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Original Article

Effect of initial lactate level on short-term survival in patients with out-of-hospital cardiac arrest

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ABSTRACT

Purpose: This study evaluated whether serum lactate levels (SLL) at admission in patients with cardiac arrest (CA) can predict successful return of spontaneous circulation (ROSC) or short-term survival, especially within the first 24 h.
Materials and methods: This prospective, observational study was conducted in the emergency department (ED) of a training and research hospital from April 2015 through February 2016. It included all patients older than 18 years who presented to the ED during the study period with non-traumatic out-of-hospital cardiac arrest (OHCA). The study measured two outcomes: whether ROSC was achieved and whether short-term survival was achieved. ROSC was defined as the presence of spontaneous circulation for the first hour after cardiopulmonary resuscitation (CPR). Survival was defined as having survived for a minimum of 24 h after ROSC.
Results: The study included 140 patients who were admitted to the ED with OHCA. ROSC was achieved in 55 patients (39.3%), and survival for 24 h following CA was achieved in 42 patients (30%). The mean SLL in the ROSC (+) and ROSC (-) groups were 9.1 ± 3.2 mmol/L and 9.8 ± 2.9 mmol/L, respectively. The mean SLL in the survivor and non-survivor groups were 8.6 ± 2.9 mmol/L and 10 ± 3.1 mmol/L, respectively. These differences were not statistically significant ($p = 0.1$). A multivariate regression model assessing the factors that predicted both ROSC and 24-h survival showed the odds ratio (OR) of initial SLL was 1.3 (95% CI: 1.05–1.6) and 1.1 (95% CI: 0.9–1.3), respectively.
Conclusions: This study showed that in OHCA patients, SLL on admission was not associated with increased ROSC achievement or 24-h survival.

1. Introduction

Cardiac arrest (CA) events, especially out-of-hospital cardiac arrest (OHCA), remain a major public health problem, with high mortality and morbidity rates.[1,2] Despite advances in resuscitation, the rates of survival and hospital discharge for OHCA patients are lower than 16.2%.[3] Although the prognostic potential of several markers and tools has been studied, it remains difficult to predict return of spontaneous circulation (ROSC) and short-term survival.[4–6] Previous studies have shown that serum lactate level (SLL) may increase in several critical illnesses, including septic shock, severe trauma, and major surgery.[7–9] It is known that lactate is a product of anaerobic metabolism, and lactic acidosis, which causes hypoxia, can be seen in several diseases. Therefore, in recent years, the potential of SLL on admission to predict survival in CA patients has been studied. However, the varying results of such studies mean that it is still difficult to make definitive decisions based on SLL.[10–13] In addition, in previous studies, the populations have generally consisted only of patients who achieved ROSC after OHCA, not all patients with OHCA. Therefore, we believe that new studies on this topic are warranted, and the present study evaluated whether CA patients' SLL on admission can predict ROSC or short-term survival, especially within the first 24 h.

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2. Materials and methods

This prospective, observational study was conducted in the emergency department (ED) of a training and research hospital from April 2015 through February 2016. The local ethics committee approved the study, and the researchers obtained written informed consent from patients' legally authorized relatives.

2.1. Study population

The study included all patients older than 18 years who presented to the ED with OHCA during the study period. It excluded patients younger than 18 years, those who were pregnant, those who presented with CA secondary to trauma, drowning, hypothermia, and drug over-dose, and those who achieved ROSC before reaching the hospital. In addition, patients who did not have any legally authorized relatives were excluded from this study.

2.2. Study protocol

When OHCA patients presented to the ED, they were admitted to the resuscitation area and advanced cardiovascular life support (ACLS) was performed on them based on the 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care.[14] – While this study was working, update of ACLS 2015 was published. However, this update did not have any important changes which cause change of our study protocol – An independent observer researcher obtained patient characteristics and details regarding the CA in the pre-hospital period from emergency medical service (EMS) providers and patients' relatives. The same researcher also observed and recorded details regarding cardiopulmonary resuscitation (CPR), including drugs used, amount and dosage of defibrillations, duration of CPR, and CPR results (death or ROSC).

In each patient, venous blood samples were obtained within 10 min after the start of CPR by puncturing a femoral vein with heparinized syringes. The SLL was measured with a bedside blood gases analyzer (Techno Medica GASTAT-1800 pH/Blood Gas Analyzer, St. Ingbert, Germany). Other routine blood tests, including whole blood count and biochemistry tests, were performed, and all test results were recorded on the study forms.

The study measured two outcomes: whether ROSC was achieved and whether short-term survival was achieved. ROSC was defined as the presence of spontaneous circulation for the first hour after CPR. Short-term survival was defined as survival for a minimum of 24 h after ROSC. For purposes of statistical analyses, all patients were grouped according to the success of ROSC (ROSC + or ROSC -) and as survivors or non-survivors.

2.3. Statistical analyses

Statistical analyses were performed using SPSS version 16.0 (Chicago, IL, USA). The Shapiro-Wilk test was used to assess the normal distribution of all parameters related to patients. Patients' parametric data were expressed as mean values and standard deviation (SD). Non-parametric data were expressed as median values and inter-quartile range (IQR) (25–75%). The Pearson Chi-Square test was used to analyze the groups' categorical data. Continuous parametric group data were analyzed using the Student T-test, and non-parametric group data were analyzed using the Mann-Whitney *U* test. To determine the predictive value of several variables, a multivariate regression model was created using variables whose p-value was <0.2 in univariate analyses. The presence of correlation among these variables was analyzed using a Spearman test, and in each pair, the variable that detected correlation with the other variable was excluded from the regression model. To assess the model's goodness of fit, the Hosmer-Lemeshow test was performed. The 95% confidence intervals (95% CIs) were calculated whenever appropriate, and a two-tailed p-value < 0.05 was considered statistically significant.

3. Results

The study included 140 patients who were admitted to the ED with OHCA during the study period. The median age was 72 (IQR 25–75%: 63–80), and 74 patients (53%) were male. Shockable rhythm (ventricular fibrillation or ventricular tachycardia) on admission was detected in only 7 patients (5%). When rates of ROSC and survival were evaluated, ROSC was achieved in 55 patients (39.3%) and survival for 24 h after CA was achieved in 42 patients (30%). Table 1 presents all patient demographic data.

When SLL and other patient parameters were evaluated according to whether ROSC was achieved, mean SLE in the ROSC (+) and ROSC (-) groups were 9.1 ± 3.2 mmol/L and 9.8 ± 2.9 mmol/L, respectively. However, this difference was not statistically significant ($p = 0.1$). When differences in other parameters were considered, the presence of witnessed CA was higher in the ROSC (+) group than in the ROSC (-) group (60% and 34%, respectively; $p = 0.003$), but no other parameters had statistically significant differences (Table 2). A multivariate regression model created to assess the factors predicting failure of ROSC showed that SLL and bicarbonate levels on admission were poor indicators (Hazard Ratio (HR): 1.3 and 95% CI: 1.05–1.6 and HR: 1.1 and 95% CI: 1.01–1.2, respectively). In addition, the presence of witnessed CA was found

Table 1
General characteristics of patients.

Sex *n (%)*	
•Female	66 (47)
•Male	74 (53)
Age *median (IQR%25-75)*	72 (63 – 80)
Comorbidities *n (%)*	
•Chronic Hypertension	92 (65.7)
•Coronary Artery Disease	57 (40.7)
•Diabetes Mellitus	48 (34.3)
•Chronic Obstructive Pulmonary Disease	33 (23.6)
•Hyperlipidemia	29 (20.7)
•Congestive Hearth Failure	25 (17.9)
•Malignity	19 (13.6)
•Cerebrovascular disease	9 (6.4)
•Atrial Fibrillation	8 (5.7)
•Parkinson	6 (4.3)
•Chronic Kidney Disease	5 (3.6)
•Epilepsy	4 (2.9)
Witnessed arrest *n (%)*	
•Presence	62 (44.3)
•Absence	78 (65.7)
Intubation in pre-hospital period *n (%)*	
•Intubated	58 (41.4)
•Not intubated	82 (58.6)
Initial cardiac rhythm *n (%)*	
•Asystole	124 (88.6)
•Pulseless Electrical Activity	9 (6.4)
•Ventricular fibrillation/tachycardia	7 (5)
EMS's time of arrival to patient after arrest calling *median (IQR%25-75)*	10 (5 – 10)
EMS's time of arrival to ED after contact to patient *median (IQR%25-75)*	5 (5 – 10)
Returned of Spontaneous Circulation *n (%)*	
•Yes	55 (39.3)
•No	85 (60.7)
24 h survival *n (%)*	
•Yes	42(30)
•No	98(70)

EMS: Emergency Medical Services, **ED**: Emergency Department.

Table 2
Characteristics and laboratory data of patients according to success ROSC

	ROSC (+)	ROSC (-)	P Value
Sex *n (%)*			
•Female	28(50.9)	38(44.7)	0.47
•Male	27(49.1)	47(55.3)	
Age *median (IQR%25-%75)*	74(63-80)	71(63-80)	0.95
Comorbidities *n (%)*			
•Diabetes Mellitus	17(30.9)	31(36.3)	0.5
•Chronic Hypertension	39(70.9)	53(62.4)	0.29
•Coronary Artery Disease	26(47.3)	31(36.5)	0.2
•Congestive Heart Failure	13(23.6)	12(14.1)	0.15
•Atrial Fibrillation	5(9.1)	3(3.5)	0.16
•Hyperlipidemia	14(25.5)	15(17.6)	0.26
•Cerebrovascular Disease	3(3.6)	7(8.2)	0.28
•Chronic Obstructive Pulmonary Disease	14(25.5)	19(22.4)	0.67
•Chronic Kidney Disease	2(3.6)	3(3.5)	0.97
•Parkinson	3(5.5)	3(3.5)	0.58
•Malignity	11(20)	8(9.4)	0.07
•Epilepsy	1(1.8)	3(3.5)	0.55
Witnessed Arrest *n (%)*			
•Presence	33(60)	29(34.1)	0.003
•Absence	21(38.2)	53(62.4)	
Intubation in pre-hospital period *n (%)*			
•Intubated	22(40)	36(42.4)	0.89
•Not intubated	28(50.9)	48(56.5)	
EMS's time of arrival to patient after arrest calling *median (IQR%25-75)*	10 (5-10)	10 (5-10)	0.9
EMS's time of arrival to ED after contact to patient *median (IQR%25-75)*	5(5-10)	5(5-10)	0.49
Initial cardiac rhythm *n (%)*			
•Asystole	47 (85.5)	77(90.6)	0.33
•Pulseless Electrical Activity	4 (7.2)	5(5.9)	
•Ventricular fibrillation/tachycardia	4 (7.3)	3(3.5)	
Laboratory data *mean ± standard deviation*			
pH	6.98 ± 0.20	6.97 ± 0.18	0.9
PCO2 (mmHg)	71.5 ± 34.1	76.5 ± 29.2	0.2
HCO3 (mmol/L)	15.7 ± 7.15	18.07 ± 11.99	0.1
Lactate (mmol/L)	9.1 ± 3.2	9.8 ± 2.9	0.1
Glucose (mg/dL)	240 ± 131	233 ± 138	0.8
Hemoglobin (g/dL)	12.5 ± 2.6	12 ± 3.4	0.5
Creatinin (mg/dL)(median-IQR%25-%75)	1.3(0.9-2.2)	1.3(1.0-1.9)	0.5
White Blood Cell (10^{-3}/μl) (median-IQR%25-%75)	14.35 (9.8-19.5)	12.3 (9.3-18.2)	0.7
Sodium (mmol/L)(median-IQR%25-%75)	140 (137-144)	139.5 (137-143)	0.4
Potassium (mmol/L) (median-IQR%25-%75)	5.4(4.5-6.5)	5.2(4.6-6.9)	0.9

to be a good predictor (Odds Ratio (OR): 0.2 and 95% CI: 0.1–0.6) (Table 3).

When SLLs and other patient parameters were evaluated according to whether survival was achieved, the mean SLL in the survivor and non-survivor groups were 8.6 ± 2.9 mmol/L and 10 ± 3.1 mmol/L, respectively, a difference that was not statistically significant ($p = 0.1$). When the differences for other parameters were considered, the presence of witnessed CA was higher in the survivor group than in the non-survivor group (59% and 37%, respectively; $p = 0.001$). In addition, the rate of ventricular fibrillation on admission was higher in the survivor group than in the non-survivor group (9.5% and 3.1%, respectively; $p = 0.04$). No statistically significant difference was detected for other parameters (Table 4). A multivariate regression model created to assess the factors predicting non-survival showed that SLL was not a predictor (OR: 1.1 and 95% CI: 0.9–1.3). However, gender and hemoglobin levels were found to be predictors of non-survival (OR: 3.8 and 95% CI: 1.15–12.6 and 0.8 and 95% CI: 0.6–0.9, respectively) (Table 5).

Table 3
Multivariate logistic regression to predict failure ROSC in patients with OHCA

	Wald	P value	OR (95% CI)
Age	0.589	0.4	0.8 (0.3-1.6)
Sex	2.982	0.08	2.1 (0.9-5.2)
CAD	5.673	0.6	0.8 (0.3-1.9)
Malignity	3.077	0.07	0.3 (0.1-1.1)
PCO_2	1.571	0.2	0.9(0.9-1.1)
HCO_3	4.553	0.03	1.1(1-1.2)
Lactate	6.209	0.01	1.3 (1.05-1.6)
Witnessed arrest	9.519	0.002	0.2 (0.1-0.6)

CAD: Coronary Artery Disease.

4. Discussion

The present study showed no statistically significant difference in SLL on admission between either ROSC (+) and ROSC (-) groups or between survivor and non-survivor groups in patients with non-traumatic OHCA when using univariate analysis. However, a multivariate model created to determine predictive factors in ROSC failure found that SLL was a predictor. But, considering that the OR value of SLL on admission was 1.3 (95% CI 1.05–1.6), we believe it is clear that although the OR value of SLL was statistically significant, it is a poor predictor of ROSC failure and is not useful in daily clinical practice. Similarly, a multivariate model created to determine predictive factors for non-survival found that SLE was not a predictor. Therefore, although it is thought that SLL is a good predictor for tissue hypoxia and lack of perfusion, results of the present study showed that SLL alone predicted neither ROSC nor 24-h survival.

Although several studies have investigated the association between SLL and survival, results of those studies are confusing. River et al. studied 23 OHCA patients who had achieved ROSC after successful resuscitation and reported that mean SLL alone did not differ significantly between the survivor (for 6 h) and non-survivor groups (10.4 ± 1.3 and 13.3 ± 1.3, respectively, $p = 0.13$).[15] Similarly, Donino et al. studied 79 OHCA patients who achieved sustained ROSC to evaluate the prognostic value of SLE on 24-h survival. They reported mean SLL of 14.4 ± 5.1 mmol/dl in the survivor group and 16 ± 5.3 mg/dl in the non-survivor group ($p > 0.05$). However, they reported that lactate clearance at both 6 and 12 h was higher in the survivor group than in the non-survivor group.[11] Starodup et al. studied 199 patients who presented with CA and achieved ROSC, performing therapeutic hypothermia and evaluating the association between SLL and survival outcome, which was defined as survival to hospital discharge. They reported that initial and 6-h SLL was not associated with survival to hospital discharge. However, they reported that SLE at 12 and 24 h was associated with survival to hospital discharge in patients with CA on whom therapeutic hypothermia[16] was performed. Similar to these previous studies, the present study showed that OHCA patients' SLL on admission had no predictive value for ROSC or 24-h survival. As the present study did not measure SLL or lactate clearance, it did not evaluate whether lactate clearance predicted 24-h survival.

In contrast, some studies have shown that SLL may have prognostic value in CA patients. Kliegel et al. studied 394 CA patients who survived 48 h after successful resuscitation, finding that SLL on admission, at 24 h, and at 48 h was higher in 6-month survivors than in non-survivors. However, using multivariate analyses, they found that only SLL at 48 h was significant as an independent predictor of 6-month survival (OR: 1.49 and 95% CI: 1.17–1.89), not SLL on admission or at 24 h.[12] In the present study, SLL on admission was an independent factor for ROSC, but we believe that it is not helpful in clinical practice because of its low OR value. Similarly, the Donino et al. study, which included 100 patients with OHCA who had achieved ROSC for a minimum of 20 min, reported that initial SLL was lower in survivors (survival to hospital discharge) than in non-survivors. However, they reported that in multivariate analyses, initial SLL predicted neither survival to hospital discharge

Table 4
Characteristics and laboratory data of patients according to success 24h survival

	Survivor	Non-survivor	P Value
Sex *n (%)*			
•Female	21 (50)	45 (45.9)	0.65
•Male	21 (50)	53 (54.1)	
Age *median (IQR%25-%75)*	74 (63-80)	70 (63-79)	0.63
Comorbidities *n (%)*			
•Diabetes Mellitus	12 (28.6)	36 (36.7)	0.35
•Chronic Hypertension	30 (71.4)	62 (63.3)	0.35
•Coronary Artery Disease	20 (47.6)	37 (37.8)	0.27
•Congestive Heart Failure	11 (26.2)	14 (14.3)	0.09
•Atrial Fibrillation	5 (11.9)	3 (3.1)	0.04
•Hyperlipidemia	11 (26.2)	18 (18.4)	0.29
•Cerebrovascular Disease	2 (4.8)	7 (7.1)	0.6
•Chronic Obstructive Pulmonary Disease	13 (31)	20 (20.4)	0.18
•Chronic Kidney Disease	2 (4.8)	3 (3.1)	0.62
•Parkinson	3 (7.1)	3 (3.1)	0.27
•Malignity	5 (11.9)	14 (14.3)	0.7
•Epilepsy	1 (2.4)	3 (3.1)	0.82
Witnessed Arrest *n (%)*			
•Presence	25 (59.5)	37 (37.8)	0.01
•Absence	16 (38.1)	58 (59.2)	
Intubation in pre-hospital period *n (%)*			
•Intubated	18 (42.9)	40 (40.8)	0.55
•Not intubated	20 (47.6)	56 (57.1)	
EMS's time of arrival to patient after arrest calling *median (IQR%25-75)*	10(5-10)	10(5-10)	0.68
EMS's time of arrival to ED after contact to patient *median (IQR%25-75)*	5(5-10)	10(5-10)	0.21
Initial cardiac rhythm *n (%)*			
•Asystole	34(81)	90(91.8)	0.04
•Pulseless Electrical Activity	4(9.5)	5(5.1)	
•Ventricular fibrillation/tachycardia	4(9.5)	3(3.1)	
Laboratory data *mean ± standard deviation*			
pH	7.02 ± 0.20	6.96 ± 0.17	0.7
PCO_2 (mmHg)	68.7 ± 26.6	73.6 ± 33.4	0.8
HCO_3 (mmol/L)	16.4 ± 7.24	15.8 ± 6.9	0.4
Lactate (mmol/L)	8.67 ± 2.94	10 ± 3.1	0.1
Glucose (mg/dL)	233 ± 107	237 ± 135	0.6
Hemoglobin (g/dL)	12.5 ± 2.6	11.9 ± 3.2	0.2
Creatinin (mg/dL)(median-IQR%25-%75)	1.27(0.9-1.6)	1.3(1.0-2.1)	0.4
White Blood Cell (10^{-3}/μl) (median-IQR%25-%75)	14.3(11.7-17.7)	13(9.3-17.3)	0.2
Sodium (mmol/L)(median-IQR%25-%75)	140(138-143)	139(137-143)	0.4
Potassium (mmol/L)(median-IQR%25-%75)	5.1(4.5-5.9)	5.2(4.6-6.5)	0.5

nor good neurological outcome.[17] Shinozaki et al. evaluated whether initial SLL and ammonia levels predicted poor neurological outcome in OHCA patients who achieved sustained ROSC. They found that median SLL was lower in the group with favourable outcomes than in the one with unfavourable outcomes (9.2 mmol/dl [2.6–11.5] and 12.1 mmol/dl [9.5–14], respectively). In addition, their logistic regression analyses showed that SLL of less than 12 mmol could predict favourable neurological outcomes in OHCA patients who achieved sustained ROSC.[10] Finally, in another retrospective cohort analysis of 518 OHCA patients, Williams et al. reported that initial SLLs were lower in patients who survived to hospital discharge than in non-survivors (6.9 ± 4.7 and 12.2 ± 5.5 mmol/L, $p < 0.001$). In addition, the adjusted OR value of the initial SLL that predicted survival was 0.82 (95% CI 0.75–0.89).[13] Contrary to these positive results, especially those of Williams et al., the results of the present study showed that initial SLL was not useful in clinical practice. We believe that an important cause of this difference in results was that the population in the present study was older than those in the other studies.

Another important result of the present study was that presence of witnessed CA was higher in the ROSC (+) and survivor groups than in the ROSC (-) and non-survivor groups. Multivariate analysis found that witnessed CA was a predictor for ROSC (OR: 0.2 and 95% CI: 0.1–0.6), but not for survival. Williams et al. reported similar findings.[13] We believe that one probable cause of this might be early EMS and early basic life support performed by patients' relatives. According to results of the present study, another predictor of 24-h survival was haemoglobin level on admission (OR: 0.8 and 95% CI: 06–0.9). Haemoglobin level is one of the parameters that provides adequate tissue oxygen supply, which is known to be crucial to successful resuscitation. Therefore, we believe that it is reasonable that haemoglobin level is a predicting factor.

Table 5
Multivariate logistic regression to predict failure 24h survival in patients with OHCA

	Wald	P value	OR (95% CI)
Age	0.225	0.6	1.00 (0.9-1.04)
Sex	4.805	0.02	3.8 (1.15-12.6)
CHF	1.009	0.3	2.2 (0.4-10)
COPD	3.666	0.06	0.3 (0.09-1.05)
Hemoglobin	4.186	0.04	0.8 (0.6-0.9)
White Blood Cell	0.236	0.6	1.01 (0.9-1.05)
Lactate	2.087	0.1	1.1 (0.9-1.3)
Witnessed arrest	1.193	0.2	0.5 (0.1-1.5)

CHF: Congestive Heart Failure, **COPD**: Chronic Obstructive Pulmonary Disease.

5. Limitations

The present study had some limitations. Most importantly, we did not calculate sample size, thus, power of our negative results is not clear. Second, SLL was measured only on admission, not serially. Therefore, the present study did not evaluate the association between serum lactate clearance and ROSC or survival, as previous studies did. However, this limitation was ignored because we wanted to evaluate all patients with OHCA, not just those who sustained ROSC after OHCA. Third, although all resuscitation interventions were performed according to modern guidelines, our hospital was not technically able to induce therapeutic hypothermia in ROSC patients. Fourth, the present study's population was older than those of previous studies. Therefore, the population might have been more critically ill, which could be a possible cause of OHCA, and which might also cause their SLL measures to be higher than those in previous studies. Finally, we could not review data of patients including exactly starting time of CPR after CA or quality of CPR in prehospital period.

6. Conclusions

The present study showed that in OHCA patients, SLL on admission was not associated with achieving ROSC or 24-h survival. However, the study found that witnessed CA was a predictor of ROSC and that haemoglobin level on admission was a predictor of 24-h survival.

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