Original Article

Impact of Admission Calcium-phosphate Product on 1-year Mortality among Hospitalized Patients

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Abstract

Background: Calcium-phosphate product is associated with mortality among patients with end-stage kidney disease on dialysis. However, clinical evidence among hospitalized patients is limited. The objective of this study was to investigate the relationship between admission calcium-phosphate product and 1-year mortality in hospitalized patients. **Materials and Methods:** All adult patients admitted to a tertiary referral hospital in 2009–2013 were studied. Patients who had both available serum calcium and phosphate measurement within 24 h of hospital admission were included. Admission calcium-phosphate product (calcium × phosphate) was stratified based on its distribution into six groups: <21, 21–<27, 27–<33, 33–<39, 39–<45, and ≥45 mg^2/dL^2. Multivariate cox proportional hazard analysis was performed to evaluate the association between admission calcium-phosphate product and 1-year mortality, using the calcium-phosphate product of 33–<39 mg^2/dL^2 as the reference group. **Results:** A total of 14,772 patients were included in this study. The mean admission calcium-phosphate product was 34.4 ± 11.3 mg^2/dL^2. Of these patients, 3194 (22%) died within 1 year of hospital admission. In adjusted analysis, admission calcium-phosphate product of ≥45 mg^2/dL^2 was significantly associated with increased 1-year mortality with hazard ratio of 1.41 (95% 95% confidence interval 1.25–1.67), whereas lower admission calcium-phosphate product was not significantly associated with 1-year mortality. **Conclusion:** Elevated calcium-phosphate product was significantly associated with increased 1-year mortality in hospitalized patients.

Keywords: *Calcium phosphate, hospital mortality, patients*

Introduction

Calcium and phosphate are essential elements for the human body and their derangements have adverse clinical effects.[1-4] Hypocalcemia and hypercalcemia are both associated with poor clinical outcomes including increased hospital mortality.[3,5,6] Elevated serum calcium may enhance vascular atherogenesis and tissue hypoxia via calcification and increased coagulability.[7] Increase in serum calcium is also associated with incident heart failure[7] and acute ischemic stroke.[8] Elevated serum phosphorus levels are associated with increased mortality across diverse population groups, regardless of chronic kidney disease (CKD) status.[9-16] Elevated serum phosphate is also an important risk factor for accelerated vascular calcification and cardiovascular events in patients with CKD and end-stage kidney disease (ESKD).[17]

Studies have demonstrated that elevated calcium-phosphate product (a multiplication of serum calcium and serum phosphate concentration) of >55 mg^2/dL^2 is associated with increased calcification of blood vessels and soft tissues and translates to poor cardiovascular and mortality outcomes,[9,18-30] especially in ESKD patients on maintenance hemodialysis.[9] While elevated serum calcium-phosphate product has correlated with poor short-term outcomes including acute kidney injury (AKI) and in-hospital mortality, little is known about the effects of calcium-phosphate product on 1-year mortality. This additional clinical knowledge would further impact the management of both calcium and phosphate derangement in different clinical settings.

Thus, we conducted this study to evaluate the impact of admission

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calcium-phosphate product on hospitalized patients' 1-year mortality.

Materials and Methods

Study population

This was a single-center cohort study conducted at Mayo Clinic Hospital, Rochester, Minnesota, USA. All hospitalized adult patients who had available admission serum calcium and phosphate between January 2009 and December 2013 were included in this study. In patients with multiple admissions during the study period, only the first hospitalization was included. The Mayo Clinic Institutional Review Board approved this study and exempted the need for informed consent due to the minimal risk nature of the study. All included patients provided research authorization for data use.

Data collection

Clinical characteristics, demographic information, and laboratory data were abstracted from the institutional electronic medical record system. The admission serum calcium and phosphate was obtained within 24 h of hospitalization. Serum calcium and phosphate levels were measured using a photometric method. This method was used throughout the study period. The admission calcium-phosphate product, which was obtained by multiplying total serum calcium and phosphate levels (calcium × phosphate), was the predictor of interest. Estimated glomerular filtration rate (eGFR) was calculated using the CKD Epidemiology Collaboration equation.[31] The Charlson comorbidity score was calculated to evaluate the burden of comorbidities at the time of admission.[32] Principal diagnoses were grouped based on admission ICD-9 codes.

The primary outcome was 1-year mortality. Patients' vital status was derived from our institutional registry and social security death index database.

Statistical analysis

All continuous variables were summarized as mean ± standard deviation. All categorical variables were summarized as counts with percentage. Patient characteristics were compared among admission serum calcium-phosphate product groups using ANOVA for continuous variables and Chi-square test for categorical variables. Admission calcium-phosphate product was categorized based on its distribution into six groups (<21, 21–<27, 27–<33, 33–<39, 39–<45, and ≥45 mg^2/dL^2). Given its lowest 1-year mortality, calcium-phosphate product of 33–<39 mg^2/dL^2 was selected as the reference group for outcome comparison. Patient survival was initiated at hospital admission and followed until death or the last inpatient/outpatient follow-up visit. One-year mortality risk was estimated using Kaplan–Meier plot and compared between admission serum calcium-phosphate product groups using a log-rank test. Multivariable cox proportional hazard analysis was constructed to adjust for priori-defined covariates when assessing the independent association between admission calcium-phosphate product and 1-year mortality. The hazard ratio (HR) was adjusted for age, sex, race, eGFR, principal diagnosis, Charlson score, history of coronary artery disease, congestive heart failure, peripheral vascular disease, stroke, diabetes mellitus, chronic obstructive pulmonary disease, cirrhosis, AKI, mechanical ventilation, vasopressor use at admission, calcium supplement use prior to admission, and year of hospitalization. A two-tailed $P < 0.05$ was considered statistically significant. All analyses were performed using JMP statistical software (version 10, SAS Institute, Cary, NC, USA).

Results

Clinical characteristics

A total of 14,772 patients were studied. About 54% were male. The mean age was 62 ± 18 years. The mean eGFR was 67 ± 35 ml/min/1.73 m^2. The mean admission calcium-phosphate product was 34.4 ± 11.3 mg^2/dL^2. The distribution of admission calcium-phosphate product was as follows: 8% with calcium-phosphate product of <21 mg^2/dL^2, 15% with 21–<27 mg^2/dL^2, 26% with 27–<33 mg^2/dL^2, 25% with 33–<39 mg^2/dL^2, 14% with 39–<45 mg^2/dL^2, and 12% with ≥45 mg^2/dL^2. Table 1 summarizes patient clinical characteristics based on admission calcium-phosphate product levels.

Admission serum calcium phosphate levels and 1-year mortality

Of 14,772 patients, 3194 (22%) died within 1 year of hospital admission. Based on the Kaplan–Meier plot in Figure 1, the cumulative 1-year mortality was 24.7% with admission calcium-phosphate product of <21 mg^2/dL^2, 26.0% with 21–<27 mg^2/dL^2, 23.9% with 27–<33 mg^2/dL^2, 22.9% with 33–<39 mg^2/dL^2, 25.0% with 39–<45 mg^2/dL^2, and 29.3% with ≥45 mg^2/dL^2 ($P < 0.001$). In unadjusted analysis, admission calcium-phosphate

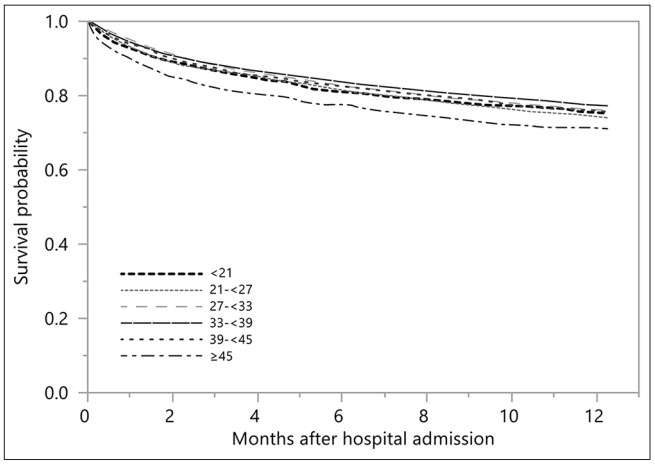

Figure 1: Kaplan–Meier plot showing 1-year mortality among patients with various admission serum calcium phosphate levels

product of 21–<27 and ≥45 mg^2/dL^2 was significantly associated with increased 1-year mortality. However, in adjusted analysis, only admission calcium-phosphate product of ≥45 mg^2/dL^2 was significantly associated with increased 1-year mortality with HR of 1.41 (95% confidence interval 1.25–1.67), while lower admission calcium-phosphate product was not significantly associated with 1-year mortality [Table 2]. A subgroup analysis of hospital survivors showed a similar association between admission calcium-phosphate product and 1-year mortality.

Subgroup analysis based on the chronic kidney disease status

In a subgroup analysis of patients without CKD, calcium-phosphate product of <21, 21–<27, and ≥45 mg^2/dL^2 was significantly associated with increased 1-year mortality [Table 3a]. In patients with CKD, only calcium-phosphate product of ≥45 mg^2/dL^2 was significantly associated with increased 1-year mortality [Table 3b]. There was an interaction between GFR and calcium-phosphate product on 1-year mortality (*P* for interaction = 0.001).

Discussion

By analyzing 14,772 patients, we demonstrated that calcium-phosphate product ≥45 mg^2/dL^2 was significantly associated with a 1.4-fold increased risk of mortality within 1 year. The increased 1-year mortality risk remained significant after adjustment for multiple clinical variables and regardless of CKD status.

Among patients with ESKD patients on maintenance hemodialysis, data from the US Renal Data System has suggested that an elevated calcium-phosphate product level was associated with increased mortality risk.[9] This risk was more pronounced in those with a calcium phosphorus product ≥72 mg^2/dL^2.[9] In line with our study, we have further shown that high calcium-phosphate product is detrimental in both CKD and non-CKD patients.

Table 1: Baseline clinical characteristics

Variables	All	Calcium-phosphate product at hospital admission (mg^2/dL^2)						
		<21	21-<27	27-<33	33-<39	39-<45	≥45	*P*
n	14772	1162	2219	3875	3631	2046	1839	
Age (years)	62±18	60±18	63±17	63±17	61±18	60±18	60±18	<0.001
Male	7937 (54)	565 (49)	1251 (56)	2116 (55)	1902 (52)	1041 (51)	1062 (58)	<0.001
Race								
Caucasian	13391 (91)	1041 (90)	2050 (92)	3553 (92)	3269 (90)	1822 (89)	1656 (90)	<0.001
African American	291 (2)	26 (2)	33 (1)	64 (2)	59 (2)	64 (3)	45 (2)	
Asian	169 (1)	19 (2)	11 (1)	39 (1)	50 (1)	25 (1)	25 (1)	
Others	921 (6)	76 (7)	125 (6)	219 (6)	253 (7)	135 (7)	113 (6)	
eGFR (ml/min/1.73 m^2)	67±35	78±32	77±30	73±30	70±33	62±38	36±36	<0.001
Principal diagnosis								
Cardiovascular	2787 (19)	136 (12)	336 (15)	768 (20)	802 (22)	404 (20)	341 (19)	<0.001
Endocrine/metabolic	864 (6)	75 (6)	132 (6)	195 (5)	189 (5)	111 (5)	162 (9)	
Gastrointestinal	1820 (12)	197 (17)	395 (18)	523 (13)	375 (10)	181 (9)	149 (8)	
Hematology/oncology	2412 (16)	146 (13)	357 (16)	663 (17)	637 (18)	358 (17)	251 (14)	
Infectious disease	744 (5)	158 (14)	148 (7)	166 (4)	124 (3)	70 (3)	78 (4)	
Respiratory	777 (5)	75 (6)	135 (6)	249 (6)	157 (4)	89 (4)	72 (4)	
Injury/poisoning	2343 (16)	178 (15)	328 (15)	633 (16)	627 (17)	333 (16)	244 (13)	
Other	3025 (20)	197 (17)	388 (17)	678 (17)	720 (20)	500 (24)	542 (29)	
Charlson score	2.4±2.7	2.2±1.7	2.3±2.7	2.3±2.7	2.3±2.6	2.4±2.7	2.7±2.7	<0.001
Comorbidities								
Coronary artery disease	3166 (21)	185 (16)	464 (21)	841 (22)	808 (22)	446 (22)	422 (23)	<0.001
Congestive heart failure	1316 (9)	56 (5)	148 (7)	338 (9)	352 (10)	196 (10)	226 (12)	<0.001
Peripheral vascular disease	569 (4)	30 (3)	63 (3)	133 (3)	154 (4)	83 (4)	106 (6)	<0.001
Stroke	1188 (8)	86 (7)	178 (8)	330 (9)	297 (8)	163 (8)	134 (7)	0.65
Diabetes mellitus	3524 (24)	221 (19)	470 (21)	862 (22)	868 (24)	544 (27)	559 (30)	<0.001
COPD	1448 (10)	90 (8)	241 (11)	407 (11)	347 (10)	181 (9)	182 (10)	0.02
Cirrhosis	648 (4)	73 (6)	105 (5)	188 (5)	125 (3)	60 (3)	97 (5)	<0.001
AKI	4378 (30)	219 (19)	412 (19)	825 (21)	951 (26)	773 (38)	1198 (65)	<0.001
Mechanical ventilation	998 (7)	122 (10)	175 (8)	239 (6)	191 (5)	121 (6)	150 (8)	<0.001
Vasopressor	698 (5)	82 (7)	88 (4)	144 (4)	148 (4)	89 (4)	147 (8)	<0.001
Calcium supplement	4590 (31)	365 (31)	661 (30)	1198 (31)	1115 (31)	612 (30)	639 (35)	0.01

Continuous data are presented as mean±SD, categorical data are presented as count (%). SD: Standard deviation, AKI: Acute kidney injury, COPD: Chronic obstructive pulmonary disease, eGFR: Estimated glomerular filtration rate

Table 2: The association between admission calcium-phosphate product levels and 1-year mortality

Calcium-phosphate product at hospital admission (mg^2/dL^2)	1-year mortality (%)	Univariate analysis		Multivariate analysis	
		HR (95% CI)	*P*	#Adjusted HR (95% CI)	*P*
<21	24.7	1.11 (0.96-1.29)	0.14	1.09 (0.94-1.26)	0.28
21-<27	26.0	1.16 (1.03-1.30)	0.01	1.09 (0.97-1.23)	0.13
27-<33	23.9	1.05 (0.95-1.16)	0.34	0.99 (0.90-1.10)	0.97
33-<39	22.9	1 (reference)	-	1 (reference)	-
39-<45	25.0	1.10 (0.98-1.24)	0.10	1.10 (0.98-1.24)	0.10
≥45	29.3	1.39 (1.24-1.56)	<0.001	1.41 (1.25-1.67)	<0.001

#Adjusted for age, sex, race, GFR, principal diagnosis, Charlson comorbidity score, coronary artery disease, congestive heart failure, peripheral vascular disease, stroke, diabetes mellitus, COPD, cirrhosis, AKI, mechanical ventilation, vasopressor use at admission, calcium supplement use prior to admission, and year of hospitalization. GFR: Glomerular filtration rate, HR: Hazard ratio, CI: Confidence interval, AKI: Acute kidney injury, COPD: Chronic obstructive pulmonary disease

Table 3: Subgroup analysis based on the chronic kidney disease

Calcium-phosphate product at hospital admission (mg^2/dL^2)	1-year mortality (%)	Univariate analysis		Multivariate analysis	
		HR (95% CI)	*P*	#Adjusted HR (95% CI)	*P*
a. eGFR ≥60 (*n*=8701)					
<21	24.4	1.38 (1.15-1.66)	0.001	1.29 (1.07-1.56)	0.01
21-<27	24.7	1.37 (1.18-1.60)	<0.001	1.25 (1.07-1.46)	0.004
27-<33	21.2	1.15 (0.99-1.32)	0.054	1.05 (0.92-1.21)	0.46
33-<39	19.0	1 (reference)	-	1 (reference)	-
39-<45	21.6	1.16 (0.97-1.39)	0.10	1.18 (0.99-1.41)	0.06
≥45	23.1	1.29 (1.02-1.63)	0.03	1.40 (1.11-1.78)	0.005
b. eGFR <60 (*n*=6071)					
<21	25.5	0.87 (0.67-1.11)	0.26	0.79 (0.62-1.03)	0.08
21-<27	28.8	0.99 (0.83-1.19)	0.91	0.94 (0.79-1.14)	0.54
27-<33	29.2	1.00 (0.86-1.16)	0.96	0.97 (0.83-1.12)	0.67
33-<39	28.8	1 (reference)	-	1 (reference)	-
39-<45	28.3	0.97 (0.82-1.14)	0.69	1.02 (0.87-1.20)	0.79
≥45	31.3	1.13 (0.98-1.30)	0.09	1.27 (1.09-1.48)	0.002

#Adjusted for age, sex, race, GFR, principal diagnosis, Charlson comorbidity score, coronary artery disease, congestive heart failure, peripheral vascular disease, stroke, diabetes mellitus, COPD, cirrhosis, AKI, mechanical ventilation, and vasopressor use at admission, calcium supplement use prior to admission, and year of hospitalization. GFR: Glomerular filtration rate, eGFR: Estimated GFR, HR: Hazard ratio, CI: Confidence interval, AKI: Acute kidney injury, COPD: Chronic obstructive pulmonary disease

However, our study contradicts the findings obtained from the Modification of Diet in Renal Disease (MDRD) Study cohort where elevated serum calcium-phosphate product had a trend toward increased cardiovascular disease (CVD)-related mortality in CKD patients but did not reach statistical significance after adjustment for GFR and other confounders.[33] However, the MDRD cohort was underpowered with a sample size of 840 patients. Furthermore, our patient cohort may represent a population at greater medical risk to disturbances of calcium and phosphorus balance, as indicated by the need for hospitalization. Our study comprising a large patient cohort across several years demonstrates that elevated calcium-phosphate product in hospitalized patients should warrant increased clinical attention and management.

The pathophysiologic mechanism for an elevation of serum calcium-phosphate product on adverse 1-year mortality outcome is not fully clear and likely multifactorial. High serum calcium and phosphate levels are associated with accelerated aortic and coronary calcification, especially in patients with CKD and ESKD.[9,18-30,34] This calcification predisposes patients to increased CVD-related mortality.[35] From an *in vitro* study, Reynolds *et al*. found that human vascular smooth muscle cells underwent vesicle-mediated calcification in response to changes in extracellular calcium and phosphate concentrations.[36] Prior studies have also revealed that elevated admission serum calcium-phosphate product is an independent risk factor for AKI in hospitalized patients,[29] and AKI *per se* is an independent risk factor itself for increased mortality with an adjusted relative risk varying from 1.6–3.9.[37,38]

It is worth noting that non-CKD patients with low admission calcium-phosphate product <27 mg^2/dL^2 also had an elevated risk of death within 1 year. We hypothesize that the underlying mechanism is related to the effects of hypocalcemia and hypophosphatemia. Hypocalcemia causes prolonged QT interval and other arrhythmias, which predispose patients to increased incidence of cardiac

death.[3,39] Likewise, hypophosphatemia is associated with ventricular ectopic activity,[40] rhabdomyolysis, metabolic encephalopathy, and respiratory failure.[41] However, we did not observe the statistical significance of low serum calcium-phosphate product and mortality rate in CKD patients. This could be due to the lack of statistical power from a small sample size.

Our study has several limitations. First, this is a single-center, retrospective cohort study. A causal relationship between calcium-phosphate product and mortality cannot be established. Second, the study population was predominantly Caucasian. Therefore, generalizability of this study may be limited. Third, although we extensively adjusted for potential confounders, this association may remain confounded by unmeasured or unknown factors. For example, information regarding the severity of illness and cause of calcium-phosphate product disturbance was lacking. The cause of death was also unknown, and this limits the ability to understand the pathological consequence of an abnormal calcium-phosphate product. Future studies consisting of a more diverse population and increased clinical data are needed to further assess this association.

Conclusion

This study comprises a large cohort demonstrating that an elevation of calcium-phosphate product ≥45 mg^2/dL^2 was significantly associated with increased 1-year mortality, whereas lower admission calcium-phosphate product was not significantly associated with 1-year mortality. Our results suggest that calcium-phosphate product should be calculated and taken into consideration for patient care.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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