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Nutritional Assessment in Autosomal Dominant Polycystic Kidney Disease Patients

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ABSTRACT

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Introduction: In patients with autosomal dominant polycystic kidney disease (ADPKD), malnutrition may develop as renal function declines and the abdominal organs become enlarged. The nutritional status of ADPKD patients was assessed using Subjective Global Assessment (SGA) and the impact of intra-abdominal mass on nutritional status were investigated. SGA is well validated and known as gold standard method in nutritional assessment. However with non-continuous interrupted scale, BIA has limitation in detecting small changes in nutritional status of a patient during follow up. Bioelectrical Impedance Analysis (BIA) is an objective measurement tool, expected to detect the subtle change of nutritional status by repeating

measurements during follow ups. Therefore, in this study BIA was used to assess the efficacy as a nutritional assessment tool compared to SGA and analyzed the correlations with abdominal kidney and liver volume and renal function in ADPKD patients.

Methods: This cross-sectional study was performed at a tertiary hospital outpatient clinic. Anthropometric and laboratory data including serum creatinine, albumin, and cholesterol were collected, and kidney and liver volumes were measured. Total kidney and liver volume was defined as the sum of kidney and liver volume and adjusted by height (htTKLV). Nutritional status was evaluated by using modified SGA, which has been validated in many studies of CKD patients and BIA, a tool used for objective and quantitative nutritional assessment in outpatient clinic. Measurement of BIA was done using Inbody S10, an 8 point tactile multi-frequency segmental BIA. The result of BIA measurement in ADPKD patients were compared with result from healthy population pool after 1:1 matching with age, sex and height.

Results: In a total of 288 patients (47.9% female), the mean age was 48.3±12.2 years and the mean estimated glomerular filtration rate (eGFR) was 65.3±25.3 mL/min/1.73 m^2. Of these patients, 21 (7.3%)

were mildly to moderately malnourished and 63 (21.7%) were at risk of malnutrition. Overall, patients with or at risk of malnutrition were older, had a lower body mass index, lower hemoglobin levels, and poor renal function compared to the well-nourished group. However, statistically significant differences in these parameters were lost in female patients, except for eGFR. In contrast, a higher htTKLV was correlated with a lower SGA score, even in subjects with an eGFR ≥ 45 mL/min/1.73 m2. Subjects with an htTKLV ≥ 2,340 mL/m showed an 8.7-fold higher risk of malnutrition, after adjusting for sex, age, hemoglobin, albumin, and serum creatinine. BIA was measured in same patients with SGA assessment in outpatient setting and compared with healthy population data. In ADPKD patients, compared to control healthy population, the ratio of extracellular water to total body water (ECW/TBW) of whole body and lower extremity were increased but body fat were decreased. Among BIA parameters, ECW/TBW of whole body, trunk and lower extremity and phase angle (PhA) of lower extremity were related to nutritional status. Using ROC curve analysis for malnutrition, whole body ECW/TBW showed highest area under curve (0.762) with cutoff value >0.389 among BIA parameters. Whole body ECW/TBW can predict malnutrition with OR 9.52 for 0.01 increases after adjusting sex, age, Hgb and either sCr or lnhtTKLV. Trunk ECW/TBW correlated with eGFR (r=-0.307) and lnhtTKLV (r=0.466) the most.

Conclusion: Nutritional risk was detected in 30% of ambulatory patients with ADPKD and relatively good renal function. Intra-abdominal organomegaly affected nutritional status independently from renal function deterioration. In ADPKD patients, segmental BIA can be a useful tool for nutritional assessment. High level of ECW/TBW of whole body, trunk and lower extremity and low level of lower extremity PhA can be used as the indicators for malnutrition in ADPKD patients.

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Keywords: Autosomal dominant polycystic kidney disease, malnutrition, subjective global assessment, bioelectrical impedance analysis

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INTRODUCTION

Malnutrition increases mortality, morbidity, and the duration of the hospital stay in various clinical settings in general (1). In chronic kidney disease (CKD), the prevalence of malnutrition increases to 30%–40% of patients, and protein-energy malnutrition is one of the strongest predictors of morbidity and mortality (2),(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). Pre-transplant nutritional status also influences the outcomes of kidney transplantations (6). Therefore, efforts have been made to establish guidelines for properly assessing the nutritional status of CKD patients and intervening to improve their outcomes (7).

Autosomal dominant polycystic kidney disease (ADPKD) is the most common hereditary kidney disease, and can progress to end-stage renal disease (ESRD) as kidney cysts grow. Liver cysts occur in 70%–83% of ADPKD patients (8). Many uncontainable complications can develop as cysts grow to cause massive organomegaly. Organomegaly may cause gastrointestinal symptoms (early satiety, abdominal distension, abdomen and flank pain) and obstructive

complications (hepatic venous outflow obstruction and compression of the inferior vena cava, portal vein, and bile duct), which can lead to ascites, infection, and thrombus. In these patients, pressure effects from the enlarged organs may also result in poor oral intake and eventually malnutrition. Occasionally, massive organomegaly requires volume reduction interventions to relieve symptoms and to improve the patient's quality of life.

In ADPKD, the increasing volumes of the kidney and liver can aggravate malnutrition in addition to the progression of CKD, even in the early stages of disease. Therefore, assessment of nutritional status in the early stages of ADPKD is mandatory to ensure timely interventions that result in the subsequent improvement of clinical outcomes. However, traditional anthropometric parameters, such as body weight and BMI, are of limited value because of the fluid-filled kidneys and liver. In this study, the nutritional status of ambulatory ADPKD patients was evaluated using SGA as a standard method, and identified intra-abdominal organ volume as an independent risk factor for malnutrition for the first time.

Also bioelectrical impedance analysis (BIA) was used to assess the body composition and nutritional status in ADPKD patients, which has been validated in the ESRD or CKD patient. As disease progress in ADPKD patients, renal function decreases and volumes of the

kidney and liver can increase. Therefore regular assessment of nutritional status will be important in ADPKD patients. SGA is an easy and well validated method for nutritional assessment, which is known to correlate with patient's outcome in cross-sectional studies. However, practical application of SGA is limited in detecting subtle change during regular follow up, because it is non-continuous 7 score rating, and subjective scoring system that result might varies due to different evaluators. Additive to SGA, other methods for monitoring ADPKD patients' nutritional status are required and we tested BIA as an option.

BIA is a method that uses the impedance vector, resistance (R) and reactance (Xc), which occur when the small amount of current pass the human body (9). By using the principle that level of electrical resistivity changes according to amount of water in the body, BIA can calculate fluid distribution and body composition. Since accuracy and reproducibility of BIA in ESRD patients has been validated, nowadays, BIA is one of method used to measure body fluid status of pre- and post hemodialysis and estimate the dry body weight (10, 11). BIA has been widely used for nutritional assessments in various disease conditions such as liver cirrhosis, cancer and chronic kidney disease (12-15). Easy to use, short measuring time and non-invasiveness are the main advantages for BIA and also by using quantified continuous parameter, BIA are suitable to detect the subtle changes over time.

Among BIA parameters, increased ratio of extracellular water to total body water (ECW/TBW), also known as edema index, and decreased phase angle (PhA) are related to malnutrition. (13) (16)

Previously, Eugenie C.H. et al, conducted a study to see the correlation between isotope dilution, DEXA, anthropometry method with BIA in renal transplantation patients (17). In his subgroup analysis using nine polycystic kidney disease patients, he suggested that BIA might underestimate total body water (TBW), since cystic water in abdominal organs contributes little to whole body resistance compared to extremities. To overcome this possible shortcoming of one-cylinder model BIA, segmental BIA was employed which use 5-cylinder model that consider upper extremities, lower extremities and trunk as 5 separate cylinders and measure impedance independently. By using segmental BIA, segmental data of ECW/TBW, lean mass and PhA from right arm, left arm, trunk, right leg and left leg could be obtained separately. BIA is one of non-invasive, low cost, and easy to perform methods for nutritional assessment. To evaluate the nutritional status in ADPKD patients, BIA was First, the BIA data of ADPKD patients were compared with healthy population's one to figure out the characteristics of BIA in ADPKD. After then, relationships between BIA parameters and SGA were assessed to find out most suitable BIA parameters for the nutritional assessment in ADPKD.

METHODS

Patient population

ADPKD patients who visited polycystic kidney disease clinic in Seoul National University Hospital from December 2013 to March 2014 were included in this study. Patients of age 18 years and older were enrolled and underwent a standardized evaluation protocol including abdominal computed tomography (CT) scan (18). Patients with active cancer, active infection, CKD stage 5 at the time of enrollment, ESRD treated with renal replacement therapy, or a history of liver resection or liver transplantation due to severe polycystic liver disease were excluded. Electronic medical records were reviewed retrospectively and a total of 288 patients were analyzed.

Since this study was a retrospective one using clinical data, and it did not involve further invasive intervention, treatment, or costs to patients, the study received a consent exemption and it was approved by the Institutional Review Board of Seoul National University Hospital (H-1407-083-594). The patient's record was de-identified and analyzed anonymously. This study was performed in accordance with the Declaration of Helsinki.

Control population

To compare the BIA data of ADPKD patients with normal population data, healthy population data from Inbody Co., Ltd. was used for the 1:1 matched case-control study. 281 people were enrolled from the healthy population data pool, match with sex, age and height ± 2 cm of case patients.

Anthropometric measurement

Anthropometric measurements including height, weight, were measured by standard procedures. Height and body weight were measured to the nearest 0.1 cm and 0.1 kg, respectively. Body mass index (BMI) was calculated as defined as body weight (kg) divided by the square of the body height (m), in units of Kg/m^2.

Clinical data collection

Laboratory tests, including serum hemoglobin, creatinine (sCr), total protein, albumin, and total cholesterol were simultaneously performed at regular outpatient clinic visit. Estimated glomerular filtration rates (eGFR) were calculated by the Chronic Kidney Disease Epidemiology (CKD-EPI) equation, using isotope dilution mass spectrometry-traceable creatinine (19)

Subjective global assessment (SGA)

The SGA score is currently a method of choice for nutritional assessment that has been well validated in various settings and is based on a clinical history and physical examination. Nutritional assessment has been validated in CKD patients as a predictor of complications and outcomes (20)-(21). Based on these results, SGA has been recommended in the Kidney Disease Outcomes Quality Initiative guidelines as a nutritional assessment tool, especially for CKD patients (7). SGA is frequently used as a reference method for evaluating new nutritional assessment techniques.

The modified SGA, which has been validated in many studies of CKD patients (20), was performed to evaluate the nutritional status of ADPKD patients according to the standardized protocol in our clinic from December 2013. A well-trained internist performed SGA to ensure consistency. SGA consists of a medical history (weight changes, dietary intake, gastrointestinal symptoms, functional capacity, and comorbidities related to nutritional needs) and a physical examination. In detail, a clinician inspected subcutaneous fat below the eye, triceps or biceps area or at chest area, and examined the temples, clavicles and the back of the hands for muscle wasting. The presence of edema or ascites was assessed by physical examination. Based on these components, a clinician uses a seven-point scale to reflect an overall

judgment of the patient's nutritional status. The SGA score was interpreted as follows: 7, well nourished; 6, at risk; 5, mildly malnourished; 3–4, moderately malnourished; and 1–2, extremely malnourished (**Figure 1**).

Bioelectrical impedance analysis (BIA)

Inbody S10, (Inbody Co., Ltd, Seoul, Korea) a multi-frequency, segmental BIA analysis were used in this study (22). In outpatient clinic, ambulatory patients were measure by using 4-electrode connected on both hands and feet, in standing position. The BIA data of body fluid, body composition parameters, PhA were collected.

In this study, we modified segmental BIA data; Upper extremity (UE) segmental parameters are defined as the average of left and right UE data and lower extremity (LE) segmental parameters are defined in like matter.

BIA analyzes body composition into body fluid, protein, body fat and mineral following 4-compartment model. To measure body composition it first calculates amount of body fluids by using the fact that cell membrane penetrability differs in alternating current frequency. By using multi-frequency current in the range of 1 kHz to 1 MHz, intracellular water (ICW) and extracellular water (ECW) can be measured. Total body water (TBW) is defined as summation of ICW and ECW. Fat free mass (FFM) can be predicted from TBW and after

extracting bone mineral portion, which is known to consist about 7% of FFM, lean mass (LM) can be calculated. Fat mass (FM) are calculated as FFM subtracted from body weight. Skeletal muscle mass (SMM) are defined as summation of LM of extremities. Quantitative BIA parameters such as TBW, ICW, ECW, protein, mineral, fat free mass, LM and fat mass were adjusted by height.

PhA are vector angle difference between two impedance, resistance (R) and reactance (Xc). The PhA is a parameter meaning viability of cell and cell membrane stability and it is known that lower PhA are related to malnutrition (13). PhA previously meant actually right side body PhA, calculated from right side body impedance. In this study, whole body (WB) PhA was defined as right side body PhA and calculated using right side body impedance as in previous studies.

Also mean extremity PhA was defined as average of upper and LE PhA to exclude the abdomen data which can be altered by abdomen organomegaly.

Volume measurement of kidneys and liver

In our polycystic kidney disease clinic, abdominal CT scans were taken every other year using CT scanners (Somatom Sensation 16, SIEMALES; Light speed Ultra 8, GE; Brilliance CT 64, Philips; and Somatom Definition, SIEMALES). The most recent abdominal CT scan

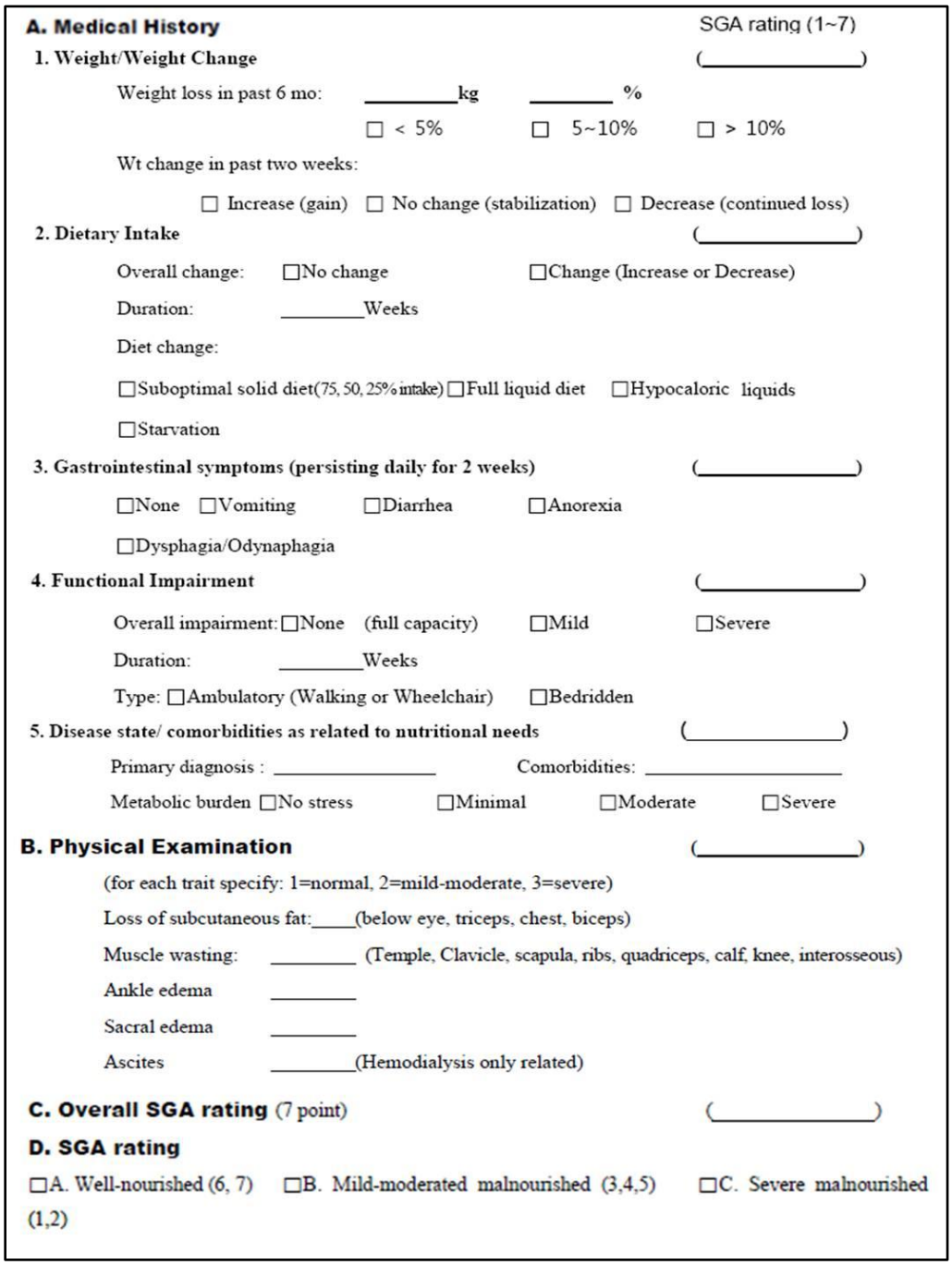
was used to measure total liver volume (TLV) and total kidney volume (TKV). The mean time interval between the CT scan and the nutritional assessment was 12.5 ± 12.6 months. TLV was calculated by adding the product of slice thickness and the area measured on a set of contiguous images generated by CT using Rapidia 2.8 CT software (INFINITT Healthcare Co. Ltd, Seoul, Korea). TKV was estimated by using the ellipsoid method (23). Height-adjusted TLV (htTLV, mL/m) and height-adjusted TKV (htTKV, mL/m) were used in this study. Height-adjusted total kidney and liver volume (htTKLV, mL/m) was defined as the sum of the htTLV and htTKV values.

Statistical analysis

For statistical analysis, analysis of variation (ANOVA) was used for variables with a normal distribution and non-parametric tests was used as appropriate for variables with a non-normal distribution (height, weight, albumin, htTLV, htTKV, htTKLV, BIA parameters). Because no subjects had an SGA score less than 4 in the outpatient environment, all patients were classified into three groups: mildly to moderately malnourished (an SGA score of 4–5), at risk (an SGA score of 6), and well nourished (an SGA score of 7). P-values <0.05 were considered to indicate statistical significance, and p-values <0.017 were used to indicate statistical significance in the post-hoc analysis using

Bonferroni correction for multiple testing.

Receiver operating characteristic (ROC) curve analysis was used to evaluate htTKLV and BIA parameters as a discriminating parameter for malnutrition (SGA score ≤5), in contrast with the well-nourished group (score 7). The Youden index was used to determine the optimal cutoff value. Binominal logistic regression was used to test the significance of the htTKLV threshold after adjusting for sex, age, hemoglobin, albumin, and CKD stage. Correlation analysis and linear logistic regression model were used to analyze the correlation between BIA parameters and htTKLV. The htTKLV was transformed to lnhtTKLV due to skewed distribution of the variable. All statistical analyses were conducted using SPSS version 22 (IBM Corporation, Armonk, NY, USA) and MedCalc for Windows version 14 (MedCalc Software, Ostend, Belgium).



A. Medical History SGA rating (1~7)

1. Weight/Weight Change (_____)

Weight loss in past 6 mo: _____kg _____ %

☐ < 5% ☐ 5~10% ☐ > 10%

Wt change in past two weeks:

☐ Increase (gain) ☐ No change (stabilization) ☐ Decrease (continued loss)

2. Dietary Intake (_____)

Overall change: ☐No change ☐Change (Increase or Decrease)

Duration: _____Weeks

Diet change:

☐Suboptimal solid diet(75, 50, 25% intake) ☐Full liquid diet ☐Hypocaloric liquids

☐Starvation

3. Gastrointestinal symptoms (persisting daily for 2 weeks) (_____)

☐None ☐Vomiting ☐Diarrhea ☐Anorexia

☐Dysphagia/Odynaphagia

4. Functional Impairment (_____)

Overall impairment: ☐None (full capacity) ☐Mild ☐Severe

Duration: _____Weeks

Type: ☐Ambulatory (Walking or Wheelchair) ☐Bedridden

5. Disease state/ comorbidities as related to nutritional needs (_____)

Primary diagnosis : _____ Comorbidities: _____

Metabolic burden ☐No stress ☐Minimal ☐Moderate ☐Severe

B. Physical Examination (_____)

(for each trait specify: 1=normal, 2=mild-moderate, 3=severe)

Loss of subcutaneous fat:____(below eye, triceps, chest, biceps)

Muscle wasting: _____ (Temple, Clavicle, scapula, ribs, quadriceps, calf, knee, interosseous)

Ankle edema _____

Sacral edema _____

Ascites _____(Hemodialysis only related)

C. Overall SGA rating (7 point) (_____)

D. SGA rating

☐A. Well-nourished (6, 7) ☐B. Mild-moderated malnourished (3,4,5) ☐C. Severe malnourished (1,2)

Figure 1. Modified subjective global assessment used in this study

PART I.

Assessment of Nutrition Status in ADPKD Patients Using SGA and Risk Factors

PURPOSE

1. Evaluation of nutritional status using SGA as a standardized method in ADPKD.
2. Evaluation of risk factors of malnutrition in ADPKD
3. Evaluation of impact of organomegaly on malnutrition in ADPKD

RESULTS

Baseline characteristics

A total of 288 patients were included in the analysis, of whom 138 (47.9%) were female. The mean age was 48.3±12.2 years, with no significant difference according to gender. The mean SGA scores were similar (6.7±0.6 vs. 6.6±0.6, p=0.197) between genders. The mean sCr level and the mean eGFR were 1.2±0.6 mg/dL and 65.3±25.3 mL/min/1.73 m^2, respectively. Mean sCr was significantly higher in male than in female patients (1.5±0.6 mg/dL vs. 1.0±0.4 mg/dL, p<0.001), but the eGFR was higher in female patients (62.3±24.5 mL/min/1.73 m^2 vs. 68.5±25.8 mL/min/1.73 m^2, p=0.035). There was no significant difference in albumin level between genders. The distribution of CKD stages was as follows: 52 patients (18.1%) were in stage 1 CKD, 116 (40.3%) were in stage 2, 53 (18.4%) were in stage 3A, 46 (16.0%) were in stage 3B, and 21 (7.3%) were in stage 4. The distribution of CKD showed no difference between genders (Table 1).

Nutritional status of subjects using SGA

Mild to moderate malnutrition was detected in 7.3% of all patients.

Only two patients (0.7%) had an SGA score of 4, and 19 patients (6.6%) had a score of 5. Sixty-three patients (21.9%) were at risk of malnutrition (a score of 6), and 204 (70.8%) were well nourished (a score of 7). No statistical difference was observed in the distribution of SGA scores between genders (**Table 2, Figure 2**)

Patients with malnutrition (SGA 4-5) or at risk for malnutrition (SGA 6) were older than the well-nourished group (SGA 7) (mean age, 53.4±11.1 years vs. 52.7±12.6 years vs. 46.4±11.7 years, respectively, $p<0.001$). In terms of anthropometric parameters, weight (59.1±8.7 kg vs. 62.3±9.7 kg vs. 67.0±12.3 kg, respectively, $p=0.003$) and BMI (22.0±2.7 kg/m^2 vs. 23.3±2.6 kg/m^2 vs. 23.7±2.9 kg/m^2, respectively, $p=0.024$) showed lower values in patients with lower SGA scores. However, this trend was observed only in male patients, and none of the anthropometric parameters was significantly different in female patients (**Figure. 3**).

With regard to laboratory parameters, increased sCr values (1.5±0.6 mg/dL vs. 1.4±0.6 mg/dL vs. 1.2±0.6 mg/dL, respectively, $p=0.004$) and decreased eGFR values (51.3±23.2 mL/min/1.73 m^2 vs. 57.1±24.9 mL/min/1.73 m^2 vs. 69.2±24.6 mL/min/1.73 m^2, respectively, $p<0.001$) were related to lower SGA scores. Hemoglobin (12.8±1.1 g/dL vs. 13.2±1.4 g/dL vs. 13.7±1.5 g/dL, respectively, $p=0.003$) also showed differences according to SGA scores. These findings were

seen only in male patients, but not in female patients. Serum total cholesterol, total protein, and albumin levels showed no differences by SGA score (**Table 2, Fig. 4**).

htTKLV was associated with SGA independently from eGFR

In order to evaluate the mass effect of kidney and liver volume on nutritional status, TKV and TLV were measured using CT scans and adjusted for height. Overall, the mean htTKLV was 2,083.8±1,071.2 mL/m, the mean htTKV was 861.7±607.1 mL/m, and the mean htTLV was 1,222.6±800.9 mL/m. Lower SGA scores corresponded to higher values of htTKLV (3,313±1,967 mL/m vs. 2,213±854 mL/m vs. 1,917±911 mL/m, respectively, $p<0.001$), htTKV (1,346±988 mL/m vs. 991±574 mL/m vs. 772±536 mL/m, respectively, $p<0.001$), and htTLV (1,966±1,515 mL/m vs.1,222±624 mL/m vs. 1,146±706 mL/m, respectively, $p=0.061$), but only htTKLV and htTKV showed a statistically significant relationship to SGA in the total population and in both genders according to Kruskal-Wallis analysis. (**Figure. 5**)

ROC curve analysis was used to compare the volume parameters to identify a threshold predictive of malnutrition (an SGA of 4–5) over a state of being well nourished (an SGA score of 7). Since SGA score category 6 can be ambiguous due to the limitations of SGA itself, ROC

curve was constructed using the data of SGA score 7 (normal) and 4-5 (malnutrition). The area under the curve (AUC) of htTKLV was larger (0.727) than that of htTKV (0.687) and htTLV (0.645). The cut-off value for htTKLV was 2,340 mL/m, with a sensitivity of 66.7% and a specificity of 81.4% (**Figure 6**). By comparison, in an ROC curve analysis between an at-risk or malnourished state over a well-nourished state (an SGA of 4-6 vs. 7), similar but less significant results were obtained (AUC of htTKLV, htTKV, and htTLV were 0.658, 0.646, and 0.571, respectively), and the cut-off value for htTKLV was 2,190 mL/m with a sensitivity of 53.6% and a specificity of 76.5% (data not shown).

It is well known that the enlargement of the kidneys is closely related to renal insufficiency in ADPKD patients (24). As expected, the eGFR fell as the SGA score decreased (**Figure 2**), and the proportion of patients with lower SGA scores increased in our patients as the CKD stages increased from 1 to 3 (**Figure 7**). When the data was stratified by CKD stage, even in stage 1 and 2 CKD, 15.4% and 20.9% of patients were either malnourished or at risk of malnutrition, respectively. Among stage 3 and 4 CKD patients, 43.4% and 42.8% were either malnourished or at risk of malnutrition, respectively. In patients with stage 4 CKD, the proportion of patients with a lower SGA score was slightly lower than among stage 3B CKD patients, which

may have been due to the relatively small number of patients in stage 4 CKD or because the patients with severe organomegaly who had already undergone intervention were excluded.

In order to minimize the confounding effect of renal failure, subgroup analysis was performed in patients with an eGFR ≥ 45 mL/min/1.73 m^2 (CKD stages 1–3A). In these patients, only htTKLV showed a significant association with SGA scores (**Figure 5D**)

Using 2,340 mL/m as the cut-off value of htTKLV based on ROC curve analysis, logistic regression analysis was used to estimate the odds ratio between the malnourished (an SGA score of 4–5) and the well-nourished group (an SGA score of 7). Patients with htTKLV ≥ 2,340 mL/m showed a higher risk of malnutrition (an SGA score of 4–5) (odds ratio= 8.74, 95% confidence interval 3.30–23.13, $p<0.001$), even after adjusting for age, gender, hemoglobin, albumin, and CKD stage. Between the age and CKD, the interaction terms was included for the binomial regression model but it did not showed statistical significance ($p=0.207$).

DISCUSSION

This study shows that the prevalence of malnutrition in ADPKD should not be ignored, since 7.3% of patients were mildly to moderately malnourished (SGA scores of 4 and 5), and 21.9% of patients were at risk of malnutrition (an SGA score of 6), even in the outpatient, non-ESRD setting. From previous studies, the prevalence of malnutrition in stage 4 and 5 CKD has been reported to be 20%–30% (25, 26), and 10%–60% of dialyzed patients have been found to have malnutrition (SGA score ≤B by using conventional SGA or ≤5 by using modified SGA) (27). Cuppari et al. (28) found that approximately 11% of patients with stage 2–5 CKD had protein-energy wasting (SGA ≤ 5) and 32% showed signs of protein-energy wasting (SGA 6). It is not proper to compare our data with those of Cuppari et al. (28), since unlike our patients (58% in stage 1–2 CKD)**,** most participants in their study were in the advanced stages of CKD (48.9% in stage 3 and 40.3% in stage 4), (**Table 1**). However, it is surprising that the prevalence of malnutrition risk is up to 30% in patients treated in an ambulatory setting with relatively good renal function. The data was further analyzed whether these findings in ADPKD could be due to the increased volume of the kidneys and liver, regardless of stages of CKD. In this study, SGA score correlated with htTKLV even in the patients

with relatively well preserved kidney function (eGFR ≥ 45 mL/min/1.73 m^2 or CKD stages 1–3A).

Renal insufficiency itself can contribute to malnutrition and protein-energy wasting (29). In this study, it was also observed that increased proportions of patients with malnutrition as the CKD stage advanced. The proportion of patients with a lower SGA score was slightly lower in stage 4 CKD than stage 3B patients, which may have been due to the relatively small number of patients in stage 4 CKD or because patients with severe organomegaly who had already undergone interventions were excluded. In addition, when the parameters were analyzed with SGA scores, most anthropometric or laboratory parameters that are widely used as markers for nutritional status failed to show an association with SGA scores, except for renal function. This finding that renal function was significantly related to SGA scores suggests regular assessment of nutritional status in ADPKD patients is needed as the disease progresses.

The association of parameters with SGA scores was different between genders. In male patients, old age, lower body weight, lower BMI, and lower hemoglobin levels were related to lower SGA scores, but these relationships were not seen in female patients. Since women have relatively less muscle mass than men, changes in body weight and BMI caused by malnutrition might be too small to be detected.

Moreover, enlarged cysts, ascites, or edemas, which are frequent complications in ADPKD patients, may mask the reduction in muscle mass or fat proportion in the body. Laboratory parameters such as hemoglobin, total protein, albumin, or total cholesterol were not sensitive enough to detect changes in nutritional status during the early stages of malnutrition. Thus, other markers for evaluation of nutritional status should be developed for patients with ADPKD, especially for female ADPKD patients.

Although previous studies have assessed the association of htTKV with renal function outcomes (30) and poor quality of life (31), this is the first study to assess the nutritional status of ADPKD patients and its relationship with htTKLV. In our previous study, an htTLV value >1,600 mL/m was associated with increased pressure-related symptoms (32). Therefore, it was hypothesized that an enlarged liver and/or kidneys may exert a mass effect on the nearby areas of the gastrointestinal tract, causing gastrointestinal symptoms and eventually affecting the nutritional status of ADPKD patients. With this in mind, htTKV and htTLV were measured, defining htTKLV to reflect the total mass effect of the enlarged kidneys and liver. This study showed that htTKLV was the sole significant predictor of malnutrition after adjusting for other risk factors, including renal function. Even in subjects with relatively good renal function (eGFR ≥45 mL/min/1.73

m^2), htTKLV was significantly associated with SGA scores of 4 and 5. Based on the ROC curve analysis and binominal logistic regression, htTKLV values ≥2,340 mL/m, which is three times larger than the mean liver volume of healthy individuals (33), raised the risk of malnutrition by more than eightfold in ADPKD patients. When compared with htTLV and htTKV, htTKLV showed a closer relationship to malnutrition on the ROC curve, suggesting that total organ volume, instead of the size of each organ, may be responsible for the mass effect and the corresponding symptoms. However, since patients with severe polycystic liver disease who underwent surgical therapy (n=16; mean htTLV, 5,136±2,563 mL/m) were excluded, the statistical association of htTLV with SGA scores could have been underestimated.

In this study, it was noticed that 23.5% of patients had nutritional problem even in early stage CKD (stage 1-3a). In addition, increased htTKLV was an independent risk factor after adjusting for kidney function by using a multivariate logistic regression model. Other nutritional biomarkers, such as prealbumin, insulin-like growth factor-1, or transferrin, were not assessed in this study. htTKLV could provide valuable information about nutritional status as well as the progression of disease, but it is cumbersome to measure with current methods. Therefore, developing new tools for the nutritional assessment of ADPKD patients is necessary, and such tools would be useful for

improving long-term patient outcomes.

Even though this is the first observational study showing the impact of abdominal mass on nutritional status in ADPKD, it has several limitations. Relatively small numbers of patients in the low-SGA group may have undermined the statistical power, especially in females. Moreover, our hypothesis that the mass effect from enlarged livers and kidneys may be related to nutrition needs to be further verified by comparing with other non-ADPKD CKD groups, which was not presented because of lack of data on nutritional status in the early CKD stages. Proper case control study with CKD cases would give us more understanding in assessing the nutritional status in ADPKD patients. Although SGA is a well-validated method for nutritional assessment in patients with a range of conditions and is easy to perform, its ability to detect subtle changes in long-term nutritional status needs to be validated. Therefore, this study should be replicated in other larger cohorts, preferably in the form of a multicenter design including non-Asian populations.

Conclusion

In conclusion, detecting marginal malnutrition in patients in ADPKD outpatient clinics and initiating proper support can play an important therapeutic role, especially in patients who have decreased renal function or an increased htTKLV. Frequent malnutrition was detected in ambulatory ADPKD patients with relatively good function. Renal function decrease was the risk factor in both gender and anthropometric parameters and laboratory parameters cannot detect the malnutrition especially in female. Measuring htTKLV is important in ADPKD patient that htTKLV ≥ 2,340 mL/m showed 8.7-fold higher risk of malnutrition.

Table 1. Baseline patient characteristics according to gender

Parameters	Male	Female	Total	P-value
Number of patients	150	138	288	
Age (years)	47.4±13.6	49.4±10.4	48.3±12.2	0.155
Height (cm)	173.2±6.8	159.1±5.7	166.4±9.5	*<0.001*
Weight (kg)	72.1±10.9	58.1±7.7	65.4±11.8	*<0.001*
BMI (kg/m^2)	23.9±2.9	22.9±2.7	23.4±2.8	*0.004*
Hemoglobin (g/dL)	14.3±1.6	12.7±1.0	13.5±1.5	*<0.001*
Serum Creatinine (mg/dL)	1.5±0.6	1.0±0.4	1.2±0.6	*<0.001*
eGFR (mL/min/1.73 m^2)	62.3±24.5	68.5±25.8	65.3±25.3	*0.035*
Serum protein (g/dL)	7.3±0.4	7.3±0.4	7.3±0.4	0.703
Serum albumin (g/dL)	4.4±0.3	4.3±0.4	4.4±0.3	0.421
Total cholesterol (mg/dL)	176.9±25.9	1,77.6±27.3	1,77.2±26.5	0.844
htTKLV (mL/m)	1,998±870	2,177±1251	2,084±1071	0.960
htTKV (mL/m)	922±631	796±575	862±607	0.057
htTLV (mL/m)	1,077±484	1,381±1020	1,223±801	0.407
SGA score				0.277
4	1	1	2	
5	11	8	19	
6	26	37	63	
7	112	92	204	
CKD stage				0.107
1	21 (14%)	31 (22.5%)	52 (18.1%)	
2	61 (40.7%)	55 (39.9%)	116 (40.3%)	
3A	29 (19.3%)	24 (17.4%)	53 (18.4%)	
3B	24 (16%)	22 (15.9%)	46 (16%)	
4	15 (10%)	6 (4.3%)	21 (7.3%)	

BMI; body mass index, CKD; chronic kidney disease, eGFR; estimated glomerular filtration rates, htTKLV; height-adjusted total abdominal volume, htTKV; height-adjusted total kidney volume, htTLV; height-adjusted total liver volume, SGA, subjective global assessment.

Table 2. Baseline patient characteristics according to nutritional status as evaluated by SGA

Parameters	Mildly to moderately malnourished (SGA 4 and 5)	At risk (SGA 6)	Well nourished (SGA 7)	P-value
Number of patients	21 (7.3%)	63 (21.9%)	204 (70.8%)	
Female	9 (42.9%)	37 (58.7%)	92 (45.1%)	0.148
Age (years)	53.4±11.1	52.7±12.6	46.4±11.7	**<0.001**
Height (cm)	164.0±7.9	163.4±7.9	167.6±9.8	**0.005**
Weight (kg)	59.1±8.7	62.3±9.7	67.0±12.3	**0.003**
BMI (kg/m^2)	22.0±2.7	23.3±2.6	23.7±2.9	**0.024**
Hemoglobin (g/dL)	12.8±1.1	13.2±1.4	13.7±1.5	**0.003**
Serum creatinine (mg/dL)	1.5±0.6	1.4±0.6	1.2±0.6	**0.004**
eGFR (mL/min/1.73 m^2)	51.3±23.2	57.1±24.9	69.2±24.6	**<0.001**
Protein (g/dL)	7.4±0.4	7.2±0.4	7.3±0.4	0.198
Albumin (g/dL)	4.4±0.3	4.3±0.3	4.4±0.4	0.605
Total cholesterol (mg/dL)	180.3±30.2	175.8 ±27.7	177.4±26.0	0.608
htTKLV (mL/m)	3,313±1967	2,213±854	1,917±911	**<0.001**
htTKV (mL/m)	1,346±988	991±574	772±536	**<0.001**
htTLV (mL/m)	1,966±1515	1,222±624	1,146±706	0.091
CKD stage				**0.001**
1	1 (4.8%)	7 (11.1%)	44 (21.6%)	
2	5 (23.8%)	19 (30.2%)	92 (45.1%)	
3A	4 (19.0%)	16 (25.4%)	33 (16.2%)	
3B	9 (42.9%)	14 (22.2%)	23 (11.3%)	
4	2 (9.5%)	7 (11.1%)	12 (5.9%)	

BMI; body mass index, CKD; chronic kidney disease, eGFR; estimated glomerular filtration rates, htTKLV; height-adjusted total abdominal volume, htTKV; height-adjusted total kidney volume, htTLV; height-adjusted total liver volume, SGA, subjective global assessment.

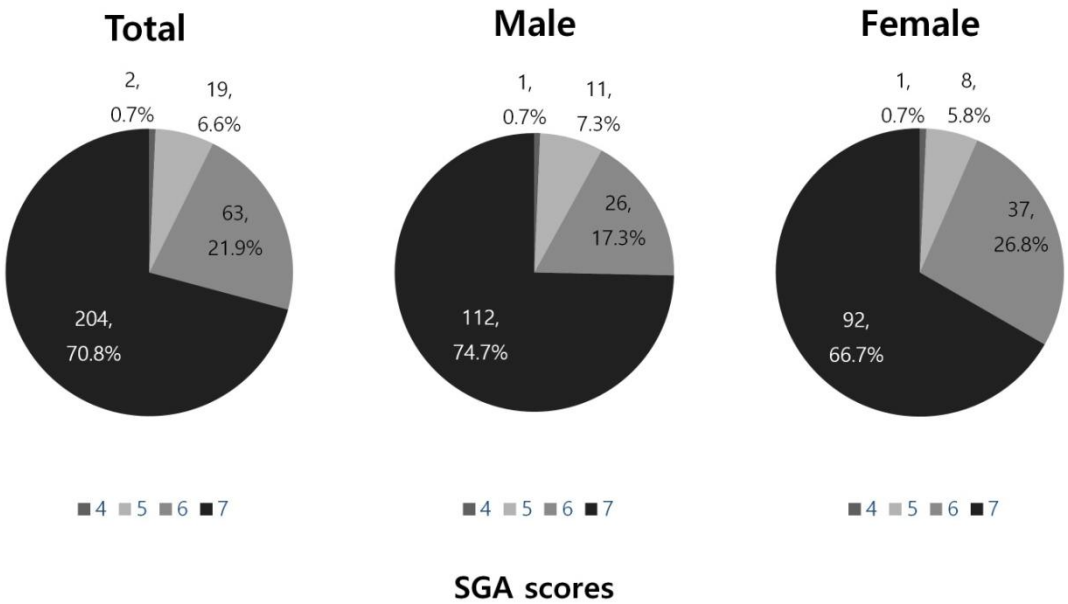


Figure 2. Distribution of SGA scores according to gender

SGA; subjective global assessment
SGA 7, well-nourished; SGA 6, at risk; SGA 5, mildly malnourished; SGA 3–4, moderately malnourished

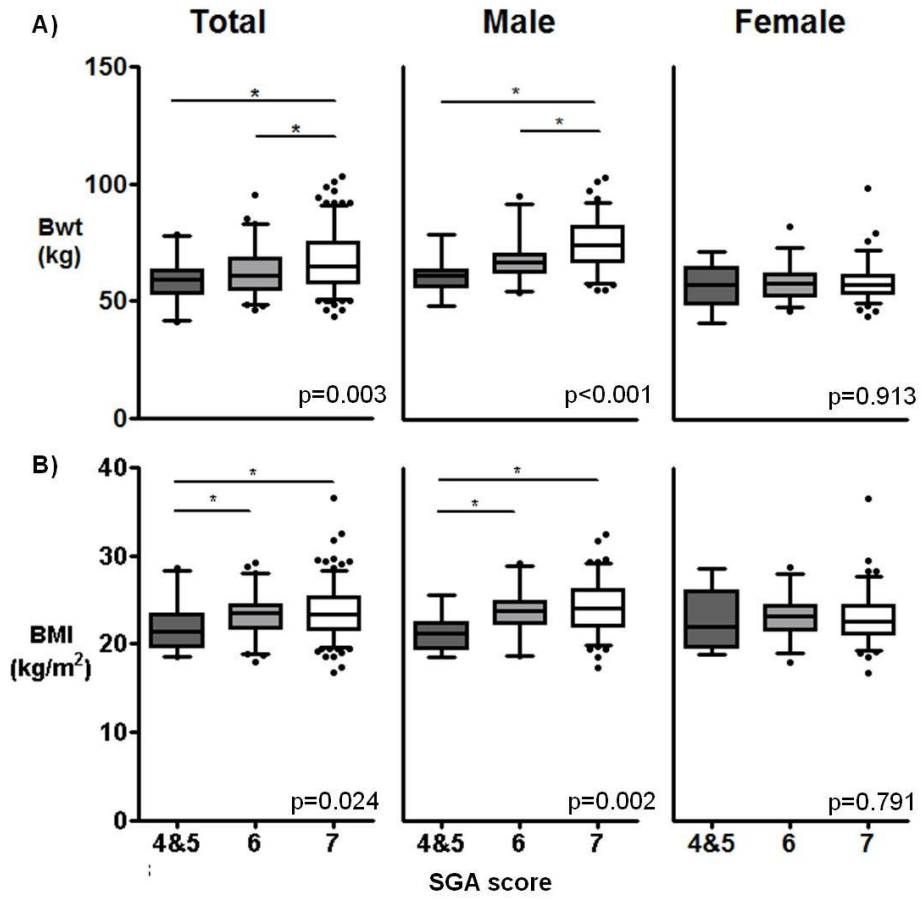


Figure 3. Correlations between the SGA score and the anthropometric nutritional parameters

(A) body weight (Bwt) and (B) body mass index (BMI)
*P<0.017 for post-hoc analysis
SGA; subjective global assessment
SGA 7, well-nourished; SGA 6, at risk; SGA 5, mildly malnourished; SGA 3–4, moderately malnourished

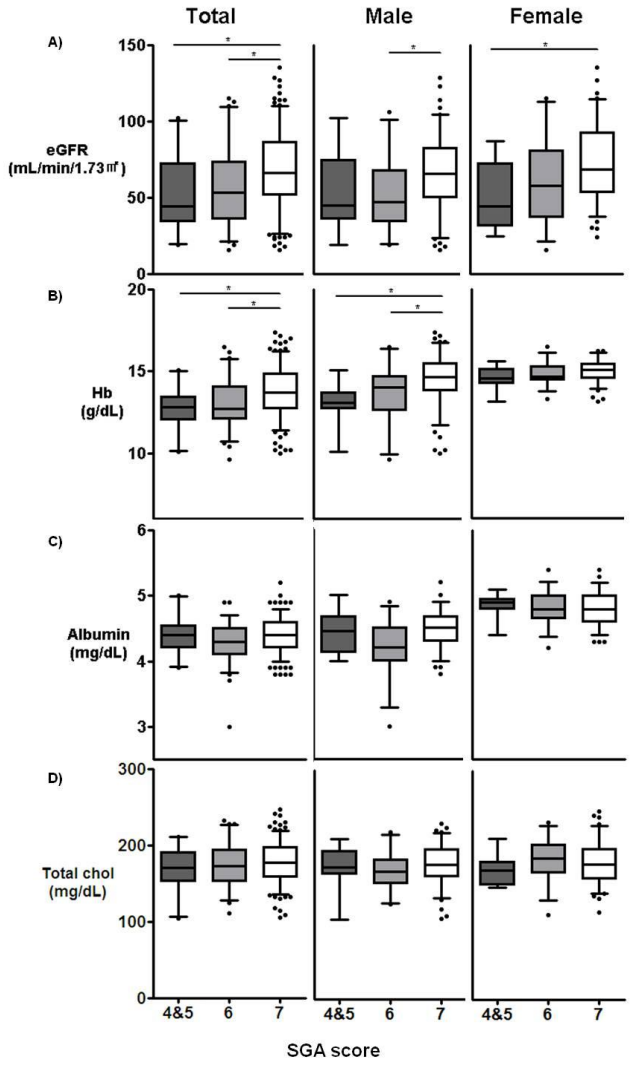


Figure 4. Correlations between the SGA score and laboratory marker

(A) Estimated glomerular filtration rate (eGFR), (B) hemoglobin (Hb), (C) albumin, and (D) total cholesterol (total chol)

*P<0.017 for post-hoc analysis

SGA: subjective global assessment

SGA 7, well-nourished; SGA 6, at risk; SGA 5, mildly malnourished; SGA 3–4, moderately malnourished

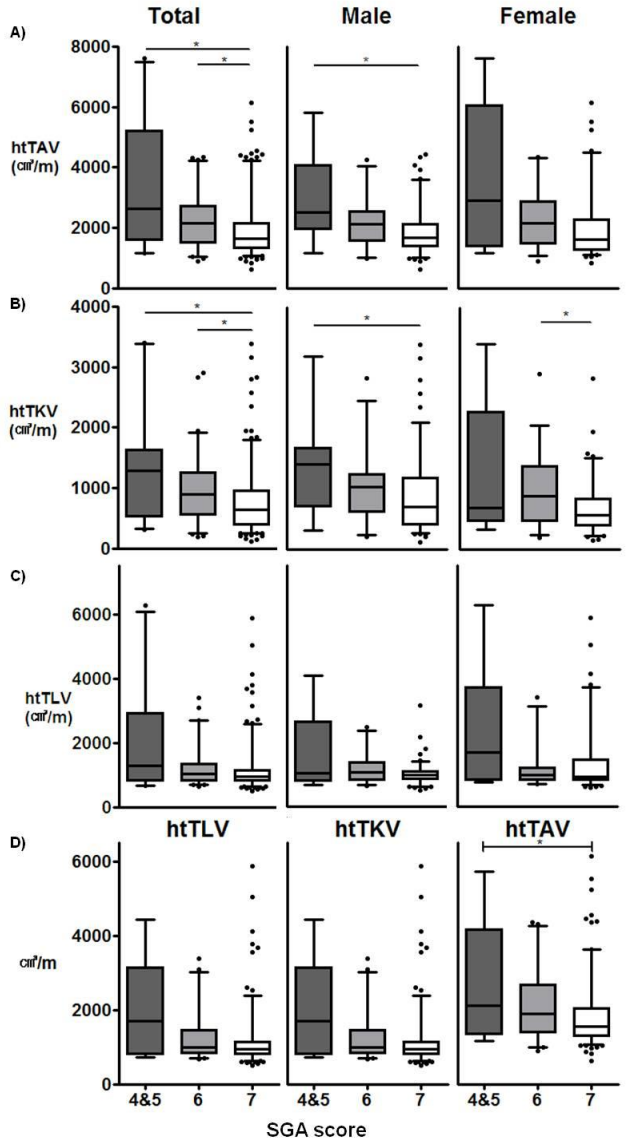


Figure 5. Correlations between the SGA score and abdominal volume

(A) height-adjusted total kidney and liver volume (htTKLV), (B) height-adjusted total kidney volume (htTKV), and (C) height-adjusted total liver volume (htTLV); (D) correlation between SGA score and abdominal volume in subjects with an eGFR ≥45 mL/min/1.73 m^2

*P<0.017 for post-hoc analysis

SGA; subjective global assessment

SGA 7, well-nourished; SGA 6, at risk; SGA 5, mildly malnourished; SGA 3–4 moderately malnourished

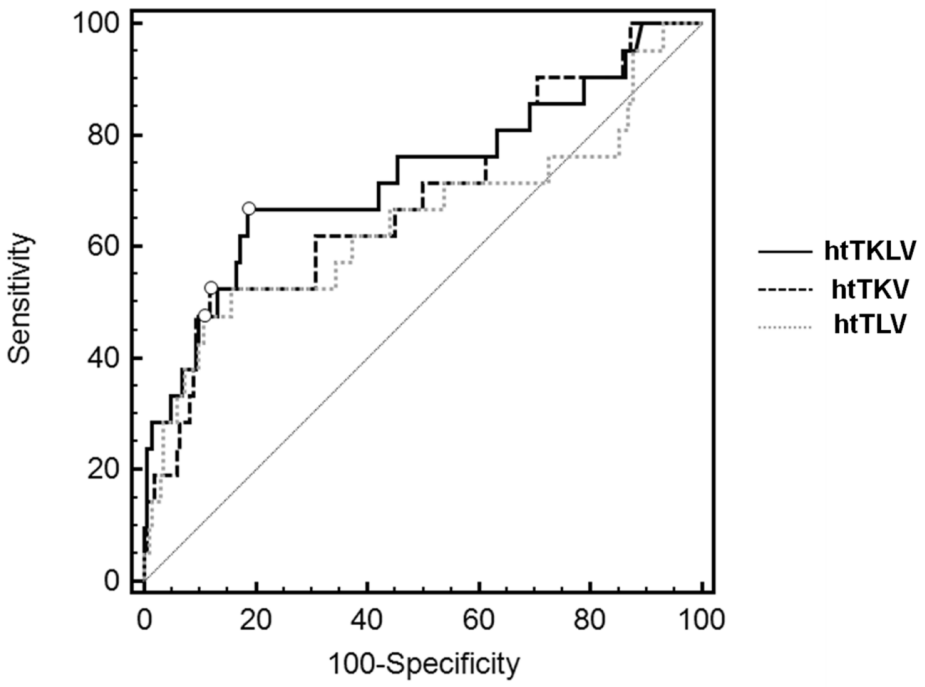


Figure 6. ROC curve of htTKLV, comparing SGA scores of 4 and 5 to 7

htTKLV; height-adjusted total abdominal volume, htTKV; height-adjusted total kidney volume, htTLV; height-adjusted total liver volume, ROC; receiver-operating characteristics, SGA; subjective global assessment

SGA 7, well-nourished; SGA 6, at risk; SGA 5, mildly malnourished; SGA 3–4, moderately malnourished

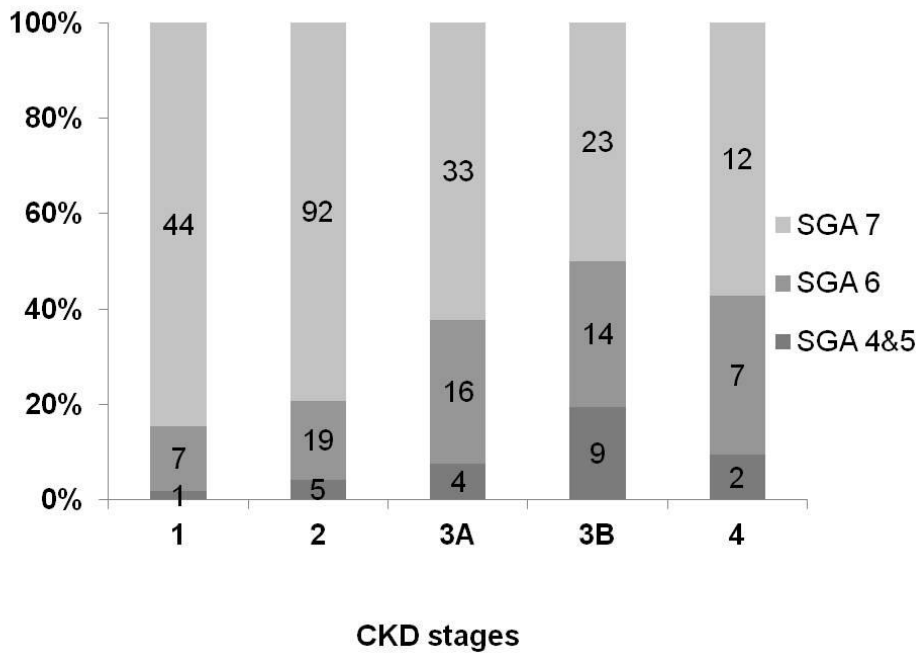


Figure 7. SGA score distribution according to CKD stages

P-values were obtained using the Fisher's exact test
Bars indicate the percentage of patients in each category
CKD; chronic kidney disease, SGA; subjective global assessment

PART II

Efficacy of Bioelectrical Impedance Analysis in

Nutritional Assessment of ADPKD patients

PURPOSE

The regular assessment of nutritional status is important especially in ADPKD patients, as renal function decreases and abdominal organ volume increases. SGA has limitations in detecting subtle changes in a patient during follow up, since it is non-continuous 7 score rating, and subjective scoring system. Most routine laboratory parameters are not sensitive enough to detect nutritional insufficiency, especially in a female. Therefore, other methods for monitoring nutritional status in ADPKD patients are required.

BIA is a non-invasive, low cost, and easy-to-perform method for nutritional assessment. This study was performed to evaluate the BIA as a tool for nutritional assessment in ADPKD. First, the BIA data of ADPKD patients were compared with those of healthy general population to figure out the characteristics of BIA in ADPKD. Then, relationships between various BIA parameters and SGA were assessed to find out most suitable BIA parameters reflecting nutritional status in subjects with ADPKD.

RESULTS

Differences in BIA Parameters between healthy population and ADPKD

To characterize the BIA parameters in ADPKD, 1:1 matched case-control study was conducted using data obtained from 281 healthy subjects, 1:1 matching with sex, age and height ±2 cm from Inbody Co., Ltd,. After matching with sex, age and height, there was no significant difference in weight and BMI between two groups (p=0.086 and 0.088, respectively). (**Table 3**)

All body fluid parameters, ICW/Ht (13.6±2.2 L/m vs13.2±2.1 L/m, p<0.001 for case versus control), ECW/Ht (8.5±1.2 L/m vs. 8.2±1.2 L/m, <0.001) and TBW/Ht (22.1±3.4 L/m vs. 21.4±2.3 L/m, p<0.001) were increased in ADPKD patients. ECW/TBW of the whole body (WB, 0.385±0.007 vs. 0.382±0.007, p<0.001), and the lower extremity (LE, 0.388±0.008 vs. 0.384±0.008, p<0.001) were also increased in ADPKD patients in total and both genders. However, between ADPKD and healthy population, no differences in the upper extremity (UE) ECW/TBW in male gender and no differences in trunk ECW/TBW in male and total subjects were noted.

In body composition parameters, fat free mass normalized to height (FFM/Ht) were increased in ADPKD patients (33.6±3.3 kg/m vs.

32.4±3.1 kg/m, 26.4±2.3 kg/m vs. 25.6±2.4 kg/m and 30.1±4.6 kg/m vs. 29.1±4.4 kg/m, all p<0.001) in total and both genders. Since the weight in two groups were similar and FFM/Ht were increased in ADPKD patients, relatively fat mass normalized to height (FM/Ht) was significantly decreased in ADPKD patients in total and both genders (7.6±3.1 kg/m vs. 8.9±2.9 kg/m in total, 10.1±3.3 kg/m vs. 11.3±3.0 kg/m in male and 8.8±3.4 kg/m vs. 10.1±3.2 kg/m in female, all p<0.001).

Lean mass normalized to height (LM/Ht) of WB, which consists of body fluid, protein and non-osseous mineral, is also increased in ADPKD patients, compared with healthy population (31.6±3.4 kg/m vs. 30.7±2.9 kg/m, 24.8±2.1 kg/m vs. 24.1±2.3 kg/m and 28.3±4.4 kg/m vs. 27.5±4.2 kg/m, p<0.001). LE LM/Ht was increased likewise (10.7±1.2 kg/m vs. 10.1±1.0 kg/m, 8.0±0.9 kg/m vs. 7.7±0.9 kg/m and 9.4±1.7 kg/m vs. 8.9±1.5 kg/m, with all p<0.001). On the contrary, trunk LM/ht were decreased in ADPKD patients in total and both genders (14.5±1.4 kg/m vs. 14.7±1.4 kg/m, p=0.008, 11.2±1.0 kg/m vs. 11.6±1.2 kg/m, p<0.001 and 12.9±2.0 kg/m vs13.2±2.0 kg/m, p<0.001). UE LM/Ht did not show statistical difference between two groups in total and male patients (p=0.447 and 0.123, respectively) and in female ADPKD patients, it was decreased in the patient group (2.5±0.4 vs. 2.6±0.4, p=0.002). skeletal muscle mass normalized to height (SMM/Ht), which

means sum of LM in extremities, was increased in ADPKD group in male, (18.8±2.0 kg/m vs. 18.2±1.9 kg/m, p<0.001), but it did not show difference in total and female gender (p-value 0.170 and 0.939, respectively)

Association of Body Fluid Parameters with SGA in ADPKD

When we analyzed body fluid BIA parameters across SGA score groups, lower SGA scores group exhibited increased ECW/TBW ratios of the whole body (0.391±0.009 vs. 0.387±0.007 vs. 0.383±0.007, respectively, p<0.001), trunk (0.391±0.01 vs. 0.387±0.008 vs. 0.382±0.007, respectively, p<0.001) and the lower extremity (0.395±0.010 vs. 0.391±0.008 vs. 0.387±0.007, respectively, p<0.001). UE ECW/TBW did not show a significant difference between the three SGA score groups (p=0.099). For the detailed distribution of body water, low SGA scores group was associated with lower ICW/Ht (13.0±1.8 L/m vs. 13.0±1.9 L/m vs. 13.9±2.3 L/m for SGA 4&5 vs. SGA 6 vs. SGA 7 respectively, p=0.012) and TBW/Ht (21.3±2.9 L/m vs. 21.3±3.0 L/m vs. 22.6±3.6 L/m, respectively, p=0.024). However, ECW/Ht was marginally higher in well-nourished group (SGA 7), which was not statistical significant in total population (p=0.076). (**Table 4**)

Subgroup analysis with respect to the gender was conducted. (**Table 5**) As in total population, correlations of increased ECW/TBW of WB, trunk and LE with low SGA scores were observed in both genders. (**Figure 7**) UE ECW/TBW did not show statistically significant differences between SGA score groups in both genders. In male, ICW/Ht (13.9±1.6 L/m vs. 14.8±1.3 L/m vs. 15.6±1.5 L/m, respectively, p=0.001), ECW/Ht (8.8±1.2 L/m vs. 9.2±0.7 L/m vs. 9.6±0.9 L/m, respectively, p=0.009) and TBW/Ht (22.6±2.7 L/m vs. 24.0±2.0 L/m vs. 25.2±2.5 L/m, respectively, p=0.002) were larger in higher SGA score groups, which difference was not seen in female (p=0.753, 0.591 and 0.849 for ICW/Ht, ECW/Ht and TBW/Ht, respectively).

Association of Body Composition Parameters with SGA in ADPKD

We analyzed the body composition parameters among three SGA groups, where FM/Ht (7.0±3.7 kg/m vs. 9.0±3.4 kg/m vs. 8.9±3.4 kg/m, respectively, p=0.011), FFM/Ht (29.0±4.0 kg/m vs. 29.0±4.1 kg/m vs. 30.8±4.8 kg/m, respectively, p=0.024), LM/Ht (27.3±3.7 kg/m vs. 27.2±3.9 kg/m vs. 28.9±4.7 kg/m, respectively, p=0.028) and SMM/Ht (15.7±2.4 kg/m vs. 15.8±2.6 kg/m vs. 17.0±3.0 kg/m, respectively, p=0.011) had statistically significant differences between three groups.

However, only SMM/Ht showed definite trend of decreasing mean mass as SGA score gets lower and significant difference between malnourished group (SGA 4&5) with the other groups. (**Table 4**)

All the segmental parameters of LM, such as trunk LM/Ht (p=0.007), UE LM/Ht (p=0.011) and LE LM/Ht (p=0.020) showed differences according to SGA scores but only trunk LM/ht showed definite decreasing trends with the lowering of SGA scores.

In subgroup analysis according to gender, male had definite decreasing trends of FM/Ht (5.3±1.9 kg/m vs. 7.3±3.7 kg/m vs. 8.1±3.0 kg/m, respectively, p=0.006), FFM/Ht (30.8±3.7 kg/m vs. 32.7±2.8 kg/m vs. 34.3±3.4 kg/m, respectively, p=0.002), LM/Ht (29.0±3.5 kg/m vs. 30.8±2.6 kg/m vs. 32.2±3.5 kg/m, respectively, p=0.002) and SMM/Ht (16.9±2.1 kg/m vs. 18.1±1.7 kg/m vs. 19.2±2.0 kg/m, respectively, p=0.001) with the lowering of SGA scores.. Also segmental LM/Ht showed difference between SGA groups (p<0.001 for both trunk and UE LM/Ht and p=0.001 for LE LM/Ht). However, in female, all the body composition parameters did not show differences between SGA score groups (p=0.363, 0.863, 0.847, 0.769, 0.707, 0.762 and 0.809 for FM/Ht, FFM/Ht, LM/Ht, SMM/Ht, trunk LM/Ht, UE LM/Ht and LE LM/Ht). (**Table 6, Figure 9**)

Association of Nutritional Parameters with SGA in ADPKD

Phase angle (PhA), the BIA parameter representing nutritional status, were evaluated for correlation with SGA scores. Mean extremity PhA (4.7±0.7 θ vs. 5.0±0.7 θ vs. 5.3±0.7 θ, respectively, p<0.001), trunk PhA (8.6±1.4 θ vs. 8.6±1.3 θ vs. 9.0±1.3 θ, respectively, p=0.049), UE PhA (5.0±0.5 θ vs. 5.0±0.6 θ vs. 5.3±0.7 θ, respectively, p=0.001) and LE PhA (5.0±0.5 θ vs. 5.0±0.6 θ vs. 5.3±0.7 θ, respectively, p=0.001) showed significant differences between three SGA groups. However only mean extremity PhA and LE PhA definitely showed trends of decreasing values as SGA score lowers. WB PhA, reported as nutritional marker in previous studies (13), did not show statistical significant difference among three groups (p=0.064). (**Table 4**)

Mean extremity PhA (5.1±0.6 θ vs. 5.4±0.7 θ vs. 5.8±0.5 θ, p=0.001 in male and 4.3±0.4 θ vs. 4.7±0.5 θ vs. 4.8±0.4 θ, p=0.013 in female) and LE PhA (10.3±1.1 θ vs. 10.9±1.2 θ vs. 11.5±1.0 θ, p<0.001 in male and 8.1±1.3 θ vs. 9.3±1.3 θ vs. 9.6±1.0 θ, p=0.004 in female) are the only parameters showing significant difference in both genders. UE PhA failed to show differences in female (p=0.267). The statistical significance of trunk PhA seen in total group, was lost in both genders (p=0.108 for male and p=0.750 for female). (**Table 7, Figure 10**).

ROC Curve Analysis of BIA Parameters with SGA in ADPKD

The Receiver Operating Characteristic (ROC) curve analysis was undertaken to compare various BIA parameters to identify the most suitable BIA parameter to predict malnourished group (SGA 4&5). ECW/TBW of WB, trunk, LE, mean extremity PhA and LE, which showed statistically significant difference between malnourished group (SGA 4&5), at risk group (SGA 6) and well-nourished group (SGA 7) in both genders were analyzed. The ROC curve was generated using the data of SGA score 7 (well nourished) and 4-5 (malnutrition).

The area-under-the-curve (AUC) of all parameters were above 0.7. AUC of WB ECW/TBW was the largest (0.762) and AUC of other parameters decreased in following order; trunk ECW/TBW (0.758), LE ECW/TBW (0.747), LE PhA (0.741) and mean extremity PhA (0.726). The cut-off value for WB ECW/TBW was 0.389 with a sensitivity of 71.4% and specificity of 80.4% and the cut-off for LE PhA was 8.6 with the sensitivity of 57.1% and specificity of 91.2%. (**Table 8, Figure 11**)

Logistic Regression Model to Predict Malnutrition Using BIA Parameters

The logistic regression analysis was conducted using WB ECW/TBW, to estimate the odds ratio between the malnourished (an SGA score of 4–5) and the well-nourished group (an SGA score of 7). In model 1, after adjustment with age, sex, hemoglobin, and sCr, higher WB ECW/TBW was significantly associated with malnutrition (for 0.01 increase of WB ECW/TBW, the odds ratio of 9.52, 95% confidence interval 3.78–23.9, p<0.001). In the model 2, after adjustment with age, sex, hemoglobin, and lnhtTKLV, the result was the same. In both model, interaction terms between WB ECW/TBW with sCr (model 1) and lnhtTKLV (model 2) respectively for the binominal regression model, did not show a statistical significance (p=0.957 for model 1, and p=0.214 for model 2).

Association between BIA Parameters and Renal Function

The scatter plots between eGFR with BIA parameters were shown in **Figure 12A** to see the effect of kidney function on BIA parameters. ECW/TBW of WB, trunk and LE showed negative correlation with eGFR with r=-0.292, r=-0.307 and r=-0.299 respectively. While LE PhA showed statistically significant positive correlation with eGFR (r=0.187), trunk PhA did not show significant correlation (p=0.635). When we

categorized kidney function into CKD stages and investigated the relationship with BIA parameters, trends for increased ECW/TBW of WB, trunk, LE were noticed as CKD progress. In LE PhA, this trend was weak and trunk PhA did not show a significant relationship with CKD stage. (**Figure 13**)

Association between BIA Parameters and Abdominal Organ Volume

Study in part I showed that among various markers of abdominal organ volume, htTKLV showed better correlation with SGA score than htTKV and htTLV. Using segmental BIA data, correlation analysis between various BIA parameters and htTKLV were undertaken. Since htTKLV has a skewed distribution, the natural log transformation of htTKLV (lnhtTKLV) was used. **Figure 12B** shows the scatter plot of htTKLV with BIA parameters such as ECW/TBW of WB, trunk and LE, trunk PhA and LE PhA. Trunk ECW/TBW showed a higher correlation (r=0.466) than other parameters, followed by WB ECW/TBW (r=0.407), LE ECW/TBW (r=0.385) and trunk PhA (r=0.215). LE PhA showed a negative correlation with lnhtTKLV (r=-0.279). To preclude the possible effect of decreased kidney function on the various BIA parameters, correlation analysis between htTKLV

and various BIA parameters were undertaken in a subgroup of patients with eGFR ≥45 mL/min/1.73 m^2. In this subgroup with relatively preserved renal function, the correlation between htTKLV and various BIA parameters were also observed with the following order; trunk ECW/TBW (r=0.416), WB ECW/TBW (r=0.357), LE ECW/TBW (r=0.337), trunk PhA (r=0.232) and LE PhA (r=-0.250).

Partial correlation analysis was conducted after adjustment with eGFR to exclude the effect of eGFR on BIA parameters, where trunk ECW/TBW showed higher correlation (r=0.378) than other parameters - WB ECW/TBW (r=0.317), LE ECW/TBW (r=0.284), trunk PhA (0.233) and LE PhA (r=-0.218). To investigate whether BIA parameters such as the trunk ECW/TBW can predict the lnhtTKLV, simple regression model was used. By the model, trunk ECW/TBW could predict lnhtTKLV at 21.7% ($p<0.001$) with linear function, lnhtTKLV = -1.825 + 24.4 x trunk ECW/TBW.

DISCUSSION

In this section of study, we used BIA to evaluate nutritional status in ADPKD patients. SGA is an easy and well validated method, but has limitation in detecting subtle change during regular follow up due to crude scale and subjectivity of the study. Therefore BIA was assessed as an additional quantitative tool for nutritional evaluation. We first compared BIA measurement data between ADPKD patients and healthy population and then explored suitable nutritional BIA parameters based on the SGA scores. Also we tried to investigate the correlation between BIA parameters and abdominal volume. This is the first study to evaluate the efficacy of BIA in ADPKD patients and identify the meanings of BIA parameters

Using the multi-frequency BIA, ICW and ECW can be measured accurately. When we compared the BIA parameters of the ADPKD patients with healthy subjects, all the body fluid compositions, ICW/Ht, ECW/Ht and TBW/Ht, were increased in ADPKD patients. (**Table 3**) This result would reflect the fluid filled cysts in kidney and liver organs in ADPKD patients with. Besides, decreased renal function in ADPKD patients may lead to increased body fluid components in ADPKD patients. When we analyzed the correlation between abdominal cystic

organ mass and body fluids, lnhtTKLV correlated with ECW (r= 0.134, p=0.023) but not with ICW (p=0.295) nor with TBW (p=0.134). This is also the same with eGFR. eGFR correlated with ECW (r=-0.150, p=0.011) but not with ICW (p=0.117) and TBW (p=0.053). (Data not shown) From this result, in ADPKD patients, abdominal cystic masses and decreased renal function would influence the ECW as compared to ICW and TBW.

Also from the data, WB ECW/TBW was increased in ADPKD patients. Increased ECW/TBW reflects the edematous status and it is an important clinical factor related with patient's outcome in various clinical settings. (16) Using the segmental BIA, not only WB ECW/TBW but, UE, trunk and LE ECW/TBW could be measured separately and showed different results between segments. It is important in ADPKD patients to evaluate the trunk region separately and analyze the data with abdominal organ mass volume. Overall WB and LE ECW/TBW ratios were increased in ADPKD patients in total and both genders. The edema concentrated on LE might be due to gravity effect and/or compression of IVC caused by organomegaly due to cysts. Trunk ECW/TBW was increased in total and female ADPKD groups but not in male. (**Table 3**) Since this is the first study on using segmental BIA in ADPKD patients, the effects of abdominal organomegaly with fluid filled cysts on the BIA measurement results of ECW and ICW are

unknown. However, there is a report of BIA study done in liver cirrhosis patients where trunk ECW/TBW was increased compared to the extremities in patients with ascites.(35) Also in this study, correlation between trunk ECW/TBW and lnhtTKLV was observed (r=0.466). (**Figure 12B**) Further studies to find out the effect of abdominal organ cysts on BIA parameters are needed.

BIA used in this study, adopted 2-compartment body composition model. Unlike 3-compartment model, it has such a limitation that it cannot distinguish overhydration from lean tissue mass (LTM). Instead lean mass (LM) is defined as the sum of the body water, protein and mineral, which also includes overhydration. Therefore, in patients with edema (i.e. patients with increased ECW/TBW in this study) LM/Ht and FFM/Ht are also increased. FM/Ht, which is the subtraction of FFM/Ht from Bwt/Ht was decreased accordingly. However trunk LM/Ht was decreased in all groups unlike the LM/Ht of WB and LE, which were increased in all groups. Opposite trend of trunk ECW/TBW and trunk LM/Ht would suggest that skeletal muscle mass in trunk would be decreased and this might be due to the pressure effect of organomegaly in ADPKD patients. (**Table 3**)

In this study, segmental parameters at the UE were not increased as in WB and LE. ECW/TBW at the UE was even decreased in female ADPKD group and other groups did not show differences. UE LM/Ht

showed the same trend. Further studies exhibited that, UE segmental BIA results did not show differences among SGA groups especially in the female subjects. This would show the distribution of edema, concentrated on the dependent portion such as LE due to gravity effect. Also, the differences in UE might be too small to be detected because the absolute LM/Ht of UE are smaller than LE (3.1±0.7 kg/m vs 9.4±1.7 kg/m $p<0.001$ in total ADPKD patients). (**Table 3**)

When we compared the body fluid parameters among the three SGA groups, increased ECW/TBW ratios of the WB, trunk and LE were related with low SGA scores. (**Table 4**) These findings were similar in both genders. (**Table 5**) This would be due to the decreased renal function in ADPKD that would also affect the increase of ECW/TBW. It is known that in CKD patients, increased ECW/TBW is associated with lower renal function probably due to hypoalbuminemia in association with proteinuria. (16) However, even in ESRD patients, increased ECW/TBW is related with hypoalbuminemia and malnutrition and can predict the mortality. Therefore, not only decreased renal function but also malnutrition status would affect the increase of the ECW/TBW. Also in ADPKD patients, organomegaly caused by fluid filled cysts would affect ECW/TBW by itself and/or by compressing the IVC. As in the **Figure 12 and 13**, both decrement of the renal function and increased lnhtTKLV were related with increment of WB, trunk, and

LE ECW/TBW ratios. The effects of abdominal organ volume on ECW/TBW remained significant even in the subgroup analysis among eGFR ≥45 mL/min/1.73 m^2 for whom the renal function was relatively preserved. From these findings, in ADPKD patients, it might be said that abdominal organomegaly due to fluid cysts affect the ECW/TBW parameters, independent from the decreased renal function.

In the analysis of body composition parameter, gender differences were observed. In male, decreased FM/Ht, FFM/Ht, LM/Ht and SMM/Ht were associated with low SGA scores. However these findings were not observed in female. (**Table 6**) In CKD patients, changes of metabolism cause the protein-energy malnutrition. Pereira et al reported, using BIA, that about 5.9% of non-dialysis dependent CKD patients had sarcopenia defined as reduced muscle function plus diminished muscle mass. (36) In this study, sarcopenia was an independent predictor of poor patient outcome. However, in our patient group, sarcopenia acts as an indicator of malnutrition only in male group. 2-compartment body composition model has limitation in distinguishing edema from LTM, that LM is overestimated by the overhydration in the BIA measurement of 2-compartment. In male, decreased lean tissue mass would be enough to show decreased LM in our analysis but in women, with relatively small amount of muscle mass it would not be sufficient to overcome the increment of edema to

show net decrement of LM. Also our study was undertaken in Koreans with relatively small muscle mass compared to the western people. Another reason would come from the fact that the study patients were enrolled in the outpatient clinic and no one was severely malnourished in this setting. If the patients were more severely malnourished, such BIA parameters might show significant differences.

PhA, a well-known nutritional BIA parameter was analyzed in this study. PhA is directly measured with BIA without using Bwt and Ht. When alternating current passes through the human body, time delay occurs between the current and voltage due to lipid bilayer of cellular membrane. This time delay expressed as an angle is called PhA and calculated as capacitance (Xc)/resistance (R) which is expressed in degrees. From this principle, PhA is an indicator of cellular health and integrity. In this study, not WB PhA but mean extremity and LE PhA showed correlation with SGA scores. Previously used WB PhA in other studies is actually right side PhA measured in the right side of human body. Therefore, in ADPKD patients, abdominal cystic masses would influence the result. (13) When we analyzed trunk PhA separately, it did not show the associations with SGA scores and eGFR. However it showed correlation with lnhtTKLV in total (r=0.215) and subgroup of eGFR ≥45 mL/min/1.73 m^2 (r=0.232) which implicate the independent effect of abdominal cystic mass on the trunk BIA. With the other

segmental PhA data, low mean extremity PhA and LE PhA, were associated with low SGA scores as in other malnutrition studies using PhA which can be useful in ADPKD replacing WB PhA.

To find out the most relevant malnutrition BIA parameters in ADPKD patients, ROC curve was conducted and ECW/TBW of WB, trunk, LE, mean extremity PhA and LM PhA all showed AUC above 0.7. WB ECW/TBW showed highest sensitivity (71.4%) and LE PhA showed highest specificity (91.2%). (**Table 8, Figure 11**) Also on the binominal logistic regression analysis using WB ECW/TBW, which has highest AUC, the odds ratio was 9.52 (confidence interval 3.78–23.9, $p<0.001$) for 0.01 increment of WB ECW/TBW. Because, WB ECW/TBW were more influence by eGFR and lnhtTKLV and LE PhA showed low sensitivity (57.1%) in detecting malnutrition, not a sole parameter should be used as a nutritional parameter but interpreting in total would be important.

The correlation between segmental BIA parameters with renal function and lnhtTKLV were analyzed. (**Figure 12, 13**) ECW/TBW showed associations with eGFR and CKD stage but this association was weak in LE PhA. Trunk PhA did not show correlation with kidney function. Trunk ECW/TBW showed highest correlation with eGFR and lnhtTKLV. By using simple regression analysis, trunk ECW/TBW could predict lnhtTKLV 21.7% ($p<0.001$) with linear function. This relationship

would be associated with malnutrition since decreased renal function and increased lnhtTKLV were risk factors for the malnutrition and trunk ECW/TBW are also one of nutritional BIA as showed in this study. Otherwise, trunk ECW/TBW could directly represent the fluid filled cysts in kidney and liver as disease progress in ADPKD. The result that trunk ECW/TBW correlated the most with EGFR and lnhtTKLV instead of ECW/TBW of WB and LE or PhA, would indicate the latter possibility as well. ECW/TBW would show combined result of decreased renal function, increased abdominal cystic mass and malnutrition but PhA meaning cellular membrane integrity would detect malnutrition more specifically with less influence from other factors. Further study would be needed to clarify the meanings of trunk segmental parameters in ADPKD patients and it could be an indicator for abdomen organ volume so that by using BIA, we could both assess the nutritional status and predict the volume of enlarged abdomen organs.

This is the first study to evaluate the BIA as a nutritional assessment tool in ADPKD patients. Also in all the patients, abdominal kidney and liver volume were measured using the latest CT images and the relationship between BIA parameters and htTKLV was analyzed. However there are a few limitations in this study. Since this study was conducted in outpatient clinic, patients with malnutrition were in largely excluded. Although we compared ADPKD patients with

healthy subjects, there is no CKD control. Comparing BIA data with CKD control group would give in-depth understanding in interpreting BIA data in ADPKD patients. We are now using BIA as a routine nutritional assessment tool along with SGA assessment in CKD outpatient clinic and this would give us useful data in the future. Further studies to see the association of malnutrition with clinical outcome, other nutritional biomarkers (i.e. prealbumin, insulin-like growth factor-1, or transferring) and body composition assessment methods would improve the understanding of malnutrition status in ADPKD patients and management to improve outcomes.

CONCLUSION

This study is the first study to use the BIA as a nutritional assessment method in ADPKD patients. In ADPKD patients overall body fluids (ICW, ECW and TBW) and ECW/TBW of WB and LE were increased compared to healthy population. Also FM/Ht was decreased in ADPKD patients. Increased ECW/TBW of WB, trunk and LE and decreased mean extremity PhA and LE PhA were associated with low SGA scores. However sarcopenia did not predict malnutrition in ADPKD female patients. WB ECW/TBW showed highest AUC (0.762) and sensitivity (71.4%) and predicted malnutrition with odd ratio 9.52 for 0.01 increase after adjusting sex, age, hemoglobin and either sCr or lnhtTKLV. In ADPKD patients both renal function and abdominal organ volume influenced the trunk ECW/TBW parameters the most and, there were correlation between lnhtTKLV with BIA parameters independently from eGFR. In conclusion, segmental BIA is an efficient method in assessing nutritional status in ADPKD patient, and further studies are needed to find out the meanings of parameters in depth.

Table 3. Comparison of BIA parameter s between ADPKD patients and healthy population control

	Male (n=144)			Female (n=137)			Total (n=281)		
	ADPKD patients	healthy population	p-value	ADPKD patients	healthy population	p-value	ADPKD patients	healthy population	p-value
Age (years)	47.4±13.2	47.4±13.2	0.250	49.5±10.3	49.5±10.3	0.828	48.4±11.9	48.4±11.9	0.385
Weight (kg)	71.4±10.4	71.4±9.8	0.980	58.0±7.8	58.7± 7.0	0.198	64.9±11.3	65.2±10.6	0.230
Height (cm)	172.6±6.1	172.6±6.0	0.253	159.0±5.6	158.9±5.6	0.125	166.0±9.0	165.9±9.0	0.086
BMI (kg/m^2)	23.8±2.9	23.9±2.6	0.515	23.0±2.7	23.2±2.3	0.090	23.4±2.8	23.6±2.5	0.088
ICW/Ht (L/m)	15.3±1.5	14.8±1.5	**<0.001**	11.8±1.0	11.6±1.1	**0.004**	13.6±2.2	13.2±2.1	**<0.001**
ECW/Ht (L/m)	9.4±0.9	9.0±0.8	**<0.001**	7.5±0.7	7.2±0.6	**<0.001**	8.5±1.2	8.2±1.2	**<0.001**
TBW/Ht (L/m)	24.7±2.4	23.9±2.3	**<0.001**	19.4±1.7	18.8±1.8	**<0.001**	22.1±3.4	21.4±2.3	**<0.001**
Whole body ECW/TBW	0.381±0.007	0.379±0.007	**0.003**	0.389±0.006	0.380±0.003	**<0.001**	0.385±0.007	0.382±0.007	**<0.001**
Trunk ECW/TBW	0.380±0.007	0.379±0.007	0.135	0.389±0.006	0.386±0.006	**<0.001**	0.384±0.008	0.382±0.007	**<0.001**
Upper extremity ECW/TBW	0.377±0.004	0.377±0.005	0.862	0.378±0.005	0.389±0.006	**0.022**	0.378±0.004	0.378±0.005	0.085
Lower extremity ECW/TBW	0.385±0.008	0.380±0.008	**<0.001**	0.392±0.006	0.387±0.007	**<0.001**	0.388±0.008	0.384±0.008	**<0.001**
FM/Ht (kg/m)	7.6±3.1	8.9±2.9	**<0.001**	10.1±3.3	11.3±3.0	**<0.001**	8.8±3.4	10.1±3.2	**<0.001**
FFM/Ht (kg/m)	33.6±3.3	32.4±3.1	**<0.001**	26.4±2.3	25.6±2.4	**<0.001**	30.1±4.6	29.1±4.4	**<0.001**
SMM/Ht (kg/m)	18.8±2.0	18.2±1.9	**<0.001**	14.2±1.3	14.2±4.9	0.939	16.5±2.9	16.2±4.2	0.170
LM/Ht (kg/m)	31.6±3.4	30.7±2.9	**<0.001**	24.8±2.1	24.1±2.3	**<0.001**	28.3±4.4	27.5±4.2	**<0.001**
Trunk LM/Ht (kg/m)	14.5±1.4	14.7±1.4	**0.008**	11.2±1.0	11.6±1.2	**<0.001**	12.9±2.0	13.2±2.0	**<0.001**
UE LM/Ht (kg/m)	3.6±0.5	3.6±0.4	0.123	2.5±0.4	2.6±0.4	**0.002**	3.1±0.7	3.1±0.6	0.447
LE LM/Ht (kg/m)	10.7±1.2	10.1±1.0	**<0.001**	8.0±0.9	7.7±0.9	**<0.001**	9.4±1.7	8.9±1.5	**<0.001**

BIA; bioelectrical impedance analysis, ICW; intracellular water, ECW; extracellular water, TBW; total body water, Ht; height, ECW/TBW; ratio of extracellular water to total body water, SGA; subjective global assessment

Table 4. Association of BIA parameters with SGA scores in total population

Parameters	Mildly to moderately malnourished (SGA 4 and 5)	At risk (SGA 6)	Well nourished (SGA 7)	Total	P-value
Number of patients	21	63	204	288	
Body fluid parameters					
ICW/Ht (L/m)	13.0±1.8	13.0±1.9	13.9±2.3	13.7±2.2	**0.012**
ECW/Ht (L/m)	8.3±1.1	8.2±1.1	8.6±1.3	8.5±1.3	0.076
TBW/Ht (L/m)	21.3±2.9	21.3±3.0	22.6±3.6	22.2±3.4	**0.024**
WB ECW/TBW	0.391±0.009	0.387±0.007	0.383±0.007	0.384±0.007	**<0.001**
Trunk ECW/TBW	0.391±0.01	0.387±0.008	0.382±0.007	0.384±0.008	**<0.001**
UE ECW/TBW	0.379±0.004	0.379±0.004	0.378±0.004	0.378±0.004	0.099
LE ECW/TBW	0.395±0.010	0.391±0.008	0.387±0.007	0.388±0.008	**<0.001**
Body composition					
FM/Ht (kg/m)	7.0±3.7	9.0±3.4	8.9±3.4	8.8±3.4	**0.011**
FFM/Ht (kg/m)	29.0±4.0	29.0±4.1	30.8±4.8	30.2±4.7	**0.024**
LM/Ht (kg/m)	27.3±3.7	27.2±3.9	28.9±4.7	28.4±4.5	**0.028**
SMM/Ht (kg/m)	15.7±2.4	15.8±2.6	17.0±3.0	16.6±2.9	**0.011**
Trunk LM/Ht (kg/m)	12.2±1.5	12.4±1.8	13.2±2.1	12.9±2.1	**0.007**
UE LM/Ht (kg/m)	2.9±0.5	2.9±0.6	3.2±0.8	3.1±0.7	**0.011**
LE LM/Ht (kg/m)	9.0±1.8	8.9±1.5	9.6±1.8	9.4±1.7	**0.020**
Nutritional parameters					
Whole PhA (θ)	5.4±0.8	5.3±0.8	5.4±0.7	5.4±0.7	0.634
Mean extremity PhA (θ)	4.7±0.7	5.0±0.7	5.3±0.7	5.2±0.7	**<0.001**
Trunk PhA (θ)	8.6±1.4	8.6±1.3	9.0±1.3	8.9±1.3	**0.049**
UE PhA (θ)	5.0±0.5	5.0±0.6	5.3±0.7	5.2±0.7	**0.001**
LE PhA (θ)	4.6±0.9	5.0±0.8	5.4±0.8	5.2±0.9	**<0.001**

BIA; bioelectrical impedance analysis, ICW; intracellular water, ECW; extracellular water, TBW; total body water, Ht; height, ECW/TBW; ratio of extracellular water to total body water, PhA; Phase angle, SGA; subjective global assessment

Table 5. Association of body water parameters of BIA with SGA scores

Parameters	Male				Female			
	Mildly to moderately malnourished (SGA 4 and 5)	At risk (SGA 6)	Well nourished (SGA 7)	P-value	Mildly to moderately malnourished (SGA 4 and 5)	At risk (SGA 6)	Well nourished (SGA 7)	P-value
Number of patients	12	26	112		9	37	92	
ICW/ht (L/m)	13.9±1.6	14.8±1.3	15.6±1.5	**0.001**	11.8±1.3	11.8±1.1	11.9±1.0	0.754
ECW/ht (L/m)	8.8±1.2	9.2±0.7	9.6±0.9	**0.009**	7.7±0.9	7.5±0.7	7.5±0.6	0.691
TBW/ht (L/m)	22.6±2.7	24.0±2.0	25.2±2.5	**0.002**	19.5±2.1	19.3±1.8	19.4±1.6	0.849
Whole ECW/TBW	0.388±0.009	0.384±0.008	0.380±0.006	**0.002**	0.396±0.005	0.390±0.006	0.388±0.005	**<0.001**
Trunk ECW/TBW	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**
Upper extremity ECW/TBW	0.378±0.004	0.378±0.005	0.377±0.004	0.126	0.381±0.002	0.379±0.003	0.379±0.003	0.198
Lower extremity ECW/TBW	0.391±0.010	0.388±0.010	0.383±0.007	**0.016**	0.400±0.006	0.393±0.007	0.391±0.006	**<0.001**

BIA; bioelectrical impedance analysis, ICW; intracellular water, ECW; extracellular water, TBW; total body water, Ht; height, ECW/TBW; ratio of extracellular water to total body water, SGA; subjective global assessment

Table 6. Association of body composition parameters of BIA with SGA scores

Parameters	Male				Female			
	Mildly to moderately malnourished (SGA 4 and 5)	At risk (SGA 6)	Well nourished (SGA 7)	P-value	Mildly to moderately malnourished (SGA 4 and 5)	At risk (SGA 6)	Well nourished (SGA 7)	P-value
Number of patients	12	26	112		9	37	92	
Fat mass/Ht (kg/m)	5.3±1.9	7.3±3.7	8.1±3.0	**0.006**	9.3±4.3	10.3±2.7	10.0±3.5	0.363
Fat free mass/Ht (kg/m)	30.8±3.7	32.7±2.8	34.3±3.4	**0.002**	26.7±3.0	26.3±2.5	26.5±2.1	0.863
Lean mass/Ht (kg/m)	29.0±3.5	30.8±2.6	32.2±3.5	**0.002**	24.9±2.7	24.7±2.4	24.9±2.0	0.847
Skeletal muscle mass/Ht (kg/m)	16.9±2.1	18.1±1.7	19.2±2.0	**0.001**	14.1±1.7	14.1±1.5	14.2±1.3	0.769
Trunk lean mass/Ht (kg/m)	13.0±1.1	14.1±1.1	14.8±1.4	**<0.001**	11.0±1.1	11.2±1.0	11.3	0.707
Upper extremity Lean mass/Ht (kg/m)	3.1±0.4	3.5±0.4	3.7±0.5	**<0.001**	2.5±0.4	2.5±0.4	2.5±0.4	0.762
Lower extremity Lean mass/Ht (kg/m)	9.8±1.8	10.2±1.0	11.0±1.1	**0.001**	7.9±1.0	8.0±1.1	8.0±0.8	0.809

BIA; bioelectrical impedance analysis, Ht; height, SGA; subjective global assessment

Table 7. Association of nutritional parameters of BIA with SGA scores

Parameters	Male				Female			
	Mildly to moderately malnourished (SGA 4 and 5)	At risk (SGA 6)	Well nourished (SGA 7)	P-value	Mildly to moderately malnourished (SGA 4 and 5)	At risk (SGA 6)	Well nourished (SGA 7)	P-value
Number of patients	12	26	112		9	37	92	
Whole body PhA (θ)	5.3±0.7	5.3±0.9	5.4±0.7	0.810	5.5±0.9	5.3±0.8	5.4±0.7	0.622
Mean extremity PhA (θ)	5.1±0.6	5.4±0.7	5.8±0.5	**0.001**	4.3±0.4	4.7±0.5	4.8±0.4	**0.013**
Trunk PhA (θ)	8.8±1.4	9.3±1.5	9.5±1.2	0.108	8.4±1.4	8.3±1.0	8.4±1.2	0.750
Upper extremity PhA (θ)	10.3±1.1	10.9±1.2	11.5±1.0	**0.001**	9.1±0.5	9.4±0.8	9.4±0.8	0.267
Lower extremity PhA (θ)	10.0±1.7	10.8±1.8	11.7±1.4	**<0.001**	8.1±1.3	9.3±1.3	9.6±1.0	**0.004**

BIA; bioelectrical impedance analysis, PhA, phase angle, SGA; subjective global assessment.

Table 8. Results of ROC analysis of BIA parameters

	AUC	Cut-off value	Sensitivity	Specificity
Whole body ECW/TBW	**0.762**	>0.389	**71.40%**	80.40%
Trunk ECW/TB	0.758	>0.388	66.70%	80.40%
Lower extremity ECW/TBW	0.747	>395	57.10%	88.70%
Lower extremity PhA (θ)	0.741	≤8.6	57.10%	**91.20%**
Mean extremity PhA (θ)	0.726	≤4.9	**71.40%**	69.10%

AUC; area under curve, BIA; bioelectrical impedance analysis, ECW/TBW; ratio of extracellular water to total body water, PhA; phase angle, ROC; receiver-operating characteristics,

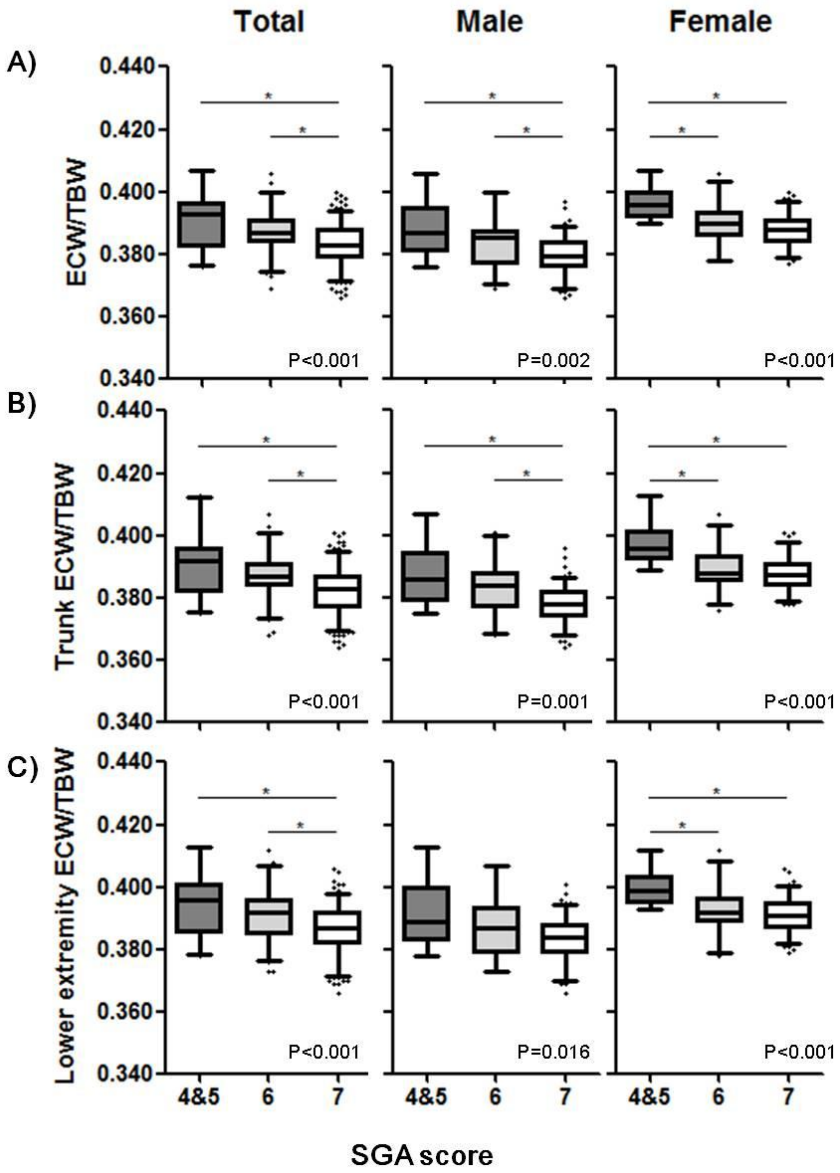


Figure 8. Association of ECW/TBW with SGA scores

(A) Whole body ECW/TBW, (B) Trunk ECW/TBW, and (C) Lower extremity ECW/TBW;
*P<0.017 for post-hoc analysis
ECW/TBW; ratio of extracellular water to total body water, SGA; subjective global assessment
SGA 7, well-nourished; SGA 6, at risk; SGA 5, mildly malnourished; SGA 3–4, moderately malnourished

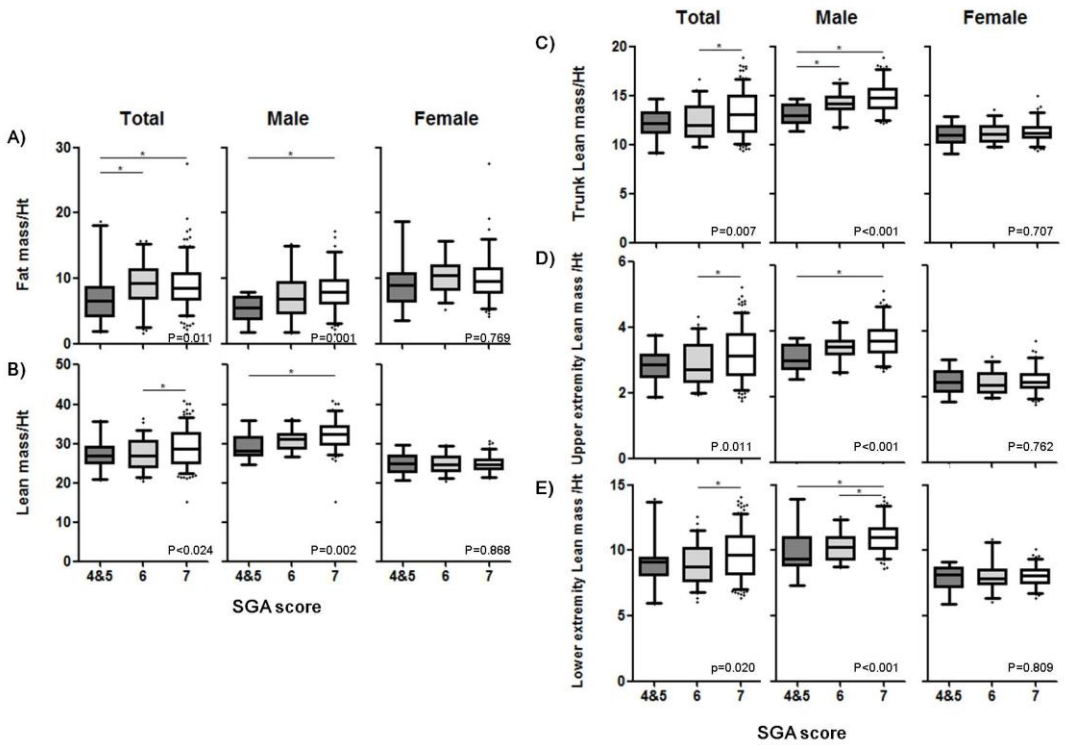


Figure 9. Association of body composition parameters with SGA scores

(A) Whole body Fat mass/Ht (kg/m), (B) Whole body Lean mass/Ht (kg/m),, (C) Trunk Lean mass/Ht (kg/m),, (D) Upper extremity Lean mass/Ht (kg/m),, and (E) Lower extremity Lean mass/Ht (kg/m).

*P<0.017 for post-hoc analysis

Ht; height, SGA; subjective global assessment

SGA 7, well-nourished; SGA 6, at risk; SGA 5, mildly malnourished; SGA 3–4, moderately

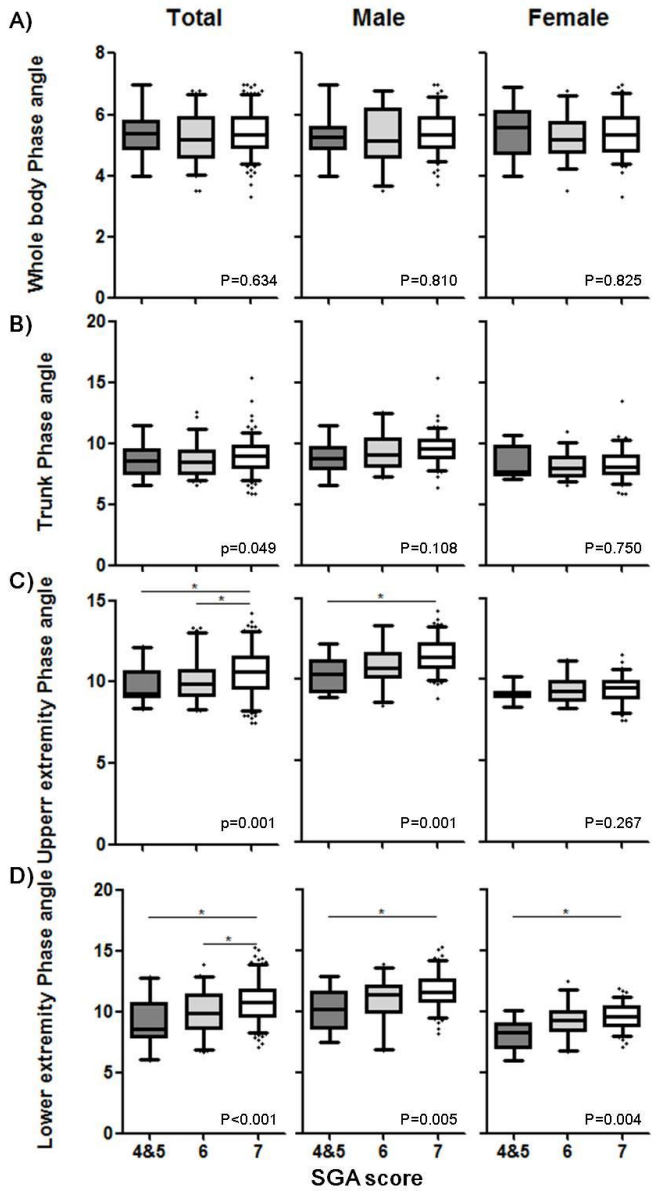


Figure 10. Association of Phase angle with SGA scores

(A) Whole body PhA (θ), (B) Trunk PhA (θ), (C) Upper extremity PhA (θ), and (D) Lower extremity PhA (θ)
*P<0.017 for post-hoc analysis
PhA; phase angle, SGA; subjective global assessment
SGA 7, well-nourished; SGA 6, at risk; SGA 5, mildly malnourished; SGA 3–4, moderately

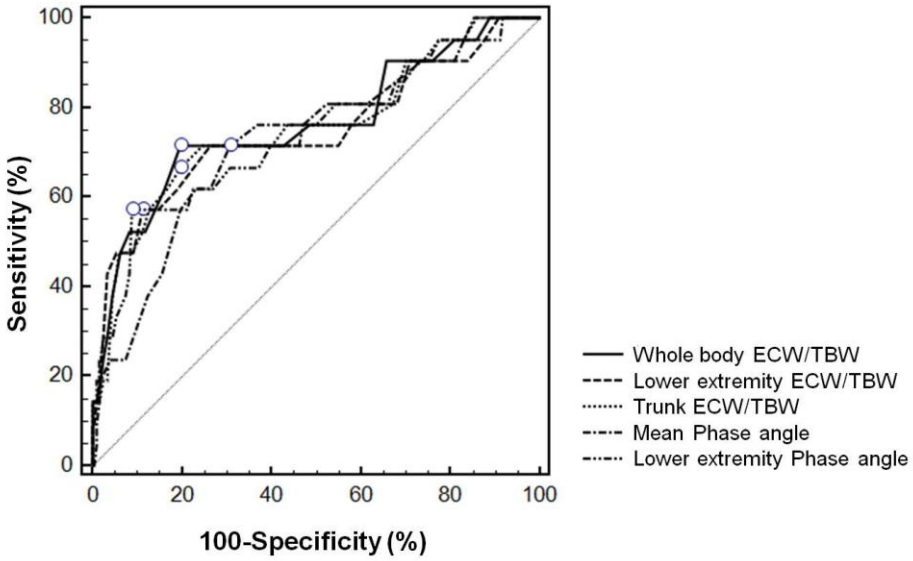


Figure 11. ROC curve of BIA parameters comparing SGA scores of 4 and 5 to 7

BIA; bioelectrical impedance analysis, ECW/TBW; ratio of extracellular water to total body water, PhA; phase angle, ROC; receiver-operating characteristics, SGA; subjective global assessment,
SGA 7, well-nourished; SGA 6, at risk; SGA 5, mildly malnourished; SGA 3–4, moderately malnourished

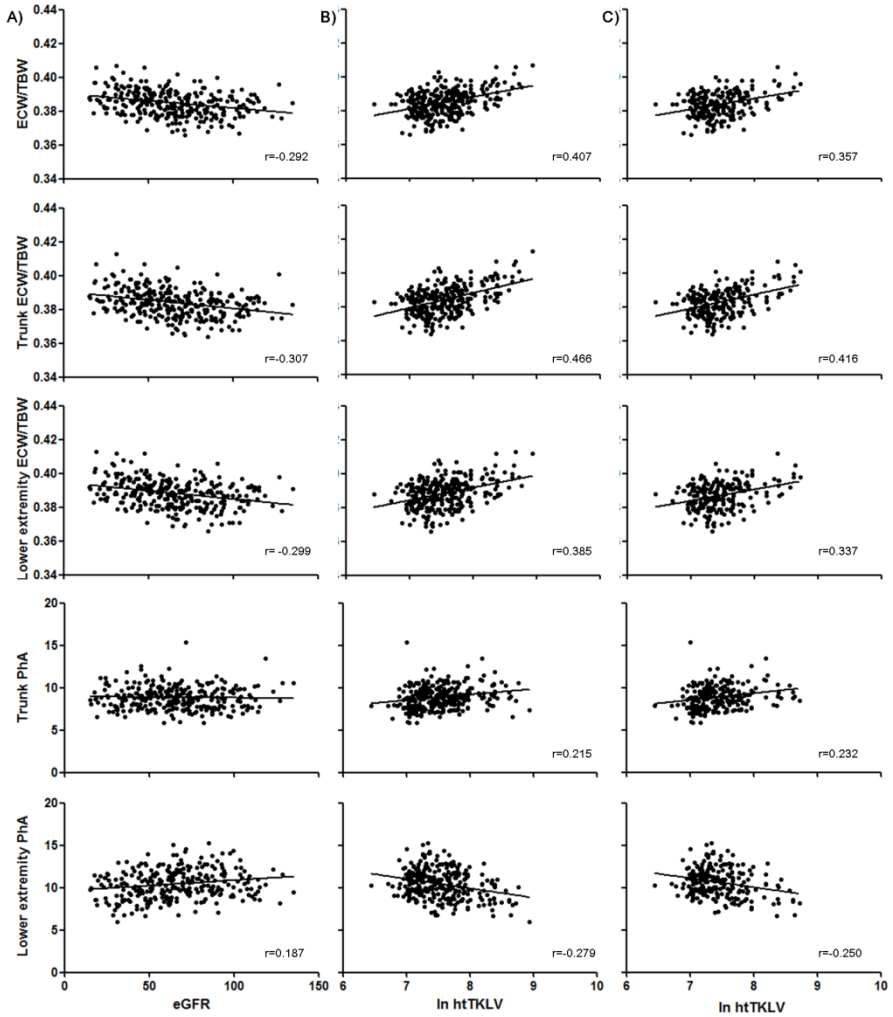


Figure 12. Scatter plot of BIA parameters with eGFR and lnhtTKLV

Scatter plot of BIA parameters with (A) eGFR (B) lnhtTKLV and (C) lnhtTKLV in eGFR ≥45 mL/min/1.73 m^2 patients

BIA; bioelectrical impedance analysis, ECW/TBW; ratio of extracellular to total body water, eGFR; estimated glomerular filtration rates, lnhtTKLV; natural log value of height adjusted total kidney and liver volume, PhA; Phase angle

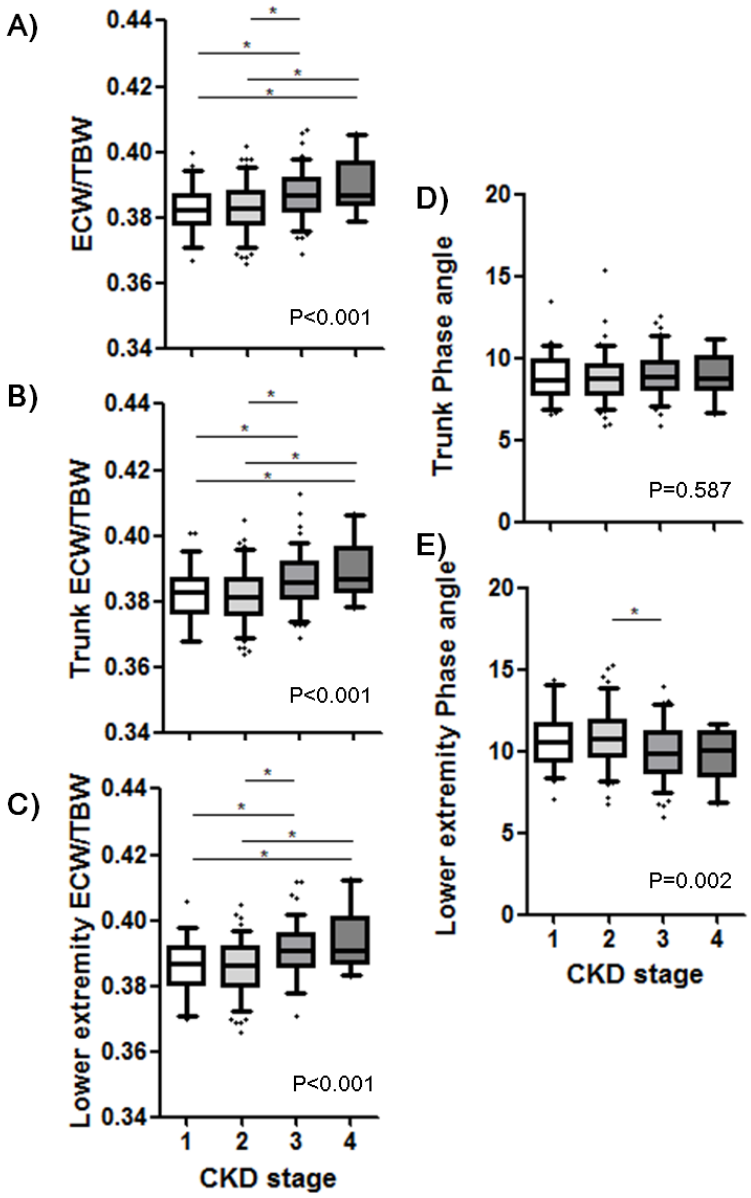


Figure 13. Association of BIA parameters with CKD stages
(A) Whole body ECW/TBW (B) trunk ECW/TBW, (C) Lower extremity ECW/TBW, (D) trunk PhA and (E) Lower extremity PhA

BIA; bioelectrical impedance analysis, CKD; chronic kidney disease, eGFR; estimated glomerular filtration rate, ECW/TBW; extracellular to total body water, PhA; phase angle

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국문초록

배경: 상염색체 우성 다낭신병증(ADPKD) 환자에서 질병의 진행에 따른 신기능의 감소와 복부 장기의 비대로 인하여 영양불균형이 발생할 수 있다. 본 연구에서는 이러한 상염색체 우성 다낭신 환자들의 영양불균형 상태에 대해 조사하고, 그 위험인자로써의 복부내 장기의 부피의 영향을 살펴보았다. 또한 상염색체 우성 다낭신병증 환자에서 생체전기저항분석법(BIA)을 이용하여 영양상태에 대한 평가를 시행하였고 그 효용성에 대해 연구하였다.

방법: 본 연구는 3차병원의 외래 다낭신클리닉을 방문하는 상염색체 우성 다낭신병증 환자에서 진행한 단면적 연구이다. 신체계측값과 혈청 크레아티닌, 알부민, 콜레스테롤을 포함한 혈액검사결과들을 수집하였고 컴퓨터 단층촬영 결과에서부터 신장과 간의 부피를 측정하였다. 신장과 간의 부피를 합한 값인 총 신장, 간 부피를 정의하였고 각각의 부피들은 신장으로 보정하여 연구에 사용하였다 (htTKV, htTLV, htTKLV). 영양상태는 만성콩팥병증 환자에서 그 효용성이 입증된 주관적 전반적 평가 (SGA)를 통해 시행하였고, 정량적이고 객관적인 측정방법인 생체전기저항분석법을 시행하여 SGA에 따른 비교 및 일반인 군과의 비교연구를 진행하였다.

결과: 총 288명 (여성 47.9%)이 연구에 참여하였으며, 평균 연령은 48.3±12.2, 평균 예측 사구체 여과율은 65.3±25.3 mL/min/1.73 m^2이었다. 이 환자중, 21명 (7.3%)가 경도 및 중증도 영양불균형 상태였으며, 63명 (21.7%)가 영양불균형 위험군이었다. 전체 환자에서 영양불균형 상태군은 고령, 낮은 체질량지수 (BMI), 낮은 헤모글로빈 수치 그리고 신기능 저하를 보였다. 하지만 여성에 시행한 하위집단 분석에서는 신기능의 저하만이 낮은 SGA 점수와의 연관성을 보였다. 증가된 htTKLV와 낮은 SGA 점수와의 연관성이 관찰되었는데 이는 신기능이 보존된 군, 즉 예측사구체 여과율이 45 이상인 군에서도 이러한 연관성이 보존되었다. 성별, 나이, 헤모글로빈, 알부민, 그리고 혈청 크레아티닌으로 보정 후에도 htTKLV가 2,340mL이상인 군이 그렇지 않은 군에 비해 8.7배의 영양불균형 위험성이 관찰되었다. 이러한 상염색체 우성 다낭신병증 환자군에서의 BIA 데이터를, 건강한 집단과의 비교를 하였을때, 체수분지표와 (ICW,ECW,TBW) 전신 및 하반신 체포외수분비 (ECW/TBW)가 증가되어있으나 지방량은 감소되어있음을 확인 할 수 있었다. SGA와 BIA 지표들과의 연관성을 살펴보았을 때, 전신, 복부, 하반신의 체포외수분비와 복부, 하반신 위상각 (Phase angle)이 의미가 있었다. ROC 곡선 분석을 시행하였을 때, BIA 지표 중 전신 체포외수분비가 가장 넓은 그래프 면적 (AUC)인 0.762로

>0.389의 절단값이 가장 높은 민감도 71.4%을 보였다. 또한 전신 체포외수분비의 0.01의 증가는 성별, 나이, 헤모글로빈 및 혈청 크레아티닌 또는 lnhtTKLV의 보정 후에도, 영양불균형상태의 위험성을 9.52의 승산비로 증가시킴을 확인하였다. 복부 체포외수분비는 잔여신기능과, 복부장기부피와의 연관성이 가장 컸으며, 잔여신기능에 무관하게, lnhtTKLV와의 연관성이 관찰되었다.

결론: 외래로 내원한 비교적 신기능이 보존되어 있는 상염색체 우성 다낭신병증 환자군에서 약 30%가 영양불균형 상태 및 위험군이었다. 이러한 환자군에서 복부내 장기의 비대가 신기능의 저하와 독립적으로 영양불균형 상태의 위험인자가 될 수 있음을 본연구에서 확인하였다. 또한 상염색체 우성 다낭신병증군에서 부위별 생체전기저항분석법이 영양상태평가에 있어서의 효용성을 확인 할 수 있었다. 전신, 복부, 하반신의 체포외수분비의 증가와, 하반신의 위상각의 감소가 상염색체 우성 다낭신병증 환자에서 영양불균형 상태를 예측하는 좋은 지표이다.

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주요어: 상염색체 우성 다낭신병증, 영양불균형, 주관적전반적평가, 생체전기저항분석법

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