

ORIGINAL ARTICLE

Intra-individual fluctuations in alkaline phosphatase predict mortality and CKD progression: insights from a large CKD cohort

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ABSTRACT

Background. Elevated alkaline phosphatase (ALP) levels are associated with mortality. However, the significance of ALP variability, particularly in chronic kidney disease (CKD), has not been well explored. This study examined the associations of baseline ALP and its variability with all-cause mortality and end-stage kidney disease (ESKD) in patients with CKD.

Methods. This retrospective cohort study analyzed data from tertiary hospitals in Taiwan and Korea (2001–2021). Adults with CKD, defined by at least two estimated glomerular filtration rate (eGFR) values <60 ml/min/1.73 m² obtained ≥3 months apart, were included. ALP variability was measured using the standard deviation (SD), coefficient of variance (CoV), and variance, categorized into quartiles. The Cox proportional hazards model evaluated the associations between ALP indices, mortality, and ESKD.

Results. In the baseline ALP cohort ($n = 14\,862$), higher ALP levels were associated with progressively increased risks of mortality and ESKD, with the highest quartile showing a 1.47-fold higher mortality risk [95% confidence interval (CI) 1.32–1.64] than the lowest. In the variability cohort ($n = 12\,531$), greater ALP variability was significantly associated with increased all-cause mortality (SD, aHR: 1.82, 95% CI: 1.61–2.05; CoV, aHR: 1.50, 95% CI: 1.34–1.68; variance, aHR: 1.81, 95% CI: 1.60–2.04) and showed directionally consistent, although attenuated, associations with ESKD risk. Subgroup analysis stratified by hypertension, diabetes, and cardiovascular disease demonstrated consistent association across comorbidities.

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Conclusion. Given the significant impact of ALP levels and their variability on mortality and kidney disease progression, targeted monitoring and stabilization of ALP over time may help improve long-term outcomes in patients with CKD.

Keywords: alkaline phosphatase, chronic kidney disease, mortality, variability

KEY LEARNING POINTS

What was known:

- While ALP is a key liver marker, elevated ALP levels in CKD patients are associated with increased mortality risk and progression to end-stage kidney disease (ESKD)

This study adds:

- The study shows that not only high ALP levels but also variability in these levels significantly increase the risks of mortality and ESKD progression.

Potential impact:

- Monitoring ALP variability, along with baseline levels, could improve patient management and outcomes, potentially reducing mortality and disease progression in CKD.

INTRODUCTION

Alkaline phosphatase (ALP) is an enzyme widely distributed throughout the body, with the highest concentrations found in the liver, bone, bile ducts, and kidney, corresponding to the tissue-nonspecific ALP (TNALP) isoenzyme [1]. ALP plays a central role in bone mineralization and is involved in hepatic metabolism and detoxification processes [2, 3]. Accordingly, ALP is frequently used as a biomarker for diagnosing and monitoring hepatic and bone disorders [4, 5]. Although serum ALP mainly reflects activity derived from the liver and bone, intestinal ALP can also contribute modestly to circulating ALP activity. Impaired kidney function is closely associated with systemic fluctuations in ALP levels, particularly in chronic kidney disease (CKD) [6, 7].

CKD is a rapidly growing medical condition worldwide that contributes significantly to both medical and socioeconomic burdens [8, 9]. As critical end organs, the kidneys have complex interactions with other systems, and their impairment leads to a cascade of systemic health issues, including cardiovascular complications, mineral and bone disorders, anemia, and fluid overload [10–12]. These complications not only worsen patient health but also intensify the clinical burden of CKD, resulting in increased healthcare costs and resource use [13]. Therefore, identifying and managing modifiable risk factors are crucial for controlling CKD and improving outcomes.

In CKD, mineral and bone disorder (CKD-MBD) and vascular calcification are major complications that correlate with altered ALP levels [14]. Elevated ALP levels are associated with an increased risk of mortality and progression to end-stage kidney disease (ESKD) [7]. However, as with serum creatinine and other laboratory biomarkers, ALP levels fluctuate over time owing to multiple biological and clinical factors, including aging, nutritional status, and comorbid bone or liver diseases [15]. In this context, it is imperative to shift the focus from single-point measurements of ALP levels to an appreciation of their variability, thereby enhancing the clinical interpretation and management of CKD-related complications.

While previous studies in CKD patients have investigated time-varying ALP levels in relation to mortality [16–18], evidence on intra-individual ALP variability, particularly among non-dialysis CKD patients, remains limited. Given that elevated

ALP levels in patients with CKD are associated with increased mortality and progression to ESKD, we examined the impact of ALP levels and their variability on these outcomes in patients with CKD.

MATERIALS AND METHODS

Study populations

This retrospective cohort study utilized data from Taiwan (hospital care system of Kaohsiung Medical University) and Korea (hospital care system of Seoul National University) collected between January 2001 and December 2021. We included adult patients aged 18 years or older with CKD confirmed by at least two measurements of estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m² or the presence of proteinuria obtained at intervals of at least 3 months, in accordance with KDIGO criteria. Only patients who were regularly followed at the nephrology clinic on at least two occasions were eligible, and the second qualifying measurement was defined as the baseline time point. The eGFR was calculated using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation [19]. Patients were excluded if they had no data on ALP values or if they progressed to ESKD within the first 3 months of follow-up.

Data acquisition and definition

By reviewing the electronic medical record database, we obtained clinical data for all patients from the retrospective cohorts. Clinical data included demographic details, such as age, sex, and body mass index (BMI), and laboratory data, such as hemoglobin, serum albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), ALP, total calcium, phosphorus, uric acid, electrolytes, total cholesterol, and eGFR. We also obtained diagnostic information on hypertension, diabetes, and cardiovascular disease based on the International Classification of Diseases 9th version (ICD-9), International Classification of Diseases 10th version (ICD-10) codes, or a history of taking medication.

To evaluate ALP variability, we collected ALP values from measurements taken at least three times, with an interval of

6 ± 2 months between each measurement. ALP variability was defined using the standard deviation (SD), coefficient of variance (CoV), and variance. The formulas used to calculate these metrics were as follows: SD is calculated by taking the square root of the average of the squared differences between each data point and the mean of the dataset. The CoV was calculated by dividing the SD by the mean, and then multiplying the result by 100 to express it as a percentage. The variance was calculated by averaging the squared differences between each data point and the mean of the dataset. ALP variability was categorized into quartiles for analysis, with the first quartile serving as the reference. The main results are presented based on the analyses using SD as the primary metric.

The primary outcome was all-cause mortality, while the risk of ESKD was assessed as a secondary outcome. In the Korean cohort, mortality was confirmed through linkage with the Statistics Korea National Death Registry, which provides complete cause-of-death data for all registered residents. In the Taiwanese cohort, cause of death was fully ascertained through linkage with the Taiwan National Death Registry. In both cohorts, ESKD events were identified from electronic medical record data, defined as initiation of chronic dialysis or kidney transplantation. The outcomes were tracked and confirmed based on the data collected on 31 December 2022. We initially conducted an analysis to determine the impact of baseline ALP levels on outcomes, followed by a comprehensive evaluation of the effects of ALP variability on these outcomes.

Measurement of serum ALP

In both the Korean and Taiwanese cohorts, the measurement method for ALP has remained consistent since 2001, following the International Federation of Clinical Chemistry (IFCC)-recommended kinetic colorimetric principle using p-nitrophenyl phosphate as the substrate at 37°C. In Korea, ALP was analyzed at each participating center using automated clinical chemistry analyzers (typical reference range 40–130 IU/l; detection range 10–4000 IU/l), and all laboratories participated in the Korean Association of External Quality Assessment Service program to ensure calibration consistency. In Taiwan, ALP was measured in the central biochemistry laboratory of Kaohsiung Medical University Hospital using automated chemistry analyzers, most recently the Abbott Alinity ci Total Laboratory Automation system (reference range 40–150 IU/l; detection range 9–4555 IU/l). All ALP concentrations were expressed in units per liter (U/l).

Statistical analysis

The baseline characteristics were compared according to the quartiles of ALP variability using SD values. Continuous variables were analyzed using ANOVA and are presented as the mean ± SD, while categorical variables were analyzed using the chi-square test and are presented as numbers (percentages). We performed multivariate Cox proportional hazards regression analysis to evaluate the impact of ALP and its variability on all-cause mortality and ESKD development. The variables used for adjustment in the multivariate analysis included age, sex, BMI, comorbidities (e.g. hypertension, diabetes, and cardiovascular disease), and laboratory parameters (e.g. hemoglobin, serum albumin, uric acid, total calcium, total cholesterol, ALP, AST, ALT, and eGFR). To explore the varying effects of ALP variability based on underlying comorbidities, we conducted subgroup analyses stratified by hypertension, diabetes, and cardiovascular disease.

A time-dependent Cox proportional hazards model was then applied to assess the association between ALP levels and the risk of all-cause mortality and ESKD. To incorporate ALP as a time-varying covariate, the data were structured in a start-stop format. Each time interval was defined from the previous ALP measurement to the next, and the final interval extended to the occurrence of the event of interest (mortality or ESKD) or the end of follow-up, whichever came first.

To explore potential nonlinear relationships between ALP and the outcomes, restricted cubic spline functions were applied and plotted. The ALP threshold with statistical significance was defined as the first point at which the lower bound of the 95% CI for the hazard ratio exceeded 1.0. In addition, to examine the robustness of the associations over the long inclusion period (2001–2021), supplementary analyses were performed after stratifying participants by enrollment era (ERA I: 2001–2007, ERA II: 2008–2014, and ERA III: 2015–2021). The same multivariate Cox regression models were applied within each era to evaluate whether temporal trends in measurement or clinical practice affected the observed relationships between ALP variability and outcomes.

To assess the combined effect of baseline ALP levels and ALP variability on mortality and ESKD, patients were categorized into two groups based on ALP levels (high and low) and ALP variability (high and low) using the SD. This yielded four combined groups: low ALP and low variability, low ALP and high variability, high ALP and low variability, and high ALP and high variability. The ALP-low/low variability group served as a reference. *P* values < .05 were defined as significant when they were set to two-sided. Logistic regression analysis was performed to evaluate the factors associated with ALP variability. In the multivariate analysis, we included variables with a *P* value of < .1 from the univariate analysis. Statistical analyses were performed using SPSS (version 23.0; IBM Corp., Armonk, NY, USA), and survival analyses were performed using R software (version 4.5.1; R Project for Statistical Computing, Vienna, Austria).

Ethical consideration

The study protocol was approved by the Institutional Review Boards of the participating hospitals at Kaohsiung Medical University Hospital (KMUHIRB-E(I)-20200062), Seoul National University Hospital (no. J-2310-035-1473) and Seoul National University Boramae Medical Center (no. 20-20223-46). The requirement for informed consent was waived by the IRB given the retrospective data used. This study was conducted in accordance with the principles of the Declaration of Helsinki.

RESULTS

Study populations

Among the 23 767 patients with CKD, 14 862 were included in the analysis assessing the association between baseline ALP levels and clinical outcomes (Fig. 1). The mean age was 64.0 ± 13.6 years, with 9089 (61.2%) male participants. The mean eGFR was 36.4 ± 14.0 ml/min/1.73 m². Among the participants, 10 018 (67.4%), 3566 (24.0%), and 1278 (8.6%) had CKD stages 3, 4, and 5, respectively (Table 1). According to the quartile range of ALP, patients in the highest quartile tended to be older and exhibited higher levels of systolic blood pressure, serum potassium, AST, ALT, and ALP, as well as a higher prevalence of hypertension, diabetes, and cardiovascular disease. Conversely, these patients demonstrated lower values of BMI, hemoglobin, serum

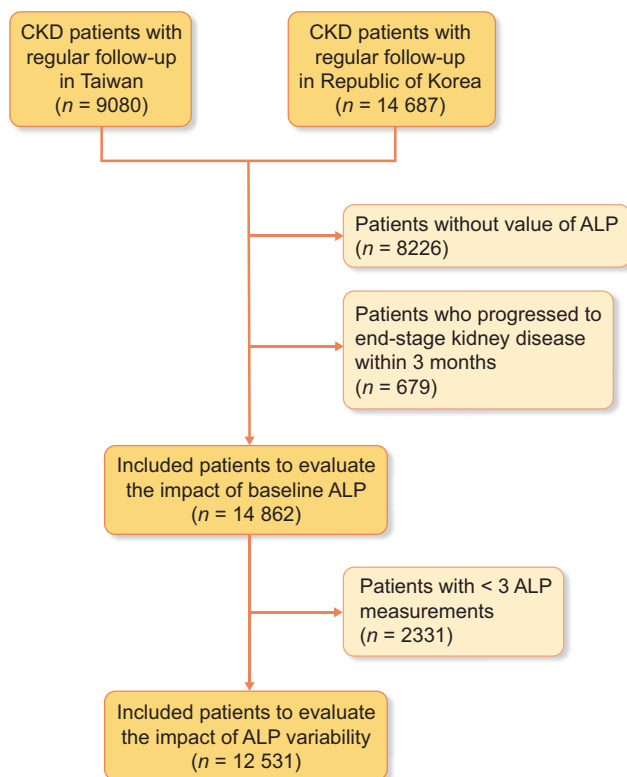


Figure 1: Flow diagram of the study.

albumin, total calcium, serum sodium, total cholesterol, and eGFR (Table 1).

The baseline characteristics of the 12 531 patients included in the ALP variability analysis were similar to those of the overall patient population; detailed results are provided in [Supplementary Table S1](#).

Impact of ALP on all-cause mortality and ESKD

During a follow-up period of 9.1 ± 5.5 years, a total of 3568 patients (24.0%) experienced mortality. The risk of mortality increased progressively across the quartiles of ALP, with the highest quartile exhibiting a 1.47-fold increase in risk [95% confidence interval (CI): 1.32, 1.64] compared to the first quartile (Fig. 2a). In addition, 6147 patients (41.4%) progressed to ESKD over a follow-up period of 7.7 ± 5.5 years. Higher quartiles of ALP were associated with a significantly increased risk of ESKD compared to the first quartile (aHR 1.19, 95% CI 1.03, 1.36) (Fig. 2b). Restricted cubic spline analysis further demonstrated a gradual, nonlinear increase in both mortality and ESKD risk beginning at ~ 70 –80 U/l, which lies within the conventional normal range (40–129 U/l) ([Supplementary Fig. S1](#)). This indicates that higher ALP levels, even within the normal range, were associated with progressively elevated risks of mortality and kidney disease progression.

Index of ALP variability

ALP variability was evaluated using three metrics: SD, CoV, and variance. The mean values of each measurement according to the quartile range of ALP levels are shown in [Supplementary Table S2](#). Both SD and variance showed a con-

sistent increasing pattern across the ALP quartiles, whereas CoV did not exhibit this trend. For the analysis of ALP variability, 12 531 patients who had at least three ALP measurements during follow-up were included.

Impact of ALP variability on all-cause mortality

Compared to the first quartile of the ALP variability group, the higher quartiles showed an incrementally increased risk of all-cause mortality, regardless of the measurement method used ([Supplementary Fig. S2](#)). These results remained consistent after adjusting for age, sex, blood pressure, BMI, comorbidities, and laboratory parameters, especially when SD or variance measurements were used (Table 2). Specifically, the fourth quartile of ALP variability showed a 1.82 times increased risk (95% CI: 1.61, 2.05) with SD, a 1.50 times increased risk (95% CI: 1.34, 1.68) with CoV, and a 1.82 times increased risk (95% CI: 1.61, 2.05) with variance measurements.

In supplementary time-dependent Cox analyses incorporating ALP as a time-updated covariate, the associations with mortality remained robust and directionally consistent, further supporting the prognostic relevance of ALP variability independent of temporal fluctuation in ALP levels ([Supplementary Table S3](#)).

Subgroup analyses stratified by enrollment era (2001–2007, 2008–2014, and 2015–2021) demonstrated consistent associations across periods, indicating that the long inclusion period did not materially influence the observed relationship between ALP variability and mortality ([Supplementary Table S4](#)).

Impact of ALP variability on ESKD

Increased ALP variability represented by the quartile range significantly increased the risk of ESKD, regardless of the measurement method used ([Supplementary Fig. S3](#)). Although the pattern of incrementally increased risk was maintained in model 3, which was adjusted for anthropometric parameters and comorbidities, this pattern disappeared after additional adjustments for laboratory parameters (Table 3). Specifically, the second to fourth quartile of ALP variability showed a 1.32-, 1.24-, and 1.29-times increased risk with SD, respectively, and a 1.33-, 1.25-, and 1.20-times increased risk with variance measurements, respectively, with all results being statistically significant ($P < .05$).

Consistent findings were observed in time-dependent Cox analyses accounting for temporal changes in ALP levels ([Supplementary Table S3](#)), indicating that the observed association between ALP variability and kidney disease progression was not driven by short-term ALP fluctuation or measurement timing.

Similarly, the associations between ALP variability and ESKD risk were directionally consistent across enrollment eras ([Supplementary Table S5](#)), supporting the robustness of these findings against potential temporal or methodological bias.

Differential impact of ALP variability according to underlying comorbidities

For the risk of all-cause mortality, the incrementally increased risk according to the quartile range of SD values for ALP variability was maintained after adjusting for all variables, regardless of the presence of underlying comorbidities, such as hypertension,

Table 1: Baseline characteristics according to the quartile of ALP^a.

	Total (n = 14 862)	First quartile (n = 3 757)	Second quartile (n = 3 610)	Third quartile (n = 3 743)	Fourth quartile (n = 3 752)	P value
Age, years	64.0 ± 13.6	63.3 ± 14.3	64.1 ± 13.6	64.2 ± 13.4	64.4 ± 13.1	.002
Male	9 089 (61.2)	2 306 (61.4)	2 282 (63.2)	2 317 (61.9)	2 184 (58.2)	<.001
Systolic blood pressure, mmHg	134.7 ± 22.3	133.3 ± 20.1	134.5 ± 21.9	135.4 ± 23.0	135.7 ± 23.9	<.001
Diastolic blood pressure, mmHg	78.1 ± 13.1	78.1 ± 12.8	78.4 ± 13.2	78.3 ± 13.3	77.7 ± 13.3	.293
BMI, kg/m ²	23.8 ± 3.9	24.2 ± 3.8	23.9 ± 3.9	23.7 ± 3.8	23.4 ± 4.0	<.001
Hemoglobin, mg/dl	11.8 ± 2.2	12.0 ± 2.2	12.1 ± 2.2	11.7 ± 2.2	11.3 ± 2.1	<.001
Serum albumin, g/dl	3.9 ± 0.5	4.0 ± 0.5	4.0 ± 0.5	3.9 ± 0.5	3.8 ± 0.6	<.001
Total calcium, mg/dl	9.0 ± 0.7	9.1 ± 0.6	9.1 ± 0.6	9.0 ± 0.6	8.9 ± 0.7	<.001
Phosphorus, mg/dl	3.7 ± 0.8	3.6 ± 0.8	3.7 ± 0.8	3.7 ± 0.8	3.8 ± 0.9	<.001
Alkaline phosphatase, U/l	87.4 ± 61.9	49.1 ± 8.1	67.1 ± 4.3	83.8 ± 5.9	148.9 ± 97.1	<.001
Aspartate aminotransferase, U/l	25.2 ± 19.6	23.6 ± 15.4	23.1 ± 13.7	23.8 ± 14.3	30.1 ± 29.5	<.001
Alanine aminotransferase, U/l	22.3 ± 21.8	20.2 ± 17.6	20.6 ± 16.9	21.7 ± 21.2	26.6 ± 28.7	<.001
Uric acid, mg/dl	7.1 ± 2.1	7.0 ± 2.0	7.1 ± 2.1	7.1 ± 2.0	7.1 ± 2.1	.135
Sodium, mEq/l	139.5 ± 3.6	139.8 ± 3.8	139.8 ± 3.1	139.6 ± 3.4	138.9 ± 4.0	<.001
Potassium, mEq/l	4.6 ± 0.7	4.6 ± 0.8	4.6 ± 0.6	4.7 ± 0.7	4.7 ± 0.7	<.001
Total cholesterol, mg/dl	178.7 ± 50.9	181.6 ± 53.2	180.6 ± 48.7	178.6 ± 50.0	174.2 ± 51.3	<0.001
eGFR, ml/min/1.73 m ²	36.4 ± 14.0	38.5 ± 13.4	37.7 ± 13.6	36.3 ± 13.7	33.0 ± 14.5	<0.001
Hypertension, n (%)	8 069 (54.3)	1 985 (52.8)	1 926 (53.4)	2 056 (54.9)	2 102 (56.0)	.022
Diabetes, n (%)	6 398 (43.0)	1 502 (40.0)	1 456 (40.3)	1 677 (44.8)	1 763 (47.0)	<.001
Cardiovascular disease, n (%)	2 410 (16.2)	534 (14.2)	555 (15.4)	638 (17.0)	683 (18.2)	<.001
CKD stage						
3	10 018 (67.4)	2 744 (73.0)	2 606 (72.2)	2 530 (67.6)	2 138 (57.0)	<.001
4	3 566 (24.0)	784 (20.9)	754 (20.9)	919 (24.6)	1 109 (29.6)	
5	1 278 (8.6)	229 (6.1)	250 (6.9)	294 (7.9)	505 (13.5)	
Death, n (%)	3 568 (24.0)	781 (20.8)	785 (21.7)	951 (25.4)	1 051 (28.0)	<.001
Follow-up for death, years	9.1 ± 5.5	9.4 ± 5.2	9.6 ± 5.5	9.3 ± 5.6	8.0 ± 5.7	<.001
ESKD, n (%)	6 147 (41.4)	1 164 (31.0)	1 330 (36.8)	1 630 (43.5)	2 023 (53.9)	<.001
Follow-up for ESKD, years	7.7 ± 5.5	8.2 ± 5.2	8.3 ± 5.5	7.7 ± 5.5	6.5 ± 5.5	<.001

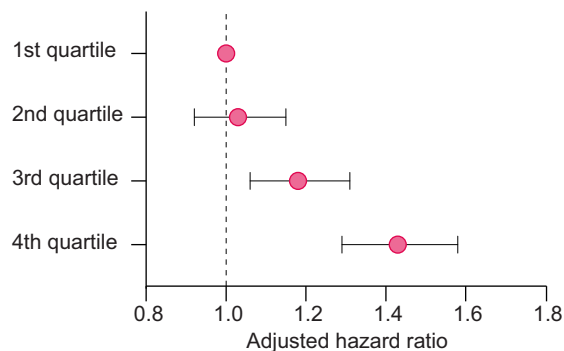
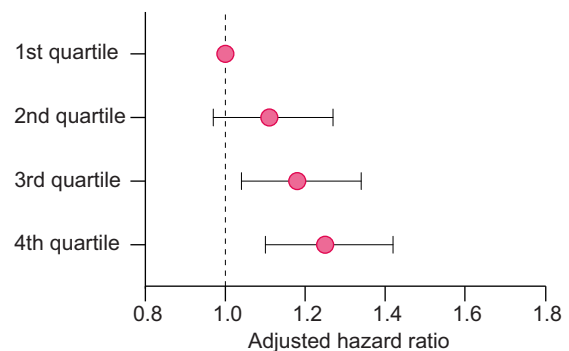
^aALP variability was assessed by SD**a All-cause mortality****b End-stage kidney disease**

Figure 2: Risk of (a) all-cause mortality and (b) ESKD according to the quartile range of ALP. The x-axis represents the adjusted hazard ratio and the y-axis represents the quartile range of ALP. The analysis was adjusted for age, sex, BMI, comorbidities (hypertension, diabetes, and cardiovascular disease), and laboratory parameters (hemoglobin, serum albumin, uric acid, total calcium, total cholesterol, ALP, AST, ALT, and eGFR).

diabetes, and cardiovascular disease, consistent with the main results (Supplementary Table S6).

By contrast, for ESKD outcomes, a significantly increased risk was observed only in patients with comorbidities. Specifically, the risk was highest in those with cardiovascular disease, with patients in the fourth quartile having a 2.23-times (95% CI: 1.47, 3.37) higher risk than those in the first quartile (Supplementary Table S7).

Combined effect of baseline ALP values and ALP variability

We found that higher variability was significantly associated with an increased risk of mortality, regardless of the ALP levels (Fig. 3a and b). In addition, even in the ALP-low group, patients with high variability had a higher mortality risk than those in the ALP high/variability low group. Although the significance of ESKD outcome was attenuated after adjusting for all laboratory

Table 2: Impact of ALP variability on the all-cause mortality according to different measures of variability.

SD	Model 1			Model 2			Model 3			Model 4		
	HR (95% CI)	P value		aHR (95% CI)	P value		aHR (95% CI)	P value		aHR (95% CI)	P value	
first quartile	Reference		first quartile	Reference		first quartile	Reference		first quartile	Reference		
second quartile	1.16 (1.07, 1.27)	<.001	second quartile	1.13 (1.04, 1.23)	.004	second quartile	1.09 (0.99, 1.21)	.092	second quartile	1.04 (0.92, 1.19)	.520	
third quartile	1.63 (1.50, 1.76)	<.001	third quartile	1.68 (1.55, 1.82)	<.001	third quartile	1.46 (1.33, 1.61)	<.001	third quartile	1.31 (1.16, 1.48)	<.001	
fourth quartile	2.44 (2.26, 2.64)	<.001	fourth quartile	2.62 (2.42, 2.83)	<.001	fourth quartile	2.28 (2.07, 2.50)	<.001	fourth quartile	1.78 (1.57, 2.01)	<.001	
CoV	HR (95% CI)	P value		aHR (95% CI)	P value		aHR (95% CI)	P value		aHR (95% CI)	P value	
first quartile	Reference		first quartile	Reference		first quartile	Reference		first quartile	Reference		
second quartile	1.01 (0.97, 1.14)	.240	second quartile	1.07 (0.98, 1.16)	.120	second quartile	0.98 (0.89, 1.08)	.734	second quartile	0.93 (0.83, 1.06)	.278	
third quartile	1.33 (1.23, 1.44)	<.001	third quartile	1.42 (1.31, 1.53)	<.001	third quartile	1.26 (1.15, 1.39)	<.001	third quartile	1.11 (0.99, 1.25)	.081	
fourth quartile	1.94 (1.80, 2.09)	<.001	fourth quartile	2.11 (1.96, 2.28)	<.001	fourth quartile	1.84 (1.68, 2.01)	<.001	fourth quartile	1.45 (1.29, 1.63)	<.001	
Variance	HR (95% CI)	P value		aHR (95% CI)	P value		aHR (95% CI)	P value		aHR (95% CI)	P value	
first quartile	Reference		first quartile	Reference		first quartile	Reference		first quartile	Reference		
second quartile	1.15 (1.06, 1.26)	.001	second quartile	1.12 (1.03, 1.22)	.009	second quartile	1.08 (0.97, 1.20)	.163	second quartile	1.04 (0.92, 1.19)	.520	
third quartile	1.63 (1.50, 1.77)	<.001	third quartile	1.68 (1.54, 1.82)	<.001	third quartile	1.47 (1.33, 1.62)	<.001	third quartile	1.31 (1.16, 1.48)	<.001	
fourth quartile	2.46 (2.27, 2.66)	<.001	fourth quartile	2.64 (2.44, 2.86)	<.001	fourth quartile	2.27 (2.06, 2.50)	<.001	fourth quartile	1.78 (1.57, 2.01)	<.001	
VIM	HR (95% CI)	P value		aHR (95% CI)	P value		aHR (95% CI)	P value		aHR (95% CI)	P value	
first quartile	Reference		first quartile	Reference		first quartile	Reference		first quartile	Reference		
second quartile	0.95 (0.88, 1.02)	.155	second quartile	0.98 (0.90, 1.05)	.531	second quartile	0.95 (0.86, 1.04)	.231	second quartile	0.95 (0.85, 1.07)	.377	
third quartile	1.13 (1.05, 1.22)	.001	third quartile	1.22 (1.13, 1.32)	<.001	third quartile	1.13 (1.04, 1.24)	.006	third quartile	1.11 (1.00, 1.24)	<.055	
fourth quartile	1.45 (1.35, 1.56)	<.001	fourth quartile	1.60 (1.48, 1.72)	<.001	fourth quartile	1.45 (1.33, 1.58)	<.001	fourth quartile	1.21 (1.09, 1.35)	.001	

Model 1: Non-adjusted

Model 2: Adjusted for age, sex

Model 3: Adjusted for variables in model 2, systolic blood pressure, BMI, and comorbidities such as hypertension, diabetes, and cardiovascular disease

Model 4: Adjusted for variables in model 3 and laboratory variables such as hemoglobin, serum albumin, uric acid, total calcium, total cholesterol, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, and eGFR

Table 3: Impact of ALP variability on progression to ESKD according to different measures of variability.

SD	Model 1		Model 2		Model 3		Model 4	
	HR (95% CI)	P value	aHR (95% CI)	P value	aHR (95% CI)	P value	aHR (95% CI)	P value
first quartile	Reference		first quartile		first quartile		first quartile	
second quartile	1.45 (1.30, 1.61)	<.001	second quartile	<.001	second quartile	<.001	second quartile	<.001
third quartile	2.02 (1.83, 2.25)	<.001	third quartile	<.001	third quartile	<.001	third quartile	.003
fourth quartile	2.57 (2.32, 2.85)	<.001	fourth quartile	<.001	fourth quartile	<.001	fourth quartile	<.001
CoV	HR (95% CI)	P value	aHR (95% CI)	P value	aHR (95% CI)	P value	aHR (95% CI)	P value
first quartile	Reference		first quartile		first quartile		first quartile	
second quartile	1.41 (1.27, 1.57)	<.001	second quartile	<.001	second quartile	.002	second quartile	.053
third quartile	1.96 (1.77, 2.18)	<.001	third quartile	<.001	third quartile	<.001	third quartile	.012
fourth quartile	2.25 (2.03, 2.49)	<.001	fourth quartile	<.001	fourth quartile	<.001	fourth quartile	.135
Variance	HR (95% CI)	P value	aHR (95% CI)	P value	aHR (95% CI)	P value	aHR (95% CI)	P value
first quartile	Reference		first quartile		first quartile		first quartile	
second quartile	1.47 (1.32, 1.65)	<.001	second quartile	<.001	second quartile	<.001	second quartile	<.001
third quartile	2.04 (1.83, 2.27)	<.001	third quartile	<.001	third quartile	<.001	third quartile	.003
fourth quartile	2.60 (2.33, 2.89)	<.001	fourth quartile	<.001	fourth quartile	<.001	fourth quartile	<.001
VIM	HR (95% CI)	P value	aHR (95% CI)	P value	aHR (95% CI)	P value	aHR (95% CI)	P value
first quartile	Reference		first quartile		first quartile		first quartile	
second quartile	1.47 (1.32, 1.65)	<.001	second quartile	<.001	second quartile	<.001	second quartile	<.001
third quartile	2.04 (1.83, 2.27)	<.001	third quartile	<.001	third quartile	<.001	third quartile	.003
fourth quartile	2.60 (2.33, 2.89)	<.001	fourth quartile	<.001	fourth quartile	<.001	fourth quartile	<.001
first quartile	Reference		first quartile		first quartile		first quartile	
second quartile	1.27 (1.15, 1.40)	<.001	second quartile	<.001	second quartile	.053	second quartile	.076
third quartile	1.66 (1.51, 1.83)	<.001	third quartile	<.001	third quartile	<.001	third quartile	.021
fourth quartile	1.95 (1.77, 2.14)	<.001	fourth quartile	<.001	fourth quartile	<.001	fourth quartile	.496

Model 1: Non-adjusted

Model 2: Adjusted for age, sex

Model 3: Adjusted for variables in model 2, systolic blood pressure, BMI, and comorbidities such as hypertension, diabetes, and cardiovascular disease

Model 4: Adjusted for variables in model 3 and laboratory variables such as hemoglobin, serum albumin, uric acid, total calcium, total cholesterol, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, and estimated glomerular filtration rate

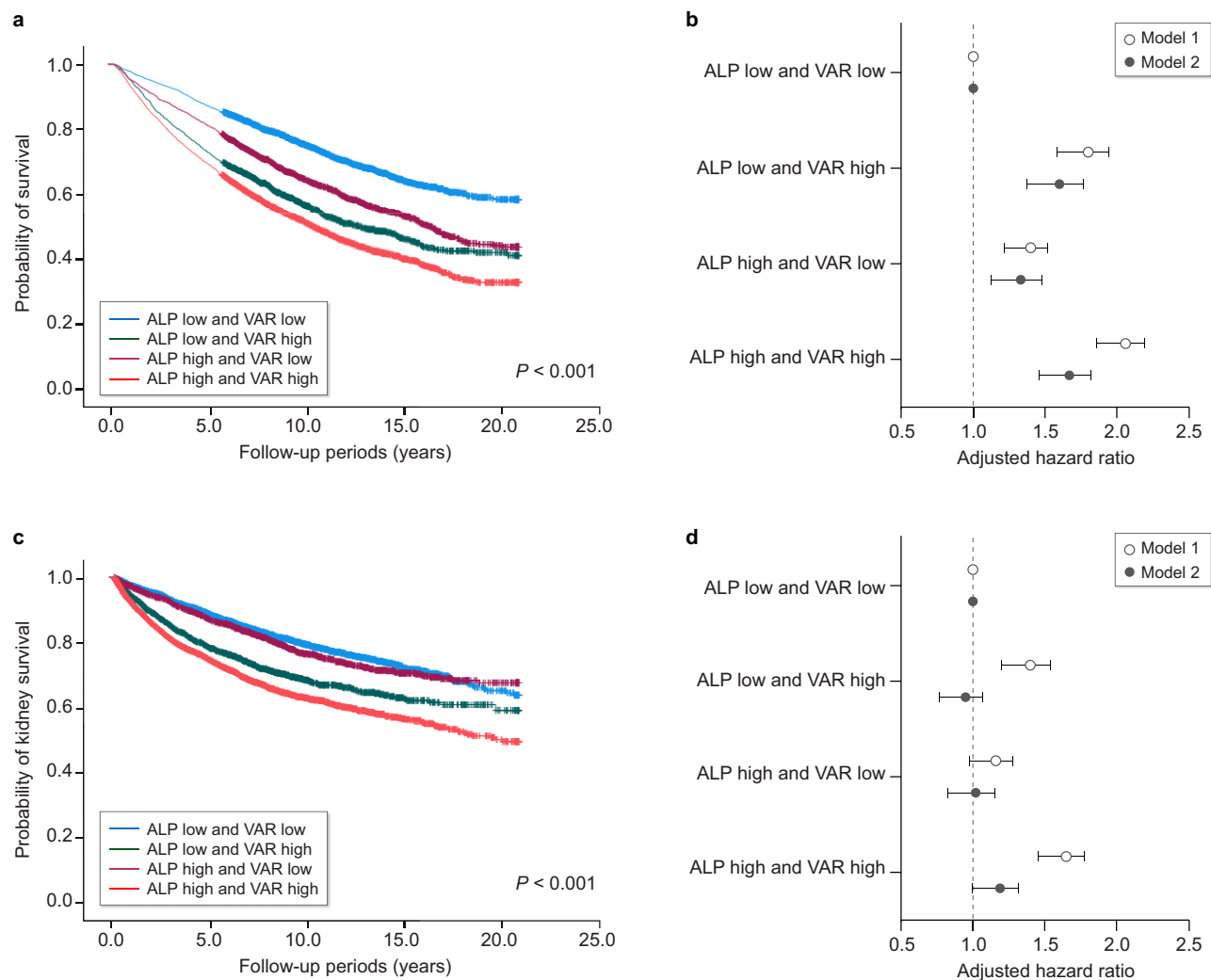


Figure 3: Kaplan-Meier survival curves and Cox proportional hazards models stratified by baseline ALP levels and ALP variability for mortality and ESKD outcomes. (a) The Kaplan-Meier survival curves for all-cause mortality. (b) The results from the Cox proportional hazards model for the same outcome. (c) The Kaplan-Meier survival curves for ESKD. (d) The corresponding Cox proportional hazards model results. The groups were defined as follows: ALP-Low & Variability Low (blue), ALP-Low & Variability High (green), ALP High & Variability Low (purple), and ALP High & Variability High (red). In the Cox proportional hazards models, the ALP-Low & Variability Low groups were used as references. Model 1 was adjusted for age, sex, systolic blood pressure, BMI, and comorbidities including hypertension, diabetes, and cardiovascular disease. Model 2 included additional adjustments for laboratory variables, such as hemoglobin, serum albumin, uric acid, total calcium, total cholesterol, ALP, AST, ALT, and eGFR.

covariates, it remained evident that the impact of higher variability was greater than that of ALP levels, similar to the findings for mortality (Fig. 3c and d).

Factors associated with baseline ALP values and ALP variability

Most variables showed a significant association with both ALP levels (Table 4) and variability (Table 5). Among these, lower BMI, serum albumin, sodium, and eGFR were consistently associated with higher ALP levels and greater ALP variability. In addition, the presence of cardiovascular disease and higher potassium, AST, and total cholesterol levels were significantly associated with increased ALP levels. Conversely, the presence of diabetes, male sex, lower hemoglobin levels, and higher ALT and ALP levels were significantly associated with increased ALP variability.

DISCUSSION

Higher ALP levels, even those within the normal range, significantly increased the risk of all-cause mortality and progression to ESKD. In addition, increased variability in ALP levels was associated with a progressively elevated risk of all-cause mortality regardless of the measurement method used. Although the pattern of incrementally increasing risk for ESKD diminishes, higher ALP variability significantly increases the risk of this outcome. Moreover, the combined effect of ALP levels and their variability further underscores the critical role of variability, suggesting that greater attention should be paid to fluctuations in ALP levels as key factors in risk assessment and patient monitoring. These findings highlight the importance of monitoring not only baseline ALP levels, but also their variability over time, as both are crucial predictors of all-cause mortality and ESKD progression in the CKD population.

Table 4: Relative factors associated with increased ALP.

Variables	Model 1		Model 2	
	OR (95% CI)	P value	aOR (95% CI)	P value
Age, year	1.00 (1.00, 1.01)	.047	1.00 (1.00, 1.00)	.881
Female	0.85 (0.79, 0.92)	<.001	0.96 (0.84, 1.09)	.500
Systolic blood pressure, mmHg	1.00 (1.00, 1.01)	.008	1.00 (1.00, 1.00)	.627
BMI, kg/m ²	0.96 (0.95, 0.98)	<.001	0.97 (0.96, 0.99)	.001
Hemoglobin, mg/dl	0.86 (0.85, 0.88)	<.001	0.95 (0.92, 0.99)	.005
Albumin, g/dl	0.52 (0.49, 0.55)	<.001	0.78 (0.69, 0.88)	<.001
Uric acid, mg/dl	0.99 (0.97, 1.01)	.439		
Total calcium, mg/dl	0.62 (0.58, 0.65)	<.001	0.87 (0.79, 0.96)	.005
Phosphorus, mg/dl	1.19 (1.14, 1.24)	<.001	1.03 (0.96, 1.11)	.425
Aspartate aminotransferase, U/l	1.02 (1.02, 1.02)	<.001	1.01 (1.01, 1.02)	<.001
Alanine aminotransferase, U/l	1.01 (1.01, 1.01)	<.001	1.00 (1.00, 1.01)	.017
Sodium, mEq/l	0.93 (0.92, 0.94)	<.001	0.97 (0.96, 0.99)	<.001
Potassium, mEq/l	1.13 (1.07, 1.20)	<.001	1.06 (0.97, 1.15)	.209
Total cholesterol, mg/dl	1.00 (1.00, 1.00)	<.001	1.00 (1.00, 1.00)	.002
eGFR, ml/min/1.73 m ²	0.98 (0.97, 0.98)	<.001	0.99 (0.98, 0.99)	<.001
Hypertension	1.10 (1.02, 1.18)	.014	0.98 (0.86, 1.11)	.739
Diabetes	1.24 (1.15, 1.33)	<.001	1.19 (1.06, 1.34)	.004
Cardiovascular disease	1.21 (1.10, 1.33)	<.001	1.19 (1.03, 1.38)	.019

Table 5: Relative factors associated with increased ALP variability.

Variables	Model 1		Model 2	
	OR (95% CI)	P value	aOR (95% CI)	P value
Age, year	1.00 (1.00, 1.01)	.005	1.00 (0.99, 1.00)	.869
Female	0.71 (0.65, 0.77)	<.001	0.77 (0.66, 0.90)	.001
Systolic blood pressure, mmHg	1.00 (1.00, 1.00)	.555		
BMI, kg/m ²	0.95 (0.94, 0.96)	<.001	0.98 (0.96, 1.00)	.023
Hemoglobin, mg/dl	0.79 (0.77, 0.80)	<.001	0.89 (0.86, 0.93)	<.001
Albumin, g/dl	0.44 (0.41, 0.47)	<.001	0.66 (0.56, 0.78)	<.001
Uric acid, mg/dl	0.98 (0.96, 1.00)	.069	1.01 (0.97, 1.05)	.598
Total calcium, mg/dl	0.56 (0.53, 0.60)	<.001	1.02 (0.89, 1.16)	.801
Phosphorus, mg/dl	1.13 (1.07, 1.19)	<.001	0.95 (0.86, 1.05)	.329
Alkaline phosphatase, U/l	1.03 (1.03, 1.04)	<.001	1.03 (1.03, 1.03)	<.001
Aspartate aminotransferase, U/l	1.01 (1.01, 1.01)	<.001	1.00 (0.99, 1.00)	.264
Alanine aminotransferase, U/l	1.01 (1.01, 1.01)	<.001	1.01 (1.00, 1.01)	.030
Sodium, mEq/l	0.91 (0.90, 0.92)	<.001	0.97 (0.95, 0.99)	.003
Potassium, mEq/l	1.16 (1.09, 1.24)	<.001	0.94 (0.84, 1.05)	.240
Total cholesterol, mg/dl	1.00 (1.00, 1.00)	<.001	1.00 (1.00, 1.00)	.356
eGFR, ml/min/1.73 m ²	0.98 (0.97, 0.98)	<.001	0.99 (0.99, 1.00)	.008
Hypertension	0.97 (0.89, 1.05)	.411		
Diabetes	1.34 (1.24, 1.45)	<.001	1.15 (1.00, 1.33)	.049
Cardiovascular disease	1.18 (1.06, 1.31)	.003	1.00 (0.84, 1.19)	.977

Previous studies have consistently demonstrated that elevated ALP levels are associated with increased mortality in both the general population and patients with CKD, independent of liver function and traditional cardiovascular risk factors [20, 21]. In CKD, phosphate retention, secondary hyperparathyroidism, and altered vitamin D metabolism lead to increased bone turnover and elevated ALP levels, which may further contribute to vascular calcification and cardiovascular fibrosis through metabolic and inflammatory pathways [22–25]. The prognostic value of ALP has also been confirmed in patients with ESKD, where higher baseline ALP levels have been linked to greater mortality risks [26, 27]. However, evidence regarding ALP as a

risk factor for kidney disease progression has been less consistent [28]. Our findings extend these previous observations by demonstrating that higher ALP levels are associated not only with mortality but also with progression to ESKD across different ethnic cohorts. Importantly, the association with ESKD became less pronounced after adjustment for metabolic and laboratory parameters, suggesting that the relationship between ALP and kidney outcomes may be mediated through disturbances in mineral metabolism, nutritional status, or systemic inflammation rather than representing a direct causal effect [29, 30]. This attenuation highlights the complex interplay between ALP activity and the metabolic milieu in CKD. Taken together, these

results indicate that ALP reflects multiple underlying pathophysiologic processes and serves as a useful prognostic marker in patients with CKD.

Restricted cubic spline analysis further demonstrated a gradual, nonlinear increase in mortality and ESKD risk beginning at ~70–80 U/l, which lies well within the conventional normal range (40–129 U/l). Given that the cutoff level for the reference group was 59.0 U/l, these findings indicate that maintaining ALP levels near the lower end of the normal range may be associated with lower risk. Although these results are based on an observational design and should be interpreted as data-driven prognostic points rather than causal thresholds, they highlight the potential value of early detection and longitudinal monitoring of ALP elevation in assessing adverse outcomes among patients with CKD. Consistent with these findings, additional time-dependent Cox analyses confirmed that the association between ALP and adverse outcomes persisted when ALP was modeled as a time-updated covariate, indicating that the observed relationship reflects a sustained, rather than transient, effect of ALP elevation during follow-up.

Despite numerous studies demonstrating the association between ALP levels and mortality, the role of ALP as a risk factor for ESKD progression has not been consistently established in the literature [28]. However, the findings of this study, provide robust evidence that elevated ALP levels are associated with increased risk of ESKD in different ethnic groups. Importantly, the observed similar elevation in risk from the second to fourth quartiles, compared to the first quartile, highlights the critical importance of maintaining ALP levels at the lower limit of the normal range to mitigate the risk of ESKD progression. Although the exact mechanisms have not been fully elucidated, increased ALP levels are associated with vascular calcification, inflammation, and oxidative stress. These biological processes may also underlie the link between ALP variability and kidney function instability, suggesting its potential role as a marker of CKD progression.

One of the key findings of this study was the effect of ALP variability on mortality and progression to ESKD. Although the exact mechanisms underlying ALP variability and kidney function instability remain uncertain, several plausible biological pathways may explain this association. ALP fluctuations may reflect dynamic alterations in systemic inflammation, oxidative stress, and nutritional status, all of which are closely linked to CKD progression [29, 30]. Variability in ALP could also mirror oscillations in bone-mineral metabolism, such as intermittent activation of parathyroid hormone or vitamin D deficiency, which influence phosphate homeostasis and vascular calcification [31]. These findings suggest that ALP variability captures a broader spectrum of systemic metabolic stress rather than a single organ-specific process. Considering the physiology of ALP generation, fluctuations in ALP levels can result from changes in bone or hepatic metabolism, and intestinal ALP have also been reported to contribute a small proportion of circulating ALP activity, which may represent another physiological source of intra-individual variation [32, 33].

However, ALP variability may also reflect other factors, such as aging, changes in weight, and nutritional status [34–36]. Elevated or fluctuating ALP levels have been linked to reduced muscle mass, lower physical performance, and increased adiposity, suggesting that ALP may serve as an indirect marker of nutritional and metabolic status. Based on the results of this study, it is crucial to recognize that ALP variability has a greater impact than baseline ALP levels alone in predicting and reducing the risk of major outcomes. Common factors influenc-

ing both ALP levels and ALP fluctuations include lower BMI, serum albumin level, sodium level, and eGFR, which may be linked to nutritional status. Although the exact reasons for ALP fluctuations remain unclear, these findings underscore the importance of considering comorbidities, nutritional status, and metabolic conditions as contributing factors. Importantly, longitudinal changes in relatively lower blood ALP levels reflect changes in nutritional status over time in hemodialysis patients, independent of bone metabolism markers, inflammation, and liver enzymes [17]. Higher ALP levels have been linked to malnutrition in hemodialysis patients, unlike the association with insulin resistance and high-fat mass in the general population [34]. Importantly, various fibrates treatments primarily targeting lipid metabolism have been shown to improve liver function, including ALP levels, particularly in patients with metabolic syndrome [37]. These findings highlight the multifaceted nature of ALP regulation in CKD and suggest that both the static and dynamic aspects of ALP should be considered when evaluating patient risk and designing management strategies.

Although specific treatment strategies aimed at lowering ALP levels have not yet been established, targeting ALP could be more effective than focusing on PTH levels in managing disturbed bone turnover in CKD [38, 39]. In patients with ESKD, bone-specific ALP has shown greater predictive power for CKD-MBD-related outcomes [40], and TNAP has also been identified as a more specific marker of cardiovascular disease in patients with CKD [41]. While these findings underscore the bone-related and cardiovascular implications of ALP, total ALP as measured in this study likely represents a composite signal reflecting hepatic function, systemic inflammation, and nutritional status in addition to bone turnover. Its elevation should therefore be interpreted within the broader context of metabolic and inflammatory disturbances commonly observed in CKD. From a translational perspective, although our observational data do not directly evaluate therapeutic modulation of ALP, several experimental approaches have targeted tissue-nonspecific ALP (TNAP) activity. In particular, various epigenetic therapies designed to inhibit vascular calcification without affecting bone mineralization have been developed [42–44]. Beyond bone metabolism, decreasing circulating ALP activity itself may have broader clinical implications. Lowering ALP levels through improvement of metabolic and inflammatory status, such as optimizing lipid and glucose control, maintaining bone-mineral balance, and reducing systemic inflammation, could contribute to better kidney and cardiovascular outcomes. Furthermore, emerging pharmacological strategies including epigenetic, antifibrotic, and anti-calcific agents, may offer novel therapeutic avenues to mitigate disease progression in CKD [41, 44, 45]. Thus, focusing on both metabolic optimization and targeted ALP modulation could be a powerful strategy for improving the outcomes of patients with CKD.

This study highlights the clinical importance of considering baseline ALP levels and their variability. Specifically, the finding that elevated ALP levels additively contribute to variability underscores the need for a dual approach for risk evaluation and clinical monitoring. These results indicate that a multifaceted strategy is essential for addressing modifiable metabolic and inflammatory factors associated with ALP elevation and for exploring potential upstream mechanisms, including epigenetic regulation, that may influence ALP activity. By integrating these perspectives, clinicians may better identify high-risk individuals and monitor disease trajectories, ultimately improving patient outcomes. The strength of this study include its large multi-ethnic cohort and long-term follow-up, which enhance

the generalizability and reliability of the findings. Detailed analysis of ALP variability provides valuable insights into its role in CKD progression and mortality. Nevertheless, several limitations should be acknowledged. First, ALP variability was measured at three fixed intervals, and more frequent monitoring may have affected the outcomes. Second, bone-specific or liver-specific ALP isoenzymes, as well as related biomarkers such as parathyroid hormone and 25-hydroxyvitamin D, were unavailable, limiting the ability to distinguish tissue-specific sources of ALP variation. Third, given the multicenter design and extended inclusion period (2001–2021), minor differences in analyzers, reagents, or site-specific calibration could not be fully excluded, although the same IFCC-recommended kinetic colorimetric method was consistently applied across all centers. Fourth, despite adjusting for confounders, residual confounding from unmeasured factors remained possible. Finally, as a retrospective observational study, this work is subject to inherent biases and cannot establish causality. While it identifies key associations, further research is needed to explore the underlying mechanisms and validate these findings in other populations.

CONCLUSION

This study highlights the significant impact of the ALP level and variability on mortality and CKD progression. ALP may serve as a prognostic biomarker reflecting systemic metabolic and inflammatory dysregulation in patients with CKD. Further studies are required to explore the underlying mechanisms and to validate these findings in prospective settings.

SUPPLEMENTARY DATA

Supplementary data are available at *Clinical Kidney Journal* online.

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AUTHORS' CONTRIBUTIONS

Conceptualization was carried out by Y.K. and J.P.L. Study design and analysis plan were developed by Y.K. and P.H.W. Statistical analysis was performed by S.K., J.L., M.Y.L., and N.H.S. Funding was acquired by P.H.W. The manuscript was written by Y.K. and P.H.W. Writing—review & editing were carried out by Y.W.C., J.H.P., D.K.K., S.H., C.S.L., S.J.H., and J.P.L.

DATA AVAILABILITY STATEMENT

The data underlying this article will be shared on reasonable request to the corresponding author.

CONFLICT OF INTEREST STATEMENT

None declared.

REFERENCES

- McComb RB, Bowers GN Jr, Posen S. *Alkaline Phosphatase*. New York: Springer Science & Business Media; 2013.
- Pekarthy JM, Short J, Lansing AI et al. Function and control of liver alkaline phosphatase. *J Biol Chem* 1972;247:1767–74. [https://doi.org/10.1016/S0021-9258\(19\)45541-5](https://doi.org/10.1016/S0021-9258(19)45541-5)
- Masrou Roudsari J, Mahjoub S. Quantification and comparison of bone-specific alkaline phosphatase with two methods in normal and Paget's specimens. *Caspian J Intern Med* 2012;3:478–83.
- Shamban L, Patel B, Williams M. Significantly elevated liver alkaline phosphatase in congestive heart failure. *Gastroenterology Res* 2014;7:64–68.
- Vimalraj S. Alkaline phosphatase: structure, expression and its function in bone mineralization. *Gene* 2020;754:144855. <https://doi.org/10.1016/j.gene.2020.144855>
- Jackson EK, Zhang Y, Cheng D. Alkaline phosphatase inhibitors attenuate renovascular responses to norepinephrine. *Hypertension* 2017;69:484–93. <https://doi.org/10.1161/HYPERTENSIONAHA.116.08623>
- Taliercio JJ, Schold JD, Simon JF et al. Prognostic importance of serum alkaline phosphatase in CKD stages 3–4 in a clinical population. *Am J Kidney Dis* 2013;62:703–10. <https://doi.org/10.1053/j.ajkd.2013.04.012>
- Bae EH, Lim SY, Yang EM et al. The effects of socioeconomic status on major adverse cardiovascular events: a nationwide population-based cohort study. *Kidney Res Clin Pract* 2023;42:229–42. <https://doi.org/10.23876/j.krcp.21.249>
- Makmun A, Satirapoj B, Tuyen DG et al. The burden of chronic kidney disease in Asia region: a review of the evidence, current challenges, and future directions. *Kidney Res Clin Pract* 2025;44:411–33. <https://doi.org/10.23876/j.krcp.23.194>
- Zoccali C, Vanholder R, Massy ZA et al. The systemic nature of CKD. *Nat Rev Nephrol* 2017;13:344–58. <https://doi.org/10.1038/nrneph.2017.52>
- Kim JH, Kang M, Kang E et al. Comparison of cardiovascular event predictability between the 2009 and 2021 Chronic Kidney Disease Epidemiology Collaboration equations in a Korean chronic kidney disease cohort: the KoreaN Cohort Study for Outcome in Patients With Chronic Kidney Disease. *Kidney Res Clin Pract* 2023;42:700–11. <https://doi.org/10.23876/j.krcp.22.206>
- Cho JM, Han K, Joo KW et al. Associations of metabolic variabilities and cardiovascular outcomes according to estimated glomerular filtration rate in chronic kidney disease: a nationwide observational cohort study. *Kidney Res Clin Pract* 2025;44:265–76. <https://doi.org/10.23876/j.krcp.23.135>
- Deng H, Zou Q, Chen Z et al. Global burden and risk factors of chronic kidney disease in adolescents and young adults: a study from 1990 to 2019. *Kidney Res Clin Pract* 2025;44:588–601.
- Nizet A, Cavalier E, Stenvinkel P et al. Bone alkaline phosphatase: an important biomarker in chronic kidney disease—mineral and bone disorder. *Clin Chim*

- Acta 2020;501:198–206. <https://doi.org/10.1016/j.cca.2019.11.012>
15. Brichacek AL, Brown CM. Alkaline phosphatase: a potential biomarker for stroke and implications for treatment. *Metab Brain Dis* 2019;34:3–19. <https://doi.org/10.1007/s11011-018-0322-3>
 16. Liu Y, Zhu JG, Cheng BC 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. <https://doi.org/10.1038/srep43314>
 17. Beberashvili I, Samogalska O, Azar A et al. Nutritional status and mortality predictability for time-varying serum alkaline phosphatase in hemodialysis patients: a longitudinal study. *J Ren Nutr* 2020;30:452–61. <https://doi.org/10.1053/j.jrn.2019.10.004>
 18. Kovesdy CP, Ureche V, Lu JL et al. Outcome predictability of serum alkaline phosphatase in men with pre-dialysis CKD. *Nephrol Dial Transplant* 2010;25:3003–11. <https://doi.org/10.1093/ndt/gfq144>
 19. Levey AS, Stevens LA, Schmid CH et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009;150:604–12. <https://doi.org/10.7326/0003-4819-150-9-200905050-00006>
 20. Park JB, Kang DY, Yang HM et al. Serum alkaline phosphatase is a predictor of mortality, myocardial infarction, or stent thrombosis after implantation of coronary drug-eluting stent. *Eur Heart J* 2013;34:920–31. <https://doi.org/10.1093/eurheartj/ehs419>
 21. Tonelli M, Curhan G, Pfeffer M et al. Relation between alkaline phosphatase, serum phosphate, and all-cause or cardiovascular mortality. *Circulation* 2009;120:1784–92. <https://doi.org/10.1161/CIRCULATIONAHA.109.851873>
 22. Moe S, Drüeke T, Cunningham J et al. Definition, evaluation, and classification of renal osteodystrophy: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int* 2006;69:1945–53. <https://doi.org/10.1038/sj.ki.5000414>
 23. Blayney MJ, Pisoni RL, Bragg-Gresham JL et al. High alkaline phosphatase levels in hemodialysis patients are associated with higher risk of hospitalization and death. *Kidney Int* 2008;74:655–63. <https://doi.org/10.1038/ki.2008.248>
 24. Maruyama Y, Taniguchi M, Kazama JJ et al. A higher serum alkaline phosphatase is associated with the incidence of hip fracture and mortality among patients receiving hemodialysis in Japan. *Nephrol Dial Transplant* 2014;29:1532–8. <https://doi.org/10.1093/ndt/gfu055>
 25. Haarhaus M, Brandenburg V, Kalantar-Zadeh K et al. Alkaline phosphatase: a novel treatment target for cardiovascular disease in CKD. *Nat Rev Nephrol* 2017;13:429–42. <https://doi.org/10.1038/nrneph.2017.60>
 26. Regidor DL, Kovesdy CP, Mehrotra R et al. Serum alkaline phosphatase predicts mortality among maintenance hemodialysis patients. *J Am Soc Nephrol* 2008;19:2193–203. <https://doi.org/10.1681/ASN.2008010014>
 27. Soohoo M, Feng M, Obi Y et al. Changes in markers of mineral and bone disorders and mortality in incident hemodialysis patients. *Am J Nephrol* 2016;43:85–96. <https://doi.org/10.1159/000444890>
 28. Zhang Y, He P, Wang G et al. Interaction of serum alkaline phosphatase and folic acid treatment on chronic kidney disease progression in treated hypertensive adults. *Front Pharmacol* 2021;12:753803. <https://doi.org/10.3389/fphar.2021.753803>
 29. Podkowińska A, Formanowicz D. Chronic kidney disease as oxidative stress- and inflammatory-mediated cardiovascular disease. *Antioxidants (Basel)* 2020;9:752.
 30. Graterol Torres F, Molina M, Soler-Majoral J et al. Evolving concepts on inflammatory biomarkers and malnutrition in chronic kidney disease. *Nutrients* 2022; 14 4297. <https://doi.org/10.3390/nu14204297>
 31. Tunbridge MJ, Jardine AG. Atherosclerotic vascular disease associated with chronic kidney disease. *Cardiol Clin* 2021;39:403–14.
 32. Lallès JP. Intestinal alkaline phosphatase: multiple biological roles in maintenance of intestinal homeostasis and modulation by diet. *Nutr Rev* 2010;68:323–32.
 33. Nakano T, Shimanuki T, Matsushita M et al. Involvement of intestinal alkaline phosphatase in serum apolipoprotein B-48 level and its association with ABO and secretor blood group types. *Biochem Biophys Res Commun* 2006;341:33–38. <https://doi.org/10.1016/j.bbrc.2005.12.145>
 34. Kang SH, Do JY, Kim JC. Association between alkaline phosphatase and muscle mass, strength, or physical performance in patients on maintenance hemodialysis. *Front Med* 2021;8:657957. <https://doi.org/10.3389/fmed.2021.657957>
 35. Kim MK, Baek KH, Kang MI et al. Serum alkaline phosphatase, body composition, and risk of metabolic syndrome in middle-aged Korean. *Endocr J* 2013;60:321–8. <https://doi.org/10.1507/endocrj.EJ12-0331>
 36. Zhang Z, Zhou J, Ma A et al. The correlation between serum alkaline phosphatase and grip strength in middle-aged and elderly people: NHANES 2011–2014. *BMC Musculoskelet Disord* 2025;26:191. <https://doi.org/10.1186/s12891-025-08408-2>
 37. Gandhi N, Lenton R, Bhartia M et al. Effect of fibrate treatment on liver function tests in patients with the metabolic syndrome. *Springerplus* 2014;3:14. <https://doi.org/10.1186/2193-1801-3-14>
 38. Garrett G, Sardiwal S, Lamb EJ et al. PTH—a particularly tricky hormone: why measure it at all in kidney patients? *Clin J Am Soc Nephrol* 2013;8:299–312. <https://doi.org/10.2215/CJN.09580911>
 39. Lamb EJ, Delaney MP. Does PTH offer additive value to ALP measurement in assessing CKD-MBD? *Perit Dial Int* 2014;34:687–91. <https://doi.org/10.3747/pdi.2014.00246>
 40. Sardiwal S, Magnusson P, Goldsmith DJ et al. Bone alkaline phosphatase in CKD-mineral bone disorder. *Am J Kidney Dis* 2013;62:810–22. <https://doi.org/10.1053/j.ajkd.2013.02.366>
 41. Goettsch C, Strzelecka-Kiliszek A, Bessueille L et al. TNAP as a therapeutic target for cardiovascular calcification: a discussion of its pleiotropic functions in the body. *Cardiovasc Res* 2022;118:84–96. <https://doi.org/10.1093/cvr/cvaa299>
 42. Sheen CR, Kuss P, Narisawa S et al. Pathophysiological role of vascular smooth muscle alkaline phosphatase in medial artery calcification. *J Bone Miner Res* 2015;30:824–36. <https://doi.org/10.1002/jbmr.2420>
 43. Picaud S, Wells C, Felletar I et al. RVX-208, an inhibitor of BET transcriptional regulators with selectivity for the second bromodomain. *Proc Natl Acad Sci USA* 2013;110:19754–9. <https://doi.org/10.1073/pnas.1310658110>

44. Dhulkifle H, Diab MI, Algoniaiah M et al. Apabetalone (RVX-208): a potential epigenetic therapy for the treatment of cardiovascular, renal, neurological, viral, and cancer disorders. *ACS Pharmacol Transl Sci* 2024;7:546–59. <https://doi.org/10.1021/acsptsci.3c00219>
45. Gao L, Wang LY, Liu ZQ et al. TNAP inhibition attenuates cardiac fibrosis induced by myocardial infarction through deactivating TGF- β 1/Smads and activating P53 signaling pathways. *Cell Death Dis* 2020;11:44. <https://doi.org/10.1038/s41419-020-2243-4>

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