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The Sequential Evaluation of Static and Kinetic Lactate Levels as a Predictor of Mortality in Patients with Septic Shock in the Intensive Care Unit

Ibrahim Mungan,[1] Cilem Bayindir Dicle,[2] Derya Ademoglu,[3] Busra Tezcan,[2] Hayriye Cankar Dal,[2] Sema Turan[2]

Abstract

Aim: Screening and initial resuscitation are key aspects of sepsis guidelines, with lactate levels being central to discussions on sepsis management. We aimed to elucidate the relationship between mortality and lactate levels in septic shock patients and to evaluate the efficacy of static lactate levels versus lactate kinetics at specific time points.

Study Design: This retrospective cohort study was based on the archived records of patients admitted to the intensive care unit (ICU) from July 2019 to December 2019. Serum lactate levels were measured at ICU admission, and after 2, 6, 12, 24, and 48 hours.

Results: During the six-month study period, 90 patients managed in the intensive care unit and diagnosed with septic shock met the eligibility criteria. Lactate levels at admission and six hours later did not differ between the nonsurvivor and survivor groups (2.8 mmol/L vs. 2.42 mmol/L and 3.38 mmol/L vs. 2.61 mmol/L, respectively). Lactate levels at 2, 12, 24, and 48 hours after admission were higher in the nonsurvivor group, and the differences were statistically significant. Delta lactate levels at all time points did not differ between groups statistically. The analysis of the Receiver Operating Characteristic (ROC) curve for 28-day mortality showed that the lactate level at 48 hours had the best predictive value, with an Area Under the Curve (AUC) of 0.728.

Conclusions: Our study showed that in septic shock patients, lactate levels at a relatively late stage—48 hours after admission—could be utilized as a prognostic marker. New advances in the management of septic shock shifted focus from resuscitation endpoints to microcirculation parameters. The lactate kinetics of patients with critical illnesses might be investigated according to disease classification in the future.

Keywords: Static; Kinetic; Lactate levels; Mortality; Septic shock; Intensive care.

[1]Department of Intensive Care Unit, Kocaeli Darıca Farabi Training and Research Hospital, Kocaeli, Türkiye
[2]Department of Intensive Care Unit, Ankara Training and Research City Hospital, Ankara, Türkiye
[3]Department of Intensive Care Unit, İstanbul Çam & Sakura Training and Research Hospital, Istanbul, Türkiye

Address for correspondence:
Ibrahim Mungan, MD.
Department of Intensive Care Unit, Kocaeli Darıca Farabi Training and Research Hospital, Kocaeli, Turkiye.
E-mail:
imungan@gmail.com

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Introduction

In 2016, the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) introduced a significant change in the diagnostic criteria and definition of sepsis and septic shock.[1] The consensus added serum lactate concentration greater than 2 mmol/L as a criterion to define septic shock, and recent guidelines have proposed using lactate decrement to guide resuscitation in sepsis patients.[1,2] The combined incidence of 189 hospital-treated adult sepsis cases per 100,000 person-years and an approximate 30% mortality rate highlight the importance of effective management in sepsis.[3] Screening and initial resuscitation were emphasized in the guidelines, with lactate level being central to discussions on sepsis management.[1]

Hyperlactatemia has traditionally been considered solely as a byproduct of anaerobic metabolism associated with tissue hypoxia in sepsis, while recent studies have shed light on additional factors. Increased β-adrenergic stimulation, whether of endogenous or exogenous origin, leads to an increased glycolytic flux and subsequent lactate accumulation. Decreased serum lactate clearance due to hepatic or renal dysfunction or defects in microcirculation is another contributing factor for hyperlactatemia.[4] In sepsis, the crucial oxygen (O_2) extraction ratio, normally about 70%, decreases to about 50%, which impairs the O_2 demand response. Microcirculatory and mitochondrial dysfunction exacerbate this impairment, and adequate oxygenation fails to meet the tissue's oxygen needs.[5]

Although static lactate indices, particularly the lactate level at admission, which show the relationship between sepsis and mortality, have been widely studied and accepted as a poor prognostic indicator, the kinetic changes in lactate levels have not been adequately clarified and have not been compared with static levels. Our study aims to reveal the association between mortality and lactate levels in septic shock patients and to evaluate the efficacy of static lactate levels versus lactate kinetics at specific time points.

Materials and Methods

Our study was conducted in a retrospective manner based on the archive records of patients followed in the intensive care unit (ICU) between July 2019 and December 2019. We evaluated not only demographic and clinical information but also serum lactate levels. Arterial blood gas analysis was performed through episodic blood sampling using co-oximetry (Blood Gas Analyzer; Techno Medica, St. Ingbert, Germany). The primary parameters investigated were 28-day mortality and its relationship with lactate levels. Additional clinical parameters included:

a) Clinical and demographic characteristics of the patients such as age, gender, Acute Physiology and Chronic Health Evaluation II (APACHE II) score at admission, vital signs at shock recognition, and past medical history.

b) Baseline laboratory values.

c) Outcomes, such as 28-day mortality, the need for mechanical ventilation, length of stay in the hospital and in the ICU, and management strategies of septic shock patients.

d) Static and kinetic lactate levels of septic shock patients.

Definitions and Inclusion Criteria

1. **Static Lactate Levels:** Absolute lactate levels at admission (L0), and at 2, 6, 12, 24, and 48 hours after admission to the ICU (L2, L6, L12, L24, and L48, respectively).

2. **Kinetic Lactate Levels:** Changes in serum lactate levels at the specified time points (2, 6, 12, 24, and 48 hours after admission to the ICU) were defined as delta lactate 2, 6, 12, 24, and 48, respectively, according to their chronological order. It was calculated as the initial lactate level (L0) minus the lactate levels at the specified times mentioned above.

In accordance with the Sepsis-3, we first classified patients with sepsis based on an elevation in the Sequential Organ Failure Assessment (SOFA) score of ≥2 points following a proven or suspected infection. Proven or suspected infection was defined as the initiation of therapeutic antibiotic or antiviral therapy within 24 hours after ICU admission. Both the APACHE II score and the SOFA score were used to evaluate the severity of critical illness. We then recategorized these patients based on whether they had septic shock or not according to the Sepsis-3 criteria, defined as the need for vasopressor support to maintain a mean arterial pressure of ≥65 mm Hg or a serum lactate level ≥2 mmol/L in the absence of hypovolemia.[1] All patients were managed according to the

standard practices in the ICU in line with the Surviving Sepsis Campaign (SSC) guidelines, which include fluid resuscitation, serial lactate measurement, blood culture, and the administration of broad-spectrum antibiotics.[2]

Patients older than 18 years, who met the septic shock criteria and were diagnosed with new-onset infection, were included in this study. The exclusion criteria were as follows: patients younger than 18 years, trauma patients, patients with a "do not attempt resuscitation" status, and patients who lacked data for repeated lactate measurements. Patients who died within 48 hours after admission were also excluded from the study because data on their lactate levels at 48 hours (L48) would be lacking. Our study was conducted in accordance with international standards and the Declaration of Helsinki, and the Ankara City Hospital Clinical Research Ethics Committee approved the study with a waiver of informed consent (Approval Number: E1-19-213, Date: 24.12.2019).

Statistical Analysis

The normality of the data was assessed using the Kolmogorov-Smirnov test, which indicated that the data were not normally distributed; therefore, non-parametric tests were used. Data are expressed as median and interquartile range values for continuous variables and as numbers and percentages for categorical variables. The Spearman Rho correlation coefficient and the Mann-Whitney U test were utilized to evaluate the correlation between variables and mortality. The prognostic power of lactate kinetic and static levels was compared using receiver operating characteristic (ROC) curves and area under the curve (AUC). The ROC curves were cross-verified using Hanley's method. Statistical analysis was conducted using SPSS software (version 25.0; IBM, Armonk, NY) and MedCalc Statistical Software (version 15.2.2; MedCalc Software, Ostend, Belgium). In all analyses, a p-value of less than 0.05 indicated statistical significance.

Results

During the six-month study period, a total of 121 patients were admitted to the ICU with a diagnosis of sepsis, and the standard sepsis management protocol described earlier was applied. Septic shock was present in 74.4% (n=90) of these patients, meeting the eligibility criteria.

The demographic variables are outlined in Table 1. The median age was 66.5 years, with no difference between groups based on this variable. The majority of patients were admitted from the emergency department (n=52, 57.8%) and no significant differences were observed between groups (p=0.781). Congestive heart failure and oncologic diseases were the most common comorbidities. A history of malignancy was predominantly observed in the nonsurvivor group, with this difference reaching statistical significance (p=0.042). Both the APACHE II score and the SOFA score were used to evaluate the severity of critical illness. The APACHE II score was higher in the nonsurvivor group (p=0.025), while the SOFA score did not show a statistically significant difference between groups (p=0.261).

The most common underlying infection of sepsis at admission for both groups was pneumonia, as shown in Table 1. While pneumonia was more prevalent in the survivor group, the difference was not statistically significant between groups (p=0.058). Intra-abdominal infections as a cause of septic shock were more commonly identified in the nonsurvivor group, but the difference between groups was not statistically significant (p=0.107). Culture results were positive (+) in 82 cases (91.1%), while blood cultures were positive (+) in 72 of the total cases (80%). There were no statistically significant differences between the groups regarding these variables (p=0.275 and p=0.131, respectively).

In Table 2, the outcomes and management strategies of patients with septic shock are detailed. The length of stay in the hospital and ICU was longer in the survivor group, and this difference was statistically significant (p<0.001). Additionally, the duration of mechanical ventilator-free days was longer in the survivor group (p<0.001). The duration of vasopressor requirement was similar between groups, with no significant difference (p=0.574).

As shown in Table 3, the lactate levels at admission and six hours later did not differ between the nonsurvivor and survivor groups (2.8 mmol/L vs. 2.42 mmol/L and 3.38 mmol/L vs. 2.61 mmol/L, respectively). Lactate levels measured 2, 12, 24, and 48 hours after admission were higher in the nonsurvivor group, and these differences were statistically significant (p=0.018, p=0.002, p=0.002, p≤0.001, respectively). Delta lactate levels at all time points did not differ significantly between groups. The predictive power of static and kinetic lactate levels was compared in Table 4, Figure 1, and Figure 2 according to their AUC values. Table 4 also presents the optimal cutoff values for

Table 1. Clinical characteristics and baseline laboratory values in septic shock patients on admission to the intensive care unit (ICU)

Variables	Total (n=90)	Survivors (n=34, 37.8%)	Non-survivors (n=56, 62.2%)	p
Male Gender	58 (64.4%)	21 (61.8%)	37 (66.1%)	0.683
Age, years	66.5 (55.5-80)	65.5 (42.7-74.2)	68 (57.5-81)	0.161
Characteristics on ICU Admission				
Glascow Coma Score	11 (6-14.2)	11 (7-15)	9 (3.2-13)	0.062
APACHE II Score	23 (18-28.2)	21.5 (16.8-24.3)	25 (18-34)	0.025
SOFA Score	10 (8-12)	8 (8-11)	10 (7.3-12.8)	0.261
Vital Signs at Shock Recognition				
Mean Arterial Pressure (mmHg)	70 (60-80)	70 (57.3-75.3)	70 (62.8-82)	0.455
Heart Rate (beats/min)	111 (97.8-124.2)	111 (97.8-123)	111 (96.5-125.5)	0.977
Arterial Oxygen Saturation	91 (87-95)	92 (88-95)	91 (85-95)	0.144
Past Medical History				
Cardiovascular Disease	43 (47.8%)	19 (55.9%)	24 (42.9%)	0.235
Diabetes Mellitus Type 2	30 (33.3%)	14 (41.2%)	16 (28.6%)	0.223
Chronic Kidney Disease	17 (18.9%)	7 (20.6%)	10 (17.9%)	0.752
Chronic Obstructive Pulmonary				
Disease	6 (6.7%)	1 (2.9%)	5 (8.9%)	0.275
Malignancy	36 (40%)	9 (26.5%)	27 (48.2%)	0.042
Stroke	8 (8.9%)	5 (14.7%)	3 (5.4%)	0.134
Sites of Infection				
Pneumonia	44 (48.9%)	21 (61.8%)	23 (41.1%)	0.058
Urinary Tract Infection	19 (21.1%)	6 (17.6%)	13 (23.2%)	0.53
Intra-abdominal Infection	12 (13.3%)	2 (5.9%)	10 (17.9%)	0.107
Other Infections	12 (13.3%)	4 (11.8%)	8 (14.3%)	0.737
Transferred from				
Emergency Department	52 (57.8%)	19 (55.9%)	33 (58.9%)	0.781
Hospital Ward	25 (27.8%)	7 (20.6%)	18 (32.1%)	0.24
Operating Room	1 (1.1%)	1 (2.9%)	0	0.202
Other Sources	12 (13.3%)	7 (20.6%)	5 (8.9%)	0.115
Baseline Laboratory Values				
Hemoglobin, g/dL	9 (7.9-10.8)	9 (7.9-11)	8.9 (7.8-10.5)	0.924
Platelet Count (×109/L)	186.5 (77-307)	241.5 (108.5-319)	161 (70.5-274.5)	0.057
White Blood Cell Count, (×103/μL)	12420 (7500-1600)	12070 (8175-15300)	12760 (5115-16000)	0.99
Creatinine, mg/dL	1.91 (0.9-3.1)	1.75 (0.6-3.5)	2 (1-2.95)	0.644
C-Reactive Protein, mg/dL	17.3 (12.5-24.1)	17.3 (14.1-23.4)	17.3 (11.9-25.4)	0.609
Culture Positive	82 (91.1%)	50 (89.3%)	32 (94.1%)	0.275
Blood Culture Positive	72 (80%)	42 (75%)	30 (88.2)	0.131

Data are expressed as median and interquartile range values or numbers and percentages. ICU: Intensive Care Unit; SOFA: Sequential Organ Failure Assessment; APACHE II: Acute Physiology and Chronic Health Evaluation II.

static and kinetic lactate levels to predict mortality in patients with septic shock.

In Figure 3, the analysis of the ROC curve for 28-day mortality showed that lactate at 48 hours (Lactate48), which had the best predictive value (AUC, 0.728) with a cut-off value of 4.29, has a sensitivity of 53.57% and a specificity of 94.12%. Lactate levels at 24 hours (Lactate24) and 12 hours (Lactate12) have the same AUC value (0.696), while the other static lactate levels (Lactate0, Lactate2, and Lactate6) and all kinetic lactate levels have smaller predictive power respectively, as

Table 2. Outcomes and management strategies of septic shock patients admitted to the intensive care unit (ICU)

	Total (n=90)	Survivors (n=34, 37.8%)	Non-survivors (n=56, 62.2%)	p
Fluid Balance in the First 24 Hours, mL	2151 (1646-3000)	2357 (1800-3285)	2100 (1512-3000)	0.244
ICU Length of Stay (days)	13.5 (4-30)	24 (12-48.8)	7.5 (3-18)	<0.001
Length of Stay in Hospital (days)	21.5 (9.5-42)	33.5 (20-56.3)	15 (5-30)	<0.001
Mechanical Ventilation-Free Days	1 (0-8)	5 (3-15)	1 (0-2)	<0.001
Need for Vasopressors	88 (97.8%)	32 (94.1%)	56 (100%)	0.068
Hydrocortisone Use	15 (16.7%)	5 (14.7%)	10 (17.9%)	0.701
Invasive Mechanical ventilation	75 (83.3%)	23 (67.6%)	52 (92.9%)	0.002
Renal Replacement Therapy	43 (47.8%)	15 (44.1%)	28 (50%)	0.593

Data are expressed as median and interquartile range or numbers and percentages. Abbreviations: CRRT: Continuous Renal Replacement Therapy; ICU: Intensive Care Unit.

Table 3. Static and kinetic lactate levels of septic shock patients admitted to the intensive care unit (ICU)

Lactate Metrics	Total (n=90)	Survivors (n=34, 37.8%)	Non-survivors (n=56, 62.2%)	p
Lactate0 (Lactate at Admission), mmol/L	2.66 (1.91-4.26)	2.42 (1.8-4.1)	2.8 (2-4.9)	0.089
Lactate2, mmol/L	2.61 (2-4.2)	2.23 (1.4-3.2)	2.96 (2.1-4.3)	0.018
Lactate6, mmol/L	3 (2-5.1)	2.61 (1.9-4.1)	3.38 (2.3-5.6)	0.102
Lactate12, mmol/L	3 (1.9-4.3)	2.03 (1.5-3.7)	3.74 (2.2-4.8)	0.002
Lactate24, mmol/L	2.69 (1.73-5.27)	1.98 (1.4-2.9)	4.1 (1.9-7.1)	0.002
Lactate48, mmol/L	2.38 (1.5-5.81)	1.88 (1.3-2.3)	4.5 (2-8.65)	<0.001
Delta Lactate2	0 (-0.52-0.5)	0 (-0.61-0.42)	0 (-0.52-0.6)	0.590
Delta Lactate6	0.05 (-0.8-1.4)	0.33 (-1-1.18)	0.02 (-0.8-1.4)	0.947
Delta Lactate12	0.03 (-0.9-1.4)	-0.1 (-1-0.83)	0.43 (-0.95-1.7)	0.367
Delta Lactate24	0 (-1.2-1.8)	-0.22 (-1.5-0.67)	0.2 (-1.1-2.53)	0.162
Delta Lactate48	-0.05 (-1-2.3)	-0.26 (-1.4-0.1)	0.56 (-1-4.28)	0.057

Data are expressed as median and interquartile range values.

Table 4. Area under the receiver operating characteristic (ROC) curves for static and kinetic lactate levels of septic shock patients admitted to the intensive care unit (ICU)

Variable	95% CI								
	AUC	SE	Lower Bound	Upper Bound	Cut-off Value	Sensitivity	Specificity	p	Youden Index J
Lactate0	0.607	0.0620	0.499	0.709	2.46	62.5	55.9	0.081	0.183
Lactate2	0.649	0.0619	0.541	0.747	2.5	64.29	67.65	0.0151	0.319
Lactate6	0.603	0.0617	0.495	0.705	2.5	75.00	50.00	0.0921	0.25
Lactate12	0.696	0.0589	0.590	0.789	2.1	78.57	61.76	0.0008	0.403
Lactate24	0.696	0.0577	0.590	0.788	2.95	58.93	79.41	0.0006	0.383
Lactate48	0.728	0.0557	0.624	0.817	4.29	53.57	94.12	<0.0001	0.476
Delta Lactate2	0.534	0.0629	0.426	0.640	0.7	21.43	91.18	0.5833	0.1261
Delta Lactate6	0.505	0.0640	0.397	0.612	0.96	82.14	29.41	0.9407	0.1155
Delta Lactate12	0.557	0.0619	0.448	0.661	0.02	55.36	61.76	0.3011	0.1712
Delta Lactate24	0.588	0.0607	0.479	0.691	0.2	46.43	76.47	0.1229	0.2290
Delta Lactate48	0.620	0.0596	0.512	0.721	1.33	42.86	91.18	0.0422	0.3403

Abbreviations: AUC: Area Under The Curve; CI: Confidence Interval; SE: Standard Error.

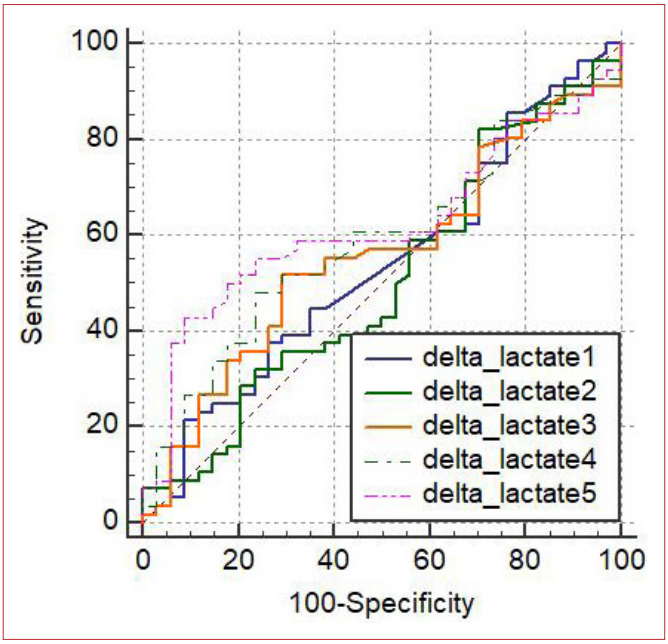

Figure 1. Receiver operating characteristic (ROC) curves of kinetic lactate values for mortality prediction in septic shock patients admitted to the the intensive care unit (ICU).

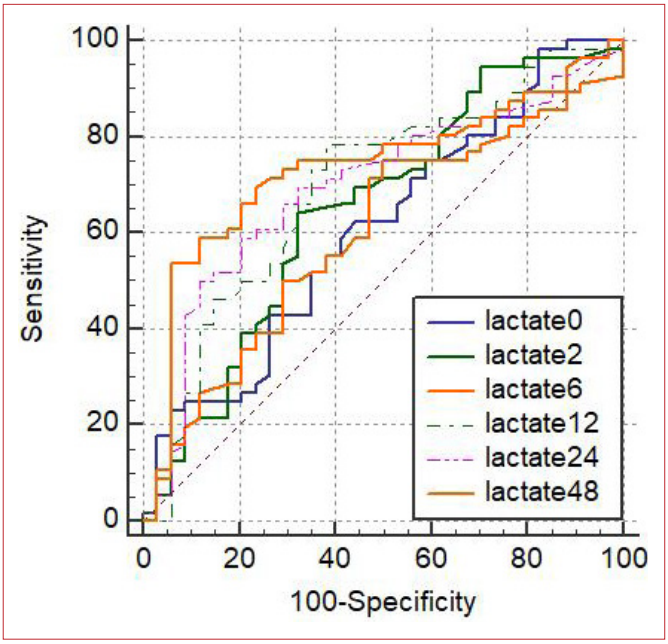

Figure 2. Receiver operating characteristic curves of static lactate values for mortality prediction in septic shock patients admitted to the ICU.

detailed in Table 4. In Figures 4 and 5, both the static and kinetic lactate levels at different time periods are displayed, comparing the differences between the non-survivor and survivor groups. The differences were particularly notable for Lactate48 and delta lactate at 48 hours (Delta Lactate48).

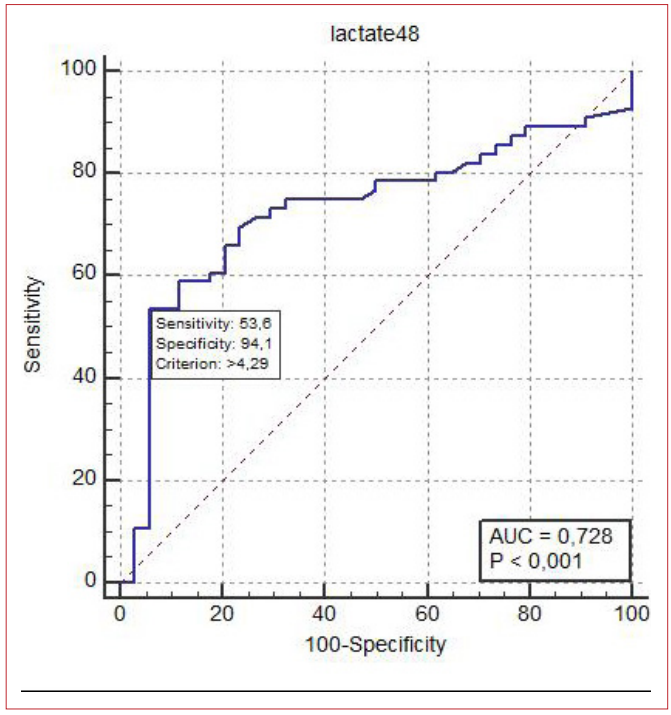

Figure 3. Receiver operating characteristic curve lactate value 48 hours after admission to the ICU for mortality prediction in septic shock

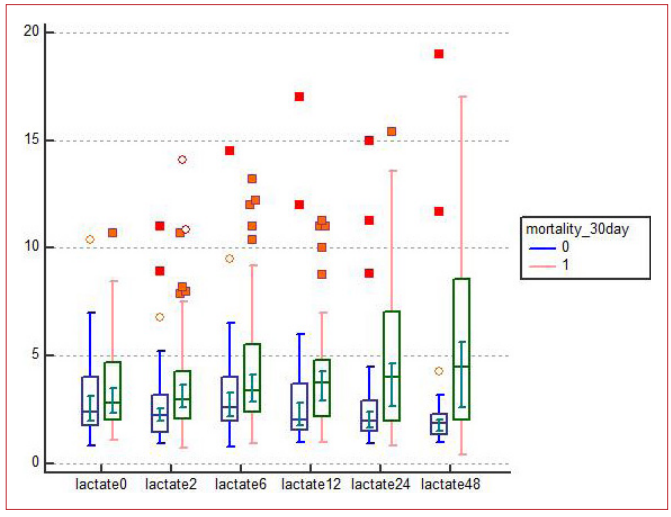

Figure 4. The static lactate levels and the difference between nonsurvivor and survivor groups in septic shock patients admitted to the ICU.

Discussion

The Surviving Sepsis Campaign recommended an initial lactate measurement and a follow-up test six hours later if the lactate level at admission was greater than 2 mmol/L.[2] The term "lactate clearance" is debatable as it is typically defined as the volume of plasma from which

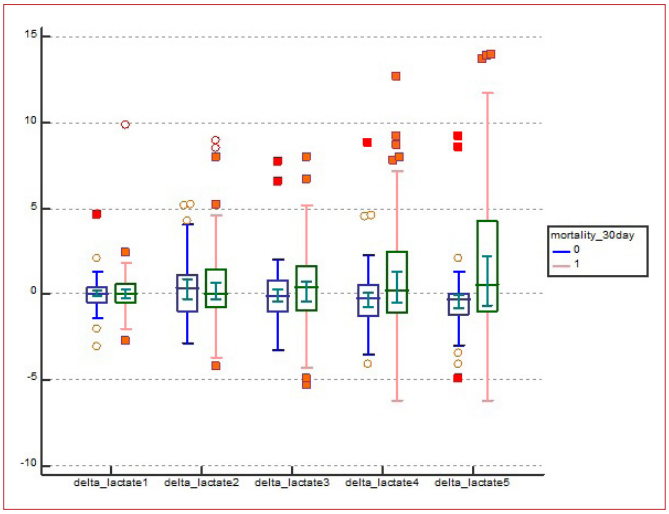

Figure 5. The kinetic lactate levels and the difference between nonsurvivor and survivor groups in septic shock patients admitted to the ICU.

lactate has been completely removed per unit of time.[6] In the context of lactate, variations in the ongoing production of lactate and its utilization as an energy source by other tissues at different levels influenced both the plasma lactate level and its clearance by the kidney or liver.[7] Consequently, we use the term "lactate kinetics" instead of "lactate clearance" in this study.

The evaluation of lactate kinetics was first recommended by Vincent et al.[6] as an indicator of response to therapy in critically ill patients. Subsequently, Yu et al.[8] measured the blood lactate level at admission, and 2, 4, 6, and 12 hours later, assessing the predictive power of each lactate level, the maximum lactate level, and the lactate area score, which was derived from the AUC of serial lactate levels. They found that both static lactate levels and lactate area score were related to mortality, with the lactate area score exhibiting the highest AUC on the ROC curve.

Even though some authors have proposed monitoring static lactate levels and employing lactate-guided therapies in sepsis management,[9,10]] lactate clearance, also referred to as lactate kinetics, has emerged as another point of interest, with researchers drawing various conclusions.[5,6,11] Levraut et al.[12] evaluated serum lactate level changes by modeling the lactate kinetics and concluded that in stable sepsis cases, impaired lactate clearance was the reason for mild hyperlactatemia. Vandewalle et al.[13] highlighted another aspect of sepsis—metabolic dysregulation with a strong starvation reaction leading to lactate accumulation.

We found that the lactate level at 48 hours was superior to other static lactate levels and kinetic lactate levels, a finding not parallel to other researchers' conclusions. Not only did Herwanto et al.[14] claim that lactate clearance at the 24th hour was the best parameter associated with mortality, but Marty et al.[15] also supported the claim. Bruno et al.[4] concluded that lactate clearance six hours after admission was an independent factor for outcome prediction, irrespective of the SOFA score and the need for organ support. In contrast, Lee et al.[16] claimed the opposite and found that Lactate6 proved to be more accurate in predicting 30-day mortality than either lactate clearance at six hours or the initial lactate level at admission.

Nazir et al.[17] also concluded that lactate kinetics were associated with mortality and the length of hospital stay in pediatric septic shock cases. They claimed that the change in lactate level at the 24th hour was superior for predicting mortality compared to the change at the 6th hour (referred to as delta lactate 24 and delta lactate 6 in the study). A recent study identified heart rate, blood glucose level, SOFA score, and APACHE II score as independent risk factors influencing lactate kinetics.[18] We found that only the APACHE II score differed between nonsurvivor and survivor groups, while the other parameters were statistically similar.

New advances in the management of septic shock shifted the focus from resuscitation endpoints and macrocirculation parameters, primarily cardiac output and mean arterial pressure, to microcirculation parameters, such as video microscopes for hemodynamic monitoring.[7,19,20] Yajnik et al.[21] proposed microcirculatory bedside tools to guide the resuscitation of septic shock. The lactate kinetics of patients with critical illnesses might be investigated according to disease classification in the future.

Limitations

The retrospective nature of this study was the main limitation, coupled with a relatively small patient cohort. One might be concerned about missing data in a retrospective study; however, septic shock was the inclusion criterion for the study, and lactate levels were analyzed in a standard manner in the ICU in cases of septic shock, thereby minimizing the risk of missing data.

Conclusion

Sepsis remains a complex puzzle that we have just begun to unravel. Following the Sepsis-3 guidelines, the rela-

tionship between lactate levels and mortality has been intensely studied. This study demonstrated that in patients with septic shock, lactate levels measured at a relatively late stage—48 hours after admission—could be used as a prognostic marker.

Ethics Committee Approval: The Ankara City Hospital Clinical Research Ethics Committee approved the study (Approval Number: E1-19-213, Date: 24.12.2019).
Informed Consent: Patient consent was not required as only de-identified data were utilized.
Peer-review: Externally peer-reviewed.
Author Contribution: Concept – I.M., S.T.; Design – I.M., S.T., B.T.; Supervision – S.T, I.M.; Resource – C.B.D., D.A., H.C.D.; Materials – C.B.D, D.A, H.C.D.; Data Collection and/or Processing - I.M., C.B.D., D.A.; Analysis and/or Interpretation - I.M.; Literature Review – I.M., H.C.D.; Writing – I.M.; Critical Review – I.M., S.T., B.T.
Conflict of Interest: The authors declare they have no conflict of interest relevant to this article.
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