



The relation between serum phosphorus levels and long-term mortality in Chinese patients with ST-segment elevation myocardial infarction

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Abstract

Background Elevated serum phosphorus levels may be associated with adverse outcomes in cardiovascular disease. This study aimed to investigate the relation between serum phosphorus levels and risk of all-cause mortality in Chinese patients with ST-segment elevation myocardial infarction (STEMI) who had preserved renal function at baseline. **Methods** We enrolled patients with STEMI who had preserved renal function at baseline in Xuanwu Hospital from January 2011 to December 2016. Those patients were divided into four groups based on serum phosphorus levels. All-cause mortality rates were compared between groups. Mean duration of follow up was 54.6 months. We used Cox proportional-hazards models to examine the relation between serum phosphorus levels and all-cause mortality after adjustment for potential confounders. **Results** 1989 patients were involved and 211 patients (10.6%) died during follow-up. Based on serum phosphorus levels, patients were categorized into the following groups: < 2.50 mg/dL ($n = 89$), 2.51–3.50 mg/dL ($n = 1066$), 3.51–4.50 mg/dL ($n = 672$) and > 4.50 mg/dL ($n = 162$), respectively. The lowest mortality occurred in patients with serum phosphorus levels between 2.51–3.50 mg/dL, with a multivariable-adjusted hazard ratio of 1.19 (95% CI: 0.64–1.54), 1.37 (95% CI: 1.22–1.74), and 1.46 (95% CI: 1.35–1.83) in patients with serum phosphorus levels of < 2.50 mg/dL, 3.51–4.50 mg/dL and > 4.50 mg/dL, respectively. **Conclusions** Elevated serum phosphorus levels were associated with all-cause mortality in Chinese patients with STEMI who had preserved renal function at baseline.

J Geriatr Cardiol 2019; 16: 775–781. doi:10.11909/j.issn.1671-5411.2019.10.004

Keywords: Mortality; Serum phosphorus levels; ST-segment elevation myocardial infarction

1 Introduction

Phosphorus is an essential element in the human body, which plays an important role in physiological processes, such as cell metabolism, intracellular signaling, bone structure, and protein synthesis.^[1] Approximately 80%–85% of total body phosphorus is stored in bone as hydroxyapatite, 14%–15% in soft tissue and less than 1% in the extracellular space.^[2] In normal adults, the fasting plasma phosphorus concentration ranges from 2.50 mg/dL to 4.50 mg/dL,^[3] and the major determinants of this physiologic range include daily dietary absorption, bone formation, urinary phosphate excretion, shifts between the intracellular and extracellular spaces, as well as phosphate-responsive hormones (such as fibroblast growth factor-23, parathyroid hormone and calcitriol). Thus, elevated serum phosphorus levels are ob-

served in many clinical setting such as chronic kidney disease (CKD) and secondary hyperparathyroidism.^[4,5]

There is controversy in the relation between elevated serum phosphorus levels and adverse cardiovascular outcomes. Both animal models and human studies have reported elevated serum phosphorus levels as strongly being associated with increased mortality and cardiovascular events in patients with cardiovascular disease (CVD),^[6–9] and recent studies have extended those observations to the general population.^[10–13] By contrast, several large studies found inconsistent associations between elevated serum phosphorus levels and CVD.^[14,15] Although the relationship and underlying biological mechanisms remain unclear, several potential factors have been postulated, such as vascular calcification, endothelial dysfunction, ventricular hypertrophy and atherosclerosis, of which vascular calcification appears to be the most important.^[6,16] Vascular calcifications due to elevated serum phosphorus levels may potentially interact and aggravate several cardiovascular risk factors. In the present study, we used a retrospective database to investigate the relation between elevated serum phosphorus levels and risk of all-cause mortality in Chinese patients with

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Received: June 9, 2019

Revised: July 26, 2019

Accepted: September 24, 2019

Published online: October 28, 2019

ST-segment elevation myocardial infarction (STEMI) who had preserved function at baseline.

2 Methods

2.1 Study population

This was a single-center, retrospective analysis. We enrolled 1989 patients with STEMI who had preserved renal function at baseline in Xuanwu Hospital from January 2011 to December 2016. STEMI is a clinical syndrome defined by characteristic symptoms of myocardial ischemia in association with persistent electrocardiographic ST-segment elevation and subsequent release of biomarkers of myocardial necrosis. Coronary angiography was performed for clinical purposes and CVD prospectively assessed as normal (0% to < 10% stenosis), mild/moderate (10% to < 70% stenosis), or severe (\geq 70% stenosis). The inclusion criteria was an estimated Glomerular Filtration Rate (eGFR) > 60 mL/min per 1.73 m², as calculated by the Modification of Diet in Renal Disease formula, these patients were considered to have preserved renal function as per recent guidelines.^[17] We excluded patients with any renal, hepatic, autoimmune diseases, malignancy, and current use of bisphosphonates, calcium supplements, vitamin D supplements, steroids, or anticonvulsants. Baseline blood analyses were measured on admission. Demographic data (including age, gender, diabetes, hypertension, dyslipidemia and so on) and comorbidities (prior myocardial infarction and history of cerebrovascular disease) were also recorded (Figure 1).

2.2 Classification of serum phosphorus levels

Baseline serum phosphorus levels were measured on admission using XE-5000 automated hematology analyzer (Sysmex, Kobe, Japan) and considered as a continuous

variable (normal range, 2.50–4.50 mg/dL).^[3] To evaluate relation between serum phosphorus levels and clinical outcome, the 1989 patients were categorized into the following groups: < 2.50 mg/dL ($n = 89$), 2.51–3.50 mg/dL ($n = 1066$), 3.51–4.50 mg/dL ($n = 672$) and > 4.50 mg/dL ($n = 162$), respectively.

2.3 Clinical outcome

The end-point of this study was the incidence of all-cause death. Cardiac death was defined as death caused by recurrent myocardial infarction (RMI), heart failure, serious cardiac arrhythmias and sudden death.^[18] Clinical outcome data were collected until November 1, 2018 and mean duration of follow up was 54.6 months after hospital discharge. Clinical event data were fully collected during the follow-up period for all patients by reviewing the national death registry and by contacting each patient individually and independently reviewing the hospital course for major clinical events if the patient had been rehospitalized.

2.4 Statistical analysis

For baseline characteristics, variables are summarized as percentages for discrete variables and means \pm SD for continuous variables (median with standard error for non-normally distributed variables). We used χ^2 test or analysis of variance, respectively, to test for differences in categorical or continuous factors between different groups of phosphorus.

The association between serum phosphorus level and clinical and biochemical variables was assessed by univariable linear regression for each variable separately. The following variables were considered for multivariable linear regression model: age, gender, creatinine, blood urea nitrogen, eGFR, serum calcium levels, and history of hypertension, diabetes mellitus.

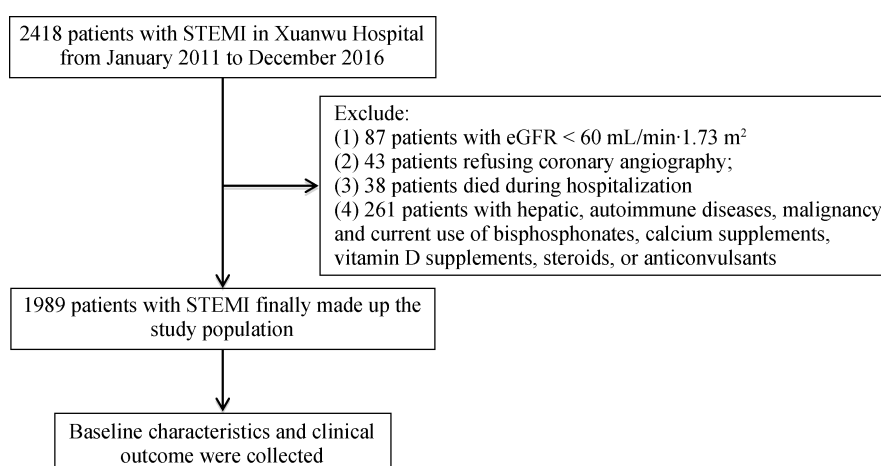


Figure 1. Flowchart depicting the inclusion and exclusion of the patients in the present study. eGFR: estimated Glomerular Filtration Rate; STEMI: ST-segment elevation myocardial infarction.

Survival curves were constructed using the Kaplan-Meier method, and comparisons were made using the log-rank test. Cox proportional hazards models with enter selection were used to calculate hazard ratios (HRs) and 95% confidence intervals (CI) for serum phosphorus groups adjusted for age, gender, creatinine, blood urea nitrogen, eGFR, serum calcium levels, coronary revascularization, and history of hypertension, diabetes mellitus, dyslipidemia, prior myocardial infarction and cerebrovascular disease. Statistical analyses were performed using the SPSS statistical software version 17.0 (Chicago, IL). Differences were considered statistically significant at the two-sided $P < 0.05$.

3 Results

3.1 Baseline characteristics

Baseline characteristics and medications are shown in Table 1. We enrolled 1989 patients with STEMI who had preserved renal function at baseline in Xuanwu Hospital from January 2011 to December 2016. The majority of patients ($n = 1738$, 87.4%) had serum phosphorus levels within the normal range, while 89 (4.5%) patients had hypophosphatemia and 162 (8.1%) had hyperphosphatemia. Compared with the lowest serum phosphorus level, those with higher concentrations had higher blood urea nitrogen,

Table 1. Baseline characteristics.

Variable	Serum phosphorus				P-value
	< 2.50 mg/dL (n = 89)	2.51–3.50 mg/dL (n = 1066)	3.51–4.50 mg/dL (n = 672)	> 4.50 mg/dL (n = 162)	
Age, yrs	68.1 ± 11.1	66.7 ± 10.0	65.3 ± 9.4	62.8 ± 11.1	< 0.01
Female	12 (13.5%)	245 (23.0%)	209 (31.1%)	76 (46.9%)	< 0.01
Hypertension	52 (58.9%)	556 (52.2%)	356 (53.0%)	99 (61.4%)	0.03
Diabetes mellitus	24 (26.7%)	240 (22.5%)	125 (18.6%)	54 (33.1%)	0.01
Dyslipidemia	47 (52.4%)	607 (56.9%)	372 (55.3%)	95 (58.8%)	0.27
Prior MI	6 (6.7%)	95 (8.9%)	48 (7.1%)	14 (8.6%)	0.08
Cerebrovascular disease	12 (13.5%)	174 (16.3%)	97 (14.4%)	26 (15.8%)	0.16
Cr, mg/dL	0.85 ± 9.5	0.88 ± 11.4	0.86 ± 10.3	0.92 ± 11.2	< 0.01
BUN, mg/dL	13.88 ± 1.3	14.44 ± 1.3	14.78 ± 1.5	15.0 ± 1.5	< 0.01
eGFR, mL/min-1.73 m ²	108.7 ± 20.6	102.3 ± 22.5	104.2 ± 25.8	93.4 ± 29.4	< 0.01
ALT, U/L	22.0 ± 10.7	21.5 ± 12.4	21.2 ± 11.5	23.7 ± 14.3	0.14
AST, U/L	24.7 ± 11.4	24.9 ± 14.7	23.1 ± 12.5	23.2 ± 11.8	0.26
T-Cho, mg/dL	165.1 ± 1.0	170.1 ± 1.0	194.9 ± 1.3	181.0 ± 1.1	0.53
TG, mg/dL	163.8 ± 1.2	167.4 ± 1.5	160.3 ± 1.1	171.8 ± 1.1	0.19
HDL-C, mg/dL	36.7 ± 0.2	40.6 ± 0.3	42.1 ± 0.3	41.0 ± 0.3	0.43
LDL-C, mg/dL	92.4 ± 0.8	93.2 ± 0.7	94.7 ± 0.6	98.6 ± 0.7	0.76
Fasting plasma glucose, mg/dL	113.4 ± 2.4	108.5 ± 2.3	104.0 ± 1.8	103.9 ± 2.1	0.85
Serum calcium, mg/dL	8.6 ± 0.15	8.78 ± 0.13	8.9 ± 0.14	9.1 ± 0.12	0.01
Coronary revascularization	73 (82.4%)	851 (79.8%)	541 (80.5%)	131 (80.9%)	0.08
Aspirin	86 (96.8%)	1030 (96.6%)	640 (95.3%)	157 (97.2%)	0.67
DAPT	83 (92.8%)	995 (93.3%)	625 (93.0%)	150 (92.6%)	0.49
Statin	75 (84.2%)	906 (85.0%)	569 (84.7%)	138 (85.4%)	0.74
β-blocker	58 (64.9%)	674 (63.2%)	435 (64.7%)	102 (62.8%)	0.77
Ca-blocker	37 (41.9%)	442 (41.5%)	285 (42.4%)	68 (42.1%)	0.24
ACE-I/ARB	56 (63.3%)	671 (62.9%)	423 (63.0%)	103 (63.7%)	0.31
OHA	22 (24.5%)	252 (23.6%)	153 (22.7%)	41 (25.2%)	0.10
Insulin	16 (17.8%)	176 (16.5%)	110 (16.4%)	30 (18.6%)	0.09

Data are presented as means ± SD or n (%). ACE-I: angiotensin-converting enzyme inhibitor; ALT: glutamic-pyruvic transaminase; ARB: angiotensin receptor blocker; AST: glutamic-oxaloacetic transaminase; BUN: blood urea nitrogen; Cr: creatinine; DAPT: dual antiplatelet therapy; eGFR: estimated Glomerular Filtration Rate; HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol; MI: myocardial infarction; OHA: oral hypoglycemic agents; T-Cho: total cholesterol; TG: triglyceride.

Table 2. Multiple linear regression analysis with serum phosphorus levels as the dependent variable.

Independent variable	Regression coefficient (SE)	95% CI	P-value
Age, per decade	-0.05 (0.02)	-0.08–0.02	< 0.01
Female gender	0.16 (0.02)	0.08–0.24	< 0.01
Hypertension	0.14 (0.05)	0.07–0.21	0.04
Diabetes mellitus	0.12 (0.05)	0.06–0.15	0.02
eGFR	-0.04 (0.02)	-0.06–0.02	< 0.01

eGFR: estimated glomerular filtration rate; SE: standard error.

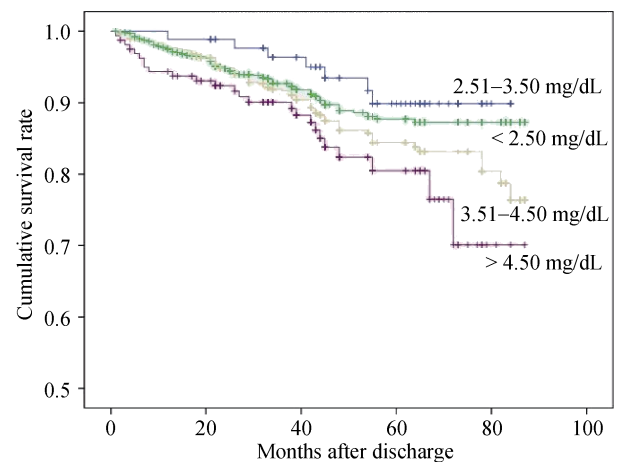
higher creatinine and lower eGFR. Patients with higher phosphorus levels also were more likely to be younger and females, and had higher prevalence of hypertension, diabetes mellitus, and had reduced renal function and hemoglobin levels. No significant differences in baseline medication were identified between the groups.

In a multivariable linear regression model, serum phosphorus levels were associated with age, female gender, hypertension, diabetes mellitus, and eGFR (Table 2).

3.2 Clinical outcomes

Patients were followed between two years and seven years (mean 54.6 months). 211 patients (10.6%) died, including 158 deaths from cardiac causes (RMI, $n = 43$; heart failure, $n = 79$; serious cardiac arrhythmias, $n = 29$; and sudden death, $n = 7$) during the follow-up period. Kaplan-Meier curves showed that the lowest mortality occurred in patients with serum phosphorus levels between 2.51–

3.50 mg/dL. Mortality was higher in patients with hypophosphatemia and in patients with serum phosphorus between 3.51–4.50 mg/dL, with a marked increase in mortality among patients with hyperphosphatemia (Figure 2). The results of the Cox proportional hazards model examining the relationship between serum phosphorus levels and all-cause mortality using 2.51–3.50 mg/dL as the reference group. After adjustment for other factors independently associated with mortality, the risk associated with low phosphorus level was no longer significant. The risk associated with elevated phosphorus levels was attenuated but remained statistically significant with increased risk for mortality even for patients with phosphorus levels within the normal range (Table 3).

**Figure 2. Kaplan-Meier curves of mortality****Table 3. Cox proportional hazards models of clinical outcome.**

Variable	Regression coefficient (SE)	Hazard ratio	95% CI	P-value
Age	-0.02 (0.01)	0.98	0.97–0.99	< 0.01
Gender, female	0.06 (0.06)	1.06	1.01–1.12	0.02
Creatinine	-0.00 (0.00)	1.00	0.99–0.01	0.45
Blood urea nitrogen	-0.03 (0.04)	0.97	0.91–1.04	0.38
eGRF	0.03 (0.02)	1.03	1.00–1.06	0.20
Serum calcium level	0.01 (0.01)	1.01	0.99–1.02	0.33
Coronary revascularization	-0.01 (0.07)	0.98	0.86–1.14	0.86
Hypertension	0.07 (0.06)	1.08	0.97–1.20	0.18
Diabetes mellitus	-0.01 (0.05)	0.99	0.90–1.09	0.86
Dyslipidemia	0.15 (0.06)	1.17	1.04–1.29	< 0.01
Prior myocardial infarction	0.10 (0.08)	1.10	0.94–1.29	0.23
Prior cerebrovascular disease	0.01 (0.08)	1.01	0.86–1.18	0.92
Phosphorus levels				
< 2.50 mg/dL	0.17 (0.03)	1.19	0.64–1.54	0.06
2.51–3.50 mg/dL	-	-	1.0 (Referent)	-
3.51–4.50 mg/dL	0.32 (0.04)	1.37	1.22–1.74	< 0.01
> 4.50 mg/dL	0.38 (0.01)	1.46	1.35–1.83	< 0.01

eGFR: estimated glomerular filtration rate; SE: standard error.

4 Discussion

To our knowledge, many but not all studies have found an association between baseline higher serum phosphorus and an increased risk of mortality in subjects with CKD or with normal renal function. The main finding in the present study also is that elevated serum phosphorus levels are associated with all-cause mortality in patients with STEMI from the point of statistical view. The association remained significant even after adjustment for other independent variables.

Phosphorus is micronutrient traditionally viewed in relation to bone health or CKD. It was not until recently that phosphorus was identified as a marker of increased morbidity and mortality. The association between serum phosphorus levels and cardiovascular risk was first demonstrated in the CKD population. Several recent studies demonstrated that elevated serum phosphorus levels were associated with an increased risk of all-cause and cardiovascular death when kidney function is impaired, especially in people with end-stage renal disease.^[6-9] Subsequent studies have extended those observations to the general population.^[10-13] A large community based cohort study demonstrated that serum phosphate levels were associated with cardiovascular events in both people with normal renal function and those with CKD.^[19] Tonelli M, *et al.*^[20] and Aronson D, *et al.*^[21] reported a graded independent relation between elevated serum phosphorus levels and the risk of death and cardiovascular events in people with prior myocardial infarction. Our study enrolled patients with STEMI who had preserved function at baseline, and the finding is consistent with previous studies.

Serum phosphorus level is determined by regulating intestinal absorption, bone mobilization, and renal excretion,^[22] and may be affected factors such as complications, gender, and smoking.^[23,24] In current study, we also observe that serum phosphorus is associated with age, gender, hypertension, diabetes mellitus and eGFR according to the analysis of baseline characteristics and following multivariable linear regression model. This result suggests that renal function is still an important factor for serum phosphorus even in patients with preserved eGFR, while the underlying mechanism of other factors remains unclear. Prior studies may provide some reasonable assumptions. Dietary intake is the main source of serum phosphorus, thus poor appetite and low protein intake poor may have a great effect on serum phosphorus levels, particularly in elderly patients.^[25] Females experience a decrease in estrogen and a subsequent increase in serum phosphorus concentration after menopause,^[12] for estrogen may directly induce renal phosphorus

excretion, playing an important role on phosphorus homeostasis.^[24] As for hypertension and diabetes, they both may be involved in the regulation of blood phosphorus through chronic inflammation and insulin resistance.^[26]

Although recent studies have showed that phosphorus is a prognostic factor for CVD, the underlying biological mechanisms have not yet been fully understood. Several potential factors have been postulated, such as vascular calcification, endothelial dysfunction, ventricular hypertrophy and atherosclerosis, of which vascular calcification appears to be the most important.^[27-31] And reducing phosphorus absorption may significantly decreased calcification.^[32] Vascular calcification is a complex process regulated by several mediators, including fibroblast growth factor-23 (FGF-23), uncarboxylated matrix Gla protein, bone morphogenetic protein-2 inorganic pyrophosphate, and fetuin-A.^[33] The hallmark of vascular calcification is calcium phosphate deposition, which can occur in the vasculature, myocardium, and cardiac valves. Elevated serum phosphorus levels can induce a phenotypic transformation of a cultured smooth muscle cell into an osteoblast-like cell that initiates calcification of the extracellular milieu.^[29,34] Vascular calcification occurs independently of atheroma and is an important cause of vascular stiffness leading to increased pulse wave velocity, increased left ventricular hypertrophy.^[35,36] Alternatively, phosphorus may induce direct vascular damage via deposition of hydroxyapatite crystals in the context of the arterial wall and this in turn may induce a self-sustaining process of crystals deposition and inflammation, as shown in experimental models.^[37]

Whether elevated serum phosphorus levels contribute to atherosclerosis is also unclear. High dietary phosphate intake has recently been shown to accelerate atherogenesis in ApoE knockout mice, independently of calcification.^[38] Among patients with minimal impairment of kidney function, Kanbay, *et al.*^[39] found that FGF-23 also independently predicted coronary atheroma burden. A number of mechanisms may link phosphate exposure with atherosclerosis, these can be divided into direct effects of phosphate and those mediated by compensatory changes in phosphate-regulating hormones.

By contrast, several large studies found inconsistent associations between elevated serum phosphorus levels and CVD. In 15,732 participants of the Atherosclerosis Risk in Communities Study with mean follow-up of 12.6 years, higher serum phosphorus was associated with increased risk for mortality but not of coronary disease.^[9] An analysis of 7,259 postmenopausal women reported no associations between serum phosphorus levels and incident cardiovascular events during four years of follow-up.^[14] In a recent nested

case-control study of men without CKD from the Health Professionals Follow-up Study, serum phosphorus levels were not associated with the development of incident CVD during ten years of follow-up.^[15] Thus, further studies are needed to clarify the relationship between serum phosphorus levels and different clinical endpoints.

4.1 Limitations

Some limitations in the present study must be considered. Firstly, this was a single-center, retrospective analysis. Residual confounding factors might thus have affected the results, regardless of the adjusted analysis. Secondly, laboratory data including parathyroid hormone, vitamin D and FGF-23 also associated with adverse outcomes were not measured. Last but not least, further studies are needed to clarify the mechanisms underlying the relationship between serum phosphorus levels and mortality.

4.2 Conclusions

In conclusion, elevated serum phosphorus levels were associated with all-cause mortality in Chinese patients with STEMI who had preserved renal function at baseline. Serum phosphorus levels might be useful as a marker for risk stratification in Chinese patients with STEMI.

Acknowledgments

All authors had no conflicts of interest to disclose.

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