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Original Investigation

Association of Fluid Overload With Kidney Disease Progression in Advanced CKD: A Prospective Cohort Study

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Background: Fluid overload is a common phenomenon in patients in a late stage of chronic kidney disease (CKD). However, little is known about whether fluid overload is related to kidney disease progression in patients with CKD. Accordingly, the aim of the study was to assess the association of the severity of fluid status and kidney disease progression in an advanced CKD cohort.

Study Design: Prospective observational cohort study.

Setting & Participants: This cohort study enrolled 472 non−dialysis-dependent patients with CKD stages 4-5 who were in an integrated CKD care program from January 2011 to December 2011 and followed up until December 2012 or initiation of renal replacement therapy (RRT).

Predictors: Tertile of fluid overload, with cutoff values at 0.6 and 1.6 L.

Outcomes: RRT, rapid estimated glomerular filtration rate (eGFR) decline (faster than 3 mL/min/1.73 m^2 per year), and change in eGFR.

Measurements: The severity of fluid overload was measured by a bioimpedance spectroscopy method. eGFR was computed using the 4-variable MDRD (Modification of Diet in Renal Disease) Study equation.

Results: During a median 17.3-month follow-up, 71 (15.0%) patients initiated RRT and 187 (39.6%) experienced rapid eGFR decline. The severity of fluid overload was associated with increased risk of RRT (tertile 3 vs tertile 1: adjusted HR, 3.16 [95% CI, 1.33-7.50]). Fluid overload value was associated with increased risk of rapid eGFR decline (tertile 3 vs tertile 1: adjusted OR, 4.68 [95% CI, 2.30-9.52]). Furthermore, the linear mixed-effects model showed that the reduction in eGFR over time was faster in tertile 3 than in tertile 1 ($P = 0.02$).

Limitations: The effect of fluid volume variation over time must be considered.

Conclusions: Fluid overload is an independent risk factor associated with initiation of RRT and rapid eGFR decline in patients with advanced CKD.

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INDEX WORDS: Fluid overload; chronic kidney disease; dialysis; kidney disease progression.

Fluid overload is a common phenomenon in patients with late-stage chronic kidney disease (CKD). Abnormal hydration status has been correlated with hypertension, as well as some symptoms and signs of left ventricular hypertrophy, congestive heart failure, pulmonary edema, peripheral edema, and other adverse cardiovascular sequelae.[1,2] Several observational studies have reported the association between hydration status and poor clinical outcome in

dialysis patients.[3-5] Wizemann et al[6] indicated that relative hydration status >15%, defined as severe fluid overload, was associated independently with mortality in long-term hemodialysis patients. Paniagua et al[7] also showed that the ratio of extracellular water to total-body water is a significant predictor of all-cause and cardiovascular mortality in dialysis patients. Previous research has supported the finding that strict volume control would increase the survival of dialysis patients. Hence, in addition to many traditional risk factors, such as diabetes mellitus (DM), hypertension, hyperlipidemia, and advanced age, fluid overload is an important element of progression to adverse clinical outcomes in dialysis patients.

Decreased kidney function contributes to decreased water excretion and excess fluid overload; however, whether fluid overload itself has an influence on kidney disease progression in patients with CKD not receiving dialysis is not well understood. Chen et al[8] found that an enlarged left atrium diameter, an indicator of volume overload and impaired diastolic function, was associated with faster decline in estimated glomerular filtration rate (eGFR). TREAT

(Trial to Reduce Cardiovascular Events With Aranesp Therapy) demonstrated that a high level of N-terminal pro−brain natriuretic peptide, as a clinical marker of volume overload, was associated significantly with increased risk of maintenance dialysis in diabetic patients with CKD.[9] However, left atrium diameter and N-terminal pro−brain natriuretic peptide level are indicators of volume, not measurements of volume status. To measure volume status, we used the bio-impedance spectroscopy method. In the present study, we attempted to analyze the association of the severity of fluid overload and kidney disease progression in non−dialysis-dependent patients with CKD stages 4-5.

METHODS

Study Participants

This observational study was conducted at a tertiary hospital in southern Taiwan. Our integrated CKD program included 612 patients with CKD stages 4-5, and all of them were invited to participate in the study from January 2011 to December 2011. CKD was staged according to KDOQI (Kidney Disease Outcomes Quality Initiative) definitions,[10] and eGFR was calculated using the 4-variable MDRD (Modification of Diet in Renal Disease) Study equation.[11] Of these patients, 115 with disabilities, 5 with pacemaker implantation, and 12 with decreased skin integrity were excluded. After informed consent, 480 patients were enrolled and scheduled for a study interview. We also excluded 8 patients requiring maintenance dialysis within 30 days after enrollment. The final study population comprised 472 patients with CKD stages 4-5 in the subsequent analysis (Fig 1). This study was approved by the Institutional Review Board at Kaohsiung Medical University Hospital.

Measurement of Hydration and Body Composition

We used a bioimpedance spectroscopy device, the BCM Body Composition Monitor (Fresenius Medical Care), to determine the severity of fluid overload of patients at enrollment. The body composition monitor measures impedance spectroscopy at 50 different frequencies between 5 kHz and 1 MHz. According to the difference in impedance in each tissue, it provides information regarding normohydrated lean tissue, normohydrated adipose tissue, and extracellular fluid overload in the whole body. Normal extracellular and intracellular water can be determined for a given weight and body composition. Fluid overload can be calculated
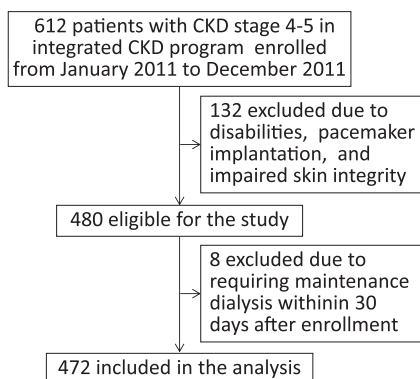
from the difference between normal expected extracellular water and measured extracellular water.[12] Hence, the body composition monitor can detect specific body fluid compartments more precisely than traditional methods. It has been validated intensively against all available gold-standard methods in the general population and patients on dialysis therapy.[13-16]

In the present study, clinical relevant parameters were registered in the case report form. Electrodes were attached to one hand and one foot at the ipsilateral side, after the patient had been in the recumbent position for at least 5 minutes. Only parameters of fluid status for which measurement quality was ≥95% were included in the analysis. Fluid overload value, as absolute change in tissue hydration, extracellular water, intracellular water, and total-body water, was determined from the measured impedance data following the model of Moissl et al.[14] The category was based on the 10th (corresponding to −1.1 L) and 90th (corresponding to 1.1 L) percentiles of a population of the same sex distribution and with a similar age band of a healthy reference cohort, in which hydration status was measured with the identical technology.[17] We used absolute change in tissue hydration and relative hydration status (fluid overload/extracellular water) as an indicator of fluid status.

Assessment of Pulse Wave Velocity

Pulse wave velocity (PWV) was measured by an ankle-brachial index device, which automatically and simultaneously measured blood pressures in both arms and ankles using an oscillometric method.[18] After obtaining bilateral PWV values, the higher one was used as the representative value for each participant. PWV measurement was done once at the same time as fluid measurement for each patient.

Data Collection

Demographic and clinical data were obtained from medical records and interviews with patients at enrollment. Participants were asked to fast for at least 12 hours before blood sample collection for the biochemistry study. Protein in urine was measured using an immediate semiquantitative urine protein dipstick test and graded as negative, trace, 1+, 2+, 3+, or 4+. The severity of leg edema was measured and graded individually on a 4-point system as follows: none (0 point), mild (1 point), moderate (2 points), or severe (3 points).[19] DM and hypertension were defined as medical history of these conditions through chart review. Cardiovascular disease was defined as history of heart failure, acute or chronic ischemic heart disease, and myocardial infarction. Cerebrovascular disease was defined as history of cerebral infarction or hemorrhage. Blood pressure was recorded as the mean of 2 consecutive measurements with a 5-minute interval, using a single calibrated device. Information regarding patient medications, including diuretics, β-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, and angiotensin II receptor blockers, before and after enrollment was obtained from medical records.

Kidney Disease Progression

Two major outcomes were accessed: renal replacement therapy (RRT) and rapid eGFR decline. RRT was confirmed by reviewing medical charts or catastrophic illness certificates (issued by the Bureau of National Health Insurance in Taiwan) and defined as requiring maintenance hemodialysis, peritoneal dialysis, or kidney transplantation. The timing for RRT was considered according to the regulations of the Bureau of the National Health Insurance of Taiwan regarding laboratory data, eGFR, uremic status, and nutritional status.[8]

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│ 612 patients with CKD stage 4-5 │
│ in integrated CKD program       │
│ enrolled from January 2011 to   │
│ December 2011                   │
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            │
            │    ┌──────────────────────────┐
            │    │ 132 excluded due to      │
            ├───▶│ disabilities, pacemaker  │
            │    │ implantation, and        │
            │    │ impaired skin integrity  │
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│ 480 eligible for the study      │
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            │    │ 8 excluded due to        │
            ├───▶│ requiring maintenance    │
            │    │ dialysis withinin 30     │
            │    │ days after enrollment    │
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│ 472 included in the analysis    │
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Figure 1. Flowchart of participants analyzed in this study.

The decline in eGFR was assessed by eGFR slope, defined as the regression coefficient between eGFR and time in units of mL/min/1.73 m^2 per year. At least 3 eGFR values were required to estimate eGFR slope. All eGFR values available from ascertainment of fluid status to the end of the observation period were included for calculation. Rapid eGFR decline was defined as the quartile with the steepest eGFR slope (eGFR decline >3 mL/min/1.73 m^2 per year, for which 3 is an integer near the cutoff point between the quartile with the steepest eGFR slope and the quartile with the next steepest slope).[8] Decline in eGFR also was assessed by change in eGFR over time. Patients were censored at the end of observation on December 31, 2012.

Statistical Analysis

Statistical results of baseline characteristics of all participants were stratified by tertiles of fluid overload, cut at 0.6 and 1.6 L. Continuous variables were expressed as mean ± standard deviation or median (interquartile range [IQR]), as appropriate, and categorical variables were expressed as percentages. Continuous variables with skewed distribution were log-transformed to approximate normal distribution. The significance of differences in continuous variables between groups was tested using one-way analysis of variance or Kruskal-Wallis H test, as appropriate. The difference in the distribution of categorical variables was tested using χ^2 test. Time-to-event survival analysis by Kaplan-Meier survival curve was used to test fluid overload as a predictor of risk of RRT. Cox regression models were used to examine the relationship between RRT and fluid overload. Multivariable logistic regression models also were used to evaluate the association of rapid eGFR decline with fluid overload. A linear mixed-effects model analysis was used to identify factors associated with change in eGFR, controlling for internal correlations and other covariates. All variables in Table 1 were tested by univariate analysis, and variables with $P < 0.05$, including eGFR, DM, cardiovascular disease, anemia (hemoglobin <9.0 g/dL),[20] hypoalbuminemia (serum albumin <3.5 g/dL), calcium-phosphorus product (cut at 50 mg^2/dL^2), proteinuria (urine protein excretion >1+), systolic blood pressure (cut at 140 mm Hg), age, sex, and medication, including angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers and diuretics, were selected for multivariate analysis. We also did subgroup analysis to diminish the effect of confounding factors on RRT. Statistical analyses were conducted using SPSS 18.0 for Windows (SPSS Inc). Statistical significance was set at 2-sided $P < 0.05$.

RESULTS

Cohort Characteristics

Mean age was 65.4 ± 12.7 years, and 54.4% were men. Median level of fluid overload was 0.9 (IQR, 0.4-2.2) L. Table 1 lists baseline clinical characteristics organized by tertiles of fluid overload, for which cut points were 0.6 and 1.6 L. Among our patients, 43.9% had diabetes and 85.0% had hypertension. Pre-existing and documented cardiovascular disease and cerebrovascular disease were noted in 18.4% and 9.5% of patients, respectively.

Tertile 3 (most severe fluid overload) had a higher percentage of DM (66.0% vs 31.7%), cardiovascular disease (25.2% vs 15.9%), and cerebrovascular disease (14.5% vs 4.3%) than tertile 1. Patients in tertile 3 received more diuretics, calcium channel blockers, and β-blockers (45.9% vs 18.3%, 74.8% vs 48.8%,

and 37.1% vs 19.5%, respectively) than those in tertile 1. Tertile 3 had a higher percentage of urine protein excretion >1+ (70.0% vs 36.2%) than tertile 1. Comparing fluid overload tertiles 1, 2, and 3, there were corresponding stepwise increases in levels of systolic blood pressure, extracellular water, total-body water, serum blood urea nitrogen, glycated hemoglobin, and uric acid and stepwise declines in fat tissue index, serum hemoglobin, albumin, and cholesterol levels.

Fluid Overload and RRT

During a median follow-up of 17.3 (IQR, 14.0-19.1) months, 71 (15.0%) patients progressed to RRT initiation, comprising 65 starting hemodialysis and 6 beginning peritoneal dialysis (Table 2). There were no deaths. Patients in the highest tertile of fluid overload were more likely to initiate RRT than those in the lowest tertile of fluid overload (26.4% vs 7.9%; Table 2). Figure 2 presents estimates of survival free of RRT by tertiles of fluid overload.

Multivariate regression analysis showed that the highest tertile of fluid overload was associated with significantly increased risk of RRT initiation versus the lowest tertile of fluid overload (hazard ratio [HR], 3.16; 95% confidence interval [CI], 1.33-7.50; $P = 0.01$; Table 3). The highest tertile of fluid overload/extracellular water (tertile thresholds were 4% and 11%) was associated with significantly increased risk of RRT initiation compared with the lowest tertile of fluid overload/extracellular water (HR, 3.08; 95% CI, 1.33-7.16; $P = 0.01$; Table S1 [available as online supplementary material]). Similarly, relative hydration status ≥7% was associated significantly with higher risk of RRT initiation (HR, 2.73; 95% CI, 1.34-5.55; $P = 0.01$; Table S2).

Because DM, cardiovascular disease, and malnutrition might affect fluid status, we performed further subgroup analysis. For fluid overload tertile 3 compared with tertile 1 in patients without cardiovascular disease, without DM, and with serum albumin level >3.5 g/dL, the adjusted HRs of RRT were 3.53 (95% CI, 1.43-8.69), 6.38 (95% CI, 1.44-28.32), and 2.77 (95% CI, 1.09-7.01), respectively.

Fluid Overload and eGFR

There were 187 (39.6%) participants in our cohort who had rapid eGFR decline (>3 mL/min/1.73 m^2 per year decline in eGFR). Decrease in eGFR in the highest tertile of baseline fluid overload was significantly faster than in the lowest tertile of fluid overload (median eGFR slope, −3.5 [IQR, −7.2 to −0.6] vs −1.4 [IQR, −3.3 to 0.6] mL/min/1.73 m^2 per year; Table 2). Patients with rapid decline in eGFR were more likely to have had higher baseline fluid overload than

Table 1. Clinical Characteristics of Study Participants Stratified by Fluid Overload Tertile

	Total Cohort (N=472)	Fluid Overload[a]			P Trend
		Tertile 1 (n=164)	Tertile 2 (n=149)	Tertile 3 (n=159)	
Demographics					
Age (y)	65.4 ± 12.7	63.1 ± 13.0	68.0 ± 11.8	65.3 ± 12.8	0.1
Male sex	54.4	44.5	49.7	69.2	<0.001
Smoking[b]	20.6	20.7	14.1	26.4	0.1
Alcohol drinking[b]	9.7	9.1	8.7	11.3	0.3
Cardiovascular disease	18.4	15.9	14.1	25.2	0.03
Cerebrovascular disease	9.5	4.3	10.1	14.5	0.002
Hypertension	85.0	81.1	83.2	90.6	0.02
Diabetes mellitus	43.9	31.7	33.6	66.0	<0.001
Hyperlipidemia	52.1	54.9	45.6	55.3	0.9
CKD					0.2
Stage 4	49.8	50.6	55.7	43.4	
Stage 5	50.2	49.4	44.3	56.6	
Body mass index (kg/m^2)	24.3 ± 3.8	24.6 ± 3.8	23.9 ± 3.6	24.5 ± 3.9	0.6
SBP (mm Hg)	139.6 ± 20.3	132.9 ± 16.3	137.9 ± 19.8	148.3 ± 21.5	<0.001
DBP (mm Hg)	75.6 ± 11.6	76.6 ± 10.8	74.1 ± 11.1	75.9 ± 12.6	0.6
PWV (per 100 cm/s)	18.6 ± 3.9	17.4 ± 3.4	18.7 ± 3.8	19.8 ± 4.3	<0.001
Leg edema score ≥1	18.4	5.4	10.8	42.1	<0.001
Body composition					
Lean tissue Index (kg/m^2)	13.7 ± 2.6	14.0 ± 2.6	13.3 ± 2.3	13.8 ± 2.9	0.5
Fat tissue index (kg/m^2)	9.8 ± 4.2	10.5 ± 4.6	9.9 ± 4.0	9.1 ± 4.0	0.004
Total-body water (L)	32.6 ± 6.7	31.6 ± 5.6	31.3 ± 5.7	35.2 ± 7.8	<0.001
ICW (L)	17.1 ± 3.6	17.3 ± 3.5	16.4 ± 3.3	17.4 ± 4.0	0.8
ECW (L)	15.6 ± 3.6	14.2 ± 2.3	14.8 ± 2.8	17.7 ± 4.2	<0.001
ECW:ICW ratio	0.9 ± 0.1	0.8 ± 0.1	0.9 ± 0.1	1.0 ± 0.1	<0.001
ECW:TBW ratio	47.7 ± 3.5	45.2 ± 2.3	47.5 ± 2.8	50.5 ± 3.1	<0.001
Fluid overload (L)	0.9 (0.4 to 2.2)	0.1 (−0.2 to 0.4)	1.0 (0.9 to 1.3)	2.8 (2.1 to 4.1)	<0.001
Medications used					
Diuretic	29.0	18.3	22.8	45.9	<0.001
Calcium channel blocker	59.7	48.8	55.7	74.8	<0.001
β-Blocker	27.8	19.5	26.8	37.1	0.001
ACEi/ARB	53.0	53.0	46.3	59.1	0.3
Laboratory parameters					
SUN (mg/dL)	47.3 (34.3 to 64.9)	43.2 (33.2 to 62.4)	44.4 (32.5 to 61.2)	52.2 (37.9 to 71.5)	0.01
eGFR (mL/min/1.73 m^2)	15.4 ± 7.5	15.7 ± 7.8	16.5 ± 7.7	14.2 ± 6.7	0.06
Fasting glucose (g/dL)	102 (93 to 121)	102 (94 to 115)	100 (96 to 112)	107 (90 to 130)	0.1
Glycated hemoglobin (%)	5.9 (5.6 to 6.8)	5.8 (5.6 to 6.4)	5.8 (5.6 to 6.4)	6.3 (5.6 to 7.2)	0.01
Hemoglobin (g/dL)	10.4 ± 1.7	10.8 ± 1.7	10.4 ± 1.6	10.0 ± 1.7	<0.001
Albumin (g/dL)	4.0 ± 0.4	4.2 ± 0.3	4.1 ± 0.3	3.8 ± 0.5	<0.001
Ca × P (mg^2/dL^2)	38.5 (34.2 to 44.0)	38.9 (33.9 to 44.0)	37.7 (33.9 to 42.3)	38.6 (34.4 to 44.0)	0.9
Uric acid (mg/dL)	7.7 ± 1.7	7.4 ± 1.7	7.7 ± 1.7	8.0 ± 1.7	0.004
Cholesterol (mg/dL)	180 (153 to 210)	186 (162 to 214)	181 (158 to 210)	173 (139 to 202)	0.02
Triglycerides (mg/dL)	116 (80 to 166)	123 (87 to 165)	106 (77 to 169)	112 (72 to 158)	0.3
hs-CRP (mg/L)	1.3 (0.6 to 3.6)	1.4 (0.7 to 2.9)	1.5 (0.6 to 4.3)	1.3 (0.5 to 3.6)	0.5
PTH (pg/mL)	95 (50 to 238)	87 (45 to 228)	77 (44 to 145)	123 (62 to 286)	0.05
Urine protein >1+[c]	49.0	36.2	40.3	70.0	<0.001

Note: Values for categorical variables are given as percentages; values for continuous variables are given as mean ± standard deviation or median [interquartile range]. Conversion factors for units: cholesterol in mg/dL to mmol/L, ×0.02586; triglycerides in mg/dL to mmol/L, ×0.01129; uric acid in mg/dL to μmol/L, ×59.48.

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; Ca × P, calcium-phosphorus product; CKD, chronic kidney disease; DBP, diastolic blood pressure; ECW, extracellular water; eGFR, estimated glomerular filtration rate; hs-CRP, high-sensitivity C-reactive protein; ICW, intracellular water; PTH, parathyroid hormone; PWV, pulse wave velocity; SBP, systolic blood pressure; SUN, serum urea nitrogen; TBW, total-body water.

[a]Fluid overload tertile cut at 0.6 and 1.6 L; ie, tertile 3 corresponds to most severe fluid overload.
[b]Current.
[c]Urine protein was measured using dipstick test.

Table 2. Events for All Participants

	Total Cohort (N=472)	Fluid Overload[a]			P Trend
		Tertile 1 (n=164)	Tertile 2 (n=149)	Tertile 3 (n=159)	
Follow-up time (mo)	17.3 [14.0 to 19.1]	17.9 [14.7 to 19.3]	17.9 [15.1 to 19.1]	15.5 [10.0 to 19.3]	<0.001
No. of SCr measurements	7 [4 to 10]	7 [4 to 11]	7 [4 to 11]	7 [4 to 10]	0.9
ΔeGFR (mL/min/1.73 m²/y)	−2.0 [−5.2 to 0.1]	−1.4 [−3.3 to 0.6]	−1.8 [−4.4 to 0.7]	−3.5 [−7.2 to −0.6]	0.004
Dialysis initiation	71 (15.0)	13 (7.9)	16 (10.7)	42 (26.4)	<0.001

Note: Values for categorical variables are given as number (percentage); values for continuous variables, as median [interquartile range].

Abbreviations: ΔeGFR, change in estimated glomerular filtration rate; SCr, serum creatinine.

[a]Fluid overload tertile cut at 0.6 and 1.6 L; ie, tertile 3 corresponds to most severe fluid overload.

those of without rapid decline in eGFR (Table S3). At baseline, patients who subsequently had a rapid decline in eGFR had higher systolic blood pressure, lower serum albumin level, and higher proportion of urine protein excretion >1+ than those whose eGFR decline was not rapid. There was no significant different in baseline eGFR between the 2 groups.

Multivariate regression analysis showed that the highest tertile of fluid overload was associated with significant increased risk of rapid eGFR decline compared with the lowest tertile of fluid overload (odds ratio [OR], 4.68; 95% CI, 2.30-9.52; Table 3). The highest tertile of fluid overload/extracellular water was associated with a significantly increased odds of rapid eGFR decline compared with the lowest tertile of fluid overload/extracellular water (OR, 4.15; 95% CI, 2.06-8.36; Table S1).

The effect of study group on eGFR change was studied by a linear mixed-effects model. The highest tertile of fluid overload was associated with a significant decrease in eGFR over time compared with the lowest tertile of fluid overload (unstandardized coefficient $\beta = -1.10$; 95% CI, −2.06 to −0.13; $P = 0.02$; Table 3). The association between fluid overload/extracellular water and decrease in eGFR over time (tertile 3 vs tertile 1: unstandardized

coefficient $\beta = -0.89$; 95% CI, −1.79 to 0.00) was at the border of statistical significance ($P = 0.05$).

DISCUSSION

To our knowledge, this study is the first to show that fluid overload is associated with initiation of RRT and rapid eGFR decline in patients with CKD stages 4-5. Patients with the highest tertile of baseline fluid overload have more than a 3-fold increase in risk of RRT and rapid eGFR decline after adjustment for other risk factors. Furthermore, the linear mixed-effects model shows a faster decline in eGFR over time in patients with the highest tertile of fluid overload than in those with the lowest tertile of fluid overload.

Fluid overload has an independent influence on vascular and endothelial level, leading to arterial stiffness, atherosclerosis, and left ventricular hypertrophy.[21] The excess volume status would increase renal efferent pressure, decrease renal blood flow, and finally cause progressive eGFR decline.[22] Positive sodium and fluid balance, frequently related to decreased kidney function, also may contribute to pressure-independent alterations in artery structure and function.[23] The present study showed the association
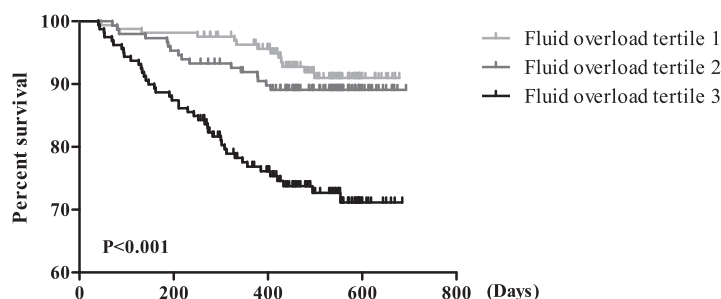
Figure 2. Kaplan-Meier survival curve for renal replacement therapy.

Table 3. Adjusted Risks According to Fluid Overload Tertile

	RRT		Rapid eGFR Decline		Change in eGFR	
Fluid Overload[a]	HR (95% CI)	*P*	OR (95% CI)	*P*	β[b] (95% CI)	*P*
Tertile 1	1.00 (reference)	—	1.00 (reference)	—	Reference	—
Tertile 2	2.01 (0.85 to 4.74)	0.1	2.00 (1.07 to 3.76)	0.03	−0.19 (−0.99 to 0.61)	0.6
Tertile 3	3.16 (1.33 to 7.50)	0.01	4.68 (2.30 to 9.52)	<0.001	−1.10 (−2.06 to −0.13)	0.02

Note: Adjusted for age, sex, cardiovascular disease, diabetes mellitus, medication including angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers and diuretics, eGFR, anemia (hemoglobin < 9 g/dL), hypoalbuminemia (serum albumin <3.5 g/dL), calcium-phosphorus product cut at 50 mg^2/dL^2, proteinuria (urine protein >1+), and systolic blood pressure cut at 140 mm Hg.

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio; OR, odds ratio; RRT, renal replacement therapy.

[a]Fluid overload tertile cut at 0.6 and 1.6 L; ie, tertile 3 corresponds to most severe fluid overload.

[b]Unstandardized coefficient β expressed as eGFR in mL/min/1.73 m^2 per year.

of fluid overload and PWV, a clinical indicator of arterial stiffness, and Chen et al[24] have demonstrated that arterial stiffness is associated independently with kidney disease progression in patients with CKD. Increased arterial stiffness might result in greater transmission of elevated systemic blood pressure to the glomerular capillaries, and in so doing, worsening glomerular hypertension, a key determinant of progressive kidney damage.[25] The interaction between fluid overload and arterial stiffness may be one of the major causes of kidney disease progression in patients with CKD.

Cardiomyocyte elongation and dysfunction are found during the left ventricle remodeling and decompensation response to fluid overload.[26,27] Previous studies also have demonstrated that removal of excess volume leads to regression of left ventricular mass.[28,29] The interaction among fluid overload, cardiac function, and kidney disease progression is close and complex. In our study, patients with fluid overload had a higher proportion of cardiovascular disease and use of diuretics, which are important associated factors of initiating dialysis therapy. In addition, a number of comorbid conditions, such as DM, might confound the association between CKD progression and fluid overload.[30] This complex interaction between traditional risk factors, fluid overload, and CKD led us to adjust for DM status, cardiovascular disease status, and diuretic use. In addition, we also performed subgroup analyses in non-DM and non—cardiovascular disease patients. Our findings showed that fluid overload remained correlated independently with initiation of maintenance dialysis therapy. Therefore, fluid overload itself could be an independent mediator of kidney disease progression in a CKD cohort.

Accumulating evidence has documented that malnutrition-inflammation correlates with volume expansion in dialysis patients.[31,32] This relationship may be bidirectional, in which the expanded volume behaves as an malnutrition-inflammatory stimulus.

Conversely, the malnutrition-inflammatory process itself might have a role in increased volume.[33] In patients with chronic congestive heart failure with fluid overload, bowel-wall edema might contribute to increased gut permeability and bacterial endotoxin translocation.[34] Inflammation suppresses water channel aquaporin 1, a molecular counterpart of the ultrasmall pore responsible for transcellular water permeability.[35] The intricate correlation between fluid overload, malnutrition, and inflammation in dialysis patients also attracts clinicians' attention.[36,37] For patients with non—dialysis-dependent CKD, our present study showed an association between fluid overload and hypoalbuminemia. Hypoalbuminemia may be the presentation of malnutrition-inflammation that has been known to be a risk factor for kidney disease progression.[38] However, our results showed that there was no significant association between fluid overload and high-sensitivity C-reactive protein level. Further study of other inflammatory markers is needed to evaluate the relationship between malnutrition-inflammation and fluid overload.

For clinical practice, evaluation of volume status is an important issue in patients with CKD. Physical examination is not enough to detect small increases in volume status efficiently. Small increases in volume status can be measured using multifrequency spectroscopic bioimpedance, which provides information on both hydration status and body composition.[30]

Patients with CKD with fluid overload have expanded extravascular volume and decreased intravascular volume. This imbalance in fluid distribution of the body alters kidney perfusion, thereby further deteriorating kidney function. Furthermore, because fluid overload status may lead to underestimates of creatinine level, clinicians should use particular care in monitoring kidney function in patients with possible fluid overload. Our results show that fluid overload increases the risk of RRT and we therefore recommend that the care team begin preparation for RRT earlier, such as arteriovenous fistula creation or

Tenckhoff catheter implantation. Further studies also are needed to test whether relieving fluid overload might improve outcomes in patients with CKD.

Some limitations of this study must be considered. First, fluid status was measured only at enrollment. Thus, the effect of time-varying fluid status on CKD outcome could not be estimated. Second, the body composition monitor has been validated in the dialysis population, but not in the CKD population. This limitation means that it is not yet known if parameters recorded by the body composition monitor are authentic measures of the fluid status of patients with CKD. However, our findings showed that a stepwise increase in leg edema score corresponded to greater fluid overload as assessed by the body composition monitor. This suggests that the severity of fluid status measured by body composition monitor is compatible with an accepted indicator of actual fluid status in patients with CKD.

In conclusion, our study demonstrates that fluid overload is associated with increased risks of maintenance dialysis and rapid eGFR decline in patients with CKD stages 4-5. Future studies to investigate the pathogenic link between fluid overload and kidney disease progression are needed, so that failing kidneys might be salvaged through this factor common in almost all kidney diseases.

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SUPPLEMENTARY MATERIAL

Table S1: Adjusted risks of RRT, rapid eGFR decline, and change of eGFR.

Table S2: Risks for RRT and rapid eGFR decline by relative hydration status.

Table S3: Baseline characteristics of patients with and without rapid eGFR decline.

Note: The supplementary material accompanying this article (http://dx.doi.org/10.1053/j.ajkd.2013.06.011) is available at www.ajkd.org

REFERENCES

1. Wizemann V, Schilling M. Dilemma of assessing volume state—the use and the limitations of a clinical score. *Nephrol Dial Transplant*. 1995;10(11):2114-2117.

2. Wizemann V, Leibinger A, Mueller K, Nilson A. Influence of hydration state on plasma volume changes during ultrafiltration. *Artif Organs*. 1995;19(5):416-419.

3. Saran R, Bragg-Gresham JL, Levin NW, et al. Longer treatment time and slower ultrafiltration in hemodialysis: associations with reduced mortality in the DOPPS. *Kidney Int*. 2006;69(7):1222-1228.

4. Movilli E, Gaggia P, Zubani R, et al. Association between high ultrafiltration rates and mortality in uraemic patients on regular haemodialysis. A 5-year prospective observational multi-centre study. *Nephrol Dial Transplant*. 2007;22(12):3547-3552.

5. Ozkahya M, Ok E, Toz H, et al. Long-term survival rates in haemodialysis patients treated with strict volume control. *Nephrol Dial Transplant*. 2006;21(12):3506-3513.

6. Wizemann V, Wabel P, Chamney P, et al. The mortality risk of overhydration in haemodialysis patients. *Nephrol Dial Transplant*. 2009;24(5):1574-1579.

7. Paniagua R, Ventura MD, Avila-Diaz M, et al. NT-proBNP, fluid volume overload and dialysis modality are independent predictors of mortality in ESRD patients. *Nephrol Dial Transplant*. 2010;25(2):551-557.

8. Chen SC, Su HM, Hung CC, et al. Echocardiographic parameters are independently associated with rate of renal function decline and progression to dialysis in patients with chronic kidney disease. *Clin J Am Soc Nephrol*. 2011;6(12):2750-2758.

9. Desai AS, Toto R, Jarolim P, et al. Association between cardiac biomarkers and the development of ESRD in patients with type 2 diabetes mellitus, anemia, and CKD. *Am J Kidney Dis*. 2011;58(5):717-728.

10. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis*. 2002;39(2)(suppl 1):S1-S266.

11. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Inter Med*. 1999;130(6):461-470.

12. Hur E, Usta M, Toz H, et al. Effect of fluid management guided by bioimpedance spectroscopy on cardiovascular parameters in hemodialysis patients: a randomized controlled trial. *Am J Kidney Dis*. 2013;61(6):957-965.

13. 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.

14. Moissl UM, Wabel P, Chamney PW, et al. Body fluid volume determination via body composition spectroscopy in health and disease. *Physiol Meas*. 2006;27(9):921-933.

15. Crepaldi C, Soni S, Chionh CY, Wabel P, Cruz DN, Ronco C. Application of body composition monitoring to peritoneal dialysis patients. *Contrib Nephrol*. 2009;163:1-6.

16. Wizemann V, Rode C, Wabel P. Whole-body spectroscopy (BCM) in the assessment of normovolemia in hemodialysis patients. *Contrib Nephrol*. 2008;161:115-118.

17. Wieskotten S, Heinke S, Wabel P, et al. Bioimpedance-based identification of malnutrition using fuzzy logic. *Physiol Meas*. 2008;29(5):639-654.

18. Yokoyama H, Shoji T, Kimoto E, et al. Pulse wave velocity in lower-limb arteries among diabetic patients with peripheral arterial disease. *J Atheroscler Thromb*. 2003;10(4):253-258.

19. Nakayama M, Kawaguchi Y. Multicenter survey on hydration status and control of blood pressure in Japanese CAPD patients. *Perit Dial Int*. 2002;22(3):411-414.

20. Drüeke TB, Parfrey PS. Summary of the KDIGO guideline on anemia and comment: reading between the (guide) line(s). *Kidney Int*. 2012;82(9):952-960.

21. Bock JS, Gottlieb SS. Cardiorenal syndrome: new perspectives. *Circulation*. 2010;121(23):2592-2600.

22. Guyton AC. Roles of the kidneys and fluid volumes in arterial pressure regulation and hypertension. *Chin J Physiol*. 1989;32(2):49-57.

23. Safar ME, London GM, Plante GE. Arterial stiffness and kidney function. *Hypertension*. 2004;43(2):163-168.

24. Chen SC, Chang JM, Liu WC, et al. Brachial-ankle pulse wave velocity and rate of renal function decline and mortality in chronic kidney disease. *Clin J Am Soc Nephrol*. 2011;6(4):724-732.

25. Griffin KA, Picken MM, Churchill M, et al. Functional and structural correlates of glomerulosclerosis after renal mass reduction in the rat. *J Am Soc Nephrol*. 2000;11:497-506.

26. Ryan TD, Rothstein EC, Aban I, et al. Left ventricular eccentric remodeling and matrix loss are mediated by bradykinin and precede cardiomyocyte elongation in rats with volume overload. *J Am Coll Cardiol*. 2007;49(7):811-821.

27. Grossman W, Jones D, McLaurin LP. Wall stress and patterns of hypertrophy in the human left ventricle. *J Clin Invest*. 1975;56(1):56-64.

28. Fagugli RM, Reboldi G, Quintaliani G, et al. Short daily hemodialysis: blood pressure control and left ventricular mass reduction in hypertensive hemodialysis patients. *Am J Kidney Dis*. 2001;38(2):371-376.

29. Zamboli P, De Nicola L, Minutolo R, et al. Effect of furosemide on left ventricular mass in non-dialysis chronic kidney disease patients: a randomized controlled trial. *Nephrol Dial Transplant*. 2011;26(5):1575-1583.

30. Essig M, Escoubet B, de Zuttere D, et al. Cardiovascular remodelling and extracellular fluid excess in early stages of chronic kidney disease. *Nephrol Dial Transplant*. 2008;23(1):239-248.

31. Vicente-Martinez M, Martinez-Ramirez L, Munoz R, et al. Inflammation in patients on peritoneal dialysis is associated with increased extracellular fluid volume. *Arch Med Res*. 2004;35(3):220-224.

32. Gangji AS, Brimble KS, Margetts PJ. Association between markers of inflammation, fibrosis and hypervolemia in peritoneal dialysis patients. *Blood Purif*. 2009;28(4):354-358.

33. Avila-Diaz M, Ventura MD, Valle D, et al. Inflammation and extracellular volume expansion are related to sodium and water removal in patients on peritoneal dialysis. *Perit Dial Int*. 2006;26(5):574-580.

34. Niebauer J, Volk HD, Kemp M, et al. Endotoxin and immune activation in chronic heart failure: a prospective cohort study. *Lancet*. 1999;353(9167):1838-1842.

35. Stoenoiu MS, Ni J, Verkaeren C, et al. Corticosteroids induce expression of aquaporin-1 and increase transcellular water transport in rat peritoneum. *J Am Soc Nephrol*. 2003;14(3):555-565.

36. Demirci MS, Demirci C, Ozdogan O, 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):1708-1716.

37. Cheng LT, Tang W, Wang T. Strong association between volume status and nutritional status in peritoneal dialysis patients. *Am J Kidney Dis*. 2005;45(5):891-902.

38. Tsai YC, Hung CC, Kuo MC, et al. Association of hsCRP, white blood cell count and ferritin with renal outcome in chronic kidney disease patients. *PLoS One*. 2012;7(12):e52775.