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ORIGINAL RESEARCH

Association Between the Serum Phosphate Levels and Hospital Mortality as Well as 90-Day Mortality Among Critically Ill Patients with Chronic Obstructive Pulmonary Disease: A Retrospective Cohort Study

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Purpose: COPD patients frequently have abnormal serum phosphorus levels. The objective of this study was to examine the correlation between serum phosphorus levels with hospital and 90-day mortality in critically ill patients with COPD.

Patients and Methods: The MIMIC IV database was used for this retrospective cohort analysis. We extracted demographics, vital signs, laboratory tests, comorbidity, antibiotic usage, ventilation and scoring systems within the first 24 hours of ICU admission. Restricted cubic splines and multivariate cox regression analysis models were used to evaluate the connection between serum phosphorus with hospital and 90-day mortality. We assessed and classified various factors including gender, age, renal disease, severe liver disease, the utilization of antibiotics and congestive heart failure.

Results: We included a total of 3611 patients with COPD, with a median age of 70.7 years. After adjusting for all other factors, we observed a significant positive association between serum phosphate levels with both hospital mortality (HR 1.19, 95% CI: 1.07–1.31, p<0.001) and 90-day mortality (HR 1.15, 95% CI: 1.06–1.24, p<0.001). Compared to the medium group (Q2 ≥3.15, <4.0), the adjusted hazard ratios for hospital mortality were 1.47 (95% CI: 1.08–2, p=0.013), and 1.31 (95% CI: 1.06–1.61, p=0.013) for 90-day mortality in the high group (Q3≥4.0). Hospital mortality decreased at serum phosphate levels below 3.8 mg/dl (HR 0.664, 95% CI: 0.468–0.943, p=0.022), but increased for both hospital (HR 1.312, 95% CI: 1.141–1.509, p<0.001) and 90-day mortality (HR 1.236, 95% CI: 1.102–1.386, p<0.001) when levels were above 3.8 mg/dl. Subgroup and sensitivity analyses yielded consistent results.

Conclusion: In critical ill COPD patients, this study demonstrated a non-linear association between serum phosphate levels and both hospital and 90-day mortality. Notably, there was an inflection point at 3.8 mg/dl, indicating a significant shift in outcomes. Future prospective research is necessary to validate this correlation.

Keywords: COPD, serum phosphate, mortality, MIMIC-IV, critically ill

Introduction

Chronic obstructive pulmonary disease (COPD), a widely prevalent respiratory condition, is associated with significant morbidity and mortality rates. It is estimated to affect more than 350 million people globally and account for 32 million deaths annually. Globally, chronic obstructive pulmonary disease (COPD) is ranked as the third leading cause of death, making it a significant public health concern.[1,2] In addition to genetic, developmental, and social variables, characterized by persistent respiratory

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symptoms and progressive airflow blockage, chronic obstructive pulmonary disease (COPD) is primarily caused by prolonged exposure to inhaled particulate matter, such as cigarette smoke and air pollutants.[3] Beyond its direct effects on human suffering, COPD increases the chance of lung cancer, cardiovascular disease, COVID-19, pneumonia, and other major causes of death by two to four times.[1] These illnesses also have an impact on other major causes of mortality.[1] This has put a strain on people and society.[4] ICU admissions are desperately needed for a large number of patients. According to existing literature, the prevalence of acute exacerbations of chronic obstructive pulmonary disease (AECOPD) necessitating hospitalization varies from 2% to 19% among ICU admissions.[5] These exacerbations are associated with an in-hospital mortality rate ranging from 20% to 40%.[5] Furthermore, there is an observed re-hospitalization rate of 18% for new severe events related to AECOPD.[5] Individuals with COPD had greater death rate in the ICU when compared to individuals without the disease.[6] Hence, identifying reliable indicators for predicting the clinical outcomes of critically ill patients who have comorbid chronic obstructive pulmonary disease (COPD) becomes crucial.

Despite making up just about 1% of the total phosphorus in the human body, serum phosphate is essential for several physiological functions, such as energy metabolism, bone mineralization, membrane transport, and intracellular signaling.[7–9] The content of serum phosphorus in the blood of normal adult is between 2.7 and 4.5mg/dL. Phosphorus metabolism disorder is a frequently encountered electrolyte disorder observed in intensive care units (ICUs). Several studies have indicated a correlation between serum phosphate levels and increased mortality rates in various diseases.[10–14] Disruption of phosphorus metabolic balance may have serious clinical consequences and affect various physiologic functions and organ systems. Acute changes in serum phosphate levels can lead to life-threatening complications such as respiratory failure and arrhythmias.[15] A few studies have indicated a relation between the severity and prognosis of COPD and the serum phosphate level.[16–18] For instance, In the study conducted by Li et al,[18] a positive relationship was observed between elevated serum phosphate levels and a higher risk of in-hospital mortality among patients experiencing acute exacerbation of AECOPD. In individuals with severe COPD, the serum phosphate level may act as an indicator of the severity of the disease. Nevertheless, no studies have been conducted to investigate the correlation between serum phosphate levels and hospital or 90-day mortality in ICU patients with COPD. Therefore, the objective of this study was to investigate the correlation between serum phosphorus levels and mortality rates, both in-hospital and at 90 days, in patients diagnosed with COPD. The findings of this research aim to provide valuable insights for guiding the clinical management of these individuals.

Materials and Methods

Data Sources

A population-based cohort investigation was conducted using critical care databases in the Medical Information Mart for Intensive Care (MIMIC)-IV (version 2.2). The study covered 73,181 ICU admissions between 2008 and 2019. Shuang Du received authorization to access and employ this database (certification number 12069720). The collection of patient information and establishment of the research resource underwent a thorough review by the Institutional Review Boards (IRB) of the Massachusetts Institute of Technology (No. 0403000206) and Beth Israel Deaconess Medical Center (2001-P-001699/14). It approved the data sharing program and waived informed consent (https://doi.org/10.13026/6mm1-ek67).

Selection of Study Population

Patients identified as having COPD according to the tenth revision of the International Classification of Diseases (ICD10) (J44, J440, J441, J449). All participants in this study were above the age of 18. Only initial admissions and initial ICU admissions were considered for inclusion. Patients with incomplete serum phosphorus data on the first day of ICU admission were excluded from our analysis.

Variable Extraction

PostgreSQL (version 16.0) was used to acquire baseline features directly, we extracted study variables, which encompassed demographic characteristics (age, gender) as well as vital signs (respiratory rate, heart rate, mean blood pressure, systolic blood pressure, diastolic blood pressure, and temperature), initial laboratory data (hematocrit, hemoglobin, WBC, BUN, chloride, creatinine, sodium, calcium, platelets, potassium), ventilation status [oxygen inhalation (high-flow

oxygen inhalation as well as nasal cannula oxygen, face mask oxygen, venti mask and so on), mechanical ventilation (non-invasive ventilation, invasive ventilation and tracheostomy)], comorbidities [myocardial infarct, congestive heart failure, peripheral vascular disease, dementia, cerebrovascular disease, rheumatic disease, peptic ulcer disease, diabetes without chronic complication(cc), diabetes with cc, paraplegia, renal disease, malignant cancer, severe liver disease, metastatic solid tumor, sepsis3], severity of illness [Charlson comorbidity index, simplified acute physiology score II (SAPSII)] and antibiotic usage.[7,12,19] Together with the mean and initial values of serum phosphate, the data from further laboratory tests conducted on the first day were also retrieved, as were the mean values of vital signs. For missing data in the database, the predicted mean matching method (normal distribution) or median (skewed distribution) was used to impute the missing values. Additionally, sensitivity analyses were performed separately for the first serum phosphate results and the average serum phosphate levels on the first day for those patients.

Hospital mortality was this study's main outcome. Ninety-day mortality was one of the secondary outcomes.

Statistical Analysis

A descriptive analysis was done on each participant. Categorical variables were presented using frequencies and percentages, while continuous variables were expressed as either mean and standard deviation (SD) or median and interquartile range (IQR) based on the distribution of the data, whether it was normally distributed or skewed. To compare categorical variables, the chi-square test was employed. For continuous variables with skewed distributions, the Kruskal–Wallis test was utilized, and the *t*-test was used for regularly distributed variables. Five Cox regression models were employed to calculate the hazard ratio (HR) along with the corresponding 95% confidence intervals (CI) for the continuous and tri-categorized variation of serum phosphate linked to hospital mortality and 90-day mortality: (1) unadjusted; (2) model 1, adjusted for age, sex; (3) model 2, adjusted for MI, CHF, dementia, CVD, paraplegia, renal disease, severe liver disease, metastatic solid tumor, sepsis and model 1; (4) model 3, adjusted for HR, MBP, SBP, DBP, Temperature, RR, Hematocrit, Hemoglobin, WBC, BUN, Chloride, Creatinine, Calcium, Platelets, Potassium and model 2; (5) model 4, adjusted for Charlson comorbidity index, SAPSII, antibiotic usage, ventilation status and model 3.

A confounder was based on clinical significance and variables less than 0.05 in one-way linear regression analysis. Additionally, in order to flexibly examine the correlation between hospital mortality and 90-day mortality with serum phosphate, we implemented restricted cubic splines with four knots placed at the 5th, 35th, 65th, and 95th percentiles. To visually represent these relationships, we also utilized the Kaplan-Meier (K-M) curve. Moreover, through subgroup analyses employing stratified Cox regression models, we explored the association between serum phosphate levels and both hospital mortality and 90-day mortality within various subgroups, including sex, age, renal disease, severe liver disease, antibiotic usage and congestive heart failure. The R 4.2.2 was utilized for performing all statistical analyses. Additionally, the Free Statistics software version 1.9 was employed. For determining statistical significance, p-values <0.05 (two-sided) were considered.

Results

Study Population

14,070 patients diagnosed with COPD were extracted from the MMIC-IV database for the period from 2008 to 2019. Among these patients, 6992 were found to have duplicates in the database, we excluded individuals multiple hospitalizations and ICU admissions (n=3178), individuals with incomplete data of serum phosphate (n=286), and outlier in follow-up time (n=3). In the final analysis, a total of 3611 COPD patients were enrolled. Figure 1 illustrates the detailed inclusion and exclusion procedure for the study.

Baseline Characteristics

Table 1 presents the baseline characteristics of all subjects categorized based on serum phosphorus tertiles. The average age of the patients was 70.7 years, with 1888 male (52.3%) and 1723 (47.7%) female. The mean heart rate of the patients was 84.9, and the mean temperature was 36.8, respiratory rate was 19.7. The MBP and DBP, SBP of group Q3 were all lower than those of Q1 and Q2. Greater serum phosphorus levels were found to be associated with higher values of white blood cell count (WBC), blood urea nitrogen (BUN), creatinine, and potassium in patients, but lower values of hematocrit, hemoglobin, and chloride.

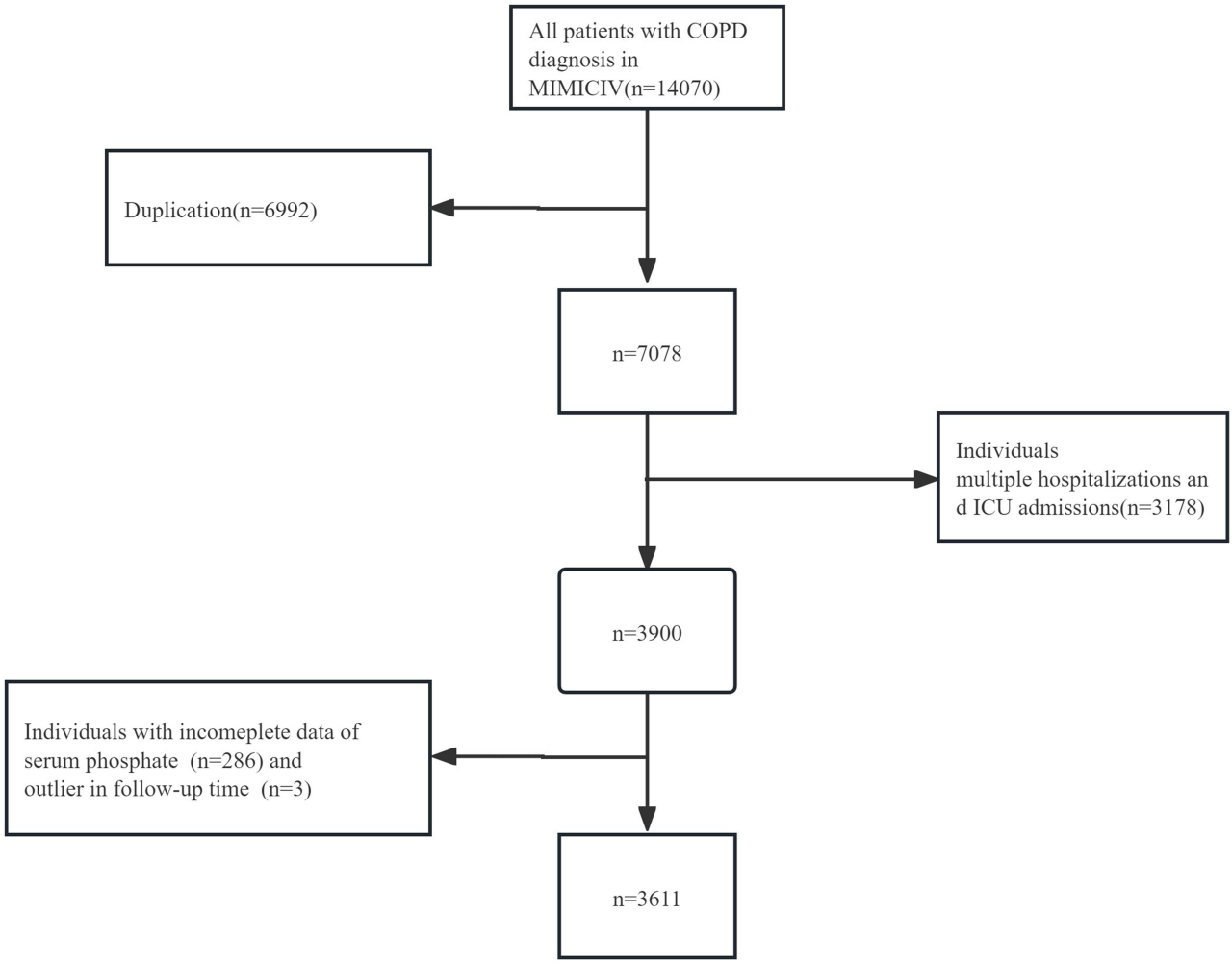

Figure 1 Flowchart of the patient selection process.

Among these patients, there was a higher incidence of comorbidities such as congestive heart failure (41.6%) and sepsis (49.1%). However, the prevalence of severe liver disease (4.0%) was relatively low.

Group Q3 was higher than group Q1 and Q2 in Charlson comorbidity index, SAPSII and antibiotic usage. In addition, mechanical ventilation ratio of Q3 group (38.2%) was higher than Q1 group (27.9%) and Q2 group (29.7%). Hospital mortality was greater in group Q3 (15.5%, $p < 0.001$) than in groups Q1 and Q2 (6.5% and 5.8%, $p < 0.001$), and similar outcomes were discovered for 90-day mortality.

Univariate Analysis for Hospital Mortality and 90-Day Mortality

The univariate analysis demonstrated that age, heart rate, MBP, DBP, SBP, temperature, respiratory rate, hematocrit, hemoglobin, WBC, BUN, chloride, creatinine, calcium, platelets, potassium, myocardial infarct, congestive heart failure, dementia, cerebrovascular disease, paraplegia, renal disease, severe liver disease, metastatic solid tumor, sepsis, Charlson comorbidity index, SAPSII, ventilation and antibiotic usage were associated with hospital mortality and 90-day mortality (Supplementary Table 1). The survival of patients diagnosed with COPD, based on different serum phosphate levels in groups Q1, Q2, and Q3, was illustrated using Kaplan-Meier survival curves. These curves depicted the patients' survival over a period of hospital admission and 90 days within the intensive care unit (ICU). The Kaplan-Meier survival analysis revealed that the hospital survival rate and the 90-day survival rate (Supplementary Figure) of patients in the Q1 and Q2 groups were significantly higher ($p<0.0001$, Log rank test) compared to those in the Q3 group.

Table 1 Baseline Characteristics of Participants

Variables	Total (n = 3611)	Q1 (n = 1180) (<3.133mg/dl)	Q2 (n = 1215) (≥3.15 mg/dl, <4.0 mg/dl)	Q3 (n = 1216) (≥4.0 mg/dl)	*p*
Sex, n (%)					0.179
Female	1723 (47.7)	540 (45.8)	602 (49.5)	581 (47.8)	
Male	1888 (52.3)	640 (54.2)	613 (50.5)	635 (52.2)	
Age, Mean ± SD	70.7 ± 11.7	70.2 ± 12.0	71.3 ± 11.8	70.6 ± 11.4	0.079
Vital sign					
Heart rate, Mean ± SD (bpm)	84.9 ± 15.9	86.4 ± 15.8	83.8 ± 15.3	84.5 ± 16.5	< 0.001
MBP, Mean ± SD (mmHg)	78.8 ± 10.8	80.0 ± 11.4	79.1 ± 10.2	77.1 ± 10.6	< 0.001
DBP, Mean ± SD (mmHg)	63.5 ± 11.0	65.2 ± 11.4	63.6 ± 10.6	61.8 ± 10.8	< 0.001
SBP, Mean ± SD (mmHg)	118.7 ± 16.2	119.6 ± 16.2	119.7 ± 15.6	116.8 ± 16.6	< 0.001
Temperature, Mean ± SD (°C)	36.8 ± 0.4	36.9 ± 0.4	36.8 ± 0.4	36.8 ± 0.4	< 0.001
Respiratory rate, Mean ± SD (bpm)	19.7 ± 3.7	20.0 ± 3.8	19.4 ± 3.4	19.8 ± 3.9	0.001
Laboratory data					
Hematocrit, Mean ± SD (%)	31.3 ± 6.9	31.7 ± 6.5	31.8 ± 6.8	30.4 ± 7.4	< 0.001
Hemoglobin, Mean ± SD (g/L)	10.1 ± 2.3	10.4 ± 2.2	10.3 ± 2.3	9.7 ± 2.4	< 0.001
WBC, Median (IQR) ($\times10^9$/L)	12.3 (8.8, 16.8)	11.9 (8.4, 16.2)	11.8 (8.6, 16.1)	13.0 (9.5, 18.0)	< 0.001
BUN, Median (IQR) (mg/dl)	22.0 (15.0, 36.0)	19.0 (13.0, 27.0)	21.0 (15.0, 30.0)	32.0 (20.0, 54.0)	< 0.001
Chloride, Mean ± SD (mEq/L)	100.2 ± 6.3	100.9 ± 6.6	100.7 ± 5.8	99.1 ± 6.2	< 0.001
Creatinine, Median (IQR) (mg/dl)	1.1 (0.8, 1.6)	0.9 (0.7, 1.2)	1.0 (0.8, 1.4)	1.5 (1.0, 2.7)	< 0.001
Sodium, Mean ± SD (mmol/L)	136.7 ± 5.2	136.8 ± 5.5	136.9 ± 4.8	136.4 ± 5.1	0.02
Calcium, Mean ± SD (mmol/L)	8.2 ± 0.8	8.1 ± 0.8	8.3 ± 0.7	8.2 ± 0.8	< 0.001
Platelets, Mean ± SD ($\times10^9$/L)	191.6 ± 93.1	187.1 ± 94.1	195.5 ± 89.8	192.1 ± 95.2	0.088
Potassium, Mean ± SD (mmol/L)	4.0 ± 0.6	3.8 ± 0.5	4.0 ± 0.5	4.3 ± 0.6	< 0.001
Comorbidities					
Myocardial infarct, n (%)					< 0.001
No	2805 (77.7)	968 (82)	942 (77.5)	895 (73.6)	
Yes	806 (22.3)	212 (18)	273 (22.5)	321 (26.4)	
Congestive heart failure, n (%)					< 0.001
No	2109 (58.4)	791 (67)	718 (59.1)	600 (49.3)	
Yes	1502 (41.6)	389 (33)	497 (40.9)	616 (50.7)	
Peripheral vascular disease, n (%)					0.185
No	2954 (81.8)	985 (83.5)	987 (81.2)	982 (80.8)	
Yes	657 (18.2)	195 (16.5)	228 (18.8)	234 (19.2)	
Dementia, n (%)					0.053
No	3420 (94.7)	1103 (93.5)	1154 (95)	1163 (95.6)	
Yes	191 (5.3)	77 (6.5)	61 (5)	53 (4.4)	
Cerebrovascular disease, n (%)					< 0.001
No	3086 (85.5)	997 (84.5)	1011 (83.2)	1078 (88.7)	
Yes	525 (14.5)	183 (15.5)	204 (16.8)	138 (11.3)	
Rheumatic disease, n (%)					0.996
No	3440 (95.3)	1124 (95.3)	1158 (95.3)	1158 (95.2)	
Yes	171 (4.7)	56 (4.7)	57 (4.7)	58 (4.8)	
Peptic ulcer disease, n (%)					0.068
No	3500 (96.9)	1138 (96.4)	1189 (97.9)	1173 (96.5)	
Yes	111 (3.1)	42 (3.6)	26 (2.1)	43 (3.5)	
Diabetes without cc, n (%)					0.935
No	2713 (75.1)	891 (75.5)	911 (75)	911 (74.9)	
Yes	898 (24.9)	289 (24.5)	304 (25)	305 (25.1)	

(*Continued*)

Table 1 (Continued).

Variables	Total (n = 3611)	Q1 (n = 1180) (<3.133mg/dl)	Q2 (n = 1215) (≥3.15 mg/dl, <4.0 mg/dl)	Q3 (n = 1216) (≥4.0 mg/dl)	*p*
Diabetes with cc, n (%)					< 0.001
No	3055 (84.6)	1034 (87.6)	1068 (87.9)	953 (78.4)	
Yes	556 (15.4)	146 (12.4)	147 (12.1)	263 (21.6)	
Paraplegia, n (%)					0.948
No	3490 (96.6)	1142 (96.8)	1173 (96.5)	1175 (96.6)	
Yes	121 (3.4)	38 (3.2)	42 (3.5)	41 (3.4)	
Renal disease, n (%)					< 0.001
No	2663 (73.7)	978 (82.9)	948 (78)	737 (60.6)	
Yes	948 (26.3)	202 (17.1)	267 (22)	479 (39.4)	
Malignant cancer, n (%)					0.47
No	3100 (85.8)	1023 (86.7)	1044 (85.9)	1033 (85)	
Yes	511 (14.2)	157 (13.3)	171 (14.1)	183 (15)	
Severe liver disease, n (%)					0.018
No	3467 (96.0)	1138 (96.4)	1177 (96.9)	1152 (94.7)	
Yes	144 (4.0)	42 (3.6)	38 (3.1)	64 (5.3)	
Metastatic solid tumor, n (%)					0.394
No	3389 (93.9)	1113 (94.3)	1144 (94.2)	1132 (93.1)	
Yes	222 (6.1)	67 (5.7)	71 (5.8)	84 (6.9)	
Sepsis3, n (%)					< 0.001
No	1839 (50.9)	627 (53.1)	677 (55.7)	535 (44)	
Yes	1772 (49.1)	553 (46.9)	538 (44.3)	681 (56)	
Severity of disease					
Charlson comorbidity index, Mean ± SD	7.1 ± 2.6	6.6 ± 2.6	7.0 ± 2.6	7.7 ± 2.7	< 0.001
SAPSII, Mean ± SD	37.3 ± 13.0	34.4 ± 11.1	35.3 ± 11.6	42.1 ± 14.8	< 0.001
Others					
Ventilation, n (%)					< 0.001
No	571 (15.8)	243 (20.6)	210 (17.3)	118 (9.7)	
Oxygen	1885 (52.2)	608 (51.5)	644 (53)	633 (52.1)	
Mechanical Ventilation	1155 (32.0)	329 (27.9)	361 (29.7)	465 (38.2)	
Antibiotic, n (%)					0.017
No	1143 (31.7)	374 (31.7)	417 (34.3)	352 (28.9)	
Yes	2468 (68.3)	806 (68.3)	798 (65.7)	864 (71.1)	
Outcome					
Mortality hospital, n (%)					< 0.001
No	3275 (90.7)	1103 (93.5)	1145 (94.2)	1027 (84.5)	
Yes	336 (9.3)	77 (6.5)	70 (5.8)	189 (15.5)	
Mortality 90 days, n (%)					< 0.001
No	2993 (82.9)	1031 (87.4)	1047 (86.2)	915 (75.2)	
Yes	618 (17.1)	149 (12.6)	168 (13.8)	301 (24.8)	

Abbreviations: BUN, Blood urea nitrogen; SAPS, Simplified acute physiology score; MBP, mean blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; WBC, white blood cell; CC, chronic complication; SD, standard deviation; IQR, Interquartile Range.

Correlation Between Serum Phosphate Levels and the Risk of Hospital Mortality and 90-Day Mortality

After adjusted for all the covariates in multivariate cox regression analysis, the hazard ratios between hospital mortality and 90-day mortality with the serum phosphate respectively were 1.19 (95% CI: 1.07–1.31 P<0.001) and 1.15 (95% CI: 1.06–1.24 p<0.001). Compared with the medium group Q2 (≥3.15, <4.0), the adjusted hazard ratio values for the serum phosphate and hospital mortality in Q1 (<3.133), and Q3 (≥4.0) were 1.32 (95% CI: 0.95–1.84, p=0.102), and 1.47 (95%

CI: 1.08–2, P<0.013), respectively. Likewise, the adjusted hazard ratio values for the serum phosphate and 90-day mortality in Q1 (<3.133), and Q3 (≥4.0), were 1.04 (95% CI: 0.83–1.3, p=0.763), and 1.31 (95% CI:1.06–1.61, p=0.013), respectively (Table 2). The non-linearity curve depicted the relationship between serum phosphate levels with hospital mortality and 90-day mortality (Figure 2). Hospital mortality (HR 0.664, 95% CI, 0.468–0.943, p=0.022) and 90-day mortality (HR 0.842, 95% CI, 0.662–1.072, p=0.1629) showed a downward trend when the serum phosphate level was less than 3.8 mg/dl. Furthermore, when the serum phosphate level was higher than 3.8 mg/dl, there was an increase in 90-day mortality (HR 1.236, 95% CI, 1.102–1.386, p<0.001) and hospital mortality (HR 1.312, 95% CI, 1.141–1.509, p<0.001) (Table 3).

Stratified Analysis

Stratified analysis was performed in several subgroups to assess any alterations in the relationship between serum phosphate levels and hospital mortality, as well as 90-day mortality (Figure 3). No significant interactions were observed in any of the subgroups when stratified by gender, age, renal disease, severe liver disease, antibiotic usage and congestive heart failure.

Sensitivity Analysis

The first serum phosphorus results after first 24 hours in ICU admission were analyzed by univariate cox regression analysis, the hospital mortality and 90-day mortality increased (HR 1.32, 95% CI:1.25–1.4, p<0.001), (HR 1.34, 95% CI:1.28–1.41, p<0.001), respectively. After adjusted for all the covariates in multivariate cox regression analysis, the results were generally consistent in hospital mortality (HR 1.17, 95% CI: 1.07–1.27 P<0.001) and 90-day mortality (HR 1.16, 95% CI: 1.09–1.24 p<0.001) with the serum phosphate (Supplementary Table 2). In addition, serum phosphate was according to values with 2.7–4.5mg/dl, after adjusted for all the covariates in multivariate cox regression analysis, the results were generally consistent between serum phosphate with hospital mortality (HR 1.17, 95% CI: 1.07–1.27 P<0.001) and 90-day mortality (HR 1.16, 95% CI: 1.09–1.24 p<0.001) (Supplementary Table 3).

Discussion

This retrospective cohort study provided evidence of a positive correlation between elevated serum phosphate levels and increased hospital and 90-day mortality in critically ill COPD patients using Cox multivariable regression analysis. Additionally, we found a non-linear relationship between serum phosphate levels and mortality, with a distinct inflection point at 3.8 mg/dl. When these patients were divided into three groups according to their serum phosphate levels within 24 hours of ICU admission, hospital and 90-day mortality rates were significantly higher in the elevated phosphate group compared to the control group. In the subgroup analysis, the relationship between age and kidney disease groups had a P-value below 0.05. Taking into account the issue of multiple testing[20] and applying the Bonferroni correction,[21] a P-value of less than 0.05 for the interaction between age and kidney disease may not be clinically significant between serum phosphate and mortality.

Based on a comprehensive review of recent literature, several findings have suggested a potential association between hyperphosphatemia and all-cause mortality in critically ill patients.[7,22] For example, In a study conducted by Wei Cao,[23] it was discovered that elevated levels of serum phosphorus were significantly associated with an augmented probability of heart failure during hospitalization, as well as overall mortality and mortality specifically related to the heart. Kyung Hoon Yang conducted a retrospective cross-sectional analysis involving 173 individuals undergoing hemodialysis. The study revealed that for every increase of 1 mg/dL in serum phosphorus levels, the likelihood of intradialytic hypotension increased by 2.1-fold.[24] Likewise, individuals with elevated serum phosphate levels also had worse outcomes in 28-day mortality and 90-day mortality in intensive care unit and metabolic syndrome.[7,25] Very few epidemiological studies have explored an association between serum phosphate and COPD, previous similar study has shown that comprehensive retrospective analysis involving 1199 hospitalized patients revealed a positive association between elevated serum phosphate levels and increased in-hospital mortality among individuals diagnosed with acute exacerbation of chronic obstructive pulmonary disease (AECOPD).[18] Our study results were consistent with this, showing that for each 1 mg/dL increase in serum phosphorus, in-hospital mortality increases by 19%, and 90-day mortality increases by 15%. Upon

Table 2 COX Regression Models to Assess the Association of the Average Level of Serum Phosphate with Hospital Mortality and 90-Day Mortality

			Crude		Model 1		Model 2		Model 3		Model 4	
	Variable	**n**	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
Hospital mortality	**Serum phosphate Quartile**	3611	1.35 (1.27~1.43)	<0.001	1.37 (1.29~1.46)	<0.001	1.36 (1.27~1.45)	<0.001	1.27 (1.15~1.41)	<0.001	1.19 (1.07~1.31)	0.001
	Q1 (<3.133)	1180	1.12 (0.81~1.55)	0.485	1.18 (0.85~1.63)	0.315	1.15 (0.83~1.6)	0.389	1.21 (0.87~1.68)	0.266	1.32 (0.95~1.84)	0.102
	Q2 (≥3.15,<4.0)	1215	1(Ref)		1(Ref)		1(Ref)		1(Ref)		1(Ref)	
	Q3 (≥4.0)	1216	2.24 (1.7~2.95)	<0.001	2.41 (1.83~3.18)	<0.001	2.37 (1.79~3.14)	<0.001	1.73 (1.27~2.34)	<0.001	1.47 (1.08~2)	0.013
90-day mortality	**Serum phosphate Quartile**	3611	1.38 (1.32~1.46)	<0.001	1.42 (1.35~1.5)	<0.001	1.35 (1.27~1.42)	<0.001	1.22 (1.12~1.32)	<0.001	1.15 (1.06~1.24)	<0.001
	Q1 (<3.133)	1180	0.92 (0.73~1.14)	0.434	0.95 (0.76~1.19)	0.662	0.95 (0.76~1.19)	0.648	0.96 (0.77~1.21)	0.758	1.04 (0.83~1.3)	0.763
	Q2 (≥3.15,<4.0)	1215	1(Ref)		1(Ref)		1(Ref)		1(Ref)		1(Ref)	
	Q3 (≥4.0)	1216	1.96 (1.62~2.37)	<0.001	2.09 (1.73~2.52)	<0.001	1.91 (1.57~2.31)	<0.001	1.45 (1.18~1.79)	<0.001	1.31 (1.06~1.61)	0.013

Notes: Model 1: Adjusted for sex and age. Model 2: Adjusted for covariates in Model 1 plus MI, CHF, dementia, CVD, paraplegia, Renal disease, Severe liver disease, Metastatic solid tumor and sepsis3. Model 3: Adjusted for covariates in Model 2 plus Heart rate, MBP, SBP, DBP, Temperature, RR, Hematocrit, Hemoglobin, WBC, BUN, Chloride, Creatinine, Calcium, Platelets and Potassium. Model 4: Adjusted for covariates in Model 3 plus CCI, SAPSII, Ventilation and Antibiotic.

Abbreviations: CI, confidence interval; BUN, Blood urea nitrogen; ICU, Intensive care unit; SAPS, Simplified acute physiology score; MBP, mean blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; WBC, white blood cell; MI, Myocardial infarct; CHF, Congestive heart failure; CVD, Cerebrovascular disease; RR, Respiratory rate; CCI, Charlson comorbidity index; HR, hazard ratio.

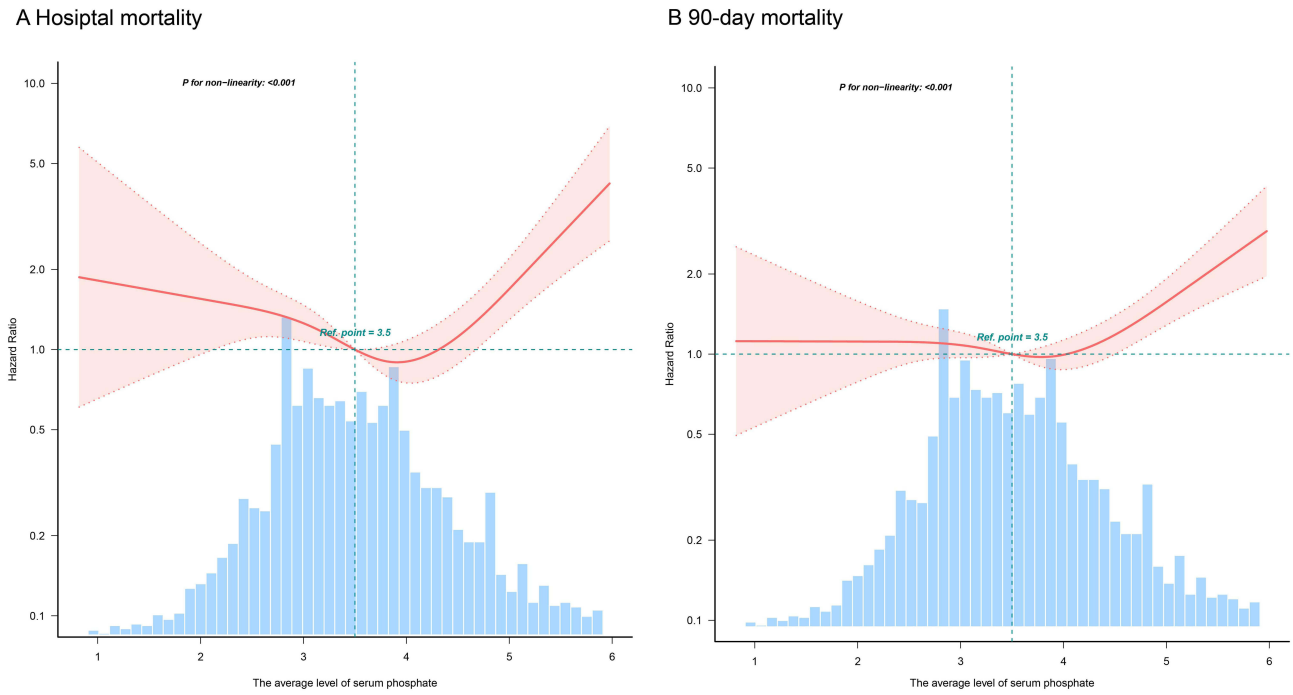

Figure 2 Association between serum phosphate and hospital mortality hazard ratio (**A**) and 90-day mortality hazard ratio (**B**). Solid lines signify the predicted values, while the 95% confidence intervals are marked with dashed lines. They were adjusted for sex, age, MI, CHF, dementia, CVD, paraplegia, renal disease, severe liver disease, metastatic solid tumor, sepsis3, Heart rate, MBP, SBP, DBP, temperature, RR, hematocrit, hemoglobin, WBC, BUN, chloride, creatinine, calcium, platelets, potassium, CCI, SAPSII, ventilation, antibiotic. Only 95% of data is showing.

categorizing serum phosphorus levels, we observed that the high serum phosphorus group, when compared to the second quartile, was associated with a higher risk for in-hospital mortality (HR 1.47, 95% CI 1.08–2) and mortality within 90 days (HR 1.31, 95% CI 1.06–1.61).

Numerous clinical studies have demonstrated that electrolyte disorders are common in COPD patients.[26–29] In COPD patients admitted to ICU, electrolyte disorders are often caused by various factors such as the disease itself or treatment. More important, the influence of serum phosphorus is often ignored in clinic. Serum phosphate disorder is a prevalent electrolyte imbalance that has been consistently linked to heightened mortality rates. To prevent raising the risk of disease progression, maintaining its concentration within the normal homeostatic range was essential. The reasons for heightened mortality in COPD patients with elevated serum phosphate levels were uncertain, but several potential explanations could exist. Primarily, parathormone, FGF23, and 1.25-dihydroxyvitamin D are important

Table 3 Threshold Effect Analysis of the Relationship of Serum Phosphate with Hospital Mortality and 90-Day Mortality in Patients of COPD

Serum Phosphate (mg/dl)	Hospital Mortality		90-Day Mortality	
	HR (95% CI)	*P*_ value	HR (95% CI)	*P*_ value
<3.8mg/dl	0.664 (0.468,0.943)	0.022	0.842 (0.662,1.072)	0.1629
≥3.8mg/dl	1.312 (1.141,1.509)	< 0.001	1.236 (1.102,1.386)	< 0.001
Likelihood Ratio test		0.004		0.016

Notes: Adjusted for sex, age, MI, CHF, dementia, CVD, paraplegia, renal disease, severe liver disease, metastatic solid tumor, sepsis3, Heart rate, MBP, SBP, DBP, temperature, RR, hematocrit, hemoglobin, WBC, BUN, chloride, creatinine, calcium, platelets, potassium, CCI, SAPSII, ventilation, antibiotic.

Abbreviations: COPD, Chronic obstructive pulmonary disease; CI, confidence interval; BUN, Blood urea nitrogen; ICU, Intensive care unit; SAPS, Simplified acute physiology score; MBP, mean blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; WBC, white blood cell; MI, Myocardial infarct; CHF, Congestive heart failure; CVD, Cerebrovascular disease; RR, Respiratory rate; CCI, Charlson comorbidity index; HR, hazard ratio.

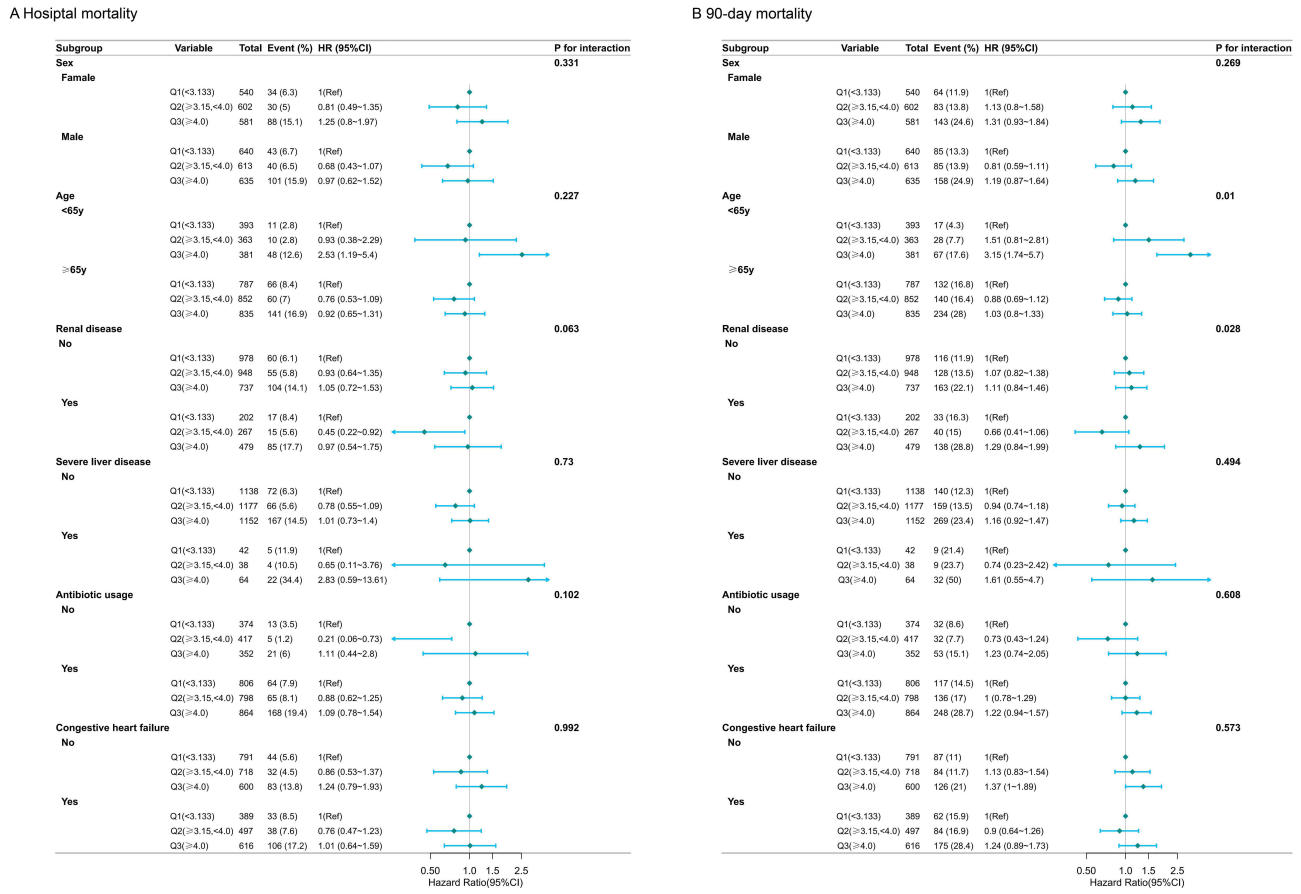

Figure 3 Subgroup analysis of the relationship between serum phosphate and hospital mortality (**A**) and 90-day mortality (**B**). They were adjusted for MI, CHF, dementia, CVD, paraplegia, metastatic solid tumor, sepsis3, Heart rate, MBP, SBP, DBP, temperature, RR, hematocrit, hemoglobin, WBC, BUN, chloride, creatinine, calcium, platelets, potassium, CCI, SAPSII, ventilation.

regulators of phosphate homeostasis that react to changes in serum phosphate levels by modifying the transcellular transporters occurs at both the intestinal and renal tubular levels.[8] The elevation of phosphorus levels could result in dysregulation of FGF23, an imbalance in parathyroid hormone, vascular calcification, and dysfunction of endothelial cells.[30] Secondly, cigarette smoking is widely recognized as the primary causative factor for COPD.[31] The act of smoking triggers the activation of the mitogen-activated protein kinase (MAPK) or extracellular signal-regulated kinase 1/2 (ERK1/2) signaling network, consequently resulting in amplified production of proinflammatory cytokines such as IL1B, IL6, and IL8.[32,33] Cigarette smoke has a pronounced impact on bronchial epithelial cells, rendering them particularly susceptible to its deleterious effects.[32,34] Furthermore, pathological alterations also observed in individuals with COPD encompass thickening of the airway walls, hyperplasia of goblet cells, and an augmented fractional volume of bronchial epithelial cells.[35,36] Meanwhile, for high serum phosphorus, it directly induced inflammation, cell apoptosis, cellular senescence, injury and epithelial-mesenchymal transition, oxidative stress.[35–37] Considering that this identical signaling pathway has been implicated as a crucial contributor to inflammation mediated by phosphates and FGF23.[33] Lack of FGF23 may lead to hyperphosphatemia and hyperphosphatemia may be involved in the pathogenesis of COPD.[38,39] Therefore, we considered that the influence of serum phosphorus on the mortality of COPD patients may be plausible.

An enormous percentage of people worldwide suffer from COPD, a prevalent and dangerous illness. The health and respiratory function of patients frequently deteriorate as they get sicker, which frequently results in death. There is a need for quick and inexpensive surveys that can predict mortality in patients with acute exacerbations. Previous studies have examined the prognostic significance of various easily assessable predictors, including eosinophil concentrations,[40] neutrophil-lymphocyte ratio,[41,42] red blood cell distribution width,[43] platelet lymphocyte ratio[44] and Serum Sodium.[45]

Our study indicated that a serum phosphorus concentration of 3.8 mg/dl is optimal, potentially serving as a reference for correcting serum phosphorus to reduce mortality in critically ill patients with COPD. Consequently, monitoring serum phosphorus could be a useful option for evaluating the prognosis of these patients.

The study leveraged data from MIMIC-IV (version 2.2), involving 3611 patients, thus benefiting from a large sample size that enhanced the validity of the findings. However, certain limitations should be acknowledged. Firstly, the study design was retrospective and limited to a single center, which may introduce bias and limit the generalizability of the results. Additionally, as the data were extracted from a public database, many indicators had missing values. Despite efforts to adjust for known confounders, there is a possibility of unmeasured variables impacting the results. Furthermore, a notable drawback of the study was the absence of lung function testing for most patients, preventing the classification of airflow restriction severity for all cases of COPD. Meanwhile, we only measured serum phosphorus levels in patients with COPD in the ICU. We did not investigate trends in serum phosphorus, which might provide more information. Additional prospective studies should be conducted in the future to investigate the clinical significance of blood phosphorus levels in individuals with severe COPD.

Conclusion

In critical care units, this study identified a non-linear correlation between serum phosphate levels and both hospital mortality and 90-day mortality in patients with COPD. An inflection point at 3.8mg/dL was observed. Elevated serum phosphate levels appear to be associated with higher rates of hospital mortality and 90-day mortality, although further confirmation is necessary through future prospective investigations.

Abbreviations

COPD, Chronic obstructive pulmonary disease; AECOPD, acute exacerbation chronic obstructive pulmonary disease; ICD, International Classification of Diseases; MIMIC, Medical Information Mart for Intensive Care; CI, confidence interval; BUN, Blood urea nitrogen; ICU, Intensive care unit; SAPS, Simplified acute physiology score; MBP, mean blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; WBC, white blood cell; MI, Myocardial infarct; CHF, Congestive heart failure; CVD, Cerebrovascular disease; RR, Respiratory rate; CCI, Charlson comorbidity index; HR, hazard ratio; FGF23, fibroblast growth factor 23; CC, chronic complication; SD, standard deviation; IQR, Interquartile Range.

Data Sharing Statement

Publicly available datasets were analyzed in this study. This data can be found here: https://physionet.org/content/mimiciv.

Ethics Statement

The research involving human participants underwent review and approval by the Institutional Review Board of the Massachusetts Institute of Technology and Beth Israel Deaconess Medical Center. Written informed consent for participation was not deemed necessary for this study in compliance with national legislation and institutional requirements. Additionally, this study was approved by the ethics review committee of The First People's Hospital of Jin tang County (No.20240423010).

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Author Contributions

All authors made a significant contribution to the work reported, whether in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas. They took part in drafting, revising, or critically

reviewing the article, gave final approval of the version to be published, agreed on the journal to which the article has been submitted, and agreed to be accountable for all aspects of the work.

Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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