

Original Paper

# Evaluation of the Relationship between the Serum Alkaline Phosphatase Level at Dialysis Initiation and All-Cause Mortality: A Multicenter, Prospective Study

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## Keywords

Alkaline phosphatase · Mortality · Hemodialysis

## Abstract

**Background/Aim:** High serum alkaline phosphatase (ALP) levels predict mortality independent of bone metabolism parameters and liver function test results in patients on hemodialysis. The relationship between serum ALP at dialysis initiation and mortality during maintenance dialysis is unknown; therefore, we aimed to identify an association. **Methods:** This multicenter, prospective cohort study analyzed 1,213 patients registered in the Aichi Cohort Study of Prognosis in Patients Newly Initiated into Dialysis from October 2011 to September 2013. Patients were divided into 2 groups based on serum ALP levels. All-cause mortality and incidences of cardiovascular events after dialysis initiation were compared using the log-rank test and multivariate Cox proportional hazard regression analysis. We performed stratified analysis based on parathyroid hormone (PTH) levels. **Results:** During the follow-up, 109 (18.0%) and 86 (14.1%) patients died in the high ALP group (232  $\geq$ IU/L; High ALP group) and low ALP group (232  $<$ IU/L; Low ALP group), respectively. All-cause mortality was significantly higher in the High ALP group than in the Low ALP group ( $p = 0.014$ ). The serum ALP level was significantly correlated with the all-cause mortality rate (hazard ratio = 1.17 per 100 IU/L increase of ALP, 95% confidence interval: 1.11–1.24,  $p < 0.001$ ). The all-cause mortality rate was significantly higher in the High ALP group among patients with low ( $<150$  pg/mL) or normal (150–300 pg/mL) PTH levels ( $p = 0.012$  and  $p = 0.005$ , respectively) than in the Low ALP group; there was no significant difference among patients with a high ( $\geq 300$  pg/mL) PTH level ( $p = 1.000$ ). **Conclusion:** The serum ALP level at dialysis initiation is associated with all-cause mortality during maintenance dialysis.

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## Introduction

Chronic kidney disease (CKD)-mineral and bone disorder is a systemic disorder of mineral and bone metabolism due to CKD. CKD-mineral and bone disorder induces abnormalities in bone turnover, mineralization, and vascular or other tissue calcification, and it develops during the early stage of CKD [1]. Serum alkaline phosphatase (ALP) is an enzyme measurable in most body fluids, and the serum ALP activity is increased in hepatobiliary or bone disease. In patients with CKD without liver disease, the ALP level can be increased in high-turnover bone disease [2, 3]. In patients on hemodialysis, the serum parathyroid hormone (PTH) and phosphate are associated with all-cause mortality. Additionally, PTH has a U-shaped or J-shaped association with mortality, and low PTH levels have long been associated with an older age, malnutrition, and calcium (Ca)-containing phosphate binder and vitamin D overuse. Compared with serum PTH, serum ALP seems to have a linear and incremental association with mortality [4–8].

Serum ALP is a biomarker of bone turnover, and it is increased in patients with CKD. Serum ALP is independently associated with increased all-cause mortality and the incidence of cardiovascular (CV) disease in patients on hemodialysis [9–12]. However, there are no previous reports concerning the association between the serum ALP level at dialysis initiation and outcomes, such as all-cause mortality and the incidence of CV events.

The aim of this study was to identify the association between serum ALP levels at dialysis initiation and all-cause mortality, and the incidence of CV events.

## Materials and Methods

### *Study Population*

Study subjects were patients in whom dialysis had recently been initiated at 17 centers that participated in the Aichi Cohort Study of Prognosis in Patients Newly Initiated into Dialysis (AICOPP) between October 2011 and September 2013. This study was a multicenter, prospective cohort analysis, and we screened 1,524 patients who were at least 20 years old, had CKD, and provided written informed consent. We excluded 53 patients whose serum ALP levels and 191 patients whose serum PTH levels were not assessed. We also excluded patients whose serum ALP levels were affected by comorbid liver disease (16 who were hepatitis B virus [HBV] antigen positive, 70 who were hepatitis C virus [HCV] antibody positive, 25 with aspartate aminotransferase [AST] level >80 IU/L, and 22 with serum alanine aminotransferase [ALT] level >80 IU/L), and 2 with serum C-reactive protein (CRP)  $\geq$ 30 mg/dL. In addition, we excluded 25 patients who had undergone kidney transplantation, 4 patients who recovered from hemodialysis, and 7 patients who were not followed up. Finally, we excluded 347 patients and enrolled 1,177 patients in this study.

### *Patients' Characteristics and Data at the Time of Dialysis Initiation (Baseline)*

Baseline was defined as the time of dialysis initiation. The body mass index (BMI) was measured at the first dialysis session. The patients' CV history was determined from their medical records and included coronary artery disease, heart valve disease, congestive heart failure requiring hospitalization, cerebral infarction, cerebral hemorrhage, or aortic disease. Information about medication use was also obtained from the medical records. Medication use refers to the drugs taken at the time of dialysis initiation. Laboratory tests were performed using blood samples taken before the first dialysis session. Blood pressure was also measured before the first dialysis session.

### *Classification according to the Serum ALP Level*

We divided patients into 2 groups according to serum ALP levels. We set the cutoff point as a median serum ALP level of 232 IU/L. Previous studies on hemodialysis patients set cutoffs at around 120, but this study population included patients in whom dialysis had recently been initiated and the average ALP levels varied. Hence, we set the median ALP level as the cutoff point.

### *Outcomes*

Data were obtained from the AICOPP database, and we evaluated patients' clinical outcome, including all-cause mortality and the incidence of CV events. CV events were defined as heart failure requiring hospitalization, acute coronary syndrome, stroke, or peripheral artery disease requiring hospitalization. Heart failure was defined as hypoxemia and pulmonary congestion, pulmonary edema, or pleural effusion on a chest radiograph. Acute coronary syndrome was defined as stenosis or occlusion detected by coronary angiography or percutaneous coronary intervention, a record of coronary artery bypass surgery, or electrocardiogram findings consistent with acute coronary syndrome. Stroke was defined as the presence of neurological symptoms and brain computed tomography or magnetic resonance imaging findings indicative of hemorrhage or infarction.

### *Ethical Approval and Consent to Participate*

This study was approved by the ethics committee of Nagoya Daini Red Cross Hospital (approval No. 20110823-3), and it was conducted in accordance with the principles of the Declaration of Helsinki (revised 2013) and Ethical Guidelines for Clinical Research by the Japanese Ministry of Health, Labor, and Welfare (created July 30, 2003; full revision December 28, 2004; full revision July 31, 2008). Subjects received oral and written explanations of the purpose of the study, and all subjects provided consent to participate. The trial was registered on January 18, 2012 (UMIN 7096).

### *Statistical Analysis*

The Easy R program was used for statistical processing [13]. Categorical data are presented as frequencies (percentages), and continuous data are presented as means  $\pm$  standard deviations. Data were compared using the Mann-Whitney U test for continuous variables and the Fisher exact test for categorical variables. Kaplan-Meier curves and the log-rank test were used to evaluate the long-term all-cause mortality and the incidence of CV events between the two serum ALP groups. Factors contributing to the all-cause mortality rates were analyzed using univariate Cox proportional hazard regression analysis. In addition to the serum-adjusted Ca level, factors that were significant in univariate analysis served as explanatory variables in multivariate Cox proportional hazard analysis using the stepwise method. Stepwise multivariate logistic regression analysis was performed for age, sex, BMI, estimated glomerular filtration rate (eGFR), hemoglobin (Hb) level, albumin level, ALP level, PTH level, phosphate level, CRP level, comorbidity of diabetes, history of CV disease, and Ca channel blocker (CCB) use. In univariate and multivariate analyses, we used the continuous value for serum ALP. We conducted the stratified analysis using the following PTH levels:  $<150$  pg/mL and  $150 \leq$  PTH level  $<300$  pg/mL. Significance was defined as a probability value  $<0.05$ .

**Table 1.** Baseline characteristics of all patients

Characteristics	All (n = 1,177)	Low ALP group (n = 591)	High ALP group (n = 586)	p value
Age, years	67.6±12.9	66.7±13.5	68.8±11.7	0.008
Female, %	67.2	71.7	65.9	0.042
Hemodialysis, %	91.8	92.9	90.6	0.292
BMI	23.6±4.5	23.9±4.7	23.4±4.2	0.195
Diabetes mellitus, %	51.2	49.7	52.0	1.000
CVD, %	44.0	41.8	45.2	0.190
Atrial fibrillation, %	5.8	4.6	6.6	0.095
eGFR, mL/min/1.73 m <sup>2</sup>	5.3±2.1	5.1±1.9	5.5±2.2	<0.001
Creatinine, mg/dL	9.1±3.2	9.6±3.4	8.6±2.9	<0.001
BUN, mg/dL	91.1±29.3	91.0±27.6	91.3±30.9	0.429
Hemoglobin, g/dL	9.4±1.5	9.3±1.4	9.5±1.5	0.299
Albumin, g/dL	3.2±0.6	3.2±0.6	3.2±0.6	0.236
AST, IU/L	17.9±10.2	16.1±8.3	19.7±11.5	<0.001
ALT, IU/L	13.6±10.5	12.0±9.0	15.4±12.0	<0.001
ALP, IU/L	256±157	181±35	332±190	<0.001
Uric acid, mg/dL	8.7±2.3	8.8±2.3	8.6±2.3	0.405
Na, mEq/L	138±4.3	138±4.3	138±4.3	0.271
Potassium, mEq/L	4.5±0.8	4.5±0.8	4.5±0.8	0.933
Adjusted Ca, mg/dL	8.6±1.0	8.6±1.0	8.5±1.0	0.186
Phosphorus, mg/dL	6.4±1.9	6.5±1.9	6.3±1.9	0.006
LDL cholesterol, mg/dL	90±35	92±35	88±36	0.204
HDL cholesterol, mg/dL	44±16	45±16	44±16	0.701
Triglycerides, mg/dL	126±74	125±66	127±81	0.874
HbA1c, %	5.6±0.9	5.5±0.8	5.8±1.0	0.001
BNP, pg/mL	537±965	438±548	637±1,230	0.042
PTH, pg/mL	355±293	301±184	413±360	<0.001
CRP, mg/dL	1.5±3.4	1.2±2.7	1.9±4.6	0.004
Use of ARBs or ACEIs, %	61.4	63.8	59.4	0.091
Use of CCBs, %	80.5	73.5	70.8	0.152
Use of statins, %	41.5	40.8	42.4	0.289
Use of VDRA, %	28.5	30.9	26.9	0.180
Cardio thoracic ratio, %	54.1±9.5	53.7±10.2	54.4±8.7	0.410
Ejection fraction, %	61.0±11.8	61.8±11.3	60.1±12.3	0.049

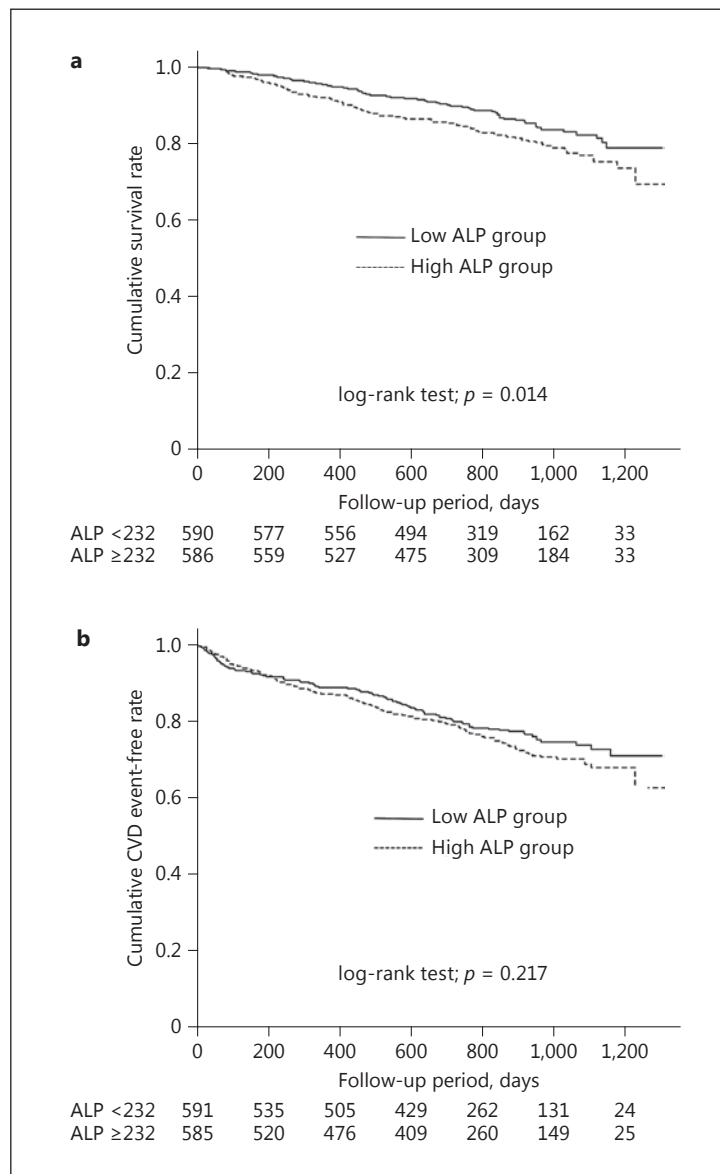
Mean ± standard deviation. ALP, alkaline phosphatase; BMI, body mass index; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; BUN, blood urea nitrogen; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDL, low-density lipoprotein; HDL, high-density lipoprotein; BNP, brain natriuretic peptide; PTH, parathyroid hormone; CRP, C-reactive protein; ARBs, angiotensin receptor blockers; ACEIs, angiotensin-converting enzyme inhibitor; CCBs, calcium channel blockers; VDRA, vitamin D receptor agonists.

## Results

The serum ALP level of 591 patients was ≤232 IU/L (Low ALP group), and the serum ALP level of 586 patients was >232 IU/L (High ALP group).

### Comparison of Patients' Characteristics and Baseline Data

Table 1 shows the patient characteristics and baseline data of the 2 groups. Significant differences between the 2 groups were observed for age, sex, eGFR, serum AST level, serum ALT level, serum creatinine level, serum phosphorus level, HbA1c level, serum brain natriuretic peptide level, serum CRP level, serum PTH level, and left ventricular ejection fraction on echocardiogram. There were no significant differences in the adjusted Ca level between the 2 groups.



**Fig. 1.** All-cause mortality and incidence of cardiovascular disease (CVD). ALP, alkaline phosphatase.

#### Comparison of Mortality and Incidence of CV Disease

Figure 1a and b illustrate the all-cause mortality and incidence of CV events. There were 195 deaths during the follow-up period (Low ALP group, 82 patients; High ALP group, 113 patients). Significant differences in the cumulative survival rates were observed between the 2 groups ( $p = 0.014$ ). There were 273 incidences of CV events during the follow-up period (Low ALP group, 128 patients; High ALP group, 145 patients). No significant differences were observed in the incidence of CV disease ( $p = 0.217$ ).

#### Factors Affecting All-Cause Mortality

In the univariate analysis, older age, male sex, hemodialysis, lower BMI, more comorbidities, including CV disease, atrial fibrillation, no CCB use, lower Hb level, lower albumin level, higher ALP level, higher AST level, lower creatinine level, higher eGFR, higher adjusted Ca level, lower PTH level, higher brain natriuretic peptide level, lower total cholesterol level,

**Table 2.** Single regression analysis

	HR	95% CI	p value
Age, years	1.059	1.042–1.076	<0.001
Female, %	0.548	0.373–0.805	0.002
Hemodialysis, %	0.269	0.099–0.726	0.010
BMI	0.917	0.877–0.958	<0.001
Diabetes mellitus, %	1.150	0.840–1.575	0.384
CVD, %	2.315	1.674–3.201	<0.001
Atrial fibrillation, %	2.092	1.228–3.563	0.007
eGFR, mL/min/1.73 m <sup>2</sup>	1.131	1.076–1.189	<0.001
Creatinine, mg/dL	0.850	0.792–0.912	<0.001
BUN, mg/dL	1.003	1.076–1.189	0.242
Hemoglobin, g/dL	0.852	0.763–0.952	0.005
Albumin, g/dL	0.564	0.434–0.732	<0.001
AST, IU/L	1.026	1.012–1.039	<0.001
ALT, IU/L	1.010	0.996–1.024	0.164
ALP/100, IU/L	1.124	1.072–1.179	<0.001
Adjusted Ca, mg/dL	1.318	1.119–1.554	<0.001
Phosphorus, mg/dL	0.949	0.863–1.042	0.272
LDL cholesterol, mg/dL	0.998	0.993–1.004	0.545
HDL cholesterol, mg/dL	0.988	0.976–0.999	0.036
HbA1c, %	0.989	0.805–1.213	0.912
BNP, pg/mL	1.011	1.002–1.020	0.022
PTH, pg/mL	0.999	0.999–1.000	0.109
CRP, mg/dL	1.061	1.021–1.102	0.002
Use of CCBs, %	0.481	0.338–0.685	<0.001

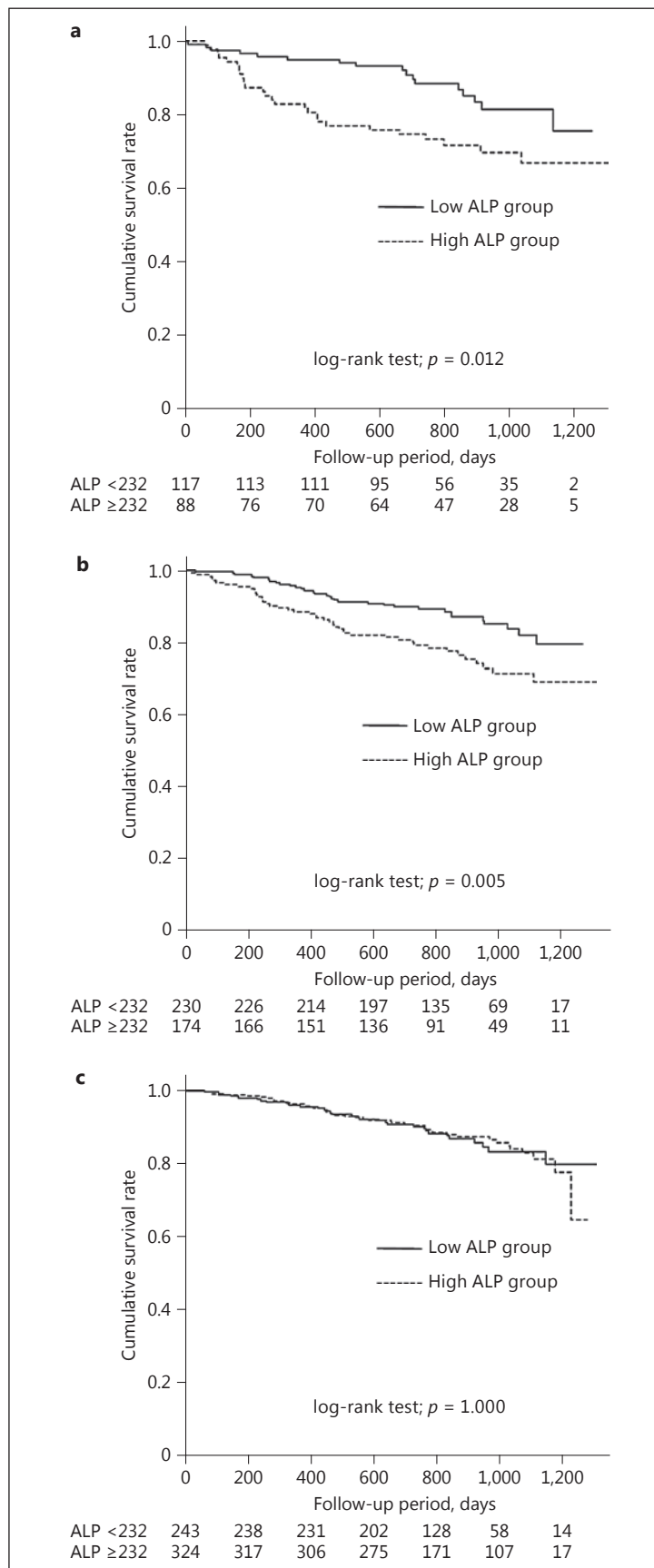
Other than that above, uric acid level, sodium level, potassium level, triglyceride level, use of angiotensin receptor blockers or angiotensin-converting enzyme inhibitor, statins and vitamin D receptor agonists are not risk factors for all-cause mortality. HR, hazard ratio; CI, confidence interval; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; BUN, blood urea nitrogen; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; LDL, low-density lipoprotein; HDL, high-density lipoprotein; BNP, brain natriuretic peptide; PTH, parathyroid hormone; CRP, C-reactive protein; CCBs, calcium channel blockers.

lower high-density lipoprotein cholesterol level, and higher CRP level were risk factors for all-cause mortality (Table 2).

Results of the multivariate Cox proportional hazard analysis using the stepwise method are shown in Table 3. A higher serum ALP was associated with all-cause mortality (hazard ratio [HR]: 1.17, 95% confidence interval [CI]: 1.11–1.24 per 100 IU/L increase of ALP). In addition, a high mortality rate was associated with advanced age (HR: 1.06, 95% CI: 1.04–1.08), female sex (HR: 0.61, 95% CI: 0.41–0.93), higher eGFR (HR: 1.09, 95% CI: 1.02–1.16), higher phosphorus level (HR: 1.13, 95% CI: 1.02–1.25), history of CV disease (HR: 1.67, 95% CI: 1.18–2.37), and no CCB use (HR: 0.52, 95% CI: 0.36–0.77).

#### Stratified Analyses

We also stratified data according to the serum PTH levels. Figure 2a–c illustrate all-cause mortality by the log-rank test between the 3 groups according to the serum PTH levels. In patients with PTH levels <150 pg/mL and 150 ≤ PTH levels <300 pg/mL, significant differences between the cumulative survival rates were observed for the 2 groups ( $p = 0.012$  and  $p = 0.005$ , respectively). However, in patients with PTH levels ≥300 pg/mL, no significant differences were observed ( $p = 1.000$ ). Results of multivariate Cox proportional hazard analysis between the 3 groups according to the serum PTH levels using the stepwise method



**Fig. 2.** All-cause mortality between the 3 groups according to the serum parathyroid hormone (PTH) levels. ALP, alkaline phosphatase.

**Table 3.** Multiple regression analysis

	HR	95% CI	p value
Age, years	1.058	1.040–1.077	<0.001
Female, %	0.614	0.407–0.926	0.020
CV disease, %	1.669	1.175–2.373	0.004
eGFR, mL/min/1.73 m <sup>2</sup>	1.087	1.015–1.163	0.017
ALP/100, IU/L	1.170	1.106–1.236	<0.001
Phosphorus, mg/dL	1.132	1.024–1.251	0.015
Use of CCBs, %	0.524	0.358–0.768	<0.001

Adjusted for sex, age, body mass index (BMI), diabetes mellitus, cardiovascular (CV) disease, estimated glomerular filtration rate (eGFR), hemoglobin (Hb), albumin (Alb), alkaline phosphatase (ALP), parathyroid hormone (PTH), phosphorus, C-reactive protein (CRP), and calcium channel blocker (CCB). HR, hazard ratio; CI, confidence interval.

**Table 4.** Multiple regression analysis

	HR	95% CI	p value
<i>PTH &lt;150 pg/mL</i>			
Age, years	1.062	1.014–1.130	0.010
Hemoglobin, g/dL	0.680	0.509–0.910	0.009
Diabetes mellitus, %	2.572	1.099–6.016	0.029
ALP/100, IU/L	1.598	1.249–2.045	<0.001
Use of CCBs, %	0.343	0.153–0.769	0.009
<i>150 ≤ PTH &lt;300 pg/mL</i>			
Age, years	1.056	1.025–1.087	<0.001
Female, %	0.377	0.149–0.950	0.039
CV disease, %	1.874	1.059–3.318	0.031
ALP/100, IU/L	1.171	1.102–1.244	<0.001
CRP, mg/dL	1.103	0.008–1.207	0.033
<i>PTH ≥300, pg/mL</i>			
Age, years	1.057	1.031–1.084	<0.001
eGFR, mL/min/1.73 m <sup>2</sup>	1.196	1.003–1.426	0.046
Use of CCBs, %	0.494	0.271–0.899	0.021

Adjusted for sex, age, body mass index (BMI), diabetes mellitus, cardiovascular (CV) disease, estimated glomerular filtration rate (eGFR), hemoglobin (Hb), albumin (Alb), alkaline phosphatase (ALP), parathyroid hormone (PTH), phosphorus, C-reactive protein (CRP), calcium channel blockers (CCB). HR, hazard ratio; CI, confidence interval.

are shown in Table 4. In patients with PTH levels <150 pg/mL and 150 ≤ PTH levels <300 pg/mL, higher serum ALP levels were significantly associated with all-cause mortality (HR: 1.60, 95% CI: 1.25–2.05 and HR: 1.17, 95% CI: 1.10–1.24, respectively). However, in patients with PTH levels ≥300 pg/mL, serum ALP levels were not associated with all-cause mortality.

## Discussion

In this cohort study, we showed that the serum ALP level at dialysis initiation is associated with all-cause mortality during maintenance dialysis. Especially in patients with a serum PTH level <300 pg/mL, a higher serum ALP level is significantly associated with



mortality. This is the first report to demonstrate that a higher serum ALP level at dialysis initiation is associated with a higher risk of all-cause mortality.

Some studies have reported that the serum PTH level has a U-shaped or J-shaped association with mortality in patients on hemodialysis. They have also reported that a higher serum ALP level is a risk factor for mortality between 3 groups stratified by the serum PTH level (low group <150 pg/mL, middle group 150–300 pg/mL, and high group >300 pg/mL), which is similar to the findings in our study [14, 15]. Patients on hemodialysis seem to have an increased serum PTH level due to secondary hyperparathyroidism. The current study showed no relationship between the serum PTH level and all-cause mortality in multivariate analysis, which is different than that previously found for patients on hemodialysis. Since ALP is expressed in the liver, kidneys, bones, intestines, and leukocytes, high serum ALP levels may be a marker of inflammation and neutrophil activation in addition to the liver function disorder and abnormal bone metabolism [16]. Besides abnormal bone metabolism being associated with CKD, chronic inflammation may have a relationship with a higher risk of mortality, because a higher serum ALP level is associated with the risk of mortality, especially in those with a lower serum PTH level [17].

The Prospective Registry of the Working Group of Epidemiology of Dialysis Region Calabria, a cohort study involving 35 dialysis units in two regions of southern Italy, showed that oxidative stress is a strong modifier of the adverse biological effects of a high serum ALP level [18]. In in-vitro experiments of vascular and bone cells, oxidative stress is a strong inducer of ALP and a key event promoting the transition of the vascular cell phenotype into calcifying cells. A higher serum ALP level is associated with the inflammatory response, because ALP is potently induced by interleukin-6, tumor necrosis factor- $\alpha$ , and bacterial lipopolysaccharide, which are all factors typically associated with high oxidative stress induced by inflammation and cancer [19]. Damera et al. [20] reported that the serum ALP level is strongly associated with the serum CRP level, both in the CKD and non-CKD population. A high serum ALP level also induces polyphosphoric acid and promotes vascular calcification. Experimental studies have shown that proinflammatory cytokines stimulate the production of an active metabolite of vitamin D in vascular smooth muscle cells and subsequently promote vascular smooth muscle cell calcification through the upregulation of ALP expression [21, 22]. Particularly in patients with a high serum ALP level (>120 IU/L), the serum ALP is a risk factor for coronary calcification [23].

In previous reports, a higher serum ALP level was associated with an increased risk of both all-cause and CV disease mortalities in patients on hemodialysis [7, 8, 14, 24, 25]. In the current study of patients with CKD newly initiating hemodialysis, a higher serum ALP level was the risk factor for all-cause mortality, but there was no significant difference in those with CV disease. We considered the reasons for differences in CV disease mortality between patients with newly initiated hemodialysis and those on maintenance hemodialysis. Drechsler et al. [6] reported that bone-specific alkaline phosphatase (BAP) levels were strongly associated with all-cause and CV disease mortality and that low BAP levels may reflect good vitamin D supplementation, with a beneficial effect on non-CV mortality. It is believed that cytokines associated with inflammation and cancer have a greater association with all-cause mortality than coronary calcification in CKD patients with newly initiated hemodialysis, in contrast with those on maintenance dialysis. We showed that a higher serum ALP level is a risk factor for all-cause mortality, but can also be a risk factor for CV disease mortality in the long-term because of coronary calcification.

This study has some limitations. First, this was an observational analysis, and there were some differences in the baseline characteristics and laboratory data among the 4 groups. Therefore, we performed adjusted analyses. Second, although we excluded patients with HBV antigen positivity, HCV antigen positivity, an AST level >80 U/L, and an ALT level >80 U/L, we

could not perfectly exclude those with liver disease, and liver function affects the serum ALP level in many ways. Finally, we collected data for the total ALP level only, thus the absence of BAP is an important limitation of this study.

## Conclusions

We found that a higher serum ALP level at dialysis initiation is significantly associated with all-cause mortality. We hope that further studies will confirm the relationship between long-term mortality and the serum ALP level.

## Statement of Ethics

This study was approved by the ethics committee of Nagoya Daini Red Cross Hospital (approval No. 20110823-3), and all subjects provided informed consent. The trial was registered on January 18, 2012 (UMIN 7096).

## Disclosure Statement

The authors declare no conflicts of interest.

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