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Electrolyte and mineral disturbances in septic acute kidney injury patients undergoing continuous renal replacement therapy

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Abstract

Electrolyte and mineral disturbances remain a major concern in patients undergoing continuous renal replacement therapy (CRRT); however, it is not clear whether those imbalances are associated with adverse outcomes in patients with septic acute kidney injury (AKI) undergoing CRRT. We conducted a post-hoc analysis of data from a prospective randomized controlled trial. A total of 210 patients with a mean age of 62.2 years (136 [64.8%] males) in 2 hospitals were enrolled. Levels of sodium, potassium, calcium, and phosphate measured before (0 hour) and 24 hours after CRRT initiation. Before starting CRRT, at least 1 deficiency and excess in electrolytes or minerals were observed in 126 (60.0%) and 188 (67.6%) patients, respectively. The excess in these parameters was greatly improved, whereas hypokalemia and hypophosphatemia became more prevalent at 24 hours after CRRT. However, 1 and 2 or more deficiencies in those parameters at the 2 time points were not associated with mortality. However, during 28 days, 89 (71.2%) deaths occurred in patients with phosphate levels at 0 hour of ≥4.5 mg/dL as compared with 49 (57.6%) in patients with phosphate levels <4.5 mg/dL. The 90-day mortality was also significantly higher in patients with hyperphosphatemia. Similarly, in 184 patients who survived at 24 hours after CRRT, hyperphosphatemia conferred a 2.2-fold and 2.6-fold increased risk of 28- and 90-day mortality, respectively. The results remained unaltered when the serum phosphate level was analyzed as a continuous variable. Electrolyte and mineral disturbances are common, and hyperphosphatemia may predict poor prognosis in septic AKI patients undergoing CRRT.

Abbreviations: AKI = acute kidney injury, APACHE II = acute physiology and chronic health evaluation II, CCI = Charlson comorbidity index, CI = confidence interval, CRP = C-reactive protein, CRRT = continuous renal replacement therapy, eGFR = estimated glomerular filtration rate, FiO_2 = fraction of inspired oxygen, HR = hazard ratio, ICU = intensive care unit, MAP = mean arterial pressure, SOFA = sequential organ failure assessment.

Keywords: acute kidney injury (AKI), continuous renal replacement therapy (CRRT), electrolyte, mineral

1. Introduction

Acute kidney injury (AKI) commonly occurs in critically ill patients in the intensive care unit (ICU).[1] The incidence rate of AKI varies depending on the definition used and is reported to be 7% in all hospitalized patients[2] and up to 60% in ICU patients.[3] The importance of AKI has been highlighted because it is associated with high morbidity and mortality rates.[4] It is also associated with increased costs[5] and length of hospital stay.[6] Moreover, patients with AKI are more likely to develop chronic kidney disease, including end-stage renal disease than those without AKI.[7] Sepsis is a devastating medical condition triggered by an immune response to infection, leading to multiple complications. AKI frequently develops as a consequence of sepsis, and its incidence has been reported to be 19% in patients with sepsis, 23% in those with severe sepsis, and 51% in those with septic shock, when blood cultures are positive.[8] Notably, septic AKI is one of the life-threatening manifestations of multiple organ dysfunction syndrome and has been shown to be independently associated with adverse clinical outcomes.[9]

Electrolyte or mineral imbalances are common findings in many serious conditions, including septic AKI. However, the incidence of these alterations in critically ill patients is unclear. Adekola et al[10] reported that >66.78% of patients in the ICU had multiple electrolyte and acid-base abnormalities. It is important to maintain these parameters within the physiologic levels to prevent complications and adverse outcomes because electrolytes and minerals play important roles in protecting cellular function, tissue perfusion, and acid–base homeostasis.[11,12] Not surprisingly,

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continuous renal replacement therapy (CRRT) has become the modality of choice in critically ill patients with AKI as it is more effective in correcting uremia, electrolyte and mineral disturbances, acid-base disorder, and volume overload. In addition, CRRT can provide immune modulation through the convective and adsorptive removal of various immune mediators.[13]

Although electrolyte and mineral disturbances are largely improved with dialysis treatment, this issue has not yet been completely resolved even in patients undergoing CRRT. In fact, overcorrection often causes serious problems such as neurologic dysfunction, conductance abnormalities, arrhythmia, and gastrointestinal hypomotility.[14–16] On the other hand, insufficient correction remains despite CRRT and is sometimes ignored in clinical practice. When septic AKI occurs, the clinical outcomes are primarily determined by the proper management of primary illness and the presence or absence of multiorgan involvement. However, it is not clear whether electrolyte and mineral disturbances are associated with adverse outcomes in patients with septic AKI undergoing CRRT. Therefore, we aimed to investigate the incidence, clinical course, and clinical utility as prognostic markers of the altered levels of electrolytes and minerals in these patients.

2. Materials and methods

2.1. Patient selection

We performed a post-hoc analysis of data from our recent study, "Effects of High-volume Continuous Renal Replacement Therapy on Inflammatory Mediators and Outcomes in Patients with Septic Acute Kidney Injury" (NCT01191905). Briefly, this prospective randomized controlled open-label trial was conducted at Yonsei University Health System Severance Hospital and Seoul National University Hospital between January 2011 and August 2014. The aim of the study was to compare high and conventional doses of CRRT in patients with septic AKI who underwent CRRT. The detailed treatment was described elsewhere.[17] Patients were included if they met the following criteria: consensus criteria for sepsis,[18] injury stage of the RIFLE (risk, injury, failure, loss, end stage) criteria[19] or more (>2-fold increase in serum creatinine or urine output of <0.5 mL/kg/h for 12 hours), and absence of other established nonsepsis-related cause of AKI. Patients were excluded if they met the following criteria: age <20 years or >80 years, with a life expectancy of <3 months, with Child-Pugh class C liver cirrhosis, pregnant or lactating, and with a history of dialysis before the study. Finally, a total of 210 patients were enrolled excluding 2 patients with missing data. The study was approved by the institutional review board of the 2 participating hospitals and followed the provisions of the Declaration of Helsinki. We obtained informed written consent from all the enrolled participants.

2.2. Clinical and biochemical data collection

Demographic and clinical data such as age, sex, body mass index, and comorbidities were recorded at the time of CRRT initiation. Biochemical data for electrolyte and mineral levels, such as sodium, potassium, calcium, and phosphate, were measured before starting CRRT (0 hour) and at 24 hours after CRRT initiation. Calcium levels were corrected by using serum albumin levels (corrected calcium = calcium [mg/dL] + 0.8 × [4 – serum albumin {g/dL}]). The reference ranges of each electrolyte and mineral are as follows: sodium, 135–145 mEq/L; potassium, 3.5–5.5 mEq/L; calcium and corrected calcium, 8.5–10.5 mg/dL; and phosphate, 2.5–4.5 mg/dL. In addition, the following biochemical laboratory data were collected at both time points: hemoglobin, white blood cell, serum creatinine, albumin, lactate, aspartate aminotransferase, alanine aminotransferase, and total bilirubin levels. The estimated glomerular filtration rate (eGFR) was calculated by using the chronic kidney disease epidemiology collaboration equation.[20] The data also included the age-adjusted Charlson comorbidity index (CCI), Sequential Organ Failure Assessment (SOFA) score, and Acute Physiology and Chronic Health Evaluation II (APACHE II) score. Although the APACHE II is the most well-known system that provides prognostic information for ICU patients, the score does not include specific criteria for kidney function.[21] Thus, we used the SOFA score for this study analysis.

2.3. Study end points

The study end point was death that occurred within 28 and 90 days after CRRT initiation. In addition, the duration of CRRT and length of hospital stay after CRRT initiation were also analyzed.

2.4. Statistical analysis

All statistical analyses were performed by using SPSS for Windows version 23.0 (IBM Corp., Armonk, NY). Continuous variables are expressed as the mean ± standard deviation or median (interquartile range), whereas categorical variables are expressed as a number (percentage). Comparisons between 2 groups or among 3 groups were done through an analysis of variance or Student's *t* test for continuous variables, and with the chi-squared test or Fisher's exact test for categorical variables. The normality of distribution was confirmed by using the Kolmogorov–Smirnov test. Cumulative survival curves were derived by using the Kaplan–Meier method, and differences between curves were compared through the log-rank test. Cox proportional hazards analysis was performed to determine the relationship between the abnormality in each electrolyte and mineral, and mortality. *P*-values <0.05 were considered statistically significant.

3. Results

3.1. Patient characteristics

The baseline clinical characteristics and laboratory findings of the study subjects are shown in Table 1. The mean age of the participants was 62.2 ± 12.9 years, and 136 (64.8%) of them were men. Among the 210 patients, 57 (27.3%) had diabetes and 17 (8.0%) had cardiovascular diseases. The mean baseline eGFR at the time of CRRT initiation was 26.30 ± 22.39 mL/min 1.73 m^{-2}. The mean age-adjusted CCI was 4.64 ± 2.62. The SOFA score was 14.18 ± 3.10, and the APACHE II score was 28.72 ± 7.30. The mean arterial pressure (MAP) at 0 hour was 78.81 ± 14.49 mm Hg. A total of 175 (83.3%) patients received mechanical ventilation, and the mean fraction of inspired oxygen (FiO_2) was 0.58 ± 0.24. The mean white blood cell count and C-reactive protein levels were 11,350 μL (5,037–18,815 μL) and 18.43 mg/L (9.35–39.80 mg/L), respectively.

3.2. Electrolyte or mineral deficiencies and excess before and 24 hour after CRRT initiation

Table 2 shows the deficiencies and excess of each electrolyte and mineral at 0 and 24 hours after CRRT application. Overall deficiencies or excesses in a single electrolyte or mineral were observed in 126 (60.0%) and 188 (67.6%) patients, respectively, before starting CRRT (0 hour). The most frequent disturbances

Table 1

Baseline characteristics of subjects.

	Total (n = 210)
Age, y	62.2 ± 12.9
Male, %	136 (64.8)
Hypertension, %	100 (47.6)
Diabetes mellitus, %	57 (27.3)
Heart failure, %	18 (8.6)
Ischemic heart disease, %	13 (6.2)
Myocardial infarction, %	4 (1.9)
Cerebrovascular disease, %	11 (5.3)
COPD, %	12 (5.7)
Mechanical ventilation, %	175 (83.3)
CCI	2.94 ± 2.15
Age-adjusted CCI	4.64 ± 2.62
BMI (kg/m^2) at ICU admission	23.26 ± 4.22
eGFR (mL/min/1.73 m^2) at admission	72.58 ± 45.10
eGFR at CRRT initiation (mL/min/1.73 m^2)	26.30 ± 22.39
SOFA score	14.18 ± 3.10
APACHE II score	28.72 ± 7.30
Systolic blood pressure, mm Hg	111.72 ± 20.52
Diastolic blood pressure, mm Hg	62.30 ± 13.90
Mean arterial pressure, mm Hg	78.81 ± 14.49
Hemoglobin, g/dL	9.42 ± 1.93
White blood cell, μL	11350 [5037 – 18815]
Albumin, g/dL	2.47 ± 0.53
Blood urea nitrogen, mg/dL	62.48 ± 32.60
Creatinine, mg/dL	3.09 ± 1.77
Aspartate aminotransferase, IU/L	89.50 [38.00–356.00]
Alanine transaminase, IU/L	39.50 [16.00–185.00]
Bilirubin, mg/dL	1.90 [0.90–5.65]
CRP, mg/L	18.43 [9.35–39.80]
Lactate, mmol/L	6.60 ± 5.11
FiO_2	0.58 ± 0.24
pH	7.30 ± 0.11
PaO_2, mm Hg	103.97 ± 81.88
$PaCO_2$, mm Hg	38.71 ± 16.27
Base excess, mmol/L	−6.90 [−11.13 to −3.80]

Data are expressed as mean ± standard deviations, median (interquartile range), or numbers (%). APACHE II = acute physiology and chronic health evaluation II, BMI = body mass index, CCI = Charlson comorbidity index, COPD = chronic obstructive pulmonary disease, CRP = C-reactive protein, CRRT = continuous renal replacement therapy, eGFR = estimated glomerular filtration rate, FiO_2 = fraction of inspired oxygen, ICU = intensive care unit, SOFA = sequential organ failure assessment score.

(deficiency or excess) were hypocalcemia (37%) and hyperphosphatemia (59.5%) (Table 2).

CRRT during the first 24 hours greatly improved the excess in electrolytes and minerals. However, disturbances in these parameters were still common at 24 hours (Fig. 1). For deficiencies, hyponatremia, hypokalemia, hypocalcemia, and hypophosphatemia were found in 35 (19.4%), 51 (28.3%), 15 (8.5%), and 36 (19.6%) patients, respectively. In contrast, for excess, hypernatremia (n = 8, 4.4%), hyperkalemia (n = 2, 1.1%), and hyperphosphatemia (n = 57, 31.0%) occurred at lesser rates than those at 0 hour (Table 2).

3.3. CRRT duration, hospital stays, and mortality

Among the 210 patients, 138 (65.7%) and 162 (77.1%) deaths occurred during 28 and 90 days. Twenty-two (10.5%) patients died during 24 hours after CRRT initiation. Overall, the median duration of CRRT and the median length of hospital stay after CRRT initiation were 3.90 (2.20–7.24) and 10.45 (2.97–31.33) days, respectively. The duration of CRRT (3.94 [3.21–5.18] vs 3.91 [1.81–8.99], $P = 0.003$) and hospital stay (34.53 [19.40–70.16] vs 6.20 [2.33–19.74], $P < 0.001$) were significantly longer in survivors than in nonsurvivors (Supplementary Table 1, http://links.lww.com/MD/B261).

3.4. Clinical outcomes according to electrolyte or mineral disturbances before and at 24 hours after CRRT initiation

We compared the mortality rates according to the deficiencies and excesses of electrolytes and minerals (Supplementary Table 2, http://links.lww.com/MD/B261). Any alterations in sodium, calcium, and potassium levels at 0 and 24 hours were not associated with mortality (data not shown). In addition, the serum levels of these parameters at 0 hour did not differ between survivors and nonsurvivors (Supplementary Table 3, http://links.lww.com/MD/B261). However, 89 (71.2%) deaths occurred in hyperphosphatemic patients as compared with 2 (33.3%, $P = 0.08$) in hypophosphatemic patients and 47 (59.5%, $P = 0.02$) in normophosphatemic patients during 28 days. During 90 days, 105 (84.0%) patients with hyperphosphatemia died as compared with 57 (67.1%) patients with phosphate levels <4.5 mEq/L ($P = 0.03$). The serum phosphate levels were also higher in nonsurvivors than in survivors (4.97 ± 2.78 mg/dL vs 5.79 ± 2.53 mg/dL, $P = 0.04$). This pattern was consistent when analyzed by using phosphate levels at 24 hours (3.42 ± 1.37 mg/dL vs 4.21 ± 1.84 mg/dL, $P = 0.01$) (Supplementary Table 3, http://links.lww.com/MD/B261). The length of hospital stay after CRRT initiation was shorter in patients with hyperphosphatemia at 24 hours than those for the normal or low-level group (19.63 [6.28–35.53] days vs 15.81 [6.39–33.58] days vs 3.94 [1.91–22.70] days, $P = 0.02$) (Supplementary Table 4, http://links.lww.com/MD/B261). This finding was not observed for sodium, potassium, and calcium. We further analyzed whether 2 or more deficiencies in electrolytes and minerals could predict adverse

Table 2

Electrolyte or mineral deficiencies and excess before starting continuous renal replacement therapy and 24 h after continuous renal replacement therapy initiation.

	0 h	24 h		Deficiency		Excess	
	Mean ± SD	Mean ± SD	*P*	0 h	24 h	0 h	24 h
Sodium	138.24 ± 8.25	137.54 ± 4.34	0.22	58 (27.6)	35 (19.4)	30 (14.3)	8 (4.4)
Potassium	4.39 ± 0.94	3.83 ± 0.73	<0.001	26 (12.4)	51 (28.3)	24 (11.4)	2 (1.1)
Calcium, Ca	7.61 ± 1.20	8.35 ± 0.78	<0.001	168 (80.8)	95 (54.0)	5 (2.4)	2 (1.1)
Corrected Ca	8.82 ± 1.16	9.46 ± 0.74	<0.001	77 (37.0)	15 (8.5)	12 (5.8)	11 (6.3)
Phosphate	5.66 ± 2.48	3.99 ± 1.76	<0.001	6 (2.9)	36 (19.6)	125 (59.5)	57 (31.0)

Data are expressed mean ± standard deviations and numbers (%).
Calcium (mg/dL); corrected Ca (mg/dL); phosphate (mg/dL); potassium (mEq/L); sodium (mEq/L).
SD = standard deviation.

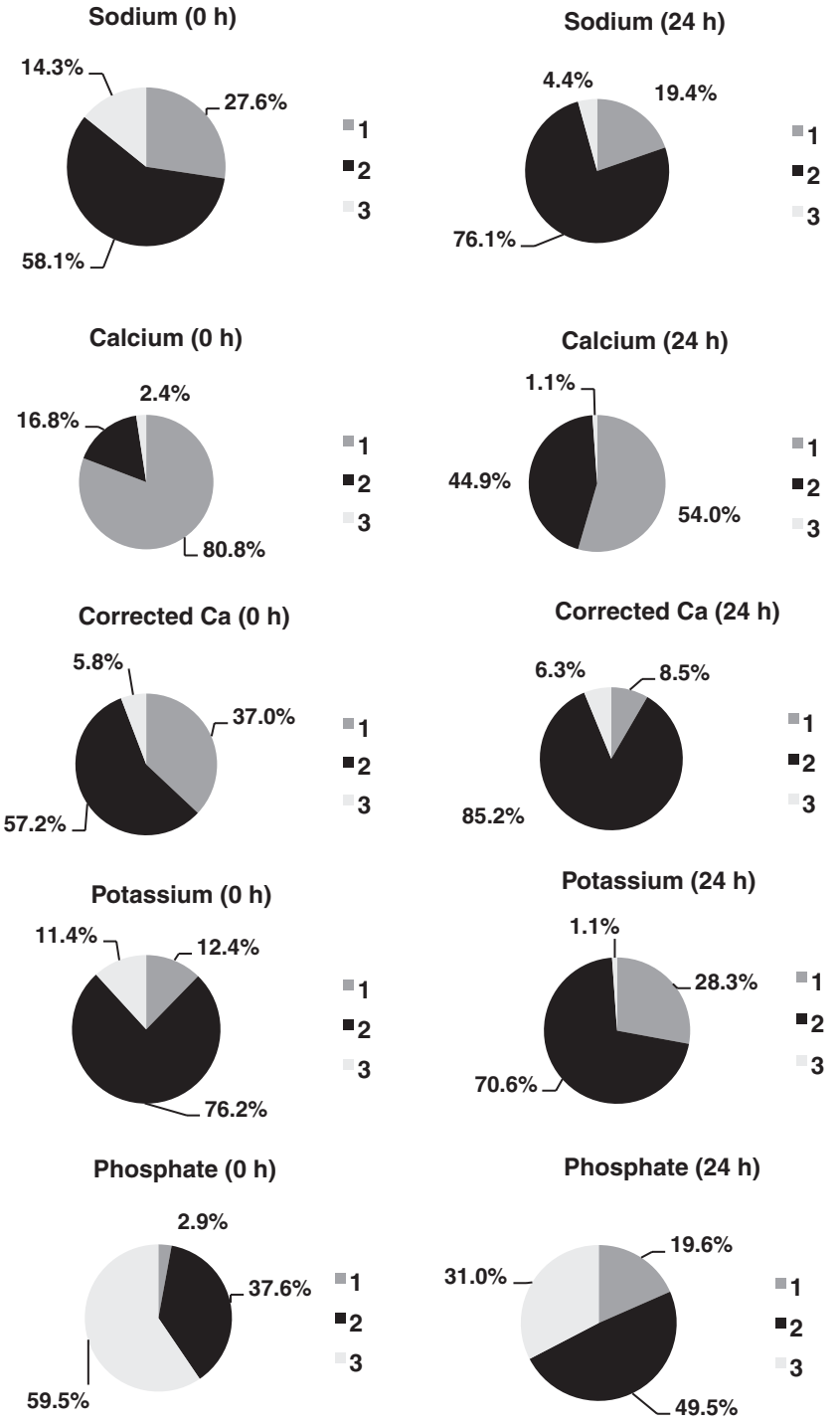

Figure 1. Electrolyte or mineral deficiencies and excess before starting CRRT and 24 hours after CRRT initiation: 1, deficiency; 2, normal; 3, excess. CRRT = continuous renal replacement therapy.

outcomes. Compared with a single-deficiency group, groups with 2 or more deficiencies did not show an increased mortality rate (Fig. 2).

3.5. Hyperphosphatemia predicts adverse outcomes

Because more deaths occurred in the hyperphosphatemic group than in the other 2 groups, we further investigated whether phosphate levels could predict clinical adverse outcomes. First, there were only 6 patients with phosphate levels <2.5 mg/dL at 0 hour; thus, the patients were divided into 2 groups: <4.5 mg/dL and ≥4.5 mg/dL. Most baseline characteristics were comparable between groups before CRRT initiation (Supplementary Table 5, http://links.lww.com/MD/B261). However, eGFR was significantly lower in patients with hyperphosphatemia (31.5 ± 30.7 vs 22.7 ± 13.2 mL/min 1.73 m^{-2}, $P = 0.01$). We constructed 3 different Cox models, as presented in Table 3. The crude hazard ratios (HRs) for

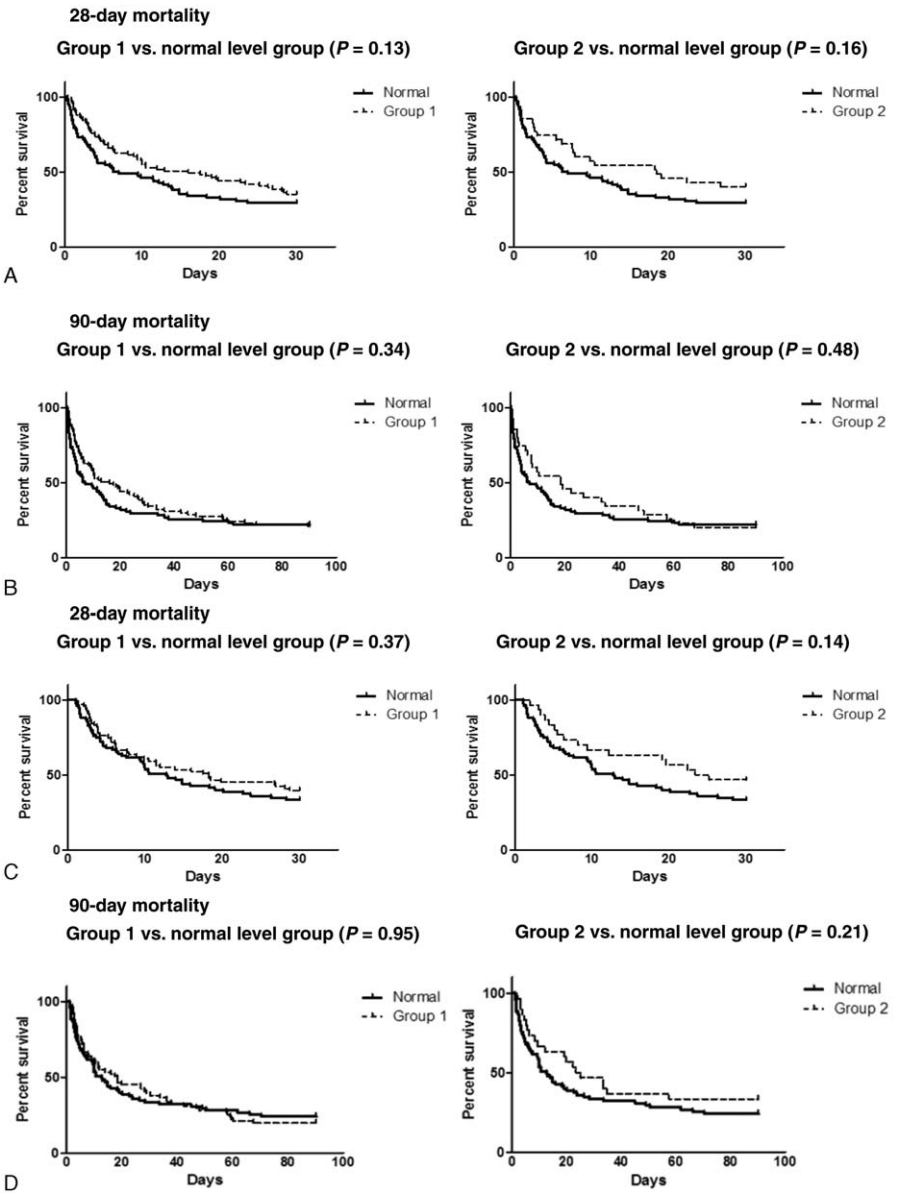

Figure 2. Kaplan–Meier plots for 28- and 90-day mortality according to single and 2 or more deficiencies in electrolytes or minerals before starting CRRT (A and B) and 24 hours after CRRT initiation (C and D), Group 1 (single deficiency); Group 2 (2 or more deficiencies), CRRT = continuous renal replacement therapy.

the 28- and 90-day mortality rates compared with normophosphatemia or hypophosphatemia were 1.44 and 1.47 (95% confidence interval [CI], 1.01–2.03, $P = 0.04$; 95% CI, 1.07–2.02, $P = 0.02$), respectively. In a model 2 adjusted for age, sex, and body mass index (BMI), hyperphosphatemia was also associated with an increased risk of death. Finally, in a fully adjusted model after additional adjustment for CCI, SOFA score, and residual kidney function, this association became more evident (Table 3). Next, patients were classified into 3 groups according to deficient, normal, and excess phosphate levels at 24 hours after CRRT (Supplementary Table 6, http://links.lww.com/MD/B261). The hyperphosphatemic group was younger ($P = 0.18$), had higher BMI ($P = 0.01$) and SOFA score ($P < 0.001$), and had lower MAP ($P = 0.002$). After full adjustment of these factors, hyperphosphatemia conferred a 2.2-fold and 2.6-fold increased risk of 28-day (HR, 2.25; 95% CI, 1.40–3.61; $P < 0.001$) and 90-day mortality (HR, 2.65; 95% CI, 1.71–4.12; $P < 0.001$) compared with normophosphatemia. When the phosphate level was treated as a continuous variable, hyperphosphatemia was a significant predictor of 28-day mortality (HR, 1.36 per 1 mg/dL increase; 95% CI, 1.20–1.54; $P < 0.001$) and 90-day mortality (HR, 1.32 per 1 mg/dL increase; 95% CI, 1.17–1.48; $P < 0.001$) (Table 4 and Fig. 3).

4. Discussion

Electrolyte, mineral, and acid–base disturbances commonly occur in AKI patients.[22] Much effort has been made to maintain homeostasis in clinical practice. In particular, CRRT greatly improves the abnormalities of these parameters; however, it can often cause overcorrection, and suboptimal correction remains a concern. This study evaluated the incidence, clinical course, and prognostic implication of electrolyte and mineral disturbances in septic AKI patients undergoing CRRT. We found that, as expected, electrolyte and mineral disturbances were common and

Table 3

Cox proportional hazard regression analysis for 28- and 90-day mortality before starting continuous renal replacement therapy with all-cause mortality.

	Phosphate as a categorical variable (≥ 4.5 vs <4.5 mg/dL)*		Phosphate as a continuous variable (per 1 mg/dL increase)	
	HR (95% CI)	*P*	HR (95% CI)	*P*
28-day				
Model 1	1.44 (1.01–2.03)	0.04	1.04 (0.98–1.10)	0.24
Model 2	1.46 (1.03–2.07)	0.04	1.05 (0.99–1.11)	0.14
Model 3	1.59 (1.10–2.29)	0.01	1.08 (1.00–1.15)	0.04
90-day				
Model 1	1.47 (1.07–2.02)	0.02	1.05 (1.00–1.10)	0.07
Model 2	1.49 (1.08–2.06)	0.02	1.06 (1.00–1.11)	0.05
Model 3	1.64 (1.18–2.29)	0.003	1.09 (1.02–1.16)	0.01

* Phosphate level <4.5 mg/dL is a referent.

Model 1: unadjusted.

Model 2: Age, gender, BMI at ICU admission.

Model 3: Model 2 + CCI, SOFA score, eGFR (0 h).

BMI = body mass index, CCI = Charlson comorbidity index, CI = confidence interval, eGFR = estimated glomerular filtration rate, HR = hazard ratio, ICU = intensive care unit, SOFA = sequential organ failure assessment.

CRRT largely corrected these abnormalities in the analyzed patients. Notably, a single deficiency and 2 or more deficiencies of electrolytes or minerals were not associated with adverse outcomes. However, hyperphosphatemia was significantly associated with an increased risk of 28- and 90-day mortality rates in septic AKI patients undergoing CRRT.

It is well known that deficiencies in electrolytes and minerals can increase morbidity, if not properly treated.[23] In addition, many studies have shown that critically ill patients with hypokalemia[24] or hypophosphatemia[25,26] are more likely to die than patients without these abnormalities. In contrast to these previous studies, in this study, any deficiencies in sodium, potassium, calcium, and phosphate were found not to be related to increased mortality rates in septic AKI patients undergoing CRRT. Before initiating CRRT, deficiencies in sodium and calcium were more common than deficiencies in potassium and phosphate. However, hyponatremia and hypocalcemia were much improved after CRRT. In general, a CRRT solution contains 140 mEq/L sodium and 2.5–3.5 mEq/L calcium; thus, sodium and calcium deficiencies can be corrected by diffusion. In contrast, hypokalemia and hypophosphatemia became more prevalent 24 hours after CRRT. This overcorrection can commonly occur during CRRT. To prevent this, CRRT solutions containing potassium and phosphate have been commercially available. Unfortunately, our centers do not have these solutions and thus cannot use them in the ICU. Even though the samples were collected and stored at 0 and 24 hours according to the original study protocol, we additionally measured serum levels of electrolytes and minerals at 10–12 hours after CRRT initiation for early detection of disturbances in these parameters in AKI patients, particularly those on CRRT. Presumably, prompt correction of potassium and phosphate deficiencies might be helpful to avoid serious complications. Another possible explanation is the unique patient inclusion of this study; we only included patients with septic AKI requiring CRRT. In fact, septic AKI is apparently distinct from nonseptic AKI in pathophysiology and severity.[27] In sepsis, the systemic inflammatory response triggered by infectious insult deteriorates failure in multiple organs and systems, subsequently resulting in catastrophic physiological derangements. Therefore, it can be presumed that the hemodynamic alteration and deterioration due to sepsis-induced systemic inflammatory response syndrome might overwhelm the impact of electrolyte and mineral disturbances in terms of affecting mortality.

In this study, we showed that hyperphosphatemia was significantly associated with an increased risk of death. In

Table 4

Cox proportional hazard regression analysis for 28- and 90-day mortality in 184 patients who survived 24 h after continuous renal replacement therapy initiation.

	Phosphate as a categorical variable (≥4.5 vs 2.5 to 4.5 vs <2.5 mg/dL)*		Phosphate as a continuous variable (per 1 mg/dL increase)	
	HR (95% CI)	*P*	HR (95% CI)	*P*
28-day				
Model 1	2.11 (1.41–3.16)	<0.001	1.33 (1.20–1.47)	<0.001
Model 2	3.12 (2.01–4.86)	<0.001	1.46 (1.31–1.62)	<0.001
Model 3	2.25 (1.40–3.61)	<0.001	1.36 (1.20–1.54)	<0.001
90-day				
Model 1	2.54 (1.76–3.67)	<0.001	1.36 (1.21–1.47)	<0.001
Model 2	3.52 (2.24–5.30)	<0.001	1.43 (1.29–1.59)	<0.001
Model 3	2.65 (1.71–4.12)	<0.001	1.32 (1.17–1.48)	<0.001

* Phosphate level of 2.5–4.5 mg/dL is a referent.

Model 1: unadjusted.

Model 2: Age, gender, BMI at ICU admission.

Model 3: Model 2 + CCI, SOFA score, urine output (24 h).

BMI = body mass index, CCI = Charlson comorbidity index, CI = confidence interval, HR = hazard ratio, ICU = intensive care unit, SOFA = sequential organ failure assessment.

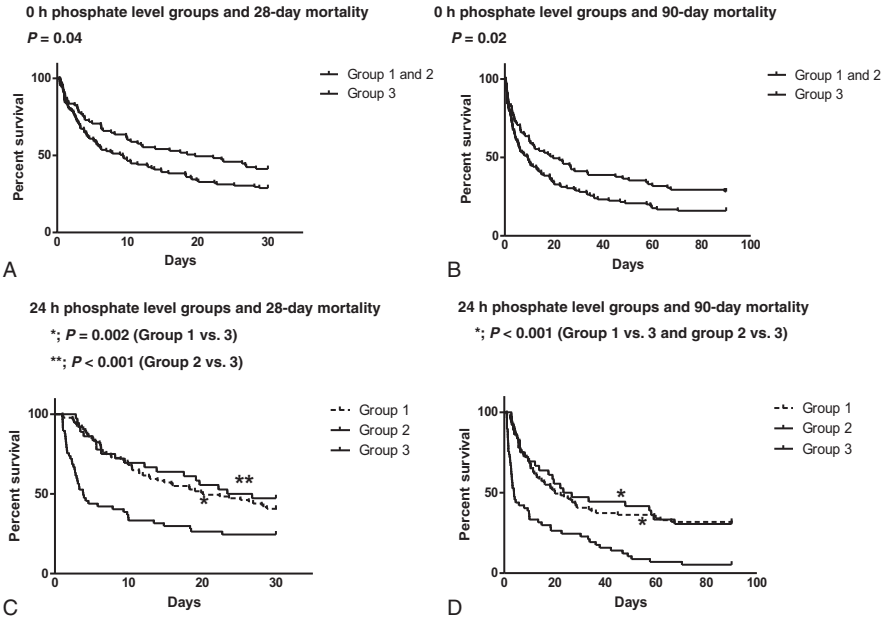

Figure 3. Kaplan–Meier plots for 28- and 90-day mortality according to phosphate levels before starting CRRT (A and B) and 24 hours after CRRT initiation (C and D), Group 1 (below normal levels) <2.5 mg/dL; Group 2 (normal levels) 2.5–4.5 mg/dL; Group 3 (elevated levels) >4.5 mg/dL. CRRT = continuous renal replacement therapy.

contrast to our findings, several previous studies have shown that hypophosphatemia was a significant predictor of adverse outcomes in critically ill patients. In fact, phosphate is a key component of bone and cell membranes, is essential in all body functions requiring energy (as adenosine triphosphate), and is especially important in nerve and muscle function.[28] Hypophosphatemia is caused by various conditions in ICU patients, such as sepsis, diuretic use, total parenteral nutrition, and gastrointestinal wasting.[29–32] Its harmful effects can be exemplified by decreased myocardial contraction, increased development of arrhythmia, impaired response to vasopressors, and decreased granulocyte phagocytic activity.[33–37] The reason for the discrepancy in findings concerning phosphate levels and mortality among studies is unclear. Interestingly, most of the adverse effects caused by hypophosphatemia result from very severe phosphate deficiency. In many previous studies, severe hypophosphatemia was defined as a serum phosphate level of <1.0 mg/dL.[38–40] By using this definition in our study, severe hypophosphatemia was not observed in our subjects at 24 hours after CRRT. In addition, most patients with phosphate levels <2.5 mg/dL at 0 hour had phosphate levels of 2.0–2.5 mg/dL and only 10 patients had phosphate levels <2.0 mg/dL at 24 hours. We strictly followed a protocol concerning the supplementation for deficiencies in electrolytes and minerals, and this can explain the rare incidence of severe hypophosphatemia in our study.

An acute decrease in phosphate levels during dialysis treatment is also important in determining adverse outcomes. Demirjian et al[41] showed that patients with a decline in phosphate to <2 mg/dL during CRRT had prolonged respiratory failure requiring tracheostomy. In our study, there were only 10 patients whose phosphate levels declined to <2 mg/dL at 24 hours after CRRT. These patients were not significantly associated with an increased mortality as compared with patients with phosphate levels >2 mg/dL (HR, 1.12; 95% CI, 0.80–1.57; $P = 0.50$, data not shown).

The underlying mechanism responsible for the high mortality in hyperphosphatemic patients is largely presumptive. It is possible that phosphate simply reflects disease severity because it is released from damaged cells. Various types of cell death have been suggested in sepsis.[42] Besides phosphate, other danger signals and inflammatory cytokines are also released upon cell death and may play more important roles in the development of life-threatening conditions.[43–45] Direct phosphate toxicity is also plausible. Increased phosphate from dead cells subsequently promotes vascular inflammation[46,47] and triggers phosphate influx into cells, resulting in increased mitochondrial membrane potential and reactive oxygen species production.[48] This can produce a vicious cycle and further aggravate cell death. In fact, a number of studies have shown that patients with increased phosphate levels are more likely to develop cardiovascular diseases[47,49,50] and chronic kidney disease,[51] even end-stage renal disease.[51]

This study has some limitations. First, as this is a post-hoc analysis of our prior randomized controlled trial, causality is uncertain and the results should be interpreted with caution. In addition, the small sample size is another limitation, as it may result in a lack of statistical power. Second, magnesium is also an important mineral and its deficiency is common in AKI patients; however, we did not include magnesium imbalance in the reported data because magnesium levels were not measured in >50% of the patients. Nevertheless, we performed further analysis in this limited number of patients and found that magnesium disturbances did not affect mortality (data not shown). Third, further analysis with extended follow-up data, such as phosphate levels measured at 72 hours, would be helpful to confirm our findings. However, septic AKI is a devastating medical condition and many patients have died while receiving CRRT. We analyzed 146 patients who survived at 72 hours after CRRT, by collecting additional blood samples, and found that hyperphosphatemia still remained a significant risk factor of death (HR, 2.25; 95% CI, 0.13–4.89; $P = 0.04$, data not shown). Finally, the original study aimed to evaluate effects of high (80 mL/kg/h) versus conventional (40 mL/kg/h) volume on clinical outcomes; thus, the greater deficiencies in electrolytes and minerals might be attributed to high-volume treatment. However, there were no differences in the changes of these parameters

after 24-h CRRT between the 2 groups. This finding suggests that disturbances in electrolytes and minerals are not further improved by high-volume treatment compared with treatment with the conventional volume.

In conclusion, this study showed that electrolyte and mineral disturbances are common and hyperphosphatemia may portend a poor prognosis in septic AKI patients undergoing CRRT. If phosphate is a biomarker that can reflect disease severity, then more careful attention should be paid to patients with increased phosphate levels.

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