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Peer reviewed

*Original Articles*

## Mineral and bone disorders and survival in hemodialysis patients with and without polycystic kidney disease

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### Abstract

**Background.** Maintenance hemodialysis (MHD) patients with polycystic kidney disease (PKD) have better survival than non-PKD patients. Mineral and bone disorders (MBD) are associated with accelerated atherosclerosis and cardiovascular death in MHD patients. It is unknown whether the different MBD mortality association between MHD populations with and without PKD can explain the survival differential.

**Methods.** Survival models were examined to assess the association between different laboratory markers of MBD [such as serum phosphorous, parathyroid hormone (PTH), calcium and alkaline phosphatase] and mortality in a 6-year cohort of 60 089 non-PKD and 1501 PKD MHD patients.

**Results.** PKD and non-PKD patients were  $57 \pm 13$  and  $62 \pm 15$  years old and included 46 and 45% women and 14 and 32% Blacks, respectively. Whereas PKD individuals with PTH 150 to <300 pg/mL (reference) had the lowest risk for mortality, the death risk was higher in patients with PTH <150 [hazard ratio (HR): 2.16 (95% confidence interval 1.53–3.06)], 300 to <600 [HR: 1.30 (0.97–1.74)] and  $\geq 600$  pg/mL [HR: 1.46 (1.02–2.08)], respectively. Similar patterns were found in non-PKD patients. Fully adjusted death HRs of time-averaged serum phosphorous increments <3.5, 5.5 to <7.5 and  $\geq 7.5$  mg/dL (reference: 3.5 to <5.5 mg/dL) for PKD patients were 2.82 (1.50–5.29), 1.40 (1.12–1.75) and 2.25 (1.57–3.22). The associations of alkaline phosphatase and calcium with mortality were similar in PKD and non-PKD patients.

**Conclusion.** Bone-mineral disorder markers exhibit similar mortality trends between PKD and non-PKD MHD patients, although some differences are observed in particular in low PTH and phosphorus ranges.

**Keywords:** hemodialysis; mineral and bone disorders; mortality; parathyroid hormone; polycystic kidney disease

### Introduction

Although maintenance dialysis prevents death from uremia, patient survival remains an important issue. Once renal replacement therapy is initiated, the range of the expected remaining life span in the United States Renal Data System (USRDS) report was ~8 years (varies with race) for dialysis patients aged 40–44 years and ~4.5 years for those aged 60–64 years [1]. Cardiovascular disease accounts for ~50% of deaths. While a decline in cardiovascular deaths has occurred in the general population, a similar trend has not been observed in dialysis patients [1]. Accelerated atherosclerosis is an important cause of cardiovascular death in long-term dialysis patients [2] and shows strong association with mineral and bone disorders (MBD) in these patients [3]. Serum phosphorous, calcium and parathyroid hormone (PTH) levels help us to assess MBD in these patients; however, a recent meta-analysis in chronic kidney disease (CKD) patients suggested that only serum phosphorous level was a strong and independent predictor of mortality [4].

Approximately 5% of end-stage renal disease (ESRD) patients in the USA suffer from polycystic kidney disease (PKD) [5]. There is a relative paucity of data for ESRD patients with PKD [6–8]. Those PKD patients who require maintenance hemodialysis (MHD) treatment seem to be different from other MHD patients: they report a better quality of life [9] and have greater survival than non-PKD patients, including non-diabetic MHD patients

[10–14]. The relative risk of death is substantially lower among MHD patients with PKD compared to non-diabetic dialysis patients [10, 12], a survival advantage that is also observed among peritoneal dialysis patients with PKD [15]. Orskov *et al.* [16] demonstrated that in Danish patients with PKD, the prognosis had significantly improved during the last decade. There are certain factors that may potentially affect the association between MBD markers and mortality in ESRD patients with PKD. Fibroblast growth factor 23 level was substantially elevated in PKD patients compared with glomerular filtration rate-matched CKD patients and was associated with an apparent renal phosphate leak, while PTH and vitamin D metabolite levels remained in the normal range [17]. However, this difference might not be true in patients on maintenance dialysis. These differences raise questions as to whether the MBD mortality association is different in PKD patients and in the general MHD population and if the survival difference between PKD and general MHD patients is due to the consequence of different MBD mortality association between these groups.

Given the greater survival and lower comorbidity burden in PKD patients compared to other MHD patients, we hypothesized that associations of PTH, calcium and phosphorus with mortality are different in MHD patients with PKD and without PKD.

## Materials and methods

### Patients

We extracted, refined and examined data from all individuals with ESRD who underwent dialysis treatment from July 2001 through June 2006 in any one of the 580 outpatient dialysis facilities of DaVita, a large dialysis organization in the USA (prior to its acquisition of units owned by Gambro). Of the 164 789 cumulative patients treated in all DaVita units over the 5-year period, we excluded 13 312 patients without quarterly baseline data, 19 652 patients who were on peritoneal dialysis or in whom the method of renal replacement therapy was unknown and 802 patients aged >99 years or <18 years. From these 131 023 patients, 60 089 did not have PTH data; therefore, our study population of PTH analysis consisted of 1501 MHD patients with PKD and 69 433 MHD patients without PKD. In our calcium, phosphorus and alkaline phosphatase analysis, we included 119 128, 111 587 and 115 432 patients, respectively, who had calcium, phosphorus and alkaline phosphatase time-averaged data. The study was approved by relevant Institutional Review Committees.

### Clinical and demographic measures

The creation of the cohort has been described previously [18–25]. To minimize measurement variability, all repeated measures for each patient during any given calendar quarter, i.e. over a 13-week interval, were averaged and the summary estimate was used in all models. Average PTH, calcium, phosphorus and alkaline phosphatase values were obtained from up to 20 calendar quarters (q1 through q20). The first (baseline) studied quarter for each patient was the calendar quarter in which the patient's dialysis vintage was >90 days. The presence or absence of diabetes at baseline and history of tobacco smoking were obtained by linking the DaVita database to the data from Medical Evidence Form 2728 from the USRDS. The presence of preexisting comorbid conditions was similarly ascertained and grouped into nine categories: ischemic heart disease, congestive heart failure, history of hypertension, history of other cardiac disease, cerebrovascular events, peripheral vascular disease, chronic obstructive pulmonary disease, ability to ambulate and cancer [26]. We did not use HIV/AIDS status in this analysis due to large amount of missing data on these conditions as well as due to the fact that many available data had HIV/AIDS status listed as 'undisclosed'. Patients were followed for outcomes through 30 June 2007.

### Laboratory measures

Blood samples were drawn using uniform techniques in all dialysis clinics and were transported to the DaVita Laboratory in Deland, Florida within 24 h. All laboratory values, including PTH, calcium, phosphorus and alkaline phosphatase, were measured by automated and standardized methods. The 3-month-averaged PTH, calcium, phosphorus and alkaline phosphatase for each quarter were used in our analyses. We divided PTH a priori into four categories (<150, 150 to <300, 300 to <600 and  $\geq 600$  pg/mL). We have used the following equation to calculate the corrected calcium level 'corrected calcium =  $\{0.8 \times [\text{normal albumin (4 g/dL)} - \text{patients' albumin}]\} + \text{serum calcium}$ '. We divided corrected calcium level a priori into four categories (<8.4, 8.4 to <9.5, 9.5 to <10.2 and  $\geq 10.2$  mg/dL), phosphorus level a priori into four categories (<3.5, 3.5 to <5.5, 5.5 to <7.5 and  $\geq 7.5$  mg/dL) and alkaline phosphatase level a priori into four categories (<80, 80 to <120, 120 to <160 and  $\geq 160$  U/L).

### Epidemiologic and statistical methods

Data were summarized using proportions and means ( $\pm$ SD). The significance of the difference between categorical variables was determined using the chi-square test and between continuous variables using analysis of variance, as appropriate. Survival analysis was performed by fitting time-averaged Cox proportional hazard models to examine whether PTH, corrected calcium, phosphorus and alkaline phosphatase predicted survival in PKD and non-PKD patients. The presence of non-linearity in the survival associations was tested by adding the quadratic term of markers of MBD to the models already containing the linear term. For each analysis, including subgroup analyses, three models were examined:

- (1) Unadjusted or minimally adjusted models included PTH, corrected calcium, phosphorus and alkaline phosphatase categories and entry calendar quarter (q1 through q20).
- (2) Case-mix adjusted models that included all variables included in minimally adjusted model plus age, gender, presence of diabetes, race/ethnicity (African-Americans and other self-categorized Blacks, non-Hispanic Caucasians, Asians, Hispanics and others), categories of dialysis vintage (<6 months, 6–12 months, 12–24 months and  $\geq 2$  years), primary insurance (Medicare, Medicaid and others) and marital status (married, single, divorced or widowed), type of vascular access (catheter, arteriovenous fistula or graft), dialysis dose as indicated by  $Kt/V$  (single pool), nine preexisting comorbid conditions and history of tobacco smoking.
- (3) Case-mix plus malnutrition–inflammation complex syndrome (MICS) adjusted models included all the covariates in the case-mix model as well as body mass index (BMI) and nine laboratory surrogates with known association with clinical outcomes in hemodialysis (HD) patients including serum levels of albumin, total iron binding capacity (TIBC), creatinine, calcium (except model where calcium was predictor), phosphorous (except model where phosphorous was predictor), bicarbonate, normalized protein catabolic rate as an indicator of daily protein intake, also known as the normalized protein nitrogen appearance, white blood cell count (WBC) and lymphocyte percentage.

For all analysis, two-sided P-values are reported and results were considered statistically significant if  $P < 0.05$ . All statistical analyses were carried out with the SAS, version 9.1 (SAS Institute Inc., Cary, NC).

## Results

The baseline demographic, clinical and laboratory characteristics of the 1501 PKD and 69 433 non-PKD patients, divided into four subgroups based on PTH categories, are summarized in Table 1. PKD and non-PKD patients were  $57 \pm 13$  and  $62 \pm 15$  years old and included 46 and 45% women and 14 and 32% Blacks, respectively. In the PKD and non-PKD populations, higher PTH level was associated with younger age, higher proportion of Blacks and higher serum phosphorous and

**Table 1.** Baseline characteristics of patients across baseline intact parathyroid hormone categories in 70 934 MHD patients, including 1501 MHD patients with PKD and 69 433 MHD<sup>a</sup>

	PKD					Non-PKD				
	PTH <150 (pg/mL); n = 357	PTH 150 to <300 (pg/mL); n = 468	PTH 300 to <600 (pg/mL); n = 407	PTH ≥600 (pg/mL); n = 269	P*	PTH <150 (pg/mL); n = 20 503	PTH 150 to <300 (pg/mL); n = 23 171	PTH 300 to <600 (pg/mL); n = 16 950	PTH ≥600 (pg/mL); n = 8809	P**
Age (years)	60 ± 13	59 ± 13	57 ± 13	53 ± 13	<0.001	65 ± 15	64 ± 15	60 ± 15	55 ± 16	<0.001
Gender (% female)	49	46	50	42	0.19	46	44	45	47	<0.001
Diabetes mellitus (%)	13	16	13	14	0.33	60	64	61	47	<0.001
Race (%)										
White	70	68	61	54	<0.001	51	43	34	27	<0.001
Black	11	13	19	23	<0.001	22	29	39	51	<0.001
Hispanic	9	9	13	18	0.003	16	17	17	13	<0.001
Asian	2	3	1	2	0.14	4	3	3	2	<0.001
Other	8	7	6	3	0.14	7	8	7	7	0.20
Vintage [time on dialysis (%)]										
0–6 Months	9	14	16	11	0.02	17	18	17	13	<0.001
6–24 Months	20	17	15	13	0.06	21	18	18	15	<0.001
2–5 Years	40	45	42	44	0.40	42	43	42	39	<0.001
>5 Years	31	24	27	32	0.06	20	21	23	33	<0.001
Primary insurance (%)										
Medicare	59	53	58	58	0.39	69	68	66	65	<0.001
Medicaid	4	5	3	6	0.28	6	6	7	10	<0.001
Other	9	18	14	12	0.005	8	9	10	10	<0.001
Marital status (%)										
Married	60	62	59	45	<0.001	51	50	45	39	<0.001
Divorced	8	7	12	10	0.21	8	8	9	9	<0.001
Single	19	21	20	36	<0.001	23	24	30	40	<0.001
Widowed	13	9	9	10	0.45	19	18	16	12	<0.001
Other variables (mean ± SD)										
Kt/V (dialysis dose)	1.60 ± 0.32	1.59 ± 0.37	1.52 ± 0.34	1.47 ± 0.32	<0.001	1.56 ± 0.36	1.53 ± 0.35	1.49 ± 0.35	1.46 ± 0.34	<0.001
BMI (kg/m <sup>2</sup> )	25.5 ± 5.3	26.0 ± 6.2	26.8 ± 6.0	26.5 ± 4.5	0.03	25.8 ± 6.5	26.7 ± 6.7	27.4 ± 7.3	27.7 ± 7.7	<0.001
Vascular access (%)										
Catheter	27	26	31	35	0.07	41	39	41	40	<0.001
AVF	39	43	37	36	0.30	25	26	26	27	<0.001
Graft	34	31	32	29	0.78	34	35	33	33	<0.001
Comorbid conditions (%)										
Cancer	2.8	3.2	2.7	2.2	0.89	5.3	4.3	3.6	3.1	<0.001
Atherosclerotic heart disease	11.8	11.3	10.6	11.2	0.96	23.7	22.6	18.7	13.5	<0.001
Heart failure	10.9	9.8	8.4	9.7	0.69	30.0	30.1	26.6	21.3	<0.001
Chronic obstructive pulmonary disease	5.9	4.3	3.0	1.1	0.01	6.4	5.9	5.3	3.5	<0.001
Cerebrovascular disease	5.0	5.6	3.2	3.0	0.20	8.3	7.8	6.6	5.4	<0.001
History of hypertension	77.6	78.2	76.9	72.9	0.40	77.1	78.9	79.3	78.1	<0.001
Other heart diseases	5.3	3.9	4.7	4.1	0.76	6.2	6.0	4.7	3.6	<0.001
Non-ambulatory	0	1.5	0.3	1.5	0.03	4.1	3.0	2.6	2.0	<0.001
Peripheral vascular disease	5.3	2.8	3.0	2.2	0.11	13.5	12.7	10.1	7.2	<0.001
Smoker	4.8	4.3	5.4	3.7	0.75	4.2	4.8	5.1	5.7	<0.001
Serum levels (at baseline)										

(continued)

Table 1. Continued

	PKD					Non-PKD				
	PTH <150 (pg/mL); n = 357	PTH 150 to <300 (pg/mL); n = 468	PTH 300 to <600 (pg/mL); n = 407	PTH ≥600 (pg/mL); n = 269	P*	PTH <150 (pg/mL); n = 20 503	PTH 150 to <300 (pg/mL); n = 23 171	PTH 300 to <600 (pg/mL); n = 16 950	PTH ≥600 (pg/mL); n = 8809	P**
Albumin (g/dL)	3.90 ± 0.4	3.89 ± 0.4	3.91 ± 0.3	3.86 ± 0.4	0.31	3.60 ± 0.5	3.68 ± 0.4	3.71 ± 0.4	3.77 ± 0.4	<0.001
Creatinine (mg/dL)	9.09 ± 2.9	9.12 ± 2.9	9.42 ± 2.8	10.57 ± 3.6	<0.001	7.31 ± 3.1	7.80 ± 3.1	8.68 ± 3.3	10.16 ± 3.7	<0.001
TIBC (mg/dL)	211 ± 43	214 ± 41	216 ± 42	209 ± 42	0.16	203 ± 47	209 ± 45	210 ± 45	207 ± 43	<0.001
Bicarbonate (mmol/L)	22.08 ± 2.4	21.82 ± 2.7	21.64 ± 3.1	21.03 ± 2.9	<0.001	22.7 ± 2.9	22.36 ± 2.9	21.99 ± 2.9	21.46 ± 3.1	<0.001
Calcium (mg/dL)	9.61 ± 0.7	9.40 ± 0.6	9.37 ± 0.8	9.34 ± 0.8	<0.001	9.34 ± 0.7	9.11 ± 0.6	9.05 ± 0.7	9.11 ± 0.8	<0.001
Phosphorous (mg/dL)	5.35 ± 1.4	5.58 ± 1.4	6.02 ± 1.4	6.78 ± 1.5	<0.001	5.04 ± 1.3	5.45 ± 1.4	5.93 ± 1.5	6.60 ± 1.7	<0.001
Ferritin (ng/mL)	518 ± 436	471 ± 388	434 ± 388	465 ± 406	0.05	568 ± 536	530 ± 482	506 ± 469	525 ± 519	<0.001
Protein catabolic rate (g/kg/day)	0.97 ± 0.23	0.96 ± 0.24	0.98 ± 0.24	1.04 ± 0.23	0.001	0.93 ± 0.26	0.96 ± 0.25	0.98 ± 0.25	0.99 ± 0.25	<0.001
Blood hemoglobin (g/dL)	12.45 ± 1.3	12.33 ± 1.3	12.31 ± 1.4	12.13 ± 1.5	0.03	12.02 ± 1.4	12.05 ± 1.3	11.91 ± 1.4	11.70 ± 1.4	<0.001
WBC (×10 <sup>3</sup> /μL)	6.63 ± 1.8	6.78 ± 2.1	6.82 ± 2.1	6.76 ± 2.0	0.63	7.77 ± 2.8	7.51 ± 2.6	7.41 ± 2.4	7.15 ± 2.3	<0.001
Lymphocyte (% of total WBC)	20.87 ± 6.7	20.63 ± 5.5	21.27 ± 7.6	20.08 ± 6.9	0.19	19.59 ± 7.8	20.36 ± 7.7	20.76 ± 7.8	21.50 ± 8.0	<0.001

AVF, arteriovenous fistula.

\*P-value shows the difference in each PTH categories in PKD patients.

\*\*P-value shows the difference in each PTH categories in non-PKD patients.

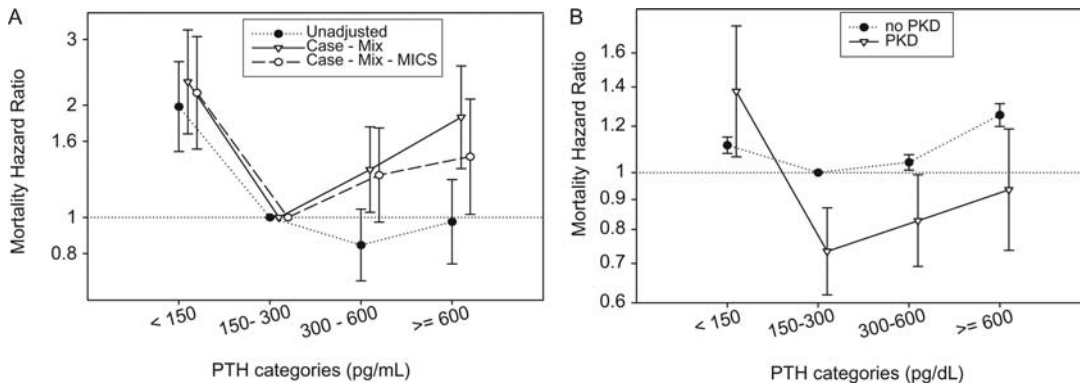
creatinine levels (Table 1). Additionally, in the non-PKD population, it was associated with higher BMI and serum calcium level (Table 1). In contrast, in the PKD population, it was associated with a lower serum calcium level (Table 1). The median follow-up time for the cohort was 686 days (interquartile range: 332–1195 days).

Figure 1A shows unadjusted, case-mix and MICS adjusted death hazard ratios (HRs) for time-averaged PTH levels in PKD patients. The association was U-shaped in both subgroups. While PKD individuals with PTH 150–300 pg/mL (as reference) had the lowest risk for mortality, the death risk was higher in patients with PTH <150 [HR: 2.16; 95% confidence interval (CI) 1.53–3.06], 300–600 (HR: 1.30; 95% CI 0.97–1.74) and ≥600 (HR: 1.46; 95% CI 1.02–2.08) pg/mL, respectively, in our fully adjusted model (P > 0.05 for the quadratic PTH term in case-mix and P > 0.05 in MICS models) (Figure 1A). A similar pattern was found in non-PKD patients. The association between PTH and mortality was not modified by the presence of PKD (P > 0.05 for interaction term). Figure 1B shows pooled analyses comparing mortality predictability of PTH increments in PKD versus non-PKD patients (PTH reference: 150 to <300 pg/mL in non-PKD patients). PKD patients have lower mortality risk than non-PKD patients in higher PTH categories (>150 pg/mL).

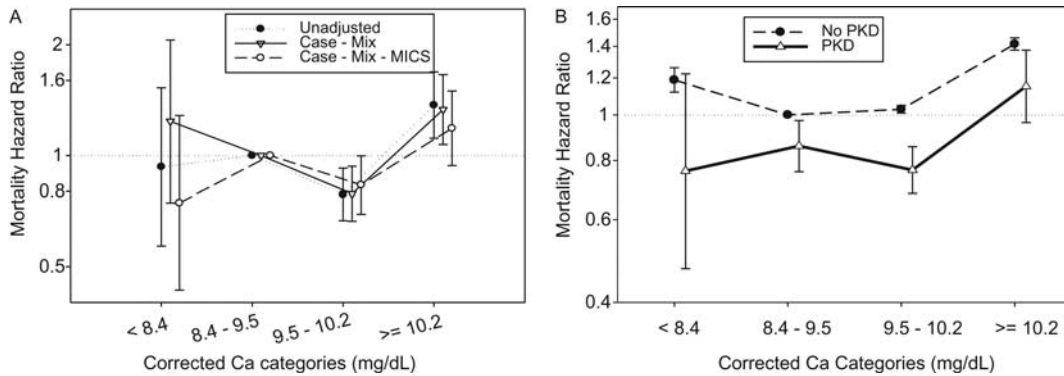
Figure 2A shows unadjusted, case-mix and MICS adjusted death HR for time-averaged corrected calcium levels in PKD patients. Fully adjusted death HRs (95% CI) associated with time-averaged corrected calcium levels of <8.4, 9.5 to <10.2 and ≥10.2 mg/dL (reference: 8.4 to <9.5 mg/dL) for PKD patients were 0.75 (0.43–1.29), 0.83 (0.69–1.00) and 1.19 (0.94–1.50) (P = 0.02 for the quadratic corrected calcium term in case-mix and MICS models), respectively, and similar pattern was found in non-PKD patients. The association between corrected calcium and mortality was not modified by presence of PKD (P > 0.05 for interaction term). Figure 2B shows pooled analyses comparing mortality predictability of corrected calcium increments in PKD versus non-PKD patients (corrected calcium reference: 8.4 to <9.5 mg/dL in non-PKD patients). PKD patients have lower mortality risk than non-PKD patients in all corrected calcium categories.

Figure 3A shows unadjusted, case-mix and MICS adjusted death HR for time-averaged serum phosphorous levels in PKD patients. Fully adjusted death HRs (95% CI) associated with time-averaged serum phosphorous levels of <3.5, 5.5 to <7.5 and ≥7.5 mg/dL (reference: 3.5 to <5.5 mg/dL) for PKD patients were 2.82 (1.50–5.29), 1.40 (1.12–1.75) and 2.25 (1.57–3.22) (P < 0.001 for the quadratic phosphorous term in case-mix and MICS models), respectively, and a similar pattern was found in non-PKD patients. The association between phosphorous and mortality was not modified by presence of PKD (P > 0.05 for interaction term). Figure 3B shows pooled analyses comparing mortality predictability of serum phosphorous increments in PKD versus non-PKD patients (corrected calcium reference: 3.5 to <5.5 mg/dL in non-





**Fig. 1.** HRs of all-cause mortality of the entire range of time-averaged intact parathyroid hormone (iPTH) using time-averaged Cox model in PKD patients (A) and comparing mortality predictability of PKD versus non-PKD HD patient in fully (case-mix and MICS) adjusted models using and time-averaged Cox regression analyses in different iPTH categories (B). Case-mix model is adjusted for age, gender, presence of diabetes, race/ethnicity, categories of dialysis vintage, primary insurance and marital status, type of vascular access, dialysis dose as indicated by *Kt/V*, nine preexisting comorbid conditions and history of tobacco smoking. MICS-adjusted model includes all of the case-mix covariates as well as BMI, serum levels of albumin, TIBC, creatinine, calcium, phosphorous, bicarbonate, normalized protein catabolic rate as an indicator of daily protein intake, also known as the normalized protein nitrogen appearance, WBC and lymphocyte percentage.



**Fig. 2.** HRs of all-cause mortality of the entire range of time-averaged corrected calcium level using time-averaged Cox model in PKD patients (A) and comparing mortality predictability of PKD versus non-PKD HD patient in fully (case-mix and MICS) adjusted models using and time-averaged Cox regression analyses in different corrected serum calcium categories (B). Case-mix model is adjusted for age, gender, presence of diabetes, race/ethnicity, categories of dialysis vintage, primary insurance and marital status, type of vascular access, dialysis dose as indicated by *Kt/V*, nine preexisting comorbid conditions and history of tobacco smoking. MICS-adjusted model includes all of the case-mix covariates as well as BMI, serum levels of albumin, TIBC, creatinine, phosphorous, bicarbonate, normalized protein catabolic rate as an indicator of daily protein intake, also known as the normalized protein nitrogen appearance, WBC and lymphocyte percentage.

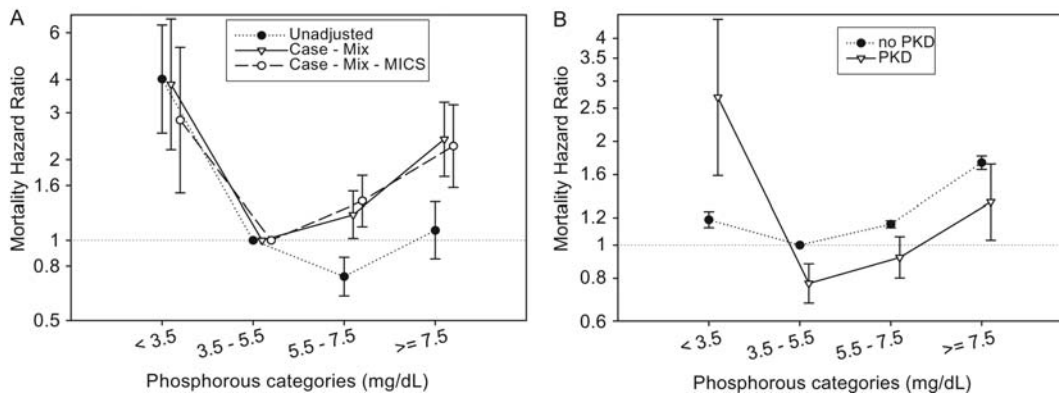
PKD patients). PKD patients had lower mortality risk than non-PKD patients in higher phosphorous categories ( $\geq 3.5$  mg/dL), but PKD patients had higher mortality risk in the lower phosphorous categories ( $< 3.5$  mg/dL).

Figure 4A shows unadjusted, case-mix and MICS adjusted death HRs associated with time-averaged serum alkaline phosphatase levels in PKD patients. Fully adjusted death HRs (95% CI) associated with time-averaged serum alkaline phosphatase levels of  $< 80$ , 120 to  $< 160$  and  $\geq 160$  U/L (reference: 80 to  $< 120$  U/L) for PKD patients were 0.98 (0.74–1.30), 0.96 (0.68–1.34) and 1.14 (0.80–1.64) ( $P > 0.05$  for the quadratic alkaline phosphatase term in case-mix and MICS models), respectively, and similar pattern was found in non-PKD patients. The association between alkaline phosphatase and mortality was not modified by presence of PKD ( $P > 0.05$  for interaction term). Figure 4B shows pooled analyses comparing mortality predictability of serum alkaline phosphatase increments in PKD versus non-PKD patients (serum

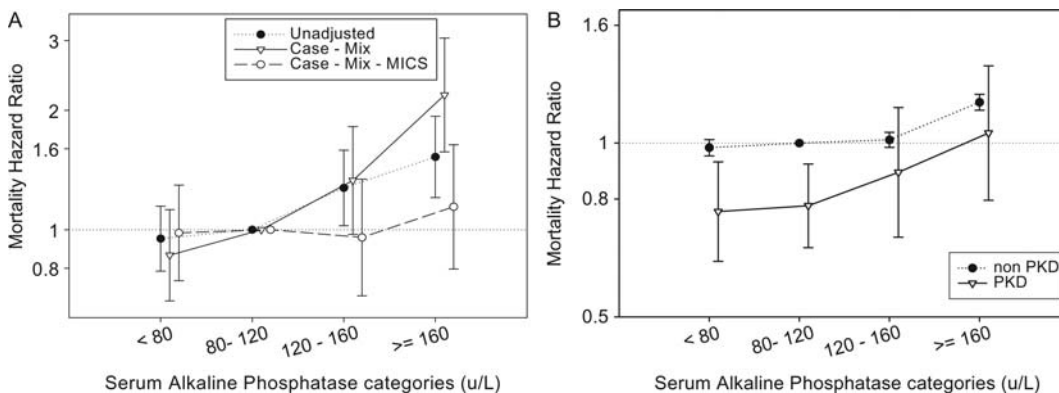
alkaline phosphatase reference: 80 to  $< 120$  U/L in non-PKD patients). PKD patients had lower mortality risk than non-PKD patients when serum alkaline phosphatase was  $< 120$  U/L.

**Discussion**

The analyses of data from a large and nationally representative contemporary cohort of  $> 100,000$  non-PKD MHD patients and  $> 1500$  PKD MHD patients allow us to make several important observations. Firstly, we confirm the previous findings of an association between higher serum phosphorous level and higher risk for death in MHD patients using a time-averaged analysis. Secondly, the association of different bone-mineral markers and mortality was not modified by presence PKD. Thirdly, despite a similar relationship between bone-mineral markers and mortality in PKD and non-PKD MHD patients, PKD patients had superior survival to non-PKD patients with higher levels of different bone-mineral markers.



**Fig. 3.** HRs of all-cause mortality of the entire range of time-averaged serum phosphorous using time-averaged Cox model in PKD patients (A) and comparing mortality predictability of PKD versus non-PKD HD patient in fully (case-mix and MICS) adjusted models using and time-averaged Cox regression analyses in different serum phosphorous categories (B). Case-mix model is adjusted for age, gender, presence of diabetes, race/ethnicity, categories of dialysis vintage, primary insurance and marital status, type of vascular access, dialysis dose as indicated by  $Kt/V$ , nine preexisting comorbid conditions and history of tobacco smoking. MICS-adjusted model includes all of the case-mix covariates as well as BMI, serum levels of albumin, TIBC, creatinine, calcium, bicarbonate, normalized protein catabolic rate as an indicator of daily protein intake, also known as the normalized protein nitrogen appearance, WBC and lymphocyte percentage.



**Fig. 4.** HRs of all-cause mortality of the entire range of time-averaged serum alkaline phosphatase using time-averaged Cox model in PKD patients (A) and comparing mortality predictability of PKD versus non-PKD HD patient in fully (case-mix and MICS) adjusted models using and time-averaged Cox regression analyses in different serum alkaline phosphatase categories (B). Case-mix model is adjusted for age, gender, presence of diabetes, race/ethnicity, categories of dialysis vintage, primary insurance and marital status, type of vascular access, dialysis dose as indicated by  $Kt/V$ , nine preexisting comorbid conditions and history of tobacco smoking. MICS-adjusted model includes all of the case-mix covariates as well as BMI, serum levels of albumin, TIBC, creatinine, calcium, phosphorous, bicarbonate, normalized protein catabolic rate as an indicator of daily protein intake, also known as the normalized protein nitrogen appearance, WBC and lymphocyte percentage.

In our study, we found a U-shape association between serum PTH and phosphorous level and death risk in PKD and non-PKD patients. However, a recent meta-analysis in CKD patients indicated that only high serum phosphorous level was a strong and independent predictor of mortality [4]. In the Netherlands Cooperative Study on the Adequacy of Dialysis study, in incident HD patients, Noordzij *et al.* [27] reported that the presence of plasma phosphorous concentrations greater than the Kidney Disease Outcomes Quality Initiative targets increased all-cause mortality risk in HD and peritoneal dialysis patients. This observation was confirmed by others [28, 29]. Here, we reported a similar relationship between serum phosphorous/PTH levels and mortality in MHD patients and showed that this association is not modified by the presence of PKD. Of note, a survival difference between PKD and non-PKD patients still exists in high serum phosphorous and PTH categories. While the high serum phosphorous level is a strong predictor of mortality

in both subgroups, the lower death risk of PKD patients compared to non-PKD patients was only present in those with high serum phosphorous level, but not in patients with low phosphorous level. This may indicate that PKD patients are healthier, and high phosphorous level still exists as a risk factor in this subgroup of MHD patients.

Low serum phosphorous/PTH levels were also associated with mortality in both PKD and non-PKD MHD patients. In MHD patients, a serum PTH between 150 and 300 pg/mL is considered a reasonable target zone [30]. A low serum PTH <150 pg/mL, however, may not necessarily be due to the so-called 'adynamic bone' but may be another facet of the malnutrition–inflammation complex syndrome (MICS) [31]. An observational study of HD patients by Dukkipati *et al.* [31] studied the relationship between low PTH and protein–energy malnutrition and inflammation and found that patients with low PTH in the range of 150–200 pg/mL had the greatest survival in this cohort. PTH stimulates lipogenesis through influx of

calcium into the adipocytes [32] and it is thus reasonable to suggest that a low PTH may prevent the accumulation of adipose tissue which may serve as a mechanism for protein–energy wasting in low PTH states. A recent study by Kovcsdy *et al.* [33] showed an association of PTH with obesity in patients with non-dialysis dependent-CKD. *In vitro* PTH secretion is suppressed by interleukin (IL)-6 [34], a strong pro-inflammatory cytokine that is associated with poor outcome in maintenance dialysis patients [35]. IL-1 $\beta$ , another pro-inflammatory cytokine, inhibits PTH secretion in cultured parathyroid tissue slices [36]. This effect may be mediated through the specific IL-1 receptors that upregulate calcium-sensing receptor messenger RNA leading to apparent low bone turnover [36]. Indeed, in the foregoing study, the inhibitory effect of IL-1 $\beta$  could be counteracted by the IL-1 receptor antagonist [36], indicating that the inflammation induced suppression of PTH can potentially be overcome by treatment of malnutrition–inflammation complex in individuals with CKD. Interestingly, we found the worst survival in the lowest levels of PTH and phosphorus, likely markers of inflammation, in PKD patients. Moreover, in these categories, PKD patients had worse survival than non-PKD patients. This might mean that inflammation has bigger impact on survival in PKD than in non-PKD patients. This observation needs further confirmation and more studies.

In the present study, we found U-shape association between serum calcium and mortality in PKD patients, but it was not significant due to the lack of statistical power. A similar U-shaped association was observed previously by our group [23]. Since enhanced calcification of blood vessels, including coronaries, often occurs in CKD patients and is a strong death predictor [37], the hypercalcemia–death associations are often attributed to vascular calcification upon higher calcium load. There have been mixed data about the mortality predictability of low serum calcium in CKD patients. Lowrie and Lew [38] were the first to report increased mortality with calcium <9.0 mg/dL in over 12 000 HD patients. However, Block *et al.* [28] did not find an increased mortality risk with hypocalcemia in 40 538 HD patients from the Fresenius Dialysis Clinics. Young *et al.* [39] found that serum calcium concentrations <7.8 mg/dL were associated with lower mortality compared to 9.0–9.5 mg/dL. We also showed this association in non-dialysis-dependent CKD patients, but only when analyzing calcium in time-dependent models, not in time-averaged models [40]. There is a physiological explanation for this short-term mortality caused by acutely lower calcium only, due to arrhythmias [40].

In our study, the association between serum alkaline phosphatase and survival was monotonic, almost strictly upgoing and independent of the level of multivariate adjustment in both PKD and non-PKD patients >120 U/L. Similar associations were found in our previous study analyzed >70 000 MHD patients [41]. A linear association indicative of the relation between the worsening severity of high-turnover bone disease and increased risk for death [42–44]. However, it is important to note that in our models, there was almost no association between serum alkaline phosphatase values <120 U/L and survival in

both subgroups. The lack of survival improvement trend of lower serum alkaline phosphatase levels may be related to the higher likelihood of adynamic bone disease in such low ranges [45–47]. Hence, a low serum alkaline phosphatase can herald adynamic bone, which may *per se* be associated with greater vascular calcification, thereby counteracting the expectedly improving effect of lowering serum alkaline phosphatase. Such a hypothesis, even though biologically plausible and consistent with our discrepant findings pertaining to lower levels of serum alkaline phosphatase, needs to be verified in future studies. There is another potential explanation. Severe acute illnesses (such as sepsis) are associated with alkaline phosphatase depletion. There is literature on benefits of alkaline phosphatase supplementation in patients with acute kidney injury [48].

Our study is notable for its large sample size. The detailed information on baseline covariates allowed us to control for a range of factors known to be related to the mortality of MHD patients. It is important to note that observational studies, such as ours, cannot prove causality. The information on comorbidities in our study was limited to that obtained from Medical Evidence Form 2728, a form in which comorbid conditions may be underreported [49]. Another potential limitation is the lack of information about explicit laboratory markers of inflammation such as C-reactive protein. However, we used data on serum albumin, TIBC, WBC and lymphocyte percentage, which have significant associations with inflammation in dialysis patients [50]. Moreover, we do not have data about treatment of MBD in these patients, which might have confounded our results.

## Conclusions

A U-shaped association for serum phosphorous, PTH and calcium mortality was observed in MHD independently their PKD status. Additionally, the association between serum alkaline phosphatase and survival was monotonic, almost strictly upgoing and independent of the level of multivariate adjustment in both PKD and non-PKD patients >120 U/L. PKD did not appear to be an effect modifier in the association between MBD markers and mortality in MHD patients. Despite a similar relationship between bone–mineral markers and mortality in PKD and non-PKD MHD patients, PKD patients had superior survival to non-PKD patients with higher levels of different bone–mineral markers.

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*Conflict of interest statement.* Dr K.K.-Z. is the medical director of DaVita Harbor-UCLA/MFI in Long Beach, CA, none of the other authors declare a conflict of interest.

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