNIHSS scores were similar in patients with anterior and posterior infarcts (p=0.913). There were no significant differences in ΔNIHSS scores based on the different etiological risk factors (p=0.333). The door-to-needle time as <60 min and ≥60 min had no impact on the ΔNIHSS scores' values (p=0.417). Table 7 shows the statistical analysis of time × group inter-actions of the NIHSS scores according to age groups, infarct area, etiological risk factors, and the door-to-needle time. There was no significant impact of age, infarct area, and etiological risk factors on the amount of change in the NIHSS score (Table 7). The door-to-needle time had significantly impacted the change of NIHSS score (interaction p=0.008).

DISCUSSION

The study's initial objective was to analyze the clinical and demographical findings and and evaluate the relationships between NIHSS and mrRS scores, and NLR,PLR and CAR ratios of acute ischemic stroke patients treated with iv-tPA in a secondary-state facility. Most of our patients were above 65 years old, and the female-to-male ratio was evenly distributed. Atherosclerotic diseases were more frequent etiological risk factor; hypertension and atrial fibrillation were detected as the most common comorbidities. Carotid artery stenosis was detected

Table 5. Correlation of baseline and post-treatment NIHSS and 1st and 3rd month mRS scores

	Baseline NIHSS		mRs -1st month	
	Spearman's rho	p	Spearman's rho	p
Symptom to door time	0.023	0.873	0.201	0.171
Door to needle time	-0.038	0.798	0.211	0.150
Symptom to neddle time	0.002	0.990	0.155	0.292
CAR (Post-treatment)	0.174	0.233	0.233	0.112
PLR (Post-treatment)	0.079	0.591	0.270	0.064
NLR (Post-treatment)	-0.019	0.895	0.125	0.399
	Post-treatment NIHSS		mRS - 3rd month	
Symptom to door time	0.114	0.437	0.179	0.223
Door to needle time	0.104	0.475	0.265	0.069
Symptom to neddle time	0.090	0.541	0.145	0.325
CAR (Post-treatment)	0.444	**0.001**	0.268	0.065
PLR (Post-treatment)	0.414	**0.003**	0.467	**<0.001**
NLR (Post-treatment)	0.384	**0.007**	0.364	**0.011**

Table 6. Analysis of Δ NIHSS score according to demographic and clinical variables

Variable	Δ NIHSS‡	p
Age groups		
<65 years (n=15)	50 [20–80]	0.343
≥65 years (n=34)	37.5 [25–61.11]	
Area of infarct		
Anterior system (n=41)	40 [20–66.67]	0.913
Posterior system (n=8)	38.75 [33.33–50]	
Etiology		
Atherosclerotic (n=21)	47.37 [25–66.67]	0.333
Cardiogenic (n=14)	33.33 [0–50]	
Lacunar (n=10)	50 [40–83.33]	
Others (n=4)	19.65 [-32.86–50]	
Door-to-needle time (min)		
<60 min (n=47)	40 [20–66.67]	0.417
≥60 min (n=2)	57.5 [40–75]	

‡: Median [Q1–Q3].

in almost half of the patients, and most of the infarcts were located at the anterior system. There was a decrease in the post-treatment NIHSS scores according to the baseline. Similarly, the first-month's median mRS score decreased in the third-month follow-up. This decrease could be explained by the fact that our patients significantly benefitted from the iv-tPA treatment. Therefore, our results match those observed in earlier studies [1, 7].

As mentioned in the literature review, iv-tPA's initial administration is related to reduced mortality and better prognosis [8]. The aim is to get door-to-needle time within 60 minutes [8–10]. The importance of door-to-needle time is directly under the control of physicians [8, 11]. In our study, our patients' door-to-needle time was 15 minutes. We believe there are several reasons for how we achieved this duration. A possible explanation for this might be that is, the early interference. After the CT scan and informed consent, the intravenous infusion was administrated in the emergency department, and during the initiation of alteplase, CT-angiography was performed. Another probable rationalization is, the closest stroke unit was 2-hours away; therefore, it was crucial to decide, begin the treatment, and transfer the patient if necessary.

We noticed considerable alterations among the baseline and post-treatment laboratory measures. There was a decrease in lymphocyte and albumin counts; however, an increase in neutrophile, NLR, CRP, and CAR values [12]. The inflammation has been related to secondary brain damage after stroke. Prior studies have noted the importance of neutrophil and lymphocyte values related to this manner. In the early-period of stroke, neutrophils begin to accumulate and discharge mediators to aggra-

Table 7. Analysis of time × group inter-actions of the NIHSS scores according to age groups, infarct area, etiological risk factors and door-to-needle time

	Baseline NIHSS ‡	Post-treatment NIHSS ‡	Main effect p	Interaction
Age groups				
<65 years (n=15)	8 [5–10]	3 [1–6]	**<0.001**	0.578¥
≥65 years (n=34)	11.5 [8–15]	6.5 [4–10]		
Area of infarct				
Anterior system (n=41)	10 [6–13]	6 [1–10]	**<0.001**	0.322¥
Posterior system (n=8)	10.5 [7–13]	6 [3.5–9]		
Etiology				
Atherosclerotic (n=21)	10 [6–16]	6 [2–9]	**<0.001**	0.124¥
Cardiogenic (n=14)	10.5 [8–13]	6 [4–10]		
Lacunar (n=10)	7 [6–10]	3.5 [1–6]		
Others (n=4)	9 [6–12]	9 [3.5–15]		
Door to needle time (min)				
<60 min (n=47)	10 [6–13]	6 [1–10]	**<0.001**	**0.008¥**
≥60 min (n=2)	8 [8–10]	4 [2–6]		

¥: Nonparametric Analytical Method of Longitudinal Data in Factor Experiments.

vate the destruction in the ischemic area, therefore reveals poor clinical outcomes [12, 13]. Also, after the excessive triggering of the sympathetic system, the catecholamines release. This release causes a decrease in lymphocytes and a reduction in neuroprotection. Consequently, due to excessive inflammation and immunosuppression, NLR can be related to poor outcomes [12, 14, 15]. CRP is also released after stroke as an inflammatory response. Elevated levels trigger blood-brain barrier breakdown and cause the loss of the neurons. Besides, numerous researches found that it accelerates atherosclerosis, carotid artery stenosis, and stroke progression [16, 17]. As a reaction to inflammation, albumin levels decrease and stand out as an anti-inflammatory mediator. It attenuates the activation of microglia and T cells [12, 16]. There has been a confirmed association among CAR and 3-month mortality; therefore, CAR could further predict stroke prognosis [18]. Hence, the findings observed in this study mirror those of the previous studies. This study has been unable to demonstrate that elevated levels of PLR are associated with acute stroke. Platelets contribute to atherosclerosis, and elevated levels are related to ischemic stroke. Recently, there has been an uncovered relationship between elevated PLR levels and stenosis severity in carotid arteries [19]. However, we did not find any association; the possible explanation for these results may be the lack of adequate patients. One more of the issues that emerge from our findings is revealing significant positive correlations between post-treatment NIHSS score and CAR, PLR, and NLR. As the values of CAR, PLR, and NLR elevated, post-treatment NIHSS score increased. Moreover, PLR and NLR were significantly correlated with the third-month mRS scores. Our findings accord with previous observations, which showed that elevated levels of NLR, PLR, and CAR predict poor outcomes [12, 17, 18].

There were no significant differences in the amount of change of NIHSS scores based on the different risk factors as age, infarct area, and etiology; however, the door-to-needle time had significantly impacted the change of NIHSS score as <60 minutes, but ≥60 minutes did not affect. Thefore, the findings of the current study are consistent with those of Fonarow et al. [9] (2020) who advised rapid alteplase infusion treatment in acute stroke is sufficient and, can be achieved not only without increasing rates of symptomatic intracranial hemorrhage, but with actual reductions in complications.

Finally, several significant limitations need to be considered. First, the study is cross-sectional, non-randomized, and the number of patients is small. Future studies on the current topic are therefore recommended and supported by multi-center studies with more participants. Secondly, the study did not evaluate the use of endovascular treat-

ment due to the lack of a stroke unit. Further work is required to establish the effect of mechanic trombectomy.

In conclusion, although the current study is based on a small sample of participants, the findings suggest that elevated levels of NLR, PLR, and CAR predict modest consequences. Rapid treatment is sufficient and can reduce complications and poor outcomes. Taken together, our results suggest that it would be beneficial to treat the patients with iv-tPA in secondary-staged hospitals and should be widespread.

Ethics Committee Approval: The Siirt University Clinical Research Ethics Committee granted approval for this study (date: 2020, number: 1302).

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