Clinical Research

Evaluation of the Relationship Between Arterial Lactate Level and Mortality in Septic Patients Hospitalized in the Tertiary Intensive Care Unit

Ali İhsan SERT[1], Koray ALTUN[1], Burhan Sami KALIN[1,a], Esra AKTİZ BIÇAK[2]

[1]*Gazi Yaşargil Eğitim ve Araştırma Hastanesi, Yoğun Bakım Kliniği, Diyarbakır, Türkiye*
[2]*Gazi Yaşargil Eğitim ve Araştırma Hastanesi, Anesteziyoloji ve Reanimasyon Kliniği, Diyarbakır, Türkiye*

ABSTRACT

Objective: Elevated lactate has been found to be associated with a higher mortality in a various patient population of intensive care unit (ICU). Our aim is to review the relationship between arterial blood lactate level and the mortality rate in septic cases admitted to the ICU.
Material and Method: Hundred and ten septic patients who were followed up in ICU between March 2021 and November 2021 were included in this study. The patients included in the study were divided into two groups as survivors and deceased and all the parameters studied were statistically analyzed for both groups.
Results: Sixty-six (60%) were male of 110 patients. The mean age was 62(49-72) years. Mortality rate was 58%. LOS (length of stay) in ICU was 4(2-6) days. Septic shock was diagnosed in 60 (54.5%) of the patients upon admission to the ICU. The requirements for IMV (invasive mechanical ventilation) and NIMV non- invasive mechanical ventilation) for patients were 70(63.6%) and 43(39.1%), respectively. APACHE-II score was 24±9. Mean arterial lactate level was 3.5(2.4-5.2). As a result of the logistic regression analysis, Glasgow coma scale (GCS), requirement for IMV, arterial lactate level and LOS in ICU were determined as independent risk variables for mortality (OR =1.304 (1.073-1.586), p =0.008, OR =5.747 (1.501-22.002), p =0.011, OR =1.703 (1.190-2.518), p =0.004, OR =1.472 (1.042-2.213), p =0.04), respectively.
Conclusion: As a result of the logistic regression analysis, GCS, requirement for IMV, arterial lactate level and LOS in ICU were determined as independent risk variables for mortality.

Keywords: *Intensive Care Unit, Lactate, Mortality, Sepsis.*

ÖZ

Üçüncü Basamak Yoğun Bakım Ünitesinde Yatan Septik Hastalarda Arteriyel Laktat Düzeyi ile Mortalite Arasındaki İlişkinin Değerlendirilmesi

Amaç: Yüksek laktat düzeyi, yoğun bakım ünitesindeki (YBÜ) hasta popülasyonunda yüksek ölüm oranı ile ilişkili bulunmuştur. Amacımız, yoğun bakım ünitesine kabul edilen septik olgularda arteriyel kan laktat düzeyi ile ölüm oranı arasındaki ilişkiyi gözden geçirmektir.
Gereç ve Yöntem: Mart 2021- Kasım 2021 tarihleri arasında YBÜ'nde izlenen 110 septik hasta bu çalışmaya dahil edildi. Çalışmaya dahil edilen hastalar sağ kalanlar ve ölenler olarak iki gruba ayrıldı ve çalışılan tüm parametreler her iki grup için istatistiksel olarak analiz edildi.
Bulgular: Yüzon hastanın 66(%60)' sı erkekti. Ortalama yaş 62(49-72) idi. Ölüm oranı %58 idi. YBÜ'de kalış süresi 4(2-6) gündü. 60(%54,5) hastaya YBÜ'ye kabulde septik şok tanısı konuldu. Hastalarda IMV (invaziv mekanik ventilasyon) ve NIMV (invaziv olmayan mekanik ventilasyon) gereksinimleri sırası ile 70(%63,6) ve 43(%39,1) idi. APACHE-II skoru 24±9 idi. Ortalama arteriyel laktat değeri 3.5(2.4-5.2) idi. Lojistik regresyon analizi sonucunda Glasgow koma skalası (GKS), IMV gereksinimi, arteriyel laktat seviyesi ve YBÜ'de kalış süresi mortalite için bağımsız risk faktörleri olarak belirlendi. Sırasıyla (OR =1.304 (1.073-1.586), p =0.008, OR =5.747 (1.501-22.002), p =0.011, OR =1.703 (1.190-2.518), p =0.004, OR =1.472 (1.042-2.213), p =0.04).
Sonuç: Lojistik regresyon analizi sonucunda GKS, IMV gereksinimi, arteriyel laktat seviyesi ve YBÜ'de kalış süresi mortalite için bağımsız risk faktörleri olarak belirlendi.

Anahtar Sözcükler: *Yoğun Bakım Ünitesi, Laktat, Mortalite, Sepsis.*

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ORCID IDs: A.İ.S. 0000-0002-9300-2456, K.A. 0000-0001-6916-8408, B.S.K. 0000-0003-2624-6175, E.A.B. 0000-0003-1976-1179.

Sepsis is defined as a syndrome characterized by life-threatening organ dysfunction due to dysregulated host response to infection (1). Sepsis is a global health problem that causes the death of more than five million people a year and is frequently observed in intensive care units. Even though ratio varies among countries, its incidence has been reported to continue to increase in the last 40 years. In addition to potential distinctions in case populations, change in noticed ratios also projects diversity in recognition strategies, reach to healthcare and awareness of diagnosis. Factors such as age, gender, socioeconomic situation, comorbidities, type and location of infection influence the improvement of sepsis and also its results. Many biomarkers

[a]Yazışma Adresi: Burhan Sami KALIN, Gazi Yaşargil Eğitim ve Araştırma Hastanesi, Yoğun Bakım Kliniği, Diyarbakır, Türkiye
Tel: 0538 978 7180 e-mail: bskalin@windowslive.com
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and scoring systems are used to estimate the prognosis of septic cases due to the rapid increase in mortality and the significance of initial diagnosis and therapy. Hyperlactatemia is a widespread finding in cases with sepsis and appears in thereabout one-third of cases accepted to the critical care units (2, 3). Although serum lactate increase is not a direct measurement of tissue perfusion, it can be used in diagnosis, follow-up and prognosis as it may indicate tissue hypoxia, accelerated aerobic glycolysis caused by excessive beta-adrenergic stimulation (4, 5). Updated in October 2021 Sepsis and Septic Shock guideline suggest measuring blood lactate and guiding resuscitation to reduce serum lactate in cases with raised lactate level for adults suspected of having sepsis with weak recommendation and low quality of evidence (6). This study aimed to evaluate mortality status according to arterial lactate in septic cases hospitalized in the tertiary critical care unit.

MATERIAL AND METHOD

This retrospective and single-centre study was carried out at tertiary ICU. The study was ratified by the institutional ethic committee of our hospital (date: April 07, 2022; no.60) and informed consent from patients was not provided because of the retrospective investigation. The cases were appreciated retrospectively from March 2021 and November 2021. The critically ill patients were excluded if they were not at least 18 years of age, and were not expected to remain 24-hour critical care unit support. One hundred and ten septic patients diagnosed with sepsis followed in our intensive care unit were included in the study. Sepsis and/or septic shock was identified accordingly to the International Sepsis Definitions Conference criteria (1). The data were collected from medical electronic patient records at hospital. Patient age, gender, Acute Physiologic and Chronic Health Evaluation score (APACHE II), Sequential Organ Failure Assessment score (SOFA), Glasgow Coma scale (GCS), need for invasive mechanical ventilation (IMV) and noninvasive mechanical ventilation (NIMV) and hemodialysis (IHD: intermittent haemodialysis and/or CRRT: continuous renal replacement therapy), length of stay (LOS) in ICU, comorbid conditions, admission reasons to ICU, arterial lactate level at the time of admission to ICU and mortality status were enrolled. APACHE II score was computed by looking at the some laboratory and physiological parameters in the first 24 hours after ICU admission.

Statistical analysis

Kolmogorov-Smirnov test was used to investigate the conformity of the data to the normal distribution and continuous data were given as mean ± standard deviation or median and interquartile range. In the comparison of measurement data, independent samples t-test was used in independent groups and Mann-Whitney-U test was used in cases where normal distribution could not be achieved. Pearson Chi-Square and Fisher's exact tests analyzes were used in the analysis of the created cross tables. Binary logistic regression was applied to determine association between mortality and covariates. Patients were divided into two groups as the survivors and nonsurvivors and the differences between the two groups were analyzed for all variables. The outcomes of the regression analyses were expressed as odds ratio (OR) and 95% confidence interval (CI). A p-value less than 0.05 were presumed statistically significant. Statistical analyses were carried out using IBM SPSS version 22.0.

Power analysis

The group of patients included in this study provided 0.98 actual power and 0.72 effect size according to conventional acceptable values that for power and α are 80% or above and 5% or below, respectively. In summary, this study has sufficient power and level of effect size. The power level and effect size calculated in this study were determined using the G* Power Version 3.1.9.4.

RESULTS

Forty-four (40%) were female of 110 septic patients participated in this study. The mean age was 62 (49-72) years. Mortality rate was 58%. LOS in ICU was 4 (2-6) days. The number of patients undergoing hemodialysis (IHD and/or CRRT) was 31(28.2%). Sixty (54.5%) of the patients was diagnosed as septic shock on ICU admission. ARDS diagnosis had been in eleven of the patients on admission to ICU. The need for IMV was 70 (63.6%) and the need for NIMV was 43 (39.1%). APACHE-II score was 24±9. GCS was 11 (8-15). SOFA score was 9 (6-12). Mean lactate value was 3.5 (2.4-5.2) mmol/L. In this study, 48 (43.6%) patients had hypertension, 32(29%) patients had coronary artery disease and 27 (24.5%) patients had chronic obstructive pulmonary disease. The frequency of comorbidities was not different between survivors and nonsurvivors. Acute respiratory failure 90 (81.8%), acute renal failure 31 (28.2%) and acute coronary syndrome 20 (18.2%) were the leading reasons for admission to ICU. The frequency of admission reason to ICU was not different between survivors and nonsurvivors. Survivors had lower APACHE II score (19±6 versus 27±9, p =0.001), SOFA score (7 (5-9) versus 11 (7-14), p = 0.001) and lactate value (3 (2-4) versus 3.8 (2.8-6.4), p =0.001) as compared to nonsurvivors. Survivors had higher GCS (15 (13-15) versus 9 (6-11), p =0.001) and need for NIMV (24 (52.2%) versus 19 (29.7%), p =0.017) as compared to nonsurvivors. Nonsurvivors had higher need for IMV (57 (89.1%) versus 13 (28.3%), p =0.001), need for hemodialysis (IHD and/or CRRT) (23 (35.9%) versus 8 (17.4%), p =0.033), rate of septic shock diagnosis on admission to ICU (40 (62.5%) versus 20 (43.5%), p =0.04) and arterial lactate value (3.8 (2.8-6.4) versus 3 (2-4), p =0.001) as

compared to survivors. Detailed demographic characteristics were described in table 1.

Table 1. *Baseline characteristics of the patients.*

Variables	Total n =110	Survivors n =46	Nonsurvivors n =64	p
Age, (year), median (IQR)	62 (49-72)	63 (54-69)	61 (43-74)	0.513
Female, n (%)	44 (40)	18 (39.1)	26 (40.6)	0.875
APACHE II score, (mean±SD)	24±9	19±6	27±9	**0.001**
GCS, median (IQR)	11 (8-15)	15 (13-15)	9 (6-11)	**0.001**
SOFA score, median (IQR)	9 (6-12)	7 (5-9)	11 (7-14)	**0.001**
Need for IMV, n(%)	70 (63.6)	13 (28.3)	57 (89.1)	**0.001**
Need for NIMV, n(%)	43 (39.1)	24 (52.2)	19 (29.7)	**0.017**
Need for hemodialysis (IHD and/or CRRT), n(%)	31 (28.2)	8 (17.4)	23 (35.9)	**0.033**
Lactate level (mmol/L), median (IQR)	3.5 (2.4-5.2)	3 (2-4)	3.8 (2.8-6.4)	**0.001**
Comorbidity, n(%)				
COPD	27 (24.5)	9 (19.6)	18 (28.1)	0.443
CAD	32 (29)	12 (26)	20 (31.2)	0.303
HTN	48 (43.6)	19 (41.3)	29 (45.3)	0.704
CVD	11 (10)	5 (10.9)	6 (9.4)	0.797
CRF	23 (20.9)	8 (17.4)	15 (23.4)	0.442
DM	18 (16.4)	8 (17.4)	10 (15.6)	0.875
Malignant disease	7 (6)	3 (6.5)	4 (6.2)	0.493
Admission reason to ICU				
Renal complications, n(%)	31 (28.2)	12 (26.1)	19 (29.7)	0.679
Respiratory complications, n(%)	90 (81.8)	35 (76.1)	55 (85.9)	0.186
Cardiac complications, n(%)	20 (18.2)	10 (21.7)	10 (15.6)	0.412
Gastrointestinal complications, n(%)	14 (12.7)	3 (6.5)	11 (17.2)	0.098
Hepatobiliary complications, n(%)	13 (11.8)	5 (10.9)	8 (12.5)	0.794
Neurological complications, n(%)	19 (17.3)	5 (10.9)	14 (21.9)	0.132
Presence of septic shock diagnosis on admission to ICU	60 (54.5)	20 (43.5)	40 (62.5)	**0.04**
Presence of ARDS diagnosis on admission to ICU	11 (10)	3 (6.5)	8 (12.5)	0.354
LOS in ICU, days, median (IQR)	4 (2-6)	4 (3-5)	5 (3-13)	**0.001**

Abbreviations: n: number, y: year, p: probability, APACHE II: Acute physiologic and chronic health evaluation, GCS: Glasgow coma scale, SOFA: Sequential organ failure assessment, IMV: Invasive mechanical ventilation, NIMV: Noninvasive mechanical ventilation, IHD: Intermittent haemodialysis, CRRT: Continuous renal replacement therapy, COPD: Chronic obctructive pulmonary disease, CAD: Coronary artery disease, HTN: Hypertension, CVD: Cerebrovascular disease, CRF: Chronic renal failure, DM: Diabetes mellitus, ARDS: Acute respiratory distress syndrome, LOS: Length of stay, ICU: Intensive care unit.

In the binary logistic regression analysis, GCS, need for IMV, arterial lactate and LOS in ICU were found to be independent risk factors for mortality (OR =1.304 (1.073-1.586), p =0.008, OR =5.747 (1.501-22.002), p =0.011, OR =1.703 (1.190-2.518), p =0.004, OR =1.472 (1.042-2.213), p =0.04), respectively (Detailed demographic characteristics were described in table 2).

Table 2. *Multivariable binary logistic regression modeling of parameters for mortality.*

Variables	OR	%95 CI	p
APACHE II score	0.938	0.850-1.035	0.204
GCS	1.304	1.073-1.586	**0.008**
SOFA score	0.986	0.806-1.207	0.891
Need for IMV	5.747	1.501-22.002	**0.011**
Need for NIMV	0.778	0.232-2.610	0.684
Need for hemodialysis (IHD and/or CRRT)	0.795	0.170-3.721	0.771
Lactate	1.703	1.190-2.518	**0.004**
Presence of septic shock diagnosis on admission to ICU	0.873	0.259-2.944	0.826
LOS in ICU	1.472	1.042-2.213	**0.04**

Abbreviations: OR: Odds ratio, CI: Confidence interval, p:probability, APACHE II: Acute physiologic and chronic health evaluation, GCS: Glasgow coma scale, SOFA: Sequential organ failure assessment, IMV: Invasive mechanical ventilation, NIMV: Noninvasive mechanical ventilation, IHD: Intermittent haemodialysis, CRRT: Continuous renal replacement therapy, LOS: Length of stay, ICU: Intensive care unit.

DISCUSSION

Sepsis, which is very common in ICUs around the world, increases the mortality, causes deterioration of general condition especially in elderly patients and causes long-term acute care hospitalization and also causing serious harm to the patients and their relatives and the country's economy (7). Different factors that increase mortality can be observed in each ICU and awareness of these causes and timely intervention seriously contribute to a reduce in death ratios in the ICU. As an example, if gram-negative bacterias are the most detected agents as a source of sepsis in the ICU, mortality rates may be reduced by empirically initiated antibiotherapy for gram-negative active agents. Apart from individual factors, factors such as high lactate parameter value, use of vasopressors, or prolonged invasive mechanical ventilator support, which have been shown to be effective many times in previous studies, increase mortality (8-10). Villar et al (11) showed that invasive mechanical ventilation is one of the best predictors of mortality in ICU in their study called biological or clinical indicators for estimating ARDS and outcomes in septic cases. In the study of Clar et al (12) in which they investigated the prognostic values in community-acquired sepsis, they observed GCS<13 as a factor that increases in-hospital mortality.

In the study of Peng et al (13) it was shown that prolonged hospital stay in cases with chronic obstructive pulmonary disease increases mortality independently of other risk factors. We evaluated prognostic factors, including lactate, to identify causes of mortality in critically septic patients and similar to the results of these mentioned studies, we found that the combination of low GCS, need for IMV, LOS in ICU and arterial lactate level can predict mortality risk for ICU admission.

Lactate level is used as a global indicator of perfusion and oxygenation adequacy and microcirculatory dysfunction. A rised lactate >2 mmol/L has been associated with increased death rates. According to Surviving Sepsis Campaign Guidelines, in case of lactate levels of >4 mmol/L or systolic blood pressure of less than 90 mmHg, it should be started directly the resuscitation of the cases (6). The cause of lactate elevation may be a decrease in clearance from the body, an increase in the amount produced, or it may be possible for every two conditions to occur together. The combination of increased lactate production and decreased lactate clearance can also be observed in severe liver failure, and this condition may become more obvious with hypoperfusion due to multi-organ failure observed in sepsis. Effectively, the clearance of lactate from the body is associated with a decrease in mortality rates. Therefore, the failure to clear serum lactate level turns into a poor prognosis and understanding the cause of lactate elevation is important for increasing treatment success. Lactate levels may rise due to ischemic bowel disease, permanent mitochondrial injury, a severe untreated infection, trauma, multi-organ failure, insufficient cardiac output, damage secondary to a pharmacological agent (for example, caused by metformin), lack of thiamine levels, or other conditions (14). Filho et al (15) in their study in the ICU, showed that a lactate level of more than 2.5 mmol/L at the time of hospitalization was associated with a significant increase in 28-day mortality. Yao et al (16) demonstrated that 24 h lactate clearance rate is independent factor that influence the prognosis of critical care cases. Schork et al (17) demonstrated that one of the best indicators of death defined by ROC (Receiver Operating Characteristic) were maximum lactate in 24 hour. Kliegel et al (18) in their study of patients who survived at least 48 hours after successful cardiopulmonary resuscitation from cardiac arrest, they deduced that hyperlactatemia worsens the neurological prognosis and is also an important predictor of mortality. Lactate level may vary with laboratory derangements, vasopressor use, steroid use, drug use, trauma, multi-organ failure, infection, excessive muscle activity, burns, smoke inhalation, seizure, regional ischemia, liver dysfunction, diabetic ketoacidosis, and intravenous fluid use. The mentioned parameters could not be evaluated clearly since it is a retrospective study. The number of patients included in the study can be considered insufficient in terms of generalizing the results. The study was carried out retrospectively by scanning the files of the patients in the ICU of a single-center hospital and selection bias cannot be ruled out, making it difficult to generalize the findings to all patients.

In conclusion, our study showed that lactate level was an independent predictor of mortality in septic ICU patients.

Ethical Approval: The study was ratified by the institutional ethic committee of our hospital (date: April 07, 2022; no.60) and informed consent from patients was not provided because of the retrospective investigation.

Conflict of Interest: Authors declared no conflict of interest.

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