Mortality of Combined Serum Phosphorus and Parathyroid Hormone Concentrations and their Changes over Time in Hemodialysis Patients

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Abstract

Background—Mineral and bone disorder (MBD) is common and associated with mortality in patients with chronic kidney disease (CKD). Given that disarrays in serum phosphorus (P) and parathyroid hormone (PTH) levels and their changes over time are closely interrelated, modeling mortality-predictability of their combinations may help improve CKD patient management.
Methods—A historical cohort study was undertaken to evaluate the joint effect of serum P and PTH levels on mortality in 107,299 chronic hemodialysis (HD) patients. Changes in serum P and PTH levels over 6 months, in particular discordant changes, were also modeled with mortality.

Results—HD patients were 64±15 (mean±SD) years old and included 45% women, 33% African–American, and 59% diabetic. Compared with serum P level ≥7.0 mg/dL and PTH level ≥600 pg/mL, adjusted hazard ratio (HR) tended to be lowest in patients with serum P level of 3.5–<5.5 mg/dL combined with PTH level of 150–<300 pg/mL (HR 0.64, 95% confidence interval 0.61–0.67). A change over time in serum P level towards the 3.5–<5.5 mg/dL range from higher or lower ranges was associated with a decreased mortality, whereas only change in PTH level from <150 pg/mL to 150–<300 pg/mL range was associated with a lower risk of mortality. Upon discordant changes of PTH and P, i.e., decrease in one of the two measures while the other increased, no change in mortality risk was observed.

Conclusion—In CKD–MBD management, patent survival is the greatest with controlling both serum P and PTH levels in balance. Tailoring an individualized treatment strategy in CKD-MBD may benefit patients. Further studies are needed.

Keywords
bone; hemodialysis; hyperparathyroidism; mineral; phosphorus

Introduction
Abnormalities in serum calcium, phosphorus (P), and parathyroid hormone (PTH) levels are common in patients with chronic kidney disease (CKD). These biochemical changes together with elevation of fibroblast growth factor-23 (FGF-23) and abnormalities in vitamin D metabolism constitute a systemic syndrome known as chronic kidney disease mineral and bone disorder (CKD-MBD). Observational studies have found associations of serum phosphorus (P) and parathyroid hormone (PTH) with mortality in patients with CKD [1, 2] and in patients on maintenance dialysis [3–11]. Although no conclusive clinical trials have been conducted yet, hyperphosphatemia and secondary hyperparathyroidism have been recommended as major targets to treat CKD–MBD [12, 13]. Since serum P and PTH levels are physiologically interrelated, [14, 15] it may be plausible that both parameters be considered simultaneously in risk stratification, planning and adjusting treatments for CKD–MBD. In this respect, a model combining serum P with PTH level as a “bivariate” predictor may fit a survival model better than a model that treats each parameter separately. In addition to static levels of serum P and PTH, dynamic change over time may be also important. However, effect of changes in serum P and PTH levels on mortality has been insufficiently evaluated, especially in discordant (i.e. increase in serum P level but decrease in PTH level or vice versa) changes. [16]

We hypothesized that concurrent preferable levels of serum P and PTH are associated with better survival in hemodialysis (HD) patients, and that changes in serum P and PTH levels to a preferable level would be also associated with lower mortality. Evaluation for discordant changes may give insight about situations faced during treatment of CKD–MBD in clinical practice. We evaluated our hypothesis with a large and contemporary cohort of HD patients.
Materials and Methods

Patients

We retrospectively examined data from all patients receiving HD treatment from July 1, 2001, to June 30, 2006 in a large dialysis care organization in the United States (DaVita Inc.). As a dialysis population is a dynamic cohort with a high turnover rate, a non-concurrent cohort was formed. Prevalent patients as of July 1, 2001 and incident patients from July 1, 2001 to June 30, 2006 were included, which has been described in our previous studies. [17, 18] The first (baseline) quarter for each patient was the calendar quarter in which the patient’s dialysis duration was longer than 90 days. Patients were considered to be treated with HD if they were on the therapy at entry into cohort. During the cohort period, a total of 164,789 patients received dialysis treatment, among whom 130,087 had both serum P and intact PTH measures. After excluding 22,788 patients on PD or without data for dialysis modality at cohort entry, 107,299 HD patients were selected for the study. There was no significant difference in demographics between included and excluded HD patients. Follow-up time began on the date of entry into the cohort. Date and cause of death were recorded. Patients were censored at time of renal transplantation, departure from DaVita facilities, or end of the study period (June 30, 2006). The study was approved by the relevant Institutional Review Committees with exemption for a written consent.

Demographic and Clinical Measures

Information on dialysis modality and treatment, body weights, laboratory values, and intravenous medications were obtained from DaVita Inc. databases. These data were merged with data from the US Renal Data System (USRDS) to obtain information on date of first dialysis treatment, race/ethnicity, marital status, insurance, and co-morbid conditions. The following comorbid conditions were considered: diabetes mellitus, hypertension, ischemic heart disease, congestive heart failure, cerebrovascular accident, peripheral vascular disease, chronic obstructive pulmonary disease, malignancy, non-ambulatory state, and current smoking. Information on comorbidities was collected at the start of dialysis based on the Medical Evidence Report for ESRD (Form 2728). Dialysis duration was defined as the time between the first day of dialysis treatment and the first day that the patient entered the cohort.

Laboratory Values

Most blood samples were collected by uniform techniques in all dialysis clinics at the beginning of HD treatment. All samples were transported within 24 hours to a single laboratory center (DaVita Laboratory, Deland, FL), and then were measured by automated and standardized methods. Serum intact PTH level was measured by immunoradiometric assay utilizing a polyclonal 1–84 PTH Label Antibody, labeled with $^{125}$I, with a tendency to bind in the N terminal region on 1–84 PTH, and a Capture Antibody, polyclonal goat anti-PTH (39–84) fixed to the tubes, with a tendency to bind in the C terminal region of 1–84 PTH (Nichols, San Juan Capistrano, CA, USA). Precision inter- and intra-assay coefficient of variation was evaluated by performing 20 different assays on 3 EDTA plasma samples. The mean coefficient of variation for inter-assays was 4.68% and for intra-assays 2.47%. Serum P, calcium, urea, albumin, bicarbonate and total iron binding capacity were measured.
monthly. Serum intact PTH and ferritin were measured at least quarterly. Hemoglobin was measured weekly to bi-weekly in most patients. Delivered dialysis dose was estimated by single-pooled Kt/V using the urea kinetic model. Normalized protein nitrogen appearance (nPNA) was used as indicator of dietary protein intake. The 3-month-averaged values during the patient’s first eligible quarter were used as baseline values in order to attenuate an effect of short-term variation in laboratory measurements.

**Composite Ranking Score Analysis**

Changes in serum P level (Δ P) and intact PTH level (Δ intact PTH) were calculated as a mean of third quarter measured values minus a mean of first quarter measured values in each patient (ie. change during the first 6 months after entry into the cohort). We chose the first 6-month interval because serum P and PTH levels tend to be high before start of maintenance dialysis treatment and then are gradually controlled usually within 6 months in incident HD patients. Eligible patients were ranked with respect to Δ P and Δ intact PTH. We ranked these change values as −100th to 0th percentiles for declines and 0th to +100th percentiles for rises. We then subtracted these two change scores (ie. rank of Δ P minus rank of Δ intact PTH) for each patient to create composite ranking scores (a number between −200 to +200 for each subject). The difference reflects discordant changes; with a decrease in serum P level but an increase in intact PTH level predominating below −100, while with an increase in serum P level but a decrease in intact PTH level predominating above 100. Using composite ranking scores enabled us to distinguish which lab measurement predominated in a discordant change. Examples using derived composite ranking score have been described in our previous papers. [19, 20]

**Statistical Methods**

Data were summarized using proportions, means (±standard deviation, SD) and medians (interquartile range, IQR) as appropriate. We divided serum P levels a priori into 4 categories (<3.5, 3.5 to <5.5, 5.5 to <7.0 and ≥7.0 mg/dL) and intact PTH levels into 4 categories (<150, 150 to <300, 300 to <600, and ≥600 pg/mL) based on Kidney Disease Outcomes Quality Initiative (KDOQI) clinical practice guidelines for mineral bone disease because patients in our cohort were enrolled from 2001 to 2006 and were treated according to this guideline. [12] Patients were then divided into 16 groups according to their serum P and intact PTH levels (4 × 4 groups). Patients with serum P level of ≥7.0 mg/dL and intact PTH level of ≥600 pg/mL were considered as the reference group, for which we expected the worst outcome. For analysis of change in serum P level, we stratified patients based on their baseline values (<3.5, 3.5 to <5.5 and ≥5.5 mg/dL), and then further divided these groups into 3 strata based on their 3rd quarter serum P levels (<3.5, 3.5 to <5.5 and ≥5.5 mg/dL). Patients who did not change the category of serum P level between baseline and 3rd quarter were treated as the reference group. We similarly analyzed change in serum intact PTH level using 3 categories (<150, 150 to <300 and ≥300 pg/mL). The method for calculating composite ranking score is mentioned above. Survival analysis was performed by fitting Cox proportional hazard models with all-cause mortality as the outcome. The predictors were baseline serum P and intact PTH levels (4 × 4 groups), change in serum P level (3 × 3 groups), change in serum intact PTH level (3 × 3 groups) and composite ranking score. For composite ranking score analysis, Cox regression with restricted cubic splines
was used. The assumption of proportional hazard was assessed by log-log plots and Schoenfeld residuals after fitting models.

For each analysis, 3 levels of multivariable adjustment were examined: 1) an unadjusted model that included only the main predictor variable(s) and calendar quarter of entry; 2) case-mix adjusted models that additionally included age, gender, race/ethnicity, comorbidities, primary insurance, marital status, dialysis duration, vascular access type, single-pool Kt/V and serum total calcium level as covariates; and 3) case-mix plus malnutrition-inflammation cachexia syndrome (MICS) adjusted models which included all of the covariates in the case-mix model as well as 8 surrogates of nutritional and inflammatory status: hemoglobin, serum albumin, total iron binding capacity, ferritin, bicarbonate, peripheral white blood cell count, lymphocyte percentage and nPNA. In an attempt to mitigate the impact of regression to the mean, the model with composite ranking score analysis also adjusted for baseline serum P and intact PTH values.

Data for age, gender, race/ethnicity, diabetes, dialysis duration and laboratory variables were missing for <1% of patients in the cohort. Data on insurance were missing for 8%; marital status for 19%; comorbidities for 5%; and vascular access for 16% of patients. Missing values were handled using the following strategies: for categorical variables, creating a missing indicator; and for continuous variables, imputing with mean or median of existing values during the baseline quarter by serum P and intact PTH categories. Analyses were carried out with SAS version 9.1 (SAS Institute, Inc., Cary, North Carolina) and Stata version 10.1 (Stata Corporation, College Station, Texas).

**Results**

**Baseline characteristics**

The cohort included 107,299 HD patients, who were 64±15 (mean±SD) years old, 45% women, 42% Caucasian, 33% African-American, and 15% Hispanic. At the start of dialysis, 59% of HD patients had diabetes mellitus and 80% had hypertension. Mean baseline serum P level was 5.6 mg/dL (SD, 1.5) and median intact PTH level was 244 pg/dL (IQR, 144–417). Baseline characteristics stratified by each baseline serum P and intact PTH level are presented in Table 1. Patients with higher serum P level tended to be younger, male, have longer dialysis duration before cohort entry, and a lower prevalence of diabetes, ischemic heart disease and congestive heart failure. Serum P level was correlated positively with intact PTH level. Patients with higher intact PTH levels tended to be younger, African American, have longer dialysis duration, and also a lower prevalence of diabetes, ischemic heart disease and congestive heart failure.

**Joint levels of serum P and intact PTH and all-cause mortality**

Median duration of follow-up was 1.4 years (IQR, 0.6–2.8). During follow-up, 58,208 patients died (54%) and the crude mortality rate was 294 per each 1,000 person-year. In the unadjusted model, higher serum P and PTH levels were linearly associated with better survival, in which mortality risk tended to be highest in patients with a combination of serum P <3.5 mg/dL and intact PTH <150 pg/mL [hazard ratio (HR) 2.20, 95% confidence
interval (CI) 2.08–2.34 when compared with patients with serum P ≥7.0 mg/dL and intact PTH level of ≥600 pg/mL (reference group). This association, however, was reversed after adjustment with additional covariates. In the fully adjusted model (case-mix plus MICS adjusted), compared to the reference group, patients with serum P level of 3.5 to <5.5 mg/dL combined with intact PTH of 150 to <300 pg/mL tended to have the lowest estimated HR (HR 0.64, 95% CI 0.61–0.67). The HR for this group was also significantly lower than the HRs for the groups with serum P of 3.5 to <5.5 mg/dL but intact PTH of ≥600 pg/mL; with serum P of 5.5 to <7.0 mg/dL and intact PTH of ≥300 pg/mL; and with serum P of ≥7.0 mg/dL and any intact PTH level, when CIs for each HR were compared (Table 2).

Within each intact PTH stratum, the association between serum P level and mortality followed a J-shaped curve (Figure 1). In addition, the trend of increasing mortality risk with higher serum intact PTH level existed in the three serum P strata ≥3.5 mg/dL. In particular, serum intact PTH level ≥600 pg/mL was associated with significantly higher mortality compared to other intact PTH levels, as indicated by CIs that did not overlap for HRs, in all 3 strata where serum P level was ≥3.5 mg/dL (Table 2). This effect was attenuated in serum P stratum <3.5 mg/dL.

**Mortality prediction with changes in serum P and intact PTH levels**

Mortality predictability by change in serum P or intact PTH level during the first 6 months of dialysis treatment in our cohort was evaluated in a total of 66,084 HD patients who had serum P and intact PTH measures in both the first and the third quarter, and survived for at least 6 months after cohort entry. Compared with patients whose serum P level was sustained greater than 5.5 mg/dL, survival benefit was revealed in patients with decrease in serum P level from ≥5.5 mg/dL to 3.5–<5.5 mg/dL (HR 0.93, 95% CI 0.90–0.96). In the same vein, increase in serum P level from 3.5–<5.5 mg/dL to ≥5.5 mg/dL tended to be associated with higher mortality compared with no change for patients with serum P level values 3.5–<5.5 mg/dL (HR 1.03, 95% CI 0.99–1.06) (Table 3). In contrast, a decrease to low level serum P (<3.5 mg/dL) was paradoxically associated with increased mortality when compared to those who did not change from this serum P level strata from baseline (HR 1.40, 95% CI 1.24–1.58 for change from ≥5.5 mg/dL to <3.5 mg/dL; HR 1.28, 95% CI 1.21–1.36 for change from 3.5–<5.5 mg/dL to <3.5 mg/dL).

Compared with patients who maintained a high serum intact PTH level ≥300 pg/mL, patients whose serum intact PTH decreased from ≥300 pg/mL to 150–<300 pg/mL did not show a significantly lower mortality risk (HR 1.03, 95% CI 0.99–1.08). The only change in serum intact PTH level that was associated with a significant decrease in mortality was for those with a baseline <150 pg/ml and experienced an increased to 150–<300 pg/ml (HR 0.94, 95% CI 0.90–0.99) (Table 4).

**Discordant changes in serum P and intact PTH levels and mortality: Composite ranking score analysis**

The composite ranking score analysis reported that a fall in serum P level over 6 months, even in patient whose serum intact PTH level rises at the same time, tended to be associated with lower mortality (left side of the Figure 2), whereas an increase in serum P level, even if
it occurred concurrently with a fall in serum intact PTH level, tended to be associated with higher risk of death (right side of the Figure 2). However, this association was not significant overall, suggesting that lowering one of the two measures while the other one increases, is not related to significant improvement in survival.

Discussion

This study provides detailed information on mortality outcomes according to the combination of serum P and PTH levels in a large cohort of HD patients. Patients with a combination of preferable serum P (3.5–<5.5 mg/dL) and preferable PTH (150–<300 pg/mL) levels tended to have the lowest mortality risk. Change in serum P level to this preferable range was associated with low risk of mortality, whereas only increase in low serum PTH level to its preferable range was significantly associated with lower mortality.

Previous studies have shown a consistent association between higher serum P concentrations and the increased relative risk of mortality in dialysis patients. [4–11] Secondary hyperparathyroidism has also been found to be related to higher mortality. [4–6, 8–10] These studies suggest that serum P and PTH levels are independently associated with mortality. With a larger number of patients than those in previous studies, we modeled mortality risk with joint levels of serum P with PTH ("bivariate" predictor). This approach may have an advantage in risk stratification because both measures are main targets of CKD-MBD treatment and various combinations of serum P and PTH levels are observed in clinical practice. Adjusted HR for all-cause mortality tended to be lowest in patients having serum P level of 3.5–<5.5 mg/dL and intact PTH level of 150–<300 pg/mL simultaneously. The results presented in Table 2 suggest that the treatment of CKD–MBD should be balanced to achieve these preferred serum P and PTH levels together as long as possible. Recently, advances in CKD-MBD treatment with medications such as sevelamer, lanthanum, paricalcitol and cinacalcet, allow us to manipulate serum calcium, P and PTH separately. In this era, a detailed and individually tailored treatment for CKD-MBD could be possible and potentially helpful to improve a patient’s outcome.

Serum P level more than 7.0 mg/dL was significantly associated with increased risk of mortality in each intact PTH stratum. 600 pg/mL Mortality risk was significantly increased with serum P level more than 600 pg/mL in normal and high serum P strata (≥3.5 mg/dL). However, the association was attenuated when serum P level was low (<3.5 mg/dL). These observations were comparable with previous reports. Block et al. reported that serum P concentrations >5.0 mg/dL were associated with an increased relative risk of death. This study additionally reported that moderate to severe hyperparathyroidism (PTH ≥600 pg/mL) was associated with an increase in relative risk of death, whereas more modest increases in PTH were not. [4] Young et al. demonstrated that all-cause mortality was significantly and independently associated with serum concentration of P (relative risk (RR): 1.04 per 1 mg/dL, p = 0.0003) and PTH (RR: 1.01 per 100 pg/dL, p=0.04). [5] Furthermore, studies using time-varying survival models have shown similar associations. Kalantar-Zadeh et al. reported that hyperphosphatemia (>6 mg/dL) and high serum PTH value (≥300 pg/mL) were strong correlates of higher death risk in time-dependent Cox regression analyses. [6] Floege et al. recently showed that serum PTH concentration above 600 pg/mL and P concentration...
above 5.5 mg/dL were associated with an increased risk of mortality in fixed Cox analyses [adjusted HR 2.10 (95% CI 1.62–2.73) and 1.32 (1.13–1.55), respectively]. [10]

Our results corroborate the findings of previous studies and additionally suggest that there is a mechanism attenuating the effect of PTH on mortality in patients with lower serum P concentrations. One possible explanation for this finding is due to the association between serum P level and dietary protein intake. [21] Previous studies have reported that an association between low serum P level and high mortality may be explained by low serum P level being a proxy of poor dietary protein intake [22] and protein–energy wasting [6], both known strong predictors of mortality. [23–26] In low serum P level, an association between PTH level and mortality may be masked by a strong association of protein-energy wasting with mortality. [27]

Our results showed that patients whose serum P level decreased from ≥5.5 mg/dL to 3.5–<5.5 mg/dL have 7% lower risk of mortality compared to those with persistently high serum P level ≥5.5 mg/dL. In the same vein, rise in serum P level from 3.5–<5.5 mg/dL to ≥5.5 mg/dL showed a non-significant trend toward increased mortality risk when compared with patients whose serum P stayed within 3.5–<5.5 mg/dL (HR 1.03, 95% CI 0.99–1.06). A previous study reported that both drop and rise in serum P out of 3.5–5.5 mg/dL were associated with additional risk of mortality. [6] Although there is no conclusive clinical trial demonstrating the impact of lowering serum P or PTH level on outcomes in ESRD patients, [9, 28] maintaining serum P level within the 3.5–5.5mg/dL range may be beneficial for patient-level outcomes. Unlike change in serum P level, a change in serum intact PTH level did not show an association with mortality in our analysis. Caution should be used in interpreting this observation because use of active vitamin D therapy could not be incorporated in our analysis. In previous studies, vitamin D analogs therapy was associated with favorable outcomes in CKD [29, 30] and dialysis patients. [31–33] Active vitamin D therapy may impact outcomes independently of its effect on serum PTH. Patients having persistent high serum PTH tended to be continuously treated with high dose of active vitamin D, which could attenuate a harmful effect from uncontrolled serum PTH. In addition to reporting on the mortality associations for change in serum P or PTH level separately, our study also showed decreasing one of the two measures while the other increases, was not significantly associated with mortality. It suggests that conflicting change in serum P and PTH compete for survival.

Strengths of our study include the use of a large sample size of patients representative of US hemodialysis population [34] and use of uniform laboratory measurements. However, some limitations should be noted. First, our cohort consisted of both prevalent and incident HD patients, where 60% of patients had a less than 6-month dialysis duration at entry into cohort. Although we adjusted for dialysis duration in our case-mix and case-mix plus MICS adjusted analyses, patients who have been on dialysis longer may have conditions or body chemistry that may differ from incident patients. The inability to account for these differences with available lab data may lead to residual confounding. Secondly, information on comorbid conditions was obtained at the time of dialysis initiation. Median lag time between dialysis initiation and baseline was 3 months (IQR 1–26). A variation in the time
from comorbidity measurement to cohort entry could be a source of potential error or confounding.

In addition our study was limited by lack of available data on a number of measurements which may lead to residual confounding. Data on phosphate binders and vitamin D receptor activators was not available. We are therefore unable to determine whether observed associations with mortality were driven by actual serum concentrations themselves or by pharmacologic interventions that influence serum concentrations. Data on FGF-23 level was also not available. Given rising evidence for the mortality association of FGF-23, [35–37] our study should have but could not incorporate its potential pathophysiologic role, especially in association between serum P and mortality. Additionally, there were no data on residual renal function. Residual renal function is an important covariate influencing biomarkers of CKD-MBD and mortality even in HD patients. [38] It should be noted that change in score is not a validated parameter in either healthy subjects of hemodialysis patients against any outcomes. Lastly, because this is an observational cohort study, control for confounders is limited to those that are recognized and measured and we cannot assume that associations imply causal relationships.

In conclusion, our findings for serum P and intact PTH largely support current practical guidelines for CKD-MBD. We demonstrate that balanced control of serum P and PTH level may lead better outcomes in ESRD patients. Further studies, particularly clinical trials, examining the physiological mechanisms behind the relationship between serum P and PTH level with mortality are needed.

Acknowledgments

We thank DaVita Clinical Research (DCR) for providing the clinical data for this research. The work is supported by Dr. KKZ’s NIH (NIDDK) grants K24-DK091419, R01-DK078106, a philanthropic grant from Mr. Harold Simmons and research grants from DaVita Clinical Research. Dr. KKZ was the medical director of DaVita Harbor-UCLA/MFI in Long Beach, CA during 2007–2012.

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Highlights

- A large cohort of hemodialysis patients
- We model mortality of combined serum phosphorus and parathyroid hormone levels.
- Survival may be greatest with controlling both serum P and PTH levels in balance.
Figure 1.
Association of combined levels of baseline serum phosphorus and intact parathyroid hormone with all-cause mortality in 107,299 maintenance hemodialysis patients

Note: Patients with serum phosphorus level of ≥7.0 mg/dL and intact parathyroid hormone level of ≥600 pg/mL were considered as the reference. Hazard ratios were estimated by case-mix plus MICS adjusted Cox regression models. Abbreviations: P, phosphorus; PTH, parathyroid hormone; MICS, malnutrition–inflammation cachexia syndrome.
Figure 2.
Mortality association of discordant change in serum phosphorus and intact parathyroid hormone levels during the first 6 months after entry (n = 66,084)

Note: Each patient received a percentile score between −100 and +100 according to the change in serum phosphorus or intact parathyroid hormone level. Difference of the scores created composite ranking score between −200 and +200. The Y-axis shows the logarithm of hazard ratio from Cox regression using restricted cubic splines, adjusted for case-mix plus MICS covariates. Dashed lines are 95% point-wise confidence levels.
Table 1

Baseline characteristics stratified by baseline serum P and intact PTH levels in 107,299 HD patients

| Variables          | Total | Phosphorus (mg/dL) | Intact PTH (pg/mL) |
|--------------------|-------|--------------------|--------------------|
|                    |       | <3.5               | 3.5–<5.5           | 5.5–<7.0 | ≥7.0 | <150 | 150–<300 | 300–<600 | ≥600 |
| N                  | 107,299 | 5,694            | 50,632             | 34,275   | 16,698 | 28,149 | 36,788   | 27,639   | 14,723 |
| Age (year)         | 64 (15) | 70 (13)           | 67 (14)            | 62 (15)  | 55 (15) | 66 (15) | 66 (15)  | 62 (15)  | 57 (16) |
| Female (%)         | 45     | 48                | 46                 | 45       | 41     | 46     | 44       | 45       | 46     |
| Race/ethnicity (%) |        |                   |                    |          |        |        |          |          |        |
| Caucasian          | 42     | 42                | 44                 | 40       | 38     | 51     | 44       | 36       | 27     |
| African American   | 33     | 35                | 31                 | 33       | 34     | 22     | 29       | 38       | 51     |
| Hispanic           | 15     | 14                | 14                 | 16       | 17     | 15     | 16       | 16       | 13     |
| Asian              | 3      | 2                 | 3                  | 3        | 3      | 4      | 3        | 3        | 2      |
| Dialysis duration (%) |       |                   |                    |          |        |        |          |          |        |
| <6 mo              | 60     | 62                | 64                 | 59       | 49     | 62     | 63       | 60       | 47     |
| 6 mo – <2 yrs      | 16     | 16                | 16                 | 16       | 19     | 18     | 16       | 16       | 14     |
| 2 – <5yrs          | 15     | 14                | 13                 | 16       | 20     | 14     | 14       | 16       | 21     |
| ≥5 yrs             | 8      | 8                 | 7                  | 9        | 12     | 6      | 6        | 8        | 18     |
| Primary insurance (%) |       |                   |                    |          |        |        |          |          |        |
| Medicare           | 68     | 71                | 69                 | 67       | 66     | 69     | 69       | 67       | 66     |
| Medicaid           | 6      | 5                 | 5                  | 6        | 8      | 5      | 5        | 6        | 8      |
| Other              | 21     | 17                | 21                 | 22       | 21     | 20     | 21       | 22       | 21     |
| Marital status (%) |        |                   |                    |          |        |        |          |          |        |
| Married            | 44     | 42                | 46                 | 44       | 39     | 47     | 47       | 42       | 36     |
| Divorced           | 8      | 7                 | 7                  | 9        | 10     | 7      | 8        | 9        | 9      |
| Single             | 27     | 21                | 23                 | 28       | 36     | 22     | 24       | 29       | 39     |
| Widowed            | 16     | 23                | 19                 | 14       | 10     | 18     | 17       | 15       | 12     |
| Vascular access (%) |       |                   |                    |          |        |        |          |          |        |
| AV fistula         | 22     | 16                | 21                 | 23       | 25     | 21     | 22       | 22       | 23     |
| AV graft           | 25     | 24                | 25                 | 25       | 24     | 25     | 25       | 24       | 25     |
| Catheter           | 35     | 42                | 36                 | 34       | 32     | 37     | 35       | 36       | 33     |
| Comorbid conditions (%) |       |                   |                    |          |        |        |          |          |        |
| Variables   | Total | <3.5 | 3.5–<5.5 | 5.5–<7.0 | ≥7.0 | <150 | 150–<300 | 300–<600 | ≥600 |
|------------|-------|------|----------|----------|------|------|----------|----------|------|
| DM         | 59    | 58   | 61       | 59       | 53   | 59   | 63       | 60       | 47   |
| HTN        | 80    | 78   | 79       | 80       | 79   | 78   | 80       | 81       | 80   |
| IHD        | 22    | 26   | 25       | 20       | 15   | 24   | 23       | 20       | 14   |
| CHF        | 29    | 34   | 31       | 27       | 23   | 30   | 30       | 27       | 22   |
| PVD        | 12    | 14   | 13       | 11       | 9    | 14   | 13       | 10       | 8    |
| CVA        | 8     | 12   | 9        | 7        | 5    | 9    | 8        | 7        | 6    |
| Malignancy | 5     | 7    | 5        | 4        | 3    | 6    | 5        | 4        | 3    |
| COPD       | 6     | 8    | 7        | 5        | 4    | 7    | 6        | 6        | 4    |
| Non-ambulatory | 3 | 7    | 4        | 3        | 2    | 4    | 3        | 3        | 2    |
| Current smoking | 5 | 3    | 4        | 3        | 2    | 4    | 3        | 5        | 6    |

| Variables | Total | <3.5 | 3.5–<5.5 | 5.5–<7.0 | ≥7.0 | <150 | 150–<300 | 300–<600 | ≥600 |
|-----------|-------|------|----------|----------|------|------|----------|----------|------|
| Phosphorus (mg/dL) | 5.6 (1.5) | 3.0 (0.4) | 4.6 (0.5) | 6.1 (0.4) | 8.1 (1.0) | 5.0 (1.3) | 5.4 (1.3) | 5.8 (1.5) | 6.5 (1.6) |
| Intact PTH (pg/mL) | 244 (144–417) | 151 (78–253) | 213 (126–336) | 274 (167–456) | 396 (226–711) | 90 (55–121) | 217 (184–226) | 401 (344–480) | 872 (704–1215) |
| Total calcium (mg/dL) | 9.2 (0.7) | 9.2 (0.9) | 9.2 (0.7) | 9.2 (0.7) | 9.0 (0.8) | 9.2 (0.7) | 9.3 (0.7) | 9.1 (0.6) | 9.1 (0.7) |
| Albumin (g/dL) | 3.7 (0.5) | 3.6 (0.5) | 3.7 (0.4) | 3.8 (0.4) | 3.7 (0.5) | 3.6 (0.5) | 3.7 (0.5) | 3.7 (0.5) | 3.7 (0.5) |
| TIBC (μg/dL) | 209 (46) | 208 (44) | 213 (45) | 212 (44) | 209 (46) | 204 (48) | 211 (46) | 212 (45) | 212 (45) |
| Ferritin (ng/mL) | 384 (182–713) | 508 (259–889) | 388 (187–713) | 362 (170–687) | 376 (174–703) | 415 (198–765) | 372 (178–693) | 360 (171–678) | 403 (189–723) |
| Total CO₂ (mEq/L) | 22.4 (3.0) | 21.7 (3.1) | 23.1 (2.8) | 21.9 (2.8) | 20.6 (2.9) | 22.4 (3.0) | 22.8 (3.0) | 22.5 (3.0) | 22.1 (3.0) |
| Hemoglobin (g/dL) | 12.0 (1.4) | 11.8 (1.4) | 12.0 (1.4) | 12.1 (1.3) | 12.0 (1.4) | 12.0 (1.4) | 12.0 (1.4) | 12.1 (1.3) | 12.0 (1.4) |
| WBC (x10⁹/μL) | 7.5 (2.5) | 7.1 (2.3) | 7.4 (2.5) | 7.4 (2.4) | 7.6 (2.3) | 7.5 (2.5) | 7.8 (2.8) | 7.5 (2.5) | 7.3 (2.4) |
| Lymphocyte (%) | 20 (8) | 22 (8) | 20 (8) | 21 (8) | 21 (8) | 20 (8) | 20 (8) | 20 (8) | 21 (8) |
| Single pool Kt/V | 1.53 (0.35) | 1.58 (0.39) | 1.56 (0.36) | 1.51 (0.34) | 1.45 (0.32) | 1.56 (0.36) | 1.54 (0.35) | 1.50 (0.35) | 1.47 (0.34) |
| nPNA (g/kg/day) | 0.95 (0.26) | 0.98 (0.25) | 0.90 (0.24) | 0.99 (0.24) | 1.06 (0.25) | 0.95 (0.26) | 0.92 (0.26) | 0.95 (0.25) | 0.96 (0.25) |

Note: Categorical variables are given as percentage; continuous variables as mean (standard deviation) or median (interquartile range) as appropriate. Laboratory measures are represented as averages of repeated measures during the first quarter of entry to cohort. Conversion factors for units: albumin and hemoglobin in g/dL to g/L, ×10; calcium in mg/dL to mmol/L, ×0.2495; phosphorus in mg/dL to mmol/L, ×0.3229; TIBC in μg/dL to μmol/L, ×0.179. No conversion necessary for intact PTH in pg/mL and ng/L, ferritin in ng/mL and μg/L, and WBC count in 10⁹/μL and 10³/L. Abbreviations: PTH, parathyroid hormone; P, phosphorus; AV, arteriovenous; DM, diabetes mellitus; HTN, hypertension; IHD, ischemic heart disease; CHF, congestive heart failure; PVD, peripheral vascular disease; CVA, cerebrovascular accident; COPD, chronic obstructive pulmonary disease; TIBC, total iron-binding capacity; WBC, white blood cells; nPNA, normalized protein nitrogen appearance.
Table 2

Association of combined serum P and intact PTH levels with all-cause mortality (n = 107,299)

| Phosphorus (mg/dL) | Intact PTH (pg/mL) | <150 | 150–<300 | 300–<600 | ≥600 |
|-------------------|--------------------|------|----------|----------|------|
| Unadjusted        |                    |      |          |          |      |
| <3.5              | 2.20 (2.08–2.34)   | 1.97 (1.83–2.11) | 1.83 (1.66–2.02) | 1.75 (1.48–2.07) |
| 3.5–<5.5          | 1.51 (1.45–1.58)   | 1.33 (1.27–1.39) | 1.29 (1.23–1.35) | 1.30 (1.23–1.38) |
| 5.5–<7.0          | 1.24 (1.18–1.30)   | 1.15 (1.09–1.20) | 1.11 (1.06–1.17) | 1.08 (1.02–1.14) |
| ≥7.0              | 1.20 (1.12–1.29)   | 1.19 (1.12–1.26) | 1.07 (1.01–1.13) | Reference |
| Case-mix adjusted |                    |      |          |          |      |
| <3.5              | 1.01 (0.95–1.07)   | 0.88 (0.82–0.94) | 0.93 (0.85–1.03) | 1.01 (0.85–1.19) |
| 3.5–<5.5          | 0.77 (0.74–0.81)   | 0.69 (0.66–0.72) | 0.71 (0.67–0.74) | 0.87 (0.82–0.92) |
| 5.5–<7.0          | 0.72 (0.69–0.76)   | 0.70 (0.66–0.73) | 0.72 (0.69–0.76) | 0.87 (0.83–0.92) |
| ≥7.0              | 0.83 (0.77–0.89)   | 0.83 (0.78–0.88) | 0.84 (0.79–0.88) | Reference |
| Case-mix plus MICS adjusted | |      |          |          |      |
| <3.5              | 0.71 (0.67–0.76)   | 0.69 (0.64–0.74) | 0.74 (0.67–0.81) | 0.77 (0.65–0.91) |
| 3.5–<5.5          | 0.68 (0.65–0.71)   | 0.64 (0.61–0.67) | 0.66 (0.63–0.70) | 0.79 (0.74–0.83) |
| 5.5–<7.0          | 0.69 (0.65–0.72)   | 0.69 (0.66–0.72) | 0.72 (0.68–0.75) | 0.85 (0.80–0.89) |
| ≥7.0              | 0.77 (0.72–0.83)   | 0.83 (0.78–0.88) | 0.86 (0.81–0.91) | Reference |

Note: Case-mix adjusted model included age, gender, race/ethnicity, diabetes mellitus, dialysis vintage, comorbidities, primary insurance, marital status, vascular access type, dialysis dose estimated by single-pool Kt/V and serum total calcium level as covariates. Case-mix and MICS adjusted models included all of the covariates in the case-mix model as well as 8 surrogates of nutritional status and inflammation: serum albumin, total iron-binding capacity, ferritin, bicarbonate, peripheral white blood cell count, lymphocyte percentage, hemoglobin, and normalized protein nitrogen appearance. Abbreviations: PTH, parathyroid hormone; MICS, malnutrition-inflammation cachexia syndrome.
### Table 3

Adjusted hazard ratios for all-cause mortality by change in serum P level during the first 6 months after entry (n = 66,084)

| Baseline P (mg/dL) | 3rd quarter P (mg/dL) | n   | HR (95% CI)       |
|-------------------|------------------------|-----|------------------|
| ≥5.5              | <3.5                   | 396 | 1.40 (1.24–1.58) |
|                   | 3.5–<5.5               | 9,525 | 0.93 (0.90–0.96) |
|                   | ≥5.5                   | 22,720 | Ref              |
| 3.5–<5.5          | <3.5                   | 1,789 | 1.28 (1.21–1.36) |
|                   | 3.5–<5.5               | 19,723 | Ref              |
|                   | ≥5.5                   | 9,225 | 1.03 (0.99–1.06) |
| <3.5              | <3.5                   | 669  | Ref              |
|                   | 3.5–<5.5               | 1,689 | 0.78 (0.69–0.87) |
|                   | ≥5.5                   | 348  | 0.86 (0.73–1.02) |

*Note:* Patients who did not change serum P category during 6 months were treated as the reference in each baseline serum P category. Abbreviations: P, phosphorus; HR, hazard ratio; CI, confidence interval.
Table 4

Adjusted hazard ratios for all-cause mortality by change in serum intact PTH level during the first 6 months after entry (n = 66,084)

| Baseline intact PTH (pg/mL) | 3rd quarter intact PTH (pg/mL) | n    | HR (95% CI)          |
|----------------------------|-------------------------------|------|----------------------|
| ≥300                       | <150                          | 3,461| 1.04 (0.98–1.10)     |
| 150–<300                   |                               | 6,567| 1.03 (0.99–1.08)     |
| ≥300                       |                               | 15,853| Ref                 |
| 150–<300                   | <150                          | 7,238| 1.04 (0.99–1.08)     |
| 150–<300                   |                               | 10,504| Ref                 |
| ≥300                       |                               | 5,497| 1.00 (0.96–1.05)     |
| <150                       | <150                          | 10,042| Ref                 |
| 150–<300                   |                               | 5,312| 0.94 (0.90–0.99)     |
| ≥300                       |                               | 1,610| 1.02 (0.95–1.09)     |

Note: Patients who did not change serum intact PTH category during 6 months were treated as the reference in each baseline serum intact PTH category. Abbreviations: PTH, parathyroid hormone; HR, hazard ratio; CI, confidence interval.