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Novel Protein to Phosphorous Ratio Score Predicts Mortality in Hemodialysis Patients

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Objective: Lowering serum phosphorus in people on hemodialysis may improve their survival. However, prior studies have shown that restricting dietary protein intake, a major source of phosphorus, is associated with higher mortality. We hypothesized that a novel metric that incorporates both these values commensurately can improve survival prediction.

Methods: We used serum phosphorous and normalized protein catabolic rate (nPCR), a surrogate of dietary protein intake, to form a new metric R that was used to examine the associations with mortality in 63,016 people on hemodialysis (HD) of one year after treatment initiation. Survival models were adjusted for case-mix, malnutrition-inflammation cachexia syndrome (MICS), and residual kidney function (RKF).

Results: Individuals treated with hemodialysis were divided into five groups in accordance with R value. Group 1 included sick individuals with high phosphorous and low nPCR. Group 5 included individuals with low phosphorous and high nPCR. After 1-year follow-up, survival difference between the groups reflected R value, where an increase in R was associated with improved survival. The association of R with mortality was strengthened by adjustment in demographic variables and attenuated after adjustment to MICS. Mortality associations in accordance with R were not influenced by residual kidney function (RKF).

Conclusion: The novel protein to phosphorus ratio score R predicts mortality in people on dialysis, probably reflecting both nutrition and inflammation state independent of RKF. The metric enables better phosphorus monitoring, although adequate dietary protein intake is ensured and may improve the prediction of outcomes in the clinical setting.

Introduction

PEOPLE WITH CHRONIC kidney disease (CKD) have higher incidence of malnutrition than the general population. Malnutrition and protein-energy wasting have been strongly related to mortality in CKD patients,[1,2] whereas surrogates of over-nutrition, e.g., obesity or hyperlipidemia improved their survival.[3–6] Hence, dietary protein intake should be increased following initiation of dialysis to improve their survival.[7,8]

Hyperphosphatemia, per se, is usually asymptomatic, yet it is widely appreciated as a major cardiovascular risk and linked to increased mortality in people with CKD and people on maintenance hemodialysis (MHD).[9,10] Elevated phosphorus levels as high as 6.5 mg/dL are associated with mortality[10–12] in people on hemodialysis (HD) causing vascular damage by endothelial dysfunction, leading to vascular calcification.[13–16] Dietary phosphate restriction and use of phosphate binders are still considered the most effective strategies for the prevention of vascular calcification in CKD,[9,17] whereas MHD treatment may contribute to lower phosphorous burden to a less extent.

Reducing the amount of phosphorus load while raising the amount of dietary protein intake is recommended as per both American and European guidelines for the management of people on MHD.[18] In addition, reduced phosphorus intake in people on MHD correlates with an increase in mortality.[8] This could be indicative of the difficulty in maintaining the balance between reduced phosphorus and adequate protein intake. Low phosphorus

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values are considered as a marker of protein-energy malnutrition and poor food intake, as well as other comorbidities.[19] Since foods with high protein content tend to have high phosphorus content, an increase in dietary protein has been shown to correlate with an increase in serum phosphorus levels.[20]

Noori et al concluded both higher dietary phosphorus intake and a greater dietary phosphorus to protein ratio are associated with an increased risk of death in people on MHD[16] based on food frequency questioner (FFQ) data. They also mentioned the uncertainty of using dietary questionnaires as a valid information source and the need for caution when inferring dietary intake to mortality.[16]

Therefore, this relationship needs further validation by using laboratory data from people on MHD.

Our objective was to combine the two, protein consumption and phosphorous levels, in one novel parsimonious metric and assess the relative contribution of each to mortality in people on MHD.

Material and Methods

Cohort Construction

We extracted, refined, and examined electronic data from all the people treated with incident dialysis who received conventional HD treatment in a total of 1,737 facilities operated by a large dialysis organization in the USA from January 1, 2007, to December 31, 2011. The construction of the cohort has previously been described.[5] In brief, 208,820 people initiated dialysis treatment. After excluding people who received <60 days of thrice-weekly HD treatment at the time of study entry (first quarter of serum phosphorus and normalized protein catabolic rate measurements), or people treated with dialysis modality other than IHD, 145,972 people treated with incident HD remained. After excluding people with missing phosphorus and nPCR data after a year from dialysis initiation, the final study population consisted of 63,016 people treated with incident HD (Supplementary Figure1).

Demographic and Clinical Measures

Follow-up time was divided into 91-day intervals (patient quarters) from the time of the first dialysis treatment. Information on race/ethnicity, primary insurance, access type, and the occurence of diabetes at baseline was obtained from the large dialysis organization database. The following coexisting comorbidities were considered: (1) diabetes, (2) hypertension, (3) dyslipidemia, (4) atherosclerotic heart disease, (5) other cardiac disease (pericarditis and cardiac arrhythmia), (6) congestive heart disease, and (6) cerebrovascular disease.

Laboratory Measures

Blood samples were drawn using standardized techniques in all dialysis clinics and were transported to a central laboratory in Deland, FL typically within 24 hours. Most laboratory values including serum creatinine, albumin, hemoglobin, calcium, phosphorus, bicarbonate, and alkaline phosphatase were measured monthly. Serum intact parathyroid hormone (PTH) and ferritin levels were usually measured at least once during each calendar quarter. Blood samples were collected before dialysis. nPCR, a surrogate of dietary protein intake, was measured monthly as an indicator of daily protein intake. Dialysis dose was estimated by a single-pool Kt/V using the urea kinetic model. The 3-month-averaged values during the first quarter of dialysis treatment were used as baseline values to address the measurement variability in laboratory parameters.

Metrics Creation

We suggest that a mathematical way to give each of the two variables the same weight in a metric is by dividing them by one another. If they get distributed in the same range, the change in size will affect the distance of the ratio from 1. Both variables, phosphorus and nPCR, distributed normally, although the range of the distributions were different. Phosphorous levels ranged between 1.1 and 13.8, whereas nPCR distributed between 0.2 and 2.37. To overlap the ranges of these distributions, we compared the minimum, maximum, and mean values of both the variables. The mean of these differences was 5.4. Therefore, we created a modified phosphorous which is the original value divided by 5.4, termed as nP (new phosphorous). Elaboration of these calculations and modification is presented in Supplementary Figure 2.

In addition, we divided nPCR by nP to create the new variable R. We chose to split our patient population into five equal groups in accordance with R value to characterize the differences and trends along with the variable R (Supplementary Figure 3).

Statistical Analysis

Analyses were conducted by using STATA MP version 13.1 (StataCorp, College Station, TX).

The characteristics of people comprising the final cohort are expressed as means ± standard deviation, medians (interquartile range), or percentages, as appropriate. Follow-up time started after 91 days from HD initiation.

Survival Analysis

The cumulative incidence of all-cause death as per the R groups was assessed using the Kaplan-Meier method and the log-rank test.

Cox proportional hazards models were used to determine the relationship between R values and all-cause mortality. For each analysis, 3 levels of hierarchical adjustments were examined, and the reference group was the first R group, representing the sickest patients (low nPCR and high phosphorous):

(I) Unadjusted models included the entry of calendar quarter.

(II) Case-mix adjusted models that include all variables were included in the unadjusted model plus age, sex, race/ethnicity (White, African American, Hispanic, Asian, and other), preexisting comorbidities described above (see demographic and clinical measures) and primary insurance (Medicare, Medicaid, and other), vascular access (catheter, arteriovenous fistula, or graft), and dialysis dose as indicated by single-pool Kt/V (spKt/V).

(III) Models adjusted for case-mix and malnutrition-inflammation complex syndrome (MICS) covariates included all of the covariates in the case-mix model and the following quarterly averaged variables: body mass index and laboratory surrogates associated with clinical outcomes in people on HD including serum concentrations of (1) albumin, (2) creatinine, (3) hemoglobin, (4) ferritin, (5) bicarbonate, (6) calcium, (7) phosphorus, (8) intact PTH, and (9) normalized protein catabolic rate.

We also examined the effect of residual kidney function (RKF; less than 3 mL/minute and greater than or equal to 3 mL/minute) on the association between R and mortality in subgroup analysis and evaluated the significance of an interaction term in the case-mix model.

Results

We constructed a historical cohort of 63,016 people on dialysis, followed for 1 year after initiation of treatment that had the data of phosphorous and nPCR in the first 90 days (Supplementary Figure 1). They were divided into five groups as per R values, labeled from 1 to 5. The demographic and laboratory characteristics of people in different R groups are illustrated in Table 1. People in group 1, total of 12,603, are the sickest individuals, i.e., have high phosphorous and low nPCR values, and hence, have the lowest R values. These people were young (mean age 56 ± 16), more likely to be women, and initiate dialysis therapy with a catheter. They also had the highest prevalence of Black individuals compared to other groups. People in group 5, who were considered the healthiest (low phosphorous and high nPCR values) were older, more likely to be White, use a permanent access, and less likely to be hypertensive. Their laboratory workup also reflected a different survival potential because they had higher serum albumin, lower serum phosphorus, lower ferritin, and

Table 1. Demographic and Laboratory Data of 63,016 Maintenance Hemodialysis Patients, Divided Into 5 Groups According to R Value

Variables	R1 (N = 12,605)	R2 (N = 12,605)	R3 (N = 12,600)	R4 (N = 12,603)	R5 (N = 12,603)
Age (y)	56 ± 16	61 ± 15	62 ± 14	64 ± 14	65 ± 14
Female (%)	48	46	44	42	40
White (%)	41	41	42	43	43
African American (%)	42	37	35	31	26
Hispanic (%)	11	15	16	18	21
Asian (%)	2	2	3	4	6
Other race (%)	4	4	4	4	4
CVC	76	72	70	70	71
AVF	13	16	17	18	18
AVG	4	4	5	5	4
AV other	0	0	0	0	0
Access unknown	8	7	7	7	7
Medicare (%)	50	52	53	54	54
Medicaid (%)	10	7	7	7	8
Other insurance (%)	41	41	40	39	39
Albumin (g/dL)	3.69 ± 0.47	3.81 ± 0.41	3.85 ± 0.38	3.88 ± 0.37	3.88 ± 0.38
Calcium (mg/dL)	9.05 ± 0.60	9.05 ± 0.53	9.06 ± 0.51	9.04 ± 0.49	9.04 ± 0.49
Phosphorus (mg/dL)	6.24 ± 1.50	5.50 ± 1.12	5.13 ± 0.99	4.78 ± 0.87	4.25 ± 0.84
PTH (pg/mL)	309 (212,468)	284 (202,404)	278 (198,381)	266 (189,361)	248 (176,338)
Ferritin (ng/L)	488 (296,727)	539 (348,765)	553 (365,776)	606 (405,835)	552 (357,782)
BMI (kg/m^2)	28.74 ± 7.81	28.75 ± 7.46	28.64 ± 7.25	28.23 ± 7.10	27.51 ± 6.78
Hypertension (%)	56	54	53	53	50
Diabetes (%)	67	69	68	69	69
CHF (%)	49	47	44	42	42
ASHD (%)	17	17	17	17	17
CVD (%)	2	2	2	2	2
Other cardiovascular (%)	17	16	17	17	16
SPKTV	1.42 ± 0.32	1.45 ± 0.31	1.47 ± 0.31	1.49 ± 0.31	1.53 ± 0.32

ASHD, atherosclerotic heart disease; AVF, arteriovenous fistula; AVG, arteriovenous graft; CHF, congestive heart failure; CVC, central venous catheter; CVD, cardiovascular disease; PTH, parathyroid hormone; SPKTV, single pool kTV.

Body mass index (BMI) was calculated using post-HD body weight and height. Data are presented as proportions, mean ± SD, or median (IQR) where applicable.

higher PTH levels, despite similar calcium values across the groups.

Survival Analysis

After 1 year of follow-up, the survival curve for the people in group 1, who are the sickest individuals, split from the other curves that were associated with worse survival (Fig. 1). This notion was reinforced when we numerically examined death rates per group (Supplementary Figure 4) and saw that they are lower in group 5 compared with group 1.

Figure 2 and Supplementary Table 1 shows 3 different models of hazard ratios of death risk according to R value. In an unadjusted model with people in group 1 as the reference, the hazard ratio for death decreases as R value increases. People in group 5 had 37% (CI 34%–40%) higher chances of survival than people in group 1. Survival differences were statistically significant among groups.

After adjustment for Case-Mix variables, the association of R value with survival was strengthened. According to this model, compared to the reference, people in group 5 had 49% higher chance of survival (CI 46%–52%). After further adjustment for MICS covariates in the fully adjusted model, this association was attenuated to chances of survival of 35% for people in group 5 (CI 31%–39%).

Adjustment to RKF

Our cohort data of RKF were available only for 21,756 people. Survival differences among R groups were not affected by the presence or absence of RKF (Fig. 3) in either unadjusted (*P* for interaction = .6383) or Case-Mix models (*P* for interaction = .4765).

Discussion

We have created a new metric in people on dialysis according to the ratio between phosphorous and nPCR that is associated with survival in a cohort of 63,016 people on incident HD after 1 year from initiation of dialysis. We divided this population into 5 groups; people in group 1, the sickest individuals with low nPCR and high phosphorous were given an R score lower than 1 (Fig. 4). They were younger, more likely to be Black, and their albumin and BMI were lower. Compared to them, people in group 5 were healthier with high nPCR, low phosphorus, and R score higher than 1. Their demographic characteristics were the mirror image of people in group 1 and were more likely to have AVF as an access for dialysis. Kaplan–Meier curves showed a clear difference in survival among groups, after 1 year of follow-up, with survival improving as R value increases. Association of R with survival was even more robust after the adjustment for socio-demographic variables irrelevant of residual kidney function. However, adjustment for inflammatory profile attenuated this association.

Our results reflect the complex interplay among different nutritional elements in people on MHD and the constant struggle between competing risks. For people on MHD, higher phosphorous is detrimental not only to the bone metabolism, enhancing PTH production, and dissolving the bone, but also to the cardiovascular system where it promotes vascular calcification.[21] On the other hand, as the major source of phosphorous is protein from animal, limiting its consumption may be harmful to this fragile population.[22]

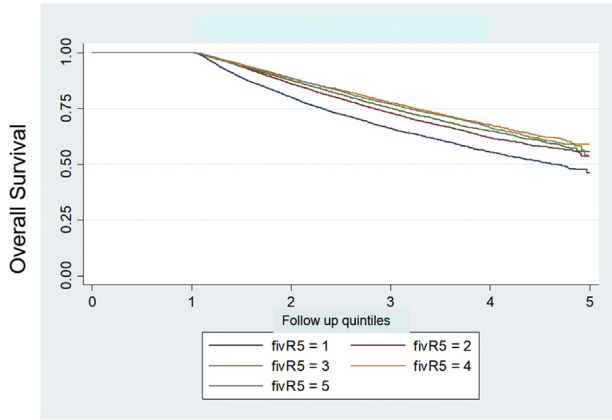

Figure 1. Survival rates after 1 year of follow-up according to R groups. A total of 63,016 MHD patients survived 1 year after initiation of dialysis from a preliminary cohort of 108,308 patients. Numbering of R5 group is according to the ratio between phosphorous and nPCR. R1 patients have high phosphorous and low nPCR, and R5 patients have low phosphorous and high nPCR.

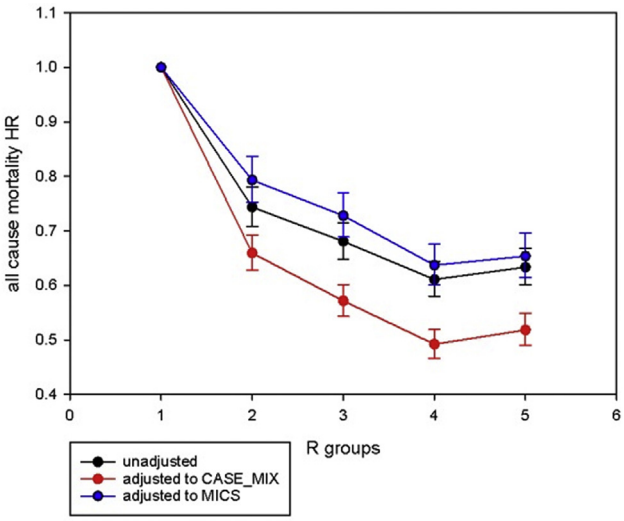

Figure 2. Cox regression analysis shows the hazard ratio for mortality across R groups in 63,016 MHD patients. The black curve shows the unadjusted model of hazard ratio for each group. The red curve shows the hazard ratio after adjustment to Case-Mix variables. The blue curve shows the hazard ratio after adjustment to MICS variables. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article).

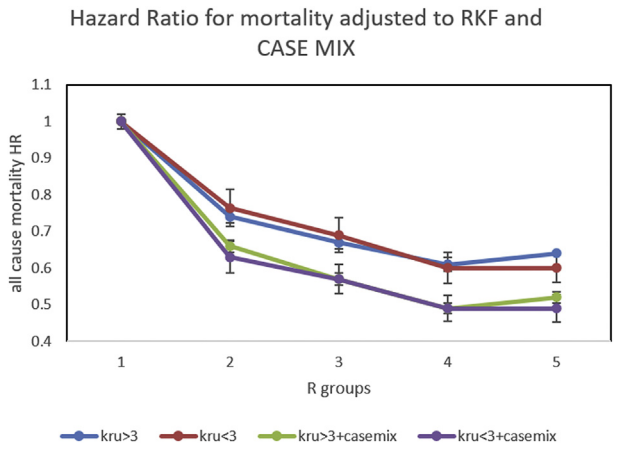

Figure 3. Cox regression analysis shows the hazard ratio for mortality across R groups in 21,756 MHD patients. The blue curve shows the unadjusted model of hazard ratio for patients with residual kidney function. The red curve shows the unadjusted model of hazard ratio for patients without residual kidney function. The green curve shows the hazard ratio after adjustment to Case-Mix variables for patients with residual kidney function. The purple curve shows the hazard ratio after adjustment to Case-Mix variables for patients without residual kidney function. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article).

Restriction of dietary intake of phosphorus generally requires some reduction in the allowable protein intake[17] and restricted consumption of highly processed, fast, and convenient foods.[23] However, imposing dietary reduction of protein intake is associated with protein-energy wasting (PEW)[24] and increased mortality.[17] Is there a difference between protein from animals versus protein from plants? Phosphorous in meat is easily hydrolyzed and readily absorbed, whereas phosphorous in plants has relatively low, usually <50% bioavailability.[25-27] Hence, despite the "apparently" higher phosphorous content of some plants, the actual result may be a lower rate of intestinal phosphorous absorption per gram of plant protein than animal based protein.[23] Therefore, it seems that a vegetarian diet may be beneficial for people with end-stage kidney disease (ESKD) because it allows for increased protein consumption without increasing phosphorus levels above the required value.[28]

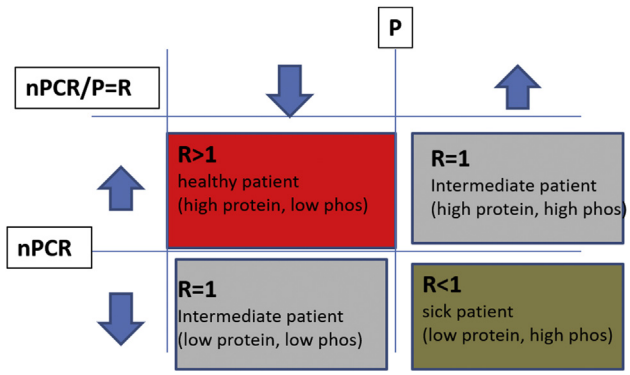

Figure 4. A 2×2 table shows the hypothesis of relation between phosphorous and nPCR and patients' status. X axis represents phosphorous (P) and Y axis represents nPCR. The red box contains patients with high values of protein and low phosphorous. The olive box contains patients with low protein and high phosphorous. Gray boxes represent intermediate states where only one of the desired conditions is met. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article).

It is not surprising that socio-demographic factors contribute to the mortality prediction of nutrition, as they indicate a person's awareness to health, compliance to treatment, and support system. This is in alignment with our observation that socio-demographic variables intensify the effect of nutrition on mortality. Successful dialysis in ESKD largely depends on the person's ability to adhere to several clinical requirements and lifestyle changes. Social support has been consistently linked to better health outcomes in several chronic diseases.[29] Precision nutrition management should also take into account, patient demographics, social, psychological, education, and compliance factors, all of which may influence the therapeutic needs and responses to the nutritional therapy prescribed.[30]

Yet it is unexpected that minorities scored low R values, as it was shown that they had better survival on dialysis than Whites.[31-33] Black ethnicity was shown to be associated with a lower prevalence of atherosclerotic cardiovascular disease at the start of dialysis and a lower incidence of new or recurrent cardiovascular events after starting dialysis.[34]

The survival advantage for Black individuals on dialysis may be due, at least in part, to a lower risk of cardiovascular disease. This is surprising given the higher incidence of diabetes and hypertension within the same population, both of which are known to be cardiovascular risk factors both in the general population and among those on dialysis.[35] People on dialysis from an underprivileged background such as ethnic minorities, those with low education, or no health insurance are significantly less likely to access cardiovascular healthcare compared to the more advantaged dialysis counterparts.[36] Our results might reflect this gap so that young and Black people lose their relative advantage of survival on dialysis. The influence of socioeconomic factors on survival prediction was irrelevant of RKF (Fig. 3).

In contrast, we saw that inflammation attenuates mortality prediction by R value, as it creates a constant catabolic state, unrectified by nutrition. People undergoing MHD have a high prevalence of protein-energy malnutrition and inflammation.[37] This confounds the association between traditional risk factors such as obesity and clinical outcome, and even reverses them.[38]

Inflammation also effects the relation between high protein intake and mortality in people on MHD. The discrepancy between protein and phosphorus in relation to mortality[39,40] can be mediated by PEW. Phosphorus induces systemic inflammation and oxidative stress dose-dependently, without affecting kidney function, resulting in the development of the phenotypes of PEW including weight loss, hypoalbuminemia, and decreased urinary creatinine excretion.[41]

Kidney clearance of urea leads to the underestimation of nPCR values,[42] most likely because of the kidney component of urea clearance that is overlooked in dialysis patients with residual kidney function. Hence, the lack of effect by RKF on our association is a supportive finding of the suggested model. It implies that regardless of other venues to dispose off urea, the relation between protein and its by-product, phosphorous, is the major player in mortality prediction of MHD patients. This is in contrast to the commonly accepted concept of RKF being a major determinant of survival in MHD patients.[5,43] Calculation of catabolic rate is different in the presence of urea clearance by urine.[42] This probably results from the overpowering effect that phosphorus has on RKF. Higher phosphorus levels were associated with a steeper 6-month RKF slope compared with the reference category and were independently associated with decline in RKF in people on incident HD.[44]

Our study should be qualified to several limitations. At first, because of the observational nature of our study, we can neither exclude the presence of residual confounders and unmeasured confounders nor prove causality between R and outcomes. Further studies are needed to examine these relationships. Second, we did not have precise data on medications that could have influenced serum phosphorous levels and all-cause mortality. Our cohort did not have elaborated information regarding source of protein, and it might be interesting to test our metric on two patient populations, one feeding on vegetarian diet and the other on meat base nutrition.

Another limitation of our study is the lack of a longer follow-up. The chance of surviving 4 or more years on dialysis therapy decreases in association with older age, White race, history of smoking, unemployed status, low systolic blood pressure, and low albumin level.[45] Increased age was a risk factor in each follow-up interval, whereas White race was a risk factor in only the later years. The apparent different risk factors for mortality in long-term dialysis survivors relative to patients in earlier phases of ESKD may reflect the characteristics of patients who survived the effects of earlier risk factors.[45]

The strengths of our study include a large nationally representative incident MHD population with detailed personal level data, which allowed us to rigorously account changes in nutritional markers and mortality for a range of clinically relevant factors. Essentially, all people on incident MHD in the original cohort were included in our analyses, and thus, the likelihood of selection bias is minimized. In addition, all the dialysis facilities were under uniform administrative care, and all laboratory tests were performed in one single laboratory with an optimal quality assurance monitoring. We have used quarterly averaged measurements rather than one single baseline measurement to minimize the effects of short-term variations.

Conclusion

The relationship of nutritional status and mortality in people on MHD is multifaceted and involves multiple influencing factors. Scaling people on MHD according to R value might provide the clinician insight into nutritional status that will mandate intervention and direct the intensity. People scoring low on the R value are being persistently attacked by two competing threats to their survival–they have low nutritional status as indicated by nPCR and a high phosphorous level. This combination is the result of not only low compliance to medical therapy and dietary counseling but also of a high inflammatory state. Intervention in these people could affect survival. Therefore, R value may be a useful predictor of mortality in people on hemodialysis among others (3,33) and should be included in composite nutritional scores (34,35).

Practical Application

We have created a new metric in dialysis patients as per the ratio between phosphorous and nPCR that is associated with their survival. Scaling patients according to this metric might provide the clinician insight into nutritional status that will mandate intervention and direct the intensity of treatment. The metric we propose may be a useful predictor of mortality in patients on HD and should be included in composite nutritional scores.

Data Sharing

Data, analytic methods, and study materials will not be made available to other researchers for the purpose of reproducing the results or replicating the procedure. Data are provided under contract with a large dialysis organization and are at their disposal. Hence, this center may not over-ride the contractual agreements. Additional details regarding the analytical methods can be provided on request.

Credit Authorship Contribution Statement

Dana Bielopolski: designed and conducted the analysis, Writing – original draft. **Cachet Wenziger:** conducted a part of the analysis. **Tali Steinmetz:** contributed to the final version of the manuscript. **Benaya Rozen Zvi:** contributed to the final version of the manuscript. **Kamyar Kalantar-Zadeh:** designed the research project. **Elani Streja:** Supervision, Formal analysis.

Supplementary Data

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1053/j.jrn.2021.08.008.

References

1. Kalantar-Zadeh K. Recent advances in understanding the malnutrition-inflammation-cachexia syndrome in chronic kidney disease patients: what is next? *Semin Dial*. 2005;18:365-369.
2. Kalantar-Zadeh K, Supasyndh O, Lehn RS, McAllister CJ, Kopple JD. Normalized protein nitrogen appearance is correlated with hospitalization and mortality in hemodialysis patients with Kt/V greater than 1.20. *J Ren Nutr*. 2003;13:15-25.
3. Noce A, Vidiri MF, Marrone G, et al. Is low-protein diet a possible risk factor of malnutrition in chronic kidney disease patients? *Cell Death Discov*. 2016;2:16026.
4. Kalantar-Zadeh K, Kovesdy CP, Derose SF, Horwich TB, Fonarow GC. Racial and survival paradoxes in chronic kidney disease. *Nat Clin Pract Nephrol*. 2007;3:493-506.
5. Obi Y, Rhee CM, Mathew AT, et al. Residual kidney function decline and mortality in incident hemodialysis patients. *J Am Soc Nephrol*. 2016;27:3758-3768.
6. Kalantar-Zadeh K, Kilpatrick RD, Kuwae N, Wu DY. Reverse epidemiology: a spurious hypothesis or a hardcore reality? *Blood Purif*. 2005;23:57-63.
7. Uribarri J. Phosphorus homeostasis in normal health and in chronic kidney disease patients with special emphasis on dietary phosphorus intake. *Semin Dial*. 2007;20:295-301.
8. Lynch KE, Lynch R, Curhan GC, Brunelli SM. Prescribed dietary phosphate restriction and survival among hemodialysis patients. *Clin J Am Soc Nephrol*. 2011;6:620-629.
9. Reiss AB, Miyawaki N, Moon J, et al. CKD, arterial calcification, atherosclerosis and bone health: Inter-relationships and controversies. *Atherosclerosis*. 2018;278:49-59.
10. Block GA, Klassen PS, Lazarus JM, Ofsthun N, Lowrie EG, Chertow GM. Mineral metabolism, mortality, and morbidity in maintenance hemodialysis. *J Am Soc Nephrol*. 2004;15:2208-2218.
11. Kestenbaum B, Sampson JN, Rudser KD, et al. Serum phosphate levels and mortality risk among people with chronic kidney disease. *J Am Soc Nephrol*. 2005;16:520-528.
12. Block GA, Hulbert-Shearon TE, Levin NW, Port FK. Association of serum phosphorus and calcium x phosphate product with mortality risk in chronic hemodialysis patients: a national study. *Am J Kidney Dis*. 1998;31:607-617.
13. Martínez-Moreno JM, Herencia C, de Oca AM, et al. High phosphate induces a pro-inflammatory response by vascular smooth muscle cells and modulation by vitamin D derivatives. *Clin Sci*. 2017;131:1449-1463.
14. Six I, Maizel J, Barreto FC, et al. Effects of phosphate on vascular function under normal conditions and influence of the uraemic state. *Cardiovasc Res*. 2012;96:130-139.
15. Shanahan CM, Crouthamel MH, Kapustin A, Giachelli CM. Arterial calcification in chronic kidney disease: key roles for calcium and phosphate. *Circ Res*. 2011;109:697-711.
16. Noori N, Kalantar-Zadeh K, Kovesdy CP, Bross R, Benner D, Kopple JD. Association of dietary phosphorus intake and phosphorus to protein ratio with mortality in hemodialysis patients. *Clin J Am Soc Nephrol*. 2010;5:683-692.
17. Shinaberger CS, Greenland S, Kopple JD, et al. Is controlling phosphorus by decreasing dietary protein intake beneficial or harmful in persons with chronic kidney disease? *Am J Clin Nutr*. 2008;88:1511-1518.
18. Isakova T, Nickolas TL, Denburg M, et al. KDOQI US Commentary on the 2017 KDIGO clinical Practice guideline update for the Diagnosis, evaluation, prevention, and treatment of chronic kidney disease-mineral and bone disorder (CKD-MBD). *Am J Kidney Dis*. 2017;70:737-751.
19. Fernández-Martín JL, Martínez-Camblor P, Dionisi MP, et al. Improvement of mineral and bone metabolism markers is associated with better survival in haemodialysis patients: the COSMOS study. *Nephrol Dial Transpl*. 2015;30:1542-1551.
20. Fouque D, Horne R, Cozzolino M, Kalantar-Zadeh K. Balancing nutrition and serum phosphorus in maintenance dialysis. *Am J Kidney Dis*. 2014;64:143-150.
21. Elder GJ, Malik A, Lambert K. Role of dietary phosphate restriction in chronic kidney disease. *Nephrology (Carlton)*. 2018;23:1107-1115.
22. Kalantar-Zadeh K, Tortorici AR, Chen JLT, et al. Dietary restrictions in dialysis patients: is there anything left to eat? *Semin Dial*. 2015;28:159-168.
23. Sullivan C, Sayre SS, Leon JB, et al. Effect of food additives on hyperphosphatemia among patients with end-stage renal disease: a randomized controlled trial. *JAMA*. 2009;301:629-635.
24. Fouque D, Kalantar-Zadeh K, Kopple J, et al. A proposed nomenclature and diagnostic criteria for protein-energy wasting in acute and chronic kidney disease. *Kidney Int*. 2008;73:391-398.
25. Bohn L, Meyer AS, Rasmussen SK. Phytate: impact on environment and human nutrition. A challenge for molecular breeding. *J Zhejiang Univ Sci B*. 2008;9:165-191.
26. Sandberg AS, Andersson H, Kivistö B, Sandström B. Extrusion cooking of a high-fibre cereal product. 1. Effects on digestibility and absorption of protein, fat, starch, dietary fibre and phytate in the small intestine. *Br J Nutr*. 1986;55:245-254.
27. Lei XG, Porres JM. Phytase enzymology, applications, and biotechnology. *Biotechnol Lett*. 2003;25:1787-1794.
28. Gluba-Brzózka A, Franczyk B, Rysz J. Vegetarian diet in chronic kidney disease-A Friend or Foe. *Nutrients*. 2017;9:374.
29. Sousa H, Ribeiro O, Paúl C, et al. Social support and treatment adherence in patients with end-stage renal disease: a systematic review. *Semin Dial*. 2019;32:562-574.
30. Wang AY-M, Kalantar-Zadeh K, Fouque D, et al. Precision medicine for nutritional management in end-stage kidney disease and Transition to dialysis. *Semin Nephrol*. 2018;38:383-396.
31. Cole N, Bedford M, Cai A, Jones C, Cairns H, Jayawardene S. Black ethnicity predicts better survival on dialysis despite greater deprivation and co-morbidity: a UK study. *Clin Nephrol*. 2014;82:77-82.
32. Pei YP, Greenwood CM, Chery AL, Wu GG. Racial differences in survival of patients on dialysis. *Kidney Int*. 2000;58:1293-1299.
33. Collins AJ, Foley RN, Chavers B, et al. United States renal data system 2011 Annual data Report: Atlas of chronic kidney disease & end-stage renal disease in the United States. *Am J Kidney Dis*. 2012;59(1 Suppl 1):e1-e420. A7.
34. Parekh RS, Zhang L, Fivush BA, Klag MJ. Incidence of atherosclerosis by race in the dialysis morbidity and mortality study: a sample of the US ESRD population. *J Am Soc Nephrol*. 2005;16:1420-1426.
35. Xue JL, Frazier ET, Herzog CA, Collins AJ. Association of heart disease with diabetes and hypertension in patients with ESRD. *Am J Kidney Dis*. 2005;45:316-323.
36. Morton RL, Schlackow I, Mihaylova B, Staplin ND, Gray A, Cass A. The impact of social disadvantage in moderate-to-severe chronic kidney disease: an equity-focused systematic review. *Nephrol Dial Transpl*. 2016;31:46-56.
37. Kalantar-Zadeh K, Ikizler TA, Block G, Avram MM, Kopple JD. Malnutrition-inflammation complex syndrome in dialysis patients: causes and consequences. *Am J Kidney Dis*. 2003;42:864-881.
38. Kalantar-Zadeh K, Kopple JD, Humphreys MH, Block G. Comparing outcome predictability of markers of malnutrition-inflammation complex syndrome in haemodialysis patients. *Nephrol Dial Transpl*. 2004;19:1507-1519.
39. Streja E, Lau WL, Goldstein L, et al. Hyperphosphatemia is a combined function of high serum PTH and high dietary protein intake in dialysis patients. *Kidney Int Suppl (2011)*. 2013;3:462-468.

40. Lertdumrongluk P, Rhee CM, Park J, et al. Association of serum phosphorus concentration with mortality in elderly and nonelderly hemodialysis patients. *J Ren Nutr.* 2013;23:411-421.

41. Obi Y, Qader H, Kovesdy CP, Kalantar-Zadeh K. Latest consensus and update on protein-energy wasting in chronic kidney disease. *Curr Opin Clin Nutr Metab Care.* 2015;18:254-262.

42. Eriguchi R, Obi Y, Streja E, et al. Longitudinal associations among renal urea clearance-Corrected normalized protein catabolic rate, serum albumin, and mortality in patients on hemodialysis. *Clin J Am Soc Nephrol.* 2017;12:1109-1117.

43. Mathew AT, Fishbane S, Obi Y, Kalantar-Zadeh K. Preservation of residual kidney function in hemodialysis patients: reviving an old concept. *Kidney Int.* 2016;90:262-271.

44. Lee Y-J, Okuda Y, Sy J, et al. Association of mineral bone disorder with decline in residual kidney function in incident hemodialysis patients. *J Bone Miner Res.* 2020;35:317-325.

45. Plantinga LC, Fink NE, Levin NW, et al. Early, intermediate, and long-term risk factors for mortality in incident dialysis patients: the Choices for Healthy Outcomes in Caring for ESRD (CHOICE) Study. *Am J Kidney Dis.* 2007;49:831-840.