

Original Article

Clinical prognostic role of bioimpedance phase angle in diabetic and non-diabetic hemodialysis patients

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Background and Objectives: Bioelectrical-impedance analysis (BIA) is frequently used to estimate dry weight in hemodialysis (HD) patients. However, the clinical prognostic significance of BIA indicators is unclear. As a nutritional index, low phase angle (PA) might be an independent risk factor for predicting death in multiple chronic diseases. We performed this study to find relative influence factors of PA and other clinical prognostic significance. **Methods and Study Design:** The study involved 87 HD patients, 33 of whom were diabetic and 54 of whom were not. We measured body composition index, body water index and nutritional indicators and collected biochemical criteria. Then, we statistically analyzed the associations of these indices. After 1 year of follow-up, we recorded death, heart failure, hospitalization, cerebrovascular and cardiovascular events and other clinical outcomes. **Results:** We found a significant difference between the two groups in visceral-fat area, extracellular water/total body water (ECW/TBW) ratio and PA value. Two factors were negatively associated with PA: ECW/TBW ratio and HCO₃⁻ before HD. At 1 year, we noted that PA was associated with events such as heart failure or hospitalization. By further stratification and multivariate analysis adjusting for age, sex and months of dialysis, we found that low PA was an independent predictor of heart failure for diabetic HD patients. **Conclusions:** PA value was lower in Diabetic nephropathy (DN) HD patients, than that in non-DN HD patients. PA was mainly negatively associated with ECW/TBW ratio. It is a useful index for predicting heart failure in diabetic HD patients.

Key Words: phase angle, prognostic role, diabetic, hemodialysis patient, heart failure

INTRODUCTION

Diabetic nephropathy (DN), a serious complication of diabetes, is defined as the functional, structural and clinical abnormalities of the kidney caused by type II diabetes.¹ DN is a clinical syndrome characterized by persistent albuminuria (>300 mg/24 hours or 300 mg/g creatinine), a progressive decline in glomerular filtration rate (GFR), arterial hypertension and increased cardiovascular morbidity and mortality. Over the recent decades, DN has become the primary cause of chronic renal-replacement therapy due to end-stage kidney disease (ESRD) in both Western countries and worldwide.² One study revealed that the total prevalence of type II diabetes in China's adult population was 11.6%, approximately 30%–40% of which progressed into DN.³ Mortality is significantly higher in DN patients on maintenance hemodialysis (HD) than in non-DN patients on maintenance HD. Hu Chen et al⁴ reported a multicenter, cross-sectional survey of clinical characteristics of DN patients on maintenance HD in Anhui Province, China. These patients presented higher rates of cardiovascular complications and lower levels of serum albumin and parathyroid hormone (iPTH) than non-DN patients on maintenance HD. But this survey did not analyze or form conclusions about the relative risk factors of all causes of death in DN patients on maintenance HD. Unlike their non-diabetic counterparts, DN

patients on HD are also at high risk of HD-induced unstable blood glucose levels, which are associated with poor clinical outcomes that include a high risk of death,⁵ cardiovascular and cerebrovascular events (C-events) and heart failure. Glenn M et al⁶ found that age-, sex-, race- and diabetes-related differences could be elucidated in patients on maintenance HD by measuring bioimpedance parameters and derived estimates of body composition. They revealed that phase angle (PA) and body cell mass are correlated directly with serum creatinine (Scr), albumin and pre-albumin concentrations. In their study, they measured bioelectrical-impedance analysis (BIA) parameters and analyzed potential causal relationships. However, there were not follow-up data in that study.

Of numerous BIA parameters, we mainly focused on PA, which might be a latent biomarker predictive of adverse endpoints in maintenance HD patients. PA is related

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to cell size or integrity of the cell membrane and is calculated as the arctangent of the directly measured reactance-to-resistance ratio.⁷ If reactance increases, PA increases; if reactance decreases, PA decreases. Therefore, cell membrane damage and a decrease in cell function cause a decrease in PA. In general, the PA of most healthy adults is 3–15°, larger in men than in women. The PA of the Asian population is the smallest.⁸ Recently, PA has been used to estimate nutritional status and to predict mortality in various diseases, especially cachexia in HIV infection⁹ or certain cancers.¹⁰ Some studies have also confirmed its survival prediction value in other chronic diseases.¹¹ Most type II DN patients on maintenance HD have had diabetes for >10 years. Long-term hyperglycemia and HD result in poor nutrition and vascular condition. However, the significance of PA in patients with DN on maintenance HD has not been elaborated.

In this study, we analyzed PA and its associated impact factors in detail. At 1 year, we confirmed that PA might predict various adverse clinical outcomes, including heart failure, hospitalization or death from all causes.

METHODS

Subjects

Eighty-seven patients on maintenance HD participated in this study. All participants signed the informed consent. This study was complied with the Declaration of Helsinki and approved by the Ethics Committee of our hospital. We measured and collected BIA parameters and clinical data from them from December 2015 to June 2016. Inclusion criteria were as follows: (1) maintenance HD patients (3×/week); (2) dialysis >3 months; (3) no adverse clinical events in recent 3 months; (4) agreed to sign the informed consent. Exclusion criteria were as follows: (1) dialysis <3 months; (2) have occurred adverse clinical events in recent 3 months; (3) New York Heart Association (NYHA) class III or IV, or acute heart failure; (4) presence of malignant tumor, serious infection or severe liver failure; (5) could not complete the BIA measurements; (6) age <18 years or >85 years; (7) refused to sign the informed consent. We followed various clinical outcomes over the course of 1 year, including death from all causes, cardiovascular events, hospitalization frequency and heart failure.

Of the 87 subjects, 33 were diagnosed with chronic renal failure due to DN. Diagnostic criteria for DN were as reported by Mogensen CE.¹² All diabetic patients had DN.

Methods of bioelectrical-impedance measurement

All measurements were performed by trained renal physicians using an InBody S10 Body Water Analyzer (InBody Co., Ltd, Seoul, Korea) per manufacturer's instructions. All patients were measured while lying down after HD. We input name, sex, date and dry weight into the InBody S10 before taking measurements. If the data were extremely unusual, the patient was asked to repeat the measurement the following week. All data were exported into Microsoft Excel. PAs were analyzed for the whole body. We measured impedance (Xc) and reactance (Z) via the InBody S10, then calculated PAs by the formula below:

$$\text{Phase Angle} = \arctan [\text{Reactance (Xc)/Resistance (R)}]$$

Clinical-data collection

All laboratory examinations and blood sample collection were performed before BIA measurement on the same day. We measured serum levels of K⁺, Na⁺, HCO₃⁻, Ca²⁺, P³⁺, Scr and other biochemical indices using a Modular Analyzer (Cobas 8000, Roche, Basel, Switzerland). intact parathyroid hormone (iPTH) concentrations were detected by immunoradiometric or immunochemiluminometric assays. All laboratory tests were performed in the clinical laboratories. The biochemical index included such measures as blood routine, blood biochemistry and iPTH. All clinical data were recorded and checked by trained renal physicians.

Statistical analysis

We divided the subjects into two groups, diabetic and non-diabetic, by leading cause of maintenance HD. For continuous variables, the normal distribution indices were represented by mean ± standard deviation (SD), and we compared the 2 groups using independent-sample t-tests. The skewed distribution indices were shown by median and compared using a Wilcoxon rank sum test. Categorical variables were presented as absolute and relative frequencies using a chi-square test or Fisher's exact test. We used Pearson's correlation coefficient (PCC) to analyze factors associated with PA and performed multiple linear-regression analyses to obtain adjusted (partial) correlations, obtaining 95% confidence intervals for PAs. The final multivariate model included variables selected by the 2 previous steps and was proven by the enter method. We used logistic-regression analysis on the relationship between clinical-outcome events and parameters measured by BIA. Finally, we calculated crude and adjusted odds ratios (ORs). $p < 0.05$ were considered statistically significant.

RESULTS

Demographic and baseline clinical data

We reviewed each patient's medical records to collect data, including age, gender, weight, height, body mass index (BMI, calculated as body weight [kg] divided by height [m²]), months of dialysis, primary diseases (diabetes or non-diabetes) and blood biochemical indicators before dialysis (e.g., K⁺, Na⁺, HCO₃⁻, Ca²⁺, P³⁺, Scr, iPTH). These baseline data are shown in Table 1. There were differences in the following data between the non-diabetic and diabetic groups: age ($p < 0.001$), months of dialysis ($p = 0.003$), white blood cell (WBC) and red blood cell (RBC) counts ($p = 0.035$), Scr before HD ($p < 0.001$), Na⁺ ($p = 0.004$) and iPTH ($p = 0.035$). That diabetic kidney disease patients started earlier on dialysis than non-diabetic patients might partly explain the lower levels of Scr before HD and iPTH in diabetic HD patients.

Main indicators measured by BIA equipment

Important indicators are shown in Table 2. The whole-body PA of non-diabetic patients was larger than that of diabetic patients (5.92±0.14 vs. 4.79±0.20, respectively; $p < 0.001$). Most body composition indices were higher in the diabetic group than in the non-diabetic group. However, among these, only visceral-fat area differed significantly between the 2 groups (non-diabetic vs. diabetic:

Table 1. Patient characteristics and blood before dialysis

Variable	Non-diabetic (n=54)	Diabetic (n=33)	p value
Age	51.39±14.86	64.45±11.92***	<0.001
Gender (M/F)	21/33	19/14	
Weight (kg)	56.25±10.52	56.68±9.74	0.132
Height (m ²)	1.60±10.56	1.63±0.07	0.570
BMI	21.44±3.60	22.36±2.95	0.219
Dialysis (months)	52.18±46.01	22.36±27.32**	0.003
WBC (*10 ⁹ /L)	6.25±0.22	7.04±0.30*	0.035
RBC (*10 ¹² /L)	3.39±0.06	3.65±0.13*	0.035
HGB (g/L)	99.24±1.53	107.21±3.47	0.019
Scr (μmol/L)	1095.80±27.46	894.27±38.68***	<0.001
K ⁺ (mmol/L)	5.20±0.08	5.45±0.18	0.139
Na ⁺ (mmol/L)	138.52±0.31	136.72±0.57**	0.004
HCO ₃ ⁻ (mmol/L)	19.65±0.31	20.34±0.46	0.199
Ca ²⁺ (mmol/L)	2.37±0.03	2.34±0.03	0.581
P ³⁺ (mmol/L)	2.02±0.09	1.98±0.11	0.778
Ca ²⁺ *P ³⁺	59.51±2.63	59.81±4.26	0.949
iPTH (ng/L)	477.48±75.89	258.06±40.91*	0.035
β2MG (mg/L)	48.21±9.43	38.18±1.90	0.413
FER (ng/mL)	252.52±23.41	256.28±34.59	0.906

BMI: body mass index; WBC: white blood cell count; RBC: red blood cell count; HGB: hemoglobin; Scr: serum creatinine; iPTH: parathyroid hormone; β2MG: serum β2 microglobulin; FER: serum ferritin.

For continuous variables, the normal distribution indices were represented by mean ± standard deviation (SD) and compared by independent-sample t-tests between the two groups.

Compared with non-diabetic group **p*<0.05, ***p*<0.01, ****p*<0.001.

Table 2. BIA data measurements (body composition indices, body water indices and nutritional information) in non-diabetic and diabetic HD patients

Variable	Non-diabetic (n = 54)	Diabetic (n = 33)	p value
PA	5.92±0.14	4.79±0.20***	<0.001
Body composition indices			
Soft lean mass (L)	38.92±1.07	40.01±1.30	0.526
Skeletal muscle mass (L)	22.63±0.71	22.74±0.82	0.921
Body fat (%)	26.05±1.32	28.52±1.52	0.235
Fat-free mass (kg)	41.27±1.12	42.43±1.36	0.521
Visceral-fat area (cm ²)	72.41±5.76	93.02±8.40*	0.040
Body water indices			
Intracellular water (L)	18.87±0.54	18.97±0.63	0.905
Extracellular water (L)	11.40±0.31	12.35±0.40	0.058
Total body water (L)	30.27±0.82	31.31±1.01	0.430
ECW/TBW	0.38±0.00	0.39±0.00***	<0.001
Nutritional information			
Body cell mass (kg)	27.02±0.77	27.15±0.90	0.916
UAC (cm)	28.32±0.46	28.73±0.46	0.560
UAMC (cm)	23.05±0.34	23.77±0.39	0.179
Bone mineral content (kg)	2.35±0.06	2.41±0.06	0.534
Basal metabolic rate (kcal)	1261.48±24.27	1286.36±29.36	0.521
TBW/FFM	73.33±0.09	73.76±0.06***	<0.001

PA: phase angle; ECW/TBW: extracellular water/total body water; TBW/FFM: total body water/fat-free mass; UAC: upper-arm circumference; UAMC: upper-arm muscle circumference.

For continuous variables, the normal distribution indices were represented by mean ± standard deviation (SD) and compared by independent-sample t-test between the two groups.

Compared with the non-diabetic group, **p*<0.05, ****p*<0.001

72.41±5.76 vs. 93.02±8.40; *p*<0.05). For body water indices, there were no differences between the 2 groups in intracellular water (*p*=0.905), extracellular water (ECW) (*p*=0.058) or total body water (TBW) (*p*=0.430). However, the ECW/TBW ratio in the diabetic group was higher than in the non-diabetic group (0.39±0.00 vs. 0.38±0.00, respectively; *p*<0.001). In the nutritional-information index, the statistical difference in TBW/fat-free mass (FFM) ratio between groups was significant (non-diabetic

vs. diabetic: 73.33±0.09 vs. 73.76±0.06, *p*<0.001). On other indices, there was no difference between the groups.

Phase angles and associated factors

PA in the diabetic HD group was notably lower than in the non-diabetic group. We therefore explored potential factors that might affect PA. PCCs are shown in Table 3. Notably, the PCC for the association between ECW/TBW ratio and PAs was -0.8850 (*p*<0.01; Figure 1). Other indices such as Scr (before and after HD), skeletal muscle

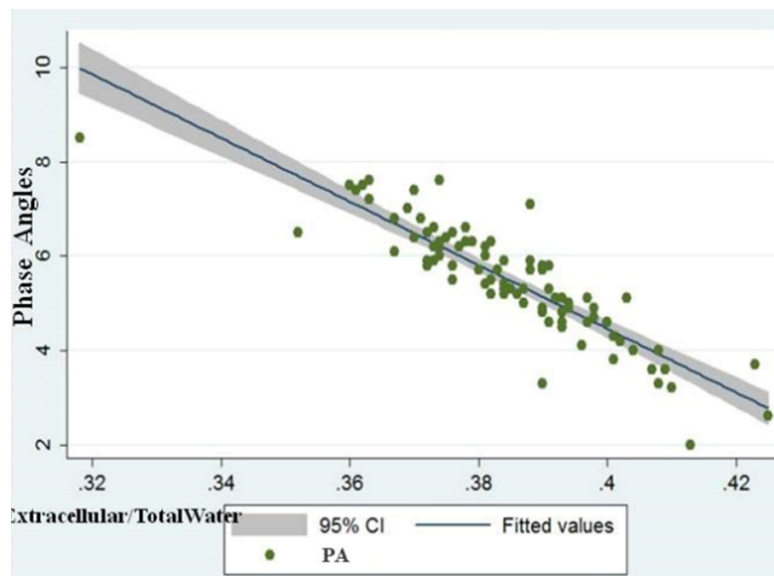


Figure 1. PA, phase angle; ECW/TBW, extracellular water/total body water; The Pearson's correlation coefficient for the association between ECW/TBW ratio and PAs was -0.8850 ($p < 0.01$).

mass and intracellular water were positively correlated with PA, while age, hemoglobin (HGB), hematocrit (Hct), Na^+ , and HCO_3^- were negatively correlated (Table 3). We screened possible influencing factors using the stepwise-regression method; we then included sex, age, months of dialysis and other potential influences in multiple linear regressions. The resulting analyses indicated that PA was independently associated with ECW/TBW ratio and HCO_3^- (all $p < 0.05$, R^2 0.9, adjusted R^2 0.78; Table 3). The PCC for ECW/TBW ratio was -65.1780 ± 5.8237 (95% CI, -75.2859 to -53.0703) while that of HCO_3^- was -0.0562 ± 0.02795 (95% CI, -0.1118 to -0.00118). From this data, we concluded that PA was mainly negatively associated with ECW/TBW ratio, and we confirmed this finding by reviewing ECW/TBW ratio data in diabetic and non-diabetic patients.

Phase angles and clinical outcomes

After 1 year, we followed up with patients and recorded main clinical outcomes, which included death, heart fail-

ure, hospitalization and cardiovascular and cerebrovascular events (C-events). Results are shown in Tables 4 and 5. The incidence rate of heart failure after 1 year was significantly higher in the diabetic group ($p < 0.001$). All cases of heart failure were caused by capacity overload. By strengthening ultrafiltration, the heart function of all patients was improved significantly. More diabetic patients were hospitalized over the course of the year due to heart failure or unstable vital signs than non-diabetic patients (20/33 vs. 17/54, respectively; $p = 0.008$). One non-diabetic patient and 2 diabetic patients died during the year; we recorded the causes of death. The cause of the non-diabetic patient's death was unclear. One diabetic patient died from esophageal cancer, and the other from multiple-organ failure. There was no statistically significant difference between the two groups in death events ($p = 0.297$). For C-events other than heart failure, two diabetic HD patients suffered strokes, but no non-diabetic HD patients experienced C-events during the follow-up period. Using Fisher's exact test, we found no statistically

Table 3. Linear-regression model of PA and i

Variable	Coefficient	<i>p</i> value	CI	R^2	Adj. R^2
ECW/TBW	-65.18 ± 5.8	< 0.001	-75.29 to -53.07	0.80	0.78
HCO_3^-	-0.06 ± 0.03	0.048	-0.11 to -0.001		

PA: phase angle; CI: confidence interval; ECW/TBW: extracellular water/total body water. Multiple linear-regression analyses were performed to obtain adjusted (partial) correlations.

Table 4. Clinical outcomes

Variable	Non-diabetic (n=54)	Diabetic (n=33)	<i>p</i> value
Heart failure	4	13 ^{***}	< 0.001
Hospitalization	17 (31.48%)	20 (60.61%) ^{**}	0.008
All causes of death	1 (18.52%)	2 (6.06%)	0.297
C-events	0 (0)	2 (6.06%)	0.152

C-events, cardiovascular (except heart failure) and cerebrovascular events.

Categorical variable was presented as absolute and relative frequencies. Chi-square or Fisher's exact test was used. Compared with the non-diabetic group, ^{**} $p < 0.01$, ^{***} $p < 0.001$.

Table 5. Possible relationships of PA and clinical outcomes

Variable	Crude OR	<i>p</i> value	95% CI
Heart failure	0.42±0.11	<0.001***	0.24–0.71
Hospitalization	0.41±0.10	<0.001***	0.25–0.66
All causes of death	0.03±0.05	<0.001***	0.00–0.98
C-events	0.46±0.26	0.170	0.15–1.41

PA: phase angle; C-events: cardiovascular (except heart failure) and cerebrovascular events.

Logistic-regression analysis was used to analyze the relationships between clinical-outcome events and PA.

****p*<0.001.

significant difference between the two groups in C-events (both cardiovascular and cerebrovascular events, (*p*=0.152).

PA has been associated with survival in various advanced cancers.¹⁰ Lower PAs might predict worse clinical outcomes. Therefore, we analyzed the relationships between PA and several common adverse clinical outcomes. Crude ORs, *p* value and 95% CI are shown in Table 5. From the results, we could conclude that lower PAs might predict more occurrences of heart failure (crude OR 0.415±0.114; 95% CI, 0.242–0.710; *p*<0.001), frequent hospitalization (crude OR 0.405±0.100; 95% CI, 0.250–0.656; *p*<0.001), and death from all causes (crude OR 0.029±0.052; 95% CI, 0.001–0.975; *p*<0.001). However, PA was not associated with C-events (95% CI, 0.151–1.405; *p*=0.170).

For the most common adverse clinical outcome, heart failure, we performed detailed logistic-regression and stratified analyses; results are shown in Table 6. We found that age, diabetes vs. non-diabetes, PA degree, visceral-fat area, ECW/TBW ratio and TBW/FFM ratio might be factors associated with heart failure. After adjustment for age, sex, months of dialysis and other baseline indices, all factors became non-significant for heart

failure. However, after stratified analysis based on presence or absence of diabetes, we found that months of dialysis, PA, and ECW/TBW ratio found that months of dialysis (*p*=0.029), PA (*p*=0.022), and ECW/TBW ratio (*p*=0.016) might be associated with heart failure in diabetic patients. After adjusting for age, sex, months of dialysis and other baseline indices, we calculated that the adjusted OR of PAs for heart failure was 0.42±0.12 (95% CI, 0.24–0.74; *p*<0.01, Table 7).

DISCUSSION

BIA, in clinical practice, is mainly used to help estimate the dry weight and dialysis sufficiency of dialysis patients upon HD or peritoneal dialysis (PD). We found some differences in BIA indices between diabetic and non-diabetic patients (Table 2). Based on our analysis of participants' baseline data, diabetic patients entered HD earlier than non-diabetic patients at Shenzhen Traditional Chinese Hospital, which was consistent with data from other dialysis centers. Therefore, some indicators in the diabetic group, such as months of dialysis, Scr before HD and iPTH, were lower than in the non-diabetic group. By taking BIA measurements, we found significant differences in PA, visceral-fat area and ECW/TBW and

Table 6. Parameters that might be associated with heart failure in HD patients and adjusted odds ratio

Variable	Crude OR	<i>p</i> value	95% CI	Adjusted OR	<i>p</i> value	CI
Age	1.05±0.21*	0.014	1.01-1.09	1.00±0.03	0.975	0.94–1.07
Diabetes	8.13±5.12**	0.001	2.36-27.9	4.21±3.39	0.074	0.87–20.4
PA	0.41±0.11**	0.001	0.24-0.71	0.66±0.40	0.493	0.20–2.19
Visceral-fat area	1.02±0.01**	0.004	1.01-1.03	1.01±0.01	0.391	0.99–1.02
ECW/TBW	3.52e + 35 ± 8.56e + 36**	0.001	7.20e+14 to 1.72e+56	1.60e–10±1.17e–08	0.759	5.38e–73 to 4.74e + 52
TBW/FFM	11.7±9.76**	0.003	2.29-60.0	24.8±42.0	0.058	0.90–683

PA: phase angle; ECW/TBW: extracellular water/total body water; TBW/FFM: total body water/fat-free mass.

Crude and adjusted ORs, *p* value and 95% CI are shown.

Logistic-regression analyses were performed to obtain crude and adjusted (partial) correlations.

Age, sex, months since diabetes diagnosis and other factors were used to adjust the model in Table 7.

p*<0.05, *p*<0.01.

Table 7. Parameters that might be associated with heart failure in non-diabetic vs. diabetic HD patients

Variable	Non-diabetic		Diabetic	
	Crude OR	<i>p</i> value	Crude OR	<i>p</i> value
Age	1.05±0.04	0.172	1.02±0.03	0.626
Months of dialysis	0.96±0.03	0.207	1.07±0.03*	0.029
PA	0.91±0.45	0.847	0.39±0.16*	0.022
Visceral-fat area	1.02±0.01*	0.035	1.01±0.01	0.136
ECW/TBW	7.06e + 09±2.55e + 11	0.530	4.25e + 48±1.98e + 50*	0.016
TBW/FFM	2.84±4.10	0.471	8.17±9.67	0.076

PA: phase angle; ECW/TBW: extracellular water/total body water; TBW/FFM: total body water/fat-free mass.

Shown are crude ORs and *p* values after analysis was stratified by non-diabetic or diabetic.

**p*<0.05.

TBW/FFM ratios in the two groups. For the nutritional index, PA was smaller in diabetic HD patients than in non-diabetic HD patients after we adjusted for age, months of dialysis and sex. PA is calculated from resistance and reactance as follows: $(\text{Reactance}/\text{Resistance}) \times (180^\circ/\pi)$.

This means that the capacitance behavior of tissues is associated with cellularity, cell size and integrity of the cell membrane.¹³ In previous studies, the ECW/TBW ratio has also been found to be a good prognostic factor for various diseases such as acute heart failure,¹⁴ renal disease¹⁵ and liver disease. In our study, PA showed a significantly negative correlation with ECW/TBW ratio for HD patients. In particular, the average degree of PA differed significantly between non-diabetic and diabetic HD patients. Low PA can imply significant malnutrition.¹⁶ We considered that for diabetic HD patients, duration of elevated blood sugar increased vascular permeability and induced vascular endothelial-cell injury.

In previous studies, PA has been considered a factor predictive of cell survival in most terminal diseases. In following up after 1 year, we found that a small PA was associated with frequent capacity-induced heart failure in HD patients, especially diabetic HD patients. Thus, for diabetic HD patients, PA might be an independent risk factor of heart failure. By analyzing causes of hospitalization, we found that most of our subjects had been hospitalized for heart failure. All heart failure patients had exacerbation of symptoms, fluid retention and elevated brain natriuretic peptide (BNP; >2000 pg/mL). Strengthening dialysis enabled them to get better and be discharged. In hospitalized patients, by repeating measurements and comparing BIA indices, we found that PA did not change significantly (<1°) but was relatively stable.

Alves FD et al¹⁷ reported that in multivariate analysis adjusted for age, left-ventricular ejection fraction (LVEF) and urea nitrogen level, a PA of <4.8° was independently associated with increased mortality (hazard ratio [HR] 2.67; $p=0.015$). PA seems to be a prognostic marker in patients with acute decompensated heart failure (ADHF) independent of other known risk factors. Colín-Ramírez E et al¹⁸ also found that a PA <4.2 was an independent predictor of all-cause mortality in chronic heart failure. In our study, by stratified analysis, we first confirmed that for diabetic patients, low PA was a prognostic marker independently associated with heart failure. For cardiovascular events, there was no difference between the two groups; in addition, PA was not associated with cardiovascular events.

Conclusion

From this study, we concluded that PA value was lower in DN HD patients, than that in non-DN HD patients. PA was mainly negatively associated with ECW/TBW ratio. It is an important index for predicting heart failure event in diabetic HD patients. Nonetheless, we believe that with an extension of follow-up time, researchers will find PA and other BIA indices to have more-significant predictive value.

AUTHOR DISCLOSURES

There is no conflict of interest.

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