Is Monitoring for Phosphate a Necessary Measure in Critical Ill Patients ?

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Abstract

Background: In recent years, some studies have shown that hyperphosphatemia and hypophosphatemia are associated with high mortality in intensive care unit (ICU) patients. Based on this, we speculated that the abnormalities of serum phosphate when patients enter the ICU had an adverse effect on the mortality of ICU patients and conducted our study.

Methods: For our retrospective cohort study, we collected the data from a publicly accessible critical care database. We selected adult patients admitted to ICU with some inclusion criteria. And we extracted a large number of clinical variables. Using multivariate Cox regression and other statistical methods, we assessed the association between serum phosphate and primary endpoints.

Results: Of 27131 eligible patients, the patients with hyperphosphatemia or hypophosphatemia had poorer clinical outcomes. After adjustment for potential confounders, there was no significant association between abnormalities phosphate and 28 or 90-day ICU mortality. Nevertheless, at the medical intensive care unit, hyperphosphatemia was associated with a 37% higher risk of 28-day mortality or a 25% higher risk of 90-day mortality.

Conclusion: After adjustment for potential confounders, hypophosphatemia and hyperphosphatemia at ICU admission were not the independent risk factors of 28 or 90-day mortality for general ICU patients. However, hyperphosphatemia at admission increased the risk of 28 or 90-day mortality among patients admitted to the medical intensive care unit.

Background

In the human body, phosphorus is in the form of phosphate, most of which (about 85%) is stored in bones and teeth, and the rest (about 14%) is mainly in cells and the extracellular fluid. Phosphorus only accounts for 1% (of which 70% exists in organic form, and 30% exists in inorganic form). Inorganic phosphate is the value of serum phosphate measured in the clinic [1−5]. Although serum phosphate is very low, it plays an important role in the body [1−3, 6−9]. For example, (I) participating in the composition of cell membranes in the form of phospholipids to maintain the integrity and function of the cell structure; (II) regulating hemoglobin release oxygen in the form of 2,3-Diphosphoglycerate; (III) directly participating in energy storage and metabolism in the form of adenosine triphosphate. At present, the more generally accepted normal range of phosphate is 0.8 mmol/L ~ 1.5 mmol/L (2.5 mg/dL ~ 4.5 mg/dL)[3, 4, 6]. In addition, phosphate homeostasis is a complicated process [1−3, 5, 7, 10−12], phosphate is mainly absorbed in the intestine, and then reabsorbed or excreted in the kidney, which is mainly related to the following three factors: (I) 1,25-Dihydroxy Vitamin D [1,25(OH)2D]: up-regulating the expression of sodium-dependent phosphate co-transporter 2b (NPT2b) to stimulate the absorption of phosphate by the intestine; (II) Fibroblast Growth Factor-23 (FGF23): reducing 1,25(OH)2D and NPT2b to inhibition intestinal transport of phosphate; (III) Parathyroid Hormone (PTH): indirectly increasing the absorption of phosphate in the intestine through the action of 1,25(OH)2D. Phosphate abnormalities can cause dysfunction of multiple organ systems, including the respiratory system, cardiovascular system, immune system, urinary system, hematology, or neuromuscular [1, 3−6, 11, 13−16].

The Intensive Care Unit (ICU) is distinct from the emergency department ward. It is a department that provides medical services for patients who need life support and have a very high risk of death. It is mainly divided into five adult ICU departments[17]: coronary care unit (CCU), cardiac surgery recovery unit (CSRU), medical intensive care unit (MICU), surgical intensive care unit (SICU), trauma surgical intensive care unit (TSICU). As we all know, patients often have electrolyte disturbances during ICU, the hypophosphatemia and hyperphosphatemia are common electrolyte disturbances. Recent studies have shown that ICU patients have a higher prevalence of hypophosphatemia and hyperphosphatemia[1, 3, 6, 8, 18, 19]. It has varying degrees of impact on clinical outcomes, but due to its atypical clinical symptoms, it has not received much attention.

In the past few decades, there were some researches about the associations between abnormal serum phosphate levels and clinical outcomes. For hyperphosphatemia, most studies had proved that hyperphosphatemia was an independent risk factor for mortality or morbidity[1, 7, 11, 14, 15, 20−26]. For hypophosphatemia, some studies showed that it was an independent risk factor for mortality or morbidity[1, 8, 23, 27], but some studies showed that it was not significantly associated with mortality or morbidity[15, 20, 22, 28]. Thus, it was not determined whether serum phosphate abnormalities are directly related to the increase in mortality in ICU patients or merely a sign of the severity of disease for ICU patients. We reviewed the previous literature and found that the relationship between serum phosphate levels and the prognosis of the ICU population at the time of initial admission to the ICU had been poorly studied in the past, and the sample size was small. Based on the above, we speculated that the abnormalities of serum phosphate when patients enter the ICU had an adverse effect on the mortality of ICU patients, and the impact of abnormal serum phosphate levels on the mortality of patients at various ICU departments was different. To confirm this hypothesis, we conducted a single-center retrospective cohort study. Our primary study endpoints were 28-day mortality and 90-day mortality after ICU admission.

Methods

Sources of Data

The data for our study were collected from a publicly accessible critical care database named Multiparameter Intelligent Monitoring in Intensive Care Database III (MIMIC-III, version 1.4)[29]. MIMIC III is a large, single-centre database containing information of 61532 ICU admissions to Beth Israel Deaconess Medical Center (a teaching hospital of Harvard Medical School in Boston, Massachusetts) between 2001 and 2012. This database is approved by the institutional review boards of the Massachusetts Institute of Technology (MIT) and Beth Israel Deaconess Medical Center (BIDMC). Because all the data is de-identified, no informed consent is required. In recent years, some high-quality papers using this database's data have been published[30]. In this study, data presented were extracted by author Chen, who completed the National Institutes of Health (NIH) Web-based training course and the Protecting Human Research Participants examination (No. 36328122). Data extraction was performed using structure query language (SQL) with pgAdmin4 PostgreSQL.

Selection of Participants and Stratification Method

In our study, all patients admitted to ICU in this database were included. Exclusion criteria as follows: (I) age<18 years; (II) patients who did not complete serum phosphate measurement within the first day after admission to the ICU or had unclear records of the first serum phosphate measured value; (III) patients who received phosphate supplementation during the ICU stay; (IV) for patients with multiple records of ICU admission, excluding records other than the first ICU admission. Finally, the total number of 27131 patients were included. The detail was shown in Figure 1.

(Figure 1 should be placed here).

According to the normal range of serum phosphate as mentioned before, we divided patients into six groups based on the admission serum phosphate levels: G1: hypophosphatemia group (<2.5mg/L); G2: very-low-normal phosphate group (≥2.5mg/dL and <3.0mg/dL); G3: low-normal phosphate group (≥3.0mg/dL and <3.5mg/dL); G4: high-normal phosphate group (≥3.5mg/dL and <4.0mg/dL); G5: very-high-normal phosphate group (≥4.0mg/dL and <4.5mg/dL); G6: hyperphosphatemia group (≥4.5mg/dL). The data were also analyzed in terms of subgroups based on different ICU departments: CCU、CSRU、MICU、SICU、TSICU.

Extraction of variables

As mentioned before, using SQL with pgAdmin4 PostgreSQL, we extracted the following data: (I) age; (II) gender; (III) ethnicities; (IV) admission types; (V) ICU types; (VI) vital signs (within the first day at ICU admission): heart rate, mean arterial pressure, respiratory rate, temperature, oxygen saturation; (VII) severity at ICU admission: Sequential Organ Failure Assessment (SOFA) score, Simplified Acute Physiology Score II (SAPS II), Overall Anxiety Severity and Impairment Scale (OASIS) score; (VIII) comorbidities: congestive heart failure, coronary artery disease, hypertension, diabetes, chronic pulmonary disease, atrial fibrillation, liver disease, fluid and electrolyte disorder, malignant tumor, chronic kidney disease, (IX) laboratory results (within the first day at ICU admission): serum phosphate, serum sodium, serum potassium, serum calcium, serum creatinine, blood urea nitrogen, serum bicarbonate, serum chloride, white blood cell, hemoglobin, platelet; (X) interventions (within the first day at ICU admission): use of mechanical ventilation, renal replacement therapy, vasopressor. For some patients whose multiple laboratory measurements within the first day at ICU admission were available, the first measurement was used in our study. Because all variables included less than 3% of missing observations, missing values were imputed as the mean values.

Outcome Variables

We extracted the following outcomes variables: (I) all-cause 28-day mortality after ICU admission; (II) all-cause 90-day mortality after ICU admission; (III) all-cause mortality during ICU stay; (IV) length of ICU stay. Among the four, all-cause 28-day ICU mortality and 90-day ICU mortality were the primary endpoints, all-cause mortality during ICU stay and length of ICU stay were the secondary endpoints. Moreover, the secondary endpoints were extracted only for descriptive purposes. The data for the 28 or 90-day ICU mortality was confirmed by inspection of the death records in the database.

Statistical Analysis

Patient characteristics were described using descriptive statistics. Continuous variables were examined for normality using the Shapiro–Wilk test. According to the types and distributions of variables, normally distributed continuous variables are presented in the tables as the mean with standard deviation (SD). Skewed variables were presented as the median with interquartile ranges (IQR). Categorical variables are presented as a percentage. Analysis of variance (or the Kruskal-Wallis test) and Chi-square (or Fisher's exact) tests were used for comparisons between groups.

Kaplan-Meier survival analysis for the cumulative rate of all-cause 28 or 90-day mortality after ICU admission was used to compare the death distributions of patients among six groups of serum phosphate at admission.

We used the restricted cubic spline functions to explore nonlinear relationships between the different levels of the serum phosphate at ICU admission as a continuous variable and our primary endpoints after ICU admission.

In order to evaluate independent associations between serum phosphate levels at ICU admission and the primary endpoints, we used univariate and multivariable Cox regression models. We used two different models to adjust potential confounders. Model 1: including age, gender, ethnicities, heart rate, mean arterial pressure, respiratory rate, temperature, oxygen saturation; Model 2: including the same as Model 1, furthermore, including admission types, ICU types, SOFA score, SAPS II, OASIS score, congestive heart failure, coronary artery disease, hypertension, diabetes, chronic pulmonary disease, atrial fibrillation, liver disease, fluid and electrolyte disorder, malignant tumor, chronic kidney disease, serum sodium, serum potassium, serum calcium, serum creatinine, blood urea nitrogen, serum bicarbonate, serum chloride, white blood cell, hemoglobin, platelet, use of mechanical ventilation on the first day, use of renal replacement therapy on the first day, use of vasopressor on the first day. We chose the G2 as the model's reference group and calculated adjusted hazard ratios (HRs) for the other groups in comparison to the reference group. In addition, we used the same way to evaluate independent associations between serum phosphate levels at ICU admission and the primary endpoints at the different ICU departments.

Software Stata version 16.0 and R version 3.6.3 were used for statistical analyses. P-values of less than 0.05 was considered to indicate statistical significance in all analyses.

Results

Baseline Characteristics of the Study Population

In the end, a total of 27131 patients were enrolled (Fig. 1), among which 3060 patients in G1 (11.28%), 4257 patients in G2 (15.69%), 5804 patients in G3 (21.39%), 5395 patients in G4 (19.89%), 3584 patients in G5 (13.21%) and 5031 patients in G6 (18,54%). The mean age of the study population was 64.00 ± 17.94 years. More patients were males (55.60%), but the gender distribution among the six groups was not significant. 19387 patients (71.46%) were White, and emergency admission (85.61%) was the most common of the admission types. The patients who admitted to the MICU (39.45%), CCU (17.28%), SICU (18.21%) accounted for a higher proportion. However, when we compared the six groups with each other, we found that the patients of G6 (hyperphosphatemia group) had higher SOFA score, SAPS II, OASIS score on ICU admission, higher prevalence of chronic kidney disease (28.82%), a higher value of serum creatinine (2.66 ± 2.50) and blood urea nitrogen (43.65 ± 31.06). Also, the patients of G6 had higher usage of mechanical ventilation (44.27%) or renal replacement therapy (1.89%) or vasopressor (32.96%). The detail was shown in Table 1.

Characteristics	All	G1	G2	G3	G4	G5	G6	P-value
N	27131	3060	4257	5804	5395	3584	5031	
Age (years), mean ± SD	64.00 ± 17.94	61.27 ± 18.25	64.60 ± 17.85	64.38 ± 18.06	64.30 ± 18.21	63.87 ± 18.15	64.50 ± 17.08	< 0.001
Male, n (%)	15086 (55.60%)	1719 (56.18%)	2384 (56.00%)	3219 (55.46%)	2934 (54.38%)	2004 (55.92%)	2826 (56.17%)	0.443
Ethnicities,n (%)								< 0.001
White	19387 (71.46%)	2104 (68.76%)	3119 (73.27%)	4236 (72.98%)	3875 (71.83%)	2545 (71.01%)	3508 (69.73%)	
Black	2291 (8.44%)	248 (8.10%)	343 (8.06%)	422 (7.27%)	456 (8.45%)	319 (8.90%)	503 (10.00%)	
Other	3758 (13.85%)	466 (15.23%)	543 (12.76%)	781 (13.46%)	742 (13.75%)	504 (14.06%)	722 (14.35%)	
Admission Types, n (%)								< 0.001
Elective	3192 (11.77%)	323 (10.56%)	420 (9.87%)	664 (11.44%)	688 (12.75%)	480 (13.39%)	617 (12.26%)	
Emergency	23228 (85.61%)	2665 (87.09%)	3737 (87.78%)	5011 (86.34%)	4573 (84.76%)	2996 (83.59%)	4246 (84.40%)	
Urgent	711 (2.62%)	72 (2.35%)	100 (2.35%)	129 (2.22%)	134 (2.48%)	108 (3.01%)	168 (3.34%)	
ICU Types, n (%)								< 0.001
CCU	4688 (17.28%)	386 (12.61%)	641 (15.06%)	1001 (17.25%)	1000 (18.54%)	698 (19.48%)	962 (19.12%)	
CSRU	2899 (10.69%)	351 (11.47%)	447 (10.50%)	649 (11.18%)	605 (11.21%)	391 (10.91%)	456 (9.06%)	
MICU	10704 (39.45%)	1435 (46.90%)	1811 (42.54%)	2123 (36.58%)	1918 (35.55%)	1286 (35.88%)	2131 (42.36%)	
SICU	4940 (18.21%)	528 (17.25%)	761 (17.88%)	1106 (19.06%)	1002 (18.57%)	659 (18.39%)	884 (17.57%)	
TSICU	3900 (14.37%)	360 (11.76%)	597 (14.02%)	925 (15.94%)	870 (16.13%)	550 (15.35%)	598 (11.89%)	
Vital Signs, mean ± SD								
Heart rate (beat/min)	84.70 ± 15.88	87.52 ± 15.88	84.65 ± 15.56	83.07 ± 15.58	83.46 ± 15.43	84.29 ± 15.87	86.52 ± 16.55	< 0.001
Mean arterial pressure (mmHg)	78.54 ± 11.28	78.89 ± 11.08	79.28 ± 11.12	79.02 ± 10.98	78.55 ± 10.97	78.64 ± 11.11	77.07 ± 12.15	< 0.001
Respiratory rate (time/min)	18.86 ± 3.99	19.18 ± 4.09	18.85 ± 3.86	18.65 ± 3.88	18.62 ± 3.85	18.73 ± 3.98	19.23 ± 4.29	< 0.001
Temperature (°C)	36.82 ± 0.62	36.99 ± 0.65	36.89 ± 0.59	36.84 ± 0.58	36.79 ± 0.57	36.78 ± 0.60	36.70 ± 0.69	< 0.001
Oxygen saturation (%)	97.09 ± 2.52	97.15 ± 2.28	97.24 ± 1.93	97.20 ± 2.03	97.16 ± 2.15	97.10 ± 2.20	96.68 ± 3.80	< 0.001
Severity score, mean ± SD								
SOFA	3.86 ± 3.06	3.67 ± 2.83	3.25 ± 2.52	3.17 ± 2.51	3.37 ± 2.67	3.85 ± 2.97	5.82 ± 3.75	< 0.001
SAPS II	34.51 ± 14.83	32.39 ± 13.62	32.18 ± 12.89	32.03 ± 13.36	33.02 ± 13.78	34.57 ± 14.73	42.20 ± 17.09	< 0.001

Notes: Data are expressed as mean ± SD, or n (%). Analysis of variance (or the Kruskal-Wallis test) and Chi-square (or Fisher's exact) tests were used for comparisons among groups. Statistical significance (P < 0.05). G1: hypophosphatemia group (< 2.5 mg/L); G2: very-low-normal phosphate group (≥ 2.5 mg/dL and < 3.0 mg/dL); G3: low-normal phosphate group (≥ 3.0 mg/dL and < 3.5 mg/dL); G4: high-normal phosphate group (≥ 3.5 mg/dL and < 4.0 mg/dL); G5: very-high-normal phosphate group (≥ 4.0 mg/dL and < 4.5 mg/dL); G6: hyperphosphatemia group (≥ 4.5 mg/dL).

Abbreviations: ICU, intensive care unit; CCU, coronary care unit; CSRU, cardiac surgery recovery unit; MICU, medical intensive care unit; SICU, surgical intensive care unit; TSICU, trauma surgical intensive care unit; SD, standard deviation; SOFA, Sequential Organ Failure Assessment; SAPS II, Simplified Acute Physiology Score II; OASIS, Overall Anxiety Severity and Impairment Scale.

Characteristics	All	G1	G2	G3	G4	G5	G6	P-value
OASIS	30.77 ± 9.03	30.11 ± 8.73	30.20 ± 8.30	29.81 ± 8.55	30.09 ± 8.53	30.74 ± 9.22	33.50 ± 10.14	< 0.001
Comorbidities, n (%)								
Congestive heart failure	6878 (25.35%)	539 (17.61%)	875 (20.55%)	1263 (21.76%)	1365 (25.30%)	1049 (29.27%)	1787 (35.52%)	< 0.001
Coronary artery disease	8868 (32.69%)	909 (29.71%)	1371 (32.21%)	1903 (32.79%)	1704 (31.58%)	1189 (33.18%)	1792 (35.62%)	< 0.001
Hypertension	14200 (52.34%)	1438 (46.99%)	2261 (53.11%)	2999 (51.67%)	2792 (51.75%)	1911 (53.32%)	2799 (55.64%)	< 0.001
Diabetes	6737 (24.83%)	689 (22.52%)	915 (21.49%)	1296 (22.33%)	1309 (24.26%)	946 (26.40%)	1582 (31.45%)	< 0.001
Chronic pulmonary disease	5614 (20.69%)	529 (17.29%)	757 (17.78%)	1172 (20.19%)	1170 (21.69%)	807 (22.52%)	1179 (23.43%)	< 0.001
Atrial fibrillation	6891 (25.40%)	677 (22.12%)	1075 (25.25%)	1478 (25.47%)	1335 (24.75%)	868 (24.22%)	1458 (28.98%)	< 0.001
Liver disease	2595 (9.56%)	323 (10.56%)	327 (7.68%)	438 (7.55%)	420 (7.78%)	316 (8.82%)	771 (15.32%)	< 0.001
Fluid and electrolyte disorder	7960 (29.34%)	1015 (33.17%)	1144 (26.87%)	1413 (24.35%)	1341 (24.86%)	994 (27.73%)	2053 (40.81%)	< 0.001
Malignant tumor	3905 (14.39%)	401 (13.10%)	566 (13.30%)	736 (12.68%)	760 (14.09%)	555 (15.49%)	887 (17.63%)	< 0.001
Chronic kidney disease	3955 (14.58%)	252 (8.24%)	399 (9.37%)	569 (9.80%)	701 (12.99%)	584 (16.29%)	1450 (28.82%)	< 0.001
Laboratory results, mean ± SD								
Phosphate (mg/dL)	3.68 ± 1.28	2.03 ± 0.36	2.72 ± 0.14	3.21 ± 0.14	3.69 ± 0.14	4.18 ± 0.14	5.66 ± 1.39	< 0.001
Sodium (mmol/L)	138.42 ± 4.65	138.59 ± 5.18	138.59 ± 4.48	138.47 ± 4.31	138.51 ± 4.36	138.45 ± 4.49	138.00 ± 5.21	< 0.001
Potassium (mmol/L)	4.16 ± 0.71	3.87 ± 0.66	3.95 ± 0.63	4.05 ± 0.62	4.17 ± 0.64	4.25 ± 0.68	4.54 ± 0.83	< 0.001
Calcium (mg/dL)	8.32 ± 0.82	8.08 ± 0.86	8.23 ± 0.79	8.34 ± 0.74	8.41 ± 0.74	8.43 ± 0.78	8.36 ± 0.99	< 0.001
Creatinine (mg/dL)	1.37 ± 1.44	0.97 ± 0.64	0.98 ± 0.64	1.00 ± 0.66	1.14 ± 0.85	1.33 ± 1.12	2.66 ± 2.50	< 0.001
Blood urea nitrogen (mg/dL)	25.47 ± 21.06	18.16 ± 12.15	19.18 ± 12.67	20.13 ± 13.67	22.81 ± 16.16	26.34 ± 19.43	43.65 ± 31.06	< 0.001
Bicarbonate (mmol/L)	23.70 ± 4.53	23.23 ± 4.50	23.88 ± 3.95	24.33 ± 3.99	24.26 ± 4.15	24.15 ± 4.41	22.18 ± 5.57	< 0.001
Chloride (mmol/L)	105.10 ± 5.90	106.40 ± 6.55	105.84 ± 5.60	105.35 ± 5.41	105.09 ± 5.44	104.66 ± 5.71	103.70 ± 6.54	< 0.001
White blood cell (× 10^3/μL)	11.83 ± 6.64	11.54 ± 6.39	11.36 ± 6.14	11.21 ± 5.73	11.45 ± 6.12	12.15 ± 6.72	13.29 ± 8.24	< 0.001
Platelet (× 10^3/μL)	225.19 ± 109.04	205.93 ± 97.88	216.53 ± 99.33	223.61 ± 101.03	230.85 ± 108.24	238.25 ± 114.93	230.69 ± 125.41	< 0.001
Hemoglobin (g/dL)	11.06 ± 2.03	11.01 ± 1.99	11.18 ± 2.03	11.23 ± 1.99	11.16 ± 2.01	11.10 ± 2.08	10.68 ± 2.02	< 0.001
Interventions (1st 24 h), n (%)								

Notes: Data are expressed as mean ± SD, or n (%). Analysis of variance (or the Kruskal-Wallis test) and Chi-square (or Fisher's exact) tests were used for comparisons among groups. Statistical significance (P < 0.05). G1: hypophosphatemia group (< 2.5 mg/L); G2: very-low-normal phosphate group (≥ 2.5 mg/dL and < 3.0 mg/dL); G3: low-normal phosphate group (≥ 3.0 mg/dL and < 3.5 mg/dL); G4: high-normal phosphate group (≥ 3.5 mg/dL and < 4.0 mg/dL); G5: very-high-normal phosphate group (≥ 4.0 mg/dL and < 4.5 mg/dL); G6: hyperphosphatemia group (≥ 4.5 mg/dL).

Abbreviations: ICU, intensive care unit; CCU, coronary care unit; CSRU, cardiac surgery recovery unit; MICU, medical intensive care unit; SICU, surgical intensive care unit; TSICU, trauma surgical intensive care unit; SD, standard deviation; SOFA, Sequential Organ Failure Assessment; SAPS II, Simplified Acute Physiology Score II; OASIS, Overall Anxiety Severity and Impairment Scale.

Characteristics	All	G1	G2	G3	G4	G5	G6	P-value
Mechanical ventilation	9643 (35.54%)	1054 (34.44%)	1383 (32.49%)	1855 (31.96%)	1799 (33.35%)	1325 (36.97%)	2227 (44.27%)	< 0.001
Renal replacement therapy	127 (0.47%)	5 (0.16%)	5 (0.12%)	2 (0.03%)	9 (0.17%)	11 (0.31%)	95 (1.89%)	< 0.001
Vasopressor	6136 (22.62%)	681 (22.25%)	795 (18.68%)	1097 (18.90%)	1090 (20.20%)	815 (22.74%)	1658 (32.96%)	< 0.001

Notes: Data are expressed as mean ± SD, or n (%). Analysis of variance (or the Kruskal-Wallis test) and Chi-square (or Fisher's exact) tests were used for comparisons among groups. Statistical significance (P < 0.05). G1: hypophosphatemia group (< 2.5 mg/L); G2: very-low-normal phosphate group (≥ 2.5 mg/dL and < 3.0 mg/dL); G3: low-normal phosphate group (≥ 3.0 mg/dL and < 3.5 mg/dL); G4: high-normal phosphate group (≥ 3.5 mg/dL and < 4.0 mg/dL); G5: very-high-normal phosphate group (≥ 4.0 mg/dL and < 4.5 mg/dL); G6: hyperphosphatemia group (≥ 4.5 mg/dL).

Abbreviations: ICU, intensive care unit; CCU, coronary care unit; CSRU, cardiac surgery recovery unit; MICU, medical intensive care unit; SICU, surgical intensive care unit; TSICU, trauma surgical intensive care unit; SD, standard deviation; SOFA, Sequential Organ Failure Assessment; SAPS II, Simplified Acute Physiology Score II; OASIS, Overall Anxiety Severity and Impairment Scale.

ICU Outcomes of the Study Population

Overall, 3776 patients (13.92%) of the study population died within 28 days after ICU admission. We found that the 28-day ICU mortality of G2 (10.74%), G3 (10.91%), G4 (10.70%) was close, while the comparison of 28-day ICU mortality among the six groups was G6 (24.41%) > G5 (14.17%) > G1 (12.19%) > G2, G3, G4. In addition, similar results were found for 90-day ICU mortality, mortality at ICU, and the median lengths of ICU stay. The detail was shown in Table 2

Table 2
ICU outcomes of patients.

Outcomes	All	G1	G2	G3	G4	G5	G6	P-value
Mortality, n (%)								
28-day after ICU admission	3776 (13.92%)	373 (12.19%)	457 (10.74%)	633 (10.91%)	577 (10.70%)	508 (14.17%)	1228 (24.41%)	< 0.001
90-day after ICU admission	5202 (19.17%)	510 (16.67%)	647 (15.20%)	905 (15.59%)	871 (16.14%)	696 (19.42%)	1573 (31.27%)	< 0.001
Stay at ICU	2198 (8.10%)	215 (7.03%)	252 (5.92%)	297 (5.12%)	311 (5.76%)	284 (7.92%)	839 (16.68%)	< 0.001
Length of stay, median (IQR)								
Stay at ICU (day)	2.04 (1.18,3.90)	2.01 (1.23,3.77)	1.94 (1.16,3.44)	1.93 (1.13,3.42)	1.96 (1.13,3.67)	2.10 (1.19,3.99)	2.62 (1.38,5.16)	< 0.001

Notes: Data are expressed as mean ± SD, median (IQR) or n (%). Analysis of variance (or the Kruskal-Wallis test) and Chi-square (or Fisher's exact) tests were used for comparisons among groups. Statistical significance (P < 0.05). G1: hypophosphatemia group (< 2.5 mg/L); G2: very-low-normal phosphate group (≥ 2.5 mg/dL and < 3.0 mg/dL); G3: low-normal phosphate group (≥ 3.0 mg/dL and < 3.5 mg/dL); G4: high-normal phosphate group (≥ 3.5 mg/dL and < 4.0 mg/dL); G5: very-high-normal phosphate group (≥ 4.0 mg/dL and < 4.5 mg/dL); G6: hyperphosphatemia group (≥ 4.5 mg/dL).

Abbreviations: ICU, intensive care unit; SD, standard deviation; IQR, interquartile ranges.

As shown in Fig. 2, the Kaplan-Meier curves of all-cause 28 or 90-day mortality after ICU admission intuitively reflected the death distributions of the six groups' patients and showed the result as before (P < 0.0001).

Cubic spline analysis demonstrated that the relationship between serum phosphate and the probability of 28 or 90-day ICU mortality had a linear relationship. The detail was shown in Fig. 3.

Associations Between Serum Phosphate and Clinical Outcomes

The multivariable Cox regression analyses were used to indicate the relationship between serum phosphate levels and all-cause 28 or 90-day ICU mortality. Compared with patients of G2, patients of G1, G5 and G6 had increased 28-day ICU mortality with a non-adjusted hazard ratio (G1: HR = 1.15, 95%CI 1.00 to 1.32, P = 0.0481; G5: HR = 1.34, 95%CI 1.18 to 1.52, P < 0.0001; G6: HR = 2.50, 95%CI 2.25 to 2.79, P < 0.0001, respectively). After being adjusted by the two different models, the associations were no statistical significant [(G1: HR = 1.07, 95%CI 0.93 to 1.22, P = 0.3638; G5: HR = 1.02, 95%CI 0.89 to 1.15, P = 0.8187; G6: HR = 1.04, 95%CI 0.91 to 1.17, P = 0.5785, respectively), adjusted by Model 2]. Besides, we also found that the G4 had a beneficial effect on the 28-day ICU mortality (HR = 0.87, 95%CI 0.77 to 0.98, P = 0.0243, adjusted by Model 2). The relationship between serum phosphate and 90-day ICU mortality had a similar pattern to that of 28-day ICU mortality, with increased risk for events in patients of G5 and G6 with a non-adjusted hazard ratio (G5: HR = 1.31, 95%CI 1.18 to 1.46, P < 0.0001; G6: HR = 2.32, 95%CI 2.12 to 2.54, P < 0.0001, respectively). After being adjusted by the two different models, the associations were no statistically significant [(G5: HR = 1.02, 95%CI 0.91 to 1.14, P = 0.7523; G6: HR = 1.05, 95%CI 0.95 to 1.17, P = 0.3354, respectively), adjusted by Model 2]. The detailed results are shown in Table 3.

Outcomes	G1	P-value	G2	G3	P-value	G4	P-value	G5	P-value	G6	P-value
28-day mortality, HR (95%CI)											
Non-adjusted	1.15 (1.00,1.32)	0.0481	Reference	1.01 (0.90,1.14)	0.8497	0.99 (0.88,1.12)	0.9340	1.34 (1.18,1.52)	< 0.0001	2.50 (2.25,2.79)	< 0.0001
Model 1	1.14 (1.00,1.31)	0.0566	Reference	1.02 (0.90,1.15)	0.7414	0.96 (0.85,1.09)	0.5518	1.32 (1.16,1.50)	< 0.0001	2.20 (1.97,2.45)	< 0.0001
Model 2	1.07 (0.93,1.22)	0.3638	Reference	0.98 (0.87,1.10)	0.7104	0.87 (0.77,0.98)	0.0272	1.02 (0.89,1.15)	0.8187	1.04 (0.91,1.17)	0.5785
90-day mortality, HR (95%CI)											
Non-adjusted	1.11 (0.99,1.25)	0.0751	Reference	1.02 (0.93,1.13)	0.6407	1.06 (0.96,1.18)	0.2395	1.31 (1.18,1.46)	< 0.0001	2.32 (2.12,2.54)	< 0.0001
Model 1	1.13 (1.01,1.27)	0.0372	Reference	1.04 (0.94,1.15)	0.5026	1.03 (0.93,1.14)	0.5266	1.30 (1.17,1.44)	< 0.0001	2.09 (1.91,2.30)	< 0.0001
Model 2	1.06 (0.94,1.19)	0.3261	Reference	0.99 (0.90,1.10)	0.9100	0.93 (0.84,1.03)	0.1619	1.02 (0.91,1.14)	0.7523	1.05 (0.95,1.17)	0.3354

Notes: G1: hypophosphatemia group (< 2.5 mg/L); G2: very-low-normal phosphate group (≥ 2.5 mg/dL and < 3.0 mg/dL); G3: low-normal phosphate group (≥ 3.0 mg/dL and < 3.5 mg/dL); G4: high-normal phosphate group (≥ 3.5 mg/dL and < 4.0 mg/dL); G5: very-high-normal phosphate group (≥ 4.0 mg/dL and < 4.5 mg/dL); G6: hyperphosphatemia group (≥ 4.5 mg/dL). G2 was the reference group.

Model 1 was adjusted by age, gender, ethnicities, heart rate, mean arterial pressure, respiratory rate, temperature, oxygen saturation;

Model 2 was adjusted by age, gender, ethnicities, heart rate, mean arterial pressure, respiratory rate, temperature, oxygen saturation, admission types, ICU types, Sequential Organ Failure Assessment score, Simplified Acute Physiology Score II, Overall Anxiety Severity and Impairment Scale score, congestive heart failure, coronary artery disease, hypertension, diabetes, chronic pulmonary disease, atrial fibrillation, liver disease, fluid and electrolyte disorder, malignant tumor, chronic kidney disease, serum sodium, serum potassium, serum calcium, serum creatinine, blood urea nitrogen, serum bicarbonate, serum chloride, white blood cell, hemoglobin, platelet, use of mechanical ventilation on the first day, use of renal replacement therapy on the first day, use of vasopressor on the first day. Statistical significance (P < 0.05).

Abbreviations: ICU, intensive care unit; HR, hazard ratio; CI, confidence interval.

As shown in Table 4, at the different ICU departments, the multivariable Cox regression analyses showed that the estimates of the association between serum phosphate and 28 or 90-day ICU mortality were broadly consistent. Nevertheless, at the MICU, patients of G6 had increased risk of 28 or 90-day mortality [(HR = 1.37, 95%CI 1.15 to 1.63, P = 0.0005; HR = 1.25, 95%CI 1.08 to 1.44, P = 0.0035, respectively), adjusted by Model 2]. Moreover, at the SICU, a significant inverse association between patients of G4 and 28 or 90-day mortality was observed [(HR = 0.64, 95%CI 0.48 to 0.84, P = 0.0017; HR = 0.72, 95%CI 0.57 to 0.91, P = 0.0067, respectively), adjusted by Model 2]. There were two interesting findings: Firstly, hyperphosphatemia (G6) exerted a beneficial effect on the 28 or 90-day mortality of patients at the SICU [(HR = 0.54, 95%CI 0.40 to 0.74, P < 0.0001; HR = 0.69, 95%CI 0.53 to 0.89, P = 0.0042, respectively), adjusted by Model 2]. Secondly, hyperphosphatemia(G6) also made a beneficial effect on the 28-day ICU mortality of patients at the TSICU (HR = 0.62, 95%CI 0.42 to 0.91, P = 0.0160, adjusted by Model 2).

ICU departments	28-day mortality after ICU admission						90-day mortality after ICU admission					
	Non-adjusted		Model 1		Model 2		Non-adjusted		Model 1		Model 2	
	HR, 95%CI	P-value	HR, 95%CI	P-value	HR, 95%CI	P-value	HR, 95%CI	P-value	HR, 95%CI	P-value	HR, 95%CI	P-val
CCU												
G1	1.25 (0.82,1.90)	0.2975	1.27 (0.83,1.93)	0.2731	1.00 (0.65,1.53)	0.9920	1.44 (1.02,2.05)	0.0408	1.51 (1.06,2.14)	0.0222	1.28 (0.90,1.83)	0.1
G2	Reference						Reference					
G3	1.26 (0.90,1.76)	0.1798	1.29 (0.92,1.81)	0.1395	1.21 (0.86,1.71)	0.2620	1.27 (0.95,1.70)	0.1137	1.29 (0.96,1.73)	0.0859	1.24 (0.92,1.66)	0.1
G4	1.12 (0.79,1.58)	0.5147	1.05 (0.74,1.48)	0.7969	0.83 (0.58,1.18)	0.2928	1.26 (0.94,1.69)	0.1161	1.19 (0.89,1.60)	0.2400	0.97 (0.72,1.31)	0.8
G5	1.82 (1.29,2.55)	0.0005	1.73 (1.23,2.43)	0.0015	1.20 (0.85,1.70)	0.3042	1.90 (1.42,2.55)	< 0.0001	1.82 (1.36,2.44)	< 0.0001	1.31 (0.97,1.76)	0.0
G6	3.36 (2.48,4.55)	< 0.0001	2.77 (2.04,3.77)	< 0.0001	1.11 (0.79,1.57)	0.5426	3.40 (2.62,4.43)	< 0.0001	2.83 (2.17,3.69)	< 0.0001	1.19 (0.89,1.60)	0.2
CSRU												
G1	1.98 (1.07,3.64)	0.0290	1.81 (0.98,3.34)	0.0581	1.76 (0.94,3.30)	0.0779	1.70 (1.02,2.84)	0.0406	1.58 (0.95,2.64)	0.0783	1.56 (0.93,2.64)	0.0
G2	Reference						Reference					
G3	1.25 (0.69,2.27)	0.4538	1.27 (0.70,2.30)	0.4300	1.16 (0.63,2.14)	0.6273	1.25 (0.77,2.02)	0.3619	1.27 (0.78,2.05)	0.3318	1.12 (0.68,1.82)	0.6
G4	1.13 (0.61,2.08)	0.6928	1.10 (0.59,2.03)	0.7658	1.07 (0.57,2.01)	0.8333	1.37 (0.85,2.21)	0.1933	1.31 (0.81,2.12)	0.2653	1.18 (0.72,1.92)	0.5
G5	1.77 (0.96,3.26)	0.0681	1.71 (0.93,3.16)	0.0851	1.37 (0.72,2.58)	0.3342	1.84 (1.12,3.00)	0.0152	1.79 (1.09,2.93)	0.0207	1.37 (0.82,2.27)	0.2
G6	4.36 (2.57,7.41)	< 0.0001	3.65 (2.13,6.25)	< 0.0001	1.65 (0.91,3.00)	0.1016	3.84 (2.48,5.93)	< 0.0001	3.33 (2.14,5.18)	< 0.0001	1.41 (0.86,2.31)	0.1
MICU												
G1	1.00 (0.82,1.22)	0.9913	1.05 (0.86,1.28)	0.6539	1.04 (0.85,1.27)	0.6809	0.90 (0.77,1.06)	0.2244	0.97 (0.82,1.14)	0.7177	0.97 (0.82,1.14)	0.7
G2	Reference						Reference					
G3	1.10 (0.93,1.31)	0.2754	1.08 (0.90,1.28)	0.4181	1.02 (0.86,1.22)	0.8183	1.06 (0.92,1.22)	0.4395	1.04 (0.90,1.20)	0.6123	0.98 (0.85,1.13)	0.7
G4	1.27 (1.06,1.51)	0.0077	1.21 (1.02,1.44)	0.0307	1.08 (0.90,1.28)	0.4206	1.22 (1.06,1.41)	0.0061	1.17 (1.01,1.35)	0.0323	1.03 (0.89,1.19)	0.7
G5	1.71 (1.43,2.05)	< 0.0001	1.58 (1.32,1.90)	< 0.0001	1.13 (0.94,1.36)	0.1975	1.55 (1.34,1.80)	< 0.0001	1.46 (1.26,1.69)	< 0.0001	1.07 (0.92,1.25)	0.3
G6	3.11 (2.68,3.62)	< 0.0001	2.67 (2.29,3.11)	< 0.0001	1.37 (1.15,1.63)	0.0005	2.56 (2.26,2.91)	< 0.0001	2.28 (2.01,2.59)	< 0.0001	1.25 (1.08,1.44)	0.0
SICU												
G1	1.17 (0.88,1.56)	0.2701	1.18 (0.89,1.57)	0.2504	1.15 (0.86,1.53)	0.3540	1.27 (0.99,1.62)	0.0616	1.30 (1.01,1.66)	0.0404	1.26 (0.98,1.62)	0.0

Notes: G1: hypophosphatemia group (< 2.5 mg/L); G2: very-low-normal phosphate group (≥ 2.5 mg/dL and < 3.0 mg/dL); G3: low-normal phosphate group (≥ 3.0 mg/dL and < 3.5 mg/dL); G4: high-normal phosphate group (≥ 3.5 mg/dL and < 4.0 mg/dL); G5: very-high-normal phosphate group (≥ 4.0 mg/dL and < 4.5 mg/dL); G6: hyperphosphatemia group (≥ 4.5 mg/dL). G2 was the reference group.

Model 1 was adjusted by age, gender, ethnicities, heart rate, mean arterial pressure, respiratory rate, temperature, oxygen saturation;

Model 2 was adjusted by age, gender, ethnicities, heart rate, mean arterial pressure, respiratory rate, temperature, oxygen saturation, admission types, Sequent Organ Failure Assessment score, Simplified Acute Physiology Score II, Overall Anxiety Severity and Impairment Scale score, congestive heart failure, coronary artery disease, hypertension, diabetes, chronic pulmonary disease, atrial fibrillation, liver disease, fluid and electrolyte disorder, malignant tumor, chronic kidne disease, serum sodium, serum potassium, serum calcium, serum creatinine, blood urea nitrogen, serum bicarbonate, serum chloride, white blood cell, hemoglobin, platelet, use of mechanical ventilation on the first day, use of renal replacement therapy on the first day, use of vasopressor on the first day. Statistical significance (P < 0.05).

Abbreviations: ICU, intensive care unit; HR, hazard ratio; CI, confidence interval; CCU, coronary care unit; CSRU, cardiac surgery recovery unit; MICU, medical intensive care unit; SICU, surgical intensive care unit; TSICU, trauma surgical intensive care unit.

ICU departments	28-day mortality after ICU admission						90-day mortality after ICU admission					
	Non-adjusted		Model 1		Model 2		Non-adjusted		Model 1		Model 2	
	HR, 95%CI	P-value	HR, 95%CI	P-value	HR, 95%CI	P-value	HR, 95%CI	P-value	HR, 95%CI	P-value	HR, 95%CI	P-val
G2	Reference						Reference					
G3	0.85 (0.66,1.10)	0.2176	0.91 (0.71,1.18)	0.4805	0.91 (0.71,1.18)	0.4942	0.95 (0.76,1.18)	0.6506	1.02 (0.82,1.27)	0.8878	1.00 (0.80,1.25)	0.9
G4	0.65 (0.49,0.86)	0.0022	0.70 (0.53,0.92)	0.0108	0.64 (0.48,0.84)	0.0017	0.77 (0.61,0.97)	0.0292	0.82 (0.64,1.03)	0.0898	0.72 (0.57,0.91)	0.0
G5	0.84 (0.63,1.12)	0.2254	0.97 (0.72,1.30)	0.8429	0.86 (0.64,1.16)	0.3328	0.91 (0.71,1.17)	0.4833	1.05 (0.82,1.35)	0.7067	0.88 (0.68,1.14)	0.3
G6	1.17 (0.91,1.50)	0.2258	1.28 (0.99,1.65)	0.0586	0.54 (0.40,0.74)	< 0.0001	1.36 (1.10,1.68)	0.0052	1.48 (1.19,1.84)	0.0005	0.69 (0.53,0.89)	0.0
TSICU												
G1	1.38 (0.94,2.01)	0.1006	1.17 (0.80,1.72)	0.4138	0.94 (0.64,1.40)	0.7760	1.29 (0.92,1.82)	0.1383	1.10 (0.78,1.56)	0.5741	0.92 (0.65,1.31)	0.6
G2	Reference						Reference					
G3	0.86 (0.62,1.21)	0.3894	0.75 (0.54,1.06)	0.0995	0.76 (0.54,1.08)	0.1233	0.95 (0.71,1.28)	0.7543	0.84 (0.62,1.12)	0.2261	0.82 (0.61,1.10)	0.1
G4	0.85 (0.61,1.20)	0.3583	0.76 (0.54,1.07)	0.1143	0.71 (0.50,1.01)	0.0570	1.05 (0.78,1.40)	0.7563	0.93 (0.70,1.25)	0.6479	0.88 (0.65,1.18)	0.3
G5	0.85 (0.58,1.25)	0.4179	0.88 (0.60,1.29)	0.5064	0.74 (0.50,1.09)	0.1303	0.80 (0.57,1.13)	0.2051	0.84 (0.60,1.19)	0.3367	0.73 (0.51,1.04)	0.0
G6	1.50 (1.08,2.09)	0.0164	1.31 (0.93,1.83)	0.1169	0.62 (0.42,0.91)	0.0160	1.63 (1.22,2.17)	0.0009	1.43 (1.07,1.91)	0.0166	0.74 (0.53,1.02)	0.0

Notes: G1: hypophosphatemia group (< 2.5 mg/L); G2: very-low-normal phosphate group (≥ 2.5 mg/dL and < 3.0 mg/dL); G3: low-normal phosphate group (≥ 3.0 mg/dL and < 3.5 mg/dL); G4: high-normal phosphate group (≥ 3.5 mg/dL and < 4.0 mg/dL); G5: very-high-normal phosphate group (≥ 4.0 mg/dL and < 4.5 mg/dL); G6: hyperphosphatemia group (≥ 4.5 mg/dL). G2 was the reference group.

Model 1 was adjusted by age, gender, ethnicities, heart rate, mean arterial pressure, respiratory rate, temperature, oxygen saturation;

Model 2 was adjusted by age, gender, ethnicities, heart rate, mean arterial pressure, respiratory rate, temperature, oxygen saturation, admission types, Sequential Organ Failure Assessment score, Simplified Acute Physiology Score II, Overall Anxiety Severity and Impairment Scale score, congestive heart failure, coronary artery disease, hypertension, diabetes, chronic pulmonary disease, atrial fibrillation, liver disease, fluid and electrolyte disorder, malignant tumor, chronic kidney disease, serum sodium, serum potassium, serum calcium, serum creatinine, blood urea nitrogen, serum bicarbonate, serum chloride, white blood cell, hemoglobin, platelet, use of mechanical ventilation on the first day, use of renal replacement therapy on the first day, use of vasopressor on the first day. Statistical significance (P < 0.05).

Abbreviations: ICU, intensive care unit; HR, hazard ratio; CI, confidence interval; CCU, coronary care unit; CSRU, cardiac surgery recovery unit; MICU, medical intensive care unit; SICU, surgical intensive care unit; TSICU, trauma surgical intensive care unit.

Discussion

After reviewing the literature in recent years, we found that few studies have focused on the association between serum phosphate and ICU patients' clinical outcomes. Compared with these studies, our study seemed to be the only one study currently available with a large sample for patients in ICU, and it was the advantage of our study. In addition, the results of these studies in the past were partly consistent and partly controversial. Suzuki et al.'s study[28] showed the

relationship between hypophosphatemia and 28-day ICU mortality among 2730 ICU patients. They found higher ICU mortality of patients with hypophosphatemia (12% versus 7%) and a longer ICU stay [(3.6, 2.2 to 6.8) versus (1.7, 0.9 to 3.1)], but the incidence of hypophosphatemia was not an independent risk factor for ICU mortality (OR = 0.86, 95%CI 0.66 to 1.10, adjusted). Also, they found the timing or the duration of hypophosphatemia had no significant association with ICU mortality. Another retrospective cohort study among 946 ICU patients performed by Wang et al.'s[8] indicated that patients in ICU with hypophosphatemia had higher 28-day ICU mortality (35.3% versus 24%) and longer ICU stay [(5.5, 2.8 to 10.6) versus (1.7, 1.5 to 3.4)]. According to the results of their study, hypophosphatemia was an independent risk factor for 28-day ICU mortality (OR = 1.5, 95%CI 1.1 to 2.1, P = 0.01, adjusted). Haider et al.' s[22] reported that the ICU stay of patients with hyperphosphatemia was longer than patients with hypophosphatemia or normal phosphate [(6, 1 to 14) versus (3, 0 to 8) or (3, 0 to 3)] among 2390 ICU patients. On the one hand, hyperphosphatemia was a predictor for 28-day ICU mortality(OR = 3.29, 95%CI 1.8 to 6.1, P < 0.001, adjusted), on the other hand, hypophosphatemia was not associated with 28-day ICU mortality (OR = 1.24, 95%CI 0.66 to 2.30, P = 0.51, adjusted). Another study conducted by Broman et al[1].' s[1] was similar to the Haider's. In this research with 4656 samples, hyperphosphatemia was associated with a higher risk of 180-day ICU death (HR = 1.2, 98.3%CI 1.0 to 1.5, P = 0.0089, adjusted) compared to controls. The risk of death in the hypophosphatemia group did not differ significantly from controls (HR = 0.90, 98.3%CI 0.72 to 1.1, P = 0.2650, adjusted). In summary, the association between abnormal serum phosphate and clinical outcomes was still controversial.

Our study selected patients with serum phosphate measurements (within the first day at ICU admission) as the study population and explored the associations between serum phosphate at ICU admission and clinical outcomes to verify the hypothesis mentioned above. We retrospectively analyzed the data from a large critical care database (MIMIC-III database). Through our study, we found that the comparison of the clinical outcomes (ICU mortality,28-day ICU mortality,90-day ICU mortality, ICU stay) among the six groups was G6 > G5 > G1 > G2, G3, G4 approximately. Unlike previous results, we found that very-high-normal phosphate (G5) was also associated with worse clinical outcomes in critically ill patients. It seemed to remind us whether it was necessary to redefine the normal range of ICU admission phosphate. The results of the multivariable Cox regression analysis showed that hypophosphatemia (G1) and hyperphosphatemia (G6) at ICU admission were not the independent risk factors of 28 or 90-day mortality for critically ill patients admitted to the ICU in total. It showed that the abnormal phosphate seemed to be just a marker of illness severity. And monitoring for phosphate might not be necessary for ICU patients. Besides, high-normal phosphate (G4) was the independent protection factor of 28-day ICU mortality. However, after being stratified by types of ICU, this association only appeared at the SICU. It showed that controlling the phosphate value at 3.0-4.5 mg/dL might have a positive effect on reducing short-term mortality at the SICU. Moreover, we found that hyperphosphatemia was an independent risk factor of 28 or 90-day mortality at the MICU, which would increase the risk of 28 or 90-day mortality after MICU admission by about 35% or 25%. It indicated that timely adjustment of hyperphosphatemia after MICU admission might be a necessary treatment. However, our study had not studied whether correcting hyperphosphatemia would improve the prognosis of patients at the MICU. So, this issue would be further explored in future research. In addition, some results need to be discussed were: (I) the inverse association between hyperphosphatemia and 28 or 90-day ICU mortality for the SICU patients; (II) the inverse association between hyperphosphatemia and 28-day ICU mortality for the TSICU patients. These results seemed to be contrary to intuition, which we thought were related to the selection of participants. In our study, for patients with multiple ICU admission records, only the first ICU admission was analyzed. As we all know, the SICU and TSICU mainly aimed at surgical critically ill patients. They stayed in the ICU for a relatively short term. Generally, they would be transferred out of the ICU within 1−2 days after the operation. So, we thought it was not accurate to define clinical outcomes based on the first ICU admission. We speculated that a more reasonable approach was when critically ill patients were prepared for the operation in the SICU or TSICU, and then transferred out of the ICU for the operation. In this circumstance, it was more accurate to use hospital mortality as the clinical outcome. In the future, we need to target the patients of SICU or TSICU to verify our speculation.

The most obvious advantage of this study was the large ICU sample size, which performed for subgroup analysis and adjustment for confounding factors. And another important finding was that hyperphosphatemia was not an independent risk factor for ICU clinical outcomes, which was contrary to the results of previous studies. In addition, hypophosphatemia was also not an independent risk factor for ICU clinical outcomes. This was the same as the results of some previous studies. Our study provided clinical evidence for this conclusion. However, there were several limitations to our study. Firstly, this was a single-centre, a retrospective study based on the MIMIC-III database. Wherefore, the additional investigation was required to generalize our findings to other institutions. Secondly, because of the missing observations of albumin measurement up to 45.7%, we did not adjust our model for serum albumin. Thirdly, the main ethnicity in our study was white. We also required further studies with a more heterogeneous ethnicity population. Fourthly, we only evaluated the baseline measurements of the serum phosphate level at ICU admission, but we ignored the evaluation of serum phosphate levels over time. Finally, although we found hyperphosphatemia was an independent risk factor of 28 or 90-day mortality at the MICU, whether correcting hyperphosphatemia would improve patients' outcomes at the MICU was unknown. Therefore, prospective studies were still needed to confirm the results of our study further.

Conclusion

After adjustment for potential confounders, hypophosphatemia and hyperphosphatemia at ICU admission were not the independent risk factors of 28 or 90-day mortality for general critically ill patients but were still a sign of worse clinical outcomes. It leads us to consider whether monitoring for phosphate is not a necessary measure in general ICU patients, at least we concluded that it might not be necessary. After being stratified by types of ICU, hyperphosphatemia at admission increased the risk of 28 or 90-day mortality among patients admitted to the MICU, which emphasizes the potential importance of early monitoring for phosphate and treatments of hyperphosphatemia for the MICU patients.

Abbreviations List

ICU, intensive care unit; 1,25(OH)2D, 1,25-Dihydroxy Vitamin D; NPT2b, sodium-dependent phosphate co-transporter 2b; FGF23, Fibroblast Growth Factor-23; CCU, coronary care unit; CSRU, cardiac surgery recovery unit; MICU, medical intensive care unit; SICU, surgical intensive care unit; TSICU, trauma/surgical intensive care unit; MIMIC-III, Medical Information Mart for Intensive Care III; MIT, Massachusetts Institute of Technology; BIDMC, Beth Israel Deaconess Medical Center; NIH, National Institutes of Health; SQL, structure query language; SOFA, Sequential Organ Failure Assessment; SAPS II, Simplified Acute

Physiology Score II; OASIS, Overall Anxiety Severity and Impairment Scale; SD, standard deviation; IQR, interquartile ranges; HR, hazard ratio; CI, confidence interval; OR, odds ratio.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

The full data set generated and/or analyzed during the present study is publicly available in the MIMIC-III Database. https://physionet.org/content/mimiciii/1.4/.

Conflict of Interest

The authors declare that they have no conflicts of interest.

Authors' contributions

Chen and He designed the study. Chen extracted the data. Huang, Zhao, Xu analyzed the data. Chen and Luo drafted the manuscript. Chen and He revised the text for critical content. All authors read and approved the final manuscript.

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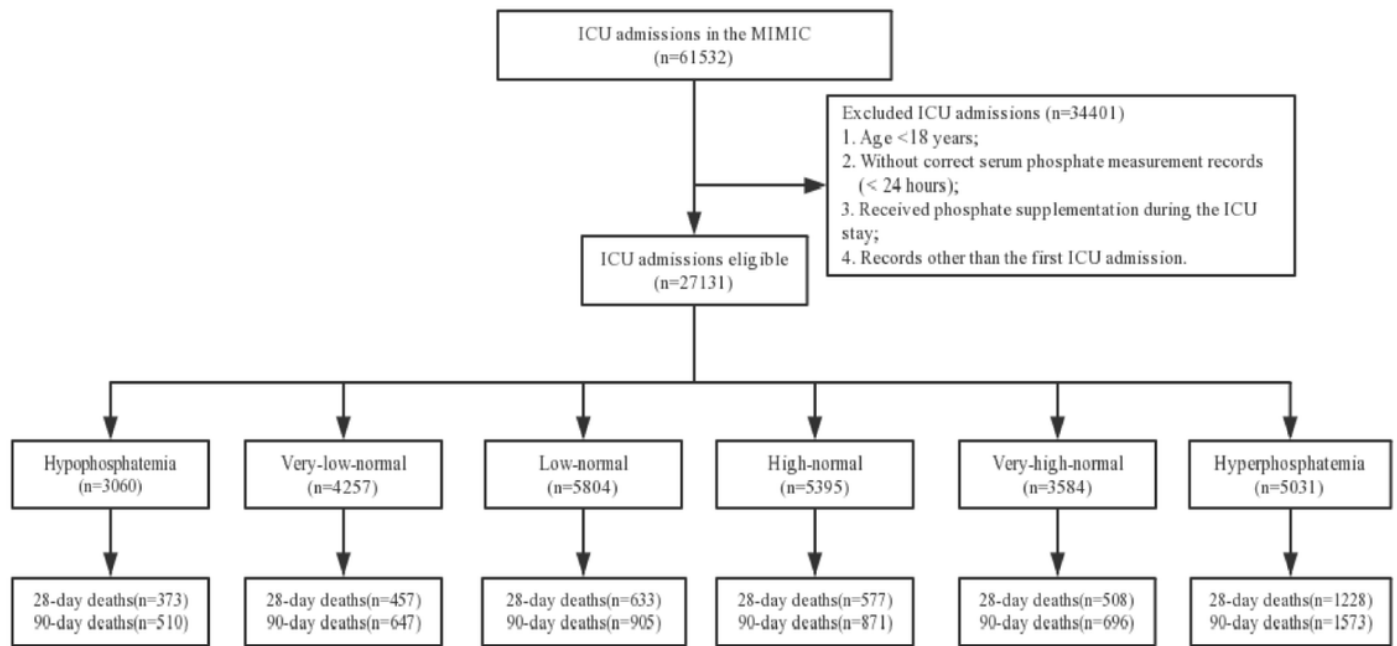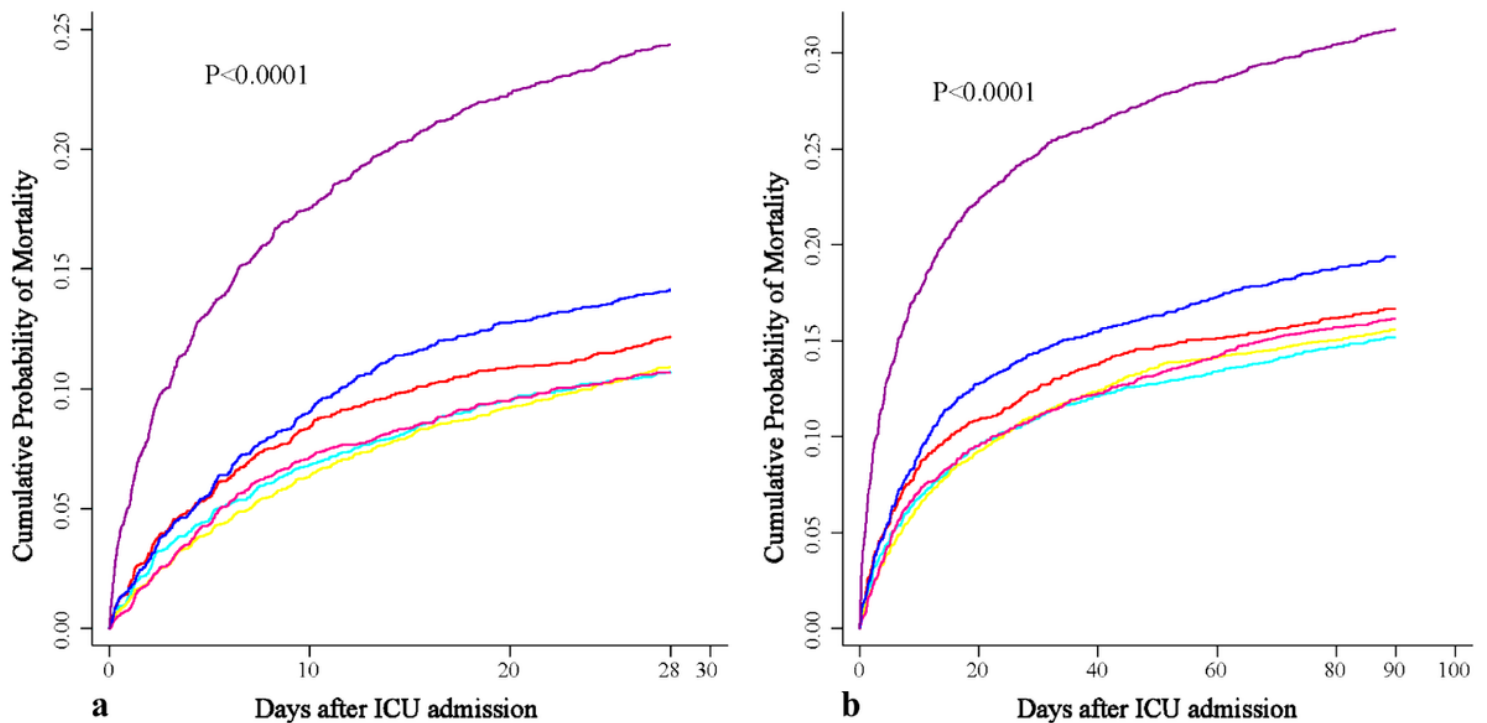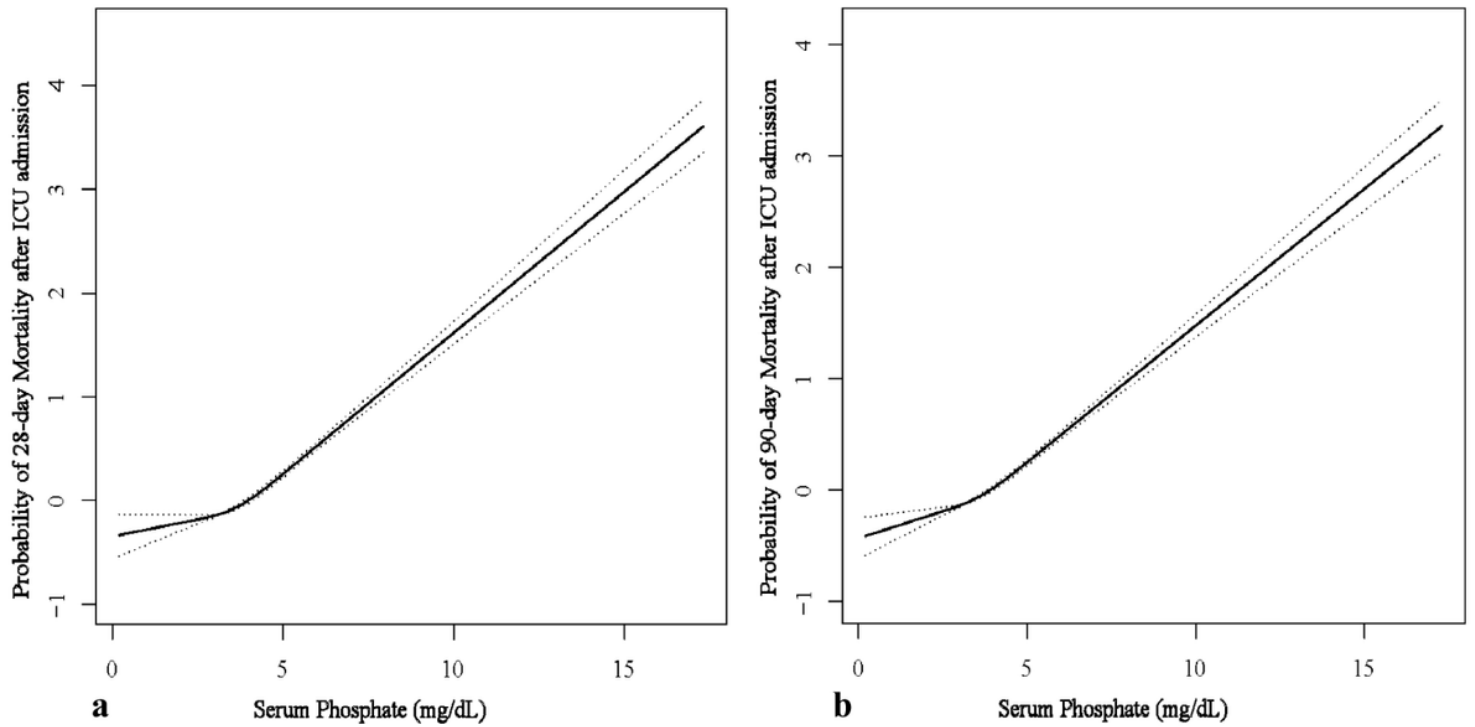
Figures

Figure 1

Figure 2

Kaplan-Meier survival plot of mortality (P<0.0001). The death distributions of patients among six groups of serum phosphate at admission within 28 days (a) or 90 days (b) after ICU admission. G1 (red): hypophosphatemia group (<2.5mg/L); G2 (cyan): very-low-normal phosphate group (≥2.5mg/dL and <3.0mg/dL); G3 (yellow): low-normal phosphate group (≥3.0mg/dL and <3.5mg/dL); G4 (pink): high-normal phosphate group (≥3.5mg/dL and <4.0mg/dL); G5 (blue): very-high-normal phosphate group (≥4.0mg/dL and <4.5mg/dL); G6 (purple): hyperphosphatemia group (≥4.5mg/dL).

Figure 3

Cubic spline analysis. The plot described the relationship between serum phosphate as a continuous variable and the probability of 28-day (a) or 90-day (b) mortality after ICU admission. The dashed area indicated the 95% confidence interval (CI).