

Association between serum phosphorus levels and adverse outcomes in chronic kidney disease: an observational cohort study

Akira Oda

Fukushima Medical University

Kenichi Tanaka (✉ kennichi@fmu.ac.jp)

Fukushima Medical University <https://orcid.org/0000-0003-4655-9355>

Hiroataka Saito

Fukushima Medical University

Tsuyoshi Iwasaki

Fukushima Medical University

Shuhei Watanabe

Fukushima Medical University

Makoto Kanno

Fukushima Medical University

Hiroshi Kimura

Fukushima Medical University

Michio Shimabukuro

Fukushima Medical University

Koichi Asahi

Iwate Medical University: Iwate Ika Daigaku

Tsuyoshi Watanabe

Fukushima Medical University

Junichiro James Kazama

Fukushima Medical University

Research article

Keywords: Cardiovascular event, Chronic kidney disease, End-stage renal disease, Kidney event, Mortality, Phosphorus

Posted Date: March 18th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-329816/v1>

License:  This work is licensed under a Creative Commons Attribution 4.0 International License. [Read Full License](#)

Abstract

Background

Although an association between serum phosphorus levels and poor prognosis has been noted in dialysis patients, these associations have been insufficiently reported in non-dialysis dependent chronic kidney disease (NDD-CKD) patients. This study attempted to determine the association between serum phosphorus levels and adverse outcomes in Japanese NDD-CKD patients.

Methods

We investigated the relationships between serum phosphorus levels and adverse outcomes such as kidney events, cardiovascular events, and all-cause death in Japanese NDD-CKD patients, using the longitudinal data of the Fukushima CKD Cohort Study. The study evaluated 822 patients with NDD-CKD enrolled between June 2012 and July 2014. A kidney event was defined as a combination of doubling of the baseline serum creatinine or end-stage renal disease. Cox regression was performed to analyze the relationships of the quartile of the serum phosphorus with kidney events, cardiovascular events, and all-cause death.

Results

Over a median follow-up period of 2.8 years, 46 patients died, there were 50 cardiovascular events, and 102 kidney events occurred. Increased risk of kidney events was observed in patients with higher serum phosphorus, with the lowest risk shown to be a second quartile of serum phosphorus level of 2.9–3.2 mg/dL. Multivariable Cox regression analysis showed an increased risk of kidney events for the highest quartile of the serum phosphorus levels (≥ 3.7 mg/dL) versus the second quartile (2.9–3.2 mg/dL, hazard ratio, 3.62; 95% confidence interval, 1.65–7.94; $P = 0.001$). A 1 mg/dL increase of the serum phosphorus was associated with an adjusted hazard ratio of 1.66 (95% CI; 1.24–2.20) for the kidney events. There were no significant associations between the serum phosphorus levels at baseline and the risk of cardiovascular events and all-cause death.

Conclusions

Serum phosphorus levels were associated with an increased risk of CKD progression in Japanese NDD-CKD patients.

Background

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 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 phosphorus or calcium, and all-cause and cardiovascular mortality in dialysis patients [2–4]. Recent studies have demonstrated that elevated serum levels of 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 phosphorus levels and CKD progression and mortality in NDD-CKD patients [10, 11]. However, some studies have reported finding no independent associations for serum phosphorus levels with the risk for cardiovascular death or CKD progression in these patients [12, 13]. In addition, since the serum

phosphorus levels associated with increased risk for these adverse outcomes has varied from study to study, the optimal range of serum 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 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 phosphorus levels and adverse outcomes in Japanese patients. Therefore, the aim of the present study was to investigate the relevance of serum 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, described in detail [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 $eGFR \geq 60 \text{ mL/min/1.73 m}^2$ or patients who did not have positive proteinuria at the time of registration. After the exclusion of those without serum calcium and phosphorus data, a total of 822 participants were evaluated in the present study (Fig. 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, 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 $\geq 126 \text{ mg/dL}$, or a glycosylated hemoglobin (HbA1c) value (National Glycohemoglobin Standardization) $\geq 6.5\%$, or as patients who used insulin or oral antihyperglycemic drugs. Dyslipidemia was defined as patients with either a triglyceride concentration $\geq 150 \text{ mg/dL}$, low-density lipoprotein cholesterol concentration $\geq 140 \text{ mg/dL}$, high-density lipoprotein cholesterol concentration $< 40 \text{ mg/dL}$, 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, 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 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 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 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 phosphorus. Subjects with higher serum 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 phosphorus level ≥ 4.5 mg/dL and 25 hypercalcemia patients (3% of the total) with a serum calcium level ≥ 10 mg/dL.

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.					

Serum phosphorus and calcium 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 phosphorus categories at baseline, U-shaped relationships were observed for the kidney events (Table 2). A significant difference ($P < 0.001$) was found for the incidence of kidney events among the NDD-CKD patients with different serum phosphorus levels at baseline, but not for the incidence of cardiovascular events and all-cause death (Fig. 2A, B, C). The multivariate Cox regression analysis results showed that higher serum phosphorus was significantly associated with an increased risk of kidney events, with the lowest risk shown to be a serum 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 1.72 (95% confidence interval (CI); 0.72–4.09) for serum

phosphorus ≤ 2.8 mg/dL, 2.04 (95% CI; 0.87–4.64) for 3.3–3.6 mg/dL, and 3.62 (95% CI; 1.65–7.94) for ≥ 3.7 mg/dL (Model 3 in Table 2). A 1 mg/dL increase of the serum phosphorus was associated with an adjusted hazard ratio of 1.66 (95% CI; 1.24–2.20) for the kidney events. There were no significant associations between the serum phosphorus levels at baseline and the risk of cardiovascular events and all-cause death.

Table 2

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)	<i>P</i>						
<i>All-cause death</i>									
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	1.35 (0.58–3.14)	0.486
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	0.66 (0.25–1.72)	0.390
≥ 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	1.73 (0.75–4.00)	0.197
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	1.16 (0.68–1.96)	0.595
<i>Cardiovascular event</i>									
Serum phosphorus									
< 2.8 mg/dL	20.9	1.44 (0.60–3.48)	0.416	1.45 (0.60–3.48)	0.416	0.32 (0.54–3.21)	0.543	1.32 (0.53–3.78)	0.549
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	1.60 (0.68–4.11)	0.285
≥ 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	1.65 (0.66–4.11)	0.285
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	1.11 (0.71–1.74)	0.637
<i>Kidney event</i>									

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, and serum calcium.

	Incident rate	Univariate		Model 1		Model 2		Model 3	
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	1.72 (0.72–4.09)	0.224
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	2.04 (0.87–4.64)	0.090
≥ 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	3.62 (1.65–7.94)	0.001
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	1.66 (1.24–2.20)	0.001
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, and serum calcium.									

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 A, B, C). 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 S2).

Discussion

The present study investigated serum phosphorus and calcium associations with mortality, cardiovascular, and kidney events in Japanese NDD-CKD patients, and demonstrated that serum phosphorus levels were independently associated with kidney events, but not with either mortality or cardiovascular events. U-shaped relationships were observed between the serum phosphorus levels and the incidence of kidney events, with the best outcomes seen with serum phosphorus levels of 2.9–3.2 mg/dL. A serum 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 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 phosphorus levels ranging from 3.5–4.6 mg/dL or more were associated with these adverse outcomes. Although the serum phosphorus

levels that contributed to this increased risk for these adverse outcomes varied according to the study, the cut-off values of serum 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 phosphorus levels are within the normal 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 phosphorus levels had serum phosphorus levels that were within the normal range. In addition, it has also been reported that there was an association between the phosphorus levels and kidney events in Japanese NDD-CKD patients [22], with a phosphorus level of ≥ 3.4 mg/dL shown to be a risk factor for CKD progression to ESRD. Therefore, higher serum phosphorus levels that are still within the normal range could be a risk of adverse kidney outcomes in the NDD-CKD patients. The present results suggest the importance of serum 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 phosphorus levels.

The present study found that there were no significant associations observed between serum phosphorus levels at baseline and the risk of cardiovascular events or all-cause mortality. Other previous studies have reported finding associations between higher serum 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 phosphorus levels and these events in Japanese NDD-CKD patients.

The association of higher serum 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. A recent study reported that elevated phosphaturia accelerated CKD progression due to renal tubular injury even in the absence of hyperphosphatemia in animal model [25]. Fibroblast growth factor 23 (FGF23), a peptide hormone inducing phosphaturia through its effects on proximal renal tubules, increases prior to the elevation of serum phosphorus levels in the patients with NDD-CKD maintaining the serum phosphorus levels to the normal range by promoting excretion per nephron. Thus, increased phosphaturia could explain the mechanisms on the associations between the normal range of serum 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 [26]. In a randomized control trial in NDD-CKD patients with normal ranges of serum phosphorus levels, phosphorus binders significantly reduced serum phosphorus levels. In contrast, significant deteriorations of vascular calcification were observed in the calcium-based phosphorus binder group [27]. Further studies will need to be conducted to reveal the best strategy against elevated serum phosphorus during daily activities, such as dietary phosphorus restriction and the administration of phosphorus binders. These changes could improve renal prognosis and mortality in NDD-CKD patients.

The present study had several limitations. First, only a small sample size was evaluated. Moreover, the number of all-cause deaths and cardiovascular events were much lower than expected. 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. Second, the serum phosphorus levels were only measured at baseline. Therefore, single measurements of serum

phosphorus might have led to some misclassification of hyperphosphatemia or the serum phosphorus category. Third, we did not collect any data on the serum FGF23 levels or the medication use, such as phosphorus binders and activated vitamin D, which could relate to both the serum phosphorus levels and outcomes in CKD patients. These limitations of our present study will need to be addressed in future studies.

Conclusions

In summary, the present study showed that serum phosphorus levels were significantly associated with kidney events, but not with all-cause death and cardiovascular events in Japanese NDD-CKD patients. Serum 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 phosphorus levels within the normal range can be associated with adverse outcomes in CKD, and whether lowering serum levels of phosphorus will delay CKD progression and improve renal prognosis.

Abbreviations

NDD: Non-dialysis dependent; CKD: Chronic kidney disease; ESRD: End-stage renal disease; CVD: Cardiovascular disease; PTH: Parathyroid hormone; CI: Confidence interval; FGF23: Fibroblast growth factor 23

Declarations

Ethics approval and consent to participate

This study protocol complied with the Declaration of Helsinki and was approved by the ethics committee at Fukushima Medical University (acceptance no. 1456, 2001). All patients received an explanation of the procedures and possible risks of this study and gave their written, informed consent to participate in this study.

Consent for publication

Not applicable.

Availability of data and materials

The dataset generated and/or analyzed during the current study are available from corresponding author on reasonable request.

Competing interest

None.

Funding

The authors received no funding for this work.

Authors' contributions

AO wrote the paper with input from all authors. All authors have approved the manuscript.

Research idea and study design: KT; data acquisition: HS, TI, AO, SW, MK, HK; data analysis/interpretation: KT, AO, MS, KA, TW; statistical analysis: KT, HK; supervision or mentorship: JK.

Acknowledgements

The authors would like to thank Ayumi Kanno for her assistance in data collection.

References

1. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY: **Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization.** *The New England journal of medicine* 2004, **351**(13):1296-1305.
2. Block GA, Klassen PS, Lazarus JM, Ofsthun N, Lowrie EG, Chertow GM: **Mineral metabolism, mortality, and morbidity in maintenance hemodialysis.** *J Am Soc Nephrol* 2004, **15**(8):2208-2218.
3. Melamed ML, Eustace JA, Plantinga L, Jaar BG, Fink NE, Coresh J, Klag MJ, Powe NR: **Changes in serum calcium, phosphate, and PTH and the risk of death in incident dialysis patients: a longitudinal study.** *Kidney Int* 2006, **70**(2):351-357.
4. Natoli JL, Boer R, Nathanson BH, Miller RM, Chiroli S, Goodman WG, Belozeroff V: **Is there an association between elevated or low serum levels of phosphorus, parathyroid hormone, and calcium and mortality in patients with end stage renal disease? A meta-analysis.** *BMC nephrology* 2013, **14**:88.
5. Kestenbaum B, Sampson JN, Rudser KD, Patterson DJ, Seliger SL, Young B, Sherrard DJ, Andress DL: **Serum phosphate levels and mortality risk among people with chronic kidney disease.** *Journal of the American Society of Nephrology : JASN* 2005, **16**(2):520-528.
6. Schwarz S, Trivedi BK, Kalantar-Zadeh K, Kovesdy CP: **Association of disorders in mineral metabolism with progression of chronic kidney disease.** *Clinical journal of the American Society of Nephrology : CJASN* 2006, **1**(4):825-831.
7. Eddington H, Hoefield R, Sinha S, Chrysochou C, Lane B, Foley RN, Hegarty J, New J, O'Donoghue DJ, Middleton RJ *et al*: **Serum phosphate and mortality in patients with chronic kidney disease.** *Clinical journal of the American Society of Nephrology : CJASN* 2010, **5**(12):2251-2257.
8. Kovesdy CP, Anderson JE, Kalantar-Zadeh K: **Outcomes associated with serum phosphorus level in males with non-dialysis dependent chronic kidney disease.** *Clinical nephrology* 2010, **73**(4):268-275.
9. Chartsrisak K, Vipattawat K, Assanatham M, Nongnuch A, Ingsathit A, Domrongkitchaiporn S, Sumethkul V, Disthabanchong S: **Mineral metabolism and outcomes in chronic kidney disease stage 2-4 patients.** *BMC nephrology* 2013, **14**:14.
10. Palmer SC, Hayen A, Macaskill P, Pellegrini F, Craig JC, Elder GJ, Strippoli GF: **Serum levels of phosphorus, parathyroid hormone, and calcium and risks of death and cardiovascular disease in individuals with chronic kidney disease: a systematic review and meta-analysis.** *Jama* 2011, **305**(11):1119-1127.
11. Da J, Xie X, Wolf M, Disthabanchong S, Wang J, Zha Y, Lv J, Zhang L, Wang H: **Serum Phosphorus and Progression of CKD and Mortality: A Meta-analysis of Cohort Studies.** *American journal of kidney diseases : the official journal of the National Kidney Foundation* 2015, **66**(2):258-265.
12. Mehrotra R, Peralta CA, Chen SC, Li S, Sachs M, Shah A, Norris K, Saab G, Whaley-Connell A, Kestenbaum B *et al*: **No independent association of serum phosphorus with risk for death or progression to end-stage renal disease in a large screen for chronic kidney disease.** *Kidney Int* 2013, **84**(5):989-997.
13. Menon V, Greene T, Pereira AA, Wang X, Beck GJ, Kusek JW, Collins AJ, Levey AS, Sarnak MJ: **Relationship of phosphorus and calcium-phosphorus product with mortality in CKD.** *Am J Kidney Dis* 2005, **46**(3):455-463.
14. Tanaka K, Watanabe T, Takeuchi A, Ohashi Y, Nitta K, Akizawa T, Matsuo S, Imai E, Makino H, Hishida A: **Cardiovascular events and death in Japanese patients with chronic kidney disease.** *Kidney Int* 2017, **91**(1):227-234.

15. Inaguma D, Imai E, Takeuchi A, Ohashi Y, Watanabe T, Nitta K, Akizawa T, Matsuo S, Makino H, Hishida A: **Risk factors for CKD progression in Japanese patients: findings from the Chronic Kidney Disease Japan Cohort (CKD-JAC) study.** *Clin Exp Nephrol* 2017, **21**(3):446-456.
16. Saito H, Tanaka K, Iwasaki T, Oda A, Watanabe S, Kanno M, Kimura H, Shimabukuro M, Asahi K, Watanabe T *et al.*: **Xanthine oxidase inhibitors are associated with reduced risk of cardiovascular disease.** *Sci Rep* 2021, **11**(1):1380.
17. Tanaka K, Saito H, Iwasaki T, Oda A, Watanabe S, Kanno M, Kimura H, Shimabukuro M, Asahi K, Watanabe T *et al.*: **Association between serum potassium levels and adverse outcomes in chronic kidney disease: the Fukushima CKD cohort study.** *Clin Exp Nephrol* 2021.
18. Janmaat CJ, van Diepen M, Gasparini A, Evans M, Qureshi AR, Ärnlöv J, Barany P, Elinder CG, Rotmans JI, Vervloet M *et al.*: **Lower serum calcium is independently associated with CKD progression.** *Scientific reports* 2018, **8**(1):5148.
19. Lim LM, Kuo HT, Kuo MC, Chiu YW, Lee JJ, Hwang SJ, Tsai JC, Hung CC, Chen HC: **Low serum calcium is associated with poor renal outcomes in chronic kidney disease stages 3-4 patients.** *BMC nephrology* 2014, **15**:183.
20. Voormolen N, Noordzij M, Grootendorst DC, Beetz I, Sijkens YW, van Manen JG, Boeschoten EW, Huisman RM, Krediet RT, Dekker FW: **High plasma phosphate as a risk factor for decline in renal function and mortality in pre-dialysis patients.** *Nephrol Dial Transplant* 2007, **22**(10):2909-2916.
21. Bellasi A, Mandreoli M, Baldrati L, Corradini M, Di Nicolo P, Malmusi G, Santoro A: **Chronic kidney disease progression and outcome according to serum phosphorus in mild-to-moderate kidney dysfunction.** *Clinical journal of the American Society of Nephrology : CJASN* 2011, **6**(4):883-891.
22. Chang WX, Xu N, Kumagai T, Shiraishi T, Kikuyama T, Omizo H, Sakai K, Arai S, Tamura Y, Ota T *et al.*: **The Impact of Normal Range of Serum Phosphorus on the Incidence of End-Stage Renal Disease by A Propensity Score Analysis.** *PLoS One* 2016, **11**(4):e0154469.
23. McGovern AP, de Lusignan S, van Vlymen J, Liyanage H, Tomson CR, Gallagher H, Rafiq M, Jones S: **Serum phosphate as a risk factor for cardiovascular events in people with and without chronic kidney disease: a large community based cohort study.** *PLoS one* 2013, **8**(9):e74996.
24. Kuro OM: **Phosphate as a Pathogen of Arteriosclerosis and Aging.** *J Atheroscler Thromb* 2020.
25. Santamaría R, Díaz-Tocados JM, Pendón-Ruiz de Mier MV, Robles A, Salmerón-Rodríguez MD, Ruiz E, Vergara N, Aguilera-Tejero E, Raya A, Ortega R *et al.*: **Increased Phosphaturia Accelerates The Decline in Renal Function: A Search for Mechanisms.** *Scientific reports* 2018, **8**(1):13701.
26. Kovesdy CP, Kuchmak O, Lu JL, Kalantar-Zadeh K: **Outcomes associated with phosphorus binders in men with non-dialysis-dependent CKD.** *American journal of kidney diseases : the official journal of the National Kidney Foundation* 2010, **56**(5):842-851.
27. Block GA, Wheeler DC, Persky MS, Kestenbaum B, Ketteler M, Spiegel DM, Allison MA, Asplin J, Smits G, Hoofnagle AN *et al.*: **Effects of phosphate binders in moderate CKD.** *Journal of the American Society of Nephrology : JASN* 2012, **23**(8):1407-1415.

Figures

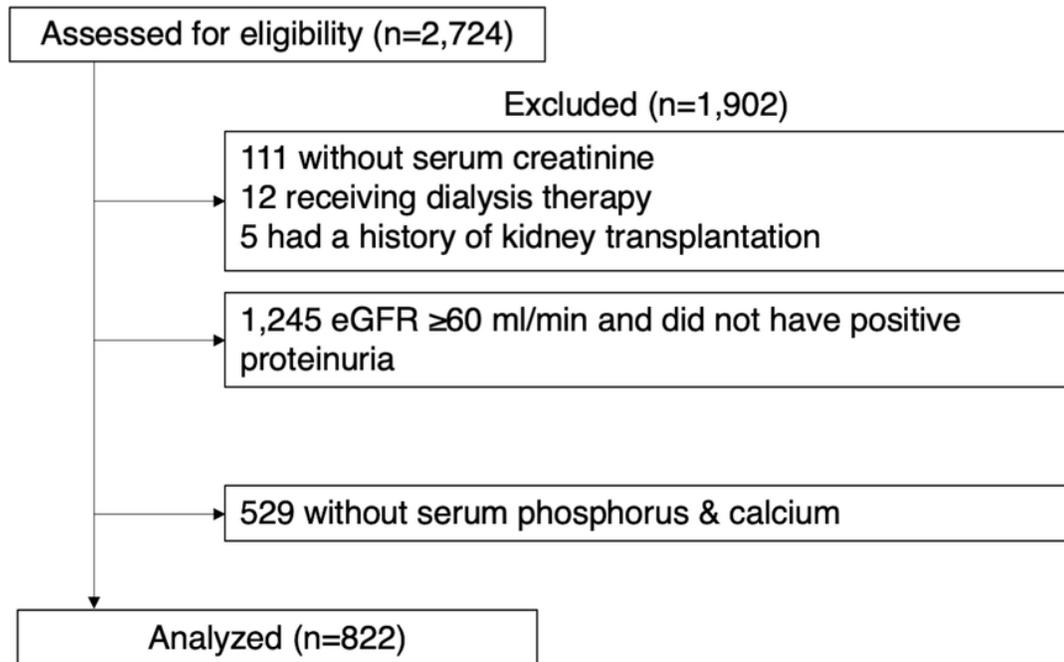


Figure 1

Participant flowchart for the present study.

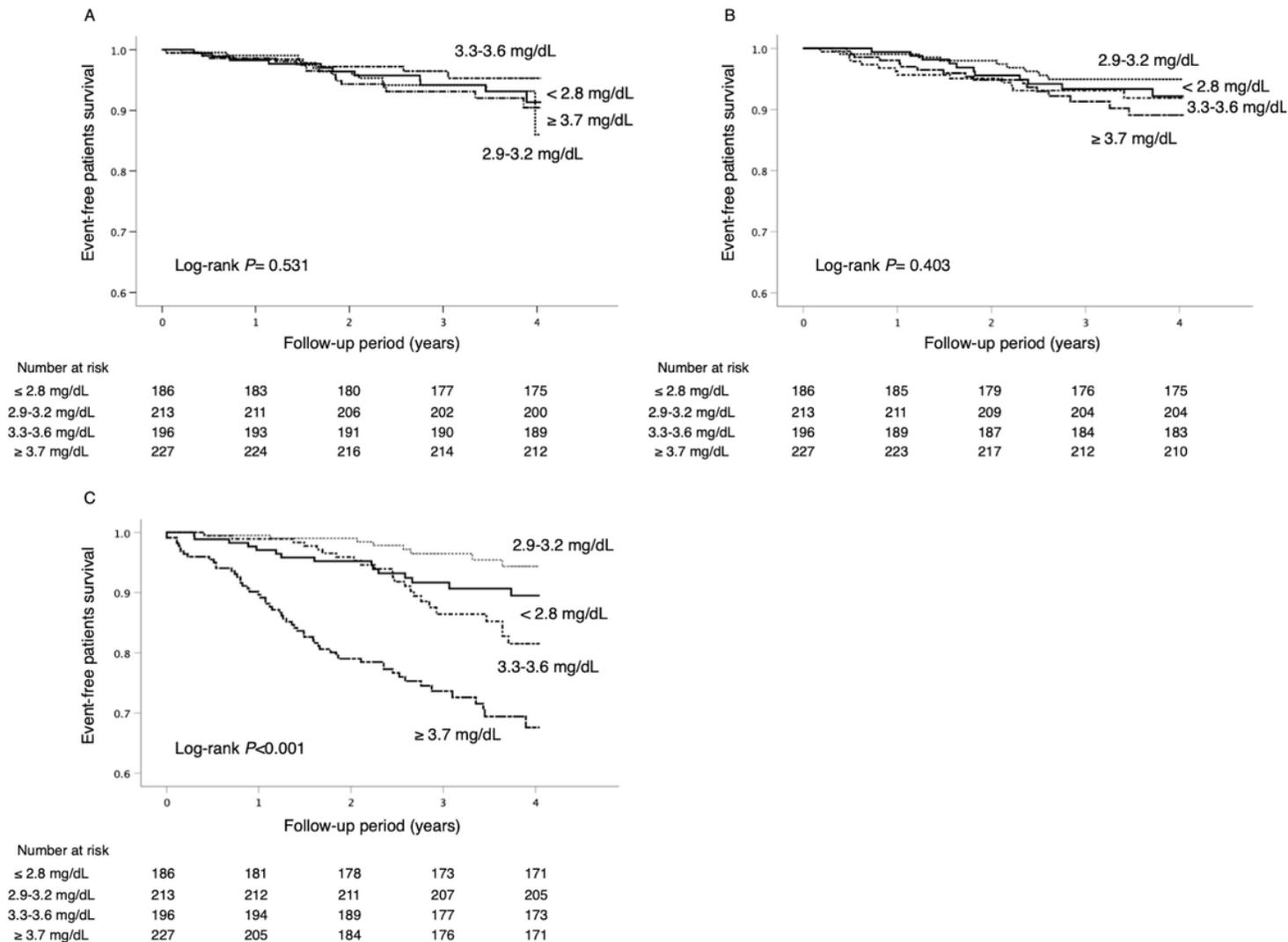


Figure 2

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

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [SupplementalFigure.tiff](#)
- [SupplementalTablesPi.docx](#)