



## Applied nutritional investigation

# Predicting clinical outcomes using phase angle as assessed by bioelectrical impedance analysis in maintenance hemodialysis patients



Jung-ho Shin M.D., Ph.D., Chae Rim Kim M.D., Ki Hyun Park M.D.,  
Jin Ho Hwang M.D., Su Hyun Kim M.D., Ph.D.\*

Division of Nephrology, Department of Internal Medicine, Chung-Ang University Hospital, Seoul, Korea

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## ABSTRACT

**Objective:** Protein–energy wasting is common in patients on hemodialysis and is an independent risk factor for adverse events. The aim of this study was to retrospectively investigate whether phase angle (PA), known as a nutritional marker, can predict various clinical outcomes in patients with end-stage renal disease (ESRD) who are receiving hemodialysis.

**Methods:** Using bioelectrical impedance analysis (BIA), PA was obtained every 6 mo, and patients were divided into two groups according to baseline PA: group A included patients with  $PA \geq 4.5^\circ$ , and group B included patients with  $PA < 4.5^\circ$ .

**Results:** We followed 142 patients for a median of 29 mo (12–42 mo). We found that a decrease in PA was associated with an increased risk for death that persisted after adjusting for age, sex, and comorbidities (hazard ratio [HR], 0.56; 95% confidence interval [CI], 0.33–0.97). Cardiovascular events were not associated with PA ( $P = 0.685$ ). We found that PA predicted the occurrence of infection, independent of age, sex, and comorbidities (HR, 0.65; 95% CI, 0.45–0.94). Although levels of hemoglobin did not differ between groups during the study period, patients in group B received higher doses of erythropoiesis-stimulating agents and intravenous iron than those in group A ( $P = 0.004$  and  $0.044$ , respectively). In longitudinal analyses, we did not find increases in PA over time in patients who had a mean dialysis adequacy  $\geq 1.4$ , daily protein catabolic rate  $\geq 1.2$  g/kg, or total carbon dioxide level  $\geq 22$  mmol/L.

**Conclusions:** PA assessed in a simple manner using BIA provides practical information to predict clinical outcomes in ESRD patients on maintenance hemodialysis.

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## Introduction

Protein–energy wasting (PEW) is a syndrome characterized by decreased body stores of protein and energy sources [1]. This condition is prevalent in patients with chronic kidney disease (CKD), especially those with end-stage renal disease (ESRD)

requiring maintenance dialysis. Although the prevalence of this condition varies depending on the assessment method, previous surveys have reported that 18 to 75% of dialysis patients are malnourished [2,3]. PEW is an important determinant of mortality and morbidity in patients on dialysis. Several studies have demonstrated that it is closely associated with increased rates of hospitalization and death [4,5]. Furthermore, studies have shown that it may be a contributing factor in the development of cardiovascular disease (CVD) and infection [6,7], which are major concerns in patients with CKD. However, improving nutritional status is challenging in patients with ESRD who are undergoing maintenance dialysis because PEW can be induced by several factors including not only inadequate diet, but also uremia-induced alterations such as increased energy expenditure,

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\* Corresponding author. Tel.: +82 2 6299 1440; fax: +82 2 6299 2626.

E-mail address: [sh76so@cau.ac.kr](mailto:sh76so@cau.ac.kr) (S. H. Kim).

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chronic inflammation, metabolic acidosis, endocrine disorders, comorbid conditions, and dialysis per se [7]. Accordingly, an integrated approach ranging from identification of malnourished patients to treatment of wasting is required.

Although several clinical, nutritional, and biochemical parameters have been used, no single parameter has been established to provide reliable information on the overall nutritional status patients on maintenance dialysis [1,8]. Bioelectrical impedance analysis (BIA), which is a fast, noninvasive, and reproducible technique, appears to be a promising tool for monitoring the nutritional status of these patients [9]. Among various parameters obtained from BIA, phase angle (PA) is assumed to indicate cell integrity and shows a good correlation with other nutritional parameters [10,11]. Moreover, previous studies have confirmed that PA can be used as a nutritional indicator to predict mortality in ESRD patients on maintenance dialysis [11–13]. Nevertheless, although studies have shown an association between PA and mortality, the correlations between PA and other important clinical outcomes such as CVD, infection, or anemia are unclear.

In this study, we retrospectively evaluated whether low PA was associated with the occurrence of CVD, infection, and mortality among ESRD patients receiving maintenance hemodialysis. Differences in anemia management according to PA also were explored. Furthermore, we assessed longitudinal changes in PA over time with a specific focus on whether optimizing CKD management can improve PA in patients on hemodialysis.

## Materials and methods

### Patients

Patients with ESRD who are receiving outpatient maintenance hemodialysis at Chung-Ang University Hospital in Seoul, Korea, were recruited between October 2011 and October 2015. The study included adult patients who had been on hemodialysis for  $\geq 3$  mo. Among 147 patients on maintenance hemodialysis,

body composition was evaluated in 145 patients. We excluded three patients for the following reasons: One did not have baseline laboratory data and two were followed up for  $< 1$  mo after body composition analysis. Thus, the study included 142 ESRD patients on maintenance hemodialysis.

After examination of body composition, patients were followed up until death, hospitalization due to cardiovascular events or infection, or loss to follow-up. This study was approved by the Institutional Review Board of Chung-Ang University Hospital.

### Data collection

All demographic and clinical data were collected from electronic medical records. Age, sex, height, body weight, causes of ESRD, duration of renal replacement therapy, types of dialysis access, and intradialytic weight gain in kilograms were collected. Comorbidity burden was assessed using the modified Charlson comorbidity index (CCI) [14]. Age was excluded to calculate the modified CCI, but was used for adjustment in multivariate analyses. Additionally, information regarding the use of erythropoiesis-stimulating agents (ESAs) and intravenous (IV) iron was reviewed.

All blood samples were drawn under fasting conditions before the first-in-week dialysis sessions, except postdialysis blood urea nitrogen (BUN). Dialysis adequacy ( $Kt/V_{\text{urea}}$ ) and protein catabolic rate (PCR) also were estimated using a single pool urea kinetic model [15]. Laboratory results were measured every 6 mo during the study period.

### Body composition analysis

Body composition was assessed every 6 mo using a multifrequency BIA device (InBody S10, Biospace, Seoul, South Korea), with the measurement performed within 30 min after the start of dialysis on the day of the first dialysis session after the weekend [16]. Eight electrodes were placed on the surface of the thumb, fingers of the hand, and ball of the foot and heel with the patient in the supine position. Using reactance (Xc) and resistance (R) obtained from BIA at 50 kHz, PA was estimated by the following formula:  $PA (^{\circ}) = \arctangent(Xc/R) \times (180^{\circ}/\pi)$ . Patients were divided into two groups based on the initial PA value: group A included patients who had a  $PA \geq 4.5^{\circ}$  and group B included patients with a  $PA < 4.5^{\circ}$  [17,18].

### Outcome measurements

The correlation of PA with several variables known to be associated with nutritional conditions was evaluated. We then explored whether PA could

**Table 1**  
Baseline characteristics of ESRD patients receiving maintenance hemodialysis

Variables	Total (N = 142)	Group A* (n = 77)	Group B* (n = 65)	P Value
Age, y	64 $\pm$ 13	61 $\pm$ 12	67 $\pm$ 13	0.007
Male, n (%)	75 (52.8)	51 (66.2)	24 (36.9)	<0.001
Dialysis duration, mo	22 (5–57)	19 (7–46)	25 (3–64)	0.954
Diabetes, n (%)	81 (55.9)	36 (46.8)	45 (69.2)	0.007
Charlson comorbidity index	7 $\pm$ 2	6 $\pm$ 2	7 $\pm$ 2	0.006
Central venous access, n (%)	5 (3.5)	0 (0.0)	5 (7.7)	0.018
BMI, kg/m <sup>2</sup>	22.5 (20.4–24.9)	23.4 (21.5–25.8)	21.1 (19.4–23.4)	0.018
Intradialytic weight gain, kg	1.8 $\pm$ 0.7	1.9 $\pm$ 0.7	1.6 $\pm$ 0.7	0.011
Hemoglobin, g/dL	10.6 $\pm$ 1	10.8 $\pm$ 0.9	10.5 $\pm$ 1.1	0.071
Albumin, g/dL	3.8 $\pm$ 0.3	3.9 $\pm$ 0.3	3.7 $\pm$ 0.4	<0.001
Glucose, mg/dL	153.0 (124–242.3)	140.0 (118.5–195.5)	180.0 (134–274)	0.002
BUN, mg/dL	68.6 $\pm$ 18.9	73.3 $\pm$ 18.6	63 $\pm$ 18	0.001
Creatinine, mg/dL	9.0 $\pm$ 2.6	10.1 $\pm$ 2.6	7.6 $\pm$ 2.1	<0.001
Total cholesterol, mg/dL	139.5 (121.5–163.3)	143.0 (123–168)	135.0 (118.5–161)	0.347
Triacylglycerol, mg/dL	108.5 (81.8–149.3)	114.0 (85.5–150.5)	105.0 (76–143)	0.759
LDL cholesterol, mg/dL	72.5 (61.8–95)	75.0 (61.5–96.5)	72.0 (62–93)	0.314
Uric acid, mg/dL	7.9 $\pm$ 1.6	8.4 $\pm$ 1.5	7.2 $\pm$ 1.5	<0.001
CRP, mg/L	1.9 (0.8–4.5)	1.8 (0.8–3.9)	2.0 (0.8–4.8)	0.200
TCO <sub>2</sub> , mEq/L	23.1 $\pm$ 3.1	22.6 $\pm$ 2.9	23.6 $\pm$ 3.2	0.063
Intact PTH, pg/mL	214.3 (132.2–351.6)	240.3 (151.4–378.4)	201.5 (115.1–304.2)	0.690
Calcium, mg/dL	8.6 $\pm$ 0.7	8.7 $\pm$ 0.7	8.5 $\pm$ 0.7	0.277
Phosphorus, mg/dL	5.0 $\pm$ 1.5	5.4 $\pm$ 1.5	4.6 $\pm$ 1.4	0.001
$Kt/V_{\text{urea}}$	1.6 $\pm$ 0.3	1.6 $\pm$ 0.3	1.7 $\pm$ 0.2	0.076
PCR, g/kg daily	1.0 $\pm$ 0.2	1.0 $\pm$ 0.2	0.9 $\pm$ 0.2	0.072
PA, $^{\circ}$	4.6 $\pm$ 1.0	5.3 $\pm$ 0.7	3.7 $\pm$ 0.6	<0.001

BMI, body mass index; BUN, blood urea nitrogen; CRP, C-reactive protein; LDL, low-density lipoprotein; PA, phase angle; PCR, protein catabolic rate; PTH, parathyroid hormone; TCO<sub>2</sub>, total carbon dioxide

Continuous variables are expressed as mean value  $\pm$  standard deviation or median (interquartile range), and categorical variables are expressed as number (percentage)

\* Group A included patients who had a  $PA \geq 4.5^{\circ}$  and group B included patients with a  $PA < 4.5^{\circ}$ .

predict various clinical outcomes in patients on maintenance hemodialysis with respect to all-cause death, hospitalization due to cardiovascular events or infection, and anemia. Cardiovascular events referred to cardiac death, acute coronary syndrome, cerebrovascular accident, acute exacerbation of heart failure, or acute peripheral artery occlusion. Additionally, differences in anemia management according to hemoglobin level and doses of ESAs and IV iron were compared between groups A and B. Dose of ESA was converted to the equivalent units of epoetin alfa, and then weekly dose of ESA was computed. Monthly IV iron was used in comparisons.

We also determined whether improvement in management quality could positively influence PA over time. We classified patients into two subgroups according to mean values of  $Kt/V_{urea}$ , PCR, and total carbon dioxide content ( $TCO_2$ ) during the study period as follows: Those with  $Kt/V_{urea} \geq 1.4$  or  $< 1.4$ ; daily PCR  $\geq 1.2$  or  $< 1.2$  g/kg; and those with  $TCO_2 \geq 22$  or  $< 22$  mEq/L. Thereafter, changes in the PA over time were compared between each subgroup. Those cutoff values conform to the recommendations of the National Kidney Foundation and the International Society of Renal Nutrition and Metabolism [19,20].

#### Statistical analysis

Continuous variables, expressed as mean  $\pm$  SD or median (interquartile range) when the data showed non-normal distribution, were compared using the independent *t* test or the Wilcoxon rank-sum test. Normality assumption was confirmed through the Shapiro–Wilk test. Categorical variables, expressed as number (percentage), were analyzed using the  $\chi^2$  test. Associations between PA and variables were assessed using Pearson correlation coefficients. Cumulative incidence of death, cardiovascular events, and infection was estimated by the Kaplan–Meier method and was compared between groups using the log-rank test. Univariate and multivariate Cox regression analyses were conducted to determine the hazard ratio (HR) of PA for events. Age, sex, and modified CCI were adjusted for in multivariate analyses. A linear mixed-effect model was used to compare the pattern of PA changes over time according to the quality of management with regard to  $Kt/V_{urea}$ , PCR, and  $TCO_2$ . All statistical analyses were performed using SPSS Statistics version 18.0 (IBM Corp., Armonk, NY, USA). A two-sided *P* value  $< 0.05$  was considered significant.

## Results

### Patient characteristics

In all, 142 patients with ESRD who were receiving maintenance hemodialysis were analyzed in this study, and the mean PA at baseline was  $4.6 \pm 1^\circ$ . Of the 142 patients, 77 (54.2%) and 65 (45.8%) were classified into groups A and B, respectively. Table 1 presents baseline characteristics according to PA group. Patients in group B had a higher comorbidity index and less interdialytic weight gain than those in group A ( $P = 0.006$  and  $0.011$ , respectively). Among baseline laboratory results, serum levels of albumin, glucose, BUN, creatinine, uric acid, and phosphorus differed significantly between the two groups (all  $P < 0.05$ ).

### Correlation analysis

We evaluated the relationship between PA and several variables in the patients on hemodialysis. Aging, female sex, the presence of diabetes, and a high modified CCI were associated with a significantly decreased PA ( $r = -0.29, -0.40, -0.21$ , and  $-0.21$ , respectively; all  $P < 0.05$ ). Body mass index and interdialytic weight gain were also associated with PA ( $r = 0.27$  and  $0.22$ ;  $P = 0.001$  and  $0.009$ ). We found positive correlation between PA and various nutritional parameters such as albumin, BUN, creatinine, uric acid, and phosphorus ( $r = 0.37, 0.31, 0.50, 0.46$ , and  $0.20$ ; all  $P < 0.05$ ). Conversely, glucose and  $TCO_2$  had negative correlation with PA ( $r = -0.22$  and  $-0.19$ ;  $P = 0.009$  and

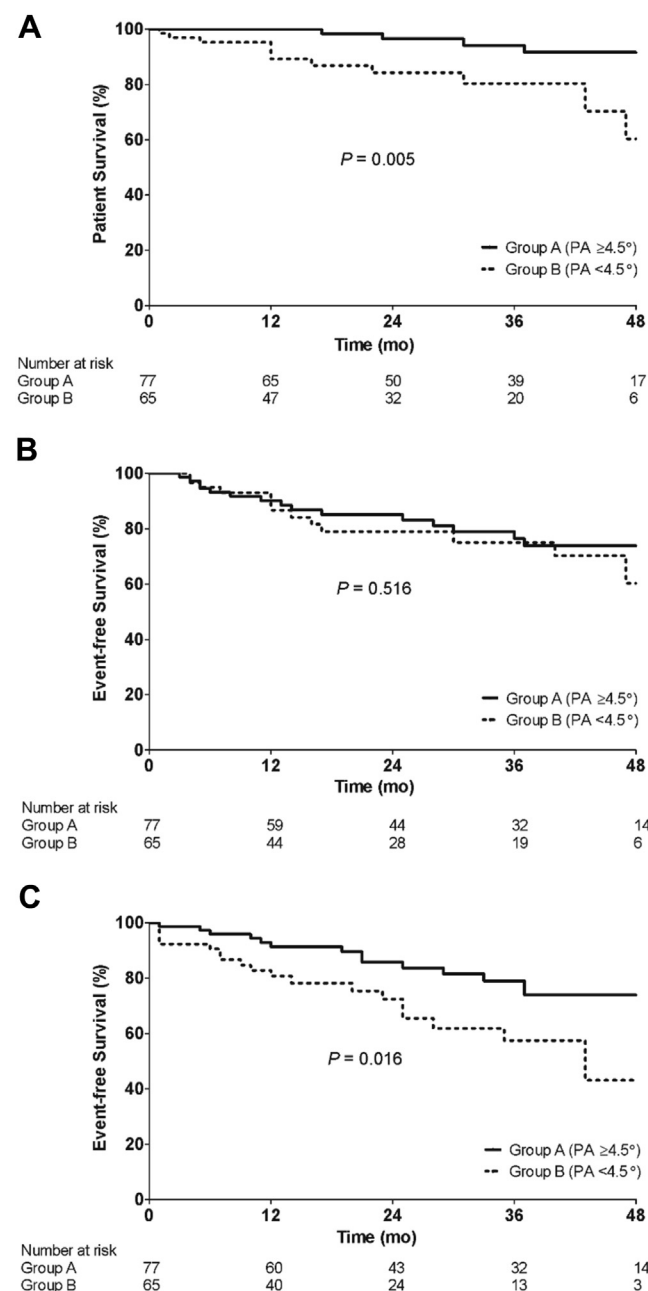
**Table 2**

PA as a predictor for clinical outcomes such as death, cardiovascular events, and infection in ESRD patients on maintenance hemodialysis

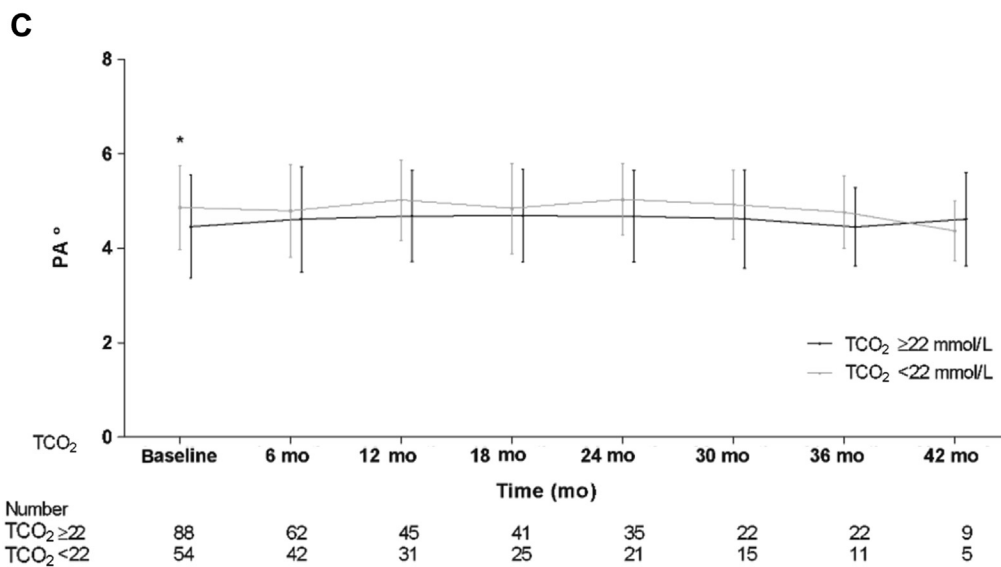
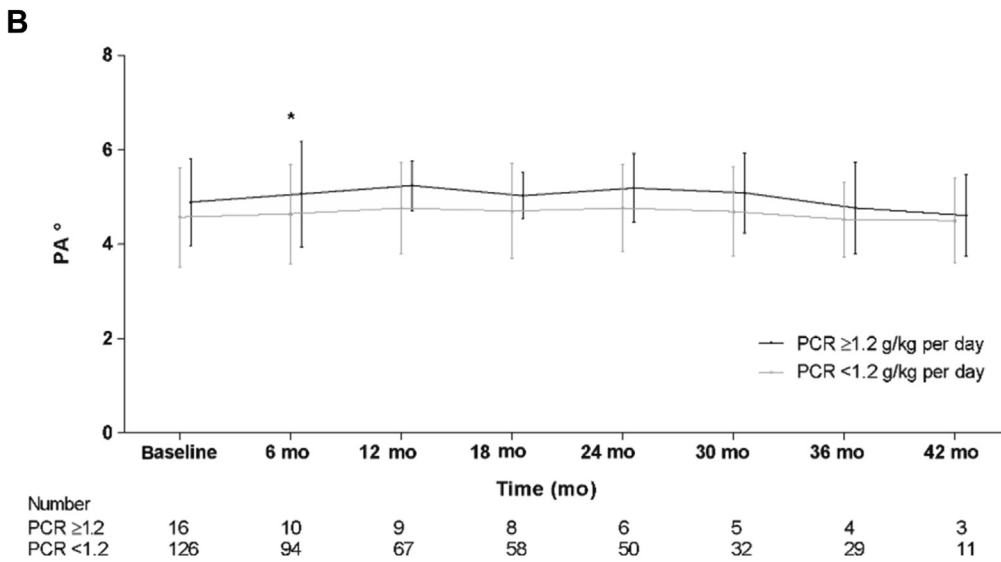
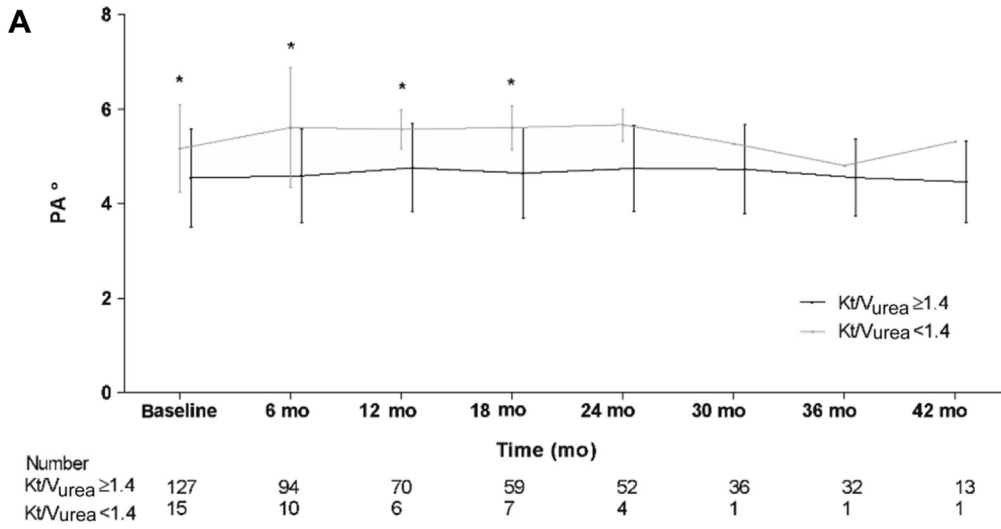
Variables	Univariate HR (95% CI)	<i>P</i> Value	Multivariate* HR (95% CI)	<i>P</i> Value
Death	0.54 (0.32–0.92)	0.023	0.56 (0.33–0.97)	0.039
Cardiovascular events	0.89 (0.61–1.30)	0.544	0.92 (0.43–2.14)	0.917
Infection	0.63 (0.45–0.89)	0.009	0.65 (0.45–0.94)	0.021

CI, confidence interval; ESRD, end-stage renal disease; HR, hazard ratio; PA, phase angle

\* Adjusted for age, sex, and modified Charlson comorbidity index.



**Fig. 1.** Cumulative incidence of all-cause mortality, cardiovascular events, and infection according to PA group. (A) Rate of survival was higher in patients in group A than those in group B ( $P = 0.005$ ). The 3-y survival rate was 94.1 and 80.4% in groups A and B, respectively. (B) Cumulative incidence of cardiovascular events did not differ between PA groups ( $P = 0.516$ ). (C) Infection rate differed between groups A and B ( $P = 0.016$ ). Infection-free survival at 3 y was 79.1% in group A and 57.5% in group B. Group A included patients who had a PA  $\geq 4.5^\circ$ , whereas patients in group B had a PA  $< 4.5^\circ$ .



0.025). Total cholesterol, triacylglycerols, and low-density lipoprotein cholesterol levels were not associated with PA ( $P = 0.369$ ,  $0.929$ , and  $0.257$ , respectively).

### Clinical outcomes

The 142 patients were followed for a median period of 29 mo (12–42 mo), and 15 (10.3%) died during the study period. Cumulative all-cause mortality differed between groups A and B ( $P = 0.005$ ; Fig. 1A). Furthermore, we evaluated PA as a predictor of cardiovascular events and infection, which occurred in 28 (19.3%) and 33 (22.8%) patients, respectively. Cumulative incidence of cardiovascular events did not differ according to PA group, but that of infection did ( $P = 0.516$  and  $0.016$ ; Fig. 1B, C).

HRs for clinical outcomes including all-cause death, cardiovascular events, and infection were estimated (Table 2). In univariate analysis, PA predicted mortality, and this association persisted in multivariate analysis after adjustment for age, sex, and modified CCI (HR, 0.56; 95% confidence interval [CI], 0.33–0.97;  $P = 0.039$ ). Cardiovascular events were not associated with PA in the analyses. In contrast, PA was a predictor of infection independent of age, sex, and modified CCI (HR, 0.65; 95% CI, 0.45–0.94;  $P = 0.021$ ).

Additionally, we compared the levels of hemoglobin every 6 mo between the two groups. Baseline hemoglobin was  $10.8 \pm 0.9$  g/dL in group A and  $10.5 \pm 1.1$  g/dL in group B ( $P = 0.071$ ). There were no significant differences in hemoglobin levels between groups during the study period. However, patients in group B received higher weekly doses of ESAs and monthly doses of IV iron than those in group A (ESAs: 4313 [3245–5439] versus 5647 [4262–7150] U/wk, IV iron: 42 [21–64] versus 58 [31–100] mg/mo;  $P = 0.004$  and  $0.044$ , respectively).

### Longitudinal changes in PA

To determine the factors that can influence PA over time, we analyzed longitudinal data. Body composition analysis was conducted a median of three (one to six) times in the 142 patients during the study period. PA changed over time by  $-0.1^\circ/\text{y}$  (95% CI,  $-0.2$  to  $-0.1^\circ/\text{y}$ ;  $P < 0.001$ ). Age, sex, and modified CCI did not influence the PA slope in this study ( $P = 0.085$ ,  $0.584$ , and  $0.593$ , respectively).

We evaluated whether an improvement in ESRD management increased PA. Figure 2 shows the longitudinal PA results according to the average values of  $\text{Kt}/V_{\text{urea}}$ , PCR, and  $\text{TCO}_2$ . Although there were differences at some time points, we did not find a change in the PA slope according to  $\text{Kt}/V_{\text{urea}} \geq 1.4$ , daily PCR  $\geq 1.2$  g/kg, or  $\text{TCO}_2 \geq 22$  mmol/L ( $P = 0.689$ ,  $0.134$ , and  $0.713$ , respectively).

### Discussion

We retrospectively investigated the usefulness of PA measured by a multifrequency BIA device in ESRD patients on maintenance hemodialysis. PA was associated with age, sex, and comorbidities, and it also had good correlation with several nutritional parameters such as serum albumin, BUN, creatinine, and uric acid. We found that PA was a predictor of all-cause

mortality in the included patients on hemodialysis. Notably, the incidence of infection increased as the PA decreased independent of age, sex, and comorbidities. Furthermore, patients with a lower PA needed higher doses of ESAs and IV iron to maintain proper levels of hemoglobin than those with a higher PA. However, no associations were observed between PA and cardiovascular events. We evaluated whether management quality influenced PA over time and found that there were no significant increases in PA among patients with mean  $\text{Kt}/V_{\text{urea}} \geq 1.4$ , daily PCR  $\geq 1.2$  g/kg, or  $\text{TCO}_2 \geq 22$  mmol/L over the study period.

Multiple studies have reported that PEW is an important predictor of morbidity and mortality in patients with CKD [4,5,21]. Therefore, diagnosis of PEW is crucial in managing these populations, but it is problematic because there is no single gold standard to assess their nutritional status. Several studies have focused on finding more simple and accurate tools to detect PEW [22–24]. BIA is an attractive method because it is safe, easy to use, noninvasive, and relatively low cost. BIA-derived parameters have therefore been investigated as novel nutritional markers, especially in patients with ESRD who are receiving maintenance hemodialysis [25,26]. PA measured by BIA is a particularly promising marker. Although the biological meaning of PA is not well understood, it is assumed to indicate cell membrane function and body cell mass, which reflects nutritional status [10,27]. Various studies using PA, including the present study, have shown an association between PA and several nutritional parameters [11,28,29]. PA may be a useful tool to assess nutritional status. Nevertheless, there are challenges for the practical application of PA measurements. One of them is the lack of consensus on cut-points to be used to identify PEW. Although we used PA of  $4.5^\circ$  as the cutoff value to show the differences according to the PA groups [17,18], the cut-points have been shown to be variable in the different studies [30,31]. Given this problem, studies have made great efforts to determine the reference cutoffs, which can serve for future clinical studies investigating the applications of PA [30,32].

PA has been demonstrated to have prognostic utility in multiple patient populations [11–13,29,33–36]. However, few studies have evaluated the incidence of specific events according to PA. Because CVD and infection are major causes of morbidity and mortality in patients with CKD [37,38], the relationship of PA with these events should be investigated in these populations. Thus, we explored whether PA could predict the occurrence of cardiovascular events and infection requiring hospitalization in addition to all-cause death and found an association between PA and infection, but no association with cardiovascular events.

Malnutrition may play a role in the development of CVD, which can be explained by the malnutrition–inflammation–atherosclerosis syndrome [6]. In contrast to our findings, some studies have reported an association between low PA and increased cardiovascular morbidity [11,39]. However, atherosclerosis is not the only reason for CVD; various complex mechanisms such as vascular calcification can result in cardiovascular complications in patients with CKD [40]. We hypothesized that we did not find an association between PA and cardiovascular

**Fig. 2.** Comparison of PA over time according to average management quality values for  $\text{Kt}/V_{\text{urea}}$ , PCR, and  $\text{TCO}_2$ . We compared the longitudinal data between the groups. The low numbers of patients in the later period might make meaningful comparisons difficult. (A) PA in patients with a mean  $\text{Kt}/V_{\text{urea}} \geq 1.4$  were higher than those in patients with mean  $\text{Kt}/V_{\text{urea}} < 1.4$  at baseline, 6, 12, and 18 mo ( $P = 0.028$ ,  $0.003$ ,  $0.002$ , and  $0.001$ , respectively). However, changes in PA did not differ according to  $\text{Kt}/V_{\text{urea}}$  ( $P = 0.526$ ). (B) We compared PA over time according to mean PCR. Although PA values at 12 mo differed ( $P = 0.037$ ), a mean PCR  $\geq 1.2$  g/kg daily did not increase PA in comparison with a mean daily PCR  $< 1.2$  g/kg ( $P = 0.583$ ). (C) Baseline PA was different between patients with a mean  $\text{TCO}_2 \geq 22$  mEq/L and  $< 22$  mEq/L ( $4.9 \pm 0.9^\circ$  versus  $4.5 \pm 1.1^\circ$ ;  $P = 0.023$ ). In contrast, maintaining  $\text{TCO}_2 \geq 22$  mEq/L in hemodialysis patients did not improve PA over time ( $P = 0.659$ ). BMI, body mass index; BUN, blood urea nitrogen; CRP, C-reactive protein; LDL, low-density lipoprotein; PA, phase angle; PCR, protein catabolic rate;  $\text{TCO}_2$ , total carbon dioxide. \* $P < 0.05$ .

events because other confounding factors than malnutrition affected the occurrence of these events.

PEW alters patient immune function and can increase the risk for infection [41]. In this study, we assessed nutritional status by PA and then demonstrated that ESRD patients with low PA are at increased risk for infection. To our knowledge, few studies have investigated nutritional markers as predictors of infection. A previous study investigated which nutrition-related tests best predicted mortality and morbidity in hemodialysis patients and conducted subgroup analysis with respect to specific outcomes including all-cause mortality, cardiovascular events, and infection [42]. Of the eight tests evaluated, malnutrition inflammation score and albumin predicted infection and mortality. Although we did not compare the prediction power of PA with other nutritional markers, we did compare PA with albumin and found that PA was superior to albumin at predicting death and infection ( $P$  of albumin = 0.909 and 0.972, respectively, in multivariate analyses).

Additionally, we evaluated differences in anemia management according to PA level. Despite similar hemoglobin levels between the PA groups, patients with a low PA received greater weekly doses of ESAs and monthly doses of IV iron than those with a high PA. This can be explained by the association between PEW and inflammation in hemodialysis patients [43]. Previous studies have shown that ESA resistance is related to mortality, and that the malnutrition–inflammation complex is a predictor of ESA resistance [44]. Additionally, recent studies have raised concerns about the relationship between IV iron and adverse outcomes [45]. To date, it remains unclear whether IV iron has toxic effects. However, PEW might act as a confounder when investigating the relationship between higher doses of ESAs, IV iron, and adverse outcomes. The present study found that hemodialysis patients with low PA have poor responsiveness to anemia management including ESAs and IV iron and demonstrated that responsiveness to anemia management in ESRD patients can be assessed simply by PA.

To manage PEW in patients with CKD, the International Society of Renal Nutrition and Metabolism proposed continuous preventive measures including optimizing dietary nutrient intake, appropriate treatment of metabolic disturbances such as metabolic acidosis, systemic inflammation, hormonal deficiencies, and optimized dialytic regimens [19], although evidence of the effectiveness of these preventive measures is lacking. Accordingly, we investigated which measures positively influence nutritional status and then evaluated the effects of optimizing dialysis ( $Kt/V_{\text{urea}} \geq 1.4$ ) and nutrient intake (PCR  $\geq 1.2$  g/kg daily) as well as managing acidosis ( $\text{TCO}_2 \geq 22$  mmol/L) on PA. We did not find that optimized management increased PA over time, although the distinct power might be weakened as the sample size decreased on longer follow-up. A previous study by Beberashvili et al. [46] prospectively observed changes in PA and found that they were associated with daily energy intake and daily protein intake, but not with PCR. Although continuous preventive measures are essential in patients with CKD, further studies are needed to confirm that these can actually prevent PEW.

This study had several limitations that should be taken into consideration. First, we used retrospective data, which could have resulted in information bias. However, we included outpatients undergoing maintenance hemodialysis at our hospital; these patients were followed up twice or thrice weekly, and their medical records were regularly recorded. Thus, missing or incorrect information was likely minimized. The retrospective design also limited our ability to analyze the association between

PA and other nutritional parameters because medical records did not include all subjective or objective data reflecting nutritional status. Second, this was not a controlled trial, which may have resulted in selection bias, especially with regard to analyses of longitudinal PA because the included patients were not equally divided according to  $Kt/V_{\text{urea}}$ , PCR, and  $\text{TCO}_2$ . Further studies are needed to ascertain the effects of management quality on nutrition, but it is hard to conduct a controlled trial with these essential strategies. Third, we included only Korean dialysis patients; thus, the associations between PA and clinical outcomes cannot be generalized to other populations. PA values also may differ between races as well as sexes.

## Conclusion

Results of the present study demonstrated that PA as determined by BIA is associated with markers reflecting nutritional status in ESRD patients undergoing maintenance hemodialysis. Moreover, it can predict clinical outcomes such as infection and all-cause death. Additionally, PA might help estimate responsiveness to anemia management with ESAs and IV iron. There were no significant changes in PA according to quality of management in ESRD patients. These findings have practical clinical implications for the treatment of ESRD patients on maintenance hemodialysis and will help inform further research into ideal nutritional management strategies for patients with CKD.

## References

- [1] Fouque D, Kalantar-Zadeh K, Kopple J, Cano N, Chauveau P, Cuppari L, et al. A proposed nomenclature and diagnostic criteria for protein-energy wasting in acute and chronic kidney disease. *Kidney Int* 2008;73:391–8.
- [2] Kopple JD. McCollum Award Lecture, 1996: protein-energy malnutrition in maintenance dialysis patients. *Am J Clin Nutr* 1997;65:1544–57.
- [3] 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;42:864–81.
- [4] Pifer TB, McCullough KP, Port FK, Goodkin DA, Maroni BJ, Held PJ, et al. Mortality risk in hemodialysis patients and changes in nutritional indicators: DOPPS. *Kidney Int* 2002;62:2238–45.
- [5] Kalantar-Zadeh K, Block G, McAllister CJ, Humphreys MH, Kopple JD. Appetite and inflammation, nutrition, anemia, and clinical outcome in hemodialysis patients. *Am J Clin Nutr* 2004;80:299–307.
- [6] Stenvinkel P, Heimbürger O, Paulter F, Diczfalussy U, Wang T, Berglund L, et al. Strong association between malnutrition, inflammation, and atherosclerosis in chronic renal failure. *Kidney Int* 1999;55:1899–911.
- [7] Carrero JJ, Stenvinkel P, Cuppari L, Ikizler TA, Kalantar-Zadeh K, Kaysen G, et al. Etiology of the protein-energy wasting syndrome in chronic kidney disease: a consensus statement from the International Society of Renal Nutrition and Metabolism (ISRNM). *J Ren Nutr* 2013;23:77–90.
- [8] Druml W. Malnutrition is bad, but how can one detect malnutrition? *Nephrol Dial Transplant* 1997;12:2225–7.
- [9] Toigo G, Aparicio M, Attman PO, Cano N, Cianciarusio B, Engel B, et al. Expert Working Group report on nutrition in adult patients with renal insufficiency (part 1 of 2). *Clin Nutr* 2000;19:197–207.
- [10] Bosy-Westphal A, Danielzik S, Dorhofer RP, Piccoli A, Muller MJ. Patterns of bioelectrical impedance vector distribution by body mass index and age: implications for body-composition analysis. *Am J Clin Nutr* 2005;82:60–8.
- [11] Pupim LB, Caglar K, Hakim RM, Shyr Y, Ikizler TA. Uremic malnutrition is a predictor of death independent of inflammatory status. *Kidney Int* 2004;66:2054–60.
- [12] Johansen KL, Kaysen GA, Young BS, Hung AM, da Silva M, Chertow GM. Longitudinal study of nutritional status, body composition, and physical function in hemodialysis patients. *Am J Clin Nutr* 2003;77:842–6.
- [13] Mushnick R, Fein PA, Mittman N, Goel N, Chattopadhyay J, Avram MM. Relationship of bioelectrical impedance parameters to nutrition and survival in peritoneal dialysis patients. *Kidney Int Suppl* 2003;87:S53–6.
- [14] Beddhu S, Bruns FJ, Saul M, Seddon P, Zeidel ML. A simple comorbidity scale predicts clinical outcomes and costs in dialysis patients. *Am J Med* 2000;108:609–13.
- [15] Depner TA, Daugirdas JT. Equations for normalized protein catabolic rate based on two-point modeling of hemodialysis urea kinetics. *J Am Soc Nephrol* 1996;7:780–5.

- [16] Kyle UG, Bosaeus I, De Lorenzo AD, Deurenberg P, Elia M, Manuel Gomez J, et al. Bioelectrical impedance analysis-part II: Utilization in clinical practice. *Clin Nutr* 2004;23:1430–53.
- [17] Wirth R, Volkert D, Rosler A, Sieber CC, Bauer JM. Bioelectric impedance phase angle is associated with hospital mortality of geriatric patients. *Arch Gerontol Geriatr* 2010;51:290–4.
- [18] Norman K, Stobaus N, Zocher D, Bopsy-Westphal A, Szramek A, Scheufele R, et al. Cutoff percentiles of bioelectrical phase angle predict functionality, quality of life, and mortality in patients with cancer. *Am J Clin Nutr* 2010;92:612–9.
- [19] Ikizler TA, Cano NJ, Franch H, Fouque D, Himmelfarb J, Kalantar-Zadeh K, et al. Prevention and treatment of protein energy wasting in chronic kidney disease patients: a consensus statement by the International Society of Renal Nutrition and Metabolism. *Kidney Int* 2013;84:1096–107.
- [20] National Kidney Foundation. KDOQI Clinical Practice Guideline for Hemodialysis Adequacy: 2015 update. *Am J Kidney Dis* 2015;66:884–930.
- [21] Ikizler TA, Hakim RM. Nutrition in end-stage renal disease. *Kidney Int* 1996;50:343–57.
- [22] Steiber A, Leon JB, Secker D, McCarthy M, McCann L, Serra M, et al. Multicenter study of the validity and reliability of subjective global assessment in the hemodialysis population. *J Ren Nutr* 2007;17:336–42.
- [23] Rambod M, Kovesdy CP, Bross R, Kopple JD, Kalantar-Zadeh K. Association of serum prealbumin and its changes over time with clinical outcomes and survival in patients receiving hemodialysis. *Am J Clin Nutr* 2008;88:1485–94.
- [24] Rambod M, Bross R, Zitterkoph J, Benner D, Pithia J, Colman S, et al. Association of Malnutrition-Inflammation Score with quality of life and mortality in hemodialysis patients: a 5-year prospective cohort study. *Am J Kidney Dis* 2009;53:298–309.
- [25] Chertow GM, Lowrie EG, Wilmore DW, Gonzalez J, Lew NL, Ling J, et al. Nutritional assessment with bioelectrical impedance analysis in maintenance hemodialysis patients. *J Am Soc Nephrol* 1995;6:75–81.
- [26] Madore F, Wuest M, Ethier JH. Nutritional evaluation of hemodialysis patients using an impedance index. *Clin Nephrol* 1994;41:377–82.
- [27] Barbosa-Silva MC, Barros AJ. Bioelectrical impedance analysis in clinical practice: a new perspective on its use beyond body composition equations. *Curr Opin Clin Nutr Metab Care* 2005;8:311–7.
- [28] Oliveira CM, Kubrusly M, Mota RS, Silva CA, Choukroun G, Oliveira VN. The phase angle and mass body cell as markers of nutritional status in hemodialysis patients. *J Ren Nutr* 2010;20:314–20.
- [29] Maggiore Q, Nigrelli S, Ciccarelli C, Grimaldi C, Rossi GA, Michelassi C. Nutritional and prognostic correlates of bioimpedance indexes in hemodialysis patients. *Kidney Int* 1996;50:2103–8.
- [30] Bopsy-Westphal A, Danielzik S, Dorhofer RP, Later W, Wiese S, Muller MJ. Phase angle from bioelectrical impedance analysis: population reference values by age, sex, and body mass index. *JPEN J Parenter Enteral Nutr* 2006;30:309–16.
- [31] Genton L, Graf CE, Karsgaard VL, Kyle UG, Pichard C. Low fat-free mass as a marker of mortality in community-dwelling healthy elderly subjects. *Age Ageing* 2013;42:33–9.
- [32] Kuchnia AJ, Teigen LM, Cole AJ, Mulasi U, Gonzalez MC, Heymsfield SB, et al. Phase angle and impedance ratio: reference cut-points from the United States National Health and Nutrition Examination Survey 1999–2004 from bioimpedance spectroscopy data. *JPEN J Parenter Enteral Nutr*; 2016 [Epub ahead of print].
- [33] Schwenk A, Beisenherz A, Romer K, Kremer G, Salzberger B, Elia M. Phase angle from bioelectrical impedance analysis remains an independent predictive marker in HIV-infected patients in the era of highly active antiretroviral treatment. *Am J Clin Nutr* 2000;72:496–501.
- [34] Selberg O, Selberg D. Norms and correlates of bioimpedance phase angle in healthy human subjects, hospitalized patients, and patients with liver cirrhosis. *Eur J Appl Physiol* 2002;86:509–16.
- [35] Gupta D, Lis CG, Dahlk SL, King J, Vashi PG, Grutsch JF, et al. The relationship between bioelectrical impedance phase angle and subjective global assessment in advanced colorectal cancer. *Nutr J* 2008;7:19.
- [36] Colin-Ramirez E, Castillo-Martinez L, Orea-Tejeda A, Vazquez-Duran M, Rodriguez AE, Keirns-Davis C. Bioelectrical impedance phase angle as a prognostic marker in chronic heart failure. *Nutrition* 2012;28:901–5.
- [37] Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med* 2004;351:1296–305.
- [38] U.S. Renal Data System. USRD 2015 Annual Data Report: epidemiology of kidney disease in the United States. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Disease; 2015.
- [39] Beberashvili I, Azar A, Sinuani I, Shapiro G, Feldman L, Stav K, et al. Bioimpedance phase angle predicts muscle function, quality of life and clinical outcome in maintenance hemodialysis patients. *Eur J Clin Nutr* 2014;68:683–9.
- [40] Giachelli CM. The emerging role of phosphate in vascular calcification. *Kidney Int* 2009;75:890–7.
- [41] Mattern WD, Hak LJ, Lamanna RW, Teasley KM, Laffell MS. Malnutrition, altered immune function, and the risk of infection in maintenance hemodialysis patients. *Am J Kidney Dis* 1982;1:206–18.
- [42] de Roij van Zuijdewijn CL, ter Wee PM, Chapdelaine I, Bots ML, Blankestijn PJ, van den Dorpel MA, et al. A comparison of 8 nutrition-related tests to predict mortality in hemodialysis patients. *J Ren Nutr* 2015;25:412–9.
- [43] Kalantar-Zadeh K, Kopple JD, Block G, Humphreys MH. A malnutrition-inflammation score is correlated with morbidity and mortality in maintenance hemodialysis patients. *Am J Kidney Dis* 2001;38:1251–63.
- [44] Zhang Y, Thamer M, Stefanik K, Kaufman J, Cotter DJ. Epoetin requirements predict mortality in hemodialysis patients. *Am J Kidney Dis* 2004;44:866–76.
- [45] Agarwal R, Kusek JW, Pappas MK. A randomized trial of intravenous and oral iron in chronic kidney disease. *Kidney Int* 2015;88:905–14.
- [46] Beberashvili I, Azar A, Sinuani I, Kadoshi H, Shapiro G, Feldman L, et al. Longitudinal changes in bioimpedance phase angle reflect inverse changes in serum IL-6 levels in maintenance hemodialysis patients. *Nutrition* 2014;30:297–304.