Initial Blood Ammonia Level Is a Useful Prognostication Tool in Out-of-Hospital Cardiac Arrest — Multicenter Prospective Study (SOS-KANTO 2012 Study) —

SOS-KANTO 2012 Study Group

**Background:** Initial blood ammonia level is associated with neurologic outcomes in out-of-hospital cardiac arrest (OHCA). We tested the usefulness of blood ammonia for prediction of long-term neurological outcome of OHCA.

**Methods and Results:** A total of 3,011 hospitalized adult OHCA patients were enrolled. Blood samples were obtained at the ED. Cut-offs (ammonia <100 μmol/L and lactate <12 mmol/L) were determined in a previous study. Neurological outcomes in survivors were assessed at 3 months. A logistic regression model with adjustment for within-hospital clustering and other risk factors was used to evaluate the association between biomarkers and outcomes. Of 3,011 patients, 380 (13.8%) had favorable neurological outcomes. Ammonia and lactate predicted neurological outcome with an AUC of 0.80 (95% CI: 0.76–0.84) and 0.77 (95% CI: 0.72–0.82), respectively. Adjusted OR for ammonia <100 μmol/L (4.55; 95% CI: 2.67–7.81) was higher than that for lactate <12 mmol/L (2.63; 95% CI: 1.61–4.28) and most other risk factors, such as cardiac etiology (3.47; 95% CI: 2.55–4.72), age<80 years (3.16; 95% CI: 2.17–4.61), bystander CPR (2.39; 95% CI: 1.70–3.38), and initial rhythm shockable (1.66; 95% CI: 1.16–2.37). The combination of ammonia and lactate had an increased predictive value (AUC, 0.86; 95% CI: 0.85–0.87) compared with that without biomarkers (AUC, 0.81; 95% CI: 0.80–0.82).

**Conclusions:** Initial blood ammonia level is as useful as other traditional prognostic indicators such as lactate. Measurement of both initial blood ammonia and lactate helped accurately predict neurological outcomes after OHCA.

**Key Words:** Biomarker; Heart arrest; Prognosis; Risk factor
spontaneous circulation (ROSC). In order to help with the decision-making in post-CA care, subjects should be restricted to those who have successfully gained ROSC. Because patients without ROSC are automatically withdrawn from post-CA care, it is important to delineate ROSC survivals from non-ROSC deaths. Restriction of subject enrollment lowers the study volume, therefore it has not been studied much in the past.

The purpose of this study was therefore to test whether initial blood ammonia level is independently associated with long-term neurological outcome of OHCA when it is adjusted for lactate and other risk indicators. In addition, we compared the predictability of blood ammonia level with that of blood lactate level and other clinical risk factors. This is the first study to test this hypothesis using a multicenter large-scale prospective cohort.

**Methods**

**Setting and Design**

The Survey of Survivors after Out-of-Hospital Cardiac Arrest in KANTO Area 2012 (SOS-KANTO 2012) is an observational, prospective survey conducted by 67 emergency hospitals in the Kanto region, Japan. We previously described this survey in detail. In brief, all OHCA patients who were transported to hospital by emergency medical services were included in this cohort. From January 2012 to March 2013, a total of 16,452 patients were recruited. This study was approved by the Institutional Review Boards of all institutions, which waived the requirement for informed patient consent to ensure participant anonymity, stipulated in Japanese government guidelines.

Resuscitation attempts were documented by both paramedics and attending physicians, and data were obtained following Utstein definitions: precisely defined variables for uniform reporting of CA developed by international experts. Bystander cardiopulmonary resuscitation (CPR) was defined as CPR performed by a person who was not responding as part of an organized medical response system to a CA. Shockable rhythms were defined as the first recorded rhythms of ventricular fibrillation (VF) or pulseless ventricular tachycardia presented on the monitor or defibrillator. Data for individual patients were entered into a database by SOS-KANTO 2012 members at each hospital and were independently cross-checked by different investigators. Original data were made available to the Data and Safety Monitoring Committee for independent scrutiny.

**Subjects**

The subjects consisted of adult patients (≥18 years) with non-traumatic CA. Patients with initial resuscitation performed inside the hospital were excluded. Patients who were successfully resuscitated and admitted to a participating hospital were included in the analysis (Figure 1).

**Lactate and Ammonia Measurement**

Blood samples were obtained and lactate and ammonia concentration were measured after the patient presented to hospital. In the study period, physicians in charge provided post-CA care independent of biomarker concentration, because the investigational cut-offs for lactate and ammonia were not relayed to physicians until the study was finished.

Lactate and ammonia concentration were measured with instruments available for normal clinical use in each institution. This was an observational data-registration study, spontaneous circulation (ROSC). In order to help with the decision-making in post-CA care, subjects should be restricted to those who have successfully gained ROSC. Because patients without ROSC are automatically withdrawn from post-CA care, it is important to delineate ROSC survivals from non-ROSC deaths. Restriction of subject enrollment lowers the study volume, therefore it has not been studied much in the past.

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Lactate and ammonia concentration were measured with instruments available for normal clinical use in each institution. This was an observational data-registration study,
therefore all procedures were performed according to the standard of care clarified in the institution(s). Blood sampling and measurement were also performed as part of standard care. The reference range (lower limit-upper limit) of lactate and ammonia concentration was dependent on the measurement system in each hospital. The median lower lactate limit in participating institutions was 0.5 mmol/L (IQR, 0.4–0.5 mmol/L) and the upper limit was 1.6 mmol/L (IQR, 1.6–1.9 mmol/L). For ammonia measurements, the median lower limit was 7 μmol/L (IQR, 7–11 μmol/L) and the upper limit was 39 μmol/L (IQR, 39–41 μmol/L).

Neurological Outcome Assessment
The cerebral performance of an individual patient was evaluated using Glasgow-Pittsburgh cerebral performance categories (CPC; categories 1–5). All patients received follow-up care 3 months after CA. CPC at the end of the follow-up period was recorded. If a patient had died before the follow-up visit, his/her CPC was defined as CPC5. The investigators assigning neurological outcome were not blinded to biomarker concentration. Patients were assigned into 2 groups based on neurological outcome: favorable neurological outcome (CPC1–2) and poor neurological outcome (CPC3–5).

Statistical Analysis
Data were missing for lactate in 33%, and for ammonia in 52%, therefore the number of valid samples for both was limited to 33% of patients. Despite the high proportion of patients with missing data for either lactate or ammonia (67%), there were no significant differences in the distribution of neurological outcomes or baseline characteristics with regard to data status (Table S1). Based on the assumption that missing data occurred at random, we used multiple imputation in order to increase the precision of calculated statistics. Multiple imputation is performed to impute missing values with estimated values by creating 5 filling-in copies to reduce bias caused by incomplete data.18,19

To analyze the ability of biomarkers to predict neurological outcome, we constructed an ROC curve and calculated the AUC. A multivariable logistic regression model was used to evaluate the association between biomarker concentration and neurological outcome, with adjustment for prospectively designated, clinically relevant prognostic indicators of neurological outcome, and within-institutional clustering effect using a generalized estimating equation.20 Cut-offs for numerical data were defined as follows: lactate, 12 mmol/L; ammonia, 100 μmol/L, determined in the previous study;14 an age of 80 years was used according to the previously reported value for age categorization;12 the median time interval from call receipt to emergency room (ER) arrival was used. We calculated the c-statistic using predicted probability of the model. Before a logistic regression model was made, multi-collinearity between biomarkers was assessed to determine whether the variance inflation factor was ≥10. Median (IQR) blood concentration of lactate and ammonia according to the time interval from witnessed arrest to ROSC was evaluated in patients who had bystander witnessed arrest and achieved ROSC in the pre-hospital setting. Spearman correlation coefficient was calculated to assess the correlation between biomarker concentration and the time interval from witnessed arrest to ROSC. P<0.05 was considered statistically significant. All statistical analysis was performed using IBM SPSS for Mac, version 22.0 (IBM, Armonk, NY, USA).

Results
A total of 3,011 patients with admission to 67 hospitals were included in the present study (Figure 1). Baseline characteristics were compared between the 2 different neurological outcomes (Table 1). The median time interval from ER arrival to blood sampling was 8 min (IQR, 5–14 min). A total of 991 patients had valid initial blood lactate and ammonia concentrations and these were used for the ROC analysis. Of those patients, 345 patients had ROSC before hospital arrival. In addition, of patients who had ROSC after hospital arrival, the number of patients with blood tests performed after ROSC was 122. Therefore, the total number of patients with blood collected after ROSC was 467. The number of patients with blood collected before ROSC was 432. Ninety-two patients did not have data on blood sampling or ROSC time. The median blood concentration of ammonia (72 μmol/L; IQR, 38–129 μmol/L) and lactate (9.2 mmol/L; IQR, 6.3–12.9 mmol/L) in patients with blood sampling after ROSC was significantly lower than in patients with blood sampling before ROSC (ammonia: 118 μmol/L; IQR, 63–172 μmol/L; lactate: 11.9 mmol/L; IQR, 9.1–15.0 mmol/L; P<0.001, P=0.001, respectively).

Lactate and Ammonia Blood Concentration vs. Outcome
The median blood concentration of ammonia (44 μmol/L; IQR, 24.8–72 μmol/L) and lactate (6.4 mmol/L; IQR, 4.5–10.2 mmol/L) in surviving patients with favorable neurological outcome was significantly lower than in those with poor neurological outcome (ammonia: 108 μmol/L; IQR, 61–172 μmol/L; lactate: 11.5 mmol/L; IQR, 8.7–14.9 mmol/L; P<0.001, P<0.001, respectively; Figure S1). The median blood concentration of ammonia (78 μmol/L; IQR, 44–125 μmol/L) and lactate (10.5 μmol/L; IQR, 8.1–14.0 mmol/L) in patients who received targeted temperature management was lower than in those who did not receive targeted temperature management (ammonia: 98 μmol/L; IQR, 49–165 μmol/L; lactate: 10.8 mmol/L; IQR, 7.6–14.6 mmol/L). There were statistically significant differences in ammonia but not in lactate (P=0.006, P=0.469, respectively).

Predictive Accuracy of Biomarkers Compared With Other Risk Factors
The AUC calculated on ROC analysis was 0.799 (95% CI: 0.763–0.835, P<0.001) in ammonia and 0.768 (95% CI: 0.720–0.816, P<0.001) in lactate, respectively (Figure 2). There were no significant differences between the 2 AUC (P=0.201). Patients with blood ammonia concentration lower than the cut-off of 100 μmol/L and lactate lower than 12 mmol/L had a significantly high frequency of favorable neurological outcome (Table S2). The AUC of patients with blood sampling after ROSC was 0.790 for ammonia (95% CI: 0.744–0.836, P<0.001) and 0.767 for lactate (95% CI: 0.714–0.820). The AUC of patients who had blood sampling before ROSC was 0.793 for ammonia (95% CI: 0.710–0.876, P<0.001) and 0.755 for lactate (95% CI: 0.637–0.872).

On multivariable logistic regression analysis with adjustment for the hospital clustering effect, lower blood ammonia and lactate concentration correlated with favorable neurological outcome. The adjusted OR for ammonia was higher than that for lactate and most other risk factors (Table 2). The median of 32 min (IQR, 26–39 min) for time interval from call receipt to ED arrival was used as a cut-off for patient classification. The c-statistic (AUC) of this model
Biomarker Blood Concentration and Witnessed Arrest-ROSC Time Interval

In the subgroup of patients with bystander-witnessed CA and pre-hospital ROSC (246/991), blood ammonia and lactate concentration according to the time interval from witnessed arrest to ROSC is shown in Figure 3. The Spearman correlation coefficient for ammonia and lactate with the time interval was 0.417 (P<0.001) and 0.333 (P<0.001), respectively. Biomarker concentrations measured at the time of patient arrival to the ED moderately, but significantly correlated with the time interval from the start of ischemia to successful resuscitation.
Discussion

In this study, the ability of initial blood ammonia and lactate to prognosticate neurological outcome of OHCA was high, as shown by the AUC of 0.80 for ammonia and 0.77 for lactate, respectively. The large sample numbers allowed for comparison of predictive accuracy between the biomarkers and other risk factors. On multivariable logistic regression analysis with adjustment for the clustering effect of hospitals, the initial blood ammonia level might have higher predictive ability than that of lactate or other traditional risk factors. This is the first study to validate the predictive accuracy of ammonia for long-term (3-month) neurological outcome using a multicenter large-scale observational cohort.

Risk estimation at admission would assist not only in physician decision-making but also in the stratification of patients screened for randomized studies and in the interpretation of the results of epidemiological studies.11,12 Prognostic indicators used for the purpose of early risk stratification need to be collected by the time of hospital admission. For this reason, there are few prognostic indicators available and useful for early risk estimation. Biomarkers that are readily reproduced across different ED, such as blood lactate and ammonia, have a certain advantage over the other risk factors, because these clinical variables, obtained from such as the Utstein templates,21,22 performed poorly due to inaccurate recall or recording of times during the highly stressful situation.11,12 Therefore, several researchers have tested the performance of initial blood lactate as an early prognostic indicator.13,22,23 It is not yet, however, a gold standard procedure in post-CA care, mainly due to its insufficient specificity for outcome prognostication.8,24

Our previous work was conducted 5 years earlier, and we studied the ability of blood ammonia and lactate to predict OHCA neurological outcome.13 According to that previous data, the AUC of ammonia and lactate were 0.714 (95% CI: 0.584–0.845) and 0.735 (95% CI: 0.574–0.896), respectively, and these were significant in the differentiation of neurological outcome of OHCA.13 On multivariate logistic regression analysis, however, there was no statistical significance due to the small size of the study. Therefore, we conducted the present study with a large-scale cohort in order to test whether blood ammonia and lactate are independently associated with OHCA outcome. The AUC reported in other studies, such as the Kasai et al and Moon et al studies,14,25 are higher than those from the current and previous studies.13,14,25 Moon et al investigated the predictive accuracy of survival outcome regardless of neurological function.25 Kasai et al included all of their patients, even those not admitted to hospital.14 It is possible that the differences in AUC are caused by differences in selection of the primary outcomes or of the subjects.

In contrast, Donnino et al reported an AUC of 0.67 for initial blood lactate.26 They also found that initial lactate level could dramatically decrease in patients with favorable neurological outcome.

Table 2. Predictors Associated With Favorable Neurological Outcome 3 Months After CA

| Predictor                          | Adjusted OR (95% CI) | P-value |
|-----------------------------------|----------------------|---------|
| Ammonia ≤100 μmol/L               | 4.55 (2.65–7.81)     | 0.001   |
| Lactate ≤12 mmol/L                | 2.63 (1.61–4.28)     | 0.003   |
| CA in an EMS vehicle              | 4.95 (2.71–9.04)     | <0.001  |
| Cardiac origin                    | 3.47 (2.55–4.72)     | <0.001  |
| Age ≤80 years                     | 3.16 (2.17–4.61)     | <0.001  |
| Bystander CPR                     | 2.39 (1.70–3.38)     | <0.001  |
| Male gender                       | 1.90 (1.47–2.46)     | <0.001  |
| First ECG as shockable rhythm     | 1.66 (1.16–2.37)     | 0.007   |
| TTM                               | 1.60 (1.08–2.36)     | 0.025   |
| Bystander witnessed               | 1.40 (1.07–1.85)     | 0.016   |
| Call receipt to ER arrival ≤32 min| 0.99 (0.75–1.30)     | 0.926   |

The c-statistic (AUC) of this model including all the 11 factors is 0.858 (95% CI: 0.850–0.866). Using a predicted probability of survival with favorable neurological outcome, the sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of this model are 36.7, 96.5, 64.4, 89.8, and 87.7, respectively. CA, cardiac arrest; ER, emergency room. Other abbreviations as in Table 1.

Figure 3. Blood ammonia and lactate vs. time from collapse to return of spontaneous circulation (ROSC) in patients with bystander-witnessed cardiac arrest who achieved pre-hospital ROSC. Correlation coefficient (R2) for the time interval and ammonia was 0.417 (P<0.001) and that for lactate was 0.333 (P<0.001). (∗): 1.5-fold higher than 75th percentile or <25th percentile; (★): 3-fold higher than 75th percentile or <25th percentile.
outcomes. The blood samples in that study were collected within the first 3h of patient arrival. It is possible that the wide time window for blood sampling might have decreased the sensitivity of outcome prediction because CA is recognized as 1 of the most time-sensitive diseases. In the present study, the blood was sampled immediately after patient arrival (median, 8min; IQR, 5–14min). The narrower time window might have improved the biomarker predictive accuracy.

The blood levels of lactate and ammonia are important prognostic indicators in resuscitation. Lactate, with a molecular weight of 89.0, is a metabolite produced by anaerobic glycolysis. Blood lactate level is considered a good index of tissue dysoxia and can indicate perfusion deficit. Ammonia, with a molecular weight of 17.0, is a component of the physiological buffer system that maintains pH homeostasis. The majority of body ammonia is metabolized with the ornithine cycle if the metabolism works normally. Blood ammonia level increases in patients with shock and hypoxia. Dysfunction of the metabolism in glycolysis (the Krebs cycle) and the ornithine cycle involve the same issue: mitochondria dysfunction in cardiac arrest, which is well studied in animal models. An animal model paradigm, however, regardless of how well it is studied, is not the same as the in vivo metabolism of these molecules in humans. Lactate does have a large network that shuttles and metabolizes it everywhere. Therefore, the difference in clearance of the blood levels is likely attributed to the differences in metabolism of the molecules and it might be the reason for the different time relationship between the biomarkers (Figure 3).

The present paper shows moderate to weak correlation between blood lactate or ammonia level and the time interval from witnessed arrest to ROSC. Blood lactate and ammonia levels might reflect the duration of ischemia/CA. Mullner et al found a moderate correlation (Spearman correlation coefficient, 0.49) between blood lactate concentration and total duration of CA in VF witnessed CA patients. Carden et al reported that blood lactate concentration and duration of CA were well fitted on a linear regression model (R², 0.86) using induced-VF animals. The present findings are consistent with these analyses. To the best of our knowledge, there have been no clinical studies on the correlation of blood ammonia concentration with CA ischemia time.

Study Limitations
This study had several limitations. The analysis was specific to the KANTO region, Japan and may not be universal. Cut-offs of lactate and ammonia may change in different communities depending on ethical issues such as how many FPR are required to predict poor outcome. Also, cut-offs may need to be changed based on the timing of blood sampling, that is, whether it is before or after ROSC. Because both ammonia and lactate were lower in patients with blood sampling after ROSC compared with before ROSC, the optimal cut-offs are different in those conditions. The outcome predictive ability, as reflected by AUC, was the same in both conditions. In addition, we used a cut-off defined in our preliminary study, therefore the present conclusion is not affected by the differences in sample timing. Second, there were a large number of patients missing biomarker data. The baseline characteristics (except the time interval from call receipt to ED arrival) or the distribution of neurological outcomes were not significantly different between the patients with and without biomarker data. Based on the assumption that missing data occurred at random, we used multiple imputation in order to increase the precision of calculated statistics. A possible unknown bias, however, still remains. Last, we are not able to rule out the possibility that initial ammonia level might affect physician decision-making of targeted temperature management. This is because the physicians were not blinded to biomarker levels. Therefore, multivariate analysis was carried out to decrease the confounding effects of other factors.

Conclusions
Initial blood ammonia level is independently associated with long-term neurological outcome, and the predictive accuracy of ammonia is higher than that of most other traditional risk factors of OHCA. Initial blood ammonia and lactate helped to accurately predict long-term neurological outcome after CA. Prognostication using these biomarkers is reasonable and they might be useful in most clinical settings.

Acknowledgments
This study was supported by the Japanese Association for Acute Medicine of Kanto. We thank Joshua W. Lampe and Sara Lampe for English editing assistance. The list of contributors is given in Appendix S1.

Author Contributions
K. Shinozaki and M. Suzuki as principal investigators, contributed to the design of study, acquisition, analysis and interpretation of data for this study, and critical revision of the manuscript for important intellectual content. K. Shinozaki contributed to drafting the work. L.B. Becker contributed to the design of study, interpretation of results, and critical revision of the manuscript for important intellectual content. T. Tagami contributed to statistical analysis and critical revision of the manuscript for important intellectual content. N. Yonemoto participated in study design, management of data, and critical revision of the manuscript. S. Oda, A. Sakurai, Y. Tahara, K. Nagao, A. Yaguchi, and N. Morimura participated in the conception of the study, the acquisition and management of data, and revision of the manuscript. All contributors approved the final version of the report.

Conflicts of Interests
This study was supported by Japanese Association for Acute Medicine of Kanto. SOS-KANTO 2012 Study group declares no conflicts of interest.

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Supplementary Files

Appendix S1. SOS-KANTO 2012 Investigators

Figure S1. Median (IQR) blood ammonia and lactate level differed significantly with regard to neurological outcome (P<0.001, P<0.001, respectively).

Table S1. Subject characteristics vs. biomarker data status

Table S2. Predictive accuracy of lactate and ammonia for favorable neurological outcome

Please find supplementary file(s); http://dx.doi.org/10.1253/circj.CJ-17-0335