Submitted: 17 February, 2022 Accepted: 07 May, 2022 Published: 08 March, 2023 DOI:10.22514/sv.2022.047

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ORIGINAL RESEARCH

Prognostic value of serum phosphate level in elderly post-cardiac arrest patients

Hee Eun Kim[1], Young Taeck Oh[2,*,†], You Hwan Jo[1,3], Jonghwan Shin[3,4], Seung Min Park[1,3,*,†], Dong Keon Lee[1,3], Yoon Sun Jung[5], Dong-Hyun Jang[6] on behalf of the SNU CARE Investigators

[1]Department of Emergency Medicine, Seoul National University Bundang Hospital, 13620 Seongnam-si, Republic of Korea
[2]Department of Emergency Medicine, Hallym University Dongtan Sacred Heart Hospital, 18450 Hwaseong, Republic of Korea
[3]Department of Emergency Medicine, Seoul National University College of Medicine, 03080 Seoul, Republic of Korea
[4]Department of Emergency Medicine, Seoul Metropolitan Government—Seoul National University Boramae Medical Center, 07061 Seoul, Republic of Korea
[5]Division of Critical Care Medicine, Seoul National University Hospital, 03080 Seoul, Republic of Korea
[6]Department of Emergency Medicine, Uijeongbu Eulji Medical Center, Eulji University, 11759 Uijeongbu, Republic of Korea

***Correspondence**
powerfreeze@hanmail.net
(Young Taeck Oh);
aukawa1227@gmail.com
(Seung Min Park)

† These authors contributed equally.

Abstract

Prognosticating the neurological outcomes of cardiac arrest is important. A recent study has shown that serum phosphate (SP) may be a prognostic indicator for poor neurological outcomes in cardiac arrest patients. Due to advancements in medicine, more elderly patients survive cardiac arrest than ever before, and prognostication of the markers in this population has not been studied previously. We aimed to confirm the hypothesis that a higher SP level predicts a poor neurological outcome of cardiac arrest, even in elderly patients. This retrospective observational study included post-cardiac arrest elderly patients (aged $\geq$ 65 years) who were admitted to three hospitals in urban areas in South Korea from December 2013 to February 2020. Data regarding patient characteristics, laboratory values, and neurological outcomes at 28 days were collected from patients' medical records. The primary outcome was poor neurological outcome (Cerebral Performance Category scores 3–5) at 28 days. Of the 389 eligible patients, 334/389 had poor neurological outcomes at 28 days. SP levels were significantly higher in those with poor neurological outcomes than in those with good neurological outcomes (7.32 *vs.* 5.01, $p < 0.001$). Multivariate logistic regression analysis also showed that SP levels were independently associated with neurological outcomes. Receiver operating characteristic curve analysis of SP levels showed an area under the curve of 0.772. Higher SP levels are associated with poor neurological outcomes after cardiac arrest in the elderly population.

Keywords

Heart arrest; Prognosis; Phosphates; Aged

1. Introduction

Life expectancy is increasing, and aging has become a global issue. Due to advancements in medicine, more elderly patients survive cardiac arrest than ever before. Some studies even show a survival rate of 10%, even in patients aged over 90 years of age, showing that age has no predictive value for mortality [1].

In resuscitated patients, neurological outcome is an important factor. Although various biomarkers have been studied to predict the neurological outcomes of resuscitated patients, such biomarkers are not available during the early stages of post-cardiac arrest care [2]. To develop early treatment strategies and to counsel patients and their families on the course of treatment, early prognostication is of paramount importance.

Serum phosphate (SP) levels have been associated with the severity of ischemia, as seen in traditional animal models, and have even been found to be predictive of bowel ischemia [3–6]. It has also been associated with poor outcomes of limb ischemia in humans [7]. A recent study [8] has shown that SP levels may serve as a prognostic indicator for poor neurological outcomes in adult patients with cardiac arrest. Some studies have even demonstrated that higher phosphate level has been shown to be linked with higher morbidity and coronary disease [9]. As well as correlation with higher mortality rates in patients admitted to the intensive care unit [10].

Prognostic markers for neurological outcomes have not been studied previously in the isolated elderly population. This study hypothesized that a higher SP level would predict poor neurological outcomes, even in elderly patients.

2. Materials and Methods

2.1 Design, Settings, and Participants

This was a retrospective observational study in which a registry of post-cardiac arrest patients across three urban hospitals

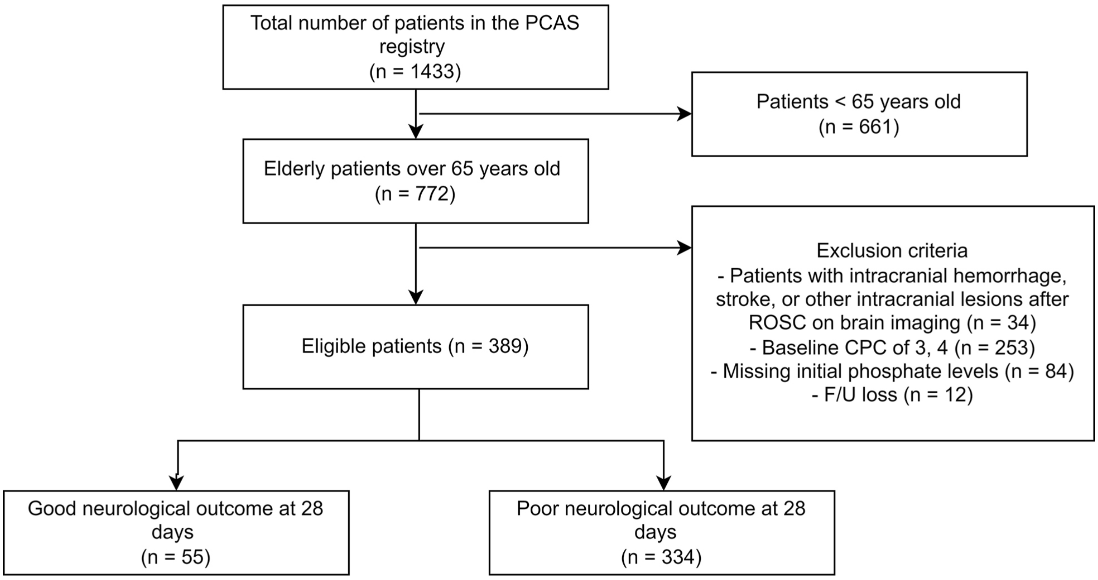

FIGURE 1. Flowchart of the study process. PCAS, post-cardiac arrest syndrome; ROSC, restoration of spontaneous circulation; CPC, Cerebral Performance Category; F/U, Follow-up.

in South Korea (Seoul National University Bundang Hospital, Seoul National University Hospital, and Seoul National University Boramae Medical Center), from December 2013 to February 2020, was analyzed. Patients included in the registry were aged $\geq$ 65 years with a return of spontaneous circulation (ROSC). Patients were excluded if: (1) they were aged <65 years, (2) post-resuscitation brain imaging showed an intracranial hemorrhage or stroke, (3) initial SP levels were missing, (4) their baseline Cerebral Performance Category (CPC) score was already at 3 or 4, or (5) they were lost to follow-up at 28 days (Fig. 1).

2.2 Data Collection

Data including age, sex, witnessed arrest, bystander cardiopulmonary resuscitation, initial rhythm (shockable or nonshockable), execution of hypothermia treatment, cause of arrest, low flow time and no-flow time, presence of comorbidities, laboratory values (phosphate, blood urea nitrogen, creatinine, glucose, pH, lactate) at presentation, and neurological outcome at 28 days, were collected from the registry. The labs that were used are the first labs that were drawn when the patient arrived at the emergency department. Total cardiopulmonary resuscitation (CPR) time refers to the time of total CPR duration in the emergency department. Low flow time is the duration between the time of arrest to the start of bystander CPR or CPR by emergency medical services (EMS) personnel. Low flow time refers to the time from the start of bystander CPR or CPR by EMS personnel to emergency department (ED) arrival. Data for the registry were collected by researchers across the three hospitals. Follow-up was conducted through phone interviews with either the patient or the caretakers and was conducted by researchers. The primary outcome was poor neurological outcome (CPC scores 3–5) at 28 days.

2.3 Statistical Analyses

All continuous variables were non-normally distributed. The Mann-Whitney U test was used to compare continuous variables; these are presented as medians and interquartile ranges. Categorical variables are presented as frequencies and percentages and were analyzed using the chi-squared test. Multiple logistic regression analysis was performed using SP levels and other statistically significant factors with a $p < 0.05$ (shockable rhythm, no flow time, low flow time, blood urea nitrogen (BUN), creatinine, pH, and lactate) to determine whether they were independently associated with poor neurological outcomes. Receiver operating characteristic curve (ROC) analyses were performed to assess the prognostic value of SP levels. All variables with $p < 0.05$ were included in the ROC analysis. Phosphate levels between the younger group and the elder group were compared using student t-test. Data were analyzed using Statistical Package for the Social Sciences (SPSS) for Windows (version 27.0, IBM Corp, Armonk, NY, USA) and MedCalc Statistical Software version 20.011 (MedCalc Software bv, Ostend, Belgium). A two-sided $p < 0.05$ was considered statistically significant.

3. Results

A total of 1433 patients were registered in the post-cardiac arrest syndrome registry of the three hospitals. Moreover, 661 patients were aged <65 years. Thus, only 772 elderly patients were considered in this study. Upon exclusion of those who did not meet the inclusion criteria, 389 eligible patients remained. Of these patients, 334 had poor neurological outcomes, and 55 had good neurological outcomes at 28 days (Fig. 1).

Patient characteristics stratified according to neurological outcomes are shown in Table 1. Patients with poorer neurological outcomes had a lower percentage of shockable rhythm, longer CPR time, no flow time, and low flow time. Patients in the good neurological outcome group also had a significantly higher percentage of cardiac etiology of the arrest. All patients

TABLE 1. Patient characteristics and serum phosphate, calcium, and lactate levels.

Variable	Total (n = 389)	Good neurological outcome (n = 55)	Poor neurological outcome (n = 334)	*p*-value
Age	76.97 (71.00–82.00)	73.91 (73.00–79.00)	77.48 (72.00–82.00)	0.646
Male	251 (64.5%)	37 (67.3%)	214 (64.1%)	0.838
Comorbidity	257 (66.1%)	37 (67.3%)	220 (65.9%)	0.838
Witnessed arrest	298 (76.6%)	45 (81.8%)	253 (75.7%)	0.324
Bystander CPR	186 (47.8%)	31 (56.4%)	155 (46.4%)	0.348
Shockable rhythm	26 (6.8%)	9 (16.4%)	20 (6.0%)	0.008
Total CPR time (min)	11.54 (1.00–14.00)	1.50 (0.00–3.00)	13.10(4.00–15.00)	<0.001
Total no flow time (min)	3.83 (0.00–7.00)	2.25 (0.00–4.50)	4.09 (0.00–7.00)	0.039
Total low flow time (min)	27.33 (13.75–37.25)	11.48 (6.00–15.00)	29.89 (17.00–39.00)	<0.001
Cause of arrest				<0.001
Cardiac	144 (37.0%)	44 (80.0%)	100 (29.9%)	
Noncardiac	245 (63.0%)	11 (20.0%)	234 (70.1%)	
TTM	163 (41.9%)	23 (41.8%)	140 (41.9%)	0.989
BUN (mg/dL)	31.83 (18.00–38.75)	22.40 (17.00–24.00)	33.36 (18.00–41.25)	<0.001
Cr (mg/dL)	2.13 (1.11–2.34)	1.49 (0.90–1.28)	2.24 (1.14–2.50)	<0.001
Glucose (mg/dL)	262.2 (163.0–334.0)	232.7 (165.5–279.0)	267.0 (161.0–347.0)	0.207
Phosphate (mg/dL)	6.99 (5.25–8.50)	5.01 (3.70–6.30)	7.32 (5.50–8.70)	<0.001
0–5.2	97 (24.9%)	28 (50.9%)	69 (20.7%)	
5.3–6.8	103 (26.5%)	20 (36.4%)	83 (24.9%)	
6.9–8.4	90 (23.1%)	6 (10.9%)	84 (25.1%)	
8.5–17.0	99 (25.4%)	1 (1.8%)	98 (29.3%)	
pH	6.95 (6.83–7.04)	7.12 (6.94–7.28)	6.94 (6.82–7.03)	<0.001
Lactate (mmol/dL)	12.68 (8.76–15.00)	8.54 (4.32–11.72)	12.98 (9.37–15.00)	<0.001

CPR, cardiopulmonary resuscitation; TTM, targeted temperature management; BUN, blood urea nitrogen; Cr, creatinine.

had out-of-hospital cardiac arrests.

SP was divided into 4 levels according to quartiles. A higher level of SP was related to a worse neurological outcome ($p <$ 0.001). Multivariate logistic regression analysis also showed that SP levels were independently associated with neurological outcomes (Table 2). Higher SP levels were associated with poor neurological outcomes at 28 days (odds ratio, 1.722; 95% confidence interval (CI): 1.083–2.738, $p = 0.022$), while factors other than total CPR time, low flow time, creatinine, and pH were no longer associated. Fig. 2 shows the frequencies of each category of phosphate levels grouped according to quartiles. With a higher SP quartile, a higher frequency of poor neurological outcome was observed. Fig. 3 shows a univariate analysis of initial SP. A ROC curve analysis of SP levels showed an area under the curve (AUC) of 0.772 (95% CI: 0.719–0.830). The optimal cutoff value for serum phosphate level showing specificity and sensitivity for poor neurological outcome was 6.5 (Fig. 4). We also compared the mean SP levels of the younger population in the same registry (Table 3). There was no significant difference in SP levels between the two groups.

4. Discussion

This study analyzed whether SP levels could predict neurological outcomes after cardiac arrest in the elderly population. SP levels at cardiac arrest were higher in patients with poor neurological outcomes than in those with good neurological outcomes. Even after adjusting for confounders, including shockable rhythm and cause of arrest, SP levels remained higher in those with poor neurological outcomes than in those with good neurological outcomes. The ROC curve for SP levels yielded an AUC of 0.772.

The characteristics of the study population showed characteristics different from those that are commonly known. This group had a higher percentage of witnessed arrest, which can be attributable to the fact that only resuscitated patients were included in the registry.

Phosphate is filtered in the glomeruli, and renal absorption is the main mechanism by which phosphate levels are regulated [11]. Patients with chronic kidney disease and end-stage renal failure requiring hemodialysis often have hyperphosphatasemia, and increased SP levels have been found to be associated with higher mortality in patients with end-stage renal disease (ESRD) [12]. It has also been shown, in a study by Xu *et al.* [13], that abnormal SP levels were associated with

TABLE 2. Multivariate logistic regression analysis.

Variable	Crude OR (95% CI)	*p*-value	Adjusted OR (95% CI)	*p*-value
Phosphate	1.345 (1.280–1.420)	<0.001	1.722 (1.083–2.738)	0.022
Shockable rhythm	6.88 (2.01–9.30)	<0.001	14.241 (0.985–205.855)	0.051
Total CPR time (min)	1.465 (1.337–1.605)	<0.001	1.537 (1.112–2.125)	0.009
Total low flow time	1.11 (1.08–1.13)	<0.001	1.120 (1.009–1.243)	0.033
Total no flow time	1.36 (1.25–1.48)	<0.001	1.128 (0.880–1.446)	0.342
Cause of arrest	21.27 (11.62–38.94)	<0.001	1.410 (0.203–9.807)	0.728
BUN	1.070 (1.057–1.840)	<0.001	1.043 (0.988–1.102)	0.124
Cr	2.82 (2.32–3.42)	<0.001	0.603 (0.381–0.953)	0.030
pH	1.44 (1.34–1.54)	<0.001	0.286 (0.129–0.635)	0.002
Lactate	1.28 (1.21–1.36)	<0.001	1.117 (0.918–1.359)	0.269

CPR, cardiopulmonary resuscitation; BUN, blood urea nitrogen; CI, confidence interval; OR, odds ratio; Cr, creatinine.

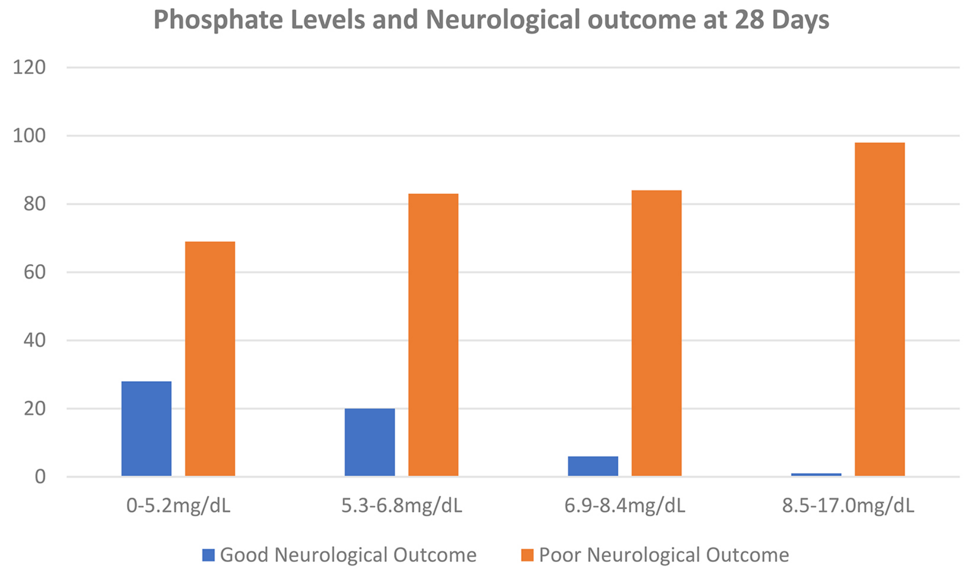

FIGURE 2. Phosphate levels and neurological outcome at 28 days according to quartiles of SP levels. X-axis: phosphate levels by quartile; Y-axis: frequency.

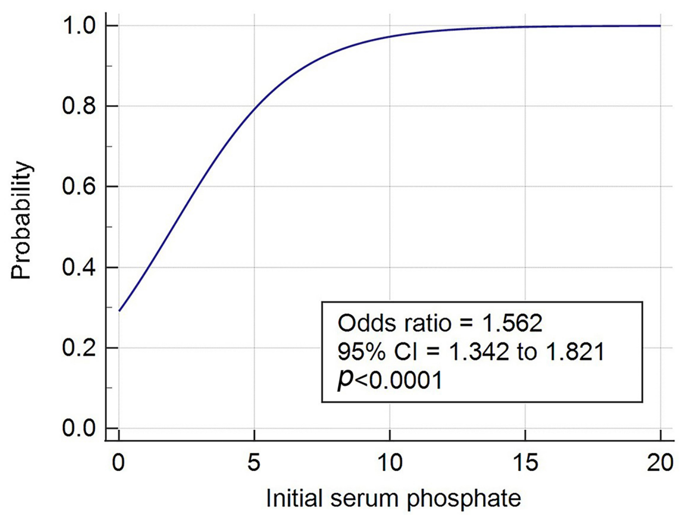

FIGURE 3. Univariate analysis of initial serum phosphate. X-axis, initial SP level; Y-axis, probability of poor neurological outcome. CI, confidence interval.

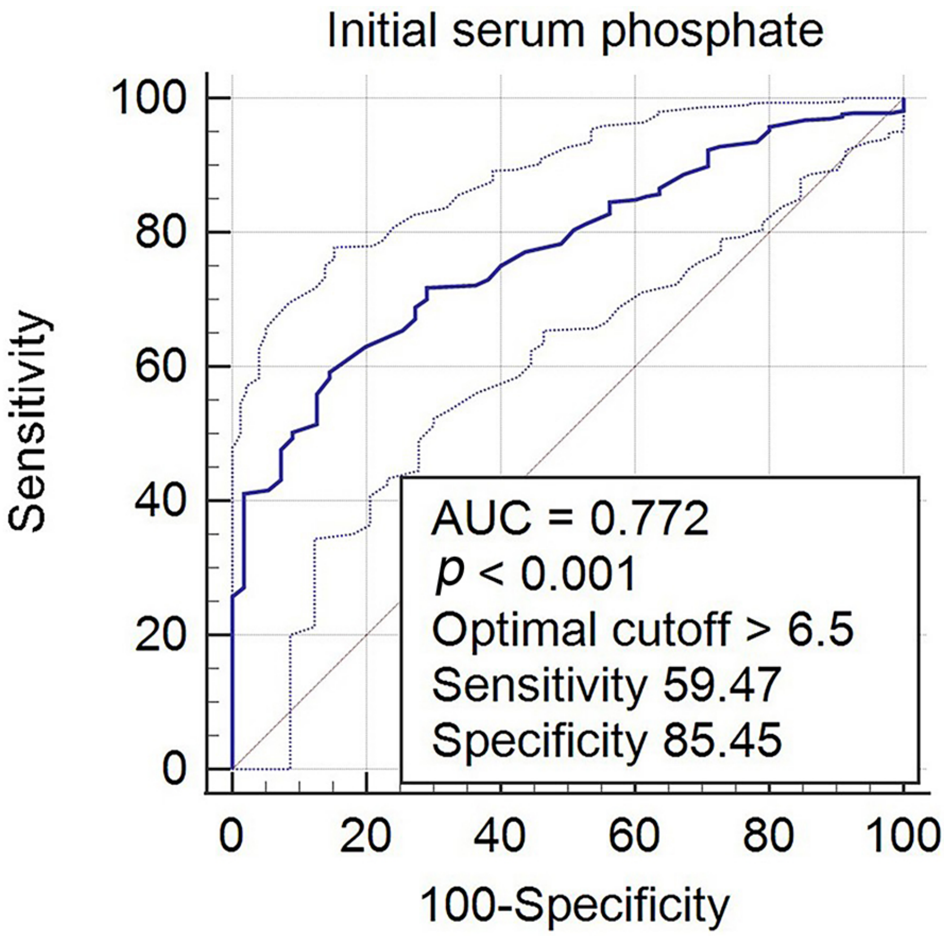

FIGURE 4. Receiver operating characteristic curve of serum phosphate levels and neurological outcomes. Area under the curve, 0.772. AUC, area under the curve.

TABLE 3. Comparison between serum phosphate levels in the younger population.

	Age <65 (n = 215)	Age ≥65 (n = 294)	*p*-value
Mean Serum Phosphate (SD)	6.88 (3.06)	6.99 (2.56)	0.301

SD, standard deviation.

a higher likelihood of acute coronary syndrome, possibly due to the effects of phosphate on endothelial dysfunction, vascular calcification, and left ventricular dysfunction.

SP is known to vary not only with existing medical disease, but also with homeostatic mechanisms, along with various endogenous factors such as age, genetics, and diet [14]. Age is a known factor in differences in SP levels. Phosphate level is high in infancy, which is critical to bone formation during the neonatal period, and rapidly fall with age. Menopausal women tend to show an increase in SP levels as compared to men of the same age group [14].

Although the exact pathophysiology of ischemia and SP levels has not been identified, previous animal studies have shown an association between ischemic injury in both the bowel and myocardium and SP levels [3, 4]. In a study by Neumar *et al.* [5], SP and lactate levels have been used as metabolic markers in myocardial ischemic injury during ventricular fibrillation in swine models. It has been hypothesized that intracellular phosphate is released into the bloodstream after cellular damage [3]. In addition, higher SP levels have been associated with coronary artery disease and aortic calcification in patients with ESRD on dialysis [15], and in the general population in a cross-sectional study [16].

Neuron-specific enolase (NSE) has been used as a predictor of hypoxic brain damage. Serum NSE levels at 72 hours after ROSC are significantly higher in patients with a higher level of hypoxic brain damage than in those with a lower level of hypoxic brain damage [17]. However, NSE levels are usually not immediately available in cardiac arrest settings. In a previous study by Lee *et al.* [18], patients with lower serum potassium and cardiac troponin I levels were associated with a higher rate of ROSC. However, both serum levels were not associated with survival. Traditional biomarkers for neurological outcomes have not been studied in the geriatric population. As observed in this study, SP levels may shed some light on neurological outcomes in the early phase of post-cardiac arrest.

SP levels have been shown to be an independent predictor of poor neurological outcomes. However, the AUC was 0.772, indicating only a modest prognostic value for neurological outcomes. In a retrospective study of patients with traumatic brain injury [19], as each quartile of serum glucose-phosphate ratio levels increased, the Glasgow Coma Scale score, overall probability, and mortality worsened, with an AUC of approximately 0.885 in all categories. In a study by Jung *et al.* [8], the ROC curve showed an AUC of 0.805 for SP levels, poor neurological outcomes, and hospital discharge. An AUC of 0.772 reflects that SP levels show a modest predictive level in terms of prognosticating neurological outcome after cardiac arrest.

5. Limitations

This study had several limitations. First, this was a retrospective study. Second, the comorbidity data in the registry only included diabetes, hypertension, and dyslipidaemia. It did not include chronic kidney disease, ESRD, malignancy, or parathyroid conditions, and could not be included in the data analysis. Baseline SP levels may have been higher in patients with chronic kidney disease and ESRD, which was not considered in this study. Further review of medical records and patients' kidney disease status need to be incorporated for a more precise analysis of the association between SP levels and neurological outcomes after cardiac arrest. Third, the severity of individual patients was not assessed in the data analysis. Sequential Organ Failure Assessment scores can be incorporated to adjust for severity in critically ill patients. Critically ill patients with sepsis or septic shock and their mortality rates are associated with different SP levels [3]. Additionally, only SP levels measured at initial presentation were analyzed in this study. Because single measurements of SP levels were found to be associated with neurological outcomes, serial measurements of SP levels may be of assistance, and could be analyzed in subsequent studies. Lastly, the registry included only cardiac arrest patients that achieved ROSC. Therefore, selection bias may exist. Nonetheless, SP predicted neurological prognosis more strongly than other commonly known variables. This study is the first study to examine the association between serum phosphate and good neurological prognosis in elderly patients, and further studies are likely to be needed in the future.

6. Conclusions

Higher serum phosphate levels were found to be associated with poor neurological outcomes at 28 days post-cardiac arrest in the elderly population. However, the prognostic performance of SP level is only modest, and considering the complex pathology of cardiac arrest, no single variable can be used in isolation to predict neurological outcome after cardiac arrest. SP levels can be used as an ancillary measure to known prognosticating variables to predict the outcomes of cardiac arrest in the elderly.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

AUTHOR CONTRIBUTIONS

SMP—conception of the study; SMP, YTO—design; YHJ, JHS, YSJ, DKL, DHJ—data collection; YTO, HEK—data analysis and interpretation; HEK, YTO, SMP—drafting and revising the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

All procedures performed in this study were in accordance were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. The study design was approved by the Institutional Review Boards (IRB) of each institution (IRB Nos. H-1408-012-599, J-1408-012-599, and B-1401-234-402). The requirement for written informed consent was waived by the review boards owing to the retrospective nature of the study.

ACKNOWLEDGMENT

We would like to thank Editage (www.editage.com) for their writing support.

FUNDING

This research received no external funding.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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How to cite this article: Hee Eun Kim, Young Taeck Oh, You Hwan Jo, Jonghwan Shin, Seung Min Park, Dong Keon Lee, *et al*. Prognostic value of serum phosphate level in elderly post-cardiac arrest patients. Signa Vitae. 2023; 19(2): 97-103. doi: 10.22514/sv.2022.047.