THE EFFECT OF FLUID OVERLOAD ON CLINICAL OUTCOME IN SOUTHERN CHINESE PATIENTS UNDERGOING CONTINUOUS AMBULATORY PERITONEAL DIALYSIS

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◆ **Background:** Fluid overload is frequently present in dialysis patients and one of the important predictors of patient outcome. This study aimed to investigate the influence of fluid overload on all-cause mortality and technique failure in Southern Chinese continuous ambulatory peritoneal dialysis (CAPD) patients.

◆ **Methods:** This was a *post hoc* study from a cross-sectional survey originally designed to investigate the prevalence and associated risk factors of fluid overload defined by bioimpedance analysis (BIA) in CAPD patients from January 1, 2008, to December 31, 2009. All 307 CAPD patients completing the original study were followed up until December 31, 2012.

◆ **Results:** With a median follow-up period of 38.4 (19.2 – 47.9) months, 52 patients died. Patients with fluid overload (defined by extracellular water/total body water [ECW/TBW] ≥ 0.40) had a significantly higher peritonitis rate (0.016 vs 0.011 events/month exposure, $p = 0.018$) and cerebrovascular event rate (3.9 vs 1.1 events/100 patient years, $p = 0.024$) than the normal hydrated patients. Moreover, the results showed a significant rising of all-cause mortality (log-rank test = 5.59, $p = 0.018$), and a trend of increasing cardiovascular disease (CVD) mortality (log-rank test = 2.90, $p = 0.089$) and technique failure (log-rank test = 3.78, $p = 0.052$) in the patients with fluid overload. Fluid overload independently predicted all-cause mortality (hazard ratio [HR] = 12.98, 95% confidence interval [CI] = 1.06 – 168.23, $p = 0.042$) and technique failure (HR = 13.56, 95% CI = 2.53 – 78.69, $p = 0.007$) in CAPD patients after adjustment for confounders.

◆ **Conclusions:** Fluid overload defined by BIA was an independent predictor for all-cause mortality and technique failure in CAPD patients. Continuous ambulatory peritoneal dialysis patients with fluid overload had a higher peritonitis rate, cardiovascular event rate, and poorer clinical outcome than those patients with normal hydration.

KEY WORDS: Fluid overload; bioimpedance analysis; mortality; outcome; peritoneal dialysis; technique failure; nutrition.

Fluid overload is frequently present in dialysis patients (1), which is closely associated with cardiovascular complication (2,3), inflammation (4), and mortality in dialysis patients (5,6). Usually in peritoneal dialysis (PD) patients, practitioners rely most on routine physical examination, observation of dry weight, blood pressure, urine, and ultrafiltration output to diagnose overhydration (7), which provide a useful but imprecise picture of hydration.

Multi-frequency bioelectrical impedance analysis (BIA) is an extensively studied technique to evaluate fluid status in patients. Recent studies demonstrate that it is of potential value to provide a precise and sensitive method for detecting longitudinal changes in hydration (8–10). Using BIA, the European Body Composition Monitoring study demonstrated that fluid overload is present in 53.4% (341/639) of PD patients (2). Our previous cross-sectional study also showed that the prevalence of fluid overload is 66.8% in a cohort of 307 southern Chinese continuous ambulatory peritoneal dialysis (CAPD) patients (11).

Although Wizemann *et al.* (12) and Paniagua *et al.* (5) found overhydration defined by BIA was a predictor of mortality in the dialysis population, whether fluid overload defined by BIA can predict clinical events, technique failure, and mortality is still not clear. Thus we performed a *post hoc* analysis from a cross-sectional study, which was originally designed to investigate the prevalence and associated risk factors of fluid overload in CAPD patients, to understand the effect of fluid

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overload on clinical events, technique survival, and patient survival.

SUBJECTS AND METHODS

PARTICIPANTS

All patients came from the PD center at The First Affiliated Hospital, Sun Yat-sen University, Guangzhou, China. The original patient inclusion criteria were: 1) undergoing CAPD ≥ 3 months; 2) age > 18 years; 3) signed informed consent form. The exclusion criteria were: 1) patients with pacemakers; 2) patients with amputation; 3) patients who were not able to accomplish the analysis of body composition in standing position for 3 minutes. A total of 307 CAPD patients completing the original study were recruited in the present study and followed up till December 31, 2012. The study protocols were approved by the Ethics Committee of The First Affiliated Hospital of Sun Yat-sen University. An informed consent form was obtained from all the participants.

PATIENT INFORMATION

Patients were evaluated for clinical and biochemical data, fluid status, body composition, nutritional status, and comorbidity during a routine clinical visit, from January 1, 2008, to December 31, 2009.

All 307 patients were using dialysis systems from Baxter Healthcare Corp. The program uses a variety of 2-L dextrose glucose solutions. However, icodextrin was not used in this program as icodextrin was not commercially available in China. All the patients underwent CAPD therapy, none underwent automated peritoneal dialysis (APD). Peritoneal dialysis prescription dosage included 4 L per day (7, 2.3%), 6 L per day (48, 15.7%), 8 L per day (222, 72.3%), 10 L per day (27, 8.8%), and 12 L per day (3, 1.0%).

Blood was taken from patients to measure biochemical markers, including high sensitive C-reactive protein (hsCRP), hemoglobin, creatinine, albumin, transferrin, total cholesterol, triglyceride, serum phosphate, calcium, intact-PTH, sodium, chloride, potassium, carbon dioxide, and glucose. At the same time, patient demographic data and PD prescription and medication information were collected. Ultrafiltration and residual urine output were calculated from the patient's charts as a daily mean of ultrafiltration and urine volume obtained during the last week preceding the measurement. Solution glucose concentration (%) was calculated by dividing the total daily amount of glucose in dialysate by the total PD solution volume.

Patients provided a 24-hour collection of urine and effluent, completed in the morning of the study visit date, to evaluate Kt/V and residual renal function (RRF). Adequest 2.0 software (Baxter Healthcare, Deerfield, IL, USA) was applied to make the calculation. Dialysate-to-plasma ratio of creatinine (D/P_{cr}) was determined based on results of the last available *peritoneal equilibration test* (PET) preceding the BIA measurement.

BIOIMPEDANCE ANALYSIS

Total body water, extracellular water (ECW), intracellular water (ICW), and body composition were measured by multi-frequency bioelectrical impedance model InBody 720 (Biospace, Seoul, Korea). InBody 720 uses state-of-the-art technology, and an 8-point tactile electrode system that measures the total and segmental impedance and phase angle of alternating electric current at 6 different frequencies (1 kHz, 5 kHz, 50 kHz, 250 kHz, 500 kHz, and 1,000 kHz). All the subjects underwent BIA analysis in the morning during a routine clinical visit. They were instructed to fast and to avoid exercise 8 hours before measurement and had been resting for at least 30 minutes before measurement according to the manufacturer's instructions. When the measurement was performed, the patients had completed their first dwelling, and PD fluid was not drained from the abdomen as it has been previously shown that there is no significant effect on BIA measures (2,13,14). All patients had the same infill volume of 2 L. Impedance measurements were made with the subject standing in an upright position, on 4 foot electrodes in the platform of the instrument, and gripping 2 Palm-and-Thumb electrodes in order to yield 2 thumb electrodes and 2 palm electrodes. All the body composition data were performed in the instrument by inner software and entered on the result sheet immediately after measuring. This tool has been assessed in normal populations, renal transplant patients, hemodialysis (HD) patients, and PD patients, and closely correlates with the gold standard measurement by isotope dilution (15–19).

The ratio of ECW/TBW ≥ 0.4 , suggested by the manufacturer (Biospace, Seoul, Korea), was used to define overhydration. This cut-off was based on a fluid status measurement in 6,520 normal healthy Koreans. The threshold of 0.4 represented mean + 2 standard deviation (SD), i.e. $> 95^{\text{th}}$ percentile for normal Asian people.

NUTRITIONAL STATUS

Subjective global assessment (SGA) was performed to assess nutritional status by one experienced nurse

blinded to all clinical and biochemical variables of the patients. The method was based on the patient's history and physical examination as described by Detsky (20). The history focuses on gastrointestinal symptoms (anorexia, nausea, vomiting, and diarrhea) and weight loss in the preceding 6 months. The physical examination is graded by muscle wasting, loss of subcutaneous fat, and the presence of ankle edema. The nutritional status was scored on the 7-point scale of the SGA. Subjective global assessment scores of 5 or lower were defined as malnutrition.

COMORBIDITY

The comorbidity of each patient was determined according to the Charlson Comorbidity Index (CCI). This index is one of the most commonly used comorbidity models, and is based on comorbid conditions with varying assigned weights, resulting in a composite score. The CCI score was calculated by assigning a weight of 2 to diabetes, stroke, renal insufficiency, and malignancy, and a weight of 1 to the other comorbidities (21,22). Cardiovascular disease (CVD) was defined as a history of myocardial infarction, angina, congestive heart failure, cerebrovascular event, and peripheral vascular disease.

CLINICAL OUTCOME

All the patients were regularly followed up every 3 to 6 months until December 31, 2012. Patient survival, cardiac event, cerebrovascular event, peritonitis, non-peritonitis infection, and anuria were recorded. The last residual renal function was calculated by the last 24-hour urine and effluent collection performed within 6 months before the observational end-point. Cardiac event was defined as myocardial infarction, angina, arrhythmia, and congestive heart failure. Cerebrovascular event was defined as stroke and transient ischemic attack (TIA). Anuria was defined as urine volume less than 100 mL. The definition of peritonitis in CAPD requires 2 of the 3 criteria listed as follows: 1) presence of clinical manifestations of peritonitis; 2) dialysate white cell count over 100/ μ L, of which at least 50% are polymorphonuclear leukocytes; 3) positive culture (23). Cerebrovascular death included deaths from myocardial infarction, heart failure, arrhythmia, invasive cardiovascular interventions, stroke, unexpected death presumed to be from ischemic CVD occurring within 24 hours after the onset of symptoms, and death from other vascular diseases (24). Technique failure was defined as death and permanent HD transfer (25).

STATISTICAL ANALYSES

Patient characteristics were presented as mean $\pm$ SD for continuous variables, and percentages and frequencies for categorical variables. An independent sample *t*-test was used for a comparison of normally distributed continuous variables. A comparison of non-normally distributed continuous variables was performed using a Mann-Whitney U test. For categorical variables, Chi-squared test was used. Clinical event rate was compared by Poisson analysis. Mortality and technique failure was constructed using the Kaplan-Meier method. Center transfer, transplantation, HD transfer, and loss to follow-up led to censoring. Factors that reached statistical significance $p < 0.1$ in univariate analysis were selected for further multivariable analyses for all-cause and CVD mortality, PD technique failure by Cox-proportion hazard models. A 2-sided p value < 0.05 was considered statistically significant. The statistical analyses were conducted using SPSS 13.0 software (SPSS, Chicago, IL, USA).

RESULTS

COMPARISON BETWEEN SURVIVAL AND DEATH

A total of 307 CAPD patients (43% male) were enrolled, their mean age was 47.8 ± 15.3 , with a median PD duration of 38.4 (19.2 – 47.9) months. By the end of follow-up, of the 307 CAPD patients, 52 patients died, 28 patients transferred to HD, 44 patients were transplanted, 7 patients transferred to other centers, 1 patient withdrew for renal function recovery, 3 patients were lost to follow-up.

Compared with the survivors, the non-survivors were significantly older (58 ± 15 vs 46 ± 14 years, $p < 0.001$), and had significantly higher diabetic percentage (36.5% vs 12%, $p < 0.001$), malnourishment percentage (54% vs 36%, $p = 0.03$), ECW/TBW ratio (0.41 ± 0.01 vs 0.40 ± 0.01 , $p = 0.01$), CCI (6 [5 – 7] vs 4 [3 – 5], $p < 0.001$), solution glucose concentration (1.75% [1.5 – 2.0] vs 1.5% [1.5 – 1.75], $p = 0.003$), hsCRP level (6.75 mg/L [1.51 – 11.28] vs 1.89 mg/L [0.72 – 6.49], $p < 0.001$), but significantly lower diastolic blood pressure (80 ± 14 vs 86 ± 15 mmHg, $p = 0.004$), residual urine volume (399 ± 382 vs 546 ± 470 mL/24 hours, $p = 0.04$), and serum albumin level (36 [33 – 40] vs 41 [38 – 43] g/L, $p < 0.001$), as shown in Table 1.

DIAGNOSTIC TOOL FOR ALL-CAUSE MORTALITY

As shown in Figure 1, we used receiver-operating characteristic curve (ROC) analysis to calculate the sensitivity

TABLE 1
Baseline of Clinical, Demographic, and Laboratory Characteristics in All Patients

	All patients <i>n</i> =307	Non-survivor <i>n</i> =52	Survivor <i>n</i> =255	<i>P</i> value
Baseline of demographics				
Male (%)	132/307 (43%)	25/52 (48%)	107/255 (42%)	0.42
Age (years)	47.8±15.3	58±15	46±14	<0.001**
Duration of CAPD (months)	14.6 (5.9–30.9)	17.2 (10.0–37.7)	13.7 (5.4–28.3)	0.13
BMI (kg/m ²)	22.7±3.9	23.0±3.1	22.6±4.0	0.53
Diabetes (%)	49/307 (16%)	19/52 (36.5%)	30/255 (12%)	<0.001**
Systolic blood pressure (mmHg)	137±22	142±20	136±22	0.08
Diastolic blood pressure (mmHg)	85±15	80±14	86±15	0.004**
Residual urine volume (mL/24 hours)	522±459	399±382	546±470	0.04
D/P _{cr}	0.68±0.11	0.71±0.10	0.69±0.11	0.30
RRF (mL/min/1.73 m ²)	2.66 (0.31–3.28)	3.54 (0.92–5.85)	2.52 (1.18–4.00)	0.63
SGA score≤5 percentage (%)	120/307 (39%)	28/52 (54%)	92/255 (36%)	0.03*
CCI score	4 (3–6)	6 (5–7)	4 (3–5)	<0.001**
ECW (L)	13.9±3.1	13.8±2.7	13.9±3.2	0.79
ICW (L)	20.8±4.5	20.2±3.9	20.9±4.7	0.36
ECW/height	0.085±0.017	0.086±0.014	0.085±0.017	0.86
ECW/TBW	0.40±0.01	0.41±0.01	0.40±0.01	0.01*
PD prescription				
Solution glucose concentration (%)	1.5 (1.5–1.8)	1.75 (1.5–2.0)	1.5 (1.5–1.75)	0.003**
Kt/V	2.45±1.10	2.76±1.10	2.38±0.62	0.06
Ultrafiltration (mL/24 hours)	496±476	601±390	474±490	0.18
Salt restriction (yes/no)	177/130	44/8	194/61	0.46
Biochemical markers				
hsCRP (mg/L)	2.00 (0.80–8.30)	6.75 (1.51–11.28)	1.89 (0.72–6.49)	<0.001**
Creatinine (μmol/L)	923±353	847±363	941±349	0.08
Albumin (g/L)	39 (36–42)	36 (33–40)	41 (38–43)	<0.001**
Transferrin (g/L)	2.3 (1.9–2.6)	2.1 (1.9–2.5)	2.3 (2.0–2.6)	0.14
Phosphate (mmol/L)	1.67±0.58	1.63±0.56	1.67±0.58	0.63
Potassium (mmol/L)	3.8 (3.3–4.2)	3.8 (3.4–4.1)	3.8 (3.3–4.3)	0.58
Carbon dioxide (mmol/L)	25±4	26±4	25±4	0.37
Glucose (mmol/L)	4.5 (3.9–5.3)	4.9 (4.3–7.2)	4.5 (3.8–5.2)	0.005**
Medications				
Number of anti-hypertension drugs	2 (1–3)	3 (2–3)	2 (1–3)	0.59
Calcium channel blockers (%)	199/307 (65%)	40/52 (77%)	159/255 (63%)	0.39
Diuresis (%)	19/307 (6.0%)	2/52 (4.0%)	17/255 (6.7%)	0.50
Antiplatelet agents	26/307 (8.5%)	6/52 (11.5%)	20/255 (7.8%)	0.38
HMG CoA reductase inhibitors	28/307 (9.1%)	4/52 (7.7%)	24/255 (9.4%)	1.00

CAPD = continuous ambulatory peritoneal dialysis; BMI = body mass index; RRF = residual renal function; SGA = subjective global assessment; CCI = Charlson Comorbidity Index; ECW = extracellular water; ICW = intracellular water; TBW = total body water; PD = peritoneal dialysis; hsCRP = high-sensitivity C-reactive protein.

* *P*<0.05.

** *P*<0.01.

and specificity of ECW/TBW (area under the curve [AUC] = 0.64, cut-off 0.40, sensitivity 0.61, specificity 0.60, *p* = 0.002), ICW (AUC = 0.46, *p* = 0.42), ECW (AUC = 0.49, *p* = 0.84), and ECW/height (AUC = 0.51, *p* = 0.79) as a

diagnostic tool to diagnose all-cause mortality in 307 CAPD patients.

In our previous cross-sectional study (11) and present study, the ratio of ECW/TBW ≥ 0.4, suggested by the

Figure 1 — ROC analysis of ECW/TBW (AUC=0.64, cut-off 0.40, sensitivity 0.61, specificity 0.60, $p=0.002$), ICW (AUC=0.46, $p=0.42$), ECW (AUC=0.49, $p=0.84$), and ECW/height (AUC=0.51, $p=0.79$) for all-cause mortality. ROC = receiver-operating characteristic curve; ECW = extracellular water; TBW = total body water; AUC = area under the curve; ICW = intracellular water.

manufacturer (Biospace, Seoul, Korea), was used to define overhydration. The threshold of 0.4 represented mean + 2 SD, i.e. > 95th percentile for normal Asian people. We certified in this study that the threshold of 0.40 was a sensitive and specific cut-off for all-cause mortality in southern Chinese CAPD patients.

CHANGE OF RESIDUAL RENAL FUNCTION

The baseline percentage of anuric patients was comparable in the overhydrated and normal hydrated patients (19.0% [39/205] vs 22.5% [23/102], $p=0.47$). After a median follow-up period of 38.4 (19.2 – 47.9) months, the change of residual urine volume (-160 [-500 – 0] vs -70 [-450 – 0] mL/24 hours, $p=0.36$) and residual renal function (-1.50 [-3.0 to -0.31] vs -1.07 [-3.01 to -0.24] mL/min/1.73 m², $p=0.35$) were comparable in the patients with fluid overload and normal hydration after a median follow-up of 38.4 months, as shown in Figure 2. In addition, during the period of follow-up, anuria occurred in 36.5% (73/205) of overhydrated patients, and 25.5% (26/102) of normal hydrated patients ($p=0.074$).

PERITONITIS, CARDIAC EVENT, AND CEREBROVASCULAR EVENT

During a median follow-up period of 38.4 (19.2 – 47.9) months, 111 peritonitis episodes happened in 62 of 205 overhydrated patients; 39 patients had 1 episode, 7 patients had 2 episodes, 8 patients had 3 episodes, 6 patients had 4 episodes, and 2 patients had 5 episodes. During the same period, 37 peritonitis episodes

Figure 2A — Change of urine volume (mL/24 hours) in the 307 CAPD patients with fluid overload (ECW/TBW $\geq$ 0.4, $n=205$) and normal hydration (ECW/TBW<0.4, $n=102$) followed for a median of 38.4 months (-160 [-500–0] vs -70 [-450–0] mL/24 hours, $p=0.36$). CAPD = continuous ambulatory peritoneal dialysis; ECW = extracellular water; TBW = total body water.

Figure 2B — Change of residual renal function (mL/min/1.73 m²) in the 307 CAPD patients with fluid overload (ECW/TBW $\geq$ 0.4, $n=205$) and normal hydration (ECW/TBW<0.4, $n=102$) followed for a median of 38.4 months (-1.50 [-3.0 to -0.31] vs -1.07 [-3.01 to -0.24] mL/min/1.73 m², $p=0.35$). CAPD = continuous ambulatory peritoneal dialysis; ECW = extracellular water; TBW = total body water.

happened in 25 of 102 normal hydrated patients: 17 patients had 1 episode, 4 patients had 2 episodes, and 4 patients had 3 episodes.

Compared with normal hydrated patients, patients with fluid overload had significantly higher peritonitis rate (0.016 vs 0.011 episodes/month exposure, $p=0.018$,

odds ratio [OR] = 1.57, 95% CI 1.08 – 2.28), and higher non-peritonitis infection rate, but not statistically significant (11.1 vs 8.7 events/100 patient years, $p = 0.19$, OR = 1.36, 95% CI 0.86 – 2.16), as shown in Table 2.

The cerebrovascular event rate (3.9 vs 1.1 events/100 patient years, $p = 0.024$, OR = 1.97, 95% CI 1.12 – 3.48), cardiac and cerebrovascular event rate (10.1 vs 5.2 events/100 patient years, $p = 0.019$, OR = 3.98, 95% CI 1.20 – 13.26) were significantly higher in patients with fluid overload than that of normal hydrated patients. Although the cardiac event rate was higher in the overhydrated patients (6.1 vs 4.2 events/100 patient years, $p = 0.18$, OR = 1.56, 95% CI 0.81 – 3.00), it was not statistically significant, as shown in Table 2.

INCIDENCE OF ALL-CAUSE MORTALITY, CVD MORTALITY, AND TECHNIQUE FAILURE

The all-cause mortality was 5.9 events/100 patient years in 307 CAPD patients (Table 2). The cumulative all-cause mortality at the first, second and third year was 8%, 14%, and 20% in the overhydrated group, as well as 2%, 5%, and 10% in the normal hydrated group. Kaplan-Meier mortality curves showed a significant rising all-cause mortality in the subjects with fluid overload (log-rank test = 5.59, $p = 0.018$, Figure 3A). The cumulative CVD mortality at the first, second, and third year was 6%, 10%, and 14% in the overhydrated group, as well as 2%, 5%, and 9% in the normal hydrated group.

Kaplan-Meier mortality curves showed a trend of increasing CVD mortality in the patients with fluid overload (log-rank test = 2.90, $p = 0.089$, Figure 3B). Moreover, the cumulative technique failure at the first, second, and third year was 11%, 20%, and 27% in the overhydrated group, and 4%, 9%, and 18% in the normal hydrated group. Kaplan-Meier mortality curves also showed a trend of increasing technique failure in the patients with fluid overload (log-rank test = 3.78, $p = 0.052$, Figure 3C)

RISK FACTORS FOR ALL-CAUSE MORTALITY, CVD MORTALITY, AND TECHNIQUE FAILURE

By performing Cox proportional hazards models in a step backward method, we found that fluid overload (ECW/TBW ≥ 0.4) independently predicted all-cause mortality (HR = 12.98, 95% CI = 1.06 – 168.23, $p = 0.042$) in CAPD patients after adjustment for age, sex, diabetes mellitus (DM), Charlson Comorbidity Index (CCI), residual renal function (RRF), Log hsCRP, albumin, diastolic blood pressure, D/P_{cr}, Kt/V, and solution glucose concentration. Moreover, fluid overload (ECW/TBW ≥ 0.40) also independently predicted PD technique failure (HR = 13.56, 95% CI = 2.53 – 78.69, $p = 0.007$) in CAPD patients after adjustment for age, sex, DM, CCI, RRF, Log hsCRP, albumin, diastolic blood pressure, D/P_{cr}, Kt/V, and solution glucose concentration, as shown in Table 3A. A separate model including SGA as an independent nutritional marker was shown in Table 3B.

TABLE 2
Clinical Events and Outcome in All 307 Participants

Clinical outcome	Total population (n=307)	Fluid status		P value
		ECW/TBW ≥ 0.4 (n=205)	ECW/TBW < 0.4 (n=102)	
Peritonitis (episodes/month exposure)	148 (0.014)	111 (0.016)	37 (0.011)	0.018*
Non-peritonitis infection (events/100 patient years)	90 (10.3)	65 (11.1)	25 (8.7)	0.19
Cardiac and cerebrovascular events (events/100 patient years)	74 (8.5)	59 (10.1)	15 (5.2)	0.019*
Cardiac events (events/100 patient years)	48 (5.5)	36 (6.1)	12 (4.2)	0.18
Cerebrovascular events (events/100 patient years)	26 (3.0)	23 (3.9)	3 (1.0)	0.024*
Ischemic cerebrovascular events (events/100 patient years)	18 (2.1)	16 (2.7)	2 (0.7)	0.057
Haemorrhagic cerebrovascular events (events/100 patient years)	8 (0.9)	7 (1.2)	1 (0.3)	0.227
All-cause mortality (events/100 patient years)	52 (5.9)	43 (7.3)	9 (3.1)	0.018*
CVD mortality (events/100 patient years)	37 (4.2)	30 (5.1)	7 (2.4)	0.089
Cardiac diseases mortality (events/100 patient years)	28 (3.2)	22 (3.7)	6 (2.1)	0.242
Stroke mortality (events/100 patient years)	9 (1.0)	8 (1.4)	1 (0.3)	0.168
Peripheral vascular diseases mortality (events/100 patient years)	0 (0)	0 (0)	0 (0)	—
Infectious diseases mortality (events/100 patient years)	10 (1.1)	9 (1.5)	1 (0.3)	0.129
Other diseases mortality (events/100 patient years)	5 (0.6)	4 (0.7)	1 (0.3)	0.406

CVD = cardiovascular disease.

* $P < 0.05$.

Figure 3 — Kaplan-Meier survival curves for the patients with ECW/TBW above or below the ROC-derived cut-off for all-cause mortality (A), CVD mortality (B), technique failure (C) in the 307 CAPD patients followed for a median of 38.4 months. ECW = extracellular water; TBW = total body water; CVD = cardiovascular disease; ROC = receiver-operating characteristic curve; CAPD = continuous ambulatory peritoneal dialysis.

DISCUSSION

In this study, we demonstrated that overhydrated (ECW/TBW ≥ 0.40) patients defined by BIA had a significant increase of all-cause mortality, and a trend of increasing CVD mortality and technique failure. Fluid overload independently predicted all-cause mortality and technique failure in CAPD patients after adjustment for confounders. Moreover, patients with fluid overload had significantly higher peritonitis rates, cerebrovascular events, cardiac and cerebrovascular event rate than those of normally hydrated patients.

One important finding of this study was that fluid overload defined by BIA independently predicted all-cause

mortality and technique failure in CAPD patients. Our results, which showed that overhydrated patients had significantly higher all-cause mortality, was consistent with Wizemann *et al.*'s reported results, who found a marked higher gross mortality in hydrated HD patients. Moreover, they found overhydration was a significant predictor of mortality in the HD population (HR = 2.102, $p = 0.003$) (12). Paniagua *et al.* also investigated the effect of fluid overload on mortality in 753 HD and PD patients. They found that ECW/TBW was an independent predictor for CVD mortality (5). In a recent randomized trial, Onofriescu *et al.* showed that BIA-guided ultrafiltration in HD patients helped to decrease blood pressure and improve hydration status

TABLE 3A
Hazard Ratios of ECW/TBW for All-Cause Mortality, CVD Mortality, and PD Technique Failure
Adjusted for Albumin (A) and SGA (B)

Multivariate model A	All-cause mortality			CVD mortality			PD technique failure		
	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P
Crude									
ECW/TBW (above vs below 0.40)	9.01	1.20–67.53	0.032*	7.97	1.06–60.13	0.044*	3.87	1.16–12.90	0.027*
Model 1									
ECW/TBW (above vs below 0.40)	7.07	0.92–54.47	0.060	6.16	0.79–47.98	0.082	3.61	1.06–12.29	0.040*
Model 2									
ECW/TBW (above vs below 0.40)	9.73	1.15–82.56	0.037*	7.56	0.89–64.54	0.064	5.40	1.45–20.16	0.012*
Model 3									
ECW/TBW (above vs below 0.40)	13.58	1.08–170.11	0.042*	9.20	0.68–124.29	0.094	13.33	2.12–83.68	0.007**
Age (years)	1.03	0.97–1.09	0.390	1.04	0.97–1.11	0.288	1.02	0.97–1.07	0.542
Sex (female vs male)	0.74	0.23–2.31	0.599	0.65	0.19–2.23	0.488	0.98	0.38–2.52	0.961
DM	0.91	0.19–4.47	0.906	1.20	0.20–7.38	0.842	1.05	0.25–4.34	0.945
CCI	5.89	0.13–274.33	0.324	5.24	0.09–300.11	0.409	2.64	1.16–44.46	0.047*
Residual renal function (mL/min/1.73 m ²)	1.27	0.95–1.71	0.105	1.36	1.05–1.78	0.022*	1.32	1.02–1.70	0.032*
Log hsCRP	1.36	0.57–3.28	0.546	1.28	0.92–1.78	0.596	0.88	0.42–1.82	0.488
Albumin (g/L)	1.00	0.86–1.16	0.984	1.02	0.90–1.17	0.730	1.00	0.89–1.13	0.957
Diastolic blood pressure (mmHg)	0.995	0.95–1.05	0.84	1.02	0.96–1.08	0.527	0.98	0.94–1.02	0.238
D/P _{cr}	109.07	0.11–113,508	0.19	140.71	0.16–127,924	0.155	4314	10.79–1,723,874	0.006**
Kt/V	1.34	0.72–2.50	0.36	1.43	0.73–2.81	0.293	1.23	0.71–2.12	0.469
Solution glucose concentration (%)	2.56	0.25–26.01	0.428	1.63	0.13–19.91	0.702	1.62	0.31–8.62	0.570

Model 1: after adjustment for age, sex.

Model 2: after adjustment for age, sex, DM, CCI.

Model 3: after adjustment for age, sex, DM, CCI, RRF, log hsCRP, albumin, diastolic blood pressure, D/P_{cr}, Kt/V, and solution glucose concentration.

R² values for all-cause mortality crude model, model 1, 2, and 3 were 6.74, 10.56, 22.78, 31.72, respectively. R² values for CVD mortality crude model, model 1, 2, and 3 were 5.74, 9.32, 18.36, 28.02, respectively. R² values for technique failure crude model, model 1, 2, and 3 were 5.65, 7.18, 21.71, 36.10, respectively.

ECW = extracellular water; TBW = total body water; CVD = cardiovascular disease; PD = peritoneal dialysis; HR = hazard ratio; CI = confidence interval; DM = diabetes mellitus; CCI = Charlson comorbidity index; hsCRP = high sensitivity C-reactive protein; D/P_{cr} = dialysate-to-plasma ratio of creatinine; RRF = residual renal function.

* *P* < 0.05.

** *P* < 0.01.

TABLE 3B
Hazard Ratios of ECW/TBW for All-Cause Mortality, CVD Mortality, and PD Technique Failure
Adjusted for Albumin (A) and SGA (B)

Multivariate model B	All-cause mortality			CVD mortality			PD technique failure		
	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P
Crude									
ECW/TBW (above vs below 0.40)	9.24	1.23–69.23	0.030*	8.18	1.08–61.68	0.042*	3.61	1.08–12.11	0.038*
Model 1									
ECW/TBW (above vs below 0.40)	7.29	0.95–56.10	0.057	6.36	0.82–49.47	0.077	3.32	0.97–11.43	0.057*
Model 2									
ECW/TBW (above vs below 0.40)	9.83	1.16–83.20	0.036*	7.66	0.90–65.19	0.062	4.89	1.28–18.61	0.020*
Model 3									
ECW/TBW (above vs below 0.40)	13.12	1.35–128	0.027*	7.97	0.82–77.77	0.074	10.34	1.88–57.02	0.007**
Age (years)	1.03	0.97–1.09	0.370	1.04	0.97–1.11	0.251	1.02	0.97–1.07	0.546
Sex (female vs male)	0.69	0.21–2.23	0.532	0.55	0.16–1.98	0.363	0.95	0.34–2.66	0.924
DM	0.98	0.19–5.12	0.98	1.35	0.22–8.46	0.747	1.30	0.26–6.46	0.752
CCI	4.04	0.06–26	0.513	2.84	0.39–207	0.633	5.31	0.1–282	0.410
Residual renal function (mL/min/1.73 m ²)	1.26	0.94–1.69	0.128	1.37	1.06–1.76	0.016*	1.26	0.97–1.66	0.089
Log hsCRP	1.56	0.63–2.87	0.576	1.33	0.71–1.87	0.643	0.81	0.38–1.89	0.461
SGA (score)	0.77	0.24–2.43	0.654	0.70	0.22–2.25	0.550	1.01	0.35–2.95	0.986
Diastolic blood pressure (mmHg)	0.995	0.95–1.05	0.836	1.02	0.96–1.08	0.538	0.99	0.95–1.03	0.622
D/P _{cr}	120.24	0.20–74,217	0.144	117	0.16–127,924	0.139	6108	21.86–1,706,708	0.002**
Kt/V	1.38	0.74–2.59	0.316	1.47	0.76–2.87	0.255	1.28	0.72–2.28	0.403
Solution glucose concentration (%)	2.60	0.28–24.28	0.402	1.55	0.14–17.30	0.702	1.27	0.21–8.62	7.91

Model 1: after adjustment for age, sex.

Model 2: after adjustment for age, sex, DM, CCI.

Model 3: after adjustment for age, sex, DM, CCI, RRF, log hsCRP, SGA, diastolic blood pressure, D/P_{cr}, Kt/V, and solution glucose concentration.

R² values for all-cause mortality crude model, model 1, 2, and 3 were 6.96, 10.59, 22.22, 31.02, respectively. R² values for CVD mortality crude model, model 1, 2, and 3 were 5.93, 9.34, 17.91, 28.57, respectively. R² values for technique failure crude model, model 1, 2, and 3 were 4.95, 6.37, 23.15, 36.24, respectively.

ECW = extracellular water; TBW = total body water; CVD = cardiovascular disease; PD = peritoneal dialysis; SGA = subjective global assessment; HR = hazard ratio; CI = confidence interval; DM = diabetes mellitus; CCI = Charlson comorbidity index; hsCRP = high sensitivity C-reactive protein; D/P_{cr} = dialysate-to-plasma ratio of creatinine; RRF = residual renal function.

* P < 0.05.

** P < 0.01.

and arterial stiffness, thus decreasing CVD risk factors (26). However, they did not report the effect of this BIA-guided therapy on mortality. Furthermore, we found that fluid overload was an independent predictor for technique failure, the patients with overhydration having a higher technique failure rate ($p = 0.052$). Indeed, Nakayama showed that fluid overload for all reasons constituted 31.8% of all withdrawals occurring within the first year, 17.8% within 1 to 4 years, and 12.5% within 4 to 8 years of PD in Japanese patients (27). Additionally, a recent randomized controlled study showed that use of icodextrin-containing solutions to improve fluid status has a beneficial effect on PD technique survival (28). However, whether controlling fluid overload by bioimpedance monitoring can decrease mortality and technique failure in PD patients warrants a prospective, randomized study.

The novel finding of this study is that patients with fluid overload had obvious increasing peritonitis rates and CVD event rates compared with those in normally hydrated patients. Why the patients with overhydration associated with higher peritonitis rates is unclear. Our previous study showed that protein-energy wasting was independently associated with fluid overload in CAPD patients (11). These malnourished patients with fluid overload may be more susceptible to infection, and had higher risk of peritonitis (29). Moreover, to our knowledge, our study is the first to report that overhydrated dialysis patients defined by BIA had higher cerebrovascular event and CVD event rates than normally hydrated dialysis patients. Indeed, Demirci *et al.* showed that fluid overload defined by ECW/height is significantly correlated with malnutrition, inflammation, and atherosclerosis. Their patients with fluid overload were more inflamed, had higher carotid artery intima-media thickness, left ventricular end-diastolic diameter, and left atrium diameter (4). Lin *et al.* also found left ventricular mass (LVM) was significantly positively related to extracellular fluid (ECF) (30). On the other hand, Machek *et al.* found that HD patients that were closer to the bioimpedance target of normohydration had better control of hypertension and less intradialytic adverse events (31). Whether improving fluid status guided by BIA could decrease cerebrovascular and cardiac events in PD patients needs further prospective study to confirm. Furthermore, although it is known that hemorrhagic cerebrovascular events are more common in the Chinese population, ischemic cerebrovascular events were more common in our group of CAPD patients. Our results suggest that patients with overhydration had a significantly higher ischemic and hemorrhagic cerebrovascular event rate than that of normally hydrated patients.

Of note, fluid overload has a very close relationship with malnutrition. The denominator of the ECW/TBW ratio contains ICW, which reflects body cell mass; thus it is not surprising that this ratio inversely reflects nutritional state. Nevertheless, a PD patient developing malnutrition may gradually acquire extracellular water accumulation to balance loss of body cell mass or body fat mass, while this hydration fails to become clinically obvious until fluid excess is considerably overt. Thus BIA helps to identify early or occult overhydration. Furthermore, the lower serum albumin level of malnourished patients inevitably caused a lower colloid osmotic pressure in the blood, which certainly aggravated the fluid retention in the tissue space. Our previous study (11) showed that the ECW/TBW ratio was inversely associated with good surrogate markers of protein-energy wasting, including BMI, SGA score, body fat mass, serum albumin, and creatinine; furthermore, lower serum albumin and body fat mass were independent associated factors of overhydration. In the present study, neither ICW nor ECW or ECW/height were predictors of adverse outcomes on their own. Therefore, the ECW/TBW ratio may be of greater significance as a predictor of poorer outcomes as a composite of overhydration and wasting. Nevertheless, the ratio of ECW/TBW was still an independent predictor of clinical outcome after adjustment for SGA and albumin as an independent nutritional marker (as shown in Tables 3A and B). In other words, fluid status represented as ECW/TBW remained an independent predictor of mortality and technique failure in PD patients even after adjustment for nutritional status.

Our previous study used an ECW/TBW cut-off of 0.4 to diagnose fluid overload and got a prevalence of 66.8% in CAPD patients, which was notably higher than the diagnosis rate of 45% by routine physical examination (11). In the present study, we used ROC analysis to calculate the sensitivity and specificity of ECW/TBW, ICW, ECW, and ECW/height as a diagnostic tool to diagnose all-cause mortality and certified that only the ECW/TBW cut-off value of 0.4 predicted all-cause mortality in PD patients. As we showed that fluid overload guided by BIA was significantly associated with overall mortality, technique failure, and clinical events, it is necessary to pay more attention to the high prevalence and to identify the clinical occult overhydration before notable clinical edema appears, in order to make the appropriate therapeutic changes. Our survey supported that ECW/TBW defined by BIA used in this study could be used as a simple bedside screening tool in clinical evaluation of fluid overload in CAPD patients. As fluid status predicted clinical outcome, more attention is needed to improve the patients' fluid status, including optimizing sodium and water removal,

controlling sodium and water intake, and administering diuretics to enhance residual urine output.

Considering the measurement by BIA, Davenport reported that BIA measurements made in PD patients with fluid instilled may overestimate ECW and ECW/TBW and suggested the dialysate should be drained out for more accurate BIA measurement (32). However, segmental bioimpedance spectroscopy does not measure sequestered fluid in the trunk for bio-physical reasons. Thus presence or absence of PD fluid in the abdomen does not influence the reading of hydration status (2,33). Davison *et al.* confirmed this result by taking readings with and without indwelling dialysate for PD patients, and no differences in readings were observed (34).

LIMITATIONS

This is a single-center, observational study without intervention in a prevalent cohort. Furthermore, the ROC value for ECW/TBW is 0.64, which is <0.7 . Therefore, further randomized control study is needed to testify whether interventions guided by BIA have a positive effect on reducing CVD event, technique failure, peritonitis rate and mortality in CAPD patients. In addition, the cut-off value we have explored (0.4) is only a threshold for the InBody BIA device we used in this study, which might be very different for other devices.

CONCLUSION

In conclusion, bioimpedance analysis is a valuable bedside tool, not only to diagnose fluid overload and nutritional status, but also to predict clinical outcome in PD patients. Peritoneal dialysis patients with a higher ratio of ECW/TBW (as composite of overhydration and wasting) had poor patient survival and technique survival, higher peritonitis rates, higher cardiac and cerebrovascular event rates than patients with lower value. After adjustment for nutritional status, fluid overload represented by ECW/TBW was still an independent predictor for all-cause mortality and technique failure in CAPD patients.

DISCLOSURES

The authors have no financial conflicts of interest to declare.

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REFERENCES

- Lo WK, Bargman JM, Burkart J, Krediet RT, Pollock C, Kawanishi H, *et al.* Guideline on targets for solute and fluid removal in adult patients on chronic peritoneal dialysis. *Perit Dial Int* 2006; 26(5):520–2.
- Van Biesen W, Williams JD, Covic AC, Fan S, Claes K, Lichodziejewska-Niemierko M, *et al.* Fluid status in peritoneal dialysis patients: the European Body Composition Monitoring (EuroBCM) study cohort. *PLoS one* 2011; 6(2):e17148.
- Cheng LT, Tian JP, Tang LJ, Chen HM, Gu Y, Du FH, *et al.* Why is there significant overlap in volume status between hypertensive and normotensive patients on dialysis? *Am J Nephrol* 2008; 28(3):508–16.
- Demirci MS, Demirci C, Ozdogan O, Kircelli F, Akcicek F, Basci A, *et al.* Relations between malnutrition-inflammation-atherosclerosis and volume status. The usefulness of bioimpedance analysis in peritoneal dialysis patients. *Nephrol Dial Transplant* 2011; 26(5):1708–16.
- Paniagua R, Ventura MD, Avila-Diaz M, Hinojosa-Heredia H, Mendez-Duran A, Cueto-Manzano A, *et al.* NT-proBNP, fluid volume overload and dialysis modality are independent predictors of mortality in ESRD patients. *Nephrol Dial Transplant* 2010; 25(2):551–7.
- Chen W, Gu Y, Han QF, Wang T. Contrasting clinical outcomes between different modes of peritoneal dialysis regimens: two center experiences in China. *Kidney Int Suppl* 2008; 108:S56–62.
- Cocchi R, Degli Esposti E, Fabbri A, Lucatello A, Sturani A, Quarello F, *et al.* Prevalence of hypertension in patients on peritoneal dialysis: results of an Italian multicentre study. *Nephrol Dial Transplant* 1999; 14(6):1536–40.
- Woodrow G. Methodology of assessment of fluid status and ultrafiltration problems. *Perit Dial Int* 2007; 27(Suppl 2):S143–7.
- Moissl UM, Wabel P, Chamney PW, Bosaeus I, Levin NW, Bosy-Westphal A, *et al.* Body fluid volume determination via body composition spectroscopy in health and disease. *Physiol Meas* 2006; 27(9):921–33.
- Wabel P, Chamney P, Moissl U, Jirka T. Importance of whole-body bioimpedance spectroscopy for the management of fluid balance. *Blood Purif* 2009; 27(1):75–80.
- Guo Q, Yi C, Li J, Wu X, Yang X, Yu X. Prevalence and risk factors of fluid overload in Southern Chinese continuous ambulatory peritoneal dialysis patients. *PLoS one* 2013; 8(1):e53294.
- Wizemann V, Wabel P, Chamney P, Zaluska W, Moissl U, Rode C, *et al.* The mortality risk of overhydration in

- haemodialysis patients. *Nephrol Dial Transplant* 2009; 24(5):1574–9.
13. Boudville NC, Cordy P, Millman K, Fairbairn L, Sharma A, Lindsay R, *et al.* Blood pressure, volume, and sodium control in an automated peritoneal dialysis population. *Perit Dial Int* 2007; 27(5):537–43.
 14. Rallison LR, Kushner RF, Penn D, Schoeller DA. Errors in estimating peritoneal fluid by bioelectrical impedance analysis and total body electrical conductivity. *J Am Coll Nutr* 1993; 12(1):66–72.
 15. Bioelectrical impedance analysis in body composition measurement: National Institutes of Health Technology Assessment Conference Statement. *Am J Clin Nutr* 1996; 64(Suppl):524S–32S.
 16. van den Ham EC, Kooman JP, Christiaans MH, Nieman FH, Van Kreel BK, Heidendal GA, *et al.* Body composition in renal transplant patients: bioimpedance analysis compared to isotope dilution, dual energy X-ray absorptiometry, and anthropometry. *J Am Soc Nephrol* 1999; 10(5):1067–79.
 17. Chertow GM, Lowrie EG, Wilmore DW, Gonzalez J, Lew NL, Ling J, *et al.* Nutritional assessment with bioelectrical impedance analysis in maintenance hemodialysis patients. *J Am Soc Nephrol* 1995; 6(1):75–81.
 18. Jones CH, Smye SW, Newstead CG, Will EJ, Davison AM. Extracellular fluid volume determined by bioelectric impedance and serum albumin in CAPD patients. *Nephrol Dial Transplant* 1998; 13(2):393–7.
 19. Cooper BA, Aslani A, Ryan M, Zhu FY, Ibels LS, Allen BJ, *et al.* Comparing different methods of assessing body composition in end-stage renal failure. *Kidney Int* 2000; 58(1):408–16.
 20. Detsky AS, McLaughlin JR, Baker JP, Johnston N, Whittaker S, Mendelson RA, *et al.* What is subjective global assessment of nutritional status? 1987. Classical article. *Nutr Hosp* 2008; 23(4):400–7.
 21. Volk ML, Hernandez JC, Lok AS, Marrero JA. Modified Charlson comorbidity index for predicting survival after liver transplantation. *Liver Transpl* 2007; 13(11):1515–20.
 22. Yong DS, Kwok AO, Wong DM, Suen MH, Chen WT, Tse DM. Symptom burden and quality of life in end-stage renal disease: a study of 179 patients on dialysis and palliative care. *Palliat Med* 2009; 23(2):111–9.
 23. Li PK, Szeto CC, Piraino B, Bernardini J, Figueiredo AE, Gupta A, *et al.* Peritoneal dialysis-related infections recommendations: 2010 update. *Perit Dial Int* 2010; 30(4):393–423.
 24. Pop-Busui R, Evans GW, Gerstein HC, Fonseca V, Fleg JL, Hoogwerf BJ, *et al.* Effects of cardiac autonomic dysfunction on mortality risk in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. *Diabetes care* 2010; 33(7):1578–84.
 25. Van Biesen W, Vanholder RC, Veys N, Dhondt A, Lameire NH. An evaluation of an integrative care approach for end-stage renal disease patients. *J Am Soc Nephrol* 2000; 11(1):116–25.
 26. Onofriescu M, Mardare NG, Segall L, Voroneanu L, Cusai C, Hogas S, *et al.* Randomized trial of bioelectrical impedance analysis versus clinical criteria for guiding ultrafiltration in hemodialysis patients: effects on blood pressure, hydration status, and arterial stiffness. *Int Urol Nephrol* 2012; 44(2):583–91.
 27. Nakayama M. Fluid status and its management in Japanese peritoneal dialysis patients. *Perit Dial Int* 2006; 26(2):144–9.
 28. Takatori Y, Akagi S, Sugiyama H, Inoue J, Kojo S, Morinaga H, *et al.* Icodextrin increases technique survival rate in peritoneal dialysis patients with diabetic nephropathy by improving body fluid management: a randomized controlled trial. *Clin J Am Soc Nephrol* 2011; 6(6):1337–44.
 29. Dong J, Li Y, Xu Y, Xu R. Daily protein intake and survival in patients on peritoneal dialysis. *Nephrol Dial Transplant* 2011; 26(11):3715–21.
 30. Lin YP, Chen CH, Yu WC, Hsu TL, Ding PY, Yang WC. Left ventricular mass and hemodynamic overload in normotensive hemodialysis patients. *Kidney Int* 2002; 62(5):1828–38.
 31. Machek P, Jirka T, Moissl U, Chamney P, Wabel P. Guided optimization of fluid status in haemodialysis patients. *Nephrol Dial Transplant* 2010; 25(2):538–44.
 32. Davenport A. Does peritoneal dialysate affect body composition assessments using multi-frequency bioimpedance in peritoneal dialysis patients? *Eur J Clin Nutr* 2013; 67(2):223–5.
 33. Foster KR and Lukaski HC. Whole body impedance—what does it measure? *Am J Clin Nutr* 1996; 64(Suppl):388S–96S.
 34. Davison SN, Jhanqri GS, Jindal K, Pannu N. Comparison of volume overload with cycler-assisted versus continuous ambulatory peritoneal dialysis. *Clin J Am Soc Nephrol* 2009; 4(6):1044–50.