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Association between serum phosphate and in-hospital mortality of patients with AECOPD: A retrospective analysis on eICU database

Siqi Li [a,b,c,1], Qiong Huang [a,b,c,1], Wenbin Nan [d], Baimei He [a,b,c,*]

[a] Department of Geriatric Respiratory and Critical Care Medicine, Xiangya Hospital, Central South University, Changsha 410008, China
[b] Department of Geriatric Medicine, Xiangya Hospital, Central South University, Changsha 410008, China
[c] National Clinical Research Center for Geriatric Disorders, Xiangya Hospital, Central South University, Changsha 410008, China
[d] Department of Emergency Medicine, Second Xiangya Hospital, Central South University, Changsha 410011, China

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ABSTRACT

Acute exacerbation of chronic obstructive pulmonary disease (AECOPD) is an important adverse event in the development of chronic obstructive pulmonary disease (COPD). Hyperphosphatemia is associated with higher mortality in patients with multiple diseases. In this study, we aimed to determine the relationship between serum phosphate and the risk of in-hospital mortality in patients with AECOPD. **Methods**: In the present study, patients with AECOPD were enrolled in the electronic Intensive Care Unit Collaborative Research Database (eICU-CRD), and divided into three groups according to the tertiles of serum phosphate level. The primary outcome measure was all-cause in-hospital mortality. The association between serum phosphate level and in-hospital mortality was investigated using multivariate logistic regression analysis. Moreover, subgroup analysis was performed to explore whether the relationship was consistent among different subgroups. **Results:** A total of 1199 AECOPD patients were included in this study. Non-survivors had higher serum phosphate levels than survivors. All patients were classified into lowest tertile, median tertile, and highest tertile, respectively. Multivariate logistic regression analysis indicated that serum phosphate was positively associated with in-hospital mortality after adjusting for confounders. Moreover, there was a significant trend across tertiles when serum phosphate level was diverted as a categorical variable. In addition, subgroup analysis demonstrated that serum phosphate was consistently associated with a higher risk of in-hospital mortality in different subgroups. **Conclusion:** Higher serum phosphate was positively associated with the increased in-hospital mortality in patients with AECOPD. Hyperphosphatemia may be an underlying high-risk factor for in-hospital mortality owing to AECOPD.

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a term used to describe persistent respiratory symptoms and airflow limitation caused by abnormalities of the airway or alveolus due to noxious particles and gases [1,2]. Acute exacerbation of COPD (AECOPD) is defined as an acute worsening of respiratory symptoms and is regarded as an important event in the progression of COPD [3]. It has

* Corresponding author. Department of Geriatric Medicine, Xiangya Hospital, Central South University, Changsha 410008, China.
E-mail addresses: lsq199706@163.com (S. Li), huangqiong1998@163.com (Q. Huang), 598570948@qq.com (W. Nan), hebaimei@126.com (B. He).
[1] These authors have contributed equally to this work and share the first authorship.

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been reported that AECOPD accelerates lung function decline, reduces exercise capacity, and increases the risk of hospitalization [4,5]. Several recent studies have shown that acute exacerbations are associated with increased mortality in patients with COPD [6–8]. Despite many efforts, the mortality rate of patients with AECOPD remains high [9]. Hence, it is crucial to identify the potential risk factors for patients with AECOPD, which may improve the outcomes of high-risk patients.

Phosphorus is involved in various aspects of physiological processes, including energy metabolism, bone mineralization, membrane transport, and intracellular signaling [10–13]. Numerous studies have shown that higher serum phosphate level is associated with increased mortality in many diseases [14–18]. Recently, a few studies have indicated that the serum phosphate level is related to the severity and outcomes of COPD [19,20]. However, it is not clear whether serum phosphate level is associated with short-term mortality in patients with AECOPD in the intensive care unit (ICU). Therefore, in this retrospective study, we investigated the relationship between serum phosphate level and the in-hospital mortality of AECOPD patients based on the electronic Intensive Care Unit Collaborative Research Database (eICU-CRD).

2. Materials and methods

2.1. Data sources

The eICU-CRD, created by Philips Healthcare in collaboration with the Massachusetts Institute of Technology (MIT) Computational Physiology Laboratory, contains important clinical data on more than 200,000 inpatients in 335 ICUs at 208 hospitals in the United States during the period 2014–2015. This study utilized anonymous data available in the eICU database with pre-existing institutional review board approval from the institutional review board of MIT. As all the data were anonymously recorded, informed consent and ethical approval are not required for this study. The corresponding author (Baimei He) completed the "Protecting Human Research Participants" curriculum and was granted access to the database (Record ID: 50055924). All methods were performed in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.

2.2. Population selection

In this retrospective observational study, we included all adult patients with a primary diagnosis of AECOPD according to the International Classification of Diseases (ICD) code (ICD code: 491.21) from the eICU-CRD. The following exclusion criteria were used: (1) the length of ICU stay < 24 h; (2) repeated ICU admission; (3) missing serum phosphate values within the first 24 h of ICU admission.

2.3. Data extraction

We used PostgreSQL (version 10, www.postgresql.org) to extract data of patients with AECOPD from the eICU-CRD. Study covariates included demographic data, vital signs, blood biochemistry, comorbidities, severity score, treatment, and outcome. The following information was extracted: age, gender, body mass index (BMI), temperature, heart rate, respiratory rate, mean arterial pressure (MAP), saturation of peripheral oxygen (SpO_2), white blood cells (WBC), hemoglobin, platelets, creatinine, calcium, potassium, sodium, hypertension, coronary artery disease (CAD), diabetes, chronic kidney disease (CKD), cirrhosis, stroke, renal replacement therapy (RRT), ventilation, vasoactive drugs, sequential organ failure assessment (SOFA), acute physiology and chronic health evaluation (APACHE) IV, length of stay (LOS) in ICU, LOS in hospital, ICU mortality and in-hospital mortality. If vital signs were collected multiple times or if patients underwent more than one laboratory test during the hospitalization, the initial data within the first 24 h after ICU admission were extracted for subsequent analysis. Dummy variables were used to represent missing covariate values.

2.4. Outcomes

The primary outcome in the present study was all-cause in-hospital mortality, defined as survival to hospital discharge. Secondary outcomes included LOS in ICU, LOS in the hospital, and all-cause ICU mortality. The LOS in ICU and LOS in the hospital were measured as the total time spent in the ICU and hospital, respectively. ICU mortality referred to the proportion of patients who died before discharge from the ICU. Patients with no survival outcome data were excluded from the final analysis.

2.5. Statistical analysis

Continuous variables following a Gaussian distribution were described as mean $\pm$ standard deviation (SD). In contrast, if the requirement was not satisfied, the data were represented as medians (25th and 75th percentiles). Categorical variables were expressed as absolute values and percentages. The data were analyzed using the Kruskal-Wallis H test, Chi-squared test, or One way ANOVA, appropriately. The patients diagnosed with AECOPD were separated into three groups according to tertiles of serum phosphate level, including lowest tertile (serum phosphate ≤ 3.0 mg/dL, $n = 445$), median tertile (3.0 mg/dL $<$ serum phosphate ≤ 4.0 mg/dL, $n = 378$) and highest tertile (serum phosphate > 4.0 mg/dL, $n = 376$). Box plots were used to compare serum phosphate level between the survival and non-survival groups. To investigate whether serum phosphate level was correlated with in-hospital mortality, statistical analysis was performed in two key steps. Step 1: Univariate and multivariate logistic regression analyses were constructed to exclude

the confounding factors. Specifically, we used all selected clinically relevant variables for the univariate logistic regression analysis. The variables with $P < 0.2$ in the univariate logistic regression analysis were selected for the multivariate logistic regression analysis. Three different multivariate models were presented in this study. A crude model was created without adjusting for covariates. Model I was adjusted for demographic data. Model II was adjusted for the covariates included in Model I and the covariates with $P < 0.2$ in the univariate logistic regression analysis. Step 2: Subgroup analysis was conducted to further validate the robust association between serum phosphate level and in-hospital mortality and the potential interaction between serum phosphate and the stratified variables based on gender, age, BMI, sodium, potassium, calcium, hypertension, diabetes, CKD, ventilation, and vasoactive drugs. All statistical analyses were performed using the R software version 4.2.0 (http://www.r-project.org). A two-sided significance threshold of $P < 0.05$ was considered statistically significant.

3. Results

3.1. Basic characteristics

The flow chart of patients' enrollment process was illustrated in Fig. 1. A total of 5285 patients diagnosed with AECOPD were included in the eICU-CRD. Sequentially, we excluded 4086 patients based on the exclusion criteria. The final analysis included 1199 participants in this study. As shown in Supplementary Table 1, the in-hospital mortality was 11.1% (133/1199), with 133 non-survivors and 1066 survivors. As shown in Fig. 2, non-survivors had higher serum phosphate level than survivors. Moreover, we divided the AECOPD patients into three groups (lowest tertile, median tertile, and highest tertile) according to the tertiles of the serum phosphate level within 24 h of ICU admission. The baseline characteristics of the final cohort were shown in Table 1, which indicated that the patients in the highest tertile of serum phosphate group had significantly higher BMI ($P < 0.001$), lower temperature ($P < 0.001$), lower heart rate ($P < 0.001$), lower MAP ($P = 0.011$), higher creatinine ($P < 0.001$), higher potassium ($P < 0.001$), higher SOFA ($P < 0.001$), higher APACHE IV ($P < 0.001$), and higher ICU mortality ($P < 0.001$). Moreover, patients with higher serum phosphate levels were more likely to receive RRT ($P < 0.001$) and vasoactive drugs ($P = 0.003$) than those in the lower serum phosphate group. There were significant differences in age ($P = 0.021$), calcium level ($P = 0.023$), sodium level ($P = 0.039$), hypertension ($P = 0.014$), CAD ($P = 0.004$), diabetes ($P = 0.017$), and CKD ($P < 0.001$) among the three groups. However, no significant differences were observed for gender, respiration rate, SpO_2, WBC count, hemoglobin, platelets, cirrhosis, stroke, ventilation, LOS in ICU, and LOS in hospital ($P > 0.05$) among the three groups.

3.2. Univariate analysis

Univariate logistic regression analysis was performed to determine the relationship between serum phosphate level and risk of in-hospital mortality. As shown in Table 2, univariate logistic regression analysis revealed that serum phosphate level correlated with increased in-hospital mortality (odds ratio [OR] 1.30, 95% confidence interval [CI] 1.16–1.46, $P < 0.001$). Moreover, the univariate logistic regression analysis demonstrated that age (OR 1.04, 95% CI 1.02–1.06, $P < 0.001$), heart rate (OR 1.01, 95% CI 1.00–1.02, $P = 0.004$), WBC (OR 1.06, 95% CI 1.03–1.09, $P < 0.001$), creatinine (OR 1.16, 95% CI 1.00–1.34, $P = 0.044$), invasive ventilation (OR 1.83, 95% CI 1.18–2.82, $P = 0.007$), vasoactive drugs (OR 4.13, 95% CI 2.60–6.54, $P < 0.001$), SOFA (OR 1.26, 95% CI 1.17–1.35, $P < 0.001$), and APACHE IV (OR 1.04, 95% CI 1.03–1.05, $P < 0.001$) were positively associated with the in-hospital mortality. Additionally, BMI (OR 0.97, 95% CI 0.96–0.99, $P = 0.008$), MAP (OR 0.98, 95% CI 0.97–0.99, $P = 0.002$), SpO_2 (OR 0.96, 95% CI 0.92–1.00, $P = 0.038$), hemoglobin (OR 0.90, 95% CI 0.83–0.98, $P = 0.016$), and calcium (OR 0.66, 95% CI 0.51–0.85, $P = 0.001$) were negatively associated with the in-hospital mortality. However, gender, temperature, respiration rate, platelets, potassium, sodium, hypertension, CAD, diabetes, CKD, cirrhosis, stroke, RRT, and non-invasive ventilation were not associated with in-hospital mortality ($P > 0.05$).

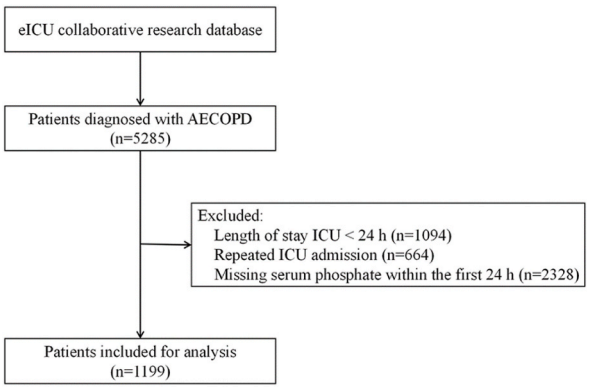

Fig. 1. Flow chart of patients' enrollment process. AECOPD, acute exacerbation of chronic obstructive pulmonary disease; ICU, intensive care unit.

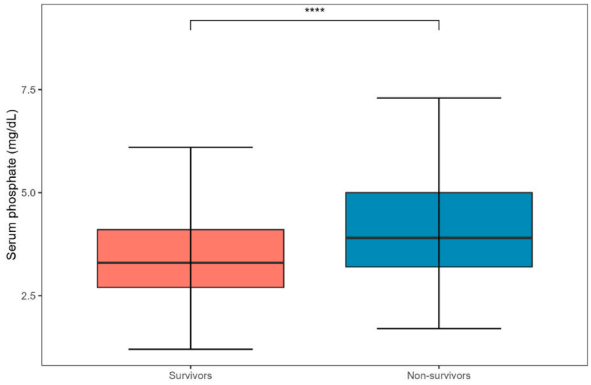

Fig. 2. Serum phosphate values in survivors group and non-survivors group. ****P < 0.0001.

Table 1
Baseline characteristics of the patients grouped by the tertiles of serum phosphate.

	Lowest tertile (n = 445)	Median tertile (n = 378)	Highest tertile (n = 376)	*P* value
Age (years)	67 (58, 75)	69 (60, 78)	68 (62, 75)	0.021
Gender, n (%)				0.411
Female	250 (56.18)	213 (56.35)	196 (52.13)	
Male	195 (43.82)	165 (43.65)	180 (47.87)	
BMI (kg/m^2)	25.86 (21.25, 33.35)	28.1 (22.49, 34.39)	29.07 (23.27,38.11)	<0.001
Temperature (°C)	36.50 (36.20, 36.80)	36.40 (36.10, 36.60)	36.38 (36, 36.60)	<0.001
Heart rate (bpm)	98 (87, 111)	95 (81, 108)	92 (79, 106)	<0.001
Respiration rate (bpm)	21 (18, 25)	22 (18, 27)	22 (18, 26)	0.654
MAP (mm Hg)	82 (72, 93)	85 (74, 99)	80 (70, 96)	0.011
SpO_2 (%)	97 (95, 99)	97 (93, 99)	97 (93, 100)	0.508
WBC (10^9/L)	10.62 (7.40, 14.30)	9.50 (7.20, 14.03)	10.68 (7.61, 15.03)	0.053
Hemoglobin (g/dL)	11.62 ± 2.01	11.51 ± 2.13	11.54 ± 2.44	0.743
Platelets (10^9/L)	195 (156, 243.50)	206 (162.75, 264.25)	195.50 (156, 256)	0.207
Creatinine (mg/dL)	0.78 (0.60, 1.01)	0.99 (0.73, 1.38)	1.60 (1, 2.58)	<0.001
Calcium (mg/dL)	8.5 (8.10, 9)	8.7 (8.20, 9.1)	8.55 (8.10, 9)	0.023
Potassium (mmol/L)	4.10 (3.70, 4.50)	4.20 (3.80, 4.52)	4.60 (4.17, 5.10)	<0.001
Sodium (mmol/L)	139 (136, 141)	138 (135, 141)	138 (135, 141)	0.039
Hypertension, n (%)	75 (16.85)	91 (24.07)	90 (23.94)	0.014
CAD, n (%)	21 (4.72)	13 (3.44)	33 (8.78)	0.004
Diabetes, n (%)	63 (14.16)	56 (14.81)	79 (21.01)	0.017
CKD, n (%)	26 (5.84)	36 (9.52)	68 (18.09)	<0.001
Cirrhosis, n (%)	2 (0.45)	5 (1.32)	0 (0)	0.052
Stroke, n (%)	14 (3.15)	11 (2.91)	3 (0.80)	0.057
RRT, n (%)	5 (1.12)	4 (1.06)	34 (9.04)	<0.001
Ventilation, n (%)				0.273
Oxygen therapy	191 (42.92)	185 (48.94)	163 (43.35)	
Non-invasive	151 (33.93)	126 (33.33)	130 (34.57)	
Invasive	103 (23.15)	67 (17.72)	83 (22.07)	
Vasoactive drugs, n (%)	36 (8.09)	23 (6.08)	49 (13.03)	0.003
SOFA	4 (2, 6)	3 (2, 5)	5 (3, 6.25)	<0.001
APACHE IV	57 (45, 71)	56 (44, 72.50)	64 (50, 80)	<0.001
LOS in ICU (days)	3.13 (1.86, 5.77)	3.03 (1.89, 5.08)	3.04 (1.92, 6.03)	0.281
LOS in hospital (days)	7.15 (4.85, 10.80)	7.31 (4.85, 10.45)	7.88 (4.89, 11.80)	0.265
ICU mortality, n (%)	14 (3.15)	20 (5.29)	40 (10.64)	<0.001
In-hospital mortality, n (%)	31 (6.97)	42 (11.11)	60 (15.96)	<0.001

BMI, body mass index; MAP, mean arterial pressure; SpO_2, saturation of peripheral oxygen; WBC, white blood cell; CAD, coronary artery disease; CKD, chronic kidney disease; RRT, renal replacement therapy; SOFA, sequential organ failure assessment; APACHE, acute physiology and chronic health evaluation; LOS, length of stay; ICU, intensive care unit.

3.3. Multivariate analysis

The variables with $P < 0.2$ in univariate logistic regression analysis were selected for multivariate logistic regression analysis. As shown in Table 3, three models were constructed to validate the independent association between serum phosphate level and in-hospital mortality after modification for potential confounding factors. In the Crude model, the serum phosphate level was positively associated with in-hospital mortality (OR 1.30, 95% CI 1.16–1.46, $P < 0.001$) after adjustment for none. In Model I, the serum phosphate level was also positively associated with in-hospital mortality (OR 1.32, 95% CI 1.18–1.49, $P < 0.001$) after adjustment for

Table 2
Univariate logistic regression analysis of serum phosphate for in-hospital mortality.

	OR	95% CI	*P* value
Age (years)	1.04	1.02–1.06	<0.001
Gender, n (%)	1.07	0.75–1.54	0.698
BMI (kg/m^2)	0.97	0.96–0.99	0.008
Temperature (°C)	1.01	0.98–1.04	0.463
Heart rate (bpm)	1.01	1.00–1.02	0.004
Respiration rate (bpm)	1.02	0.99–1.05	0.196
MAP (mm Hg)	0.98	0.97–0.99	0.002
SpO_2 (%)	0.96	0.92–1.00	0.038
WBC (10^9/L)	1.06	1.03–1.09	<0.001
Hemoglobin (g/dL)	0.90	0.83–0.98	0.016
Platelets (10^9/L)	1.00	1.00–1.00	0.716
Creatinine (mg/dL)	1.16	1.00–1.34	0.044
Serum phosphate (mg/dL)	1.30	1.16–1.46	<0.001
Calcium (mg/dL)	0.66	0.51–0.85	0.001
Potassium (mmol/L)	1.11	0.86–1.43	0.417
Sodium (mmol/L)	1.00	0.96–1.04	0.974
Hypertension, n (%)	1.14	0.74–1.74	0.559
CAD, n (%)	1.26	0.61–2.61	0.531
Diabetes, n (%)	1.26	0.80–2.00	0.318
CKD, n (%)	1.14	0.65–1.99	0.641
Cirrhosis, n (%)	1.34	0.16–11.20	0.788
Stroke, n (%)	1.35	0.46–3.94	0.587
RRT, n (%)	0.82	0.29–2.32	0.704
Ventilation, n (%)			
Oxygen therapy	Reference		
Non-invasive	0.94	0.61–1.46	0.798
Invasive	1.83	1.18–2.82	0.007
Vasoactive drugs, n (%)	4.13	2.60–6.54	<0.001
SOFA	1.26	1.17–1.35	<0.001
APACHE IV	1.04	1.03–1.05	<0.001

ICU, intensive care unit; AECOPD, acute exacerbation of chronic obstructive pulmonary disease; OR, odds ratio; CI, confidence interval; BMI, body mass index; MAP, mean arterial pressure; SpO_2, saturation of peripheral oxygen; WBC, white blood cell; CAD, coronary artery disease; CKD, chronic kidney disease; RRT, renal replacement therapy; SOFA, sequential organ failure assessment; APACHE, acute physiology and chronic health evaluation.

Table 3
Multivariate logistic regression analysis of serum phosphate for in-hospital mortality.

	Crude model		Model I		Model II	
	Crude OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value
Serum phosphate	1.30 (1.16, 1.46)	<0.001	1.32 (1.18–1.49)	<0.001	1.28 (1.09–1.51)	0.003
Lowest tertile	Reference		Reference		Reference	
Median tertile	1.67 (1.03–2.71)	0.039	1.63 (1.00–2.67)	0.051	1.99 (1.16–3.43)	0.012
Highest tertile	2.54 (1.60–4.01)	<0.001	2.68 (1.68–4.27)	<0.001	2.72 (1.55–4.76)	<0.001
P for trend	<0.001		<0.001		<0.001	

The variables with $P < 0.2$ in Table 2 were selected for multivariate logistic regression analysis. Crude model: all results were adjusted for none. Model I: all results were adjusted for age, BMI. Model II: all results were adjusted for age, BMI, heart rate, respiration rate, MAP, SpO_2, WBC, hemoglobin, calcium, creatinine, oxygen therapy, vasoactive drugs, SOFA, APACHE IV. OR, odds ratio; CI, confidence interval; BMI, body mass index; MAP, mean arterial pressure; SpO_2, saturation of peripheral oxygen; WBC, white blood cell; SOFA, sequential organ failure assessment; APACHE, acute physiology and chronic health evaluation.

age and BMI. In Model II, the correlations were significant (OR 1.28, 95% CI 1.09–1.51, $P = 0.003$) when covariates were adjusted for age, BMI, heart rate, respiration rate, MAP, SpO_2, WBC, hemoglobin, calcium, creatinine, oxygen therapy, vasoactive drugs, SOFA, and APACHE IV. Additionally, there was a significant trend across the tertiles (*P* for trend: <0.001) when serum phosphate was used as a categorical variable. When the lowest tertile was used as a reference in Model I and Model II, higher serum phosphate level (highest tertile vs. lowest tertile) was still associated with an increased risk of in-hospital mortality in AECOPD patients.

3.4. Subgroup analysis

We further performed a stratified analysis to investigate whether the relationship between serum phosphate level and in-hospital mortality was consistent among the different subgroups. As shown in Fig. 3, subgroup analysis revealed a significant association between the increased serum phosphate level and in-hospital mortality in different subclasses. The interaction was not significant after

stratified by gender, age, BMI, sodium, potassium, calcium, hypertension, diabetes, CKD, ventilation, and vasoactive drugs, which indicated that serum phosphate was consistently associated with a higher risk.

4. Discussion

COPD affects 10% of the world's population and remains the third leading cause of death worldwide [21]. It is estimated that AECOPD is one of the most common causes of hospitalization and mortality among COPD patients [22]. Therefore, early identification of high-risk patients with AECOPD is important to guide clinical therapy and improve prognosis. In the present study, we analyzed 1199 patients with AECOPD from the eICU-CRD and found that serum phosphate level was significantly increased in patients who died from AECOPD. Moreover, high serum phosphate level was independently associated with in-hospital mortality of patients with AECOPD. Additionally, the subgroup analysis demonstrated that the effect of serum phosphate on the in-hospital mortality of patients

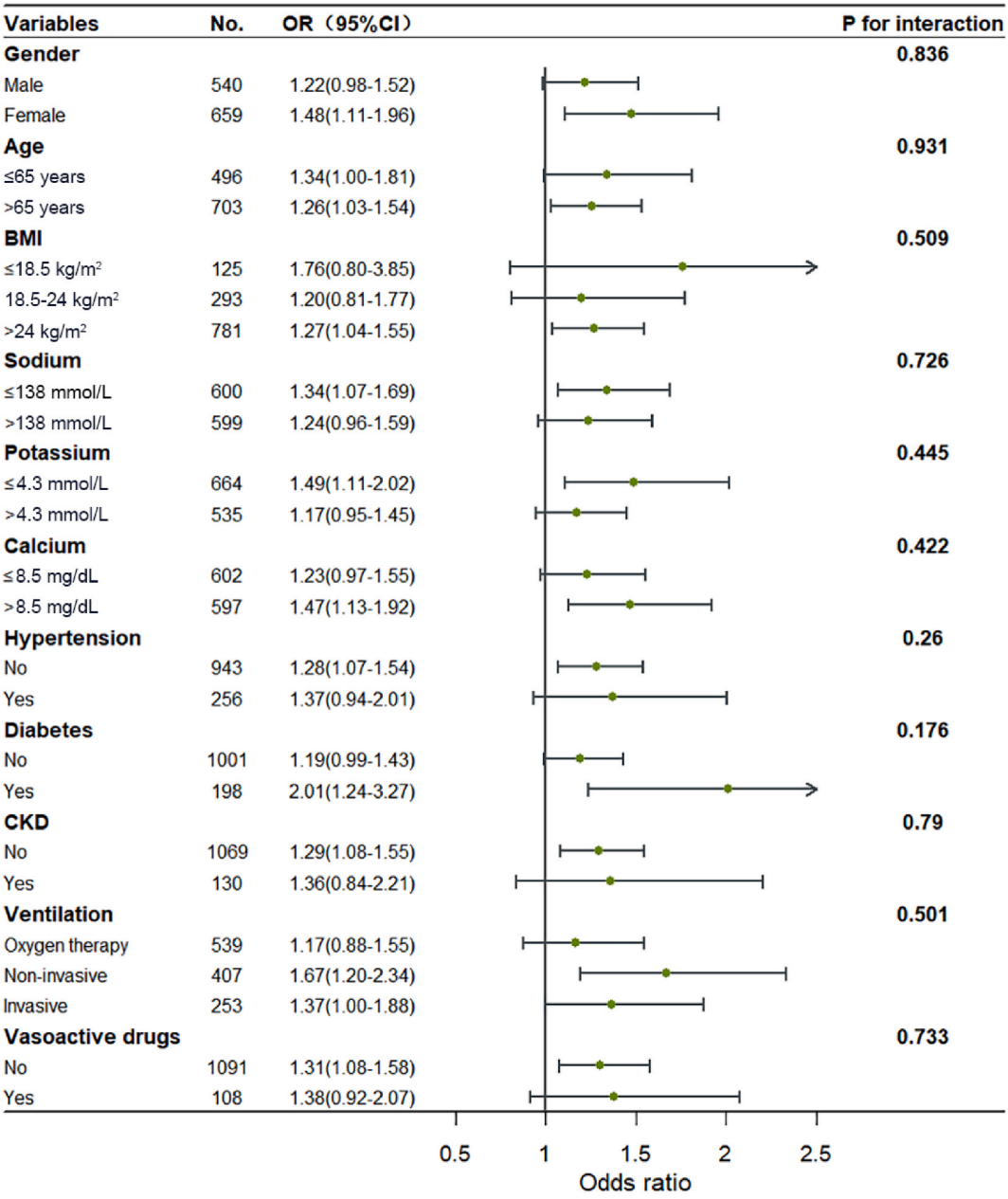

Fig. 3. Results of subgroup analysis and interaction analysis. Odds ratio per 1 mg/dL serum phosphate increase in predicted in-hospital mortality. OR, odds ratio; CI, confidence interval; BMI, body mass index; CKD, chronic kidney disease.

with AECOPD was consistent in different subgroups. Therefore, higher serum phosphate level is a potential high-risk factor for in-hospital mortality in patients with AECOPD.

Phosphorus is a common and crucial mineral in the body. Inorganic phosphate, the ionized form of phosphorus, plays an important role in maintaining normal cellular functions [23]. Phosphate also affects the respiratory muscle contractility, electrolyte transport, and inflammation-related response [24–27]. Recently, numerous studies have demonstrated that disturbances in phosphate homeostasis contribute to poor prognosis in many diseases [26,28–30]. Several studies have shown that patients admitted to the ICU tend to have abnormal serum phosphate level due to gastrointestinal tract absorption, kidney excretion, sepsis, trauma, drugs, and so on [31]. Zheng et al. found that higher serum phosphate level was observed in critically ill patients and was associated with a higher risk of all-cause mortality [32]. Additionally, a meta-analysis of 12 cohort studies revealed that hypophosphatemia was a common marker of disease severity rather than an independent predictor of ICU or in-hospital mortality [33]. A prospective population-based cohort study by Campos-Obando et al. indicated that serum phosphate was higher in male COPD patients who died [20]. However, it is not clear whether abnormal serum phosphate level exists in survivors and non-survivors of AECOPD. In this study, we found that serum phosphate level was elevated in non-survivors of AECOPD compared to those in survivors. It was previously reported that respiratory infection, hypoxemia, and respiratory acidosis were the main causes of death in AECOPD [34–36]. Moreover, many studies revealed that hypoxia and infection caused rhabdomyolysis and led muscle cells to release phosphate [37]. Thompson et al. found that respiratory acidosis promoted the efflux of phosphate from skeletal muscle cells into the blood [38]. Thus, hypoxia, infection, and respiratory acidosis possibly contributed to hyperphosphatemia in the AECOPD patients who died.

AECOPD is an acute event with worsening symptoms that contributes to adverse outcomes for COPD patients [39]. Multiple studies demonstrated that exacerbation frequency, severity, Charlson comorbidity index, C-reactive protein (CRP), soluble urokinase plasminogen activator receptor, serum IgG, and neutrophil-to-lymphocyte ratio were associated with mortality of AECOPD [40–43]. However, the indicators that predict the prognosis of COPD vary substantially. Recently, an increasing number of studies have indicated that elevated serum phosphate level is related to all-cause mortality in numerous diseases. Bai et al. indicated that higher serum phosphate level was one of the risk factors for mortality from cardiovascular diseases [44]. Moreover, hyperphosphatemia was a major complication in patients with CKD and was also regarded as a predictor of mortality in CKD [45]. Similarly, hyperphosphatemia was associated with increased in-hospital mortality in patients with severe sepsis [32]. In addition, Thongprayoon et al. showed that high serum phosphate level was associated with the risk of respiratory failure requiring mechanical ventilation [46]. Recently, Campos-Obando et al. found that higher phosphate levels increased the risk of COPD mortality in male patients [20]. However, there are no published studies on whether serum phosphate level is correlated with the poor prognosis of AECOPD. Renal insufficiency can lead to hyperphosphatemia and may be considered an independent risk factor for in-hospital mortality. Nevertheless, we adjusted for serum creatinine in Model II and further performed a subgroup analysis and found that there was no significant interaction in most subgroups including CKD. The findings of our study confirmed that increased serum phosphate was independently associated with in-hospital mortality in patients with AECOPD after adjusting for confounders, without the influence of renal function. Therefore, serum phosphate was an independent and stable high-risk factor for in-hospital mortality of patients with AECOPD.

Numerous studies have demonstrated that hyperphosphatemia is involved in the pathophysiology of adverse events in several diseases. Our findings indicated that high serum phosphate level was a high-risk factor for mortality of patients with AECOPD. Several mechanisms can explain this phenomenon. First, increased serum phosphate induces vascular calcification and endothelial dysfunction, leading to organ dysfunction [47–49]. Second, there is increasing evidence that hyperphosphatemia results in oxidative stress, cell apoptosis, and inflammation [50–53], which are involved in the pathogenesis of AECOPD. Third, a higher phosphate diet exacerbates aging and lung emphysema phenotypes, whereas restriction of phosphate intake and absorption relieves these phenotypes and alveolar destruction [54–56], which might contribute to the development of AECOPD. Therefore, reducing serum phosphate levels may be a therapeutic strategy to improve the prognosis of AECOPD patients.

There are several strengths in this study. First, the present study was based on a large population from various units in the United States, reflecting the real-world clinical practice. Second, serum phosphate was easy to measure and regarded as a cost-effective parameter in the clinic, which was beneficial for identifying high-risk AECOPD patients. Third, logistic regression analysis and subgroup analysis were used to minimize residual confounders, which increased the robustness and drew a stable conclusion in our study.

Meanwhile, there are also several limitations that should be considered. First, as a retrospective study, potential confounders could exist in our study that might affect our findings. Second, serum phosphate level changed dynamically in AECOPD patients. It is better to evaluate the association between dynamic changes in serum phosphate level and in-hospital mortality during hospitalization. Third, many variables, such as smoking, exacerbation frequency, severity, PH, PaO_2, $PaCO_2$ and lactate, were not included in this study owing to more than 20% missing values. Therefore, multicenter prospective trials are required for future investigation.

5. Conclusions

Serum phosphate level was elevated in non-survivors with AECOPD compared to those in survivors. In addition, there was a positive and stable association between serum phosphate level and in-hospital mortality. In conclusion, higher serum phosphate level was a potential high-risk factor for in-hospital mortality of AECOPD patients.

Author contribution statement

Wrote the paper and performed the experiments, Siqi Li and Qiong Huang; Analyzed and interpreted the data, Wenbin Nan; Contributed reagents, materials, analysis tools or data and conceived and designed the experiments, Baimei He. All authors have read

and agreed to the published version of the manuscript.

Data availability statement

Data associated with this study has been deposited at https://eicu-crd.mit.edu/.

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Informed consent statement

This study utilized the anonymous data available in the eICU database with pre-existing institutional review board approval, an institutional review board of MIT. Since all the data are anonymously recorded, the informed consent and ethical approval are not required for this study. The corresponding author (Baimei He) finished the "Protecting Human Research Participants" curriculum and was granted access to the database (Record ID: 50055924).

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e19748.

Abbreviations

eICU-CRD	electronic Intensive Care Unit Collaborative Research Database
ICU	intensive care unit
AECOPD	acute exacerbation of chronic obstructive pulmonary disease
MIT	Massachusetts Institute of Technology
STROBE	strengthening the reporting of observational studies in epidemiology
ICD	international classification of diseases
SD	standard deviation
OR	odds ratio
CI	confidence interval
BMI	body mass index
MAP	mean arterial pressure
SpO_2	saturation of peripheral oxygen
WBC	white blood cell
CAD	coronary artery disease
CKD	chronic kidney disease
RRT	renal replacement therapy
SOFA	sequential organ failure assessment
APACHE	acute physiology and chronic health evaluation
LOS	length of stay
CRP	C-reactive protein

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