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Title

Impact of nutritional index on the association between phosphorus concentrations and mortality in hemodialysis patients: a cohort study from Dialysis Outcomes and Practice Pattern Study in Japan

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ABSTRACT

Objectives: While maintenance of both phosphorus concentration and nutritional status is a major concern in managing hemodialysis patients, little is understood regarding interaction between these parameters. The aim of this study was to assess whether or not nutritional index influences the association between phosphorus concentration and all-cause mortality.

Design: A cohort study.

Setting: The Dialysis Outcomes and Practice Pattern Study which include 99 representative dialysis facilities in Japan between 1997 and 2010.

Participants: 6,230 adult hemodialysis patients who had spent at least 6 months on hemodialysis.

Main predictors: 6 categories based on time-averaged factors of nutritional risk index (GNRI; lower two and the highest tertiles) and phosphorus concentration (<3.5, 3.5 to <6.0, and ≥6.0 mg/dl).

Primary outcome measure: all-cause mortality rate

Analysis: Time-dependent Cox regression adjusting for potential confounders.

Results: During the follow-up period (12,294 person-years), we noted 561 deaths (4.6 per 100 person-years), and both high phosphorus concentrations and low-middle GNRI were separately associated with all-cause mortality. The harmful effect of high phosphorus concentrations on all-cause mortality was stronger in patients with high GNRI than in those with low-middle GNRI. On the other hand, the harmful effect of low phosphorus concentrations was stronger in those with low-middle GNRI than in those with high GNRI. Relative excess risk due to interaction (RERI) was -0.57 between high phosphorus concentrations and low-middle GNRI, indicating negative biological interaction. We also observed a significant statistical interaction between phosphorus concentrations and GNRI (P=0.05 by likelihood ratio test).

Conclusions: The associations between time-averaged serum phosphorus concentration and all-cause mortality were found to differ across nutritional index. We should consider the nutritional index when evaluating the impact of phosphorus concentration on mortality in hemodialysis patients.

Strength and limitations of this study

- While a number of previous studies have examined the associations between phosphorus concentration and mortality after adjusting for nutritional indices, these studies failed to account for the interaction between the nutritional index and phosphorus concentration.
- We analyzed large size (>6,000) representative dialysis population in Japan.
- We defined exposure categories based on two categorical factors (phosphorus concentration and nutritional index), which allowed us to examine the separate and combined effects of these components and to examine their biological interaction by calculating the relative excess risk due to interaction (RERI).
- We specifically used time-averaged phosphorus concentration and nutritional index, as subsequent values of phosphorus and nutritional index dramatically changed from baseline values.
- A limitation of this study is that this is an observational study and residual confounding due to unmeasured factors may affect the association between exposure categories and mortality.

INTRODUCTION

Both phosphorus concentration and nutritional status have attracted attention in hemodialysis patients in light of their association with mortality.[1-5] However, while preventing hyperphosphatemia[6-8] and improving nutritional status[4 9 10] are therefore understandably major concerns in the management of hemodialysis patients, simultaneously accomplishing both tasks has largely proven difficult.[11] Reducing phosphorus concentration is mainly accomplished via phosphate binders and phosphate restriction,[11] the latter of which often involves protein restriction and may thereby worsen nutritional status.[12] In light of these difficulties in managing these side effects, physicians have pondered whether or not reducing phosphorus concentration actually improves survival in patients at risk of nutrition-related morbidity and mortality.[12 13] However, at present, little is known regarding whether or not the association between phosphorus concentration and mortality differs across nutritional index.

Because nutritional index and phosphorus concentration may change greatly over time and are associated with each other, the interaction between time-dependent nutritional index and phosphorus concentration must be carefully considered when evaluating their separate and combined effects on mortality.[14] Although the Geriatric Nutritional Risk Index (GNRI)[15] was originally intended for use as a screening tool for predicting risk of morbidity and mortality in elderly patients, it has been validated for use in whole hemodialysis patients as well.[16 17] Low GNRI is indicative of having nutrition-related risk for mortality and morbidity. As such, clarifying its effect on the association between phosphorus concentration and mortality will aid in determining the effectiveness of outcome-oriented phosphorus management in hemodialysis patients.

Here, to clarify whether or not time-averaged GNRI modifies the association between time-averaged phosphorus concentration and mortality, we conducted a cohort study using data from the Dialysis Outcomes and Practice Pattern Study (DOPPS) in Japan (1997-2010).

METHODS

Study population and data sources

Our cohort study used Japan-derived data from DOPPS, an international longitudinal study of hemodialysis patients to identify practice patterns associated with improved patient outcomes. Participants in DOPPS were randomly selected from representative dialysis facilities within participating countries. Details regarding the design of DOPPS have been described in full previously.[18]

From 99 representative dialysis facilities in Japan, this study involved 6,230 hemodialysis patients aged ≥18 years who had spent at least 6 months on hemodialysis. All eligible patients were selected from DOPPS I (1997-2001), II (2002-2004), III (2005-2007) and IV (2008-2010). Baseline data regarding demographic information, comorbid conditions, medication for mineral bone disorder, and laboratory values were obtained at enrollment. Time-dependent data (GNRI and phosphorus concentration) and mortality data (time and cause) were obtained from the database during the follow-up period. GNRI was calculated as follows:

$$\text{GNRI} = (14.89 \times \text{albumin[g/dl]}) + [41.7 \times (\text{body weight} / \text{ideal body weight})]$$

where "ideal body weight" was calculated using the Lorentz formula as follows:

$$\text{Ideal body weight for men} = \text{height} - 100 - [(\text{height} - 150) / 4]$$

$$\text{Ideal body weight for women} = \text{height} - 100 - [(\text{height} - 150) / 2.5]$$

We set (body weight/ideal body weight) as "1" when "body weight" exceeded "ideal body weight" [15].

Definition of exposure

Exposure categories were defined based on the categorical factors of GNRI (low-middle, lower two tertiles; high, the highest tertile) and serum phosphorus concentrations (low, <3.5 mg/dl; middle, 3.5 to <6.0 mg/dl; high, ≥6.0 mg/dl). We evaluated GNRI and serum phosphorus concentrations in two ways: first using time-averaged variables, which were updated every four months to the mean values up to that time after study entry, and then using fixed baseline variables measured at study entry. Based on these parameters, we were able to define six exposure categories: "low-middle GNRI and low phosphorus", "low-middle GNRI and middle phosphorus", "low-middle GNRI and high phosphorus", "high GNRI and low phosphorus", "high GNRI and middle phosphorus", and "high GNRI and high phosphorus". The cut-off values for phosphorus concentration were defined according to the Japanese clinical guidelines.[19] The cut-off values for GNRI were defined based on the highest tertile established in this study, with the category of "high GNRI and middle phosphorus" defined as our reference, as previous studies have suggested that this category has the lowest mortality risk.[2 16 18 20-22]

Outcomes

The primary outcome measure was hazard ratio for all-cause mortality. Patients were followed from study entry until death, transplantation, transfer to another facility, modality change, withdrawal, or study end, whichever came first. The secondary outcome measure was hazard ratio for cardiovascular mortality, which included sudden deaths, deaths from heart failure, acute myocardial infarction, cerebrovascular disease, and other vascular disease.

Statistical analysis

We conducted baseline and time-dependent Cox regression to estimate hazard ratios and their 95% confidence intervals (CIs) for the association between exposure categories and all-cause mortality. The baseline Cox regression used baseline fixed exposure categories and the time-dependent Cox regression used time-averaged exposure categories. In our analyses using these combination categories of phosphorus concentration and GNRI, the hazard ratio for "high phosphorus concentration and high GNRI" compared with the reference category of "middle phosphorus concentration and high GNRI" indicate the effect of high phosphorus concentration on outcomes. The hazard ratio for "low-middle GNRI and middle phosphorus concentration" compared with the reference category indicate the effect of low-middle GNRI on outcomes. Our Cox model included adjustment for age, gender, time on dialysis, 11 comorbid conditions, single-pool Kt/V (quintiles), phosphate binder use, oral or intravenous vitamin D receptor activator (VDRA) use, and DOPPS phase, all of which had been indicated as potential confounding factors in previous studies.[2 3 22-27] Given their potential to function as intermediate factors between phosphorus concentration and mortality, we used fixed baseline variables of these covariates in the model. For Cox models, we used robust variance estimate to consider cluster effects at the facility level (correlation between patients).

We examined interaction between GNRI and phosphorus concentration in two ways. First, we assessed statistical interaction using the likelihood ratio test, which compares models with and without interaction terms. Second, to assess biological interaction between high phosphorus concentration and low-middle GNRI, we first estimated relative excess risk due to interaction (RERI) using the methodology of Rothman.[28 29] RERI between two factors (A and B) is defined as "departure from additive effects" and is calculated as follows using adjusted hazard ratios (HRs): [30]

$$RERI = HR(A\&B) - HR(A) - HR(B) + 1$$

RERI < 0, RERI = 0, and RERI > 0 indicate negative interaction, absence of interaction, and positive interaction, respectively.

To examine how the effects of phosphorus concentration change by GNRI levels, we estimated the effect of a discrete change of the phosphorus categories across GNRI levels. After conducting time-dependent Cox regression with interaction term of continuous GNRI and categorical phosphorus concentration, we estimated average marginal effect of phosphorus categories (high and low phosphorus concentration) on all-cause mortality at each GNRI level (GNRI levels at 85, 90, 95, 100, and 105). The reference level of GNRI was set to 100 based on the highest tertile. We used "MARGINS" and "MARGINSPLOT" commands in STATA.

All analyses were performed using STATA (Version 14.2, STATA, College Station, TX, USA) software.

RESULTS

Baseline patient characteristics

Figure 1 shows selection process. A total of 6,230 hemodialysis patients were included in this study. Overall, the mean (±SD) age was 61.1 ± 12.5 years, 60.8% of patients were male, the median (interquartile range) dialysis duration was 5.8 (Interquartile range; 2.6 to 11.3) years, and 29.7% of patients had diabetes. With regard to GNRI values, the lower tow tertiles of this study was <97.5, indicating patients at nutrition-related mortality risk according to the original study [15]. A total of 6.0% of patients had low phosphorus concentration while 35.6% had high phosphorus concentration. Baseline characteristics by combinations of GNRI and phosphorus concentration are shown in TABLE 1.

Association between GNRI, phosphorus concentrations, and all-cause mortality

TABLE 2 shows incidence rates and HRs for all-cause mortality according to baseline and time-averaged exposure categories. Median follow-up time was 2.1 years. During the follow-up period (total: 12,294 person-years), we recorded 561 all-cause deaths (4.6 per 100 person-years) from all causes.

In the time-dependent Cox model, both time-averaged factors of high phosphorus concentration and low-middle GNRI were found to be associated with all-cause mortality after adjusting for potential confounders. The hazard ratio for "high GNRI and high phosphorus" indicate the effect of high phosphorus concentration on all-cause mortality (HR: 1.66, 95% CI: 1.01 to 2.73), compared with the reference of "high GNRI and middle phosphorus". The hazard ratio for "low-middle GNRI and middle phosphorus" indicate the effect of low-middle GNRI on all-cause mortality (HR: 2.12, 95% CI: 1.51 to 2.96), compared with the reference category. We found the highest mortality rate in patients with both

"low-middle GNRI and low phosphorus" (HR: 4.28, 95% CI: 2.66 to 6.88), indicating the combined effect of low-middle GNRI and low phosphorus concentration.

In the baseline Cox model, both baseline fixed factors of high phosphorus concentration and low-middle GNRI level were found to be associated with all-cause mortality after adjusting for potential confounders. We found the highest mortality rate in patients with both "low-middle GNRI and low phosphorus".

Interaction between GNRI and phosphorus concentrations on all-cause mortality

In the time-dependent Cox model, the RERI was -0.57 between time-averaged high phosphorus concentration and low-middle GNRI level with respect to all-cause mortality, indicating negative biological interaction between them. We also observed a significant statistical interaction between these factors and all-cause mortality (P=0.05 by likelihood ratio test).

Figure 2 shows hazard ratios of the high and low phosphorus concentrations by GNRI levels. We see that the harmful effect of high phosphorus concentration increase as GNRI level increase. On the other hand, the harmful effect of low phosphorus concentration decrease as GNRI level increase.

Association between GNRI, phosphorus concentrations, and cardiovascular mortality

TABLE 2 shows incidence rates and HRs for cardiovascular mortality according to baseline and time-averaged exposure categories. We observed 286 cardiovascular deaths (2.3 per 100 person-years) during the follow-up period.

In the time-dependent Cox model, high phosphorus concentration and low GNRI was found to be associated with cardiovascular mortality. The hazard ratio for "high GNRI and high phosphorus" indicate the effect of high phosphorus concentration on cardiovascular

mortality (HR: 2.02, 95% CI: 1.18 to 3.45), compared with the reference of "high GNRI and middle phosphorus". The hazard ratio for "low-middle GNRI and middle phosphorus" indicate the effect of low-middle GNRI on cardiovascular mortality (HR: 1.80, 95% CI: 1.20 to 2.70). We found the highest cardiovascular mortality rate in patients with "low-middle GNRI and low phosphorus" (HR: 3.04, 95% CI: 1.62 to 5.67).

In the baseline Cox model, the associations of baseline fixed factors of high phosphorus ("high GNRI and high phosphorus" vs "high GNRI and middle phosphorus") and low GNRI ("low-middle GNRI and middle phosphorus" vs "high GNRI and middle phosphorus") with cardiovascular mortality were not statistically significant. We found the highest cardiovascular mortality rate in patients with "low-middle GNRI and low phosphorus" (HR: 2.39, 95% CI: 1.33 to 4.30).

Interaction between GNRI and phosphorus concentrations on cardiovascular mortality

In the time-dependent Cox model, the RERI was -0.47 between time-averaged high phosphorus concentration and low-middle GNRI level with respect to cardiovascular mortality, indicating negative biological interaction. However, we did not find significant statistical interaction between these factors and cardiovascular mortality (P=0.22 by likelihood ratio test).

DISCUSSION

In this cohort study, we found that both phosphorus concentration and nutritional index were separately associated with all-cause mortality and, more importantly, that interactions existed between these two factors. The association between high phosphorus concentrations and mortality was stronger in patients with high nutritional index than in those with low-middle nutritional index, with opposite findings for low phosphorus concentrations and mortality (Figure 2). These results suggest that the association between phosphorus concentration and mortality is indeed modified by nutritional index, suggesting that nutritional index should therefore be considered in the management of phosphorus concentration in hemodialysis patients.

Two third of hemodialysis patients here had risk of nutrition-related mortality (low-medium GNRI [<97.5] which was found to be associated with increased mortality rate).[15] We also found that abnormalities in phosphorus concentration, which have been shown to be associated with mortality,[22 31 32] were highly prevalent regardless of GNRI category (TABLE1). Taken together, these results suggest the clinical importance of our results showing the separate and combined association of these time-averaged factors with clinical outcomes.

While a number of previous studies have examined the associations between phosphorus concentration and mortality after adjusting for nutritional indices such as serum albumin concentration,[1 2 31 32] these studies failed to account for the interaction between the nutritional index and phosphorus concentration. A recent study in Austria noted statistical interactions between *time-varying* phosphorus and albumin, in which *time-varying* factors were updated to the most recent values every 3 months.[14] Here, we confirmed a statistical interaction on all-cause mortality between *time-averaged* phosphorus concentration and GNRI value.

Of note, two different concepts of interaction have been posited: statistical interaction and biological interaction, with the two concepts often confounding one another. Statistical interaction refers to any departure of the value of the combined effect from that of additive or multiplicative effects of the two risk factors, depending on the statistical model used. In contrast, biological interaction always refers to departure from additive effects, regardless of the statistical model used. Further, the degree of biological interaction may be estimated by calculating measures of biological interaction, such as the RERI.[28 29] In the present study, results of RERI calculation[30] showed negative biological interaction between high phosphorus concentrations and low GNRI.

Several plausible reasons have been proposed to explain the interaction between phosphorus concentration and GNRI: First, the influence of low-middle GNRI may outweigh the association between high phosphorus concentration and mortality should the association of low-middle GNRI and mortality be stronger than that of high phosphorus concentration and mortality; second, the mechanism of the association between phosphorus concentration and mortality may differ by GNRI category. In patients in high GNRI categories, high phosphorus concentration could be a risk factor as a promoter of vascular calcification. However, in those with low-middle GNRI, high phosphorus concentration may denote sufficient dietary intake and improving nutrition.

Clinical guidelines and previous papers recommended regular assessment of nutritional status for all hemodialysis patients, one method of which includes GNRI.[6-8 15-17] We used GNRI as a nutritional index to classify patients according to nutrition-related mortality risk in the present study for a number of reasons. First, GNRI can be calculated relatively simply using available objective data and does not require subjective assessment or judgment—an aspect which makes it a particularly useful index in clinical practice. Second, clinical guidelines recommended nutritional assessment by multidisciplinary methods, a criterion

which GNRI satisfies, being calculated using multidisciplinary factors, including gender, body weight, height, and serum albumin concentration. Finally, a number of previous studies have determined GNRI to be an accurate index for identifying hemodialysis patients at risk of malnutrition[17] and mortality.[16] However, it should be noted that low-middle GNRI is not necessarily indicative of a patient having malnutrition, as the GNRI formula includes serum albumin concentration, which is affected by chronic inflammation and fluid volume expansion.[33-35] Further, some investigators have suggested that malnutrition may be a consequence of chronic inflammation,[36-38] and dividing inflammation from malnutrition and examining their independent effect on mortality is therefore decidedly difficult.

Several strengths to the present study warrant mention. The major strength is that we analyzed large size (>6,000) representative dialysis population in Japan from DOPPS. Participants in DOPPS are representative dialysis patients in each country via a stratified random sampling method.[39] Second, we defined exposure categories based on two categorical factors (phosphorus concentration and GNRI), which allowed us to examine the separate and combined effects of these components and to examine their biological interaction by calculating the RERI. Third, we specifically used *time-averaged* phosphorus concentration and GNRI, as subsequent values of phosphorus and GNRI dramatically changed from baseline values. However, it should be noted that we used fixed baseline covariates for laboratory values and medications, as these can represent intermediate factors between phosphorus concentration and mortality. A fourth strength is that we confirmed the interaction between GNRI and phosphorus concentration via several methods, thereby underscoring the validity of our results.

However, several limitations to our study also warrant mention. First, residual confounding due to unmeasured factors may affect the association between exposure categories and mortality. To help combat this potential confounding, we included in our

multivariable model available baseline data. However, given that we also found consistent associations even after adding other covariates to the model, we believe that our findings are still sound. Second, we lacked data from other nutritional scoring tools, such as subjective global assessment (SGA)[40] and malnutrition-inflammation score (MIS).[41] However, GNRI can be calculated more simply than SGA and MIS, using the available data which are often measured in daily practice. Third, we lacked data on types and dose of phosphate binders, which might confound the association between phosphorus concentration and mortality. Fourth, results of time-dependent analysis are heavily affected by clinical conditions before death. For example, patients who experience acute drops in phosphorus concentration or GNRI are known to be likely to die more quickly. We believe that using time-averaged categories of phosphorus concentration and GNRI allows us to detect accumulated effects on mortality in time-dependent analysis after dealing with subsequent changes of these factors during the follow-up period. We also found similar associations between baseline fixed exposure categories and outcomes. Finally, this study included only Japanese hemodialysis patients and may therefore not be representative of findings in other countries. As such, interpreting and generalizing these results should be conducted with care.

CONCLUSION

We found that GNRI modified the association between phosphorus concentration and mortality, with both high phosphorus concentration and low-medium GNRI being found to be associated with mortality. We noted significant statistical interaction between phosphorus concentration and GNRI on all-cause mortality. We also noted negative biological interaction between high phosphorus concentration and low-medium GNRI. Taken together, these findings suggest that impact of phosphorus concentration on mortality is not consistent across nutritional status. Further, nutritional index should be considered when evaluating impact of

phosphorus concentration on mortality and making decisions regarding treatment with phosphorus management in hemodialysis patients.

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Contributors

The author's contributions were as follows: S. Fukuma designed research; S. Fukuma and T.I conducted research; S. Fukuma and T.I analyzed data; S. Fukuma wrote the paper; S.Fukuhara and T.A provided critical review of the manuscript; S. Fukuma had primary responsibility for final content.

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Competing interests

S. Fukuma is an advisor on epidemiology studies for Kyowa Hakko Kirin and receives consulting fees from Kyowa Hakko Kirin. T. A receives consulting fees from Chugai, Kirin, and Abbott, and grants/funds from Chugai and Kirin. Other authors have nothing to declare.

Data sharing statement

No additional data are available.

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TABLE 1 Baseline characteristics by combinations of GNRI and phosphorus concentrations

	Low-Middle GNRI			*High GNRI*		
	Low Phosphorus (N=342)	***Middle Phosphorus*** (N=2,557)	***High Phosphorus*** *(N=1,331)*	***Low phosphorus*** *(n=83)*	***Middle Phosphorus*** *(n=1,070)*	***High Phosphorus*** *(n=847)*
Age (years)	67.4 ± 11.6[2]	64.4 ± 11.7	59.6 ± 12.4	60.2 ± 15.0	59.0 ± 12.2	55.0 ± 11.8
Male (%)	59.1	56.3	55.9	71.2	69.3	69.6
Dialysis duration (years)	6.6 (2.5 to 11.7)[3]	5.9 (2.7 to 12.2)	6.8 (3.0 to 12.8)	5.0 (2.8 to 9.8)	5.0 (2.0 to 9.5)	5.5 (2.7 to 10.1)
BMI (kg/m^2)	19.5 ± 2.5	19.7 ± 2.8	19.8 ± 3.0	21.8 ± 2.9	22.3 ± 2.6	22.5 ± 2.7
Serum albumin (g/dl)	3.5 ± 0.4	3.6 ± 0.3	3.7 ± 0.3	4.2 ± 0.3	4.1 ± 0.3	4.2 ± 0.3
Calcium (mg/dl)	8.9 ± 0.7	8.9 ± 0.7	9.1 ± 0.9	9.5 ± 0.7	9.2 ± 0.7	9.1 ± 0.9
iPTH (pg/ml)	106 (41 to 240)	140 (56 to 262)	120 (54 to 256)	159 (67 to 262)	139 (54 to 252)	131 (50 to 265)
Single-pool Kt/V	1.37 ± 0.29	1.37 ± 0.28	1.36 ± 0.29	1.33 ± 0.27	1.36 ± 0.28	1.33 ± 0.29
nPNA (g/kg per day)	0.93 ± 0.23	1.01 ± 0.21	1.11 ± 0.21	0.94 ± 0.24	1.02 ± 0.19	1.10 ± 0.19
Medications (%)						
Phosphate binder	75.1	80.2	79.8	82.2	84.9	86.3
Oral VDRA	42.9	46.0	46.6	41.1	50.1	42.8

Intravenous VDRA	5.3	13.0	15.8	11.0	13.8	18.6
Comorbid conditions (%)						
Diabetes mellitus	38.6	29.7	25.3	37.0	32.6	28.9
Hypertension	68.3	69.2	65.9	76.7	67.3	67.2
Coronary heart disease	37.6	32.6	26.2	35.6	29.6	25.5
Other cardiovascular disease	39.3	33.2	31.3	32.9	26.2	21.2
Congestive heart failure	21.5	18.1	17.7	21.9	15.4	14.2
Cerebrovascular disease	21.5	16.7	11.9	13.7	11.4	8.8
Peripheral vascular disease	23.1	16.8	13.1	16.4	13.5	12.2
Recurrent cellulitis	7.3	4.0	3.0	5.5	2.8	3.2
Lung disease	3.0	2.9	1.9	2.7	1.7	0.9
Neurological disorder	13.2	8.7	5.3	9.6	4.9	3.2
Psychiatric disorder	5.3	4.0	4.4	4.1	3.6	2.9

GNRI, Geriatric Nutritional Risk Index; iPTH, intact parathyroid hormone; nPNA, normalized protein nitrogen appearance; VDRA, Vitamin D receptor activator; SD, standard deviation; IQR, interquartile range

Low-Middle GNRI: < highest tertile of GNRI; high GNRI: ≥ highest tertile of GNRI; low phosphorus: <3.5 mg/dl; middle phosphorus: 3.5 to <6.0 mg/dl; high phosphorus: ≥6.0 mg/dl, [1]Mean ± SD (all such values), [2]Median; IQR in parentheses (all such values)

TABLE 2 Hazard ratios for all-cause and cardiovascular mortality by baseline and time-averaged exposure categories

GNRI	Phosphorus	All-cause mortality					Cardiovascular-mortality				
		Baseline			Time-averaged		Baseline			Time-averaged	
		Incidence Rate[1]	HR[2]	95% CI	HR[3]	95% CI	Incidence Rate[1]	HR[2]	95% CI	HR[3]	95% CI
Low-Middle	***Low***	12.1	3.43	2.11 to 5.58	4.28	2.66 to 6.88	4.7	2.39	1.33 to 4.30	3.04	1.62 to 5.67
	Middle	5.5	1.93	1.33 to 2.79	2.12	1.51 to 2.96	2.6	1.57	0.95 to 2.59	1.80	1.20 to 2.70
	High	4.6	2.18	1.41 to 3.37	2.20	1.45 to 3.35	2.5	1.97	1.07 to 3.65	2.35	1.43 to 3.84
High	***Low***	3.3	1.14	0.49 to 2.70	0.93	0.22 to 3.87	1.6	1.01	0.32 to 3.24	0.83	0.12 to 5.57
	Middle	2.1	1.00	reference	1.00	reference	1.4	1.00	reference	1.00	reference
	High	2.6	1.59	1.03 to 2.45	1.66	1.01 to 2.73	1.8	1.71	0.94 to 3.11	2.02	1.18 to 3.45

GNRI, geriatric nutritional risk index; VDRA, Vitamin D receptor activator; DOPPS, the Dialysis Outcomes and Practice Pattern Study; HR, hazard ratio; CI, confidence interval

Low-Middle GNRI: < highest tertile of GNRI; high GNRI: ≥ highest tertile of GNRI; low phosphorus: <3.5 mg/dl; middle phosphorus: 3.5 to <6.0 mg/dl; high phosphorus: ≥6.0 mg/dl.

[1]Incidence rate per 100 person-years.

[2]Cox proportional hazards model adjusted for age, sex, time on dialysis, 11 comorbid conditions listed in Table 1, single-pool Kt/V, oral or intravenous VDRA use, phosphate binder use, and DOPPS phase.

[3]Time-dependent Cox proportional hazards model adjusted for age, sex, time on dialysis, 11 comorbid conditions listed in Table 1, single-pool Kt/V, oral or intravenous VDRA use, phosphate binder use, and DOPPS phase

Figure 1.

Selection process for study population.

DOPPS, the Dialysis Outcomes and Practice Pattern Study; GNRI, Geriatric Nutritional Risk Index.

Figure 2.

Effect of nutritional index on hazard ratios for the association between phosphorus concentrations and mortality

Hazard ratios of the high (≥6.0 mg/dl) and low (<3.5 mg/dl) phosphorus concentrations on all-cause mortality by GNRI level (GNRI levels at 85, 90, 95, 100, and 105). The reference level of GNRI was set to 100 based on the highest tertile.

GNRI, Geriatric Nutritional Risk Index.

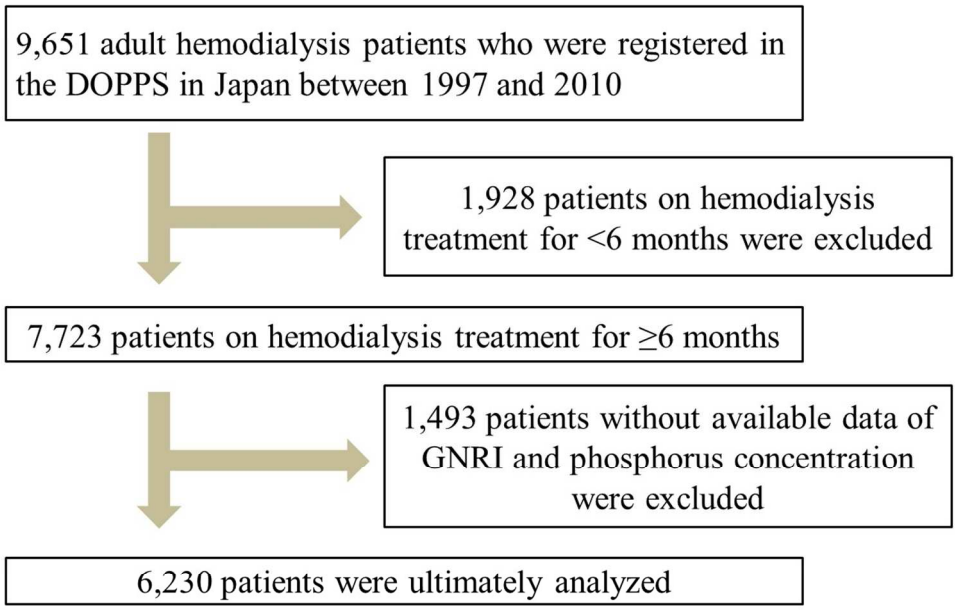
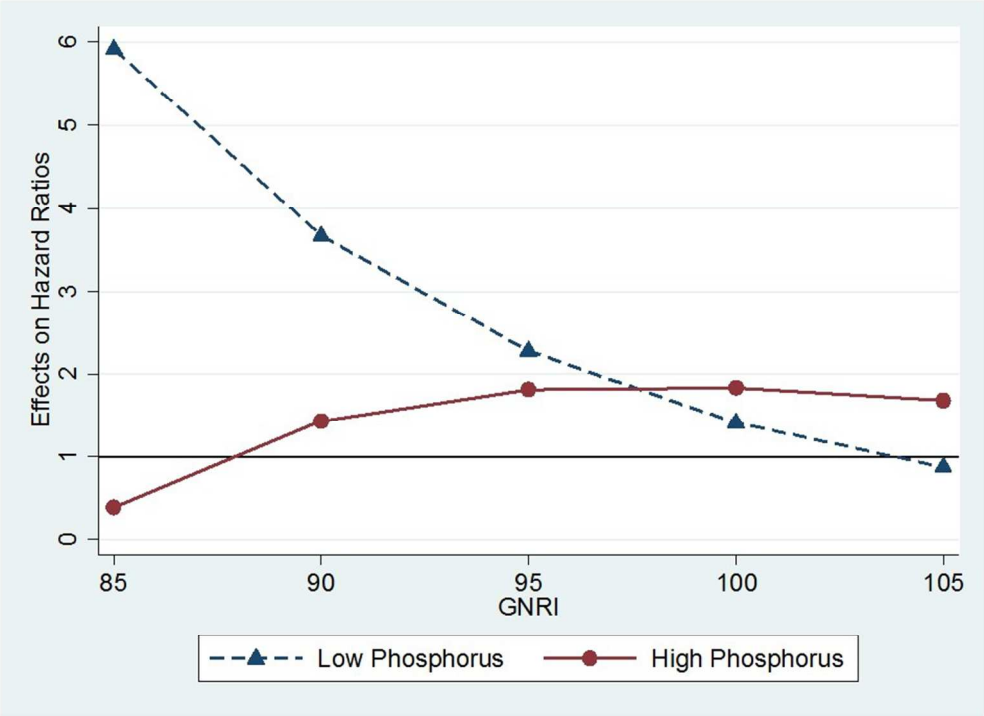


Figure 1

Selection process for study population.
DOPPS, the Dialysis Outcomes and Practice Pattern Study; GNRI, Geriatric Nutritional Risk Index.

355x266mm (96 x 96 DPI)



Effect of nutritional index on hazard ratios for the association between phosphorus concentrations and mortality

Hazard ratios of the high (≥6.0 mg/dl) and low (<3.5 mg/dl) phosphorus concentrations on all-cause mortality by GNRI level (GNRI levels at 85, 90, 95, 100, and 105). The reference level of GNRI was set to 100 based on the highest tertile.

GNRI, Geriatric Nutritional Risk Index.

254x190mm (96 x 96 DPI)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	na
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7
Bias	9	Describe any efforts to address potential sources of bias	8
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	8-9
		(*c*) Explain how missing data were addressed	8
		(*d*) If applicable, explain how loss to follow-up was addressed	8
		(*e*) Describe any sensitivity analyses	8
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10
		(b) Give reasons for non-participation at each stage	10
		(c) Consider use of a flow diagram	10
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10
		(b) Indicate number of participants with missing data for each variable of interest	10
		(c) Summarise follow-up time (eg, average and total amount)	10
Outcome data	15*	Report numbers of outcome events or summary measures over time	10
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10-12
		(*b*) Report category boundaries when continuous variables were categorized	10
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	na
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	na
Discussion			
Key results	18	Summarise key results with reference to study objectives	13
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13, 16
Generalisability	21	Discuss the generalisability (external validity) of the study results	15-16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	18

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Title

Impact of nutritional index on the association between phosphorus concentrations and mortality in hemodialysis patients: a cohort study from Dialysis Outcomes and Practice Pattern Study in Japan

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ABSTRACT

Objectives: While maintenance of both phosphorus concentration and nutritional status is a major concern in managing hemodialysis patients, the interaction between these parameters is not well understood. The aim of this study was to assess whether or not nutritional index influences the association between phosphorus concentration and all-cause mortality.

Design: A cohort study.

Setting: The Dialysis Outcomes and Practice Pattern Study, which included 99 representative dialysis facilities in Japan between 1997 and 2010.

Participants: A total of 6,230 adult hemodialysis patients who had spent at least six months on hemodialysis.

Main predictors: Six categories based on time-averaged factors of the geriatric nutritional risk index (GNRI; the lowest two and highest tertiles) and phosphorus concentration (<3.5, 3.5 to <6.0, and ≥6.0 mg/dl).

Primary outcome measure: All-cause mortality rate.

Analysis: Time-dependent Cox regression adjusting for potential confounders.

Results: During the follow-up period (12,294 person-years), we noted 561 deaths (4.6 per 100 person-years), and both high phosphorus concentrations and low-middle GNRI were separately associated with all-cause mortality. The harmful effect of high phosphorus concentrations on all-cause mortality was stronger in patients with high GNRI than in those with low-middle GNRI. On the other hand, the harmful effect of low phosphorus concentrations was stronger in those with low-middle GNRI than in those with high GNRI. Relative excess risk due to interaction (RERI) between high phosphorus concentrations and low-middle GNRI was -0.57, indicating an antagonistic interaction. We also observed a significant statistical multiplicative interaction between phosphorus concentrations and GNRI (P=0.05 by likelihood ratio test).

Conclusions: The association between time-averaged serum phosphorus concentration and all-cause mortality differs across the nutritional index. Accordingly, nutritional index should be considered when the impact of phosphorus concentration on mortality in hemodialysis patients is evaluated.

Strengths and limitations of this study

- While a number of previous studies have examined the association between phosphorus concentration and mortality after adjusting for nutritional indices, these studies failed to account for the interaction between nutritional index and phosphorus concentration.
- We analyzed a large (>6,000) representative dialysis population in Japan.
- We defined exposure categories based on two categorical factors (phosphorus concentration and nutritional index), which allowed us to examine the separate and combined effects of these components and to examine their additive interaction by calculating the relative excess risk due to interaction (RERI).
- We specifically examined time-averaged phosphorus concentration and nutritional index because subsequent phosphorus and nutritional index values changed dramatically from those at baseline.
- A limitation of this study is that it is an observational study and residual confounding due to unmeasured factors may affect the association between exposure categories and mortality.

INTRODUCTION

Both phosphorus concentration and nutritional status have attracted attention in the management of hemodialysis patients due to their association with mortality.[1-5] However, while preventing hyperphosphatemia[6-8] and improving nutritional status[4 9 10] are understandably major concerns, accomplishing both tasks simultaneously has largely proven difficult.[11] Reducing phosphorus concentration is primarily accomplished using phosphate binders and phosphate restriction,[11] the latter of which often involves protein restriction and may thereby worsen nutritional status.[12] In light of the difficulties associated with managing these side effects, physicians have concerns as to whether or not reducing phosphorus concentration actually improves survival in patients at risk of nutrition-related morbidity and mortality.[12 13] However, at present, it is unclear whether or not the association between phosphorus concentration and mortality differs across the nutritional index.

As nutritional index and phosphorus concentration are linked and may change dramatically over time, the interaction between time-dependent nutritional index and phosphorus concentration must be carefully considered when evaluating their separate and combined effects on mortality.[14] Although the Geriatric Nutritional Risk Index (GNRI)[15] was originally intended for use as a screening tool for predicting risk of morbidity and mortality in elderly patients, it has since been validated for use in whole hemodialysis patients.[16 17] Low GNRI is indicative of nutrition-related risk for mortality and morbidity. As such, clarifying its effect on the association between phosphorus concentration and mortality will aid in determining the effectiveness of outcome-oriented phosphorus management in hemodialysis patients.

Here, to clarify whether time-averaged GNRI modifies the association between time-averaged phosphorus concentration and mortality, we conducted a cohort study using data from the Dialysis Outcomes and Practice Pattern Study (DOPPS) in Japan (1997-2010).

METHODS

Study population and data sources

Our cohort study used Japan-derived data from DOPPS, an international longitudinal study of hemodialysis patients which aims to identify practice patterns associated with improved patient outcomes. Participants in DOPPS were randomly selected from representative dialysis facilities within participating countries. Details regarding the design of DOPPS have been described in full elsewhere.[18]

The study included 6,230 hemodialysis patients aged ≥18 years from 99 representative dialysis facilities in Japan who had spent at least six months on hemodialysis (Figure 1). All eligible patients were selected from DOPPS I (1997-2001), II (2002-2004), III (2005-2007) and IV (2008-2010). Baseline data regarding demographic information, comorbid conditions, medication for mineral bone disorder, and laboratory values were obtained at enrollment. Time-dependent data (GNRI and phosphorus concentration) and mortality data (time and cause) were obtained from the database during the follow-up period. GNRI was calculated as follows:

$$\text{GNRI} = (14.89 \times \text{albumin [g/dl]}) + [41.7 \times (\text{body weight} / \text{ideal body weight})]$$

where "ideal body weight" was calculated using the Lorentz formula as follows:

$$\text{Ideal body weight for men} = \text{height} - 100 - [(\text{height} - 150) / 4]$$

$$\text{Ideal body weight for women} = \text{height} - 100 - [(\text{height} - 150) / 2.5]$$

We set (body weight/ideal body weight) as "1" when "body weight" exceeded "ideal body weight" [15]. In this cohort, "body weight" exceeded "ideal body weight" in 26.0% of patients.

Definition of exposure

Exposure categories were defined based on the categorical factors of GNRI (low-middle, lower two tertiles; high, the highest tertile) and serum phosphorus concentrations (low, <3.5 mg/dl; middle, 3.5 to <6.0 mg/dl; high, ≥6.0 mg/dl). We evaluated GNRI and serum phosphorus concentrations by first using time-averaged variables, which were updated every four months to obtain the most recent mean values after study entry, and then using fixed baseline variables measured at study entry. The reference category for GNRI was the highest tertile, and the lower two tertiles were regarded as the high-risk category. The reference category for phosphorus concentration was the middle category (3.5 to <6.0 mg/dl) and the low (<3.5 mg/dl) and high (≥6.0 mg/dl) categories were regarded as high-risk categories. Based on these two risk categories, we defined six exposure categories: "low-middle GNRI and low phosphorus", "low-middle GNRI and middle phosphorus", "low-middle GNRI and high phosphorus", "high GNRI and low phosphorus", "high GNRI and middle phosphorus", and "high GNRI and high phosphorus". The cut-off values for phosphorus concentration were defined according to the Japanese clinical guidelines.[19] The cut-off values for GNRI were defined based on the highest tertile established in this study, with "high GNRI and middle phosphorus" defined as the reference category, as previous studies have suggested that this category has the lowest mortality risk.[2 16 18 20-22]

Outcomes

The primary outcome measure was hazard ratio for all-cause mortality. Patients were followed from study entry until death, transplantation, transfer to another facility, modality change, withdrawal, or study end, whichever came first. The secondary outcome measure was hazard

ratio for cardiovascular mortality, which included sudden deaths, deaths from heart failure, acute myocardial infarction, cerebrovascular disease, and other vascular diseases.

Statistical analysis

We conducted baseline and time-dependent Cox regression to estimate hazard ratios and their 95% confidence intervals (CIs) for the association between exposure categories and all-cause mortality. The baseline Cox regression used baseline fixed exposure categories, and the time-dependent Cox regression used time-averaged exposure categories. In our analyses using the combined phosphorus concentration and GNRI categories, the hazard ratio for "high phosphorus concentration and high GNRI" to "middle phosphorus concentration and high GNRI" (the reference category) indicates the effect of high phosphorus concentration on outcomes. The hazard ratio for "low-middle GNRI and middle phosphorus concentration" to the reference category indicates the effect of low-middle GNRI on outcomes. Our Cox model included adjustments for age, gender, time on dialysis, 11 comorbid conditions, single-pool Kt/V (quintiles), phosphate binder use, oral or intravenous vitamin D receptor activator (VDRA) use, and DOPPS phase, all of which were indicated as potential confounding factors in previous studies.[2 3 22-27] Given their potential to function as intermediate factors between phosphorus concentration and mortality, we used fixed baseline variables of these covariates in the model. For Cox models, we used robust variance estimates to consider cluster effects at the facility level (correlation between patients).

We examined interactions between GNRI and phosphorus concentration in two ways. First, we assessed a statistical multiplicative interaction using the likelihood ratio test, which compares models with and without interaction terms. Second, to assess an additive interaction between high phosphorus concentration and low-middle GNRI, we estimated the relative excess risk due to interaction (RERI) using the method described by Rothman.[28 29] RERI

between two factors (A and B) is defined as "departure from additive effects" and is calculated as follows using adjusted hazard ratios (HRs): [30]

$$RERI = HR(A\&B) - HR(A) - HR(B) + 1$$

RERI < 0, RERI = 0, and RERI > 0 indicate an antagonistic interaction, absence of interaction, and synergistic interaction, respectively.

To examine how the effects of phosphorus concentration changes according to GNRI levels, we estimated the effect of a discrete change in phosphorus category across GNRI levels. Hazard ratios of "low phosphorus" and "high phosphorus" were estimated by comparing with the reference category of "middle phosphorus". Therefore, we reported hazard ratios for "low phosphorus" and "high phosphorus" from 2 phosphorus categories. After conducting time-dependent Cox regression with the interaction term for continuous GNRI and categorical phosphorus concentration, we estimated the average marginal effect of phosphorus categories (high and low phosphorus concentration) on all-cause mortality at each GNRI level (GNRI levels: 85, 90, 95, 100, and 105). The reference GNRI level was set at 100 based on the highest tertile. We used "MARGINS" and "MARGINSPLOT" commands in STATA for Figure 2.

All analyses were performed using STATA (Version 14.2, STATA, College Station, TX, USA) software.

RESULTS

Baseline patient characteristics

Figure 1 shows the participant selection process. A total of 6,230 hemodialysis patients were included in this study. The mean (±SD) age was 61.1 (±12.5) years, 60.8% of patients were male, median (interquartile range) dialysis duration was 5.8 (2.6 to 11.3) years, and 29.7% of patients had diabetes. The median GNRI value was 94.9 (low GNRI, 53.4 to 91.8; middle GNRI, 91.8 to 97.5; high GNRI, 97.5 to 125.9) and the range of the lower two tertiles was <97.5, indicating patients with nutrition-related mortality risk, according to the original study.[15] A total of 6.0% of patients had low phosphorus concentrations while 35.6% had high phosphorus concentrations. Baseline characteristics by combined GNRI and phosphorus concentration categories are shown in TABLE 1. Associations between GNRI values and phosphorus concentration and nPNA are summarized in Supplementary TABLE 1.

Association between GNRI, phosphorus concentration, and all-cause mortality

TABLE 2 shows incidence rates and HRs for all-cause mortality according to baseline and time-averaged exposure categories. Median follow-up time was 2.1 years. During the follow-up period (total: 12,294 person-years), we recorded 561 all-cause deaths (4.6 per 100 person-years).

In the time-dependent Cox model, both time-averaged factors of high phosphorus concentration and low-middle GNRI were associated with all-cause mortality after adjusting for potential confounders. The hazard ratio for “high GNRI and high phosphorus” indicated that there was an effect of high phosphorus concentration on all-cause mortality (HR: 1.66, 95% CI: 1.01 to 2.73) compared with “high GNRI and middle phosphorus” (the reference category). The hazard ratio for “low-middle GNRI and middle phosphorus” indicated that there was an effect of low-middle GNRI on all-cause mortality (HR: 2.12, 95% CI: 1.51 to

2.96) compared with the reference category. We found the highest mortality rate in patients with both "low-middle GNRI and low phosphorus" (HR: 4.28, 95% CI: 2.66 to 6.88), highlighting the combined effect of low-middle GNRI and low phosphorus concentration.

In the baseline Cox model, both baseline fixed factors of high phosphorus concentration and low-middle GNRI level were associated with all-cause mortality after adjusting for potential confounders. We found the highest mortality rate in patients with both "low-middle GNRI and low phosphorus".

Interaction between GNRI and phosphorus concentration on all-cause mortality

In the time-dependent Cox model, the RERI was -0.57 between time-averaged high phosphorus concentration and low-middle GNRI with respect to all-cause mortality, indicating an antagonistic interaction. We also observed a significant statistical multiplicative interaction between these factors and all-cause mortality (P=0.05 by a likelihood ratio test).

Figure 2 shows the hazard ratios for high and low phosphorus concentrations across the GNRI. The harmful effect of high phosphorus concentration increases with increasing GNRI. On the other hand, the harmful effect of low phosphorus concentration decreases with increasing GNRI.

Association between GNRI, phosphorus concentration, and cardiovascular mortality

TABLE 2 shows the incidence rates and HRs for cardiovascular mortality according to baseline and time-averaged exposure categories. We observed 286 cardiovascular deaths (2.3 per 100 person-years) during the follow-up period.

In the time-dependent Cox model, high phosphorus concentration and low GNRI was associated with cardiovascular mortality. The hazard ratio for "high GNRI and high phosphorus" indicates that there was an effect of high phosphorus concentration on

cardiovascular mortality (HR: 2.02, 95% CI: 1.18 to 3.45) compared with "high GNRI and middle phosphorus" (the reference category). The hazard ratio for "low-middle GNRI and middle phosphorus" indicates that there was an effect of low-middle GNRI on cardiovascular mortality (HR: 1.80, 95% CI: 1.20 to 2.70). We found the highest cardiovascular mortality rate in patients with "low-middle GNRI and low phosphorus" (HR: 3.04, 95% CI: 1.62 to 5.67).

In the baseline Cox model, baseline fixed factors of high phosphorus ("high GNRI and high phosphorus" vs "high GNRI and middle phosphorus") and low GNRI ("low-middle GNRI and middle phosphorus" vs "high GNRI and middle phosphorus") were not significantly associated with cardiovascular mortality. We found the highest cardiovascular mortality rate in patients with "low-middle GNRI and low phosphorus" (HR: 2.39, 95% CI: 1.33 to 4.30).

Interaction between GNRI and phosphorus concentration on cardiovascular mortality

In the time-dependent Cox model, the RERI was -0.47 between time-averaged high phosphorus concentrations and low-middle GNRI with respect to cardiovascular mortality, indicating an antagonistic interaction. However, we did not find a significant statistical multiplicative interaction between these factors and cardiovascular mortality (P=0.22 by a likelihood ratio test).

DISCUSSION

In this cohort study, we found that both phosphorus concentration and nutritional index were separately associated with all-cause mortality and, more importantly, that there were interactions between these two factors. The association between high phosphorus concentrations and mortality was stronger in patients with a high nutritional index than in those with a low-middle nutritional index, with opposite findings for low phosphorus concentrations and mortality (Figure 2). These results suggest that the association between phosphorus concentration and mortality is indeed modified by nutritional index, suggesting that nutritional index should be considered in the management of phosphorus concentration in hemodialysis patients.

Two-thirds of hemodialysis patients here were at risk of nutrition-related mortality (low-medium GNRI [<97.5] was associated with increased mortality rate).[15] We also found that abnormalities in phosphorus concentration, which have been shown to be associated with mortality,[22 31 32] were highly prevalent regardless of GNRI category (TABLE 1). Taken together, these results indicate the clinical importance of both the separate and combined association of these time-averaged factors with clinical outcomes.

While a number of previous studies have examined the associations between phosphorus concentration and mortality after adjusting for nutritional indices such as serum albumin concentration,[1 2 31 32] these studies failed to account for the interaction between nutritional index and phosphorus concentration. A recent study in Austria noted statistical multiplicative interactions between time-varying phosphorus and albumin, in which time-varying factors were updated to the most recent values every three months.[14] Here, we confirmed a statistical multiplicative interaction between *time-averaged* phosphorus concentration and GNRI on all-cause mortality.

Two different types of interaction have been posited: statistical interaction and additive interaction, with the two concepts often confounding one another. Statistical interaction refers to any departure of the value of the combined effect from that of additive or multiplicative effects of the two risk factors, depending on the statistical model used. In contrast, additive interaction always refers to departure from additive effects, regardless of the statistical model used. Further, the degree of additive interaction may be estimated by calculating measures of additive interaction, such as the RERI.[28 29] In the present study, RERI calculations[30] showed antagonistic interactions between high phosphorus concentrations and low GNRI.

Two plausible reasons have been proposed to explain the interaction between phosphorus concentration and GNRI. First, the influence of low-middle GNRI may outweigh the association between high phosphorus concentration and mortality if the association between low-middle GNRI and mortality is stronger than that of high phosphorus concentration and mortality. Second, the mechanism of the association between phosphorus concentration and mortality may differ by GNRI category. In patients in high GNRI categories, high phosphorus concentration could be a risk factor as a promoter of vascular calcification. However, in those with low-middle GNRI, high phosphorus concentration may denote sufficient dietary intake and improving nutrition.

Clinical guidelines and previous studies recommend regular assessment of nutritional status for all hemodialysis patients, which can be conducted using GNRI, among other methods.[6-8 15-17] We used GNRI as a nutritional index to classify patients according to nutrition-related mortality risk for a number of reasons. First, GNRI can be calculated relatively simply using available objective data and does not require subjective assessment or judgment—an aspect that makes it a particularly useful index in clinical practice. Second, clinical guidelines recommend nutritional assessment by multiple measurements, a criterion which GNRI satisfies as it is calculated using multiple factors, including gender, body weight,

height, and serum albumin concentration. Finally, a number of previous studies have found GNRI to be an accurate index for identifying hemodialysis patients at risk of malnutrition[17] and mortality.[16] However, it should be noted that low-middle GNRI is not necessarily indicative of malnutrition, as the GNRI formula includes serum albumin concentration, which is affected by chronic inflammation and fluid volume expansion.[33-35] Further, some investigators have suggested that malnutrition may be a consequence of chronic inflammation,[36-38] making it difficult to separate inflammation from malnutrition and to examine their independent effects on mortality.

Several strengths of the present study warrant mention. The major strength is the analysis of a large (>6,000) representative dialysis population in Japan from DOPPS. Participants in DOPPS are representative dialysis patients of a particular country selected via a stratified random sampling method.[39] Second, we defined exposure categories based on two categorical factors (phosphorus concentration and GNRI), which allowed us to examine the separate and combined effects of these components and to examine their additive interaction by calculating the RERI. Third, we specifically used *time-averaged* phosphorus concentration and GNRI, as subsequent values of phosphorus and GNRI changed dramatically from baseline values. Fourth, we confirmed the interaction between GNRI and phosphorus concentration via several methods, thereby underscoring the validity of our results.

Several limitations of our study also warrant mention. First, residual confounding due to unmeasured factors may affect the association between exposure categories and mortality. To minimize the effects of this potential confounding, we included available baseline data in our multivariable model. Given that we found consistent associations even after the addition of other covariates to the model, we believe that our findings are sound. Second, we lacked data from other nutritional scoring tools, such as subjective global assessment (SGA)[40] and malnutrition-inflammation score (MIS).[41] However, GNRI can be calculated more simply

than SGA and MIS, using available data which are often measured in daily practice. Third, we lacked data on the type and dose of phosphate binders, which might confound the association between phosphorus concentration and mortality. Fourth, results of time-dependent analysis are heavily affected by clinical conditions before death. For example, patients who experience acute drops in phosphorus concentration or GNRI are known to be likely to die more quickly. We believe that using time-averaged categories of phosphorus concentration and GNRI allowed us to detect accumulated effects on mortality in time-dependent analysis after changes in these factors during the follow-up period. We also found similar associations between baseline fixed exposure categories and outcomes. It should be noted that we used fixed baseline covariates for laboratory values and medications, as these can represent intermediate factors between phosphorus concentration and mortality. Finally, this study included only Japanese hemodialysis patients and our findings may therefore not be representative of those from other countries. As such, interpreting and generalizing these results should be conducted with care.

CONCLUSION

We found that GNRI modified the association between phosphorus concentration and mortality, with both high phosphorus concentration and low-medium GNRI associated with mortality. We noted a significant statistical multiplicative interaction between phosphorus concentration and GNRI on all-cause mortality. We also noted an antagonistic interaction between high phosphorus concentration and low-medium GNRI. Taken together, these findings suggest that the impact of phosphorus concentration on mortality is not consistent across nutritional status. Therefore, nutritional index should be considered when evaluating the impact of phosphorus concentration on mortality, and when making decisions regarding treatment with phosphorus management in hemodialysis patients.

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Contributors

The author's contributions were as follows: S. Fukuma designed research; S. Fukuma and T.I conducted research; S. Fukuma and T.I analyzed data; S. Fukuma wrote the paper; S. Fukuhara and T.A provided critical review of the manuscript; and S. Fukuma had primary responsibility for final content.

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Competing interests

S. Fukuma is an advisor on epidemiology studies for Kyowa Hakko Kirin and receives consulting fees from Kyowa Hakko Kirin. T. A. receives consulting fees from Chugai, Kirin, and Abbott, and grants/funds from Chugai and Kirin. The other authors have nothing to declare.

Data sharing statement

No additional data are available.

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TABLE 1 Baseline characteristics by combined GNRI and phosphorus concentration categories

	Total	*Low-Middle GNRI*			*High GNRI*		
		Low Phosphorus	*Middle Phosphorus*	*High Phosphorus*	*Low phosphorus*	*Middle Phosphorus*	*High Phosphorus*
	(N=6230)	(N=342)	(N=2,557)	*(N=1,331)*	*(n=83)*	*(n=1,070)*	*(n=847)*
Age (years)	61.1±12.5	67.4 ± 11.6[2]	64.4 ± 11.7	59.6 ± 12.4	60.2 ± 15.0	59.0 ± 12.2	55.0 ± 11.8
Male (%)	60.8	59.1	56.3	55.9	71.2	69.3	69.6
Dialysis duration (years)	5.8	6.6	5.9	6.8	5.0	5.0	5.5
	(2.6 to 11.3)	(2.5 to 11.7)[3]	(2.7 to 12.2)	(3.0 to 12.8)	(2.8 to 9.8)	(2.0 to 9.5)	(2.7 to 10.1)
BMI (kg/m^2)	20.7±3.1	19.5 ± 2.5	19.7 ± 2.8	19.8 ± 3.0	21.8 ± 2.9	22.3 ± 2.6	22.5 ± 2.7
Serum albumin (g/dl)	3.8±0.4	3.5 ± 0.4	3.6 ± 0.3	3.7 ± 0.3	4.2 ± 0.3	4.1 ± 0.3	4.2 ± 0.3
Calcium (mg/dl)	9.0±0.8	8.9 ± 0.7	8.9 ± 0.7	9.1 ± 0.9	9.5 ± 0.7	9.2 ± 0.7	9.1 ± 0.9
iPTH (pg/ml)	133	106	140	120	159	139	131
	(53 to 260)	(41 to 240)	(56 to 262)	(54 to 256)	(67 to 262)	(54 to 252)	(50 to 265)
Single-pool Kt/V	1.36±0.29	1.37 ± 0.29	1.37 ± 0.28	1.36 ± 0.29	1.33 ± 0.27	1.36 ± 0.28	1.33 ± 0.29
nPNA (g/kg per day)	1.04±0.21	0.93 ± 0.23	1.01 ± 0.21	1.11 ± 0.21	0.94 ± 0.24	1.02 ± 0.19	1.10 ± 0.19
Medications (%)							

Phosphate binder	81.6	75.1	80.2	79.8	82.2	84.9	86.3
Oral VDRA	46.2	42.9	46.0	46.6	41.1	50.1	42.8
Intravenous VDRA	14.2	5.3	13.0	15.8	11.0	13.8	18.6
Comorbid conditions (%)							
Diabetes mellitus	29.7	38.6	29.7	25.3	37.0	32.6	28.9
Hypertension	67.9	68.3	69.2	65.9	76.7	67.3	67.2
Coronary heart disease	30.0	37.6	32.6	26.2	35.6	29.6	25.5
Other cardiovascular disease	30.1	39.3	33.2	31.3	32.9	26.2	21.2
Congestive heart failure	17.2	21.5	18.1	17.7	21.9	15.4	14.2
Cerebrovascular disease	13.8	21.5	16.7	11.9	13.7	11.4	8.8
Peripheral vascular disease	15.0	23.1	16.8	13.1	16.4	13.5	12.2
Recurrent cellulitis	3.6	7.3	4.0	3.0	5.5	2.8	3.2
Lung disease	2.2	3.0	2.9	1.9	2.7	1.7	0.9
Neurological disorder	6.7	13.2	8.7	5.3	9.6	4.9	3.2
Psychiatric disorder	3.9	5.3	4.0	4.4	4.1	3.6	2.9

GNRI, Geriatric Nutritional Risk Index; iPTH, intact parathyroid hormone; nPNA, normalized protein nitrogen appearance; VDRA, Vitamin D receptor activator; SD, standard deviation; IQR, interquartile range

Low-Middle GNRI: < highest tertile of GNRI; high GNRI: ≥ highest tertile of GNRI; low phosphorus: <3.5 mg/dl; middle phosphorus: 3.5 to <6.0 mg/dl; high phosphorus: ≥6.0 mg/dl, [1]Mean ± SD (all such values), [2]Median; IQR in parentheses (all such values)

TABLE 2 Hazard ratios for all-cause and cardiovascular mortality by baseline and time-averaged exposure categories

GNRI	Phosphorus	All-cause mortality					Cardiovascular-mortality				
		Baseline			Time-averaged		Baseline			Time-averaged	
		Incidence Rate[1]	HR[2]	95% CI	HR[3]	95% CI	Incidence Rate[1]	HR[2]	95% CI	HR[3]	95% CI
Low-Middle	***Low***	12.1	3.43	2.11 to 5.58	4.28	2.66 to 6.88	4.7	2.39	1.33 to 4.30	3.04	1.62 to 5.67
	Middle	5.5	1.93	1.33 to 2.79	2.12	1.51 to 2.96	2.6	1.57	0.95 to 2.59	1.80	1.20 to 2.70
	High	4.6	2.18	1.41 to 3.37	2.20	1.45 to 3.35	2.5	1.97	1.07 to 3.65	2.35	1.43 to 3.84
High	***Low***	3.3	1.14	0.49 to 2.70	0.93	0.22 to 3.87	1.6	1.01	0.32 to 3.24	0.83	0.12 to 5.57
	Middle	2.1	1.00	reference	1.00	reference	1.4	1.00	reference	1.00	reference
	High	2.6	1.59	1.03 to 2.45	1.66	1.01 to 2.73	1.8	1.71	0.94 to 3.11	2.02	1.18 to 3.45

GNRI, geriatric nutritional risk index; VDRA, Vitamin D receptor activator; DOPPS, the Dialysis Outcomes and Practice Pattern Study; HR, hazard ratio; CI, confidence interval

Low-Middle GNRI: < highest tertile of GNRI; high GNRI: ≥ highest tertile of GNRI; low phosphorus: <3.5 mg/dl; middle phosphorus: 3.5 to <6.0 mg/dl; high phosphorus: ≥6.0 mg/dl.

[1]Incidence rate per 100 person-years.

[2]Cox proportional hazards model adjusted for age, sex, time on dialysis, 11 comorbid conditions listed in Table 1, single-pool Kt/V, oral or intravenous VDRA use, phosphate binder use, and DOPPS phase.

[3]Time-dependent Cox proportional hazards model adjusted for age, sex, time on dialysis, 11 comorbid conditions listed in Table 1, single-pool Kt/V, oral or intravenous VDRA use, phosphate binder use, and DOPPS phase

Figure 1.

Selection process for study population.

DOPPS, the Dialysis Outcomes and Practice Pattern Study; GNRI, Geriatric Nutritional Risk Index.

Figure 2.

Effect of nutritional index on hazard ratios for the association between phosphorus concentration and mortality

Hazard ratios of high (≥6.0 mg/dl) and low (<3.5 mg/dl) phosphorus concentrations on all-cause mortality by GNRI level (GNRI levels: 85, 90, 95, 100, and 105). The reference GNRI level was set at 100 based on the highest tertile.

GNRI, Geriatric Nutritional Risk Index.

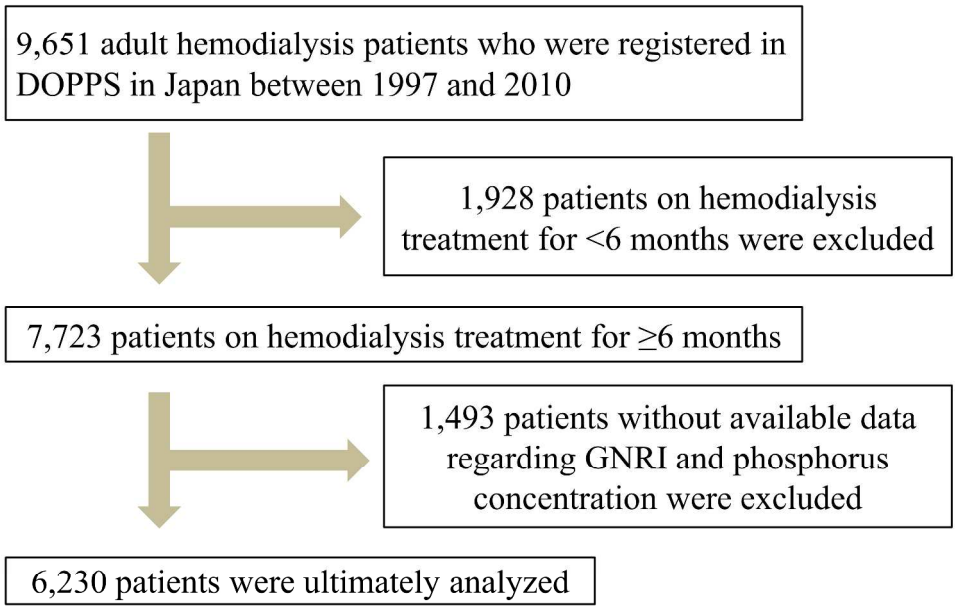

Figure 1

Selection process for study population.
DOPPS, the Dialysis Outcomes and Practice Pattern Study; GNRI, Geriatric Nutritional Risk Index.

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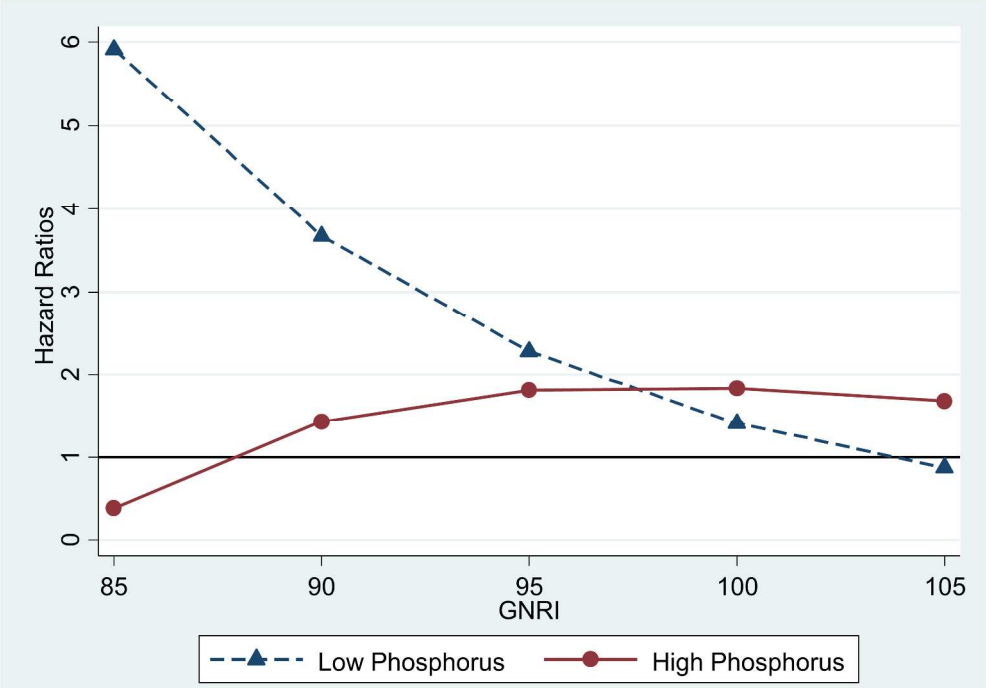

Effect of nutritional index on hazard ratios for the association between phosphorus concentration and mortality

Hazard ratios of high (≥6.0 mg/dl) and low (<3.5 mg/dl) phosphorus concentrations on all-cause mortality by GNRI level (GNRI levels: 85, 90, 95, 100, and 105). The reference GNRI level was set at 100 based on the highest tertile.

GNRI, Geriatric Nutritional Risk Index.

254x190mm (300 x 300 DPI)

Supplementary TABLE 1 Association between GNRI and phosphorus or nPNA

	Phosphorus (mg/dL)		*nPNA (g/kg per day)*	
	Coefficient	**95%CI**	**Coefficient**	**95%CI**
GNRI	0.35	0.30 to 0.40	0.02	0.01 to 0.03

GNRI, Geriatric Nutritional Risk Index; nPNA, normalized protein nitrogen appearance.

Coefficients are estimated by linear regression and the values indicate the mean change in phosphorus or nPNA for every 10-point increase in GNRI.

Supplementary TABLE 2 Hazard ratios for all-cause and cardiovascular mortality by time-averaged exposure categories adjusting for time-varying phosphate binder use

GNRI	Phosphorus	All-cause mortality		Cardiovascular-mortality	
		HR[1]	95% CI	HR[1]	95% CI
Low-Middle	***Low***	4.04	2.48 to 6.59	2.79	1.49 to 5.25
	Middle	2.06	1.45 to 2.92	1.69	1.11 to 2.57
	High	2.03	1.31 to 3.17	2.12	1.27 to 3.54
High	***Low***	1.00	0.24 to 4.17	0.88	0.13 to 5.98
	Middle	1.00	reference	1.00	reference
	High	1.76	1.07 to 2.91	2.12	1.23 to 3.65

GNRI, geriatric nutritional risk index; HR, hazard ratio; CI, confidence interval

Low-Middle GNRI: < highest tertile of GNRI; high GNRI: ≥ highest tertile of GNRI; low phosphorus: < 3.5 mg/dl; middle phosphorus: 3.5 to < 6.0 mg/dl; high phosphorus: ≥ 6.0 mg/dl.

[1]Time-dependent Cox proportional hazards model adjusted for time-varying phosphate binder use in addition to baseline covariates (age, sex, time on dialysis, 11 comorbid conditions listed in Table 1, single-pool Kt/V, oral or intravenous VDRA use, and DOPPS phase)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	na
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7
Bias	9	Describe any efforts to address potential sources of bias	8
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	8-9
		(*c*) Explain how missing data were addressed	8
		(*d*) If applicable, explain how loss to follow-up was addressed	8
		(*e*) Describe any sensitivity analyses	8
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10
		(b) Give reasons for non-participation at each stage	10
		(c) Consider use of a flow diagram	10
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10
		(b) Indicate number of participants with missing data for each variable of interest	10
		(c) Summarise follow-up time (eg, average and total amount)	10
Outcome data	15*	Report numbers of outcome events or summary measures over time	10
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10-12
		(*b*) Report category boundaries when continuous variables were categorized	10
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	na
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	na
Discussion			
Key results	18	Summarise key results with reference to study objectives	13
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13, 16
Generalisability	21	Discuss the generalisability (external validity) of the study results	15-16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	18

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Impact of nutritional index on the association between phosphorus concentrations and mortality in hemodialysis patients: a cohort study from Dialysis Outcomes and Practice Pattern Study in Japan

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Title

Impact of nutritional index on the association between phosphorus concentrations and mortality in hemodialysis patients: a cohort study from Dialysis Outcomes and Practice Pattern Study in Japan

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ABSTRACT

Objectives: While maintenance of both phosphorus concentration and nutritional status is a major concern in managing hemodialysis patients, the interaction between these parameters is not well understood. The aim of this study was to assess whether or not nutritional index influences the association between phosphorus concentration and all-cause mortality.

Design: A cohort study.

Setting: The Dialysis Outcomes and Practice Pattern Study, which included 99 representative dialysis facilities in Japan between 1997 and 2010.

Participants: A total of 6,230 adult hemodialysis patients who had spent at least six months on hemodialysis.

Main predictors: Six categories based on time-averaged factors of the geriatric nutritional risk index (GNRI; the lowest two and highest tertiles) and phosphorus concentration (<3.5, 3.5 to <6.0, and ≥6.0 mg/dl).

Primary outcome measure: All-cause mortality rate.

Analysis: Time-dependent Cox regression adjusting for potential confounders.

Results: During the follow-up period (12,294 person-years), we noted 561 deaths (4.6 per 100 person-years), and both high phosphorus concentrations and low-middle GNRI were separately associated with all-cause mortality. The harmful effect of high phosphorus concentrations on all-cause mortality was stronger in patients with high GNRI than in those with low-middle GNRI. On the other hand, the harmful effect of low phosphorus concentrations was stronger in those with low-middle GNRI than in those with high GNRI. Relative excess risk due to interaction (RERI) between high phosphorus concentrations and low-middle GNRI was -0.57, indicating an antagonistic interaction. We also observed a significant statistical multiplicative interaction between phosphorus concentrations and GNRI (P=0.05 by likelihood ratio test).

Conclusions: The association between time-averaged serum phosphorus concentration and all-cause mortality differs across the nutritional index. Accordingly, nutritional index should be considered when the impact of phosphorus concentration on mortality in hemodialysis patients is evaluated.

Strengths and limitations of this study

- While a number of previous studies have examined the association between phosphorus concentration and mortality after adjusting for nutritional indices, these studies failed to account for the interaction between nutritional index and phosphorus concentration.
- We analyzed a large (>6,000) representative dialysis population in Japan.
- We defined exposure categories based on two categorical factors (phosphorus concentration and nutritional index), which allowed us to examine the separate and combined effects of these components and to examine their additive interaction by calculating the relative excess risk due to interaction (RERI).
- We specifically examined time-averaged phosphorus concentration and nutritional index because subsequent phosphorus and nutritional index values changed dramatically from those at baseline.
- A limitation of this study is that it is an observational study and residual confounding due to unmeasured factors may affect the association between exposure categories and mortality.

INTRODUCTION

Both phosphorus concentration and nutritional status have attracted attention in the management of hemodialysis patients due to their association with mortality.[1-5] However, while preventing hyperphosphatemia[6-8] and improving nutritional status[4 9 10] are understandably major concerns, accomplishing both tasks simultaneously has largely proven difficult.[11] Reducing phosphorus concentration is primarily accomplished using phosphate binders and phosphate restriction,[11] the latter of which often involves protein restriction and may thereby worsen nutritional status.[12] In light of the difficulties associated with managing these side effects, physicians have concerns as to whether or not reducing phosphorus concentration actually improves survival in patients at risk of nutrition-related morbidity and mortality.[12 13] However, at present, it is unclear whether or not the association between phosphorus concentration and mortality differs across the nutritional index.

As nutritional index and phosphorus concentration are linked and may change dramatically over time, the interaction between time-dependent nutritional index and phosphorus concentration must be carefully considered when evaluating their separate and combined effects on mortality.[14] Although the Geriatric Nutritional Risk Index (GNRI)[15] was originally intended for use as a screening tool for predicting risk of morbidity and mortality in elderly patients, it has since been validated for use in whole hemodialysis patients.[16 17] Low GNRI is indicative of nutrition-related risk for mortality and morbidity. As such, clarifying its effect on the association between phosphorus concentration and mortality will aid in determining the effectiveness of outcome-oriented phosphorus management in hemodialysis patients.

Here, to clarify whether time-averaged GNRI modifies the association between time-averaged phosphorus concentration and mortality, we conducted a cohort study using data from the Dialysis Outcomes and Practice Pattern Study (DOPPS) in Japan (1997-2010).

METHODS

Study population and data sources

Our cohort study used Japan-derived data from DOPPS, an international longitudinal study of hemodialysis patients which aims to identify practice patterns associated with improved patient outcomes. Participants in DOPPS were randomly selected from representative dialysis facilities within participating countries. Details regarding the design of DOPPS have been described in full elsewhere.[18]

The study included 6,230 hemodialysis patients aged ≥18 years from 99 representative dialysis facilities in Japan who had spent at least six months on hemodialysis (Figure 1). All eligible patients were selected from DOPPS I (1997-2001), II (2002-2004), III (2005-2007) and IV (2008-2010). Baseline data regarding demographic information, comorbid conditions, medication for mineral bone disorder, and laboratory values were obtained at enrollment. Time-dependent data (GNRI and phosphorus concentration) and mortality data (time and cause) were obtained from the database during the follow-up period. GNRI was calculated as follows:

$$\text{GNRI} = (14.89 \times \text{albumin [g/dl]}) + [41.7 \times (\text{body weight} / \text{ideal body weight})]$$

where "ideal body weight" was calculated using the Lorentz formula as follows:

$$\text{Ideal body weight for men} = \text{height} - 100 - [(\text{height} - 150) / 4]$$

$$\text{Ideal body weight for women} = \text{height} - 100 - [(\text{height} - 150) / 2.5]$$

We set (body weight/ideal body weight) as "1" when "body weight" exceeded "ideal body weight" [15]. In this cohort, "body weight" exceeded "ideal body weight" in 26.0% of patients.

Definition of exposure

Exposure categories were defined based on the categorical factors of GNRI (low-middle, lower two tertiles; high, the highest tertile) and serum phosphorus concentrations (low, <3.5 mg/dl; middle, 3.5 to <6.0 mg/dl; high, ≥6.0 mg/dl). We evaluated GNRI and serum phosphorus concentrations by first using time-averaged variables, which were updated every four months to obtain the most recent mean values after study entry, and then using fixed baseline variables measured at study entry. The reference category for GNRI was the highest tertile, and the lower two tertiles were regarded as the high-risk category. The reference category for phosphorus concentration was the middle category (3.5 to <6.0 mg/dl) and the low (<3.5 mg/dl) and high (≥6.0 mg/dl) categories were regarded as high-risk categories. Based on these two risk categories, we defined six exposure categories: "low-middle GNRI and low phosphorus", "low-middle GNRI and middle phosphorus", "low-middle GNRI and high phosphorus", "high GNRI and low phosphorus", "high GNRI and middle phosphorus", and "high GNRI and high phosphorus". The cut-off values for phosphorus concentration were defined according to the Japanese clinical guidelines.[19] The cut-off values for GNRI were defined based on the highest tertile established in this study, with "high GNRI and middle phosphorus" defined as the reference category, as previous studies have suggested that this category has the lowest mortality risk.[2 16 18 20-22]

Outcomes

The primary outcome measure was hazard ratio for all-cause mortality. Patients were followed from study entry until death, transplantation, transfer to another facility, modality change, withdrawal, or study end, whichever came first. The secondary outcome measure was hazard

ratio for cardiovascular mortality, which included sudden deaths, deaths from heart failure, acute myocardial infarction, cerebrovascular disease, and other vascular diseases.

Statistical analysis

We conducted baseline and time-dependent Cox regression to estimate hazard ratios and their 95% confidence intervals (CIs) for the association between exposure categories and all-cause mortality. The baseline Cox regression used baseline fixed exposure categories, and the time-dependent Cox regression used time-averaged exposure categories. In our analyses using the combined phosphorus concentration and GNRI categories, the hazard ratio for "high phosphorus concentration and high GNRI" to "middle phosphorus concentration and high GNRI" (the reference category) indicates the effect of high phosphorus concentration on outcomes. The hazard ratio for "low-middle GNRI and middle phosphorus concentration" to the reference category indicates the effect of low-middle GNRI on outcomes. Our Cox model included adjustments for age, gender, time on dialysis, 11 comorbid conditions, single-pool Kt/V (quintiles), phosphate binder use, oral or intravenous vitamin D receptor activator (VDRA) use, and DOPPS phase, all of which were indicated as potential confounding factors in previous studies.[2 3 22-27] Given their potential to function as intermediate factors between phosphorus concentration and mortality, we used fixed baseline variables of these covariates in the model. For Cox models, we used robust variance estimates to consider cluster effects at the facility level (correlation between patients).

We examined interactions between GNRI and phosphorus concentration in two ways. First, we assessed a statistical multiplicative interaction using the likelihood ratio test, which compares models with and without interaction terms. Second, to assess an additive interaction between high phosphorus concentration and low-middle GNRI, we estimated the relative excess risk due to interaction (RERI) using the method described by Rothman.[28 29] RERI

between two factors (A and B) is defined as "departure from additive effects" and is calculated as follows using adjusted hazard ratios (HRs): [30]

$$RERI = HR(A\&B) - HR(A) - HR(B) + 1$$

RERI < 0, RERI = 0, and RERI > 0 indicate an antagonistic interaction, absence of interaction, and synergistic interaction, respectively.

To examine how the effects of phosphorus concentration changes according to GNRI levels, we estimated the effect of a discrete change in phosphorus category across GNRI levels. Hazard ratios of "low phosphorus" and "high phosphorus" were estimated by comparing with the reference category of "middle phosphorus". Therefore, we reported hazard ratios for "low phosphorus" and "high phosphorus" from 2 phosphorus categories. After conducting time-dependent Cox regression with the interaction term for continuous GNRI and categorical phosphorus concentration, we estimated the average marginal effect of phosphorus categories (high and low phosphorus concentration) on all-cause mortality at each GNRI level (GNRI levels: 85, 90, 95, 100, and 105). The reference GNRI level was set at 100 based on the highest tertile. We used "MARGINS" and "MARGINSPLOT" commands in STATA for Figure 2.

All analyses were performed using STATA (Version 14.2, STATA, College Station, TX, USA) software.

RESULTS

Baseline patient characteristics

Figure 1 shows the participant selection process. A total of 6,230 hemodialysis patients were included in this study. The mean (±SD) age was 61.1 (±12.5) years, 60.8% of patients were male, median (interquartile range) dialysis duration was 5.8 (2.6 to 11.3) years, and 29.7% of patients had diabetes. The median GNRI value was 94.9 (low GNRI, 53.4 to 91.8; middle GNRI, 91.8 to 97.5; high GNRI, 97.5 to 125.9) and the range of the lower two tertiles was <97.5, indicating patients with nutrition-related mortality risk, according to the original study.[15] A total of 6.0% of patients had low phosphorus concentrations while 35.6% had high phosphorus concentrations. Baseline characteristics by combined GNRI and phosphorus concentration categories are shown in TABLE 1. Associations between GNRI values and phosphorus concentration and nPNA are summarized in Supplementary TABLE 1.

Association between GNRI, phosphorus concentration, and all-cause mortality

TABLE 2 shows incidence rates and HRs for all-cause mortality according to baseline and time-averaged exposure categories. Median follow-up time was 2.1 years. During the follow-up period (total: 12,294 person-years), we recorded 561 all-cause deaths (4.6 per 100 person-years).

In the time-dependent Cox model, both time-averaged factors of high phosphorus concentration and low-middle GNRI were associated with all-cause mortality after adjusting for potential confounders. The hazard ratio for “high GNRI and high phosphorus” indicated that there was an effect of high phosphorus concentration on all-cause mortality (HR: 1.66, 95% CI: 1.01 to 2.73) compared with “high GNRI and middle phosphorus” (the reference category). The hazard ratio for “low-middle GNRI and middle phosphorus” indicated that there was an effect of low-middle GNRI on all-cause mortality (HR: 2.12, 95% CI: 1.51 to

2.96) compared with the reference category. We found the highest mortality rate in patients with both "low-middle GNRI and low phosphorus" (HR: 4.28, 95% CI: 2.66 to 6.88), highlighting the combined effect of low-middle GNRI and low phosphorus concentration.

In the baseline Cox model, both baseline fixed factors of high phosphorus concentration and low-middle GNRI level were associated with all-cause mortality after adjusting for potential confounders. We found the highest mortality rate in patients with both "low-middle GNRI and low phosphorus".

Interaction between GNRI and phosphorus concentration on all-cause mortality

In the time-dependent Cox model, the RERI was -0.57 between time-averaged high phosphorus concentration and low-middle GNRI with respect to all-cause mortality, indicating an antagonistic interaction. We also observed a significant statistical multiplicative interaction between these factors and all-cause mortality (P=0.05 by a likelihood ratio test).

Figure 2 shows the hazard ratios for high and low phosphorus concentrations across the GNRI. The harmful effect of high phosphorus concentration increases with increasing GNRI. On the other hand, the harmful effect of low phosphorus concentration decreases with increasing GNRI.

Association between GNRI, phosphorus concentration, and cardiovascular mortality

TABLE 2 shows the incidence rates and HRs for cardiovascular mortality according to baseline and time-averaged exposure categories. We observed 286 cardiovascular deaths (2.3 per 100 person-years) during the follow-up period.

In the time-dependent Cox model, high phosphorus concentration and low GNRI was associated with cardiovascular mortality. The hazard ratio for "high GNRI and high phosphorus" indicates that there was an effect of high phosphorus concentration on

cardiovascular mortality (HR: 2.02, 95% CI: 1.18 to 3.45) compared with "high GNRI and middle phosphorus" (the reference category). The hazard ratio for "low-middle GNRI and middle phosphorus" indicates that there was an effect of low-middle GNRI on cardiovascular mortality (HR: 1.80, 95% CI: 1.20 to 2.70). We found the highest cardiovascular mortality rate in patients with "low-middle GNRI and low phosphorus" (HR: 3.04, 95% CI: 1.62 to 5.67).

In the baseline Cox model, baseline fixed factors of high phosphorus ("high GNRI and high phosphorus" vs "high GNRI and middle phosphorus") and low GNRI ("low-middle GNRI and middle phosphorus" vs "high GNRI and middle phosphorus") were not significantly associated with cardiovascular mortality. We found the highest cardiovascular mortality rate in patients with "low-middle GNRI and low phosphorus" (HR: 2.39, 95% CI: 1.33 to 4.30).

Interaction between GNRI and phosphorus concentration on cardiovascular mortality

In the time-dependent Cox model, the RERI was -0.47 between time-averaged high phosphorus concentrations and low-middle GNRI with respect to cardiovascular mortality, indicating an antagonistic interaction. However, we did not find a significant statistical multiplicative interaction between these factors and cardiovascular mortality (P=0.22 by a likelihood ratio test).

DISCUSSION

In this cohort study, we found that both phosphorus concentration and nutritional index were separately associated with all-cause mortality and, more importantly, that there were interactions between these two factors. The association between high phosphorus concentrations and mortality was stronger in patients with a high nutritional index than in those with a low-middle nutritional index, with opposite findings for low phosphorus concentrations and mortality (Figure 2). These results suggest that the association between phosphorus concentration and mortality is indeed modified by nutritional index, suggesting that nutritional index should be considered in the management of phosphorus concentration in hemodialysis patients.

Two-thirds of hemodialysis patients here were at risk of nutrition-related mortality (low-medium GNRI [<97.5] was associated with increased mortality rate).[15] We also found that abnormalities in phosphorus concentration, which have been shown to be associated with mortality,[22 31 32] were highly prevalent regardless of GNRI category (TABLE 1). Taken together, these results indicate the clinical importance of both the separate and combined association of these time-averaged factors with clinical outcomes.

While a number of previous studies have examined the associations between phosphorus concentration and mortality after adjusting for nutritional indices such as serum albumin concentration,[1 2 31 32] these studies failed to account for the interaction between nutritional index and phosphorus concentration. A recent study in Austria noted statistical multiplicative interactions between time-varying phosphorus and albumin, in which time-varying factors were updated to the most recent values every three months.[14] Here, we confirmed a statistical multiplicative interaction between *time-averaged* phosphorus concentration and GNRI on all-cause mortality.

Two different types of interaction have been posited: statistical interaction and additive interaction, with the two concepts often confounding one another. Statistical interaction refers to any departure of the value of the combined effect from that of additive or multiplicative effects of the two risk factors, depending on the statistical model used. In contrast, additive interaction always refers to departure from additive effects, regardless of the statistical model used. Further, the degree of additive interaction may be estimated by calculating measures of additive interaction, such as the RERI.[28 29] In the present study, RERI calculations[30] showed antagonistic interactions between high phosphorus concentrations and low GNRI.

Two plausible reasons have been proposed to explain the interaction between phosphorus concentration and GNRI. First, the influence of low-middle GNRI may outweigh the association between high phosphorus concentration and mortality if the association between low-middle GNRI and mortality is stronger than that of high phosphorus concentration and mortality. Second, the mechanism of the association between phosphorus concentration and mortality may differ by GNRI category. In patients in high GNRI categories, high phosphorus concentration could be a risk factor as a promoter of vascular calcification. However, in those with low-middle GNRI, high phosphorus concentration may denote sufficient dietary intake and improving nutrition.

Clinical guidelines and previous studies recommend regular assessment of nutritional status for all hemodialysis patients, which can be conducted using GNRI, among other methods.[6-8 15-17] We used GNRI as a nutritional index to classify patients according to nutrition-related mortality risk for a number of reasons. First, GNRI can be calculated relatively simply using available objective data and does not require subjective assessment or judgment—an aspect that makes it a particularly useful index in clinical practice. Second, clinical guidelines recommend nutritional assessment by multiple measurements, a criterion which GNRI satisfies as it is calculated using multiple factors, including gender, body weight,

height, and serum albumin concentration. Finally, a number of previous studies have found GNRI to be an accurate index for identifying hemodialysis patients at risk of malnutrition[17] and mortality.[16] However, it should be noted that low-middle GNRI is not necessarily indicative of malnutrition, as the GNRI formula includes serum albumin concentration, which is affected by chronic inflammation and fluid volume expansion.[33-35] Further, some investigators have suggested that malnutrition may be a consequence of chronic inflammation,[36-38] making it difficult to separate inflammation from malnutrition and to examine their independent effects on mortality.

Several strengths of the present study warrant mention. The major strength is the analysis of a large (>6,000) representative dialysis population in Japan from DOPPS. Participants in DOPPS are representative dialysis patients of a particular country selected via a stratified random sampling method.[39] Second, we defined exposure categories based on two categorical factors (phosphorus concentration and GNRI), which allowed us to examine the separate and combined effects of these components and to examine their additive interaction by calculating the RERI. Third, we specifically used *time-averaged* phosphorus concentration and GNRI, as subsequent values of phosphorus and GNRI changed dramatically from baseline values. Fourth, we confirmed the interaction between GNRI and phosphorus concentration via several methods, thereby underscoring the validity of our results.

Several limitations of our study also warrant mention. First, residual confounding due to unmeasured factors may affect the association between exposure categories and mortality. To minimize the effects of this potential confounding, we included available baseline data in our multivariable model. Given that we found consistent associations even after the addition of other covariates to the model, we believe that our findings are sound. Second, we lacked data from other nutritional scoring tools, such as subjective global assessment (SGA)[40] and malnutrition-inflammation score (MIS).[41] However, GNRI can be calculated more simply

than SGA and MIS, using available data which are often measured in daily practice. Third, we lacked data on the type and dose of phosphate binders, which might confound the association between phosphorus concentration and mortality. Fourth, results of time-dependent analysis are heavily affected by clinical conditions before death. For example, patients who experience acute drops in phosphorus concentration or GNRI are known to be likely to die more quickly. We believe that using time-averaged categories of phosphorus concentration and GNRI allowed us to detect accumulated effects on mortality in time-dependent analysis after changes in these factors during the follow-up period. We also found similar associations between baseline fixed exposure categories and outcomes. It should be noted that we used fixed baseline covariates for laboratory values and medications, as these can represent intermediate factors between phosphorus concentration and mortality. Finally, this study included only Japanese hemodialysis patients and our findings may therefore not be representative of those from other countries. As such, interpreting and generalizing these results should be conducted with care.

CONCLUSION

We found that GNRI modified the association between phosphorus concentration and mortality, with both high phosphorus concentration and low-medium GNRI associated with mortality. We noted a significant statistical multiplicative interaction between phosphorus concentration and GNRI on all-cause mortality. We also noted an antagonistic interaction between high phosphorus concentration and low-medium GNRI. Taken together, these findings suggest that the impact of phosphorus concentration on mortality is not consistent across nutritional status. Therefore, nutritional index should be considered when evaluating the impact of phosphorus concentration on mortality, and when making decisions regarding treatment with phosphorus management in hemodialysis patients.

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Contributors

The author's contributions were as follows: S. Fukuma designed research; S. Fukuma and T.I conducted research; S. Fukuma and T.I analyzed data; S. Fukuma wrote the paper; S. Fukuhara and T.A provided critical review of the manuscript; and S. Fukuma had primary responsibility for final content.

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Competing interests

S. Fukuma is an advisor on epidemiology studies for Kyowa Hakko Kirin and receives consulting fees from Kyowa Hakko Kirin. T. A. receives consulting fees from Chugai, Kirin, and Abbott, and grants/funds from Chugai and Kirin. The other authors have nothing to declare.

Data sharing statement

No additional data are available.

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TABLE 1 Baseline characteristics by combined GNRI and phosphorus concentration categories

	Total	*Low-Middle GNRI*			*High GNRI*		
		Low Phosphorus	*Middle Phosphorus*	*High Phosphorus*	*Low phosphorus*	*Middle Phosphorus*	*High Phosphorus*
	(N=6230)	(N=342)	(N=2,557)	*(N=1,331)*	*(n=83)*	*(n=1,070)*	*(n=847)*
Age (years)	61.1±12.5	67.4 ± 11.6[2]	64.4 ± 11.7	59.6 ± 12.4	60.2 ± 15.0	59.0 ± 12.2	55.0 ± 11.8
Male (%)	60.8	59.1	56.3	55.9	71.2	69.3	69.6
Dialysis duration (years)	5.8	6.6	5.9	6.8	5.0	5.0	5.5
	(2.6 to 11.3)	(2.5 to 11.7)[3]	(2.7 to 12.2)	(3.0 to 12.8)	(2.8 to 9.8)	(2.0 to 9.5)	(2.7 to 10.1)
BMI (kg/m^2)	20.7±3.1	19.5 ± 2.5	19.7 ± 2.8	19.8 ± 3.0	21.8 ± 2.9	22.3 ± 2.6	22.5 ± 2.7
Serum albumin (g/dl)	3.8±0.4	3.5 ± 0.4	3.6 ± 0.3	3.7 ± 0.3	4.2 ± 0.3	4.1 ± 0.3	4.2 ± 0.3
Calcium (mg/dl)	9.0±0.8	8.9 ± 0.7	8.9 ± 0.7	9.1 ± 0.9	9.5 ± 0.7	9.2 ± 0.7	9.1 ± 0.9
iPTH (pg/ml)	133	106	140	120	159	139	131
	(53 to 260)	(41 to 240)	(56 to 262)	(54 to 256)	(67 to 262)	(54 to 252)	(50 to 265)
Single-pool Kt/V	1.36±0.29	1.37 ± 0.29	1.37 ± 0.28	1.36 ± 0.29	1.33 ± 0.27	1.36 ± 0.28	1.33 ± 0.29
nPNA (g/kg per day)	1.04±0.21	0.93 ± 0.23	1.01 ± 0.21	1.11 ± 0.21	0.94 ± 0.24	1.02 ± 0.19	1.10 ± 0.19
Medications (%)							

Phosphate binder	81.6	75.1	80.2	79.8	82.2	84.9	86.3
Oral VDRA	46.2	42.9	46.0	46.6	41.1	50.1	42.8
Intravenous VDRA	14.2	5.3	13.0	15.8	11.0	13.8	18.6
Comorbid conditions (%)							
Diabetes mellitus	29.7	38.6	29.7	25.3	37.0	32.6	28.9
Hypertension	67.9	68.3	69.2	65.9	76.7	67.3	67.2
Coronary heart disease	30.0	37.6	32.6	26.2	35.6	29.6	25.5
Other cardiovascular disease	30.1	39.3	33.2	31.3	32.9	26.2	21.2
Congestive heart failure	17.2	21.5	18.1	17.7	21.9	15.4	14.2
Cerebrovascular disease	13.8	21.5	16.7	11.9	13.7	11.4	8.8
Peripheral vascular disease	15.0	23.1	16.8	13.1	16.4	13.5	12.2
Recurrent cellulitis	3.6	7.3	4.0	3.0	5.5	2.8	3.2
Lung disease	2.2	3.0	2.9	1.9	2.7	1.7	0.9
Neurological disorder	6.7	13.2	8.7	5.3	9.6	4.9	3.2
Psychiatric disorder	3.9	5.3	4.0	4.4	4.1	3.6	2.9

GNRI, Geriatric Nutritional Risk Index; iPTH, intact parathyroid hormone; nPNA, normalized protein nitrogen appearance; VDRA, Vitamin D receptor activator; SD, standard deviation; IQR, interquartile range

Low-Middle GNRI: < highest tertile of GNRI; high GNRI: ≥ highest tertile of GNRI; low phosphorus: <3.5 mg/dl; middle phosphorus: 3.5 to <6.0 mg/dl; high phosphorus: ≥6.0 mg/dl, [1]Mean ± SD (all such values), [2]Median; IQR in parentheses (all such values)

TABLE 2 Hazard ratios for all-cause and cardiovascular mortality by baseline and time-averaged exposure categories

GNRI	Phosphorus	All-cause mortality					Cardiovascular-mortality				
		Baseline			Time-averaged		Baseline			Time-averaged	
		Incidence Rate[1]	HR[2]	95% CI	HR[3]	95% CI	Incidence Rate[1]	HR[2]	95% CI	HR[3]	95% CI
Low-Middle	***Low***	12.1	3.43	2.11 to 5.58	4.28	2.66 to 6.88	4.7	2.39	1.33 to 4.30	3.04	1.62 to 5.67
	Middle	5.5	1.93	1.33 to 2.79	2.12	1.51 to 2.96	2.6	1.57	0.95 to 2.59	1.80	1.20 to 2.70
	High	4.6	2.18	1.41 to 3.37	2.20	1.45 to 3.35	2.5	1.97	1.07 to 3.65	2.35	1.43 to 3.84
High	***Low***	3.3	1.14	0.49 to 2.70	0.93	0.22 to 3.87	1.6	1.01	0.32 to 3.24	0.83	0.12 to 5.57
	Middle	2.1	1.00	reference	1.00	reference	1.4	1.00	reference	1.00	reference
	High	2.6	1.59	1.03 to 2.45	1.66	1.01 to 2.73	1.8	1.71	0.94 to 3.11	2.02	1.18 to 3.45

GNRI, geriatric nutritional risk index; VDRA, Vitamin D receptor activator; DOPPS, the Dialysis Outcomes and Practice Pattern Study; HR, hazard ratio; CI, confidence interval

Low-Middle GNRI: < highest tertile of GNRI; high GNRI: ≥ highest tertile of GNRI; low phosphorus: <3.5 mg/dl; middle phosphorus: 3.5 to <6.0 mg/dl; high phosphorus: ≥6.0 mg/dl.

[1]Incidence rate per 100 person-years.

[2]Cox proportional hazards model adjusted for age, sex, time on dialysis, 11 comorbid conditions listed in Table 1, single-pool Kt/V, oral or intravenous VDRA use, phosphate binder use, and DOPPS phase.

[3]Time-dependent Cox proportional hazards model adjusted for age, sex, time on dialysis, 11 comorbid conditions listed in Table 1, single-pool Kt/V, oral or intravenous VDRA use, phosphate binder use, and DOPPS phase

Figure 1.

Selection process for study population.

DOPPS, the Dialysis Outcomes and Practice Pattern Study; GNRI, Geriatric Nutritional Risk Index.

Figure 2.

Effect of nutritional index on hazard ratios for the association between phosphorus concentration and mortality

Hazard ratios of high (≥6.0 mg/dl) and low (<3.5 mg/dl) phosphorus concentrations on all-cause mortality by GNRI level (GNRI levels: 85, 90, 95, 100, and 105). The reference GNRI level was set at 100 based on the highest tertile.

GNRI, Geriatric Nutritional Risk Index.

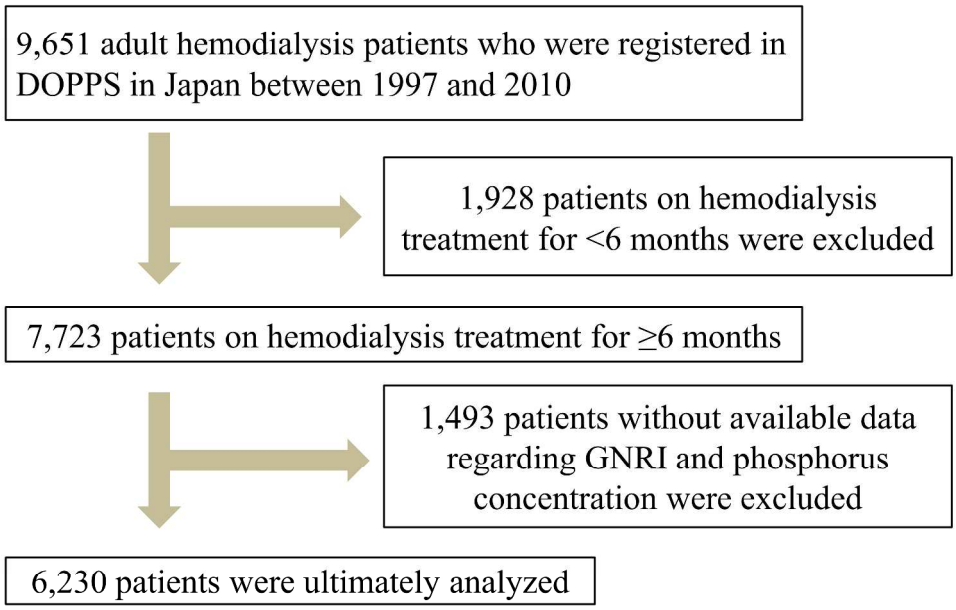

Figure 1

Selection process for study population.
DOPPS, the Dialysis Outcomes and Practice Pattern Study; GNRI, Geriatric Nutritional Risk Index.

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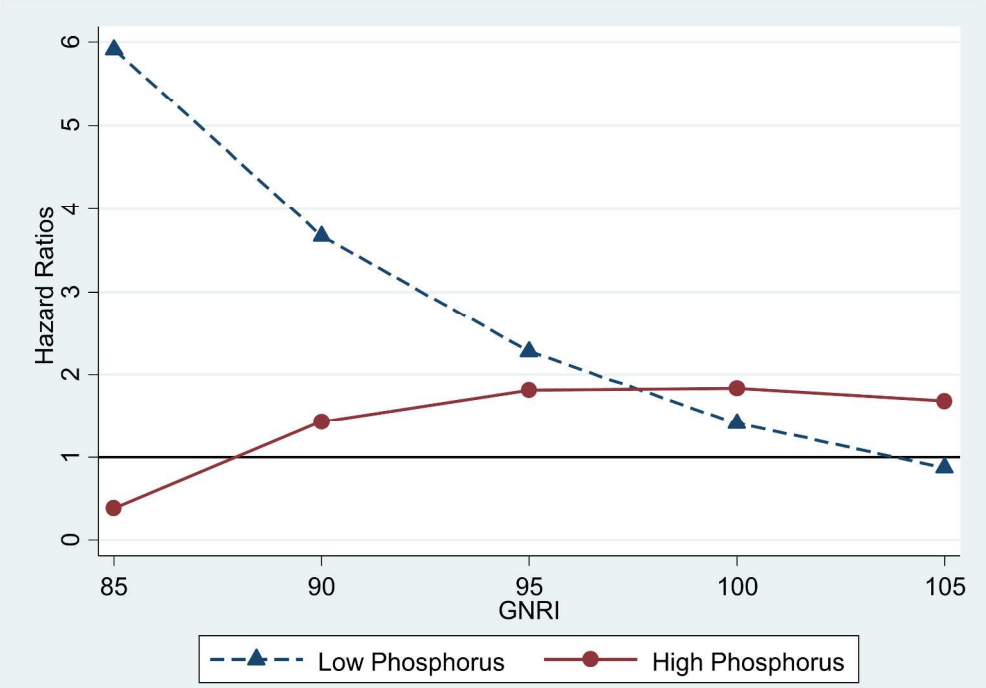

Effect of nutritional index on hazard ratios for the association between phosphorus concentration and mortality

Hazard ratios of high (≥6.0 mg/dl) and low (<3.5 mg/dl) phosphorus concentrations on all-cause mortality by GNRI level (GNRI levels: 85, 90, 95, 100, and 105). The reference GNRI level was set at 100 based on the highest tertile.

GNRI, Geriatric Nutritional Risk Index.

254x190mm (300 x 300 DPI)

Supplementary TABLE 1 Association between GNRI and phosphorus or nPNA

	Phosphorus (mg/dL)		*nPNA (g/kg per day)*	
	Coefficient	**95%CI**	**Coefficient**	**95%CI**
GNRI	0.35	0.30 to 0.40	0.02	0.01 to 0.03

GNRI, Geriatric Nutritional Risk Index; nPNA, normalized protein nitrogen appearance.

Coefficients are estimated by linear regression and the values indicate the mean change in phosphorus or nPNA for every 10-point increase in GNRI.

Supplementary TABLE 2 Hazard ratios for all-cause and cardiovascular mortality by time-averaged exposure categories adjusting for time-varying phosphate binder use

GNRI	Phosphorus	All-cause mortality		Cardiovascular-mortality	
		HR[1]	95% CI	HR[1]	95% CI
Low-Middle	***Low***	4.04	2.48 to 6.59	2.79	1.49 to 5.25
	Middle	2.06	1.45 to 2.92	1.69	1.11 to 2.57
	High	2.03	1.31 to 3.17	2.12	1.27 to 3.54
High	***Low***	1.00	0.24 to 4.17	0.88	0.13 to 5.98
	Middle	1.00	reference	1.00	reference
	High	1.76	1.07 to 2.91	2.12	1.23 to 3.65

GNRI, geriatric nutritional risk index; HR, hazard ratio; CI, confidence interval

Low-Middle GNRI: < highest tertile of GNRI; high GNRI: ≥ highest tertile of GNRI; low phosphorus: < 3.5 mg/dl; middle phosphorus: 3.5 to < 6.0 mg/dl; high phosphorus: ≥ 6.0 mg/dl.

[1]Time-dependent Cox proportional hazards model adjusted for time-varying phosphate binder use in addition to baseline covariates (age, sex, time on dialysis, 11 comorbid conditions listed in Table 1, single-pool Kt/V, oral or intravenous VDRA use, and DOPPS phase)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	na
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7
Bias	9	Describe any efforts to address potential sources of bias	8
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	8-9
		(*c*) Explain how missing data were addressed	8
		(*d*) If applicable, explain how loss to follow-up was addressed	8
		(*e*) Describe any sensitivity analyses	8
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10
		(b) Give reasons for non-participation at each stage	10
		(c) Consider use of a flow diagram	10
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10
		(b) Indicate number of participants with missing data for each variable of interest	10
		(c) Summarise follow-up time (eg, average and total amount)	10
Outcome data	15*	Report numbers of outcome events or summary measures over time	10
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10-12
		(*b*) Report category boundaries when continuous variables were categorized	10
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	na
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	na
Discussion			
Key results	18	Summarise key results with reference to study objectives	13
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13, 16
Generalisability	21	Discuss the generalisability (external validity) of the study results	15-16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	18

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.