ORIGINAL ARTICLE

Serum lactate level may predict the development of acute kidney injury in acute decompensated heart failure

Serum laktat seviyesi, akut dekompanse kalp yetersizliğinde akut böbrek hasarının gelişmesini öngördürebilir

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ABSTRACT

Objective: Acute decompensated heart failure (ADHF) is a life-threatening medical condition and more than 30% of patients hospitalized for ADHF develop acute kidney injury (AKI), which increases the rate of both mortality and morbidity. Previous research has indicated that several biomarkers may help to predict the development of AKI. The aim of this study was to investigate the relationship between lactate level at the time of admission and AKI in ADHF patients.

Methods: A total of 154 consecutive ADHF patients were prospectively enrolled from June 2018 to December 2018, and after applying the exclusion criteria, a total of 91 patients were included in the study. The patients were divided into 2 groups: those with and without AKI.

Results: There were 63 patients in the group without AKI and 28 patients in the group with AKI. The AKI group had a higher percentage of a history of chronic kidney disease (CKD), a higher creatinine level, lower glomerular filtration rate level, lower bicarbonate level, higher lactate level, and a lower left ventricular ejection fraction compared with the non-AKI group ($p<0.05$ for all parameters). Multiple logistic regression analysis determined that CKD history (odds ratio [OR]: 4.003, 95% confidence interval [CI]: 1.295–12.371; p=0.016) and lactate level (OR: 1.545, 95% CI: 1.222–1.954; $p<0.001$) were independent predictive parameters for developing AKI.

Conclusion: An elevated lactate level may help to make an early diagnosis of AKI, an important concern in ADHF.

ÖZET

Amaç: Akut dekompanse kalp yetersizliği (ADKY) hayati tehlike arz eden bir tıbbi durumdur ve akut böbrek hasarı (ABH), ADKY nedeniyle hastaneye yatırılan hastaların %30'undan fazlasında gelişerek hem mortalite hem de morbidite oranlarını arttırmaktadır. Önceki çalışmalar ABH'nin gelişimini öngörmek için çeşitli biyobelirteçler kullanılabileceğini bildirmiştir. Biz bu çalışmada, ADKY hastalarında başvuru sırasındaki laktat düzeyleri ile ABH arasındaki ilişkiyi araştırmayı amaçladık.

Yöntemler: Haziran 2018 ile Aralık 2018 arasında ardışık toplam 154 ADKY hastası çalışmaya ileriye yönelik olarak alındı ve dışlama kriterleri sonrasında toplam 91 hasta incelendi. Hastalar ABH gelişen ve gelişmeyen olmak üzere iki gruba ayrıldı.

Bulgular: Hastalar ABH gelişmeyen 63, ABH gelişen 28 hasta olmak üzere iki gruba ayrıldı. ABH gelişen grupta, ABH gelişmeyen gruba göre daha yüksek kronik böbrek hastalığı öyküsü, daha yüksek kreatinin seviyeleri, daha düşük GFR seviyeleri, daha düşük HCO3 seviyeleri, daha yüksek laktat seviyeleri ve daha düşük LVEF değerleri vardı (tüm parametreler için $p<0.05$). Akut böbrek hasarının gelişmesinde bağımsız belirleyicileri belirlemek için çoklu lojistik regresyon analizi yapıldı. KBH öyküsü (odds oranı [OO] 4.003, %95 GA [güven aralığı] 1.295–12.371, p=0.016) ve laktat seviyeleri (OO 1.545, %95 GA 1.222–1.954, $p<0.001$) akut böbrek hasarının gelişmesinde bağımsız öngördürücü parametreler olarak saptandı.

Sonuç: Akut böbrek hasarı ADKY hastalarında en büyük sorunlardan biridir ve yüksek laktat seviyeleri akut böbrek hasarının erken teşhisinde yardımcı olabilir.

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Acute decompensated heart failure (ADHF) is a life-threatening medical condition defined as the sudden onset or worsening of the symptoms and signs of heart failure.[1] Early recognition of ADHF and early application of pharmacological and non-pharmacological treatment are of great importance in the prognosis.[1] Despite appropriate medical treatment, the 1-year mortality rate of ADHF in various registries is approximately 20% to 30%.[2,3] Furthermore, acute kidney injury (AKI) develops in more than 30% of patients hospitalized for ADHF, which increases both mortality and morbidity. A diagnosis of AKI would be considered in the decision-making process for the selection or withdrawal of therapeutic agents used in the treatment of ADHF, such as diuretics and renin-angiotensin-aldosterone system (RAAS) blockers.[4–6] Therefore, prevention and early recognition of AKI in ADHF patients are important.

In ADHF patients, arterial blood gas (ABG) test parameters deteriorate due to both impaired gas exchange in the lungs and decreased tissue perfusion resulting from the low cardiac output.[7] It has been suggested that they may be utilized to evaluate the efficacy of ADHF treatment as many studies have shown that ABG parameters, including the levels of pH, lactate, and partial pressure of carbon dioxide, were of prognostic value in ADHF patients.[8,9] Decreased oxygen delivery, reduced cardiac output, and subsequent tissue hypoperfusion elevate the serum lactate level in ADHF.[10,11] One of the pathomechanisms in the development of AKI in ADHF patients, as in lactate elevation, is organ hypoperfusion and renal hypoperfusion, and consequently, these changes may be reflected in deterioration of kidney function.[12]

Previous studies have determined that the level of lactate may serve as a useful marker for predicting AKI in patients undergoing cardiac surgery.[13] The objective of this study was to investigate the relationship between lactate level at the time of hospital admission and AKI in ADHF patients.

METHODS

A total of 154 consecutive ADHF patients were prospectively enrolled from June 2018 to December 2018 at a single study center. ADHF was diagnosed based on the current European Society of Cardiology guidelines.[1] ADHF was defined as the sudden onset or worsening of the symptoms and signs of heart failure.[1] Patients who had acute coronary syndrome; had undergone invasive procedures requiring contrast administration; had received intermittent/continuous renal placement therapy; had a systolic blood pressure <90 mmHg; had a diagnosis of sepsis or systemic inflammatory, hepatic, or neoplastic disease; and those for whom an ABG test was performed after receiving initial treatment were excluded from the study. This study was performed according to the principles of the Declaration of Helsinki after receiving the approval of our institutional ethics committee.

Abbreviations:

ABG	*Arterial blood gas*
ADHF	*Acute decompensated heart failure*
AKI	*Acute kidney injury*
AUC	*Area under the curve*
CKD	*Chronic kidney disease*
CI	*Confidence interval*
eGFR	*Estimated glomerular filtration rate*
GFR	*Glomerular filtration rate*
HCO3	*Bicarbonate*
KDIGO	*Kidney Disease: Improving Global Outcomes*
LVEF	*Left ventricular ejection fraction*
OR	*Odds ratio*
RAAS	*Renin-angiotensin-aldosterone system*

In the emergency setting and at the time of admission, all of the study patients underwent an ABG analysis, including evaluation of the pH, lactate, bicarbonate (HCO3), and oxygen saturation levels. Other blood samples were also collected on admission to carry out hematologic tests and biochemistry tests. The estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation.[14] AKI was defined according to the Kidney Disease: Improving Global Outcomes (KDIGO) criteria as a creatinine increase of more than 0.3 mg/dL or a 20% reduction in eGFR during the hospital stay.[15] Chronic kidney disease (CKD) was defined according to current international guidelines: decreased kidney function evidenced by a GFR of <60 mL/min/1.73 m^2.[15] Echocardiography was performed on all of the study patients, and the left ventricular ejection fraction (LVEF) was assessed with the Simpson method.

Statistical analysis

All values were expressed as mean±SD or median (25^{th}-75^{th} percentile), or as a percentage. The normality of the distribution of the data was assessed with the Kolmogorov-Smirnov test. For the non-normally distributed variables, the comparison of groups was performed using nonparametric tests. Comparisons of continuous variables between the 2 study groups were performed using Student's t-test or the Mann-Whit-

ney U test. The distribution of categorical variables was compared with a chi-square test. Finally, multiple logistic regression analysis was performed to determine independent predictors of developing AKI. The correlation of continuous variables was analyzed using Spearman and Pearson correlation analyses. All of the statistical analyses were performed with IBM SPSS Statistics for Windows, Version 21.0 software (IBM Corp., Armonk, NY, USA). A p value of <0.05 was considered statistically significant.

RESULTS

A total of 154 patients were enrolled during the study period. The exclusion criteria eliminated 26 patients because the ABG test was performed after initial treatment, 12 patients due to acute coronary syndrome or invasive procedures requiring contrast administration, 6 patients who had received intermittent/continuous renal placement therapy, 12 patients with a systolic blood pressure <90 mmHg, and 7 patients due to a diagnosis of sepsis or systemic inflammatory, hepatic, or neoplastic disease. A total of 91 patients were included in the study. The patients were divided into 2 groups: 63 patients without AKI were designated as the non-AKI group, and 28 patients with AKI were allocated to the second group. The clinical and demographic characteristics and laboratory findings of the patients are summarized in Table 1. The normal

Table 1. Baseline clinical, echocardiographic, and laboratory characteristics of the study population

Variable	All (n=91)	AKI (-) (n=63)	AKI (+) (n=28)	*p*
Demographics				
Age, years	71.4±10.4	70.6±11.4	73.3±7.5	0.251
Gender, n (%)				
Male	45 (49)	32 (51)	13 (46)	0.821
Female	46 (51)	31 (49)	15 (54)	
DM, n (%)	38 (42)	25 (40)	13 (46)	0.646
Smoker, n (%)	42 (46)	32 (51)	10 (36)	0.255
Previous coronary artery disease, n (%)	61 (67)	43 (68)	18 (64)	0.810
Chronic kidney disease history, n (%)	41 (45)	22 (35)	19 (68)	0.006
Laboratory values				
Creatinine (mg/dL)	1.38±0.71	1.25±0.47	1.68±1.01	0.007
GFR (mL/min/1.73 m^2)	53.8±21.8	57.7±21.8	45.2±19.7	0.011
Hemoglobin (g/dL)	11.8±1.9	12±2.2	11.5±1.4	0.297
WBC (10^9/L)	12.7±4.4	12.3±4.5	13.6±4.1	0.208
AST (U/L)	37.2±36.3	33.8±23.7	45.1±54.8	0.171
ALT (U/L)	28.4±32.2	26.1±17.8	33.9±51.8	0.284
Arterial blood gas values				
SaO2 (%)	83.2±6	83±6.2	83.6±5.9	0.681
pH	7.24±0.09	7.26±0.09	7.22±0.08	0.116
HCO3 (mmol/L)	19.1±3.6	19.8±3.6	17.2±3	0.001
Lactate (mmol/L)	3.9±2.6	3.1±1.9	5.7±3	<0.001
LVEF (%)	37.4±10.8	39.3±10.8	33.2±9.8	0.013
Clinical outcomes				
Length of hospital (days)	7.2±3.5	5.5±2.1	10.9±2.9	<0.001
Renal replacement therapy, n (%)	8 (9)	–	8 (29)	<0.001
In-hospital mortality, n (%)	16 (18)	4 (6)	12 (43)	<0.001

AKI: Acute kidney injury; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; DM: Diabetes mellitus; GFR: Glomerular filtration rate; HCO3: Bicarbonate; LVEF: Left ventricular ejection fraction; SaO2: Oxygen saturation; WBC: White blood cell.

Table 2. The result of multivariate logistic regression analysis for the prediction of acute kidney injury

Variable	Odds ratio	Confidence interval	*p*
History of chronic kidney disease	4.003	1.295–12.371	0.016
Left ventricular ejection fraction	0.966	0.916–1.019	0.205
Lactate	1.545	1.222–1.954	<0.001

reference range of the lactate value in our laboratory was 0.5–1.6 mmol/L. Values above this reference were considered high. The AKI group had a higher percentage of CKD history, a higher creatinine level, lower GFR level, lower HCO3 level, higher lactate level, and lower LVEF compared with the non-AKI group (p<0.05 for all parameters). Also, the length of hospital stay was longer in the AKI group (5.5±2.1 days vs. 10.9±2.9 days, respectively; p<0.001). Renal replacement therapy was performed in 8 (29%) AKI patients, which was a significant difference between the groups (29% vs. 0%; p<0.001). In-hospital mortality was also significantly greater in the AKI patients compared with the non-AKI group (43% vs. 6%, respectively; p<0.001).

Univariate correlation analysis revealed a moderately inverse correlation between the lactate and HCO3- levels (r=-0.657; p<0.001). No significant correlations were found between the lactate and creatinine levels (r=0.040; p=0.708).

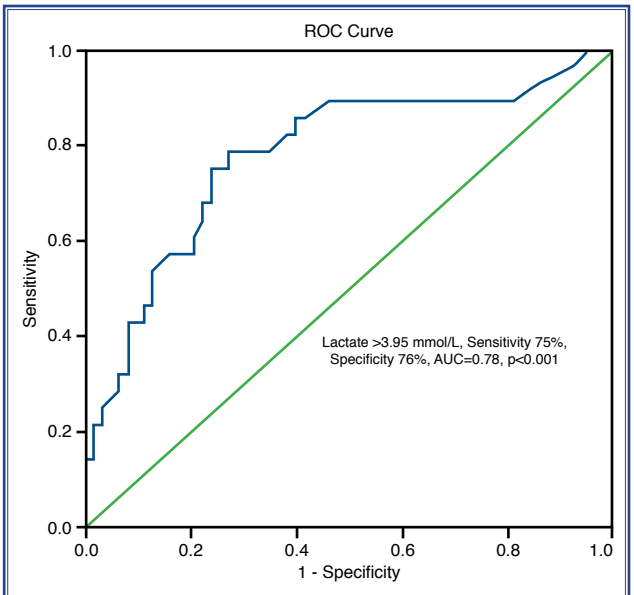

Figure 1. Receiver operating characteristic (ROC) curve analysis of the lactate level to predict the development of acute kidney injury. AUC: Area under the curve.

Multiple binary logistic regression analysis was performed to determine independent predictors of developing AKI. In the univariate correlation analysis, a close relationship was observed between the lactate and HCO3 levels. Therefore, HCO3 was excluded from the multivariate analysis. CKD history, LVEF, and lactate level were evaluated with multivariate binary logistic regression analysis, which revealed that CKD history (OR: 4.003, 95% CI: 1.295–12.371; p=0.016) and lactate level (OR: 1.545, 95% CI: 1.222–1.954; p<0.001) were independent predictive parameters for developing AKI (Table 2).

Receiver operating characteristic curve analysis demonstrated that a lactate level of >3.95 mmol/L predicted the development of AKI with 75% sensitivity and 76% specificity (area under the curve [AUC]: 0.78; p<0.001) (Fig. 1).

DISCUSSION

ADHF is a life-threatening clinical disorder with a poor prognosis.[16,17] AKI develops in approximately 30% of ADHF patients in the hospital, resulting in increased rates of mortality and morbidity.[4–6] As a result of AKI development, therapeutic agents such as diuretics and RAAS inhibitors may be excluded from the treatment regimen for ADHF.[4–6] The length of stay in the hospital and the intensive care unit is prolonged in these patients, which also contributes to increased morbidity and mortality.

The development of acute renal failure in ADHF patients complicates patient management and worsens the prognosis. The ability to identify patients with a high risk of AKI may help to reduce the mortality and morbidity of ADHF. Previous studies have shown that patient follow-up monitoring the creatinine level and urine output was too limited to make an early diagnosis of AKI.[18,19] Both of these parameters change slowly with AKI, and they are not sufficiently sensitive to draw conclusions. Therefore, various urinary and plasma markers have been studied to de-

termine whether their use would be more beneficial in establishing an early diagnosis of AKI in ADHF patients. Studies have reported that urinary biomarkers, such as neutrophil gelatinase-associated lipocalin, urinary angiotensinogen, and brain natriuretic peptide; serum albumin; and risk scoring methods could be used to predict the development of AKI.[19,20] Research has also shown that ABG parameters, such as acid-base balance, hypoxia, and hypercarbia, and increasing lactate levels can be beneficial in making a differential diagnosis, performing a risk classification, and evaluating treatment efficacy in ADHF patients.[8,9,21,22] However, the relationship between lactate level and AKI has not yet been examined. In our study, we initially hypothesized that the lactate level measured in an ABG test on admission might predict AKI development, and our results showed that the lactate level demonstrated an independent predictive value of AKI development.

A high lactate level has been shown to have independent predictive value for mortality in various clinical situations, including acute coronary syndrome, trauma, intensive care unit stay, and cirrhosis.[22–25] Furthermore, many studies have reported that a high lactate level was an independent predictor of hospital mortality in ADHF patients. Kawase et al.[22] found that a lactate level of >3.2 mmol/L in ADHF patients significantly contributed to a high in-hospital mortality rate. Our findings also revealed that the initial lactate level may allow for the identification of those ADHF patients at the greatest risk for developing AKI.

Several components may clarify the relationship between lactate level and AKI. The causes of AKI in ADHF are multifactorial. One major cause is the low cardiac output.[12] The kidneys are highly prone to ischemic injury.[26] AKI caused by renal hypoperfusion develops due to a reduction in cardiac output in ADHF patients.[26] Based on this information, we thought that the lactate level, which is an indicator of tissue hypoperfusion, might predict AKI. The tissue hypoperfusion and anaerobic respiration in ischemic tissues due to low cardiac output in ADHF causes the lactate levels to increase.[10,11]

The relationship between lactate level and acute renal failure has been in examined several studies. Mitchell et al.[13] showed that an intraoperatively elevated lactate level (mean: 2.7±2 mmol/L, OR: 1.44, 95% CI: 1.15–1.82) was a risk factor for developing postoperative AKI in patients undergoing elective coronary artery bypass grafting. In another study, a peak lactate level of >4 mmol/L was associated with a high probability for AKI in low-risk cardiac surgery patients (OR: 6.330, 95% CI: 1.957–20.473; p<0.001).[27] In our study, the lactate level (OR: 1.545, 95% CI: 1.222–1.954; p<0.001) was determined to be an independent predictive parameter for the development of AKI and a lactate level of >3.95 mmol/L predicted AKI with 75% sensitivity and 76% specificity (AUC: 0.78; p<0.001).

In addition to the level of lactate, our results demonstrated that a positive history of CKD had predictive value in the development of AKI. The relationship between basal renal function and AKI is controversial. Some studies have shown that basal creatinine and GFR values were not associated with AKI, though they are accepted as risk factors for death and rehospitalization.[26,28] In the ESCAPE trial (Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness), Nohria et al.[28] observed that basal renal parameters did not have a predictive value for declining renal function in patients with decompensated heart failure. However, other studies have shown that impaired renal function on admission had an independent predictive value for AKI. In the Pre-RELAX study (Preliminary study of RELAXin in Acute Heart Failure), Voors et al.[29] found that the basal creatinine level was a risk factor for deterioration in renal function (OR: 1.41, 95% CI: 1.04–1.93; p<0.0297). Similarly, in our study, a positive CKD history was determined to be an independent predictor for the development of AKI. In our opinion, it is not surprising that a pre-existing diagnosis of CKD is an independent marker of AKI in patients with ADHF.

There are several limitations to our study. First, the number of patients included was relatively small. Second, the data analysis was performed only to evaluate outcomes during hospitalization (the development of AKI, the emerging need for renal replacement therapy, and in-hospital mortality), which did not allow for compiling detailed information about short- and long-term prognosis. Perhaps the major limitation of our study is that only creatinine and GFR values were taken into consideration while evaluating AKI; urine output was not evaluated. Previous reports have

shown that an increase in creatinine and kidney function known as pseudo-worsening renal function was not associated with a poor prognosis in ADHF.[26] The primary means of discerning pseudo-worsening renal function status from AKI is to assess whether increased urine output continues. Finally, hemodynamic parameters that could account for the development of AKI, such as stroke volume and cardiac output, could not be assessed in this study.

Conclusion

AKI is a significant problem in ADHF and contributes to greater morbidity and mortality. Early detection of patients with acute renal failure may play an important role in improving disease outcomes in patients with ADHF. An elevated lactate level observed in an ABG test at admission may help to make an early diagnosis of AKI. However, further investigations are needed to support this conclusion.

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Keywords: Acute decompensated heart failure; acute kidney injury; lactate.

Anahtar sözcükler: Akut dekompanse kalp yetersizliği; akut böbrek hasarı; laktat.