

Bioelectrical Impedance Analysis-derived Phase Angle as a Determinant of Protein-energy Wasting, Frailty, and Worse Outcome in Maintenance Hemodialysis Patients: retrospective cohort study

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Abstract

Background

To evaluate the relationship between phase angle (PA) measured by bioimpedance electrical analysis and protein-energy wasting (PEW) or frailty, and its impact on 2-year mortality in patients with hemodialysis (HD).

Methods

This retrospective observational study included 116 adult HD patients (35% female, 64 ± 12 years of age) in a single dialysis center. Patients were classified according to the PA quartiles into four groups (quartile 1, lowest; quartile 4, highest). International Society of Renal Nutrition and Metabolism (ISRNM) criteria and Japanese version of Cardiovascular Health Study (J-CHS) criteria were used to identify PEW and frailty.

Results

The lower PA group was associated with a greater risk of PEW (35% vs. 24% vs. 21% vs. 3%; $p = 0.032$), frailty (59% vs. 40% vs. 21% vs. 3%; $p < 0.001$). In multivariate logistic regression analysis, the first quartile group ($PA < 3.7^\circ$) was at a significantly greater risk of both PEW and frailty compared with the fourth quartile group ($PA \geq 5.0^\circ$) after adjusting for other confounding factors. In addition, Kaplan-Meier survival analysis showed a worse survival rate in the first quartile group than in the third quartile group ($PA 4.2-5.0^\circ$) and fourth quartile group (Log-rank test $p = 0.05$, respectively). The Cox regression analysis found that the first quartile group had a significantly greater risk of all-cause mortality than the patients in the fourth quartile group (HR 5.461 95%CI 1.180–25.280).

Conclusions

Lower PA was associated with a greater risk of PEW and frailty and found to have prognostic significance for 2-year all-cause mortality in HD patients.

Introduction

Protein-energy wasting (PEW), defined as the loss of somatic and circulation body protein and energy reserves, is a common complication among hemodialysis (HD) patients.¹ Frailty can be defined as a biological syndrome of decreased reserve and resistance to stressors that results from cumulative decline across multiple physiological systems and is highly prevalent in patients with HD. HD patients accompanied by PEW or frailty are associated with accelerated biological ageing, and an increased risk

of death.^{1,2} A more recent proposal suggests early screening and diagnosis of PEW and frailty are important in clinical practice among HD patients.¹⁻³

Bioimpedance electrical analysis (BIA) is a noninvasive, validated assessment of body composition and hydration status in patients with chronic kidney disease (CKD) and in HD patients. Phase angle (PA) measured by BIA reflects the resistance and reaction of the body in response to the application of an external current. A lower PA level indicates decreased cell integrity or cell death, whereas higher PA suggests large quantities of intact cell membranes.⁴ Moreover, PA has been recently found to be a predictor of survival in many clinical situations.⁵ However, the prognostic significance of PA for PEW, frailty, and all-cause mortality remains uncertain among HD patients. The main purpose of the present study was to assess the validity of PA in predicting PEW, frailty, and all-cause mortality in patients with HD.

Methods

Subjects

The present study included 116 adult HD patients (35% female, 64 ± 12 years of age) from a single unit of the Meisei-kai Toyo Clinic Yachimata, Chiba, Japan between January 2018 and March 2018. Patients were eligible to participate if they were over 18 years of age, had received maintenance HD at least 3 times per week for more than 6 months, and had no contraindications for BIA including patients with pacemakers or were not limbless. The exclusion criteria of present study were comorbidities malignant tumors and recent surgical intervention that might influence nutritional or functional status. Study collaborators interviewed patients before or during a HD session, obtained recent clinical and laboratory data from medical records, and measured muscle strength and physical performance prior to the start of the HD session. In addition, study collaborators measured the body composition using a BIA after a midweek dialysis session.

Clinical outcomes and other criteria

All-cause mortality during 2-year follow-up periods were collected using medical records or the hospital database. Cardiovascular (CV) risk score was calculated using new risk model developed by Japan Dialysis Outcomes and Practice Patterns Study (J-DOPPS)⁶. This CV risk model had a more accurate dose-dependent association with observed CV events than the Framingham risk score among HD patients. The J-DOPPS CV risk model contained only six variables: age, diabetes mellitus, history of CV events, dialysis time per session, phosphorus level, and albumin level, ranging from 0 to 20 points with higher scores reflecting greater risk of CV events.

Diagnosis Of Protein-energy Wasting

International Society of Renal Nutrition and Metabolism (ISRNM) criteria were used to identify PEW,⁷ which has been described elsewhere.⁸ PEW was scored as the grading of 1 selected item in each of the four categories of wasting syndrome as follows: serum albumin, body mass index (BMI) or unintentional weight loss, pre-dialysis serum creatinine normalized by the body surface area (sCr/BSA), and normalized protein nitrogen appearance (nPNA). The cutoff values were as follows: serum albumin, 3.8 g/dL; BMI, 23 kg/m² or unintentional weight loss (5% over 3 months or 10% over 6 months); sCr/BSA, 380 µmol/L/m²; and nPNA, 0.8 g/kg per day. BSA was estimated by the following formula:

$$\text{Body surface (cm}^2\text{)} = [0.425 \times (\text{weight})] \times [0.725 \times (\text{height})] \times 0.007184.$$

A lower value than the cutoff value was scored as 1 point, and the PEW score was calculated as the sum of the four-item score. PEW was defined as a PEW score \geq 3 points.

Diagnosis Of Frailty

Frailty was evaluated based on the Japanese version of Cardiovascular Health Study (J-CHS) criteria consisting of 5 components: weight loss, exhaustion, low physical activity, slowness and weakness.⁹ (1) Weight loss was evaluated using the question "Have you lost 2 kg or more in the past 6 months?". (2) Exhaustion was measured using the question: "In the past 2 weeks, have you felt tired without a reason?". (3) Low physical activity was measured using the two questions: "Do you engage in moderate levels of physical exercise or sports aimed at health?", and "Do you engage in low levels of physical exercise aimed at health?". (4) Slowness was measured using usual gait speed: patients were asked to 5 m-walk at their comfortable pace using any walking aids to maintain balance and function. (5) Weakness was evaluated by measuring handgrip strength in the sitting position. The J-CHS comprises the following: (1) Weight loss: 1 point for "yes" to the question; (2) Exhaustion: 1 point for "yes" to the question; (3) Low physical activity: 1 point for "no" to both questions; (4) Slowness: 1 point if gait speed < 1.0 m/s; (5) Weakness: 1 point if handgrip strength < 26 kg in men and < 18 kg in women. Summing up the J-CHS scores, we calculated a total J-CHS score; a cut off of \geq 3 was used to identify frailty.

Bioelectrical Impedance Analysis

The seca mBCA515 (seca®, Hamburg, Germany), an integrated platform with a handrail system was used. Electrodes were placed in the ascending handrail, of which two were chosen depending on the subject's height. Another two pairs of electrodes contacted the soles of the feet. The prediction equations for total body water, and extracellular water (ECW) were validated by a prior study.¹⁰ Resistance (R), the opposition of an ionic solution in both intra and extracellular spaces and reactance (Xc), representing the capacitance from cell membranes values obtained at 5 and 50 kHz for different body segments were used in the prediction equations. BIA was performed under standardized conditions according to the manufacturer's protocol. The PA was calculated using the following equation:

PA (degree) = $\arctan(Xc/R) \times (180/\pi)$, is related to body cell mass and soft tissue composition.

Quartiles were obtained for the PA (25th, 3.7°; 50th, 4.2°; 75th, 5.0), and the patients were classified in four groups: first quartile group (PA < 3.7°), second quartile group (3.7 ≤ PA < 4.2°), third quartile group (4.2 ≤ PA < 5.0°), and fourth quartile group (PA ≥ 5.0°).

To examine the PA values adjusting for age, sex, and body mass index, the PA values were converted into s.d. score by the following equation:

Standard deviation score (SDS) = $(X - \text{average } X)/\text{s.d.}$

Where X is the observed value, average X is the mean of the normal value at the respective age, sex, and body mass index, and s.d. is the standard deviation from the mean.

Statistical Analysis

Continuous variables are expressed at mean ± standard deviation and as counts and percentages as appropriate. For the comparison of continuous variables among PA groups, one-way analysis of variance was used, and for categorical variables, the Pearson chi-square test was performed. To adjust for effects due to potential confounders for PA, multivariate logistic regression models of PEW, and frailty were performed, and odds ratios (ORs) and 95% confidence intervals (95% CI) were determined. A Kaplan-Meier survival analysis with the log-rank significance test, and univariate Cox regression analysis were performed. The PA ≥ 5.0° (fourth quartile group) was considered the reference for this analysis. In the analysis for the CV event risk, we compared the CV event risk model score among PA groups using Kruskal-Wallis test. Statistical analyses were performed using SPSS software, version 21, and in all statistical calculations, a two-tailed p < 0.05 was considered statistically significant.

Results

The average age of HD patients in the analysis was 64 ± 12 years; 35% of patients were female; dialysis vintage was 7 ± 6 years; PA score was 4.3 ± 1.1°, and PA SDS was -1.1 ± 1.8; 65% of the patients had PA SDS < -1 s.d., and 17% had PA SDS between -1 and 0 s.d. and 18% had PA SDS > 0 s.d..

The clinical characteristics of the study population according PA groups are shown in Table 1. HD patients with lower PA were significantly older, had a higher proportion of females, and lower BMI, serum creatinine level, albumin level, modified creatinine index, and handgrip strength. Our findings demonstrated that 35% of patients in the first quartile group, 24% in the second quartile group, 21% in the third quartile group, and 3% in the fourth quartile group exhibited PEW based on ISRNM criteria (p = 0.032). Moreover, the prevalence of frailty was 59% in the first quartile group, 40% in the second quartile group, 21% in the third quartile group, and 3% in the fourth quartile group (p < 0.001). The remaining clinical variables were not significantly different among PA groups.

Table 1
Clinical characteristics.

	First quartile group (PA < 3.7) n = 29	Second quartile group (3.7 ≤ PA < 4.2) n = 29	Third quartile group (4.2 ≤ PA < 5.0) n = 29	Fourth quartile group (PA ≥ 5.0) n = 29	P-value among groups
Age, years	58 ± 12	62 ± 11	67 ± 11	70 ± 10	< 0.001
Female, n (%)	4 (14)	9 (31)	13 (43)	15 (52)	0.015
BMI, kg/m ²	24.6 ± 3.0	25.1 ± 5.6	24.6 ± 4.5	20.5 ± 3.2	< 0.001
HD vintage, years	6.0 ± 4.7	7.3 ± 4.3	7.1 ± 5.5	6.9 ± 7.6	0.833
Hypertension, n (%)	27 (93)	27 (93)	29 (97)	28(97)	0.864
Diabetes mellitus, n (%)	11 (38)	17 (59)	20(67)	17 (59)	0.147
Hb, g/dL	10.9 ± 0.9	10.7 ± 1.5	10.2 ± 1.0	10.2 ± 1.2	0.054
sCr, mg/dL	13.4 ± 2.4	11.6 ± 1.9	9.7 ± 2.1	8.8 ± 1.9	< 0.001
Alb, mg/dL	3.9 ± 0.3	3.7 ± 0.3	3.7 ± 0.2	3.6 ± 0.4	0.005
P, pg/dL	6.0 ± 1.6	5.6 ± 1.1	5.8 ± 1.2	5.2 ± 1.2	0.104
Ca, mg/dL	8.9 ± 0.6	9.0 ± 0.7	8.8 ± 0.8	8.6 ± 0.7	0.129
K, mg/dL	5.0 ± 0.7	4.9 ± 0.5	4.8 ± 0.8	5.1 ± 0.7	0.308
CRP, mg/dL	0.20 ± 0.20	0.26 ± 0.33	0.33 ± 0.44	0.58 ± 0.88	0.045
Kt/V	1.3 ± 0.2	1.3 ± 0.2	1.3 ± 0.2	1.4 ± 0.3	0.667
nPNA, g/kg/day	0.9 ± 0.2	0.8 ± 0.1	0.8 ± 0.1	0.8 ± 0.2	0.088
EAT-10, points	0.9 ± 2.8	0.6 ± 2.8	1.3 ± 2.9	1.6 ± 4.4	0.702
SNAQ, points	14.8 ± 1.6	15.0 ± 1.5	14.2 ± 3.2	14.4 ± 2.6	0.563
Modified creatinine index, mg/kg/day	24.3 ± 2.4	22.0 ± 2.8	20.5 ± 2.1	19.5 ± 1.9	< 0.001
PA, °	5.7 ± 0.5	4.7 ± 0.2	3.9 ± 0.2	3.0 ± 0.6	< 0.001

BMI body mass index, HD hemodialysis, Hb hemoglobin, sCr serum creatinine, BUN blood urine nitrogen, Alb albumin, P phosphorus, Ca calcium, K potassium, CRP C-reactive protein, KT/V K-dialyzer clearance of urea, t dialysis time, V volume of distribution of urea, nPNA normalized protein nitrogen appearance, SNAQ Simplified Nutritional Appetite Questionnaire, PA phase angle, SDS standard deviation score, ECT extracellular water, TBW total body water, SPPB short physical performance battery.

	First quartile group (PA < 3.7) n = 29	Second quartile group (3.7 ≤ PA < 4.2) n = 29	Third quartile group (4.2 ≤ PA < 5.0) n = 29	Fourth quartile group (PA ≥ 5.0) n = 29	P-value among groups
PA SDS	1.08 ± 1.14	-0.56 ± 1.07	-1.77 ± 1.17	-2.15 ± 1.60	< 0.001
ECW/TBW	41.4 ± 2.2	45.3 ± 2.0	48.0 ± 2.7	51.6 ± 0.7	< 0.001
Handgrip strength, kg	32.9 ± 7.6	26.3 ± 7.7	22.0 ± 7.4	17.8 ± 6.2	< 0.001
SPPB score, points	11.6 ± 0.9	11.0 ± 1.8	10.9 ± 1.7	10.3 ± 2.1	0.055
BMI body mass index, HD hemodialysis, Hb hemoglobin, sCr serum creatinine, BUN blood urine nitrogen, Alb albumin, P phosphorus, Ca calcium, K potassium, CRP C-reactive protein, KT/V K-dialyzer clearance of urea, t dialysis time, V volume of distribution of urea, nPNA normalized protein nitrogen appearance, SNAQ Simplified Nutritional Appetite Questionnaire, PA phase angle, SDS standard deviation score, ECT extracellular water, TBW total body water, SPPB short physical performance battery.					

Table 2 shows the results of logistic regression analysis of the predictive variables related to PEW in HD patients. The univariate logistic regression analysis showed that the first quartile group (OR 14.737, 95%CI 1.740-124.827, p = 0.014) and second quartile group (OR 8.909, 95%CI 1.019–77.905, p = 0.048) were at significantly greater risk of PEW compared with fourth quartile group. Moreover, multivariate logistic regression analysis showed that first quartile group remained a predictor of PEW after adjusting for other confounding factors, compared to the fourth quartile group (model 2: OR 10.967, 95%CI 1.124-107.014, p = 0.039; model 3: OR 11.099, 95%CI 1.101-111.926, p = 0.041).

Table 2
Logistic regression analysis of the predictive variables related to PEW in hemodialysis patients.

	Odds ratio	95% CI	P-value
Model 1	1 (ref)	0.819–65.114	0.075
Fourth quartile group (PA ≥ 5.0°)	7.304	1.019–77.905	0.048
Third quartile group (PA 4.2 to < 5.0°)	8.909	1.740-124.827	0.014
Second quartile group (PA 3.7 to < 4.2°)	14.737		
First quartile group (PA < 3.7°)			
Model 2	1 (ref)	0.954–92.786	0.055
Fourth quartile group (PA ≥ 5.0°)	9.410	0.847–81.215	0.069
Third quartile group (PA 4.2 to < 5.0°)	8.294	1.124-107.014	0.039
Second quartile group (PA 3.7 to < 4.2°)	10.967		
First quartile group (PA < 3.7°)			
Model 3	1 (ref)	0.581–64.777	0.131
Fourth quartile group (PA ≥ 5.0°)	6.137	0.757–76.454	0.085
Third quartile group (PA 4.2 to < 5.0°)	7.607	1.101-111.926	0.041
Second quartile group (PA 3.7 to < 4.2°)	11.099		
First quartile group (PA < 3.7°)			
Model 1: PA class			
Model 2: PA class + age, sex, HD vintage			
Model 3: PA class + age, sex, HD vintage, diabetes mellitus, hemoglobin, C-reactive protein			
PA, phase angle; HD, hemodialysis			

Table 3 shows the results of logistic regression analysis of the predictive variables associated with frailty in HD patients. In univariate logistic regression analysis, the first quartile group (OR 40.727, 95%CI 4.805-345.219, p = 0.001) and the second quartile group (OR17.111, 95%CI 2.031-144.136, p = 0.009) were at a significantly greater risk of frailty compared with the 4th quartile group. In multivariate analysis, the first quartile group (OR 36.770, 95%CI 3.906–346.140, p = 0.002) and the second quartile group (OR 16.525, 95%CI 1.867-146.285, p = 0.012) remained predictors of frailty after adjusting for age, sex, and HD vintage compared with fourth quartile group (model 2). Similarly, the first quartile group (OR 15.612, 95%CI 1.194–204.120, p = 0.036) was significantly associated with frailty after adjusting for age, sex, HD vintage, diabetes mellitus, hemoglobin level, grip strength than the fourth quartile group (model 3).

Table 3
Logistic regression analysis of the predictive variables related to frailty in hemodialysis patients.

	Odds ratio	95% CI	P-value
Model 1	1 (ref)	0.819–65.114	0.075
Fourth quartile group (PA $\geq 5.0^\circ$)	7.304	2.031-144.136	0.009
Third quartile group (PA 4.2 to $< 5.0^\circ$)	17.111	4.805-345.219	0.001
Second quartile group (PA 3.7 to $< 4.2^\circ$)	40.727		
First quartile group (PA $< 3.7^\circ$)			
Model 2	1 (ref)	0.791–65.885	0.080
Fourth quartile group (PA $\geq 5.0^\circ$)	7.219	1.867-146.285	0.012
Third quartile group (PA 4.2 to $< 5.0^\circ$)	16.525	3.906–346.140	0.002
Second quartile group (PA 3.7 to $< 4.2^\circ$)	36.770		
First quartile group (PA $< 3.7^\circ$)			
Model 3	1 (ref)	0.383–61.527	0.223
Fourth quartile group (PA $\geq 5.0^\circ$)	4.855	0.803-108.108	0.074
Third quartile group (PA 4.2 to $< 5.0^\circ$)	9.315	1.194–204.120	0.036
Second quartile group (PA 3.7 to $< 4.2^\circ$)	15.612		
First quartile group (PA $< 3.7^\circ$)			
Model 1: PA class			
Model 2: PA class + age, sex, HD vintage			
Model 3: PA class + age, sex, HD vintage, diabetes mellitus, hemoglobin, C-reactive protein			
PA, phase angle; HD, hemodialysis			

During the 2-year follow-up, 19 deaths (16%) occurred among the present study patients. The Kaplan-Meier survival analysis showed a worse survival rate in the first quartile group compared with that in the third quartile and fourth quartile groups (Log-rank test, $p = 0.030$ and $p = 0.009$) (Fig. 1). Cox regression analysis including only PA groups demonstrated that the first quartile group was at a significantly greater risk of all-cause mortality compared to fourth quartile group (Hazard ratio 5.461, 95%CI 1.180–25.280, $p = 0.030$), as well as frailty (Hazard ratio 2.464, 95% CI 1.025–5.922, $p = 0.044$) and PEW (Hazard ratio 4.579, 95%CI 1.901–11.031, $p = 0.001$) (Table 4). Moreover, age, body mass index, Cr, albumin, calcium, C-reactive protein, and handgrip strength were also associated with all-cause mortality among HD patients.

Multivariate Cox regression analyses were not performed because of the small number of all-cause deaths in the present study.

Table 4

Predictors of all-cause mortality in univariate Cox regression analysis in hemodialysis patients.

	Odds ratio	95% CI	P-value
Age [every 1 year increase]	1.083	1.035–1.133	0.001
Female [reference male]	0.800	0.307–2.081	0.647
BMI [every 1 kg/m ² increase]	0.850	0.749–0.965	0.012
HD vintage [every 1 year increase]	0.948	0.865–1.040	0.257
Diabetes mellitus	0.782	0.326–1.879	0.583
Hb [every 1 g/dL increase]	0.886	0.613–1.282	0.521
sCr [every 1 mg/dL increase]	0.749	0.624–0.899	0.002
Alb [every 1 mg/dL increase]	0.254	0.078–0.832	0.024
P [every 1 pg/dL increase]	0.792	0.557–1.126	0.194
Ca [every 1 mg/dL increase]	0.442	0.230–0.847	0.014
K [every 1 mg/dL increase]	0.753	0.400–1.416	0.378
CRP [every 1 mg/dL increase]	1.729	1.166–2.563	0.006
Kt/V [every 1 unit increase]	0.193	0.036–1.041	0.056
nPNA [every 1 g/kg/day increase]	0.173	0.010–3.088	0.233
EAT-10 [every 1 point increase]	1.032	0.914–1.164	0.613
SNAQ [every 1 point increase]	1.078	0.857–1.356	0.520
Modified creatinine index [each 1 mg/kg/day increase]	0.799	0.689–0.927	0.003
PA quartile class	1 (ref)	0.265–9.476	0.615
Fourth quartile group (PA ≥ 5.0°)	1.583	0.644–15.807	0.155
Third quartile group (PA 4.2 to < 5.0°)	3.190	1.180–25.280	0.030
Second quartile group (PA 3.7 to < 4.2°)	5.461		
First quartile group (PA < 3.7°)			

BMI body mass index, HD hemodialysis, Hb hemoglobin, sCr serum creatinine, BUN blood urine nitrogen, Alb albumin, P phosphorus, Ca calcium, K potassium, CRP C-reactive protein, KT/V K-dialyzer clearance of urea, t dialysis time, V volume of distribution of urea, nPNA normalized protein nitrogen appearance, SNAQ Simplified Nutritional Appetite Questionnaire, PA phase angle, SDS standard deviation score, ECT extracellular water, TBW total body water, SPPB short physical performance battery, PEW protein energy wasting.

	Odds ratio	95% CI	P-value
ECW/TBW [every 1 unit increase]	1.105	0.984–1.240	0.090
Handgrip strength [every 1 kg increase]	0.930	0.879–0.983	0.011
SPPB score [every 1 point]	0.832	0.663–1.043	0.111
PEW	4.579	1.901–11.031	0.001
Frailty	2.464	1.025–5.922	0.044

BMI body mass index, HD hemodialysis, Hb hemoglobin, sCr serum creatinine, BUN blood urine nitrogen, Alb albumin, P phosphorus, Ca calcium, K potassium, CRP C-reactive protein, KT/V K-dialyzer clearance of urea, t dialysis time, V volume of distribution of urea, nPNA normalized protein nitrogen appearance, SNAQ Simplified Nutritional Appetite Questionnaire, PA phase angle, SDS standard deviation score, ECT extracellular water, TBW total body water, SPPB short physical performance battery, PEW protein energy wasting.

Figure 2 shows the relationship between phase angle and four quartile subgroups of CV risk model score among HD patients. The first quartile and second quartile groups were significantly higher CV risk score compared with fourth quartile groups ($p = 0.001$ and $p = 0.003$).

Discussion

PEW and frailty are common complication associated with functional decline, and worse prognosis in HD patients.^{7,11,12} The present study demonstrated that a low PA measured by BIA as a simple alternative screening tool is an independent predictor of PEW and frailty as well as worse outcome in HD patients.

The biological meaning of the PA remains uncertain; however, it seems to reflect body cell mass, or cell membrane function.⁵ Increased ECW is associated with poor nutritional status, and reduced total body water (TBW), an indicator of lower body cellular mass. Therefore, an increase in the ECW/TBW may be explained by malnutrition or skeletal muscle mass loss, as well as by fluid overload status.¹³ Our findings also demonstrated that lower PA tended to have a significantly higher ECW/TBW ratio among HD patients. Moreover, a low PA showed a tendency for association with lower BMI, hand grip strength, and higher ECW-TBW and C-reactive protein levels, which are included in the PEW or frailty diagnostic criteria and were consistent with results from prior studies.^{14,15} Moreover, a lower PA correlated with PEW, the highest OR in the multivariate models was 10.967 and 11.099 in the first quartile group compared to the reference group (fourth quartile group). Ruperto et al. subsequently confirmed that $PA < 4^\circ$ was an independent risk predictor for HD patients with PEW,¹⁶ and is in line with our results. Thus, we also recognized that a low PA was an important indicator of malnutrition and hydration in HD patients. In addition, we showed that a low PA was associated with low TBW as an indicator of skeletal muscle mass in HD patients. Moreover, low PA was a greater risk factor for frailty even after adjusting for other clinical indicators. Several prior studies have reported an association between low PA and frailty phenomenon in older subjects,^{17,18} or cardiac surgery patients,¹⁹ although very few studies have focused on HD

patients.²⁰ In the present study, we also determined that low PA is a representative comprehensive biomarker of malnutrition, skeletal muscle wasting, frailty, as well as hydration in HD patients.

Few studies have evaluated the association between PA and mortality or CV event in HD patients, however, we demonstrated that first quartile group had a greater risk of all-cause mortality and higher CV risk score. More recently, Bansal et al. and Segall et al. demonstrated that PA was significantly associated with mortality in CKD patients²¹ and HD patients.²² Beberashvili et al. reported that each 1° increase in PA was associated with a reduced risk of all-cause death in HD patients (Hazard ratio 0.65, 95%CI 0.48–0.81).¹⁴ Moreover, Varan et al. reported a significant increase in the risk of death among HD patients with PA < 4°, even after adjustment of several nutritional indicators.²³ In present study, the first quartile group (PA < 3.7°) was associated with worse outcome and higher CV risk score, which is nearly consistent with the results of Varan et al.²³ However, given the relatively small number of patients and few events in present study, we could not perform multivariate analyses to identify factors related to all-cause mortality or CV event.

Thus, we propose that regular screening would be essential to monitor the progression of PEW or frailty over time, and to avoid the development of the vicious cycle of PEW or frailty. Regular screening may help in the early identification of patients accompanied by PEW or frailty when they are the most treatable as well as provide prognostic information. We therefore suggest that PA could be a useful, simple indicator to predict PEW, frailty, and all-cause mortality among HD patients.

Study Limitations

Several limitations of our present study should be noted. First, our findings are limited to a relatively small number of patients at a single HD center, though most of the results are comparable to those from prior clinical studies. The small sample size study may not allow sufficient statistical power, therefore we could not perform the multivariate cox regression analyses in order to evaluate the significant prognostic factors among HD patients; further studies are therefore needed to assess outcomes. Second, it has suggested that PEW is cachexia and should be termed kidney disease cachexia as a continuum with PEW first followed by cachexia. Our findings are limited to a small number of patients with severe PEW or kidney disease cachexia, therefore we could not assess the relationship between phase angle and severity of PEW including kidney disease cachexia. Future research needs to evaluate the diagnostic, prognostic, and predictive accuracy of phase angle on severe PEW or kidney disease cachexia status.

In conclusion, PA could be a useful, simple indicator to predict PEW, frailty, and all-cause mortality among HD patients. Lower PA was associated with a greater risk of PEW and frailty and found to have prognostic significance for all-cause mortality in hemodialysis patients.

List Of Abbreviations

BIA, Bioimpedance electrical analysis; BMI, body mass index; BSA, body surface area; CKD, chronic kidney disease; CV, Cardiovascular; ECW, extracellular water; HD, hemodialysis; ISRNM, International Society of Renal Nutrition and Metabolism; J-CHS, Japanese version of Cardiovascular Health Study; J-DOPPS, Japan Dialysis Outcomes and Practice Patterns Study; nPNA, normalized protein nitrogen appearance; ORs, odds ratios; PA, Phase angle; PEW, Protein-energy wasting; SDS, standard deviation score; TBW, total body water.

Declarations

Ethics approval and consent to participate

This study was approved by the institutional review board at the Meisei-kai Toyo Clinic, Chiba, Japan, and informed consent was obtained before data collection. The ethics committee granted approval to waive the requirement for written informed consent for the additional follow-up from 2018–2020 because of the retrospective nature of this study.

Consent for publication

Not applicable

Availability of data and materials

The data that support the findings of the study are not publicly available due to privacy restrictions (the data contains information that could compromise the privacy of the study participants).

Competing interests

The authors declare that they have no competing interests

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Author's contribution

SM provided the research design, data measurements and analysis, and wrote the manuscript. OM and KH provided the interpretation of data. TT provided the substantially contributed the analysis and revised the manuscript. SK, IH, and TY participated in the research design and substantially contributed to the study concept. All authors read and approved the final manuscript.

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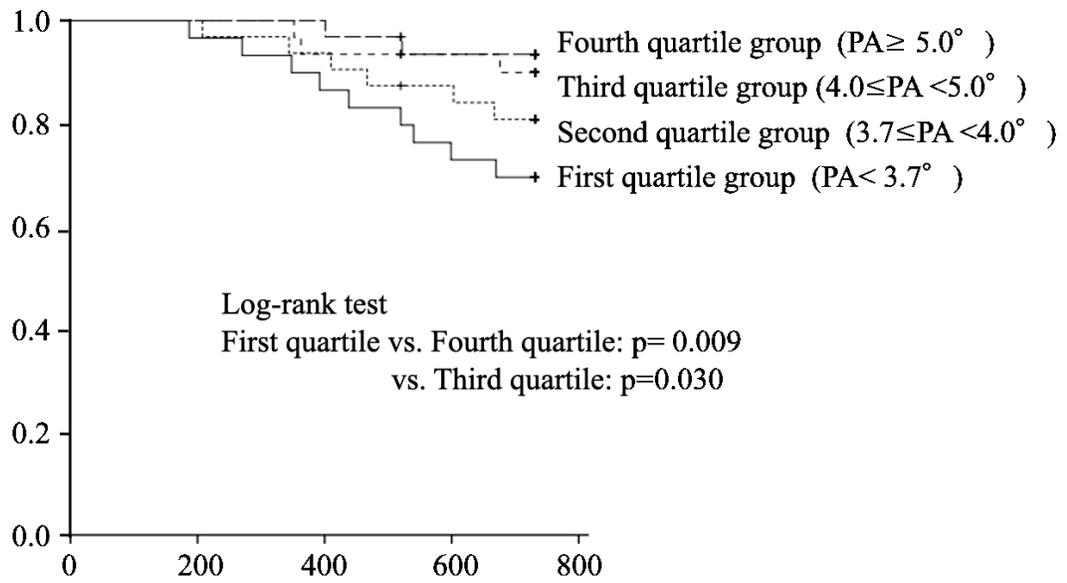
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Figures



Number of risk

First quartile group	29	27	24	20	18
Second quartile group	29	29	28	24	22
Third quartile group	29	29	27	24	23
Fourth quartile group	29	29	29	26	25

Figure 1

Kaplan-Meier curves at 2-year for all-cause mortality.

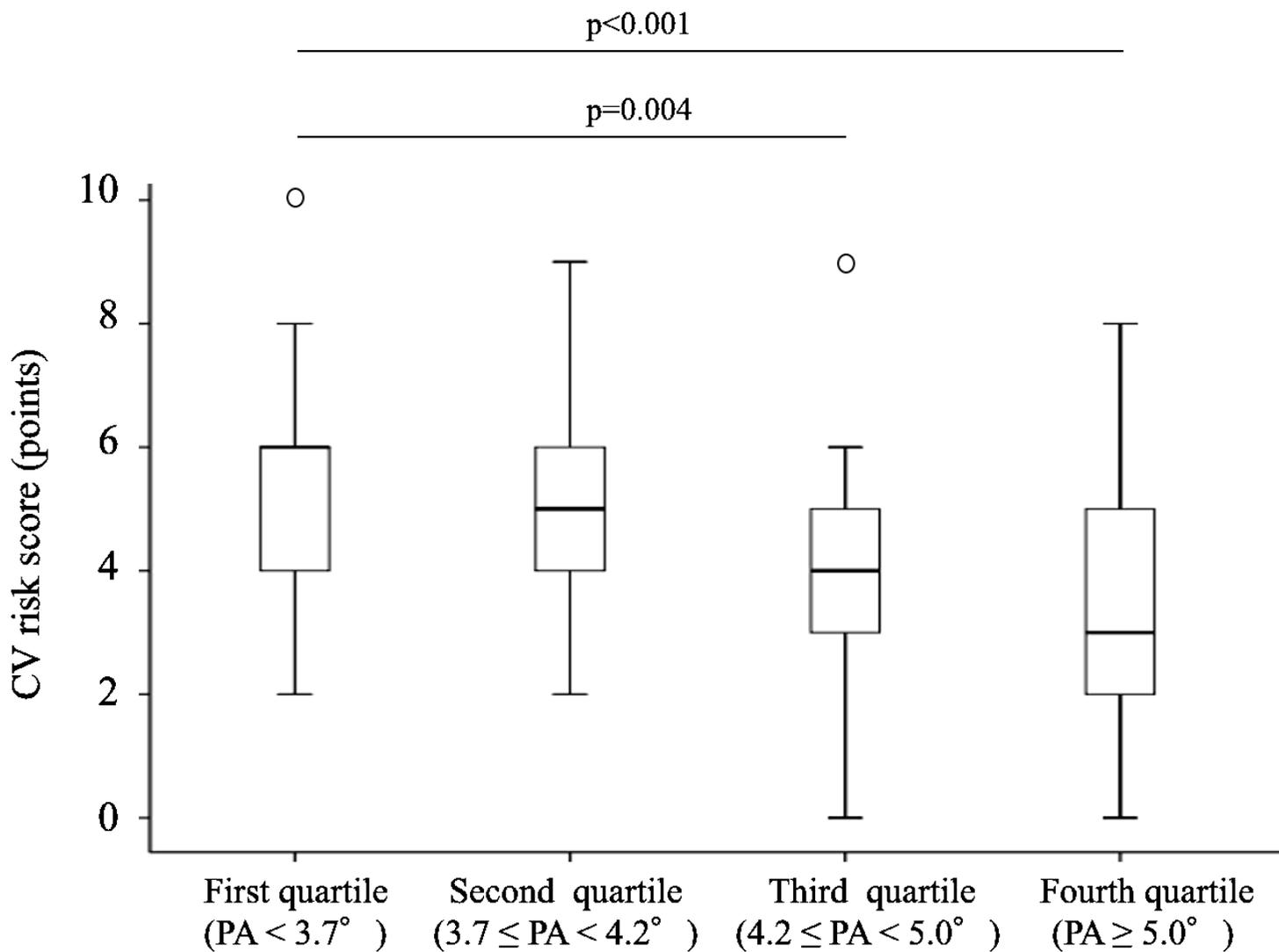


Figure 2

Phase angle and CV risk model score developed by J-DOPPS among HD patients