# Asymptomatic fluid volume imbalance and peridialysis blood pressure independently predict cardiovascular and all-cause mortality in patients undergoing hemodialysis

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Chronic fluid overload (FO) is a well-known factor which contributes to the high morbidity and mortality of patients undergoing hemodialysis (HD).[1] Higher blood pressure (BP) is commonly associated with overload volume.[1-4] Thus, the measurement time point (*eg*, pre-dialysis and post-dialysis) and volume status may affect the prognostic value of BP in HD patients. This study aimed to examine the correlation between fluid volume and BP, as well as their prognostic effects in HD patients who were free of coronary artery disease (CAD).

We retrospectively included 101 patients aged 18 to 90 years who received HD for at least 3 months and underwent bio-impedance analysis (BIA) measurement at the Hemodialysis Center in our hospital between August 2017 and February 2018. The exclusion criteria were as follows: (1) HD combined with peritoneal dialysis; (2) history of cancer, systemic vasculitis, or congenital heart disease; (3) preexisting CAD diagnosed by radiology, or suspected CAD manifested by frequent angina; (4) unstable vital signs or symptoms such as chest pain and palpitations during the HD session; and (5) the patient refused consent for the study.

All baseline demographic and clinical data were obtained from the electronic medical records. Dialysis parameters and BP records at enrollment day were extracted from dialysis electronic files. BIA measurements (InBodyS10, Biospace, Seoul, South Korea) within 30 min after HD, including extracellular fluid (ECF), intracellular fluid (ICF), total body fluid (TBF), and dry weight, were collected. Post-dialysis FO was calculated as: FO (kg) = post-dialysis weight (kg) − dry weight (kg). The primary outcomes were cardiovascular death (CVD) and all-cause death. CVD was defined as death from congestive heart failure, cardiogenic or hypovolemic shock, myocardial infarction, arrhythmia, or stroke. All-cause death was death due to any cause. The investigators adhered to the *Declaration of Helsinki* during the study and all patients included in the study provided informed consent before the BIA measurement. The study protocol was approved by the Review Board of West China Hospital of Sichuan University (No. 2017-204).

Continuous variables were presented as mean ± standard deviation (SD) or median (interquartile range) for non-normally distributed variables. Categorical variables were presented as percentages. A two-sample *t* test or Wilcoxon rank-sum test was used to compare continuous variables, and the Chi-square test was applied for comparing proportions. Bivariate correlation analyses were utilized to test the correlations between BIA measurements and baseline variables. The receiver operating characteristic (ROC) curve with area under the curve (AUC) was generated to determine the optimal cutoff value of the ECF/ICF ratio for mortality. Multivariate regression analysis was conducted to determine the relationship between BP and ECF/ICF ratio. The Kaplan–Meier method was used to estimate the survival, which was analyzed using the log-rank test. The Cox proportional hazard regression model was fitted to explore the predictors for cardiovascular and all-cause mortality, with hazard ratios (HRs) and 95% confidence intervals (CIs) being reported. The level of significance was set to a two-sided *P* value of $<0.05$. Data

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Quick Response Code:

Website: www.cmj.org

DOI: 10.1097/CM9.0000000000001337

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Chinese Medical Journal 2021;134(3)
**Received:** 22-10-2020 **Edited by:** Ning-Ning Wang

**Table 1: Cox proportional hazard regression analysis for cardiovascular (model a) and all-cause (model b) death.**

| Variable | HR (a) | 95% CI | *P* | HR (b) | 95% CI | *P* |
|---|---|---|---|---|---|---|
| Age (/1 year) | 1.01 | 0.89–1.14 | 0.92 | 0.97 | 0.89–1.06 | 0.49 |
| Male (1 = yes) | 3.56 | 0.11–112.69 | 0.47 | 0.31 | 0.04–2.63 | 0.28 |
| Diabetes (1 = yes) | 6.36 | 0.72–56.43 | 0.10 | 2.61 | 0.71–9.6 | 0.15 |
| PAD (1 = yes) | 1.08 | 0.08–14.23 | 0.95 | 2.34 | 0.45–12.1 | 0.31 |
| LVEF (/0.01) | 0.94 | 0.85–1.04 | 0.21 | 0.97 | 0.91–1.03 | 0.28 |
| Dialysis vintage (/1 month) | 0.95 | 0.9–1.01 | 0.13 | 1.00 | 0.98–1.03 | 0.81 |
| TDC use (1 = yes) | 0.26 | 0.01–5.8 | 0.40 | 0.59 | 0.10–3.32 | 0.55 |
| Pre-dialysis SBP (/1 mmHg) | 1.12 | 0.97–1.29 | 0.11 | 1.07 | 1.00–1.15 | 0.04 |
| Pre-dialysis DBP (/1 mmHg) | 0.89 | 0.77–1.04 | 0.14 | 0.86 | 0.76–0.97 | 0.02 |
| Post-dialysis SBP (/1 mmHg) | 0.80 | 0.67–0.95 | 0.01 | 0.86 | 0.78–0.95 | <0.01 |
| Post-dialysis DBP (/1 mmHg) | 1.10 | 0.84–1.44 | 0.48 | 1.12 | 0.98–1.27 | 0.09 |
| Hemoglobin (/1 g/L) | 1.10 | 1.01–1.21 | 0.03 | 1.01 | 0.97–1.05 | 0.56 |
| Albumin (/1 g/L) | 1.05 | 0.85–1.30 | 0.63 | 0.94 | 0.84–1.05 | 0.30 |
| LDL (/1 mmol/L) | 0.88 | 0.14–5.58 | 0.89 | 1.61 | 0.75–3.44 | 0.22 |
| ECF/ICF ratio (/0.01) | 1.65 | 1.02–2.68 | 0.04 | 1.27 | 1.02–1.57 | 0.03 |

Model a: overall (score) $\chi^2 = 46$, $P < 0.001$. Model b: overall (score) $\chi^2 = 39$, $P = 0.001$. CI: Confidence interval; DBP: Diastolic blood pressure; ECF: Extracellular fluid; HR: Hazard ratio; ICF: Intracellular fluid; LDL: Low-density lipoprotein; LVEF: Left ventricular ejection fraction; PAD: Peripheral artery disease; SBP: Systolic blood pressure; TDC: Tunneled dialysis catheter.

were analyzed using SPSS version 22.0 (IBM Corp, Armonk, NY, USA).

A total of 101 eligible patients (63.4% male) with a median age of 48 (35–62) years were included in the study, among which 21.8% had diabetes. The main etiology of end-stage renal disease (ESRD) was glomerulonephritis (38.6%: 12.9% confirmed by histology and 25.7% diagnosed by medical history and previous clinical data), followed by hypertensive nephropathy (25.7%), diabetic nephropathy (17.8%), and others (17.8%).

The median dialysis vintage of study patients was 10.0 (3.2–60.1) months, and they underwent HD treatment *via* autogenous arteriovenous fistula (52.5%) or tunneled dialysis catheters (47.5%). The mean ECF/ICF ratio was $0.66 \pm 0.04$ and 40 patients (39.6%) had post-dialysis ECF/TBF ratio ≥0.4.

The mean pre- and post-dialysis systolic blood pressure (SBP)/diastolic blood pressure (DBP) was $135.9 \pm 18.7$/$79.5 \pm 12.9$ mmHg and $134.3 \pm 17.4$/$78.1 \pm 11.3$ mmHg, respectively. The median absolute value of the change between pre-dialysis and post-dialysis BP was 7 (3–11) mmHg in SBP and 9 (4–14) mmHg in DBP. Yet, there was no correlation between ECF/ICF ratio and peridialysis BPs, or the absolute change in BP after dialysis in logistic regression analyses.

Based on the optimal cutoff value of ECF/ICF ratio for discriminating CVD from the ROC analysis (AUC = 0.76, $P = 0.011$), the patients were stratified into groups of ECF/ICF ≥0.65 or ECF/ICF <0.65. Compared with the low ECF/ICF group, the high group exhibited a higher post-dialysis DBP ($78.3 \pm 12.8$ *vs.* $77.8 \pm 9.5$; $P = 0.016$), a higher prevalence of diabetes (35.8% *vs.* 6.3%; $P < 0.001$) and peripheral artery disease, and a lower level of serum potassium at baseline. ECF/ICF ratio significantly correlated with serum albumin ($r = -0.47$), hemoglobin ($r = -0.31$), and potassium ($r = -0.33$).

During a median follow-up period of 26.4 (13–27.7) months (until March 2020), 13 patients received allogeneic kidney transplants at the Urology Department in our hospital, and 2 switched to peritoneal dialysis. Twelve (11.9%) deaths were recorded, of which nine (8.9%) were cardiovascular. Other causes of death were severe pneumonia (two cases) and esophageal cancer (one case). Compared with the low ECF/ICF ratio group, the high group had higher cardiovascular (15.1% *vs.* 2.1%; $P = 0.022$) and all-cause mortality (20.8% *vs.* 2.1%; $P = 0.004$), as well as worse survivals (curves not shown). ECF/ICF ratio was an independent predictor for CVD (HR = 1.65, $P = 0.043$) and all-cause death (HR = 1.27, $P = 0.033$). Peridialysis BPs showed diverse prognostic effects in Cox regression models [Table 1].

Although ultrafiltration volume was set by the nephrologists of our center mainly based on the patient's interdialysis weight gain, 39.6% of patients remained overhydrated after HD (ECF/TBF ratio ≥0.4). This underlined the importance of objective volume evaluation in HD patients. A single measurement of fluid distribution at volume peak cannot accurately reflect the patient's usual volume status, especially in a retrospective study without water intake intervention. Therefore, we used the post-dialysis volume parameters for the relatively less intra-individual variations.

Inflammation-induced hypoalbuminemia and increased vascular permeability in ESRD patients can cause a fluid shift from intracellular to extracellular, and malnutrition-related body cell mass depletion can lead to a decrease in ICF. Moreover, our study showed positive correlations of the ECF/ICF ratio with serum hemoglobin and albumin. Thus, the increase in ECF/ICF volume ratio is likely to be an integrated marker that simultaneously reflects ECF overload, renal anemia, and malnutrition. For every 1% increase in post-dialysis ECF/ICF ratio, the cardiovascular and all-cause mortality were increased by 65% and 27%, respectively.

Among peridialysis BPs, pre-dialysis SBP, and post-dialysis DBP acted as risk factors in prognosis, whereas pre-dialysis DBP and post-dialysis SBP were protective factors. Only post-dialysis DBP showed significant predictive effects both for CVD and all-cause death. Losito *et al*[5] suggested that BP had no direct relationship with mortality in patients who were taking antihypertensive medications. Since antihypertensive agents could be cleared by HD, post-dialysis BP was more likely to represent the patient's actual heart and vessel function, when compared to pre-dialysis. Notably, this was the first study that demonstrated that in HD patients, post-dialysis fluid distribution was irrelevant to BP. The reason for the negative result may be the study population. ECF/ICF ratio and peridialysis BPs may affect outcomes through independent mechanisms without interaction in patients with no coexisting CAD. Hence, volume evaluation based on BP should be cautiously undertaken for such patients.

The present study has some limitations. First, inherent biases exist in a retrospective study since the selection bias cannot be eliminated. For example, patients who were unsuitable for BIA measurement (e.g., amputee) could not be included in this study. Second, the sample size was small, which limited the exploration of the combined prognostic value of the ECF/ICF ratio and BP. Third, serial data of the ECF/ICF ratio that reflects changes over time or time-averaged exposure were lacking, although a recent study showed that the baseline FO could also predict long-term survival of HD patients, similar to chronic FO.[1] Finally, the study population, consisting of Chinese patients in a major tertiary hospital, may not reflect a nationwide or multiethnic cohort, thereby limiting the generalizability of the results.

This retrospective study shows that ECF/ICF volume ratio and peridialysis BPs can independently predict cardiovascular and all-cause mortality in an adult HD population without CAD. Moreover, there is no statistical correlation between fluid volume and peridialysis BPs, or the change of BP after HD. The relationship among volume, BP, and mortality needs to be identified in HD patients with different characteristics.

### Acknowledgements

We gratefully acknowledge the clinicians and technicians in the West China Hospital who contributed to this study.

### Funding

This work was financially sponsored by the National Clinical Research Center for Geriatrics, the West China Hospital, Sichuan University (No. Z2018B10), the Key Project of Research and Development of Science and Technology Department of Sichuan Province (No. 2018FZ0102), the Science and Technology Achievement Transformation Fund of West China Hospital of Sichuan University (No. CGZH19006), and the World-Class University Construction Fund of Sichuan University (No. 2040204401012).

### Conflicts of interest

None.

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**How to cite this article:** Yu Y, Liao RX, Li YP, Xiong YQ, Su BH. Asymptomatic fluid volume imbalance and peridialysis blood pressure independently predict cardiovascular and all-cause mortality in patients undergoing hemodialysis. Chin Med J 2021;134:356–358. doi: 10.1097/CM9.0000000000001337