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THE ASSOCIATIONS OF MALNUTRITION AND AGING WITH FLUID VOLUME IMBALANCE BETWEEN INTRA- AND EXTRACELLULAR WATER IN PATIENTS WITH CHRONIC KIDNEY DISEASE

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Abstract: *Objectives:* Fluid imbalance due to sodium retention and malnutrition can be characterized by the ratio of extracellular water (ECW) to intracellular water (ICW). We investigated whether the ECW/ICW ratio is a risk factor for adverse outcomes. *Design:* Retrospective cohort study. *Setting and Participants:* 149 patients with chronic kidney disease from 2005 to 2009, who were followed until August 2013. *Measurements:* Body fluid composition was measured by bioelectrical impedance analysis. Patients were categorized according to the ECW/ICW ratio tertile. Daily nutrient intake was estimated from 24-h dietary recall and analyzed using standard food composition tables. The main outcomes were adverse renal outcomes, as defined by a decline of 50% or more from the baseline glomerular filtration rate or initiation of renal replacement therapy, cardiovascular events, and all-cause mortality. *Results:* The ECW/ICW ratio increased with downward ICW slope with age and renal dysfunction besides ECW excess with massive proteinuria. Sodium intake, protein intake, and calorie intake were negatively correlated with the ECW/ICW ratios due to the steeper decreasing ICW content with the decreased dietary intake than the decreasing ECW content. During a median 4.9-year follow up, patients in the highest tertile had the worst adverse renal outcomes (15.9 vs. 5.1 per 100 patient-years, P <0.001), cardiovascular events (4.1 vs. 0.3 per 100 patient-years, P = 0.002), and mortality (11.2 vs. 1.3 per 100 patient-years, P <0.001). The adjusted hazard ratio (95% confidence intervals) for adverse renal outcomes, cardiovascular events, and mortality were 1.15 (1.03 – 1.26), 1.12 (0.93 – 1.31), and 1.29 (1.11 – 1.50), respectively. *Conclusions:* Fluid imbalance between ICW and ECW occurring in malnourished and elderly patients with chronic kidney disease may explain the reserve capacity for volume overload and is associated with adverse renal outcomes and all-cause mortality.

Key words: Aging, bioelectrical impedance analysis, chronic kidney disease, fluid/electrolytes, protein-energy malnutrition.

Introduction

Fluid volume imbalance commonly occurs in chronic kidney and cardiovascular diseases; however, whether it is a risk factor for end-stage renal disease remains unclear (1). Fluid imbalance in patients with chronic kidney disease (CKD) is primarily characterized by excess extracellular water (ECW) content associated with sodium retention (2, 3) and a decreased body cell mass associated with malnutrition (4). Cells are also known to shrink with aging through apoptosis (5-9). The prevalence of patients with protein–energy wasting increases progressively along with the loss of residual renal function, which can result in an increased risk of cardiovascular disease and mortality (10, 11). Among dialysis patients, those with a leaner body mass have a higher prevalence of hypertension, poorer control of hypertension, and greater left ventricular hypertrophy (12). In this regard, we hypothesized that malnourished patients with CKD are more susceptible to volume overload than patients with overall good nutritional status.

Multifrequency bioelectrical impedance analysis (MFBIA) can effectively distinguish between intra- and extracellular components. The values of total body water (TBW), intracellular water (ICW), and ECW content measured by MFBIA have a high correlation with those values measured by the isotopic dilution technique and dual-energy X-ray absorptiometry (13). Using this method, the ratio of ECW to ICW may be associated with excess ECW volume and decreased cell volume in patients with CKD.

The goals of the present study were to (1) identify the factors associated with the ratio of ECW to ICW, (2) determine the association between the ECW/ICW ratio and renal outcomes, cardiovascular events, and mortality in patients with CKD, and (3) evaluate the prognostic performance of the ECW/ICW ratio for the investigated adverse outcomes.

Materials and Methods

Study design

Of 170 patients with CKD aged ≥20 years with MFBIA body composition measurements obtained from August 2005 to January 2009, we identified 149 patients with complete clinical data for whom we simultaneously assessed anthropometric measurements, blood pressure, proteinuria, and kidney function. The surveyed patient characteristics included age, gender, height, body weight, body mass index, underlying

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disease, office blood pressure, serum albumin, total cholesterol, triglyceride, fasting blood glucose, uric acid, creatinine, estimated glomerular filtration rate (eGFR), the ratio of urinary protein to creatinine in a random urine sample (UPCR), and the prescription of diuretics and antihypertensive agents. Hyperuricemia was diagnosed for a uric acid level >7.0 mg/dL in men and >5.7 mg/dL in women according to population surveys (14). The stage of CKD was classified based on the GFR category (1), and the eGFR was calculated according to the revised formula of (194 × Creatinine – 1.094 × Age – 0.287) (× 0.739 for women) for Japanese patients according to the Modification of Diet in Renal Disease method (15). Daily nutrient intake was estimated from 24-h dietary recall and analyzed using standard food composition tables by a registered dietitian at the time of body composition measurements. Nutrition counseling was appropriately conducted for our patients at their own physician's discretion in the followed-up period. Treatment-resistant high blood pressure was defined as a systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥80 mmHg in patients receiving three or more hypertension medications, including diuretics. Blood pressure control requiring four or more drugs was also considered treatment resistant (16, 17). Patients were followed-up until death, loss to follow-up, or August 2013 (median, 1,789 days; 10th–90th percentile; 422–2,689 days).

Endpoints

The endpoint of the study was the time to the first recorded adverse event. Time-dependent Cox proportional hazards models were used to compare adverse renal outcomes, cardiovascular events, hospitalization, and all-cause mortality. Adverse renal outcomes were defined as a decline of 50% or more compared with baseline GFR or initiation of either dialysis therapy or renal transplantation (18, 19). Cardiovascular events were also defined as a composite of hospital-treated myocardial infarction or coronary intervention, hospital-treated heart failure, or hospital-treated stroke.

Assessment of body fluid composition

Standard MFBIA was performed with the patient lying in the supine position on a flat nonconductive bed for at least 15 minutes. For body composition measurements, we used a segmental MFBIA instrument (Inbody S20®; Biospace Co. Ltd., Seoul, Korea; www.biospaceamerica.com), which has eight tactile electrodes. The microprocessor-controlled switches and impedance analyzer were activated and the segmental resistances of the arms, trunk, and legs were measured at four frequencies (5, 50, 250, and 500 kHz). Thus, the resistance of 20 segments was measured for each individual. The sum of the measurements for each body segment was then used to calculate TBW, ICW, and ECW using MFBIA software. Patients were categorized according to the ECW/ICW ratio tertile.

Statistical analyses

Data were analyzed using JMP 9.0 statistical software (SAS Institute, Inc., Cary, NC, USA). The measured values were expressed as the means ± standard deviations and percentages. Statistical significance was assessed using a linear regression model to compare the mean values of possible risk factors among the tertile groups (20) for continuous variables and Pearson's chi-squared test for categorical variables. Correlations between variables were determined using the Pearson product-moment correlation coefficient. Logistic and linear regression analyses were used to identify associations between the ratio of ECW to ICW and demographic factors. Explanatory variables that had a significant correlation ($P < 0.10$) to the ratio of ECW to ICW were analyzed using multivariate analysis to evaluate independent associations. The Kaplan–Meier survival analysis was used to generate the investigated outcomes. The Cox regression model with time-dependent covariates was used to identify the association of the ECW/ICW ratio with the investigated outcomes, and the analyzed values were expressed as HR and 95% confidence intervals (CI). The receiver operating characteristic (ROC) curve analysis was used to identify the best prognostic value for renal outcomes and death. A probability (P) value of <0.05 was considered statistically significant.

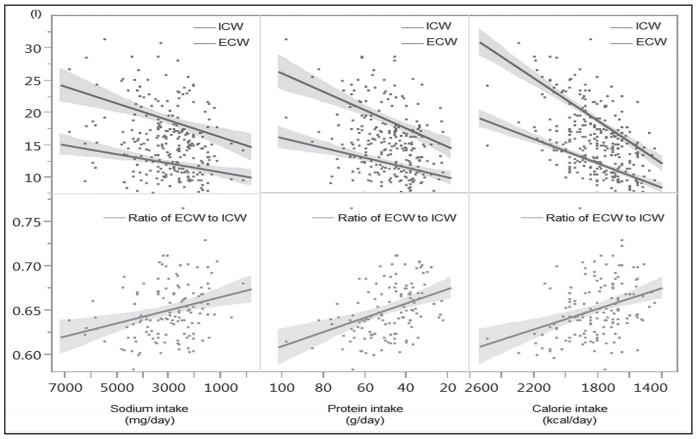
Results

Population characteristics at the time of bioimpedance analysis

The population characteristics of the subjects (80 men and 69 women; mean age, 63.7 ± 16.1 years) are presented by the ratio of ECW to ICW tertiles in Table 1. The tertile values were 0.636 and 0.663. Patients in the higher tertile of ECW/ICW ratios tended to be older and have diabetes mellitus, treatment-resistant high blood pressure, higher serum creatinine, lower eGFR, lower serum albumin, higher UPCR levels, and higher usage of furosemide and other antihypertensive agents besides angiotensin-converting enzyme inhibitors and angiotensin II type 1 receptor blockers ($P < 0.01$). In body fluid composition analysis, the percentage of ECW in body weight increased along with decreased TBW in patients in the higher tertile of ECW/ICW ratios (P for Trend < 0.01). Sodium intake, protein intake, and calorie intake were negatively correlated with the ECW/ICW ratios due to the steeper decreasing ICW content with the decreased dietary intake than the decreasing ECW content (Figure 1). The averages of the nonprotein calorie to nitrogen ratios increased along with decreased protein intake in patients in the higher tertile of ECW/ICW ratios ($P < 0.01$). However, calorie intake was below 35 kcal/kg/day of the target level in all groups.

Figure 1

Effects of all of sodium intake, protein intake, and calorie intake on the imbalance between ICW and ECW. Influence of dietary intake on the slope of imbalance between ICW and ECW content



Abbreviations: ICW, intracellular water; ECW, extracellular water

Correlations between age, kidney dysfunction, and proteinuria with an imbalance between ICW and ECW

As shown in Figure 2A, the G1 or G2 of CKD and the G3 to G5 of CKD were present in 33 patients and in 116 patients, respectively. Both intra- and extracellular water volumes decreased with age, although the trend was predominantly observed in ICW content in those with the G3 to G5 of CKD ($r = –0.27$ in a correlation between ICW and age, $P < 0.01$ vs. $r = –0.16$ in a correlation between ECW and age, $P = 0.08$). Consequently, the ECW/ICW ratios had a moderate positive correlation with age in those with the G3 to G5 of CKD ($r = 0.53$, $P < 0.001$). On the other hand, there was no significant correlation between age and the ECW/ICW ratios in those of the G1 or G2 of CKD ($r=0.18$, $P = 0.34$). Moreover, each of the correlations in age, eGFR, and UPCR with an imbalance between ICW and ECW are presented in Figure 2B, 2C, and 2D, respectively. The imbalance between ICW and ECW was observed even in the eGFR levels and the proteinuria levels. The eGFR levels showed a weak positive correlation to ICW content ($r = 0.17$, $P = 0.04$) but no correlation to ECW ($r = 0.06$, $P = 0.47$). Both of the ICW content and ECW content demonstrated a slightly upward trend with the UPCR levels, especially in ECW content. As a result, the ECW/ICW ratios had a moderate positive correlation with age ($r = 0.60$, $P < 0.001$), a moderate negative correlation with GFR ($r = –0.52$, $P < 0.001$), and a weak positive correlation with massive UPCR ($r = 0.29$, $P < 0.001$).

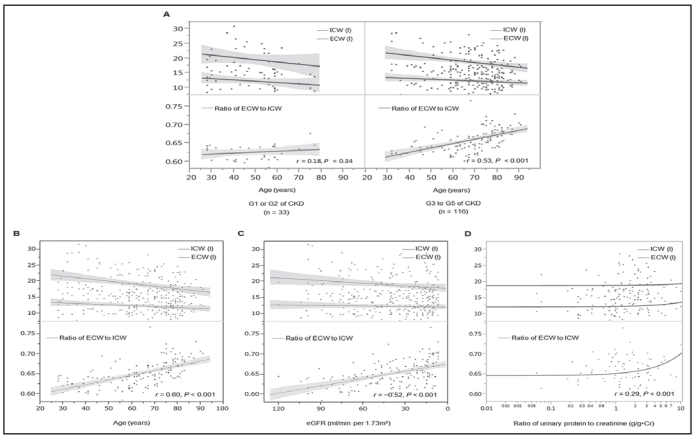
Age, diabetes mellitus, eGFR, UPCR, and the nonprotein calorie to nitrogen ratios were correlated with the ECW/ICW ratios in univariate analysis. In multivariate analysis, age and eGFR remained independently associated with the ECW/ICW ratios (Table 2).

Association of ICW and ECW imbalance with renal outcomes, cardiovascular events, hospitalization, and all-cause mortality

During a median 4.9-year follow-up period, 52 patients had adverse renal outcomes, 18 patients experienced cardiovascular events, 83 patients were hospitalized, and 25 patients died.

Figure 2

Effects of age, renal function, and proteinuria on the imbalance between ICW and ECW. Influence of (A) age by the stage of chronic kidney disease, (B) age, (C) glomerular filtration, and (D) ratio of urinary protein to creatinine on the slope of imbalance between ICW and ECW content



Abbreviations: ICW, intracellular water; ECW, extracellular water; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.

As shown in Figure 3, patients in the highest tertile of ECW/ICW ratios (15.9 per 100 patient-years) were at a greater risk for the development of the composite renal end point compared with those in the lowest tertile (5.1 per 100 patient-years) and the second tertile (6.5 per 100 patient-years) ($P < 0.001$). After adjustment for covariates, including age, diabetes mellitus, systolic blood pressure, UPCR, and baseline eGFR, the ratio of ECW to ICW was associated with adverse renal outcomes [hazard ratio (HR) = 1.15; 95% CI = 1.03–1.26, $P = 0.01$) (Table 3). The Kaplan–Meier analysis curves also exhibited significant differences in cardiovascular events, hospitalization, and all-cause mortality in the highest tertile of ECW/ICW ratios (Figure 3). First, the 10 patients in the highest tertile of ECW/ICW ratios (4.1 per 100 patient-years) developed cardiovascular event, whereas only one patient in the lowest tertile of ECW/ICW ratios experienced a cardiovascular event (0.3 per 100 patient-years) ($P = 0.002$). Second, the frequency of hospitalization gradually increased along with the higher tertile of ECW/ICW ratios (5.9, 14.2, and 20.1 per 100 patient-years for the lowest, second, and highest tertiles, respectively) ($P < 0.001$). Finally, there was a noticeable difference in the frequency of all-cause mortality. Mortality was significantly higher in the highest tertile of ECW/ICW ratios (11.2 per 100 patient-years) than in the lowest and second tertiles (1.3 and 1.8

Table 1
Sample characteristics by tertile of the ratio of extracellular water to intracellular water levels at the time of bioimpedance analysis

Sample characteristics	Ratio of extracellular water to intracellular water			
	Tertile 1 (n = 50, <0.636)	Tertile 2 (n = 49, 0.636–0.662)	Tertile 3 (n = 50, 0.663≤)	P for Trend
Age, years	52.7 ± 13.4	62.2 ± 15.4	76.0 ± 9.6	<0.001
Male sex, n (%)	34 (68.0)	19 (38.8)	27 (54.0)	0.28
Diabetes mellitus, n (%)	3 (6.0)	5 (10.2)	16 (32.0)	<0.001
BMI, kg/m2	23.7 ± 4.1	21.9 ± 3.3	22.0 ± 3.5	0.15
Systolic blood pressure, mmHg	125 ± 18	123 ± 16	130 ± 22	0.06
Diastolic blood pressure, mmHg	74 ± 9	71 ± 10	70 ± 11	0.03
Resistant high blood pressure, n (%)	9 (18.0)	9 (18.4)	19 (38.0)	<0.01
Serum creatinine, mg/dL	1.50 ± 1.17	1.68 ± 1.09	2.80 ± 1.74	<0.001
eGFRMDRD, mL/min per 1.73 m2	53.8 ± 26.7	42.5 ± 26.8	24.7 ± 18.0	<0.001
Serum albumin, mg/dL	4.2 ± 0.4	3.9 ± 0.4	3.6 ± 0.5	<0.001
Total cholesterol, mg/dL	196 ± 29	197 ± 41	192 ± 55	0.81
Triglyceride, mg/dL	147 ± 95	138 ± 73	130 ± 86	0.61
Fasting blood glucose, mg/dL	109 ± 37	133 ± 45	135 ± 40	0.05
UPCR, g/g·Cr	0.6 ± 1.0	1.0 ± 1.7	1.6 ± 2.0	<0.001
Uric acid >7.0 mg/dL in males or >6.0 mg/dL in females, n (%)	24 (49.0)	30 (61.2)	29 (58.0)	0.49
Total body water, L	34.8 ± 7.9	29.4 ± 5.0	29.5 ± 6.0	<0.001
(% in body weight)	(54.8 ± 6.8)	(54.2 ± 6.1)	(54.6 ± 6.9)	0.81
Intracellular water, L	21.5 ± 4.9	17.8 ± 3.0	17.5 ± 3.5	<0.001
(% in body weight)	(33.8 ± 4.3)	(32.9 ± 3.7)	(32.2 ± 4.1)	0.03
Extracellular water, L	13.3 ± 3.0	11.5 ± 1.9	12.0 ± 2.5	0.11
(% in body weight)	(20.9 ± 2.6)	(21.3 ± 2.4)	(22.2 ± 2.9)	<0.01
Free water contents, kg	29.0 ± 8.9	25.2 ± 6.6	25.2 ± 7.3	0.07
(% in body weight)	(45.2 ± 6.9)	(45.8 ± 6.1)	(45.7 ± 6.9)	0.74
Sodium intake, mg/day	3,453 ± 1,216	3,007 ± 1,240	2,660 ± 987	<0.01
Protein intake, g/day	56 ± 13	48 ± 15	43 ± 9	<0.001
Protein intake, g/kg/day	0.8 ± 0.2	0.8 ± 0.3	0.7 ± 0.2	0.02
Calorie intake, kcal/day	1,911 ± 196	1,780 ± 153	1,740 ± 157	<0.001
Ratio of nonprotein calorie to nitrogen	198 ± 51	233 ± 102	243 ± 56	<0.01
Furosemide, n (%)	3 (6.0)	5 (10.2)	21 (42.0)	<0.001
Other diuretics, n (%)	4 (8.0)	10 (20.4)	6 (12.0)	0.18
ACE inhibitors, n (%)	18 (36.0)	16 (32.7)	13 (26.0)	0.55
AT1-receptor blockers, n (%)	32 (64.0)	25 (51.0)	26 (52.0)	0.55
Other antihypertensives	17 (34.0)	25 (51.0)	34 (68.0)	<0.01

Abbreviations: BMI, body mass index; eGFRMDRD, estimated glomerular filtration rate by the Modification of Diet in Renal Disease method; UPCR, urinary protein-to-creatinine ratio; ACE inhibitors, angiotensin- converting enzyme inhibitors; AT1-receptor blockers, angiotensin II type 1 receptor blockers

Table 2
Independent factors associated with the ratio of extra- to intracellular water levels

Variables	Univariate analysis		Multivariate analysis*	
	ß (95% CI)	P-value	ß (95% CI)	P-value
Age, per 10 years of age	0.56 (0.83–1.35)	<0.001	0.35 (0.30–1.02)	<0.001
Diabetes mellitus	0.31 (0.68–2.01)	<0.001	0.12 (–0.18–1.23)	0.14
eGFRMDRD, ml/min per 1.73 m^2	–0.52 (–0.08––0.04)	<0.001	–0.23 (–0.05––0.00)	0.03
UPCR, g/g·Cr	0.29 (0.25–0.85)	<0.001	0.06 (–0.21–0.47)	0.46
Ratio of nonprotein calorie to nitrogen	0.24 (0.00–0.02)	<0.01	0.10 (–0.01–0.01)	0.22

Abbreviations: eGFRMDRD, estimated glomerular filtration rate by the Modification of Diet in Renal Disease method; UPCR, urinary protein-to-creatinine ratio; β= standardized regression coefficients; CI, confidence interval; *Factors associated with the ratio of extra- to intracellular water levels in univariate analysis (P < 0.10) were entered in the multivariable model.

Table 3
Hazard risks of the ratio of extracellular water to intracellular water content on adverse renal outcomes, cardiovascular disease events, hospitalization rates, and all-cause mortality

Variables	HR (95% CI)	P-value
50% eGFR decline or renal replacement therapy		
Unadjusted	1.26 (1.16–1.37)	<0.001
Age- and gender-adjusted	1.27 (1.16–1.38)	<0.001
Multivariable-adjusted[a]	1.15 (1.03–1.26)	0.01
Cardiovascular disease event		
Unadjusted	1.21 (1.06–1.36)	0.006
Age- and gender-adjusted	1.14 (0.97–1.32)	0.10
Multivariable-adjusted[b]	1.12 (0.93–1.31)	0.22
Hospitalization		
Unadjusted	1.25 (1.17–1.34)	<0.001
Age- and gender-adjusted	1.22 (1.13–1.30)	<0.001
Multivariable-adjusted[c]	1.18 (1.08–1.28)	<0.001
Death		
Unadjusted	1.33 (1.22–1.45)	<0.001
Age- and gender-adjusted	1.30 (1.15–1.46)	<0.001
Multivariable-adjusted[d]	1.29 (1.11–1.50)	<0.001

Abbreviations: HR, hazard ratio; CI, confidence interval; a. Adjusted for age, diabetes mellitus, systolic blood pressure, urinary protein-creatinine ratio, and baseline estimated glomerular filtration rate (variables associated with renal outcomes in univariate analysis (P < 0.10) were entered in the multivariable model); b. Adjusted for age, systolic blood pressure, urinary protein-creatinine ratio, and baseline estimated glomerular filtration rate (variables associated with cardiovascular event in univariate analysis (P < 0.10) were entered in the multivariable model); c. Adjusted for age, diabetes mellitus, man sex, systolic blood pressure, and baseline estimated glomerular filtration rate (variables associated with hospitalization in univariate analysis (P < 0.10) were entered in the multivariable model); d. Adjusted for age, diabetes mellitus, and baseline estimated glomerular filtration rate (variables associated with death in univariate analysis (P < 0.10) were entered in the multivariable model).

per 100 patient-years, respectively) (P < 0.001). After adjusting for covariates, the ratio of ECW to ICW was associated with hospitalization (HR = 1.18; 95% CI = 1.08–1.28, P < 0.001) and all-cause mortality (HR = 1.29; 95% CI = 1.11–1.50, P < 0.001), while there was no significant difference in the incidence of cardiovascular events (HR = 1.12; 95% CI = 0.93–1.31, P = 0.22) (Table 3).

Prognostic performance of ECW to ICW ratio to predict renal outcomes and death

We constructed ROC curves to derive the cut-off values of ECW/ICW ratios that predict the risks of optimal adverse renal outcomes and death. The best cut-off values of ECW/ICW ratios for adverse renal outcomes and death were 0.66 and 0.67, respectively. Using these cut-off values, the area under curves were 0.665 (95% Cl: 0.567–0.751) for adverse renal outcomes and 0.842 (95% CI: 0.729–0.914) for death. These data suggest that an imbalance in the ICW to ECW ratio >3:2 is a risk for adverse renal outcomes and all-cause mortality (Figure 4).

Figure 3

Kaplan–Meier survival curves for renal outcomes, cardiovascular event, hospitalization, and all-cause mortality by tertiles of the ECW to ICW ratios. Patients were categorized according to the ECW/ICW ratio tertile

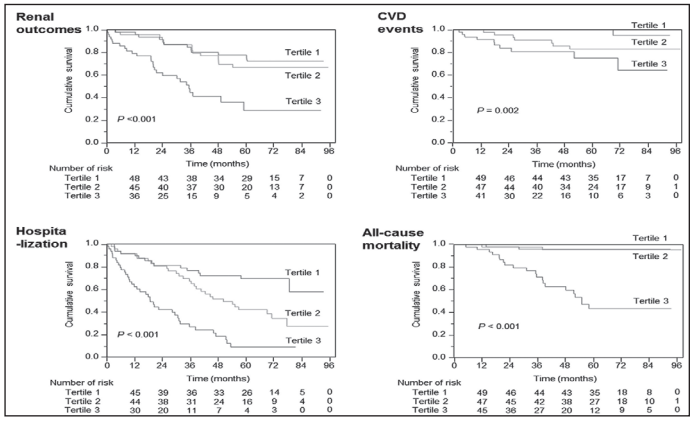
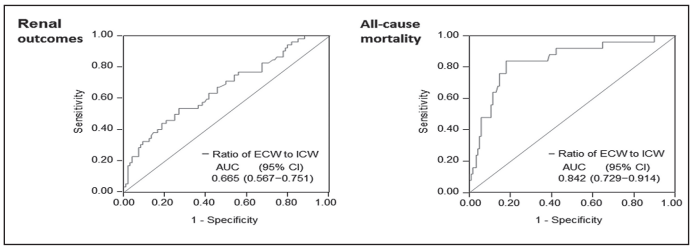


Figure 4

Receiver operating characteristic curves for the ECW to ICW ratios as a prognostic factor of adverse renal outcomes and all-cause mortality



Abbreviations: ICW, intracellular water; ECW, extracellular water; AUC, area under curve; CI, confidence interval

Renal outcomes and all-cause mortality by each ICW content and ECW content

There were no significant differences in renal outcomes and all-cause mortality by the percentage of ICW in body weight tertiles; while patients in the highest tertile percentage of ECW in body weight had the worst adverse renal outcomes but there were no significant differences in all-cause mortality by those tertiles.

Discussion

The results of this study revealed that a fluid volume imbalance between ICW and ECW in patients with CKD was significantly associated with increased age and decreased GFR, which indicated that the ECW to ICW ratio was primarily driven by decreased intracellular volume as well as extracellular volume excess and that the fluid volume imbalance was associated with adverse renal outcomes and all-cause mortality.

Bioimpedance analysis methods are used to noninvasively measure ECW, ICW, and TBW content, and to calculate free fat mass and fat based on empirical equations (21). In addition, the ratio of ECW to TBW has been used as a marker of ECW excess (22-27). However, the ECW/TBW ratio, which is substantially the same as the ECW/ICW ratio, may not be a reliable measurement of ECW excess (28). Our proposal marker expresses an imbalance between ICW and ECW, and the marker may have potential value to assess the reserve capacity for volume overload in patients with CKD. Intriguingly, despite the fact that the ratios of ECW to ICW express a relative increase in ECW content by decreased intracellular volume, the marker was well correlated with many clinical factors associated with volume overload; diabetes mellitus, treatment-resistant high blood pressure, lower serum albumin and higher proteinuria levels, and higher usage of furosemide and other antihypertensive agents. More importantly, the ECW to ICW ratio was an independent risk factor for adverse renal outcomes and mortality, although the content of ICW and ECW were not risks for mortality.

Agarwal (12) reported that leaner dialysis patients have a higher prevalence of hypertension and greater left ventricular hypertrophy, thereby describing an obesity paradox in dialysis patients. Furthermore, Weir (29) commented on the obesity paradox reported by Agarwal. For this clinical question, we developed a unique consideration that leaner patients may be directly susceptible to hemodynamic instability. In the present study, patients in the higher tertile of ECW/ICW ratios tended to have a low-protein diet without optimal calorie intake by strengthening of protein restriction or deterioration of protein–energy wasting, which led to a relative increase in ECW content. In contrast, sodium intake was not associated with fluid excess. Younger subjects and those without uremia consume a higher variety of foods with various levels of sodium, protein, and total calories than do elderly people and patients with uremia. These biases may have hampered studies in this area (30-32).

About 75% and 22% of muscle and viscera and of bone consist of water content, respectively (33), and organ aging (34) and a decrease of bone mass related to the low 25-OH-vitamin D levels (35) may be associated with the loss of ICW content. The decreasing ICW slope with age and renal dysfunction was steeper than the decreasing ECW slope. The shift in the balance between ICW and ECW led to an increase in the ECW to ICW ratio. Cell volume is regulated by apoptosis, which is a morphological hallmark of programmed cell death (5). This universal loss of cell volume during apoptosis may play a role in the change in balance between ICW and ECW content. In addition, uremic status may be also associated with cell shrinkage. Previous studies reported that erythrocytes may undergo suicidal death or eryptosis associated with cell shrinkage (36, 37), which can be stimulated by uremic toxins (38, 39). Lin et al. (40) reported that hemodialysis patients were more probable to have lower percentages of ICW and ECW in body weight and a higher ratio of ECW to ICW than healthy

subjects. Thus, apoptosis, uremic status, and protein–energy wasting are less probable to preserve fluid volume within the cells of patients with advanced CKD.

The fluid volume can be distributed on the basis of age, sex, and body size in everyone including healthy subjects, especially in patients with CKD. If they are exposed to fluid volume excess, most likely the excessive fluid volume is redistributed on the basis of the ratio of ICW to ECW (e.g., a ratio of 1:2 for ECW/ICW; 3 L of free water is redistributed in 2 L and 1 L in ICW and in ECW, respectively, or a ratio of 2:3 for ECW/ICW; the 3 L is redistributed in 1.8 L and 1.2 L in ICW and in ECW, respectively). Thus, we assume that the excessive fluid volume is redistributed on the basis of the baseline fluid volume balance when they are exposed to fluid accumulation. In addition, hypoalbuminemia, mostly in association with massive proteinuria, produces an increased interstitial fluid volume and a contracted intravascular volume contraction by a diminished oncotic pressure gradient, thus inducing renal sodium retention by activation of the renin-angiotensin-aldosterone system (41).

The best cut-off ECW/ICW ratios for adverse renal outcomes and death were 0.66 and 0.67, respectively. These values were close to a ratio of 2:3 for ECW/ICW. In this regard, we should cautiously interpret ECW/ICW values. The retention of cell volume may be very important as well as the correction of ECW excess to normalize the ECW to ICW ratio. We suggest that patients with higher ECW to ICW ratios should receive nutritional support to improve the reserve capacity of cells for volume overload. This theory is supported by two previous studies that used the ECW/ICW ratio to monitor dialysis patients (40, 42). Chen et al. (42) demonstrated that the ECW/ICW ratio was correlated with nutritional markers and strongly associated with survival of peritoneal dialysis patients.

This present study had several limitations. First, this was a cohort study of only 149 patients in a single center. However, it provided detailed information of body fluid composition and had a relatively long follow-up period. Second, we acknowledge that the ICW using MFBIA may not be a precise indicator of cell volume; however, the MFBIA method can be used to noninvasively and easily assess body fluid composition, as the fluid compartments measured by MFBIA have a high correlation with those values measured using the isotopic dilution technique and dual-energy X-ray absorptiometry (13). Third, whether the imbalance between ICW and ECW was notably occurred in patients with CKD was unclear; however, the imbalance of ICW and ECW was less noticeable in patients with the G1 or G2 of CKD. Fourth, in the present study we did not regularly measure the subjects' body composition during the follow-up period and did not entirely investigate the redistribution of water by means of administering the fluid challenge test to prove our hypothesis. Finally, it was difficult to clearly differentiate between overhydration and malnutrition using the ECW/ICW ratios. It is unclear whether both adverse conditions have an equally detrimental impact on the investigated outcomes and whether the imbalance between ICW and ECW can be appropriately corrected by some kind of therapeutic intervention; therefore, additional future studies are required to clarify these issues.

In conclusion, malnourished and elderly patients with CKD may be susceptible to a volume overload along with decreased ICW content as well as increased ECW content. Fluid imbalance between ICW and ECW was independently associated with adverse renal outcomes and mortality, which may explain the reserve capacity for volume overload in patients with CKD.

Conflicts of Interest: OY, TR, AT, MS, OT, TY, OT, AA, and SK have no conflicts of interest to declare.

Ethics Statement: This study was approved by the Ethics Committee of Toho University Omori Medical Center, Tokyo, Japan (approval number: 25–252) and was in adherence with the Declaration of Helsinki. Informed consent was obtained from all participants.

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