

# Impact of age on survival predictability of bone turnover markers in hemodialysis patients

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## ABSTRACT

**Background.** Abnormalities in serum alkaline phosphatase (ALP) and intact parathyroid hormone (PTH) concentrations, as biochemical markers of bone turnover in dialysis patients, correlate with increased mortality in maintenance hemodialysis (MHD) patients. Changes in bone turnover rate vary with age. The mortality predictability of serum ALP and PTH levels in MHD patients may be different across ages.

**Methods.** We examined differences across four age groups (18 to <45, 45 to <65, 65 to <75 and ≥75 years) in the mortality predictability of serum ALP and PTH in 102 149 MHD patients using Cox models.

**Results.** Higher serum ALP levels were associated with higher mortality across all ages; however, the ALP–mortality association was much stronger in young patients (<45 years) compared with older patients. The association between higher serum PTH levels and mortality was stronger in older patients compared with the younger groups. Serum PTH levels were incrementally associated with mortality only in middle-aged and elderly patients (≥45 years). Compared with patients with serum PTH 150 to <300 pg/mL, the death risks were higher in patients with serum PTH 300 to <600 pg/mL [HRs (95% CI): 1.05 (1.01–1.10), 1.15 (1.10–1.21) and 1.25 (1.19–1.31) for patients 45 to <65, 65 to <75 and ≥75 years, respectively], and ≥600 pg/mL [HRs(95% CI): 1.07 (1.01–1.14), 1.31(1.21–1.42)

and 1.45(1.33–1.59) for age categories 45 to <65, 65 to <75 and ≥75 years, respectively]. However, no significant association between higher serum PTH levels and mortality was observed in patients <45 years.

**Conclusions.** There are important differences in mortality-predictability of serum ALP and PTH in older MHD patients compared with their younger counterparts. The effect of age needs to be considered when interpreting the prognostic implications of serum ALP and PTH levels.

## INTRODUCTION

Cardiovascular disease is the leading cause of mortality in dialysis patients [1]. Cardiovascular risk factors among dialysis patients are comprised of traditional risk factors and uremia-related risk factors; the latter includes mineral and bone disorders (MBDs) [2, 3]. Abnormalities of MBD markers including serum calcium, phosphorus and intact parathyroid hormone (PTH) levels have been shown to be associated with increased vascular calcification [4, 5], and higher risks of cardiovascular and all-cause mortality in maintenance hemodialysis (MHD) patients [6–9]. Experimental studies have investigated the role of tissue-nonspecific alkaline phosphatase (TNALP) in the pathogenesis of vascular calcification [10, 11]. TNALP is upregulated under uremic conditions in vessels from rats, which leads to the hydrolysis and inactivation of

pyrophosphate, a potent inhibitor of vascular calcification [10, 12]. Furthermore, higher serum total alkaline phosphatase (ALP) levels are independently associated with coronary artery calcification [13], increased hospitalization rates and mortality in MHD patients [14, 15].

The incidence of end-stage renal disease (ESRD) is increasing among the elderly population worldwide [16, 17]. Bone and mineral metabolism in the elderly dialysis population might differ from that of younger patients in response to reduction in dietary protein, phosphorus and calcium intake, reduced physical activity and decreased bone responsiveness to hormonal regulators [18, 19]. A large cohort of MHD patients demonstrated differences in laboratory markers, and treatment of MBD between younger and older patients. The elderly patients tended to have lower levels of serum phosphorus and PTH than the younger patients. Compared with younger MHD patients, there was significantly lower phosphorus binder and cinacalcet usage and a trend towards lower receipt of activated vitamin D compounds in older patients [20]. We recently reported differential associations between serum phosphorus levels and mortality across varying age groups in MHD patients. High serum phosphorus levels correlate with increased mortality across all ages, whereas low serum phosphorus concentrations are associated with higher risks of death only in elderly patients  $\geq 65$  years in whom there is a greater likelihood of hypophosphatemia [21]. Serum ALP and PTH levels are biochemical markers of bone turnover in chronic kidney disease (CKD) patients [22, 23], and no survival analysis based on ALP and PTH values in the elderly dialysis population has been done. We hypothesized that serum ALP and PTH levels would show differential associations with mortality across varying age groups in MHD patients.

## MATERIALS AND METHODS

### Study population

We extracted and analyzed data from a 6-year cohort of all MHD patients from 580 outpatient dialysis facilities of DaVita, a large dialysis organization in the USA. The baseline studied quarter for each patient was the earliest calendar quarter, in which the patient's HD vintage was  $>90$  days. Of the 127 304 patients who underwent HD treatment  $>90$  days during the study period, 580 patients  $>99$  or  $<18$  years or with missing age data and 19 190 patients with missing quarterly baseline data or follow-up periods were excluded. Among the remaining 107 534 patients, we excluded 930 patients for ALP and 19 178 patients for PTH outliers or missing data. For ALP analyses, 4455 patients with serum aspartate transaminase (AST)  $>40$  U/L or missing AST data were excluded. Therefore, the final study population consisted of 102 149 patients for serum ALP and 88 356 patients for serum PTH analyses (Supplementary data, Figure S1). The study was approved by the institutional review committees of the Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center and DaVita Clinical Research. The requirement for a written consent was exempted due to large sample size, patient anonymity, and the noninvasive nature of the research.

### Clinical and demographic measures

The creation of the DaVita MHD patient cohort has been described previously [24]. Average values were obtained from up to 20 calendar quarters (1 July 2001–30 June 2006) for each laboratory parameter and clinical measure for each patient during the cohort period. Patients were followed for outcomes until 30 June 2007. Dialysis vintage was defined as the duration of time between the first day of HD treatment and the day that the patient entered the cohort study. The demographic data were obtained from the DaVita database. History of preexisting comorbidities and tobacco smoking was obtained by linking the DaVita database to the data from Medical Evidence Form 2728 from the US Renal Data System (USRDS). Available preexisting comorbid conditions were grouped into nine categories: atherosclerotic heart disease, congestive heart failure, other cardiac diseases, hypertension, cerebrovascular disease, peripheral vascular disease, chronic obstructive pulmonary disease, cancer and non-ambulatory state. The causes of death were obtained from the USRDS, and cardiovascular death was defined as death due to myocardial infarction, cardiac arrest, congestive heart failure, cerebrovascular accident or other cardiac diseases.

Patients who received any activated injectable vitamin D agents (i.e. paricalcitol, calcitriol or doxercalciferol) in the dialysis facility during each calendar quarter were identified, and the administered doses were captured from the DaVita database. Over 90% of DaVita MHD patients who received any activated injectable vitamin D during the study cohort period received paricalcitol; therefore, the administered doses of calcitriol and doxercalciferol were converted to equivalent paricalcitol doses and the total doses of administered vitamin D agents for each patient over the entire cohort were calculated and included in all case-mix adjusted models. The study population was stratified into four age categories (18 to  $<45$ , 45 to  $<65$ , 65 to  $<75$ , and  $\geq 75$  years) for data analysis.

### Laboratory measures

Blood samples were drawn using standardized techniques in all DaVita dialysis clinics and were transported to the DaVita Laboratory in Deland, Florida, typically within 24 h. All laboratory values were measured using automated and standardized methods in the DaVita Laboratory. Most laboratory parameters were measured monthly, including serum levels of urea nitrogen, creatinine, albumin, ALP, AST, calcium and phosphorus. Serum PTH concentrations were measured at least quarterly using a first-generation immunoradiometric PTH assay [25]. Serum calcium levels corrected for serum albumin were calculated using the following equation: 'albumin-corrected calcium (mg/dL) =  $\{0.8 \times [4 - \text{serum albumin (g/dL)}]\} + \text{serum calcium (mg/dL)}$ .' Most blood samples were collected prior to HD, except for post-dialysis serum urea nitrogen to calculate urea kinetics. Time-averaged serum ALP and PTH values obtained from up to 20 calendar quarters for each patient during the study cohort period were used in our analyses. We divided time-averaged serum ALP levels a priori into four categories ( $<80$ , 80 to  $<120$ , 120 to  $<160$  and  $\geq 160$  U/L), and time-averaged serum PTH levels a priori into four categories ( $<150$ , 150 to  $<300$ , 300 to  $<600$  and  $\geq 600$  pg/mL). The ALP category

**Table 1. Baseline characteristics of 102 149 MHD patients according to the age category**

Age range (years)	All	18 to <45	45 to <65	65 to <75	≥75	P
<i>n</i> (%)	102 149	17 649 (17)	39 321 (39)	23 896 (23)	21 283 (21)	NA
Age (years)	60 ± 16	35 ± 7	55 ± 6	69 ± 3	80 ± 4	<0.001
Female (%)	45	40	44	49	47	<0.001
<b>Race (%)</b>						
Caucasian	46	30	38	52	67	<0.001
African American	35	48	40	29	20	<0.001
Hispanic	16	19	19	15	10	<0.001
Asian	3	3	3	4	3	0.06
<b>Dialysis duration (%)</b>						
<6 month	58	46	56	60	70	<0.001
6 to <24 months	17	16	17	18	17	0.003
2 to <5 years	16	18	18	16	11	<0.001
≥5 years	9	20	9	6	2	<0.001
<b>Primary insurance (%)</b>						
Medicare	68	60	58	78	81	<0.001
Medicaid	6	12	9	2	1	<0.001
Other	26	28	33	20	18	<0.001
<b>Marital status (%)</b>						
Divorced	8	7	12	8	4	<0.001
Single	28	58	30	15	11	<0.001
Widowed	17	1	8	23	38	<0.001
Married	47	34	50	54	47	<0.001
<b>Vascular access (%)</b>						
AVF	26	34	26	24	21	<0.001
AVG	30	26	31	33	27	0.25
Catheter	44	40	43	43	52	<0.001
<i>Kt/V</i> (single-pool)	1.52 ± 0.35	1.47 ± 0.35	1.49 ± 0.34	1.56 ± 0.36	1.58 ± 0.35	<0.001
BMI (kg/m <sup>2</sup> )	26.9 ± 6.9	27.1 ± 7.8	28.2 ± 7.4	26.6 ± 6.2	24.4 ± 5.1	<0.001
nPNA (g/kg/day)	0.95 ± 0.25	0.97 ± 0.26	0.96 ± 0.26	0.94 ± 0.25	0.91 ± 0.24	<0.001
<b>Comorbidities (%)</b>						
DM	58	34	66	68	51	<0.001
Atherosclerotic heart disease	22	4.4	18	29	33	<0.001
Cancer	4.7	1	3.1	6	9	<0.001
Congestive heart failure	29	12	26	35	38	<0.001
COPD	6	1.2	5	9	9	<0.001
Cerebrovascular disease	8	2.5	7	10	11	<0.001
Hypertension	80	76	81	81	80	<0.001
Other cardiac diseases	6	2.1	4.1	7	10	<0.001

Continued

Table 1. Continued

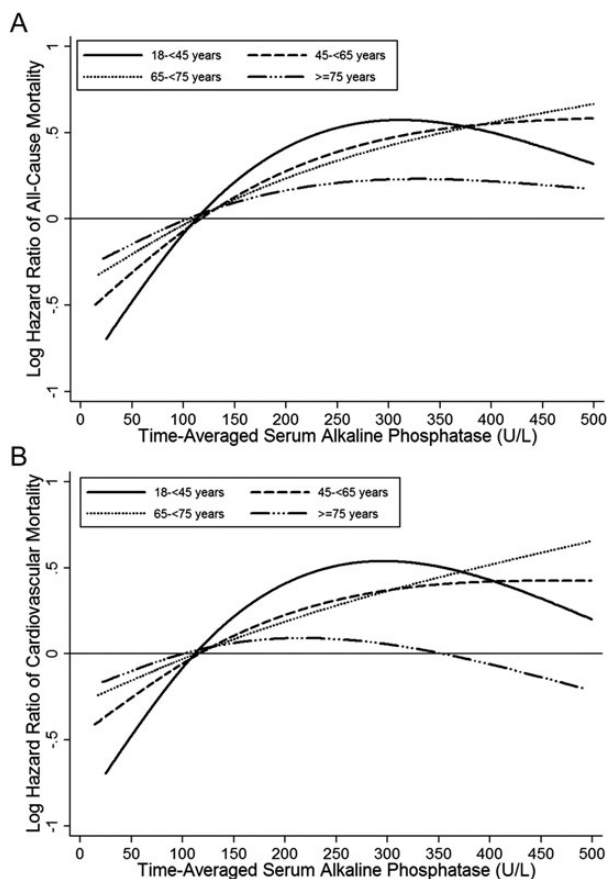
Age range (years)	All	18 to <45	45 to <65	65 to <75	≥75	P
Peripheral vascular disease	12	3.4	10	16	16	<0.001
Non-ambulatory state	3.2	1.2	2.9	3.7	4.6	<0.001
Current smoking	5	7	7	4	1.8	<0.001
Laboratory measures (baseline)						
ALP (U/L)	96 (76, 127)	96 (74, 132)	100 (78, 133)	95 (75, 123)	93 (75, 118)	<0.001
Intact PTH (pg/mL)	237 (134, 412)	326 (173, 613)	252 (144, 434)	211 (120, 347)	193 (114, 312)	<0.001
Calcium (mg/dL)	9.5 ± 0.7	9.4 ± 0.8	9.5 ± 0.7	9.5 ± 0.6	9.5 ± 0.6	<0.001
Phosphorus (mg/dL)	5.6 ± 1.5	6.3 ± 1.6	5.7 ± 1.4	5.3 ± 1.3	5.0 ± 1.2	<0.001
Albumin (g/dL)	3.7 ± 0.5	3.8 ± 0.5	3.7 ± 0.5	3.6 ± 0.4	3.6 ± 0.4	<0.001
Creatinine (mg/dL)	8.0 ± 3.3	10.8 ± 3.8	8.3 ± 3.1	7.0 ± 2.5	6.1 ± 2.2	<0.001
TIBC (mg/dL)	209 ± 46	209 ± 44	212 ± 46	208 ± 46	204 ± 46	<0.001
Ferritin (ng/mL)	373 (177, 698)	349 (159, 674)	378 (181, 707)	391 (187, 722)	361 (175, 672)	<0.001
Hemoglobin (g/dL)	12.0 ± 1.4	11.9 ± 1.5	12.0 ± 1.4	12.1 ± 1.3	12.1 ± 1.3	<0.001
WBC (×10 <sup>3</sup> /μL)	7.5 ± 2.5	7.2 ± 2.4	7.5 ± 2.4	7.5 ± 2.4	7.6 ± 2.8	<0.001
% Lymphocytes	20.5 ± 7.8	22.7 ± 8.1	20.8 ± 7.7	19.6 ± 7.6	19.0 ± 7.5	<0.001
AST (U/L)	18 ± 8	18 ± 9	18 ± 9	18 ± 7	19 ± 7	<0.001
Activated vitamin D <sup>a</sup> (%)	82	84	85	80	77	<0.001
Paricalcitol dose <sup>b</sup> (μg/week)	10 (7, 15)	13 (8, 19)	11 (8, 16)	9 (7, 14)	8 (6, 12)	<0.001
<p>AVF, arteriovenous fistula; AVG, arteriovenous graft; BMI, body mass index; nPNA, normalized protein nitrogen appearance; DM, diabetes mellitus; COPD, chronic obstructive pulmonary disease; TIBC, total iron-binding capacity; WBC, white blood cells; AST, aspartate transaminase.</p> <p>Continuous variables expressed as mean ± SD or median (interquartile range); categorical variables expressed as number (percent); P-for trend shows the differences in each age category.</p> <p><sup>a</sup>Percentages of patients who received activated vitamin D agents including paricalcitol, calcitriol and doxercalciferol.</p> <p><sup>b</sup>Weekly average dose in any patients who received paricalcitol during follow-up.</p>						

of 80 to <120 U/L and the PTH category of 150 to <300 pg/mL were designated as the reference groups.

### Statistical analysis

Data were summarized using proportions, means ± SD or medians [interquartile ranges (IQR)] as dictated by data type. We evaluated the association of time-averaged serum ALP and PTH as main predictors with all-cause and cardiovascular mortality as outcomes using Cox proportional hazard models and restricted cubic splines within each age category. For each analysis, three models with multivariable adjustments were examined:

- (i) Unadjusted models included ALP and PTH categories, and entry calendar quarter (q1–q20).
- (ii) Case-mix adjusted models included all of the variables in the unadjusted model plus sex, race/ethnicity (Caucasian, African American, Hispanic and Asian), presence of diabetes and nine preexisting comorbidities, dialysis duration (<6 months, 6 to <24 months, 2 to <5 years and ≥5 years), primary insurance (Medicare, Medicaid and others), marital status (married, single, widowed and divorced), history of tobacco smoking, types of vascular access (arteriovenous fistula, arteriovenous graft and catheter), dialysis dose as indicated by single-pool  $Kt/V$ ,



**FIGURE 1:** Cubic splines of HRs of all-cause mortality (A) and cardiovascular mortality (B) for time-averaged serum ALP levels using Cox regression analyses comparing four different age groups of 102 144 HD patients ( $n = 17\,645$  for patients 18 to <45 years old,  $n = 39\,320$  for patients 45 to <65 years old,  $n = 23\,896$  for patients 65 to <75 years old and  $n = 21\,283$  for patients  $\geq 75$  years old). Model adjusted for sex, race/ethnicity, presence of diabetes mellitus, nine pre-existing comorbidities, history of tobacco smoking, dialysis duration categories, marital status, primary insurance, types of vascular access, dialysis dose as indicated by single-pool  $Kt/V$ , the dosage of activated vitamin D agents, serum aspartate transaminase, albumin corrected calcium, phosphorus and intact PTH concentrations.

serum AST levels (only for ALP analyses) and the dosage of activated vitamin D agents.

- (iii) Case-mix plus MBD-adjusted models included all of the covariates in the case-mix model plus serum phosphorus, calcium, ALP (except for the model where serum ALP was the predictor), and PTH (except for the model where serum PTH was the predictor) concentrations.

Patients who received a kidney transplant, switched to peritoneal dialysis or left DaVita dialysis clinics were censored at the time of the event. Missing covariate data (<3% for laboratory and most demographic variables) were imputed by the means or medians of the existing values as appropriate. Two-sided  $P$ -values <0.05 were considered to be statistically significant. All statistical analyses were performed using Stata version 11.2 (Stata Corp., College Station, TX).

## RESULTS

### Cohort description

The baseline demographics, clinical and laboratory characteristics of the 102 149 MHD patients, stratified by age category, are summarized in Table 1. The mean age of the cohort at baseline was  $60 \pm 16$  years, among which there were 35% African Americans and 58% diabetics. Older MHD patients were more likely to be Caucasian, and diabetic, and had lower levels of serum ALP, PTH, phosphorus, albumin and creatinine. They were also less likely to receive activated vitamin D agents, and had a lower mean dose than younger patients (Table 1). The median follow-up time was 2.25 years (IQR 1.21–3.71 years). During the follow-up period (July 2001–June 2007), 53 184 (52%) patients died, with 21 965 (41%) deaths due to cardiovascular causes.

### Effect modification by age on serum alkaline phosphatase and mortality association

Serum ALP levels were incrementally associated with all-cause and cardiovascular mortality risks across all ages. However, in patients <45 years, there was a higher mortality risk associated with serum ALP elevation up to 300 U/L than in the other age groups. The ALP-mortality association appeared to be weaker in patients  $\geq 75$  years compared with the younger groups (Figure 1, Supplementary data, Figures S2 and S3). Compared with a serum ALP level of 80 to <120 U/L, serum ALP levels of 120 to <160 and  $\geq 160$  U/L showed a 23% [hazard ratio (HR) 1.23, 95% confidence interval (CI) 1.13–1.32], and 59% (HR 1.59, 95% CI 1.47–1.71) higher mortality risk in patients <45 years, whereas death HRs associated with serum levels of ALP 120 to <160 and  $\geq 160$  U/L were progressively lower in older age categories [HRs (95% CI): 1.16 (1.11–1.20) and 1.41 (1.35–1.47) for patients 45 to <65 years old, 1.10 (1.06–1.15) and 1.32 (1.25–1.38) for patients 65 to <75 years old, and 1.12 (1.07–1.16) and 1.21 (1.14–1.28) for patients  $\geq 75$  years, respectively] (Table 2). A similar pattern was observed with cardiovascular mortality (Supplementary data, Table S1).

### Effect modification by age on serum intact parathyroid hormone and mortality association

Higher serum PTH levels showed a significant and linear association with higher all-cause and cardiovascular mortality risks only in MHD patients  $\geq 45$  years and the PTH-mortality association was much stronger in older patients compared with the younger groups. In contrast, there was no significant association between higher serum PTH levels and mortality in patients <45 years (Figure 2, Supplementary data, Figures S4 and S5). In a case-mix and MBD-adjusted model, young patients (<45 years) with serum PTH levels of <150 pg/mL had a 15% [HRs (95% CI): 0.85 (0.76–0.95)] lower risk of all-cause mortality compared with those with serum PTH levels of 150 to <300 pg/mL; however, higher serum PTH levels ( $\geq 300$  pg/mL) were not associated with increased all-cause mortality in young patients. In older age categories ( $\geq 45$  years), the death risks were significantly higher in patients with serum PTH levels of 300 to <600 pg/

**Table 2. HRs (95% CIs) of all-cause mortality comparing time-averaged serum ALP categories (reference: 80 to <120 U/L) using Cox regression analyses in 102 149 HD patients stratified by age category**

Serum ALP (U/L)	All-cause death HRs (95% CIs)		
	Unadjusted	Case-mix adjusted	Case-mix + MBD adjusted
Age 18 to <45 years, <i>n</i> = 17 649 (unadjusted), 17 645 (case-mix), 17 645 (case-mix + MBD)			
<80	0.73 (0.66–0.81)	0.71 (0.65–0.79)	0.71 (0.65–0.79)
80 to <120	Reference	Reference	Reference
120 to <160	1.32 (1.22–1.42)	1.22 (1.13–1.32)	1.23 (1.13–1.32)
≥160	1.80 (1.67–1.93)	1.60 (1.48–1.72)	1.59 (1.47–1.71)
Age 45 to <65 years, <i>n</i> = 39 321 (unadjusted), 39 320 (case-mix), 39 320 (case-mix + MBD)			
<80	0.89 (0.85–0.93)	0.83 (0.80–0.87)	0.83 (0.80–0.87)
80 to <120	Reference	Reference	Reference
120 to <160	1.14 (1.10–1.18)	1.16 (1.12–1.21)	1.16 (1.11–1.20)
≥160	1.46 (1.41–1.52)	1.42 (1.37–1.48)	1.41 (1.35–1.47)
Age 65 to <75 years, <i>n</i> = 23 896 (unadjusted), 23 896 (case-mix), 23 896 (case-mix + MBD)			
<80	0.96 (0.92–1.00)	0.87 (0.83–0.91)	0.88 (0.85–0.92)
80 to <120	Reference	Reference	Reference
120 to <160	1.08 (1.04–1.13)	1.12 (1.07–1.17)	1.10 (1.06–1.15)
≥160	1.37 (1.31–1.44)	1.36 (1.30–1.43)	1.32 (1.25–1.38)
Age ≥75 years, <i>n</i> = 21 283 (unadjusted), 21 283 (case-mix), 21 283 (case-mix + MBD)			
<80	1.01 (0.97–1.05)	0.92 (0.88–0.96)	0.93 (0.89–0.97)
80 to <120	Reference	Reference	Reference
120 to <160	1.08 (1.04–1.13)	1.13 (1.08–1.18)	1.12 (1.07–1.16)
≥160	1.28 (1.22–1.35)	1.27 (1.20–1.34)	1.21 (1.14–1.28)

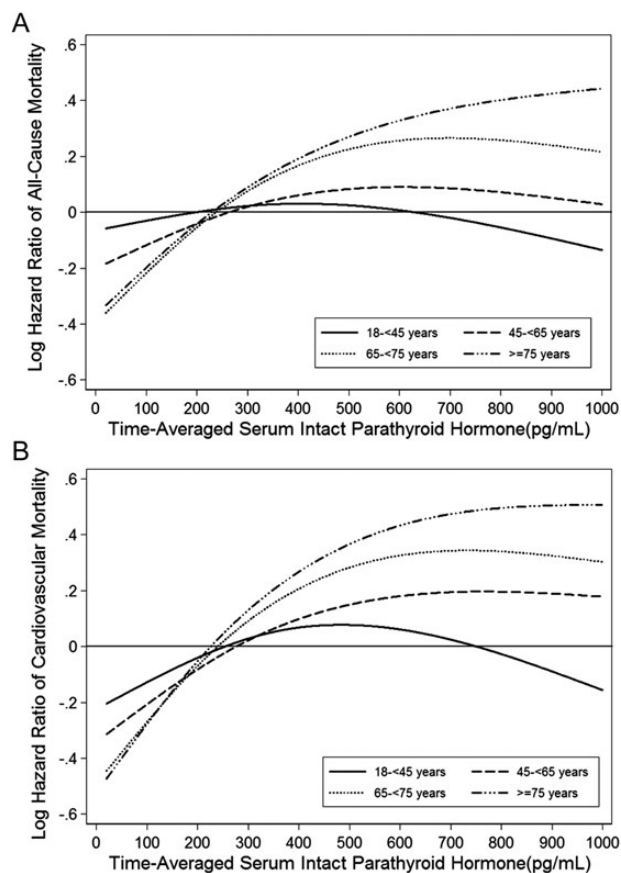
Case-mix model is adjusted for sex, race/ethnicity, presence of diabetes mellitus, nine preexisting comorbidities, history of tobacco smoking, dialysis duration categories, marital status, primary insurance, types of vascular access, dialysis dose as indicated by single-pool *Kt/V*, serum aspartate transaminase levels and the dosage of activated vitamin D agents.  
Case-mix + MBD adjusted model includes all of the case-mix covariates plus serum albumin corrected calcium, phosphorus and intact PTH concentrations.  
MBDs, mineral and bone disorders.

mL [Fully adjusted HRs (95% CI): 1.05 (1.01–1.10), 1.15 (1.10–1.21) and 1.25 (1.19–1.31) for age categories 45 to <65, 65 to <75 and ≥75 years, respectively], and ≥600 pg/mL [fully adjusted HRs (95% CI): 1.07 (1.01–1.14), 1.31 (1.21–1.42) and 1.45 (1.33–1.59) for patients 45 to <65, 65 to <75 and ≥75 years old, respectively] (Table 3). Similar results were found with cardiovascular mortality (Supplementary data, Table S2). Similar patterns were observed after additional adjustment for nutritional markers including body mass index (BMI), serum levels of albumin, creatinine and normalized protein nitrogen appearance (nPNA); however, the association seemed to be stronger across all ages (Supplementary data Table S3 and Figure S6). In models containing interaction terms for serum PTH levels and age (<45 versus ≥45 years), interaction terms were statistically

significant, confirming that there was a differential association between serum PTH levels and mortality in different age strata (P-interaction = 0.02 for all-cause mortality and P-interaction <0.001 for cardiovascular mortality).

## DISCUSSION

In this retrospective analysis of over 100 000 MHD patients, we found differential associations of mortality with serum levels of ALP and PTH across varying age categories. Although higher serum ALP levels were associated with higher risks of mortality across all ages, the strength of association was stronger in young patients (<45 years) compared with older patients. Serum PTH levels showed a linear and robust



**FIGURE 2.** Cubic splines of HRs of all-cause mortality (A) and cardiovascular mortality (B) for time-averaged serum intact PTH levels using Cox regression analyses comparing four different age groups of 88 354 HD patients ( $n = 14\,654$  for patients 18 to <45 years old,  $n = 34\,997$  for patients 45 to <65 years old,  $n = 20\,908$  for patients 65 to <75 years old and  $n = 17\,795$  for patients  $\geq 75$  years old). Model adjusted for sex, race/ethnicity, presence of diabetes mellitus, nine pre-existing comorbidities, history of tobacco smoking, dialysis duration categories, marital status, primary insurance, types of vascular access, dialysis dose as indicated by single-pool  $Kt/V$ , the dosage of activated vitamin D agents, serum albumin corrected calcium, phosphorus and ALP concentrations.

association with mortality only in middle-aged and elderly patients ( $\geq 45$  years), whereas there was a null association between higher serum PTH levels and mortality in patients <45 years. The PTH-mortality association appeared to be stronger in the older age categories compared with the younger groups. Similar patterns of association were observed with all-cause and cardiovascular mortality.

Our study is the first to compare mortality predictability of serum ALP and PTH levels across varying age categories in MHD patients. Serum ALP levels showed a monotonic and incremental association with mortality across the entire continuum of ALP levels in all age categories of MHD patients, independent of the parameters of MBDs and liver enzymes. However, the ALP-mortality association was stronger in young patients (<45 years) compared with older patients. The associations between elevated serum ALP levels and increased mortality have been observed not only in MHD [14, 15] and pre-dialysis CKD patients [26–28], but also in the general

population [29]. Drechsler *et al.* [30] found a strong association between both serum bone ALP (BAP) and total ALP levels with short-term (6 month) mortality in incident dialysis patients. However, the ALP-mortality association was attenuated to the null when long-term (4-year) mortality was examined [30]. However, this study [30] used baseline serum levels of bone-specific and total ALP (measured at a single time-point) to study the association between serum ALP levels and long-term mortality. In contrast, our study examined the ALP-mortality association using time-averaged serum ALP levels, which may better reflect the long-term associations between cumulative exposure of higher ALP levels and mortality. Similarly, a higher serum BAP level was observed to be a predictor of mortality in male HD patients [31]. Our findings of the linear ALP-mortality association even at low serum ALP levels could possibly be related to vascular calcification through its pyrophosphate link. Vascular calcification has been independently associated with adverse cardiovascular outcomes and mortality in HD patients [32–34]. Smooth muscle cells in medial vascular calcification express higher levels of ALP [35], which may promote vascular calcification by lowering inorganic pyrophosphate [36], which is a potent inhibitor of extracellular mineralization [37, 38]. Thus, increased serum ALP levels may explain the prominent ALP-mortality association in younger patients, in whom vascular calcification is usually less.

In our study, we found a robust association between higher serum PTH levels and increased mortality risks only in MHD patients  $\geq 45$  years, and the PTH-mortality association was stronger in older patients compared with the younger groups. This finding was consistent with the results from previous publications that reported an association between high serum PTH levels (but not low serum PTH levels) and increased mortality in MHD patients [6, 9, 24]. In the general population, higher serum PTH levels were associated with higher risks of all-cause and cardiovascular mortality in the elderly population ( $\geq 65$  years) [39, 40]. Serum PTH levels positively correlated with BMI, fat mass and lean mass in MHD patients [41, 42]. Elderly dialysis patients tended to have worse nutritional parameters [43, 44] that strongly correlated with increased mortality in dialysis patients [45, 46]. Nutritional factors likely did not confound the more prominent PTH-mortality association in elderly patients observed in the current study, as this association remained significant after additional adjustment for nutritional surrogates. Possible mechanisms that may explain the link between high serum PTH levels and mortality include vascular calcification, vascular remodeling [47–49] and detrimental effects on the myocardium such as left-ventricular hypertrophy and cardiac fibrosis [50–53]. However, we found that the PTH-mortality association was less prominent in young MHD patients (<45 years) compared with older patients. This finding may in part be due to differences in traditional risk factors associated with vascular calcification such as age, diabetes and hypertension [54] across age groups.

Our study found that the ALP-mortality association was stronger in younger patients, while the PTH-mortality association was more prominent in older patients ( $\geq 45$  years).

**Table 3. HRs (95% CIs) of all-cause mortality comparing time-averaged serum intact PTH categories (Reference: 150 to <300 pg/mL) using Cox regression analyses in 88 356 HD patients stratified by age category**

Serum intact PTH (pg/mL)	All-cause death HRs (95% CIs)		
	Unadjusted	Case-mix adjusted	Case-mix + MBD adjusted
Age 18 to <45 years, <i>n</i> = 14 656 (unadjusted), 14 654 (case-mix), 14 654 (case-mix + MBD)			
<150	1.66 (1.50–1.83)	0.85 (0.76–0.95)	0.85 (0.76–0.95)
150 to <300	Reference	Reference	Reference
300 to <600	0.88 (0.81–0.95)	1.01 (0.94–1.10)	0.95 (0.88–1.03)
≥600	0.93 (0.85–1.02)	1.14 (1.04–1.25)	0.92 (0.84–1.02)
Age 45 to <65 years, <i>n</i> = 34 997 (unadjusted), 34 997 (case-mix), 34 997 (case-mix + MBD)			
<150	1.55 (1.49–1.63)	0.86 (0.82–0.90)	0.86 (0.82–0.90)
150 to <300	Reference	Reference	Reference
300 to <600	0.99 (0.95–1.02)	1.11 (1.07–1.16)	1.05 (1.01–1.10)
≥600	1.09 (1.03–1.15)	1.22 (1.15–1.29)	1.07 (1.01–1.14)
Age 65 to <75 years, <i>n</i> = 20 908 (unadjusted), 20 908 (case-mix), 20 908 (case-mix + MBD)			
<150	1.47 (1.40–1.53)	0.79 (0.75–0.83)	0.79 (0.75–0.84)
150 to <300	Reference	Reference	Reference
300 to <600	1.07 (1.02–1.11)	1.22 (1.17–1.28)	1.15 (1.10–1.21)
≥600	1.32 (1.22–1.42)	1.50 (1.39–1.62)	1.31 (1.21–1.42)
Age ≥75 years, <i>n</i> = 17 795 (unadjusted), 17 795 (case-mix), 17 795 (case-mix + MBD)			
<150	1.40 (1.34–1.46)	0.84 (0.80–0.88)	0.83 (0.79–0.88)
150 to <300	Reference	Reference	Reference
300 to <600	1.14 (1.09–1.19)	1.29 (1.23–1.35)	1.25 (1.19–1.31)
≥600	1.35 (1.24–1.47)	1.59 (1.45–1.74)	1.45 (1.33–1.59)
Case-mix model is adjusted for sex, race/ethnicity, presence of diabetes mellitus, nine preexisting comorbidities, history of tobacco smoking, dialysis duration categories, marital status, primary insurance, types of vascular access, dialysis dose as indicated by single-pool <i>Kt/V</i> and the dosage of activated vitamin D agents. Case-mix + MBD adjusted model includes all of the case-mix covariates plus serum albumin corrected calcium, phosphorus and alkaline phosphatase concentrations. Intact PTH, intact parathyroid hormone; MBDs, mineral and bone disorders.			

Several reasons could explain the discrepancy in mortality between serum ALP and PTH levels across ages. Serum BAP levels were not measured in our study. ALP is produced by different organs, including bone, liver, kidney and intestines [22] and sources of ALP could be different between age groups. Besides PTH, BAP production is influenced by other hormones including growth hormone and 1,25(OH)<sub>2</sub>vitamin D<sub>3</sub>, and bone responsiveness to these hormones also changes with age [18, 55–57]. We did not have information on serum levels of growth hormone or 1,25(OH)<sub>2</sub>vitamin D<sub>3</sub> to examine this association. Additionally, an *in vitro* study investigating PTH signaling in human marrow stromal cells demonstrated that bone responsiveness to PTH varied with age [19]. It is important to stress that the PTH–survival interaction is likely more complex than its effect on bone, since the PTH has

direct effects on other tissues, including vascular smooth muscle cells and myocardium [48, 52, 58].

Several limitations of this study need to be considered. First, our analyses were based on observational data, and no causal relationships can be established from the study results. Second, information on serum BAP levels was not available; therefore, elevated levels of total serum ALP could possibly stem from liver disease or other sources. However, we excluded patients with serum AST>40 U/L or missing AST data from our analyses, and we accounted for differences in serum levels of AST across exposure groups in case-mix adjusted analyses, indicating that the ALP–mortality association is likely to be independent of liver pathology. Third, we lacked data on oral medications related to treatment of MBDs including phosphorus binders and calcimimetics. However, it is noteworthy



that calcimimetics became available in the USA during the last few months of this study cohort; hence, our cohort belongs to the pre-calcimimetic era. Fourth, serum 25(OH) vitamin D, 1,25(OH)<sub>2</sub>vitamin D<sub>3</sub> and fibroblast growth factor-23 levels were not available in our study population and may have resulted in residual confounding. Fifth, we lacked data on inflammatory markers such as C-reactive protein. However, correction for malnutrition inflammation complex syndrome (MICS) surrogates might lead to over-adjustment which could introduce sources of error/bias particularly if mortality effects of serum ALP and PTH levels are exerted through modulation of MICS-related pathways; therefore, the case-mix adjusted models should be considered more appropriate.

The strengths of our study include its large sample size with relatively long follow-up periods. Patient data were obtained from DaVita dialysis facilities which were under uniform administrative care, and all laboratory values were measured in a single laboratory with optimal quality assurance. We adjusted for multiple potential confounders including baseline comorbidities, dialysis duration, receipt of activated injectable vitamin D treatment and doses in multivariable models. We used time-averaged measures with all laboratory data, rather than a single baseline measure in our analyses. The use of time-averaged survival models in this study reduces the risk of exposure misclassification and may better reflect the association between long-term cumulative exposure to higher levels of serum ALP and PTH and mortality over time.

In conclusion, our study revealed differential associations of serum ALP and PTH with death risks among MHD patients from various age groups. The ALP–mortality association was much stronger in young patients (<45 years) compared with older patients. Serum PTH levels showed a linear and significant association with mortality only in patients ≥45 years, whereas there was no significant association between higher serum PTH levels and mortality in young patients (<45 years). Our findings suggest that age is an effect modifier of the association of serum ALP and PTH levels with mortality in MHD patients. Further prospective studies are warranted to confirm these findings.

## SUPPLEMENTARY DATA

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

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## CONFLICT OF INTEREST STATEMENT

None declared.

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## Simultaneous reversal of risk factors for cardiac death and intensified therapy in long-term survivors of paediatric end-stage renal disease over the last 10 years

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Keywords: cardioprotective management, CV disease, left ventricular hypertrophy, long-term follow-up, renal replacement therapy

### ABSTRACT

**Background.** In an extended long-term follow-up of patients on chronic renal replacement therapy (RRT) since childhood (LERIC study), we observed a substantial reduction in cardiovascular (CV) death over the last decade. In this study, we investigated the contemporaneous changes in risk factors for CV death and cardioprotective therapy.

**Methods.** The cohort consisted of 140 Dutch patients, who were born before 1979 and started RRT before 15 years of age between 1972 and 1992. We compared the prevalence of various factors in 2000 and 2010 by calculating matched odds ratios (OR<sub>matched</sub>).

**Results.** Median age of patients was 38.5 years (range 23.2–50.8) in 2010, after a median time on RRT of 28 years. The prevalence of CV risk factors decreased from 41.3% in 2000 to