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Akut Ekstremite İskemisinde Serum Laktat Düzeyinin Mortalite ve Amputasyon İle İlişkisi

Relatıonshıp Of Serum Lactate Level Wıth Mortalıty And Amputatıon In Acute Limb Ischemıa

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Öz

Amaç: Akut ekstremite iskemisi, ani ekstremite perfüzyon yetmezliği ile karakterize vasküler bir acil durumdur ve derhal tedavi edilmezse amputasyon veya mortaliteye yol açabilir. Bu çalışmada, acil embolektomi uygulanan ALI hastalarında preoperatif serum laktat düzeyleri ile amputasyon ve hastane içi mortalite arasındaki ilişki araştırılmıştır.

Gereç ve Yöntem: 2021-2023 yılları arasında akut arter oklüzyonu tanısı ile embolektomi operasyonu yapılmış hastalar retrospektif olarak değerlendirildi. Kronik periferik arter hastalığı, kronik böbrek yetmezliği olan veya ameliyat öncesi laktat verileri eksik olan hastalar çalışma dışı bırakıldı. Demografik bilgiler, komorbiditeler, motor-duyusal defisitler, Rutherford sınıflandırması, biyokimyasal parametreler ve 30 günlük postoperatif sonuçlar analiz edildi. Amputasyon ve mortalite için risk faktörlerini belirlemek üzere lojistik regresyon uygulandı.

Bulgular: Çalışmada 67 hastanın (30 kadın, 37 erkek; ort. yaş: 74.57±12.0 yıl; dağılım 48-95 yıl) verileri retrospektif incelendi. Diabetes mellitus (DM), motor defisit, duyu defisit ve Rutherford kategori IIB amputasyon ile anlamlı şekilde ilişkiliydi. Ancak, çok değişkenli analizde yalnızca DM anlamlı bir belirleyici olarak kaldı (OR: 4.923, p=0.042). Serum laktat seviyeleri amputasyon ile anlamlı bir ilişki göstermemekle birlikte hastanede ölen hastalarda anlamlı derecede yüksek bulundu (medyan 4,1'e karşı 2,15; p=0.002). Tek değişkenli analiz, yüksek laktat seviyelerinin mortalite riskini artırdığını öngördü (OR: 2.354, p=0.003). Kreatin kinaz (CK) seviyeleri de hem ampute edilen hem de ölen hastalarda daha yüksekti, ancak çok değişkenli analizde anlamlılık kayboldu.

Sonuç: Ameliyat öncesi serum laktat düzeyleri hastane içi mortalite ile anlamlı şekilde ilişkilidir ancak amputasyon ile ilişkili değildir. DM, amputasyonun güçlü bir bağımsız öngörücüsüdür. Bu bulguları doğrulamak için daha geniş örneklemli ileri çalışmalara ihtiyaç vardır.

Anahtar kelimeler: Akut ekstremite iskemisi, amputasyon, mortalite, serum laktat

Abstract

Aim; Acute limb ischemia (ALI) is a vascular emergency characterized by sudden limb perfusion failure, which may lead to amputation or mortality if not treated promptly. This study investigates the relationship between preoperative serum lactate levels and amputation and in-hospital mortality in ALI patients undergoing emergency embolectomy.

Method; Patients who underwent embolectomy operation for acute arterial occlusion between 2021 and 2023 were evaluated retrospectively. Patients with chronic peripheral arterial disease, chronic renal failure, or missing preoperative lactate data were excluded. Demographic information, comorbidities, motor-sensory deficits, Rutherford classification, biochemical parameters, and 30-day postoperative outcomes were analyzed. Logistic regression was performed to determine risk factors for amputation and mortality.

Results; Data of 67 patients (30 females, 37 males; mean age: 74.57±12,0 years; range 48-95 years) were retrospectively analyzed. Diabetes mellitus (DM), motor deficits, sensory deficits, and Rutherford category IIB were significantly associated with amputation. However, in multivariate analysis, only DM remained a significant predictor (OR: 4.923, p=0.042). Serum lactate levels showed no significant association with amputation but were significantly higher in patients who died in-hospital (median 4.1 vs. 2.15, p=0.002). Univariate analysis confirmed that elevated lactate levels increased mortality risk (OR: 2.354, p=0.003). Creatine kinase (CK) levels were also higher in both amputated and deceased patients, though significance was lost in multivariate analysis.

Conclusion; Preoperative serum lactate levels are significantly associated with in-hospital mortality but not amputation. DM is a strong independent predictor of amputation. Further studies with larger sample sizes are needed to validate these findings.

Keywords: Acute limb ischemia, amputation, mortality, serum lactate

1. Introduction

Acute limb ischemia(ALI) is defined as a sudden decrease or complete loss of limb perfusion. Ischemia can result from arterial embolization, in situ thrombosis, trauma, or various other factors. The sudden interruption in tissue perfusion usually causes new and worsening signs and symptoms of ischemia. If ischemia is not corrected, it threatens the survival of the extremity[1].

Ischemia leads to an abrupt disruption in blood flow, cutting off the supply of oxygen and nutrients to all tissues within the affected region, including muscles, nerves, and skin. As a result, aerobic metabolism shifts to an anaerobic state, leading to increased lactate production. This elevates the lactate-to-pyruvate ratio, causing a rise in hydrogen ion concentration and subsequent acidosis. Continued hypoxic muscle injury results in ATP depletion, allowing free calcium to escape into the extracellular space. This excess calcium interacts with actin, myosin, and cellular proteases, ultimately triggering skeletal muscle fiber necrosis. As necrosis progresses, intracellular potassium, phosphate, creatine kinase (CK), and myoglobin enter systemic circulation [2].

ALI is one of the most common emergencies in vascular surgery. Studies have reported its incidence as 22 per 100000 patients per year[3]. The 30-day amputation rate in ALI has been reported to be 10-30% and the mortality rate between 9% and 25%[4,5]. In different studies, major amputation rates have been reported to be up to 50%[6]. Considering the high amputation and mortality risks, ALI is a serious clinical emergency.

The objective of this study was to explore the correlation between preoperative serum lactate levels and amputation as well as in-hospital mortality in patients who presented with acute lower extremity ischemia and underwent emergency surgical embolectomy.

2. Methods

2.1 Study Design and Sample

Data of patients admitted to Konya City Hospital between January 2021 and December 2023 with acute lower extremity ischemia who underwent emergency embolectomy were retrospectively analyzed. Patients with known chronic peripheral arterial disease, upper extremity ischemia, chronic renal failure, concomitant endovascular intervention, and no preoperative lactate data in the records were excluded.

Demographic data and chronic diseases of 67 patients who met the inclusion criteria were analyzed. Motor-sensory deficit and Rutherford category were determined by evaluating the initial examination notes of the patients in the emergency department. Biochemical parameters, serum lactate level, CK level, operation notes, postoperative major amputation(below the knee/above the knee) and mortality in the first 30 days were recorded

2.2 Ethical Consideration

The study protocol was approved by KTO Karatay University Faculty of Medicine Ethics Committee (date: 06.06.2024, number: 2024/003). The study was conducted in accordance with the principles of the Declaration of Helsinki.

2.3 Statistical Analysis

The IBM SPSS 26 application (IBM Corp., 2019) was used to evaluate the data. Kolmogorov-Smirnov and Sjhapiro-Wilk tests were used to check for compliance with the normal distribution. When comparing regularly distributed data per group, the independent two-sample t test was employed, and when comparing non-normally distributed data, the Mann Whitney U test. Categorical data were compared by group using Fisher's exact test and Pearson chi-square test. Using the Bonferroni adjusted Z test, multiple comparisons were examined. Logistic regression analysis was used to examine the factors influencing mortality and amputation. The findings of the analysis were displayed as frequency (%) for categorical data and mean ± standard deviation and median (minimum-maximum) for quantitative variables. The threshold for significance was set at p<.05

3. Results

Demographic characteristics and preoperative examination results of the patients according to amputation status are given in Table 1. There was no statistically significant relationship between amputation and age, gender and smoking status (p>.05). When the distribution of chronic diseases according to the amputation status of the patients was analyzed, a significant difference was found as 66.7% of the patients with DM in the group with amputation (p=.037).

Table 1. Comparison of demographic characteristics and preoperative data of patients according to amputation

	Amputation		**stat.**	**p**
	Absent (n=55)	**Present (n=12)**		
Age	78 (48 - 93)	73.5 (63 - 95)	-0.254	0.800[m]
Gender				
Male	28 (50.9)	9 (75)	-	0.201[f]
Female	27 (49.1)	3 (25)		
Smoking				
Absent	36 (65.5)	5 (41.7)	-	0.191[f]
Present	19 (34.5)	7 (58.3)		
Chronic Diseases*				
Hypertension	42 (84)[a]	9 (75)[a]	13.400	>0.05
Hyperlipidemia	6 (12)[a]	4 (33.3)[a]		>0.05
Diabetes Mellitus	15 (30)[a]	8 (66.7)[b]		**0.037[f]**
CAD	28 (56)[a]	5 (41.7)[a]		>0.05
COPD	7 (14)[a]	3 (25)[a]		>0.05
Atrial Fibrillation	29 (58)[a]	4 (33.3)[a]		>0.05
Motor Deficit				
Absent	51 (92.7)	8 (66.7)	-	**0.029[f]**
Present	4 (7.3)[a]	4 (33.3)[b]		
Sensory Deficit				
Absent	38 (69.1)	0 (0)	-	**<0.001[f]**
Present	17 (30.9)[a]	12 (100)[b]		
Rutherford Categori				
IIA	49 (89.1)[a]	6 (50)[b]	11.150	**0.003[f]**
IIB	4 (7.3)[a]	6 (50)[b]		
III	2 (3.6)	0 (0)		

m: Mann Whitney U test, f: Fisher's exact test, a-b: No difference between groups with the same letter (Bonferroni corrected Z test), *Multiple response, median (min.-max.), n (%), CAD:Coronery artery disease, COPD:Chronic obstructive pulmonary disease

A statistically significant difference was found in the distribution of motor deficits based on amputation status (p = .029). The motor deficit rate was 7.3% in patients without amputation, while it increased to 33.3% in patients with amputation. A significant difference was also observed in the distribution of sensory deficits (p < .001). Additionally, a statistically significant difference was identified in Rutherford classifications (p = .003), particularly between IIA and IIB patients based on amputation status. The rate of IIA was 89.1% in patients without amputation, but it was lower in those with amputation.

The relationship between amputation and preoperative blood values is given in Table 2. There was a statistically significant difference between preoperative CK values according to the amputation status of the patients (p<.001). While the median preoperative CK value of patients without amputation was 120, the median preoperative CK

value of patients with amputation was higher with 807. There was no statistically significant relationship between amputation status and other preoperative blood values (p>.05).

Table 2. Analysis of preoperative biochemical parameters of patients according to amputation

	Amputation		Stat.	p
	Absent (n=55)	**Present (n=12)**		
pH	7.39 ± 0.06	7.37 ± 0.06	0.990	0.326[t]
Lactate	2.3 (0.6 - 9)	2.35 (0.9 - 4.7)	-0.425	0.671[m]
Base excess	-1 (-14 - 5)	-1.75 (-5 - 1.9)	-0.412	0.680[m]
HCO3	23.1 (13 - 29)	23 (19 - 25.2)	-0.303	0.762[m]
Creatine Kinase	120 (29 - 6875)	807 (581 - 1956)	-4.023	**<0.001[m]**
Troponin	21.8 (4.8 - 226)	22.4 (17.8 - 125)	-0.708	0.479[m]
Creatinine	1 ± 0.34	1.02 ± 0.3	-0.154	0.878[t]
Urea	22.91 ± 11.45	27.25 ± 14.3	-1.137	0.260[t]
Potassium	4.46 ± 0.62	4.48 ± 0.63	-0.109	0.914[t]

t: Independent two sample t test, m: Mann Whitney U test, mean ± s. deviation, median (min.-max.)

Factors influencing amputation status were assessed using both univariate and multivariate logistic regression models (Table 3). The univariate analysis indicated that diabetes mellitus (DM), motor deficits, and Rutherford categories were statistically significant predictors of amputation status (p < .05). The likelihood of amputation was higher in patients with DM compared to those without DM (OR: 5.333, p = .014). Patients with motor deficits had a greater risk of amputation than those without (OR: 6.375, p = .021). Additionally, patients classified as Rutherford IIB had a higher risk of amputation compared to those with IIA (p = .001). However, preoperative lactate and CK values did not have a statistically significant impact on predicting amputation (p > .05).

Table 3. Examination of factors affecting amputation

	Univariate		Multivariate	
	OR (%95 CI)	**p**	**OR (%95 CI)**	**p**
DM (Ref.: Absent)	5.333 (1.398 - 20.346)	**0.014**	4.923 (1.062 - 22.816)	**0.042**
Motor Deficit (Ref.: Absent)	6.375 (1.322 - 30.753)	**0.021**	3.426 (0.202 - 58.157)	0.394
Rutherford (Ref.: IIA)●	12.25 (2.671 - 56.173)	**0.001**	4.752 (0.49 - 46.085)	0.179
Preoperative Lactate	0.966 (0.649 - 1.439)	0.867		
Preoperative CK	1 (1 - 1.001)	0.435		

OR: Odds ratio, CI: Confidance interval, Accuracy=0.831, ●Patients with Rutherford III were not included because there were no patients with amputation.

Multivariate analysis showed that the risk of amputation was higher in patients with DM compared to patients without DM (OR: 4.923, p=.042). The combined effect of motor deficit and Rutherford characteristics on amputation status was not statistically significant (p>.05). The multivariate model correctly classified 83.1% of the cases. In the study, there were two patients with rutherford category III. the reason for surgical treatment of these patients was to salvage the amputation level.

Table 4. Examination of the relationship between in-hospital mortality status and preoperative lactate and preoperative CK values

	In-Hospital Mortality		Stat.	p[m]
	Absent (n=60)	**Present (n=7)**		
Preoperative Lactate	2.15 (0.6 - 6)	4.1 (2.2 - 9)	-3.138	**0.002**
Preoperative CK	146 (29 - 1956)	3895 (2052 - 6875)	-4.305	**<0.001**

m: Mann Whitney U test, median (min.-max.)

A significant statistical difference was observed in preoperative lactate levels based on patients' in-hospital mortality status (p = .002). The median preoperative lactate level was 2.15 in patients who survived hospitalization, whereas it was 4.1 in those who did not (Table 4). Similarly, a statistically significant difference was found in preoperative CK levels concerning in-hospital mortality (p < .001). Patients who survived had a median preoperative CK level of 146, while those who did not survive had a median value of 3895.

As shown in Table 5, as a result of univariate analysis, the risk of mortality increased as the preoperative lactate value increased (OR: 2.354, p=.003). There was no statistically significant effect of preoperative CK values on the prediction of mortality (p=.972).

Table 5. Examination of the effect of preoperative lactate and preoperative CK values in predicting mortality

	Univariate	
	OR (%95 CI)	**p**
Preoperative Lactate	2.354 (1.339 - 4.137)	**0.003**
Preoperative CK	1.295 (0 - 1906576.732)	0.972

OR: Odds ratio, CI: Confidance interval

4. Discussion

ALI is characterized by sudden tissue perfusion failure due to embolism, arterial thrombosis and trauma. The severity of tissue damage is related to the duration of ischemia and it is a serious clinical picture that may progress from the loss of the extremity to the death of the patient as a result of progressively worsening clinical and metabolic events as the duration of ischemia prolongs. As the duration of ischemia prolongs, lactate increases as a result of anaerobic respiration and metabolic acidosis is observed. In this study, we investigated the relationship between preoperative lactate levels and amputation and in-hospital mortality in acute lower extremity ischemia.

In terms of amputation, there was no significant relationship between preoperative lactate value and amputation. However, preoperative CK values, presence of DM, presence of sensory deficits, presence of motor deficits and Rutherford category IIB were significantly associated with amputation. In the univariate analysis, the preoperative CK value lost its significance and in the multivariate analysis, only the presence of DM was associated with amputation. High serum lactate and CK levels were associated with in-hospital mortality. Univariate logistic regression analysis confirmed that the significant relationship between high lactate levels and in-hospital mortality remained.

In our study, a history of DM was significantly associated with amputation. And DM continued to be a risk factor for amputation in multivariate analysis. ALI has been defined as one of the complications of Type 2 DM[7]. The mean percentage of amputations in patients with diabetes has been reported to account for 68.6% of all amputations[8]. DM is also known to cause various microvascular complications[9]. In our study, in the group of patients who underwent emergency embolectomy, the probability of amputation was found to be higher in diabetic patients than in non-diabetic patients.

There is evidence in the literature that motor and sensory loss predicts amputation[10]. In our study, the presence of motor and sensory deficits was found to be significantly associated with amputation. However, this relationship disappeared in logistic regression analysis. This could be attributed to the limited sample size of our study. Likewise, it was concluded that patients with Rutherford IIB were at risk for amputation compared to patients with IIA, but this relationship was not found in multivariate analysis. In addition, the reason why two patients with Rutherford Class III were found in the non-amputee group is that these patients had early exitus.

In our study, preoperative serum keratin kinase levels were also evaluated. As a result of ischemia in skeletal muscles, cytoplasmic molecules such as CK in the structure of myocytes enter the blood[11]. CK is an enzyme that catalyzes creatinine conversion and uses atp. Therefore, it is an indirect marker of muscle damage anywhere in the body. In studies, there is a correlation between prolonged ischemia duration and serum CK levels[12]. In ALI the risk of irreversible damage increases as the duration of ischemia prolongs and this explains the relationship between high serum CK levels and the risk of amputation. It is thought that baseline serum CK levels may help prognostic evaluation in ALI patients(10). In a retrospective study of 97 patients admitted with ALI, an increase in serum CK levels was shown to carry a 56.2% risk of amputation[13]. In the same study, it was also reported that a 10-fold increase in serum CK level predicted amputation at a rate of 100%. In our study, a significant association was observed between preoperative serum CK level and amputation and in-hospital mortality, but this association was lost in logistic regression analysis. However, a more significant association may be found in a larger sample size.

In ALI patients, certain biomarkers are crucial for predicting which limbs will not respond well to limb salvage efforts or which will experience poor outcomes post-salvage, both preoperatively and intraoperatively. Among these biomarkers, CK and lactate are currently

being explored [14]. In ALI, anaerobic metabolism is triggered by tissue hypoxia, leading to the production of lactic acid and an increase in serum lactate levels. As a result, elevated lactate levels are believed to indicate prolonged ischemia, suggesting that the damage may be irreversible. A study on limb ischemia in vasopressor-dependent sepsis patients found significantly higher serum lactate levels in those with threatened limb ischemia [15]. Another study involving 3325 patients reported that high serum lactate levels during hospitalization were linked to all-cause in-hospital mortality [16]. Furthermore, the literature highlights the relationship between lactate clearance and survival in cases of subarachnoid hemorrhage, metformin use in diabetics, and cardiogenic shock treated with extracorporeal membrane oxygenation [17-19]. In line with these findings, our study also demonstrates that increased serum lactate levels are linked to in-hospital mortality in patients with ALI.

This study has several limitations. Firstly, it follows a retrospective design.Therefore, our sample size was limited because the preoperative blood values of each patient did not meet the inclusion criteria. In addition, due to the high number of hybrid interventions in our clinic, our group of patients who underwent only surgical embolectomy is limited.

5. Concluison

This study found that preoperative serum lactate levels were significantly associated with in-hospital mortality in patients with acute limb ischemia, but not with amputation. High lactate levels suggest a higher risk of mortality, possibly reflecting the severity and duration of ischemic injury. Diabetes mellitus was identified as a strong independent predictor of amputation. These findings suggest that preoperative lactate may be a useful predictor of mortality in ALI patients.

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