Available online at www.sciencedirect.com

Resuscitation

journal homepage: www.elsevier.com/locate/resuscitation

EUROPEAN RESUSCITATION COUNCIL

Clinical paper

Ion shift index as a promising prognostic indicator in adult patients resuscitated from cardiac arrest☆

Hyoung Youn Lee [a], **Yong Hun Jung** [a], **Kyung Woon Jeung** [a,*], **Byung Kook Lee** [a], **Chun Song Youn** [b], **Najmiddin Mamadjonov** [c], **Jin Woong Kim** [d], **Tag Heo** [a], **Yong Il Min** [a]

[a] *Department of Emergency Medicine, Chonnam National University Hospital, 42 Jebong-ro, Donggu, Gwangju, Republic of Korea*

[b] *Department of Emergency Medicine, Seoul St. Mary's Hospital, The Catholic University of Korea, 222 Banpo-daero, Seocho-gu, Seoul, Republic of Korea*

[c] *Department of Medical Science, Chonnam National University Graduate School, 160 Baekseo-ro, Donggu, Gwangju, Republic of Korea*

[d] *Department of Radiology, Chosun University Hospital, 365 Pilmon-daero, Donggu, Gwangju, Republic of Korea*

Abstract

Background: Several studies reported that disturbances in cellular ion homeostasis occur following ischaemia, the magnitude of which was proportional to illness severity. The changes in serum electrolyte levels following ischaemia were minor compared with the changes in ion concentrations in the extracellular fluid. To amplify the serum electrolyte changes, we devised a new index (ion shift index), which could be calculated using commonly measured serum electrolyte levels, and explored its prognostic value in adult cardiac arrest patients.

Methods: This retrospective observational study included adult cardiac arrest survivors treated at a tertiary university hospital between January 2014 and December 2017. Using the first available serum electrolyte levels, the ion shift index was calculated as follows: ion shift index = (potassium + phosphate + magnesium) / calcium. The primary outcome was poor outcome at hospital discharge (cerebral performance categories 3–5).

Results: The area under the receiver operating characteristic curve (AUC) of ion shift index for predicting poor outcome was 0.878 (95% confidence interval [CI], 0.849–0.907). The AUC of ion shift index was greater than those of individual electrolytes (all $p < 0.001$). In multivariate analysis, higher ion shift index levels were independently associated with poor outcome (odds ratio, 2.916; 95% CI, 1.798–4.730; $p < 0.001$). The AUC of multivariate model including ion shift index was greater than that of multivariate model after excluding ion shift index ($p = 0.007$).

Conclusions: Our results suggest that the ion shift index can be helpful in the early prognostication of adult cardiac arrest patients.

Keywords: Heart, Arrest, Electrolytes, Prognosis

Abbreviations: ICF, intracellular fluid; ECF, extracellular fluid; ROS, Crestoration of spontaneous circulation; CPC, cerebral performance category; CPR, cardiopulmonary resuscitation; TTM, targeted temperature management; eGFR, estimated glomerular filtration rate; OHCA, out-of-hospital cardiac arrest; ROC, receiver operating characteristic; AUC, area under the receiver operating characteristic curve; NRI, net reclassification improvement; IDI, integrated discrimination improvement; CI, confidence interval; IHCA, in-hospital cardiac arrest; WLST, withdrawal of life-sustaining treatments.

☆ Chonnam National University Hospital Institutional Review Board Protocol No. CNUH-2018-215

* Corresponding author at: Department of Emergency Medicine, Chonnam National University Hospital, 42 Jebong-ro, Donggu, Gwangju, Republic of Korea.

E-mail address: neoneti@hanmail.net (K.W. Jeung).

https://doi.org/10.1016/j.resuscitation.2019.02.020

Received 22 October 2018; Received in revised form 5 February 2019; Accepted 11 February 2019

Introduction

The rate of survival with good neurologic outcome after cardiac arrest is still low.[1] The early prediction of outcome after cardiac arrest would help clinicians in choosing the appropriate treatment strategy and in providing early estimates of prognoses to patients' families; however, it remains a challenge.

In normal physiological state, cellular ion homeostasis is maintained primarily by energy-dependent mechanisms including cell membrane ion pumps. High-energy phosphate depletion during ischaemia leads to failure of the energy-dependent mechanisms to maintain ionic gradients across cell membranes. This, in turn, induces shifts of ions between intracellular fluid (ICF) and extracellular fluid (ECF) compartments: the ions that are predominantly present in the ICF leak from the ICF compartment, while the ions that are predominantly present in the ECF enter the cells.[2–6] Several studies have reported that the magnitude of the ion shift is proportional to the severity of ischaemic injury and that, when the injury is severe, the disturbances of ion homeostasis persist even after the restoration of blood flow.[2,7,8] In a study that investigated the changes in extracellular ion concentrations in the brains of rats during transient forebrain ischaemia,[8] the maximal extracellular potassium level was significantly higher in the animals experiencing prolonged ischaemia than in those experiencing a shorter duration of ischaemia. In a study that investigated the relationship between electrophysiological and metabolic recoveries in cats undergoing transient cerebral ischaemia,[7] animals without recovery of electroencephalographic activity after reperfusion showed a significant increase in the brain tissue calcium content, while those with recovery of electroencephalographic activity did not.

In view of the above studies,[2–8] ion concentrations in the ECF after restoration of spontaneous circulation (ROSC) may provide useful information regarding illness severity and outcome following cardiac arrest. Although serum electrolyte level is not a direct measure of ion concentrations in the ECF, it is likely to reflect the changes in ion concentrations in the ECF as the ion shift between the ICF and ECF compartments would create a concentration gradient between the ECF and blood compartments, resulting in the shift of ions between ECF and blood. In fact, a number of studies have reported changes in serum electrolyte levels following cardiac arrest in the same direction as the changes in extracellular ion concentrations following ischaemia (reported in previous experimental studies).[9–17] A few studies have examined the associations between serum electrolyte levels and outcomes in cardiac arrest patients,[18–22] but yielded conflicting results. These conflicting results may be due, in part, to the fact that only minor changes in serum electrolyte levels occur following ischaemia compared with those that occur in the ECF.[2]

We calculated the ratio between the concentration of serum electrolytes that shift from the ICF to the ECF compartment following ischaemia (potassium, phosphate, and magnesium) and the concentration of serum calcium that shifts from the ECF to the ICF compartment, and explored its prognostic value in adult cardiac arrest patients. This ratio (referred to as ion shift index) may better reflect the magnitude of ion shift following ischaemia than individual serum electrolytes, since the numerator and denominator in the ratio change in opposite directions following ischaemia. We hypothesised that the ion shift index level would be significantly associated with outcome after cardiac arrest and that it would predict the outcome better than individual electrolyte levels.

Methods

Study design, population, and setting

This study was a retrospective observational study of adult cardiac arrest patients treated at a tertiary hospital located in Gwangju, Korea, from January 2014 to December 2017. The Institutional Review Board of the Chonnam National University Hospital approved this study (CNUH-2018-215) and waived the need for informed consent.

Adult patients (aged 18 years or older) who were resuscitated after cardiac arrest were included in the study. Patients (1) who experienced cardiac arrest due to trauma; (2) who had haemorrhagic or ischaemic stroke on brain imaging obtained after ROSC; (3) who had a poor pre-arrest neurologic status (defined as cerebral performance category [CPC] 3 or 4); (4) whose serum electrolyte levels measured within 6 h after ROSC were not available; (5) who had a pre-existing medical condition that could influence the electrolyte levels; (6) whose cardiac arrest was secondary to electrolyte disturbances; (7) who received sodium bicarbonate, calcium, potassium, or magnesium prior to blood sampling; or (8) with missing data on arrest and cardiopulmonary resuscitation (CPR) were excluded.

Patients were given post-cardiac arrest care based on the recent resuscitation guidelines.[23,24] All patients who were unable to obey commands were treated with targeted temperature management (TTM) with a target core body temperature of 33 °C–36 °C, except those with active bleeding, refractory haemodynamic instability, possible causes of coma other than cardiac arrest, terminal malignancy, or poor pre-arrest neurologic status (CPC 3 or 4).

We collected the following data from patients' medical records: sex, age, comorbidities, location of arrest, presence of a witness on collapse, bystander CPR, first monitored rhythm, dose of adrenaline (epinephrine) administered during CPR, time to ROSC (time interval from recognition of cardiac arrest to ROSC), cause of arrest, Glasgow Coma Scale score upon admission, sequential organ failure assessment score within the first 24 h, TTM and CPC at hospital discharge.[25] An investigator blinded to the study hypothesis determined the CPC score by medical record review. Using the first available laboratory data after ROSC, we also collected the levels of patients' serum electrolytes (sodium, potassium, chloride, phosphate, calcium, and magnesium), levels of parameters known as outcome predictors (glucose and lactate),[26,27] levels of parameters that might affect electrolyte levels (pH, haemoglobin, albumin, and creatinine),[28,29] estimated glomerular filtration rate (eGFR), and time interval from ROSC to blood sampling. Serum electrolyte levels were determined at the hospital laboratory using UniCel DxC 800 Synchron Clinical Systems (Beckman Coulter, Fullerton, USA). The eGFR was calculated according to the Chronic Kidney Disease Epidemiology Collaboration equation.[30] The ion shift index was calculated using the following equation:

$$\text{Ion shift index (arbitrary unit)} = \frac{\text{Potassium (mmol l} - 1) + \text{Phosphate (mmol l} - 1) + \text{Magnesium (mmol l} - 1)}{\text{Calcium (mmol l} - 1)}$$

Sodium and chloride were not included in the calculation of index, because their high values and wide reference ranges might mask the effects of other electrolytes included in the index. In order to compare the prognostic performance of ion shift index with that of an existing prognostication tool, out-of-hospital cardiac arrest (OHCA) score was calculated in patients with witnessed OHCA.[31] Our primary outcome was poor outcome at hospital discharge, which was defined as CPC 3–5.

Statistical analysis

Data were analysed using R language version 3.3.3 (R Foundation for Statistical Computing, Vienna, Austria), T&F program version 2.5 (YooJin BioSoft, Goyang, Korea) and IBM SPSS Statistics for Windows version 22.0 (SPSS Inc., Chicago, USA). Comparisons of continuous variables between independent groups were performed using independent t-test or Mann–Whitney *U* test, as appropriate. Comparisons of categorical variables were performed using $\chi 2$ or Fisher's exact tests, as appropriate. Correlation between continuous variables was assessed using Spearman's rank correlation coefficient. Receiver operating characteristic (ROC) analyses were performed to examine the prognostic performances of ion shift index, individual electrolytes included in the index, and lactate. Comparisons of the areas under the ROC curves (AUC) were conducted using the method of DeLong et al.[32] A multivariate logistic regression model was constructed using backward stepwise procedure as variable selection method to minimise Akaike's information criterion (model 1). Variables with $p < 0.2$ in the univariate analyses were included in the multivariate regression model, and the ion shift index was used as a fixed covariate. Multicollinearity was assessed by calculating variance inflation factors, with a value greater than 2.0 indicating significant collinearity between variables. To determine the contribution of ion shift index in association with other predictive factors in predicting poor outcome, we constructed another multivariate prediction model (model 2) by removing the ion shift index from the multivariate logistic regression model (model 1) and assessed the prognostic performances of the multivariate models using ROC analysis. To evaluate the impact of ion shift index on outcome prediction in more detail, we calculated net reclassification improvement (NRI) (using categories based on deciles of the predicted risk estimates) and integrated discrimination improvement (IDI).[33] A two-tailed significance level of 0.05 was used for statistical significance.

Results

Patient characteristics

A total of 1048 adult cardiac arrest survivors were treated during the study period. Of these patients, 468 were excluded as described in Fig. 1. Thus, the remaining 580 patients were included in this study and were stratified into two groups based on their outcome at hospital discharge: 213 with good outcome and 367 with poor outcome. Clinical and laboratory characteristics of the included patients are shown in Table 1. The patients with poor outcomes had higher levels of glucose, lactate, creatinine, potassium, phosphate, and magnesium than those with good outcomes, but had lower levels of pH, haemoglobin, albumin, eGFR, and calcium. The ion shift index was significantly higher in patients with poor outcome than in those with good outcome ($p < 0.001$).

Prognostic performances of ion shift index

The proportion of patients with poor outcome increased as the ion shift index increased (Fig. 2). The ion shift index level was significantly correlated with time to ROSC ($r = 0.416$; $p < 0.001$) as well as lactate ($r = 0.576$; $p < 0.001$). In the ROC analysis (Table 2 and Supplemental Fig. 1), the AUC of ion shift index was 0.878 (95% confidence interval [CI], 0.849–0.907). The AUC of ion shift index was significantly greater than that of lactate as well as those of individual electrolytes that were included in the ion shift index (all $p < 0.001$). In the subgroup of patients with witnessed OHCA, the AUC of ion shift index (0.879; 95% CI, 0.838–0.920) was comparable to that of the OHCA score (0.863; 95% CI, 0.819–0.908).

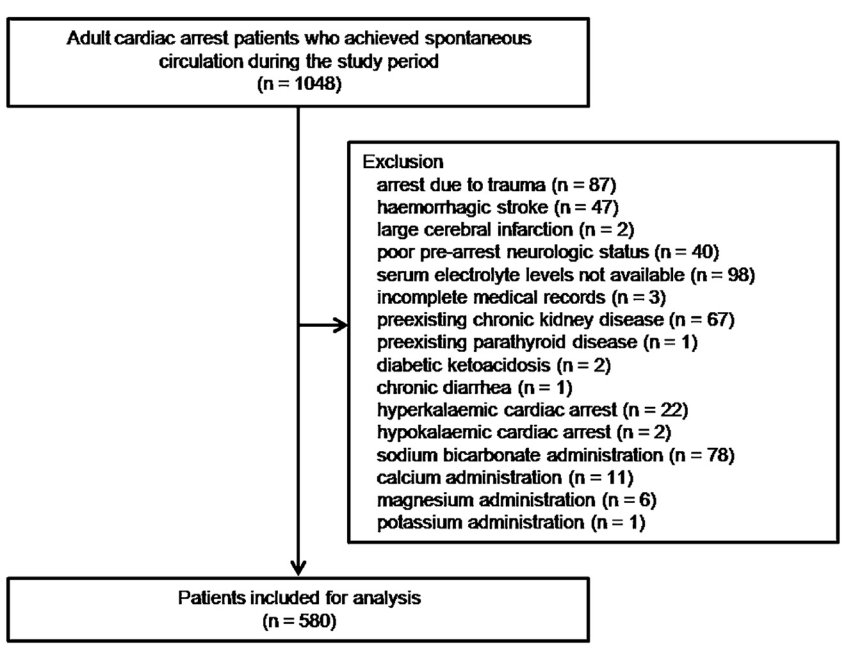

Fig. 1 – Flow diagram of the patient selection process in the present study.

Table 1 – Clinical and laboratory characteristics stratified by outcome at hospital discharge.

	Total (n = 580)	Good outcome (n = 213)	Poor outcome (n = 367)	*p*-value	OR (95% CI)
Age, years	62 (51–73)	57 (48–68)	66 (54–75)	<0.001	1.028 (1.016–1.039)
Male sex	390 (67.2)	157 (73.7)	233 (63.5)	0.012	0.620 (0.428–0.900)
Comorbidities					
Coronary artery disease	59 (10.2)	31 (14.6)	28 (7.6)	0.009	0.485 (0.282–0.834)
Arrhythmia	33 (5.7)	13 (6.1)	20 (5.4)	0.743	0.887 (0.432–1.821)
Heart failure	28 (4.8)	13 (6.1)	15 (4.1)	0.278	0.656 (0.306–1.406)
CVA	28 (4.8)	13 (6.1)	15 (4.1)	0.278	0.656 (0.306–1.406)
Hypertension	208 (35.9)	70 (32.9)	138 (37.6)	0.252	1.231 (0.863–1.757)
Diabetes	117 (20.2)	32 (15.0)	85 (23.2)	0.019	1.705 (1.090–2.667)
Pulmonary disease	43 (7.4)	9 (4.2)	34 (9.3)	0.029	2.314 (1.088–4.925)
Neurologic disease other than CVA	21 (3.6)	2 (0.9)	19 (5.2)	0.019	5.760 (1.329–24.973)
Malignancy	49 (8.4)	9 (4.2)	40 (10.9)	0.007	2.773 (1.318–5.834)
Liver cirrhosis	13 (2.2)	3 (1.4)	10 (2.7)	0.311	1.961 (0.534–7.205)
Location of arrest				0.022	
Out-of-hospital	437 (75.3)	149 (70.0)	288 (78.5)		Reference
In-hospital	143 (24.7)	64 (30.0)	79 (21.5)		0.639 (0.435–0.938)
Witnessed collapse	402 (69.3)	181 (85.0)	221 (60.2)	<0.001	0.268 (0.174–0.411)
Bystander CPR	393 (67.8)	172 (80.8)	221 (60.2)	<0.001	0.361 (0.242–0.538)
First monitored rhythm				<0.001	
Non-shockable	388 (66.9)	76 (35.7)	312 (85.0)		Reference
Shockable	192 (33.1)	137 (64.3)	55 (15.0)		0.098 (0.065–0.146)
Adrenaline administered during CPR, mg	2 (1–5)	0 (0–2)	3 (2–6)	<0.001	1.533 (1.392–1.687)
Time to ROSC, min	25 (12–40)	14 (7–23)	31 (19–45)	<0.001	1.071 (1.056–1.087)
Aetiology				<0.001	
Non-cardiac	249 (42.9)	28 (13.1)	221 (60.2)		Reference
Cardiac	331 (57.1)	185 (86.9)	146 (39.8)		0.100 (0.064–0.157)
Glasgow Coma Scale	3 (3–7)	9 (4–15)	3 (3–3)	<0.001	0.664 (0.618–0.714)
SOFA score	10 (7–13)	6 (4–9)	12 (10–13)	<0.001	1.587 (1.471–1.713)
Time from ROSC to blood sampling, min	50 (20–102)	59 (29–114)	46 (7–95)	0.054	0.998 (0.995–1.000)
Glucose, mg dl^{-1}	228 (166–307)	203 (150–265)[a]	247 (180–314)[b]	0.003	1.002 (1.001–1.004)
Lactate, mmol l^{-1}	9.0 (5.4–13.3)	5.4 (3.6–8.3)[c]	11.1 (7.9–14.8)[d]	<0.001	1.277 (1.215–1.341)
pH	7.160 (6.970–7.310)	7.319 (7.240–7.380)[e]	7.040 (6.890–7.200)[f]	<0.001	0 (0–0.002)
Haemoglobin, g dl^{-1}	12.8 (10.7–14.4)	14.2 (12.4–15.1)	12.0 (9.9–13.6)	<0.001	0.721 (0.665–0.781)
Albumin, g dl^{-1}	3.1 (2.5–3.6)	3.6 (3.2–3.9)	2.8 (2.3–3.3)	<0.001	0.182 (0.130–0.254)
Creatinine, mg dl^{-1}	1.2 (1.0–1.5)	1.0 (0.9–1.2)	1.3 (1.0–1.6)	<0.001	4.549 (2.850–7.262)
eGFR, ml min^{-1} per 1.73 m^2	63.32 ± 26.19	75.41 ± 23.29	56.31 ± 25.22	<0.001	0.969 (0.961–0.977)
Sodium, mmol l^{-1}	141 (138–144)	141 (139–143)	141 (137–145)	0.494	1.011 (0.979–1.045)
Potassium, mmol l^{-1}	4.1 (3.6–4.8)	3.7 (3.4–4.1)	4.4 (3.8–5.4)	<0.001	2.99 (2.307–3.875)
Chloride, mmol l^{-1}	107 (104–110)	107 (104–109)	107 (103–110)	0.905	0.998 (0.971–1.026)
Phosphate, mmol l^{-1}	2.1 (1.5–2.7)	1.4 (1.1–1.8)	2.5 (1.9–2.9)	<0.001	6.438 (4.627–8.959)
Calcium, mmol l^{-1}	1.9 (1.8–2.1)	2.0 (1.9–2.2)	1.9 (1.7–2.0)	<0.001	0.078 (0.036–0.172)
Magnesium, mmol l^{-1}	0.9 (0.8–1.1)	0.9 (0.8–1.0)	1.0 (0.9–1.2)	<0.001	36.387 (12.726–104.039)
Ion shift index	3.78 (3.04–4.56)	2.97 (2.68–3.37)	4.31 (3.69–4.91)	<0.001	8.424 (5.889–12.050)

Categorical variables are presented as n (%). Continuous variables are presented as medians with interquartile ranges or mean ± standard deviation. OR, odds ratio; CI, confidence interval; CVA, cerebrovascular accident; CPR, cardiopulmonary resuscitation; ROSC, restoration of spontaneous circulation; SOFA, sequential organ failure assessment; eGFR, estimated glomerular filtration rate.
Missing data; [a] n = 3; [b] n = 2; [c] n = 13; [d] n = 3; [e] n = 5; [f] n = 1.

Association between ion shift index level and outcome

In the multivariate logistic regression analysis (model 1 in the Table 3), a higher ion shift index level was independently associated with poor outcome at hospital discharge (odds ratio, 2.916; 95% CI, 1.798–4.730; $p < 0.001$). The association between ion shift index and outcome remained significant even when pH, eGFR or dose of adrenaline, all of which could affect the serum electrolyte level, was forced into the multivariate model as a fixed covariate (Supplemental Table 1). Of the 580 patients included in this study, 276 (47.6%) underwent TTM. Thus, a subgroup analysis was performed to assess TTM and non-TTM cohorts separately. In this subgroup analysis, the association between ion shift index level and outcome remained significant in both TTM and non-TTM cohorts (Supplemental Table 2). Another subgroup analysis was performed to assess OHCA and in-hospital cardiac arrest (IHCA) cohorts separately, and this revealed a significant association between ion shift index level and outcome for both OHCA and IHCA cohorts. Finally, in order to further evaluate the effect of eGFR on the association between ion shift index level and outcome, we stratified the overall cohort into two subgroups based on eGFR: ≥ 60 and <60 ml min^{-1} per 1.73 m^2,[34] and performed subgroup analysis. In this subgroup analysis, the association between ion shift index level and outcome remained significant in the both subgroups.

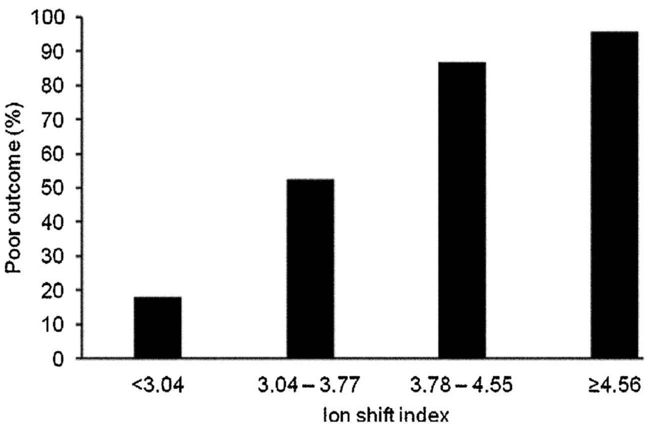

Fig. 2 – Proportion of patients with poor outcome at hospital discharge in relation to ion shift index. The overall cohort was divided into four categories based on the distribution of ion shift index, using quartiles as cut-off values between categories.

Prognostic performance of ion shift index in conjunction with other predictors

The AUC for the multivariate logistic regression model including ion shift index (model 1 in the Table 3) was 0.958 (95% CI, 0.942–0.974) (Table 4 and Supplemental Fig. 2). This value was significantly higher than the AUC for ion shift index alone ($p < 0.001$) as well as the AUC for the multivariate logistic regression model excluding the ion shift index (model 2 in the Table 3) ($p = 0.007$). On including ion shift index, the multivariate logistic regression model achieved significant NRI (0.150; 95% CI, 0.060–0.241) and IDI (0.025; 95% CI, 0.012–0.039) compared with the multivariate logistic regression model from which the ion shift index was excluded (Supplemental Table 3).

Discussion

Our multivariate analysis showed that higher ion shift index levels were significantly associated with poor outcome. This finding supports our hypothesis that the ion shift index would be significantly associated with outcome after cardiac arrest. In addition, higher ion shift index levels maintained their association with poor outcome even after forcing potentially confounding variables including pH, eGFR or dose of adrenaline into the multivariate model. These findings suggest that the ion shift index levels can be used for prognostication regardless of these factors.

Our study findings are in line with the results of previous studies that reported significant associations between serum electrolyte levels and outcomes after cardiac arrest.[18,19] In an observational study including 98 cardiac arrest patients, Skrifvars et al. reported that a higher serum potassium level during the first 72 h was independently associated with higher mortality.[18] A higher serum phosphate level was found to be independently associated with poor outcome at hospital discharge in a study including 674 cardiac arrest survivors.[19] Although several ratios of intracellular ions have been used as chemical means for the detection of early ischaemic changes in experimental studies,[6] the ion shift index is, to our knowledge, the first to combine serum electrolyte levels for the prediction of outcome after cardiac arrest. In our study, the ion shift index had significantly better performance in predicting poor outcome than the individual electrolyte levels. This finding indicates the superiority of ion shift index as a prognostic indicator compared with individual electrolytes.

Besides the changes in serum electrolyte levels, many other alterations in blood ion levels occur following cardiac arrest. In a study conducted by Makino et al. that analysed blood gas and chemistry variables using the Stewart-Figge methodology,[35] strong ion gap, reflecting unmeasured anions, was significantly increased in cardiac arrest patients compared to control patients with minor injuries, and contributed approximately 33% to the development of post-cardiac arrest acidosis. The changes in unmeasured anions after cardiac arrest may also provide important prognostic information. However, its prognostic significance has not yet been determined, and warrants further study.

The ion shift index appears valuable as an early prognostic indicator after cardiac arrest. Its prognostic performance was superior to those of other known prognostic biomarkers obtainable in the early hours after ROSC, including serum lactate and phosphate.[19,26,36] The OHCA score is a risk score for predicting outcome after OHCA based on first monitored rhythm, no-flow and low-flow intervals, and admission levels of serum creatinine and lactate, and has shown good prognostic

Table 2 – Performances of ion shift index, lactate, potassium, phosphate, magnesium, and calcium in predicting poor outcome.

	AUC (95% CI)	*p*-value	Cutoff	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	*p*-value for AUC comparison
Ion shift index	0.878 (0.849–0.907)	<0.001	3.507	82.8	82.2	69.4	73.5	Reference
Lactate	0.790 (0.750–0.829)	<0.001	8.35	71.4	75.0	68.9	60.0	<0.001
Potassium	0.748 (0.708–0.788)	<0.001	4.25	54.8	85.9	67.4	52.5	<0.001
Phosphate	0.826 (0.792–0.861)	<0.001	1.855	76.8	77.9	68.9	64.3	<0.001
Magnesium	0.681 (0.638–0.725)	<0.001	1.054	41.1	87.3	69.9	49.5	<0.001
Calcium	0.690 (0.646–0.733)	<0.001	1.913	57.8	72.3	81.7	40.2	<0.001

AUC, area under curve; CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value.

Table 3 – Multivariate logistic regression analyses of poor outcome at hospital discharge.

	OR (95% CI)	*p*-value
Model 1		
Ion shift index	2.916 (1.798–4.730)	<0.001
Age, year	1.029 (1.007–1.051)	0.008
In-hospital arrest	0.449 (0.187–1.079)	0.073
Bystander CPR	0.653 (0.313–1.364)	0.257
Shockable rhythm	0.310 (0.153–0.628)	0.001
Time to ROSC, min	1.041 (1.018–1.065)	<0.001
Cardiac aetiology	0.198 (0.090–0.433)	<0.001
Glasgow Coma Scale	0.823 (0.744–0.911)	<0.001
SOFA score	1.260 (1.118–1.420)	<0.001
Time from ROSC to blood sampling, min	1.004 (0.999–1.008)	0.101
Albumin, g dl^{-1}	0.674 (0.397–1.145)	0.145
Model 2		
Age, year	1.023 (1.003–1.044)	0.024
In-hospital arrest	0.528 (0.234–1.195)	0.126
Bystander CPR	0.756 (0.374–1.528)	0.435
Shockable rhythm	0.252 (0.130–0.491)	<0.001
Time to ROSC, min	1.047 (1.025–1.069)	<0.001
Cardiac aetiology	0.178 (0.084–0.379)	<0.001
Glasgow Coma Scale	0.816 (0.740–0.899)	<0.001
SOFA score	1.380 (1.238–1.539)	<0.001
Time from ROSC to blood sampling, min	1.002 (0.998–1.006)	0.335
Albumin, g dl^{-1}	0.484 (0.298–0.785)	0.003

The multivariate model 1 included all variables with $p < 0.2$ in univariate analyses, whereas model 2 included the variables in model 1 except ion shift index. In the Hosmer-Lemeshow test, the *p*-value of the model 1 was 0.099 and that of the model 2 was 0.086. OR, odds ratio; CI, confidence interval; CPR, cardiopulmonary resuscitation; ROSC, restoration of spontaneous circulation; SOFA, sequential organ failure assessment.

Table 4 – Prognostic performances of multivariate logistic regression model including ion shift index (model 1), multivariate logistic regression model after excluding ion shift index (model 2) and ion shift index alone.

	AUC (95% CI)	*p*-value	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	*p*-value for AUC comparison
Model 1	0.958 (0.942–0.974)	< 0.001	89.9	90.1	96.3	72.1	Reference
Model 2	0.950 (0.932–0.968)	< 0.001	89.9	86.9	95.0	70.2	0.007
Ion shift index alone	0.878 (0.849–0.907)	< 0.001	82.8	82.2	69.4	73.5	<0.001

AUC, area under curve; CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value.

performance.[31,37] Although the ion shift index exhibited comparable prognostic performance to the OHCA score, our index has many advantages over the OHCA score. The calculation of OHCA score requires knowledge of the no-flow interval, which is difficult to estimate with accuracy or even unobtainable in patients with unwitnessed collapse, as well as the natural log transformation of the variables. However, the calculation of ion shift index is relatively easy and only requires knowledge of serum electrolyte levels, which can be rapidly measured in most hospital laboratories. Furthermore, the ion shift index can be applied to both IHCA and OHCA, in contrast to the OHCA score, which was originally intended for use in OHCA. In our study, higher ion shift index levels were consistently associated with poor outcome in both IHCA and OHCA cohorts. In addition, the ion shift index can be applied irrespective of whether the patient receives TTM or not. In our study, higher ion shift index levels were consistently associated with poor outcome in both TTM and non-TTM cohorts.

In the present study, the AUC value of ion shift index indicated moderate predictive performance, and the positive predictive value of ion shift index alone was not high enough to be useful in clinical decision-making. In addition, the multivariate model including ion shift index and other significant predictors showed significantly better prognostic performance compared with the ion shift index alone or the multivariate model after excluding ion shift index. These findings suggest that the ion shift index should be used in combination with other outcome predictors. Recent resuscitation guidelines recommend delaying neurological prognostication until at least 72 h after ROSC to avoid premature withdrawal of life-sustaining treatments (WLST) in patients with a chance of neurological recovery.[23,24] In our study, the multivariate logistic regression model including ion shift index and other significant predictors was not accurate enough for use in decision-making on WLST. Thus, our findings also do not support WLST in the early hours after ROSC.

Our study had several limitations. First, it was a single-centre retrospective study. Thus, further study is needed to confirm our findings. Importantly, our findings were not validated in separate cohorts. Our index needs to be validated using independent samples. Second, among the 1048 patients reviewed for inclusion, 98 (9.4%) were excluded from the study due to lack of data on serum electrolyte levels. This might have caused selection bias. Besides these patients, a substantial number of patients were excluded according to predefined criteria, which could limit the generalisability of our findings. Third, total calcium was used for the calculation of ion shift index in this study, as ionised calcium level was not available for most patients of our study. Fourth, although we excluded patients who had experienced cardiac arrest secondary to electrolyte disturbances, some patients might have had electrolyte derangements prior to cardiac arrest, and this could have affected our results. Fifth, a single investigator determined CPC scores by reviewing medical records, and inter-reviewer reliability for this assessment was not determined. A recent study reported that using CPC scores for classifying good versus poor neurologic outcomes at hospital discharge resulted in variable inter-reviewer agreement.[38] Thus, our method for determining outcomes might have biased the results. Sixth, although the investigator who determined CPC score was blinded to the study hypothesis, other investigators were not. In addition, treating physicians were not blinded to the serum electrolyte levels. Thus, a self-fulfilling prophecy might have confounded our results.

Conclusions

The ion shift index level was independently associated with outcome at hospital discharge and appeared to provide additional prognostic information in combination with other prognostic indicators.

Conflicts of interest

None.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.resuscitation.2019.02.020.

REFERENCES

1. Lemiale V, Dumas F, Mongardon N, et al. Intensive care unit mortality after cardiac arrest: the relative contribution of shock and brain injury in a large cohort. Intensive Care Med 2013;39:1972–80.
2. Hossmann KA, Sakaki S, Zimmerman V. Cation activities in reversible ischemia of the cat brain. Stroke 1977;8:77–81.
3. Hill JL, Gettes LS. Effect of acute coronary artery occlusion on local myocardial extracellular K+ activity in swine. Circulation 1980;61:768–78.
4. Raab W. Myocardial electrolyte derangement: crucial feature of pluricausal, so-called coronary, heart disease (dysionic cardiopathy). Ann N Y Acad Sci 1969;147:627–86.
5. Jennings RB, Sommers HM, Kaltenbach JP, West JJ. Electrolyte alterations in acute myocardial ischemic injury. Circ Res 1964;14:260–9.
6. Lie JT, Pairolero PC, Holley KE, McCall JT, Thompson Jr HK, Titus JL. Time course and zonal variations of ischemia-induced myocardial cationic electrolyte derangements. Circulation 1975;51:860–6.
7. Schmidt-Kastner R, Hossmann KA, Grosse Ophoff B. Relationship between metabolic recovery and the EEG prolonged ischemia of cat brain. Stroke 1986;17:1164–9.
8. Stiefel MF, Tomita Y, Marmarou A. Secondary ischemia impairing the restoration of ion homeostasis following traumatic brain injury. J Neurosurg 2005;103:707–14.
9. Cairns CB, Niemann JT, Pelikan PC, Sharma J. Ionized hypocalcemia during prolonged cardiac arrest and closed-chest CPR in a canine model. Ann Emerg Med 1991;20:1178–82.
10. Urban P, Scheidegger D, Buchmann B, Barth D. Cardiac arrest and blood ionized calcium levels. Ann Intern Med 1988;109:110–3.
11. Niemann JT, Cairns CB. Hyperkalemia and ionized hypocalcemia during cardiac arrest and resuscitation: possible culprits for postcountershock arrhythmias? Ann Emerg Med 1999;34:1–7.
12. Gando S, Tedo I, Kubota M. A comparison of serum ionized calcium in arterial and mixed venous blood during CPR. Ann Emerg Med 1990;19:850–6.
13. Gando S, Igarashi M, Kameue T, Nanzaki S. Ionized hypocalcemia during out-of-hospital cardiac arrest and cardiopulmonary resuscitation is not due to binding by lactate. Intensive Care Med 1997;23:1245–50.
14. Youngquist ST, Heyming T, Rosborough JP, Niemann JT. Hypocalcemia following resuscitation from cardiac arrest revisited. Resuscitation 2010;81:117–22.
15. Geddes LA, Roeder RA, Rundell AE, Otlewski MP, Kemeny AE, Lottes AE. The natural biochemical changes during ventricular fibrillation with cardiopulmonary resuscitation and the onset of postdefibrillation pulseless electrical activity. Am J Emerg Med 2006;24:577–81.
16. Bleske BE, Song J, Chow MS, Kluger J, White CM. Hematologic and chemical changes observed during and after cardiac arrest in a canine model–a pilot study. Pharmacotherapy 2001;21:1187–91.
17. Martin GB, Nowak RM, Cisek JE, Carden DL, Tomlanovich MC. Hyperkalemia during human cardiopulmonary resuscitation: incidence and ramifications. J Emerg Med 1989;7:109–13.
18. Skrifvars MB, Pettilä V, Rosenberg PH, Castrén M. A multiple logistic regression analysis of in-hospital factors related to survival at six months in patients resuscitated from out-of-hospital ventricular fibrillation. Resuscitation 2003;59:319–28.
19. Jung YH, Lee BK, Jeung KW, et al. Prognostic value of serum phosphate level in adult patients resuscitated from cardiac arrest. Resuscitation 2018;128:56–62.
20. Yanagawa Y, Sakamoto T, Sato H. Relationship between laboratory findings and the outcome of cardiopulmonary arrest. Am J Emerg Med 2009;27:308–12.
21. Cho YM, Lim YS, Yang HJ, et al. Blood ammonia is a predictive biomarker of neurologic outcome in cardiac arrest patients treated with therapeutic hypothermia. Am J Emerg Med 2012;30:1395–401.
22. Perucki WH, Hiendlmayr B, O'Sullivan DM, Gunaseelan AC, Fayas F, Fernandez AB. Magnesium Levels and Neurologic Outcomes in Patients Undergoing Therapeutic Hypothermia After Cardiac Arrest. Ther Hypothermia Temp Manag 2018;8:14–7.
23. Peberdy MA, Callaway CW, Neumar RW, et al. Part 9: post-cardiac arrest care: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation 2010;122:S768–86.
24. Callaway CW, Donnino MW, Fink EL, et al. Part 8: Post-Cardiac Arrest Care: 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation 2015;132:S465–82.
25. Booth CM, Boone RH, Tomlinson G, Detsky AS. Is this patient dead, vegetative, or severely neurologically impaired? Assessing outcome for comatose survivors of cardiac arrest. JAMA 2004;291:870–9.
26. Lee DH, Cho IS, Lee SH, et al. Correlation between initial serum levels of lactate after return of spontaneous circulation and survival and neurological outcomes in patients who undergo therapeutic hypothermia after cardiac arrest. Resuscitation 2015;88:143–9.
27. Kim SH, Choi SP, Park KN, et al. Association of blood glucose at admission with outcomes in patients treated with therapeutic hypothermia after cardiac arrest. Am J Emerg Med 2014;32:900–4.
28. Lin CH, Tu YF, Chiang WC, Wu SY, Chang YH, Chi CH. Electrolyte abnormalities and laboratory findings in patients with out-of-hospital cardiac arrest who have kidney disease. Am J Emerg Med 2013;31:487–93.
29. Tonelli M, Sacks F, Pfeffer M, Gao Z, Curhan G. Cholesterol And Recurrent Events Trial Investigators. Relation between serum

phosphate level and cardiovascular event rate in people with coronary disease. Circulation 2005;112:2627–33.
30. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med 2009;150:604–12.
31. Adrie C, Cariou A, Mourvillier B, et al. Predicting survival with good neurological recovery at hospital admission after successful resuscitation of out-of-hospital cardiac arrest: the OHCA score. Eur Heart J 2006;27:2840–5.
32. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. Biometrics 1988;44:837–45.
33. Pencina MJ, D'Agostino Sr RB, D'Agostino Jr RB, Vasan RS. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. Stat Med 2008;27:157–72.
34. Kidney Disease Improving Global Outcomes. Chapter 1: Definition and classification of CKD. Kidney Int Suppl 2013;3:19–62.
35. Makino J, Uchino S, Morimatsu H, Bellomo R. A quantitative analysis of the acidosis of cardiac arrest: a prospective observational study. Crit Care 2005;9:R357–E362.
36. Shinozaki K, Oda S, Sadahiro T, et al. Blood ammonia and lactate levels on hospital arrival as a predictive biomarker in patients with out-of-hospital cardiac arrest. Resuscitation 2011;82:404–9.
37. Hunziker S, Bivens MJ, Cocchi MN, et al. International validation of the out-of-hospital cardiac arrest score in the United States. Crit Care Med 2011;39:1670–4.
38. Ajam K, Gold LS, Beck SS, Damon S, Phelps R, Rea TD. Reliability of the Cerebral Performance Category to classify neurological status among survivors of ventricular fibrillation arrest: a cohort study. Scand J Trauma Resusc Emerg Med 2011;19:38.