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Prognostic significance of pre-end-stage renal disease serum alkaline phosphatase for post-end-stage renal disease mortality in late-stage chronic kidney disease patients transitioning to dialysis

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ABSTRACT

Background. Higher serum alkaline phosphatase (ALP) levels have been associated with excess mortality in patients with non-dialysis-dependent chronic kidney disease (NDD-CKD) and end-stage renal disease (ESRD). However, little is known about the impact of late-stage NDD-CKD ALP levels on outcomes after dialysis initiation.

Methods. Among 17 732 US veterans who transitioned to dialysis between October 2007 and September 2011, we examined the association of serum ALP levels averaged over the last 6 months of the pre-ESRD transition period ('prelude period') with all-cause, cardiovascular and infection-related mortality following dialysis initiation, using Cox (for all-cause mortality) and competing risk (for cause-specific mortality) regressions adjusted for demographics, comorbidities, medications, estimated glomerular filtration rate and serum albumin levels over the 6-month prelude period, and vascular access type at dialysis initiation.

Results. During a median follow-up of 2.0 (interquartile range, 1.1–3.2) years following dialysis initiation, a total of 9196 all-cause deaths occurred. Higher ALP levels were incrementally associated with higher all-cause, cardiovascular and infection-related mortality. Compared with patients in the lowest ALP quartile (<66.0 U/L), those in the highest quartile (≥111.1 U/L) had multivariable-adjusted hazard/subhazard ratios (95% confidence interval) of 1.42 (1.34–1.51), 1.43 (1.09–1.88) and 1.39 (1.09–1.78) for all-cause, cardiovascular and infection-related mortality, respectively. The associations remained consistent in various subgroups and after further adjustment for liver enzymes, serum phosphorus and intact parathyroid hormone levels.

Conclusions. Higher pre-ESRD serum ALP levels are independently associated with higher post-ESRD mortality risk. Further studies are warranted to determine if interventions that lower pre-ESRD ALP levels reduce mortality in incident dialysis patients.

Keywords: alkaline phosphatase, chronic kidney disease, end-stage renal disease, mortality, transition

INTRODUCTION

Patients with advanced non-dialysis-dependent chronic kidney disease (NDD-CKD) transitioning to end-stage renal disease

(ESRD) suffer from an exceptionally high health and economic burden, with the highest mortality seen within the first few months after the transition to dialysis [1–3]. It is therefore important to focus on this vulnerable population and identify modifiable risk factors and interventions that could improve their clinical outcomes.

Derangements in bone and mineral metabolism are almost universally observed in patients with ESRD on dialysis therapy and have been associated with higher risk of adverse clinical outcomes [4, 5]. Elevated serum alkaline phosphatase (ALP), a known feature of mineral and bone disorders (MBD) in ESRD patients, has been shown to be associated with higher risk of cardiovascular events, hospitalization and all-cause mortality, potentially through progression of vascular calcification [6–10]. A few studies have also demonstrated its independent association with infection-related mortality in dialysis patients [6, 11, 12], suggesting that ALP is not merely a marker of bone turnover but may serve as a reliable predictor of mortality in patients with ESRD. Furthermore, recent observational studies have reported a similar ALP–mortality association in patients with NDD-CKD, mostly in those with CKD stages 3–4 [13–15].

Despite the plausible ALP–mortality association throughout all stages of CKD, no evidence, to the best of our knowledge, have been provided as to whether this association applies to the transition period from late-stage NDD-CKD to maintenance dialysis, largely due to the lack of large databases linking pre-ESRD transition data to post-ESRD registries. Therefore, the objective of this study is to investigate the impact of pre-ESRD ALP levels on post-ESRD all-cause, cardiovascular and infection-related mortality, using a large nationally representative cohort of US veterans with advanced NDD-CKD transitioning to dialysis.

MATERIALS AND METHODS

Study population

We analyzed data from the Transition of Care in CKD (TC-CKD) study, a historical cohort study examining US veterans with late-stage NDD-CKD transitioning to dialysis over the period of 1 October 2007 through 30 September 2011 [16–18]. A total of 52 172 US veterans were identified from the US Renal Data System (USRDS) [1] as a source population. In the present study, patients without any serum ALP measurements available from Veterans Affairs (VA) medical centers were excluded ($n = 23\,515$). We also excluded those who did not have any serum ALP measurements within 6 months prior to dialysis initiation (i.e. 6-month 'prelude period') ($n = 10\,672$) and who had missing follow-up data ($n = 253$), resulting in a study population of 17 732 patients (Supplementary data, Figure S1).

Exposure variable

The primary exposure of interest was serum ALP level averaged over the 6-month prelude period. We categorized ALP levels into quartiles as follows: quartile 1, <66.0; quartile 2, 66.0 to <84.8; quartile 3, 84.8 to <111.1; and quartile 4, ≥111.1 U/L. The lowest quartile (<66.0 U/L) was used as reference in all analyses under the assumption that mortality risk is the lowest in that group. The ALP level was also treated as a continuous variable to examine nonlinear associations by using fractional polynomials.

Covariates

Data from the USRDS Patient and Medical Evidence files were used to determine patients' baseline demographic data and type of vascular access at the time of dialysis initiation. Laboratory data were collected from VA research databases as previously described [19, 20], and their baseline values were defined as the average of each covariate during the 6-month prelude period preceding dialysis initiation. Using serum creatinine and demographic data, estimated glomerular filtration rate (eGFR) was calculated based on the Chronic Kidney Disease Epidemiology Collaboration equation [21]. Medication data were obtained from both Centers for Medicare and Medicaid Services (CMS) Data (Medicare Part D) and VA pharmacy dispensation records [22]. Patients who received at least one dispensation of medications within the 6-month prelude period were recorded as having been treated with these medications. Information about comorbidities at the time of dialysis initiation was extracted from the VA Inpatient and Outpatient Medical SAS Datasets [23], using the International Classification of Diseases, Ninth Revision, Clinical Modification diagnostic and procedure codes and Current Procedural Terminology codes, as well as from VA/CMS data. We calculated the Charlson Comorbidity Index score using the Deyo modification for administrative datasets, without including kidney disease [24]. Cardiovascular disease was defined as the presence of diagnostic codes for coronary artery disease, angina, myocardial infarction or cerebrovascular disease.

Outcome assessment

The co-primary outcomes of interest were all-cause, cardiovascular and infection-related mortality after dialysis initiation. All-cause mortality data, censoring events and associated dates were obtained from VA and USRDS sources [1]. Cause-specific mortality data were obtained from the USRDS source only. The start of follow-up was the date of dialysis initiation, and patients were followed up until death or other censoring events including kidney transplantation, loss of follow-up or the last date of available follow-up data (27 December 2012 and 6 October 2011 for all-cause and cause-specific mortality, respectively) [16–18].

Statistical analysis

Baseline characteristics were summarized according to quartiles of ALP level, and presented as number (percent) for categorical variables and the mean ± standard deviation (SD) for continuous variables with a normal distribution or median [interquartile range (IQR)] for those with a skewed distribution. Differences across quartiles were assessed using analysis of variance and chi-squared tests for continuous and categorical variables, respectively.

Table 1. Baseline patient characteristics according to quartiles of serum ALP level over the 6-month prelude period

	All	Quartile of serum ALP level (U/L)				P
		Q1 (lowest) <66.0	Q2 66.0 to < 84.8	Q3 84.8 to <111.1	Q4 (highest) ≥111.1	
	(N = 17 732)	(n = 4298)	(n = 4559)	(n = 4437)	(n = 4438)	
Age (years)	68.1 ± 11.4	69.4 ± 11.6	68.8 ± 11.5	67.7 ± 11.2	66.4 ± 10.9	<0.001
Sex (male)	17 394 (98.1)	4234 (98.5)	4469 (98.0)	4349 (98.0)	4342 (97.8)	0.12
Race						<0.001
White	12 105 (68.3)	2890 (67.2)	3183 (69.8)	3078 (69.4)	2954 (66.6)	
African-American	5253 (29.6)	1293 (30.1)	1279 (28.1)	1285 (29.0)	1396 (31.5)	
Asian	341 (1.9)	107 (2.5)	92 (2.0)	68 (1.5)	74 (1.7)	
Other	33 (0.2)	8 (0.2)	5 (0.1)	6 (0.1)	14 (0.3)	
Marital status						<0.001
Married	9500 (53.6)	2402 (55.9)	2505 (55.0)	2366 (53.3)	2227 (50.2)	
Divorced	4438 (25.0)	984 (22.9)	1099 (24.1)	1129 (25.5)	1226 (27.6)	
Single	1527 (8.6)	344 (8.0)	358 (7.9)	374 (8.4)	451 (10.2)	
Widow	1820 (10.3)	455 (10.6)	492 (10.8)	463 (10.4)	410 (9.2)	
Unknown	447 (2.5)	113 (2.6)	105 (2.3)	105 (2.4)	124 (2.8)	
BMI (kg/m^2)	29.9 ± 6.7	30.0 ± 6.6	30.0 ± 6.6	30.0 ± 6.7	29.8 ± 7.0	0.32
Diabetes mellitus	12 619 (71.2)	2855 (66.4)	3168 (69.5)	3262 (73.5)	3334 (75.1)	<0.001
Hypertension	17 127 (96.6)	4162 (96.8)	4422 (97.0)	4288 (96.6)	4255 (95.9)	0.11
Cardiovascular disease[a]	8273 (46.7)	1949 (45.4)	2155 (47.3)	2122 (47.8)	2047 (46.1)	0.086
Congestive heart failure	9861 (55.6)	2245 (52.2)	2486 (54.5)	2512 (56.6)	2618 (59.0)	<0.001
Peripheral vascular disease	7284 (41.1)	1671 (38.9)	1915 (42.0)	1868 (42.1)	1830 (41.2)	0.049
Liver disease	2364 (13.3)	395 (9.2)	481 (10.6)	557 (12.6)	931 (21.0)	<0.001
Dementia	456 (2.6)	104 (2.4)	125 (2.7)	128 (2.9)	99 (2.2)	0.53
Chronic pulmonary disease	7963 (44.9)	1769 (41.2)	2020 (44.3)	2049 (46.2)	2125 (47.9)	<0.001
Malignancies	4443 (25.1)	1127 (26.2)	1154 (25.3)	1100 (24.8)	1062 (23.9)	0.34
Charlson Comorbidity Index	5 (3, 7)	4 (3, 6)	5 (3, 7)	5 (3, 7)	5 (3, 7)	<0.001
Vascular access type						<0.001
Arteriovenous fistula	3402 (19.2)	978 (22.8)	888 (19.5)	812 (18.3)	724 (16.3)	
Arteriovenous graft	410 (2.3)	116 (2.7)	111 (2.4)	102 (2.3)	81 (1.8)	
Catheter	12 611 (71.1)	2832 (65.9)	3217 (70.6)	3214 (72.4)	3348 (75.4)	
Unknown	1309 (7.4)	372 (8.7)	343 (7.5)	309 (7.0)	285 (6.4)	
Medications						
ACEIs/ARBs	8862 (50.0)	2164 (50.4)	2330 (51.1)	2201 (49.6)	2167 (48.8)	0.16
Statins	11 410 (64.4)	2844 (66.2)	3007 (66.0)	2909 (65.6)	2650 (59.7)	<0.001
Vitamin D analogs	5545 (31.3)	1,572 (36.6)	1429 (31.3)	1299 (29.3)	1245 (28.1)	<0.001
Phosphate binders[b]	5940 (33.5)	1,549 (36.0)	1473 (32.3)	1466 (33.0)	1452 (32.7)	0.001
Bicarbonate	4078 (23.0)	937 (21.8)	996 (21.9)	999 (22.5)	1146 (25.8)	<0.001
ESAs	5906 (33.3)	1485 (34.6)	1457 (32.0)	1449 (32.7)	1515 (34.1)	0.030
Laboratory parameters[c]						
Serum albumin (g/dL)	3.4 ± 0.6	3.4 ± 0.6	3.4 ± 0.6	3.4 ± 0.6	3.2 ± 0.6	<0.001
Serum cholesterol (mg/dL)	155.1 ± 50.4	155.4 ± 49.8	155.3 ± 48.8	157.8 ± 51.0	151.9 ± 52.1	<0.001
Serum bicarbonate (mEq/L)	23.1 ± 4.0	23.4 ± 4.0	23.2 ± 3.9	23.0 ± 4.0	22.8 ± 4.2	<0.001
Serum potassium (mEq/L)	4.5 ± 0.6	4.5 ± 0.6	4.5 ± 0.6	4.5 ± 0.6	4.5 ± 0.6	0.26
Serum calcium (mg/dL)	8.7 ± 0.7	8.9 ± 0.7	8.8 ± 0.7	8.7 ± 0.7	8.6 ± 0.7	<0.001
Serum phosphorus (mg/dL)	5.1 ± 1.3	5.3 ± 1.4	5.1 ± 1.3	5.1 ± 1.3	5.0 ± 1.2	<0.001
Serum intact PTH (pg/mL)	220 (130, 362)	190 (112, 308)	215 (133, 348)	237 (139, 373)	243 (139, 426)	<0.001
Serum AST (U/L)	20 (16, 27)	19 (15, 24)	19 (15, 25)	20 (16, 27)	24 (18, 35)	<0.001
Serum ALT (U/L)	18 (13, 26)	16 (12, 21)	17 (13, 23)	19 (14, 27)	23 (16, 34)	<0.001
Blood hemoglobin (g/dL)	10.6 ± 1.5	10.5 ± 1.5	10.6 ± 1.5	10.6 ± 1.5	10.6 ± 1.5	<0.001
White blood cells (1000/mm^3)	7.8 ± 3.2	7.4 ± 2.6	7.7 ± 3.0	7.9 ± 3.1	8.0 ± 3.8	<0.001
Serum urea nitrogen (mg/dL)	60.9 ± 23.0	63.6 ± 24.1	60.4 ± 22.5	60.1 ± 22.3	59.6 ± 22.8	<0.001
Serum creatinine (mg/dL)	4.7 ± 2.4	5.1 ± 2.8	4.7 ± 2.4	4.6 ± 2.3	4.3 ± 2.2	<0.001
eGFR (mL/min/1.73 m^2)	13.8 (10.3, 19.4)	12.5 (9.4, 17.3)	13.6 (10.2, 18.9)	13.8 (10.6, 19.0)	15.4 (11.3, 22.2)	<0.001

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; ESA, erythropoietin-stimulating agent.
Data are presented as number (percentage), mean ± SD or median (IQR).
[a]Cardiovascular disease include coronary artery disease, angina, myocardial infarction or cerebrovascular disease.
[b]Phosphate binders include calcium acetate, sevelamer or lanthanum.
[c]All laboratory results averaged over the 6-month prelude period.

The cumulative incidence of all-cause death according to the ALP quartiles was assessed using the Kaplan–Meier method and the log-rank test. Cause-specific deaths are competing events; therefore, we fit cumulative incidence functions and performed Gray's test for the cumulative incidences of cause-specific deaths [25]. Subsequently, we estimated the association between ALP levels and mortality using Cox proportional hazards models for all-cause death and Fine and Gray competing

risks regressions for cause-specific deaths by treating deaths from other causes as competing events [26]. Models were incrementally adjusted for the following potential confounders based on theoretical considerations: model 1 adjusted for age, sex, race/ethnicity and marital status; model 2 additionally accounted for comorbidities (cardiovascular disease, congestive heart failure, peripheral vascular disease, dementia, lung disease, diabetes mellitus, liver disease, malignancy and Charlson Comorbidity Index); and model 3 additionally included medications (vitamin D analogs, phosphate binders, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, statins, bicarbonate and erythropoietin stimulating agents), eGFR and serum albumin averaged over the 6-month prelude period, and type of vascular access (arteriovenous fistula, arteriovenous graft or catheter). Tests for linear trend across quartiles were conducted by applying the median value of each quartile to relevant patients and modeling that variable as a continuous variable in the regression models. We used fractional polynomial regression models to examine nonlinear

associations between ALP levels and mortality [27], in which the ALP level was treated as a log-transformed continuous variable since the values had a highly positively skewed distribution.

We performed sensitivity analyses to evaluate the robustness of our main findings. The associations of ALP levels with outcomes were examined in subgroups of patients stratified by age, race, body mass index, presence/absence of comorbidities such as diabetes mellitus, cardiovascular disease and liver disease, and eGFR and intact parathyroid hormone (PTH) levels. To
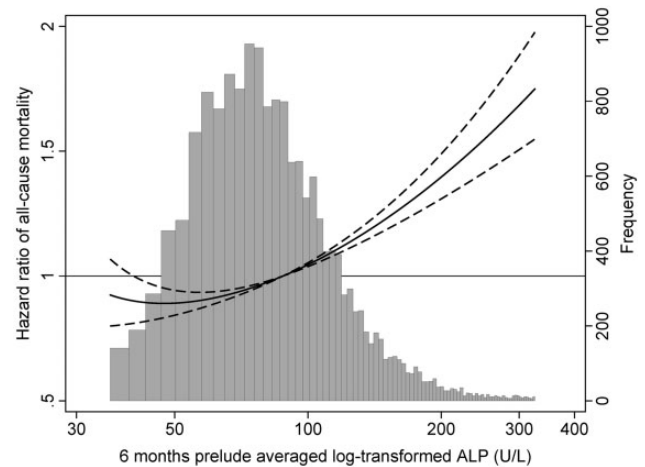
FIGURE 2: Association of serum ALP levels over the 6-month prelude period with all-cause mortality after dialysis initiation in multivariable-adjusted Cox models using fractional polynomials. Solid and dashed lines represent HR and 95% CI, respectively. A hazard reference ratio of 1 (solid horizontal line) and a histogram of observed serum ALP values are overlaid. The x-axis shows log-transformed serum ALP levels, trimmed at 1% and 99%. Model is adjusted for age, sex, race/ethnicity, marital status, comorbidities (cardiovascular disease, congestive heart failure, peripheral vascular disease, dementia, lung disease, diabetes mellitus, liver disease, malignancy and Charlson Comorbidity Index), medications (vitamin D analogs, phosphate binders, ACEIs/ARBs, statins, bicarbonate and ESAs), eGFR and serum albumin averaged over the 6-month prelude period, and vascular access type (arteriovenous fistula, arteriovenous graft or catheter). ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ESA, erythropoietin-stimulating agent.
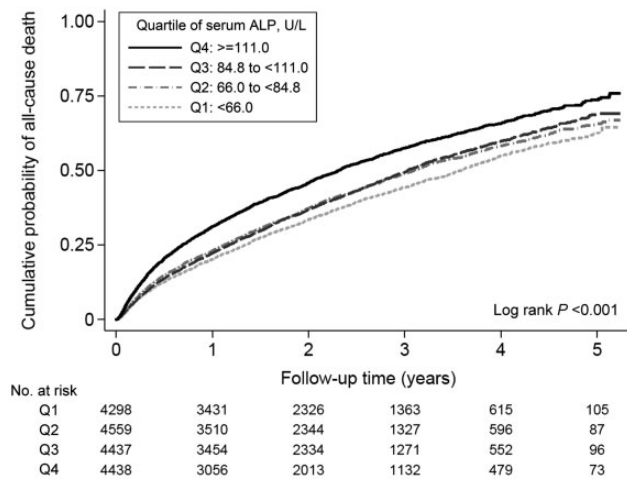

FIGURE 1: Unadjusted cumulative incidence curves for all-cause mortality after dialysis initiation by quartiles of serum ALP level over the 6-month prelude period. Estimated probabilities are presented using the Kaplan–Meier method.

Table 2. Adjusted HRs (95% CIs) for all-cause mortality after dialysis initiation by quartiles of serum ALP level over the 6-month prelude period in Cox models

	Quartile of serum ALP level (U/L)				P for trend[a]
	Q1 (lowest) <66.0	Q2 66.0 to <84.8	Q3 84.8 to <111.1	Q4 (highest) ≥111.1	
Patients (n)	4298	4559	4437	4438	
Events	1997 (46.5)	2291 (50.3)	2279 (51.4)	2679 (60.4)	
Model 1	1 [reference]	1.15 (1.09–1.23)	1.23 (1.16–1.31)	1.66 (1.56–1.76)	<0.001
Model 2	1 [reference]	1.12 (1.06–1.19)	1.17 (1.10–1.24)	1.53 (1.44–1.63)	<0.001
Model 3	1 [reference]	1.10 (1.04–1.18)	1.12 (1.05–1.19)	1.42 (1.34–1.51)	<0.001

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ESA, erythropoietin-stimulating agent.
Data are presented as number (percentage) or HR (95% CI) unless otherwise specified.
Models are as follows: model 1 is adjusted for age, sex, race/ethnicity and marital status; model 2 is adjusted for the variables in model 1 plus comorbidities (cardiovascular disease, congestive heart failure, peripheral vascular disease, dementia, lung disease, diabetes mellitus, liver disease, malignancy and Charlson Comorbidity Index); and model 3 is adjusted for the variables in model 2 plus medications (vitamin D analogs, phosphate binders, ACEIs/ARBs, statins, bicarbonate and ESAs), eGFR and serum albumin averaged over the 6-month prelude period, and vascular access type (arteriovenous fistula, arteriovenous graft or catheter).
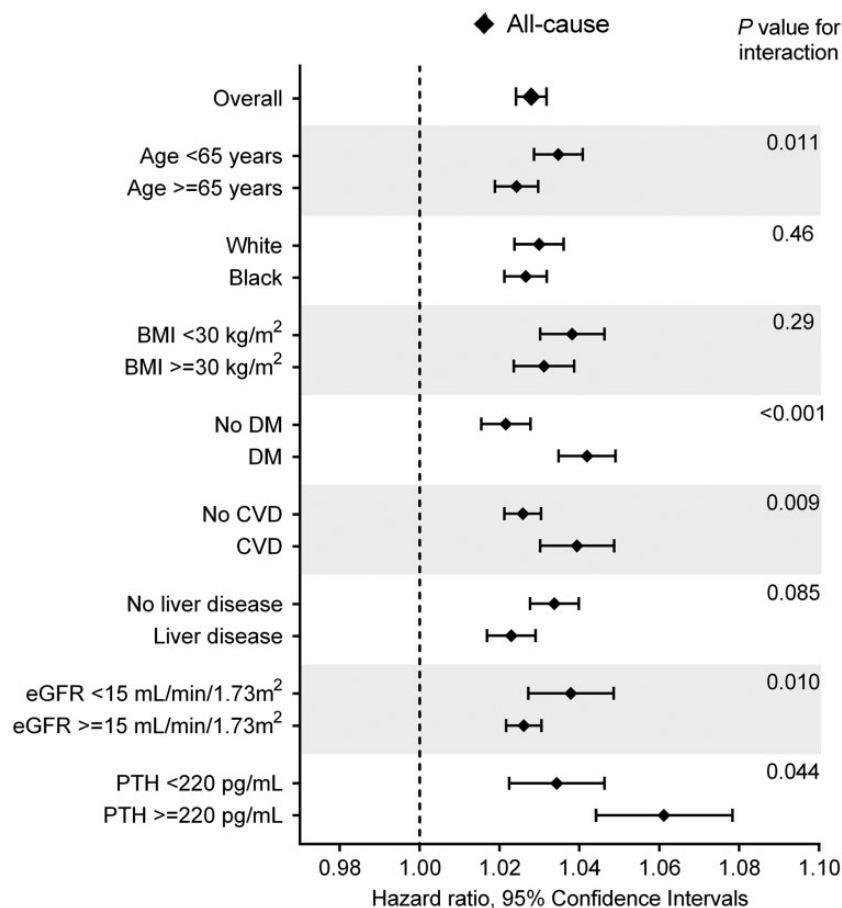[a]Linear trend across the quartiles using the median ALP value of each quartile.

FIGURE 3: Adjusted HRs (95% CIs) of all-cause mortality after dialysis initiation associated with a 20-U/L higher serum ALP level over the 6-month prelude period in selected subgroups. Model is adjusted for age, sex, race/ethnicity, marital status, comorbidities (cardiovascular disease, congestive heart failure, peripheral vascular disease, dementia, lung disease, diabetes mellitus, liver disease, malignancy and Charlson Comorbidity Index), medications (vitamin D analogs, phosphate binders, ACEIs/ARBs, statins, bicarbonate and ESAs), eGFR and serum albumin averaged over the 6-month prelude period, and vascular access type (arteriovenous fistula, arteriovenous graft or catheter). ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CVD, cardiovascular disease; DM, diabetes mellitus; ESA, erythropoietin-stimulating agent.

obtain a reliable estimate in each subgroup, the ALP level was modeled as a continuous variable and hazard ratios (HRs)/subhazard ratios (SHRs) were expressed for each 20-U/L increment. Potential interactions were formally tested by including relevant interaction terms. Although liver disease was accounted for in the multivariable models, we investigated whether accounting for liver enzymes [i.e. serum aspartate transaminase (AST) and alanine transaminase (ALT)] further attenuates the association between ALP levels and mortality (model 4). Additional adjustment for MBD markers including serum phosphorus and intact PTH was also performed in the group of 5541 patients with available phosphorus and intact PTH measurements (model 5). In order to explore the effect of inflammation as a potential pathway intermediate of the ALP–mortality association, we additionally included white blood cell count in expanded adjusted model and observed for attenuation of effect estimates (model 6).

Compared with patients in our main cohort ($n = 17\,732$), those who were excluded from the source cohort ($n = 34\,440$) were older (71.5 versus 68.1 years) and were less likely to be male (92.4% versus 98.1%) and African-American (21.4%

versus 29.6%). Of the variables included in multivariable models, data points were missing for race (0.2%), comorbidities (<0.01%), vascular access type (7.4%), eGFR (0.2%), serum albumin (1.2%), AST (3.3%), ALT (1.9%), phosphorus (48.9%), intact PTH (50.4%) and white blood cells (9.5%). Information about cause of death was also missing in 4383 (47.7%) of the 9196 who died in our main cohort. Compared with patients with missing cause of death, those without missing cause of death were less likely to be African-American (20.2% versus 24.0%) and had a slightly higher prevalence of cardiovascular disease (57.4% versus 51.8%), congestive heart failure (66.4% versus 62.5%) and peripheral vascular disease (49.9% versus 45.6%) (Supplementary data, Table S1). Of the 17 732 patients in our main cohort, 16 175 (91.2%) had complete data available for the main adjusted multivariable model (model 3). Since it is possible that missingness was not at random, and the proportion of patients with missingness was low in our main analyses, imputation was not used. The reported P-values are two-sided and reported as significant at <0.05 for all analyses. All analyses were conducted using STATA/MP Version 14 (STATA Corporation, College Station, TX, USA). The study was
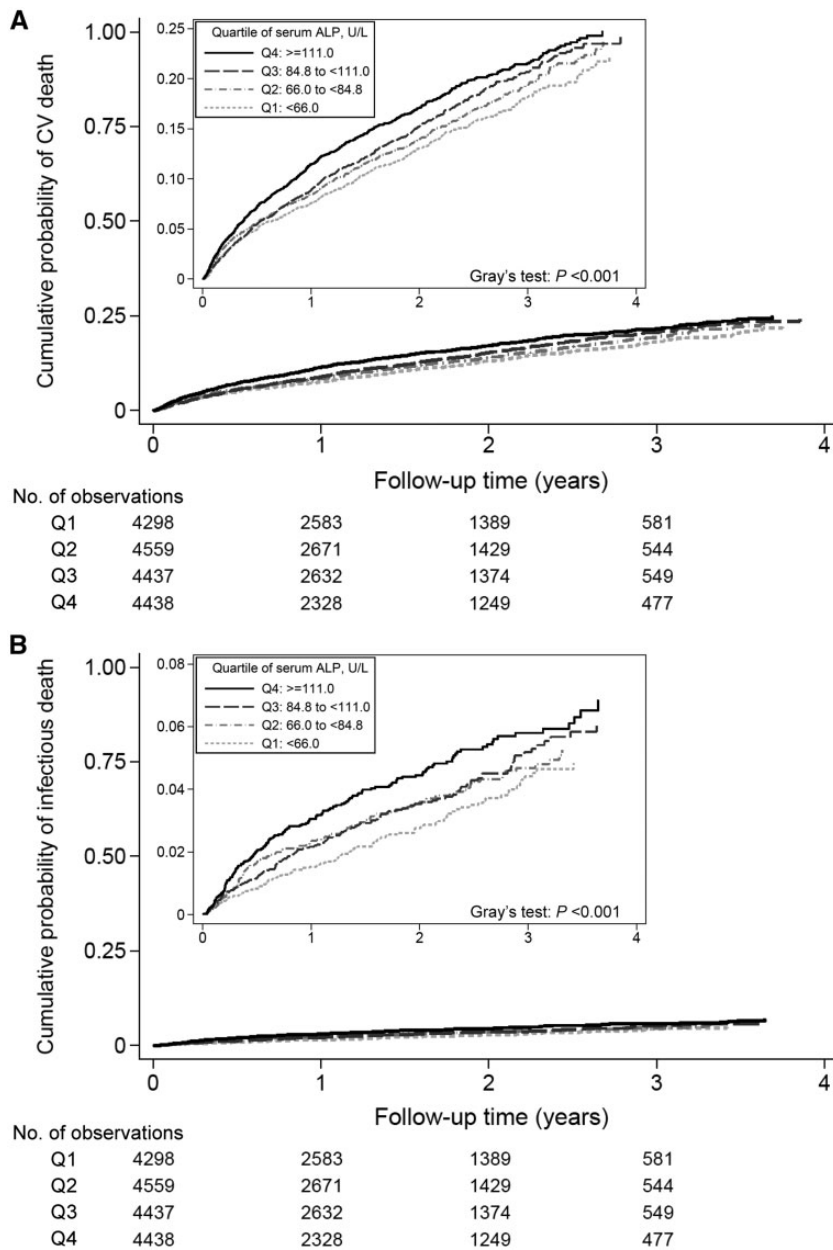
FIGURE 4: Unadjusted cumulative incidence curves for (**A**) cardiovascular and (**B**) infection-related mortality after dialysis initiation by quartiles of serum ALP level over the 6-month prelude period. Estimated probabilities are presented using cumulative incidence function. CV, cardiovascular.

approved by the Institutional Review Boards of the Memphis and Long Beach VA Medical Centers, with exemption from informed consent.

RESULTS

Baseline characteristics

Patients' baseline characteristics in the overall cohort and categorized by quartiles of ALP level are presented in Table 1. Among 17 732 patients, the mean ± SD age at baseline was 68.1 ± 11.4 years; 98.1% were male; 29.6% were African-American; and 71.2% were diabetic. The median (IQR) eGFR level averaged over

6 months prior to dialysis initiation was 13.8 (10.3, 19.4) mL/min/1.73 m². During the 6-month prelude period, there were a median (IQR) of 2 (1, 4) ALP measurements per patient, and the median (IQR) ALP level was 85 (66, 111) U/L.

Compared with patients with lower ALP levels, those with higher ALP levels: were younger; were more likely to be divorced and initiate dialysis therapy with a catheter; had a higher prevalence of diabetes, congestive heart failure, liver disease and chronic pulmonary disease; were less likely to use statins, vitamin D analogs and phosphate binders; had lower serum albumin, calcium, phosphorus, urea nitrogen and creatinine levels; and had higher serum intact PTH, AST and ALT, white blood cells and eGFR levels.

Table 3. Adjusted SHRs (95% CIs) for (A) cardiovascular and (B) infection-related mortality after dialysis initiation by quartiles of serum ALP level over the 6-month prelude period in competing risk regression models

	Quartile of serum ALP level (U/L)				P for trend[b]
	Q1 (lowest) <66.0	Q2 66.0 to < 84.8	Q3 84.8 to < 111.1	Q4 (highest) ≥111.1	
(A) Cardiovascular mortality					
Patients (*n*)	4298	4559	4437	4438	
Primary events	519 (12.1)	593 (13.0)	614 (13.8)	669 (15.1)	
Competing events[a]	527 (12.3)	608 (13.3)	571 (12.9)	712 (16.0)	
Model 1	1 [reference]	1.11 (0.99–1.25)	1.23 (1.10–1.39)	1.46 (1.30–1.64)	<0.001
Model 2	1 [reference]	1.09 (0.97–1.22)	1.17 (1.04–1.31)	1.36 (1.21–1.53)	<0.001
Model 3	1 [reference]	1.12 (0.86–1.48)	1.16 (0.88–1.52)	1.43 (1.09–1.88)	<0.001
(B) Infection-related mortality					
Patients (*n*)	4298	4559	4437	4438	
Primary events	114 (2.7)	147 (3.2)	149 (3.4)	180 (4.1)	
Competing events[a]	932 (21.7)	1054 (23.1)	1036 (23.3)	1201 (27.1)	
Model 1	1 [reference]	1.27 (0.99–1.62)	1.36 (1.06–1.73)	1.73 (1.37–2.18)	<0.001
Model 2	1 [reference]	1.23 (0.97–1.58)	1.30 (1.02–1.66)	1.61 (1.27–2.04)	<0.001
Model 3	1 [reference]	1.20 (0.93–1.55)	1.24 (0.96–1.59)	1.39 (1.09–1.78)	0.012

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ESA, erythropoietin-stimulating agent.

Data are presented as number (percentage) or SHR (95% CI) unless otherwise specified.

Models are as follows: model 1 is adjusted for age, sex, race/ethnicity and marital status; model 2 is adjusted for the variables in model 1 plus comorbidities (cardiovascular disease, congestive heart failure, peripheral vascular disease, dementia, lung disease, diabetes mellitus, liver disease, malignancy and Charlson Comorbidity Index); and model 3 is adjusted for the variables in model 2 plus medications (vitamin D analogs, phosphate binders, ACEIs/ARBs, statins, bicarbonate and ESAs), eGFR and serum albumin averaged over the 6-month prelude period, and vascular access type (arteriovenous fistula, arteriovenous graft or catheter).

[a]Competing events include deaths from other causes.

[b]Linear trend across the quartiles using the median ALP value of each quartile.

Association of pre-ESRD ALP levels with post-ESRD all-cause mortality

During a median follow-up of 2.0 years (IQR, 1.1, 3.2 years; total time at risk, 38 573 patient-years) following dialysis initiation, a total of 9196 all-cause deaths occurred [crude incidence rate, 238.4 per 1000 patient-years; 95% confidence interval (CI), 233.6–243.3]. Patients in the higher ALP quartiles had a higher 5-year unadjusted cumulative incidence of all-cause mortality (e.g. 73.6% versus 62.6% in the highest versus lowest quartiles; log-rank P < 0.001, Figure 1). In the model adjusted for demographics, compared with patients in the lowest ALP quartile, those in the higher ALP quartiles showed incrementally higher risk of all-cause mortality (Table 2). After adjustment for additional potential confounders, including comorbidities, medications, laboratory data (i.e. eGFR and serum albumin) and vascular access type, the association between ALP levels and all-cause mortality was somewhat attenuated but remained statistically significant [adjusted HRs (95% CI) for quartiles 2 through 4 (versus quartile 1), 1.10 (1.04–1.18), 1.12 (1.05–1.19) and 1.42 (1.34–1.51), in model 3; P-value for trend <0.001, Table 2]. When using multivariable-adjusted fractional polynomials, higher ALP levels were monotonically associated with higher all-cause mortality, with significantly higher death risk in those with ALP levels greater than ∼90 U/L (Figure 2).

As shown in Figure 3, a 20-U/L higher ALP level was associated with higher all-cause mortality overall and across all subgroups. Statistically significant interactions were present for age, diabetes, cardiovascular disease, eGFR and intact PTH, with greater contributions of higher ALP levels to all-cause mortality among patients younger than 65 years, those with diabetes, those with a history of cardiovascular disease, those with an eGFR of <15 mL/min/1.73 m^2 and those with

an intact PTH of ≥220 pg/mL, compared with their counterparts. Similar results were observed after further adjustment for liver enzymes (i.e. serum AST and ALT) and MBD (i.e. serum phosphorus and intact PTH) and inflammatory (i.e. white blood cell count) markers (Supplementary data, Table S2).

Association of pre-ESRD ALP levels with post-ESRD cardiovascular and infection-related mortality

During a median follow-up of 1.2 years (IQR, 0.5, 2.3 years) following dialysis initiation, 2395 and 590 deaths occurred from cardiovascular and infection-related causes, respectively, and 1828 deaths occurred from other causes. Patients in the higher ALP quartiles had a higher unadjusted cumulative incidence of cardiovascular and infection-related mortality (Gray's test P < 0.001 and 0.002, for cardiovascular and infection-related mortality, respectively, Figure 4). After multivariable adjustment, patients in the higher ALP quartiles had incrementally higher risk of cardiovascular and infection-related mortality [adjusted SHRs (95% CI) for quartiles 2 through 4 (versus quartile 1), 1.12 (0.86–1.48), 1.16 (0.88–1.52) and 1.43 (1.09–1.88); P-value for trend <0.001, for cardiovascular, and 1.20 (0.93–1.55), 1.24 (0.96–1.59) and 1.39 (1.09–1.78); P-value for trend = 0.012, for infection-related mortality, respectively, in model 3, Table 3A]. When using multivariable-adjusted fractional polynomials, similarly, higher ALP levels were monotonically associated with higher risk of cardiovascular and infection-related mortality. Higher mortality was seen in those with log-transformed ALP levels greater than ∼90 U/L (Figure 5).

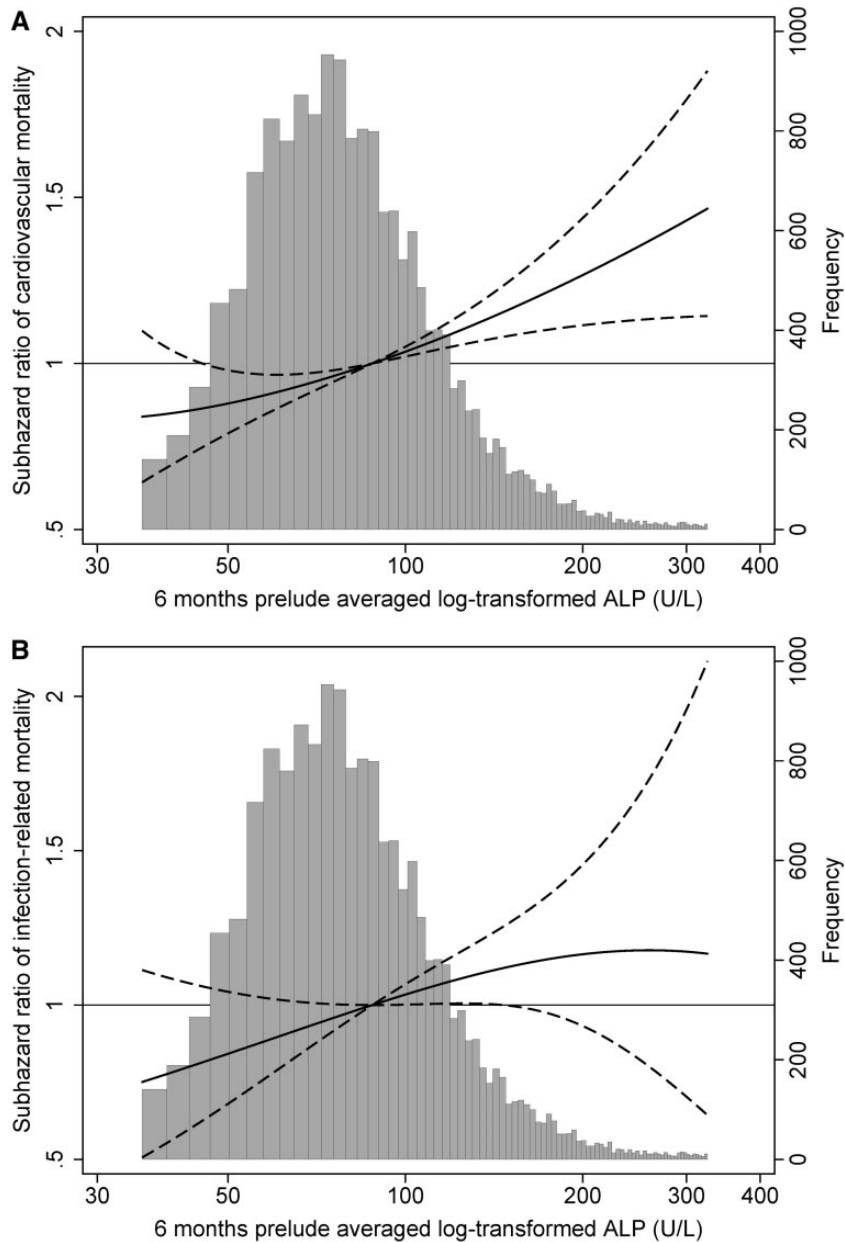In subgroup analyses, a 20-U/L increment of ALP level showed similar associations with higher cardiovascular

FIGURE 5: Association of serum ALP levels over the 6-month prelude period with (**A**) cardiovascular and (**B**) infection-related mortality after dialysis initiation in multivariable-adjusted competing risk regression models using fractional polynomials. Solid and dashed lines represent SHR and 95% CI, respectively. A subhazard reference ratio of 1 (solid horizontal line) and a histogram of observed serum ALP values are overlaid. The *x*-axis shows log-transformed serum ALP levels, trimmed at 1% and 99%. Model is adjusted for age, sex, race/ethnicity, marital status, comorbidities (cardiovascular disease, congestive heart failure, peripheral vascular disease, dementia, lung disease, diabetes mellitus, liver disease, malignancy and Charlson Comorbidity Index), medications (vitamin D analogs, phosphate binders, ACEIs/ARBs, statins, bicarbonate and ESAs), eGFR and serum albumin averaged over the 6-month prelude period, and vascular access type (arteriovenous fistula, arteriovenous graft or catheter). ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ESA, erythropoietin-stimulating agent.

mortality across all subgroups (P = Not Significant for all interaction terms). A higher ALP level only showed significant associations with higher infection-related mortality in patients younger than 65 years, those without liver disease and those with an eGFR of <15 mL/min/1.73 m², although a statistically significant interaction was present only with age (Supplementary data, Figure S2). Results were largely consistent after further adjustment for liver enzymes and MBD and inflammatory markers (Supplementary data, Table S3).

DISCUSSION

In this large national cohort of US veterans with late-stage NDD-CKD transitioning to dialysis, we found that elevated pre-ESRD serum ALP levels were independently associated with higher risk of all-cause, cardiovascular and infection-related mortality following dialysis initiation. Compared with patients in the lowest ALP quartile (<66.0 U/L), those in the

highest ALP quartile (≥111.1 U/L) had a 42% higher all-cause mortality risk, and 43% and 39% higher cardiovascular and infection-related mortality, respectively, after adjusting for demographics, comorbidities, medications, eGFR and serum albumin levels, and vascular access type. Findings were robust in several subgroups and after additional adjustment for liver enzymes and MBD and inflammatory markers.

Several epidemiologic studies have reported that elevated ALP levels are associated with higher risk of adverse clinical outcomes, such as cardiovascular events, hospitalization and mortality in dialysis patients [6, 7, 9, 10]. A few observational studies have also demonstrated a similar ALP–mortality association in NDD-CKD populations [13–15]. Most importantly, however, none of these studies has examined the ALP–mortality association during the ESRD transition period. We therefore extended the previous observations to a large and unique cohort of patients with late-stage NDD-CKD transitioning to dialysis, and for the first time demonstrated the impact of pre-ESRD ALP levels on outcomes after dialysis initiation.

Although our observational study cannot conclude a causal relationship, there are several plausible mechanisms underlying the association of pre-ESRD ALP levels with post-ESRD mortality. Growing evidence suggests that ALP may play a contributory role in the development of vascular calcification, potentially through its effects on pyrophosphate [28, 29]. Tissue-nonspecific ALP has been shown to inactivate pyrophosphate, an endogenous inhibitor of hydroxyapatite formation, resulting in medial arterial vascular calcification and thereby contributing to cardiovascular disease and mortality [30, 31]. Elevated ALP levels have also been associated with inflammation in CKD [32], which may further contribute to the progression of vascular calcification. Indeed, some studies have reported independent associations of higher ALP levels with higher risk of progressive arterial calcification [33, 34], supporting a possible direct physiological role of ALP in adverse cardiovascular outcomes. In line with these findings, our results demonstrated a significant association of elevated pre-ESRD ALP levels with higher post-ESRD cardiovascular mortality, independent of liver disease and other potential confounders.

Our findings regarding the association between ALP levels and infection-related mortality are generally consistent with a few recent reports observed in dialysis patients [6, 11, 12]. In our study, compared with patients with lower ALP levels, those with higher ALP levels had lower serum albumin, phosphorus, urea nitrogen and creatinine levels, and higher white blood cells at baseline, suggesting that they had poorer nutritional status, lower muscle mass and inflammation, and thus were more likely to be susceptible to severe infections. Furthermore, previous studies have shown that ALP interacts with the lipopolysaccharide (LPS)–Toll-like receptor 4 (TLR4) pathway and can reduce the excretion of circulating pro-inflammatory mediators, such as tumor necrosis factor-α, interleukin-6 and LPS-binding protein [35–37]. These anti-inflammatory effects resulting in unfavorable innate host defense associated with higher ALP levels could lead to higher infection rates and, consequently, contribute to the observed higher infection-related mortality.

Given the considerable uncertainty about the optimal approach to the management of patients in the transition period, our study may hold several clinical implications, suggesting the need for heightened attention to ALP levels in patients with late-stage NDD-CKD. The optimal ALP levels and potential therapeutic interventions targeting ALP to mitigate mortality risk may deserve further investigations, particularly if our findings are confirmed in other settings.

This study must be interpreted with acknowledgement of several limitations. First, most of our patients consisted of male US veterans; therefore, the results may not be generalizable to women or the general US population. Second, information about bone-specific ALP, a sensitive and specific marker of bone metabolism, was not available; hence, it is possible that elevated ALP levels reflected underlying liver disease rather than CKD-MBD. However, the elevated ALP levels remained associated with higher mortality even after adjusting for liver enzymes and also after stratification by liver disease. Third, there were large amounts of missing data relating to MBD markers such as serum phosphorus and intact PTH for the entire study population; however, the sensitivity analysis including patients with available phosphorus and PTH measurements yielded similar associations. Finally, as with all observational studies, we cannot eliminate the possibility of unmeasured confounders.

In conclusion, in this large nationwide cohort of US veterans with late-stage NDD-CKD transitioning to dialysis, we found that elevated pre-ESRD serum ALP levels were incrementally associated with higher all-cause, cardiovascular and infection-related mortality following dialysis initiation, independent of comorbid conditions and other known risk factors. Our findings highlight the significance of ALP levels in late-stage NDD-CKD, and suggest their potential value as a treatment target. Further studies are needed to determine if interventions that lower pre-ESRD ALP levels can reduce mortality after dialysis initiation.

SUPPLEMENTARY DATA

Supplementary data are available online at http://ndt.oxfordjournals.org.

government. The results of this article have not been published previously in whole or part.

REFERENCES

1. United States Renal Data System. 2014 *Annual Data Report: Epidemiology of Kidney Disease in the United States*. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 2014
2. Robinson BM, Zhang J, Morgenstern H *et al.* Worldwide, mortality risk is high soon after initiation of hemodialysis. *Kidney Int* 2014; 85: 158–165
3. Bradbury BD, Fissell RB, Albert JM *et al.* Predictors of early mortality among incident US hemodialysis patients in the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Clin J Am Soc Nephrol* 2007; 2: 89–99
4. Kalantar-Zadeh K, Kuwae N, Regidor DL *et al.* Survival predictability of time-varying indicators of bone disease in maintenance hemodialysis patients. *Kidney Int* 2006; 70: 771–780
5. Levin A, Bakris GL, Molitch M *et al.* Prevalence of abnormal serum vitamin D, PTH, calcium, and phosphorus in patients with chronic kidney disease: results of the study to evaluate early kidney disease. *Kidney Int* 2007; 71: 31–38
6. 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: 655–663
7. Regidor DL, Kovesdy CP, Mehrotra R *et al.* Serum alkaline phosphatase predicts mortality among maintenance hemodialysis patients. *J Am Soc Nephrol* 2008; 19: 2193–2203
8. Molnar MZ, Kovesdy CP, Mucsi I *et al.* Association of pre-kidney transplant markers of mineral and bone disorder with post-transplant outcomes. *Clin J Am Soc Nephrol* 2012; 7: 1859–1871
9. Lertdumrongluk P, Lau WL, Park J *et al.* Impact of age on survival predictability of bone turnover markers in hemodialysis patients. *Nephrol Dial Transplant* 2013; 28: 2535–2545
10. 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: 1532–1538
11. Ye H, Lin X, Qiu Y *et al.* Higher alkaline phosphatase was associated with the short-term adverse outcomes of peritoneal dialysis-related peritonitis. *Clin Chem Lab Med* 2015; 53: e113–e116
12. Hwang SD, Kim SH, Kim YO *et al.* Serum alkaline phosphatase levels predict infection-related mortality and hospitalization in peritoneal dialysis patients. *PLoS One* 2016; 11: e0157361
13. 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: 3003–3011
14. Beddhu S, Ma X, Baird B *et al.* Serum alkaline phosphatase and mortality in African Americans with chronic kidney disease. *Clin J Am Soc Nephrol* 2009; 4: 1805–1810
15. 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: 703–710
16. Sumida K, Molnar MZ, Potukuchi PK *et al.* Association of slopes of estimated glomerular filtration rate with post-end-stage renal disease mortality in patients with advanced chronic kidney disease transitioning to dialysis. *Mayo Clin Proc* 2016; 91: 196–207
17. Sumida K, Molnar MZ, Potukuchi PK *et al.* Association between vascular access creation and deceleration of estimated glomerular filtration rate decline in late-stage chronic kidney disease patients transitioning to end-stage renal disease. *Nephrol Dial Transplant* 30 May 2016 (Epub ahead of print)
18. Molnar MZ, Gosmanova EO, Sumida K *et al.* Predialysis cardiovascular disease medication adherence and mortality after transition to dialysis. *Am J Kidney Dis* 2016; 68: 609–618
19. Kovesdy CP, Norris KC, Boulware LE *et al.* Association of race with mortality and cardiovascular events in a large cohort of US veterans. *Circulation* 2015; 132: 1538–1548
20. Kovesdy CP, Alrifai A, Gosmanova EO *et al.* Age and outcomes associated with BP in patients with incident CKD. *Clin J Am Soc Nephrol* 2016; 11: 821–831
21. Levey AS, Stevens LA, Schmid CH *et al.* A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009; 150: 604–612
22. VA Information Resource Center (VIReC). *VIReC Research User Guide: VHA Pharmacy Prescription Data*, 2nd edn. Hines, IL: US Department of Veterans Affairs, Health Services Research and Development Service, VA Information Resource Center, 2008
23. US Department of Veterans Affairs. *VIReC Research User Guide; VHA Medical SAS Inpatient Datasets FY2006-2007*. Hines, IL: VA Information Resource Center, 2007
24. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *J Clin Epidemiol* 1992; 45: 613–619
25. Gray RJ. A class of K-sample tests for comparing the cumulative incidence of a competing risk. *Ann Stat* 1988; 16: 1141–1154
26. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc* 1999; 94: 496–509
27. Royston P, Sauerbrei W. Building multivariable regression models with continuous covariates in clinical epidemiology–with an emphasis on fractional polynomials. *Methods Inf Med* 2005; 44: 561–571
28. Schoppet M, Shanahan CM. Role for alkaline phosphatase as an inducer of vascular calcification in renal failure? *Kidney Int* 2008; 73: 989–991
29. Lomashvili KA, Garg P, Narisawa S *et al.* Upregulation of alkaline phosphatase and pyrophosphate hydrolysis: potential mechanism for uremic vascular calcification. *Kidney Int* 2008; 73: 1024–1030
30. Jono S, Shioi A, Ikari Y *et al.* Vascular calcification in chronic kidney disease. *J Bone Miner Metab* 2006; 24: 176–181
31. Nitta K. Vascular calcification in patients with chronic kidney disease. *Ther Apher Dial* 2011; 15: 513–521
32. Damera S, Raphael KL, Baird BC *et al.* Serum alkaline phosphatase levels associate with elevated serum C-reactive protein in chronic kidney disease. *Kidney Int* 2011; 79: 228–233
33. Shantouf R, Kovesdy CP, Kim Y *et al.* Association of serum alkaline phosphatase with coronary artery calcification in maintenance hemodialysis patients. *Clin J Am Soc Nephrol* 2009; 4: 1106–1114
34. Sigrist MK, Taal MW, Bungay P *et al.* Progressive vascular calcification over 2 years is associated with arterial stiffening and increased mortality in patients with stages 4 and 5 chronic kidney disease. *Clin J Am Soc Nephrol* 2007; 2: 1241–1248
35. Koyama I, Matsunaga T, Harada T *et al.* Alkaline phosphatases reduce toxicity of lipopolysaccharides in vivo and in vitro through dephosphorylation. *Clin Biochem* 2002; 35: 455–461
36. Campbell EL, MacManus CF, Kominsky DJ *et al.* Resolvin E1-induced intestinal alkaline phosphatase promotes resolution of inflammation through LPS detoxification. *Proc Natl Acad Sci USA* 2010; 107: 14298–14303
37. Peters E, Heemskerk S, Masereeuw R *et al.* Alkaline phosphatase: a possible treatment for sepsis-associated acute kidney injury in critically ill patients. *Am J Kidney Dis* 2014; 63: 1038–1048