Published in final edited form as:

Pharmacoepidemiol Drug Saf. 2012 November ; 21(11): 1232–1239. doi:10.1002/pds.3349.

Administered Paricalcitol Dose and Survival in Hemodialysis Patients: A Marginal Structural Model Analysis

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Abstract

Purpose—Several observational studies have indicated that vitamin D receptor activators (VDRA), including *paricalcitol*, are associated with greater survival in maintenance hemodialysis (MHD) patients. However, patients with higher serum parathyroid hormone (PTH), a surrogate of higher death risk, are usually given higher VDRA doses, which can lead to confounding by indication and attenuate the expected survival advantage of high VDRA doses.

Methods—We examined mortality-predictability of low (>1 but <10 µg/week) versus high (≥10 µg/week) dose of administered *paricalcitol* over time in a contemporary cohort of 15,442 MHD patients (age 64±15 years, 55% men, 44% diabetes, 35% African Americans) from all DaVita dialysis clinics across the USA (7/2001-6/2006 with survival follow-ups until 6/2007) using conventional Cox regression, propensity score (PS) matching, and marginal structural model (MSM) analyses.

Results—In our conventional Cox models and PS matching models, low dose of *paricalcitol* was not associated with mortality either in baseline (hazard ratio (HR): 1.03, 95% confidence interval (CI): (0.97-1.09)) and (HR: 0.99, 95%CI: (0.86-1.14)) or time-dependent (HR: 1.04, 95%CI: (0.98-1.10)) and (HR: 1.12, 95%CI: (0.98-1.28)) models, respectively. In contrast, compared to high dose of *paricalcitol*, low dose was associated with a 26% higher risk of mortality (HR: 1.26,

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Relevant Potential Conflict of Interest:

Dr. Kalantar-Zadeh is the medical director of DaVita Harbor-UCLA/MFI in Long Beach, CA. KKZ have received honoraria and research grants from Abbott, the manufacturer of paricalcitol (Zemplar™). CPK has received research grants from Abbott and Genzyme. Other authors have not declared any conflict of interest.

95%CI: (1.19-1.35)) in MSM. The association between dose of *paricalcitol* and mortality was robust in almost all subgroups of patients using MSMs.

Conclusions—Higher dose of *paricalcitol* appears causally associated with greater survival in MHD patients. Randomized controlled trials need to verify the survival effect of *paricalcitol* dose in maintenance hemodialysis patients are indicated.

Keywords

Mortality; propensity score; marginal structural model; mineral and bone disorders; chronic kidney disease; *paricalcitol*

Introduction

Minerals and bone disorders (MBD) are common in individuals with chronic kidney disease (CKD)¹⁻⁵ and may be related to mortality risk in this population.⁶⁻⁸ The CKD-MBD encompasses a wide range of pathologic conditions, several of which appear amenable to therapeutic interventions and, hence, have become a cornerstone of the day-to-day management of patients with CKD. One of these is secondary hyperparathyroidism (SHPT), which is assumed to be, at least in part, the result of the progressive decline in activated vitamin D levels leading to inadequate or ineffective vitamin D receptor (VDR) modulation with progression of CKD.^{3, 11} Pharmacologic replacement therapy using VDR activators (VDRA) has thus become a main strategy in the treatment of SHPT.¹² The enthusiasm for VDRA therapy has heightened by several observational studies showing its association with greater survival in CKD patients.¹³⁻¹⁷ Although meta-analyses have yielded mixed results,¹⁸ the survival advantages of VDRA have been observed in both earlier stages of CKD¹⁹ and in maintenance dialysis patients.^{6, 20-23}

Most observational studies have reported a survival advantage for any dose of VDRA versus no VDRA therapy.¹⁹⁻²¹ Given no randomized controlled trial (RCT) to examine the association of VDRA dose with survival observational data remain the main source for clinical inferences on dose-survival phenomenon. However, parathyroid hormone (PTH) level which is usually higher among African Americans or younger patients, is usually an important driving force for VDRA dose titration,^{23, 27} The latter PTH-dose association across population may overshadow the dose-survival association leading to a so-called “confounding by indication”, which may result in seemingly opposite directions of the natural associations. For instance, the association between the incremental dose categories of *paricalcitol*, a selective VDRA, and survival in dialysis patients exhibited a paradoxically mitigated survival for the highest administered *paricalcitol* dose category.⁶ This apparently counterintuitive observation, which defies the dose-response phenomenon,^{16, 28} is likely because in more severe SHPT, which is associated with worse mortality,¹⁵ higher doses of VDRA are prescribed.²² More novel statistical techniques such as propensity scores (PS)²⁹ or marginal structural models (MSM)²⁰ may be useful to mitigate the said confounding by indication. Even though the association of dialysis patient survival with any VDRA therapy or dose versus no therapy has previously been examined using some of these techniques,^{20, 30} to the best of our knowledge no study has examined the survival of high vs. low dose *paricalcitol* using such novel techniques. We, hence, hypothesized that higher dose

of prescribed *paricalcitol* is associated with greater survival in maintenance hemodialysis (MHD) patients in a large and nationally represented dialysis patient cohort in a contemporary but pre-calcimimetic era (7/2001-6/2006 with survival follow-ups until 6/2007) where injectable *paricalcitol* was the main VDRA prescribed. In order to differentiate the effect of confounding by indication, we used three statistical techniques to examine the proposed hypothesis.

Methods

Patients

A total of 164,789 individuals, from July 1, 2001 through June 30, 2006, with end stage renal disease (ESRD) received dialysis treatment in units in any one of the 580 outpatient dialysis facilities of DaVita, a large dialysis services provider in the US (prior to its acquisition of units owned by Gambro dialysis facilities). After merging the data with demographic, laboratory and *paricalcitol* data, we identified 139,068 patients undergoing MHD at the time of entry into the cohort and whose survival was followed until June 30, 2007. Inclusion criteria were patients who had been undergoing dialysis for at least 90 days, were being treated with MHD at the time of entry into the cohort, age 18-99 years, with complete (non-missing) exposure and core covariate data (ie, *paricalcitol*, phosphorous, PTH, corrected calcium) for patient study periods (n=15,503) (Figure S1 in electronic Appendix). In order to be highly conservative and focused on *paricalcitol* dose question and in order to avoid any level of imputation, we excluded 122,860 who received any other VDRA at any time or who had even a single missing value of serum calcium, phosphorous, or PTH level or missing or no *paricalcitol* dose during any calendar quarter of the 5-year cohort. The study was approved by the Institutional Review Committees of both the Los Angeles Biomedical Research Institute as Harbor-UCLA Medical Center and DaVita Clinical Research.

Clinical and Demographic Measures

The creation of the cohort has been described previously.^{15, 23, 31-33} To minimize measurement variability, all repeated measures for each patient during any given calendar quarter, i.e., over a 13-week interval, were averaged values used in all models. Average values were obtained from up to 20 calendar quarters (q1 through q20) for each laboratory and clinical measure for each patient over the 6-year cohort period. The first (baseline) studied quarter for each patient was that calendar quarter, in which patient's vintage reached >90 days. The presence or absence of diabetes at baseline was obtained from DaVita data.

Laboratory Measures and *Paricalcitol* dose

Blood samples were drawn using uniform techniques in all dialysis clinics and were transported to the DaVita Laboratory in Deland, Florida, within 24 hrs. All laboratory values were measured by automated and standardized methods. Most laboratory values were measured monthly. We divided patients into two *a priori* categories based upon *paricalcitol* dose: low dose >1 µg/week but <10 µg/week vs high dose 10 µg/week (reference). We used the following equation to calculate the corrected calcium level "corrected calcium = (0.8 * (normal albumin (4 g/dL) – patients' albumin)) + serum calcium".

Epidemiologic and Statistical Techniques

Three different survival analyses (conventional Cox proportional hazard regression, PS matched model and MSM) were used to examine whether dose of *paricalcitol* (low > 1 µg/week but <10 µg/week vs high 10 µg/week (reference)) predicted survival for up to six years of follow-up. Mortality was defined by “date of death” if it occurred during the time the patient was enrolled in the study (7/2001-6/2007). Patients lost to follow-up or transplanted were coded as censored. The primary analysis examined the associations between doses of *paricalcitol* with all-cause mortality. We also performed exploratory analyses in sub-groups of patients based on age, gender, race, diabetes, serum albumin, phosphorous, corrected calcium, PTH and alkaline phosphatase categories. The same study population was used for the analysis with the conventional time-averaged models; the PS matched time-averaged model, and the MSM.

Conventional Cox proportional hazard regression—Adjusted conventional Cox proportional hazard regression models were used to assess the association between time-averaged dose of *paricalcitol* and survival. In our adjusted conventional model we adjusted for: entry calendar quarter (q1 through q20), age, gender, race/ethnicity (African Americans and other self-categorized Blacks, Non-Hispanic Caucasians, Asians, Hispanics and others), categories of dialysis vintage (<6 months, 6 months to 2 years, 2-5 years and 5 years), serum levels of PTH, phosphorus, calcium, and presence of diabetes. The conventional model for time-averaged *paricalcitol* used time-averaged variables and adjusted for all variables used in the construction of the inverse probability of treatment weights (IPTW) for *paricalcitol*.

Propensity score matched time-averaged model—The PS matched model for time-averaged *paricalcitol* used time-averaged variables and calculated PS for receiving an average treatment of *paricalcitol* < 10 µg/week from the variables used in the construction for the IPTW for *paricalcitol*. Patients with low and high *paricalcitol* dose were matched based on $PS \pm 0.05$.

Marginal Structural Modeling—Stabilized IPTW for *paricalcitol* doses < 10 µg/week were calculated from previous *paricalcitol* treatment doses, baseline non-time varying covariate values, and time varying covariate values. Baseline non-time varying covariates included diabetes status, gender, age, race/ethnicity, and vintage. Time varying covariates included the study quarter and laboratory values for phosphorous, PTH, and corrected calcium. To account for potential selection bias, inverse probability of censoring weights (IPCW) were calculated and combined with the IPTWs. People with outliers for the final stabilized weights (IPTW-IPCW combined) greater than 10 (n=61) were excluded from the study population. These were patients with less predictable *paricalcitol* doses based on their PTH values, i.e. high PTH values but lower than expected *paricalcitol* values, which resulted in an excessive contribution of weight and an inflated mean stabilized weight. The final study population consisted of 15,442 individuals (Figure S1).

For all analyses, two-sided p-values are reported and results considered statistically significant if $p < 0.05$. All statistical analyses were carried out with SAS software, version

9.2 (SAS Institute, Inc., Cary, North Carolina). For analysis with MSM, PROC GENMOD was used to calculate odds ratios for the odds of dying given low dose *paricalcitol*, compared to high dose *paricalcitol*. For analyses with conventional models and PS models PROC PHREG was used to calculate hazard ratios for the risk of dying given low dose *paricalcitol*, compared to high dose *paricalcitol*.

Results

The median follow-up time of the final study cohort was 395 days (range 1-2187 days).

Table 1 shows baseline demographic, clinical, and laboratory characteristics of the studied MHD patients according to low (>1 but <10 µg/week) vs. high (≥10 µg/week) dose of *paricalcitol*. High dose (≥10 µg/wk) of *paricalcitol* was associated with younger age, lower percentage of White but higher percentage of Black patients, longer dialysis vintage, and higher serum creatinine and PTH levels.

Figure 1 shows hazard ratio (95% confidence intervals) of death comparing low (>1 µg/week but <10 µg/week) vs high (≥10 µg/week- as reference) dose of *paricalcitol* using different models in the same dataset. In the conventional Cox model, low dose *paricalcitol* showed no difference compared to high dose either in baseline (HR: 1.03, 95%CI: (0.97-1.09)) or time-dependent (HR: 1.04, 95%CI: (0.98-1.10)), although in the time-averaged model (HR: 1.07, 95%CI: (1.01-1.14)) the association was more distinct (Table S1). Similar results were found in PS-matched models, in that low dose *paricalcitol* was not statistically associated with mortality in baseline (HR: 0.99, 95%CI: (0.86-1.14)), time-dependent (HR: 1.12, 95%CI: (0.98-1.28)), or time-averaged models (HR: 1.10, 95%CI: (0.95-1.27)) (Table S1). In contrast, compared to high dose of *paricalcitol*, low dose was associated with a 26% higher risk of mortality (HR: 1.26, 95%CI: (1.19-1.35)) in our MSM (Table S1). Similar results were found in the subgroup analysis (Table 2). In contrast to the conventional Cox and PS matching models, where occasional trends via higher risk was observed, almost all subgroups in the MSM models showed a higher risk of death in patients with low dose *paricalcitol* compared to those with higher dose of *paricalcitol* (Figure 2).

Discussion

In 15,442 maintenance hemodialysis patients with comprehensive data and without any missing values, who were followed for up to 6 years on dialysis and who received any dose of *paricalcitol* during each calendar quarter, lower dose of *paricalcitol* was associated with increased all-cause mortality using a causal model known as MSM to adjust for confounding by indication over time. The association between lower dose of *paricalcitol* and higher mortality was observed in almost all demographic and clinical subgroups. If our findings are verified in additional studies, administration of higher doses of this selective VDRA may become an important consideration in improving care to maintenance dialysis patients.

A recent study had found that higher *paricalcitol* dose per unit of PTH, i.e., dose divided by PTH (the so-called Shinaberger Index) was associated with greater survival in MHD patients.¹⁴ However, the question pertaining to the absolute dose per patient, which is highly relevant to clinical practice, had remained unresolved until now. In our current study, the

association of lower dose of *paricalcitol* and higher mortality was not observed when using conventional Cox models or PS matching models, but a 26% higher risk of mortality in patients with low dose of *paricalcitol* compared to high dose was observed using a causal model. Pharmaco-epidemiologic studies of dose-response phenomenon using classical survival analyses may have major limitations, in particular due to confounding by indication. In our study, patients with more severe hyperparathyroidism, which is associated with higher serum PTH levels and usually worse survival, may be given higher doses of VDRA.²² Confounding by indication is a major source of bias in observational studies,³⁴ in that the degree of hyperparathyroidism may determine the dose of *paricalcitol*. Indeed as noted in Table 1, patients who received higher dose of *paricalcitol* were younger and more likely to be African American, both determinants of higher PTH level.²³ Statistical techniques such as MSM may be useful to mitigate this confounding. MSMs can be used to estimate causal effects of a time-varying exposure in the presence of time-varying covariates that may be simultaneously confounders and intermediate variables, and hence referred to as causal models.^{20, 35, 36} To our knowledge neither RCTs nor observational studies utilizing marginal structural modeling have been published to examine the survival of the dose of *paricalcitol*; therefore our study may serve as the first focused assessment of the association of dose of *paricalcitol* dose and mortality in MHD patients.

Replacement of active vitamin D has been the cornerstone of therapy for SHPT in the CKD patient population.¹⁶ SHPT develops early in the course of CKD as a result of a combination of events including deficiency of 1,25-dihydroxycholecalciferol (calcitriol), decreased expression of the vitamin D receptor and the calcium-sensing receptor, hyperphosphatemia, hypocalcemia and PTH resistance.^{9, 16} As kidney function declines in patients with CKD, their PTH levels become increasingly higher, mirrored by a progressive decline in activated vitamin D levels.³ Administration of synthetic activated vitamin D to activate VDR and to replace physiologic levels of this hormone thus appears to be a plausible strategy to treat SHPT. Nonetheless, the application of VDRA in physiologic doses often fails to correct SHPT, in part due to decreased expression of the VDR in the parathyroid gland.¹⁶ This may be overcome by the administration of higher doses of VDRA; however, such pharmacologic doses are more likely to induce undesirable side effects such as hypercalcemia and hyperphosphatemia,³⁷ which have themselves been associated with higher mortality in patients on dialysis.^{6, 7} In order to circumvent such side effects, new agents have been developed that show a more selective effect toward suppressing PTH production, with a lesser effect on intestinal and bone absorption of calcium and phosphorus.³⁸ These novel agents (*paricalcitol* and maxacalcitol) appear to have less effects on the VDR in the GI tract and bone, thus mitigating the calcium and phosphorus absorption and allowing for a wider therapeutic margin.¹⁶ Recently, Kovesdy et al. showed that *paricalcitol* is more effective than ergocalciferol at decreasing PTH levels in patients with CKD stages 3 or 4 with vitamin D deficiency and SHPT.³⁹ Moreover, *paricalcitol* prevents vascular calcification in experimental models of renal failure, compared with calcitriol.⁴⁰⁻⁴²

Several potential mechanisms can explain the association between higher dose of *paricalcitol* and decreased risk of mortality. Higher dose of *paricalcitol* might have a positive effect on left ventricular hypertrophy (LVH). PRIMO I-II (Paricalcitol Capsules

Benefits in Renal Failure Induce Cardiac Morbidity in Chronic Kidney Disease Stage) are ongoing trials, which evaluate the effects of *paricalcitol* injection on cardiac structure and function over 48 weeks in subjects with Stage 3 / 4 (PRIMO I) and 5 (PRIMO II) CKD receiving hemodialysis who have LVH.^{24, 43, 44} Higher dose of *paricalcitol* might have a positive effect on vascular calcification. In prospective, RCTs in hemodialysis patients with moderate to severe secondary hyperparathyroidism, cinacalcet plus low-dose vitamin D sterols may attenuate vascular and cardiac valve calcification.⁴⁵ Additionally administration of *paricalcitol* is associated with lower inflammation level,⁴⁶ which is an important predictor of mortality in ESRD patients.⁴⁷⁻⁵⁰ Finally, *paricalcitol* might contribute to lower residual albuminuria in patients with residual renal function.^{46, 51}

Our study should be qualified for its observational nature and lack of data on home medication including oral, multivitamins, phosphorus binders, and calcimimetics. However, most MHD patients who receive injectable VDRA do not take oral vitamin D medications in the US, and this cohort preceded the widespread use of the calcimimetics in the US. Another limitation is the PTH assay reliability and fluctuation, especially since intact PTH may yield inaccurate values.⁵² The strengths of our study include: (1) novel statistical techniques including MSMs; (2) contemporary nature, since all patient data were obtained from the 21st century (2001-2006); (3) uniform laboratory measurements, with all laboratory data obtained from one facility, (4) large sample size; (5) 3-month averaged laboratory data to minimize measurement variability; and (6) knowledge of the administered dose of VDRA and focus on patients who received a single type of VDRA.

Conclusions

In our large and contemporary cohort of 15,442 MHD patients, higher dose of *paricalcitol* appeared causally associated with greater survival. The association between dose of *paricalcitol* and mortality was robust across different subgroups of patients using MSMs. Randomized controlled clinical trials are needed to verify the association between dose of *paricalcitol* and mortality in MHD patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank DaVita Clinical Research (DCR) for providing patient data.

Funding Source:

The study was supported by an investigator initiated research grant from Abbott. KKZ's other funding sources include the National Institute of Diabetes, Digestive and Kidney Disease of the National Institute of Health (R01 DK078106), a research grant from DaVita Clinical Research, and a philanthropic grant from Mr. Harold Simmons. MZM received grants from the National Developmental Agency (KTIA-OTKA-EU 7KP-HUMAN-MB08-A-81231) from the Research and Technological Innovation Fund, and is recipient of the Hungarian Eötvös Scholarship.

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Figure 1.

Hazard ratio (95% confidence intervals) of death comparing low ($>1 \mu\text{g/week}$ but $<10 \mu\text{g/week}$) vs high ($\geq 10 \mu\text{g/week}$ - as reference) dose of *paricalcitol* using different models (Conventional Cox, PS Matching and MSM) in the same dataset

A
Conventional Time-Averaged Models

B
Marginal Structural Models

Figure 2.

Hazard ratio (95% confidence intervals) of death comparing low (>1 µg/week but <10 µg/week) vs high (>10 µg/week- as reference) dose of *paricalcitol* using Conventional Time-Averaged Cox (**A**) and MSM (**B**) models in different subgroups

Table 1

Baseline characteristics of 15,442 maintenance HD patients

	Total population	Average <i>paricalcitol</i> dose <10µg/wk	Average <i>paricalcitol</i> dose 10 µg/wk	p-value
	(n=15,442)	(n=5,885)	(n=9,557)	
Age (years)	64 ± 15	67 ± 15	62 ± 15	<.001
Gender (% female)	45	44	45	0.33
Diabetes mellitus (%)	44	46	43	<.001
Ethnicity (%):				
White	40	48	35	<.001
Black	35	23	42	<.001
Hispanic	14	16	12	<.001
Asian	2	3	2	<.001
Other	7	7	6	0.15
Dialysis Vintage (%):				
<6 months	16	19	14	<.001
6-24 months	37	42	34	<.001
2-5 years	28	27	29	0.02
>5 years	19	12	23	<.001
Primary insurance (%):				
Medicare	65	65	65	0.64
Medicaid	4	3	4	0.04
Private Insurance	12	12	12	0.86
Other	5	5	5	0.07
Missing	14	15	14	
Marital Status (%):				
Married	37	40	36	<.001
Divorced	7	6	8	<.01
Single (never married)	21	17	23	<.001
Widowed	15	16	14	<.001
Missing	20	21	19	
BMI (kg/m ²)	26.2 ± 6.9	25.4 ± 6.5	26.7 ± 7	<.001
Kt/V (dialysis dose)	1.52 ± 0.35	1.55 ± 0.37	1.50 ± 0.34	<.001
Protein Catabolic Rate (g/kg/day)	0.95 ± 0.25	0.93 ± 0.25	0.95 ± 0.25	<.001
Biochemical measures:				
Albumin (g/dL)	3.65 ± 0.46	3.6 ± 0.48	3.68 ± 0.44	<.001
Creatinine (mg/dL)	8.1 ± 3.2	7.2 ± 2.8	8.7 ± 3.2	<.001
TIBC (mg/dL)	202 ± 46	203 ± 48	201 ± 46	<.01
Phosphorus (mg/dL)	5.6 ± 1.4	5.2 ± 1.3	5.8 ± 1.4	<.001
Calcium (mg/dL)	9.5 ± 0.7	9.4 ± 0.6	9.5 ± 0.7	<.001

	Total population	Average <i>paricalcitol</i> dose <10µg/wk	Average <i>paricalcitol</i> dose 10 µg/wk	p-value
	(n=15,442)	(n=5,885)	(n=9,557)	
PTH (ng/mL)	397 ± 349	245 ± 160	491 ± 397	<.001
Alkaline phosphatase (U/L)	124 ± 96	118 ± 92	128 ± 98	<.001
Ferritin (ng/mL)	578 ± 536	559 ± 491	589 ± 561	<.01
Hemoglobin (g/dL)	11.9 ± 1.4	12.0 ± 1.4	11.8 ± 1.4	<.001
WBC (×10 ³ /ul)	7.4 ± 2.6	7.7 ± 2.6	7.3 ± 2.6	<.001
Lymphocyte (% of total WBC)	20 ± 8	19 ± 8	20 ± 8	<.001
<i>Paricalcitol</i> (µg/week)	14.4 ± 9.9	7.0 ± 2.9	18.9 ± 10	<.001

Data are presented in mean±standard deviation (SD).

Abbreviation: BMI: Body Mass Index, TIBC: total Iron Binding Capacity, WBC: White Blood Cell, PTH: parathyroid hormone

Table 2

Hazard ratio (95% confidence intervals) of death comparing low (>1 µg/week but <10 µg/week) vs high (≥ 10 µg/week- as reference) dose of *paricalcitol* using different models in different subgroups

<i>Subgroups</i>	Hazard ratio (95% confidence intervals)		
	Conventional Cox	PS matching	MSM
Female patients	1.08 (0.99-1.18)	1.22 (0.86-1.71)	1.11 (0.99-1.24)
Male patients	1.07 (0.98-1.16)	1.28 (0.97-1.70)	1.40 (1.27-1.54)
Age < 50 years	1.01 (0.81-1.24)	-	1.30 (0.94-1.78)
Age 50-< 65 years	0.99 (0.88-1.12)	0.96 (0.52-1.78)	1.04 (0.90-1.20)
Age ≥ 65 years	1.11 (1.03-1.20)	1.01 (0.80-1.27)	1.17 (1.07-1.28)
White patients	1.04 (0.95-1.14)	1.02 (0.70-1.49)	1.11 (1.01-1.22)
Black patients	1.07 (0.95-1.19)	0.78 (0.47-1.28)	1.37 (1.19-1.58)
Hispanic patients	1.11 (0.95-1.31)	1.79 (0.10-33.03)	1.25 (0.97-1.61)
Presence of diabetes	1.11 (1.01-1.21)	1.49 (1.04-2.12)	1.27 (1.14-1.41)
Absence of diabetes	1.06 (0.97-1.15)	0.87 (0.66-1.15)	1.25 (1.13-1.37)
Albumin < 3.8 g/L	1.11 (1.03-1.19)	1.13 (0.92-1.39)	1.20 (1.10-1.32)
Albumin ≥ 3.8 g/L	1.01 (0.90-1.13)	0.55 (0.29-1.07)	1.20 (1.06-1.35)
PTH < 200	0.97 (0.87-1.09)	1.13 (0.75-1.71)	1.17 (1.04-1.33)
PTH 200-<300	1.08 (0.98-1.20)	0.94 (0.63-1.42)	1.21 (1.06-1.39)
PTH ≥ 300	1.14 (1.01-1.28)	1.61 (1.06-2.46)	1.31 (1.14-1.50)
AlkPhos < 120 U/L	1.02 (0.94-1.10)	1.10 (0.86-1.39)	1.20 (1.10-1.31)
AlkPhos ≥ 120 U/L	1.21 (1.10-1.33)	1.38 (0.88-2.17)	1.45 (1.28-1.64)
Corr Ca < 8.5 mg/dL	0.99 (0.68-1.44)	-	1.00 (0.73-1.35)
Corr Ca 8.5-<10mg/dL	1.05 (0.98-1.13)	1.01 (0.83-1.23)	1.25 (1.16-1.35)
Corr Ca ≥ 10 mg/dL	1.22 (1.07-1.39)	0.36 (0.08-1.64)	1.43 (1.17-1.74)
Phosphate < 5.5 mg/dL	1.02 (0.94-1.11)	1.04 (0.79-1.34)	1.13 (1.03-1.24)
Phosphate ≥ 5.5 mg/dL	1.10 (1.01-1.20)	1.19 (0.87-1.64)	1.34 (1.19-1.50)

Abbreviation: PS: Propensity Score, MSM: Marginal Structural Model, AlkPhos: Alkaline Phosphatase, Corr Ca: Corrected Calcium, PTH: parathyroid hormone