

RESEARCH ARTICLE

Bioelectrical impedance analysis as a nutritional assessment tool in Autosomal Dominant Polycystic Kidney Disease

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Abstract

Objective

Autosomal dominant polycystic kidney disease (ADPKD) patients with massive organomegaly suffer from pressure-related complications including malnutrition. In this study, we analyzed the efficacy of segmental bioelectrical impedance analysis (BIA) for objective and quantitative nutritional assessment in ADPKD patients

Design and methods

We conducted a cross-sectional study, to evaluate the clinical utility of segmental BIA for assessing the nutritional status of ADPKD patients. BIA measurements were assessed according to modified subjective global assessment (SGA) scores and were compared with data from a healthy population. The association between BIA measurements and the height adjusted kidney and liver volumes (htTKLV), were analyzed.

Subjects

A total of 288 ADPKD patients, aged ≥ 18 years old, were analyzed

Main outcome measures

Nutritional status was evaluated with SGA and segmental BIA. The htTKLV were measured in each patients using computed tomography images.

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Competing interests: The authors have declared that no competing interests exist.

Results

Higher ratios of extracellular water to total body water (ECW/TBW) in the whole-body (ECW/TBW_{WB}), trunk (ECW/TBW_{TR}), and lower extremities (ECW/TBW_{LE}) and lower phase angle of lower extremities (PhA_{LE}) correlated with lower SGA scores in the ADPKD population and in both gender. The four parameters, ECW/TBW_{WB}, ECW/TBW_{TR}, and ECW/TBW_{LE} of >0.38 and PhA_{LE} of <5.8° were associated with malnutrition in ADPKD patients. These correlations were preserved in the subgroup analysis for chronic kidney disease stages 1-3A. Compared to healthy populations' data, body fluid parameters and segmental ECW/TBW values, except for the upper extremities (ECW/TBW_{UE}), were greater in ADPKD patients. Increased htTKLV was an independent risk factor for malnutrition in ADPKD. The highest correlation with htTKLV was observed for the ECW/TBW_{TR} ($r = 0.466$), followed by ECW/TBW_{WB} ($r = 0.407$), ECW/TBW_{LE} ($r = 0.385$), PhA_{LE} ($r = -0.279$), and PhA_{TR} ($r = 0.215$).

Conclusions

These results demonstrated that segmental BIA parameters of ECW/TBW_{WB}, ECW/TBW_{TR}, ECW/TBW_{LE} and PhA_{LE} provide useful information on nutritional status including the impact of organomegaly in ADPKD.

Introduction

Malnutrition in chronic kidney disease (CKD), also known as protein-energy wasting is one of the strongest predictors of mortality and morbidity [1, 2]. Not only anorexia or inadequate intake of nutrients due to uremic symptoms in CKD patients but also inflammatory conditions and oxidative stress increase malnutrition risk in CKD patients [3]. In previous studies, nutritional markers such as serum albumin, creatinine, body mass index (BMI), and subjective global assessment (SGA) score were independent predictors of death and treatment failure in CKD [4, 5]. Besides, the pre-transplant nutritional status in CKD patients are known to affect the outcomes of kidney transplantation [6, 7]. Therefore, efforts have been made to establish guidelines for proper nutritional assessment and intervention to improve the outcome of CKD patients [8].

In autosomal dominant polycystic kidney disease (ADPKD), renal function decreases and the kidney and/or liver volume increases as the disease progresses. In addition to decreased renal function, organomegaly due to cyst growth is another risk factor for malnutrition in ADPKD, causing pressure-related symptoms and complications [9, 10]. Therefore, regular assessment of nutritional status and timely intervention are important in ADPKD patients [11, 12].

Subjective global assessment (SGA) is a standard nutritional assessment tool that has been well-validated in CKD patients [13, 14]. However, the practical applications of SGA are limited, as it is a non-continuous and subjective scoring system that cannot detect subtle individual changes during regular follow-ups. Thus, other methods for monitoring nutritional status in ADPKD patients are required in addition to SGA.

Bioelectrical impedance analysis (BIA), which uses electrical currents and impedance to assess fluid status and body composition, could be an option for assessing nutritional status in ADPKD patients. Its use has been validated in various conditions, including CKD [15–18].

Increased ratio of extracellular water to total body water (ECW/TBW), change in body composition, and reduced phase angle (PhA) are known to be related to malnutrition [16, 19]. The main advantages of BIA over other methods (Dual-energy X-ray absorptiometry, biomarkers, etc.) are its ease of use, short measuring time, and non-invasiveness. Additionally, because it is small and mobile and quantifies continuous parameters, BIA is suitable for detecting changes over time at the outpatient clinic.

However, the one-cylinder BIA model could underestimate total body water (TBW) in ADPKD patients because they have cystic fluids in the abdomen [20]. To overcome this, we employed segmental BIA with a 5-cylinder model that considers the upper extremities (UE), lower extremities (LE), and trunk as 5 separate cylinders for independent impedance measurements. Using segmental BIA, we were able to obtain segmental data for ECW/TBW, lean mass (LM), and PhA from each of the 4-extremities and the trunk separately.

In our previous study, ADPKD patients, especially those with large abdominal cystic organ volume, are found to be at risk for malnutrition [10]. If the height-adjusted total kidney and liver volume (htTKLV), the sum of height-adjusted TKV (htTKV) and height-adjusted TLV (htTLV), is $\geq 2,340$ (mL/m), the risk of malnutrition increases 8.7 times after adjusting for renal function [10]. This is a follow-up study to evaluate segmental BIA as a nutritional assessment tool for ADPKD patients. First, we assessed the relationships of various BIA parameters with SGA to determine the most suitable BIA parameters to reflect nutritional status in ADPKD patients. Second, we compared the BIA data of ADPKD patients with those of healthy subjects from the general population. Thirdly, to analyze the effect of abdominal cystic mass on malnutrition in ADPKD patients, we obtained the htTKV and htTLV of all patients using computed tomography (CT) and analyzed the effect on segmental BIA data. We performed this study among pre-dialysis patients with stage 1 to 4 CKD to exclude the effect of severe renal dysfunction on nutritional status.

Materials and methods

This is a cross-sectional study of ambulatory patients who visited the outpatient ADPKD clinic following HOPE-PKD (coHOrt for genotype-PhenotypE correlation in ADPKD) protocol of Seoul National University Hospital. In the HOPE-PKD, a total of Korean 288 ADPKD patients were registered during December 2013 to March, 2014. Inclusion criteria of HOPE-PKD was subjects of 18 years or older and satisfied the Unified Criteria. The nutritional status of ADPKD patients were evaluated using SGA and BIA in our outpatient PKD clinic per standardized protocols. Patients with active cancer, infection, or renal replacement therapy or with a history of liver resection or transplantation were excluded. Detailed clinical information and reasons for liver resection or transplantation are discussed in a previous publication [21].

A database of BIA profiles from healthy subjects in the general population (Inbody Co., Ltd.) was used to compare with ADPKD patients after 1:1 matching. Data for 281 healthy subjects who were matched with the case patients for sex, age, and height ± 2 cm were extracted from the database of the healthy population. PhA data was not included for the healthy population.

We used modified SGA with a seven-point scale, which has been validated in various studies in CKD patients [22]. Detailed nutritional assessment using modified SGA was described in our previous report [10]. The seven-point scale reflecting the dietician's subjective judgment of the patient's overall nutritional status was interpreted as follows: 7, well-nourished; 6, at risk; 5, mildly malnourished; 3–4, moderately malnourished; and 1–2, extremely malnourished.

Inbody S10 (Inbody Co., Ltd, Seoul, Korea), a multi-frequency segmental BIA analysis instrument, was used in this study [23]. In the outpatient's clinic, the measurements were

performed in the standing position with 4-electrodes connected to both hands and feet of patient's. The BIA data of body fluid status, body composition parameters, and PhA of 50kHz were collected. In this study, we adjusted several quantitative segmental BIA parameters of the TBW, intracellular water (ICW), extracellular water (ECW), fat free mass (FFM), LM and fat mass (FM) by height, respectively (TBW/Ht, ICW/Ht, ECW/Ht, FFM/Ht, LM/Ht and FM/Ht). UE segmental parameters were defined as the average of the left and right arm data, and LE segmental parameters were defined in the same manner. Whole-body PhA (PhA_{WB}) was defined as the PhA on the right-side of the body and was calculated from right-side body impedance, as described previously [24].

In our ADPKD clinic, abdominal CT scans were performed every other year [25], and the most recent abdominal CT scan was used to measure htTLV and htTKV. Total liver volume was calculated as the sum of the products of slice thickness and area measured on a set of contiguous image using Rapidia 2.8 CT software (INFINITT Healthcare Co. Ltd, Seoul, Korea) and the total kidney volume was estimated with the ellipsoid method [26]. The htTKLV, was defined as the sum of htTLV and htTKV. [10].

Anthropometric measurements (height, weight, and body mass index (BMI)) and laboratory measurements (serum hemoglobin, creatinine, total protein, albumin, and total cholesterol) were performed on the same day as the SGA and BIA evaluation. The estimated glomerular filtration rate (eGFR) was calculated with the CKD Epidemiology Collaboration (CKD-EPI) equation [27]. Continuous variables including age, height, weight, body mass index, serum hemoglobin, eGFR, and albumin showed normal distributions and were presented as mean value and standard deviation. However, htTKV, htTLV and htTKLV showed a non-normal distribution, and were therefore expressed as median value and interquartile range (IQR).

Since no subject had an SGA score less than 4 in the outpatient environment, all patients were classified into three groups: mildly to moderately malnourished (SGA score of ≤ 5), at risk (SGA score of 6), and well-nourished (SGA score of 7). For statistical analysis, we used the linear association test or the Jonckheere-Terpstra test to evaluate the *P* for trend among the three SGA groups. The value of *P* for trend < 0.05 were interpreted as statistically significant. In the comparison study with healthy population data, paired t-test was used for normally distributed variables and Wilcoxon signed rank test for non-normally distributed variables. Receiver operating characteristic (ROC) curve analysis was used to evaluate BIA parameters for their ability to discriminate malnourished patients from well-nourished patients and to discriminate patients with significant htTKLV, which is $\geq 2,400\text{mL/m}$. The Youden index was used to determine the optimal cut-off value in MedCalc for Windows version 14 (MedCalc Software, Ostend, Belgium). Correlation analysis was performed to determine the relationships of BIA parameters with htTKLV. Due to its skewed distribution, htTKLV was natural log-transformed to \ln htTKLV. Log odds graphs of definite malnutrition over normal nutrition with respect to various BIA parameters were plotted with STATA statistical software package version 13 (Stata Corp., College Station, TX, USA). All other statistical analyses were conducted with SPSS version 22 (IBM Corporation, Armonk, NY, USA).

To exclude the renal function effect on BIA result, subgroup analysis of early stage CKD patients (CKD stage 1-3a) was conducted. In this subgroup analysis, the BIA data was compared among SGA groups and the association between BIA parameters and abdominal cystic organ volume was also analyzed. Additionally, the adjusted log odds graph of definite malnutrition over normal nutrition with respect to various BIA parameters were plotted in whole study population after adjusted with age, hemoglobin level and renal function.

This study was approved by the Institutional Review Board of Seoul National University Hospital (IRB No; 1205-112-411 and 1407-083-594). All participants provided written informed consent.

Table 1. Baseline patient characteristics according to nutritional status as evaluated by SGA.

Parameters	SGA 4 and 5	SGA 6	SGA 7	Total	P for trend
Number of patients	21 (7.3%)	63 (21.9%)	204 (70.8%)	288	
Female	9 (42.9%)	37 (58.7%)	92 (45.1%)	138 (47.9%)	0.148
Age (years)	53.4 ± 11.1	52.7 ± 12.6	46.4 ± 11.7	48.3 ± 12.2	<0.001
Height (cm)	164.0 ± 7.9	163.4 ± 7.9	167.6 ± 9.8	166.4 ± 9.5	0.002
Weight (kg)	59.1 ± 8.7	62.3 ± 9.7	67.0 ± 12.3	65.4 ± 11.8	0.001
BMI (kg/m ²)	22.0 ± 2.7	23.3 ± 2.6	23.7 ± 2.9	23.4 ± 2.8	0.044
Hemoglobin (g/dL)	12.8 ± 1.1	13.2 ± 1.4	13.7 ± 1.5	13.5 ± 1.5	<0.001
Serum creatinine (mg/dL)	1.5 ± 0.6	1.4 ± 0.6	1.2 ± 0.6	1.2 ± 0.6	0.001
eGFR (mL/min/1.73 m ²)	51.3 ± 23.2	57.1 ± 24.9	69.2 ± 24.6	65.3 ± 25.3	<0.001
Albumin (g/dL)	4.4 ± 0.3	4.3 ± 0.3	4.4 ± 0.4	4.4 ± 0.3	0.377
htTKLV (mL/m)	2,622 [1,719–4,906]	2,147 [1,535–2,687]	1,649 [1,311–2,151]	1,776 [1,361–2,381]	<0.001
htTKV (mL/m)	1,282 [524–1,574]	903 [559–1,246]	640 [394–955]	697 [415–1,133]	<0.001
htTLV (mL/m)	1,298 [830–2,831]	1,023 [816–1,322]	957 [819–1,147]	977 [819–1,196]	0.036

htTKLV, htTKV and htTLV are represented as median [interquartile value]. All other parameters are presented as mean ± standard deviation. BMI; body mass index, CKD; chronic kidney disease, eGFR; estimated glomerular filtration rates, htTKLV; height-adjusted total kidney and liver volume, htTKV; height-adjusted total kidney volume, htTLV; height-adjusted total liver volume, SGA, subjective global assessment

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Results

Baseline characteristics according to SGA score

In total, 288 patients were included in the analysis, of whom 138 (47.9%) were female (Table 1). The mean age of the total population was 48.3±12.2 years, and the mean BMI was 23.4±2.8 kg/m². In terms of CKD stage, 52 (18.1%), 116 (40.3%), 53 (18.4%), 46 (16.0%), and 21 patients (7.3%) were in stages 1, 2, 3A, 3B, and 4, respectively. The mean eGFR value was 65.3±25.3 mL/min/1.73 m². Two patients (0.7%) were moderately malnourished (SGA score of 4), 19 (6.6%) were mildly malnourished (SGA score of 5), 63 (21.9%) were at risk for malnutrition (SGA score of 6), and 204 (70.8%) were well-nourished (SGA score of 7). The distribution of SGA scores and the mean SGA score did not differ between the two genders. Older age, lower weight, and lower BMI were associated with lower SGA score (*P* for trend <0.001, 0.002, and 0.044, respectively). The distribution of CKD stages differed across the SGA score groups, and the mean eGFR was lower in subjects with lower SGA score (*P* for trend <0.001 for both).

The median values of htTKLV, htTKV, and htTLV were 1,776 mL/m (IQR 1,361–2,381 mL/m), 697 mL/m (IQR 415–1,133 mL/m), and 977 mL/m (IQR 819–1,196 mL/m), respectively. Lower SGA scores corresponded to larger values of htTKLV (*P* for trend <0.001), htTKV (*P* for trend <0.001) and htTLV (*P* for trend = 0.036) (Table 1).

Association of BIA parameters with SGA in ADPKD patients

When we analyzed segmental BIA parameters across SGA score groups (4 or 5 vs. 6 vs. 7), the groups with lower SGA scores exhibited higher ECW/TBW_{WB}, ECW/TBW_{TR}, and ECW/TBW_{LE} (all for *P* for trend <0.001). The *P* for trend was statistically significant for UE ECW/TBW (ECW/TBW_{UE}), but the trend was less robust than in the other segments of the body (*P* for trend = 0.035) (Table 2, Fig 1).

Segmental PhA values also correlated with SGA score. The UE PhA (PhA_{UE}, *P* for trend <0.001) and PhA_{LE} (*P* for trend <0.001) differed significantly among the three SGA groups, with the mean value decreasing as the SGA score decreased. The *P* for trend was also

Table 2. Association of segmental BIA parameters with SGA scores.

Parameters	Male			Female			Total						
	SGA ≤5	SGA 6	SGA 7	P for trend	SGA ≤5	SGA 6	SGA 7	P for trend	SGA ≤5	SGA 6	SGA 7	Total	P for trend
Number of patients	12	26	112		9	37	92		21	63	204	288	
ECW/TBW _{WB}	0.388 ± 0.009	0.384 ± 0.008	0.380 ± 0.006	0.001	0.396 ± 0.005	0.390 ± 0.006	0.388 ± 0.005	0.002	0.391 ± 0.009	0.387 ± 0.007	0.383 ± 0.007	0.384 ± 0.007	< 0.001
ECW/TBW _{TR}	0.387 ± 0.010	0.383 ± 0.009	0.378 ± 0.006	< 0.001	0.398 ± 0.007	0.390 ± 0.007	0.388 ± 0.005	0.001	0.391 ± 0.01	0.387 ± 0.008	0.382 ± 0.007	0.384 ± 0.008	< 0.001
ECW/TBW _{UE}	0.378 ± 0.004	0.378 ± 0.005	0.377 ± 0.004	0.051	0.381 ± 0.002	0.379 ± 0.003	0.379 ± 0.003	0.664	0.379 ± 0.004	0.379 ± 0.004	0.378 ± 0.004	0.378 ± 0.004	0.035
ECW/TBW _{LE}	0.391 ± 0.010	0.388 ± 0.010	0.383 ± 0.007	0.005	0.400 ± 0.006	0.393 ± 0.007	0.391 ± 0.006	0.002	0.395 ± 0.010	0.391 ± 0.008	0.387 ± 0.007	0.388 ± 0.008	< 0.001
PhA _{WB} (°)	5.3 ± 0.7	5.3 ± 0.9	5.4 ± 0.7	0.530	5.5 ± 0.9	5.3 ± 0.8	5.4 ± 0.7	0.753	5.4 ± 0.8	5.3 ± 0.8	5.4 ± 0.7	5.4 ± 0.7	0.478
PhA _{TR} (°)	8.8 ± 1.4	9.3 ± 1.5	9.5 ± 1.2	0.053	8.4 ± 1.4	8.3 ± 1.0	8.4 ± 1.2	0.480	8.6 ± 1.4	8.6 ± 1.3	9.0 ± 1.3	8.9 ± 1.3	0.015
PhA _{UE} (°)	5.2 ± 0.5	5.5 ± 0.6	5.7 ± 0.5	< 0.001	4.6 ± 0.2	4.7 ± 0.4	4.7 ± 0.4	0.150	4.9 ± 0.5	5.0 ± 0.6	5.3 ± 0.7	5.2 ± 0.7	< 0.001
PhA _{LE} (°)	5.0 ± 0.9	5.4 ± 0.9	5.8 ± 0.7	0.002	4.0 ± 0.6	4.6 ± 0.6	4.8 ± 0.5	0.007	4.6 ± 0.9	5.0 ± 0.8	5.4 ± 0.8	5.2 ± 0.9	< 0.001

All parameters are presented as mean ± standard deviation. BIA; bioelectrical impedance analysis, ECW/TBW_{WB}: ratio of extracellular water to total body water of whole-body, ECW/TBW_{TR}: ratio of extracellular water to total body water of trunk, ECW/TBW_{UE}: ratio of extracellular water to total body water of upper extremities, ECW/TBW_{LE}: ratio of extracellular water to total body water of lower extremities, PhA_{WB}: Phase angle of whole-body, PhA_{TR}: Phase angle of trunk, PhA_{UE}: Phase angle of upper extremities, PhA_{LE}: Phase angle of lower extremities, SGA; subjective global assessment

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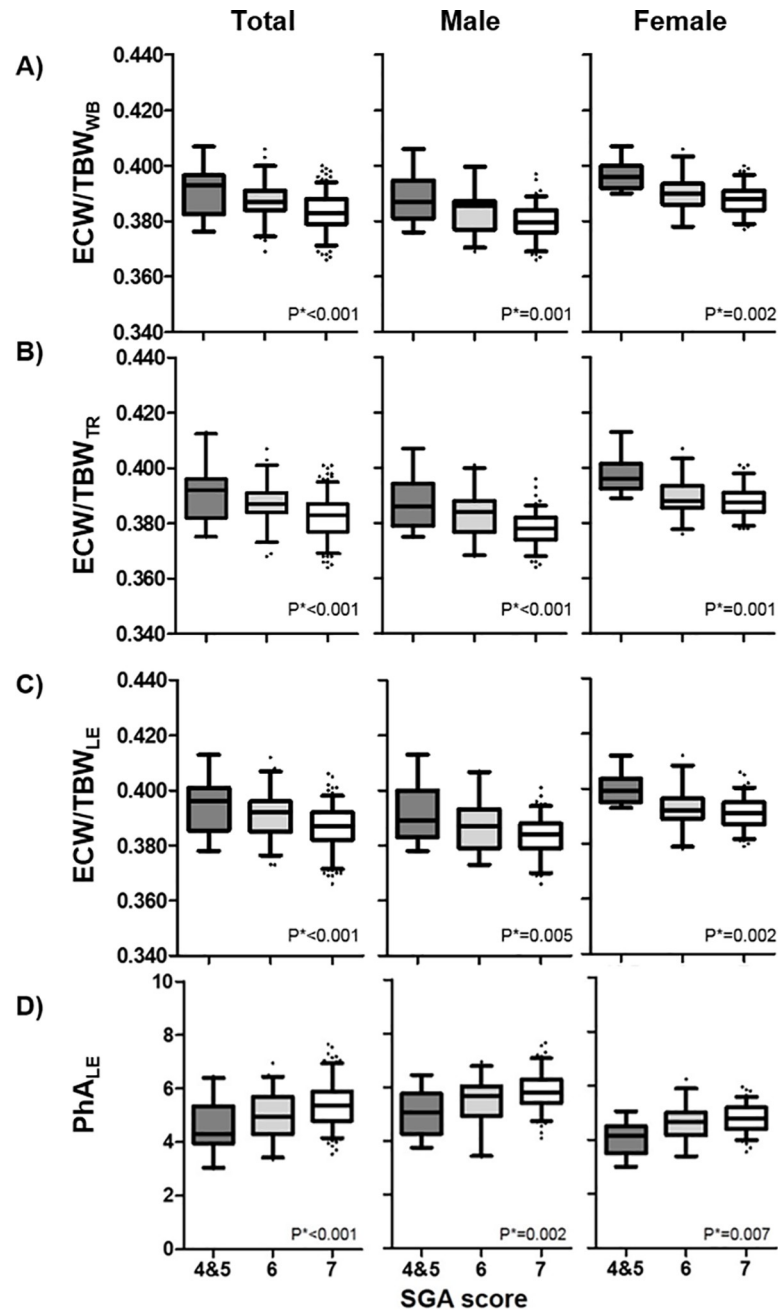


Fig 1. Associations of ECW/TBW and phase angle with SGA score. (A) ECW/TBW_{WB}, (B) ECW/TBW_{TR}, (C) ECW/TBW_{LE} and (D) PhA_{LE}. ECW/TBW_{WB}, TR and LE and PhA_{LE} associated with SGA scores in both genders. *P; P for trends, SGA 7, well-nourished; SGA 6, at risk; SGA 5, mildly malnourished; SGA 3–4, moderately malnourished, ECW/TBW_{WB}; ratio of extracellular water to total body water of whole-body, ECW/TBW_{TR}; ratio of extracellular water to total body water of trunk, ECW/TBW_{LE}; ratio of extracellular water to total body water of lower extremities, PhA_{LE}; phase angle of lower extremities, SGA; subjective global assessment.

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significant for the trunk PhA (PhA_{TR}) across the SGA score groups, but the PhA_{TR} trend was less robust than in the other segments of the body (*P* for trend = 0.015). The PhA_{WB}, which has been reported as a nutritional marker in previous studies in other disease conditions [24], did not differ significantly among the three SGA groups (*P* for trend = 0.478) (Table 2).

For each body fluid parameter, such as ICW/Ht, ECW/Ht, TBW/Ht, the P for trend was statistically significant, but the mean values failed to exhibit definite trends across the SGA score groups. Regarding body composition parameters, the FFM/Ht and the LM/Ht for the WB, UE, and LE exhibited statistically significant P for trend values (all P for trends <0.01) without definite trends in the mean values across the SGA groups. FM/Ht did not differ significantly among the three groups. Only the trunk LM/Ht (LM/Ht_{TR}) exhibited a definite trend of decreasing mean value with decreasing SGA score (P for trend = 0.002) (S1 Table and S1 Fig and S2 Fig).

Differences between the genders in the association of BIA parameters with SGA

In our previous study [10], several parameters that were associated with SGA score in males (such as age, body weight, BMI, and hemoglobin level) showed no association in females. Therefore, in this study, subgroup analyses were undertaken to determine whether there were gender differences in the associations of BIA parameters with SGA score.

Four parameters of higher ECW/TBW_{WB}, ECW/TBW_{TR}, and ECW/TBW_{LE} and lower PhA_{LE} values correlated with lower SGA score in both male and female ADPKD. However, the other body fluid parameters and body composition parameters correlated with SGA score only in the male subgroup. ECW/TBW_{UE} and PhA_{TR} values, for which the P for trend values were statistically significant in the total population, did not exhibit such trends in either gender subgroup (Table 2, S1 Table).

ROC curve analysis of BIA parameters with SGA in ADPKD patients

ROC curve analysis was conducted to identify the most suitable BIA parameter for predicting definite malnutrition (SGA ≤ 5). The parameters that differed significantly (P for trend <0.05) in both male and female patients and in the total population were analyzed, and ROC curves were generated using the data from subjects with SGA score of 7 (well-nourished) or ≤ 5 (malnutrition).

The areas under the curve (AUCs) and the ROC curves of the four relevant parameters are shown in Fig 2(A). The AUC for ECW/TBW_{WB} was the largest (0.762), and the AUCs for all the other parameters were also greater than 0.7, in the following order: ECW/TBW_{TR} (0.758), ECW/TBW_{LE} (0.747) and PhA_{LE} (0.741).

Log odds analysis of BIA parameters to predict malnutrition in ADPKD patients

When the log odds of malnutrition (SGA score of ≤ 5) were plotted across the values of each of the four BIA parameters that were significant in each sex and in the total population, the mean (95% confidence interval) log odds increased significantly as the ECW/TBW_{WB}, ECW/TBW_{TR}, and ECW/TBW_{LE} increased. On the contrary, PhA_{LE} correlated negatively with log odds (Fig 3). The cut-off values for positive likelihood of malnutrition were ECW/TBW_{WB} >0.380 , ECW/TBW_{TR} >0.379 , ECW/TBW_{LE} >0.383 and PhA_{LE} <5.8 . The same trends were observed in the subgroup analysis of both males and females (Table 3). Similar log odds graphs were obtained after adjustment for age, hemoglobin level, and renal function (S3 Fig).

Differences in BIA parameters between the healthy population and ADPKD patients

To characterize the BIA parameters in ADPKD, we compared the BIA data of ADPKD patient with healthy population's by extracting 1:1 matched, 281 healthy subjects from the database of

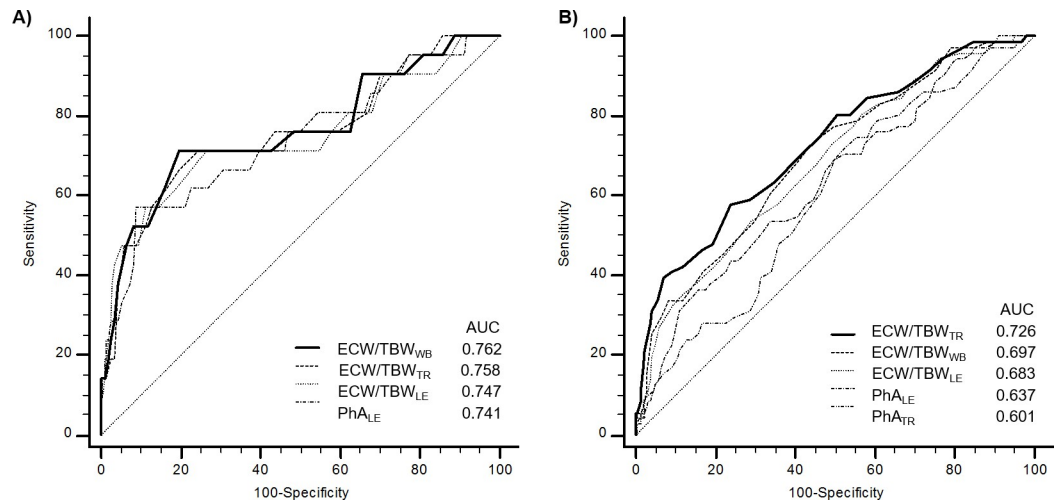


Fig 2. ROC curve of BIA parameters for the diagnosis of malnutrition and significant htTKLV. Predicting A) malnutrition defined as SGA score of 4 and 5 and B) significant htTKLV of $\geq 2,400$ mL/m using BIA parameters. In the ROC curve analysis of BIA parameters to predict malnutrition, all AUCs were larger than 0.7 and the AUC for ECW/TBW_{WB} was the largest (0.762). In the ROC curve analysis of BIA parameters to predict significant htTKLV values of $\geq 2,400$ mL/m, all AUCs of parameters shown in the figure were larger than 0.6 and the AUC for ECW/TBW_{TR} was the largest (0.726). AUC; area under curve, BIA; bioelectrical impedance analysis, ECW/TBW_{WB}; ratio of extracellular water to total body water of whole-body, ECW/TBW_{TR}; ratio of extracellular water to total body water of trunk, ECW/TBW_{LE}; ratio of extracellular water to total body water of lower extremities, PhA_{TR}; Phase angle of trunk, PhA_{LE}; Phase angle of lower extremities, ROC; receiver-operating characteristics, SGA; subjective global assessment.

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Inbody Co., Ltd, [15]. After the subjects were matched for sex, age, and height ± 2 cm, there was no significant difference in weight or BMI between the ADPKD and healthy groups ($p = 0.086$ and 0.088 , respectively).

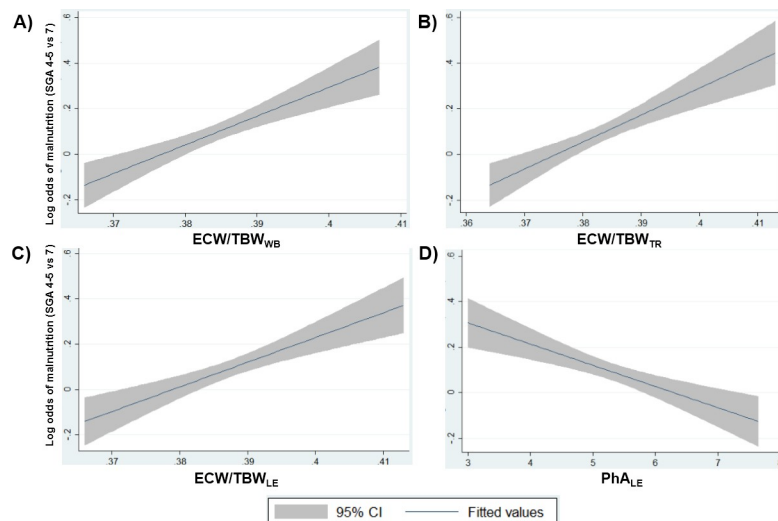


Fig 3. Likelihood (log odds) of having malnutrition (SGA 4&5 vs 7) with respect to various BIA parameters. A) ECW/TBW_{WB}, B) ECW/TBW_{TR}, C) ECW/TBW_{LE} and D) PhA_{LE} (θ). Log odds of having malnutrition increased as the ECW/TBW_{WB}, _{TR} and _{LE} increased. On the contrary, log odds decreased with PhA_{LE} increased. BIA; bioelectrical impedance analysis, ECW/TBW_{WB}; ratio of extracellular water to total body water of whole-body, ECW/TBW_{TR}; ratio of extracellular water to total body water of trunk, ECW/TBW_{LE}; ratio of extracellular water to total body water of lower extremities, PhA_{LE}; Phase angle of lower extremities, SGA; subjective global assessment.

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Table 3. Cutoff value for positive log odds of having malnutrition with respect to various BIA parameters.

	Total	Male	Female
ECW/TBW _{WB}	> 0.380	> 0.378	>0.387
ECW/TBW _{TR}	> 0.379	> 0.376	> 0.387
ECW/TBW _{LE}	> 0.383	> 0.381	> 0.390
PhA _{LE} (°)	< 5.8	< 6.1	< 4.9

BIA; bioelectrical impedance analysis, ECW/TBW_{WB}; ratio of extracellular water to total body water of whole-body, ECW/TBW_{TR}; ratio of extracellular water to total body water of trunk, ECW/TBW_{LE}; ratio of extracellular water to total body water of lower extremities, PhA_{LE}; Phase angle of lower extremities, SGA; subjective global assessment

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The mean values of body fluid parameters including ICW/Ht, ECW/Ht, and TBW/Ht were higher in ADPKD patients than in the general population ($P < 0.001$ for all). The mean values of ECW/TBW_{WB}, ECW/TBW_{TR}, and ECW/TBW_{LE} were higher in ADPKD patients than in healthy subjects ($P < 0.001$ for all).

Among the body composition parameters, FFM/Ht was higher in ADPKD patients than in healthy subjects and FM/Ht was significantly lower in ADPKD patients ($P < 0.001$ for both). Whole-body LM/Ht (LM/Ht_{WB}) and lower extremity LM/Ht (LM/Ht_{LE}) were also higher in ADPKD patients than in the healthy population ($P < 0.001$ for both). Increased LM/Ht_{WB} and LM/Ht_{LE} might reflect the edematous condition in ADPKD resulted from the decreased renal function and/or inferior vena cava compression by cystic organs. On the contrary, trunk LM/Ht (LM/Ht_{TR}) was lower in ADPKD patients ($P < 0.001$). (Table 4).

Subgroup analysis of early-stage CKD patients

We conducted subgroup analysis ($n = 221$ patients) of subjects with CKD stages 1 to 3a to exclude the effects of uremia on the nutritional and fluid status of ADPKD patients. The results of the subgroup analysis were similar to those of the overall analysis. (S2 Table and S3 Table)

Associations between BIA parameters and abdominal cystic organ volume (htTKLV)

We used segmental BIA data to elucidate the correlations of various BIA parameters with htTKLV. Fig 4 displays the scatter plots and Pearson's correlation coefficients for the relationships between ln htTKLV and BIA parameters such as the ECW/TBW_{TR}, ECW/TBW_{WB} and ECW/TBW_{LE}, PhA_{TR} and PhA_{LE}. The highest correlation was observed for the ECW/TBW_{TR} ($r = 0.466$), followed by ECW/TBW_{WB} ($r = 0.407$), ECW/TBW_{LE} ($r = 0.385$), and PhA_{TR} ($r = 0.215$). The PhA_{LE} correlated negatively with ln htTKLV ($r = -0.279$). In the subgroup analysis of patients with $eGFR \geq 45$ mL/min/1.73 m², the correlations of ln htTKLV with various BIA parameters in this subgroup were similar to those in the total population. The highest correlation was still noticed for ECW/TBW_{TR} ($r = 0.416$), followed by ECW/TBW_{WB} ($r = 0.357$), ECW/TBW_{LE} ($r = 0.337$), PhA_{LE} ($r = -0.250$) and PhA_{TR} ($r = 0.232$) in the subgroup analysis of patients with $eGFR \geq 45$ mL/min/1.73 m² (Fig 4B).

ROC curve analysis was conducted to identify the most suitable BIA parameter for predicting significant htTKLV values of $\geq 2,400$ mL/m. From previous study, htTKLV values $\geq 2,340$ mL/m increased malnutrition risk 8.7 time [10]. In this study, to simplify the number, we used the cut-off value for significant htTKLV as 2,400 mL/m. ECW/TBW_{TR} showed the largest AUC (0.726) with the following order; ECW/TBW_{WB} (0.697), ECW/TBW_{LE} (0.683), PhA_{LE}

Table 4. Comparison of BIA parameters between ADPKD patients and healthy population control.

	Total (n = 281)		
	ADPKD patients	Healthy population	P-value
Age (years)	48.4 ± 11.9	48.4 ± 11.9	0.385
Height (cm)	64.9 ± 11.3	65.2 ± 10.6	0.230
Weight (kg)	166.0 ± 9.0	165.9 ± 9.0	0.086
BMI (kg/m ²)	23.4 ± 2.8	23.6 ± 2.5	0.088
ICW/Ht (L/m)	13.6 ± 2.2	13.2 ± 2.1	<0.001
ECW/Ht (L/m)	8.5 ± 1.2	8.2 ± 1.2	<0.001
TBW/Ht (L/m)	22.1 ± 3.4	21.4 ± 2.3	<0.001
ECW/TBW _{WB}	0.385 ± 0.007	0.382 ± 0.007	<0.001
ECW/TBW _{TR}	0.384 ± 0.008	0.382 ± 0.007	<0.001
ECW/TBW _{UE}	0.378 ± 0.004	0.378 ± 0.005	0.085
ECW/TBW _{LE}	0.388 ± 0.008	0.384 ± 0.008	<0.001
FM/Ht (kg/m)	8.8 ± 3.4	10.1 ± 3.2	<0.001
FFM/Ht (kg/m)	30.1 ± 4.6	29.1 ± 4.4	<0.001
LM/Ht _{WB} (kg/m)	28.3 ± 4.4	27.5 ± 4.2	<0.001
LM/Ht _{TR} (kg/m)	12.9 ± 2.0	13.2 ± 2.0	<0.001
LM/Ht _{UE} (kg/m)	3.1 ± 0.7	3.1 ± 0.6	0.447
LM/Ht _{LE} (kg/m)	9.4 ± 1.7	8.9 ± 1.5	<0.001

All parameters are presented as mean ± standard deviation. BIA; bioelectrical impedance analysis, ECW/TBW_{WB}; ratio of extracellular water to total body water of whole-body, ECW/TBW_{TR}; ratio of extracellular water to total body water of trunk, ECW/TBW_{UE}; ratio of extracellular water to total body water of upper extremities, ECW/TBW_{LE}; ratio of extracellular water to total body water of lower extremities, FM/Ht; height-adjusted fat mass, FFM/Ht; height-adjusted fat free mass, LM/Ht_{WB}; height-adjusted lean mass of whole-body, LM/Ht_{TR}; height-adjusted lean mass of trunk, LM/Ht_{UE}; height-adjusted lean mass of upper extremities, LM/Ht_{LE}; height-adjusted lean mass of lower extremities, SGA; subjective global assessment

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(0.637) and PhA_{TR} (0.601). The cut off value of ECW/TBW_{TR} to predict significant htTKLV values ≥ 2,400 mL/m was 0.387 with sensitivity of 57.7% and specificity of 76%. (Fig 2(B))

Discussion

In a previous study, we found that even in the early stages of CKD, about 30% of patients had SGA score below 6, and that an increased htTKLV was an independent risk factor for malnutrition in ADPKD patients [10]. Therefore, nutritional assessment is important in ADPKD patients, especially for those with large abdominal volume [12]. In addition to SGA, BIA can be used as a nutritional assessment tool, with the advantage of having objective, continuous variables. In ADPKD, with cystic organs, conventional one-cylinder-model BIA might underestimate the TBW, due to the truncal geometry and tissue interfacing [20]. To overcome the limitation of one-cylinder-model BIA in the use of ADPKD patients, we evaluated segmental BIA, which is based on 5-cylinder model, as a quantitative tool for nutritional assessment in ADPKD patients in this study.

The ECW/TBW_{WB}, ECW/TBW_{TR}, and ECW/TBW_{LE} and PhA_{LE} correlated significantly with SGA score of ADPKD patients. Even though the difference was minimal, ECW/TBW_{WB} showed the best correlation with the SGA score. These findings correspond to the results of other studies in various clinical settings. ECW/TBW, which reflects an edematous status and/or malnutrition, is an important clinical factor related with the outcomes of CKD, liver cirrhosis, heart failure, and intensive care unit patients [28–31]. PhA, defined as the vector angle

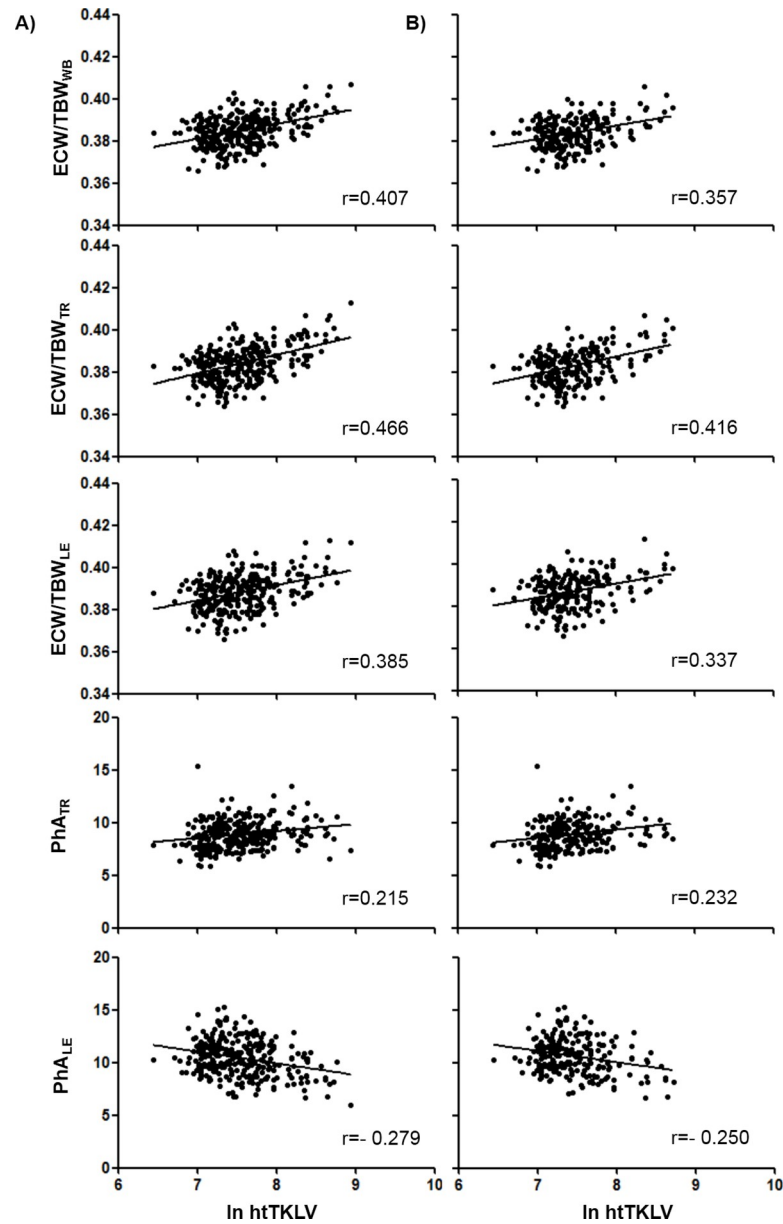


Fig 4. Scatter plot and regression line of BIA parameters with ln htTKLV. Scatter plot of BIA parameters with ln htTKLV in total population and (B) in eGFR ≥ 45 mL/min/1.73 m² patients. ECW/TBW_{WB}, _{TR} and _{LE} and PhA_{TR} showed positive correlation with ln htTKLV. On the contrary, PhA_{LE} showed negative correlation with ln htTKLV. ECW/TBW_{TR} showed highest correlation with ln htTKLV ($r = 0.466$) BIA; bioelectrical impedance analysis, ECW/TBW_{WB}; ratio of extracellular water to total body water of whole-body, ECW/TBW_{TR}; ratio of extracellular water to total body water of trunk, ECW/TBW_{LE}; ratio of extracellular water to total body water of lower extremities, eGFR; estimated glomerular filtration rates, ln htTKLV; natural log value of height-adjusted total kidney and liver volume, PhA_{TR}; Phase angle of trunk, PhA_{LE}; Phase angle of lower extremities.

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difference between the resistance (R) and reactance (Xc), reflects cell viability and membrane stability and is also known as a useful nutritional marker. Reduced PhA values are associated with malnutrition and poor outcomes in patients with CKD, cancer, and liver cirrhosis [32–35]. Our results indicated that high ECW/TBW and low PhA are clinically useful BIA parameters for the detection of malnutrition in ADPKD patients. (Fig 3).

Decreased PhA has been regarded as a one of the best nutritional marker. However, except PhA_{LE} , none of other segmental PhA parameters showed any correlation with the nutritional status in both gender of ADPKD patients. These results could represent the impact of organomegaly, since PhA_{TR} was positively correlated with htTKLV. Therefore, in ADPKD patients, among segmental PhA parameters, only PhA_{LE} , where the effect of organomegaly are minimal are suitable for nutritional parameters.

Since segmental BIA can measure the segmental fluid volume, higher ECW/TBW_{TR} was positively associated with htTKLV. Other parameters such as ECW/TBW_{WB} , ECW/TBW_{LE} , and PhA_{TR} also showed positive correlations and PhA_{LE} demonstrated negative correlations with htTKLV (Fig 4). Our previous study showed that htTKLV was an independent risk factor for malnutrition in ADPKD [10]. ROC analysis showed that ECW/TBW_{TR} of > 0.387 was related to significant htTKLV $\geq 2,400$ mL/m. These data suggested that ECW/TBW_{TR} could reflect nutritional status in ADPKD patients mainly caused by the mass effect of organomegaly.

Deterioration of renal function is another significant factor of malnutrition in ADPKD. To exclude effect of reduced renal function on nutritional status and BIA parameters, we created an adjusted likelihood graph. After adjustment for age, hemoglobin level, and CKD stage, higher ECW/TBW_{WB} , ECW/TBW_{TR} , and ECW/TBW_{LE} and lower PhA_{LE} values were associated with a greater likelihood of malnutrition (S3 Fig). Also in the subgroup analysis with CKD in stages 1-3a population, the correlations of BIA parameters with SGA scores were similar to those in the total population (S2 Table and S3 Table). This implies that, aside from reduced renal function, an increased htTKLV influences the nutritional status of ADPKD patients independently, and that segmental BIA can detect this malnutrition even in early-stage CKD patients. BIA parameters were also directly associated with \ln htTKLV in ADPKD patients even in early CKD stages (Fig 2(B)). An increased htTKLV might affect BIA parameters by causing pressure-related gastrointestinal symptoms that lead to malnutrition [9]. Other pressure-related complications such as caval compression and LE edema could also influence BIA results.

The body composition parameters did not exhibit trends of association with SGA score in ADPKD population as in other CKD patients [36]. In the male subgroup, all the body composition parameters had significant positive correlations with the SGA score, while none were meaningful in females. This discrepancy between the genders could be related to the lower muscle mass in females than in males. Since our study was undertaken in Koreans, and in an outpatient setting where only mild to moderate malnourishment was observed, the degree of sarcopenia might have been too mild to be detected with statistical significance. Also ECW increase in CKD patients due to sodium retention and volume overload can result in overestimation of LM measured by BIA adopting 2-compartment body composition model (FFM and FM) [37, 38]. However in the analysis of the study patients to see the association between ECW/TBW and skeletal muscle index, defined as the sum of appendicular lean mass divided by height square, the majority of patients were in the range of normal volume status (ECW/TBW between 0.36–0.40) and non-sarcopenic status suggesting the minimal effect of volume overload on LM value from BIA in our study patients [39, 40]. (S4 Fig)

It was previously unknown how polycystic masses would be presented in BIA, therefore we compared the BIA results between ADPKD patients and the healthy population. Greater values for body fluid parameters and ECW/TBW_{WB} , ECW/TBW_{TR} , and ECW/TBW_{LE} were observed in the ADPKD group than in the healthy population. Increased ECW/TBW_{WB} and ECW/TBW_{TR} in ADPKD may demonstrated the influence of fluid-filled cysts in the abdominal organs. In case of ECW/TBW_{LE} , where the effect of abdominal cystic mass were minimal, may represent nutritional status per se. However, compression effect of organomegaly on intra-

abdominal vessels which cause LE edema in ADPKD also participate in the increment of ECW/TBW_{LE} .

This study has a few limitations. Since this study was conducted in an outpatient clinic, patients with severe malnutrition have been excluded. Also there was no control subjects with CKD other than ADPKD. The Kidney and liver volumes were measured using CT instead of MRI. Additionally, information on the menstrual cycle in females was not gathered. Even though, this is the first study to evaluate BIA as a nutritional assessment tool in ADPKD patients and to identify the correlation of BIA parameters with abdominal cystic organ volume. In addition, the strength of the present study is that the kidney and liver volumes were measured in every patient to characterize their effect on the nutritional status and their relationship with segmental BIA parameters in ADPKD patients. Follow up studies to determine the association of malnutrition with clinical outcomes are needed. Using other malnutrition criteria such as malnutrition inflammation score [13] and newly developed GLIM criteria [41] would provide more information on the nutritional status in ADPKD patients. Studies of other nutritional biomarkers and body composition measures using a prospective cohort would enhance our understanding and management of malnutrition in ADPKD patients.

In conclusion, the ECW/TBW_{WB} and other BIA parameters of ECW/TBW_{TR} , ECW/TBW_{LE} and PhA_{LE} were qualified malnutrition parameters. The ECW/TBW_{TR} was not only associated with malnutrition, but also with htTKLV. Other parameters such as ECW/TBW_{WB} , ECW/TBW_{LE} and PhA_{LE} also showed correlation with htTKLV but with less significance.

Conclusions

These results showed that segmental BIA can be a suitable tool for assessing nutritional status as well as the impact of abdominal cystic organs in ADPKD patients, which provides continuous and segmental parameters.

Supporting information

S1 Table. Association of BIA parameters with SGA scores according to gender.
(DOCX)

S2 Table. Baseline patient characteristics according to nutritional status as evaluated by SGA in subgroup analysis among CKD stage 1-3A.
(DOCX)

S3 Table. Association of BIA parameters with SGA scores among CKD stage 1-3A.
(DOCX)

S1 Fig. Association of Body fluid parameters with SGA scores. (A) ICW/Ht (L/m), (B) ECW/Ht (L/m), (C) TBW/Ht (L/m).

ICW/Ht , ECW/Ht and TBW/Ht did not show significant association with SGA scores in female population.

*P; P for trends

SGA 7, well-nourished; SGA 6, at risk; SGA 5, mildly malnourished; SGA 3–4, moderately ICW/Ht; height-adjusted intracellular water, ECW/Ht; height-adjusted extracellular water, TBW/Ht; height-adjusted total body water, SGA; subjective global assessment.

(TIF)

S2 Fig. Association of body composition parameters with SGA scores. (A) FM/Ht_{WB} (kg/m), (B) LM/Ht_{WB} (kg/m), (C) LM/Ht_{TR} (kg/m), (D) LM/Ht_{UE} (kg/m), and (E) LM/Ht_{LE} (kg/m).

All body composition parameter did not show significant association with SGA scores in female population.

*P; P for trends

SGA 7, well-nourished; SGA 6, at risk; SGA 5, mildly malnourished; SGA 3–4, moderately FM/Ht; height-adjusted fat mass, FFM/Ht; height-adjusted fat free mass, LM/Ht_{WB}; height-adjusted lean mass of whole-body, LM/Ht_{TR}; height-adjusted lean mass of trunk, LM/Ht_{UE}; height-adjusted lean mass of upper extremities, LM/Ht_{LE}; height-adjusted lean mass of lower extremities, SGA; subjective global assessment.

(TIF)

S3 Fig. Adjusted Likelihood (log odds) of having malnutrition (SGA 4&5 vs 7) according to BIA parameters. A) ECW/TBW_{WB}, (B) ECW/TBW_{TR}, (C) ECW/TBW_{LE} and (D) PhA_{LE} (θ), after adjusted with age, hemoglobin and renal function

In the adjusted likelihood of having malnutrition showed positive correlation with ECW/TBW_{WB}, _{TR} and _{LE} and negative correlation with PhA_{LE}

BIA; bioelectrical impedance analysis, ECW/TBW_{WB}; ratio of extracellular water to total body water of whole-body, ECW/TBW_{TR}; ratio of extracellular water to total body water of trunk, ECW/TBW_{LE}; ratio of extracellular water to total body water of lower extremities, PhA_{LE}; Phase angle of lower extremities, SGA; subjective global assessment.

(TIF)

S4 Fig. Association of ECW/TBW_{WB} with skeletal muscle index. The cutoff value of ECW/TBW for edema was 0.4 and skeletal muscle index for sarcopenia was a) 7.0 kg/m² for male and 5.7 kg/m² for female, respectively.

In the subject group with both ECW/TBW_{WB} > 0.4 and skeletal muscle index higher than the cutoff for sarcopenia, the lean mass could be overestimated because over-hydration are included in the lean mass. However, in our study population, majority of subjects were not included in this group suggesting the minimal effect of volume overload on lean mass measured by BIA.

BIA; bioelectrical impedance analysis, ECW/TBW_{WB}; ratio of extracellular water to total body water of whole-body.

(TIF)

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