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Research article

A non-linear positive relationship between serum phosphate and clinical outcomes in sepsis

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ABSTRACT

Objective: This study aimed to evaluate the possible relationship between serum phosphate and short-term outcomes in sepsis.

Methods: This was a retrospective study. Sepsis patients in MIMIC-IV database were included. Based on the quartiles of serum phosphate, all sepsis patients were divided into four groups. Univariable and multivariable regression analyses were constructed for discussing the relationship between different parameters and 30-day mortality in sepsis. A generalized additive model was performed for exploring the association of serum phosphate with 30-day mortality.

Results: 6251 sepsis patients including 4368 survivors and 1883 non-survivors were included. A significant relationship between serum phosphate and 30-day mortality was found after adjusting for all potential confounders (OR = 1.19, 95%CI:1.13–1.26, P < 0.0001). The relationship was non-linear with an inflection point of 6.8 mg/dl. On the left side of the inflection point (≤6.8 mg/dl, n = 5911 (94.56%)), the OR was 1.24 (95%CI: 1.17–1.31, P < 0.0001). On the right side of the inflection point (>6.8 mg/dl, n = 340 (5.44%)), the OR was 0.94 (95%CI:0.78–1.13, P = 0.5038).

Conclusion: A non-linear positive relationship was found between serum phosphate and 30-day mortality in sepsis. Serum phosphate was associated with mortality in sepsis. Our results could be used for screening out those sepsis patients with higher risk of worse outcomes.

1. Introduction

Phosphate, as an indispensable element, takes a prominent role in various metabolic procedures in cells and regulates many physiological functions in the body [1]. Phosphate is conducive to maintaining muscle contraction and cellular integrity [2], which also helps to convey nerve stimulation and keep organ function normalization [3]. Most of phosphate, as hydroxyapatite crystals, exists in bone tissue, while serum phosphate only accounts for about 1% in total [4]. The levels of serum phosphate are mainly regulated in a comparatively stable range by the bones, kidneys and intestines [5]. Previous studies have demonstrated that serum phosphate was associated with clinical outcomes in various diseases including malignant tumor [6], pneumonia [7], acute pancreatitis [8]and metabolic syndrome [9].

Few studies explored the clinical significance of serum phosphate in sepsis. One retrospective study with 1422 sepsis patients showed that higher levels of serum phosphate was significantly associated with worse outcomes and higher risk of complications including shock and respiratory failure in sepsis [10]. Another study utilized the time-weighted phosphate level instead for a randomized level of serum phosphate and found that sepsis patients who had greater than 3.5 mg/dL of time-weighted phosphate level, 28-day mortality was significantly higher [11].

However, the evidence on the association between serum phosphate disturbances with clinical outcomes in sepsis remains controversial. In our study, we aimed to identify the effect of serum phosphate in sepsis and comprehensively explore the relationship between serum phosphate and prognosis in sepsis.

2. Materials and methods

2.1. Database and patients

This was a retrospective study based on a public database called Medical Information Mart for Intensive Care IV(MIMIC-IV) (https://

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mimic.mit.edu/iv/). This publicly and freely available database contains more than 70,000 patients in intensive care units (ICUs) encompassing around a two-decade time span [12, 13]. Information including demographic data, vital signs, laboratory parameters, imaging records and clinical outcomes was recorded.

In our research, sepsis patients in MIMIC-IV were included for analysis. The diagnosis of sepsis was based on the definition of Sepsis 3.0 [14]. We included sepsis patients that possessed serum phosphate 24 h after admission. Exclusion criteria included: 1) patients without serum phosphate and vital signs 24 h after admission; 2) data missing of other variables which were included in our research.

2.2. Data extraction and variables

Data including clinical, laboratory and outcomes of sepsis patients after admission within 24 h in MIMIC-IV were extracted by PostgreSQL 9.6 software. General characteristics including age, gender, and comorbidities (diabetes, hypertension, renal disease, and coronary artery disease (CAD)) were extracted. The days of length of stay (LOS) in ICU and hospital were collected. 30-day mortality was calculated based on the information of follow-ups. The scores of two major scoring systems for sepsis including sequential organ failure assessment (SOFA) and acute physiology and chronic health evaluation (APACHEII) were collected and calculated. Different variables including systolic blood pressure (SBP), heart rate (HR), respiratory rate (RR), diastolic blood pressure (DBP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), anion gap (AG), bicarbonate, chloride, creatinine, international normalized ratio (INR), hematocrit, hemoglobin, lactate, mean corpusular hemoglobin concentration (MCHC), mean corpuscular volume (MCV), mean corpusular hemoglobin (MCH), magnesium, platelet (PLT), total bilirubin, total calcium, potassium, prothrombin time (PT), thrombin time (TT), red blood cell distribution width (RDW), red blood cells (RBC), white blood cells (WBC), sodium, urea nitrogen, and phosphate were also collected and analyzed.

2.3. Statistical analysis

First, on the basis of quartiles of serum phosphate (25% quartile, 50% quartile and 75% quartile), sepsis patients were divided into four groups (Q1, Q2, Q3 and Q4). Baseline parameters were demonstrated as follow: 1) medians for continuous parameters; 2) percentages or frequencies for categories parameters. Different parameters between four groups were compared by Mann–Whitney U-test or Chi-squared test. Second, to investigate the relationship between different parameters and 30-day mortality in sepsis, univariable and multivariable analyses were performed.

Third, three different models were established for analyzing the relationship between serum phosphate and 30-day mortality. The models included were as follows: crude model (adjusted for none), model I (adjusted for age and gender) and model II (adjusted for all potential confounders). In addition, serum phosphate, since it was a continuous parameter, was changed into a categorical parameter (quartiles) for group analysis. Then, the P for trend of categorized serum phosphate was counted in different adjusted models.

Fourth, we constructed a generalized additive model and a smooth fitting curve for expressing the association of serum phosphate and 30-day mortality. If there was a non-linear relationship, then the inflection point of serum phosphate was ascertained by recursive algorithm. The best-fitting model was determined by the P value of the log-likelihood ratio test. If the P value > 0.05, the linear model was selected. If < 0.05, the nonlinear model was confirmed. At last, we performed the subgroups and interaction analyses between serum phosphate and different parameters by stratified models.

For illuminating the relationships between different variables, a heatmap was performed (Supplementary Figure 1). The package "corrplot" in R software was used. For demonstrating the associations between different variables and 30-day mortality in sepsis, a casual diagram was constructed (Supplementary Figure 2).

Our study was implemented by the statistical software packages R (http://www.R-project.org) and EmpowerStats (http://www. empowerstats. com). Statistically significant was determined by a P-value <0.05.

3. Results

3.1. Description of the study population

The flow chart of showed that a total number of 6251 sepsis patients including 4368 survivors and 1883 non-survivors were finally enrolled in the study. Supplementary Table 1 demonstrated the general characteristics of the cohort. The median age was 66.00 and males accounted for 56.52% in total. The incidences of comorbidities including renal disease, diabetes, CAD and hypertension were 4.26% (n = 266), 3.20% (n = 200), 9.04% (n = 565), and 20.84% (n = 1303), respectively. The median scores of SOFA and APACHEII were 4 and 12, respectively. The median days of LOS in ICU and hospital were 4.77 and 11.63, respectively. The 30-day mortality was 30.12% (n = 1883).

Table 1 illuminated different variables in four groups based on the quartiles of serum phosphate (Q1 (<2.8 mg/dl, n = 1484), Q2 (2.8–3.5 mg/dl, n = 1618), Q3 (3.6–4.6 mg/dl, n = 1571), Q4 (>4.6 mg/dl, n = 1578)). The rates of 30-day mortality in four groups were 21.50% (n = 319), 25.40% (n = 411), 30.49% (n = 479) and 42.71% (n = 674), respectively ($P < 0.001$).

3.2. Kaplan-Meier analysis for survival probability based on quartiles of serum phosphate

Figure 1 substantiated that in Q1 group, there was a significantly higher survival probability in the 30-day mortality group compared to other groups, and the lowest rate of survival in 30-day was in Q4 group by Kaplan-Meier analysis ($P < 0.0001$).

3.3. Univariable and multivariable analysis for 30-day mortality

Table 2 showed the relationships between variables and 30-day mortality by univariable and multivariable analysis. Univariable analysis indicated that factors including renal disease, CAD, diabetes, SBP, RR, AG, ALT, AST, total bilirubin, bicarbonate, creatinine, chloride, INR, hemoglobin, lactate, magnesium, MCH, MCHC, MCV, PLT, potassium, PT, TT, RBC, RDW, urea nitrogen, sodium and phosphate were associated with 30-day mortality. Multivariable analysis indicated that significant relationships between 30-day mortality and factors including renal disease, HR, RR, total bilirubin, creatinine, lactate, magnesium, TT, RDW, urea nitrogen and phosphate were found.

3.4. Relationship between serum phosphate and 30-day mortality in sepsis

We performed three models (crude model: adjusted for none, model I: adjusted for age and gender, model II: adjusted for all potential cofounders) for investigating the association of serum phosphate with 30-day mortality in sepsis (Table 3). In model II, there was still a significant association between serum phosphate and 30-day mortality (OR = 1.19, 95%CI:1.13–1.26, $P < 0.0001$). Then, when we converted the serum phosphate from a continuous variable into categorial variables (quartiles), we discovered that the risk of 30-day mortality in Q4 group was significantly higher compared with that in the Q1 group (crude model: OR = 2.72, 95%CI:2.32–3.19, model I: OR = 2.70, 95% CI:2.30–3.18, model II: OR = 1.89, 95%CI: 1.53–2.32). The values of P for trend in all three models were both <0.0001.

A smooth fitting curve for further analysis was performed in Figure 2, and a non-linear relationship was constructed. In Table 4, we utilized the two-piecewise linear regression and the linear regression models to fit the association of serum phosphate with 30-day mortality. The value of P

Table 1. Description of variables based on quartiles of serum phosphate.

Serum phosphate (mg/dl) (quartiles)					
Variables	Q1 (<2.8)	Q2 (2.8–3.5)	Q3 (3.6–4.6)	Q4 (>4.6)	P-value
Number	1484	1618	1571	1578	
Age (years)	64.50 (54.00–75.00)	67.00 (57.00–79.00)	68.00 (57.00–77.00)	66.00 (55.00–76.00)	<0.001
Gender(n,%)					0.044
Male	804 (54.18%)	895 (55.32%)	912 (58.05%)	922 (58.43%)	
Female	680 (45.82%)	723 (44.68%)	659 (41.95%)	656 (41.57%)	
Comorbidities(n,%)					
Renal disease	30 (2.02%)	37 (2.29%)	62 (3.95%)	137 (8.68%)	<0.001
CAD	135 (9.10%)	132 (8.16%)	151 (9.61%)	147 (9.32%)	0.511
Diabetes	47 (3.17%)	52 (3.21%)	45 (2.86%)	56 (3.55%)	0.754
Hypertension	378 (25.47%)	353 (21.82%)	313 (19.92%)	259 (16.41%)	<0.001
Variables					
HR (beats/min)	100.00 (86.00–115.00)	97.00 (83.00–112.00)	95.00 (82.00–111.00)	95.00 (80.00–111.00)	<0.001
SBP(mmHg)	111.00 (98.00–129.00)	110.00 (97.00–127.00)	111.00 (97.00–128.00)	110.00 (96.00–127.00)	0.311
DBP(mmHg)	64.00 (55.00–75.00)	63.00 (53.00–74.00)	63.00 (53.00–75.00)	61.00 (51.00–74.75)	0.001
RR (beats/min)	21.00 (17.00–26.00)	21.00 (17.00–25.00)	21.00 (17.00–25.00)	20.00 (16.00–25.00)	0.024
AG (mmol/l)	14.00 (12.00–17.00)	15.00 (12.00–17.00)	16.00 (13.00–18.00)	19.00 (16.00–23.00)	<0.001
ALT (IU/L)	28.00 (16.00–59.00)	27.00 (16.00–57.00)	27.00 (16.00–59.00)	35.00 (18.00–100.75)	<0.001
AST (IU/L)	39.00 (23.00–86.25)	40.00 (23.00–81.00)	40.00 (23.00–83.00)	58.00 (28.00–174.75)	<0.001
Total bilirubin (mg/dL)	0.70 (0.40–1.70)	0.70 (0.40–1.80)	0.70 (0.40–1.70)	0.80 (0.40–2.10)	0.005
Total calcium (mg/dL)	7.80 (7.30–8.40)	8.10 (7.50–8.60)	8.20 (7.60–8.70)	8.10 (7.50–8.70)	<0.001
Bicarbonate (mmol/L)	22.00 (19.00–24.00)	22.00 (19.00–25.00)	22.00 (18.00–25.00)	19.00 (15.00–23.00)	<0.001
Creatinine (mg/dL)	1.00 (0.70–1.40)	1.10 (0.80–1.50)	1.40 (1.00–2.20)	2.50 (1.60–4.20)	<0.001
Chloride (mmol/L)	105.00 (100.00–109.00)	103.00 (99.00–107.00)	103.00 (98.00–107.00)	101.00 (96.00–106.00)	<0.001
INR	1.40 (1.20–1.70)	1.40 (1.20–1.70)	1.40 (1.20–1.80)	1.50 (1.20–2.20)	<0.001
Hematocrit (%)	32.10 (27.70–36.10)	31.40 (27.13–36.20)	31.30 (27.00–36.10)	31.60 (26.90–36.77)	0.322
Hemoglobin (g/dL)	10.50 (9.10–11.90)	10.20 (8.80–11.80)	10.00 (8.70–11.70)	10.00 (8.60–11.70)	<0.001
Lactate (mmol/L)	1.95 (1.40–3.00)	1.90 (1.33–2.90)	1.90 (1.30–2.90)	2.35 (1.50–4.20)	<0.001
Magnesium (mg/dL)	1.70 (1.50–2.00)	1.80 (1.60–2.00)	1.90 (1.60–2.20)	2.10 (1.80–2.40)	<0.001
MCH(pg)	30.10 (28.40–31.80)	30.10 (28.30–31.60)	30.00 (28.20–31.60)	29.90 (28.00–31.67)	0.078
MCHC(g/dL)	32.80 (31.80–33.90)	32.50 (31.50–33.50)	32.30 (31.10–33.35)	31.85 (30.60–33.00)	<0.001
MCV(fl)	91.00 (87.00–96.00)	92.00 (87.25–97.00)	93.00 (88.00–98.00)	94.00 (88.00–99.00)	<0.001
PLT ($*10^9$/L)	164.00 (107.75–236.00)	186.00 (121.00–258.00)	196.00 (125.50–283.00)	187.00 (118.00–277.00)	<0.001
Potassium (mmol/L)	3.80 (3.40–4.20)	4.00 (3.60–4.40)	4.20 (3.80–4.70)	4.70 (4.10–5.20)	<0.001
PT(s)	15.15 (13.20–18.52)	15.00 (13.20–18.90)	15.30 (13.20–19.75)	16.20 (13.60–24.00)	<0.001
TT(s)	32.10 (28.30–38.30)	32.50 (28.50–39.30)	33.00 (28.60–40.90)	34.60 (29.33–44.60)	<0.001
RBC($*10^{12}$/L)	3.53 (3.01–4.00)	3.44 (2.94–3.99)	3.43 (2.92–3.95)	3.37 (2.89–3.98)	0.004
RDW (%)	14.90 (13.80–16.62)	15.40 (14.10–17.30)	15.80 (14.30–17.60)	16.10 (14.60–18.20)	<0.001
Urea nitrogen (mg/dL)	20.00 (13.00–29.00)	23.00 (16.00–35.00)	31.00 (20.00–47.50)	51.00 (32.00–74.00)	<0.001
WBC($*10^9$/L)	11.30 (7.00–16.40)	11.90 (7.60–17.28)	12.70 (7.90–18.80)	14.20 (9.00–20.80)	<0.001
Sodium (mmol/L)	138.00 (135.00–141.00)	137.00 (134.00–141.00)	138.00 (134.00–141.00)	137.00 (133.00–141.00)	<0.001
Clinical outcomes(days)					
LOS in ICU	3.82 (1.92–9.43)	4.33 (2.14–9.79)	5.02 (2.40–10.93)	5.79 (2.43–12.21)	<0.001
LOS in hospital	10.48 (5.98–19.86)	11.52 (6.74–20.79)	12.74 (6.99–21.68)	11.97 (5.61–21.59)	<0.001
30-day mortality(n,%)	319 (21.50%)	411 (25.40%)	479 (30.49%)	674 (42.71%)	<0.001

Abbreviations: ALT = alanine aminotransferase, AST = aspartate aminotransferase, INR = international normalized ratio, CAD = coronary artery disease, SBP = systolic blood pressure, DBP = diastolic blood pressure, HR = heart rate, RR = respiratory rate, WBC = white blood cells, PLT = platelet, RDW = red blood cell distribution width, RBC = red blood cells, MCV = mean corpuscular volume, MCH = mean corpusular hemoglobin, MCHC = mean corpusular hemoglobin concentration, PT = prothrombin time, TT = thrombin time, AG = anion gap, SOFA = sequential organ failure assessment, APACHE = acute physiology and chronic health evaluation, LOS = length of stay, ICU = intensive care unit, IQR = interquartile ranges.

for the log-likelihood ratio test was 0.010, which exemplified that the two-piecewise linear regression model was superior for indicating accurately the association between them. The inflection point of serum phosphate was 6.8 mg/dl. On the left side of inflection point (≤6.8 mg/dl, n = 5911 (94.56%)), the OR was 1.24 (95%CI:1.17–1.31, P < 0.0001). On the right side of inflection point (>6.8 mg/dl, n = 340 (5.44%)), no significant relationship was found (OR = 0.94, 95% CI:0.78–1.13, P = 0.5038).

3.5. Subgroup analysis

In Supplementary Table 2, all other variables including age, gender, renal disease, CAD, diabetes, hypertension, DBP, HR, SBP, RR, AG, ALT, AST, total bilirubin, total calcium, bicarbonate, creatinine, chloride, INR, hematocrit, hemoglobin, lactate, magnesium, MCH, MCHC, MCV, PLT, potassium, PT, TT, RBC, RDW, urea nitrogen, WBC, and sodium were

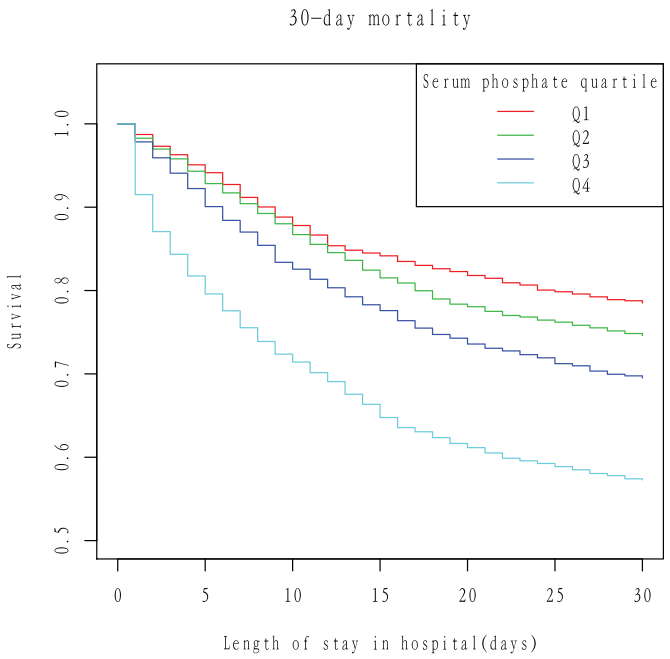

Figure 1. Kaplan-Meier analysis for survival probability in sepsis based on quartiles of serum phosphate.

stratified for subgroup analysis and the values of p for interaction in different groups were checked.

4. Discussion

In our study, several main findings were revealed. First, a significant association between serum phosphate and 30-day mortality in sepsis was identified based on the MIMIC-IV database. Even after adjusting for all potential confounders, a positive relationship was still present. It showed that a 1 mg/dl increment in serum phosphate could lead to a 19% risk increment in 30-day mortality. Second, a non-linear positive relationship was found between serum phosphate and prognosis in sepsis. The inflection point of serum phosphate was 6.8 mg/dl. When serum phosphate ≤6.8 mg/dl, with each 1 mg/dl increment in serum phosphate, the risk of mortality increased by 24%. It could be used for screening out those sepsis patients with higher risk of worse outcomes.

Phosphate is involved in various physiological procedures including oxygen supplement, homeostasis, muscle contractility, and cellular metabolism [15, 16]. Disturbances of serum phosphate including hypophosphatemia and hyperphosphatemia have impact on the body, leading to poor prognosis [17, 18, 19, 20]. In China, one study including 7,353 patients with ischemic stroke verified that a U-shaped relationship was found between serum phosphate and stroke recurrence [21]. A large-scale study with 27,131 critical ill patients observed that hyperphosphatemia was related to the increment in 28-day and 90-day mortality (hazard ratio (HR) = 0.64, 95%CI:0.48–0.84, P = 0.0017; HR = 0.72, 95% CI:0.57–0.91, P = 0.0067, respectively) [22]. Another study substantiated the positive relationship between serum phosphate and peripheral artery disease and concluded that for every 1 mg/dl increase in serum phosphate, the incidence of disease was significantly increased (HR = 1.24; 95%CI:1.10–1.39) [23]. Moreover, the larger change and the lower achievement rate of serum phosphate were also both linked with worse outcomes [24, 25]. However, few studies discovered opposite results. A cerebral hemorrhage study with 851 patients showed that lower serum phosphate was strongly associated with a higher risk of poor prognosis [26].

In sepsis, some previous studies found that low serum phosphate was also associated with a higher risk of complications and poor prognosis.

Table 2. Univariable and multivariable analysis for 30-day mortality.

Variables	Univariable (OR,95%CI, P)	Multivariable (OR,95%CI, P)
Age (years)	1.0 (1.0, 1.0) <0.001	1.0 (1.0, 1.0) <0.001
Gender		
Male	Ref.	Ref.
Female	1.0 (0.9, 1.2) 0.461	1.1 (1.0, 1.2) 0.183
Renal disease		
No	Ref.	Ref.
Yes	1.4 (1.1, 1.9) 0.005	1.4 (1.0, 1.9) 0.033
CAD		
No	Ref.	Ref.
Yes	1.2 (1.0, 1.5) 0.036	1.1 (0.9, 1.4) 0.188
Diabetes		
No	Ref.	Ref.
Yes	0.7 (0.5, 1.0) 0.039	0.8 (0.5, 1.1) 0.168
Hypertension		
No	Ref.	Ref.
Yes	1.0 (0.8, 1.1) 0.519	1.0 (0.8, 1.1) 0.796
HR (beats/min)	1.0 (1.0, 1.0) 0.127	1.0 (1.0, 1.0) <0.001
SBP(mmHg)	1.0 (1.0, 1.0) 0.002	1.0 (1.0, 1.0) 0.211
DBP(mmHg)	1.0 (1.0, 1.0) 0.052	1.0 (1.0, 1.0) 0.842
RR (beats/min)	1.0 (1.0, 1.0) <0.001	1.0 (1.0, 1.0) 0.004
AG (mmol/l)	1.1 (1.0, 1.1) <0.001	1.0 (0.9, 1.0) 0.156
ALT (IU/L)	1.0 (1.0, 1.0) <0.001	1.0 (1.0, 1.0) 0.750
AST (IU/L)	1.0 (1.0, 1.0) <0.001	1.0 (1.0, 1.0) 0.087
Total bilirubin (mg/dL)	1.1 (1.0, 1.1) <0.001	1.0 (1.0, 1.0) <0.001
Total calcium (mg/dL)	1.0 (1.0, 1.1) 0.226	1.0 (0.9, 1.0) 0.159
Bicarbonate (mmol/L)	1.0 (1.0, 1.0) <0.001	1.0 (1.0, 1.0) 0.552
Creatinine (mg/dL)	1.1 (1.0, 1.1) <0.001	0.9 (0.9, 1.0) 0.007
Chloride (mmol/L)	1.0 (1.0, 1.0) <0.001	1.0 (1.0, 1.0) 0.360
INR	1.2 (1.1, 1.3) <0.001	1.0 (0.7, 1.5) 0.824
Hematocrit (%)	1.0 (1.0, 1.0) 0.098	1.0 (0.9, 1.1) 0.865
Hemoglobin (g/dL)	1.0 (0.9, 1.0) 0.001	1.0 (0.9, 1.2) 0.504
Lactate (mmol/L)	1.2 (1.2, 1.3) <0.001	1.2 (1.1, 1.2) <0.001
Magnesium (mg/dL)	1.8 (1.6, 2.1) <0.001	1.4 (1.2, 1.6) <0.001
MCH(pg)	1.0 (1.0, 1.1) <0.001	1.0 (0.8, 1.4) 0.760
MCHC(g/dL)	0.9 (0.9, 0.9) <0.001	0.9 (0.7, 1.2) 0.600
MCV(fl)	1.0 (1.0, 1.0) <0.001	1.0 (0.9, 1.1) 0.964
PLT (*10^9/L)	1.0 (1.0, 1.0) <0.001	1.0 (1.0, 1.0) 0.055
Potassium (mmol/L)	1.2 (1.2, 1.3) <0.001	1.0 (0.9, 1.1) 0.897
PT(s)	1.0 (1.0, 1.0) <0.001	1.0 (1.0, 1.0) 0.855
TT(s)	1.0 (1.0, 1.0) <0.001	1.0 (1.0, 1.0) <0.001
RBC(*10^{12}/L)	0.8 (0.8, 0.9) <0.001	0.9 (0.5, 1.7) 0.778
RDW (%)	1.1 (1.1, 1.2) <0.001	1.1 (1.1, 1.1) <0.001
Urea nitrogen (mg/dL)	1.0 (1.0, 1.0) <0.001	1.0 (1.0, 1.0) 0.019
WBC(*10^9/L)	1.0 (1.0, 1.0) 0.225	1.0 (1.0, 1.0) 0.558
Sodium (mmol/L)	1.0 (1.0, 1.0) 0.002	1.0 (1.0, 1.0) 0.556
Phosphate (mg/dL)	1.3 (1.2, 1.3) <0.001	1.2 (1.1, 1.3) <0.001

Abbreviations: ALT = alanine aminotransferase, AST = aspartate aminotransferase, INR = international normalized ratio, CAD = coronary artery disease, SBP = systolic blood pressure, DBP = diastolic blood pressure, HR = heart rate, RR = respiratory rate, WBC = white blood cells, PLT = platelet, RDW = red blood cell distribution width, RBC = red blood cells, MCV = mean corpuscular volume, MCH = mean corpusular hemoglobin, MCHC = mean corpusular hemoglobin concentration, PT = prothrombin time, TT = thrombin time, AG = anion gap, OR = odds ratio, CI = confidential interval.

Septic patients with low serum phosphate levels had a higher risk of developing cardiac arrhythmias [27]. In addition, hypophosphatemia could be an indicator of the disease severity in sepsis [28]. Low serum phosphate might result in rhabdomyolysis, muscle weakness, and immune function impaired, leading to a higher risk of infection, organ

Table 3. Relationship between serum phosphate and 30-day mortality in different models.

OR (95%CI), P value			
Exposure	Crude model	Model I	Model II
Serum phosphate (per 1 mg/dl increment)	1.29 (1.24, 1.33) <0.0001	1.30 (1.25, 1.34) <0.0001	1.19 (1.13, 1.26) <0.0001
Serum phosphate (mg/dl) quartiles			
Q1	Ref.	Ref.	Ref.
Q2	1.24 (1.05, 1.47) 0.0105	1.17 (0.99, 1.38) 0.0734	1.07 (0.90, 1.28) 0.4479
Q3	1.60 (1.36, 1.89) <0.0001	1.53 (1.30, 1.80) <0.0001	1.37 (1.14, 1.64) 0.0007
Q4	2.72 (2.32, 3.19) <0.0001	2.70 (2.30, 3.18) <0.0001	1.89 (1.53, 2.32) <0.0001
P for trend	<0.0001	<0.0001	<0.0001

Crude model adjusted for: None; Model I adjust ed for: age; gender.
Model II adjusted for: age; gender; HR; SBP; DBP; RR; AG; ALT, AST, bicarbonate, INR, magnesium, total bilirubin; total calcium; creatinine; chloride; hematocrit; hemoglobin; lactate; MCV; MCH; MCHC; PLT; PT; TT; potassium; RBC; RDW; urea nitrogen; WBC; sodium; renal disease; CAD; diabetes; hypertension.
Abbreviations: ALT = alanine aminotransferase, AST = aspartate aminotransferase, INR = international normalized ratio, CAD = coronary artery disease, SBP = systolic blood pressure, DBP = diastolic blood pressure, HR = heart rate, RR = respiratory rate, WBC = white blood cells, PLT = platelet, RDW = red blood cell distribution width, RBC = red blood cells, MCV = mean corpuscular volume, MCH = mean corpusular hemoglobin, MCHC = mean corpusular hemoglobin concentration, PT = prothrombin time, TT = thrombin time, AG = anion gap, OR = odds ratio, CI = confidential interval.

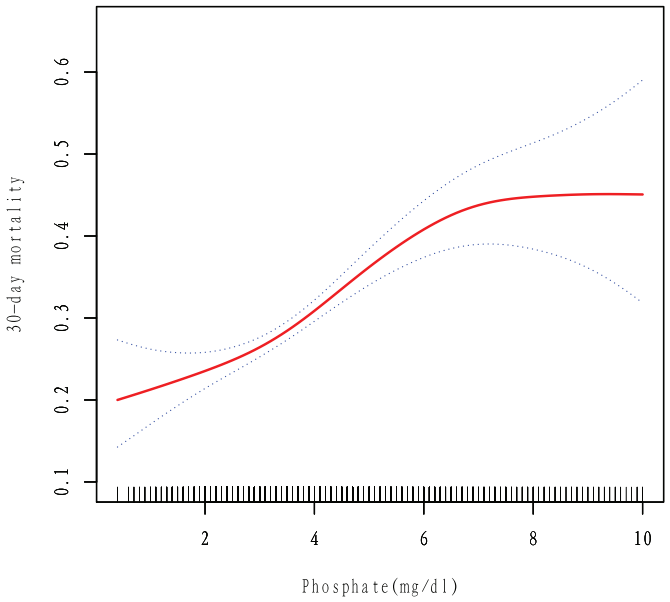

Figure 2. A non-linear association between serum phosphate and 30-day mortality in sepsis.

dysfunction and poor prognosis [1, 29]. Hypophosphatemia could enhance the virulence of bacteria and the ability of resistance to antibiotics increased due to the acidic surroundings caused by low phosphate level [30].

In the study, we found that elevated levels of serum phosphate were associated with higher risk of 30-day mortality in sepsis patients. Several possible mechanisms may be explained for our results. First, sepsis usually causes organ ischemic injury and cell damage, resulting in the release of phosphate into circulation [31]. Second, increased levels of serum phosphate is capable of producing more reactive oxygen species through disrupted mitochondrial function, which can aggravate the dysfunction of microcirculation and ischemia of organ [32]. Third, higher serum phosphate has been identified to be associated with the incidence of cardiovascular diseases [33], diabetes [34] and acute kidney injury [32], which may increase the risk of complications in sepsis.

The main strength of our research was that based on a large cohort of sepsis patients, a positive relationship was found between serum phosphate and short-term outcomes. MIMIC-IV is a large U.S public database, which could represent the general characteristics of critical ill patients in America. In our study, we adjusted for potential cofounders as much as possible to explore the relationship between serum phosphate and outcomes in sepsis. In addition, subgroups analysis with more than twenty different confounders including age, gender and comorbidities were performed for validating our results. However, there were some limitations. First, due to some data missing in the database, we only analyzed the serum phosphate of the first time in 24 h after admission. The relationship between dynamic changes of serum phosphate with outcomes wasn't investigated. Second, some factors including the level of parathyroid hormone and diet which might affect the serum phosphate were not available in the database. Hence, further study with more potential factors should be done. Third, although we adjusted for potential cofounders as much as possible in the model II, not all the confounders

Table 4. The results of the two-piecewise linear model.

	Number (%)	OR (95%CI)	P-value
Fitting model by standard linear regression	6251 (100%)	1.19 (1.13, 1.26)	<0.0001
Fitting model by two-piecewise linear regression			
The inflection point of serum phosphate (mg/dl)			
≤6.8	5911 (94.56%)	1.24 (1.17, 1.31)	<0.0001
>6.8	340 (5.44%)	0.94 (0.78, 1.13)	0.5038
P for the log-likelihood ratio test		0.010	

Model adjusted for: age; gender; HR; SBP; DBP; RR; AG; ALT, AST, bicarbonate, INR, magnesium, total bilirubin; total calcium; creatinine; chloride; hematocrit; hemoglobin; lactate; MCV; MCH; MCHC; PLT; PT; TT; potassium; RBC; RDW; urea nitrogen; WBC; sodium; renal disease; CAD; diabetes; hypertension.
Abbreviations: ALT = alanine aminotransferase, AST = aspartate aminotransferase, INR = international normalized ratio, CAD = coronary artery disease, SBP = systolic blood pressure, DBP = diastolic blood pressure, HR = heart rate, RR = respiratory rate, WBC = white blood cells, PLT = platelet, RDW = red blood cell distribution width, RBC = red blood cells, MCV = mean corpuscular volume, MCH = mean corpusular hemoglobin, MCHC = mean corpusular hemoglobin concentration, PT = prothrombin time, TT = thrombin time, AG = anion gap, OR = odds ratio, CI = confidential interval.

could be enrolled for being adjusted due to the lack of some data in MIMIC-IV. So, the limitation of generalizability of our model should be considered when applied. In addition, it was a retrospective study and selection bias couldn't be avoided due to the nature of study design.

5. Conclusion

A non-linear positive relationship was found between serum phosphate and 30-day mortality in sepsis. Serum phosphate was associated with mortality in sepsis. It could be used for screening out those sepsis patients with higher risk of worse outcomes. Physicians should pay more attention to the sepsis patients with elevated levels of serum phosphate and individualized treatment plans could be done early for improving the prognosis.

Ethics approval and consent to participate

This study was conducted in accordance with Good Clinical Practice (Declaration of Helsinki 2002). MIMIC-IV was an anonymized public database. To apply for access to the database, we passed the Protecting Human Research Participants exam (No.32900964). The project was approved by the institutional review boards of the Massachusetts Institute of Technology (MIT) and Beth Israel Deaconess Medical Center (BIDMC) and was given a waiver of informed consent.

Consent for publication

Not applicable.

Declarations

Author contribution statement

Cuirong Guo: Performed the experiments; Analyzed and interpreted the data.

Yingjie Su: Conceived and designed the experiments: Contributed reagents, materials, analysis tools or data.

Liudang He: Performed the experiments.

Zhao Zeng: Analyzed and interpreted the data.

Ning Ding: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

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Data availability statement

Data will be made available on request.

Declaration of interests statement

The authors declare no competing interests.

Additional information

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