

## The effect of blood lactate level on prognosis in cerebrovascular disease

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### Abstract

**Aim:** Cerebrovascular disease (CeVD) is "rapidly developing cerebral dysfunction, lasting 24 hours or longer or leading to death". The diagnosis and treatment of CeVD should be started quickly to prevent mortality and morbidity. Therefore, biomarkers are needed for rapid diagnosis and prognosis. The aim of this study is to describe the correlation between disease and lactate level (LL) in CeVD.

**Materials and Methods:** Our study was conducted retrospectively in an emergency service of a tertiary care hospital. One hundred thirty-eight cases meeting the study criteria were chosen from the cases applied from January 1 2017 to January 1, 2018.

**Results:** The gender distribution was as follows: 52.2% of the cases were females and 47.8% were males. The average age was 73.48±9.71 years for females and 74.13±8.73 years for males; 94.2% of the cases were ischemic and 5.8% were hemorrhagic CeVD. In ischemic cases, baseline, 4.5th hour, the first 24-hour period and the first 72-hour period's LL decreased as the infarct time passed, and mortality was observed in cases in which the height of the lactate continued ( $p<0.001$ ). The significant relationship between infarct size and LL was only in the MCA lesion and the LL was high as the lesion size increased. It was determined that NIHSS correlated with LL and NIHSS was high in patients with mortality.

**Discussion:** In stroke patient, LL will provide meaningful predictions about the time since the start of the infarct and in determining the prognosis. We think that more studies are needed for definitive comments.

### Keywords

Emergency service; Stroke; Lactate

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## Introduction

According to the World Health Organization (WHO), cerebrovascular disease (CeVD) is “rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting 24 hours or longer or leading to death, with no apparent cause other than of vascular origin” [1]. Globally, CeVD is the most common cause of mortality, other than cardiac diseases and cancer [2]. The time from the beginning of CVD to diagnosis affects the mortality and morbidity; and saving unsupplied area called ‘penumbra’ is also important to prevent the ischemic area [3].

Considering the clinical results of CeVD, the most important goal is to reach timely in order to provide effective treatment of thrombolytic therapy [4]. Therefore, rapid diagnosis and prognosis markers are needed. Lactate is a biomarker that can be pleasant in this context. In animal experimental studies by Bogousslavsky et al. and Horn et al., it has been shown that damaged and ischemic brain tissue uses lactate as an energy source and has a neuroprotective effect on nerve tissue [5,6].

In our study, we aim to benefit from the outcomes of correlation between blood gas lactate levels and prognosis, progression, early diagnosis and treatment in patients applying to emergency service with acute stroke symptoms or diagnosis of stroke, meanwhile, contributing to the literature.

## Material and Methods

### Study design

Data were collected retrospectively from blood gas lactate levels of stroke patients over the age of 18 who applied with acute stroke to Çanakkale Onsekiz Mart University Medical Faculty Research and Training, and Çanakkale Mehmet Akif Ersoy State Hospitals’ emergency services.

Participants in the study were patients who presented to the emergency room with symptoms of stroke. Performed for the diagnosis of ischemic stroke, Diffusion-weighted imaging magnetic resonance (MR DWI) and performed for the diagnosis of hemorrhagic stroke the computerized brain tomography was confirmed by a radiologist; Patients whose imaging tests could not be performed were confirmed by a neurologist by clinical evaluation.

In the study, we measured the lactate levels of stroke patients who applied at the beginning, at 4.5 hours (due to the limit hour for thrombolytic therapy), in the first 24-hour period and in the first 72-hour period. The obtained results were recorded in the previously created study form.

### Study Settings and Population

This study was planned in an approximately 300-patient applicant emergency service of a hospital with 565-bed capacity, between May 1, 2017 and December 1, 2017. Ischemic or hemorrhagic regions confirmed by a radiology or neurology specialists were recorded. CeVD diagnosis was done upon neurologist’s evaluation.

The patients who had malignancies, who were under the age of 18, with intracranial tumor, underwent cardiopulmonary resuscitation, had traumatic intracranial bleeding, pregnant women, diagnosed neither with ischemic nor with hemorrhagic cerebrovascular disease were included in the study. However, patients diagnosed with diabetic ketoacidosis, sepsis, liver

failure, pneumonia and mesenteric ischemia that changed the lactate level were not included in the study.

Patient data were collected from the automation system and patient record archive. Two hundred forty-three patients diagnosed with CeVD between May 1, 2017 and December 1, 2017 were identified. Eighty-three patients who did not meet the study criteria or whose data were missing were excluded from the study. Twenty-two of the remaining 160 patients were referred to another center due to the need for intensive care, although they met the study criteria. They were excluded from the study because they it was thought that these patients could disrupt the study data and their data would not be fully accessible.

### Study Protocol

Ethics Committee Approval was received before the collection of patients’ data (Ethics committee approval number 2011-KAEK-27/2017 - E.151568). Patients who had CeVD I67 ICD disease code and applied to the emergency service were described retrospectively via Patient Data Management System. Demographical features, vital signs (pulse, SBP, and DBP), amount of ischemia and hemorrhage, lactate levels at the beginning, at 4.5 hours, in the first 24-hour period and in the first 72-hour period, NIHSS score, comorbidities, and mortality conditions of those patients were analyzed. All data were recorded on a formerly prepared form. Patient’s lactate levels were measured at the beginning, at 4.5 hours, in the first 24-hour period and the first 72-hour period.

### Statistical analysis

SPSS (Statistical Package for Social Sciences) for Windows 23.0 software was used for the statistical analysis of all the data obtained. All data were summarized in tables during evaluation. The Mann-Whitney U test was used to compare the mean values of the data obtained, and the Pearson’s Chi-Square (and Fisher’s exact test when required) was used to compare non-parametric data.

Results were considered significant at  $p < 0.05$ , with a 95% confidence interval.

## Results

One hundred thirty-eight patients were included in the study and 52.2% ( $n = 72$ ) of the cases were females and 47.8% were males. The mean age of the patients was  $73.48 \pm 9.71$  years in females and  $74.13 \pm 8.73$  years in males. Mean ages of women and men were similar ( $p = 0.632$ ). It was found that the most common is ischemia in the area of the posterior cerebral artery (PCA) irrigation and the second is infarct in the middle cerebral artery (MCA) irrigation area. One hundred and seven of 138 patients were hospitalized in the neurology service and the remaining 31 patients were hospitalized in the intensive care unit. In the analysis of the results, it was seen that 123 patients were discharged at the end of clinical follow-up and treatment and 15 cases were mortal. Other disease descriptive data of the cases are shown in Table 1.

In our study, the ischemia type of the cases was compared with lactate levels at the beginning, at the 4.5th hour, the first 24-hour period and the first 72-hour period. We determined that lactate level decreases in ischemic strokes as time passes and this decrease is statistically significant

**Table 1.** Descriptive data of cases

Parameters	Value	p
<b>Gender</b>		
Male	72 (%52,2)	
Female	66 (%47,8)	
<b>Age (year)</b>		
Male (year)	74,13±8,73	0.632
Female (year)	73,48±9,71	
<b>CeVD Type</b>		
Ischemic CeVD	130 (%94,2)	
Hemorrhagic CeVD	8 (%5,8)	
<b>Hospitalization Status</b>		
Service Hospitalization	107 (%77,5)	
Intensive Care Unit	31 (%22,5)	
<b>Outcome Status</b>		
Discharged	123 (%89,1)	
Exitus	15 (%10,9)	
<b>Lesion Type and Size</b>		
<b>MCA Irrigation Area</b>		
<1/3	16 (%36,4)	
1/3-2/3	14 (%31,8)	
>2/3	14 (%31,8)	
<b>ACA Irrigation Area</b>		
<1/3	17 (%43,5)	
1/3-2/3	14 (%35,8)	
>2/3	8 (%20,5)	
<b>PCA Irrigation Area</b>		
<1/3	24 (%51,0)	
1/3-2/3	13 (%27,6)	
>2/3	10 (%21,2)	
SBP (mmHg)*	127,39±22,35 (70-210)	
DBP (mmHg)	76,95±13,10 (40-110)	
Pulse (Beats/min)	87,94±17,26 (55-130)	
<b>CeVD Risk Factors **</b>		
Hypertension (by history)	41 (%29,7)	
Diabetes Mellitus (by history)	40 (%28,9)	
heart failure (by history)	21 (%15,2)	
Heart Valve Disease (by history)	54 (%39,1)	

\*: SBP: Systolic blood pressure, DBP: Diastolic blood pressure; \*\*: It may be more than one marked in the same patient. ICU: Intensive care unit; Data presentation: n (%), mean ± standard deviation or median (Minimum-Maximum)

(p<0.001). Similar to ischemic stroke cases, it was observed that there was a statistically significant decrease in lactate level in hemorrhagic stroke cases (p=0.002). However, since the number of hemorrhagic stroke patients is low (n = 8), the use of this analysis will not be appropriate. There was no significant difference between lactate levels at the beginning, at the 4.5th hour, the first 24-hour period and the first 72-hour period and the gender (p>0.05). However, when lactate levels were compared according to regions where ischemia areas are present, it was observed that the initial lactate value in the infarct area of the MCA in the irrigation area decreases over time and this decrease was statistically significant (p<0.001). This relation was not statistically significant in infarcts in other irrigation areas (p> 0.05) (Table 2). When the MCA irrigation area was divided into 3 groups according to the size of ischemia

**Table 2.** Relationship between the disease data of the patients and blood lactate levels

Parameters	Lactate Level Beginning	Lactate Level 4.5th Hour	Lactate Level First 24-hour period	Lactate Level First 72-hour period	p*
<b>CeVD Type</b>					
Ischemic CeVD (mg/dL)	2,70±1,64	2,56±1,87	2,48±2,49	2,12±2,61	<0.001
Hemorrhagic CeVD (mg/dL)	5,56±2,35	5,02±1,94	4,03±1,80	3,28±1,21	0.002
<b>Outcome Status</b>					
Discharged	2,60±1,28	2,43±1,85	2,25±2,04	1,85±1,99	<0.001
Exitus	5,09±3,42	5,14±3,61	5,20±3,94	5,25±4,74	<0.001
<b>Ischemic Irrigation Area</b>					
MCA Irrigation Area	3,37±2,41	3,24±2,59	3,16±2,72	2,74±3,09	<0.001
ACA Irrigation Area	2,35±1,00	2,36±2,79	2,39±3,33	2,01±3,29	0.063
PCA Irrigation Area	2,37±0,81	2,47±1,23	1,92±1,09	1,93±0,81	0.097
<b>Gender</b>					
Male	3,03±1,84	2,93±2,41	2,86±3,01	3,32±2,84	0.367
Female	2,72±1,78	2,48±1,66	2,60±1,84	3,04±2,30	0.588

\*: Friedman Test; MCA: Middle Cerebral Artery, ACA: Anterior Cerebral Artery, PCA: Posterior Cerebral Artery; Data presentation: mean ± standard deviation

**Table 3.** Relationship between infarct size and lactate levels of cases in MCA irrigation area

Parameters	<1/3 MCA Irrigation Area	1/3-2/3 MCA Irrigation Area	>2/3 MCA Irrigation Area	p
<b>Lactate Level</b>				
Lactate Level Beginning	2,37±0,88	2,72±1,19	5,18±3,41	0.015*
Lactate Level 4.5th Hour	2,26±0,79	2,54±1,03	5,14±3,77	0.013*
Lactate Level First 24 Hour Period	2,12±0,74	2,31±1,25	5,20±3,96	0.016*
Lactate Level First 72 Hour Period	1,54±0,54	2,08±1,68	4,93±4,73	0.024*
NIHSS	11,4±4,7	18,2±4,6	25,2±5,1	<0.001**

\*: Kruskal- Wallis Test; \*\*: Mann- Whitney U Test used; MCA: Middle Cerebral Artery; Data presentation: mean ± standard deviation

and when the lactate values were compared between these groups, it was seen that the lactate levels increased at the beginning, at 4.5 hours, at the first 24-hour period and the first 72- hour period and this increase was statistically significant (Table 3). The relationship between lactate levels according to the comorbid diseases status of the cases was examined and there was no statistically significant relationship between the history of DM, HT, heart failure and heart valve disease, and lactate levels (p> 0.05).

When the relationship between the mortality status of the cases and the National Health Stroke Scale (NIHSS) scores was examined, it was observed that the NIHSS score was statistically significant in patients with high mortality (p<0.001). In addition, in this study, there was a high degree of significant correlation between the calculated NIHSS score of the cases and the lactate levels observed in beginning, at the 4.5th hour, the first 24-hour period and the first 72-hour period (pbeginner<0.001, p4.5th hour<0.001, pfirst 24 hours <0.001 and pfirst 72 hours = 0.001, respectively).

## Discussion

Stroke is the cause of serious mortality and morbidity. It is the fourth most common cause of death in the world and second in our country [7]. In the literature, ischemic stroke has been shown as 80%, hemorrhagic stroke 15%, subarachnoid hemorrhage 5% [8]. In our study, while ischemic stroke was 94.2%, hemorrhagic stroke was found to be 5.8% that is different from the literature data.

When looking at risk factors for stroke, age is an unchanged risk factor. Although more than 70% of stroke cases appear to be 65 years and older, they may be more affected by ischemic conditions due to comorbid conditions that occur with age and increased atrophies in brain tissue with age [9]. In our study, due to no difference between the mean ages in both sexes and ischemia groups, age-related differences were tried to be minimized.

Another risk factor that cannot be changed is gender. Although there are many studies showing that the effect of gender on prognosis is in favor of men, the rate of stroke for women has increased 3 times in the last 20 years, while this rate has remained constant in men. This suggests that the risk of stroke is increasing in women [11]. In our study, the relationship between the gender of the patients and lactate levels was examined, and no statistically significant relationship was detected between the two genders ( $p > 0.05$ ).

Another definite risk factor that can be changed is hypertension. It causes an increased risk of stroke, including diastolic, systolic or combined hypertension. The risk of stroke is greatest in cases with recent systolic hypertension [12]. When those with and without hypertension are compared those who have blood pressure 140/90 mmHg and above have a 3-4-times higher risk of stroke, while patients with border hypertension (blood pressure 130-139/85-89 mmHg) have been shown to increase 1.5 times the risk of stroke [13]. Another risk factor that can be changed is DM. In the study by Tireli et al., it was seen that 91 (10.7%) of 845 CeVD patients had DM [14]. In our study, it was seen that 29.7% of the cases had HT and 28.9% of them had DM, and there was no statistically significant relationship between comorbid diseases and lactate levels. Comparison could not be made because there are no studies in the literature similar to our study.

In the emergency department, both ischemic stroke and hemorrhagic stroke are important because their mortality and morbidity are high. In this process, prognostic markers can be a guide for emergency physicians. Lactate is a potential energy source for the brain [15]. In the study by Patet et al, in the presence of ischemia, it has been shown that cerebral lactate production is increased and lactate can be used as an alternative energy source [16]. In the literature, it has been shown in some studies that lactate level is measured in blood and CSF in some studies using MR spectroscopy and microdialysis methods [17]. In an animal model study conducted by Berthet, it was shown that lactate, which is given externally to the area where the ischemic area was created, had a protective effect on that region and contributed positively to the shrinkage and prognosis in the lesion area [18]. In a study by Jo, he showed that venous blood lactate level correlated positively with 3-month mortality [19]. In the thesis study by Çağlayan titled: "Effect of blood lactate

level on prognosis in patients diagnosed with hemorrhagic and ischemic cerebrovascular disease in the emergency room", there was a positive correlation between both ischemic and hemorrhagic stroke prognosis and blood lactate level. In our study, we see that the lactate level decreased statistically significantly since the beginning of infarction in patients with ischemic stroke, and high lactate levels are associated with mortality. Similarly, in Çağlayan's thesis study, it was observed that the level of lactate decreased as the onset of stroke progressed in CeVD patients. Our study data were similar to those of Çağlayan and Jo. However, it was found different from the data of Patet et al. and Berthet's studies. In contrast to the studies of Patet et al. and Berthet, the increase in lactate level was found to be a sign of poor prognosis in our study.

In our study, when the relationship between lesion size and lactate level in ischemic stroke cases was examined, this relationship was found statistically significant only in lesions in MCA infarcts within irrigation areas of ACA, PCA and MCA arteries, and not in lesions in PCA and ACA irrigation areas. When the relationship between lesion sizes and lactate levels in MCA infarct areas is examined, it is seen that lactate levels increase statistically significantly as the lesion size increases. In Çağlayan's study, although there was a statistically significant relationship between lesion size and lactate levels in all infarct regions, this relationship was not found in our study.

NIHSS is the most commonly used scale to have predictions about the prognosis of stroke patients and to contribute to the selection and follow-up of patients. With this scale, the weight and grading of the patient's clinic can be made [20]. In our study, when the outcome status of stroke patients and NIHSS were compared, mortality was also found to be high in cases with high NIHSS ( $p < 0.001$ ). The lactate level was found to be statistically significantly higher in patients with mortality ( $p < 0.001$ ). In our study, it was observed that there was a significant positive correlation between the lactate levels evaluated in the beginning, at the 4.5th hour, in the first 24 hours, and first 72-hour period, and NIHSS scores. It was seen that NIHSS was also elevated in cases where the lactate level continued to increase during this period, and this correlation was significant. In our study, the relationship between lactate level and prognosis in CeVD patients was confirmed by the NIHSS score frequently used in the evaluation of stroke patients.

### Limitations

Our study has several limitations. First, this was a single-center study, and our patient numbers were therefore low.

Secondly, in our study, we could not make an exact comment as the number of hemorrhagic CeVD patients was low. The low number of hemorrhagic CeVD patients is also a limitation of our study.

Finally, looking at the literature, if tests like MR spectroscopy, microdialysis and CSF sampling are used for lactate measurement, it is shown that lactate level was correlated with prognosis. In our study, we have used and analyzed only arterial blood gas samples for the determination of lactate levels.

### Conclusion

In our study, we thought that lactate levels in patients with ischemic stroke can provide preliminary information in terms of the duration and prognosis of the disease and that MCA could

help us estimate the size of the infarct in the irrigation area. This study is considered preliminary in this context and more extensive studies are needed to use lactate as a biomarker in CeVD patients.

#### Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

#### Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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#### Conflict of interest

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