*Original Article*

# Prognostic values of blood pH and lactate levels in patients resuscitated from out-of-hospital cardiac arrest

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*Aim:* Early prediction of prognosis after out-of-hospital cardiac arrest (OHCA) remains difficult. High blood lactate or low pH levels may be associated with poor prognosis in OHCA patients, but these associations remain controversial. We compared blood lactate and pH levels in OHCA patients transferred to our hospital to measure their prognostic performance.

*Methods:* We investigated the associations between blood lactate and pH levels on admission and neurological outcomes in 372 OHCA patients who had a return of spontaneous circulation.

*Results:* Of the 372 OHCA patients, 31 had a favorable neurological outcome. Blood lactate levels were lower in patients with a favorable outcome than in those with an unfavorable outcome, but this difference did not reach statistical significance (82 ± 49 vs. 96 ± 41 mg/dL). However, pH levels were significantly higher in patients with a favorable outcome than in those with an unfavorable outcome (7.26 ± 0.16 vs. 6.93 ± 0.19, $P < 0.001$). The relative cumulative frequency distribution curve analysis showed the optimal cut-off points of lactate and pH to be approximately 80 mg/dL and 7.05, respectively. Sensitivity and specificity to predict a favorable outcome were 61% and 64% for lactate <80 mg/dL and 84% and 80% for pH >7.05, respectively. Areas under receiver–operating characteristic curves were significantly larger for pH than for lactate levels ($P < 0.001$). In multivariate analysis, pH >7.05 was an independent predictor for a favorable outcome.

*Conclusion:* After OHCA, patients with a favorable outcome had lower lactate and higher pH levels than those with an unfavorable outcome, but pH level was a much better predictor for neurological outcome than lactate levels.

**Key words:** Blood pH, lactate, out-of-hospital cardiac arrest, predictors, prognosis

## INTRODUCTION

RECENTLY, IMPROVEMENTS IN the survival rates and the achievement of a favorable neurological outcome from out-of-hospital cardiac arrest (OHCA), which were associated with increments of cardiopulmonary resuscitation (CPR) and public-access automated external defibrillator use by bystanders,[1,2] have been reported in Japan.[3,4] However, the neurologically favorable survival rate is still low (only 2.8%),[4] and the early prediction of survival and neurological outcome after OHCA remains difficult. Cardiopulmonary arrest and the consequent interruption of blood flow to metabolically active tissues is well recognized to cause tissue oxygen deficiency, lactate accumulation, and metabolic acidosis, thereby leading to high lactate levels and low pH levels in blood. Lactate is the main metabolite of anaerobic glycolysis, and the correlation between total duration of cardiac arrest and blood lactate levels has been reported in patients resuscitated from ventricular fibrillation (VF).[5] Several studies reported that high lactate or low pH levels in arterial blood analysis were associated with a poor prognosis in patients resuscitated from OHCA,[6–8] and biomarkers, such as lactate and pH, which are commonly and easily available on hospital admission, may be helpful for predicting early prognosis and optimizing treatment in OHCA patients. However, the association between blood lactate or pH levels and a poor prognosis in OHCA patients remain controversial,[9–11] and the cut-off points of blood lactate and pH levels for determining a poor prognosis in OHCA patients vary from study to study.[12–15] Our study was done to compare prognostic performance between blood

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lactate and pH levels on hospital admission in OHCA patients transferred to our general hospital in Tokyo (Japan), to which approximately 300 OHCA patients are transferred every year.

## METHODS

WE RETROSPECTIVELY INVESTIGATED blood lactate and pH levels and prognosis in 949 consecutive OHCA patients with resuscitation attempts who were transferred to the Emergency and Critical Care Center at the National Hospital Organization Tokyo Medical Center from January 2010 December 2013. Patients with OHCA due to external causes, such as trauma or suicide, were excluded. In OHCA patients, arterial blood gas sampling was usually obtained on admission to our hospital, and blood lactate and pH levels were measured by a commercially available blood gas analyzer (RAPIDLab 1200 System; Siemens Healthcare, Erlangen, Germany). Clinical courses and blood gas data were retrospectively evaluated using patients' medical records. The neurological outcome was assessed by Glasgow–Pittsburgh Cerebral Performance Categories: CPC 1, good cerebral performance; CPC 2, moderate cerebral disability; CPC 3, severe cerebral disability; CPC 4, coma or vegetative state; and CPC 5, death.[16] The favorable neurological outcome was defined as CPC 1 and 2. Of the 949 patients resuscitated from OHCA, 375 (40%) achieved a return of spontaneous circulation (ROSC), but 65 who did not have arterial blood gas sampling were excluded, of whom three had ROSC. As a result, 372 OHCA patients who achieved ROSC were divided into two groups: 31 patients with a favorable neurological outcome (CPC 1 and 2), and 341 with an unfavorable outcome (CPC 3, 4, and 5). Our study was approved by the institutional ethics committee, and informed consent was waived because of the observational nature of the study.

### Statistical analysis

Differences between two groups were evaluated by unpaired *t*-test for parametric variables, by Mann–Whitney *U*-test for non-parametric variables, and by $\chi^2$-test for categorical variables. The receiver–operating characteristic (ROC) curves were created, and areas under ROC curves (AUC) were measured to compare the predictive abilities between lactate and pH levels for neurological outcome. The relative cumulative frequency distribution (RCD) curves were created to determine the cut-off points of lactate and pH levels for neurological outcome. The optimal cut-off point was determined as the point where the sensitivity and specificity curves intersected. Forward stepwise multiple logistic regression analysis was used to elucidate independent associations between lactate or pH levels and neurological outcome. All statistical analyses were carried out using the SPSS software package (IBM SPSS version 20, Japan). A *P*-value of <0.05 was considered statistically significant. Results are presented as either mean value ± standard deviation or median value.

## RESULTS

OF THE 372 OHCA patients who achieved ROSC, 46 survived to hospital discharge, but only 31 had a favorable neurological outcome at hospital discharge. Compared with 341 patients with an unfavorable outcome, 31 with a favorable outcome were younger (54 ± 16 vs. 75 ± 15 years) and had higher prevalence of VF or ventricular tachycardia (VT) (77% vs. 19%), bystander CPR (74% vs. 25%) and therapeutic hypothermia (45% vs. 6%) ($P < 0.001$) (Table 1). The time from collapse to ROSC was shorter in patients with a favorable outcome than in those with an unfavorable outcome (median 24.0 vs. 61.0 min, $P < 0.001$). Regarding arterial blood gas analysis, lactate levels on hospital admission tended to be lower in patients with a favorable outcome than in those with an unfavorable outcome, but this difference did not reach statistical significance (82 ± 49 vs. 96 ± 41 mg/dL) (Table 1). Notably, pH levels were significantly higher in patients with a favorable outcome than with an unfavorable outcome (7.26 ± 0.16 vs. 6.93 ± 0.19, $P < 0.001$).

To determine the optimal cut-off points for blood lactate and pH levels and to compare the predictive abilities between lactate and pH levels in order to predict a favorable neurological outcome, relative cumulative frequency distribution and ROC curve analysis was undertaken in 372 OHCA patients who achieved ROSC. As shown in Figure 1, the optimal cut-off points of lactate and pH levels were found to be approximately 80 mg/dL and 7.05, respectively. The sensitivity and specificity to predict patients with a favorable outcome were 61% and 64% for a lactate level of <80 mg/dL and 84% and 80% for a pH level of >7.05, respectively. Notably, no patient with a favorable outcome had a pH level of <6.95 (Fig. 1). Moreover, AUC for pH levels was 0.91 (95% confidence interval [CI], 0.87–0.95), which was found to be significantly larger than AUC for lactate levels (0.62; 95% CI, 0.51–0.74) ($P < 0.001$) (Fig. 2). In multivariate analysis, variables (age, VF/VT, bystander CPR, the time from collapse to ROSC <30 min, pH >7.05, and therapeutic hypothermia) in which there were significant differences between patients with a favorable outcome and those with an unfavorable outcome, were included

**Table 1.** Clinical characteristics of 372 patients with out-of hospital cardiac arrest who had a return of spontaneous circulation (ROSC), grouped according to favorable or unfavorable neurological outcome

| | All ($n$ = 372) | Favorable outcome ($n$ = 31) | $P$-value | Unfavorable outcome ($n$ = 341) |
|---|---|---|---|---|
| Age, years | 73 ± 16 | 54 ± 16 | <0.001 | 75 ± 15 |
| Gender, male | 236 (63%) | 24 (77%) | NS | 212 (62%) |
| Initial rhythm, VF/VT | 89 (24%) | 24 (77%) | <0.001 | 65 (19%) |
| Bystander CPR | 109 (29%) | 23 (74%) | <0.001 | 86 (25%) |
| Acute coronary syndrome | 51 (14%) | 17 (55%) | <0.001 | 34 (10%) |
| Time from collapse to ROSC, min | 59.0 | 24.0 | <0.001 | 61.0 |
| Time from collapse to ROSC <30 min | 52 (14%) | 18 (58%) | <0.001 | 34 (10%) |
| Blood lactate levels, mg/dL | 95 ± 42 | 82 ± 49 | NS | 96 ± 41 |
| Blood pH levels | 6.95 ± 0.21 | 7.26 ± 0.16 | <0.001 | 6.93 ± 0.19 |
| Therapeutic hypothermia | 35 (9%) | 14 (45%) | <0.01 | 21 (6%) |

Data are presented as mean ± standard deviation or the number (%) of patients, except for the time from collapse to ROSC, presented as the median value. CPR, cardiopulmonary resuscititation; VF, ventricular fibrillation; VT, ventricular tachycardia.

(Table 1). The pH level >7.05 was an independent predictor for a favorable outcome (Table 2).

## DISCUSSION

THE PRESENT STUDY investigated the prognostic value of blood lactate and pH levels in 372 OHCA patients who achieved ROSC, of whom only 31 had a favorable neurological outcome at hospital discharge. Patients with a favorable outcome showed lower lactate and higher pH levels on hospital admission than those with an unfavorable outcome. The optimal cut-off points for lactate and pH levels were 80 mg/dL and 7.05, respectively, but the AUC for pH levels was much larger than that for lactate levels. In multivariate analysis, a pH level >7.05 was an independent predictor for a favorable outcome. Blood pH levels were thus found to be a much better predictor for neurological outcome in patients resuscitated from OHCA.

Cardiopulmonary arrest causes tissue oxygen deficiency and lactate accumulation, and lactate is the main metabolite of anaerobic glycolysis. Several studies reported blood lactate levels on hospital admission to be high in OHCA patients with an unfavorable outcome,[5–8,12,14] however, the association between blood lactate levels and outcome in OHCA patients remains controversial.[9–11] Donnino *et al.*[10] investigated blood lactate levels in 79 OHCA patients. Lactate levels on admission were lower in 13 survivors than in 66 non-survivors, but this difference did not reach statistical significance. Starodub *et al.*[11] measured lactate levels on admission and at 12 and 24 h after ROSC in 199 OHCA patients who had therapeutic hypothermia. There was no significant difference in lactate levels on admission between 84 survivors and 115 non-survivors at hospital discharge, but lactate levels at 12 and 24 h after ROSC were reported to be lower in survivors than in non-survivors. In the present study, lactate levels on admission tended to be lower in 31 OHCA patients with a favorable neurological outcome than in 341 with an unfavorable outcome, but this difference did not reach statistical significance.

The cut-off point for blood lactate levels to predict a poor prognosis in OHCA patients varies from study to study.[5,12–15,17] Mullner *et al.*[5] investigated the association between lactate levels on admission and outcome in 167 survivors resuscitated from VF. They reported a very high level of lactate (>147 mg/dL) to be associated with an unfavorable neurological outcome (CPC 3–5), yielding 100% specificity with a very low sensitivity of 16%. Shinozaki *et al.*[12] also studied lactate levels on admission in 98 OHCA patients, of whom only 10 had a favorable outcome. According to ROC curve analysis, the optimal cut-off level for predicting a favorable outcome (CPC 1, 2) was 108 mg/dL. In contrast, Grimaldi *et al.*[14] reported a lactate level of <46 mg/dL to be associated with a favorable outcome at discharge from intensive care in 225 OHCA patients, of whom 57 had a

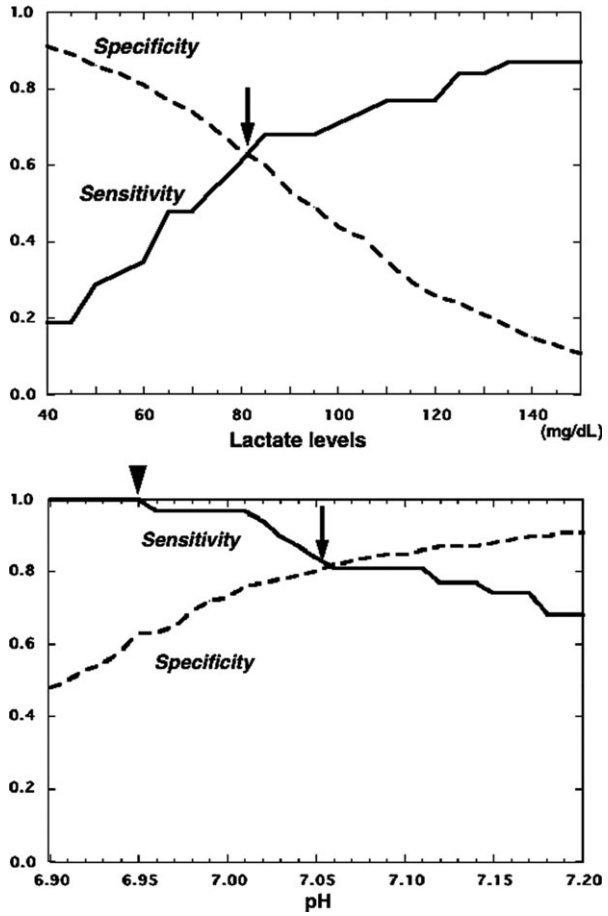


**Fig. 1.** Relative cumulative frequency distribution curves for the cut-off points of blood lactate and pH levels in 372 patients with out-of hospital cardiac arrest who had a return of spontaneous circulation. The curves indicate that optimal cut-off points of lactate and pH levels for a favorable neurological outcome were approximately 80 mg/dL and 7.05, respectively. The arrows indicate the optimal cut-off points of lactate and pH levels. The arrowhead in the lower figure suggests that no patient with a favorable outcome had a pH level <6.95.

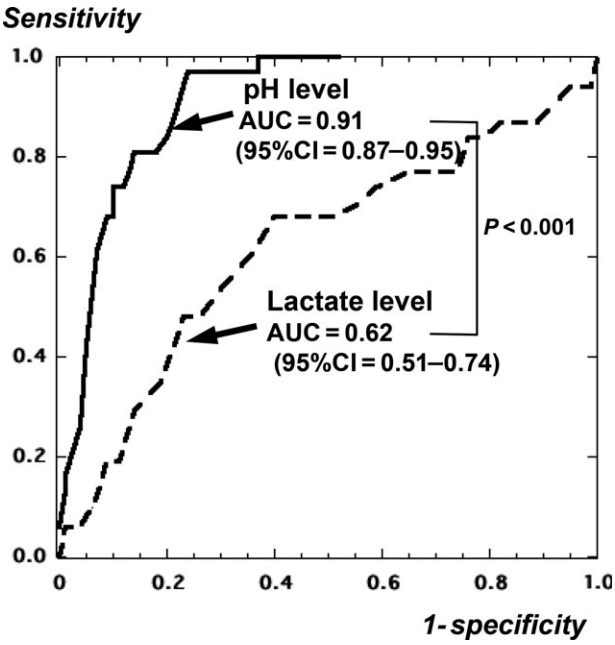


**Fig. 2.** Receiver–operating characteristic curves of lactate and pH levels for the comparison of predictive abilities of neurological outcome in 372 patients with out-of hospital cardiac arrest who had a return of spontaneous circulation. The area under the curve for pH levels was 0.91 (95% confidence interval, 0.87–0.95), which was significantly larger than that for lactate levels (0.62; 95% confidence interval, 0.51–0.74) ($P < 0.001$).

**Table 2.** Multiple logistic regression analysis of factors associated with a favorable neurological outcome in 372 patients with out-of hospital cardiac arrest who achieved return of spontaneous circulation

| Variable | Odds ratio (95%CI) | *P*-value |
|---|---|---|
| Age (1-year increase) | 0.92 (0.89–0.95) | <0.001 |
| VF/VT | 4.88 (1.59–14.98) | <0.010 |
| Bystander CPR | 5.23 (1.62–16.85) | <0.010 |
| Time from collapse to ROSC <30 min | 3.60 (1.09–11.91) | <0.050 |
| pH >7.05 | 18.56 (4.27–80.73) | <0.001 |

The dependent variable was a favorable neurological outcome. This analysis included age, ventricular fibrillation/ventricular tachycardia (VF/VT), bystander cardiopulmonary resuscititation (CPR), the time from collapse to ROSC < 30 min, pH > 7.05, and therapeutic hypothermia.
CI, confidence interval.

favorable outcome. Kaji *et al.*[17] also investigated lactate levels in 184 OHCA patients, of whom 43 had a favorable outcome at hospital discharge. They reported lactate <45 mg/dL to be predictive of a favorable outcome, with the sensitivity of 91% and the specificity of 48%. In the present study, we identified the optimal cut-off level of lactate to be 80 mg/dL, but the sensitivity and specificity to predict a favorable outcome were only 61% and 64% for lactate <80 mg/dL, respectively.

Cardiac arrest causes tissue oxygen deficiency, lactate accumulation, and metabolic acidosis, thereby leading to low pH levels in blood. Some studies reported pH levels to be higher in OHCA patients with a favorable outcome than in those with an unfavorable outcome and to be an independent factor associated with outcome in multivariate

analysis.[7,13,15] Our study also showed pH levels to be high in patients with a favorable outcome and to be an independent factor for the outcome. Takaki *et al.*[13] investigated pH levels in 50 OHCA patients undergoing therapeutic hypothermia, of whom 25 had a favorable outcome, and they reported the optimal cut-off level of pH to be 6.97 by ROC curve analysis. Seeger *et al.*[15] also studied pH levels on admission in 206 OHCA patients who achieved ROSC, of whom 137 had an unfavorable outcome. However, they reported the optimal cut-off level to be 7.21. Our study investigated pH levels in 372 OHCA patients, of whom 31 had a favorable outcome. We identified the optimal cut-off point of pH levels to be 7.05, with a sensitivity of 84% and a specificity of 80% for a pH level of >7.05 to predict a favorable outcome; all patients with a favorable outcome had a pH level >6.95. According to ROC curve analysis, the AUC for pH levels was significantly larger than that for lactate levels. Thus, pH levels on hospital admission were found to be a much better predictor for outcome than lactate levels in patients resuscitated from OHCA. However, the reason for the difference in cut-off points of pH to predict neurological outcome among studies remains unclear, but it may be due to differences in patient selection, the time of blood sampling, and the quality of in-hospital post-CPR care.

### Limitations

Our study was not without limitations. First, the number of study patients was relatively small (372 OHCA patients who achieved ROSC), and only 31 patients had a favorable outcome. Moreover, three OHCA patients with ROSC were excluded from our study because they did not have arterial blood gas sampling. This may have caused some bias. Second, the exact time at which arterial blood gas specimens were taken was not recorded. Although arterial blood gas specimens were usually obtained on hospital admission, the time of blood sampling could differ among study patients. Moreover, we could not assess serial changes in pH and lactate levels after ROSC. Third, interhospital variations in 1-month survival after successful CPR have been reported,[18] and regional differences in a neurologically favorable outcome after OHCA have recently been reported in Japan, thus suggesting regional disparities in pre-hospital care and in-hospital post-CPR care.[19] Our study was undertaken at an emergency and critical care center in Tokyo, to which approximately 300 OHCA patients are transferred every year. The results of our study may not be applicable to other hospitals, even in Japan. Moreover, therapeutic hypothermia has been reported to improve neurological outcomes after OHCA,[20] and its use is increasing in Japan. In the SOS-KANTO study, the prevalence of therapeutic hypothermia increased from 3% of patients with OHCA of cardiac etiology in 2002 to 15% in 2012.[21s] In our study, only 9% of OHCA patients who achieved ROSC had therapeutic hypothermia. This may have confounded our results. Finally, the retrospective nature of our study is another limitation. To confirm our results, further studies need to be prospectively carried out in a large number of patients resuscitated from OHCA.

## CONCLUSIONS

AFTER OHCA, PATIENTS with a favorable outcome had lower lactate and higher pH levels on hospital admission than those with an unfavorable outcome. The optimal cut-off points of lactate and pH levels were 80 mg/dL and 7.05, respectively, but the AUC for pH levels was much larger than that for lactate levels. In multivariate analysis, a pH of >7.05 was an independent predictor for a favorable outcome. Blood pH levels were therefore found to be a much better predictor for neurological outcome than lactate levels in patients resuscitated from OHCA.

## CONFLICT OF INTEREST

NONE.

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