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学　位　論　文

Association between serum inorganic phosphorus levels and adverse outcomes in chronic kidney disease: The Fukushima CKD Cohort study

（慢性腎臓病における無機リン濃度と予後との関連：福島 CKD コホート研究）

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Introduction

Chronic kidney disease (CKD) is associated with a higher risk of all-cause and cardiovascular death (1). Mineral metabolism disorders are common among patients with severe CKD, including dialysis patients, with serum inorganic phosphorus and calcium abnormality suggested as being risk factors of these events. Several observational studies, including studies based on data from the United States Renal Data System and the Dialysis Outcomes Practice Patterns Study, have reported associations between abnormalities in mineral metabolism, such as higher serum inorganic phosphorus or calcium, and all-cause and cardiovascular mortality in dialysis patients (2-4). Recent studies have demonstrated that elevated serum levels of inorganic phosphorus were an independent risk factor for all-cause death, cardiovascular events, and CKD progression even among patients with non-dialysis dependent CKD (NDD-CKD) (5-9). Meta-analyses also demonstrated that there were independent associations between higher inorganic phosphorus levels and CKD progression and mortality in NDD-CKD patients (10, 11). However, some studies have reported finding no independent associations for serum inorganic phosphorus levels with the risk for cardiovascular death or CKD progression in these patients (12, 13). In addition, since the serum inorganic phosphorus levels associated with increased risk for these adverse outcomes has varied from study to study, the optimal range of serum inorganic phosphorus levels in NDD-CKD remains controversial. The risk of end-stage renal disease (ESRD) is reportedly higher than that for death due to cardiovascular disease (CVD) in Japanese CKD patients, with the incidence of cardiovascular events much lower than that found in Western counterparts (14, 15). Since there appear to be differences between Japanese and Western CKD patients, it is crucial to elucidate the association of serum inorganic phosphorus levels in

CKD progression and other adverse events in Japanese NDD-CKD patients. However, there have been fewer evaluations of the relationships between serum inorganic phosphorus levels and adverse outcomes in Japanese patients. Therefore, the aim of the present study was to investigate the relevance of serum inorganic phosphorus levels to CKD progression, cardiovascular events, and mortality in Japanese NDD-CKD patients evaluated in the Fukushima CKD Cohort Study.

Methods

Study population (Fukushima CKD Cohort)

The Fukushima Cohort Study is a prospective survey of patient characteristics and outcomes for subjects having one or more cardiovascular risk factors, such as CKD, hypertension, diabetes, and dyslipidemia and being followed at the Fukushima Medical University Hospital enrolled between June 2012 and July 2014 (16). The Fukushima CKD Cohort Study is a sub-cohort of Fukushima Cohort Study of subjects with NDD-CKD (17).

Out of the originally recruited 2,724 patients in the Fukushima Cohort Study, subjects excluded from this analysis were: patients lacking data on serum creatinine and eGFR ≥60 mL/min/1.73 m^2 and patients who did not have positive proteinuria at the time of registration. After the exclusion of those without serum calcium and inorganic phosphorus data, a total of 822 participants were evaluated in the present study (Figure 1). This study was approved by the Ethics Committee of Fukushima Medical University (acceptance no. 1456, 2001) and carried out in accordance with the Declaration of Helsinki. The study was registered in the University Hospital Medical Information Network Clinical Trials Registry (UMIN000040848).

Measurements

Information on medication being administered at baseline, as well as history of CVD, diabetes mellitus, hypertension, and dyslipidemia were obtained from the patients' medical records or from results of blood examinations performed at registration. Serum creatinine was measured by an enzyme assay method, while serum albumin, hemoglobin, inorganic phosphorus, calcium, intact-parathyroid hormone (PTH) levels were measured according to the automated, standardized laboratory technique of the clinical laboratory of our institution. Proteinuria was detected by a urine dipstick test. Systolic blood pressure and diastolic blood pressure were measured by trained staff using a standard sphygmomanometer or an automated device with subjects in the sitting position. Body mass index was calculated as weight (kg) divided by height squared (in meters, m^2). Patients with diabetes were identified by a fasting plasma glucose concentration ≥126 mg/dL, or a glycosylated hemoglobin (HbA1c) value (National Glycohemoglobin Standardization) ≥6.5%, or as patients who used insulin or oral antihyperglycemic drugs. Dyslipidemia was defined as patients with either a triglyceride concentration ≥150 mg/dL, low-density lipoprotein cholesterol concentration ≥140 mg/dL, high-density lipoprotein cholesterol concentration <40 mg/dL, or were using antihyperlipidemic medication. CVD included myocardial infarction, angina pectoris, congestive heart failure, arrhythmias, cerebrovascular disorders, chronic arteriosclerosis obliterans, and aortic dissection.

Outcomes

Follow-up data were obtained from patients' medical records. Study endpoints were all-cause death, cardiovascular, and kidney events prior to initiating the maintenance

dialysis therapy. Cardiovascular events included fatal and nonfatal myocardial infarction, angina pectoris, sudden death, congestive heart failure which requires hospitalization, fatal arrhythmias, cerebrovascular disorder, chronic arteriosclerosis obliterans, and aortic dissection. Kidney events were defined as a composite of doubling of the serum creatinine or ESRD that required renal replacement therapy.

Statistical analyses

Participant characteristics were evaluated by dividing the study population into quartiles according to the serum inorganic phosphorus (-2.8, 2.9-3.2, 3.3-3.6, 3.7- mg/dL), and serum calcium (-9.1, 9.2-9.3, 9.4-9.6, 9.7- mg/dL) levels. Serum calcium was corrected for a low serum albumin (corrected calcium = serum calcium + (4 – serum albumin)). Data are expressed as the median and interquartile range for continuous variables and percentages for categorical data. Differences between groups were analyzed by the Kruskal-Wallis test for continuous variables and the chi-square test for categorical variables. The incidences of cardiovascular and kidney events were presented as the number of events per 1,000 person-years. The Kaplan-Meier survival plots with a log-rank test and Cox proportional hazards models were used to evaluate the association of the quartile of the serum inorganic phosphorus and serum calcium levels with all-cause death, cardiovascular, and kidney events. Data were analyzed with SPSS version 26 (IBM Corporation, Chicago, IL, USA).

Results

Baseline Characteristics

Figure 1 presents the patient disposition. Table 1 summarizes the baseline characteristics for the patient groups that were divided according to the quartiles of the serum inorganic phosphorus levels, while the information for the patient groups divided according to the quartiles of the serum calcium levels were shown in supplemental Table S1. There were no significant differences in age, diabetes, dyslipidemia, or history of CVD across quartiles of serum inorganic phosphorus. Subjects with higher serum inorganic phosphorus had a significantly lower eGFR and lower hemoglobin. In contrast, subjects with higher serum calcium had a higher eGFR, higher hemoglobin, and lower PTH. There were 37 hyperphosphatemia patients (4.5% of the total) with a serum inorganic phosphorus level ≥4.5 mg/dL, 52 hypophosphatemia patients (6.3% of the total) with a serum inorganic phosphorus level ≤2.4 mg/dL and 25 hypercalcemia patients (3% of the total) with a serum calcium level ≥10 mg/dL. Baseline patients' characteristics by quartiles of serum inorganic phosphorus level were shown in men and women, separately (Table 2, 3).

Serum inorganic phosphorus levels and adverse outcomes

Over a median follow-up period of 2.8 years, 46 patients died, there were 50 cardiovascular events, and 102 kidney events occurred. Of these patients, 35 exhibited doubling of the serum creatinine, while 67 progressed to ESRD requiring dialysis. When the incidence rates were stratified according to the serum inorganic phosphorus categories at baseline, U-shaped relationships were observed for the kidney events (Table 4). A significant difference ($P<0.001$) was found for the incidence of kidney events among the NDD-CKD patients with different serum inorganic phosphorus levels at baseline, but not for the incidence of cardiovascular events and all-cause death (Figure 2A, B, C). The

multivariate Cox regression analysis results showed that higher serum inorganic phosphorus was significantly associated with an increased risk of kidney events, with the lowest risk shown to be a serum inorganic phosphorus level of 2.9-3.2 mg/dL. When compared to the reference level of 2.9-3.2 mg/dL, the adjusted hazard ratio for the kidney events was 1.73 (95% confidence interval (CI); 0.72-4.12) for serum inorganic phosphorus ≤2.8 mg/dL, 1.98 (95% CI; 0.87-4.52) for 3.3-3.6 mg/dL, and 3.30 (95% CI; 1.50-7.28) for ≥3.7 mg/dL (Model 3 in Table 4). A 1 mg/dL increase of the serum inorganic phosphorus was associated with an adjusted hazard ratio of 1.55 (95% CI; 1.15-2.09) for the kidney events. There were no significant associations between the serum inorganic phosphorus levels at baseline and the risk of cardiovascular events and all-cause death.

There were significant differences in sex distributions across quartiles of serum inorganic phosphorus levels (Table 1), so associations of serum inorganic phosphorus levels with adverse outcomes were evaluated in men and women, separately (Table 5, 6). Significant association was observed between kidney events and higher serum inorganic phosphorus in men. U-shaped relationships were observed in the incidences of the kidney events, but due to limited number of events (no kidney events were observed in a serum inorganic phosphorus level of 2.9-3.2 mg/dL in women), cox regression could not be performed for the kidney events in women. There were no significant associations between the serum inorganic phosphorus levels and the risk of cardiovascular events and all-cause death in women but was marginal significant differences between the serum inorganic phosphorus levels and the risk of cardiovascular events in men (hazard ratio 3.22, 95% CI; 1.17-885, P=0.023, for ≥3.7 mg/dL, compared to the reference level of 2.9-3.2 mg/dL).

Kidney events were evaluated in doubling of the serum creatinine and ESRD, separately (supplemental Table S2). Due to limited number of events, multivariate adjustment was not performed for doubling of the serum creatinine, but the serum inorganic phosphorus levels had a significant association with ESRD.

Serum calcium levels and adverse outcomes

Significant differences were found in the incidence of cardiovascular (P=0.008) and kidney events (P=0.004) among the patients with different serum calcium levels, but not in the incidence of all-cause death (Supplemental Figure S1). Although univariate analysis showed that the risks of cardiovascular and kidney events were significantly higher with a serum calcium level ≤9.1 mg/dL compared to a serum calcium of 9.4-9.6 mg/dL, the significant associations for the serum calcium levels and the risk of cardiovascular and kidney events disappeared after multivariate adjustment for confounding factors (supplemental Table S3).

Discussion

The present study investigated serum inorganic phosphorus and calcium associations with mortality, cardiovascular, and kidney events in Japanese NDD-CKD patients, and demonstrated that serum inorganic phosphorus levels were independently associated with kidney events, but not with either mortality or cardiovascular events. U-shaped relationships were observed between the serum inorganic phosphorus levels and the incidence of kidney events, with the best outcomes seen with serum inorganic phosphorus levels of 2.9-3.2 mg/dL. A serum inorganic phosphorus level of ≥3.7 mg/dL was

significantly associated with an increased risk of kidney events, as compared to the reference level of 2.9-3.2 mg/dL.

There were no independent associations between the serum calcium levels and adverse outcomes in the present study. It would be expected that higher serum calcium levels contribute to adverse outcomes, due to precipitation of calcium-phosphorus product in vessels causing vascular calcification. Indeed, higher serum calcium was reportedly associated with mortality in dialysis patients (2-4). However, recent several studies reported the association between lower serum calcium and CKD progression in the patients with NDD-CKD (18) (19). As additional residual confounding factors, such as vitamin D deficiency, may influence these results in addition to sample size or observation period, further research is still needed to reveal the effects of serum calcium on CKD progression and mortality in NDD-CKD.

Previous studies have identified a relationship between serum inorganic phosphorus levels and cardiovascular events, kidney events, and all-cause mortality in NDD-CKD patients (6, 7, 11, 20, 21). These studies reported that serum inorganic phosphorus levels ranging from 3.5-4.6 mg/dL or more were associated with these adverse outcomes. Although the serum inorganic phosphorus levels that contributed to this increased risk for these adverse outcomes varied according to the study, the cut-off values of serum inorganic phosphorus reported in these studies were similar to that found in our present study. In addition, the results of the present study were approximately the same as those reported in the prior studies.

It should be noted, however, that even when serum inorganic phosphorus levels are within the reference range, these can potentially relate adverse kidney outcomes. Since our present study found that only 4.5% of the population had hyperphosphatemia (≥4.5

mg/dL), this indicates that the majority of the patients in the highest quartile of the serum inorganic phosphorus levels had serum inorganic phosphorus levels that were within the reference range. In addition, it has also been reported that there was an association between the inorganic phosphorus levels and kidney events in Japanese NDD-CKD patients (22), with a inorganic phosphorus level of ≥3.4 mg/dL shown to be a risk factor for CKD progression to ESRD. Therefore, higher serum inorganic phosphorus levels that are still within the reference range could be a risk of adverse kidney outcomes in the NDD-CKD patients. The serum inorganic phosphorus level in the previous study was based on time-averaged value up to dialysis commencement (22). Therefore, it may be uncertain whether the patients started dialysis because of a high serum phosphorus inorganic level or whether their serum phosphorus level was high on average because they were about to start dialysis. In the present study, however, such a reverse causation is unlikely to occur. The present results suggest the importance of serum inorganic phosphorus management in CKD patients with regard to kidney outcomes. However, a more detailed evaluation is still required to verify the optimal range of serum inorganic phosphorus levels.

The present study found that there were marginal significant associations observed between serum inorganic phosphorus levels at baseline and the risk of cardiovascular events only in men but were no significant associations with the risk of cardiovascular events or all-cause mortality in whole cohort. Other previous studies have reported finding associations between higher serum inorganic phosphorus levels and the risk of CVD events and all-cause death in NDD-CKD patients (5, 7, 11, 13, 20, 21, 23). However, since the incidence of cardiovascular events or all-cause death are reportedly lower in Japanese NDD-CKD patients versus their Western counterparts (14), the low frequency

of these events may have been one of the factors contributing to this lack of a significant association. In fact, the incidence rate of CVD events (22.0 per 1,000 person-years) and all-cause death (19.8 per 1,000 person-years) in the present study were much less than expected, which might be due to the small number of participants and the relatively short observation period. Further clinical studies with a larger sample size and longer follow-up period may reveal the association between serum inorganic phosphorus levels and these events in Japanese NDD-CKD patients.

The association of higher serum inorganic phosphorus to adverse renal outcome could be explained by several mechanisms. First, in addition to direct phosphorus cytotoxicity, formation of calcium-phosphate crystals, called calciprotein, particle caused by increased phosphorus load could lead tubular injury, endothelial dysfunction, and vascular calcification in the kidneys (24). Second, increased phosphaturia could be related to renal damage. Decreased urinary reabsorption of phosphate reportedly associated with decreased eGFR and increased intact PTH in NDD-CKD (25), and a recent study reported that elevated phosphaturia accelerated CKD progression due to renal tubular injury even in the absence of hyperphosphatemia in animal model (26). Fibroblast growth factor 23 (FGF23), a peptide hormone inducing phosphaturia through its effects on proximal renal tubules, increases prior to the elevation of serum inorganic phosphorus levels in the patients with NDD-CKD maintaining the serum inorganic phosphorus levels to the reference range by promoting excretion per nephron. Thus, increased phosphaturia could explain the mechanisms on the associations between the reference range of serum inorganic phosphorus levels and adverse kidney events.

An observational study reported finding that the administration of phosphorus binders was associated with lower mortality in men with NDD-CKD (27). In a randomized

control trial in NDD-CKD patients with reference ranges of serum inorganic phosphorus levels, phosphorus binders significantly reduced serum inorganic phosphorus levels. In contrast, significant deteriorations of vascular calcification were observed in the calcium-based phosphorus binder group (28). More recently, Toussaint ND et al. reported that treatment with lanthanum did not affect arterial stiffness or aortic calcification in patients with stage 3b/4 CKD who have normophosphatemia (29). Further studies will need to be conducted to reveal the best strategy against elevated serum inorganic phosphorus during daily activities, such as dietary phosphorus restriction and the administration of phosphorus binders.

The present study had several limitations. The present study had several limitations. First, only a small sample size was evaluated. The number of all-cause deaths and cardiovascular events were much lower than expected. Moreover, due to limited number of patients, sub-analyses by sex were performed insufficiently in the present study. Thus, a larger sample size or a longer observation period will be needed to analyze the variables sufficiently associated with all-cause death and cardiovascular events and investigate the differences by sex. Recently, 30% to 40% declines in eGFR reportedly could be a useful surrogate endpoint in clinical research (30), and might be suitable to evaluate renal disease progression in NDD-CKD, although these data were not available in the present study. Second, unadjusted confounding factors could have been present. During the observation period, 67 cases of ESRD requiring dialysis occurred, but the causes of dialysis induction have not been investigated in detail. Indications that led to the initiation of dialysis, such as hyperkalemia and fluid overload, may have confounded the association between serum inorganic phosphorus level and renal events in the present study. Third, the serum inorganic phosphorus levels were only measured at baseline.

Therefore, single measurements of serum inorganic phosphorus might have led to some misclassification of hyperphosphatemia or the serum inorganic phosphorus category. Fourth, we did not collect any data on the serum FGF23 levels, C-reactive protein (CRP) or the medication use, such as phosphorus binders and activated vitamin D, which could relate to both the serum inorganic phosphorus levels and outcomes in CKD patients. Fifth, exclusion of many subjects without serum calcium and inorganic phosphorus data might had been caused a selection bias in the present study. Therefore, although this study could show an association between serum inorganic phosphorus level and renal events, further studies are needed to verify the causal relationship.

Conclusions

In summary, the present study showed that serum inorganic phosphorus levels were significantly associated with kidney events, but not with all-cause death and cardiovascular events in Japanese NDD-CKD patients. Serum inorganic phosphorus levels of ≥3.7 mg/dL were related to a higher risk of CKD progression as compared with the levels that ranged from 2.9-3.2 mg/dL. Further studies will need to be conducted to examine the reason why even serum inorganic phosphorus levels within the reference range can be associated with adverse outcomes in CKD, and whether lowering serum levels of inorganic phosphorus will delay CKD progression and improve renal prognosis.

Conflict of interest

The authors declare no conflicts of interest in relation to this work.

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Table 1. Patients' characteristics by quartiles of serum phosphorus level

	Serum phosphorus (mg/dL)				*P* for trend
	≤ 2.8	2.9-3.2	3.3-3.6	3.7 ≤	
N	186	213	196	227	
Age (y)	65 (55-75)	66 (54-75)	68 (60-76)	65 (54-74)	0.587
Male sex (%)	74.7	65.7	52.6	37.4	<0.001
Body mass index (kg/m^2)	24.9 (22.0-26.9)	23.3 (20.9-25.9)	23.6 (21.2-27.4)	23.7 (20.9-26.8)	0.067
Smoking history (%)	63.2	57.7	48.1	40.3	<0.001
Diabetes (%)	41.4	43.7	46.4	46.7	0.679
Dyslipidemia (%)	62.8	67.6	62.0	71.2	0.157
Cardiovascular disease (%)	30.6	31.9	33.7	27.8	0.600
Systolic blood pressure (mmHg)	127 (120-139)	126 (118-142)	136 (126-149)	135 (122-149)	0.435
Diastolic blood pressure (mmHg)	78 (72-87)	75 (69-83)	80 (71-84)	79 (68-85)	0.080
Serum creatinine (mg/dL)	1.09 (0.92-1.44)	1.10 (0.89-1.37)	1.13 (0.76-1.75)	1.69 (0.98-3.38)	0.011
eGFR (mL/min/1.73 m^2)	49.6 (38.4-58.1)	49.5 (39.9-58.9)	46.8 (29.5-60.9)	29.9 (13.2-47.5)	<0.001
Serum albumin (g/dL)	4.0 (3.6-4.2)	4.0 (3.6-4.2)	3.9 (3.6-4.2)	3.8 (3.4-4.0)	0.050
Hemoglobin (g/dL)	13.6 (12.4-14.5)	13.0 (12.0-14.1)	12.5 (11.1-14.0)	11.3 (10.4-12.7)	<0.001
Positive proteinuria (%)	37.3	38.2	41.8	52.7	0.004
Serum phosphorus (mg/dL)	2.6 (2.4-2.8)	3.1 (3.0-3.2)	3.4 (3.3-3.5)	4.0 (3.8-4.4)	<0.001
Serum calcium (mg/dL)	9.3 (9.1-9.6)	9.4 (9.2-9.7)	9.4 (9.1-9.7)	9.3 (9.1-9.6)	0.171
intact-PTH (pg/mL)	46 (33-72)	43 (30-69)	45 (32-75)	62 (30-159)	0.104

Median (25%-75%). eGFR, estimated glomerular filtration rate; PTH, parathyroid hormone.

Table 2. Patients' characteristics by quartiles of serum phosphorus level in men

	Serum phosphorus (mg/dL)				*P* for trend
	≤ 2.8	2.9-3.2	3.3-3.6	3.7 ≤	
N	139	140	103	85	
Age (y)	65 (58-74)	70 (57-76)	68 (60-73)	63 (49-71)	0.434
Body mass index (kg/m^2)	25.1 (22.5-26.7)	23.7 (21.7-25.7)	23.9 (21.7-27.4)	23.9 (20.8-27.2)	0.108
Smoking history (%)	71.2	75.7	68.9	71.8	0.686
Diabetes (%)	43.2	49.3	47.6	51.8	0.605
Dyslipidemia (%)	62.0	68.8	56.9	67.1	0.239
Cardiovascular disease (%)	31.7	39.3	42.7	31.8	0.219
Systolic blood pressure (mmHg)	126 (120-135)	130 (119-143)	132 (118-144)	132 (124-145)	0.584
Diastolic blood pressure (mmHg)	78 (70-85)	79 (69-81)	80 (73-84)	81 (69-87)	0.315
Serum creatinine (mg/dL)	1.19 (0.97-1.58)	1.15 (1.00-1.43)	1.39 (1.09-2.09)	2.55 (1.44-3.91)	<0.001
eGFR (mL/min/1.73 m^2)	49.1 (34.8-59.2)	50.2 (39.4-58.3)	39.3 (26.0-55.4)	21.9 (13.1-40.8)	<0.001
Serum albumin (g/dL)	4.0 (3.6-4.2)	4.0 (3.5-4.2)	3.9 (3.4-4.1)	3.9 (3.3-4.1)	0.253
Hemoglobin (g/dL)	13.8 (12.5-14.7)	13.2 (12.2-14.7)	13.4 (11.7-14.3)	11.6 (10.7-12.8)	<0.001
Positive proteinuria (%)	36.9	40.7	46.1	63.5	0.002
Serum phosphorus (mg/dL)	2.6 (2.3-2.7)	3.1 (3.0-3.2)	3.4 (3.3-3.5)	3.9 (3.7-4.2)	<0.001
Serum calcium (mg/dL)	9.2 (9.0-9.5)	9.4 (9.1-9.7)	9.4 (9.0-9.7)	9.1 (8.8-9.4)	0.059
intact-PTH (pg/mL)	43 (33-69)	44 (30-66)	44 (28-69)	70 (35-181)	0.027

Median (25%-75%). eGFR, estimated glomerular filtration rate; PTH, parathyroid hormone.

Table 3. Patients' characteristics by quartiles of serum phosphorus level in women

	Serum phosphorus (mg/dL)				*P* for trend
	≤ 2.8	2.9-3.2	3.3-3.6	3.7 ≤	
N	47	73	93	142	
Age (y)	64 (47-77)	61 (45-66)	72 (59-78)	66 (57-76)	0.317
Body mass index (kg/m^2)	22.5 (19.6-27.3)	21.9 (20.3-27.3)	22.8 (20.3-27.0)	23.2 (20.8-27.1)	0.967
Smoking history (%)	23.4	13.7	21.5	18.3	0.502
Diabetes (%)	36.2	32.9	45.2	43.7	0.317
Dyslipidemia (%)	65.2	65.3	67.8	73.8	0.508
Cardiovascular disease (%)	27.7	17.8	23.7	25.4	0.567
Systolic blood pressure (mmHg)	137 (123-151)	126 (108-143)	141 (131-158)	137 (122-154)	0.654
Diastolic blood pressure (mmHg)	79 (73-94)	72 (66-84)	79 (67-86)	76 (66-85)	0.343
Serum creatinine (mg/dL)	0.92 (0.78-1.07)	0.88 (0.70-1.12)	0.83 (0.70-1.21)	1.26 (0.80-2.94)	0.073
eGFR (mL/min/1.73 m^2)	49.7 (41.2-55.9)	49.1 (40.7-69.0)	52.1 (34.5-62.3)	35.1 (12.8-53.4)	0.045
Serum albumin (g/dL)	3.9 (3.5-4.3)	3.8 (3.6-4.2)	3.9 (3.6-4.2)	3.8 (3.4-3.9)	0.369
Hemoglobin (g/dL)	13.2 (11.4-13.5)	12.7 (10.8-13.8)	11.6 (10.8-13.8)	11.2 (10.0-12.3)	0.003
Positive proteinuria (%)	30.4	33.3	36.8	46.0	0.140
Serum phosphorus (mg/dL)	2.7 (2.5-2.8)	3.1 (3.0-3.2)	3.4 (3.3-3.5)	4.1 (3.8-4.4)	<0.001
Serum calcium (mg/dL)	9.5 (9.3-9.7)	9.4 (9.3-9.6)	9.4 (9.2-9.6)	9.4 (9.2-9.7)	0.457
intact-PTH (pg/mL)	50 (40-85)	44 (31-78)	51 (37-82)	59 (28-126)	0.880

Median (25%-75%). eGFR, estimated glomerular filtration rate; PTH, parathyroid hormone.

Table 4. Associations of serum phosphorus levels with all-cause death, cardiovascular event, and kidney event in non-dialysis dependent CKD patients

	Incident rate	Univariate		Model 1		Model 2		Model 3	
	(/1,000 person-years)	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
All-cause death									
Serum phosphorus									
< 2.8 mg/dL	20.4	0.97 (0.44-2.18)	0.949	1.02 (0.46-2.28)	0.964	1.07 (0.48-2.39)	0.875	1.20 (0.52-2.77)	0.672
2.9-3.2 mg/dL	20.8	1.00 [reference]		1.00 [reference]		1.00 [reference]		1.00 [reference]	
3.3-3.6 mg/dL	12.7	0.60 (0.24-1.51)	0.279	0.66 (0.26-1.66)	0.374	0.64 (0.25-1.61)	0.337	0.58 (0.22-1.52)	0.266
≥3.7 mg/dL	24.7	1.17 (0.56-2.47)	0.674	1.49 (0.68-3.24)	0.321	1.53 (0.68-3.43)	0.302	1.26 (0.55-2.91)	0.587
per 1-mg/dL increase		1.08 (0.68-1.69)	0.754	1.23 (0.75-2.01)	0.423	1.20 (0.72-2.00)	0.489	1.00 (0.59-1.70)	0.988
Cardiovascular event									
Serum phosphorus									
< 2.8 mg/dL	20.9	1.44 (0.60-3.48)	0.416	1.45 (0.60-3.48)	0.416	1.32 (0.54-3.21)	0.543	1.36 (0.55-3.39)	0.507
2.9-3.2 mg/dL	14.6	1.00 [reference]		1.00 [reference]		1.00 [reference]		1.00 [reference]	
3.3-3.6 mg/dL	24.3	1.67 (0.72-3.91)	0.235	2.02 (0.86-4.74)	0.107	1.63 (0.69-3.83)	0.267	1.70 (0.72-4.04)	0.229
≥3.7 mg/dL	28.8	1.97 (0.88-4.43)	0.099	3.08 (1.34-7.09)	0.008	1.72 (0.71-4.18)	0.229	1.87 (0.73-4.77)	0.191
per 1-mg/dL increase		1.42 (0.95-2.12)	0.092	1.90 (1.25-2.90)	0.003	1.20 (0.78-1.85)	0.411	1.17 (0.75-1.85)	0.488
Kidney event									
Serum phosphorus									
< 2.8 mg/dL	28.6	2.20 (0.93-5.19)	0.072	2.12 (0.90-5.00)	0.086	2.19 (0.92-5.20)	0.077	1.73 (0.72-4.12)	0.218
2.9-3.2 mg/dL	12.9	1.00 [reference]		1.00 [reference]		1.00 [reference]		1.00 [reference]	
3.3-3.6 mg/dL	43.1	3.34 (1.49-7.47)	0.003	3.69 (1.65-8.26)	0.002	2.66 (1.19-5.97)	0.017	1.98 (0.87-4.52)	0.104
≥3.7 mg/dL	103.5	8.09 (3.86-16.98)	<0.001	10.70 (5.03-22.75)	<0.001	4.03 (1.87-8.66)	<0.001	3.30 (1.50-7.28)	0.003
per 1-mg/dL increase		2.80 (2.21-3.55)	<0.001	3.42 (2.67-4.39)	<0.001	1.61 (1.22-2.13)	0.001	1.55 (1.15-2.09)	0.004

HR: hazard ratio, CI: confidence interval. Model 1, adjusted for age and sex. Model 2, adjusted for Model 1 covariates plus smoking history, diabetes, history of cardiovascular disease, and eGFR. Model 3, adjusted for Model 2 covariates plus body mass index, systolic blood pressure, proteinuria positive, serum albumin, hemoglobin, and serum calcium.

Table 5. Associations of serum phosphorus levels with all-cause death, cardiovascular event, and kidney event in non-dialysis dependent CKD patients in men

	Incident rate (/1,000 person-years)	Univariate HR (95% CI)	*P*	Model 1 HR (95% CI)	*P*	Model 2 HR (95% CI)	*P*
All-cause death							
Serum phosphorus							
< 2.8 mg/dL	17.2	0.78 (0.29-2.10)	0.626	0.90 (0.34-2.43)	0.840	0.97 (0.36-2.64)	0.958
2.9-3.2 mg/dL	21.6	1.00 [reference]		1.00 [reference]		1.00 [reference]	
3.3-3.6 mg/dL	17.6	0.78 (0.26-2.34)	0.662	0.86 (0.29-2.57)	0.786	0.80 (0.27-2.40)	0.688
≥3.7 mg/dL	48.0	2.15 (0.87-5.31)	0.096	2.57 (1.04-6.36)	0.041	2.53 (0.96-6.68)	0.060
per 1-mg/dL increase		2.03 (1.15-3.56)	0.014	2.03 (1.16-3.55)	0.013	1.82 (1.01-3.29)	0.048
Cardiovascular event							
Serum phosphorus							
< 2.8 mg/dL	25.3	1.49 (0.57-3.92)	0.417	1.60 (0.61-4.21)	0.341	1.54 (0.96-1.02)	0.390
2.9-3.2 mg/dL	17.1	1.00 [reference]		1.00 [reference]		1.00 [reference]	
3.3-3.6 mg/dL	29.3	1.73 (0.63-4.76)	0.291	1.82 (0.66-5.02)	0.248	1.58 (0.57-4.37)	0.378
≥3.7 mg/dL	67.0	3.97 (1.58-9.95)	0.03	4.41(1.76-11.1)	0.002	3.22 (1.17-8.85)	0.023
per 1-mg/dL increase		2.37 (1.46-3.85)	<0.001	2.35 (1.47-3.78)	<0.001	1.64 (1.02-2.64)	0.043
Kidney event							
Serum phosphorus							
< 2.8 mg/dL	33.1	1.69 (0.700-4.08)	0.243	1.71 (0.71-4.12)	0.235	1.44 (0.59-3.51)	0.418
2.9-3.2 mg/dL	19.5	1.00 [reference]		1.00 [reference]		1.00 [reference]	
3.3-3.6 mg/dL	32.1	1.64 (0.63-4.26)	0.308	1.66 (0.638-4.293)	0.956	1.03(0.39-2.69)	0.017
≥3.7 mg/dL	193.9	10.19 (4.67-22.09)	<0.001	10.37(4.77-22.54)	<0.001	3.33 (1.46-7.62)	0.004
per 1-mg/dL increase		4.31 (3.13-5.94)	<0.001	4.32 (3.14-5.95)	<0.001	2.20 (1.49-3.25)	<0.001

HR: hazard ratio, CI: confidence interval. Model 1, adjusted for age. Model 2, adjusted for Model 1 covariates plus smoking history, diabetes, history of cardiovascular disease, and eGFR.

Table 6. Associations of serum phosphorus levels with all-cause death, cardiovascular event, and kidney event in non-dialysis dependent CKD patients in women

	Incident rate (/1,000 person-years)	Univariate HR (95% CI)	*P*	Model 1 HR (95% CI)	*P*	Model 2 HR (95% CI)	*P*
All-cause death							
Serum phosphorus							
< 2.8 mg/dL	30.1	1.58 (0.39-6.31)	0.520	1.59 (0.40-6.37)	0.511	1.39 (0.34-5.78)	0.648
2.9-3.2 mg/dL	19.2	1.00 [reference]		1.00 [reference]		1.00 [reference]	
3.3-3.6 mg/dL	7.5	0.39 (0.07-2.13)	0.277	0.34 (0.06-1.86)	0.213	0.34 (0.06-1.88)	0.218
≥3.7 mg/dL	12.5	0.65 (0.18-2.43)	0.524	0.59 (0.16-2.21)	0.434	0.61 (0.16-2.29)	0.463
per 1-mg/dL increase		0.48 (0.19-1.20)	0.117	0.44 (0.17-1.14)	0.090	0.49 (0.19-1.25)	0.136
Cardiovascular event							
Serum phosphorus							
< 2.8 mg/dL	7.6	0.80 (0.07-8.77)	0.852	0.78 (0.07-8.57)	0.835	3.10 (0.23-40.94)	0.391
2.9-3.2 mg/dL	9.7	1.00 [reference]		1.00 [reference]		1.00 [reference]	
3.3-3.6 mg/dL	19.1	1.99 (0.39-10.28)	0.409	1.57 (0.30-8.12)	0.591	2.49 (0.41-15.02)	0.318
≥3.7 mg/dL	10.1	1.03 (0.19-5.61)	0.975	0.87 (0.16-4.78)	0.876	0.56 (0.08-3.84)	0.551
per 1-mg/dL increase		1.10 (0.47-2.58)	0.828	1.09 (0.44-2.72)	0.859	0.37 (0.12-1.10)	0.072
Kidney event							
Serum phosphorus							
< 2.8 mg/dL	15.2	N/A		N/A		N/A	
2.9-3.2 mg/dL	0	1.00 [reference]		1.00 [reference]		1.00 [reference]	
3.3-3.6 mg/dL	55.2	N/A		N/A		N/A	
≥3.7 mg/dL	62.0	N/A		N/A		N/A	
per 1-mg/dL increase		2.56 (1.74-3.78)	<0.001	2.50 (1.68-3.70)	<0.001	1.23 (0.80-1.88)	0.349

HR: hazard ratio, CI: confidence interval. N/A: not applicable. Model 1, adjusted for age. Model 2, adjusted for Model 1 covariates plus smoking history, diabetes, history of cardiovascular disease, and eGFR.

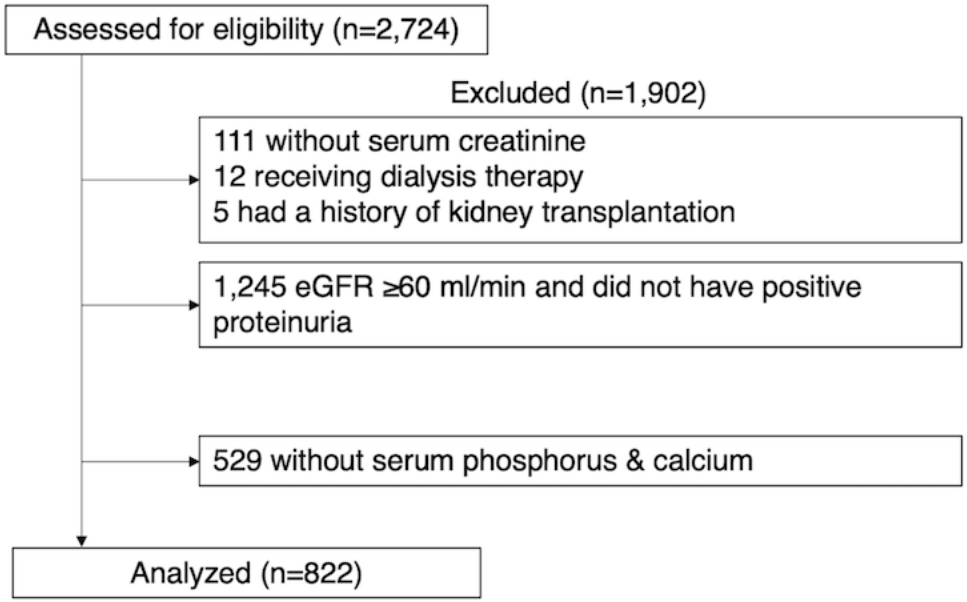


Figure 1. Participant flowchart for the present study.

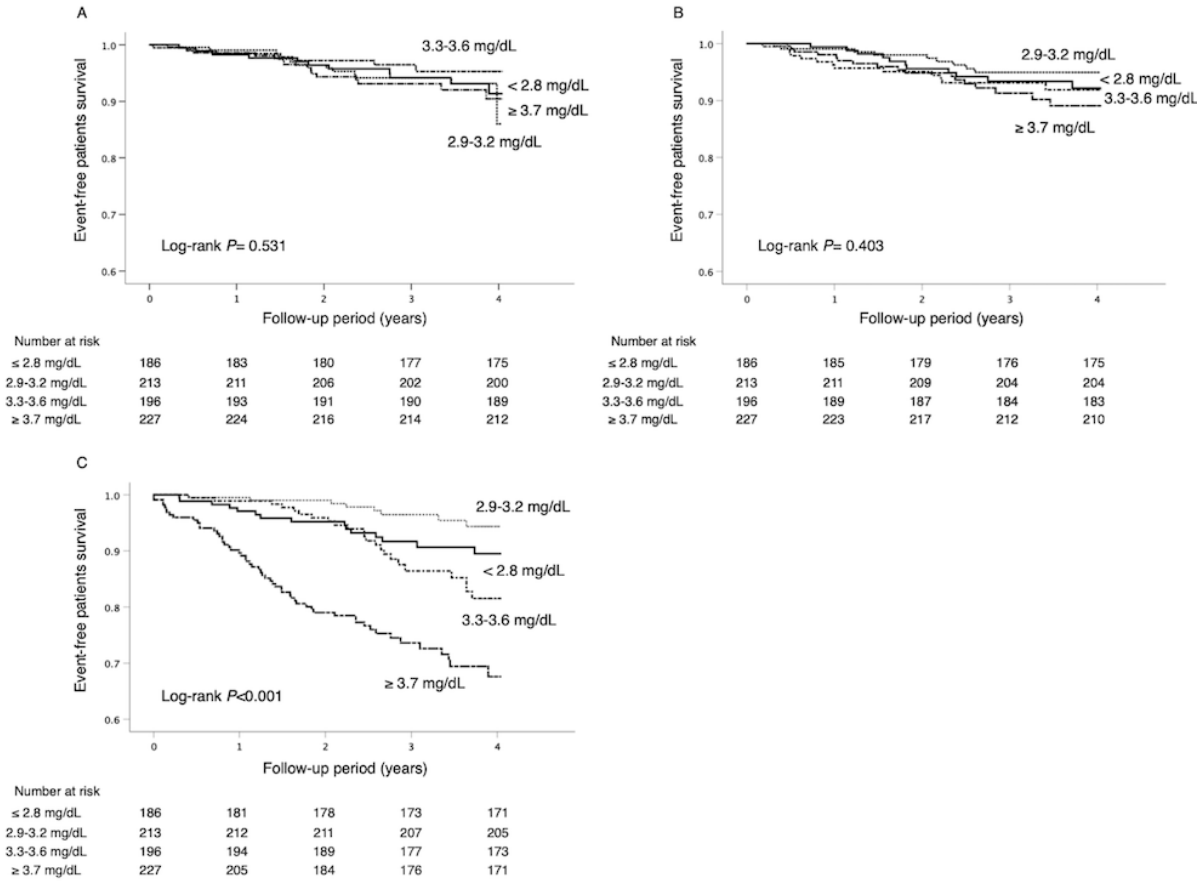


Figure 2. Kaplan-Meier curves for the incidence of all-cause death (A), cardiovascular event (B), and kidney event (C) in accordance with the serum inorganic phosphorus levels at baseline in 6 non-dialysis dependent CKD.

Supplemental Table S1. Patients' characteristics by quartiles of serum calcium level

	Serum calcium (mg/dL)				*P* for trend
	≤ 9.1	9.2-9.3	9.4-9.6	9.7 ≤	
N	224	184	225	189	
Age (y)	66 (57-74)	64 (55-75)	68 (59-75)	64(51-72)	0.172
Male sex (%)	66.5	57.1	47.1	56.6	0.001
Body mass index (kg/m2)	23.1 (20.8-26.1)	23.6 (21.8-25.9)	24.5 (21.6-27.2)	24.6 (21.3-27.4)	0.062
Smoking history (%)	56.4	50.0	46.0	55.1	0.132
Diabetes (%)	45.1	39.1	43.6	50.8	0.152
Dyslipidemia (%)	61.5	66.1	65.6	72.6	0.133
Cardiovascular disease (%)	37.9	29.3	30.2	24.9	0.034
Systolic blood pressure (mmHg)	132 (121-145)	125 (115-143)	133 (121-146)	136 (126-149)	0.297
Diastolic blood pressure (mmHg)	78 (67-86)	76 (72-80)	80 (70-83)	80 (70-87)	0.669
Serum creatinine (mg/dL)	1.68 (1.08-3.05)	1.22 (0.94-1.71)	0.99 (0.82-1.38)	1.07 (0.80-1.46)	<0.001
eGFR (mL/min/1.73 m2)	32.5 (18.4-49.9)	45.5 (25.2-55.4)	49.9 (37.7-59.1)	48.0 (34.9-65.6)	<0.001
Serum albumin (g/dL)	3.9 (3.6-4.0)	3.9 (3.7-4.1)	4.0 (3.6-4.2)	3.8 (3.1-4.4)	0.045
Hemoglobin (g/dL)	12.1 (10.6-13.5)	13.1 (11.1-14.1)	12.6 (10.9-13.8)	13.1 (11.5-14.1)	0.022
Positive proteinuria (%)	41.8	38.5	42.3	48.9	0.226
Serum phosphorus (mg/dL)	3.3 (2.9-3.9)	3.3 (2.8-3.8)	3.2 (2.9-3.6)	3.3 (3.1-3.7)	0.515
Serum calcium (mg/dL)	8.9 (8.7-9.1)	9.2 (9.2-9.3)	9.5 (9.4-9.5)	9.9 (9.8-10.1)	<0.001
intact-PTH (pg/mL)	70 (37-143)	59 (36-95)	42 (30-71)	40 (28-49)	<0.001

Median (25%-75%). eGFR, estimated glomerular filtration rate; PTH, parathyroid hormone.

Supplemental Table S2. Associations of serum phosphorus levels with doubling of the serum creatinine and ESRD in non-dialysis dependent CKD patients

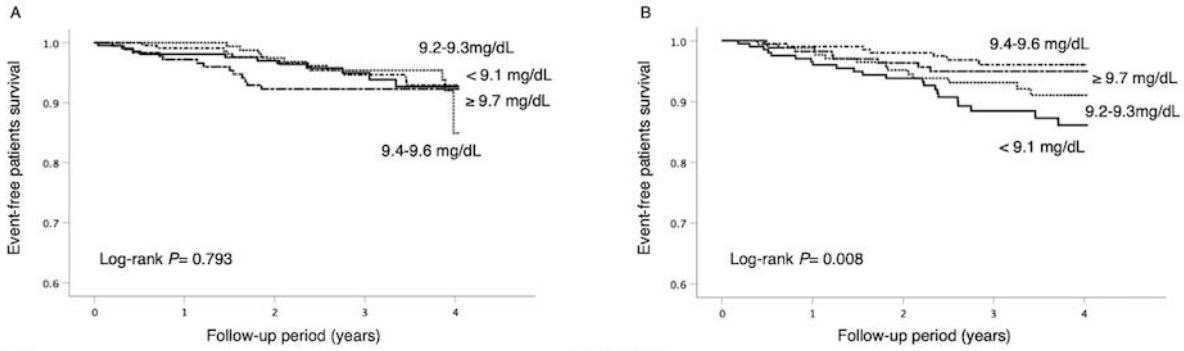
	Incident rate	Univariate		Model 1		Model 2		Model 3	
	(/1,000 person-years)	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
doubling of the serum creatinine									
Serum phosphorus									
< 2.8 mg/dL	13.4	1.63 (0.52-5.12)	0.407	1.61 (0.51-5.07)	0.419	1.62 (0.51-5.13)	0.412	N/A	
2.9-3.2 mg/dL	8.1	1.00 [reference]		1.00 [reference]		1.00 [reference]		1.00 [reference]	
3.3-3.6 mg/dL	18.7	2.38 (0.81-6.97)	0.113	2.58 (0.88-7.57)	0.085	2.24 (0.76-6.59)	0.142	N/A	
≥3.7 mg/dL	24.0	3.15 (1.12-8.85)	0.029	3.93 (1.35-11.44)	0.012	2.91 (0.99-8.53)	0.052	N/A	
per 1-mg/dL increase		1.76 (1.09-2.85)	0.021	2.07 (1.22-3.48)	0.007	1.68 (0.97-2.91)	0.066	1.43 (0.80-2.54)	
ESRD									
Serum phosphorus									
< 2.8 mg/dL	15.3	3.15 (0.84-11.87)	0.090	3.00 (0.80-11.31)	0.105	3.37 (0.88-12.88)	0.076	2.10 (0.54-8.21)	2.098
2.9-3.2 mg/dL	4.9	1.00 [reference]		1.00 [reference]		1.00 [reference]		1.00 [reference]	
3.3-3.6 mg/dL	24.3	4.97 (1.42-17.44)	0.012	5.53 (1.57-19.43)	0.008	3.54 (1.00-12.46)	0.050	2.48 (0.58-9.05)	0.170
≥3.7 mg/dL	79.5	16.16 (5.01-52.09)	<0.001	21.73 (6.66-70.88)	<0.001	4.34 (1.30-14.50)	0.017	4.17 (1.21-14.32)	0.024
per 1-mg/dL increase		3.38 (2.58-4.44)	<0.001	4.09 (3.09-5.41)	<0.001	1.15 (0.81-1.64)	0.421	1.40 (0.96-2.03)	0.082

ESRD: end-stage renal disease. HR: hazard ratio, CI: confidence interval. N/A: not applicable. Model 1, adjusted for age and sex. Model 2, adjusted for Model 1 covariates plus smoking history, diabetes, history of cardiovascular disease, and eGFR. Model 3, adjusted for Model 2 covariates plus body mass index, systolic blood pressure, proteinuria positive, serum albumin, hemoglobin, and serum calcium.

Supplemental Table S3. Associations of serum calcium levels with all-cause death, cardiovascular event, and kidney event in non-dialysis dependent CKD patients

	Incident rate (/1,000 person-years)	Univariate HR (95% CI)	*P*	Model 1 HR (95% CI)	*P*	Model 2 HR (95% CI)	*P*	Model 3 HR (95% CI)	*P*
All-cause death									
Serum calcium									
< 9.1 mg/dL	18.5	1.01 (0.45-2.30)	0.975	0.87 (0.38-1.99)	0.737	0.80 (0.35-1.86)	0.608	0.66 (0.28-1.58)	0.348
9.2-9.3 mg/dL	18.0	1.00 (0.43-2.32)	1.000	1.00 (0.43-2.32)	0.995	0.96 (0.41-2.23)	0.919	1.06 (0.44-2.55)	0.890
9.4-9.6 mg/dL	18.1	1.00 [reference]		1.00 [reference]		1.00 [reference]		1.00 [reference]	
≥ 9.7 mg/dL	25.3	1.40 (0.64-3.07)	0.402	1.44 (0.65-3.18)	0.364	1.45 (0.66-3.21)	0.354	1.55 (0.64-3.76)	0.333
per 1-mg/dL increase		1.34 (0.75-2.39)	0.320	1.48 (0.84-2.61)	0.173	1.47 (0.86-2.49)	0.158	1.47 (0.81-2.69)	0.210
Cardiovascular event									
Serum calcium									
< 9.1 mg/dL	38.3	3.58 (1.53-8.37)	0.003	2.92 (1.23-6.89)	0.015	2.01 (0.84-4.85)	0.119	2.05 (0.84-5.00)	0.115
9.2-9.3 mg/dL	24.2	2.28 (0.91-5.70)	0.079	2.23 (0.89-5.62)	0.087	1.84 (0.73-4.64)	0.198	1.93 (0.76-4.89)	0.167
9.4-9.6 mg/dL	10.7	1.00 [reference]		1.00 [reference]		1.00 [reference]		1.00 [reference]	
≥ 9.7 mg/dL	15.9	1.47 (0.53-4.06)	0.454	1.47 (0.53-4.07)	0.456	1.34 (0.48-3.71)	0.575	1.23 (0.44-3.49)	0.695
per 1-mg/dL increase		0.43 (0.26-0.71)	0.001	0.44 (0.26-0.77)	0.004	0.59 (0.34-1.04)	0.069	0.57 (0.31-1.02)	0.056
Kidney event									
Serum calcium									
< 9.1 mg/dL	72.2	2.63 (1.51-4.58)	0.001	2.53 (1.44-4.45)	0.001	1.23 (0.68-2.24)	0.490	1.11 (0.59-2.09)	0.754
9.2-9.3 mg/dL	43.8	1.58 (0.85-2.93)	0.147	1.59 (0.85-2.94)	0.144	1.18 (0.63-2.21)	0.605	1.51 (0.78-2.91)	0.224
9.4-9.6 mg/dL	27.8	1.00 [reference]		1.00 [reference]		1.00 [reference]		1.00 [reference]	
≥ 9.7 mg/dL	42.8	1.55 (0.82-2.90)	0.175	1.55 (0.82-2.92)	0.174	1.53 (0.81-2.91)	0.192	0.91 (0.45-1.86)	0.799
per 1-mg/dL increase		0.58 (0.39-0.87)	0.009	0.60 (0.39-0.90)	0.014	1.08 (0.76-1.53)	0.683	1.08 (0.74-1.59)	0.688

HR: hazard ratio, CI: confidence interval. Model 1, adjusted for age and sex. Model 2, adjusted for Model 1 covariates plus smoking history, diabetes, history of cardiovascular disease, and eGFR. Model 3, adjusted for Model 2 covariates plus body mass index, systolic blood pressure, proteinuria positive, serum albumin, hemoglobin, and serum phosphorus.

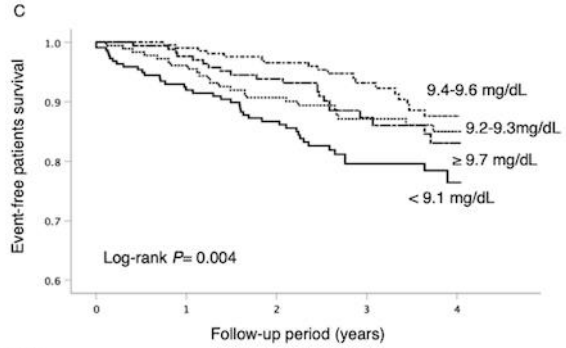


Number at risk

≤ 9.1 mg/dL	224	220	218	215	213
9.2-9.3 mg/dL	184	184	180	177	174
9.4-9.6 mg/dL	225	223	219	215	213
≥ 9.7 mg/dL	189	184	176	176	176

Number at risk

≤ 9.1 mg/dL	224	217	212	204	202
9.2-9.3 mg/dL	184	182	176	173	171
9.4-9.6 mg/dL	225	223	221	218	218
≥ 9.7 mg/dL	189	186	183	181	181



Number at risk

≤ 9.1 mg/dL	224	207	197	186	184
9.2-9.3 mg/dL	184	177	168	163	161
9.4-9.6 mg/dL	225	223	218	213	207
≥ 9.7 mg/dL	189	185	179	171	168

Supplemental Figure S1. Kaplan-Meier curves for the incidence of all-cause death (A), cardiovascular event (B), and kidney event (C) in accordance with the serum calcium levels at baseline in non-dialysis dependent CKD.