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Change trends in serum phosphate levels predict in-hospital mortality in critically ill septic patients

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Serum phosphate levels are strongly correlated with the prognosis of septic patients. However, previous studies have concentrated on individual phosphate levels, and the relationship between change trends in serum phosphate levels and in-hospital mortality has seldom been reported. We aimed to investigate whether the level and change trends of serum phosphate were associated with in-hospital mortality. We classified patients using k-means clustering analysis into clusters with changes in serum phosphate levels and used logistic regressions to explore the relationships between different clusters and in-hospital mortality, taking the cluster with the smallest change as a reference. Restricted cubic spline regression was used to examine the shape of the correlation between changes in serum phosphate levels and in-hospital mortality. Subgroup analyses and interaction analyses were performed to discover potential impact factors. A total of 1810 (21.1%) of 8586 participants died during their hospital stay. After adjustment for baseline variables, cluster 2 (OR 1.303, 95% CI 1.101–1.542, $p = 0.002$), cluster 3 (OR 1.348, 95% CI 1.158–1.57, $p < 0.001$), cluster 4 (OR 1.652, 95% CI 1.225–2.222, $p = 0.001$) and cluster 5 (OR 2.745, 95% CI 2.212–3.407, $p < 0.001$) remained associated with significantly increased mortality. The changes in serum phosphate levels and in-hospital mortality were linear according to restricted cubic spline regression. According to the subgroup analyses, the ORs of the female subgroup and mechanical ventilation subgroup were lower than those of their counterparts across all clusters. Multiplicative and additive interactions were detected between phosphate clusters and mechanical ventilation. First, a high and unstable serum phosphate level is associated with increased mortality in septic patients. Second, for those with elevated phosphate levels, treatments to lower serum phosphate may reduce mortality in septic patients. Third, an increasing trend in phosphate levels may be more important than a high level in predicting poor prognosis in septic patients.

Keywords Serum phosphate, Sepsis, Mortality, Critical care, K-means clustering

Abbreviations

ICU	Intensive care unit
MIMIC	The medical information mart for intensive care
IRB	Institutional review board
STROBE	Strengthening epidemiological observation research report
SMD	Standardized mean differences
BMI	Body mass index
CCU	Coronary care unit
CSRU	Cardiac surgery unit
MICU	Medical intensive care unit
SICU	Surgical intensive care unit
TSICU	Trauma surgical intensive care unit
SO_2	Oxygen saturation
BE	Basic excess
BUN	Blood urea nitrogen
WBC	White blood cell
SAPS II	Simplified acute physiology score ii
SIRS	Systemic inflammatory response syndrome

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SOFA	Sequential organ failure assessment
CHF	Congestive heart failure
CA	Cardiac arrhythmia
COPD	Chronic obstructive pulmonary disease
CKD	Chronic kidney disease
CLD	Chronic liver disease
AIDS	Acquired immune deficiency syndrome
RRT	Renal replacement therapy
MV	Mechanical ventilation
RCSRM	Restricted cubic spline regression model
RERI	Relative excess risk due to interaction
AP	Attributable proportion due to interaction
SI	Synergy index

With a high incidence rate, mortality, and morbidity, sepsis still poses a major challenge to intensive care units (ICUs)[1,2]. Phosphorus is a vital element for living organisms. It is mainly found in the form of phosphate in humans. Phosphate balance is crucial for maintaining bone health, energy metabolism, membrane stability, and cell signaling[3–5]. Bones and teeth store approximately 85% of calcium-binding phosphate, while tissue cells store approximately 14%. The remaining 1% is present in the extracellular fluid and serum. Only 30% of organic phosphates can be regulated and measured in clinical practice[3,4]. Phosphate is also crucial in extracellular fluid. Normal serum phosphate levels range from 2.5 mg/dL to 4.5 mg/dL[6]. The regulation of serum phosphate involves the respiratory, cardiovascular, urinary, neuromuscular, and immune systems. Various factors, such as extracellular phosphate transfer, dietary phosphate intake, tubular phosphate reabsorption, glomerular function, respiratory alkalosis, and serum insulin, influence serum phosphate levels[7]. Therefore, maintaining an appropriate phosphate concentration is crucial.

However, the role of phosphate in critically ill patients is often not given enough attention in clinical practice, which can result in phosphate disorders. Studies indicated that about approximately 20% of critically ill patients suffer from hypophosphatemia, while 45% suffer from hyperphosphatemia. These imbalances can significantly affect the outcome of critically ill patients, especially those who require mechanical ventilation (MV), leading to prolonged hospitalization and mechanical ventilation time[8].

The impact of imbalanced serum phosphate on the prognosis of septic patients has not been conclusively determined. First, although previous studies have shown that serum phosphate can predict sepsis prognosis and that elevated serum phosphate levels (within or outside the normal range) are associated with increased mortality[9,10], it is still controversial about whether hypophosphatemia is associated with increases the risk of adverse outcomes in septic patients[11,12]. Second, previous studies[9–12] mainly explored the association between the initial phosphate level and the outcomes of septic patients. Although Luo et al.[13] explored the association between septic patient outcomes and serum phosphate change, they overlooked the importance of the initial serum phosphate level. Xin Xu et al.[6] comprehensively evaluated the relationship between the serum phosphate levels in the first 2 days of ICU admission and the short-term mortality of septic patients, yet they neglected the significance of the trend in the variation of serum phosphate levels. Third, some of them have insufficient statistical power because of small sample sizes[11]. Hence we hypothesized that since both the level and changes of serum phosphate affect the prognosis of septic patients, the combined effect of the level and changes of serum phosphate has a more complicated impact on this population, and we aimed to verify this hypothesis by conducting a large cohort study.

Methods

This study was reported in accordance with the Strengthening Epidemiological Observation Research Report (STROBE) statement[14].

Data source

All the data were extracted from The Medical Information Mart for Intensive Care (MIMIC-III) using structured query languages. The MIMIC-III database includes comprehensive data on more than 60,000 ICU patients admitted to the Beth Israel Deacon Medical Center from 2001 to 2012[15]. The MIMIC III database was approved by the Beth Israel Deaconess Medical Center (Boston, MA, USA) and the Institutional Review Board (IRB) of the Massachusetts Institute of Technology (Cambridge, MA, US), and consent was obtained for the original data collection. Therefore, our institutional IRB approval, as well as the ethical approval statement and informed consent form for this manuscript, were waived.

Inclusion and exclusion criteria of the study population

Patients over 18 years old who were diagnosed with sepsis were eligible for inclusion. Sepsis was diagnosed according to the Sepsis-3 criteria[16]. In brief, patients with documented or suspected infections and an acute change in the total sequential organ failure assessment (SOFA) score of ≥ 2 points were considered to have sepsis. Infection status was determined based on the International Classification of Diseases (ICD-9) code in the MIMIC-III. We only analyzed the data of each patient's first admission to the ICU. Patients who stayed in the ICU for less than 72 h were excluded.

The outcome and exposure

In-hospital mortality was the main outcome of this study. In this study, the delta serum phosphate concentration during the first three days was collected, defined as the difference between the maximum and minimum serum

phosphate concentrations. If the time of the maximum value of serum phosphate was earlier than the minimum value, the delta serum phosphate was recorded as a negative value (decreasing in serum phosphate) or a positive value (increasing in serum phosphate) otherwise.

Covariates

Baseline demographic information (age, body mass index [BMI], sex, body temperature, ethnicity, admission type, service unit), laboratory tests (pH, oxygen saturation [SO_2], basic excess [BE], bicarbonate, calcium, potassium, sodium, chloride, albumin, bilirubin, creatinine, blood urinary nitrogen [BUN], blood glucose, lactate, platelet, white blood cell [WBC], hemoglobin), severity scores (Simplified Acute Physiology Score II [SAPS II], systemic inflammatory response syndrome [SIRS], SOFA), microbial cultivation, comorbidities (congestive heart failure [CHF], cardiac arrhythmia [CA], hypertension, paralysis, chronic obstructive pulmonary disease [COPD]; diabetes, malignancy, anemia, hypothyroidism, chronic kidney disease [CKD], chronic liver disease [CLD], peptic ulcer, acquired immune deficiency syndrome [AIDS], weight loss, drug abuse, alcohol abuse, psychoses) and interventions during the first 24 h (renal replacement treatment [RRT], MV, vasopressor). Given that patients accustomed to consuming protein-rich foods usually have higher serum phosphate levels[17], dietary habits may serve as a potential confounder, but there is no dietary habit data in MIMIC-III. Therefore, we included BMI and comorbidities such as alcohol abuse, weight loss, drug abuse, as those variables may indirectly mirror dietary habits. The clinical manifestations of some inherited diseases include hypophosphatemia or Hyperphosphatemia, but there is no genetic disease data in MIMIC-III. Therefore, we incorporated a set of comorbidities that could better characterize the physiological and pathological conditions of the patients to mitigate the confounding bias.

Statistical analysis

The datasets with the highest and lowest phosphate levels were analyzed and classified into several clusters using K-means clustering. K-means clustering is a technique that aims to divide N observations into K clusters. Each observation is assigned to the cluster with the closest mean value, which serves as the cluster prototype. The k-means clustering was selected because of its remarkable computational efficiency and its capacity to visualize the data points understandably, which can greatly facilitate the analysis and interpretation of the data[18,19].

Descriptive statistics (medians and interquartile ranges, IQRs, for continuous data, and percentages for categorical data) were used to report basic characteristics. Analysis of variance (ANOVA) or Kruskal-Wallis tests for continuous variables, as appropriate, and chi-squared tests for categorical variables were used to analyze differences in baseline characteristics between clusters. Univariable and multivariable logistic regression analyses were performed to elucidate the association between the clusters and in-hospital mortality and the association between the change in serum phosphate concentration and in-hospital mortality.

Sensitivity analysis

We conducted sensitivity analyses to evaluate the robustness of our findings.

As previous studies provide controversial evidence regarding the relationship between serum phosphate level and outcomes of septic patients, we hypothesized that this relationship is not simply a linear one. A restricted cubic spline regression model (RCSRM) with 3 knots at the 10th, 50th, and 90th was carried out to examine the shape of the correlation between phosphate change and mortality. RCSRM has found extensive application in clinical investigations aimed at exploring a continuous predictor's impact on an outcome. Its remarkable flexibility in characterizing the relationship between the predictor and the outcome is a significant advantage. Regardless of the nature of the outcome variable, in multiple linear regression, logistic regression, or survival analysis, RCSRM can be effectively employed. Moreover, the conventional techniques for making inferences regarding parameter estimates are equally applicable to RCSRM. Incorporating RCSRM offers a formal means by which to assess the presumption of a linear association between a predictor and the outcome through standard procedures. Neglect of nonlinearity, if it exists, might lead to an inaccurate estimation of the relationship, either in the form of overestimation or underestimation, or even a misidentified relationship. RCSRM proves highly effective in accurately modelling nonlinearity, thereby minimizing model misspecification and enhancing our understanding of the intricate relationship between the predictor and the outcome[20,21]. Subgroup analyses and interaction analyses were performed to discover potential impact factors. The relative excess risk due to interaction (RERI), the attributable proportion due to interaction (AP), and the synergy index (SI) were utilized to evaluate the additive interactions.

The effects of interaction analysis between phosphate clusters and covariates are reported as odds ratios (ORs) and 95% confidence intervals (CIs). Statistical analyses were performed using R software (version 4.2.3, http://www.R-project.org/). The standardized mean differences (SMDs) were calculated, and $P < 0.05$ was considered to indicate statistical significance.

Results

Selection, clusters, and baseline characteristics of the study participants

Among 61,532 admissions, we identified 22,232 patients with sepsis according to the Sepsis-3 criteria. After including the first ICU admissions of each patient and excluding patients who were younger than 18 years old, stayed in the ICU for less than 72 h and lacked serum phosphate measurements during the first 3 days, a cohort of 8586 patients was ultimately included in the present study (Fig. 1). The average age of the cohort was 66.81 (IQR, 54.29–78.59) years, and 55.5% were males. The median values of serum phosphate 1 and serum phosphate 2 were 3.7 mg/dL and 3.1 mg/dL, respectively (serum phosphate 1 and serum phosphate 2 were defined according to the time sequence in which the phosphate values were recorded), and the overall phosphate change was −0.8 (IQR −1.9–1.2).

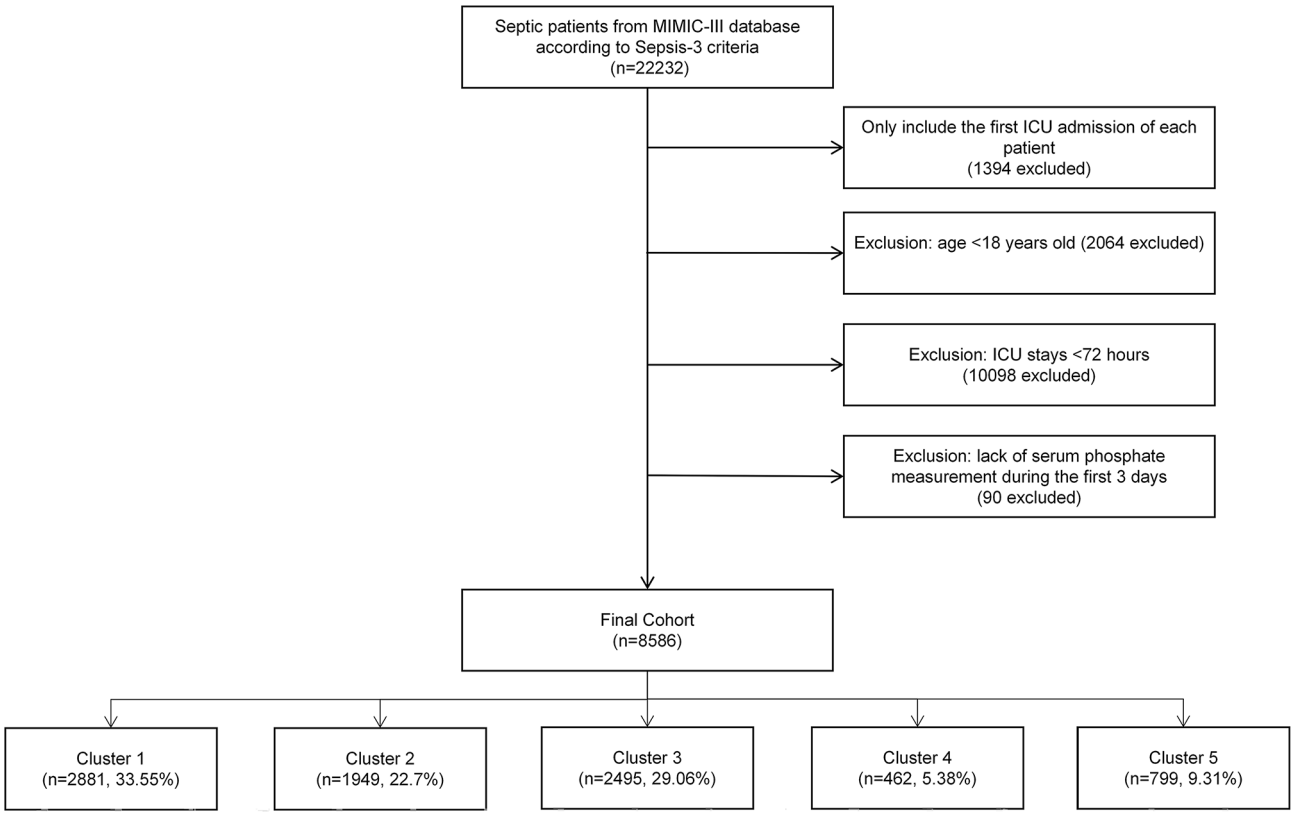

Fig. 1. Flowchart of the study population.

In the K-means clustering process, as the number of categorized clusters increased, the maximum number of clusters recruited was 5, each containing at least two data points. When the number of clusters was 5, the effect of k-means clustering was the best.

The changes in the serum phosphate concentration of each cluster are summarized as follows: in cluster 1, the phosphate concentration ranged from 3.6 mg/dL to 2.1 mg/dL; in cluster 2, the phosphate concentration ranged from 5.2 mg/dL to 3 mg/dL; in cluster 3, the phosphate concentration ranged from 2.4 mg/dL to 3.9 mg/dL; in cluster 4, the phosphate concentration ranged from 8.2 mg/dL to 4.3 mg/dL; and in cluster 5, the phosphate concentration ranged from 4.2 mg/dL to 6.7 mg/dL. A decreasing trend was shown in cluster 1, cluster 2, and cluster 4. An increasing trend was shown in cluster 3 and cluster 5. (Fig. 2).

Compared with those in cluster 1, participants in the other clusters were younger, had higher SAPS II and SOFA scores, were more likely to receive RRT and vasopressor treatment during the first 24 h, and were more likely to have a positive culture (Table 1).

Odds ratios for mortality

A total of 1810 (21.1%) participants died during their hospital stay (Table 2). Compared to cluster 1, the odds ratios for mortality were 1.542 (95% CI 1.331–1.786) for cluster 2, 1.334 (95% CI 1.159–1.536) for cluster 3, 2.242 (95% CI 1.788–2.801) for cluster 4, and 3.335 (95% CI 2.8-3.972) for cluster 5 (all $p < 0.001$).

After adjustment for baseline variables (model 2), cluster 2 (OR 1.303, 95% CI 1.101–1.542, $p = 0.002$), cluster 3 (OR 1.348, 95% CI 1.158–1.57, $p < 0.001$), cluster 4 (OR 1.652, 95% CI 1.225–2.222, $p = 0.001$) and cluster 5 (OR 2.745, 95% CI 2.212–3.407, $p < 0.001$) remained associated with significantly increased risks of death.

According to the RCSRMs, the correlation between the change in serum phosphate concentration and the risk of death was linear (Fig. 3). In Cluster 3 and Cluster 5 where the serum phosphate showed an increasing trend, the odds ratios rose as the serum phosphate change increased. Conversely, in Cluster 2 and Cluster 4 with decreasing serum phosphate, the odds ratios rose as the serum phosphate change decreased (Figs. 2 and 3).

The risk of death increased with each increase in the phosphate concentration change above 0.961 (OR 1.469, 95% CI 1.3-1.659, $p < 0.001$) and −3.692 (OR 2.537, 95% CI 1.461–4.475, $p = 0.001$) in the whole cohort and cluster 4, respectively (Table 3).

Subgroup analyses

We performed subgroup analyses to stratify the relevance between changes in serum phosphate concentration and in-hospital mortality, as shown in (Table 4). The ORs of the female subgroup were lower than those of the male subgroup across all clusters, and the ORs of the MV subgroup were lower than those of the non-MV subgroup across all clusters.

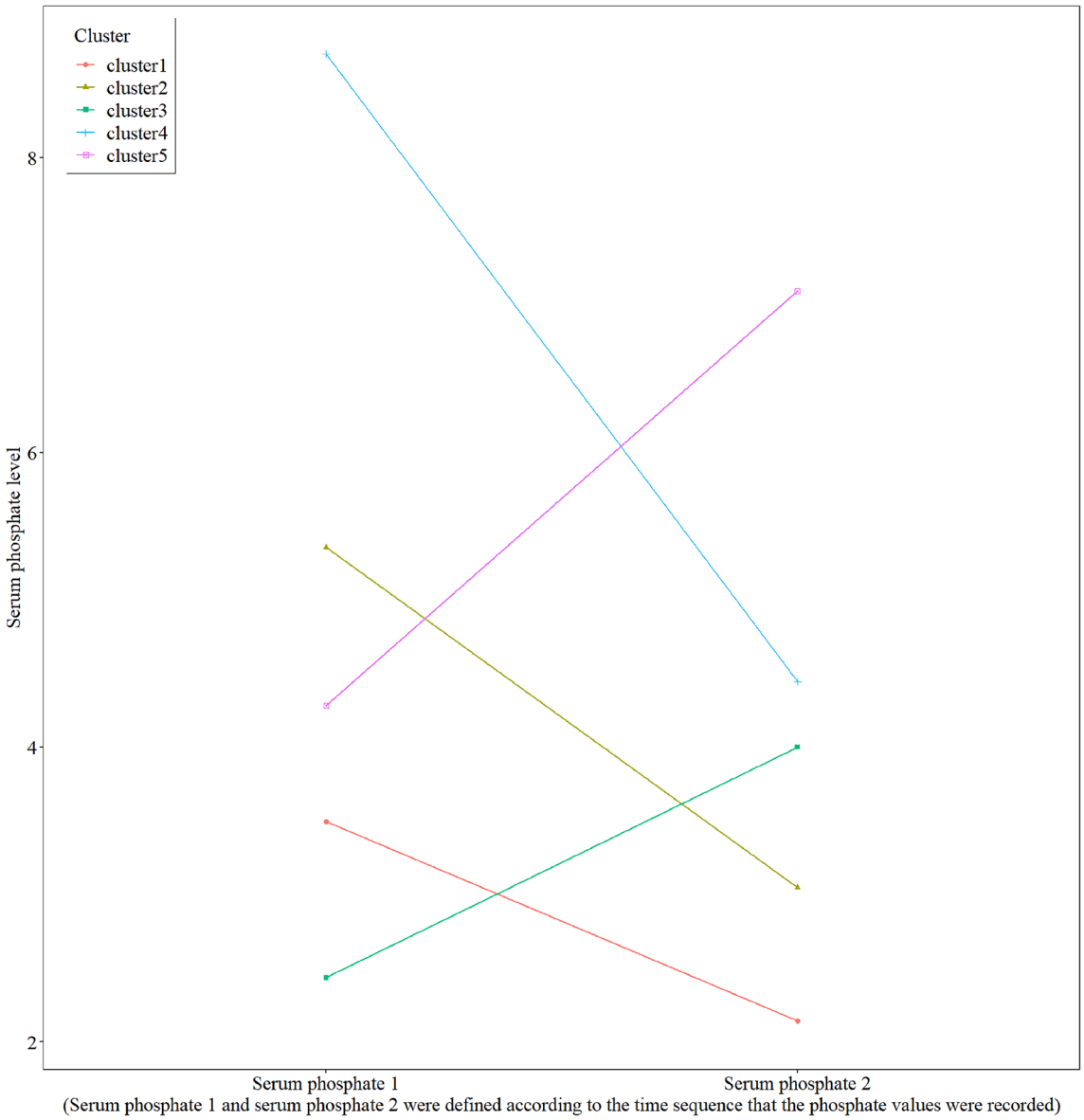

Fig. 2. The trend of serum phosphate concentration in each cluster.

Multiplicative and additive interactions were detected between phosphate clusters and mechanical ventilation (Table 5). The SI of BMI in the additive interaction analysis was null because of meaningless statistical value.

Discussion

We found in the present study that both higher and incremental serum phosphate levels were associated with increased in-hospital mortality in septic patients.

Previous studies focusing on baseline serum phosphate have proven the importance of maintaining a balance of serum phosphate since both hypophosphatemia and hyperphosphatemia are associated with poor prognosis[6,10]. Hayward et al. reported increased mortality and longer hospital stays in patients with hyperphosphatemia than in those with normal or low phosphate levels. In contrast, no similar results were observed in patients with hypophosphatemia[22]. Padelli et al. found a significant association between hypophosphatemia and a greater 90-day mortality rate in critically ill patients with bloodstream infection[23].

However, as most septic patients develop early internal environmental disturbances, resulting in fluctuations in serum ion concentrations, a single measurement may not fully reflect a patient's condition. For example, we observed an interesting phenomenon in which cluster 4 had higher serum phosphate 1 and mean phosphate levels than did cluster 5; however, cluster 4 had a lower risk of death, which may be explained by the decreasing trend in cluster 4 and the increasing trend in cluster 5. A similar phenomenon can be found between cluster 2 and cluster 3. Therefore, an increasing number of researchers have become aware of the significance of change trends in serum phosphate. It was suggested that even minor change trends within the normal range may increase the risk of mortality in sepsis patients[10]. Xu X et al. reported a greater mortality rate in patients

	Total	Cluster 1	Cluster 2	Cluster 3	Cluster 4	Cluster 5	*P* value	SMD
N	8586	2881	1949	2495	462	799		
Age (years)	66.81 (54.29, 78.59)	67.91 (55.52, 79.78)	67.44 (54.94, 78.81)	65.89 (52.48, 78.11)	63.53 (52.24, 74.83)	65.90 (53.87, 77.23)	< 0.001	0.106
BMI (kg/m^2)	27.29 (23.49, 32.15)	26.87 (23.09, 31.31)	27.99 (23.97, 33.18)	27.06 (23.47, 31.90)	27.55 (23.80, 33.50)	27.65 (24.06, 32.41)	0.346	0.05
Male (%)	4767 (55.5)	1583 (54.9)	1065 (54.6)	1340 (53.7)	290 (62.8)	489 (61.2)	< 0.001	0.1
Body temperature (℃)	37.05 (36.50, 37.70)	37.13 (36.60, 37.75)	36.98 (36.47, 37.47)	37.15 (36.60, 37.80)	36.76 (36.21, 37.40)	37.00 (36.42, 37.67)	< 0.001	0.18
Ethnicity (%)							< 0.001	0.16
Asian	214 (2.5)	84 (2.9)	33 (1.7)	60 (2.4)	9 (1.9)	28 (3.5)		
Black	839 (9.8)	207 (7.2)	201 (10.3)	258 (10.3)	71 (15.4)	102 (12.8)		
Other/unknown	1028 (12.0)	326 (11.3)	229 (11.7)	307 (12.3)	49 (10.6)	117 (14.6)		
White	6505 (75.8)	2264 (78.6)	1486 (76.2)	1870 (74.9)	333 (72.1)	552 (69.1)		
Admission type (%)							< 0.001	0.131
Elective	684 (8.0)	261 (9.1)	170 (8.7)	190 (7.6)	15 (3.2)	48 (6.0)		
Emergency	7740 (90.1)	2580 (89.6)	1735 (89.0)	2250 (90.2)	440 (95.2)	735 (92.0)		
Urgent	162 (1.9)	40 (1.4)	44 (2.3)	55 (2.2)	7 (1.5)	16 (2.0)		
Service unit (%)							< 0.001	0.208
CCU	974 (11.3)	262 (9.1)	279 (14.3)	255 (10.2)	66 (14.3)	112 (14.0)		
CSRU	890 (10.4)	283 (9.8)	193 (9.9)	288 (11.5)	33 (7.1)	93 (11.6)		
MICU	4417 (51.4)	1424 (49.4)	955 (49.0)	1354 (54.3)	256 (55.4)	428 (53.6)		
SICU	1436 (16.7)	520 (18.0)	322 (16.5)	393 (15.8)	77 (16.7)	124 (15.5)		
TSICU	869 (10.1)	392 (13.6)	200 (10.3)	205 (8.2)	30 (6.5)	42 (5.3)		
Laboratory tests								
pH	7.37 (7.32, 7.42)	7.38 (7.34, 7.42)	7.35 (7.30, 7.40)	7.39 (7.34, 7.44)	7.31 (7.25, 7.37)	7.36 (7.30, 7.41)	< 0.001	0.48
SO_2 (%)	97.00 (94.67, 98.00)	97.00 (95.00, 98.00)	96.73 (94.00, 98.00)	97.00 (94.50, 98.00)	96.00 (93.50, 98.00)	97.00 (95.00, 98.00)	< 0.001	0.102
BE (mmol/L)	−1.00 (−4.00, 1.50)	−0.44 (−3.00, 1.50)	−1.50 (−5.00, 1.00)	−0.14 (−3.04, 2.50)	−5.00 (−8.75, −1.42)	−2.50 (−6.00, 0.66)	< 0.001	0.459
Bicarbonate (mmol/L)	22.00 (18.00, 25.00)	22.00 (19.00, 25.00)	21.00 (17.00, 24.00)	22.00 (19.00, 25.00)	17.00 (14.00, 21.00)	20.00 (16.00, 23.50)	< 0.001	0.441
Calcium (mmol/L)	1.11 (1.06, 1.16)	1.12 (1.07, 1.16)	1.11 (1.06, 1.16)	1.11 (1.07, 1.16)	1.09 (1.02, 1.15)	1.11 (1.05, 1.16)	0.018	0.087
Potassium (mmol/L)	4.60 (4.10, 5.20)	4.40 (4.10, 4.90)	4.80 (4.40, 5.40)	4.40 (4.00, 4.90)	5.40 (4.70, 6.20)	4.90 (4.40, 5.60)	< 0.001	0.495
Sodium (mmol/L)	140.00 (138.00, 143.00)	141.00 (138.00, 143.00)	140.00 (138.00, 143.00)	141.00 (138.00, 143.00)	140.00 (137.00, 143.00)	140.00 (136.00, 142.00)	< 0.001	0.12
Chloride (mmol/L)	107.00 (103.00, 112.00)	108.00 (104.00, 112.00)	107.00 (102.00, 111.00)	108.00 (103.00, 112.00)	105.00 (100.00, 110.00)	106.00 (101.00, 110.00)	< 0.001	0.223
Albumin (g/dL)	3.00 (2.50, 3.40)	3.00 (2.60, 3.50)	3.00 (2.50, 3.40)	2.90 (2.50, 3.40)	2.90 (2.50, 3.30)	2.90 (2.40, 3.30)	< 0.001	0.128
Bilirubin (mg/dL)	0.70 (0.40, 1.40)	0.70 (0.40, 1.20)	0.70 (0.40, 1.50)	0.70 (0.40, 1.45)	0.80 (0.40, 1.87)	0.80 (0.40, 2.10)	< 0.001	0.185
Creatinine (mg/dL)	1.30 (0.90, 2.30)	1.00 (0.80, 1.40)	1.70 (1.10, 2.70)	1.20 (0.80, 1.80)	4.30 (2.70, 6.70)	2.80 (1.70, 4.40)	< 0.001	0.895
BUN (mg/dL)	28.00 (18.00, 47.00)	22.00 (15.00, 32.00)	36.00 (23.00, 57.00)	23.00 (16.00, 36.00)	68.00 (46.00, 100.75)	49.00 (32.50, 72.00)	< 0.001	0.856
Blood glucose (mg/dL)	166.00 (131.00, 217.00)	161.00 (131.00, 205.00)	173.00 (135.00, 227.00)	163.00 (128.00, 212.00)	177.50 (132.00, 242.50)	172.00 (135.00, 226.00)	< 0.001	0.136
Lactate (mmol/L)	2.30 (1.50, 3.80)	2.20 (1.50, 3.40)	2.40 (1.60, 4.10)	2.20 (1.50, 3.50)	3.00 (1.70, 6.27)	2.50 (1.60, 4.40)	< 0.001	0.279
Platelet (×10^9/L)	179.00 (116.00, 255.00)	184.00 (125.00, 257.00)	187.00 (116.00, 267.00)	174.00 (116.00, 245.00)	171.00 (105.25, 263.00)	156.00 (84.50, 236.50)	< 0.001	0.111
WBC (×10^9/L)	13.90 (9.80, 19.30)	13.70 (9.90, 18.60)	14.80 (10.40, 20.60)	13.30 (9.15, 18.50)	14.85 (10.60, 20.88)	13.90 (9.60, 20.00)	< 0.001	0.098
Hemoglobin (g/dL)	9.50 (8.30, 11.00)	9.90 (8.60, 11.40)	9.40 (8.20, 10.90)	9.60 (8.40, 10.90)	9.00 (7.90, 10.20)	8.90 (7.80, 10.30)	< 0.001	0.239
Severity scores								
SAPS II	42.00 (34.00, 52.00)	39.00 (31.00, 48.00)	45.00 (37.00, 55.00)	40.00 (31.00, 49.00)	52.00 (41.00, 62.00)	48.00 (39.00, 58.00)	< 0.001	0.475
SIRS	3.00 (3.00, 4.00)	3.00 (3.00, 4.00)	3.00 (3.00, 4.00)	3.00 (3.00, 4.00)	3.00 (3.00, 4.00)	3.00 (3.00, 4.00)	0.503	0.038
SOFA	6.00 (4.00, 8.00)	5.00 (3.00, 7.00)	6.00 (4.00, 9.00)	5.00 (4.00, 8.00)	9.00 (6.00, 11.00)	8.00 (5.00, 10.00)	< 0.001	0.579
Positive cultivation (%)	3451 (40.2)	1075 (37.3)	831 (42.6)	1018 (40.8)	182 (39.4)	345 (43.2)	0.001	0.061
Comorbidities (%)								
CHF	2394 (27.9)	705 (24.5)	612 (31.4)	661 (26.5)	150 (32.5)	266 (33.3)	< 0.001	0.104
CA	2310 (26.9)	784 (27.2)	549 (28.2)	636 (25.5)	129 (27.9)	212 (26.5)	0.336	0.03
Hypertension	1501 (17.5)	272 (9.4)	396 (20.3)	389 (15.6)	158 (34.2)	286 (35.8)	< 0.001	0.353

Continued

	Total	Cluster 1	Cluster 2	Cluster 3	Cluster 4	Cluster 5	*P* value	SMD
Paralysis	371 (4.3)	156 (5.4)	64 (3.3)	113 (4.5)	15 (3.2)	23 (2.9)	0.001	0.064
COPD	2004 (23.3)	666 (23.1)	505 (25.9)	557 (22.3)	113 (24.5)	163 (20.4)	0.012	0.062
Diabetes	2613 (30.4)	724 (25.1)	658 (33.8)	762 (30.5)	176 (38.1)	293 (36.7)	< 0.001	0.138
Malignancy	809 (9.4)	309 (10.7)	186 (9.5)	202 (8.1)	43 (9.3)	69 (8.6)	0.022	0.042
Anemia	2474 (28.8)	765 (26.6)	563 (28.9)	730 (29.3)	156 (33.8)	260 (32.5)	0.001	0.079
Hypothyroidism	1043 (12.1)	383 (13.3)	254 (13.0)	282 (11.3)	47 (10.2)	77 (9.6)	0.011	0.064
CKD	1840 (21.4)	316 (11.0)	499 (25.6)	476 (19.1)	201 (43.5)	348 (43.6)	< 0.001	0.42
CLD	824 (9.6)	208 (7.2)	214 (11.0)	231 (9.3)	64 (13.9)	107 (13.4)	< 0.001	0.113
Peptic ulcer	9 (0.1)	1 (0.0)	2 (0.1)	6 (0.2)	0 (0.0)	0 (0.0)	0.133	0.04
AIDS	56 (0.7)	14 (0.5)	10 (0.5)	22 (0.9)	6 (1.3)	4 (0.5)	0.131	0.044
Weight loss	646 (7.5)	208 (7.2)	143 (7.3)	197 (7.9)	27 (5.8)	71 (8.9)	0.289	0.052
Drug abuse	326 (3.8)	99 (3.4)	82 (4.2)	97 (3.9)	22 (4.8)	26 (3.3)	0.433	0.039
Alcohol abuse	694 (8.1)	247 (8.6)	148 (7.6)	205 (8.2)	32 (6.9)	62 (7.8)	0.633	0.029
Psychoses	401 (4.7)	135 (4.7)	83 (4.3)	141 (5.7)	18 (3.9)	24 (3.0)	0.019	0.06
Interventions								
RRT (1st 24 h) (%)	132 (1.5)	11 (0.4)	53 (2.7)	15 (0.6)	40 (8.7)	13 (1.6)	< 0.001	0.206
MV (1st 24 h) (%)	5710 (66.5)	1908 (66.2)	1367 (70.1)	1616 (64.8)	300 (64.9)	519 (65.0)	0.003	0.051
Vasopressor (1st 24 h) (%)	3742 (43.6)	1136 (39.4)	957 (49.1)	1015 (40.7)	262 (56.7)	372 (46.6)	< 0.001	0.174
Vasopressor duration (hours)	62.50 (18.50, 172.00)	53.25 (16.83, 140.40)	65.20 (19.33, 185.50)	59.75 (17.26, 163.18)	84.75 (25.60, 226.02)	88.00 (29.62, 253.29)	< 0.001	0.102
Phosphate1 (mg/dL)	3.70 (2.80, 4.80)	3.60 (3.10, 4.00)	5.20 (4.70, 5.90)	2.40 (1.80, 3.10)	8.20 (7.50, 9.40)	4.20 (3.40, 5.00)	< 0.001	2.423
Phosphate2 (mg/dL)	3.10 (2.30, 4.30)	2.10 (1.80, 2.50)	3.00 (2.40, 3.60)	3.90 (3.40, 4.60)	4.30 (3.40, 5.40)	6.70 (5.90, 7.80)	< 0.001	1.901
Mean serum phosphate level	3.38 (2.80, 4.21)	2.84 (2.47, 3.14)	4.03 (3.65, 4.53)	3.22 (2.70, 3.75)	6.14 (5.49, 6.96)	5.34 (4.82, 6.10)	< 0.001	2.007
Phosphate change (mg/dL)	−0.80 (−1.90, 1.20)	−1.30 (−1.90, −0.80)	−2.20 (−3.20, −1.40)	1.40 (0.90, 2.10)	−4.00 (−5.70, −2.40)	2.40 (1.55, 3.70)	< 0.001	2.319
Phosphate change quartile (%)							< 0.001	4.29
1	2181 (25.4)	660 (22.9)	1131 (58.0)	0	390 (84.4)	0		
2	2138 (24.9)	1483 (51.5)	590 (30.3)	0	65 (14.1)	0		
3	2161 (25.2)	738 (25.6)	228 (11.7)	1055 (42.3)	6 (1.3)	134 (16.8)		
4	2106 (24.5)	0	0	1440 (57.7)	1 (0.2)	665 (83.2)		

Table 1. Characteristics of included patients according to the clusters of serum phosphate levels. Phosphate1 and phosphate2 were defined according to the time sequence that the phosphate values were recorded. Data are presented as medians (interquartile range) or n (%). *SMD* standardized mean differences, *BMI* body mass index, *CCU* coronary care unit, *CSRU* cardiac surgery unit, *MICU* medical intensive care, *SICU* surgical intensive care unit, *TSICU* trauma surgical intensive care unit, SO_2 oxygen saturation, *BE* basic excess, *BUN* blood urea nitrogen, *WBC* white blood cell, *SAPS II* simplified acute physiology score II, *SIRS* systemic inflammatory response syndrome, *SOFA* sequential organ failure assessment, *CHF* congestive heart failure, *CA* cardiac arrhythmia, *COPD* chronic obstructive pulmonary disease, *CKD* chronic kidney disease, *CLD* chronic liver disease, *AIDS* acquired immune deficiency syndrome, *RRT* renal replacement therapy, *MV* mechanical ventilation.

with fluctuating serum phosphate levels than in those with stable levels[6]. Similarly, Kim et al. demonstrated the relationship between greater change trends in serum phosphate levels and increased in-hospital mortality[24]. In addition, Nan et al. reported a nonlinear relationship between serum phosphate changes and mortality among septic patients, similar to our results[25]. However, they defined phosphate change in their study as the difference between the first and last serum phosphate measurements during ICU stays, which may not reflect the true phosphate change trends and the true relationship between serum phosphate change and mortality in septic patients because some patients may start and end up with similar serum phosphate levels while fluctuating violently during their ICU stays. To overcome this shortcoming, we innovatively used the difference between the highest and lowest phosphate levels in the first three days after ICU admission to reflect change trends in the serum phosphate concentration. A recent study also used this strategy; they divided their study population into four groups according to the quartile of the serum phosphate change, and they observed that a change in the serum phosphate concentration ≥ 3.2 mg/dL was associated with increased 28-day mortality and in-hospital mortality in septic patients[13]. However, simply using quantity differences may not accurately classify patients. For example, patients in cluster 3 and cluster 5 all showed an increasing trend in serum phosphate and had similar distributions among the quartiles of the serum phosphate change, so some patients in these two clusters may be mixed into the same group if we simply used the quartiles of the serum phosphate change to group the included patients. Therefore, we innovatively used K-means clustering to capture the true characteristics of our study population and make a more accurate classification.

	Case (%)	Crude		Model 1		Model 2	
		OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Total	1810 (21.1%)	–	–	–	–	–	–
Cluster1	448 (15.6%)	Ref	Ref	Ref	Ref	Ref	Ref
Cluster2	431 (22.1%)	1.542 (1.331, 1.786)	< 0.001	1.561 (1.346, 1.809)	< 0.001	1.303 (1.101, 1.542)	0.002
Cluster3	492 (19.7%)	1.334 (1.159, 1.536)	< 0.001	1.383 (1.2, 1.594)	< 0.001	1.348 (1.158, 1.57)	< 0.001
Cluster4	135 (29.2%)	2.242 (1.788, 2.801)	< 0.001	2.417 (1.923, 3.027)	< 0.001	1.652 (1.225, 2.222)	0.001
Cluster5	304 (38%)	3.335 (2.8, 3.972)	< 0.001	3.481 (2.917, 4.153)	< 0.001	2.745 (2.212, 3.407)	< 0.001

Table 2. Logistic regression analysis for the association between different clusters and in-hospital mortality. Mode 1, adjusted for sex and age; Model 2, adjusted for age, BMI, sex, body temperature, ethnicity, admission type, service unit, pH, SO2, BE, bicarbonate, calcium, potassium, sodium, chloride, albumin, bilirubin, creatinine, BUN, blood glucose, lactate, platelet, WBC, hemoglobin, SAPS II, SIRS, SOFA, microbial cultivation, CHF, CA, hypertension, paralysis, COPD, diabetes, malignancy, anemia, hypothyroidism, CKD, CLD, peptic ulcer, AIDS, weight loss, drug abuse, alcohol abuse, psychoses and interventions during the first 24 h (RRT, MV, vasopressor). *BMI* body mass index, *CCU* coronary care unit, *CSRU* cardiac surgery unit, *MICU* medical intensive care, *SICU* surgical intensive care unit, *TSICU* trauma surgical intensive care unit, *BE* basic excess, SO_2 oxygen saturation, *BUN* blood urea nitrogen, *WBC* white blood cell, *SAPS II* simplified acute physiology score II, *SIRS* systemic inflammatory response syndrome, *SOFA* sequential organ failure assessment, *CHF* congestive heart failure, *CA* cardiac arrhythmia, *COPD* chronic obstructive pulmonary disease, *CKD* chronic kidney disease, *CLD* chronic liver disease, *AIDS* acquired immune deficiency syndrome, *RRT* renal replacement therapy, *MV* mechanical ventilation.

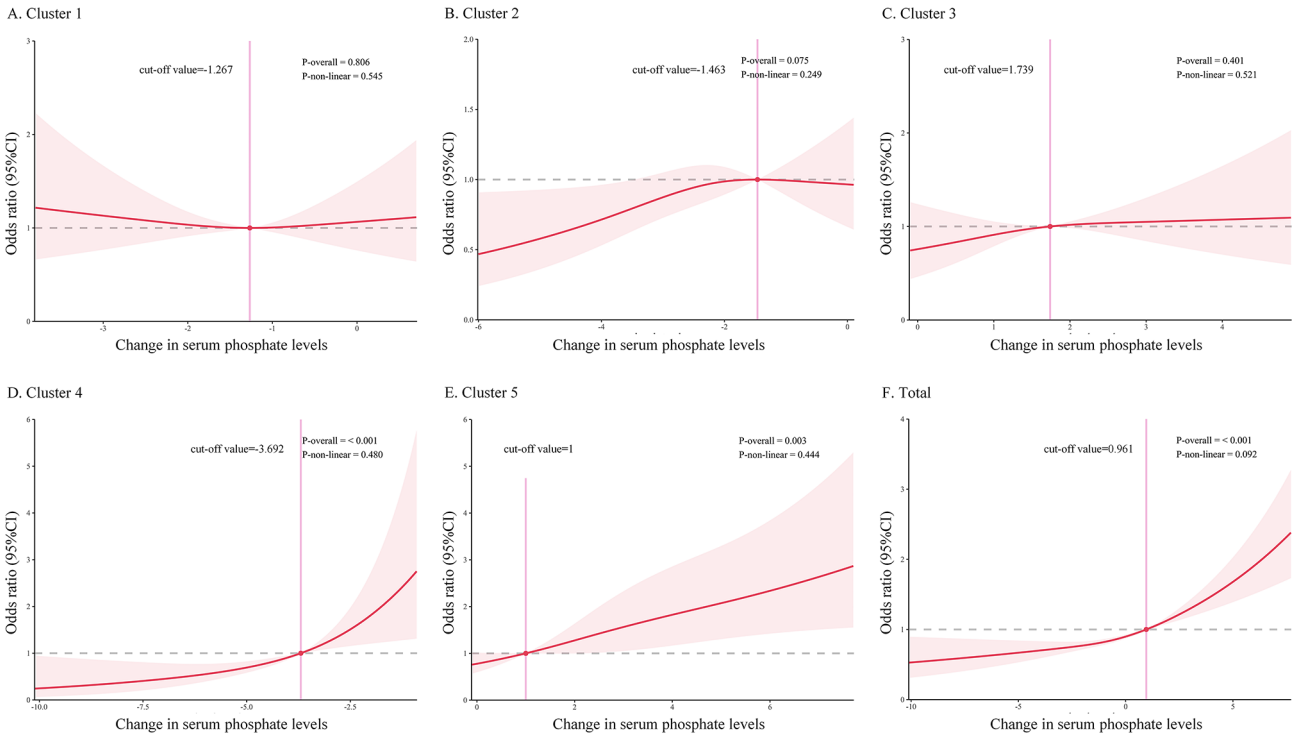

Fig. 3. Cubic model of the correlation between the change in serum phosphate concentration and in-hospital mortality after adjusting for baseline variables.

The logistic regressions in our study demonstrated a significant relationship between in-hospital mortality and the clusters, and we observed higher mortality in cluster 2, cluster 3, cluster 4, and cluster 5, patients of which had higher and more unstable serum phosphate levels than those of cluster 1, suggesting that maintaining a lower and stable serum phosphate level is crucial for surviving sepsis. For instance, testing serum phosphate dynamically and treating patients with abnormal results promptly may improve the outcome of patients with sepsis.

	OR (95% CI)	*P* value
Total	1.469 (1.3, 1.659)	< 0.001
Cluster1	1.114 (0.884, 1.404)	0.359
Cluster2	1.082 (0.807, 1.445)	0.596
Cluster3	1.181 (0.932, 1.495)	0.167
Cluster4	2.537 (1.461, 4.475)	0.001
Cluster5	1.209 (0.661, 2.25)	0.542

Table 3. Logistic regression analysis for the association between the change in serum phosphate levels and in-hospital mortality according to cut-off values from the restricted cubic spline regression models. Adjusted for age, BMI, sex, body temperature, ethnicity, admission type, service unit, pH, SO_2, BE, bicarbonate, calcium, potassium, sodium, chloride, albumin, bilirubin, creatinine, BUN, blood glucose, lactate, platelet, WBC, hemoglobin, SAPS II, SIRS, SOFA, microbial cultivation, CHF, CA, hypertension, paralysis, COPD, diabetes, malignancy, anemia, hypothyroidism, CKD, CLD, peptic ulcer, AIDS, weight loss, drug abuse, alcohol abuse, psychoses and interventions during the first 24 h (RRT, MV, vasopressor). *BMI* body mass index, *CCU* coronary care unit, *CSRU* cardiac surgery unit, *MICU* medical intensive care, *SICU* surgical intensive care unit, *TSICU* trauma surgical intensive care unit, *BE* basic excess, SO_2 oxygen saturation, *BUN* blood urea nitrogen, *WBC* white blood cell, *SAPS II* simplified acute physiology score II, *SIRS* systemic inflammatory response syndrome, *SOFA* sequential organ failure assessment, *CHF* congestive heart failure, *CA* cardiac arrhythmia, *COPD* chronic obstructive pulmonary disease, *CKD* chronic kidney disease, *CLD* chronic liver disease, *AIDS* acquired immune deficiency syndrome, *RRT* renal replacement therapy, *MV* mechanical ventilation.

	Case/total	Cluster2, OR (95% CI)	Cluster3, OR (95% CI)	Cluster4, OR (95% CI)	Cluster5, OR (95% CI)
Age, years					
≥ 60	1298/5567	1.31 (1.074, 1.597)	1.409 (1.178, 1.687)	1.522 (1.05, 2.195)	2.742 (2.112, 3.561)
<60	512/3019	1.211 (0.873, 1.678)	1.163 (0.866, 1.563)	1.579 (0.925, 2.671)	2.504 (1.684, 3.723)
Sex					
Male	1007/4767	1.362 (1.078, 1.719)	1.471 (1.192, 1.817)	1.896 (1.279, 2.799)	3.001 (2.245, 4.013)
Female	803/3819	1.246 (0.972, 1.598)	1.229 (0.983, 1.538)	1.373 (0.849, 2.195)	2.541 (1.818, 3.549)
BMI, kg/m^2					
≥ 24	1240/6178	1.276 (1.039, 1.566)	1.29 (1.069, 1.557)	1.653 (1.155, 2.356)	2.795 (2.163, 3.612)
> 24	570/2408	1.39 (1.021, 1.891)	1.487 (1.139, 1.943)	1.568 (0.89, 2.723)	2.713 (1.772, 4.151)
Cultivation					
Positive	822/3451	1.409 (1.091, 1.819)	1.28 (1.012, 1.618)	1.695 (1.066, 2.677)	2.707 (1.953, 3.754)
Negative	988/5135	1.229 (0.977, 1.544)	1.414 (1.154, 1.733)	1.613 (1.08, 2.396)	2.957 (2.204, 3.965)
CKD					
Yes	440/1840	1.239 (0.825, 1.872)	1.29 (0.87, 1.928)	1.589 (0.917, 2.759)	2.192 (1.42, 3.407)
No	1370/6746	1.312 (1.086, 1.583)	1.353 (1.146, 1.598)	1.501 (1.026, 2.181)	3.113 (2.392, 4.048)
MV					
Yes	1227/5710	1.173 (0.958, 1.435)	1.147 (0.95, 1.384)	1.361 (0.948, 1.947)	2.196 (1.676, 2.876)
No	583/2876	1.667 (1.212, 2.292)	1.882 (1.436, 2.473)	2.67 (1.537, 4.591)	4.604 (3.148, 6.75)

Table 4. Subgroup logistic regressions of different clusters and in-hospital mortality. Each subgroup analysis was adjusted (except for the subgroup variable) for age, BMI, sex, body temperature, ethnicity, admission type, service unit, pH, SO_2, BE, bicarbonate, calcium, potassium, sodium, chloride, albumin, bilirubin, creatinine, BUN, blood glucose, lactate, platelet, WBC, hemoglobin, SAPS II, SIRS, SOFA, microbial cultivation, CHF, CA, hypertension, paralysis, COPD, s diabetes, malignancy, anemia, hypothyroidism, CKD, CLD, peptic ulcer, AIDS, weight loss, drug abuse, alcohol abuse, psychoses and interventions (RRT, MV, vasopressor) during the first 24 h. *BMI* body mass index, *CKD* chronic kidney disease, *MV* mechanical ventilation. *BMI* body mass index, *CCU* coronary care unit, *CSRU* cardiac surgery unit, *MICU* medical intensive care, *SICU* surgical intensive care unit, *TSICU* trauma surgical intensive care unit, *BE* basic excess, SO_2 oxygen saturation, *BUN* blood urea nitrogen, *WBC* white blood cell, *SAPS II* simplified acute physiology score II, *SIRS* systemic inflammatory response syndrome, *SOFA* sequential organ failure assessment, *CHF* congestive heart failure, *CA* cardiac arrhythmia, *COPD* chronic obstructive pulmonary disease, *CKD* chronic kidney disease, *CLD* chronic liver disease, *AIDS* acquired immune deficiency syndrome, *RRT* renal replacement therapy, *MV* mechanical ventilation.

Variables	Multiplicative interaction	Additive interaction		
		RERI	AP	SI
Age, years	1.003 (0.912, 1.104)	0.05 (−0.098, 0.163)	0.034 (−0.021, 0.114)	1.118 (0.902, 1.385)
Sex	1.056 (0.966, 1.154)	0.032 (−0.07, 0.088)	0.029 (−0.022, 0.113)	1.451 (0.273, 7.709)
Cultivation	0.955 (0.874, 1.043)	−0.032 (−0.156, 0.031)	−0.024 (−0.072, 0.044)	0.915 (0.781, 1.072)
BMI, kg/m^2	1.012 (0.919, 1.114)	−0.042 (−0.163, 0.013)	−0.043 (−0.108, 0.062)	NA (NA, NA)
CKD	1.011 (0.914, 1.119)	0.1 (−0.101, 0.314)	0.059 (−0.025, 0.149)	1.172 (0.958, 1.435)
MV	0.838 (0.763, 0.92)	−0.134 (−0.319, −0.026)	−0.074 (−0.13, −0.017)	0.858 (0.78, 0.943)

Table 5. Interaction analysis of subgroup variables and serum phosphate clusters. *BMI* body mass index, *CKD* chronic kidney disease, *MV* mechanical ventilation, *RERI* relative excess risk due to interaction, *AP* attributable proportion due to interaction, *SI* synergy index.

In addition, according to the lower odds ratios and mortalities in cluster 2 and cluster 4 than in cluster 3 and cluster 5, respectively, we speculated that for those with high serum phosphate levels in the early stage of the ICU stay, a decreasing trend in the serum phosphate level may be associated with a better prognosis than an increasing trend. As shown in the RCSRMs, the relationship between in-hospital mortality and the change in serum phosphate, combined with the change trends of each cluster, indicated that the mortality increased with the increasing serum phosphate change in cluster 3 and cluster 5. Conversely, the mortality increased with the decreasing serum phosphate change in cluster 2 and cluster 4. These results may provide supportive evidence for treatments for lowering serum phosphate in patients with hyperphosphatemia. For those with hypophosphatemia, although phosphorus supplementation is recommended[26], correcting hypophosphatemia at a slow pace and testing serum phosphate dynamically to avoid overcorrection may be safer.

The role of change trends in serum phosphate in the progression of sepsis is complicated and still unclear. On the one hand, cellular damage and ischemic injury caused by sepsis increase phosphate release, leading to an elevated serum phosphate level[27]. On the other hand, elevated phosphate has been demonstrated to be associated with reduced muscle strength[28], vascular calcification[29], cardiovascular disease[30], and the toxic effects of phosphate[31]. Higher serum phosphate may increase the risk of microcirculatory dysfunction and cardiovascular disease via oxidative stress, endothelial dysfunction, inflammatory responses, and vascular calcification[30]. In the present study, vasopressor treatment for patients in cluster 2, cluster 3, cluster 4, and cluster 5 lasted longer, in which vascular morbidities of elevated serum phosphate may play a role. Furthermore, elevated phosphate impairs mitochondrial function, leading to increased production of reactive oxygen species, reduced endothelial nitric oxide synthase phosphorylation, and decreased nitric oxide production. Therefore, there may be reciprocal causation between change trends in serum phosphate and sepsis progression. Further research on the underlying mechanism is needed to validate this hypothesis.

According to the subgroup analyses, fluctuating serum phosphate may affect MV and non-MV patients differently. A study including only patients receiving mechanical ventilation showed that elevated maximum–minimum phosphate values and phosphate arithmetic averages were associated with increased mortality[24]. However, there is limited evidence about the different effects of serum phosphate on patients receiving different respiratory therapies, which deserves proper attention in further research. Mandy et al. reported that females may incur more risk from oral phosphate[32]. Lan et al. reported that higher serum phosphate was associated with an increased risk of developing diabetes mellitus in women[33]. Therefore, we speculated that fluctuating serum phosphate levels may exert different effects on male and female patients. Our results showed that the ORs of the female subgroup were lower than those of the male subgroup across all clusters, although no interaction was found between phosphate clusters and sex, and the sample size may account for this. Hence, a prospective cohort study with a larger sample size is needed to explore the interaction between fluctuating serum phosphate levels and sex.

The strength of our study lies in the statistical efficiency of large data from the MIMIC-III database and comprehensive analyses based on the accurate classification of patients with different characteristics of serum phosphate. The main novelty of this research lies in focusing on the dynamic processes of serum phosphate levels using the approach of K-means clustring and providing additional evidence for the association between serum phosphate levels and in-hospital mortality. Although we have made some improvements on the basis of previous studies, this study still has several limitations. First, some confounding factors were not included in the present study because of the limitations of the database. Although we have included some relevant covariates to minimize the confounding bias, the extrapolation of our findings might be restricted and the estimation of the correlation between the dynamic change trend of serum phosphate level and the outcome of septic patients might be inaccurate. Therefore, a set of customized confounding factors is needed in a prospective cohort study. Second, as an observational single-center retrospective cohort study, the generalizability may be limited. Therefore, we propose to conduct a multi-center prospective cohort study to verify our findings. In addition, a randomized controlled trial has also been put on the agenda to verify whether lowering serum phosphate concentration in septic patients with elevated initial levels can improve the clinical outcome. Third, we performed several subgroup analyses and detected multiplicative and additive interactions between phosphate clusters and mechanical ventilation, but we failed to carry out further mechanistic research due to the lack of relevant data; therefore, experimental studies are needed to explore the molecular and cytological mechanisms.

Conclusion

First, a high and unstable serum phosphate level is associated with increased mortality in septic patients. Second, for those with elevated phosphate levels, treatments to lower serum phosphate may reduce mortality in septic patients. Third, an increasing trend in phosphate levels may be more important than a high level in predicting poor prognosis in septic patients.

Data availability

The datasets generated and analyzed during the current study are available in the MIMIC-III database (https://physionet.org/content/mimiciii/1.4/).

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Author contributions

J.W. and F.G. conceptualized the research aims, planned the analyses and guided the literature review. J.W. extracted the data from the MIMIC-III database. L.C., L.J. and S.D. carried out the literature search. X.H.S and S.Y.S participated in processing the data and doing the statistical analysis. J.W. wrote the first draft of the paper and the other authors provided comments and approved the final manuscript. The authors read and approved the final manuscript.

Declarations

Competing interests

The authors declare no competing interests.

Ethics approval and consent to participate

The establishment of this database was approved by the Massachusetts Institute of Technology (Cambridge, MA) and Beth Israel Deaconess Medical Center (Boston, MA), and consent was obtained for the original data collection. Therefore, the ethical approval statement and the need for informed consent were waived for this manuscript.

Additional information

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