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The Effect of High Lactate Level on Mortality in Acute Heart Failure Patients With Reduced Ejection Fraction Without Cardiogenic Shock

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Abstract

Background We aimed to determine the effect of blood lactate levels on cardiovascular (CV) death and hospitalization for heart failure (HF) in acute HF patients with reduced left ventricular ejection fraction (EF).

Methods Eighty-five acute HF patients with reduced ejection fraction were divided into two groups according to admission blood lactate levels. 48 of them had low blood lactate levels (< 2 mmol/l) and 37 of them had high blood lactate levels (≥ 2 mmol/l). Patients with acute coronary syndrome, cardiogenic shock, sepsis and low blood pressure at admission were excluded from the study. Primary endpoint is the composite of cardiovascular (CV) death and hospitalization for heart failure (HHF) in 6-month follow-up. Secondary endpoint is the change in NT-proBNP levels from admission to 72 h.

Results Baseline characteristics of patients were similar in two groups. On baseline echocardiographic evaluation; patients with high lactate revealed a higher mitral *E*/*A* ratio (2.34 [0.43–3.31], $p = 0.008$) and a lower TAPSE ratio (14 [10–27], $p = 0.008$) than patients with low lactate levels. Over a median follow-up period of 6 months, the primary end point occurred in 28 (75.7%) of 37 patients assigned to high lactate group and in 20 (41.7%) of 48 patients assigned to low lactate group ($p = 0.006$). High lactate levels significantly increased the risk of CV death and HHF at 6 months by nearly 5.35-fold in acute HF patients with reduced EF. The change in NT-proBNP levels at 72nd hour after admission were similar between two groups.

Conclusion Higher lactate levels at admission related with higher HHF at 6 months and may be related with higher risk of CV death in acute HF patients with reduced EF.

Keywords Lactate · Acute heart failure · Hospitalization · Death

Introduction

Acute heart failure (HF) is defined as the acute onset or alteration of heart failure signs and symptoms and it is a life-threatening condition, which requires immediate medical intervention and usually hospital admission [1, 2]. The concept "acute" is variable; while deterioration of the symptoms (eg. dyspnea or edema) develops within days or weeks in some patients, HF may develop within hours or minutes in some others [e.g., acute myocardial infarction-related HF)] [2]. Patients may manifest in varying presentations from life-threatening pulmonary edema or cardiogenic shock to increased peripheral edema [2]. The number of hospitalizations for heart failure (HHF) is more than one million per annum both in the USA and Europe [3]. Hospitalization for heart failure is an indicator of unstable heart failure. Patients with acute heart failure (AHF) are re-hospitalized at a rate of 30% and the yearly mortality is about 30% [4]. Hospitalization for heart failure represents 60–74% of the total cost of heart failure due to its frequency and severity [5]. The number of the patients who present to the emergency room for AHF is gradually increasing due to the aging population and the increased number of patients with asymptomatic left ventricular dysfunction and HF [6]. It still has a high morbidity and mortality rate despite the developments in medical and device treatments. AHF is an important public health problem and has a high financial cost. The in-hospital

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mortality of acute HF is between 4 and 7% and mean duration of hospital stay is 4–11 days [7]. The thirty-day mortality rate after discharge was found to be 11.1% and one-year mortality was determined as 36% in the ADHERE study [8].

Lactate is used for determination of the disease severity and measurement of the response to therapeutic interventions. Lactate is produced by the lactate dehydrogenase enzyme from pyruvate, the final product of glycolysis. Lactate is produced in many tissues in the body, but mainly in muscle tissue. Lactate is rapidly cleared by the liver and in lower amounts by the kidneys under normal conditions [9]. Elevated lactate may result from increased production, decreased clearance or both. Although the mechanism of the development of lactic acidosis in HF is not clear, it may result from an insufficient oxygen supply to the tissues due to insufficient cardiac output and thereby hypoxia development followed by anaerobic glycolysis and conversion of pyruvate to lactate [10]. An elevated lactate level is an indicator of tissue hypoxia. A limited number of studies is available in the literature investigating the effect of the lactate level in patients with heart failure despite the large number of studies investigating the effect of the lactate level on mortality in intensive care unit patients. Kawase et al. demonstrated a significant relationship between the in-hospital mortality and the serum lactate levels in AHF patients who did not have acute coronary syndrome (ACS) [11]. The serum lactate level was reported to be useful for the prediction of the early mortality risk in patients who were hospitalized in the intensive care unit due to acute decompensated heart failure (ADHF) [11]. However, this study also included the patients in shock. Zymlinski et al. reported that an elevated serum lactate was seen frequently without the evidence of peripheral hypo-perfusion and that it was associated with a poor prognosis [12].

The present study was conducted with the aim of investigating the effect of the serum lactate level, which is an indicator of tissue hypoxia in patients hospitalized due to AHF with reduced ejection fraction without shock, on HHF.

Methods

This was a single-center prospective study conducted at the Cardiology Department of Mersin University between December 2018 and March 2019 after having obtained the ethics committee approval (date: 11.01.2018, project number: 2018/14).

The study population includes male and female patients (≥ 18 years old) admitted to the hospital for AHF with dyspnoea, congestion on chest radiograph, and elevated NT-proBNP. 85 patients without shock and whose systolic blood pressure was above 100 mmHg that had been hospitalized at the Coronary Care Unit of Mersin University Hospital were included in the study after written informed consents had been obtained. A clinical diagnosis of AHF was accepted as at least 1 sign and 1 symptom of AHF (e.g. dysponea, congestion, oedema, pulmonary rales/crackles/crepitations and with an N-terminal pro-B-type natriuretic peptide (NT-proBNP) level of 1000 pg/ml.

The inclusion criteria were as follows:

1. The patients who had been hospitalized at the Coronary Care Unit of Mersin University due to AHF.
2. Patients 18 years of age and above.
3. Patients with EF $\leq 40\%$ determined on echocardiography.
4. Patients who gave informed written consent.
5. Patients whose systolic blood pressure at admission was ≥ 100 mmHg.

The exclusion criteria were as follows:

1. Patients under 18 years of age.
2. Patients who did not give written informed consent.
3. Patients who had cardiogenic shock or a systolic blood pressure of < 100 mmHg at admission.
4. Patients with a history of acute coronary syndrome, myocardial infarction, coronary artery by-pass surgery, percutaneous coronary angioplasty and stroke during the recent 3 months.
5. Patients with EF $> 40\%$ determined on echocardiography.
6. Patients who had an active infection.
7. Patients who had a malignancy without cure during the recent 5 years.
8. Pregnant or breastfeeding women.
9. Patients who had end-stage renal failure (GFR < 15 ml/min/1.73 m^2) and who received hemodialysis.
10. Patients who were in the waiting list for cardiac transplantation, who had a supportive device or for whom receiving support was planned.
11. Patients with primary hepatic failure, biliary cirrhosis and cholestasis.

Patients with a blood pressure either systolic 140 mmHg or diastolic 90 mmHg in two or more blood pressure measurements and/or those using antihypertensive drugs were considered to have hypertension. Patients under treatment for diabetes mellitus and those with a fasting glucose above 126 mg/dl in two consecutive measurements and/or HbA1c $> 6.5\%$ were accepted as having diabetes mellitus. Atrial fibrillation/flutter was accepted as present if the patient had irregular RR intervals and no distinct *p* values on electrocardiography at admission. Chronic kidney disease was accepted as present if the patients had decreased kidney function (glomerular filtration rate below 90 ml/min per 1.73

m^2) for 3 or more months before study admission. Ischemic etiology for HF was accepted as present in patients with left ventricular dysfunction result from coronary artery disease (history of myocardial infarction or revascularization). Patients' medical history was accepted present if they were on standart HF therapy at least 1 month before qualifying HF decompensation. All patients underwent trans-thoracic echocardiography at the time of admission and at 72nd hour of hospitalization. The left ventricle diameters, volumes, diastolic filling parameters and the right ventricle functions were recorded. Biochemical values, N-terminal pro Type B natriuretic peptide (NT-proBNP), venous lactate levels and arterial blood gas values were recorded at the time of admission and at the 72nd hour of hospitalization. Treatment of the patients was carried out in accordance with the current guidelines. The patients were divided into groups according to the lactate levels on admission as those with <2 mmol/l and ≥ 2 mmol/l. The primary endpoint is the composite of CV death and HHF in the 6-month follow-up. The secondary endpoint is the change in the NT-proBNP levels from randomization to 72 h.

Patients are assessed daily while hospitalized through day 3 or discharge. They are also assessed at days 14 (phone contact), 30, 90 (phone contact), and 180. All deaths and hospitalizations reported through day 180 are adjudicated by a two cardiologist. Re-hospitalization is defined as an unplanned hospitalization (including admission to a hospital or any attendance in an acute care setting, e.g. emergency department, or in another health care facility) of 24 h or greater, regardless of whether the patient was admitted to the hospital. CV death includes death resulting from an acute myocardial infarction (MI), sudden cardiac death, death due to pump failure, death due to stroke, death due to cardiovascular (CV) procedures, and death due to other CV causes. Death reviews were conducted by two cardiologists with hospitalization and emergency department records, imaging and laboratory reports, physicians' notes, death certificates, and autopsy/medical examiners' reports. In selected cases, family members or other caregivers who were present at the time of death were interviewed to gather additional details.

Statistical Analysis

Statistical analyses were carried out using the IBM SPSS statistics 22.0 program. Variables with a normal distribution were expressed as mean ± standard deviation and the variables that were not distributed normally were expressed as median, minimum and maximum values, and the categorical variables were expressed as numbers and percentages. The statistical significance of the inter-group differences was evaluated with the *t* test, the Mann–Whitney *U* test or the chi-square test. The odds ratio and the 95% confidence interval were calculated with the multiple logistic regression analysis for all factors that affected the end points. The Kaplan–Meier curve was formed for cardiovascular death and re-hospitalization for decompensated HF. A p level of <0.05 was accepted as statistically significant.

Results

A total of 85 patients were included in the study. The serum lactate level on admission was <2 mmol/l in 48 patients and ≥ 2 mmol/l in 37 patients. The baseline patient characteristics have been summarized in Table 1. 28.2% of study patients had de novo HF and 71.8% of them had chronic HF. There was no singificant difference between two groups (Table 1). 23.5% of patients were hospitalized first in their life due to AHF in low lactate group and 21.2% of patients in high lactate group ($p=0.523$). The mean time of hospital stay due to AHF were similar between two groups (Table 1). The arterial blood gas values were found to be similar in both groups. While the median *E*/*A* value of the group with low lactate level was 1.66 [0.52–3.42], it was found to be 2.34 [0.43–3.31] for the other group ($p=0.008$). The TAPSE value was significantly higher in the group with low lactate level. The echocardiographic data have been summarized in Table 2.

Over a median follow-up period of 6 months, the primary end point occurred in 28 (75.7%) of 37 patients assigned to the high lactate group, and in 20 (41.7%) of 48 patients assigned to the low lactate group ($p=0.006$). No statistically significant difference was found between the groups with regard to CV death ($p=0.562$). A statistically significant difference was determined between the groups with regard to re-hospitalization due to decompensated HF ($p=0.006$) (Table 3). When the groups were compared with regard to the 180-day follow-up, a significant difference was determined with regard to CV death and HHF (log rank: 0.014) (Fig. 1).

In the binary logistic regression analysis, the baseline urea value, history of hypertension, the baseline albumin value, the proBNP value at the baseline and the 72nd hour and baseline serum lactate levels were found to be independent risk factors for cardiovascular death and HHF (Table 4).

The factors that influence the CV death at 180 days have been presented in Table 5. Each decrease in LVEF increases the cardiovascular death by 1.2-fold. The baseline serum urea value and the serum ALT level were found to be the other independent factors that affect the CV death (Table 5). The baseline serum lactate level of ≥ 2 mmol/l led to a 5.38-fold increase and not receiving MRAs led to a 3.5-fold increase in re-hospitalization at 180 days (Table 6).

Table 1 General characteristics of the study population and comparison of the patients whose lactate level was < 2 mmol/l and ≥ 2 mmol/l on admission

	Low lactate group, $n=48$	High lactate group, $n=37$	p value
Age	70.39 ± 12.46	67.56 ± 11.43	0.286
Male gender, *n* (%)	30, 62.50	27, 73	0.308
Systolic blood pressure	130.37 ± 22.44	125.64 ± 21.53	0.330
Diastolic blood pressure	80.75 ± 13.77	77.81 ± 14.22	0.339
Heart rate	89.43 ± 19.6	86.40 ± 16.96	0.456
History of disease, *n* (%)			
HT	28, 58.3	25, 67.6	0.384
DM	23, 47.9	18, 48.6	0.947
AF	18, 37.5	11, 29.7	0.454
CKD	14, 29.2	12, 32.4	0.746
Ischemic etiology	28, 58.3	27, 73	0.161
De novo HF, *n* (%)	14, 16.5	10, 11.8	0.829
Hospital stay (day)	5.66 ± 3.32	5.91 ± 3.36	0.731
History of medicine (%)			
ACEi/ARB	21, 43.8	20, 54.1	0.346
Beta-blocker	34, 70.8	27, 73	0.828
Furosemide	33, 68.8	30, 81.1	0.198
CaBl	9, 18.8	4, 10.8	0.313
Digoxin	7, 14.6	10, 27	0.155
MRA	15, 31.3	9, 24.3	0.482
Ivabradin	5, 10.4	4, 10.8	0.953
Long-acting nitrate	7, 14.6	9, 24.3	0.255
Laboratory results			
Creatinine	1.23 [0.45–3.71]	1.02 [0.54–3.69]	0.272
Na	136.37 ± 6.28	136.30 ± 5.96	0.956
K	4.61 ± 0.55	4.50 ± 0.45	0.313
Ca	8.94 ± 0.67	8.91 ± 0.70	0.836
Mg	2.04 ± 0.40	2.07 ± 0.33	0.677
NT-proBNP	11,150 [631–35,000]	11,200 [1533–35,000]	0.866
Arterial blood gas			
Ph	7.38 ± 0.079	7.39 ± 0.077	0.738
pCO_2	41.10 ± 13.51	38.93 ± 12.96	0.458
pO_2	73.42 ± 17.76	79.65 ± 21.10	0.144
SO_2	93.04 ± 5.33	93.44 ± 4.98	0.725
hCO_3	24.50 ± 5.72	23.42 ± 4,96	0.362

Normally distributed values are presented as mean ± standard deviation, non-normally distributed values are presented as median (minimum–maximum)

HT hypertension, *DM* diabetes mellitus, *AF* atrial fibrillation, *CKD* chronic kidney disease, *ACEi/ARB* angiotensin-converting enzyme inhibitors, *ARB* angiotensin receptor blockers, *CaBl* calcium channel blockers, *MRA* minelarocorticoid receptor antagonist, *NT-proBNP* N-terminal pro Type B natriuretic peptide, non-parametric distribution analyzed by Mann–Whitney *U* test

Discussion

In the present study, the participants were allocated to two groups according to the serum lactate level (≥ 2 mmol/l and < 2 mmol/l) and compared with regard to CV death and rate of HHF. The patients were followed up for 180 days. The patients with elevated baseline serum lactate level were found to have a higher composite end point of CV death and HHF compared to patients with low baseline lactate values. Statistical significance was found on the rate of HHF and no significant difference was determined in mortality between the groups.

Bakker et al. showed that serum lactate elevation was found to be related to survival more than the other factors [13]. In another study, the authors indicated that the serum lactate level was a parameter of risk classification, both in the emergency room and the intensive care units [14]. Khosravani et al. divided the ICU patients into those

Table 2 Echocardiography findings of the patients according to groups

Echocardiography parameters	Low lactate group, $n=48$	High lactate group, $n=37$	p value
LVEF (%)	27.79 ± 7.42	25.24 ± 8.22	0.138
Diastolic diameter (cm)	6.19 ± 0.94	6.16 ± 0.80	0.859
Mitral *E/A*	1.66 [0.52:3.42]	2.34 [0.43–3.31]	0.008
Mitral *E/e′*	17.42 [9.6–45]	17.80 [8–40]	0.554
LAV (ml)	113.5 [53–199]	117 [56–300]	0.629
LVEDV (ml)	126.5 [45–365]	133.5 [47–310]	0.971
LVESV (ml)	95 [27–342]	104,5 [33–243]	0.638
TAPSE (mm)	18 [10–27]	14 [10–27]	0.008
esPAP (mmHg)	45 [20–85]	45 [25–80]	0.161

Normally distributed values are presented as mean ± standard deviation, non-normally distributed values are presented as median (minimum–maximum)

LVEF left ventricular ejection fraction, *Mitral E/A* the ratio of peak early (E) and late (A) filling velocity, *Mitral E/e′* the ratio of early mitral inflow velocity and mitral annuler early diastolic velocity, *LAV* left atrial volume, *LVEDV* left ventricular end-diastolic volume, *LVESV* left ventricular endsystolic volume, *TAPSE* tricuspid annular plane systolic excursion, *esPAP* estimated systolic pulmonary artery pressure

Table 3 Inter-group comparisons of the study population at the end points

	Low lactate group, $n=48$	High lactate group, $n=37$	p value
Cardiovascular death, *n* (%)	8, 16.7	8, 21.6	0.562
Re-hospitalization for HF, *n* (%)	12, 25	20, 54.1	0.006
Composite end point, *n* (%)	20, 41.7	28, 75.7	0.002

HF heart failure

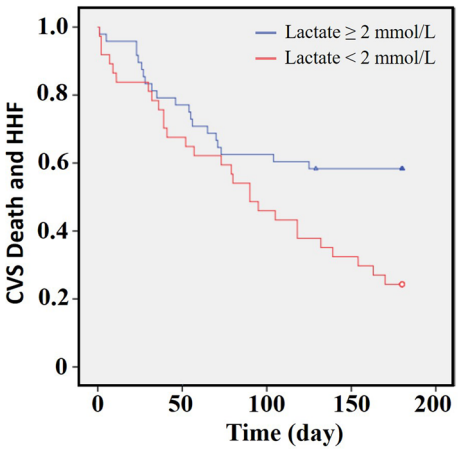

Fig. 1 Kaplan–Meier curve showing 180-day CV death and HHF in patients presenting acute heart failure with and without elevated lactate defined as blood lactate ≥ 2.0 mmol/l

Table 4 The factors influencing the composite end point of CV death and HHF in acute heart failure patients

	Odds ratio (HR)	p value
Baseline urea	1.045 (1.013–1.078)	0.006
Baseline creatinine	1.875 (0.096–36.782)	0.670
History of hypertension	23.083 (2.406–221.496)	0.007
Baseline systolic blood pressure	0.987 (0.937–1.039)	0.609
Baseline albumin	0.026 (0.002–0.293)	0.003
Baseline AST	1.020 (0.898–1.159)	0.758
Baseline serum lactate	5.35 (1.243–23.093)	0.024
Δ NT-proBNP	0.984 (0.968–1.00)	0.049
Δ lactate	0.992 (0.969–1.016)	0.507

AST aspartate aminotransferase, *NT-proBNP* N-terminal pro Type B natriuretic peptide, *Δ proBNP* the reduction in baseline proBNP rate at 72nd hour, *Δ lactate* the reduction in baseline lactate at the 72nd hour

Table 5 The factors affecting the cardiovascular death

	Odds ratio (HR)	p value
LVEF	0.833 (0.726–0.956)	0.009
Baseline urea levels	1.047 (1.014–1.080)	0.005
Baseline creatinine	0.211 (0.030–1.475)	0.117
Baseline AST	0.987 (0.973–1.000)	0.058
Baseline ALT	1.021 (1.001–1.042)	0.042
Baseline NT-proBNP	1.00 (1.00–1.00)	0.236

LVEF left ventricular ejection fraction, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *NT-proBNP* N-terminal pro Type B natriuretic peptide

who had undergone cardiac surgery, who had trauma and neurologic diseases, who had directly been transferred to the ICU from the operating room and those with APACHE score II, and evaluated the patients according to the serum lactate levels on admission and during the follow-up period. The serum lactate level was shown to be an independent risk factor for death in patients who

Table 6 The factors affecting the hospitalization for heart failure

	Odds ratio (HR)	*p* value
Baseline serum lactate	5.38 (1.915–15.138)	0.001
Usage of MRAs	3.5 (1.132–10.860)	0.030
Baseline ALT	0.999 (0.995–1.003)	0.661
Baseline albumin	0.483 (0.175–1.330)	0.159
Baseline diastolic blood pressure	0.994 (0.948–1.043)	0.820

MRA mineralocorticoid receptor antagonist, *ALT* alanin aminotransferase

had an elevated serum lactate level at the baseline and thereafter [15].

The prognostic value of the serum lactate level was also revealed in many patients with cardiac disorders. In the study of Gjesdal et al., the 30-day mortality was found to be significantly higher in patients who had acute myocardial infarction with moderate HF and without cardiogenic shock and whose lactate level was ≥2.5 mmol/l [16]. In another study conducted by Liang et al., the 30-day and 180-day mortalities were determined to be significantly higher in patients with acute coronary syndrome and with a serum lactate level of ≥2.7 mmol/l [17]. Kliegel et al. demonstrated that patients who survived had lower serum lactate levels compared to dying patients who had undergone cardiopulmonary resuscitation due to cardiac arrest [18]. In the present study, patients with acute coronary syndrome were excluded from the study. Only patients who had been hospitalized due to worsening HF without cardiogenic shock and hypotension were included in the study.

Very limited data are available about the serum lactate level in heart failure. While the 1-year mortality is 36% of patients who had been hospitalized due to AHF without hypo-perfusion and who had high baseline lactate levels, this rate was 21% in the low lactate group in the study of Zymlinski et al. [12]. The authors proposed that high vascular resistance determined with the micro-vascular tone could preserve the blood pressure despite the low cardiac output. Hence, the blood pressure was suggested to be relatively preserved in patients with low cardiac output. However, the blood pressure could be insufficient to provide sufficient tissue perfusion even if the blood pressure were preserved. Even if absence of hypo-perfusion findings on physical examination was defined as hot, it cannot be stated with certainty that there is no hypo-perfusion in these patients. In this case, the serum lactate level may be useful for making the differentiation of hypo-perfusion. In our study, the low rate of composite end point of CV death and HHF in patients with low baseline serum lactate level supported these hypotheses.

Kawase et al. found that the systolic blood pressure and the heart rate were related to early mortality in their study investigating the effect of the baseline lactate level on early mortality in patients hospitalized due to HF. The elevation in the systolic blood pressure showed a negative correlation with the in-hospital mortality [11]. Miro et al. found that a low blood pressure was related with a poor prognosis in patients who had been admitted to the emergency room due to AHF [19]. In their study investigating the clinical, hemodynamic and metabolic indicators of lactate, Biegus et al. determined that lactate was positively correlated with the heart rate. These data support the fact that the heart rate is the goal of heart failure treatment [20]. An elevated blood pressure goes together with neuro-hormonal and cytokine increase activated with an increased after-load. The likelihood of being in an advanced stage of HF with a low cardiac output and impaired organ perfusion is higher in patients with low blood pressure. In our study, no significant relationship was found between the heart rate and the blood pressure and the primary end point due to not including patients with cardiogenic shock and severe hypotension, and rather, including relatively stable patients.

Krumholz et al. found that a >0.3 mg/dl increase in the baseline creatinine level was related to both the in-hospital mortality and the 30th, 60th and the 80th-day mortality when they retrospectively evaluated the records of the patients above 65 years, who had HF and who had been hospitalized [21]. We did not detect a significant association between the baseline creatinine level and the composite end point; however, we determined that the baseline serum urea level was a factor that increased the composite end point. We also detected that the baseline serum urea level was an independent risk factor that affected the CV death. Khoury et al. retrospectively analyzed patients who had been hospitalized with HF after having been classified according to the blood urea nitrogen (BUN) values on admission and at discharge, and found that the elevated BUN values both on admission and at discharge were related with a poor prognosis [22]. Jujo et al. divided 353 patients who had been hospitalized with AHF into 4 groups according to the BUN values on admission and at discharge as "normal BUN", "preserved BUN", "elevated BUN" and "persistently elevated BUN". The authors found higher CV death and re-hospitalization rates in the persistently high-BUN group during the follow-up after discharge [23]. Ren et al. followed up 652 elderly patients who had been hospitalized with AHF for 32 months and found that the elevated BUN value was a factor that increased the all-cause mortality and furthermore, its prognostic value was determined to be the same as BNP [24]. The prognostic value of BUN may be explained with its being an indicator of neuro-hormonal activation and its relationship with increased renin–angiotensin–aldosterone system activation in AHF. Angiotensin II, endothelin, nitric oxide and prostaglandins, the values of which alter in AHF and which affect the renal perfusion, may be associated with

a poor outcome. According to these results, the BUN values and creatinine values, although not found to be significant in our study, should be monitored closely, both during the routine follow-up and at hospital admission, and treatment should be optimized according to the renal functions.

Cameli et al. found that presence of hypertension was related with mortality at the 30-day and 6-months of follow-up in their study investigating the prognostic value of the AHF score in patients hospitalized with AHF [25]. In the study of Cluzol et al. investigating the general characteristics of patients hospitalized with HF, the presence of a hypertension history, a high urea concentration on admission and a high serum creatinine level were found to be the effective factors for re-hospitalization [26]. Similarly in our study, the presence of hypertension was found to increase the CV death and re-hospitalization with AHF by 23.08-fold.

In our study, the mean mitral *E*/*A* value on admission was found to be significantly higher in the patients with high baseline serum lactate levels. However, no significant difference was found between the groups with regard to the *E*/*e*′ values. CV death and hospitalization with AHF were seen to increase as the baseline mitral *E*/*A* value increased, independent from the serum lactate level ($p = 0.046$). Treatment of AHF and the 72nd hour mitral *E*/*A* alteration were seen not to be effective on the end points. We showed that the baseline mitral *E*/*A* ratio was a parameter that predicted the CV death and HHF in the 180-day follow-up. Santos et al. found the *E*/*e*′ ratio to be significant with regard to all-cause mortality in their study investigating the prognostic value of tissue Doppler echocardiography in patients with AHF [27]. Hansen et al. found the *E*/*A* ratio to be statistically significantly higher in the group with high mortality in their study investigating the prognostic value of tissue Doppler echocardiography findings in patients with chronic HF [28].

ProBNP has a prognostic value in HF. The alteration in proBNP is a reflection of the alteration in the left ventricle filling pressure. The reduction in proBNP levels during the treatment at the hospital indicates a reduction in volume load and hemodynamic improvement. Kagiyama et al. found that the reduction in proBNP during hospitalization was significant with regard to all-cause mortality in 1028 patients who had been hospitalized with acute HF [HR 0.96 (0.93–0.99)] [29]. We determined that the reduction in proBNP at the 72nd hour compared to the baseline values was an important factor that determined the CV death and re-hospitalization with AHF [HR 0.984 (0.968–1.00)]. Khanam et al. evaluated the BNP values of 240 patients hospitalized with AHF during the 3-month follow-up after discharge with regard to all-cause mortality and found the mortality risk to be significantly higher in patients with higher BNP values ($p < 0.001$) [30]. Logeart et al. determined that the pre-discharge BNP value was an independent and a stronger parameter than the clinical findings, echocardiographic parameters and the alteration in BNP for death and re-hospitalization for decompensated HF (HR = 1.14 [1.02–1.28]) [31]. When Fonarow et al. evaluated the records of ADHERE (Acute Decompensated Heart Failure National Registry), they detected that the baseline elevated BNP value was a predictive parameter for the in-hospital mortality, independent from the clinical and laboratory values in patients who had a low ejection fraction or preserved ejection fraction (HR = 2.23 [191–2.62]) [32]. Bettencourt et al. determined that a less than 30% reduction in NT-proBNP on admission and at discharge increased the death and re-hospitalization by 2.03-fold in 182 patients who had been hospitalized due to AHF. The authors also determined that death and re-hospitalization was 5.93-fold greater in patients who had a $\geq 30\%$ increase in NT-proBNP on admission and at discharge [33]. We also demonstrated the significance of proBNP again as an indicator for predicting the response to therapy and a poor prognosis in the patients who had been hospitalized and treated for AHF.

In AHF, the lactate level increases as a result of decreased oxygen transfer due to decreased cardiac output and tissue perfusion. Organ dysfunction is encountered more frequently with the effect of congestion and hypoxia in patients with elevated serum lactate level. This may be an effective factor for a poor prognosis [12]. River et al. assumed that positive inotropic treatment improved the tissue hypo-perfusion through increasing the cardiac output in targeted treatment for patients with severe sepsis and septic shock [34]. Targeted treatment includes adjustment of the cardiac pre-load, after-load and the contractility for balancing the oxygen supply and distribution in patients with severe sepsis and septic shock. However, positive inotropic treatment was found to be associated with in-hospital and early mortality in the studies of Kawase et al. and Abraham et al. conducted with AHF patients [11, 35]. The patients who were decompensated due to acute coronary syndrome, and who had hypotension or cardiogenic shock had also been included in these studies. Positive inotropic treatment may lead to negative outcomes through increasing the myocardial oxygen consumption, heart rate and the arrhythmia risk in AHF patients. However, randomized studies are required to make a comment about whether or not these negative outcomes would persist in AHF patients whose baseline lactate level is high and who do not have hypotension or cardiogenic shock.

The serum albumin level also has a prognostic value in heart failure. Ancion et al. found that hypo-albuminemia was associated with a poor prognosis, particularly in the elderly in their study investigating the association between serum albumin level and in-hospital mortality in 546 patients with acute non-ischemic heart failure [36]. In another analysis, Ancion et al. determined that the serum albumin level had a significant prognostic value when combined with anemia in the long-term follow-up of the patients with HHF [37]. Lio et al. found that hypo-albuminemia was frequent and

together with an increased mortality risk in HF patients with preserved ejection fraction [38]. In our study, a one-unit decrease in the baseline serum albumin level was a factor that increased the CV death and re-hospitalization with heart failure by 38.46-fold. Hypo-albuminemia is an indicator of aging, malnutrition, inflammation, severity of HF and cachexia in advanced HF. Hypo-albuminemia and decreased plasma oncotic pressure are associated with pulmonary and peripheral edema. In addition, hypo-albuminemia may be a finding of excessive congestion. All these results are the potential underlying causes of a poor prognosis.

When the factors affecting the CV death and re-hospitalization due to HF were separately analyzed, the baseline EF value, the serum urea level and the serum ALT level were found to be the factors that affected the CV death. A baseline serum lactate level of ≥ 2 mmol/l and the usage of MRAs were found to be factors that affected the HHF. Biegus et al. found that the baseline AST, ALT and albumin level were associated with in-hospital mortality in re-hospitalized patients. Furthermore, AST and the albumin level were found to be associated with all-cause mortality during the 180-day follow-up [39]. Elevated liver function tests in HF are associated with reduced hepatic perfusion and increased central venous pressure. Abnormal liver function tests are an indicator of a poor hemodynamic condition.

Kim et al. determined that the LVEF fraction was a significant predictor for CV death and that a LV end-diastolic diameter was a significant predictor for re-hospitalization in their study investigating the prognostic value of echocardiography parameters in patients hospitalized due to acute decompensated HF [40]. Yeh et al. found that not the baseline LVEF, but the post-treatment LVEF improvement was related to long-term good outcomes in patients with HHF [41]. In our study, lower baseline LVEF was found to be associated with increased risk of CV death.

Limitations

This is a single-center study with relatively small sample size.

In conclusion, elevated admission serum lactate levels provide significant prognostic data in AHF patients with reduced ejection fraction without cardiogenic shock or hypotension. The serum lactate level may be an important data for AHF risk classification.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

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