ORIGINAL RESEARCH

The Relationship Between Lactate and Lactate Clearance with In-Hospital Mortality in Unselected Emergency Department Patients

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Keywords: emergency department; in-hospital mortality; lactate; lactate clearance

Abbreviations:
AUC: area under the ROC curve
ED: emergency department
HIS: hospital information system
ROC: receiver operator characteristics

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Abstract

Introduction: Lactate is a frequently used biomarker in emergency departments (EDs), especially in critically ill patients. The aim of this study is to investigate the relationship between lactate and lactate clearance with in-hospital mortality in unselected ED patients.
Methods: This study was carried out retrospectively in the ED of a tertiary hospital. Patients aged 18 years and older whose blood lactate level was obtained in the ED were included in the study. Patients whose lactate value did not have sufficient analytical accuracy, whose lactate value was recorded in the system 180 minutes after admission, who were admitted to the ED as cardiac arrest, and whose ED or hospital outcome was unknown were excluded from the study. According to the first measured lactate value, the patients were divided into three groups: < 2.0mmol/L, 2.0-3.9mmol/L, and ≥ 4.0mmol/L. Lactate clearance was calculated and recorded in patients with one-to-four hours between two lactate values.
Results: During the five-year study period, a total of 1,070,406 patients were admitted to the ED, of which 114,438 (10.7%) received blood gas analysis. The median age of 81,449 patients included in the study was 58 years (IQR: 30, min: 18–max: 117) and 54.4% were female. The study found that non-trauma patients with a lactate level between 2.0-3.9mmol/L had a 2.5-times higher mortality risk, while those with a lactate level of ≥ 4.0mmol/L had a 20.8-times higher risk, compared to those with a lactate level < 2.0mmol/L. For trauma patients, the mortality risk was three-times higher for those with lactate levels between 2.0-3.9mmol/L and nine-times higher for those with a lactate level of ≥ 4.0mmol/L, compared to those with a lactate level < 2.0mmol/L. Among patients with a first measured lactate value ≥ 4.0mmol/L and a two-hour lactate clearance < 20%, the mortality rate was 19.7%. In addition, lactate, lactate clearance, and age were independent variables for mortality in this patient group.
Conclusion: The lactate value in unselected patients in the ED is a biomarker that can be used to predict the prognosis of the patients. In addition, lactate, lactate clearance, and age are independent predictors of mortality.

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Introduction

High blood lactate level indicates tissue hypoperfusion and organ dysfunction.[1] Emergency physicians frequently measure serum lactate levels in a wide range of indications.[2] Studies have consistently demonstrated that high lactate level and low lactate clearance are associated with poor prognosis in many clinical cases, such as sepsis, trauma, shock, and cardiac arrest.[3–6] Particularly in sepsis and septic shock, a lactate value over 4.0mmol/L has been widely researched and linked to increased mortality.[7,8] In subsequent studies on sepsis, a lactate value above 2.0mmol/L has also been identified as a warning sign for poor prognosis.[9,10] Next studies have shown that lactate clearance, calculated by repeated lactate measurements, is associated with mortality.[11–13] A decrease of over 20% in lactate level within two hours has been reported as a good prognostic indicator in numerous studies.[14–16]

Early identification of patients with high lactate levels in emergency departments (EDs) is crucial for timely resuscitation of critically ill patients. While several studies have examined prognostic value of lactate in specific patient groups, research on unselected patients admitted to the ED is rare.[17–20] The aim of this study is to investigate the relationship between lactate and lactate clearance with in-hospital mortality in unselected ED patients.

Methods

This retrospective study was conducted in the Emergency Medicine Clinic of a tertiary hospital with approval from the local ethics committee (Decision No: 2019/13-23). The study drew from the ED patient records, given the large number of patients admitted to the ED in a single day and the frequent use of gas analysis in their initial evaluation and follow-up. All relevant procedures (including triage category, laboratory results, and admission times) for patients in the ED are recorded in the hospital information system (HIS).

This study included all patients aged 18 years and above who were admitted to the ED from January 1, 2015 through December 31, 2019 and had lactate values measured via blood gas analysis. Patients with missing triage category information, who admitted to the ED as cardiac arrest, who had unknown ED or hospital outcomes (eg, transferred to another medical center or discharged against medical advice), whose lactate values of insufficient analytic accuracy (eg, low sample volume, mixing of test solutions, unsuitable temperature, or sensor problem), and whose lactate value was obtained 180 minutes or more after admission were excluded from the study.

Sociodemographic characteristics, triage categories, blood lactate levels, and lactate measurement times, as well as ED and hospital outcomes of the patients were obtained from the HIS. The ED uses a color-coded triage system, where patients in need of emergency care are registered in red, those who require early evaluation and treatment in yellow, non-urgent patients in green, and trauma patients in blue. Demographic information (age, gender), triage categories (green, yellow, red, blue), ED outcomes (discharge, hospitalization, death), and hospital outcomes (discharge, death) were all recorded.

According to the World Health Organization's (WHO; Geneva, Switzerland) definition, patients were classified into three age groups: young (18-65 years), middle-aged (66-79 years), and elderly (80 years and over). Blood lactate values (the Abl800 Flex model; Hemo Cue Radiometer; Denmark) in the ED were obtained with a blood gas device that is calibrated daily by laboratory technicians. Lactate levels were obtained from 2.0cc blood samples taken with injectors containing dry, electrolyte-balanced lithium heparin. All artery and venous blood samples were included. Studies have shown that lactate values obtained from arterial and venous blood samples are perfectly correlated.[21,22] Patients were divided into three groups based on their initial lactate level: < 2.0mmol/L, 2.0-3.9mmol/L, and ≥ 4.0mmol/L. Lactate clearance was calculated in patients with at least two lactate values in the HIS, provided that the time between the two lactate measurements was one-to-four hours and the first measured lactate value was > 2.0mmol/L. Due to the small number of trauma patients for whom lactate clearance can be calculated, statistical calculations for lactate clearance were conducted exclusively for non-trauma patients. The formula used for calculating lactate clearance was:

$$[(\text{First lactate } - \text{second lactate})/\text{First lactate} \times 100) \times (60 \times \text{between lactate measurements (min)}) \times 2]$$

which was corrected for the time between the two measurements. A significant threshold was defined as a 20% decrease per two hours.

Data analysis was conducted using the SPSS for Windows Ver.20.0 (IBM Corp.; Armonk, New York USA) software. The distribution of the data was analyzed with the Shapiro-Wilk test and the Kolmogorov Smirnov test. It was determined that the data did not fit the normal distribution. Mann-Whitney U test and Kruskal Wallis tests were used in the analysis of independent quantitative data. Chi-square test was used in the analysis of qualitative data. The relations of the variables with mortality were analyzed using the receiver operator characteristics (ROC) curve. For variables associated with mortality, independent risk factors were determined by binomial univariate and multivariate regression analysis. Univariate analyses were performed using the enter method, and multivariate analyses were performed with Forward LR. All analyses were performed with a 95% confidence interval (CI), and the P <.05 value was accepted as significant.

Results

During the five-year study period, a total of 1,070,406 patients were admitted to the ED, of which 114,438 (10.7%) received blood gas analysis. After the patients' evaluation based on the eligibility criteria, 81,302 patients were ultimately included in the study. The patient flow chart is shown in Figure 1.

Of the total 81,302 admissions included in the study, the median age was 58 years (IQR: 30, min: 18–max: 117) and 54.4% (44,189) were female. The first measured median lactate values of the admissions included in the study were 1.7mmol/L (IQR: 1, min: 0.1– max: 31). There were 50,645 (62.3%) admissions with a first measured lactate value < 2.0mmol/L; 26,374 (32.4%) with 2.0-3.9mmol/L; and 4,283 (5.3%) with ≥ 4.0mmol/L. The median lactate values for patients admitted to the ward beds and intensive care unit were 1.8mmol/L (IQR: 1.2, min: 0.1–max: 25) and 2.3mmol/L (IQR: 1.9, min: 0.3–max: 27), respectively (P <.001). In-hospital mortality was 1.79% (n = 1,455). The characteristics, outcomes, and median lactate values of the admissions are shown in Table 1.

Figure 2 shows the ROC curves that illustrate the relationship between the first measured lactate value and in-hospital mortality of both trauma and non-trauma patients included in the study. The univariate two-state regression analysis was used to evaluate the relationship between the first measured lactate level and in-hospital mortality in all patients. The relationship between lactate level and in-hospital mortality in both trauma and non-trauma patients is shown in Table 2.

Lactate clearance was calculated in non-trauma patients whose first measured lactate value was > 2.0mmol/L. In 1,756 non-trauma admissions for which lactate clearance was calculated, in-hospital mortality was 4.4% (n = 78). The ROC curves of the relationship between lactate and lactate clearance and in-hospital mortality in these patients are shown in Figure 3.

In patients with an initial measured lactate value of ≥ 4.0mmol/L and a two-hour lactate clearance < 20%, the mortality rate was 19.7%. The mortality rates according to the first measured lactate and lactate clearance values of the patients are shown in Table 3.

Lactate clearance was calculated for 1,756 patients who had a lactate value measured one-to-four hours after their first lactate value. In these patients, the relationship between initial lactate value, lactate clearance, and patient age with mortality was analyzed using binomial multivariate regression analysis (Table 4).

Discussion

The study found that non-trauma patients with a lactate level between 2.0-3.9mmol/L had a 2.5-times higher mortality risk, while those with a lactate level of ≥ 4.0mmol/L had a 20.8-times higher risk, compared to those with a lactate level < 2.0mmol/L.

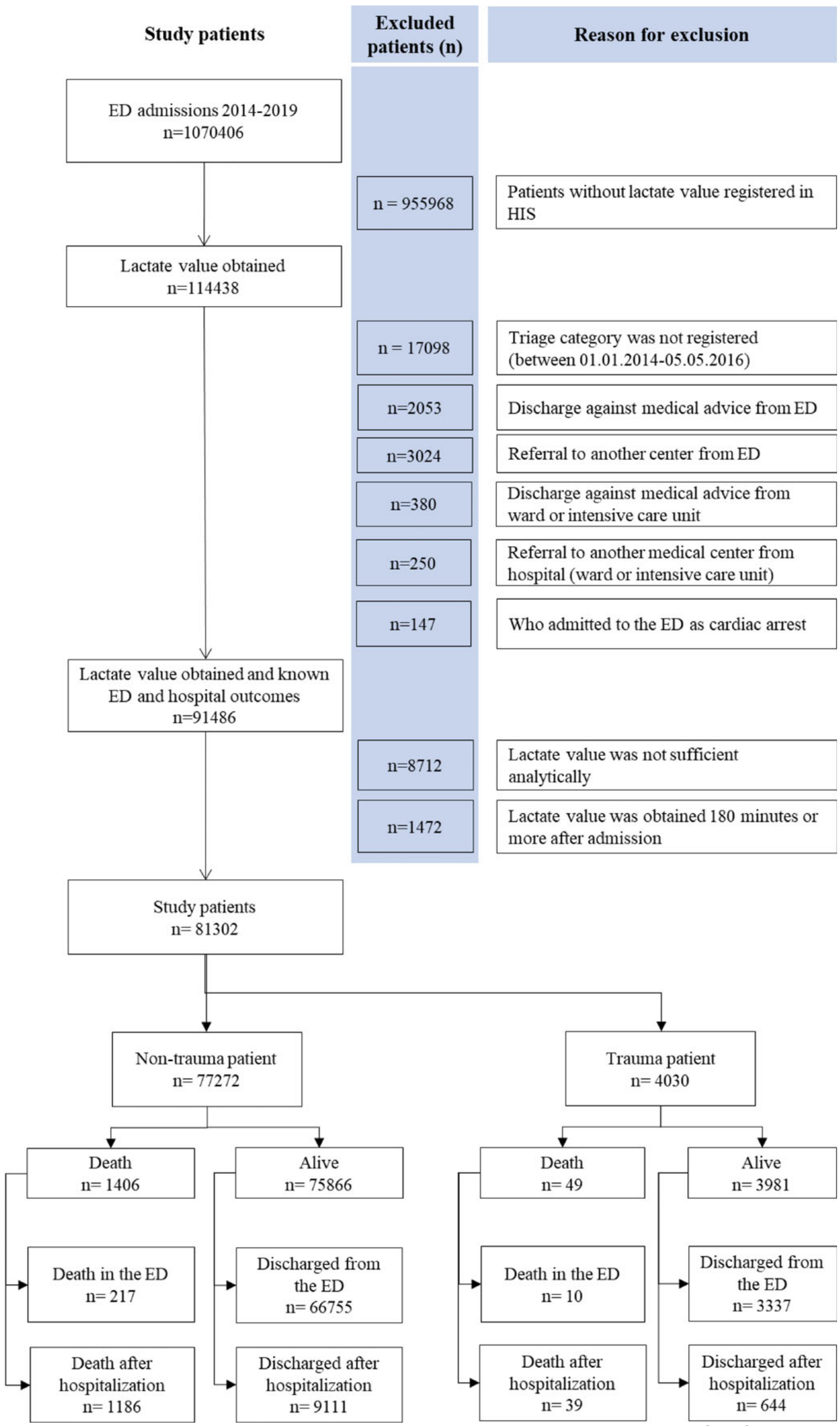

Figure 1. Patient Flow Chart.
Abbreviations: ED, emergency department; HIS, hospital information system.

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Characteristics		n (%)	Median Lactate Value (IQR; min.-max.)	P Value
Age (years)	Young (18-65)	51,623 (63.0%)	1.7 (1.1; 0.1-31)	<.001
	Middle-Aged (66-79)	19,969 (25.0%)	1.8 (1.1; 0.1-22)	
	Elderly (≥80)	9,710 (12.0%)	1.7 (1.0; 0.1-27)	
Gender	Female	44,189 (54.4%)	1.6 (1; 0.1-27)	<.001
	Male	37,113 (55.6%)	1.8 (1.1; 0.1-31)	
Triage Category	Green	7,320 (9.0%)	1.5 (0.9; 0.1-16)	<.001
	Yellow	66,747 (82.0%)	1.7 (1; 0.1-29)	
	Red	3,205 (4.0%)	2.2 (2.2; 0.3-31)	
	Trauma	4,030 (5.0%)	1.9 (1.2; 0.1-22)	
ED Outcome	Discharge	70,092 (86.2%)	1.7 (0.9, 0.1- 29)	<.001
	Hospitalization	10,980 (13.5%)	1.9 (1.4, 0.1-27)	
	Death	230 (0.3%)	7.5 (7.8, 1.1-31)	
Hospital Outcome	Discharge	9,755 (88.8%)	1.9 (1.2, 0.1-25)	<.001
	Death	1,225 (11.2%)	2.7 (3.1, 0.4-27)	

Table 1. Relationship Between Patients' Sociodemographic Characteristics, Triage Categories and Outcomes, and Lactate Values

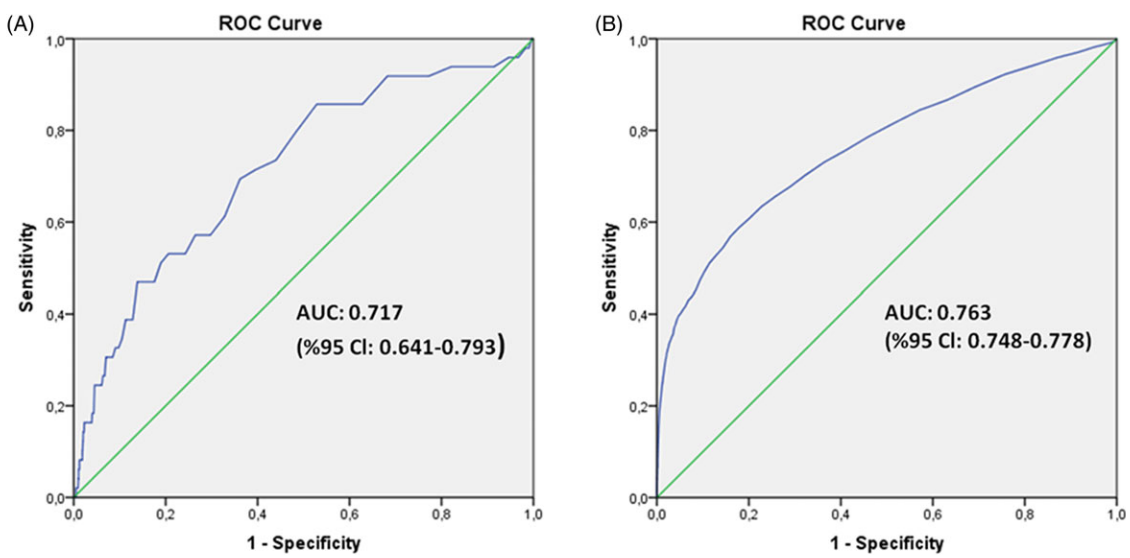

Figure 2. ROC Curves Showing the Relationship of the First Measured Lactate Values of (A) Trauma and (B) Non-Trauma Patients with In-Hospital Mortality.
Abbreviations: ROC, receiver operator characteristics; AUC, area under the ROC curve.

For trauma patients, the mortality risk was three-times higher for those with lactate levels between 2.0-3.9mmol/L and nine-times higher for those with a lactate level of ≥ 4.0mmol/L, compared to those with a lactate level < 2.0mmol/L. Among patients with a first measured lactate value ≥ 4.0mmol/L and a two-hour lactate clearance < 20%, the mortality rate was 19.7%. In addition, lactate, lactate clearance, and age were independent variables for mortality in this patient group.

The prognostic value of lactate in unselected ED patients has been proved by a limited number of studies.[17–20] Pederson, et al conducted a retrospective study in 2015 with 5,360 ED patients, where they demonstrated that high lactate levels were associated with increased mortality.[17] Lactate levels were found to be 0.0-1.9mmol/L in 77.2% of the patients, 2.0-3.9mmol/L in 16.2%, and ≥ 4.0mmol/L in 6.6% and the seven-day mortality was 2.9% (95% CI, 2.4-3.5), 7.8% (95% CI, 6.1-9.8), and 23.9% (95% CI, 19.6-28.8), respectively.[17] Datta, et al, in a prospective study that included 747 ED patients, reported that the lactate value was an indicator of 30-day mortality.[18] Compared with patients with lactate level ≥ 4.0mmol/L, odds ratios (ORs) for 30-day mortality were reported as 0.125 (95% CI, 0.068-0.229) for lactate level < 2.0mmol/L and 0.273 (95% CI, 0.140-0.533) for patients 2.0-3.9mmol/L.[18] After reported the association of mildly elevated lactate with adverse outcomes, subsequent studies attempted to determine a cut-off value for lactate.[19,20] Park, et al investigated the prognostic value of lactate as a predictor of 30-day hospital mortality in a retrospective study that included 14,015 ED patients.[19] The serum lactate OR calculated in

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Lactate Level	OR	95% CI	P Value
Binomial Univariate Regression Analysis for Trauma Patients (n = 4,030)			
< 2.0mmol/L	–	–	–
2.0-3.9mmol/L	3.028	1.437-6.381	.004
≥4.0mmol/L	9.147	4.118-20.315	<.001
Binomial Univariate Regression Analysis for Non-Trauma Patients (n = 77,272)			
< 2.0mmol/L	–	–	–
2.0-3.9mmol/L	2.518	2.198-2.884	<.001
≥4.0mmol/L	20.803	18.164-23.824	<.001

Table 2. Relationship of Lactate Level with In-Hospital Mortality

multivariate regression analysis was 1.09 (P < .001; 95% CI, 1.07-1.10) and area under the ROC curve (AUC) was 0.711 (P < .001; 95% CI, 0.703-0.718). When the lactate cut-off value was 2.6mmol/L, the sensitivity, specificity, and positive and negative predictive values for mortality were 56.7%, 74.3%, 20.8%, and 93.5%, respectively.[19] In the study conducted by Seker, et al with 1,382 unselected ED patients, the sensitivity, specificity, and positive and negative predictive values of 3.6mmol/L serum lactate cut-off value for 30-day mortality were found to be 47%, 88%, 11%, and 98%, respectively.[20] In addition, in this study, it was reported that patients with serum lactate levels of 3.6mmol/L and above had a 6.5-fold higher risk of death at 30 days (AUC: 0.722 [95% CI, 0.637-0.808]; P = .001). In recent studies, the cut-off value determined for lactate was high and its sensitivity was quite low.[19,20] A new cut-off value for lactate value was not determined in the current study. Instead, the authors referenced the previously determined and accepted lactate value in the literature. In this study, the risk of mortality was 20.8-times higher in non-trauma patients and nine-times higher in trauma patients with a lactate level ≥ 4.0mmol/L compared to those with a first measured lactate level < 2.0mmol/L.

The AUC depicting the correlation between the first measured lactate value and in-hospital mortality was consistent with the existing literature, as found in the current study (0.763 [95% CI, 0.748-0.778] in non-trauma patients and 0.717 [95% CI, 0.641-0.793] in trauma patients). In addition, in the patient group whose lactate clearance was calculated, the AUCs showing the relationship of lactate and lactate clearance value with in-hospital mortality were 0.727 (95% CI, 0.663-0.791) and 0.671 (95% CI, 0.607-0.735), respectively. This study, which included a much larger patient population (n = 81,302), adds to the literature by demonstrating the predictive power of lactate clearance for mortality in unselected ED patients.

In the logistic model of this study, age was shown to be an independent predictor of mortality along with lactate and lactate clearance. Furthermore, a retrospective study published in 2020 of 8,796 patients reported that mortality generally increased with increasing lactate levels in all age groups (P < .001).[23] In the current study, compared to patients aged 18-65 years, the mortality ORs were 2.389 in patients aged 65-79 years (95% CI, 1.362-4.190; P <.001) and 2,579 in patients aged ≥ 80 years (95% CI, 2.579-8.663; P <.001). In the ED, it is necessary to evaluate lactate together with lactate clearance and age in patient management.

Limitations

Since this study was retrospective, some admissions may belong to the same patients. The authors could not evaluate the vital parameters and co-morbidity of the patients. The absence of data on chronic illness in this study may have caused the relationship between age and increased mortality to be exaggerated. However, the authors categorized and evaluated the patients based on their triage status and whether they had experienced trauma or not. This study was conducted with ED patients (10.7% of all ED patients) whose blood gas analyses were requested by the physicians and whose results were in the system. Study results cannot be generalized to all

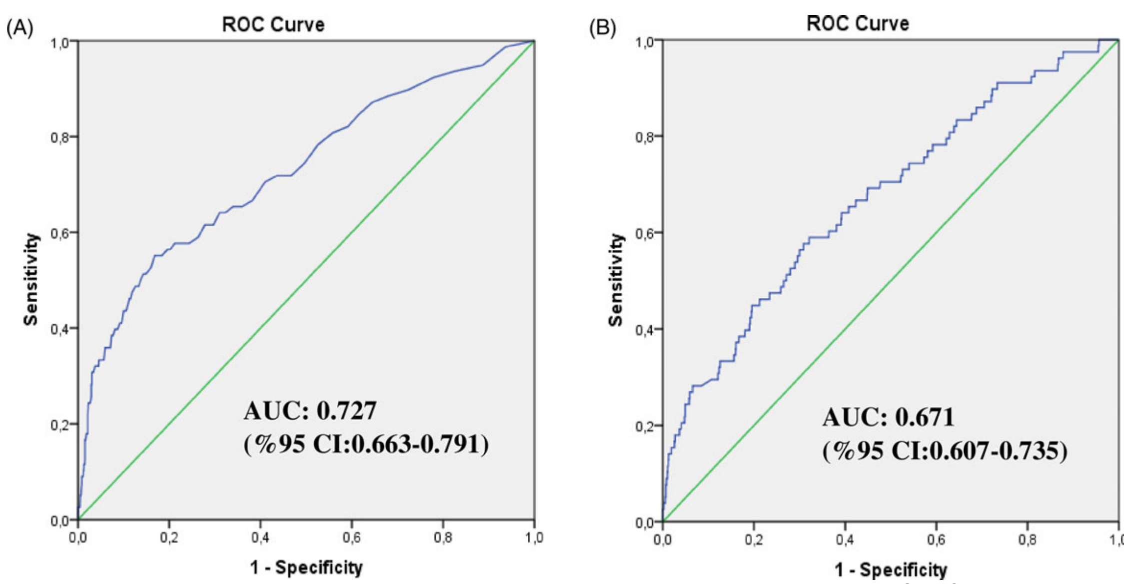

Figure 3. ROC Curves Showing the Relationship between (A) Lactate and (B) Lactate Clearance and In-Hospital Mortality for Non-Traumatic Patients.
Abbreviations: ROC, receiver operator characteristics; AUC, area under the ROC curve.

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First Lactate Level	Two-Hour Lactate Clearance	n	In-Hospital Mortality Rate (n)	P Value
2.0-3.9mmol/L	> 20%	830	1.6 (13)	<.001
	< 20%	355	4.2 (15)	
≥4.0mmol/L	> 20%	454	5.9 (27)	
	< 20%	117	19.7 (23)	

Table 3. In-Hospital Mortality Rates According to Lactate Levels and Lactate Clearance of Patients

	OR	95% CI	P Value
Lactate Level < 4.0mmol/L	–	–	<.001
Lactate Level ≥ 4.0mmol/L	4.821	2.954-7.868	
Two-Hour Lactate Clearance ≥ 20%	–	–	<.001
Two-Hour Lactate Clearance < 20%	2.917	1.804-4.717	
18-65 Years of Age	–	–	
66-79 Years of Age	2.389	1.362-4.190	<.001
≥80 Years of Age	4.727	2.579-8.663	<.001

Table 4. Binomial Multivariate Regression Analysis for First Lactate Value, Lactate Clearance, and Age

ED patients. Another limitation is that only in-hospital mortality was evaluated; no follow-up was performed after discharge.

Conclusion

The lactate value obtained at the first admission in unselected ED patients for which blood gases were drawn is a biomarker that can be used to indicate the prognosis of the patients. In the patient whose lactate level was above 2.0mmol/L at the first admission to the ED and whose blood gas analysis was performed again within one-to-four hours, initial lactate value, lactate clearance, and patient age are independent indicators of in-hospital mortality.

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