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Original Paper

Independent Association of Overhydration with All-Cause and Cardiovascular Mortality Adjusted for Global Left Ventricular Longitudinal Systolic Strain and E/E′ Ratio in Maintenance Hemodialysis Patients

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Key Words
Overhydration • Global left ventricular longitudinal systolic strain • E/E′ ratio • All-cause and cardiovascular mortality • Hemodialysis

Abstract
Background/Aims: Fluid overload is common and associated with morbidity and mortality in patients with end-stage renal disease. The relationship between fluid overload and cardiac function is complex, and whether fluid overload is associated with adverse outcomes in patients undergoing hemodialysis (HD) independently of systolic and diastolic function of the left ventricle (LV) remains unclear. ***Methods:*** The present study aimed to investigate the relationship between overhydration and all-cause and cardiovascular (CV) mortality after adjusting for LV function in 178 maintenance HD patients. The relative hydration status (overhydration/extracellular water, ΔHS) was measured using a body composition monitor, and then used to assess the fluid status. A ΔHS ≥7% was defined as fluid overload. Global left ventricular

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longitudinal systolic strain (GLS), and the early filling and early diastolic mitral annular velocity (E/E') ratio were assessed using speckle-tracking and tissue Doppler echocardiography. ***Results:*** During a mean follow-up period of 2.7 years, 24 patients died, including 11 CV deaths. An increased ΔHS was significantly associated with all-cause and CV mortality in the univariate analysis. This prognostic significance remains after multivariate adjusting for GLS and E/E' ratio for all-cause (HR, 1.123; 95% CI, 1.063–1.186; p-value <0.001) and CV (HR, 1.088; 95% CI, 1.005–1.178; p-value =0.037) mortality. Moreover, ΔHS significantly improved the prognostic value beyond conventional clinical and echocardiographic parameters. ***Conclusion:*** A higher ΔHS was independently associated with increased all-cause and CV mortality after adjusting for systolic and diastolic function of the LV. This suggests that ΔHS may be a relevant target for improving outcomes in maintenance HD patients.

Introduction

Fluid overload is a common problem in patients with end-stage renal disease (ESRD) and can result in increased cardiac load, which contributes to increased blood pressure, left ventricular hypertrophy (LVH), and congestive heart failure [1, 2]. An association between an individual's hydration status and unfavorable clinical outcomes in patients undergoing dialysis has been previously reported [3-5]. Global left ventricular longitudinal systolic strain (GLS), measured using two-dimensional (2D) speckle-tracking echocardiography, is a novel parameter for systolic function of the left ventricle (LV) [6, 7]. The early filling (E) and early diastolic mitral annular velocity (E') ratio as determined by tissue Doppler echocardiography, is an important parameter of diastolic function of the LV [8]. GLS and the E/E' ratio were reported to be associated with mortality and cardiovascular (CV) events in dialysis patients [9, 10]. Regulated volume control could increase the survival of dialysis patients by reducing their blood pressure and limiting the progression of LVH, which would improve their general wellbeing [5, 11]. Fluid overload and the systolic and diastolic function of the LV appear to be important factors associated with adverse outcomes in patients with ESRD.

The 'dry weight' is conventionally achieved in chronic hemodialysis (HD) patients through clinical judgment [12, 13]. However, fundamental issues such as hypertension, intradialytic hypotension and subclinical overhydration (OH) are rarely overcome using this approach. Recently, bioelectric impedance spectroscopy has been used to assess the fluid status of patients, and it has been shown to provide objective information with regarding body composition [14, 15]. As cardiac function and fluid overload have been significantly associated with morbidity and mortality, and as cardiac function might be associated with fluid overload [3-5, 16], complex interactions may exist between cardiac function, fluid overload, and adverse outcomes in patients with ESRD [17-19]. However, whether fluid overload may be used to predict unfavorable outcomes independently of cardiac systolic and diastolic function remains uncertain. Therefore, the present study aimed to investigate the impact of OH, as determined by bioimpedance spectroscopy, on all-cause and CV mortality in maintenance HD patients, as well as evaluating the relationship between OH and outcomes after adjusting for GLS and the E/E' ratio.

Materials and Methods

Study patients

A total of 212 patients who received maintenance HD therapy at a regional hospital in southern Taiwan in April 2014 were enrolled in the present study. The maintenance HD program included 3 sessions a week, with each session lasting 3.5–4.5 hours. Among them, 27 patients who refused examinations, 4 who had atrial fibrillation, and 3 who had below-knee amputations, were excluded. Overall, 178 study patients were included in the study. The Institutional Review Board of Kaohsiung Medical University Hospital approved the

present study, and all study participants provided written informed consent. All methods were performed in accordance with the relevant guidelines.

Measurement of fluid status

Bioelectric impedance spectroscopy (Body Composition Monitor; Fresenius Medical Care), which has previously been validated, was used to measure the severity of fluid status at study enrollment [15, 20, 21]. The patients were allowed to rest for at least 5 minutes in the supine position, and then electrodes were attached to their hand and foot on the ipsilateral side. The body composition monitor measured impedance spectroscopy at 50 different frequencies from 5 kHz to 1 MHz. At a low frequency, the current cannot penetrate cell membranes and instead passes through the extracellular water (ECW) space, whereas at a high frequency the current can flow through both ECW and intracellular water (ICW). The resulting impedance data was then used to estimate the amounts of total body water (TBW), ICW and ECW using the model reported by Moissl et al. [21]. The OH was calculated as absolute changes in tissue hydration using a model including normally hydrated lean tissue and adipose tissue, as well as excess fluid mass, which was taken to represent OH [22]. Increasing evidence has shown that the relative hydration status (ΔHS; ΔHS = OH/ECW) can be used as an indicator of fluid status [23-25]. The 90th percentile of ΔHS in a normal reference population has been reported to be -7% to 7% [24]. Accordingly, a ΔHS ≥7% is considered to represent fluid overload, as previously validated in 350 Taiwanese healthy controls and 338 patients with chronic kidney disease [24], as well as in maintenance HD [25] and peritoneal dialysis patients [23]. Therefore, in the present study ΔHS was used to represent the severity of fluid status, with ΔHS ≥7% being defined as fluid overload.

Echocardiographic evaluation

All study participants underwent echocardiographic examinations after resting in the left decubitus position for 10–30 minutes prior to the HD session. The echocardiographic evaluation was performed using a Vivid 7 system (GE Vingmed Ultrasound AS, Horten, Norway) by an experienced cardiologist who was blinded to the clinical data. 2D and anatomical M-mode images were recorded from standard views, and the Doppler sample volume was placed at the mitral leaflet tips to measure LV inflow waveforms in the apical four-chamber view. The sample volume was then placed at the lateral and septal corners of the mitral annulus to obtain pulsed Doppler tissue images in the apical four-chamber view. E' was obtained by averaging the septal and lateral values. Simpson's method was used to calculate the LV ejection fraction (LVEF), and a modification of Devereux's method was used to calculate the LV mass [26]. The LV mass index (LVMI) was calculated as LV mass/body surface area, and the left atrial volume was calculated using the biplane area-length method [27]. The left atrial volume index (LAVI) was calculated as the left atrial volume/body surface area.

A high frame rate (50–90 frames/sec) was used to acquire LV apical four-chamber, two-chamber, and long-axis views for speckle-tracking echocardiography. The endocardial border was manually identified using the point-and-click method, and epicardial surface tracing was automatically performed by the system to create a region of interest. The 6 segmental strain and strain rate curves were plotted from apical views after the LV chamber divided into six segments, and the values of maximum segmental longitudinal systolic strain were determined from these curves. GLS values were then measured in 18 LV segments from three standard apical views and then averaged for analysis [7]. A minimum of 15 LV segments were required to obtain satisfactory GLS measurements. Cine loops were used to determine which beat was used for the calculations. Study patients' raw echocardiographic data was recorded for offline analysis using EchoPAC version 08 (GE Vingmed Ultrasound AS). Dimensions of the LV, LVEF, LAVI, LVMI, and GLS were measured from the index beat [28, 29]. As E and E' could be measured easily, the data was obtained from five beats [30] and then averaged for analysis. An E/E' ratio >15 was defined as impaired diastolic function of the LV [31-33].

Demographic, medical, and laboratory data collection

The patients' age, sex, smoking history (ever *vs.* never), and co-morbidities were obtained from their medical records and interviews. Coronary artery disease was defied as a history of myocardial infarction, at least one major epicardial artery with at least 50% stenosis on coronary angiography, or a history of

coronary artery bypass surgery or coronary angioplasty. The body mass index (BMI) was calculated as the weight in kilograms divided by the height in meters squared. Laboratory tests were performed using overnight fasting blood samples, which were obtained within one month of study enrollment. Dialysis efficiency was determined using Kt/V by the Daugirdas method [34].

Definition of all-cause and CV mortality

Two cardiologists used the hospital course and medical records to define cases of all-cause and CV mortality; disagreements were resolved by discuss with a third cardiologist. CV mortality was defined as sudden cardiac death, fatal myocardial infarction, ventricular arrhythmia, fatal stroke and heart failure. The patients who reached the study endpoint were followed until death, and the survivors were followed until March 31st, 2017.

Statistical analysis

Statistical analyses were performed using SPSS version 19.0 (IBM Corp., Armonk, NY, USA) for Windows. Data were expressed as the percentage, mean ± standard deviation or median (25^{th}–75^{th} percentile) for the duration of dialysis, triglycerides and OH. The study patients were stratified into 2 groups according to their ΔHS (<7% or ≥7%). Differences between two groups were analyzed using the chi-square test for categorical variables and the independent t-test for continuous variables. Survival curves for all-cause and CV mortality were illustrated using the Kaplan-Meier method. Associations between ΔHS and all-cause and CV mortality were assessed using univariate and multivariate adjusted Cox regression analyses. Covariates were selected into multivariate backward Cox models if their p-value was < 0.05 in univariate analysis. Improvements in the performance of the models were assessed using changes in the χ^2 value. A p-value of <0.05 was considered statistically significant.

Results

A total of 178 patients (87 men and 91 women, mean age 60.9±11.6 years) were included in the study. There were 129 (72.5%) patients with ΔHS ≥7%. The patients were then stratified into two groups according to their ΔHS (<7% or ≥7%) and comparisons were made between their clinical characteristics, body composition and echocardiographic parameters as shown in Table 1. Compared with the ΔHS <7% group, the ΔHS ≥7% group were older, had a higher prevalence of diabetes mellitus (DM), a lower creatinine level, a lower lean tissue index, lower ICW, higher ECW, a higher ECW to TBW ratio and higher OH.

Predictors of all-cause mortality

The mean follow-up period was 2.7±0.5 years. During this period, 24 deaths (13.5 %) were recorded, including fatal CV events (n=11), sepsis or septic shock (n=9), gastrointestinal bleeding (n=2), liver failure (n=1), and malignancy (n=1). Predictors of all-cause mortality using the univariate and multivariate Cox proportional hazard model are listed in Table 2. In the univariate analysis, older age, DM, coronary artery disease, lower albumin level, lower creatinine level, E/E' ratio > 15, higher GLS and a higher ΔHS were associated with all-cause death. Furthermore, older age (hazard ratio [HR]: 1.086; 95% confidence interval [CI]: 1.030–1.144; p-value=0.002), E/E' ratio > 15 (HR: 3.037; 95% CI: 1.206–7.644; p-value=0.018), higher GLS (HR: 1.198; 95% CI: 1.074–1.336; p-value=0.001), and higher ΔHS (HR: 1.123; 95% CI: 1.063–1.186; p-value <0.001) were significantly associated with all-cause mortality in the multivariate adjusted Cox analysis.

Predictors of CV mortality

A total of 11 CV deaths were recorded during the follow-up period, including sudden cardiac death (n=5), myocardial infarction (n=3), ventricular arrhythmia (n=1), fatal stroke (n=1), and heart failure (n=1). Predictors of CV mortality using univariate and multivariate Cox proportional hazard models are shown in Table 3. In the univariate analysis, DM, coronary

Table 1. Comparison of baseline characteristics between patients with ΔHS <7% or ≥7%. Abbreviations: ΔHS, relative hydration status; LAVI, left atrial volume index; LVMI, left ventricular mass index; LVEF, left ventricular ejection fraction; E, peak early transmitral filling wave velocity; E', early diastolic velocity of lateral mitral annulus; GLS, global left ventricular longitudinal systolic strain

Characteristics	ΔHS <7% (n = 49)	ΔHS ≥7% (n = 129)	p-value	All patients (n = 178)
Age (years)	57.9 ± 13.5	62.1 ± 10.6	0.033	60.9 ± 11.6
Male gender (%)	42.9	54.3	0.174	51.1
Duration of dialysis (years)	7.2 (1.8–13.1)	6.4 (2.8–10.8)	0.871	6.5 (2.3–11.2)
Smoking history (%)	36.7	38.8	0.804	38.2
Diabetes mellitus (%)	30.6	54.3	0.005	47.8
Hypertension (%)	46.9	53.5	0.435	51.7
Coronary artery disease (%)	4.1	11.6	0.160	9.6
Cerebrovascular disease (%)	6.1	9.3	0.763	8.4
Systolic blood pressure (mmHg)	152.2 ± 28.4	155.4 ± 26.9	0.504	154.5 ± 27.3
Diastolic blood pressure (mmHg)	80.3 ± 17.6	81.6 ± 14.8	0.651	87.2 ± 15.6
Body mass index (kg/m^2)	24.2 ± 4.3	23.8 ± 3.7	0.513	23.9 ± 3.8
Laboratory parameters				
Albumin (g/dL)	3.9 ± 0.3	3.8 ± 0.3	0.059	3.9 ± 0.3
Triglycerides (mg/dL)	136.5 (97.5–268.5)	129 (87.5–199)	0.235	130 (91–213)
Total cholesterol (mg/dL)	185.5 ± 37.0	177.3 ± 41.6	0.232	179.5 ± 40.5
Hemoglobin (g/dL)	10.6 ± 1.0	10.6 ± 1.3	0.873	10.6±
Creatinine (mg/dL)	10.2 ± 2.3	9.4 ± 2.3	0.027	9.6 ± 2.3
Calcium-phosphorous product	39.5 ± 12.7	42.9 ± 10.8	0.082	42.0 ± 11.4
Kt/V (Daugirdas)	1.6 ± 0.3	1.6 ± 0.3	0.983	1.6 ± 0.3
Body composition				
Lean tissue index (kg/m^2)	15.4 ± 3.2	13.5 ± 3.1	0.001	14.0 ± 3.2
Fat tissue index (kg/m^2)	9.0 ± 4.8	9.1 ± 4.3	0.904	9.1 ± 4.4
Total body water (L)	34.1 ± 7.2	33.3 ± 7.7	0.567	33.5 ± 7.6
Intracellular water (L)	19.8 ± 6.7	16.9 ± 4.5	0.001	17.7 ± 5.3
Extracellular water (L)	15.0 ± 3.0	16.4 ± 3.5	0.017	16.0 ± 3.4
Extracellular water / total body water	43.2 ± 7.3	49.5 ± 3.0	< 0.001	47.8 ± 5.4
Overhydration (L)	0.6 (-0.2–0.8)	2.5 (1.8–3.5)	< 0.001	2 (1–2.9)
Echocardiographic data				
LAVI (ml/m^2)	32.8 ± 11.5	36.1 ± 23.3	0.342	35.2 ± 20.7
LVMI (g/m^2)	134.6 ± 46.1	137.3 ± 40.0	0.704	136.6 ± 41.7
LVEF (%)	67.2 ± 9.3	66.3 ± 10.3	0.568	66.5 ± 1.0
E/E' ratio > 15 (%)	26.5	30.2	0.585	29.2
GLS (%)	-17.1 ± 3.7	-16.4 ± 4.1	0.255	-16.6 ± 4.0
Death (%)	4.1	17.1	0.024	13.5
Duration of follow-up (years)	2.8 ± 0.3	2.7 ± 0.5	0.004	2.7 ± 0.5

artery disease, lower albumin level, lower total cholesterol level, lower creatinine level, an E/E' ratio >15, higher GLS and higher ΔHS were associated with CV death. In the multivariate adjusted Cox analysis, higher GLS (HR: 1.260; 95% CI: 1.090–1.457; p-value=0.002), and higher ΔHS (HR: 1.088; 95% CI: 1.005–1.178; p-value=0.037) were significantly associated with CV mortality.

Fig. 1 illustrates the Kaplan-Meier analysis of overall (log-rank p=0.024) (A) and CV survival (log-rank p=0.031) (B) according to ΔHS <7% or ≥7%. Compared to the ΔHS <7% group, the ΔHS ≥7% group had worse overall and CV survival.

Table 2. Predictors of all-cause mortality using univariate and multivariate adjusted Cox proportional hazards model

Parameters	Univariate		Multivariate (backward)	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age (per year)	1.063 (1.023–1.104)	0.002	1.086 (1.030–1.144)	0.002
Male gender (vs. female)	0.963 (0.432–2.143)	0.926	–	–
Duration of dialysis (per year)	1.185 (0.506–2.776)	0.696	–	–
Smoking history (ever vs. never)	1.174 (0.522–2.644)	0.698	–	–
Diabetes mellitus	3.588 (1.423–9.046)	0.007	–	–
Hypertension	1.671 (0.731–3.823)	0.224	–	–
Coronary artery disease	3.946 (1.562–9.969)	0.004	–	–
Cerebrovascular disease	2.461 (0.839–7.216)	0.101	–	–
Systolic blood pressure (per mmHg)	1.009 (0.992–1.026)	0.300	–	–
Diastolic blood pressure (per mmHg)	1.006 (0.977–1.036)	0.697	–	–
Body mass index (per kg/m^2)	0.929 (0.826–1.045)	0.219	–	–
Albumin (per g/dL)	0.204 (0.082–0.510)	0.001	–	–
Triglycerides (per log mg/dL)	0.842 (0.185–3.841)	0.825	–	–
Total cholesterol (per mg/dL)	0.990 (0.979–1.001)	0.073	–	–
Hemoglobin (per g/dL)	0.957 (0.690–1.327)	0.792	–	–
Creatinine (per mg/dL)	0.694 (0.576–0.837)	< 0.001	–	–
Calcium-phosphorous product (per mg^2/dL^2)	1.018 (0.983–1.054)	0.321	–	–
Kt/V	2.274 (0.540–9.577)	0.263	–	–
E/E' ratio > 15	5.599 (2.280–13.748)	< 0.001	3.037 (1.206–7.644)	0.018
GLS (per %)	1.154 (1.051–1.268)	0.003	1.198 (1.074–1.336)	0.001
ΔHS (per %)	1.101 (1.055–1.150)	< 0.001	1.123(1.063–1.186)	< 0.001

Table 3. Predictors of cardiovascular mortality using univariate and multivariate adjusted Cox proportional hazards model

Parameters	Univariate		Multivariate (backward)	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age (per year)	1.052 (0.995–1.113)	0.076	–	–
Male gender (vs. female)	1.698 (0.497–5.802)	0.398	–	–
Duration of dialysis (per year)	1.874 (0.444–7.906)	0.392	–	–
Smoking history (ever vs. never)	0.941 (0.276–3.216)	0.923	–	–
Diabetes mellitus	5.466 (1.179–25.334)	0.030	–	–
Hypertension	0.579 (0.169–1.983)	0.385	–	–
Coronary artery disease	4.509 (1.189–17.097)	0.027	–	–
Cerebrovascular disease	2.807 (0.604–13.046)	0.188	–	–
Systolic blood pressure (per mmHg)	1.016 (0.994–1.040)	0.157	–	–
Diastolic blood pressure (per mmHg)	1.026 (0.989–1.064)	0.176	–	–
Body mass index (per kg/m^2)	0.983 (0.839–1.154)	0.837	–	–
Albumin (per g/dL)	0.183 (0.051–0.649)	0.009	–	–
Triglycerides (per log mg/dL)	1.289 (0.152–10.947)	0.816	–	–
Total cholesterol (per mg/dL)	0.981 (0.965–0.997)	0.022	–	–
Hemoglobin (per g/dL)	1.201 (0.768–1.877)	0.422	–	–
Creatinine (per mg/dL)	0.733 (0.557–0.964)	0.026	–	–
Calcium-phosphorous product (per mg^2/dL^2)	1.022 (0.973–1.075)	0.384	–	–
Kt/V	0.692 (0.074–6.460)	0.747	–	–
E/E' ratio > 15	6.206 (1.602–24.050)	0.008	–	–
GLS (per %)	1.285 (1.123–1.469)	< 0.001	1.260 (1.090–1.457)	0.002
ΔHS (per %)	1.111 (1.045–1.181)	0.001	1.088 (1.005–1.178)	0.037

Incremental value of ΔHS in the prediction of all-cause and CV mortality

We further performed incremental value of ΔHS in predicting outcomes. The clinical model included age, sex, duration of dialysis, smoking history, DM, hypertension, coronary artery disease, cerebrovascular disease, systolic and diastolic blood pressures, BMI, albumin, log-transformed triglycerides, total cholesterol, hemoglobin, creatinine, calcium-phosphorous product, Kt/V and conventional echocardiographic parameters including LAVI, LVMI, LVEF and the E/E' ratio (χ^2= 45.00). Fig. 2 shows that the addition of GLS to this model

increased the predictive value for progression to all-cause mortality (χ^2=59.53, p-value <0.001), while the addition of ΔHS further improved the predictive value for all-cause mortality (χ^2=64.75, p-value=0.007). Furthermore, the addition of GLS to the clinical model containing conventional echocardiographic parameters (χ^2=48.67) improved the prediction of progression to CV mortality (χ^2=52.87, p-value <0.001), while the addition of ΔHS further improved the prediction of CV mortality (χ^2=78.05, p-value <0.001) (Fig. 3).

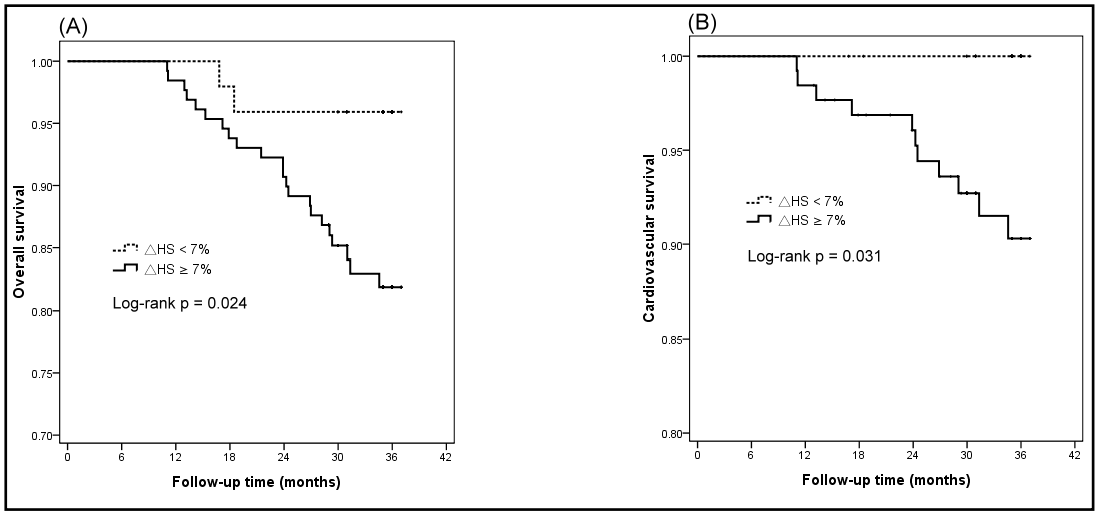


Fig. 1. Kaplan-Meier analysis of overall survival (log-rank p=0.024) (A) and cardiovascular survival (log-rank p=0.031) (B) according to ΔHS <7% or ≥7%. The group with ΔHS ≥7% had a worse overall and cardiovascular survival than that with the group of ΔHS <7%.

Fig. 2. Incremental prediction value of all-cause mortality as addition of GLS and ΔHS to clinical model containing conventional parameters of echocardiography.

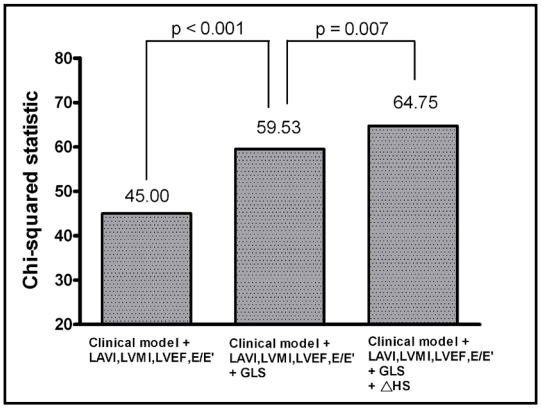
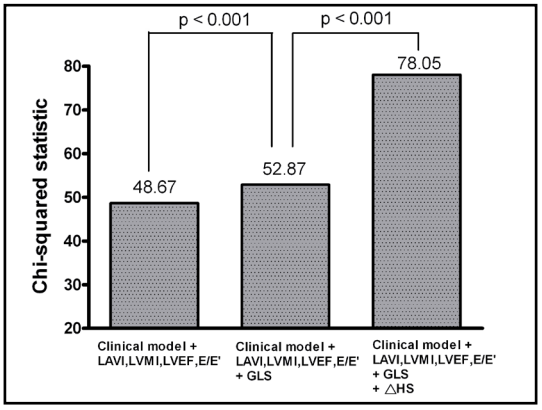


Fig. 3. Incremental prediction value of cardiovascular mortality as addition of GLS and ΔHS to clinical model containing conventional parameters of echocardiography.



Discussion

In the present study, the association between ΔHS (as assessed by bioimpedance spectroscopy) and all-cause and CV mortality was evaluated in maintenance HD patients. The results demonstrated that a higher ΔHS value was independently associated with an increased risk of all-cause and CV mortality after adjustment for GLS and the E/E' ratio. Furthermore, ΔHS significantly increased the prognostic value beyond conventional clinical and echocardiographic parameters.

The first important finding of the present study was that OH is an independent risk factor for overall and CV death in patients undergoing HD. Evaluation of volume status is an important issue in HD patients. Essig et al. suggested that an 8% increase in ECW could be easily underestimated in a clinical examination [35], and a physical examination cannot be relied on to detect small increases in volume status. ECW and TBW are frequently expressed as actual volume; however, the ratio can be affected by muscle wasting and abnormal tissue hydration. As the evaluation of dry weight in HD patients is complicated by many patient-specific factors such as atherosclerosis, structural and functional abnormalities of the heart, nutrition status and other co-morbidities, a bioimpedance analysis may help improve this essential assessment [36]. The ΔHS is therefore regarded as a better indicator of fluid status [37]. Prospective observational studies have reported the usefulness of bioimpedance in optimizing the hydration status and outcomes of dialysis patients [11, 38]. Fluid overload can affect vascular and endothelial dysfunction, and contribute to arterial stiffness, atherosclerosis and LVH [39]. In addition, fluid overload has been reported to lead to cardiomyocyte elongation, hypertrophy, and dysfunction during LV remodeling [40]. Increasing evidence suggests there is an association between fluid overload and impaired cardiac function, and that reducing excess volume can lead to a reduction in LVMI [41, 42]. In the present study, we investigated the role of ΔHS adjusted for GLS, a novel parameter of LV systolic function, and E/E' ratio as a marker of LV diastolic function in the multivariate analysis. The association between fluid overload and all-cause and CV mortality in HD patients remained significantly independent of cardiac systolic and diastolic function. Based on the survival and prognostic implication of fluid overload, physicians may have to carefully monitor and control the fluid status in maintenance HD patients.

Another important finding of the present study was that the addition of GLS to the model composed of conventional clinical characteristics and echocardiographic parameters improved the predictive ability of all-cause and CV mortality in chronic HD patients. LV systolic function is a complex process, which involves longitudinal contraction, circumferential shortening and radial thickening. Several alternative factors, however, were reported to be overweighed the role of LVEF [6]. For example, speckle-tracking imaging can provide information on multidimensional myocardial deformation [7]. In addition, compared with tissue Doppler-derived strain, speckle-derived strain is not angle-dependent and is easier to calculate. Moreover, several studies have demonstrated that GLS can improve the prediction of overall and CV mortality compared with conventional echocardiographic parameters in patients with renal insufficiency [9, 43]. Although longitudinal and radial systolic functions are decreased in patients with ESRD, LVEF may remain within normal limits due to the preservation of circumferential function. 2D speckle-tracking echocardiography may be able to detect the severity of uremic cardiomyopathy in the early stages of disease, it may also be able to provide useful information for assessing risk in patients with ESRD with preserved LVEF [44]. Therefore, the use of GLS in maintenance HD patients may help to identify those at a high risk of poor outcomes. ΔHS also significantly improved the prognostic value beyond conventional echocardiographic parameters and GLS. Although markers of cardiac systolic and diastolic function have their prognostic significance, ΔHS appears to be a more important predictor of all-cause and CV mortality in chronic HD patients.

The present study did have several limitations. Firstly, the patient's fluid status was measured only once at study enrollment, and therefore the association of fluid status over

time with outcomes could not be analyzed. Secondly, there may be some other confounding factors that were not included in the multivariate adjusted analysis. Thirdly, the number of study patients was relatively small and the follow-up period was relatively short. Only 24 patients died during the mean observation time of 2.7 years. Therefore, a larger cohort study with a longer follow-up time and an interventional study on volume status control are warranted in future studies. Finally, a new study would be necessary to address the question of whether mortality rates could be improved after decreasing the OH status.

Conclusion

An increased ΔHS was independently associated with an increased risk of all-cause and CV mortality after adjusting for GLS and the E/E' ratio. Furthermore, ΔHS significantly improved the prognostic value beyond conventional echocardiographic parameters and GLS. Therefore, hydration status, as assessed by impedance spectroscopy, may facilitate the identification of high-risk patients. ΔHS is a relevant target for improving survival outcomes in maintenance HD patients.

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Disclosure Statement

The authors declare they have no conflicts of interest.

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