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A simple protein-energy wasting score for survival prediction of maintenance hemodialysis patients

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Abstract

Background: The nutritional status of patients on maintenance hemodialysis (MHD) is a strong predictor of their survival. We assessed the reliability of a protein-energy wasting (PEW) score as a predictor of the survival of Japanese MHD patients.

Methods: The study subjects were 254 MHD patients. PEW score was from 0 (worst; group 1) to 4 (best; group 4) and was derived from four body nutrition compartments: serum albumin, body mass index, a normalized serum creatinine value, and protein intake. The main outcome was all-cause mortality.

Results: A total of 26 patients died during the follow-up period of 36 months. The Kaplan-Meier analysis revealed that the group whose score was 0–1 had a significant lower survival rate than the groups with higher (2–4) PEW scores ($P < 0.0001$). In multivariate analysis, hazard ratios (HRs) were 0.214 (confidence interval (CI) 0.068–0.610, $P < 0.005$) between group 1 and group 4, 0.176 (0.054–0.510, $P < 0.005$) between group 2 and group 4, and 0.249 (CI 0.054–0.857) between group 3 and group 4.

Conclusions: A new simple PEW score predicts the survival of MHD patients and may help to better identify subgroups of MHD patients with a high mortality rate.

Keywords: Malnutrition, Protein-energy wasting, All-cause mortality, Hemodialysis

Background

The mortality rate of maintenance hemodialysis (MHD) patients is still higher than the mortality rate of overall general population of Japan as a whole [1]. Since protein-energy wasting (PEW) is a strong predictors of MHD patient mortality [2–4], evaluation of their nutritional status is essential to optimally manage MHD patients.

Many different mechanisms, including muscle wasting, abnormalities of gastrointestinal, hematopoietic, and immune systems, and abnormal activation of the inflammatory process, have been reported to explain the link between PEW and mortality in HD patients [5, 6]. Clinical assessment of the nutritional status of MHD patients is mandatory, but since there is no single gold-standard marker, easily measured in a reproducible manner that is unaffected by confounding conditions [7], MHD patients must be screened for PEW by various measures on a regular clinical practice [8, 9].

The aim of this study was to evaluate a simple PEW score, based on various clinical and biological values, as a predictor for mortality of MHD patients.

Methods

Subjects and protocol

This was a retrospective cohort study conducted at a single center in Japan. The subjects were recruited from among patients who had been routinely dialyzed via an arteriovenous fistula in the dialysis unit of the Shinjuku Ishikawa Clinic for at least 6 months by the procedure [10]. The Institutional Review Board of the Shinjuku Ishikawa Clinic approved all study protocols (I-02-2015), and they were performed in accordance with the Declaration of Helsinki guidelines regarding ethical principles

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for medical research involving human subjects. Informed consent was obtained from every subject.

MHD patients with malignancy, active inflammation, liver cirrhosis, gastrointestinal bleeding, or severe illness were excluded from participation as subjects. The patients who were enrolled as subjects ($n = 254$) had been undergoing stable regular HD with a bicarbonate dialysate. The underlying disease was chronic glomerulonephritis in 95 cases, diabetic nephropathy in 74 cases, hypertensive nephrosclerosis in 52 cases, polycystic kidney disease in 18 cases, chronic pyeonephritis in 9 cases, and in 6 cases, the underlying disease was unknown.

All patients were on thrice-weekly HD therapy. Blood pressure (BP) was measured with a mercury sphygmomanometer with the patient in the supine position after resting for 10 to 15 min, and mean values for the 1-month period preceding enrollment were used in the statistical analysis. Dry weight was targeted to achieve a normotensive edema-free state. Information regarding previous cardiovascular disease and smoking status was collected from the patient's medical records. Diabetes was defined as a presence of diabetes and/or a fasting plasma glucose concentration >126 mg/dl or HbA1c value >6.5 % or prescription of glucose-lowering agent.

Laboratory and nutritional parameters

Blood was sampled before dialysis session after an overnight fast. Serum urea nitrogen, creatinine, albumin, and C-reactive protein (CRP) levels were measured with an autoanalyzer (Hitachi Co., Tokyo, Japan) by standard laboratory methods. Body mass index (BMI) was calculated by dividing body weight in kilograms by the square of their height in meters and was expressed in kilogram per square meter. Urea kinetics were assessed by measuring a blood-based dialysis parameter, Kt/V [11], and the mean value of the three measurements during each of the 3 months before the start of the study was used in the analysis.

We defined the PEW score as the grading of 1 selected item in each of the four categories as previously reported [12]: (1) serum albumin, (2) BMI, (3) predialysis serum creatinine normalized by body surface area (SCr/BSA), and (4) normalized protein catabolic rate (nPCR). The threshold values are shown in Table 1 and are serum albumin, 3.8 g/dL; BMI, 23 kg/m^2; SCr/BSA, 520 mmol/L/m^2; and nPNA, 0.8 g/kg/day. The nPCR was used as an indirect indicator of protein intake and was calculated by using the formula previously reported [13]. BSA was estimated by the Du Bois formula [14]. The 540 mmol/L/m^2 threshold value for the SCr/BSA variable was selected based on the results of a receiver operating characteristics (ROC) curve analysis (Fig. 1).

Table 1 Definition of protein-energy wasting score

Serum albumin (g/dL)	>3.8
Body mass index (kg/m^2)	>23
SCr/BSA (μmol/L/m^2)	>520
nPCR (g/kg/day)	>0.8

Scr/BSA predialysis serum creatinine/body surface area, *nPCR* normalized protein catabolic rate

Study outcome

Data for endpoints were obtained from hospital charts. The primary endpoint of the study was all-cause mortality during the follow-up period from January 1, 2011 to December 31, 2014. The vital status of the subjects was determined by searching the electronic dialysis records. Patients were censored if they were alive on December 31, 2014.

Statistical analysis

Normally distributed, unpaired continuous values were expressed as means ± SD and compared by performing an analysis of variance. Nonparametric values were expressed as median values and compared by performing the Kruskal-Wallis test. Categorical values were expressed as percentages and compared by performing the Fisher's exact test. We considered some variables whose P value was <0.10 according to the results of the univariate logistic regression analyses, in addition to gender, presence of diabetes and history of myocardial infarction, peripheral vascular disease and stroke, CRP, and Kt/V.

The survival analysis was based on the Kaplan-Meier curve with subjects censored for death. A log-rank test was used to compare the survival rates of two groups. A multivariate Cox proportional hazard model with adjustment for multivariate factors was used to evaluate mortality risk. Results were expressed as a hazard ratio (HR) with 95 % confidence interval (CI). A P value <0.05 was considered to be statistically significant. All statistical analyses were performed by using the SAS version 9.2 software program (SAS Institute Inc., Cary, NC, USA) for Windows personal computers.

Results

The baseline characteristics of the study cohort according to PEW score are shown in Table 2. The study cohort consisted of 70 females and 184 males. The mean age of the 254 subjects was 59.3 ± 12.8 years, and their mean dialysis vintage was 11.0 ± 7.7 years. Their mean BMI was 22.3 ± 3.7 kg/m^2. All of the subjects had an arteriovenous fistula. None of the subjects had residual renal function (urine volume ≥100 mL/day). Diabetes was present in 31.1 %. History of stroke, myocardial infarction or peripheral vascular disease was present in 17.7, 7.1, and 4.7, respectively. The mean dialysis dose was 1.45 as a single pool Kt/V, and mean protein intake was 0.93 g/kg/day. The moderate and severe wasting

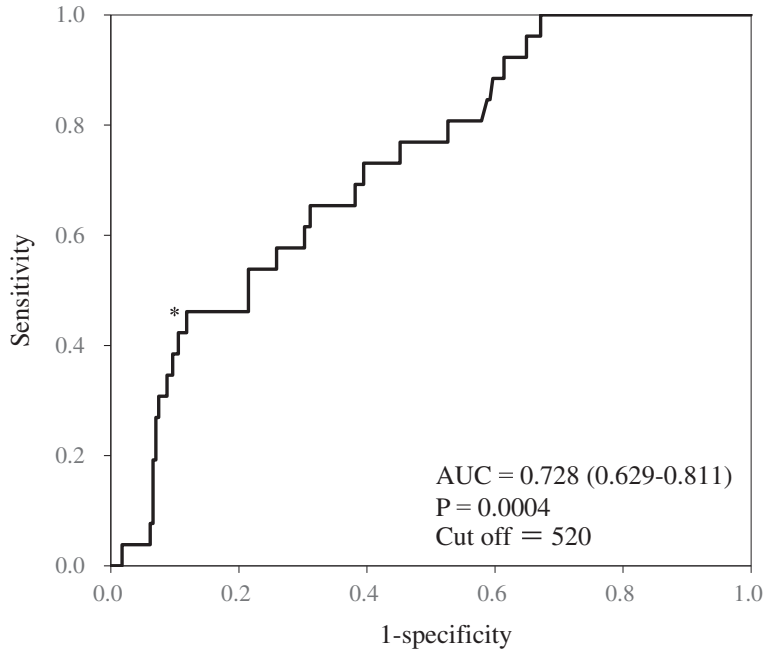

Fig. 1 Receiver operating characteristic (ROC) curve analysis to determine the optimal cut-off value of serum creatinine/body surface area (Scr/BSA) for detecting mortality rate

groups consisted of 118 patients, e.g., 46.5 % of the cohort.

During the follow-up period of 36-months, a total of 26 patients died, and a cardiovascular death occurred in 8 patients. The Kaplan-Meier analysis revealed that the group with a PEW score of 0–1 (S1) ($n = 36$) had a significant lower survival rate than the groups with higher (2–4) PEW scores (S2, S3, S4) ($P < 0.0001$, Fig. 2). Table 3 shows the survival predictive factors in MHD patients. History of peripheral vascular disease was only survival predictive factor ($P < 0.005$).

The HR was 0.239 (CI 0.088–0.607, $P < 0.005$) between the severe wasting group (score 0–1; group 1) and the normal nutritional status group (score 4; group 4), 0.131 (0.041–0.361, $P < 0.001$) between the moderate wasting group (score 2; group 2) and the normal nutritional

Table 2 Baseline characteristics of the study subjects according to the PEW score

		Scores 0–1	Score 2	Score 3	Score 4
Clinical and laboratory parameters	All	Severe wasting	Moderate wasting	Slight wasting	Normal nutritional status
Number of patients	254	36	82	97	39
Number of deaths	26	11	7	5	3
Age (years)	59.3 ± 12.8	66.2 ± 11.5**	63.1 ± 11.8**	55.9 ± 12.6	53.6 ± 11.3
Male (%)	72.8 %	75.0 %	69.5 %	70.1 %	84.6 %
Dry weight (kg)	60.2 ± 13.5	56.2 ± 9.6**	56.8 ± 14.0**	60.4 ± 13.2**	70.7 ± 10.2
BSA (m^2)	1.65 ± 0.20	1.59 ± 0.17**	1.59 ± 0.21**	1.65 ± 0.20**	1.78 ± 0.16
Dialysis vintage (years)	11.0 ± 7.7	8.8 ± 7.7	11.0 ± 6.9	12.0 ± 8.1	10.3 ± 7.8
C-reactive protein (mg/dL)	0.29 ± 0.41	0.31 ± 0.29	0.31 ± 0.43	0.26 ± 0.31	0.33 ± 0.63
Serum albumin (g/dL)	3.88 ± 0.32	3.60 ± 0.28**	3.76 ± 0.29**	3.98 ± 0.27**	4.13 ± 0.19
SCr (μmol/L)	1050 ± 217	808 ± 185**	999 ± 178**	1120 ± 173*	1208 ± 200
SCr/BSA (μmol/L/m^2)	641 ± 121	507 ± 101**	632 ± 110*	684 ± 108	678 ± 99
Kt/V	1.45 ± 0.24	1.39 ± 0.23	1.47 ± 0.24*	1.49 ± 0.24*	1.38 ± 0.19
nPCR (g protein/kg/day)	0.93 ± 0.17	0.78 ± 0.14**	0.88 ± 0.16**	1.00 ± 0.16	1.01 ± 0.13

BSA body surface area, *Scr* serum creatinine, *Kt/V* single pool urea kinetics, *nPCR* normalized protein catabolic rate
*$P < 0.001$ versus score 4; **$P < 0.05$ versus score 4

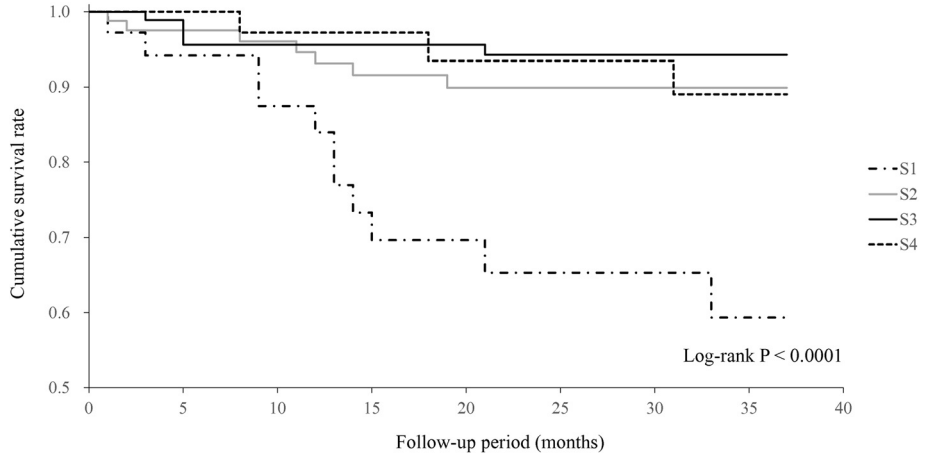

Fig. 2 Kaplan-Meier curve survival analysis according to protein-energy wasting (PEW) score. S1 (score of 0 or 1) had severe wasting, S2 (score of 2) had moderate wasting, S3 (score of 3) had slight wasting, and S4 (score of 4) had a normal nutritional status

status group (group 4) and 0.207 (CI 0.047–0.664) between slight wasting group (score 3; group 3) and the normal nutritional status group (score 4; group 4) (data not shown). In multivariate analysis, HRs were respectively 0.214 (CI 0.068–0.610, $P < 0.005$) between group 1 and group 4, 0.176 (0.054–0.510, $P < 0.005$) between group 2 and group 4, and 0.249 (CI 0.054–0.857) between group 3 and group 4 (Table 3).

Discussion

We evaluated a simple PEW score based on simple available clinical parameters and demonstrated that it can predict survival of MHD patients. Although an abnormal nutritional status is frequently reported in MHD patients, there is no single nutrition parameter that can predict PEW [15–17]. We hope to take advantage of a simple nutritional marker to make recommendations and improve the outcomes of MHD patients.

Table 3 Survival predictive factors by Cox proportional hazard models

Patients characteristics and PEW score	HR	CI min	CI max	*P* value
Gender (male/female)	1.313	0.437	4.970	
Diabetes	0.676	0.231	1.761	
Myocardial infarction	0.920	0.208	3.321	
Peripheral vascular disease	8.762	2.522	27.134	<0.005
Stroke	0.995	0.308	2.639	
C-reactive protein	1.009	0.570	1.102	
KT/V	0.176	0.019	1.766	
Score 2 versus 0–1	0.214	0.068	0.610	<0.005
Score 3 versus 0–1	0.176	0.054	0.510	<0.005
Score 4 versus 0–1	0.249	0.054	0.857	<0.05

HR hazard ratio, *CI* confidence interval, *Kt/V* single pool urea kinetics

Hypoalbuminemia is a strong predictor of mortality in MHD patients. Kalantar-Zadeh et al. [18] showed that a serum albumin levels <3.8 g/dL in MHD patients were correlated with increased cardiovascular deaths independent of demographic, clinical, or laboratory characteristics, and Malfra et al. [19] demonstrated that a serum albumin level <3.7 g/dL was a strong predictor for mortality of dialysis patients. A 10-year cohort study reported an increased risk of death in HD patients with serum albumin level below 3.8 g/dL [20]. However, Friedman and Fadem [21] have recently shown that serum albumin levels should be used cautiously as a nutritional marker in patients with chronic kidney disease (CKD) because low serum albumin levels in HD patients are known to be associated with both malnutrition and inflammation.

A lower prevalence of inflammation has been reported in dialysis patients in Asian countries, including Japan and Korea, and the lower prevalence may depend on genetic factors and cultural habits, including diet intake [22, 23]. Baseline obesity in MHD patients appears to be paradoxically associated with a higher survival rate [24, 25]. Asian-Americans have been reported to have a much lower adjusted relative mortality rate than Caucasian dialysis patients, but Asian-Americans have a significantly lower BMI [26]. The International Society of Renal Nutrition and Metabolism (ISRNM) proposed a BMI of less than 23 as a diagnostic criterion for PEW in patients with chronic kidney disease (CKD), but they have not expanded their recommendation to South Asian CKD patients [27].

nPCR is associated with dietary protein intake [28], and nPCR has been reported to be an independent predictor of mortality in MHD patients [29]. A study by Chandna et al. showed a substantial drop in the nPCR in CKD patients in the 3 months preceding the start of

dialysis [30]. The K/DOQI clinical practice guidelines recommended a daily protein intake of 1.2–1.3 g/kg/day for MHD patients and contributed to the low nPCR levels [31]. Lukowsky et al. found that a decrease in nPCR of over 0.2 g/kg/day within a 3-month period was associated with increased risk of death [4].

Because no single parameter provides a comprehensive and conclusive assessment of nutritional status, a collective evaluation of multiple nutritional markers is recommended by K/DOQI guidelines [32]. A recent panel of experts suggested using markers from four different categories (biochemistry, body mass, muscle mass, and dietary intake) for the clinical diagnosis of PEW [27]. Three out of those four categories should be selected but at least one biochemical indicator must be included. However, to the best our knowledge, their combination has not yet been tested for assessing nutritional status in HD patients.

Moreau et al. [12] developed a simple PEW score including one parameter from each major group generally identified to interfere in nutritional status: (1) biological parameters, (2) body composition, (3) muscle mass, and (4) nutrient intake. It seems important to add laboratory information, such as serum levels of albumin and Cr to other clinical information, such as BMI [19]. Since muscle mass, which is the major part of the body strongly associated with survival, is difficult to assess, they chose to use predialysis Scr values normalized by BSA. The Scr/BSA reflects the difference in Western and Asian and may differ by Cr intake and metabolism. This may be the reason why Cr is not used routinely. Indeed, SCr/BSA gave a better fit in the Cox model than raw Scr [12]. Finally, they added information on nutrient intake by entering in the score the protein intake as estimated by normalized protein nitrogen appearance (nPNA also called nPCR). This value belongs to all current international recommendations and can be calculated easily by using dialysis generator software. Added to the model, it improved survival prediction over albumin alone.

It should be noted that the score by itself was not better than the four parameters added into the model as separate variables [12]. That was not unexpected because information given by the score is already brought by all variables included into the score. However, we believe that this is the interest of this score to encourage the dialysis staff to pay attention to all these variables taken together. The PEW score could be obtained within minutes at bedside, with no additional equipment, at no expense and therefore be added to the arsenal of patient's general record and follow-up. The final patient classification we obtained corresponds well to the published literature on the prevalence of nutritional disorders in dialysis patients: 37 % of patients present with moderate and 19 % with severe impairment in their nutritional status [33].

Conclusions

The routine use of the simple nutritional score may help to identify PEW in MHD patients. Further studies may be needed to verify the robustness of the PEW score in Asian populations because of the differences in body composition and clinical practice.

Competing interests

The authors have no conflicts of interest to declare.

Authors' contributions

Kobayashi planned the study, searched the literature, assessed studies, extracted data, analyzed data and prepared article. Suzuki searched the literature, assessed studies and assisted in article preparation. Ueda assisted in the data analysis. Tanaka searched the literature and assisted in article preparation. Nitta planned the study, analyzed the data and assisted in article preparation. All authors read and approved the final manuscript.

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