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Association between modified simple protein-energy wasting (PEW) score and all-cause mortality in patients receiving maintenance hemodialysis

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Abstract

Background: Protein-energy wasting (PEW) is a frequently observed complication that leads to increased mortality in hemodialysis patients. However, a multifaceted assessment of PEW by combined objective nutritional parameters has not yet been established.

Methods: In total, 144 Japanese patients receiving maintenance hemodialysis at a hemodialysis center were retrospectively followed for 7 years. The primary outcome was all-cause death. The main exposure was a modified simple PEW score (0, 1, 2, 3, or 4), calculated from four parameters: serum albumin and creatinine levels, normalized protein catabolic rate, and body mass index. These parameters are included in the subcategories of PEW as defined by the International Society of Renal Nutrition and Management. The cutoff values of the modified simple PEW score components were based on the receiver operating characteristics curves determined by univariate logistic regression analyses. Risk estimates for all-cause mortality were calculated by the Cox proportional hazards model adjusted for potential confounding factors.

Results: During the median 5.7-years follow-up period, 37 patients died of any cause. When patients were divided into three subgroups (G1–G3) based on the modified simple PEW score, a multivariable-adjusted analysis showed that the risks of all-cause death in groups G2 and G3 were significantly higher than in the lowest score group (G1), with hazard risk (95% confidence interval) 3.10 (1.16–8.26) ($P = 0.024$) and 5.68 (1.85–17.45) ($P = 0.002$), respectively.

Conclusions: The modified simple PEW score is a useful composite indicator of nutritional status that stratifies the risk of all-cause mortality in patients undergoing maintenance hemodialysis.

Keywords: Albumin, Body mass index, Creatinine, Hemodialysis, Normalized protein catabolic rate, Protein energy wasting

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Introduction

Malnutrition or undernutrition is common in patients receiving hemodialysis [1]. The underlying causes for malnutrition in these patients are attributed to increased catabolism, decreased appetite and food intake, nutrient loss through the hemodialyzer, and dietary protein restriction for phosphate control [2]. These patients are at increased risk for morbidity and mortality [3]. To date, assessment of nutritional status in combination with effective intervention to treat malnutrition or undernutrition has been a challenging theme in this population.

Protein-energy wasting (PEW) is a term that was proposed by a panel of the International Society of Renal Nutrition and Management (ISRNM) in 2009 [4]. The ISRNM has defined PEW as a state of decreased body stores of protein and energy fuels (body protein and fat mass). The ISRNM also proposed diagnostic criteria for PEW with four distinct categories: (i) biochemical indicators such as serum albumin or prealbumin; (ii) low body weight, reduced fat, or weight loss; (iii) decreased muscle mass; and (iv) low protein or energy intake. In the clinical setting, it would be convenient to integrate all the PEW criteria into one index or risk score and use this integrated score for the periodic assessment of PEW in patients with chronic kidney disease. Recently, Moreau-Gaudry et al. reported a simple PEW score using four nutritional parameters corresponding to four categories of PEW and integrating subscores into a single value that enables semiquantitative assessment of PEW in patients undergoing hemodialysis [5]. Serum levels of albumin and creatinine (Cr), normalized protein catabolic rate (nPCR), and body mass index (BMI) were used for the score calculation. These nutritional parameters are established nutritional markers and reported to be associated with mortality in patients receiving hemodialysis [6–9]. Lopes et al. showed that the simple PEW score predicted all-cause mortality in European patients undergoing hemodialysis. However, racial, habitual, and social backgrounds make for substantial differences in the nutritional status and parameters of this patient population across countries [10]. Therefore, it is reasonable to speculate that some of the cutoff values for PEW categories should account for those differences.

The aim of the present study was threefold. The first aim was to create a modified simple PEW score (mPEW-S) for Japanese patients undergoing hemodialysis by adjusting the original simple PEW score created by Moreau-Gaudry A et al. by changing some of the cutoff values of PEW components. The second aim was to elucidate whether the mPEW-S accurately predicts all-cause mortality in Japanese patients receiving hemodialysis. The third aim was to show that some of the cutoff values of the PEW components should be determined depending on the targeting hemodialysis population. For these aims, we retrospectively recruited patients receiving maintenance hemodialysis at a single hemodialysis center in Japan. In this study, we used the geriatric nutritional risk index (GNRI) and Cr index as pre-established nutritional indexes and references in patients receiving hemodialysis [11, 12].

Patients and methods

Study design and participants

This was a single-center, retrospective, observational study consisting of 144 outpatients with end-stage kidney disease who had been receiving maintenance hemodialysis therapy at the Fukuoka Renal Clinic on December 1, 2011. Patients were followed until death, transfer to another hospital, or loss to follow-up. Patients who were lost to follow-up during the observation period were regarded as “censored” on the day of the final hospital visit and were also included in the analyses. The study was performed in accordance with the principle of the Declaration of Helsinki. The study protocol was reviewed and approved by the institutional review board at Fukuoka Dental College (2012-256). Written informed consent was obtained from each patient prior to study participation.

Primary outcomes and main exposure

The primary outcome was death by any-cause. The main exposure was the mPEW-S. The original simple PEW score proposed by Moreau-Gaudry et al. used serum albumin as serum biochemistry, BMI as body weight, serum Cr/body surface area (BSA) as skeletal muscle mass, and nPCR as protein intake [5]. BSA was calculated by the following formula: BSA (m^2) = 0.007184 × (height in centimeter)$^{0.725}$ × (body weight in kilogram)$^{0.425}$. The original cutoff values for each PEW category by Moreau-Gaudry A et al. were 3.8 g/dL, 23 kg/m^2, 380 μmol/L/m^2, and 0.8 g/kg/day, respectively. The cut-of values set for serum albumin level (3.8 g/dl) and nPCR (0.8 g/kg/day) were derived from the cutoff values set by the ISRNM [4]. As for cutoff values for serum Cr/BSA and BMI, Moreau-Gaudry A et al. determined those cutoff values based on the distribution of serum Cr/BSA and BMI among their study population [5]. However, 380 μmol/L/m^2 for serum Cr/BSA was too low and 23 kg/m^2 for BMI appeared to be too high for the Japanese population. The cutoff values were calculated by the receiver operation characteristic (ROC) curves for each nutritional surrogate by using non-adjusted logistic regression analysis for all-cause mortality and then rounded considering the distribution of those values based on the current study and database of Japanese hemodialysis patients provided by The Japanese Society for Dialysis Therapy (https://www.jsdt.or.jp/Overview_2.html). The unit of serum Cr was converted from mg/dL to μmol/L by the

following formula: serum Cr (μmol/L) = serum Cr (mg/dL) × 10000 / 113 (molecular weight for Cr).

Data collection

Demographic data, including dialysis-related parameters, were retrospectively collected by reviewing medical charts. Biochemical parameters used in the present analyses were collected at the start of the dialysis session following the longest interdialytic period (2 days) on the first week of December 2011 and December 2012. Serum calcium levels were corrected using Payne's formula only if patients had a serum albumin level < 4.0 g/dL [13]. Serum parathyroid hormone (PTH) levels were determined by immunoradiometric assay as whole PTH and were reported as intact PTH using the following formula: serum intact PTH (pg/mL) = 1.7 × whole PTH (pg/mL) [14]. Additional data collected included levels of blood hemoglobin, urea nitrogen, and calcium, as well as serum C-reactive protein.

Calculation of pre-established nutritional indexes

GNRI and modified Cr index were calculated as previously reported [11, 12]:

GNRI = 14.89 × serum albumin (g/dL) + 41.7 × body weight (kg)/ideal body weight

Modified Cr index (mg/kg/day) = 16.21 + 1.12 × (1 if male, 0 if female)

– 0.06 × age (years)

– 0.08 × single-pooled Kt/V* for urea

+ 0.009 × serum Cr level before dialysis (μmol/L).

* The Kt/V ratio represents the plasma volume (V) cleared of urea (Kt) during hemodialysis relative to the distribution volume of urea.

Body weight/ideal body weight was set to 1 when the body weight exceeded the ideal body weight. Ideal body weight was calculated as 22 × height (meters) × height (meters).

Statistical analysis

Normally distributed continuous variables, non-normally distributed continuous variables, and categorical data were described as mean (standard deviation), median (interquartile range), and percentage, respectively, unless otherwise specified.

The distribution of baseline characteristics in subgroups based on the mPEW-S (G1, G2, and G3) was compared using the following trend analyses: the Cochran–Armitage test was used for categorical variables, and the Jonckheere–Terpstra test was used for continuous variables. To determine correlation among the mPEW-S, the original simple PEW score, GNRI, or modified Cr index, Spearman's rank-order correlation was used. Unadjusted, age- and sex-adjusted, and multivariable-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for all-cause mortality were estimated using the Cox proportional hazards risk models. The multivariable-adjusted model included the following covariates: age, sex, presence of diabetic nephropathy, history of cardiovascular events, hemodialysis history, serum levels of calcium, phosphate, and PTH. To compare the predictability performance for all-cause mortality between the original simple PEW score and the mPEW-S, we calculated c-statistics by ROC, net reclassification improvement (NRI), and integrated discrimination improvement (IDI).

A two-tailed P value < 0.05 was considered statistically significant in all analyses. All statistical analyses were performed using JMP Pro 14.2.0 for Windows (SAS Institute, Inc., Tokyo, Japan) and R 3.5.1 (http://cran.r-project.org).

Results

Determination of cutoff values for each PEW parameter

In total, 144 Japanese patients undergoing maintenance hemodialysis were included in the present analysis. To determine the cutoff values for each PEW parameter appropriate for Japanese hemodialysis patients, we first conducted univariate logistic regression analyses by setting all-cause death as an endpoint and determined ROC curves. The cutoff values for serum albumin, BMI, serum Cr/BSA, and nPCR were 3.80 g/dL, 18.72 kg/m^2, 506.7 μmol/L/m^2, and 0.789 g/kg/day, respectively. Then, after considering the distribution of the four parameters of PEW in the hemodialysis patients registered in the database of the Japanese Society for Dialysis Therapy ((https://www.jsdt.or.jp/Overview_2.html) and the original cutoff values of the ISRNM, we rounded the cutoff values of BMI, serum Cr Cr/BSA, and nPCR and ultimately set the cutoff values for the four categories of PEW as 3.8 g/dL for serum albumin, 18.5 kg/m^2 for BMI, 500 μmol/L/m^2 for serum Cr/BSA, and 0.8 g/kg/day for nPCR. For the cutoff value of serum Cr/BSA, 500 μmol/L/m^2 = 5.65 mg/dL/m^2; therefore, if a patient's BSA was 1.6 m^2, the patient's serum Cr was almost 9 mg/dL.

Based on the above cutoff values, modified scoring system for PEW was created and is shown in Table 1. The lowest value was 0 and the highest value was 4. Patients with a higher mPEW-S were supposed to be more malnourished and have a higher risk of morbidity and mortality. Because the numbers of patients in mPEW-S 1, 3, and 4 were relatively small compared with those in mPEW-S 0 and 2, to further elucidate the association between mPEW-S and mortality, patients were divided into subgroups based on the mPEW-S; G1, mPEW-S 0 or 1; G2, mPEW-S 2; and G3, mPEW-S 3 or 4.

Patients' characteristics

From the cutoff values of the original simple PEW score and mPEW-S, the number and proportion of patients in each subcategory is shown in Fig. 1.

Table 1 Scoring system of the modified simple PEW score

Variable	Score
Serum albumin (g/dL)	
≥ 3.8	0
< 3.8	1
Serum Cr/BSA (μmol/L/m^2)	
≥ 500	0
< 500	1
BMI (kg/m^2)	
≥ 18.5	0
< 18.5	1
nPCR (g/kg/day)	
> 0.8	0
< 0.8	1
Total score	0-4

Total modified PEW score is the simple sum of each value of four subcategories of PEW
BMI body mass index, *BSA* body surface area, *Cr* creatinine, *nPCR* normalized protein catabolic rate, *PEW* protein-energy wasting

The scoring system for the mPEW-S is shown in Table 1. Fifty patients showed score 0, 10 patients score 1, 63 patients score 2, 18 patients score 3, and 3 patients score 4. Patients were then classified into one of three groups (G1–G3) according to the mPEW-S: G1, G2, and G3. Namely, a total of 60 patients were classified as G1 (mPEW-S 0 or 1), 63 patients were G2 (mPEW-S 2), and 21 patients were G3 (mPEW-S 3 or 4).

Table 2 shows the baseline characteristics in each subgroup divided by the mPEW-S. Patients with a higher mPEW-S were significantly ($P < 0.05$) older and showed lower nPCR, body weight, and BMI, blood hemoglobin, serum albumin, urea nitrogen, Cr, and calcium as well as a higher serum C-reactive protein. There was no tendency regarding the association between mPEW-S and medications.

Correlation between mPEW-S and two nutritional indexes

To determine the validity of our newly developed mPEW-S as a nutritional score, we examined whether the mPEW-S showed an association with the modified Cr index and GNRI, established scores for good nutrition, by using the mPEW-S as a continuous variable. As shown in Fig. 2a, b, a higher mPEW-S was significantly ($P < 0.05$) and negatively correlated with a lower Cr index and GNRI; the coefficients of determination were 0.29 and 0.54, respectively.

We also examined the correlation between the original simple PEW score and those two nutritional indexes by using the mPEW-S as a continuous variable. As shown in Fig. 2c, d, the original PEW score was significantly ($P < 0.05$) and negatively correlated with Cr index and GNRI and the coefficients of determination were 0.25 and 0.39, respectively. When coefficients of determination were compared across those PEW scores, the values were almost comparable.

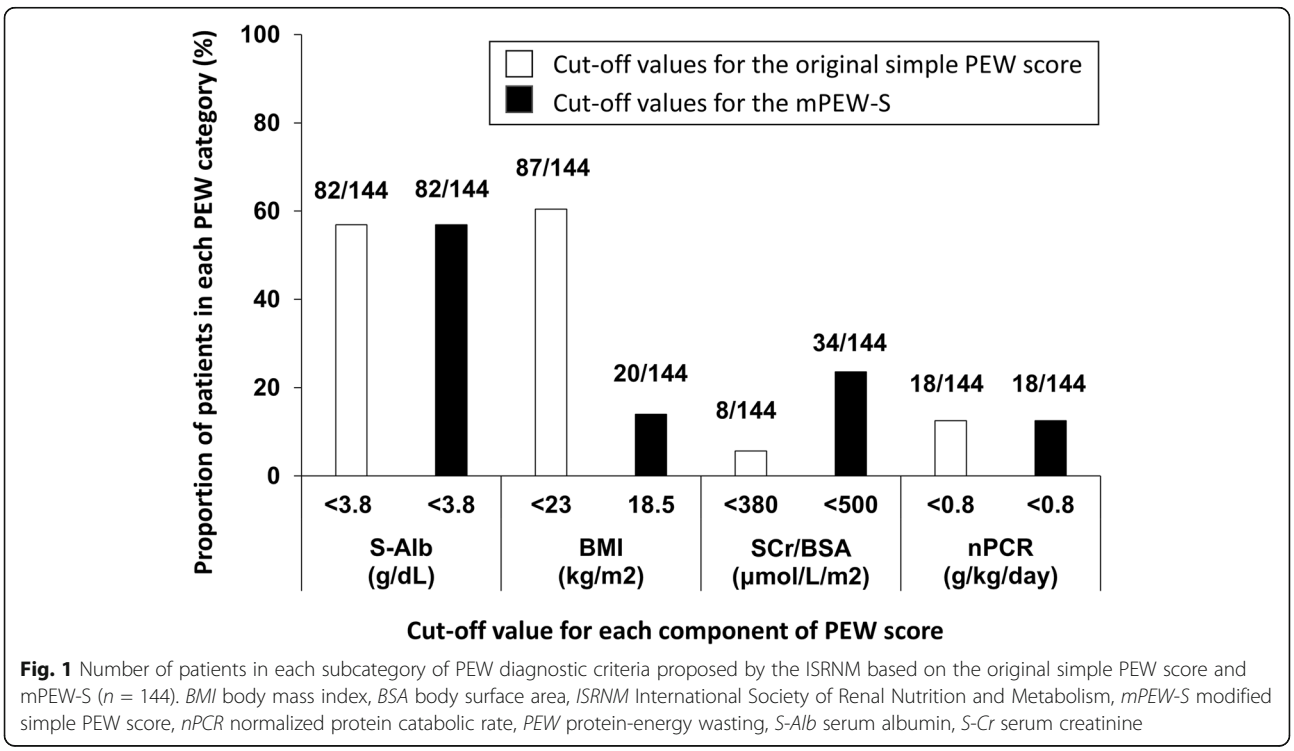

Fig. 1 Number of patients in each subcategory of PEW diagnostic criteria proposed by the ISRNM based on the original simple PEW score and mPEW-S ($n = 144$). *BMI* body mass index, *BSA* body surface area, *ISRNM* International Society of Renal Nutrition and Metabolism, *mPEW-S* modified simple PEW score, *nPCR* normalized protein catabolic rate, *PEW* protein-energy wasting, *S-Alb* serum albumin, *S-Cr* serum creatinine

Table 2 Patient characteristics at baseline stratified by mPEW-S

Risk group	Total	G1	G2	G3	*P* for trend
mPEW-S	0–4	0, 1	2	3, 4	
Patients' number	*n* = 144	*n* = 60	*n* = 63	*n* = 21	
Demographic data					
Age, years	62 ± 12	57 ± 12	63 ± 11	71 ± 12	< 0.001
Male sex, *n* (%)	85 (59)	41 (68)	32 (51)	12 (57)	0.147
Diabetic nephropathy, *n* (%)	17 (11.9)	7 (12)	6 (10)	4 (19)	0.554
History of cardiovascular diseases, *n* (%)	20 (14)	4 (7)	12 (19)	4 (19)	0.062
Dialysis history, years	11 (5-22)	14 (8-27)	7 (3-19)	8 (7-14)	0.228
Kt/V for urea	1.71 ± 0.31	1.68 ± 0.33	1.75 ± 0.27	1.66 ± 0.34	0.858
Normalized protein catabolic rate, g/kg/day	0.93 ± 0.17	0.96 ± 0.15	0.95 ± 0.15	0.78 ± 0.18	< 0.001
Dry weight, kg	57.0 ± 10.9	59.7 ± 10.5	56.8 ± 10.4	49.8 ± 10.7	< 0.001
Body mass index, kg/m^2	22.2 ± 3.5	22.7 ± 3.6	22.5 ± 3,1	19.8 ± 3.7	0.006
Blood and serum biochemical parameters					
Hemoglobin, g/dL	11.2 ± 1.1	11.4 ± 0.9	11.0 ± 1.3	10.9 ± 1.0	0.023
Albumin, g/dL	3.7 ± 0.3	4.0 ± 0.1	3.6 ± 0.3	3.4 ± 0.2	< 0.001
C-reactive protein, mg/dL	0.1 (0.1-0.3)	0.1 (0.1-0.2)	0.2 (0.1-0.4)	0.4 (0.1-1.9)	0.004
Urea nitrogen, mg/dL	64 ± 14	67 ± 12	65 ± 13	51 ± 15	< 0.001
Creatinine, mg/dL	10.7 ± 2.5	11.8 ± 2.2	10.7 ± 2.3	7.8 ± 1.6	< 0.001
Calcium, mg/dL	9.4 ± 0.5	9.6 ± 0.5	9.2 ± 0.5	9.1 ± 1.0	< 0.001
Phosphate, mg/dL	4.6 ± 0.9	4.8 ± 0.8	4.5 ± 0.9	4.6 ± 1.0	0.114
PTH (intact assay), pg/mL	72 (41–117)	82 (45–123)	62 (36–112)	76 (49–90)	0.161
Medications					
Anti-hypertensive drugs, *n* (%)	90 (54)	38 (63)	40 (63)	12 (57)	0.689
ESAs, n (%)	122 (85)	50 (83)	54 (86)	18 (86)	0.730
VDRAs, *n* (%)	106 (74)	44 (73)	47 (75)	15 (71)	0.937
Phosphate binders, *n* (%)	115 (80)	48 (80)	52 (83)	15 (71)	0.970
Cinacalcet hydrochloride, *n* (%)	36 (25)	14 (23)	14 (22)	8 (38)	0.322

Data are mean ± SD, median (interquartile range), or number (percentage)
ESAs erythropoiesis stimulating agents, *G* subgroups divided by the mPEW-S, *Kt/V* plasma volume (V) cleared of urea (Kt) during hemodialysis relative to the distribution volume of urea, *mPEW-S* modified simple protein-energy wasting score, *PTH* parathyroid hormone, *VDRAs* vitamin D receptor activators

Kaplan–Meier curves for all-cause death in the three groups divided by the mPEW-S

During the median observation period of 5.7 years, 37 patients died of any-cause. Numbers of death were 6 in G1, 19 in G2, and 12 in G3. Figure 3 shows non-adjusted Kaplan-Meier curves for all-cause death according to subgroups stratified by the mPEW-S. Patients in G2 and G3 showed a higher incidence rate of all-cause death compared with those in G1 (log-rank test, $P < 0.05$).

Association between the mPEW-S and the risk for all-cause mortality examined by Cox proportional hazards model

To further determine the association between the mPEW-S and all-cause death, we estimated the hazard risk for all-cause death in each subgroup by applying the Cox proportional hazards risk model. As shown in Table 3, unadjusted and age- and sex-adjusted hazard ratios for all-cause death in G3 were significantly higher than those in G1. The association remained significant even after adjustment for several confounding factors: HR (95% CI) for G2, 3.10 (1.16–8.26); and for G3, 5.68 (1.85–17.45), respectively. The multivariable-adjusted HR (95% CI) for every 1 score increase in the mPEW-S was 1.67 (1.16–2.40).

Comparison of the c-statistic of the ROC curves, NRI, and IDI

Finally, to compare the predictability performance for all-cause mortality between the original simple PEW score and our mPEW-S, we compared the c-statistics, NRI, and IDI by setting the original simple PEW score as reference. As shown in Fig. 4, the c-statistic of the original simple PEW score was 0.582, whereas that of mPEW-S was 0.695, and the difference was statistically significant ($P = 0.016$). The cutoff value of mPEW-S for

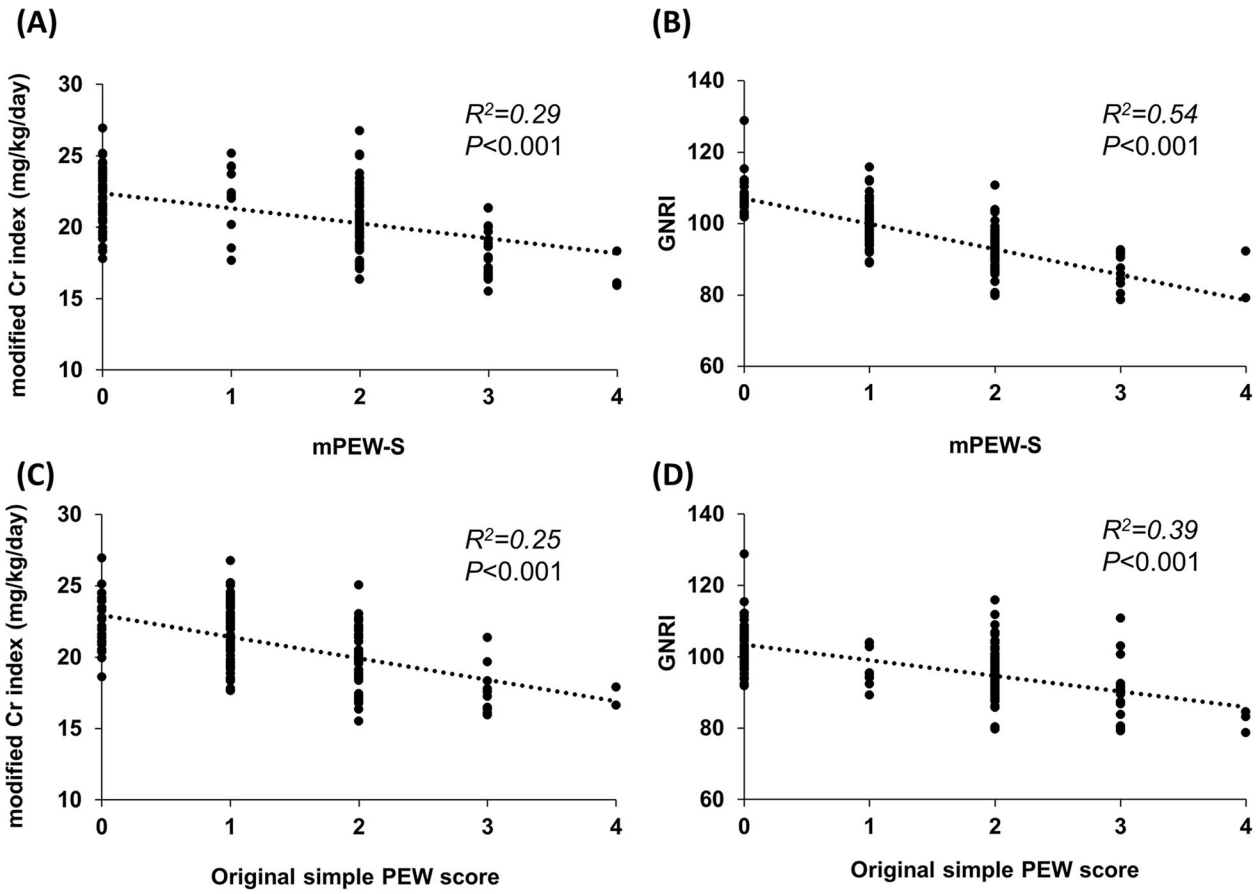

Fig. 2 Correlations between two established nutritional markers and the mPEW-S or original simple PEW score and (n = 144). **a** Correlation between mPEW-S and modified GNRI. **b** Correlation between mPEW-S and Cr index. **c** Correlation between the original simple PEW score and modified GNRI. **d** Correlation between the original simple PEW score and Cr index. Pearson's correlation coefficients were used. The mPEW-S was used as continuous variable. Spearman's rank-order correlation was used. A two-tailed $P < 0.05$ was considered statistically significant. *Cr* creatinine, *GNRI* geriatric nutritional risk index, *mPEW-S* modified simple protein-energy wasting score, *PEW* protein-energy wasting

all-cause mortality was 2, where sensitivity was 84% and specificity was 50%. The cutoff value of the original simple PEW score for all-cause mortality was 2, the sensitivity was 60%, and the specificity was 65%. Furthermore, both NRI and IDI were significantly different between the original PEW score and mPEW-S: NRI, − 0.667 (− 0.975, − 0.359), $P < 0.001$; IDI, − 0.077 (− 0.116, − 0.039), $P < 0.001$, respectively.

Discussion

In the present study, we proposed the mPEW-S, which was modified from the original simple PEW score consisting of serum albumin and Cr levels, BMI, and nPCR, by adjusting the cutoff values of those parameters suitable for Japanese patients receiving hemodialysis. The mPEW-S for these patients was significantly and negatively associated with the GNRI and modified Cr index, previously established good nutrition indexes [11, 12]. A higher mPEW-S was significantly associated with an increased risk for all-cause mortality, even after adjustment for several confounding factors. Furthermore, when predictability performance for all-cause mortality was compared, mPEW-S was superior to the original simple PEW score. Our results suggest that the mPEW-S can be a useful tool to stratify nutritional status and death risk and identify candidate patients for nutritional intervention among Japanese patients receiving hemodialysis. In addition, our study indirectly confirmed that the four nutritional parameters used in the semiquantitative assessment of PEW are valid in combination and useful for the evaluation of nutritional status of these patients.

Diagnosis of PEW is a challenging theme in patients receiving hemodialysis. Because there has been no single diagnostic marker or tool to perfectly determine whether a patient is PEW or not, clinical studies focusing on PEW inevitably require diagnostic definition of PEW by combining one or more of the nutrition-related surrogates to allocate patients into a binary variable pertaining to PEW. A variety of nutritional surrogates have been proposed for the evaluation of nutritional status in

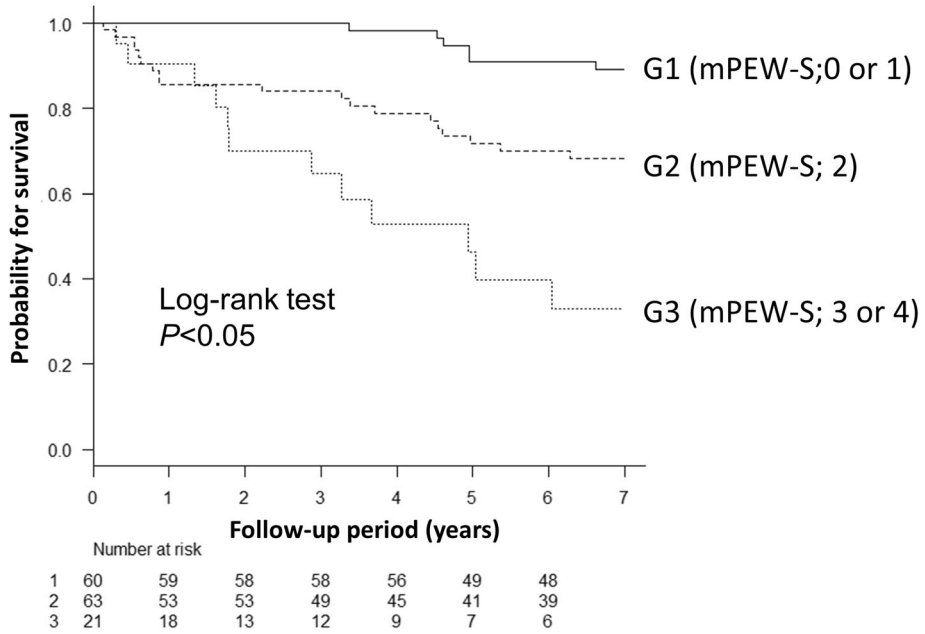

Fig. 3 Non-adjusted Kaplan-Meier curves in the three groups divided by the mPEW-S (n = 144). A log-rank test was used to compare survival curves among groups. A two-tailed $P < 0.05$ was considered statistically significant. *mPEW-S* modified simple protein-energy wasting score. G1, patients whose mPEW-S was 0 or 1; G2, patients whose mPEW-S was 2; G3, patients whose mPEW-S was 3 or 4

hemodialysis patients [3, 6–9, 15–17]. Among the potential surrogates, serum levels of albumin and Cr, BMI, and nPCR were chosen for PEW assessment. Each of the four surrogates corresponds to the component of the PEW subcategory proposed by the ISRNM and is also an established surrogate when used as a single marker. Notably, the Dialysis Outcomes and Practice Patterns Study showed that combination of two nutritional markers such as serum levels of albumin, Cr, and CRP and BMI are better than single nutritional marker [18]. These observations are acceptable because each marker provides only partial information on nutritional status. The combination of multiple surrogates enables us to assess nutritional status in a multifaceted way and offers a better prediction than a single surrogate. Indeed, the Malnutrition-Inflammation Score is another representative and gold standard tool using a multifaceted assessment of nutritional status [3]. The assessment of malnutrition-inflammation-atherosclerosis syndrome, however, contains a subjective element and interobserver differences are occasionally problematic; this assessment requires experienced staff and is unsuitable for a local dialysis center. In contrast, the mPEW-S may be useful at the level of the local dialysis clinic as a simple and objective tool for periodic nutritional assessment.

The GNRI and Cr index are established nutritional indexes often used for the evaluation of nutritional status in patients receiving hemodialysis [11, 12]. Increasing evidence has shown that those two indexes are good predictors for the development of cardiovascular events

Table 3 Hazard ratios for the incidence of all-cause death in each subgroup stratified by mPEW-S (n = 144)

Groups stratified by mPEW-S	No of events/ No of patients	Unadjusted			Age- and sex-adjusted			Multivariable- adjusted		
		HR (95% CI)	*P* value	*P* for trend	HR (95% CI)	*P* value	*P* for trend	HR (95% CI)	*P* value	*P* for trend
G1 (0, 1)	6/60	1 (reference)			1 (reference)			1 (reference)		
G2 (2)	19/63	3.63 (1.45–9.10)	0.006	< 0.001	3.25 (1.28–8.24)	0.013	0.001	3.10 (1.16–8.26)	0.024	0.005
G3 (3, 4)	12/21	9.60 (3.58–25.77)	< 0.001		5.31 (1.84–15.36)	0.002		5.68 (1.85–17.45)	0.002	
Every 1 score increase in mPEW-S		2.02 (1.47–2.85)	< 0.001		1.60 (1.17–2.27)	0.006		1.67 (1.16–2.40)	< 0.001	

Unadjusted and multivariable-adjusted HRs were analyzed by the Cox proportional hazard model. The multivariable-adjusted model included age, sex, diabetic nephropathy, history of cardiovascular events, dialysis history, blood hemoglobin, serum levels of log CRP, albumin-corrected calcium, phosphate, and parathyroid hormones. A two-tailed *P* value < 0.05 was considered statistically significant

CI confidence interval, *CRP* C-reactive protein, *HR* hazard ratio, *G* subgroups divided by the mPEW-S, *mPEW-S* modified simple protein-energy wasting score

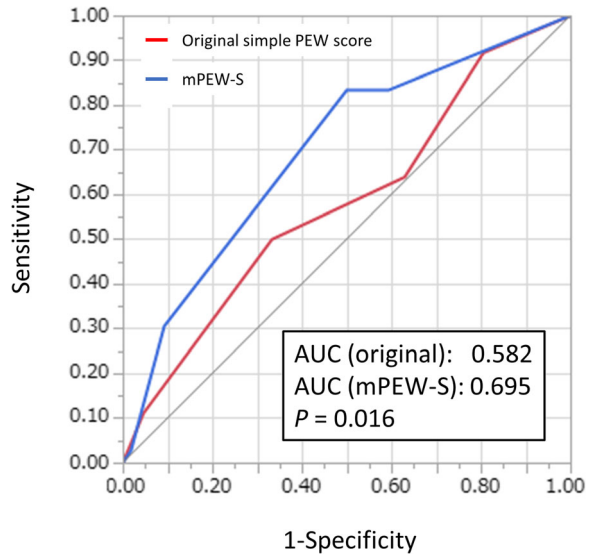

Fig. 4 Comparison of ROC curves between the original PEW score and mPEW-S (n = 144). A two-tailed $P < 0.05$ was considered statistically significant. *mPEW-S* modified original PEW score, *PEW* protein-energy wasting, *ROC* receiver operating characteristics

and bone fracture, as well as infection-related and all-cause death in patients undergoing hemodialysis [11, 12, 19–21]. The GNRI is correlated with the Malnutrition-Inflammation Score, which is now regarded as the gold standard for diagnosing PEW or malnutrition [22]. The modified Cr index is a marker of skeletal muscle mass and is also correlated with GNRI [23]. In the present study, our mPEW-S was significantly associated with both indexes. These observations suggest that our mPEW-S is a useful nutritional maker in the prediction of mortality in the hemodialysis population.

In the present study, mPEW-S was superior to the original simple PEW score. This is because the original cutoff values of the nutritional status were made for European patients and not for the Japanese. In other words, the cutoff values for each nutritional surrogate should be adjusted depending on the racial, ethnic, and social backgrounds. In this regard, our mPEW-S score was adjusted for Japanese patients receiving hemodialysis and can be used as a good surrogate for nutritional status and predictor of all-cause mortality in that population.

We are aware that our study has several limitations. First, our mPEW-S was derived from data obtained at a single Japanese hemodialysis center and comprised a relatively small sample size. Accordingly, the cutoff values of each mPEW-S parameter should be validated by a larger independent hemodialysis population such as using nationwide database of hemodialysis patients held by the Japanese Society for Dialysis Therapy. Second, because the number of death events in each mPEW-S group was very small, the patients were divided into three subgroups when Kaplan-Meier curves and hazard risk models were applied and the risk stratification in each mPEW-S group was not accomplished. Accordingly, other subgroupings based on the mPEW-S might have altered the observed association in the present study. Third, although our mPEW-S was closely associated with pre-established nutritional indexes such as the GNRI and Cr index, the cutoff values were mainly based on the dataset of our 144 Japanese hemodialysis patients and rounded after considering the distribution of those values based on the current study and database of Japanese hemodialysis patients provided by The Japanese Society for Dialysis Therapy (https://www.jsdt.or.jp/Overview_2.html). Hence, our mPEW-S should be validated with other Japanese hemodialysis populations. Fourth, because of the small sample size and outcome number, we included several confounding factors in the multi-variable adjustment. Hence, given that the known and unknown confounding factors were not adjusted, the association between the mPEW-S and all-cause death may be altered. Fifth, it is unclear whether our mPEW-S is a good predictor of other clinical outcomes such as cardiovascular disease events, bone fracture, or hospitalization. Therefore, further studies are necessary to determine the usefulness and validity of the mPEW-S developed in our study.

Conclusions

Our data showed that the mPEW-S for Japanese patients receiving maintenance hemodialysis was well correlated with pre-established nutritional risk indexes and associated with an increased risk of all-cause mortality. The mPEW-S can be a useful screening tool to detect malnutrition and identify candidates for nutritional support, especially in Japanese patients. Further studies are necessary to determine the external validity of the mPEW-S as a nutritional marker and whether the mPEW-S can be a useful tool for the prediction of other clinical outcomes in patients receiving maintenance hemodialysis. However, the mPEW-S should be cautiously used until it is validated by a larger hemodialysis population.

Supplementary information

Supplementary information accompanies this paper at https://doi.org/10.1186/s41100-020-00289-6.

Additional file 1.

Abbreviations

BMI: Body mass index; BSA: Body surface area; CI: Confidence interval; Cr: Creatinine; CKD: Chronic kidney disease; GNRI: Geriatric nutritional risk index; HR: Hazard ratio; IRI: Integrated reclassification improvement; ISRNM: International Society of Renal Nutrition and Metabolism; mPEW-S: Modified PEW score; NRI: Net reclassification improvement; PEW: Protein

energy wasting; PTH: Parathyroid hormone; ROC: Receiver operating characteristics

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Authors' contributions
Conception and study design: SY, MTo, and MTa; data acquisition: SY, ST, AH, SS, MTo, MTa, and KT; data analysis interpretation: SY, MTo, MTa, HY, HA, TN; statistical analysis: SY and TN; draft writing: SY; revision of the paper: SY, TN, ST, AH, SS, MTo, MTa, HO, HH, KT, and TK; supervision or mentorship: HO, HH, TN, KT, and TK. Each author contributed important intellectual content during manuscript drafting and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. Each author has approved the submitted version of the paper. TK takes responsibility that this study has been reported honestly, accurately, and transparently; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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Availability of data and materials
The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate
The study was conducted in accordance with the guidelines of the Declaration of Helsinki and approved by the Institutional Review Board at Fukuoka Dental College (approval number: 2012-256).

Consent for publication
Not applicable.

Competing interests
None.

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