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Evaluation of the Relationship Between Thrombolytic Treatment Complications and Laboratory Parameters in Acute Ischemic Stroke Patients

Akut İskemik İnmeli Hastalarda Trombolitik Tedavi Komplikasyonları ile Laboratuvar Parametreleri Arasındaki İlişkinin Değerlendirilmesi

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ABSTRACT

Objective: We aimed to investigate the role of serum uric acid and lactate levels and mean platelet volume in predicting treatment success in patients with ischemic stroke.

Methods: One hundred and five patients who were diagnosed with cerebrovascular disease and received thrombolytic or thrombectomy treatment were included in the study. Patients were divided into two groups as patients who developed complications and who did not develop complications. Demographical characteristics, laboratory findings, the National Institutes of Health Stroke Scale (NIHSS) scores at admission and at discharge, and Modified Rankin Scale (mRS) score were investigated retrospectively.

Results: Of all patients, 58.1% of the were male. There were no differences in terms of laboratory parameters between the groups. NIHSS score at admission, NIHSS score at discharge, and mRS score were significantly higher in the group that developed complications after treatment ($p<0.05$). Laboratory values did not differ significantly between the groups. Early mortality rate in the group which developed complications was significantly higher than the group which did not develop complications ($p<0.05$). Univariate model revealed significant effectiveness of NIHSS score at admission and at discharge, and mRS score in the differentiation of patients with and without complications ($p<0.05$). In the multivariate model, a significant and independent effectiveness of the NIHSS score at discharge was observed in the differentiation of patients with and without complications (sensitivity =83.3%, positive prediction =30.8%, specificity =57.1% and negative prediction =93.8%; $p<0.05$).

Conclusion: We found no significant associations between the development of complications after thrombolytic therapy and laboratory findings. The NIHSS score may be a suitable parameter in predicting complications.

Keywords: Acute cerebral ischemia, lactate, NIHSS score, Modified Rankin Scale, uric acid

ÖZ

Amaç: İskemik inmeli hastalarda tedavi başarısını öngörmede serum ürik asit ve laktat düzeyleri ile ortalama trombosit hacminin rolünü araştırmayı amaçladık.

Yöntemler: Çalışmaya serebrovasküler hastalık tanısı konan ve trombolitik veya trombektomi tedavisi alan 115 hasta dahil edildi. Hastalar komplikasyon gelişen ve gelişmeyen olarak iki gruba ayrıldı. Demografik özellikler, laboratuvar bulguları, Ulusal Sağlık Enstitüleri İnme Ölçeği (NIHSS) kabul ve taburculuk skoru ve Modifiye Rankin Ölçeği (mRS) skoru geriye dönük olarak incelendi.

Bulgular: Tüm hastaların %58,1'i erkekti. Gruplar arasında laboratuvar parametrelerinde fark yoktu. Başvuruda NIHSS skoru, taburculukta NIHSS skoru ve mRS skoru, tedavi sonrası komplikasyon gelişen grupta anlamlı olarak daha yüksekti ($p<0,05$). Laboratuvar değerleri gruplar arasında anlamlı farklılık göstermedi. Erken ölüm oranı komplikasyon gelişen grupta komplikasyon gelişmeyen gruba göre anlamlı derecede yüksekti ($p<0,05$). Tek değişkenli model, kabul ve taburculukta NIHSS puanının ve mRS skorunun komplikasyonlu ve komplikasyonsuz hasta ayrımında anlamlı etkinliğini ortaya koydu ($p<0,05$). Çok değişkenli modelde, taburculukta NIHSS skorunun komplikasyonlu ve komplikasyonsuz hasta ayrımında anlamlı ve bağımsız bir etkinliği gözlendi (duyarlılık =%83,3, pozitif tahmin =%30,8, özgüllük =%57,1 ve negatif tahmin =%93,8; $p<0,05$).

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ÖZ

Sonuç: Trombolitik tedavi sonrası komplikasyon gelişimi ile laboratuvar bulguları arasında anlamlı bir ilişki bulamadık. NIHSS skoru komplikasyonları öngörmede uygun bir parametre olabilir.

Anahtar kelimeler: Akut serebral iskemi, laktat, NIHSS puanı, Modifiye Rankin Ölçeği, ürik asit

INTRODUCTION

Acute cerebrovascular event (ACE) is a condition with permanent brain damage because of disruption of cerebral blood flow. Even though ACE is the second most common cause of mortality and the leading cause of disability worldwide, making decisions about the clinical course and predicting prognosis of ischemic stroke (IS) patients are still challenging (1-3).

A clinically significant relationship between serum uric acid levels and cardiovascular and cerebrovascular diseases (CVDs) has been shown (4,5). Hyperuricemia is often observed in patients with metabolic syndrome and the risk of vascular diseases is high in metabolic syndrome (6,7). Poor clinical picture after ACE has been implicated to be associated with hyperuricemia (8). There are studies showing that uric acid is a powerful antioxidant against free radicals (9,10), however, high serum uric acid levels are indicated as an independent risk factor for the development of cerebrovascular and cardiovascular disease (11). Lactate is a known by-product of anaerobic metabolism and is increased upon hypoperfusion (12). Hyperlactatemia is a biomarker of metabolic stress response and is found to be associated with mortality in critically ill patients (13,14). Several previous magnetic resonance spectroscopy and microdialysis studies have shown that lactate accumulates in ischemic brain lesions in acute stroke patients (15,16).

In our study, we aimed to investigate the role of serum uric acid and lactate levels and mean platelet volume (MPV), as well as the National Institutes of Health Stroke Scale (NIHSS) score at admission, NIHSS score at discharge, and Modified Rankin Scale (mRS) score in predicting treatment success in patients with IS.

METHODS

This retrospective study was conducted on patients who were admitted to University of Health Sciences Turkey, Şişli Hamidiye Etfal Training and Research Hospital Emergency Service within a 2-year period (between 01.01.2018-01.01.2020), diagnosed with CVD, and treated with only thrombolytic, only thrombectomy or thrombolytic + thrombectomy therapies in the emergency department and hospitalized in the neurology clinic of our hospital.

The blood pressure category (normal, stage I hypertension and stage II hypertension), electrocardiogram (ECG) and echocardiogram (ECHO) findings, presence of comorbidity, blood parameters [haemoglobin (HGB), MPV, neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), platelet (PLT) and red cell distribution width (RDW) values], serum uric acid and lactate levels, the NIHSS scores at admission and discharge, and mRS score were analysed in patients with regards to the presence of complications. This study was conducted in accordance with the Declaration of Helsinki on Ethical Principles. Ethical approval was obtained from University of Health Sciences Turkey, Şişli Hamidiye Etfal Training and Research Hospital Clinical Research Ethics Committee (decision no: 2688, date: 25.02.2020).

Statistical Analysis

In the descriptive statistics of the data, mean, standard deviation, median, minimum, maximum, frequency and ratio values were used. The distribution of variables was analysed with the Kolmogorov-Smirnov test. Independent samples t-test and Mann-Whitney U test were used in the analysis of quantitative independent data. Chi-square test was used in the analysis of qualitative independent data while Fisher's Exact test was used when the chi-square test conditions were not met. The effect level and cut-off value were investigated with the Receiver operating characteristic curve. The effectiveness of the NIHSS scores and mRS score in discriminating the complication status of the patients was investigated with univariate and multivariate logistic regression. The SPSS 26.0 program was used in the analysis.

RESULTS

A total of 105 patients were included in the study. Of the patients, 61 (58.1%) were male and 44 (41.9%) were female. Distribution of the comorbid diseases and demographic characteristics are indicated in Table 1.

Table 1. Demographic characteristics of patients

		Complication (-)	Complication (+)	p
		n (%)	n (%)	
Age	≤64	31 (29.5)	5 (20.8)	0.392$^{X^2}$
	≥65	74 (70.5)	19 (79.2)	
Gender	Female	44 (41.9)	8 (33.3)	0.440$^{X^2}$
	Male	61 (58.1)	16 (66.7)	
Comorbid chronic disease	(-)	16 (15.2)	3 (12.5)	0.733$^{X^2}$
	(+)	89 (84.8)	21 (87.5)	
Comorbid chronic disease	IHD	45 (42.9)	10 (41.7)	0.915$^{X^2}$
	HT	71 (67.6)	17 (70.8)	0.760$^{X^2}$
	DM	25 (23.8)	8 (33.3)	0.335$^{X^2}$
	CVE	19 (18.1)	5 (20.8)	0.756$^{X^2}$
	Other	18 (17.1)	4 (16.7)	0.955$^{X^2}$

CVE: cerebrovascular event, DM: diabetes mellitus, HT: hypertension, IHD: ischemic heart disease, $^{X^2}$Spearman Rho test

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The condition of blood pressure and ECG and ECHO findings did not differ significantly (p>0.05) between the groups with and without complications after thrombolytic therapy (TT). At the post-treatment period, patients who developed complications had significantly higher NIHSS score both at admission and at discharge and higher mRS score compared to the patients who did not develop any complications (p<0.05; Table 2). HGB, PLT, NLR, PLR, RDW, MPV, lactate, and uric acid values did not differ significantly between the groups with and without complications after treatment (p>0.05). The early mortality rate in the group with complications was significantly higher than the group without complications (p<0.05) (Table 2). Moreover, there were no significant associations between the presence of complications and the duration of the treatment (p>0.05; Table 2a and Table 2b).

In the analysis with univariate model, significant efficiencies of NIHSS score at admission, NIHSS score at discharge, and mRS score was observed in distinguishing patients with and without complications. In the analysis with reduced multivariate model, a significant and independent efficiency of the NIHSS score at discharge was observed in discriminating patients with and without complications (odds ratio: 1.17, 95% confidence interval: 1.07-1.28, p=0.001) (Table 3).

Table 2a. Evaluation of the post-treatment status of the patients

	Complication (-)		Complication (+)		p
	Min-max	Median	Min-max	Median	
NIHSS score at admission	4.0-22.0	10.0	4.0-42.0	16.0	0.001[m]
NIHSS score at discharge	0.0-22.0	8.0	3.0-35.0	16.5	0.001[m]
mRS score	0.0-6.0	4.0	0.0-6.0	5.0	0.008[m]
HGB	75.0-169.0	131.0	77.0-189.0	138.5	0.331[t]
PLT	97.0-592.0	219.0	101.0-609.0	221.5	0.945[m]
NLR	0.4-15.4	2.4	0.4-15.5	2.4	0.751[m]
PLR	14.5-397.3	101.8	13.8-388.6	101.5	0.444[m]
RDW	64.0-218.0	139.0	63.0-221.0	139.0	0.981[m]
MPV	7.3-12.2	9.5	7.0-13.0	9.6	0.699[t]
Lactate	0.8-7.0	1.7	1.1-7.7	1.9	0.421[m]
Uric acid	1.8-11.5	5.3	2.6-13.3	8.2	0.897[t]

HGB: haemoglobin, MPV: mean platelet volume, NIHSS: The National Institutes of Health Stroke Scale, mRS: The Modified Rankin Scale, NLR: heutrophil-to-lymphocyte ratio, PLR: platelet-to-lymphocyte ratio, PLT: platelet, RDW: red cell distribution width, [m] Mann-Whitney U test/[t]t-test

Table 2b. Evaluation of the post-treatment status of the patients

		Complication (-)	Complication (+)	p
		Mean ± SD/n (%)	Mean ± SD/n (%)	
Blood pressure	Normal	28 (26.7)	4 (16.7)	0.438[X²]
	Stage I hypertension	24 (22.9)	8 (33.3)	
	Stage II hypertension	53 (50.5)	12 (50.0)	
ECG	NSR	74 (70.5)	15 (62.5)	0.446[X²]
	AF	31 (29.5)	9 (37.5)	
ECHO findings				
Normal ECHO		68 (64.8)	18 (75.0)	0.471[X²]
Enlarged right atrium and ventricle		7 (6.7)	2 (8.3)	
Enlarged left atrium and ventricle		19 (18.1)	3 (12.5)	
Segmentary wall motion abnormality		11 (10.5)	1 (4.2)	
One-month mortality	(+)	21 (20.0)	10 (41.7)	0.025[X²]
	(-)	84 (80.0)	14 (58.3)	
Duration of treatment (min)	0-59	13 (12.4)	2 (83)	0.085[X²]
	120	51 (48.6)	9 (37.5)	
	180	26 (24.8)	12 (50.0)	
	240	15 (14.3)	1 (4.2)	

AF: atrial fibrillation, ECG: electrocardiogram, ECHO: echocardiogram, NSR: normal sinus rhythm, [X²]Spearman Rho test

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Table 3. Logistic regression analysis

	Univariate model			Multivariate model		
	OR	95% CI	p	OR	95% CI	p
NIHSS score at admission	1.164	1.059-1.279	0.002	-	-	-
NIHSS score at discharge	1.179	1.079-1.288	0.001	1.179	1.079 - 1.288	0.001
mRS score	1.532	1.088-2.156	0.014	-	-	-

NIHSS: The National Institutes of Health Stroke Scale, OR: odds ratio, CI: confidence interval

A significant efficacy of the NIHSS score at discharge was observed in the discrimination of patients who developed and did not develop complications after treatment [Area under the curve (AUC) =0.766 (0.661-0.872)]. A significant efficacy of the cut-off value of 10 in the NIHSS score at discharge was observed in the differentiation of patients with and without complications [AUC =0.702 (0.595-0.810)]. Sensitivity, positive prediction, specificity, and negative prediction were found as 83.3%, 30.8%, 57.1%, and 93.8%, respectively (Figure 1).

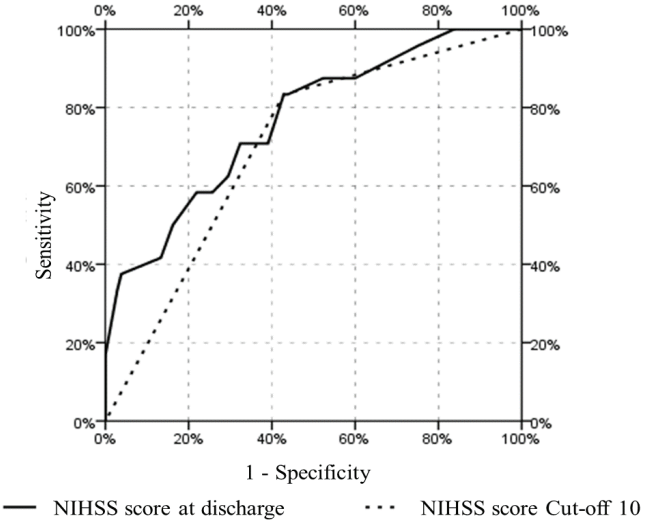

Figure 1. Sensitivity and specificity of NIHSS in predicting complication
NIHSS: The National Institutes of Health Stroke Scale

DISCUSSION

In the literature, a debate about the role of hemogram parameters on the pathogenesis of stroke is still going on. In this study, we investigated the relationship between serum uric acid, lactate and MPV values and treatment success in patients with IS. Moreover, common scales which measured the disability of the patient after stroke and severity of the stroke, including NIHSS and mRS were analysed with regards to the presence of the complications after treatment.

Previously, it was reported that the hematologic parameters were significantly altered in patients with IS (17). Yigit et al. (18) indicated that anaemia was a risk factor for recurrence of IS in patients with malignancy. Another study reported that MPV was associated with the severity of acute IS (19). On the other hand, increased NLR at the admission was reported to be an independent factor related to poor prognosis and poor 90-day outcome in patients with intracerebral haemorrhage (ICH) and it was suggested to be a prognostic marker in spontaneous ICH patients (20). In our study, no significant differences in terms of haematological parameters evaluated between the patients with and without complications after TT were found.

Lactate is produced as the result of anaerobic glycolysis. When the glucose is deprived in the brain, lactate is used as an alternative energy source for the metabolic activities in the brain (21). Previously, elevated blood lactate levels in stroke patients at admission were suggested to indicate higher risk of 1-, 3-, and 12-month mortality (22), Another study, it was shown that lactate level in cerebrospinal fluid (CSF), but not in blood, was found to be significantly higher in patients with acute stroke and it was suggested that CSF lactate level might be used as a marker for the evaluation of stroke severity (23). We also found no significant differences between the patients with and without complications with regards to serum lactate levels.

Hyperuricemia and accompanying dyslipidaemia in patients with acute stroke have been implicated to be risk factors for acute IS (24,25). Post-ischemic hyperuricemia in diabetic patients was reported to be associated with mortality and recurrent vascular events in IS patients (26). Moreover, Karagiannis et al. (27) reported a significant association between increased serum uric acid levels and early mortality. However, we did not find any significant differences in terms of uric acid levels between the patients who developed complications and the patients who did not develop complications.

Early recanalization positively affects the prognosis in patients with acute IS (28) by reducing the mortality and disability in the patients (29). Although, the risk of development of complications after intravenous recombinant tissue plasminogen activator treatment was reported to increase with older, presence of severe neurological deficit, hypertension, diabetes mellitus, and early signs of infarction in computed tomography, there were contradictory results regarding those (30-33). High NIHSS score before the TT has been implicated to be a risk factor for haemorrhagic transformation after TT (34,35). Moreover, NIHSS score higher than 25 is a contraindication for TT (33). The most common and serious complication of TT is haemorrhagic transformation and poor clinical prognosis is encountered in case of intracranial haemorrhage (36,37). The mRS is used to

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measure the disability of the patient after IS and is indicated to be an important tool for prediction outcomes after discharge (38-40). In our study, patients who developed complications after TT had higher NIHSS scores both at admission and at discharge, as well as higher mRS scores. Moreover, in the univariate model, significant efficacies of NIHSS scores both at admission and at discharge, as well as mRS scores were detected. On the other hand, NIHSS score at discharge was found to be a sensitive and specific predictor of development of complication in IS patients.

Study Limitations

This study had some limitations. First, the sample size was small, therefore, a larger group of patients could be included. Secondly, we did not measure the lactate levels in CSF or did not perform magnetic resonance spectroscopy analysis for the patients.

CONCLUSION

Predicting the development of complications after TT in patients with acute IS is crucial to prevent the complications and mortality. In the present study, NIHSS score was found to be a significant determinant in predicting complications in patients with IS. Therefore, NIHSS score may be suggested to be useful for the prediction of the development of the complications in the patients with IS. Future studies with larger populations and more detailed examinations are required to investigate the relationship between the parameters and complications and to predict the prognosis.

Ethics Committee Approval: This study was conducted in accordance with the Declaration of Helsinki on Ethical Principles. Ethical approval was obtained from University of Health Sciences Turkey, Şişli Hamidiye Etfal Training and Research Hospital Clinical Research Ethics Committee (decision no: 2688, date: 25.02.2020).

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