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Hypernatremia is associated with poor long-term neurological outcomes in out-of-hospital cardiac arrest survivors

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ABSTRACT

Background: Brain oedema after cardiac arrest is strongly associated with poor neurological outcomes. Excessive sodium supplementation may increase serum osmolarity and facilitate brain oedema development in cardiac arrest survivors. We aimed to investigate the association of serum sodium levels with long-term neurological outcomes in out-of-hospital cardiac arrest (OHCA) survivors.
Methods: This retrospective observational study used a multicentre prospective cohort registry of OHCA survivors collected between December 2013 and February 2018. We analyzed the association of serum sodium levels at the return of spontaneous circulation (ROSC) (Sodium 0H) and at 24 h after ROSC (Sodium 24H) with 1-year neurological outcomes in OHCA survivors. Patients with 1-year cerebral performance categories (CPC) 1 and 2 were included in the good outcome group while those with CPC 3, 4, and 5 were included in the poor outcome group.
Results: Among 277 patients, 84 (30.3%) and 193 (69.7%) were in the good and poor outcome groups, respectively. Compared with the good outcome group, the poor outcome group showed significantly higher Sodium 24H levels (140 mEq/L vs. 137.4 mEq/L, $p < 0.001$). Increased serum sodium levels per 1 mEq/L increased the risk of poor 1-year CPC by 13% (adjusted odds ratio = 1.13; 95% CI, 1.04 – 1.23; $p = 0.004$).
Conclusions: Relatively high Sodium 24H levels showed a strong and independent association with poor long-term neurological outcomes in OHCA survivors. These findings may be applied in therapeutic strategies for improving neurological outcomes in OHCA survivors.

1. Background

Brain oedema is a potential therapeutic target for reducing brain damage in patients with post-cardiac arrest syndrome (PCAS) [1]. Cytotoxic, ionic, and vasogenic oedema result in brain oedema after cardiac arrest [2,3]. Cytotoxic and ionic oedema occur during the no-flow and low-flow periods when the blood-brain barrier (BBB) is still intact [4]. After the return of spontaneous circulation (ROSC), the reperfusion of oxygenated blood induces endothelial dysfunction and weakens tight junctions between endothelial cells, resulting in the breakdown of the BBB, which is called vasogenic oedema [1,5-7]. In the swine and rat cardiac arrest models, this BBB injury occurred within minutes to hours after ROSC [4,8,9]. Targeted temperature management (TTM) is recommended for reducing brain injury including oedema after cardiac arrest [10-12]. However, a recent study observed significant blood-brain barrier (BBB) injury within 24 h after return of spontaneous circulation (ROSC) despite TTM [13]. Before BBB breakdown, hypertonic fluids, such as mannitol or hypertonic saline, may facilitate brain oedema reduction by drawing free water from interstitial to intravascular spaces [1,4]. In contrast, after BBB breakdown, hypertonic fluid infusion may induce extravasation of highly oncotic osmoles, draw free fluid into interstitial spaces, and aggravate brain oedema [14]. Intravascular

Abbreviations: PCAS, post-cardiac arrest syndrome; BBB, blood-brain barrier; ROSC, return of spontaneous circulation; TTM, targeted temperature management; CPC, cerebral performance categories.

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osmolarity is mainly attributed to serum sodium levels. Therefore, we hypothesized that increased serum sodium levels during the early PCAS period, particularly after BBB breakdown, would be associated with poor neurological outcomes in out-of-hospital cardiac arrest (OHCA) survivors.

2. Goals of this investigation

We aimed to investigate the association of serum sodium levels with long-term neurological outcomes in OHCA survivors.

3. Methods

3.1. Study design and setting

This retrospective observational study used a multicentre prospective cohort registry, which enrolled adult (20 years of age and older) OHCA survivors with sustained ROSC for >20 min between December 2013 and February 2018 (Clinicaltrials.gov. NCT03695718). Each hospital's institutional review boards approved the analysis and provided a waiver of informed consent (Seoul National University Hospital, 1408–012-599; Bundang Seoul National University Hospital, B-1401/234–402; Seoul Metropolitan Government Seoul National University Boramae Medical Centre, 16–2013-157). Retrospective review for this study was approved by the Seoul National University Hospital IRB (2010–052-1163). This study was based on a prospective cohort registry jointly established at three university hospitals in the Republic of Korea. Approximately 300,000 patients visit the three EDs annually. On average, approximately 300 patients are admitted to the ED due to OHCA each year. From December 2013 to the present, the OHCA survivor registry enrolled adult patients who acquired a sustained return of spontaneous circulation (ROSC) and agreed to receive post-resuscitation care in intensive care units (ICUs). Standardized post-resuscitation care was provided to patients according to the current guidelines [12,15]. For initial resuscitation and early maintenance fluid therapy, normal saline was routinely used. Hypertonic saline and mannitol were used only for patients with intracranial pathologies to reduce intracranial pressure.

3.2. Selection of participants

We reviewed patient data recorded in the OHCA registry from December 2013 to February 2018. The exclusion criteria were as follows: having a baseline cerebral performance category (CPC) 3–5 (poor status); having intracranial pathologies, including haemorrhage, infarction, or tumour; being diagnosed with central diabetes insipidus (DI) within 24 h after ROSC; and having incomplete data. Central DI was diagnosed when all of the following four conditions were met; (1) serum osmolarity >300 mmol/L, (2) urine osmolarity <300 mmol/L, (3) urine output >50 ml/kg per day or > 200 mL per hour for >4 consecutive hours, and (4) serum sodium levels >145 mEq/L.

3.3. Variables

The registry consists of 300 variables, including underlying medical conditions, prehospital resuscitation data, ED resuscitation data, and post-resuscitation care data, such as hemodynamic and laboratory parameters, severity scores, diagnostic and therapeutic interventions, and clinical outcomes. From the OHCA registry, we collected the serum sodium level and calculated the osmolarity at 0 (Sodium 0H, Osmolarity 0H) and 24 h post-ROSC (Sodium 24H, Osmolarity 24H). A formula for serum calculated osmolarity was defined as follows: serum calculated osmolarity (mmol/L) = (serum sodium (mEq/L) * 2) + (serum glucose (mg/dL)/18) + (serum blood urea nitrogen (mg/dL)/2.8). The primary outcome was the 1-year neurological outcome (1-year CPC). Patients with CPC 1–2 and 3–5 were categorized into the good and poor outcome groups, respectively. The secondary outcome was the 6-month CPC.

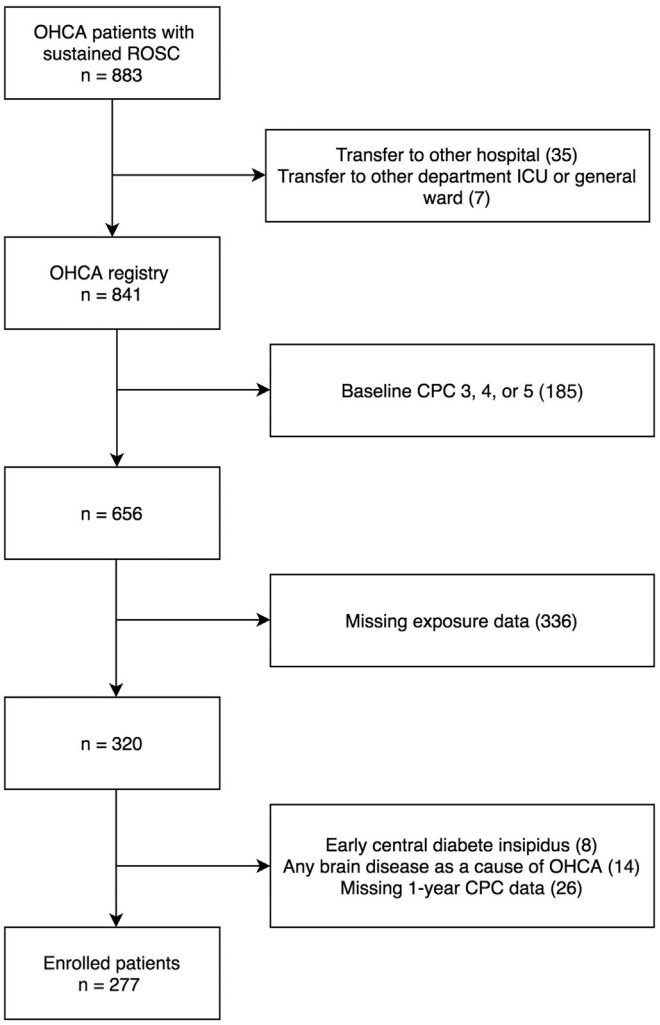

Fig. 1. Patient flow chart.
Out of 841 OHCA patients, a total of 277 patients were selected as the final study subjects.

3.4. Statistics

Parametric and non-parametric continuous variables were presented as the mean with standard deviation and median with interquartile range, respectively. Regarding categorical variables and outcomes, *chi*-square test and Fisher's exact test were performed as appropriate. Between-group comparisons of continuous variables were performed using Student's *t*-test and Mann-Whitney *U* test, as appropriate.

To assess the relationship between serum sodium levels and neurological outcomes, we applied restrictive cubic spline regression (knots, 4; a degree of polynomial, 3), univariate, and multivariate logistic regression analyses. Clinically relevant covariates with a p value <0.05 were selected by analysing all variables distributed differently according to the main outcome and primary exposure through univariate logistic regression (Table S1). Then, two primary multivariate logistic regression models were constructed for the exposure variables (model 1 for Sodium 24H level 1 mEq/L increment and model 2 for hypernatremia versus non-hypernatremia). For selecting covariates

Table 1
Baseline characteristics according to the 1-year CPC

Variable*	Missing	Good (1–2) ($n = 84$)	Poor (3–5) ($n = 193$)	p value
Demographics				
Age, year	0	54(47 – 62)	64(49 – 75)	<0.001
Female sex	0	24 (28.6%)	59 (30.6%)	0.851
Pre-existing conditions				
Diabetes mellitus	0	14 (16.7%)	65 (34.2%)	0.005
Hypertension	3	35 (41.7%)	86 (44.6%)	0.442
Hyperlipidaemia	3	8 (9.5%)	17 (8.8%)	0.512
CPR & PCAS data				
Witnessed arrest	0	74 (88.1%)	126 (65.3%)	<0.001
Bystander CPR	0	51 (60.7%)	75 (38.9%)	0.001
Non-shockable rhythm	0	9 (10.7%)	116 (60.1%)	<0.001
ROSC by EMT	0	55 (65.5%)	21 (10.9%)	<0.001
Collapse time, minute	9	15 (7 – 24)	30 (20 – 40)	<0.001
No flow time, minute	7	1 (0 – 5)	3 (0 – 9)	0.011
Low flow time, minute	3	12 (6 – 20)	25 (17 – 34)	<0.001
Mean blood pressure, mmHg	8	102.2 ± 27.5	90.7 ± 33.1	0.007
Heart rate, beat per minute	6	96.2 ± 22.3	101.8 ± 29.6	0.092
Non-reactive PLR	9	6 (7.4%)	104 (55.6%)	<0.001
Glasgow coma scale	0	6 (3 – 14)	3 (3 – 3)	<0.001
APACHE II	10	20 (13 – 24)	30 (25 – 35)	<0.001
TTM	0	41 (48.8%)	132 (68.4%)	0.003
Coronary angiography	1	32 (38.1%)	32 (16.7%)	<0.001
Renal replacement therapy	0	4 (4.8%)	45 (23.3%)	<0.001
Laboratory findings†				
Sodium 0H, mEq/L	0	138 (136.2 – 140.5)	139.5 (136 – 143)	0.158
Sodium 24H, mEq/L	0	137.4 (135 – 139)	140 (136 – 144)	<0.001
Chloride 0H, mEq/L	0	103.3 (101 – 106)	103.5 (99 – 108)	0.920
Chloride 24H, mEq/L	0	106 (103.8 – 108)	105 (100 – 110)	0.630
Osmolarity 0H, mOsm/L	0	297.3 (291.2 – 301.0)	303.5 (296.6 – 310.4)	<0.001
Osmolarity 24H, mOsm/L	0	288.4 (284.6 – 292.3)	300.5 (291.4 – 308.8)	<0.001
Glucose 0H, mg/dL	0	221 (165.5 – 275)	257 (190 – 330)	0.005
Glucose 24H, mg/dL	0	143 (122.3 – 174.5)	172 (134 – 227)	<0.001
Blood urea nitrogen 0H, mg/dL	0	17 (14 – 23)	21 (15 – 33)	0.004
Blood urea nitrogen 24H, mg/dL	0	14 (10.8 – 19.3)	27 (18 – 34)	<0.001
Creatinine 0H, mg/dL	1	1.2 (1.0 – 1.3)	1.4(1.1 – 1.9)	0.001
Creatinine 24H, mg/dL	1	0.8 (0.5 – 1.0)	1.6 (1.0 – 2.3)	<0.001

Categorical data were presented as frequency with percentage. Continuous variables were described as median with interquartile range or mean with standard deviation, as appropriate.
† Laboratory findings include the serum levels of each variable, which were measured immediately after ROSC (0H) or 24 h after ROSC (24H).
* Non-shockable rhythm includes pulseless electrical activity and asystole as the initial presentation of electrocardiographic rhythm; ROSC by EMT, return of spontaneous circulation achieved outside the hospital by emergency medical technician; Collapse time, total duration of no and low flow time; APACHE II, acute physiologic assessment and chronic health evaluation II; Coronary angiography, whether coronary angiography was implemented immediately after ROSC (with or without percutaneous coronary intervention); PLR, pupillary light reflex; TTM, targeted temperature management.

for each of these multivariate logistic regression models, a purposeful backward stepwise regression with a stopping rule, in which covariates with a p value <0.2 remained, was performed. For missing variables, we performed multiple imputations by chained equations; moreover, we repeated the multivariate analysis using five imputed datasets according to Rubin's rule to combine estimates [16,17]. In the imputation model, all clinically relevant variables that can be associated with the main exposures and outcomes were included. The chained equation was constructed using logistic regression, a multinomial logit model, and predictive mean matching for the missing values. P-values <0.05 were considered statistically significant, and the significance levels quoted are two-sided. Statistical analyses were conducted using R software version 4.0.4 (R Foundation for Statistical Computing, Vienna, Austria) and 'mice' library.

4. Results

4.1. Participants

Among 883 eligible OHCA survivors, we enrolled 277 patients. Eighty four and 193 patients were included in the good and poor outcome groups, respectively (Fig. 1). Compared with the good outcome group, the poor outcome group was older and more likely to have diabetes mellitus. Moreover, in the poor outcome group, Sodium 24H (140 mEq/L vs. 137.4 mEq/L, $p < 0.001$) and Osmolarity 24H (300.5 mmol/L vs. 288.4 mmol/L, $p < 0.001$) were significantly higher than in the good outcome group (Table 1).

4.2. Logistic regression analysis and restricted cubic spline regression analysis

Univariate logistic regression analysis and restricted cubic spline regression revealed that there was no significant increase in the poor 1-year CPC risk within the range of conventional hyponatremia (< 135 mEq/L) (Fig. 2, S1 Table). However, there was a sharp increase in the poor 1-year CPC risk from the range of conventional normonatremia (140–145 meq/L) to hypernatremia (> 145 meq/L; Fig. 2). Based on this finding, we selected a new cut-off value (140.1 mEq/L) for hypernatremia in patients with PCAS using the Youden index (J) in the receiver operating characteristic (ROC) curve (S2 Figure). In two multivariable logistic regression models, Sodium 24H per 1 mEq/L increment was associated with a 13% increase in the odds of a poor 1-year CPC (aOR, 1.13; 95% CI, 1.04 – 1.23; $p = 0.004$) (Table 2), and

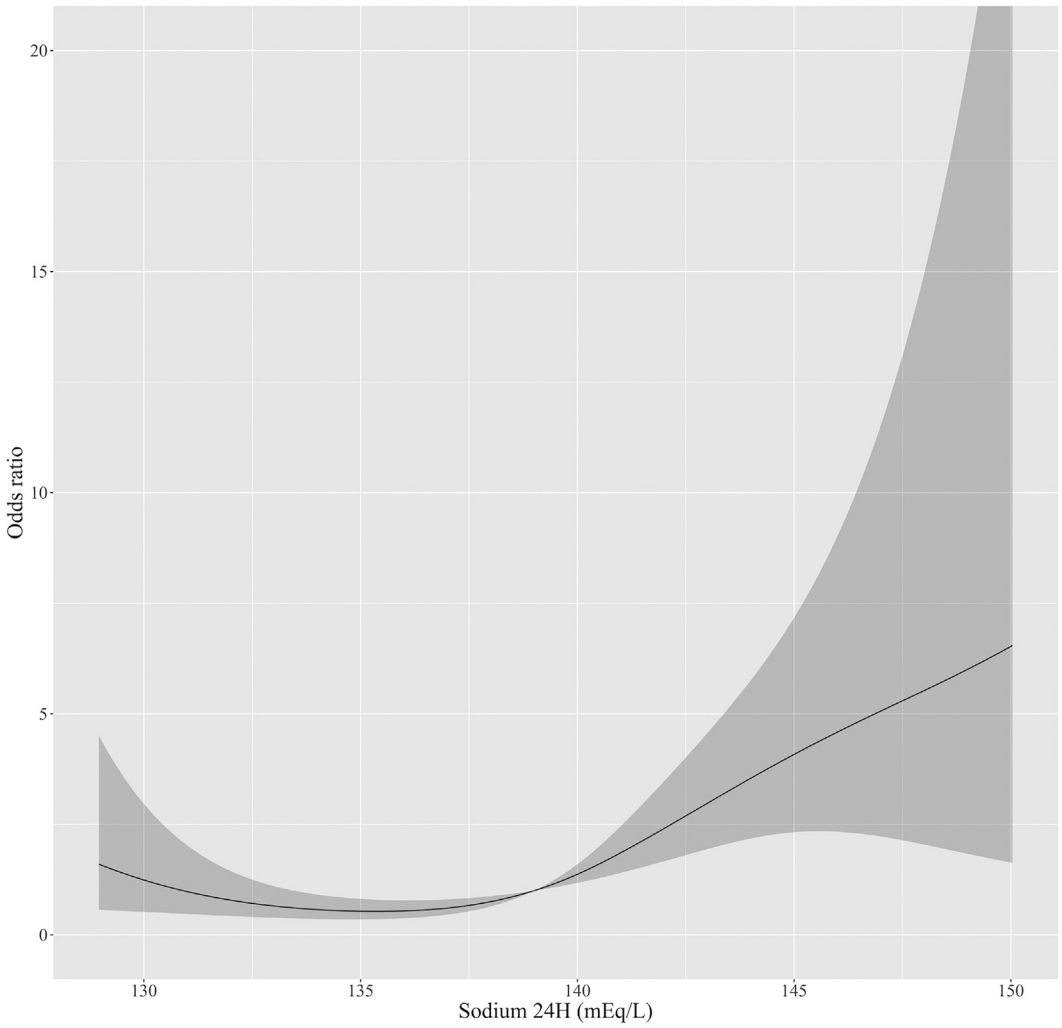

Fig. 2. Restricted cubic spline plot: Odds ratio for serum sodium level (sodium 24H).
Black line, predicted odds ratio for poor 1-year CPC; grey zones, 95% confidence intervals.
The relationship of poor long-term neurological outcomes according to serum sodium level was demonstrated using restricted cubic spline regression (4 knots, the degree of polynomial was 3). Notably, the size of the relative odds rapidly increased when the serum sodium level exceeded approximately 140 mEq/L. Contrastingly, there was a small relative change in the odds ratio for serum sodium levels below 135 meq/L (conventional cut-off value for hyponatremia).

Table 2
Logistic regression analysis for poor 1-year CPC.

Variable	Model 1		Model 2	
	OR (95% CI)	p value	OR (95% CI)	p value
Sodium 24H per 1 increment	1.13 (1.04 – 1.23)	0.004		
Hypernatremia(>140 meq/L)*			5.21 (1.84 – 14.73)	0.001
Diabete mellitus	2.72 (0.83 – 8.94)	0.091	2.55 (0.79 – 8.24)	0.119
Witnessed arrest	0.24 (0.07 – 0.78)	0.020	0.22 (0.07 – 0.66)	0.007
Non-shockable rhythm	5.78 (1.84 – 18.16)	0.002	7.64 (2.54 – 22.96)	<0.001
ROSC acheived by EMT	0.16 (0.06 – 0.44)	<0.001	0.17 (0.06 – 0.46)	<0.001
Non-reactive pupillary light reflex	2.25 (0.68 – 7.46)	0.181		
APACHE II per 1 increment	1.13 (1.06 – 1.20)	<0.001	1.14 (1.08 – 1.22)	<0.001
Mean blood pressure 1 increment	0.98 (0.97 – 1.00)	0.024	0.98 (0.97 – 1.00)	0.010
Blood urea nitrogen per 1 increment	1.08 (1.03 – 1.14)	0.004	1.08 (1.02 – 1.14)	0.006
Creatinine 1 increment	0.56 (0.34 – 0.94)	0.023	0.55 (0.33 – 0.92)	0.022

OR, odds ratio; CI, confidence intervals;
* Hypernatremia(>140 meq/L) was compared to non-hypernatremia(sodium 24H ≤ 140 mEq/L).

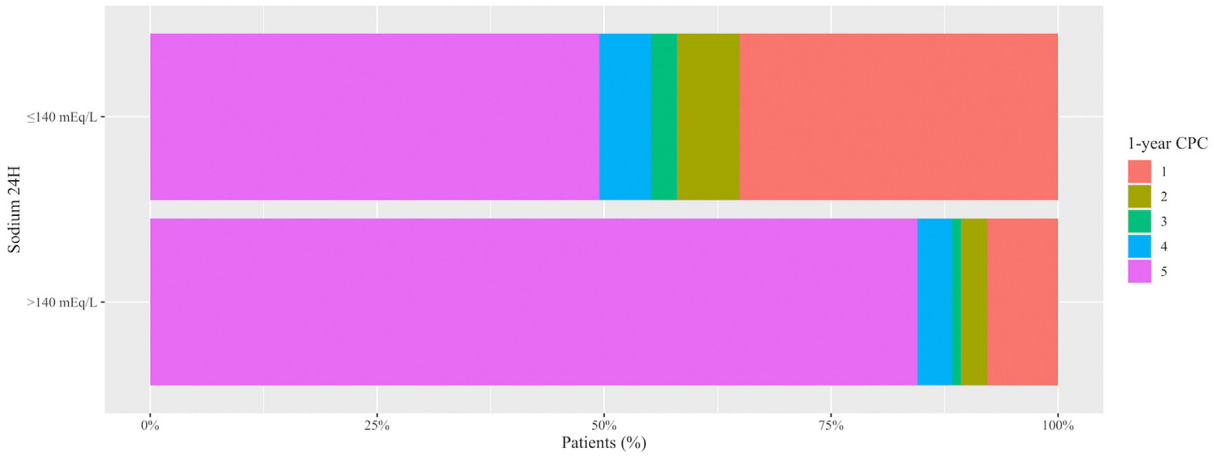

Fig. 3. CPC distribution according to Sodium 24H (>140 mEq/L vs. ≤140 mEq/L).
Among 277 patients, 103 patients had Sodium 24H >140 mEq/L. Moreover, 8 (7.7%), 3 (2.9%), 1 (0.9%), 4 (3.8%), and 87 (84.4%) patients had 1-year CPC 1, 2, 3, 4, and 5, respectively. Among 277 patients, 174 patients had sodium 24H ≤ 140 mEq/L. Further, 61 (35.0%), 12 (6.8%), 5 (2.8%), 10 (5.7%), and 86 (49.4%) patients had 1-year CPC 1, 2, 3, 4, and 5, respectively. There was a between-group differences in the distribution of 1-year CPCs ($p < 0.001$).

hypernatremia group (sodium 24H > 140 mEq/L) significantly increased the risk of poor 1-year CPC by 5 times compared to the non-hypernatremia group (sodium 24H ≤ 140 mEq/L) (aOR, 5.21; 95% CI, 1.84 – 14.73; $p = 0.001$) (Table 2).

4.3. One-year CPC distribution according to Sodium 24H

Subsequently, we compared the 1-year CPC distribution of two groups divided based on the cut-off value. Hypernatremia (Sodium 24H > 140 mEq/L) were observed in 103 patients. In patients with hypernatremia, 1-year CPCs were significantly higher than in patients without hypernatremia ($p < 0.001$) (Fig. 3, Table 3).

5. Discussion

This study observed an independent association of increased Sodium 24H levels with an increased risk of poor long-term neurological outcomes in OHCA survivors. Particularly, the risk of poor 1-year CPC rapidly increased after the serum sodium level exceeded 140 mEq/L. There was no significant difference in the risk of poor long-term neurological outcomes between patients with conventional hyponatremia and normonatremia. Although we did not elucidate the mechanism underlying the association of brain oedema with serum sodium levels, our findings support our hypothesis that under BBB breakdown, hypernatremia may induce more sodium leakage from intravascular to interstitial spaces and may worsen brain oedema in OHCA survivors.

Numerous studies have reported an association of hypernatremia with poor clinical outcomes, particularly poor neurological prognosis, in critically ill patients [18-20]; however, there has no clinical report of the association between poor neurological outcomes and hypernatremia in OHCA survivors. Additionally, previous studies on the association between hypernatremia and poor neurological prognosis in critically ill patients have indicated that central DI acts as a major confounding factor. Therefore, we excluded patients diagnosed with central DI within 24 h. In critical patients, the renin-angiotensin-aldosterone axis is activated with a potential subsequent increase in serum sodium levels [21]. In 96 included patients whose serum aldosterone levels were recorded, we further investigated the relationship between serum aldosterone and Sodium 24H levels. However, Sodium 24H levels were not significantly correlated with serum aldosterone levels (Pearson's $r = 0.05$, $p = 0.68$) (Supplementary Fig. 2).

Serum sodium levels in OHCA survivors may be attributed to fluid therapy. Isotonic 0.9% sodium chloride (NaCl) is the most commonly used fluid for OHCA victims during and after cardiopulmonary resuscitation (CPR). Recent study showed that 7% hypertonic saline during resuscitation was associated with a significant improvement in the ROSC rate and short-term survival [22]. However, this study did not investigate whether hypertonic saline during the PCAS period after successful ROSC improved neurological outcomes. An experimental study showed that isotonic crystalloid was more effective in reducing brain vasogenic oedema than hypertonic saline during the PCAS period [23]. In our study, serum chloride levels at 24 h were significantly higher in patients with hypernatremia than in patients without hypernatremia (Table 3). A recent study reported that initial hypochloraemias and subsequent increasing serum chloride levels during the 48 h of PCAS period were associated with poor neurological outcomes in OHCA survivors [24]. In the above study, the proportion and number of patients with hypernatremia and hyperchloremia were significantly lower than in our cohort. Therefore, it is possible that no statistically significant results were obtained. In addition, the role of chloride in worsening neurological outcomes has not been determined. The shift of sodium commonly accompanies that of chloride. And thus, we suggest that hypernatremia accompanied by hyperchloraemia may in part contribute to the worsening of neurological outcomes.

Current guidelines recommend the routine use of isotonic crystalloids for initial fluid therapy in patients with PCAS. Several studies have shown that balanced crystalloid fluid can facilitate better clinical outcomes in patients with sepsis [25]. However, the priority of 0.9% NaCl or balanced crystalloid in patients with PCAS remains unclear. Considering the brain oedema mechanism, our findings suggest that balanced crystalloids containing relatively low sodium levels (< 140 mEq/L) may be advantageous for reducing brain oedema and improving neurological outcomes in OHCA survivors.

6. Limitations

First, this was a retrospective study, and caution should be applied when interpreting this causal relationship. Moreover, the exclusion of patients with incomplete exposure variables might have led to selection bias. Second, we did not identify brain oedema. Brain computed tomography or magnetic resonance imaging is clinically recommended for predicting neurological outcomes [12]. However, imaging studies were not routinely performed in this study at 24 h post-ROSC. Third, during the study period, we only used 0.9% NaCl and did not use balanced crystalloid for resuscitation. Hypertonic saline or mannitol were restricted to patients with intracranial haemorrhage. Therefore, we

Table 3
Baseline characteristics according to the Sodium 24H categories

Variable*	Sodium 24H ≤140 mEq/L ($n = 174$)	Sodium 24H >140 mEq/L ($n = 103$)	p value
Demographics			
Age, year	59.0 (47.0 – 72.0)	57.0 (48.0 – 73.0)	0.963
Female sex	54 (31.0%)	29 (28.1%)	0.711
Good baseline CPC (1–2)	146 (83.9%)	79 (76.6%)	0.185
Pre-existing conditions			
Diabetes mellitus	49 (28.3%)	30 (29.7%)	0.916
Hypertension	80 (45.9%)	41 (39.8%)	0.377
Hyperlipidaemia	19 (10.9%)	6 (5.8%)	0.215
CPR & PCAS data			
Witnessed arrest	131 (75.2%)	69 (66.9%)	0.177
Bystander CPR	84 (48.2%)	42 (40.7%)	0.277
Non-shockable rhythm	68 (39.0%)	57 (55.3%)	0.026
ROSC by EMT	63 (36.2%)	13 (12.6%)	<0.001
Collapse time, minute	24.0 (11.0 – 35.0)	30.0 (18.0 – 43.0)	0.001
No flow time, minute	2.0 (0.0 – 8.0)	1.0 (0.0 – 7.0)	0.557
Low flow time, minute	18.0 (10.0 – 28.0)	25.0 (17.0 – 35.0)	<0.001
Mean blood pressure, mmHg	96.4 ± 31.6	90.0 ± 32.1	0.109
Heart rate, beat per minute	97.7 ± 26.5	103.9 ± 29.1	0.076
Non-reactive PLR	55 (32.9%)	55 (54.4%)	0.001
Glasgow coma scale	3.0 (3.0 – 6.5)	3.0 (3.0 – 3.0)	<0.001
APACHE II	27.0 (21.0 – 32.0)	29.0 (24.0 – 36.0)	0.024
TTM	101 (58.0%)	72 (69.9%)	0.066
Coronary angiography	47 (27.0%)	17 (16.6%)	<0.001
Renal replacement therapy	25 (14.3%)	24 (23.3%)	0.085
Laboratory findings			
Chloride 24H, mEq/L	104.0 (99.0 – 106.9)	110.0 (105.8 – 112.5)	<0.001
Osmolarity 24H, mOsm/L	289.9 (285.3 – 294.0)	308.3 (303.2 – 314.8)	<0.001
Glucose 24H, mg/dL	157.5 (129.0 – 210.0)	169.0 (126.0 – 226.0)	0.254
Blood urea nitrogen 24H, mg/dL	19.5 (12.0 – 31.0)	26.0 (18.0 – 32.0)	0.014
Creatinine 24H, mg/dL	1.0 (0.6 – 1.9)	1.4 (0.9 – 2.2)	0.012
Outcomes			
Good 1-year CPC (1–2)	73 (41.9%)	11 (10.6%)	<0.001
Good 6-month CPC (1–2)	73 (41.9%)	14 (13.5%)	<0.001

Categorical data were presented as frequency with percentage. Continuous variables were described as median with interquartile range or mean with standard deviation, as appropriate.

* Non-shockable rhythm includes pulseless electrical activity and asystole as the initial presentation of electrocardiographic rhythm; ROSC by EMT, return of spontaneous circulation achieved outside hospital by emergency medical technician; Collapse time, total duration of no and low flow time; APACHE II, acute physiologic assessment and chronic health evaluation II; Coronary angiography, whether coronary angiography was implemented immediately after ROSC (with or without percutaneous coronary intervention); PLR, pupillary light reflex; TTM, targeted temperature management.

could not directly examine the effect of crystalloid sodium levels on brain oedema and neurological outcomes. To confirm our hypothesis, a large-scale randomized controlled trial comparing brain oedema and neurological outcomes between OHCA survivors treated with 0.9% NaCl and balanced crystalloid is needed.

7. Conclusions

Relatively high serum sodium levels at 24 h post-ROSC were associated with poor long-term neurological outcomes in OHCA survivors.

Ethic approval and consent to participate

Each hospital's institutional review boards approved the analysis and provided a waiver of informed consent (Seoul National University Hospital, 1408–012-599; Bundang Seoul National University Hospital, B-1401/234–402; Seoul Metropolitan Government Seoul National University Boramae Medical Centre, 16–2013-157). Retrospective review for this study was approved by the Seoul National University Hospital IRB (2010–052-1163).

Consent for publication

Not applicalble.

Availability of data and materials

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Authors' contributions

EJC conceived the study idea, performed data analysis, and contributed to subsequent drafts. WYK, WJS and GY performed clinical data extraction, data analysis and contributed to subsequent drafts. YSJ, GJS and YHJ performed data collection and revised the manuscript. MSL and JS are the principal investigator and contributed to data analysis and data visualization, verified the clinical coding, and contributed to subsequent drafts.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajem.2022.06.014.

CRediT authorship contribution statement

Eun Joo Cho: Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **Min Sung Lee:** Conceptualization, Formal

analysis, Investigation, Methodology, Project administration, Writing – original draft, Writing – review & editing. **Woon Yong Kwon:** Resources, Supervision, Writing – original draft, Conceptualization. **Jonghwan Shin:** Data curation, Formal analysis, Investigation, Methodology. **Gil Joon Suh:** Resources, Supervision. **Yoon Sun Jung:** Data curation, Methodology, Resources. **Won Ji Song:** Conceptualization, Data curation, Formal analysis. **Gyeongyeon Yeo:** Conceptualization, Data curation, Formal analysis. **You Hwan Jo:** Methodology, Project administration, Resources, Supervision.

Declaration of Competing Interest

The authors declare that they have no competing interests.

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None.

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