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Changes in Markers of Mineral and Bone Disorders and Mortality in Incident Hemodialysis Patients

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Abstract

Background—Abnormalities in mineral and bone disorder (MBD) markersare common in patients with chronic kidney disease. However, previous studies have not accounted for their changes over time and it is unclear whether these changes are associated with survival.

Methods—We examined the association of change in MBD markers [serum phosphorus (Phos), albumin-corrected calcium (Ca_{Alb}), parathyroid hormone (iPTH) and alkaline phosphatase (ALP)] during the first six months of hemodialysis (HD) with all-cause mortality across baseline MBD strata using survival models adjusted for clinical characteristics and laboratory measurements in 102,754 incident HD patients treated in a large dialysis organization between 2007 and 2011.

Results—Across all MBD markers (Phos, Ca_{Alb}, iPTH, and ALP), among patients whose baseline MBD levels were higher than the reference range, increases in MBD levels were associated with higher mortality (reference group: MBD level within reference range at baseline and six months follow-up). Conversely, decreases in Phos and iPTH, among baseline Phos and iPTH levels lower than the reference range, respectively, were associated with higher mortality. An increase in baseline ALP trended towards higher mortality across all baseline ALP levels, and baseline ALP <80 U/L was associated with a lower risk of mortality irrespective of the direction of change.

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Conclusions—There is a differential association between changes in MBD markers with mortality across varying baseline levels in HD patients. Further study is needed to determine if consideration of both baseline and longitudinal changes in the management of MBD derangements improves outcomes in this population.

Keywords

Epidemiology; disorders of calcium/phosphate metabolism; parathyroid hormone; alkaline phosphatase; nutrition; statistical methods

Introduction

High serum concentrations of phosphorus (Phos), calcium, parathyroid hormone (iPTH), and alkaline phosphatase (ALP) are frequently found in patients with advanced chronic kidney disease (CKD) and are associated with increased cardiovascular disease and mortality, especially in those with end-stage renal disease (ESRD).[1–9] In addition, changes in these minerals may result in chronic kidney disease–mineral and bone disease (CKD-MBD), resulting in structural and functional abnormalities in the bone and cardiovascular system, as well as higher morbidity and mortality in ESRD patients.[10]

Although clinical practice guidelines recommend that the therapeutic management of CKD-MBD should be based on trends of these MBD markers instead of a singular laboratory result,[11–13] few studies have evaluated the association between changes in MBD markers over time with outcomes, or how baseline levels modify these relationships.[9,14] Furthermore, previous studies have examined study populations with heterogeneous dialysis vintage. Mortality is highest during the early period after hemodialysis initiation,[14,15] and thus the association of these changes with all-cause mortality may differ in long-term hemodialysis patients. Therefore, we sought to examine the association between changes in serum concentrations of corrected calcium (Ca_{Alb}), Phos, iPTH, and ALP in the first six months after dialysis initiation with all-cause mortality across varying baseline concentrations of these MBD markers in a large contemporary cohort of incident hemodialysis patients.

Methods

Study Population and Data Source

We examined data from patients who initiated treatment within a large dialysis organization (LDO) in the US between 2007–2011, with follow-up concluding on December 31, 2011.[16] This study was approved by the Institutional Review Committees of Los Angeles Biomedical Research Institute at Harbor-UCLA, University of California, Irvine and DaVita Clinical Research. The need for written consent was waived due to the study's large sample size, patient anonymity and nonintrusive nature.

Patients treated for at least 60 consecutive days were considered to be on maintenance hemodialysis. Patient follow-up was divided into consecutive calendar quarters, representing 91-day intervals from the start of dialysis treatment. The baseline quarter (Q1) for each patient was defined as the first 91-day interval in which the patient was treated with HD.

Patients were censored at the time renal transplantation, transfer to a different LDO facility, or at the end of the study period. Patients were excluded from this study if they were treated with modalities other than in-center hemodialysis, were treated for less than 91 days (only had 1 quarter of follow-up) or had missing data for Phos, Ca_{Alb}, iPTH and ALP measurements at baseline and the following quarter.

Demographic and clinical measures

The final study population was composed of 102,754 incident HD patients (Figure 1). Data obtained on baseline demographics, including self-categorized race/ethnicity and primary insurance and mortality were acquired from the LDO's electronic records database. Intravenous medications were also obtained from the LDO's records and calculated as median dose per week.

The following 11 preexisting comorbidities were obtained from ICD-9 codes from the LDO's electronic records database: (1) diabetes mellitus, (2) hypertension, (3) congestive heart failure, (4) atherosclerotic heart disease, (5) cerebrovascular disease, (6) other cardiovascular disease, (7) chronic obstructive pulmonary disease, (8) history of cancer, (9) HIV, (10) alcohol abuse, and (11) substance abuse.

Laboratory Measures

Blood samples were drawn using standard techniques in all dialysis clinics and were transported to the LDO's central laboratory in Deland, Florida within 24 hours. All laboratory values, including serum measurements of Phos, Ca_{Alb}, iPTH and ALP, were measured on a monthly basis and by automated and standardized methods. All repeated laboratory measurements were averaged during each 91-day interval to minimize the effects of short-term variability. When serum albumin concentration was <4.0 g/dL, we calculated albumin corrected calcium (Ca_{Alb}) as follows: Ca_{Alb} = serum calcium (mg/dL) + 0.8 × [4.0 – serum albumin (g/dL)].[17] Delivered dialysis dose was estimated by single-pooled Kt/V using the urea kinetic model.

We chose the first 6-month interval of HD treatment to assess changes in the baseline and follow-up levels of CKD-MBD markers because serum Phos and iPTH concentrations tended to be high prior to the initiation of maintenance dialysis treatment and then gradually decreased and stabilized usually within the first 6 months of treatment. Changes in MBD markers were calculated by subtracting the mean concentrations during the first quarter (Q1) from the mean concentrations during the second quarter (Q2).

We divided each baseline concentration of Phos, Ca_{Alb}, iPTH, and ALP into four groups (Phos: <3.5, 3.5 −<5.5, 5.5 −<7.5 and ≥7.5 mg/dL; Ca_{Alb} : <8.4, 8.4 −<9.5, 9.5 −<10.2 and ≥10.2 mg/dL; iPTH: <150, 150 −<300, 300 −<600 and ≥600 pg/mL; ALP: <80, 80 −<120, 120 −<160 and ≥160 U/L, respectively) based on prior studies.[9,18] Within each baseline category of each CKD marker, we examined the change in marker level from Q1 to Q2 across three groups: unchanged, increased and decreased, based on the following intervals per marker: Phos: ±0.5 mg/dL, Ca_{Alb}: ±0.2 mg/dL, iPTH: ±50 pg/mL, and ALP: ± 10U/L. For example, the change in Phos categories were "unchanged" (±0.5 mg/dL), "increased" (≥0.5 mg/dL), and "decreased" (≥-0.5 mg/dL). These intervals were determined by the

distribution of the change between quarters in the cohort. We categorized patients into a total of 12 groups according to baseline level and directionality of change (4-by-3) and examined their associations with all-cause mortality.

Statistical Methods

Data were summarized using proportions, means (±SD), medians (interquartile range, IQR), where appropriate. Test for trend analyses were used to quantify the relationship among baseline CKD-MBD marker groups.

Cox proportional hazards models were used to determine the relationship between change in blood concentrations of CKD-MBD related parameters (Phos, Ca_{Alb}, iPTH, and ALP) and all-cause mortality across baseline strata. Follow-up time started 91 days (1 quarter) from hemodialysis initiation. For each analysis, three levels of hierarchical adjustments were examined:

1. Unadjusted models included entry calendar quarter.
2. Case-mix adjusted models that included all variables included in the unadjusted model plus age, sex, race/ethnicity (White, African American, Hispanic, Asian and other), 11 preexisting comorbidities as well as primary insurance (Medicare, Medicaid and other), vascular access (catheter, arteriovenous fistula or graft), cause of ESRD (diabetes, hypertension, glomerulonephritis, cystic kidney disease, other), and dialysis dose as indicated by single-pool Kt/V (spKt/V). Both baseline and subsequent quarter values of vascular access and spKt/V were included in the model.
3. Models adjusted for case-mix and malnutrition-inflammation complex syndrome (MICS) covariates, which included all of the covariates in the case-mix model as well as the following quarterly averaged variables: BMI and laboratory surrogates associated with clinical outcomes in HD patients including serum concentrations of (1) albumin, (2) creatinine, (3) total iron binding capacity, (4) ferritin, (5) bicarbonate, (6) peripheral white blood cell count, (7) lymphocyte percentage, (8) hemoglobin, (9) iron saturation, (10) normalized protein catabolic rate. Models were additionally adjusted for Phos, Ca_{Alb}, iPTH, and ALP, unless the particular CKD-MBD marker was the exposure of interest. Finally, the median dose per week of active vitamin D medications administered intravenously was also included. Both baseline and subsequent quarter values were included for all laboratory covariates and medication dosages to account for the change in these variables over time.

For each MBD marker of interest, we examined for effect modification of the association between the change in MBD level with mortality according to baseline MBD level in fully adjusted case-mix and MICS model. These interaction terms were evaluated by Wald tests simultaneously for each CKD-MBD related parameters.

In each model, the referent group was the second lowest baseline concentration group and exhibiting no change in the subsequent quarter (Phos: 3.5 −<5.5 mg/dL; Ca_{Alb} : 8.4 −<9.5 mg/dL; iPTH: 150 −<300 pg/mL; ALP: 80 −<120 U/L). In sensitivity analyses, the group exhibiting no change in concentration for each baseline strata was chosen as the referent group in order to compare the association of an excessive change in MBD marker concentration within each baseline strata.

Data was missing on average, 1% for the cohort. Missing values were handled by multiple imputation. All statistical analyses were carried out with SAS, version 9.4 (SAS Institute, Inc., Cary, North Carolina).

Results

The final study population was composed of 102,754 incident HD patients with available measurements of Phos, Ca_{Alb}, iPTH, and ALP during the first six months of treatment. Patients had a mean±SD age of 63±15 years old, among whom 44% were female, 32% were African American and 60% were diabetic (Table 1). In terms of comorbid conditions, 52% of patients had hypertension, 39% had a history of congestive heart failure, and 15% had atherosclerotic heart disease prior to dialysis initiation. Overall follow-up time starting from 91 days after dialysis initiation was median (IQR) : 475 (200, 889) days.

Baseline serum concentrations of Phos, Ca_{alb}, iPTH and ALP were median (IQR): 4.8 (4.–5.6) mg/dL, 9.1 (8.8–9.4) mg/dL, 317 (201–490) pg/mL, and 87 (69–114) U/L, respectively. Changes in these concentrations from baseline to the subsequent quarter were 0.20 (−0.44–0.83) mg/dL, 0.04 (−0.20–0.30) mg/dL, −59.8 (−190.3–29.0) pg/mL, and 0 (−12.5–12.7) U/L, respectively.

The association of the change in serum Phos, Ca_{alb}, iPTH concentrations with all-cause mortality differed by baseline concentration (p-interaction <0.001 for each MBD marker). There was also effect modification of the association of change in ALP concentrations and mortality according to baseline ALP level (p-interaction=0.054). Therefore, the following survival analyses were conducted after stratifying patients into 12 groups according to four baseline groups and three levels of change in the subsequent quarter.

Changes in serum phosphorous concentrations and all-cause mortality

The median (IQR) baseline serum phosphorus concentration was 4.8 (4.2–5.6) mg/dL. Patients with higher baseline Phos concentrations were more likely to be younger, male, Hispanic, have a lower residual renal urea clearance (KRU), and have a history of congestive heart failure (Supplemental Table 1).

Table 2 shows the all-cause mortality hazard ratios for three levels of change from baseline to the next quarter across four groups of baseline serum Phos concentrations (reference: baseline serum Phos 3.5−< 5.5 mg/dL and unchanged from Q1 to Q2). Among patients whose serum concentrations did not change from baseline to the subsequent quarter of treatment, serum phosphorus concentrations showed a J-shaped association with mortality with the highest baseline group (Phos ≥7.5 mg/dL) exhibiting the highest risk of mortality

(aHR, 95%CI: 2.01(1.72–2.36)). Relative to the reference group, patients who experienced an increase or decrease in Phos in the subsequent quarter had a higher risk of mortality across all strata of baseline Phos ≥3.5 mg/dL.

Adjusted HR for all-cause mortality tended to be highest in patients who experienced an increase > 0.5 mg/dL in the subsequent quarter, especially among the highest baseline concentrations of Phos (Phos 5.5−<7.5 and ≥7.5mg/dL). Similarly, an excessive fall of >−0.5 mg/dL from low baseline Phos concentrations of <3.5 mg/dL was also associated with higher risk of mortality (aHR, 95%CI: 1.67(1.41, 1.97)) (Figure 2). This was further evident in sensitivity analysis where an increase in Phos across baseline strata Phos ≥3.5 mg/dL, as well a further decrease from Phos<3.5 mg/dL exhibited higher mortality in comparison to patients with Phos measurements that remained within the strata range (Supplemental Figure 1).

Changes in albumin-corrected serum calcium concentrations and all-cause mortality

Median (IQR) baseline serum Ca_{Alb} concentration was 9.1 (8.8–9.4) mg/dL. Patients with high baseline Ca_{Alb} concentrations were more likely to be older, female, African American and hypertensive (Supplemental Table 2).

Table 3 shows the all-cause mortality hazard ratios for three levels of change from baseline to the subsequent quarter across four groups of baseline serum Ca_{Alb} concentrations (reference: baseline serum Ca_{Alb} 8.4−< 9.5 mg/dL and unchanged from Q1 to Q2). Although unadjusted models exhibited a higher risk of mortality in patients with higher baseline Ca_{Alb} concentrations, irrespective of the nature in the change in the next quarter, this association was attenuated after fully adjusting for case-mix and MICS variables. Similar to trends seen with Phos, there was a trend towards higher risk of mortality among patients who experienced an increase in Ca_{Alb} in their subsequent quarter across all baseline groups of Ca_{Alb} ≥8.4 mg/dL (Figure 3).The highest mortality was seen in patients who experienced a further increase in Ca_{Alb} from already high baseline Ca_{Alb} concentrations (aHR, 95%CI: 1.70(1.42, 2.03)). This association is also evident when examining the association of change with respect to baseline strata (Supplemental Figure 2). In addition, a differential risk of mortality was seen in patients who experienced a decrease in Ca_{Alb} where this decrease in patients whose baseline strata were Ca_{Alb} 8.−<9.5 and ≥10.2 mg/dL was associated with a higher risk of mortality (aHR, 95%CI: 1.05(1.01, 1.09), aHR, 95%CI: 1.14(1.05, 1.24), respectively) (Figure 3).

Change in serum iPTH level and all-cause mortality

Median (IQR) baseline serum iPTH concentrations were 317 (201–490) pg/mL. Patients with high baseline iPTH concentrations were more likely to be younger, African American and hypertensive (Supplemental Table 3).

Table 4 shows the all-cause mortality hazard ratios for three levels of change from baseline to the next quarter across four groups of baseline serum iPTH concentrations (reference: baseline serum iPTH 150 −<300 pg/mL and unchanged from Q1 to Q2). In the unadjusted model, higher baseline iPTH concentrations were associated with better survival, irrespective of the direction of change in the subsequent quarter. However further adjustment

of covariates and laboratory markers reversed this association, especially among patients whose iPTH increased in the next quarter across baseline groups of iPTH ≥150 pg/mL. Patients whose levels of iPTH increased over time from baseline iPTH≥600 pg/mL experienced the highest risk of mortality (aHR, 95%CI: 1.26(1.09, 1.47)). Among patients who decreased in iPTH concentrations in the subsequent quarter, only patients whose baseline iPTH was <150 pg/mL experienced a higher risk of mortality (aHR, 95%CI: 1.16(1.06, 1.28)) (Figure 4). Similar trends were seen in sensitivity analysis, however among patients with a greater baseline iPTH (300−<600 pg/mL) were at a significantly lower risk of mortality when iPTH decreased in the next quarter in comparison to patients who did not experience a change (Supplemental Figure 3).

Change in serum alkaline phosphatase level and all-cause mortality

Median (IQR) baseline serum ALP concentrations were 87 (69–114) U/L. Patients with high baseline ALP concentrations were more likely to be younger, female, diabetic, and have history of other cardiovascular disease (Supplemental Table 4).

Table 5 shows the all-cause mortality hazard ratios for three levels of change from baseline to the next quarter across four groups of baseline serum ALP concentrations (reference: baseline serum ALP 80−<120 U/L and unchanged from Q1 to Q2).

Among patients who experienced an increase in ALP values in the subsequent quarter, greater than reference baseline groups of ALP were associated with a higher risk of mortality, especially in patients with baseline ALP ≥120 U/L after fully adjusting for case-mix and MICS covariates. In addition, a decrease in ALP was associated with a higher risk of mortality in patients with a baseline ALP ≥120 U/L. In contrast, lower baseline ALP concentrations were associated with lower mortality risk irrespective of the direction of change in ALP level in the subsequent quarter (Figure 5). Similar associations of higher mortality with an increase in ALP within baseline ALP strata was seen in sensitivity analyses in comparison to patients within the baseline strata and did not experience a change in ALP. However, lower mortality risk among patients with baseline ALP <80 U/L was not evident (Supplemental Figure 4).

Discussion

We evaluated the association of the change in concentration of four MBD markers, Phos, $Ca_{Alb,}$ iPTH, and ALP, during the first six months of maintenance hemodialysis with all-cause mortality in a cohort of 102,754 incident HD patients across strata of baseline MBD markers.

Changes deviating from KDOQI-recommended concentrations (Phos 3.5 −<5.5 mg/dL, Ca_{alb} 8.4 −<9.5 mg/dL, and iPTH 150−<300 pg/mL) were generally associated with higher mortality after adjustment for case-mix and MICS covariates.[19] In addition, both higher baseline and increased ALP ≥80 U/L concentrations showed a consistently higher risk of mortality. These findings provide additional evidence for more precise management of CKD-MBD markers during the first six months of treatment.

Previous observational studies have highlighted the importance of adherence to the KDOQI-recommended levels of serum phosphorus, calcium, and iPTH from the beginning of HD treatment, demonstrating additive effects gained by the achievement of the recommended target levels on patient survival.[20,21] In addition, one study found that patients who achieved recommended ranges for a shorter duration of time had a higher risk of death.[20] Our results were conceptually in line with these studies. Moreover, this study provided further insight about mortality risk related to changes in serum CKD-MBD markers when stratified by their baseline levels.

An increased risk in mortality in the fully adjusted model was found in patients who deviated from baseline Ca_{alb} 8.4−<9.5 mg/dL, as well as among patients who maintained a stable concentration of baseline Ca_{alb} 9.5−<10.2 mg/dL. In addition, among patients with baseline Ca_{alb} 9.5−<10.2 mg/dL, a decrease in the next quarter towards the 8.4–9.5mg/dL range trended towards lower mortality risk (Supplemental Figure 2). While these results provide support for the KDOQI guideline to maintain a lower normal range of Ca_{alb} 8.4−<9.5 mg/dL, this opposes the KDIGO guidelines with its recommendations of normal Ca_{alb} range as 8.6–10.2 mg/dL. It should be noted that this study population was composed of incident hemodialysis patients, and thus the optimal range may differ from maintenance hemodialysis.[4,11] This is also the case for iPTH where the recommended normal range is 160–720 pg/mL. Among patients who experienced an increase in iPTH, baseline iPTH levels ≥150 pg/mL were incrementally associated with higher mortality. In addition, patients with lower iPTH concentrations at baseline and who experienced a further decrease in the subsequent quarter also exhibited a higher risk of mortality, which is consistent with previous reports and the KDOQI guidelines.[4–9,11,12,19]

Among the CKD-MBD parameters examined in this study, deviations in serum phosphorus concentrations at both extremes were associated with higher all-cause mortality. Higher concentrations as well as excessive changes from the recommended range (3.5−<5.5 mg/dL) were associated with higher mortality, and the risk was dependent on the differences in concentration from that range. Meanwhile, an increase in serum ALP concentration was associated with higher mortality risk across baseline strata of ALP≥80 U/L. These results support the importance and robustness of serum ALP concentration as an MBD biomarker that predicts mortality. [4–9,11,12,19,22] Although associations between ALP and mortality were not significant in our sensitivity analyses, a previous study investigating the effect of change in ALP on mortality similarly showed results. These findings suggest that the relationship of decreased ALP and mortality may be impacted by baseline ALP concentrations. [6]

Several factors might have contributed to these findings and there are a number of limitations to this study. First, pre-dialysis care and patient condition may affect survival more potently than treatments administered after dialysis initiation in incident HD patients who bear the highest mortality risk.[4,6,23] Although we did adjust for the use intravenously delivered vitamin D medications, data on other prescription, behavior and dietary interventions were not available in this study. We cannot analyze the impact of interventions such as phosphate binders, oral active or nutritional vitamin D dose, or surgical interventions such as parathyroidectomy on the associations between CKD-MBD markers and mortality.

We also acknowledge that another limitation in this study is the inability to address other CKD-MBD related factors in the blood such as fibroblast growth factor-23 or vitamin D metabolites. Despite rigorously adjusting for markers of malnutrition and inflammation, other variables namely C - reactive protein and dialysate calcium were unavailable in this cohort and we cannot exclude residual confounding given the observational study design. Furthermore, we only evaluated changes during the first six months of dialysis treatment but not in the subsequent periods to focus on the immediate changes after dialysis initiation in CKD-MBD markers. Future studies are needed to investigate whether these associations differ according to dialysis vintage. Finally, cause of death was unavailable in our cohort.

Strengths of our study include a large nationally representative incident HD population with detailed patient-level data, which allowed us to rigorously account for a range of clinically relevant factors. Essentially all incident hemodialysis patients in the original cohort were included in our analyses, and thus the likelihood of selection bias is minimized. Additionally, all dialysis facilities were under uniform administrative care, and all laboratory tests were performed in one single laboratory with optimal quality assurance monitoring. We used quarterly averaged measurements rather than one single baseline measurement at to minimize effects of short-term variations. Furthermore, the relationship of CKD-MBD and mortality is multi-faceted and involves multiple MBD markers. In our fully adjusted models, we adjusted for the other MBD markers and their change aside from the exposure of interest, suggesting that our findings are independent of other MBD markers change and baseline measurements.

Conclusion

In conclusion, we demonstrated that baseline levels and changes in serum concentrations of CKD-MBD related parameters in the first six months after initiation of hemodialysis treatment were associated with all-cause mortality in patients with end-stage renal disease. Further studies are needed to evaluate whether stricter interventions to correct these abnormalities in the early period after hemodialysis initiation can improve patient survival.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Author’s roles: Study design: MS, MF, YO, ES, CMR, CPK and KK-Z. Study conduct: MS, MF, YO, ES and KK-Z. Data analysis: MS, MF and ES. Data Interpretation: MS, MF, YO, ES, CMR, WLL, JW, VAR, SB, CPK and KK-Z. Drafting manuscript: MS, MF, YO, ES, CMR, WLL, JW, VAR, SB, CPK and KK-Z. Revising manuscript content: MS, YO, ES and KK-Z. Approving final version of manuscript: MS, MF, YO, ES, CMR, WLL, JW, VAR, SB, CPK and KK-Z. Each author contributed important intellectual content during manuscript drafting and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. KK-Z takes responsibility for the integrity of the data analysis.

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Relevant Potential Conflict of Interest:

KKZ has received honoraria and/or support from Abbott, Abbvie, Alexion, Amgen, American Society of Nephrology, Astra-Zeneca, AVEO, Chugai, DaVita, Fresenius, Genetech, Haymarket Media, Hospira, Kabi, Keryx, National Institutes of Health, National Kidney Foundation, Relypsa, Resverlogix, Sanofi, Shire, Vifor, ZS-Pharma. CPK has received honoraria from Sanofi-Aventis, Relypsa and ZS Pharma.

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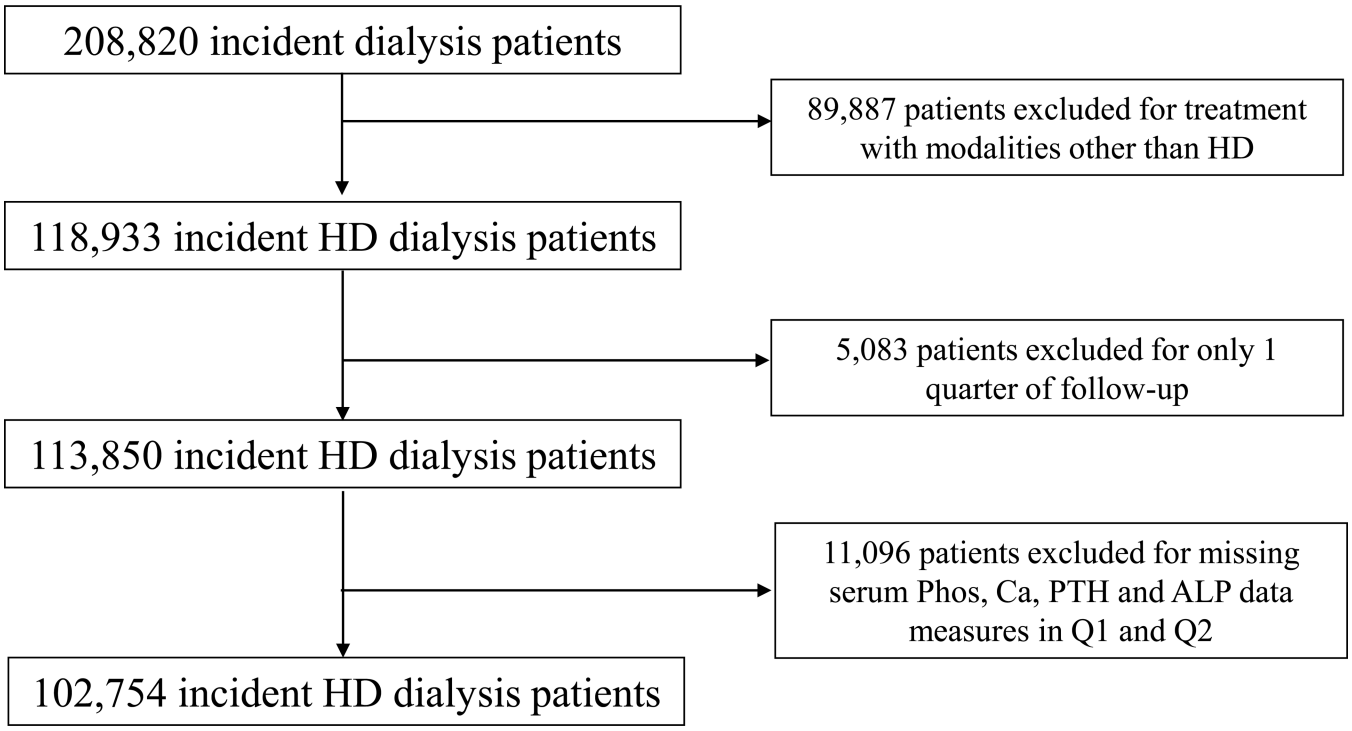

Figure 1. Cohort Construction

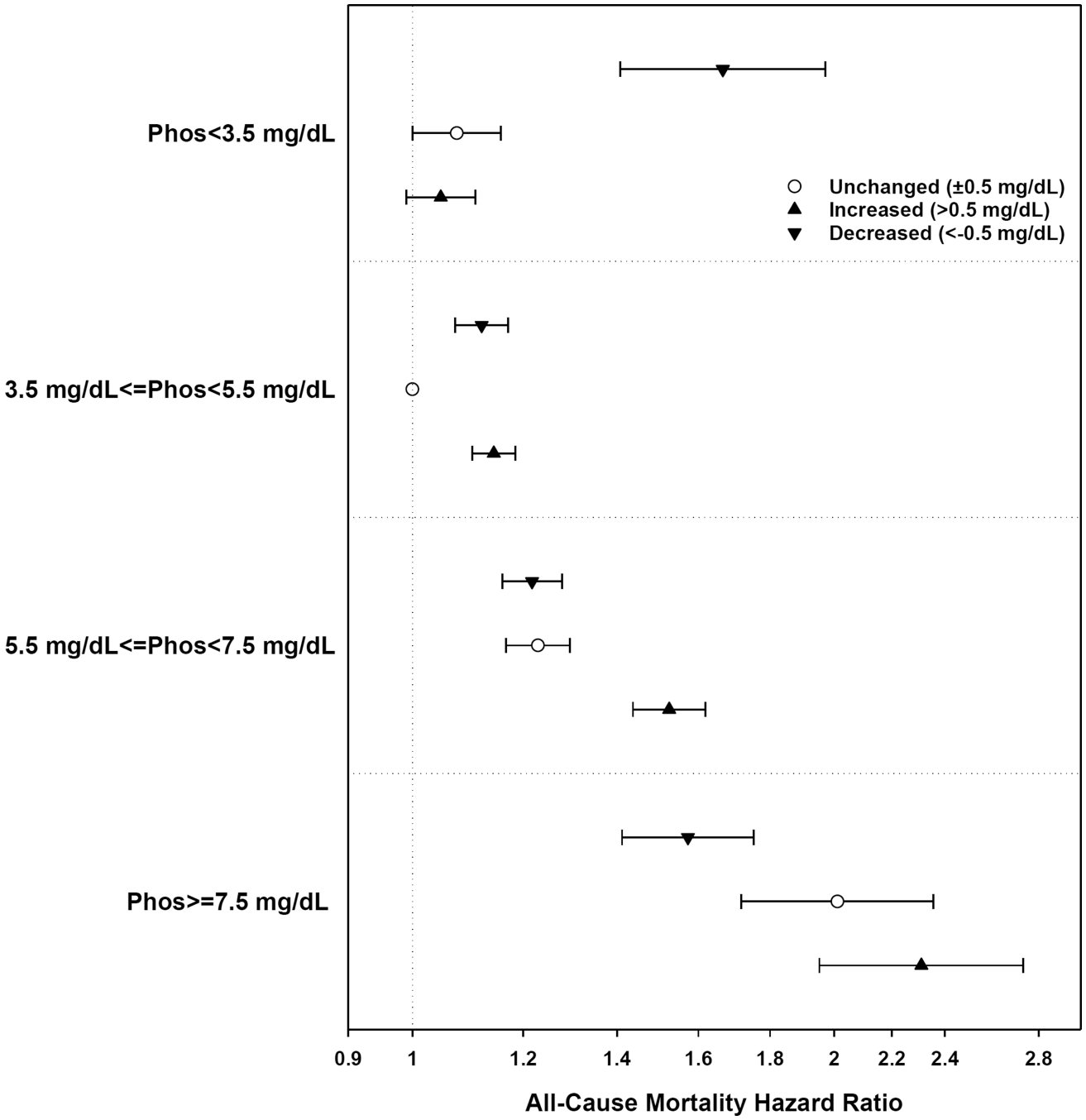

Figure 2. Association of change in serum phosphorus and all-cause mortality across strata of baseline concentration; case-mix and MICS adjusted

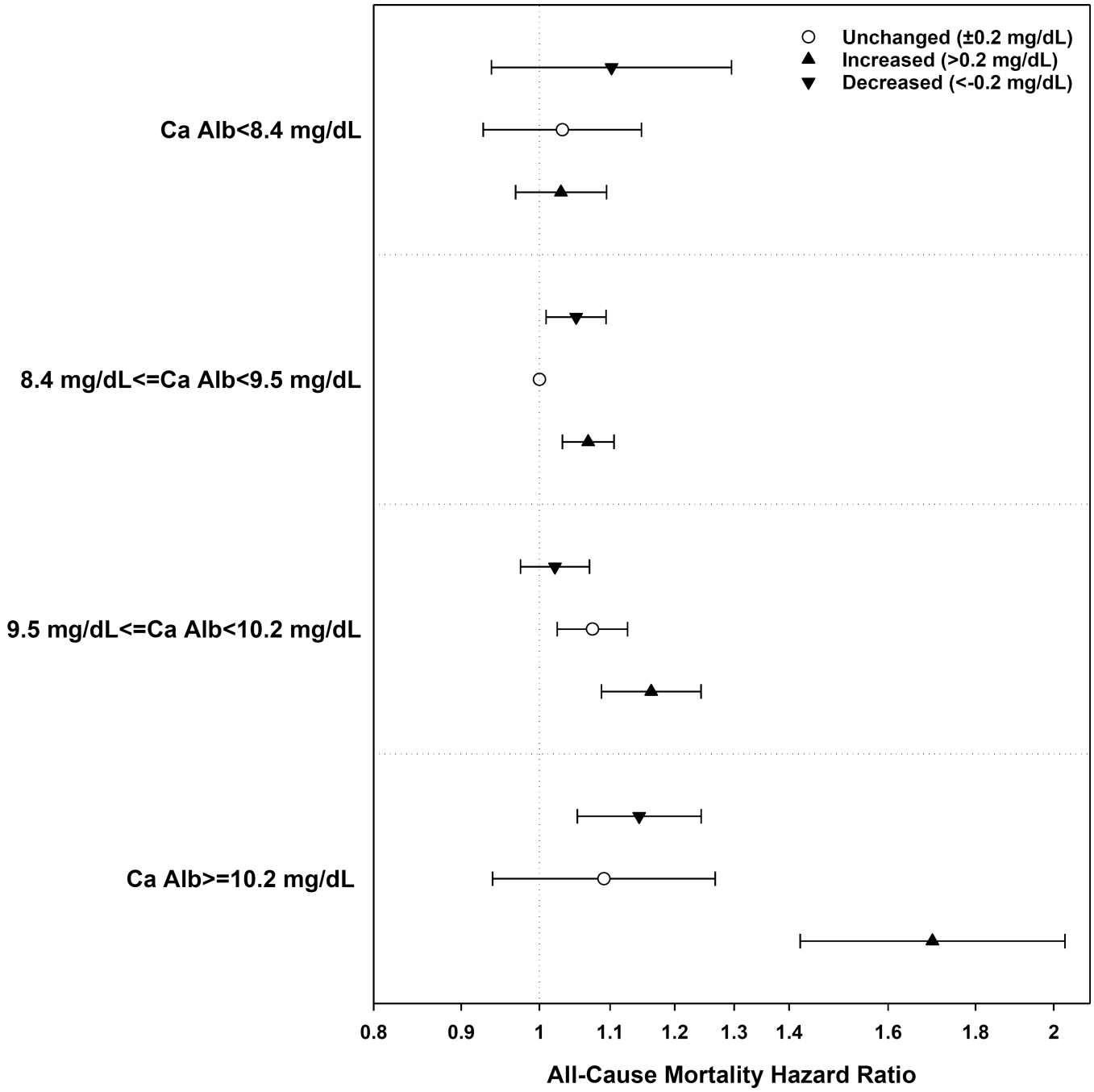

Figure 3. Association of change in serum albumin-corrected calcium and all-cause mortality across strata of baseline concentration; case-mix and MICS adjusted

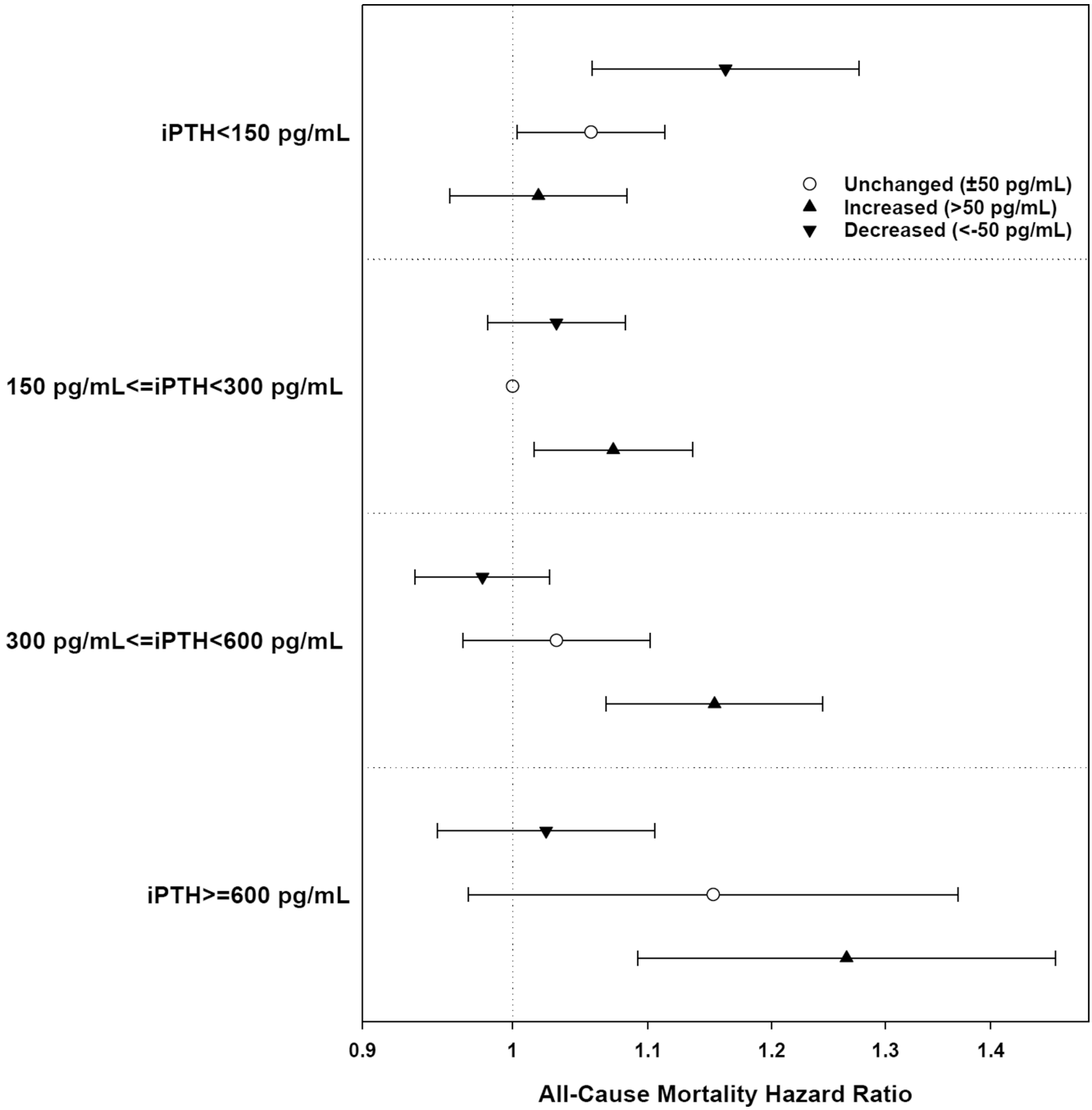

Figure 4. Association of change in serum intact parathyroid hormone and all-cause mortality across strata of baseline concentration; case-mix and MICS adjusted

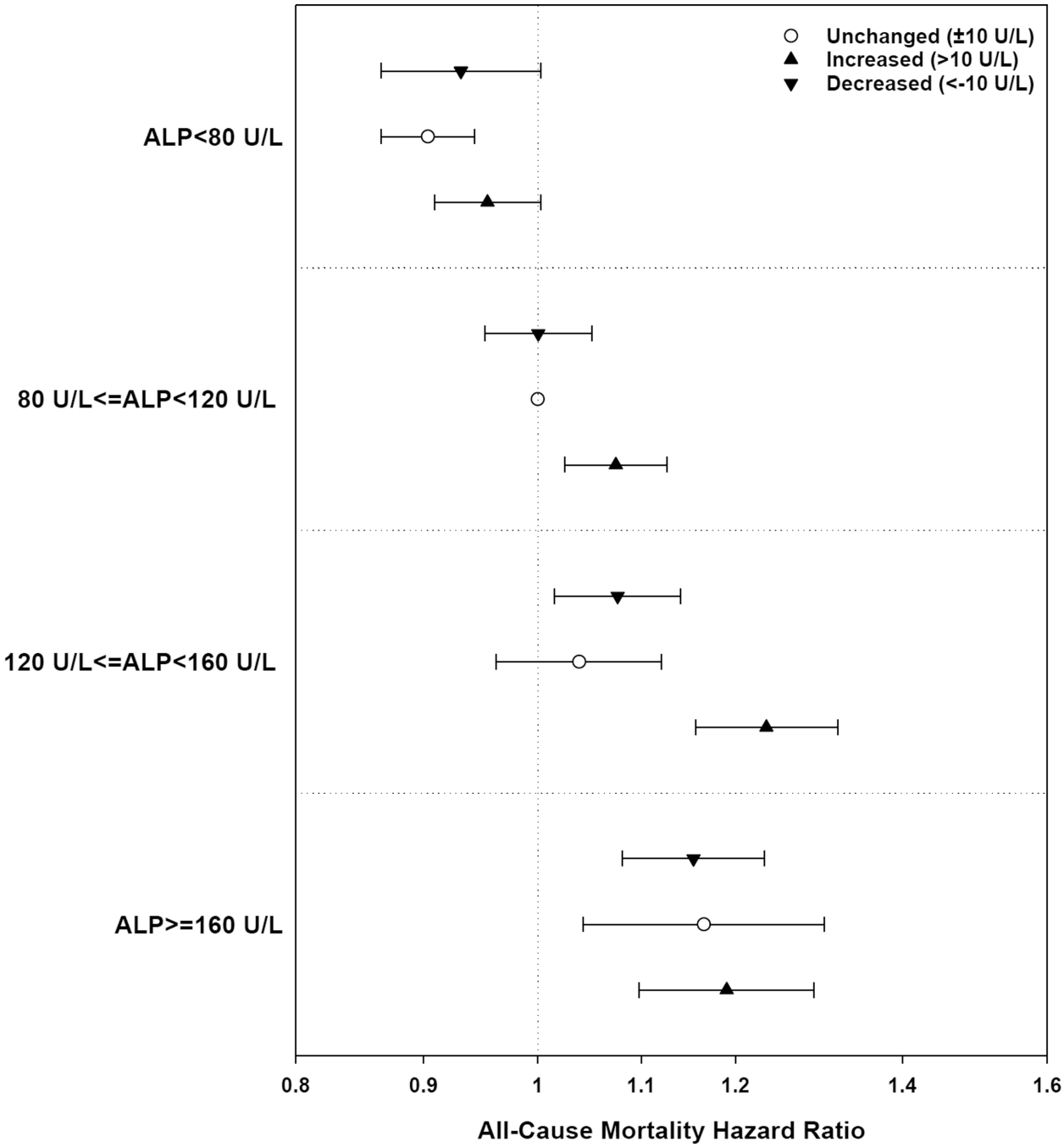

Figure 5. Association of change in serum alkaline phosphatase and all-cause mortality across strata of baseline concentration; case-mix and MICS adjusted

Table 1

Demographic and clinical characteristics of 102,754 incident HD patients.

Characteristics	**n=102,754**
Age (years)	63±15
% Women	44
Diabetes mellitus (%)	60
Median Incident Year	2009
Race (%)	
White	46
African American	32
Hispanic	15
Asian	3
Other	4
Primary insurance (%)	
Medicare	54
Medicaid	7
Other	39
Access (%)	
Central venous catheter	77
AV Fistula	15
AV Graft	4
Unknown	3
ESRD Reason (%)	
Diabetes	46
Hypertension	30
GN	9
Cystic Kidney Disease	2
Other	13
Single-pool Kt/V	1.5±0.3
KRU (mL/min)	4.1±3.4
Protein Catabolic Rate (g/kg/day)	0.8±0.2
Body Mass Index (kg/m^2)	28±7
Comorbidities (%)	
Hypertension	52
Congestive Heart Failure	39
Atherosclerotic Heart Disease	15
Other Cardiovascular Disease	15
Cerebrovascular Disease	2
COPD	5
History of Cancer	2

Characteristics	**n=102,754**
HIV	<1
Alcohol Abuse	<1
Substance Abuse	<1
Serum levels	
Albumin (g/dL)	3.5±0.5
Creatinine (mg/dL)	5.9±2.4
TIBC (mg/dL)	226.2±48.3
CO_2 (mEq/L)	23.5±2.7
Ferritin (ng/mL)	276[160,472]
White Blood Cell ($\times 10^3/mm^3$)	7.8±2.6
Iron saturation ratio (%)	23.0±8.8
Blood hemoglobin (g/dL)	11.2±1.2
Lymphocyte (%)	20.8±7.4
Phosphorus (mg/dL)	5.0±1.2
Ca_{Alb} (mg/dL)	9.1±0.6
iPTH (pg/mL)	317[201,490]
Alkaline Phosphatase (U/L)	87[69,114]
Intravenous Medication	
Active Vitamin D User (%)	64
Change in MBD levels	
Phosphorus (mg/dL)	0.20[−0.44,0.83]
Ca_{Alb} (mg/dL)	0.04[−0.20,0.30]
iPTH (pg/mL)	−59.8[−190.3,29.0]
Alkaline Phosphatase (U/L)	0[−12.5,12.7]

Table 2

All-cause mortality hazard ratios in baseline serum phosphorus groups and their changes in 102,754 incident HD patients

Baseline Phosphorus Group (mg/dL)	Phosphorus Change (mg/dL)	n	Event Rate*	Unadjusted		Case-Mix Adjusted		Case-Mix and MICS Adjusted	
				HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
<3.5	Decreased (>−0.5)	305	607	4.01 (3.40, 4.73)	<.0001	3.11 (2.63, 3.67)	<.0001	1.67 (1.41, 1.97)	<.0001
	Unchanged (± 0.5)	2583	277	1.80 (1.68, 1.94)	<.0001	149 (1.39, 1.60)	<.0001	1.08 (1.00, 1.16)	0.0486
	Increased (>0.5)	5088	233	1.51 (1.43, 1.60)	<.0001	1.31 (1.24, 1.38)	<.0001	1.05 (0.99, 1.11)	0.1061
3.5 −<5.5	Decreased (>−0.5)	11335	199	1.29 (1.24, 1.35)	<.0001	1.23 (1.18, 1.29)	<.0001	1.12 (1.07, 1.17)	<.0001
	Unchanged (±0.5)	28840	154	*Ref*	*Ref*	*Ref*	*Ref*	*Ref*	*Ref*
	Increased (>0.5)	25675	166	1.08 (1.04, 1.11)	<.0001	1.12 (1.08, 1.16)	<.0001	1.14 (1.10, 1.18)	<.0001
5.5 −<7.5	Decreased (>−0.5)	10251	143	0.92 (0.88, 0.97)	0.0006	1.07 (1.02, 1.12)	0.006	1.22 (1.16, 1.28)	<.0001
	Unchanged (±0.5)	9343	120	0.77 (0.74, 0.81)	<.0001	0.98 (0.93, 1.03)	0.5016	1.23 (1.17, 1.30)	<.0001
	Increased (>0.5)	6536	137	0.88 (0.84, 0.93)	<.0001	1.21 (1.14, 1.28)	<.0001	1.53 (1.44, 1.62)	<.0001
≥7.5	Decreased−0.5)	1607	130	0.84 (0.76, 0.93)	0.0007	1.21 (1.09, 1.34)	0.0005	1.57 (1.41, 1.75)	<.0001
	Unchanged (± 0.5)	647	139	0.90 (0.77, 1.04)	0.1597	1.33 (1.14, 1.55)	0.0004	2.01 (1.72, 2.36)	<.0001
	Increased (>0.5)	544	156	1.01 (0.86, 1.18)	0.9421	1.69 (1.44, 2.00)	<.0001	2.31 (1.95, 2.73)	<.0001

*Per 1000 patient-years

Table 3

All-cause mortality hazard ratios in baseline albumin-corrected serum calcium groups and their changes in 102,754 incident HD patients

Baseline Ca_{Alb} Group (mg/dL)	Ca_{Alb} Change (mg/dL)	n	Event Rate*	Unadjusted		Case-Mix Adjusted		Case-Mix and MICS Adjusted	
				HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
<8.4	Decreased (>−0.2)	737	156	0.99 (0.84, 1.16)	0.9089	1.21 (1.03, 1.42)	0.022	1.10 (0.94, 1.30)	0.2373
	Unchanged (± 0.2)	1844	144	0.92 (0.83, 1.02)	0.1032	1.03 (0.93, 1.15)	0.5574	1.03 (0.93, 1.15)	0.5680
	Increased (>0.2)	6460	131	0.84 (0.79, 0.89)	<.0001	0.99 (0.93, 1.05)	0.7055	1.03 (0.97, 1.09)	0.3494
8.4 −< 9.5	Decreased (>−0.2)	14425	156	0.99 (0.96, 1.03)	0.7456	1.05 (1.01, 1.09)	0.0131	1.05 (1.01, 1.09)	0.0168
	Unchanged (±0.2)	32946	156	*Ref*	*Ref*	*Ref*	*Ref*	*Ref*	*Ref*
	Increased (>0.2)	24586	163	1.05 (1.01, 1.08)	0.0071	1.09 (1.06, 1.13)	<.0001	1.07 (1.03, 1.11)	0.0003
9.5 −< 10.2	Decreased (>-0.2)	8612	158	1.02 (0.97, 1.06)	0.4651	1.03 (0.98, 1.07)	0.2593	1.02 (0.97, 1.07)	0.3738
	Unchanged (± 0.2)	7498	179	1.16 (1.10, 1.21)	<.0001	1.12 (1.07, 1.18)	<.0001	1.07 (1.02, 1.13)	0.0033
	Increased (>0.2)	3006	218	1.41 (1.33, 1.51)	<.0001	1.39 (1.30, 1.49)	<.0001	1.16 (1.09, 1.24)	<.0001
≥10.2	Decreased (>−0.2)	1844	194	1.25 (1.15, 1.36)	<.0001	1.17 (1.07, 1.27)	0.0003	1.14 (1.05, 1.24)	0.0017
	Unchanged (±0.2)	531	202	1.30 (1.12, 1.51)	0.0004	1.31 (1.13, 1.52)	0.0005	1.09 (0.94, 1.27)	0.2548
	Increased (>0.2)	265	388	2.51 (2.11, 3.00)	<.0001	2.23 (1.87, 2.67)	<.0001	1.70 (1.42, 2.03)	<.0001

*Per 1000 patient-years

Table 4

All-cause mortality hazard ratios in baseline serum parathyroid hormone groups and their changes 102,754 incident HD patients

Baseline iPTH Group (pg/mL)	iPTH Change (pg/mL)	n	Event Rate*	Unadjusted		Case-Mix Adjusted		Case-Mix and MICS Adjusted	
				HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
<150	Decreased (>−50)	1419	290	1.68 (1.54, 1.85)	<.0001	1.52 (1.39, 1.67)	<.0001	1.16 (1.06, 1.28)	0.0019
	Unchanged (±50)	8434	238	1.38 (1.31, 1.45)	<.0001	1.27 (1.20, 1.33)	<.0001	1.06 (1.00, 1.11)	0.0375
	Increased (>50)	5428	184	1.06 (1.00, 1.13)	0.053	1.05 (0.99, 1.12)	0.1109	1.02 (0.96, 1.08)	0.5653
150−< 300	Decreased (>−50)	11122	206	1.19 (1.14, 1.25)	<.0001	1.11 (1.06, 1.16)	<.0001	1.03 (0.98, 1.08)	0.2097
	Unchanged (±50)	12468	173	*Ref*	*Ref*	*Ref*	*Ref*	*Ref*	*Ref*
	Increased (>50)	8986	161	0.93 (0.88, 0.98)	0.0077	1.01 (0.95, 1.06)	0.8418	1.07 (1.02, 1.13)	0.0129
300−< 600	Decreased (>−50)	26788	142	0.82 (0.79, 0.86)	<.0001	0.92 (0.88, 0.96)	<.0001	0.98 (0.93, 1.03)	0.3784
	Unchanged (±50)	6261	137	0.79 (0.74, 0.84)	<.0001	0.94 (0.88, 1.00)	0.0414	1.03 (0.97, 1.10)	0.3578
	Increased (>50)	5115	145	0.84 (0.78, 0.90)	<.0001	1.06 (0.99, 1.14)	0.1099	1.15 (1.07, 1.24)	0.0003
≥600	Decreased (>−50)	14605	122	0.71 (0.67, 0.74)	<.0001	0.91 (0.86, 0.95)	0.0001	1.02 (0.95, 1.11)	0.5437
	Unchanged (±50)	806	132	0.77 (0.65, 0.90)	0.0013	1.05 (0.89, 1.24)	0.5417	1.15 (0.97, 1.37)	0.1076
	Increased (>50)	1324	153	0.89 (0.79, 1.00)	0.0448	1.20 (1.07, 1.36)	0.0025	1.26 (1.09, 1.47)	0.0019

*Per 1000 patient-years

Table 5

All-cause mortality hazard ratios in baseline serum alkaline phosphatase groups and their changes in 102,754 incident HD patients

Baseline ALP Group (U/L)	ALP Change (U/L)	n	Event Rate*	Unadjusted		Case-Mix Adjusted		Case-Mix and MICS Adjusted	
				HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
<80	Decreased (>−10)	4987	112	0.71 (0.66, 0.77)	<.0001	0.77 (0.72, 0.83)	<.0001	0.93 (0.87, 1.00)	0.0598
	Unchanged (±10)	24590	130	0.83 (0.80, 0.87)	<.0001	0.80 (0.77, 0.84)	<.0001	0.90 (0.87, 0.94)	<.0001
	Increased (>10)	12448	168	1.08 (1.03, 1.13)	0.0027	1.01 (0.96, 1.06)	0.778	0.95 (0.91, 1.00)	0.0631
80 −<120	Decreased (>−10)	12308	134	0.86 (0.82, 0.90)	<.0001	0.93(0.88, 0.97)	0.0021	1.00 (0.95, 1.05)	0.9847
	Unchanged (±10)	14990	156	*Ref*	*Ref*	*Ref*	*Ref*	*Ref*	*Ref*
	Increased (>10)	11194	195	1.26 (1.20, 1.32)	<.0001	1.24(1.18, 1.30)	<.0001	1.07 (1.03, 1.13)	0.003
120 −<160	Decreased (>−10)	6297	158	1.02 (0.96, 1.08)	0.5589	1.12 (1.06, 1.19)	<.0001	1.08 (1.02, 1.14)	0.0131
	Unchanged (±10)	2706	178	1.15 (1.07, 1.24)	0.0003	1.21 (1.12, 1.31)	<.0001	1.04 (0.96, 1.12)	0.3236
	Increased (>10)	3481	246	1.58 (1.49, 1.69)	<.0001	1.66 (1.56, 1.77)	<.0001	1.24 (1.16, 1.32)	<.0001
≥160	Decreased (>−10)	6009	209	1.34 (1.27, 1.42)	<.0001	1.54 (1.46, 1.62)	<.0001	1.15 (1.08, 1.23)	<.0001
	Unchanged (±10)	1034	234	1.51 (1.35, 1.68)	<.0001	1.64 (1.47, 1.83)	<.0001	1.17 (1.04, 1.30)	0.007
	Increased (>10)	2710	317	2.04 (1.91, 2.18)	<.0001	2.21 (2.07, 2.36)	<.0001	1.19 (1.10, 1.29)	<.0001

*Per 1000 patient-years