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Journal

Clinical Journal of the American Society of Nephrology, 7(11)

ISSN

1555-9041

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Publication Date

2012-11-01

DOI

10.2215/cjn.01910212

Association of Pre–Kidney Transplant Markers of Mineral and Bone Disorder with Post-Transplant Outcomes

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Summary

Background and objectives Mineral and bone disorders (MBDs) are common in long-term dialysis patients and are risk factors for unfavorable outcomes. The associations between pretransplant levels of MBD surrogates and outcomes after kidney transplantation are not clear.

Design, setting, participants, & measurements Data from the Scientific Registry of Transplant Recipients up to June 2007 were linked to the 5-year (July 2001–June 2006) cohort of a large dialysis organization in the United States. All dialysis patients who received a kidney transplant during this period were identified and divided into groups according to increments of pretransplant MBD markers. Unadjusted and multivariate adjusted predictors of transplant outcomes were examined.

Results The 11,776 patients were aged 47±14 years and 39% were women. Compared with recipients with pretransplant time-averaged serum alkaline phosphatase of 80–120 U/L, recipients with pretransplant serum alkaline phosphatase of 120–160 and ≥160 U/L had 49% and 64% higher graft failure censored all-cause mortality in multivariable adjusted models. There was no significant association between time-averaged serum alkaline phosphatase categories and risk of death censored graft failure, delayed graft function (DGF), or acute rejection (AR). Compared with recipients with pretransplant time-averaged serum parathyroid hormone (PTH) levels of 150–300 pg/ml, there was no significant association with graft censored death among recipients with pretransplant serum PTH ≥800 pg/ml. In addition, the risk of graft failure, DGF, and AR did not show any association with time-averaged serum intact PTH level. There was no significant association between time-averaged serum calcium categories and risk of graft failure censored death, DGF, and AR.

Conclusions In this cohort, hemodialysis patients with pretransplant serum alkaline phosphatase >120 U/L have unfavorable post-transplant mortality, whereas there was no association between serum PTH and serum calcium levels and post-transplant outcomes.

Clin J Am Soc Nephrol 7: 1859–1871, 2012. doi: 10.2215/CJN.01910212

Due to the number of contributing authors, the affiliations are provided in the Supplemental Material.

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Introduction

A number of reports have delineated an increased risk of all-cause and cardiovascular mortality in patients with disorders of mineral metabolism (1–5). Accelerated atherosclerosis is an important cause of cardiovascular death in long-term dialysis patients (6), and shows strong association with mineral and bone disorders (MBDs) in these patients (7). High serum alkaline phosphatase was linearly associated with increased coronary calcification (5) and mortality (8) in dialysis patients. Dysregulation of parathyroid gland function is associated with serious skeletal abnormalities, ranging from high-turnover osteodystrophy bone disease to adynamic bone disease, that have been associated with nonskeletal consequences such as cardiovascular effects, vascular calcifications, calciphylaxis, and mortality in dialysis patients (9,10).

Cardiovascular disease is the leading cause of death after kidney transplantation (11). It is therefore important to evaluate the risk factors of coronary disease before transplantation. The abnormalities of MBD are well known risk factors of mortality and coronary disease in patients on maintenance hemodialysis (4,5,8). However, only few studies aimed to analyze the association between pretransplant MBDs and post-transplant outcome. We recently examined only the association of pretransplant phosphorus level and post-transplant outcome (12). However, similar investigations for other routinely measured MBD measures, such as alkaline phosphatase, intact parathyroid hormone (iPTH), and calcium, have not yet been examined in a large cohort. Both pretransplant (13) and post-transplant (14) high serum iPTH levels were associated with inferior outcome of graft function in kidney transplant recipients. Roodnat *et al.* examined 407 kidney transplant recipients and found a significant, linear association between a higher pretransplant PTH level and higher

risk of graft failure censored death (13). Compared with a pretransplant serum PTH level of 100 pg/ml, pretransplant PTH levels of 300 pg/ml, 500 pg/ml, and 800 pg/ml were associated with approximately 20%, 40%, and 80% higher risk of graft failure censored death, respectively (13). Similarly to PTH, pretransplant (12) and post-transplant (15) serum phosphorous levels were associated with increased mortality risk in kidney transplant recipients.

Short-term delayed graft function (DGF) and acute rejection are important predictors of long-term outcome in transplant recipients. Some small studies showed that the abnormalities in markers of MBD are associated with increased risk of DGF and acute rejection (16–18).

Thus, there is very limited knowledge on the value of biochemical markers of bone and mineral metabolism (serum alkaline phosphatase, serum iPTH, and serum calcium) and short-term outcomes such as acute rejection and DGF and long-term outcomes such as mortality and graft failure after kidney transplantation. We hypothesized that higher pretransplant serum alkaline phosphatase and serum iPTH levels are associated with poor post-transplant patient and graft survival and DGF in a large prospective cohort of incident kidney transplant recipients across the United States.

Materials and Methods

Patients

We linked data on all kidney transplant recipients listed in the Scientific Registry of Transplant Recipients (SRTR) up until June 2007 to a list of individuals with CKD by using the patients' social security numbers. These CKD patients underwent maintenance hemodialysis treatment from July 2001 to June 2006 at one of the outpatient dialysis facilities of a large, US-based dialysis organization (DaVita Inc, before its acquisition of former Gambro dialysis facilities). The study was approved by the institutional review boards of both Los Angeles Biomedical Research Institute at Harbor-UCLA and DaVita Clinical Research.

Clinical and Demographic Measures

The creation of the national DaVita dialysis patient cohort has been described previously (19–23). We collected demographic data (such as age, sex, race, type of insurance, marital status, presence of diabetes, and dialysis vintage) and details of medical history data. Dialysis vintage was defined as the duration of time between the first day of dialysis treatment and the day of kidney transplantation. DGF and nonbiopsy-confirmed acute rejection data were captured from the SRTR database. In addition, medical history data (atherosclerotic heart disease, congestive heart failure, cancer, chronic obstructive pulmonary disease, cerebrovascular disease, hypertension, peripheral vascular disease, tobacco use) were captured from US Renal Data System. 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. Time-averaged values obtained from up to 20 calendar quarters (q1–q20) over the entire pretransplant period were used in our analyses. The first (baseline) studied quarter for each patient was the calendar quarter in which the patient's dialysis vintage was >90 days.

Laboratory Measures

Blood samples methods were described previously (19–23). Most blood samples were collected predialysis with the exception of postdialysis serum urea nitrogen to calculate urea kinetics. Most laboratory values were measured monthly, including serum alkaline phosphatase, calcium, phosphorus, and albumin. Serum iPTH was measured at least quarterly using a first-generation immunoradiometric PTH assay (Nichols, San Juan Capistrano, CA) as described by Nussbaum *et al*. (24). We divided patients into five *a priori*–defined categories based on pretransplant time-averaged serum iPTH level (<150 pg/ml, 150–300 pg/ml, 300–500 pg/ml, 500–800 pg/ml, and ≥800 pg/ml values) to examine the dose-response association between pretransplant time-averaged serum iPTH categories and outcome risk. We also divided patients into four *a priori*–defined categories based on pretransplant time-averaged serum alkaline phosphatase level (<80 U/L, 80–<120 U/L, 120–<160 U/L, and ≥160 U/L values), serum time-averaged calcium level (<8.4 mg/dl, 8.4–<9.5 mg/dl, 9.5–<10.2 mg/dl, and ≥10.2 mg/dl values), and serum time-averaged calcium-phosphorous level (<45 mg^2/dl^2, 45–<55 mg^2/dl^2, 55–<65 mg^2/dl^2, and ≥65 mg^2/dl^2 values), respectively, similarly to our previous article (4).

Statistical Analyses

Data were summarized using proportions (mean ± SD). We examined *P* values for trends across pretransplant serum alkaline phosphatase categories. Time to event survival analyses were done to determine association of time-averaged markers of MBDs with all-cause mortality and graft failure (defined as reinitiation of dialysis treatment or retransplantation), DGF, and acute rejection. For DGF, defined as the need for any dialysis therapy in the first week after transplantation (25), time to event was not accounted for. Survival analyses to calculate hazard ratios (HRs) and 95% confidence intervals (95% CIs) of graft failure censored death or death censored graft failure used Cox proportional hazards regression. In mortality analyses, patients were followed until event (death) or censoring (graft failure or end of follow-up period), whichever happened first. In graft failure analyses, patients were followed until event (graft failure) or censoring (death or end of follow-up period), whichever occurred first. Proportional hazard assumption was tested using log(-log) against survival plots. Logistic regression models were used to estimate the odds ratio (ORs) and 95% CIs of post-transplant DGF and acute rejection.

For each regression analysis, four levels of multivariate adjustment were examined. First, an unadjusted model included pretransplant markers of MBD categories as the predictor. Second, case-mix adjusted models included the above plus age, sex, recipient race/ethnicity (African Americans and other self-categorized blacks, non-Hispanic whites, Asians, Hispanics, and others), diabetes mellitus, dialysis vintage (<6 months, 6 months to 2 years, 2–<5 years, and ≥5 years), primary insurance (Medicare, Medicaid, private, and others), marital status (married, single,

Table 1. Baseline characteristics of 11,776 dialysis patients who underwent renal transplantation between July 2001 and June 2006

Pretransplant Serum Alkaline Phosphatase (U/L)	<80	80–<120	120–<160	≥160	*P* for Trend
n (%)	3769 (32)	4701 (40)	1833 (16)	1473 (12)	N/A
Age (yr)	48±14	48±14	47±14	42±16	<0.001
Female sex	34	40	45	47	<0.001
Race (% African American)	24	26	28	31	<0.001
Diabetes mellitus	28	36	41	35	<0.001
Proportion of peritoneal dialysis patients	18	17	17	20	0.07
BMI (kg/m^2)	26.8±5.8	26.6±5.8	26.4±5.7	25.5±6.4	<0.001
Presence of ischemic heart disease	8	9	9	7	0.24
Presence of congestive heart failure	8	10	12	10	<0.001
Presence of hypertension	78	77	75	68	<0.001
Presence of cerebrovascular events	2	3	2	2	0.60
Presence of peripheral vascular disease	3	4	4	4	0.02
Presence of chronic obstructive pulmonary disease	1	1	2	1	0.24
Presence of cancer	2	2	2	2	0.62
Tobacco use	4	4	3	3	0.78
Dialysis vintage					
0–6 mo	15	10	9	9	<0.001
6–24 mo	34	28	22	21	<0.001
2–5 yr	36	39	39	33	<0.001
>5 yr	15	23	30	37	<0.001
Kt/V	1.57±0.36	1.61±0.36	1.61±0.34	1.63±0.37	<0.001
nPCR (g/kg per day)	1.04±0.25	1.04±0.26	1.03±0.26	1.03±0.28	0.02
Serum creatinine (mg/dl)	10.9±3.5	10.6±3.4	10.3±3.3	10.1±3.3	<0.001
Serum albumin (mg/dl)	4.02±0.38	3.99±0.39	3.94±0.41	3.87±0.48	<0.001
Serum phosphate (mg/dl)	6.0±1.5	5.9±1.5	5.9±1.5	5.8±1.6	<0.001
Serum calcium (mg/dl)	9.4±0.6	9.4±0.6	9.4±0.6	9.3±0.7	<0.001
Serum iPTH (pg/ml)	305±224	386±299	499±402	727±668	<0.001
Blood hemoglobin (g/dl)	12.2±1.3	12.3±1.3	12.2±1.3	12.1±1.4	0.003
WBC (×10^3/L)	6.9±2.0	6.9±2.1	7.0±2.2	7.1±2.4	0.004
Number of HLA mismatch	3.5±1.8	3.5±1.9	3.6±1.8	3.7±1.8	<0.001
Number of HLA-DR mismatch	1.05±0.73	1.07±0.74	1.06±0.73	1.12±0.74	0.02
PRA (%)	8±21	11±25	11±25	14±28	<0.001
PRA >20%	11	15	17	20	<0.001
Donor age (yr)	39±15	39±15	39±15	38±16	0.02
Donor sex (% women)	49	47	49	46	0.08
Donor type (% living)	39	34	30	27	<0.001
EDC kidney[a]	19	19	17	16	0.07
Cold ischemia time (h)[a]	18.4±8.4	18.5±8.5	18.0±8.6	18.3±8.6	<0.001

Data are percentages or means ± SDs unless otherwise indicated. BMI, body mass index; nPCR, normalized protein catabolic rate; iPTH, intact parathyroid hormone; WBC, white blood cell count; PRA, panel reactive antibody (last value before transplant); EDC, extended donor criteria; N/A, not applicable.

[a]In recipients who received kidney from deceased donors.

divorced, widowed, and other or unknown), standardized mortality ratio of the dialysis clinic during entry quarter, dialysis dose as indicated by Kt/V (single pool), presence or absence of a hemodialysis catheter, and residual renal function during the entry quarter and eight comorbidities. Third, markers of malnutrition or inflammation (MMI) models included all of the above covariates plus 11 surrogates of nutritional status and inflammation measured during the last calendar quarter before transplantation including body mass index and 10 laboratory variables such as normalized protein catabolic rate as an indicator of daily protein intake, also known as the normalized protein nitrogen appearance (26), and serum or blood concentrations of total iron-binding capacity, ferritin, calcium (except calcium analysis), phosphorous, iPTH (except iPTH analysis), bicarbonate, peripheral white blood cell count, lymphocyte percentage, and albumin. Fourth, models adjusted for case mix, MMI, and transplant data included all of the above plus eight transplant-related variables, including donor type (deceased or living), donor age, donor sex, panel reactive antibody titer (last value before transplant), number of HLA mismatches, cold ischemia time, DGF (except when DGF was a dependent variable in logistic regression models), and extended donor criteria using standard definition (donor history of hypertension and/or serum creatinine of donor >1.5 mg/dl and/or cause of death in donor is cerebrovascular event). We repeated our alkaline phosphatase analyses in patients

without liver disease (defined if aspartate aminotransferase >40 U/L) as sensitivity analyses. All analyses were carried out with STATA software (version 11.1; STATA Corporation, College Station, TX).

Results

The original 5-year (July 2001–June 2006) national database of all DaVita patients included 164,789 adult participants. Of 65,386 DaVita patients who were identified in the SRTR database, 17,629 had undergone one or more kidney transplantations during their lifetime, but only 14,508 dialysis patients had undergone kidney transplantation for the first time. This analytic cohort was followed until death, graft failure, loss of follow-up, or survival until June 30, 2007. In the final analyses we excluded the patients who did not have serum alkaline phosphatase measurements (n=2732) or serum iPTH measurements (n=4401) or serum calcium measurements (n=2669) (Supplemental Figure 1). Accordingly, the final analyses were done in 11,776 patients for serum alkaline phosphatase, 10,107 patients for serum iPTH, and 11,839 patients for serum calcium (Supplemental Figure 1).

There were 869 deaths (7.4%) and 1320 graft failures (11.2%) irrespective of subsequent deaths in the alkaline phosphatase cohort. The median cohort time was 829 days (interquartile range, 358–1362 days). Tables 1 and 2 show the clinical, demographic, and laboratory data of the 11,776 transplanted patients across four pretransplant serum alkaline phosphatase categories. The crude all-cause mortality rate was 31.2/1000 patient-years (95% CI, 29.3–33.2).

The associations of pretransplant time-averaged serum alkaline phosphatase categories with the post-transplant risk of graft failure censored death, death censored graft failure, DGF, and acute rejection are shown in Figure 1. A higher time-averaged serum alkaline phosphatase level showed a linear and significant (P=0.04 for serum alkaline phosphatase as continuous variable) association with higher risk of graft failure censored death in our cohort (Figure 1A). Similar association was found in cardiovascular mortality (Figure 1B). Similar, but nonsignificant, association was observed for graft loss, DGF, and acute rejection (Figure 1, D–F). Table 3 shows the risk of post-transplant all-cause, cardiovascular, infectious graft failure censored death or death censored graft failure or DGF or acute rejection comparing different pretransplant time-averaged serum alkaline phosphatase categories. Compared with recipients with pretransplant time-averaged serum alkaline phosphatase of 80–120 U/L, recipients with pretransplant time-averaged serum alkaline phosphatase of 120–160 and ≥160 U/L had 41% (HR, 1.41; 95% CI, 1.17–1.69) and 57% (HR, 1.57; 95% CI, 1.30–1.91) higher graft failure censored all-cause mortality, and recipients with pretransplant time-averaged serum alkaline phosphatase of <80 U/L had 23% (HR, 0.77; 95% CI, 0.65–0.92) lower unadjusted graft failure censored death risk. After additional adjustment for case-mix, MMI, and transplant-related variables, recipients with pretransplant time-averaged serum alkaline phosphatase of 120–<160 and ≥160 U/L had 49% (HR, 1.49; 95% CI, 1.14–1.93) and 64% (HR, 1.64; 95% CI, 1.21–2.23) higher graft failure censored death risk compared with recipients with pretransplant time-averaged serum alkaline phosphatase of 80–<120 U/L (Table 3). Compared with recipients with pretransplant time-averaged serum alkaline phosphatase 80–<120 U/L, recipients with pretransplant time-averaged serum alkaline phosphatase of 120–<160 and ≥160 U/L had 111% (HR, 2.11; 95% CI, 1.26–3.52) and 100% (HR, 2.00; 95% CI, 1.10–3.65) higher graft failure censored cardiovascular mortality (Table 3). There was no significant association

Table 2. Post-transplant outcomes of 11,776 dialysis patients who underwent renal transplantation between July 2001 and June 2006

Pretransplant Serum Alkaline Phosphatase (U/L)	<80	80–<120	120–<160	≥160	P for Trend
n (%)	3769 (32)	4701 (40)	1833 (16)	1473 (12)	N/A
Deaths, n (crude death rate %)	224 (5.9)	328 (7.0)	169 (9.2)	148 (10.1)	<0.001
Crude all-cause mortality rate per 1000 patient-years (95% CI)	23 (20–26)	30 (27–33)	42 (36–49)	47 (40–55)	N/A
Cardiovascular deaths, n (crude cardiovascular death rate %)	52 (1.4)	80 (1.7)	49 (2.7)	51 (3.5)	<0.001
Crude cardiovascular mortality rate per 1000 patient-years (95% CI)	5.3 (4.0–7.0)	7.3 (5.8–9.0)	12.2 (9.2–16.1)	16.3 (12.4–21.4)	N/A
Infectious deaths, n (crude infectious death rate %)	40 (1.1)	69 (1.5)	40 (2.2)	3.7 (2.5)	<0.001
Crude infectious mortality rate per 1000 patient-years (95% CI)	4.1 (3.0–5.6)	6.3 (4.9–7.9)	9.9 (7.3–13.6)	11.8 (8.5–16.3)	N/A
Graft failure, n (crude graft failure rate %)	333 (8.8)	482 (10.3)	261 (14.2)	244 (16.6)	<0.001
Crude graft failure rate per 1000 patient-years (95% CI)	34 (30–38)	44 (40–48)	65 (57–73)	78 (69–88)	N/A
DGF, n (crude DGF %)	613 (17.0)	888 (19.9)	392 (22.8)	333 (24.5)	<0.001
History of acute rejection, n (%)	71 (3.8)	96 (3.7)	47 (4.6)	43 (5.5)	0.10

Values in parentheses indicate the crude death rate, crude graft failure rate, and crude DGF rate in the indicated group during the 6 years of observation. 95% CI, 95% confidence interval; DGF, delayed graft function; N/A, not applicable.

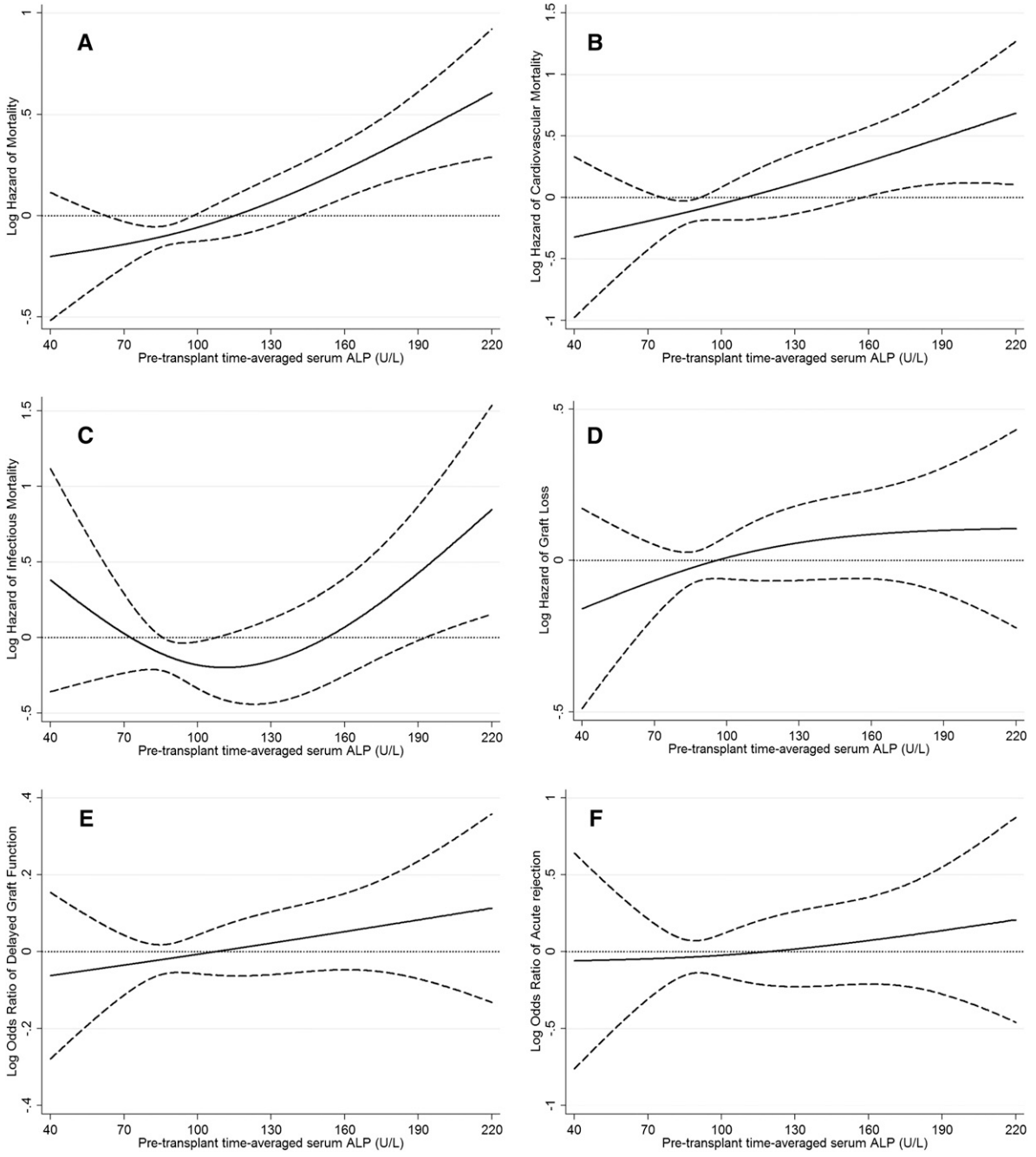

Figure 1. | Hazard/odds ratio (95% confidence intervals) of post-transplant outcomes across the entire range of pretransplant serum alkaline phosphatase level using Cox regression analyses in 11,776 long-term dialysis patients who underwent renal transplantation and who were observed over a 6-year study period (July 2001–June 2007). (A) All-cause mortality, (B) cardiovascular mortality, (C) infectious mortality, (D) graft loss, (E) delayed graft function, and (F) acute rejection. Model adjusted for age, sex, recipient race-ethnicity, diabetes mellitus, dialysis vintage, primary insurance, marital status, standardized mortality ratio of the dialysis clinic during entry quarter, dialysis dose as indicated by Kt/V (single pool), presence or absence of a hemodialysis catheter, and residual renal function during the entry quarter, eight comorbidities, body mass index, normalized protein nitrogen appearance , serum or blood concentrations of total iron-binding capacity, ferritin, calcium, phosphorous, intact parathyroid hormone, bicarbonate, peripheral white blood cell count, lymphocyte percentage, albumin, donor type, donor age, donor sex, panel reactive antibody titer (last value before transplant), number of HLA mismatches, cold ischemia time, delayed graft function, and extended donor criteria.

between time-averaged serum alkaline phosphatase categories and risk of death censored graft failure, DGF, or acute rejection (Table 3). Similar results were found in patients without liver disease (Supplemental Table 1).

The associations of pretransplant time-averaged serum iPTH categories with the post-transplant risk of graft failure censored death, death censored graft failure, DGF, and acute rejection are shown in Figure 2. Higher time-

Table 3. Hazard/odds ratios (95% confidence intervals) of post-transplant all-cause, cardiovascular, and infectious death or graft failure, delayed graft function, or acute rejection comparing pretransplant serum alkaline phosphatase categories (80–<120 U/L as reference) using Cox regression and logistic regression analyses in 11,776 dialysis patients who underwent renal transplantation and were observed for up to 6 years (July 2001–June 2007)

Pretransplant Serum Alkaline Phosphatase Level (U/L)	Unadjusted		Case-Mix Adjusted[a] (n=)		MMI Adjusted[b]		Transplant Data Adjusted[c]	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Graft failure censored all-cause death								
n	11,776		9246		7820		4852	
<80	0.77 (0.65–0.92)	0.003	0.92 (0.76–1.11)	0.37	0.89 (0.72–1.10)	0.28	0.97 (0.75–1.24)	0.80
80–<120	1.00	N/A	1.00	N/A	1.00	N/A	1.00	N/A
120–<160	1.41 (1.17–1.69)	<0.001	1.46 (1.17–1.78)	0.001	1.48 (1.19–1.85)	0.001	1.49 (1.14–1.93)	0.003
≥160	1.57 (1.30–1.91)	<0.001	1.91 (1.52–2.40)	<0.001	1.85 (1.44–2.39)	<0.001	1.64 (1.21–2.23)	0.002
Graft failure censored cardiovascular death								
<80	0.75 (0.53–1.06)	0.10	1.01 (0.68–1.50)	0.94	1.12 (0.73–1.71)	0.61	1.12 (0.67–1.89)	0.66
80–<120	1.00	N/A	1.00	N/A	1.00	N/A	1.00	N/A
120–<160	1.66 (1.16–2.37)	0.005	1.86 (1.24–2.80)	0.003	1.83 (1.19–2.83)	0.006	2.11 (1.26–3.52)	0.004
≥160	2.20 (1.55–3.13)	<0.001	2.33 (1.50–3.63)	<0.001	1.85 (1.12–3.08)	0.02	2.00 (1.10–3.65)	0.02
Graft failure censored infectious death								
<80	0.66 (0.45–0.98)	0.04	0.82 (0.52–1.27)	0.36	0.78 (0.48–1.26)	0.30	0.97 (0.53–1.77)	0.93
80–<120	1.00	N/A	1.00	N/A	1.00	N/A	1.00	N/A
120–<160	1.58 (1.07–2.33)	0.02	1.34 (0.83–2.15)	0.23	1.23 (0.74–2.04)	0.44	1.15 (0.59–2.23)	0.68
≥160	1.86 (1.25–2.78)	0.002	2.07 (1.27–3.37)	0.004	1.93 (1.12–3.32)	0.02	1.85 (0.94–3.66)	0.08
All-cause death censored graft failure								
<80	0.79 (0.69–0.91)	0.001	1.08 (0.91–1.29)	0.37	1.12 (0.93–1.35)	0.22	1.14 (0.89–1.45)	0.29
80–<120	1.00	N/A	1.00	N/A	1.00	N/A	1.00	N/A
120–<160	1.47 (1.26–1.71)	<0.001	1.30 (1.07–1.59)	0.008	1.29 (1.05–1.59)	0.01	1.23 (0.94–1.61)	0.14
≥160	1.75 (1.50–2.04)	<0.001	1.20 (0.96–1.49)	0.11	1.10 (0.86–1.40)	0.45	1.16 (0.85–1.59)	0.35
Delayed graft function								
n	11,143		8801		7457		4852	
<80	0.83 (0.74–0.93)	0.001	1.00 (0.88–1.13)	0.97	0.97 (0.84–1.11)	0.65	1.01 (0.86–1.19)	0.86
80–<120	1.00	N/A	1.00	N/A	1.00	N/A	1.00	N/A
120–<160	1.19 (1.04–1.36)	0.01	1.12 (0.96–1.31)	0.14	1.13 (0.96–1.33)	0.16	1.10 (0.91–1.33)	0.32
≥160	1.31 (1.14–1.51)	<0.001	1.20 (1.01–1.43)	0.04	1.16 (0.95–1.41)	0.14	1.14 (0.91–1.43)	0.25
Acute rejection								
n	6307		5206		4123		2793	
<80	1.04 (0.76–1.42)	0.82	1.16 (0.81–1.65)	0.41	1.16 (0.77–1.74)	0.49	1.08 (0.65–1.81)	0.77
80 –<120	1.00	N/A	1.00	N/A	1.00	N/A	1.00	N/A
120–<160	1.29 (0.90–1.84)	0.17	1.28 (0.85–1.93)	0.23	1.42 (0.90–2.22)	0.13	1.38 (0.81–2.35)	0.23
≥160	1.52 (1.05–2.20)	0.03	1.42 (0.92–2.20)	0.12	1.40 (0.83–2.35)	0.20	1.12 (0.59–2.12)	0.72

MMI, markers of malnutrition or inflammation; HR, hazard ratio; 95% CI, 95% confidence interval; iPTH, intact parathyroid hormone.

[a]Adjusted for age, sex, recipient race/ethnicity, diabetes mellitus, dialysis vintage, primary insurance, marital status, standardized mortality ratio of the dialysis clinic during entry quarter, dialysis dose as indicated by Kt/V (single pool), presence or absence of a hemodialysis catheter, and residual renal function during the entry quarter and eight comorbidities.

[b]Adjusted for all of the covariates plus body mass index, normalized protein nitrogen appearance , serum or blood concentrations of total iron-binding capacity, ferritin, calcium, phosphorous, iPTH, bicarbonate, peripheral white blood cell count, lymphocyte percentage, and albumin; N/A, not applicable.

[c]Adjusted for all of the above plus donor type, donor age, donor sex, panel reactive antibody titer (last value before transplant), number of HLA mismatches, cold ischemia time, delayed graft function (except when delayed graft function was a dependent variable in our logistic regression models), and extended donor criteria.

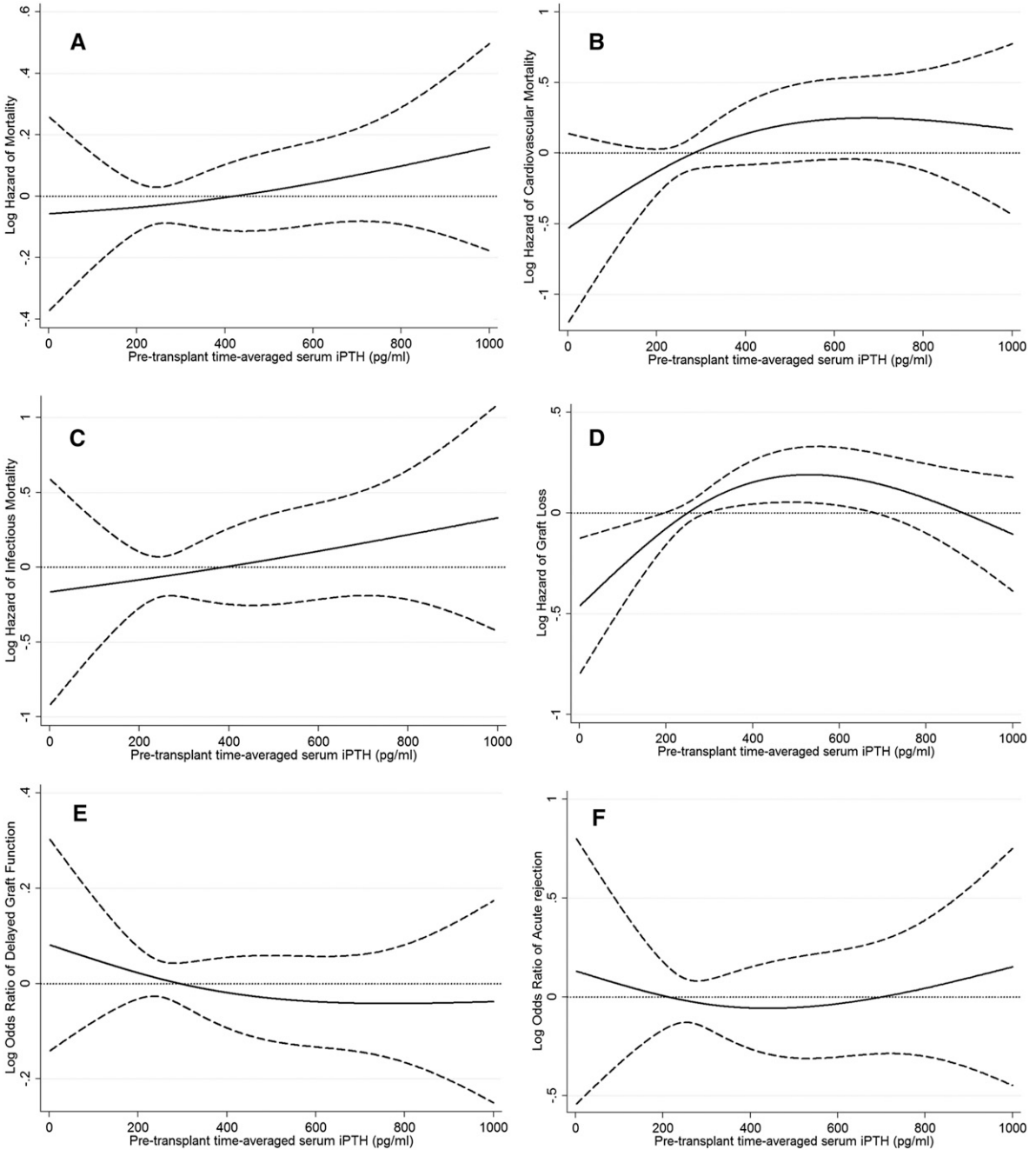

Figure 2. | Hazard/odds ratio (95% confidence intervals) of post-transplant outcomes across the entire range of pretransplant serum intact parathyroid hormone level using Cox regression analyses in 10,107 long-term dialysis patients who underwent renal transplantation and who were observed over a 6-year study period (July 2001–June 2007). (A) All-cause mortality, (B) cardiovascular mortality, (C) infectious mortality, (D) graft loss, (E) delayed graft function, and (F) acute rejection. Model adjusted for age, sex, recipient race-ethnicity, diabetes mellitus, dialysis vintage, primary insurance, marital status, standardized mortality ratio of the dialysis clinic during entry quarter, dialysis dose as indicated by Kt/V (single pool), presence or absence of a hemodialysis catheter, and residual renal function during the entry quarter, eight comorbidities, body mass index, normalized protein nitrogen appearance , serum or blood concentrations of total iron-binding capacity, ferritin, calcium, phosphorous, bicarbonate, peripheral white blood cell count, lymphocyte percentage, albumin, donor type, donor age, donor sex, panel reactive antibody titer (last value before transplant), number of HLA mismatches, cold ischemia time, delayed graft function , and extended donor criteria.

averaged serum iPTH level did not show (P=0.15 for iPTH as continuous variable) any association with risk of graft failure censored death in our cohort (Figure 2A). Similar results were found in cardiovascular and infectious mortality (Figure 2, B and C).

In addition, the risk of graft failure, DGF, and acute rejection did not show any association with time-averaged serum iPTH level (Figure 2, D–F). Table 4 shows the risk of post-transplant graft failure censored all-cause, cardiovascular, infectious death, death censored graft failure, DGF,

Table 4. Hazard/odds ratio (95% confidence intervals) of post-transplant all-cause, cardiovascular, and infectious death or graft failure, delayed graft function, or acute rejection comparing pretransplant serum iPTH categories (150–<300 pg/ml the reference) using Cox regression and logistic regression analyses in 10,107 dialysis patients who underwent renal transplantation and observed for up to 6 years (July 2001–June 2007)

Pretransplant Serum iPTH Level (pg/ml)	Unadjusted		Case-Mix Adjusted[a]		MMI Adjusted[b]		Transplant Data Adjusted[c]	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Graft failure censored all-cause death								
n	10,107		8082		7820		4852	
<150	1.05 (0.86–1.28)	0.63	0.99 (0.79–1.26)	0.97	1.04 (0.82–1.33)	0.72	1.06 (0.79–1.41)	0.70
150–<300	1.00	N/A	1.00	N/A	1.00	N/A	1.00	N/A
300–<500	0.90 (0.75–1.08)	0.24	0.99 (0.81–1.22)	0.94	0.98 (0.79–1.21)	0.83	1.12 (0.88–1.44)	0.36
500–<800	0.72 (0.56–0.92)	0.01	0.98 (0.74–1.29)	0.87	1.02 (0.76–1.37)	0.88	1.15 (0.81–1.63)	0.43
≥800	0.79 (0.61–1.03)	0.08	1.22 (0.90–1.66)	0.21	1.27 (0.92–1.75)	0.14	1.28 (0.87–1.88)	0.20
Graft failure censored cardiovascular death								
<150	1.17 (0.77–1.78)	0.46	1.09 (0.66–1.80)	0.72	1.02 (0.61–1.72)	0.94	1.00 (0.54–1.87)	0.99
150–<300	1.00	N/A	1.00	N/A	1.00	N/A	1.00	N/A
300–<500	1.12 (0.78–1.63)	0.53	1.08 (0.71–1.64)	0.74	1.03 (0.67–1.58)	0.88	1.04 (0.67–1.80)	0.79
500–<800	1.52 (1.01–2.28)	0.04	1.81 (1.14–2.89)	0.01	1.70 (1.03–2.79)	0.04	2.21 (1.24–3.91)	0.007
≥800	1.19 (0.74–1.91)	0.47	1.31 (0.72–2.39)	0.37	1.29 (0.70–2.38)	0.41	1.21 (0.58–2.54)	0.62
Graft failure censored infectious death								
<150	1.32 (0.86–2.03)	0.20	0.96 (0.57–1.63)	0.89	0.97 (0.56–1.67)	0.90	1.16 (0.59–2.29)	0.66
150–<300	1.00	N/A	1.00	N/A	1.00	N/A	1.00	N/A
300–<500	1.03 (0.69–1.54)	0.89	0.93 (0.58–1.48)	0.76	0.94 (0.58–1.52)	0.80	1.18 (0.64–2.16)	0.59
500–<800	0.92 (0.55–1.54)	0.75	1.03 (0.55–1.91)	0.93	1.05 (0.55–1.99)	0.89	1.45 (0.66–3.19)	0.36
≥800	1.07 (0.63–1.81)	0.82	1.51 (0.78–2.91)	0.22	1.52 (0.77–2.99)	0.23	1.52 (0.62–3.70)	0.36
All-cause death censored graft failure								
<150	0.88 (0.72–1.08)	0.21	0.88 (0.68–1.14)	0.34	0.87 (0.66–1.14)	0.31	0.99 (0.70–1.41)	0.96
150–<300	1.00	N/A	1.00	N/A	1.00	N/A	1.00	N/A
300–<500	1.43 (1.23–1.67)	<0.001	1.24 (1.04–1.49)	0.02	1.25 (1.04–1.51)	0.02	1.42 (1.11–1.82)	0.005
500–<800	1.34 (1.12–1.61)	0.002	1.07 (0.85–1.35)	0.58	1.03 (0.81–1.31)	0.82	1.26 (0.93–1.72)	0.14
≥800	2.10 (1.77–2.49)	<0.001	1.11 (0.87–1.42)	0.40	1.07 (0.83–1.38)	0.59	1.10 (0.79–1.55)	0.57
Delayed graft function								
n	9592		7705		7457		4852	
<150	0.90 (0.77–1.06)	0.21	1.06 (0.88–1.27)	0.52	1.10 (0.91–1.33)	0.31	1.14 (0.91–1.41)	0.26
150–<300	1.00	N/A	1.00	N/A	1.00	N/A	1.00	N/A
300–<500	1.12 (0.99–1.27)	0.08	1.12 (0.97–1.29)	0.13	1.09 (0.94–1.27)	0.24	1.10 (0.93–1.30)	0.29
500–<800	1.04 (0.89–1.22)	0.60	1.01 (0.84–1.22)	0.90	0.94 (0.77–1.14)	0.50	0.97 (0.77–1.21)	0.78
≥800	1.23 (1.04–1.45)	0.01	1.26 (1.03–1.54)	0.03	1.14 (0.92–1.41)	0.23	1.03 (0.80–1.32)	0.82
Acute rejection								
n	4985		4209		4123		2793	
<150	1.51 (0.95–2.40)	0.08	1.35 (0.78–2.32)	0.28	1.37 (0.79–2.37)	0.26	1.27 (0.65–2.51)	0.49
150–<300	1.00	N/A	1.00	N/A	1.00	N/A	1.00	N/A
300–<500	1.51 (1.05–2.18)	0.03	1.48 (0.99–2.22)	0.06	1.46 (0.97–2.20)	0.07	1.25 (0.76–2.05)	0.38

Table 4. (Continued)

Pretransplant Serum iPTH Level (pg/ml)	Unadjusted		Case-Mix Adjusted[a]		MMI Adjusted[b]		Transplant Data Adjusted[c]	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
500–<800	1.41 (0.91–2.21)	0.13	1.26 (0.75–2.11)	0.38	1.21 (0.72–2.04)	0.48	1.01 (0.52–2.00)	0.97
≥800	1.53 (0.95–2.46)	0.08	1.20 (0.67–2.16)	0.54	1.07 (0.58–1.99)	0.82	1.41 (0.70–2.85)	0.34

iPTH, intact parathyroid hormone; MMI, markers of malnutrition or inflammation; HR, hazard ratio; 95% CI, 95% confidence interval.
[a]Adjusted for age, sex, recipient race/ethnicity, diabetes mellitus, dialysis vintage, primary insurance, marital status, standardized mortality ratio of the dialysis clinic during entry quarter, dialysis dose as indicated by Kt/V (single pool), presence or absence of a hemodialysis catheter, and residual renal function during the entry quarter and eight comorbidities.
[b]Adjusted for all of the covariates plus body mass index, normalized protein nitrogen appearance , serum or blood concentrations of total iron-binding capacity, ferritin, phosphorous, calcium, bicarbonate, peripheral white blood cell count, lymphocyte percentage, and albumin.
[c]Adjusted for all of the above plus donor type, donor age, donor sex, panel reactive antibody titer (last value before transplant), number of HLA mismatches, cold ischemia time, delayed graft function (except when delayed graft function was a dependent variable in our logistic regression models), and extended donor criteria.

or acute rejection comparing different pretransplant time-averaged serum iPTH categories. Compared with recipients with pretransplant time-averaged serum PTH level of 150–300 pg/ml, there was no significant association with graft censored death among recipients with pretransplant serum PTH of ≥800 pg/ml (HR, 1.28; 95% CI, 0.87–1.88) (Table 4). Compared with recipients with pretransplant time-averaged serum iPTH level 150–300 pg/ml, recipients with pretransplant time-averaged serum iPTH of 500–800 pg/ml iPTH had higher (HR, 2.21; 95% CI, 1.24–3.91) cardiovascular mortality risk in our multivariable adjusted model (Table 4). There was no association between iPTH categories and risk of graft failure, DGF, and acute rejection.

The associations of pretransplant time-averaged serum calcium categories with the post-transplant risk of graft failure censored death, death censored graft failure, DGF, and acute rejection is shown in Figure 3. Lower time-averaged serum calcium level showed a nonsignificant trend toward higher all-cause mortality risk (P=0.10 for serum calcium as continuous variable), but there was no association between serum calcium level and the risk of DGF or acute rejection. Table 5 shows the risk of post-transplant graft failure censored all-cause, cardiovascular, and infectious death or death censored graft failure, DGF, or acute rejection comparing different pretransplant time-averaged serum calcium categories. Compared with recipients with pretransplant time-averaged serum calcium of 8.4–9.5 mg/dl, recipients with pretransplant time-averaged serum calcium of 9.5–<10.2 and ≥10.2 mg/dl calcium had 26% (HR, 0.74; 95% CI, 0.60–0.92) and 40% (HR, 0.60; 95% CI, 0.41–0.88) lower risk of graft failure in our models adjusted for case mix, MMI, and transplant variables (Table 5). There was no significant association between time-averaged serum calcium categories and risk of graft failure censored death, DGF, and acute rejection (Table 5).

In addition, there was no significant association between time-averaged serum calcium-phosphorous product levels and risk of graft failure censored all-cause, cardiovascular, infectious death, DGF, and acute rejection (Supplemental Table 2 and Supplemental Figure 2).

Discussion

In this retrospective analysis of >10,000 primary kidney transplant recipients, we describe an association between pretransplant serum alkaline phosphatase levels >120 U/L with an increased risk of graft failure censored all-cause and cardiovascular death; however, there was no association between serum iPTH and mortality. Neither pretransplant serum iPTH nor pretransplant serum alkaline phosphatase level was associated with graft loss, DGF, or acute rejection. Interestingly, pretransplant serum calcium >9.5 mg/dl was associated with decreased risk of graft loss.

The first important finding was the association of pretransplant serum alkaline phosphatase levels >120 U/L with increased risk of post-transplant graft failure

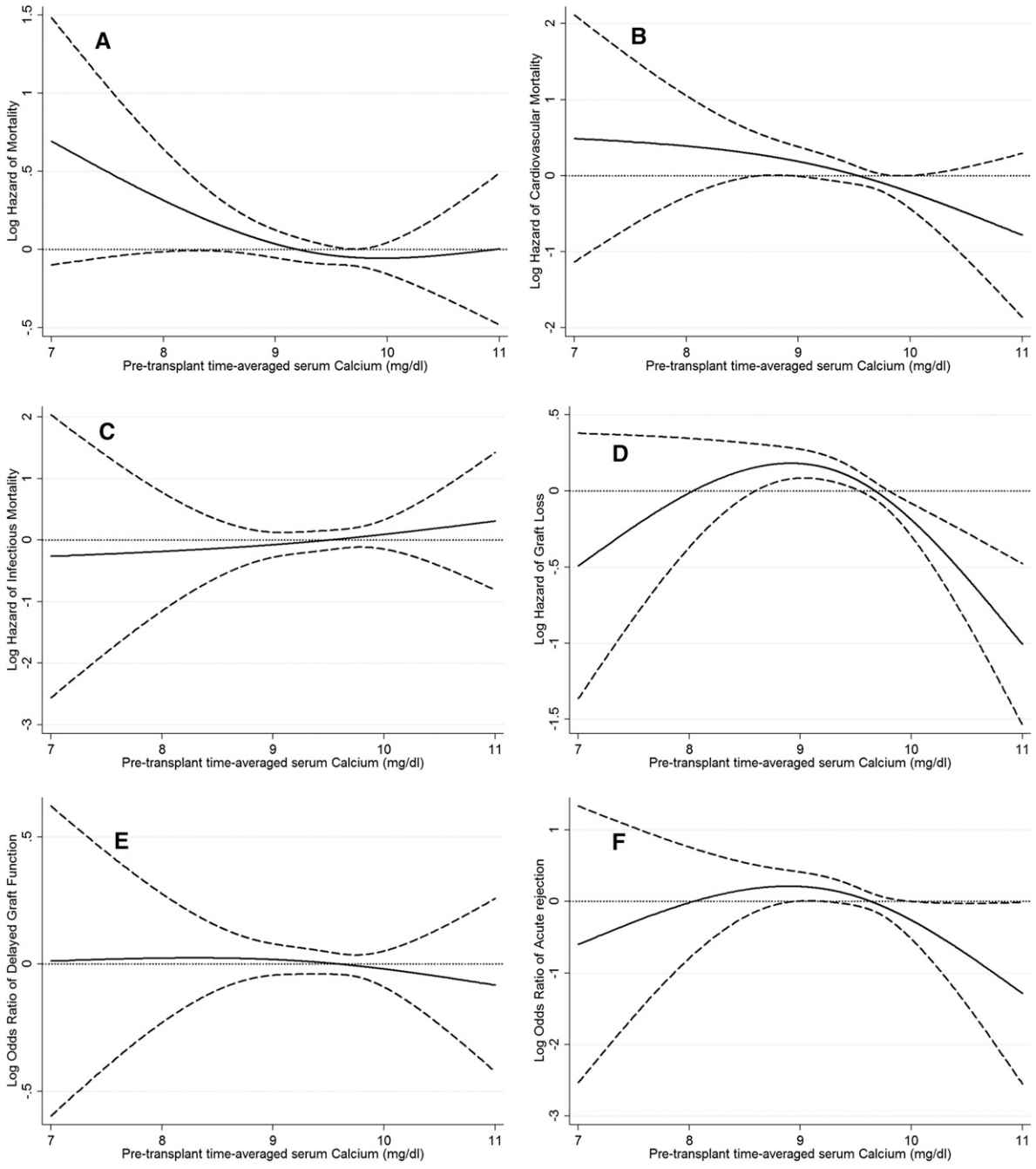

Figure 3. | Hazard/odds ratio (95% confidence intervals) of post-transplant outcomes across the entire range of pretransplant serum calcium level using Cox regression analyses in 11,839 long-term dialysis patients who underwent renal transplantation and who were observed over a 6-year study period (July 2001–June 2007). (A) All-cause mortality, (B) cardiovascular mortality, (C) infectious mortality, (D) graft loss, (E) delayed graft function, and (F) acute rejection. Model adjusted for age, sex, recipient race-ethnicity, diabetes mellitus, dialysis vintage, primary insurance, marital status, standardized mortality ratio of the dialysis clinic during entry quarter, dialysis dose as indicated by Kt/V (single pool), presence or absence of a hemodialysis catheter, and residual renal function during the entry quarter, eight comorbidities, body mass index, normalized protein nitrogen appearance , serum or blood concentrations of total iron-binding capacity, ferritin, bicarbonate, phosphorous, intact parathyroid hormone, peripheral white blood cell count, lymphocyte percentage, albumin, donor type, donor age, donor sex, panel reactive antibody titer (last value before transplant), number of HLA mismatches, cold ischemia time, delayed graft function , and extended donor criteria.

censored all-cause and cardiovascular death. The association between pretransplant serum alkaline phosphatase and survival was monotonic. Supporting this observation, the same association was detected in the cohort without liver disease. Similar associations were found in our previous studies in maintenance hemodialysis patients (4,8). This linear association is indicative of the relation between the increasing severity of high-turnover bone disease during the dialysis period and increased mortality risk in the post-transplant period (27–29).

Table 5. Hazard/odds ratio (95% confidence intervals) of post-transplant all-cause, cardiovascular, and infectious death or graft failure, delayed graft function, or acute rejection comparing pretransplant serum calcium categories (8.4–<9.5 mg/dl the reference) using Cox regression and logistic regression analyses in 11,839 dialysis patients who underwent renal transplantation and observed for up to 6 years (July 2001–June 2007)

Pretransplant Serum Calcium Level (mg/dl)	Unadjusted		Case-Mix Adjusted[a]		MMI Adjusted[b]		Transplant Data Adjusted[c]	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Graft failure censored all-cause death								
n	11,839		9255		7820		4852	
<8.4	1.27 (0.99–1.62)	0.05	1.21 (0.88–1.67)	0.23	1.12 (0.79–1.60)	0.52	1.00 (0.63–1.59)	0.99
8.4–<9.5	1.00	N/A	1.00	N/A	1.00	N/A	1.00	N/A
9.5–<10.2	0.77 (0.66–0.90)	0.001	0.76 (0.64–0.90)	0.002	0.80 (0.66–0.97)	0.02	0.81 (0.65–1.01)	0.06
≥10.2	0.94 (0.74–1.19)	0.61	0.86 (0.64–1.15)	0.31	0.95 (0.69–1.31)	0.75	1.00 (0.69–1.44)	0.97
Graft failure censored cardiovascular death								
<8.4	0.96 (0.58–1.58)	0.87	0.92 (0.48–1.78)	0.81	0.89 (0.44–1.82)	0.76	1.01 (0.42–2.44)	0.98
8.4–<9.5	1.00	N/A	1.00	N/A	1.00	N/A	1.00	N/A
9.5–<10.2	0.58 (0.43–0.79)	0.001	0.57 (0.40–0.82)	0.002	0.57 (0.40–0.86)	0.007	0.62 (0.40–0.98)	0.04
≥10.2	0.82 (0.51–1.30)	0.39	0.56 (0.30–1.06)	0.07	0.59 (0.30–1.16)	0.13	0.58 (0.25–1.32)	0.20
Graft failure censored infectious death								
<8.4	1.49 (0.49–2.50)	0.13	1.46 (0.72–2.95)	0.29	1.44 (0.67–3.11)	0.35	0.60 (0.14–2.60)	0.50
8.4–<9.5	1.00	N/A	1.00	N/A	1.00	N/A	1.00	N/A
9.5–<10.2	0.97 (0.70–1.34)	0.85	0.91 (0.62–1.33)	0.61	1.09 (0.71–1.65)	0.70	1.05 (0.63–1.76)	0.84
≥10.2	1.13 (0.68–1.88)	0.64	1.07 (0.57–2.01)	0.84	1.37 (0.70–2.67)	0.36	1.40 (0.61–3.22)	0.43
All-cause death censored graft failure								
<8.4	1.27 (1.04–1.55)	0.02	0.93 (0.63–1.26)	0.62	0.87 (0.62–1.22)	0.43	0.71 (0.44–1.17)	0.18
8.4–<9.5	1.00	N/A	1.00	N/A	1.00	N/A	1.00	N/A
9.5-<10.2	0.87 (0.77–0.98)	0.02	0.78 (0.67–0.91)	0.002	0.84 (0.71–0.99)	0.04	0.74 (0.60–0.92)	0.006
≥10.2	0.71 (0.57–0.89)	0.03	0.59 (0.44–0.78)	<0.001	0.65 (0.48–0.88)	0.005	0.60 (0.41–0.88)	0.008
Delayed graft function								
n	11,204		8810		7457		4852	
<8.4	1.14 (0.94–1.38)	0.20	1.24 (0.97–1.59)	0.08	1.20 (0.91–1.59)	0.19	1.15 (0.82–1.61)	0.43
8.4–<9.5	1.00	N/A	1.00	N/A	1.00	N/A	1.00	N/A
9.5–<10.2	1.13 (1.02–1.25)	0.02	1.01 (0.90–1.13)	0.90	1.02 (0.90–1.16)	0.71	1.00 (0.87–1.16)	0.97
≥10.2	0.95 (0.79–1.14)	0.57	0.84 (0.68–1.05)	0.12	0.85 (0.67–1.08)	0.18	0.89 (0.68–1.16)	0.37
Acute rejection								
n	6335		5210		4123		2793	
<8.4	1.27 (0.76–2.13)	0.37	1.29 (0.71–2.36)	0.40	1.39 (0.70–2.75)	0.35	1.53 (0.65–3.61)	0.33
8.4–<9.5	1.00	N/A	1.00	N/A	1.00	N/A	1.00	N/A
9.5–<10.2	1.15 (0.88–1.50)	0.31	1.06 (0.78–1.75)	0.69	0.96 (0.67–1.38)	0.83	0.73 (0.48–1.13)	0.16
≥10.2	0.88 (0.49–1.58)	0.68	0.57 (0.26–1.25)	0.16	0.53 (0.21–1.34)	0.18	0.43 (0.15–1.23)	0.12

MMI, markers of malnutrition or inflammation; HR, hazard ratio; 95% CI, 95% confidence interval; iPTH, intact parathyroid hormone.

[a]Adjusted for age, sex, recipient race/ethnicity, diabetes mellitus, dialysis vintage, primary insurance, marital status, standardized mortality ratio of the dialysis clinic during entry quarter, dialysis dose as indicated by Kt/V (single pool), presence or absence of a hemodialysis catheter, and residual renal function during the entry quarter and eight comorbidities.

[b]Adjusted for all of the covariates plus body mass index, normalized protein nitrogen appearance , serum or blood concentrations of total iron-binding capacity, ferritin, bicarbonate, phosphorous, iPTH, peripheral white blood cell count, lymphocyte percentage, and albumin.

[c]Adjusted for all of the above plus donor type, donor age, donor sex, panel reactive antibody titer (last value before transplant), number of HLA mismatches, cold ischemia time, delayed graft function (except when delayed graft function was a dependent variable in our logistic regression models), and extended donor criteria.

We did not find any association between pretransplant serum iPTH level and post-transplant outcome. In contrast, Roodnat *et al.* showed that serum pretransplant PTH levels were independently associated with the risk for graft failure censored for death in kidney transplant recipients (13). However, they did not find any association between serum iPTH level and post-transplant mortality (13). This cohort was different from our cohort in several variables: the prevalence of diabetic nephropathy was only 9.6% and the cohort was smaller (n=407).

Interestingly, pretransplant serum calcium levels >9.5 mg/dl were associated with decreased risk of graft loss. High serum calcium level during the dialysis period may be associated with usage of vitamin D and/or calcium containing phosphate binders. Vitamin D receptor is found in significant concentrations in the T lymphocyte and macrophage populations (30). The significant role of vitamin D compounds as selective immunosuppressant is illustrated by their ability to either prevent or markedly suppress animal models of autoimmune disease (30). The vitamin D hormone stimulates TGF-β1 and IL-4 production, which in turn may suppress inflammatory T cell activity (30). The decreased inflammatory T cell activity may be associated with lower risk of graft loss. Unfortunately, we do not have data about vitamin D utilization; therefore, we are not able to test this speculative hypothesis. Further studies are needed to confirm this result and develop additional hypotheses to explain this observation.

Our study should be qualified for several potential limitations. Like all observational studies, ours too cannot prove causality. Post-transplant laboratory measures, type of immunosuppressive regimen, and other relevant medications (such as vitamin D and phosphate binders) were not available in the SRTR database; however, in the full model, we did adjust for a number of transplant-related variables. We did not have access to data pertaining to death after graft loss, which is another important outcome. Patients who did not have measured serum iPTH, alkaline phosphatase, and calcium levels were excluded from the analyses. The excluded patients might have been different from those included in our study, which may have biased our results. It is important to note that missing data for covariates led to exclusion of over half of the cohort for the final multivariable models. Another potential limitation is that we did not have bone-specific alkaline phosphatase data. Moreover, we cannot exclude patients with liver disease from our analysis; however we found qualitative similar results when we reanalyzed our data with patients aspartate aminotransferase ≤40 U/L. In addition, we did not have data about 25(OH) vitamin D, 1,25(OH)2 vitamin D, fibroblast growth factor-23, and osteocalcin levels. Moreover, we do not have data about treatment of MBD in these patients.

Strengths of this study are multilevel adjustment, which includes several important pretransplant measures, the high number of patients, and the relatively long follow-up time.

Individuals with pretransplant serum alkaline phosphatase >120 U/L have increased risk of graft failure censored all-cause and cardiovascular mortality. There was no significant association between time-averaged serum alkaline phosphatase categories and risk of death censored graft failure, DGF, or acute rejection. There was no clinically meaningful association between pretransplant serum iPTH and calcium level and post-transplant outcomes. Further clinical trials are needed to better define optimal target levels of MBD markers in waitlisted dialysis patients.

Acknowledgments

We thank DaVita Clinical Research for providing the clinical data and review for this research project.

This study was supported by a research grant from the American Heart Association (0655776Y to K.K.Z). K.K.Z. has also received funding from the National Institute of Diabetes, Digestive and Kidney Diseases of the National Institutes of Health (R01 DK078106), a research grant from DaVita Clinical Research, and a philanthropic grant from Mr. Harold Simmons. M.Z.M. received grants from the National Developmental Agency (KTIA-OTKA-EU 7KP-HUMAN-MB08-A-81231) from the Research and Technological Innovation Fund, and is a recipient of the Hungarian Eötvös Scholarship (MÖB/77-2/2012).

Disclosures

K.K.Z. is the medical director of DaVita Harbor-UCLA/MFI in Long Beach, California, and received a research grant from Shire Inc. I.B.S. is the medical director of Pediatric Dialysis at DaVita Century City, Los Angeles, California.

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Received: February 24, 2012 **Accepted:** June 29, 2012

Published online ahead of print. Publication date available at www.cjasn.org.

This article contains supplemental material online at http://cjasn.asnjournals.org/lookup/suppl/doi:10.2215/CJN.01910212/-/DCSupplemental.