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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

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(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 bioimpedance 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]

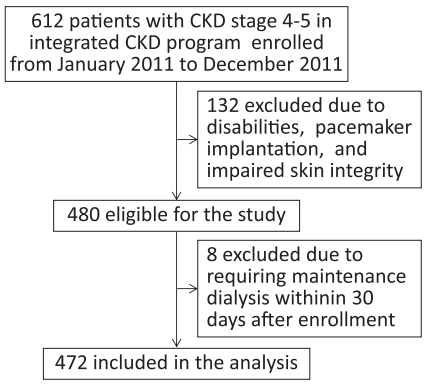

Figure 1. Flowchart of participants analyzed in this study.

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]