Original Article

KIDNEY RESEARCH
AND CLINICAL PRACTICE

Phosphate level predicts mortality in acute kidney injury patients undergoing continuous kidney replacement therapy and has a U-shaped association with mortality in patients with high disease severity: a multicenter retrospective study

Young Hwan Lee[1,*], Soyoung Lee[2,*], Yu Jin Seo[3], Jiyun Jung[4,5], Jangwook Lee[5,6], Jae Yoon Park[5,6,7], Tae Hyun Ban[8], Woo Yeong Park[9], Sung Woo Lee[10], Kipyo Kim[11], Kyeong Min Kim[2], Hyosang Kim[12], Ji-Young Choi[1], Jang-Hee Cho[1], Yong Chul Kim[13,†], Jeong-Hoon Lim[1,†]

*For further information on the authors' affiliations, see **Additional information.***

Background: This study investigated the association between serum phosphate level and mortality in acute kidney injury (AKI) patients undergoing continuous kidney replacement therapy (CKRT) and evaluated whether this association differed according to disease severity.

Methods: Data from eight tertiary hospitals in Korea were retrospectively analyzed. The patients were classified into four groups (low, normal, high, and very high) based on their serum phosphate level at baseline. The association between serum phosphate level and mortality was then analyzed, with further subgroup analysis being conducted according to disease severity.

Results: Among the 3,290 patients identified, 166, 955, 1,307, and 862 were in the low, normal, high, and very high phosphate groups, respectively. The 90-day mortality rate was 63.9% and was highest in the very high group (76.3%). Both the high and very high groups showed a significantly higher 90-day mortality rate than did the normal phosphate group (high: hazard ratio [HR], 1.35, 95% confidence interval [CI], 1.21–1.51, p < 0.001; very high: HR, 2.01, 95% CI, 1.78–2.27, p < 0.001). The low group also exhibited a higher 90-day mortality rate than did the normal group among those with high disease severity (HR, 1.47; 95% CI, 1.09–1.99; p = 0.01) but not among those with low disease severity.

Conclusion: High serum phosphate level predicted increased mortality in AKI patients undergoing CKRT, and low phosphate level was associated with increased mortality in patients with high disease severity. Therefore, serum phosphate levels should be carefully considered in critically ill patients with AKI.

Keywords: Acute kidney injury, Continuous kidney replacement therapy, Critical illness, Mortality, Phosphates

Introduction

Acute kidney injury (AKI) is a serious complication commonly observed in critically ill patients. Continuous kidney replacement therapy (CKRT), which is often required for patients with severe AKI to correct for biochemical imbalances and volume status [1], has seen increased use over the past decade [2]. Despite the advances in CKRT technology and optimization for critically ill patients, mortality rates in AKI patients requiring CKRT remain high, ranging from 30% to 60% [3]. Hence, identifying prognostic indicators of morality in these patients is essential for improving their outcomes.

Serum phosphate has emerged as a potential predictor of mortality in patients with AKI. Phosphate is an essential mineral that plays a crucial role in numerous physiological processes, including bone metabolism, energy metabolism, and intracellular signaling [4]. Numerous reports have shown that both high and low phosphate levels are associated with adverse outcomes in various clinical conditions, including chronic kidney disease, cardiovascular disease, and critical illness [5].

Several studies have investigated the association between serum phosphate and mortality in AKI patients [6–8]. Some studies have shown that hyperphosphatemia is associated with poor outcomes given that it can increase cardiovascular events and mortality [6]. On the other hand, other studies have shown that hypophosphatemia is also associated with adverse outcomes given that it can cause respiratory muscle weakness [9,10], difficulty in weaning off ventilatory support [11,12], and increased need for vasopressors [13]. The impact of these phosphate levels on patients is more devastating when the severity of the disease is high. Thus, we hypothesized that the effect of phosphate on mortality risk would be more pronounced under high disease severity condition in critically ill patients requiring CKRT.

The current study therefore aimed to investigate the association between serum phosphate level and mortality in critically ill patients with severe AKI requiring CKRT using a large multicenter CKRT cohort. In addition, we evaluated whether this association differed according to disease severity.

Methods

Study participants and data collection

This multicenter retrospective cohort study was conducted on critically ill patients with AKI requiring CKRT. Patients over 18 years of age who received CKRT for over 24 hours were included. Those who were already on maintenance dialysis before CKRT initiation were excluded. Among the 4,995 adult patients who received CKRT between 2006 and 2021 in eight university-based hospitals in South Korea (the Asan Medical Center, Daejeon Eulji Medical Center, Dongguk University Ilsan Hospital, Inha University Hospital, Keimyung University Dongsan Medical Center, Kyungpook National University Chilgok Hospital, Seoul National University Hospital, and the Catholic University of Korea, Eunpyeong St. Mary's Hospital), 651 were excluded for being on maintenance dialysis. Additionally, those without baseline phosphate data were excluded (n = 1,054). A total of 3,290 patients were included in the analysis (Fig. 1). CKRT was initiated at the discretion of a nephrologist if the patient has persistent oliguria, uncontrolled volume overload, refractory hyperkalemia, or metabolic acidosis unresponsive to conventional therapy.

Patient information at CKRT initiation, including demographics and comorbidities, clinical parameters, and laboratory results, including complete blood counts, blood urea nitrogen, creatinine, estimated glomerular filtration rate (eGFR) obtained using CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation, electrolytes such as calcium, phosphate, sodium, and potassium, C-reactive protein, albumin, and lactate at CKRT initiation, was retrospectively collected. The Charlson Comorbidity Index (CCI) and disease severity scores, such as the Acute Physiology and Chronic Health Evaluation (APACHE) II score, Sequential Organ Failure Assessment (SOFA) score, were also measured. The causes of AKI were reviewed by nephrologists to determine whether the AKI was septic or non-septic. We also collected information on critical care and mortality at 7, 30, and 90 days.

Definition

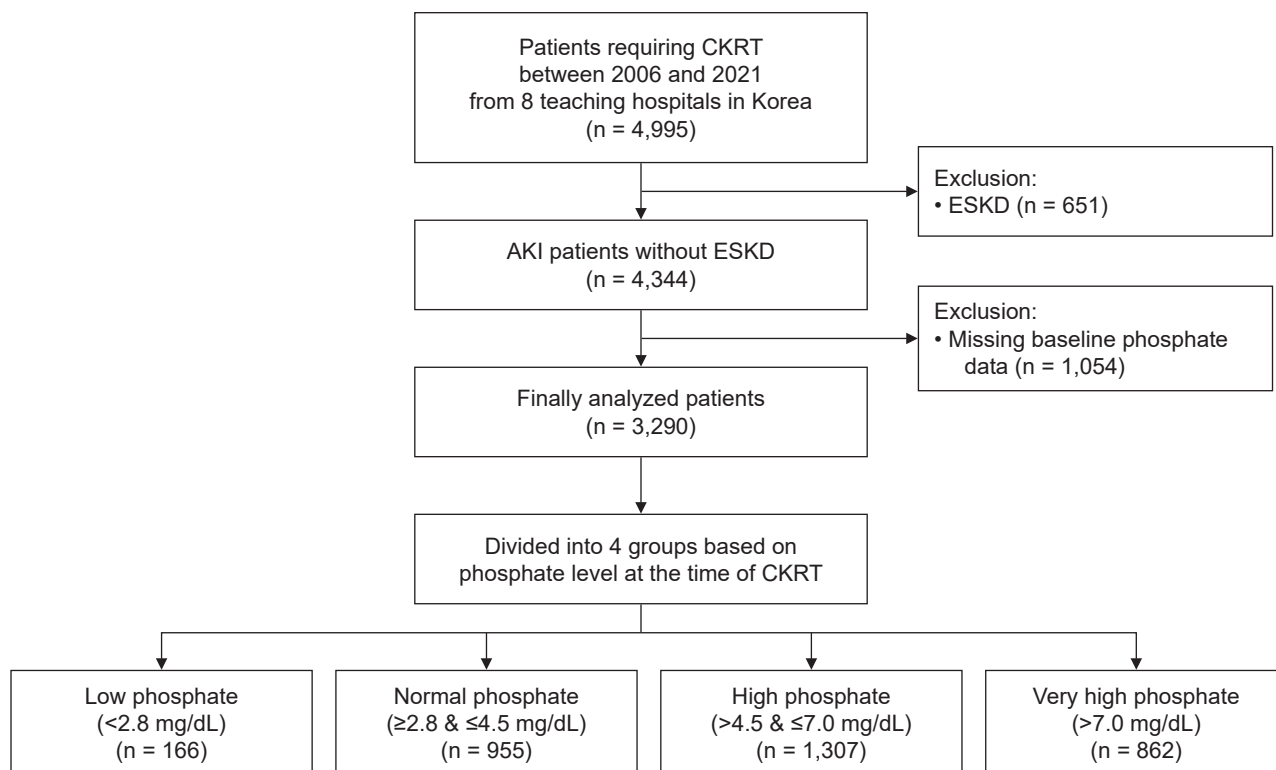The reference range for phosphate used in this study was 2.8 to 4.5 mg/dL (normal phosphate group). Study par-

Figure 1. Flow diagram for the study.
AKI, acute kidney injury; CKRT, continuous kidney replacement therapy; ESKD, end-stage kidney disease.

ticipants were divided into four groups (i.e., low, normal, high, and very high phosphate groups) according to their baseline serum phosphate levels. Baseline serum phosphate was defined as the phosphate level measured at the initiation of CKRT. Hypophosphatemia was defined as a phosphate level of <2.8 mg/dL (low phosphate group), hyperphosphatemia was defined as a phosphate level over 4.5 mg/dL but under 7.0 mg/dL (high phosphate group), and severe hyperphosphatemia was defined as a phosphate level over 7.0 mg/dL (very high phosphate group).

Disease severity was classified according to the APACHE II score at CKRT initiation. Patients with an APACHE II score of 28 (median value) or higher were classified into the high severity group, whereas those with a score of <28 were classified into the low severity group.

The CCI weights 19 different diseases to determine the severity of the underlying comorbidities [14]. Septic AKI was defined as the presence of an infection that satisfied the criteria for systemic inflammatory response syndrome [15].

The primary outcome was the 90-day mortality rate, and the secondary outcomes were the 7- and 30-day mortality rates.

Statistical analyses

Continuous variables were expressed as mean ± standard deviation, whereas categorical variables were expressed as number (percentage). Participants were divided into four groups by serum phosphate level at the time of CKRT initiation. Parameters were compared using a one-way analysis of variance for continuous variables and the Pearson chi-square test or Fisher exact test for categorical variables. We then analyzed the relationship between serum phosphate as a continuous variable and 90-day mortality using a Cox proportional hazard model with restricted cubic spline functions to capture potential nonlinear effects, with the reference value at the lower limit of reference phosphate range. Survival analyses using the Kaplan-Meier curves with log-rank tests were performed to investigate the im-

pact of phosphate levels on mortality. In addition, subgroup analysis was conducted to determine the relationship between phosphate level and mortality according to disease severity. Outcomes were compared between each group divided according to disease severity. Univariable and multivariable Cox proportional hazard regression models were used to estimate hazard ratios (HRs) for mortality according to phosphate groups and subgroups according to disease severity. The multivariable Cox regression model adjusted for clinically important variables affecting mortality and different baseline characteristics, such as age, sex, body weight, CCI, hypertension, diabetes, chronic kidney disease, congestive heart failure, SOFA score, mechanical ventilator use, vasopressor use, serum creatinine, and serum lactate. In addition, the predictive power of phosphate and traditional prognostic indicators was compared. The ability of prognostic indicators to predict mortality was determined using the area under the curve (AUC) and compared using DeLong's test [16]. We also confirmed the integrative effects of combining phosphate levels with other prognostic indicators. Net reclassification improvement (NRI) and integrated discrimination improvement (IDI) were analyzed to measure the integrative effects of combining phosphate levels with other prognostic indicators. Statistical analyses were performed using IBM SPSS for Windows version 22.0 (IBM Corp.) and R software (R Foundation for Statistical Computing). A p-value less than 0.05 was considered statistically significant.

Ethics statements

This study was approved by the Institutional Review Board of the Asan Medical Center (No. S2021-1790-0001), Daejeon Eulji Medical Center (No. 2021-07-006-002), Dongguk University Ilsan Hospital (No. 2018-12-010-001), Inha University Hospital (No. 2021-09-029-000), Keimyung University Dongsan Medical Center (No. 2021-06-057), Kyungpook National University Chilgok Hospital (No. 2021-03-024), Seoul National University Hospital (No. H-2111-057-1271), and the Catholic University of Korea, Eunpyeong St. Mary's Hospital (No. PC21RIDI0111). Informed consent was waived considering that no infringement of patient privacy or health occurred during the study. All patient data were anonymized prior to analysis. This study was conducted in accordance with the principles of the Helsin-

ki Declaration of 1975, as revised in 2013.

Results

Baseline characteristics

The baseline characteristics of the study participants and each group based on phosphate levels are presented in Table 1. Participants had a mean age of 65.7 ± 14.7 years, with males accounting for 60.9%. The number of males and body weight were significantly higher in the very high phosphate group than in the rest of the groups (both p < 0.05), but body mass index did not differ among groups. Sepsis accounted for more than half of the AKI cases in all groups. Comorbidity rates and CCI values differed significantly among the groups. Disease severity indexes, such as the APACHE II and SOFA score, were significantly higher in the very high phosphate group than in the other groups (p < 0.001). High and very high phosphate groups exhibited lower hemoglobin, eGFR, calcium, and albumin levels and higher potassium, blood urea nitrogen, creatinine, and lactate levels than did the low phosphate group (all p < 0.05).

Clinical outcomes and in-hospital course

In-hospital information is summarized in Table 2. The 90-day mortality was 63.9%, with the very high and low phosphate groups having the highest and lowest rates (76.3% and 54.8%, respectively; p < 0.001). Short-term (7- and 30-day) mortality rates were also higher in the very high phosphate group and lower in the low phosphate group than in the normal phosphate group (p < 0.001). More patients received mechanical ventilation in the low phosphate group than in the high and very high phosphate groups, whereas the high and very high phosphate groups used more vasopressors than the low phosphate group. The high and very high phosphate groups exhibited shorter hospital length of stay and CKRT duration than did the low phosphate group (p < 0.001).

Association between phosphate level and mortality

Fig. 2 displays the association between phosphate level as a continuous variable and 90-day mortality using Cox regression analysis with restricted cubic splines. After the

Table 1. Baseline characteristics in all patients

Characteristic	Total	Phosphate				p-value
		Low	Normal	High	Very high	
No. of patients	3,290	166	955	1,307	862	
Age (yr)	65.7 ± 14.7	67.9 ± 16.5	67.2 ± 14.3	65.5 ± 14.6	63.9 ± 14.8	<0.001
Male sex	2,004 (60.9)	99 (59.6)	561 (58.7)	782 (59.8)	562 (65.2)	0.03
ICU admission body weight (kg)	61.7 ± 13.2	60.3 ± 13.8	60.8 ± 12.7	61.4 ± 13.2	63.5 ± 13.4	<0.001
ICU admission BMI (kg/m^2)	23.3 ± 4.5	22.9 ± 4.9	23.0 ± 4.6	23.3 ± 4.4	23.6 ± 4.3	0.06
Systolic BP (mmHg)	113.3 ± 27.3	115.3 ± 25.8	113.8 ± 25.9	114.8 ± 27.4	112.9 ± 28.7	<0.001
Diastolic BP (mmHg)	60.4 ± 15.6	62.0 ± 16.7	60.9 ± 14.9	60.7 ± 15.0	59.2 ± 17.2	0.05
Charlson Comorbidity Index	3.6 ± 2.8	3.2 ± 2.5	3.7 ± 2.8	3.8 ± 2.8	3.3 ± 2.7	<0.001
Cause of AKI						0.24
Septic	1,822 (55.4)	104 (62.7)	528 (55.3)	710 (54.3)	480 (55.7)	
Non-septic	1,467 (44.6)	62 (37.3)	427 (44.7)	597 (45.7)	381 (44.3)	
Comorbidities						
Hypertension	1,134 (34.5)	72 (43.4)	386 (40.4)	442 (33.8)	234 (27.1)	<0.001
Diabetes	838 (25.5)	42 (25.3)	240 (25.2)	373 (28.5)	183 (21.2)	0.002
Chronic kidney disease	757 (23.0)	36 (21.7)	232 (24.3)	334 (25.6)	155 (18.0)	<0.001
Congestive heart failure	574 (17.4)	27 (16.3)	176 (18.4)	260 (19.9)	111 (12.9)	<0.001
Chronic liver disease	521 (15.8)	23 (13.9)	161 (16.9)	213 (16.3)	124 (14.4)	0.42
COPD	217 (6.6)	18 (10.8)	66 (6.9)	78 (6.0)	55 (6.4)	0.12
APACHE II score	27.6 ± 8.0	26.1 ± 7.4	25.9 ± 7.6	27.1 ± 7.8	30.5 ± 7.9	<0.001
SOFA score	12.1 ± 3.5	11.9 ± 3.3	11.9 ± 3.4	12.1 ± 3.6	12.3 ± 3.6	<0.001
Laboratory findings at CKRT initiation						
WBC count (×10^3/μL)	15.0 ± 19.4	13.1 ± 13.2	14.9 ± 21.7	14.5 ± 18.4	16.0 ± 19.1	0.20
Platelet count (×10^3/μL)	109.1 ± 91.4	94.4 ± 75.6	107.5 ± 82.5	110.7 ± 92.4	111.1 ± 101.4	0.15
Hemoglobin (g/dL)	9.5 ± 2.2	9.8 ± 1.9	9.6 ± 2.0	9.5 ± 2.1	9.2 ± 2.5	<0.001
Sodium (mEq/L)	136.9 ± 8.1	138.8 ± 6.8	137.1 ± 7.5	136.4 ± 8.0	137.2 ± 8.9	0.001
Potassium (mEq/L)	4.5 ± 1.1	3.9 ± 0.7	4.2 ± 0.9	4.5 ± 1.0	5.0 ± 1.2	<0.001
BUN (mg/dL)	53.9 ± 32.0	42.9 ± 27.0	47.3 ± 27.1	55.4 ± 30.3	61.2 ± 38.1	<0.001
Creatinine (mg/dL)	2.9 ± 2.1	2.2 ± 1.4	2.6 ± 1.8	2.9 ± 1.7	3.6 ± 2.9	<0.001
eGFR (mL/min/1.73 m^2)	31.1 ± 19.0	37.5 ± 21.2	35.2 ± 20.2	30.3 ± 18.3	27.0 ± 16.8	<0.001
Calcium (mg/dL)	7.8 ± 1.4	8.2 ± 1.1	8.1 ± 1.3	7.9 ± 1.5	7.4 ± 1.4	<0.001
Phosphate (mg/dL)	5.9 ± 2.5	2.2 ± 0.5	3.8 ± 0.5	5.7 ± 0.7	9.3 ± 2.1	<0.001
Albumin (g/dL)	2.7 ± 0.7	2.8 ± 0.6	2.7 ± 0.6	2.7 ± 0.8	2.6 ± 0.7	<0.001
CRP (mg/dL)	12.7 ± 10.9	14.5 ± 10.5	12.7 ± 10.4	12.7 ± 10.9	12.4 ± 11.5	0.17
Bicarbonate (mmol/L)	18.0 ± 5.8	21.0 ± 6.1	18.9 ± 5.5	17.6 ± 5.1	16.1 ± 6.2	<0.001
Lactate (mmol/L)	7.3 ± 5.6	4.8 ± 4.8	5.1 ± 4.2	6.6 ± 5.0	10.5 ± 6.1	<0.001

Data are expressed as number only, mean ± standard deviation, or number (%).
AKI, acute kidney injury; APACHE II, Acute Physiology and Chronic Health Evaluation II; BMI, body mass index; BP, blood pressure; BUN, blood urea nitrogen; CKRT, continuous kidney replacement therapy; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; ICU, intensive care unit; SOFA, Sequential Organ Failure Assessment; WBC, white blood cell.

reference value was set at the lower limit of normal for phosphate level (2.8 mg/dL), our results showed that a higher phosphate level was associated with increased 90-day mortality in critically ill AKI patients undergoing CKRT.

The Kaplan-Meier curves for 90-day mortality according to phosphate groups are presented in Fig. 3. Accordingly, the high and very high phosphate groups had significantly poorer survival than did the normal phosphate group, with the low phosphate group showing a survival curve similar to that for the normal phosphate group (Fig. 3A).

Table 2. In-hospital information for phosphate groups in all patients

Variable	Total (n = 3,290)	Phosphate				p-value
		Low (n = 166)	Normal (n = 955)	High (n = 1,307)	Very high (n = 862)	
Mortality						
7-Day	1,146 (34.8)	32 (19.3)	200 (20.9)	464 (35.5)	450 (52.2)	<0.001
30-Day	1,818 (55.3)	72 (43.4)	409 (42.8)	728 (55.7)	609 (70.6)	<0.001
90-Day	2,101 (63.9)	91 (54.8)	528 (55.3)	824 (63.0)	658 (76.3)	<0.001
Need for mechanical ventilation	278 (8.4)	33 (19.9)	142 (14.9)	86 (6.6)	17 (2.0)	<0.001
Vasopressor use	1,795 (54.6)	76 (45.8)	481 (50.4)	723 (55.3)	515 (59.7)	<0.001
≥2	735 (22.3)	28 (16.9)	186 (19.5)	299 (22.9)	222 (25.8)	0.004
Target clearance (mL/kg/hr)	40.8 ± 13.5	41.5 ± 14.1	40.6 ± 14.0	40.4 ± 12.8	41.3 ± 13.0	0.53
Length of hospital stay (day)	14.0 (4.0–35.0)	24.0 (9.0–42.0)	22.0 (9.0–47.0)	16.0 (4.0–34.0)	6.0 (2.0–20.0)	<0.001
CKRT duration (day)	3.0 (1.0–7.0)	4.0 (2.0–10.0)	4.0 (2.0–8.0)	3.0 (1.0–7.0)	2.0 (1.0–5.0)	<0.001

Data are expressed as number (%), mean ± standard deviation, or median (interquartile range).
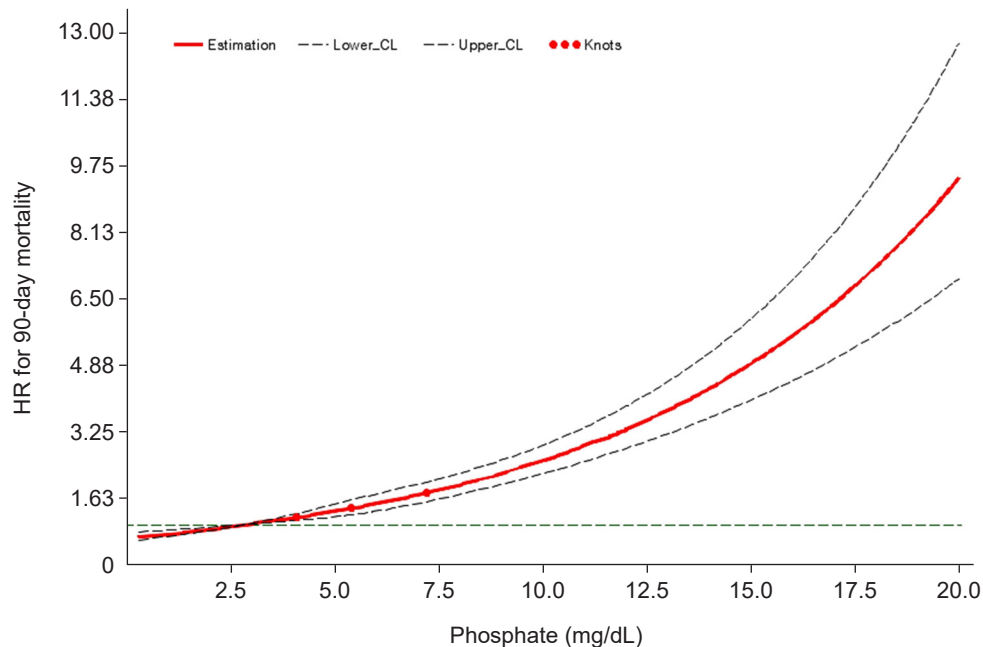CKRT, continuous kidney replacement therapy.

Figure 2. Hazard ratios (HRs) for the association between phosphate and 90-day mortality determined using the restricted cubic spline regression model. The reference value was set to the lower limit of normal for phosphate (2.8 mg/dL). The red line indicates the estimated HR; the dashed green line indicates the reference line of the null hypothesis that the HR is 1; the dashed black lines indicate the lower and upper 95% confidence limits (CLs).

In the Cox proportional hazards models, both the high and very high phosphate groups had consistently higher risk for 90-day mortality than did the normal phosphate group (model 4: high phosphate group: adjusted HR [aHR], 1.35, 95% confidence interval [CI], 1.21–1.51, p < 0.001; very high phosphate group: aHR, 2.01, 95% CI, 1.78–2.27, p < 0.001) (Table 3, Fig. 4A). No difference in mortality risk was observed between the low and normal phosphate groups.

Supplementary Table 1 (available online) details the association between phosphate level and short-term (7- and
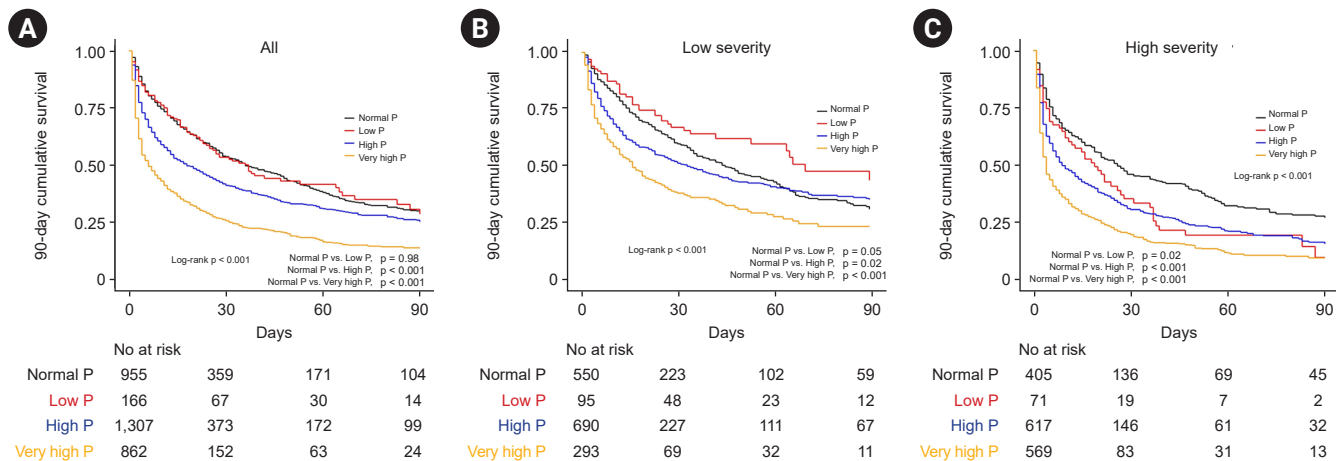
Figure 3. The Kaplan-Meier curves for 90-day mortality according to phosphate (P) level. (A) All patients, (B) patients with low disease severity, and (C) patients with high disease severity.
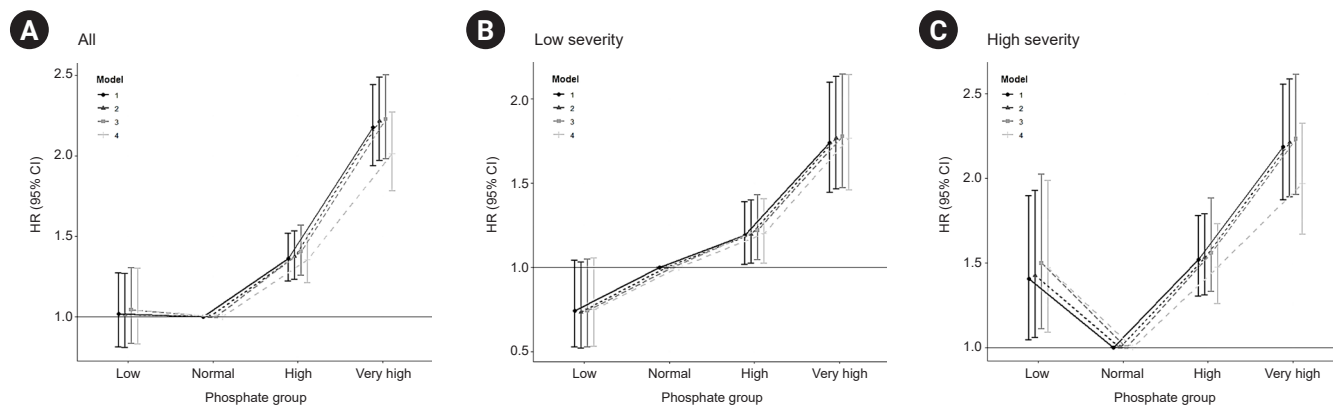

Figure 4. HRs and 95% CIs for 90-day mortality among phosphate level groups by Cox proportional hazards models. (A) All patients, (B) patients with low disease severity, and (C) patients with high disease severity. Model 1 was unadjusted. Model 2 was adjusted for age, sex, and body weight. Model 3 was adjusted for age, sex, body weight, Charlson Comorbidity Index (CCI), hypertension, diabetes, and congestive heart failure. Model 4 was adjusted for age, sex, body weight, CCI, hypertension, diabetes, congestive heart failure, mechanical ventilator use, and vasopressor use.
CI, confidence interval; HR, hazard ratio.

Table 3. Cox regression analyses for 90-day mortality among phosphate groups

Phosphate	Model 1		Model 2		Model 3		Model 4	
	HR (95% CI)	p-value	aHR (95% CI)	p-value	aHR (95% CI)	p-value	aHR (95% CI)	p-value
Low	1.02 (0.81–1.27)	0.89	1.01 (0.81–1.27)	0.92	1.04 (0.83–1.30)	0.71	1.04 (0.83–1.30)	0.75
Normal	Reference		Reference		Reference		Reference	
High	1.36 (1.22–1.52)	<0.001	1.37 (1.23–1.53)	<0.001	1.41 (1.26–1.57)	<0.001	1.35 (1.20–1.54)	<0.001
Very high	2.18 (1.94–2.44)	<0.001	2.22 (1.97–2.49)	<0.001	2.23 (1.98–2.50)	<0.001	2.01 (1.73–2.21)	<0.001

Model 1: unadjusted. Model 2: adjusted for age, sex, and body weight. Model 3: adjusted for age, sex, body weight, Charlson Comorbidity Index, hypertension, diabetes, and congestive heart failure. Model 4: adjusted for age, sex, body weight, Charlson Comorbidity Index, hypertension, diabetes, chronic kidney disease, and congestive heart failure, Sequential Organ Failure Assessment score, mechanical ventilator use, vasopressor use, serum creatinine, and serum lactate.
aHR, adjusted HR; CI, confidence interval; HR, hazard ratio.

30-day) mortality risk. Similar to the results for long-term mortality, the high and very high phosphate groups had greater 7- and 30-day mortality risk (all p < 0.001), whereas no difference in mortality risk was observed between the low and normal phosphate groups.

Association between phosphate level and mortality according to disease severity

The association between phosphate level and mortality was further analyzed according to disease severity upon CKRT initiation. Supplementary Table 2 (available online) summarizes the baseline characteristics of patients with low severity, whereas Supplementary Table 3 (available online) outlines the in-hospital information of the patients. The results of our Kaplan-Meier curve and Cox regression analyses were consistent with those for the overall patient cohort such that the high and very high phosphate groups showed an increased risk of 90-day mortality (Table 4 and Fig. 3B, 4B).

The baseline characteristics and in-hospital information of patients with high severity are shown in Supplementary Tables 4 and 5 (available online), respectively. Among patients with high severity, the normal phosphate group had the lowest 90-day mortality, whereas the low, high, and very high phosphate groups showed significantly increased 90-day mortality in the Kaplan-Meier curve analysis (Fig. 3C). Multivariable Cox regression analysis also showed that both the high and low phosphate groups showed signifi-

cantly greater risk for 90-day mortality than did the normal phosphate group (model 4: low: aHR, 1.470, 95% CI, 1.09–1.99, p = 0.01; high: aHR, 1.47, 95% CI, 1.26–1.73, p < 0.001; very high phosphate group: aHR, 1.97, 95% CI, 1.67–2.32, p < 0.001) (Table 4, Fig. 4C).

Comparison of the ability to predict mortality between phosphate and other prognostic markers

Fig. 5 shows the receiver operating characteristic curves of the prognostic parameters for 90-day mortality. Accordingly, the AUC of phosphate for 90-day mortality was 0.61 (95% CI, 0.59–0.63). The combination of phosphate and other traditional prognostic markers, such as APACHE II score, albumin, and lactate level, demonstrated significantly greater predictive power than any single marker (Table 5). The NRI for the combination of phosphate and APACHE II score or albumin level or lactate level significantly improved predictability. The IDI also revealed that the combination of phosphate and individual markers, such as the APACHE II score, albumin level, and lactate level, demonstrated significantly greater predictive power than any single marker (Table 5).

Discussion

This study investigated the relationship between serum phosphate levels at the initiation of CKRT and prognosis using nationwide multicenter cohort data of AKI patients

Table 4. Cox regression analyses for 90-day mortality among phosphate groups according to disease severity

Severity	Phosphate	Model 1		Model 2		Model 3		Model 4	
		HR (95% CI)	p-value	aHR (95% CI)	p-value	aHR (95% CI)	p-value	aHR (95% CI)	p-value
Low	Low	0.72 (0.53–1.04)	0.09	0.74 (0.52–1.03)	0.08	0.75 (0.53–1.05)	0.09	0.75 (0.53–1.06)	0.10
	Normal	Reference		Reference		Reference		Reference	
	High	1.19 (1.02–1.39)	0.03	1.20 (1.02–1.40)	0.03	1.22 (1.04–1.43)	0.01	1.20 (1.02–1.41)	0.02
	Very high	1.74 (1.44–2.10)	<0.001	1.77 (1.46–2.13)	<0.001	1.78 (1.47–2.15)	<0.001	1.77 (1.46–2.14)	<0.001
High	Low	1.41 (1.04–1.90)	0.03	1.43 (1.06–1.93)	0.02	1.50 (1.11–2.02)	0.009	1.47 (1.09–1.99)	0.01
	Normal	Reference		Reference		Reference		Reference	
	High	1.52 (1.30–1.78)	<0.001	1.53 (1.31–1.79)	<0.001	1.56 (1.33–1.88)	<0.001	1.47 (1.26–1.73)	<0.001
	Very high	2.19 (1.87–2.56)	<0.001	2.21 (1.89–2.59)	<0.001	2.23 (1.90–2.62)	<0.001	1.97 (1.67–2.32)	<0.001

Model 1: unadjusted. Model 2: adjusted for age, sex, and body weight. Model 3: adjusted for age, sex, body weight, Charlson Comorbidity Index, hypertension, diabetes, and congestive heart failure. Model 4: adjusted for age, sex, body weight, Charlson Comorbidity Index, hypertension, diabetes, chronic kidney disease, and congestive heart failure, Sequential Organ Failure Assessment score, mechanical ventilator use, vasopressor use, serum creatinine, and serum lactate.
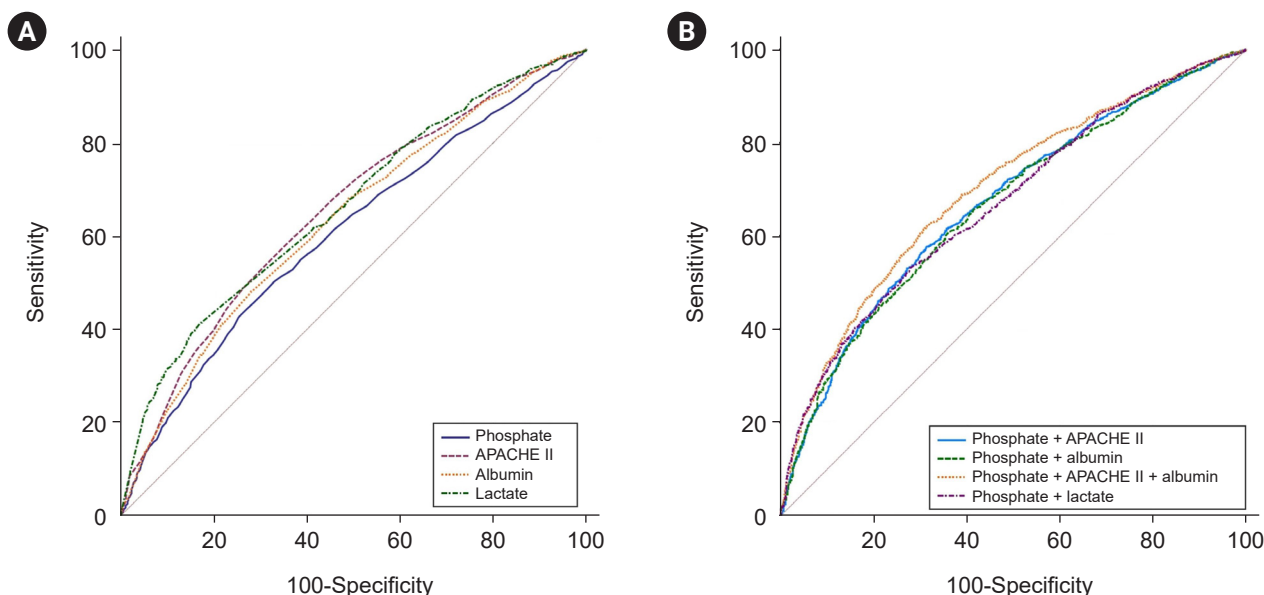aHR, adjusted HR; CI, confidence interval; HR, hazard ratio.

Figure 5. Receiver operating characteristic curves of the prognostic factors for 90-day mortality. (A) Univariate model. (B) Multivariate model. The area under the curve values are as follows: phosphate, 0.606; APACHE II score, 0.654; albumin level, 0.633; lactate level, 0.661; phosphate level + APACHE II score, 0.670; phosphate level + albumin level, 0.665; phosphate level + APACHE II score + albumin level, 0.698; phosphate level + lactate level, 0.670.
APACHE II, Acute Physiology and Chronic Health Evaluation II.

Table 5. Comparison of the AUCs and predictive power of prognostic markers for 90-day mortality

Variable	AUC (95% CI)	p-value	NRI (95% CI)	p-value	IDI	p-value
Phosphate	0.61 (0.59–0.63)					
APACHE II	0.65 (0.63–0.67)	Reference	Reference		Reference	
APACHE II + phosphate	0.67 (0.65–0.69)	<0.001	0.24 (0.17–0.31)	<0.001	0.014	<0.001
Albumin	0.63 (0.61–0.65)	Reference	Reference		Reference	
Albumin + phosphate	0.67 (0.65–0.68)	<0.001	0.32 (0.25–0.39)	<0.001	0.025	<0.001
APACHE II + albumin	0.69 (0.67–0.70)	Reference	Reference		Reference	
APACHE II + albumin + phosphate	0.70 (0.68–0.72)	<0.001	0.24 (0.17–0.31)	<0.001	0.012	<0.001
Lactate	0.66 (0.65–0.68)	Reference	Reference		Reference	
Lactate + phosphate	0.67 (0.65–0.69)	<0.001	0.35 (0.28–0.42)	<0.001	0.053	<0.001

APACHE II, Acute Physiology and Chronic Health Evaluation II; AUC, area under the curve; CI, confidence interval; IDI, integrated discrimination improvement; NRI, net reclassification improvement.

undergoing CKRT. Notably, increased phosphate levels upon CKRT initiation were associated with increased mortality. In addition, we demonstrated that low phosphate level was associated with increased mortality in patients with high disease severity. Previous studies have failed to clearly determine the relationship between phosphate levels and mortality given the limited number of available patients. This study analyzes data from a large CKRT cohort and presents a relationship clearly between phosphate

levels at the initiation of CKRT and prognosis.

Hyperphosphatemia, which is mainly caused by decreased renal excretion of phosphate, is common in AKI patients [17]. In this study, more than half of the patients had phosphate levels above the normal range. In a previous study, there were findings indicating an increased mortality rate associated with phosphate levels, particularly when phosphate levels exceeded 7 [18]. Given the number of patients with high phosphate and the reported higher risk

of mortality with very high phosphate, we divided the high phosphate population into high and very high and identified those patients with very high phosphate in particular who need more attention. Our study found that high and very high phosphate levels were associated with increased mortality risk regardless of disease severity among critically ill AKI patients, and the very high phosphate group had more risk than the high phosphate group. The shorter length of hospital stay observed in patients with higher phosphate levels in this study may be due to the high mortality rate. This is consistent with the findings of previous studies. In a meta-analysis that included 60,358 critically ill patients, hyperphosphatemia at intensive care unit admission was associated with all-cause mortality [19]. Jung et al. [6] also reported that hyperphosphatemia at CKRT initiation increased mortality risk among AKI patients undergoing CKRT, revealing that hyperphosphatemia was positively correlated with disease severity markers, such as APACHE II and the SOFA scores, and negatively correlated with mean arterial pressure and urine output. These findings suggest that phosphate levels reflect disease severity in critically ill patients with severe AKI. The association between phosphate levels at the onset of CKRT and disease severity is also supported by our findings that the group with higher phosphate levels in our study had higher APACHE II scores, SOFA scores, and serum lactate levels. However, this observational study could not prove the causal relationship, so further research is needed.

Interestingly, we also demonstrated that hypophosphatemia was a risk factor for mortality in AKI patients with high disease severity undergoing CKRT. Previous studies in CKRT have not been able to clarify the relationship between low phosphate and mortality risk due to the small number of patients with low phosphate [6,20]. Phosphate is a critical component of bone and cell membranes and plays a vital role in physiological functions requiring energy, especially in nerve and muscle function [21]. Other research has shown that hypophosphatemia can lead to respiratory muscle weakness and difficulty in the process of weaning off ventilatory support [9–12]. In our study, we also found a higher frequency of mechanical ventilator use in the low phosphate group. Various conditions, including sepsis, total parenteral nutrition, gastrointestinal wasting, diuretic usage, and prolonged mechanical ventilation, can cause hypophosphatemia in critically ill patients [8,22,23].

Hypophosphatemia can cause deleterious effects, including diminished myocardial contractility, increased risk of arrhythmia, compromised response to inotropes, and decreased granulocyte phagocytic activity [24–26].

In response to hypophosphatemia, intravenous phosphate administration or the use of phosphate-containing dialysates can reduce the risk of hypophosphatemia and reduce the variability of phosphate levels during CKRT [27,28]. However, there has been no consensus on the appropriate guidelines or protocols for treating hypophosphatemia in critically ill patients undergoing CKRT. This may be due to the lack of large-scale randomized controlled trials confirming the relationship between hypophosphatemia and mortality, as well as the inconsistent findings of retrospective studies. Some studies have indicated that hypophosphatemia increases the risk of mortality in AKI patients undergoing CKRT [7,8], whereas others have found no association between hypophosphatemia and mortality [20,29,30]. Thongprayoon et al. [7] reported that hypophosphatemia before CKRT initiation was an independent predictor of mortality in critically ill AKI patients, whereas Shor et al. [8] reported that severe hypophosphatemia was closely associated with increased mortality risk in patients with sepsis. Low phosphate levels were also associated with an increased risk of infection-related death in patients with dialysis [5]. By contrast, Kim et al. [20] reported that hypophosphatemia was not a risk factor for increased mortality in AKI patients undergoing CKRT. Their study analyzed 492 patients, of whom only 39 (7.9%) had hypophosphatemia. The current study, which analyzed the effects of hypophosphatemia in a large multicenter patient population, was able to confirm the association between hypophosphatemia and prognosis in patients with high severity. Given that patients with greater disease severity are more vulnerable, they may be more susceptible to the detrimental effects of hypophosphatemia. A recent study demonstrated that the use of phosphate-containing dialysate can effectively prevent severe hypophosphatemia in AKI patients undergoing CKRT [21]. Therefore, AKI patients with high disease severity would benefit from regularly monitoring their phosphate levels and actively using phosphate-containing dialysate to correct for low phosphate levels.

The strength of the current study lies in its multicenter cohort design, which allowed us to secure a large sample

size and resulted in significant outcomes after adjusting for various confounders. However, one limitation of our study was our failure to confirm the exact pathophysiologic mechanism for the association between phosphate levels and mortality, despite anticipating the potential mechanisms mentioned earlier. Another limitation is that the causality between phosphate at the initiation of CKRT and disease severity cannot be clearly established. In addition, the causes of AKI and the reasons for initiating CKRT are diverse, and it is expected that there may be differences in outcomes depending on these factors. However, our study was not able to take these aspects into account due to a lack of data. Furthermore, given that no data on serial changes in phosphate levels were available, it remains unclear whether correcting phosphate levels impacts mortality.

In conclusion, hyperphosphatemia was an independent predictor of mortality in critically ill AKI patients undergoing CKRT. Furthermore, hypophosphatemia was associated with increased mortality in patients with high severity. Therefore, healthcare providers must closely monitor serum phosphate levels and pay close attention to critically ill AKI patients, particularly those with greater disease severity.

Additional information

[1]Division of Nephrology, Department of Internal Medicine, Kyungpook National University School of Medicine, Kyungpook National University Hospital, Daegu, Republic of Korea

[2]Division of Nephrology, Department of Internal Medicine, Daejeon Eulji Medical Center, Eulji University School of Medicine, Daejeon, Republic of Korea

[3]Department of Statistics, Kyungpook National University, Daegu, Republic of Korea

[4]Data Management and Statistics Institute, Dongguk University Ilsan Hospital, Goyang, Republic of Korea

[5]Research Center for Chronic Disease and Environmental Medicine, Dongguk University College of Medicine, Gyeongju, Republic of Korea

[6]Department of Internal Medicine, Dongguk University Ilsan Hospital, Goyang, Republic of Korea

[7]Department of Internal Medicine, Dongguk University College of Medicine, Gyeongju, Republic of Korea

[8]Department of Internal Medicine, Eunpyeong St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea

[9]Department of Internal Medicine, Keimyung University Dongsan Medical Center, Keimyung University School of Medicine, Daegu, Republic of Korea

[10]Department of Internal Medicine, Uijeongbu Eulji University Medical Center, Uijeongbu, Republic of Korea

[11]Department of Internal Medicine, Inha University School of Medicine, Incheon, Republic of Korea

[12]Division of Nephrology, Department of Internal Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

[13]Department of Internal Medicine, Seoul National University Hospital, Seoul, Republic of Korea

Conflicts of interest

All authors have no conflicts of interest to declare.

Funding

Acknowledgments

Data sharing statement

The data presented in this study are available from the corresponding author upon reasonable request.

Authors' contributions

Conceptualization, Software, Validation: JHL
Data curation: YHL, SL, JJ, JL, JYP, THB, WYP, SWL, KK, KMK, HK, JYC, JHC, YCK, JHL
Formal analysis: YJS, JJ, JHL
Funding acquisition: JYP, JHL
Investigation: YHL, JHL
Methodology: SL, YCK, JHL
Visualization: YJS, JHL
Writing–original draft: YHL, SL, YCK, JHL
Writing–review & editing: YCK, JHL
All authors read and approved the final manuscript.

ORCID

Young Hwan Lee, https://orcid.org/0009-0008-5013-5356
Soyoung Lee, https://orcid.org/0000-0002-4344-5849
Yu Jin Seo, https://orcid.org/0009-0001-0372-179X
Jiyun Jung, https://orcid.org/0000-0002-8235-0316
Jangwook Lee, https://orcid.org/0000-0003-2181-5850
Jae Yoon Park, https://orcid.org/0000-0001-8986-7492
Tae Hyun Ban, https://orcid.org/0000-0002-2884-4948
Woo Yeong Park, https://orcid.org/0000-0003-2662-2898
Sung Woo Lee, https://orcid.org/0000-0002-4419-3938
Kipyo Kim, https://orcid.org/0000-0003-4166-1801
Kyeong Min Kim, https://orcid.org/0000-0002-5414-4339
Hyosang Kim, https://orcid.org/0000-0001-8140-9534
Ji-Young Choi, https://orcid.org/0000-0002-9774-3665
Jang-Hee Cho, https://orcid.org/0000-0002-7031-5214
Yong Chul Kim, https://orcid.org/0000-0003-3215-8681
Jeong-Hoon Lim, https://orcid.org/0000-0001-5517-9886

References

1. Karkar A, Ronco C. Prescription of CRRT: a pathway to optimize therapy. *Ann Intensive Care* 2020;10:32.
2. Park S, Lee S, Jo HA, et al. Epidemiology of continuous renal replacement therapy in Korea: results from the National Health Insurance Service claims database from 2005 to 2016. *Kidney Res Clin Pract* 2018;37:119–129.
3. Lee HJ, Son YJ. Factors associated with in-hospital mortality after continuous renal replacement therapy for critically ill patients: a systematic review and meta-analysis. *Int J Environ Res Public Health* 2020;17:8781.
4. Błaszczyk JW. Metabolites of life: phosphate. *Metabolites* 2023;13:860.
5. Lee JE, Lim JH, Jang HM, et al. Low serum phosphate as an independent predictor of increased infection-related mortality in dialysis patients: a prospective multicenter cohort study. *PLoS One* 2017;12:e0185853.
6. Jung SY, Kwon J, Park S, et al. Phosphate is a potential biomarker of disease severity and predicts adverse outcomes in acute kidney injury patients undergoing continuous renal replacement therapy. *PLoS One* 2018;13:e0191290.
7. Thongprayoon C, Radhakrishnan Y, Cheungpasitporn W, et al. Association of serum phosphate derangement with mortality in patients on continuous renal replacement therapy. *Can J Kidney Health Dis* 2022;9:20543581221114697.
8. Shor R, Halabe A, Rishver S, et al. Severe hypophosphatemia in sepsis as a mortality predictor. *Ann Clin Lab Sci* 2006;36:67–72.
9. Aubier M, Murciano D, Lecocguic Y, et al. Effect of hypophosphatemia on diaphragmatic contractility in patients with acute respiratory failure. *N Engl J Med* 1985;313:420–424.
10. Gravelyn TR, Brophy N, Siegert C, Peters-Golden M. Hypophosphatemia-associated respiratory muscle weakness in a general inpatient population. *Am J Med* 1988;84:870–876.
11. Alsumrain MH, Jawad SA, Imran NB, Riar S, DeBari VA, Adelman M. Association of hypophosphatemia with failure-to-wean from mechanical ventilation. *Ann Clin Lab Sci* 2010;40:144–148.
12. Demirjian S, Teo BW, Guzman JA, et al. Hypophosphatemia during continuous hemodialysis is associated with prolonged respiratory failure in patients with acute kidney injury. *Nephrol Dial Transplant* 2011;26:3508–3514.
13. Cohen J, Kogan A, Sahar G, Lev S, Vidne B, Singer P. Hypophosphatemia following open heart surgery: incidence and consequences. *Eur J Cardiothorac Surg* 2004;26:306–310.
14. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;40:373–383.
15. Bone RC, Balk RA, Cerra FB, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. *Chest* 1992;101:1644–1655.
16. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics* 1988;44:837–845.
17. Leaf DE, Christov M. Dysregulated mineral metabolism in AKI. *Semin Nephrol* 2019;39:41–56.
18. Achinger SG, Ayus JC. Left ventricular hypertrophy: is hyperphosphatemia among dialysis patients a risk factor? *J Am Soc Nephrol* 2006;17:S255–S261.
19. Zheng WH, Yao Y, Zhou H, Xu Y, Huang HB. Hyperphosphatemia and outcomes in critically ill patients: a systematic review and meta-analysis. *Front Med (Lausanne)* 2022;9:870637.
20. Kim SY, Kim YN, Shin HS, Jung Y, Rim H. The influence of hypophosphatemia on outcomes of low- and high-intensity continuous renal replacement therapy in critically ill patients with acute kidney injury. *Kidney Res Clin Pract* 2017;36:240–249.
21. Kim DW, Kim HJ, Kim JM, et al. Effect of Phoxilium on prognostic predictors in patients undergoing continuous venovenous hemodiafiltration. *Kidney Res Clin Pract* 2021;40:457–471.

22. Liamis G, Milionis HJ, Elisaf M. Medication-induced hypophos-phatemia: a review. *QJM* 2010;103:449–459.

23. Jung SY, Kim H, Park S, et al. Electrolyte and mineral disturbanc-es in septic acute kidney injury patients undergoing continuous renal replacement therapy. *Medicine (Baltimore)* 2016;95:e4542.

24. Craddock PR, Yawata Y, VanSanten L, Gilberstadt S, Silvis S, Ja-cob HS. Acquired phagocyte dysfunction: a complication of the hypophosphatemia of parenteral hyperalimentation. *N Engl J Med* 1974;290:1403–1407.

25. Saglikes Y, Massry SG, Iseki K, et al. Effect of phosphate deple-tion on blood pressure and vascular reactivity to norepinephrine and angiotensin II in the rat. *Am J Physiol* 1985;248:F93–F99.

26. Davis SV, Olichwier KK, Chakko SC. Reversible depression of myocardial performance in hypophosphatemia. *Am J Med Sci* 1988;295:183–187.

27. Broman M, Carlsson O, Friberg H, Wieslander A, Godaly G. Phosphate-containing dialysis solution prevents hypophos-phatemia during continuous renal replacement therapy. *Acta Anaesthesiol Scand* 2011;55:39–45.

28. Santiago MJ, López-Herce J, Urbano J, Bellón JM, del Castillo J, Carrillo A. Hypophosphatemia and phosphate supplementation during continuous renal replacement therapy in children. *Kid-ney Int* 2009;75:312–316.

29. Suzuki S, Egi M, Schneider AG, Bellomo R, Hart GK, Hegarty C. Hypophosphatemia in critically ill patients. *J Crit Care* 2013;28:536.

30. Lim C, Tan HK, Kaushik M. Hypophosphatemia in critically ill patients with acute kidney injury treated with hemodialysis is associated with adverse events. *Clin Kidney J* 2017;10:341–347.