ORIGINAL ARTICLE / ÖZGÜN ARAŞTIRMA MAKALESİ

The Effect of Lactate and Lactate Clearance on Mortality in Patients with Acute Pulmonary Embolism in Emergency Department

Acil Serviste Pulmoner Emboli Tanısı Alan Hastalarda Laktat ve Laktat Klerensinin Mortalite Üzerine Etkisinin Retrospektif Değerlendirilmesi

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ABSTRACT

Aim: Pulmonary embolism (PE) is the third leading cause of death due to cardiovascular disease. The presence of shock or hypotension remains the main prognostic clinical marker and to date, it is the only factor that indicates the need for aggressive treatment. Most patients with pulmonary embolism are normotensive. Prognostic indicators are needed to better classify patients with pulmonary embolism. This study aimed to investigate the effect of lactate level on predicting hospital mortality in patients diagnosed with pulmonary embolism in the emergency department, and the effect of lactate clearance on mortality in patients with high lactate levels (lactate ≥2 mmol/L).

Material and Methods: This study was designed as a retrospective study. Adult patients (>18-years old) who were diagnosed with PE by computed tomography angiography of the thorax in the university hospital emergency between January 1, 2018, and December 31, 2019, were analyzed.

Results: A total of 367 patients were diagnosed with pulmonary embolism in the emergency department. In-hospital mortality rate of the patients was 29.8% and the pulmonary embolism-related mortality rate was 12.4%. Lactate clearance was not significant in predicting mortality risk. In the logistic regression analysis performed among the risk factors affecting mortality in patients with pulmonary embolism, lactate ≥3 mmol/L and normotensive + lactate ≥3 mmol/L were significant in predicting in-hospital mortality.

Conclusion: The lactate level in the emergency department could be an effective screening method for identifying mortality in acute pulmonary embolism patients.

Keywords: Mortality, pulmonary embolism, emergency medicine

ÖZ

Amaç: Pulmoner emboli, kardiyovasküler hastalığa bağlı ölümlerin üçüncü önde gelen nedenidir. Pulmoner emboli de şok veya hipotansiyon varlığı ana prognostik klinik belirteç olmaya devam etmektedir ve bugüne kadar agresif tedavi ihtiyacını gösteren tek faktördür. Pulmoner embolili hastaların çoğu normotansiftir. Pulmoner emboli hastalarını daha iyi sınıflandırmak için prognostik göstergelere ihtiyaç vardır. Bu çalışmada, acil serviste pulmoner emboli tanısı konulan hastalarda laktat düzeyinin hastane mortalitesini öngörmedeki etkisi ve laktat düzeyi yüksek (laktat ≥2 mmol/L) hastalarda laktat klirensinin mortaliteye etkisi araştırıldı.

Gereç ve Yöntemler: Bu çalışma retrospektif bir çalışma olarak tasarlanmıştır. 1 Ocak 2018-31 Aralık 2019 tarihleri arasında üniversite hastanesi acilinde bilgisayarlı tomografi anjiyografisi ile pulmoner emboli tanısı alan erişkin (>18 yaş) hastalar analiz edilmiştir.

Bulgular: Acil serviste toplam 367 hastaya pulmoner emboli tanısı kondu. Hastaların hastane içi mortalite oranı %29,8, pulmoner emboli ile ilişkili mortalite oranı ise %12,4 idi. Laktat klirensi mortalite riskini öngörmede anlamlı değildi. Pulmoner emboli hastalarında mortaliteyi etkileyen risk faktörleri arasında yapılan lojistik regresyon analizinde laktat ≥3 mmol/L ve normotansif + laktat ≥3 mmol/L hastane içi mortaliteyi öngörmede anlamlı bulundu.

Sonuç: Acil serviste laktat düzeyi akut pulmoner emboli hastalarında mortaliteyi belirlemede etkili bir tarama yöntemi olabilir.

Anahtar Kelimeler: Mortalite, pulmoner emboli, acil servis

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Introduction

Pulmonary embolism (PE) is the third leading cause of death due to cardiovascular disease (1). The presence of shock or hypotension remains the main prognostic clinical marker which indicates a more aggressive treatment than heparin (2). However, shock is present in very few patients with acute PE. Most patients with PE are normotensive and are usually treated with heparin alone. There are many studies looking for new prognostic indicators to better classify normotensive patients with PE. Several evidence demonstrates that right-sided ventricular dysfunction or injury markers such as troponins and echocardiographic (Echo) evidence of right-sided ventricular dysfunction (RVH) are associated with worse prognosis (2-5). However, these markers have some important limitations. Echocardiography is generally not available 24 hours in most clinical settings. Moreover, it shares a good negative predictive value (>90%) but a low positive predictive value (approximately 10%) for short-term mortality with troponins, and these prevent both markers' usefulness to target more aggressive treatments (5).

Lactate, which is produced in almost all tissues even under conditions of sufficient oxygen, is maintained below 1 mmol/L in the blood, especially via liver metabolism and pyruvate recycling. Lactate elevation is indicative of an imbalance between tissue oxygen supply and demand, and thus lactate is possibly elevated in PE as well, which has severe hemodynamic effects. Lactate values ≥2 mmol/L predict PE-related complications in all PE patients and in PE patients who were normotensive at baseline (6-8).

There are few studies on the importance of lactate value in PE patients. In only one study, the cut-off value of lactate was found to be 2 and above in predicting PE-related complications, and other studies were based on this value (6-8). We found no studies that compares different lactate values in predicting PE-related mortality. The mortality rate may vary according to different lactate values. Lactate level may be an indicator for the patient group that will benefit from aggressive treatment (thrombolytic, intensive care unit) in PE patients.

The first aim of this study was to determine the effect of lactate value on predicting hospital mortality in patients diagnosed with PE in the emergency department. The second aim was to determine the effect of lactate clearance on mortality in patients with high lactate levels (lactate ≥2 mmol/L).

Material and Methods

The study was approved by the local ethics committee (20.03.2020 Number: 20-3.1T/5). This study was conducted between January 01, 2018, and December 31, 2019 in a university emergency department (ED). Patients aged ≥18 years who were diagnosed with PE by computed tomography angiography (CTA) of the thorax in the emergency department were analyzed retrospectively. Patients referred from another center with the diagnosis of PE, pregnant women, patients aged <18 years, and patients with incomplete data were excluded from the study. Demographic data, such as age, gender, vital parameters, laboratory values, Glasgow Coma Scale (GCS), arterial blood gas parameters, lactate values, electrocardiography (ECG), venous ultrasonography, echocardiography (Echo), and CTA findings of the patients included in the study were recorded in a report form. The data of the patients were collected from the hospital's electronic archive. The abstractors were trained and blinded before the data collection. Investigators who interpreted the patients' variables (Ecg, Echo, etc.) were blinded to the study's hypothesis and the clinical course of the patients.

Patients with high lactate levels were divided into groups as follows: lactate ≥2-3 mmol/L, lactate ≥3 mmol/L, normotensive + lactate ≥2-3 mmol/L, and normotensive + lactate ≥3 mmol/L. Patients with systolic blood pressure ≥100 mmHg were classified as the normotensive patient group. Lactate clearance was calculated using the following formula: [(lactate1 – lactate2)/lactate 1] x 100 (lactate1: initial lactate level measured in the emergency department, lactate 2: control lactate level measured at least two hours after lactate1 measurement). Patients were divided into groups according to their lactate clearance as clearance above 25% and 50%. PE-related mortality rate of the patients was considered as the endpoint for the study. PE-related death was defined as a fatal event occurring in the hours after clinical deterioration caused by pulmonary embolism.

The patient was considered unstable if there were any hypoperfusion findings, such as the need for cardiopulmonary resuscitation (CPR), systolic blood pressure <90 mmHg, or the need for an inotropic agent, and end-organ damage (such as a change in consciousness, oliguria, or anuria). Simplified Pulmonary Embolism Severity Index (sPESI) included these findings: age >80 years, malignancy, chronic pulmonary disease history, pulse >110/min, systolic blood pressure <100 mmHg, and saturation <90%. The presence of at least one of these findings was considered as the presence of sPESI.

Statistical analysis

Normally distributed data were expressed as mean ± standard deviation and percentages for continuous variables whereas data without normal distribution were expressed as medians interquartile ranges (IQR). Categorical variables were examined using frequency tables, and continuous variables were evaluated using descriptive statistics. Pearson's chi-square test was used for analyzing categorical data in terms of groups. Categorical data are reported as

ratios with 95% confidence intervals (CI). Logistic regression analysis was used to determine risk factors for mortality. The significance level (p) was set as <0.05 during hypothesis testing. IBM SPSS Version 25.0 software was used for performing statistical analysis.

The study was approved by the local ethics committee. The present study has been carried out in strict compliance with the declaration of Helsinki principles.

Results

A total of 367 patients were diagnosed with PE in our ED during the study period. Twenty-seven patients with missing data and one patient who was pregnant were excluded from the study. The remaining 339 patients were included in the study and their data were analyzed. The mean age of the patients was 69.5 ± 14.6 (18–107), and 56.6% of them were females. The most common comorbidities were arterial hypertension (73.4%, n = 249), diabetes mellitus (45.4%, n = 154), coronary artery disease (39.5%, n = 22), and cancer 27.4%, n = 100). The most common symptoms were shortness of breath (40.1%, n = 136), impaired general condition (7.1%, n = 24), fever (6.5%, n = 22), and syncope (6.2%, n = 21). The most common ECG finding was sinus tachycardia (37.8%). The most common type of PE was segmental embolism (57.8%). Also, 95.8% of patients were administered heparin and 5.9% received thrombolytic therapy. The diagnostic and therapeutic characteristics of the patients are shown in Table 1.

The median hospital length of stay of the patients was 4102 minutes [IQR 1696 to 11580 minutes]. The median second lactate measurement time was 7 hours [IQR 4 to 12 hours].

The clinical characteristics of the patients were as follows: 26.3% patients were aged >80 years, 84.7% were normotensive, 21.5% were unstable, 79.4% had sPESI ≥1, 20% had GCS <15, 80.5% had troponin T >13 ng/L, and 49% had lactate ≥2 mmol/L. Echo was performed in 54% (n=183) and compression ultrasonography (both legs popliteal and femoral vein) was performed in 19.2% (n = 65) of the patients in the emergency department.

Variable	Finding	% (n)
Electrocardiography		
	V1-4 T negative	13,3 (45)
	S1Q3T3	10,6 (36)
	Right bundle branch block	6,5 (22)
	Sinus tachycardia	37,8 (128)
	Normal	31,9 (108)
*Chest X-ray		
	Normal	25,1 (85)
	Parenchymal involvement	19,7 (67)
	Increased cardiothoracic ratio	33,3 (113)
	Pleural fluid	14,7 (50)
	Atelectasis	6,4 (22)
	No image available	9,1 (31)
Echocardiography		
	Normal	25.1 (85)
	Right-sided ventricular dysfunction	28,9 (98)
	No image available	46 (156)
Compression ultrasonography		
	Normal	3,8 (13)
	Deep vein thrombosis	15,4 (52)
	No image available	80,8 (274)
Type of pulmonary embolism		
	Segmental	57,8 (196)
	Main branch	17,7 (60)
	Massive	15,3(52)
	Lobar	9,1(31)
Systemic thrombolysis		
	Not given	94,1 (319)
	Alteplase 50 Mg	2,7(9)
	Alteplase 100 Mg	3,2(11)
Anticoagulation		
	Unfractionated Heparin	1,5 (5)
	Low-Molecular-Weight Heparin	94,3 (320)
	Not given	4,2(14)

* In some patients, more than one pathology was found together.

Table 1. Diagnostic and treatment characteristics of patients diagnosed with pulmonary embolism in the emergency department

Variable	Total	Other patients	PE Related Mortality	P value	Odds ratio (95% CI)
	339	297 (%87,6)	42 (%12,4)		
Age > 80 Year	89 (%26,3)	76	13	0,46	1,3 (0,6-2,6)
Gender Female	192 (%56,6)	168	24	0,94	0,9 (0,5-1,8)
Male	147 (%43,4)	129	18		
*SBP < 90 mmHg	26 (%7,7)	20	6	0,113	2,3 (0,8-6,1)
*SBP ≥100 mmHg(normotensive Patients)	287 (%84,7)	255	32	0,104	1,8 (0,8-4,1)
*HR ≥ 110 beats/min	134 (%39,5)	112	22	0,069	1,8 (0,9-3,4)
*sO_2(a) <%90	75 (%22,1)	60	15	0,023	2,1 (1,09-4,3)
Cancer	100 (%29,5)	82	18	0,043	1,9 (1,01-3,8)
*RVD	98(28,9)	80	18	0,047	2,5 (1,0-6,3)
GCS < 15	69 (%20,4)	51	18	0,000	3,6 (1,8-7,1)
sPESI value ≥1	269 (%79,4)	230	39	0,021	3,7 (1,1-12,6)
Cardiac arrest in the emergency department	23 (%6,8)	15	8	0,000	20 (7,8-51,6)
Mechanical ventilation	30 (%8,8)	15	15	0,000	10,4 (4,6-23,6)
Vasopressors and inotropes	41 (%12,1)	26	15	0,000	5,7 (2,7-12,2)
Systemic thrombolysis	20 (%5,9)	13	7	0,006	4,3 1,6-11,6
Unstable Patients	73 (%21,5)	53	20	0,000	4,1(2,1-8,2)
Hyponatremia (Na<135 mEq/L)	92 (%27,1)	83	9	0,374	0,7 0,3-1,5
Urea>50 mg/dl	157 (%46,3)	131	26	0,03	2 (1,06-3,9)
Troponin T level <13 ng/L	66 (%19,5)	65	1	0,003	0,08 (0,01-0,6)
Troponin T level >13 ng/L	273 (%80,5)	232	41		
*Lactate clearance≥ %50	41 (%38)	36	5	0,429	0,6 (0,2-1,9)
*Lactate clearance ≥ %25	78 (%72,2)	64	14	0,388	1,9 (0,2-1,4)
*Lactate level ≥2-3 mmol/L	73 (%21,5)	67	6	0,315	0,5 (1,04 – 4,0)
Normotensive + Lactate level ≥2-3 mmol/L	64 (%18,9)	59	5	0,293	0,5 (0,2-1,4)
Lactate level ≥3 mmol/L	93 (%27,4)	72	21	0,000	3,1 (1,6-6,0
Normotensive + Laktat level ≥3 mmol/L	73 (%21,5)	57	16	0,005	2,5 (1,3-5,1)

*SBP: Systolic blood pressure, HR: Heart Rate, sO_2(a):Arterial oxyhaemoglobin saturation, GCS: Glasgow Coma Scale , sPESI :Simplified Pulmonary Embolism Severity Index
*Lactate Level: The first lactate measurement in Emergency Department
* Lactate clearance was analyzed in 108 patients. Bedside ECHO was performed in 183 patients.
* RVD (Right-sided ventricular dysfunction) is an enlarged right ventricle parasternal long-axis view.

Table 2. Effects of variables on PE related mortality in patients diagnosed with pulmonary embolism in the emergency department

The mean lactate value of the patients who received thrombolytic medication was 7.1±6.4 mmol/L. In addition, the mean lactate value was 2.3 ± 2.2 mmol/L in patients with segmental embolism and 4.3± 4.6 mmol/L in patients with massive embolism.

The in-hospital mortality rate of the patients was 29.8% and the PE-related mortality rate was 12.4%. The PE-related mortality rate in patients with lactate ≥2-3 mmol/L and normotensive + lactate ≥2-3 mmol/L was not significant. Also, lactate clearance was not significant in predicting mortality. (Table 2)

According to logistic regression analysis, the presence of unstable patients, lactate ≥3 mmol/L and normotensive+lactate ≥3 mmol/L patient groups had significantly higher pulmonary embolism-related mortality. (Table 3)

Discussion

We found that in determining the PE related mortality risk; lactate ≥3 mmol/L, normotensive + lactate ≥3 mmol/L, sPESI>1, troponin T levels and unstable patients groups were significant.

The lactate ≥2-3 mmol/L, normotensive + lactate ≥2-3 mmol/L did not affect PE related mortality in our study. Recent studies have reported that the detection of lactate >2 mmol/L in PE, including normotensive patients, is useful for predicting mortality (6,7). In our study, according to logistic regression analysis, it was found that lactate was significant in determining mortality risk in the lactate ≥3 mmol/L patient group. Additionally, the factors affecting mortality in previous studies, such as pulse >110/min, and age >80 years, did not affect mortality in our study (6-8).

Variable	P value	Odds ratio (95% CI)	Variable	P value	Odds ratio (95% CI)
Lactate level ≥3 mmol/L	0,049	2,0 (1,004 - 4,0)	Normotensive + Lactate level ≥3 mmol/L	0,042	2,1 (1,02 - 4,3)
Troponin T level <13 ng/L	0,051	0,13 (0,01-1,0)	Troponin T level <13 ng/L	0,055	0,13(0,01 - 1,04)
Unstable patients	0,004	2,8 (1,3-5,7)	Unstable patients	0,001	3,2 (1,6 - 6,5)
sPESI value ≥1	0,162	2,4 (0,7-8,4)	sPESI value ≥1	0,135	2,5 (0,7 - 9,0)

*sPESI : Simplified Pulmonary Embolism Severity Index, normotensive patients (SBP ≥100 mmHg)

Table 3. Logistic regression analysis of lactate values affecting PE related mortality in patients diagnosed with pulmonary embolism in the ED

Galić K et al reported in their study that PE patients with a plasma lactate value >3 mmol/L had a very high mortality rate (9). In our study, the mortality risk in the group having lactate values ≥3 mmol/L was higher than the other two groups and the normotensive patient group. Therefore, considering a lactate threshold of 3 mmol/L may be more beneficial in predicting PE related mortality risk and making decisions on initiating an aggressive treatment regimen.

Although a high lactate level (>3 mmol/L) seemed as a predictor for massive PE and the need for thrombolytic therapy in this study, it cannot be used as a clinical recommendation. However, the data may help future studies to set parameters.

Decreased GCS may be associated with a higher mortality in patients with PE (10). Similarly, in our study, mortality risk was higher in the patient group diagnosed with PE with altered consciousness.

Studies have indicated that sPESI, which is a simplified version of the original Pulmonary Embolism Severity Index (PESI), can be used (11-13). We preferred to use sPESI to determine mortality risk in our study. Although we could determine the mortality risk using sPESI in our study, it was not significant according to logistic regression analysis.

Acute right ventricle (RV) failure is a determinant of critical outcomes in acute PE resulting from impaired RV filling and/or reduced RV flow output (14). In our study, the risk of mortality was higher in the patient group with Right-sided ventricular dysfunction (RVD) in Echo.

Becattani et al. showed that high troponin concentrations were associated with an increased risk of mortality in patients with PE and those who were hemodynamically stable during the initial in-hospital period (4). High-sensitivity troponin values have a good negative predictive value in acute PE (15). In our study, troponin T had a negative predictive value of 89.3% for the risk in-hospital mortality in all patient groups with low troponin T concentrations. According to logistic regression analysis, we determined that troponin T could not be used to elucidate the risk of mortality due to PE.

Lactate clearance can be used to predict treatment efficiency and mortality in patients with trauma and sepsis (16,17). However, to the best of our knowledge, there are no studies on lactate clearance in PE patients. In our study, lactate clearance was not significant in predicting mortality. Hence, further studies on lactate clearance in patients with PE may enable us to make a more accurate decision on this issue.

Limitations

The retrospective design of the study is the main limitation. Also, the sample size is small and data is collected from a single-center, so, this limits the generalizability of results.

Conclusion

The present study demonstrates that plasma lactate measurement represents a predictor of PE-related mortality. The lactate level ≥3 mmol/L and normotensive+ lactate level ≥3 mmol/L were the independent risk factors affecting mortality. Lactate clearance was not effective in predicting mortality risk, but further prospective studies are needed. The lactate level ≥3 mmol/L in the ED could be an effective screening method for predicting mortality in acute PE patients.

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