Age differences in associations of serum alkaline phosphatase and mortality among peritoneal dialysis patients

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To the Editor: Serum alkaline phosphatase (ALP) is an important bone turnover marker in chronic kidney disease (CKD) patients, with studies indicating that higher serum ALP levels are associated with increased mortality in hemodialysis (HD) patients.[1] Our previous study also showed that higher serum ALP levels were independently associated with all-cause and cardiovascular mortality in peritoneal dialysis (PD) patients.[2] Recently, a report from Taiwan (China) revealed that ALP concentrations were not associated with mortality in PD patients over a 5-year period.[3] The outcome-predictability using ALP in PD patients, therefore, remains uncertain, and the relationship between serum ALP and all-cause mortality in different ages remains unclear. Here, we investigated the relationship of serum ALP with all-cause mortality in younger and elderly PD patients.

This study was a retrospective cohort study conducted in a single PD center of The First Affiliated Hospital, Sun Yat-sen University, Guangzhou, China. The study was conducted in compliance with the ethical principles of the *Declaration of Helsinki* and approved by the Human Ethics Committees of Sun Yat-sen University. All selected patients were incident patients who started PD between 1 January 2006 and 31 December 2011. Inclusion criteria were age ≥18 years at the initiation of PD and PD treatment for more than 90 days. Patients who were catheterized in other hospitals, transferred from failed renal transplantation or permanent HD, or with malignancy, were excluded, as were patients without baseline ALP data. A total of 1273 incident PD patients were recruited and followed up until 31 December 2013.

Baseline demographic and clinical data were collected at the initiation of PD therapy. Biochemical parameters were obtained during the first 1 to 3 months after the start of PD therapy. Baseline residual renal function was assessed by 24-h urine output. The comorbidity score was estimated using the Charlson Comorbidity Index. Cardiovascular disease (CVD) was defined as a past history of or current myocardial infarction, angina, peripheral vascular disease or cerebrovascular disease.

Patients were divided into younger (age <65 years) and elderly (age ≥65 years) groups, and further stratified into quartiles (Qs) of serum ALP levels, which were calculated separately in the younger group (Q1 ≤56 U/L; Q2 56–69 U/L; Q3 70–88 U/L; Q4 ≥88 U/L) and the elderly group (Q1 ≤61 U/L; Q2 61–76 U/L; Q3 77–97 U/L; Q4 ≥97 U/L). Descriptive analyses were performed to summarize the demographic characteristics and the baseline data for the groups stratified by age and baseline ALP values. Mean ± standard deviation (SD) were calculated for normally distributed continuous variables, and medians (interquartile ranges [IQR]) were calculated for continuous variables which were not normally distributed. Categorical variables were expressed as proportions. Cumulative survival curves were calculated using Kaplan-Meier analysis, and differences in survival probabilities among groups were assessed by the log-rank test. We used Cox proportional hazard models to assess the association between serum ALP levels and all-cause mortality in the younger and elderly groups. The relationship between ALP level and all-cause mortality was evaluated by both continuous ALP and ALP quartiles. Covariates were age, sex, diabetes mellitus, CVD, 24-h urine output, hemoglobin, serum albumin levels, neutrophil to lymphocyte ratio (N/L), serum alanine aminotransferase (ALT), albumin-corrected calcium, serum phosphorus, as well as intact parathyroid hormone (iPTH), and medication use, including vitamin D analogs and phosphate binders. The results were expressed as the hazard ratio (HR) and 95% confidence interval (95% CI). All analyses were performed using SPSS software version 16.0 (SPSS, Inc., Chicago, IL, USA). Statistical significance was defined at $P < 0.05$.

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In total, 1473 incident PD patients were catheterized at our PD center, of whom 17 patients were younger than 18 years, 72 patients were on PD for less than 3 months, 9 patients were transferred after failed renal transplantation, 54 patients were transferred from permanent HD, and 26 patients had malignant disease. Of the remaining 1295 patients, 1273 had ALP measured at baseline and were eligible for the present analysis [Supplementary Figure 1, http://links.lww.com/CM9/A5].

The baseline characteristics of patients stratified by age group are shown in Supplementary Table 1, http://links.lww.com/CM9/A4. Based on the cutoff age of 65 years, there were 1068 younger patients (<65 years old), with age of 43.4 ± 12.0 years, and 205 elderly (≥65 years old) patients with age of 71.8 ± 4.6 years. The elderly patients had higher serum ALP levels and N/L, but lower 24-h urine output, diastolic blood pressure (DBP), serum albumin, phosphorus, iPTH, blood nitrogen (BUN), serum creatinine and uric acid (UA) levels than the younger patients. The elderly patients also had a higher prevalence of diabetes mellitus and CVD. The younger patients tended to be more likely to use vitamin D analogs and physiologic calcium peritoneal dialysate. Phosphate binder use was also higher in the younger patients, although the result was not statistically significant ($P = 0.051$).

In the younger group, baseline serum ALP levels ranged from 10 to 933 U/L (median 70 U/L, IQR 56–88 U/L, mean 79 U/L), and 127 (11.9%) patients had ALP levels beyond the normal range in our laboratory (0–110 U/L). Supplementary Table 2, http://links.lww.com/CM9/A4 shows the baseline data stratified by ALP Qs in the younger patients. Younger patients with higher ALP levels were older, more likely to have diabetes, and had higher comorbidity scores, N/L, iPTH, ALT, and aspartate aminotransferase (AST) levels, but lower phosphorus, BUN, serum creatinine, and UA levels. Younger patients who had higher ALP levels also had higher ratio of physiologic calcium peritoneal dialysate use. Medication use was not significantly different among each ALP Q in the younger group.

In the elderly group, baseline serum ALP levels ranged from 15 to 389 U/L (median 77 U/L, IQR 61–97 U/L, mean 86 U/L), and 36 (17.6%) patients had an ALP level over 110 U/L. Supplementary Table 3, http://links.lww.com/CM9/A4 shows the baseline data stratified by ALP Qs in the elderly patients. Elderly patients with the highest ALP Qs had the lowest systolic blood pressure. There were no significant differences among the elderly Q groups regarding other characteristics.

After a median of 34.2 (IQR 20.8–48.5) months' follow-up, 144 (13.5%) younger patients and 104 (50.7%) elderly patients died. Of 144 deaths, 77 (53.5%) in the younger group and 58 (55.8%) in the elderly group were caused by CVD.

Figure 1 shows Kaplan-Meier survival curves of ALP Qs in different groups. In the younger group, at the end of 1, 3, and 5 years, all-cause mortality was 3.0%, 7.4%, and 9.3%, respectively, in the Q1 group; 1.9%, 7.4%, and 10.7%, respectively, in the Q2 group; 2.6%, 6.7%, and 10.7%, respectively, in the Q3 group; and 3.1%, 10.0%, and 18.9%, respectively, in the Q4 group. Patient survival was significantly lower in the Q4 group compared with the other three Qs ($P = 0.014$) [Figure 1A]. In the elderly group, all-cause mortality at the end of 1, 3, and 5 years was 11.1%, 29.6%, and 51.9%, respectively, in the Q1 group; 20.0%, 44.0%, and 50.0%, respectively, in the Q2 group; 11.8%, 33.3%, and 54.9%, respectively, in the Q3 group; and 24.0%, 46% and 52.0%, respectively, in the Q4 group. There was no significant difference in survival rates among the 4 groups of elderly patients ($P = 0.683$) [Figure 1B].

After adjusting for demographics, comorbid diseases, 24-h urine output, liver function, nutrition, inflammation, bone metabolism parameters, and medication use, we found that each 10 U/L higher ALP level was associated with a 5.6% higher hazard (95% CI, 1.03–1.09; $P < 0.001$) for all-cause mortality in overall patients using Cox proportional hazards model (data not shown). Table 1 shows the results of Cox regression models that investigated the relationship of baseline serum ALP values with all-cause mortality in younger and elderly patients. Regardless of the adjustment method used, the highest quartile (Q4) was significantly associated with higher all-cause mortality compared to the lowest quartile (Q1) in the younger group. However, the risk of all-cause mortality in the middle quartile (Q2 and Q3) did not statistically significantly differ from the lowest quartile (Q1). In the multivariable adjusted model, each 10 U/L higher ALP level was associated with a 6.4% higher hazard (95% CI, 1.03–1.10; $P < 0.001$) for all-cause mortality in the younger patients. After adjustment for age, gender, comorbid diseases, 24-h urine output, hemoglobin level, serum albumin level, N/L, iPTH level, albumin-corrected calcium level, serum phosphorus level, vitamin D analog use and phosphate binder use, there was no significant association between ALP levels and all-cause mortality in the elderly group (HR: 1.04, 95% CI: 0.99–1.10; $P = 0.101$).

In this retrospective analysis of PD patients, we found that elevated serum ALP levels were associated with higher all-cause mortality in PD patients. Furthermore, we demonstrated the differences between younger and elderly populations in the impact of baseline serum ALP levels on survival. Higher serum ALP levels were incrementally associated with higher all-cause mortality only in the younger patients treated with PD, independent of potential confounders (eg, demographic characteristics, comorbidity, laboratory parameters, and medication use). There was no significant association between higher serum ALP levels and poorer survival in the elderly patients. The ALP-mortality association appeared to be stronger in the younger group compared with the elderly group.

Our previous study indicated that higher ALP levels were associated with all-cause and cardiovascular mortality in PD patients.[2] In this study, we increased the number of patients, and extended the follow-up duration, and demonstrated similar results. There are several mechanisms that can explain the contribution of elevated ALP to increased mortality. ALP is not only a marker of high bone

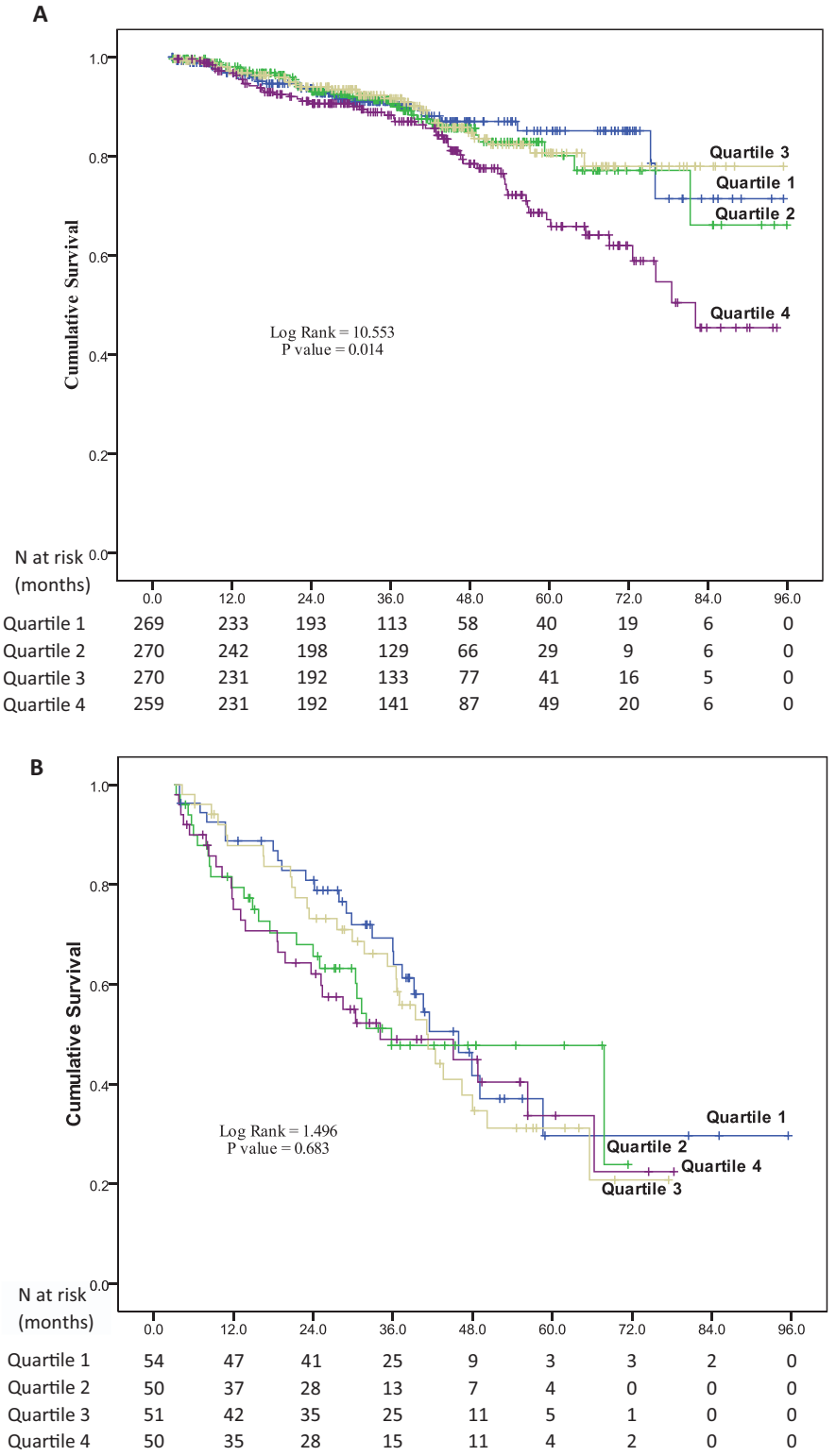

Figure 1: Survival curves for patients with different levels of serum ALP. Cumulative mortality curves for younger patients (A) and elderly patients (B) according to quartiles of ALP levels at baseline. ALP: alkaline phosphatase.

turnover, but also a mediator of vascular calcification, which is a predictor of mortality in dialysis patients.[4] ALP also has a relationship with inflammation and endothelial dysfunction, which are risk factors for mortality.[5]

Several reasons could explain the discrepancy in serum ALP-associated mortality between younger and elderly PD patients. Firstly, elderly PD patients tended to have worse nutritional parameters and a higher prevalence of

Table 1: Associations between continuous and quartiles of serum ALP and all-cause mortality in younger and elderly patients

	Model 1*		Model 2†		Model 3‡	
Items	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Younger patients						
Continuous ALP§	1.04 (1.02 to 1.07)	<0.001	1.06 (1.02 to 1.10)	0.001	1.06 (1.03 to 1.10)	<0.001
ALP Quartile 1	1.0		1.0		1.0	
ALP Quartile 2	1.12 (0.67 to 1.88)	0.663	1.68 (0.87 to 3.24)	0.125	1.71 (0.88 to 3.31)	0.112
ALP Quartile 3	1.03 (0.61 to 1.74)	0.901	0.97 (0.48 to 1.95)	0.928	0.97 (0.48 to 1.97)	0.942
ALP Quartile 4	1.81 (1.15 to 2.87)	0.011	1.94 (1.04 to 3.62)	0.038	2.01 (1.07 to 3.75)	0.030
Elderly patients						
Continuous ALP§	1.03 (0.99 to 1.08)	0.126	1.04 (0.99 to 1.09)	0.114	1.04 (0.99 to 1.09)	0.101
ALP Quartile 1	1.0		1.0		1.0	
ALP Quartile 2	1.25 (0.71 to 2.21)	0.436	1.69 (0.81 to 3.53)	0.164	1.69 (0.81 to 3.55)	0.163
ALP Quartile 3	1.21 (0.71 to 2.06)	0.494	2.12 (1.03 to 4.36)	0.041	2.14 (1.04 to 4.42)	0.040
ALP Quartile 4	1.40 (0.81 to 2.41)	0.230	1.56 (0.78 to 3.13)	0.209	1.58 (0.78 to 3.18)	0.202

ALP: alkaline phosphatase; HR: hazard ratio; 95% CI: 95% confidence interval. *Model 1: unadjusted. †Model 2: adjusted for age, gender, diabetes mellitus, cardiovascular disease, 24-h urine output, hemoglobin, serum albumin, serum alanine aminotransferase, neutrophil to lymphocyte ratio, intact parathyroid hormone, corrected calcium, and phosphorus. ‡Model 3: model 2 adjusted for vitamin D analogue and phosphate binders use. §Per 10 U/L higher ALP.

diabetes and other comorbidities with a strong correlation with increased mortality in PD patients.[6] Secondly, a high prevalence of vascular calcification may contribute to increased mortality in PD patients.[7] ALP catalyzes the hydrolysis of phosphomonoesters with releasing of inorganic phosphate (Pi) as well as hydrolyzing inorganic pyrophosphate (PPi) as pyrophosphatases.[8] Pyrophosphate, a potent inhibitor of medial vascular calcification, is controlled by hydrolysis via a tissue-nonspecific ALP.[9] Renal failure increases the expression of tissue-nonspecific ALP in vascular smooth muscle.[9] *In vivo* studies showed that tissue-nonspecific ALP deficiency could ameliorate vascular calcification.[10] Altogether, ALP hydrolyzes pyrophosphate and PPi thus increasing vascular calcification. Elevated serum ALP levels may, therefore, explain the association between ALP and mortality in younger patients, in whom vascular calcification is less.

In conclusion, our study explored the relationship between serum ALP level and all-cause mortality in younger and elderly PD patients. We found that higher serum ALP concentrations are associated with higher all-cause mortality only in younger patients treated with PD. These results suggest that serum ALP level was more valuable in predicting all-cause mortality in younger PD patients than in elderly PD patients. Further studies are warranted to confirm these findings.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

None.

Author contributions

Yang X had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Wu J, Yang X. Literature search: Wu J, Liu XH, Huang R, Wu HS. Acquisition of data: Huang R, Wu HS, Yi CY. Analysis and interpretation of data: Wu J, Liu XH. Drafting of the manuscript: Wu J. Manuscript editing and review: Liu XH, Guo QY, Yu XQ, Yang X.

References

1. Regidor DL, Kovesdy CP, Mehrotra R, Rambod M, Jing J, McAllister CJ, et al. Serum alkaline phosphatase predicts mortality among

maintenance hemodialysis patients. J Am Soc Nephrol 2008; 19: 2193–2203. doi: 10.1681/ASN.2008010014.
2. Liu X, Guo Q, Feng X, Wang J, Wu J, Mao H, et al. Alkaline phosphatase and mortality in patients on peritoneal dialysis. Clin J Am Soc Nephrol 2014;9:771–778. doi: 10.2215/CJN.08280813.
3. Liu Y, Zhu JG, Cheng BC, Liao SC, Lee CH, Chang WX, et al. An association between time-varying serum alkaline phosphatase concentrations and mortality rate in patients undergoing peritoneal dialysis: a five-year cohort study. Sci Rep 2017;7:43314. doi: 10.1038/srep43314.
4. Rhee CM, Molnar MZ, Lau WL, Ravel V, Kovesdy CP, Mehrotra R, et al. Comparative mortality-predictability using alkaline phosphatase and parathyroid hormone in patients on peritoneal dialysis and hemodialysis. Perit Dial Int 2014;34:732–748. doi: 10.3747/pdi.2013.00110.
5. Haarhaus M, Brandenburg V, Kalantar-Zadeh K, Stenvinkel P, Magnusson P. Alkaline phosphatase: a novel treatment target for cardiovascular disease in CKD. Nat Rev Nephrol 2017;13:429–442. doi: 10.1038/nrneph.2017.60.
6. Hiramatsu M, Ishida M, Tonozuka Y, Mikami H, Yamanari T, Momoki N, et al. Application of peritoneal dialysis in elderly patients by classifying the age into young-old, old, and oldest-old. Contrib Nephrol 2012;177:48–56. doi: 10.1159/000336935.
7. Wang AY. Vascular and valvular calcification in chronic peritoneal dialysis patients. Int J Nephrol 2011;2011:198045. doi: 10.4061/2011/198045.
8. Schoppet M, Shanahan CM. Role for alkaline phosphatase as an inducer of vascular calcification in renal failure? Kidney Int 2008;73:989–991. doi: 10.1038/ki.2008.104.
9. Lomashvili KA, Garg P, Narisawa S, Millan JL, O'Neill WC. Upregulation of alkaline phosphatase and pyrophosphate hydrolysis: potential mechanism for uremic vascular calcification. Kidney Int 2008;73:1024–1030. doi: 10.1038/ki.2008.26.
10. Narisawa S, Harmey D, Yadav MC, O'Neill WC, Hoylaerts MF, Millan JL. Novel inhibitors of alkaline phosphatase suppress vascular smooth muscle cell calcification. J Bone Miner Res 2007;22:1700–1710. doi: 10.1359/jbmr.070714.

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