ORIGINAL ARTICLE

Overhydration as a modifiable cardiovascular risk factor in patients undergoing hemodialysis

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KEY WORDS

bioimpedance, cardiovascular risk, end-stage renal disease, mortality, overhydration

ABSTRACT

INTRODUCTION Cardiovascular mortality in patients with end-stage renal disease (ESRD) remains high despite advances in dialysis techniques. This can be attributed to several traditional and nontraditional risk factors. Overhydration seems to be one of the promising cardiovascular risk factors that could be targeted to improve survival.

OBJECTIVES We aimed to assess the effect of chronic overhydration as well as changes in the degree of overhydration over time on cardiovascular and all-cause morbidity and mortality in patients undergoing hemodialysis.

PATIENTS AND METHODS We enrolled 511 patients with ESRD undergoing hemodialysis. The hydration status was assessed with whole-body bioimpedance spectroscopy. Patients were divided into 4 subgroups according to baseline hydration status. Additionally, patients with at least 2 follow-up visits (n = 277) were classified into 4 subgroups according to changes in the hydration status over time.

RESULTS Statistical analysis showed that male sex (P <0.001), diabetes (P <0.001), cardiac insufficiency (P <0.001), smoking (P = 0.049), and cerebrovascular events (P = 0.007) were significant risk factors for overhydration. Cardiovascular toxicity of overhydration was reflected by elevated levels of N-terminal pro-B-type natriuretic peptide (P <0.001) and cardiac troponin T (P <0.001). Albumin and total cholesterol levels were the lowest in patients with severe overhydration (P <0.001). Mortality was lower in patients with normal hydration status and mild overhydration (P <0.001) as well as in those with stable low or descending overhydration pattern (P = 0.002).

CONCLUSIONS We showed that the degree of overhydration is significantly associated with the incidence of cardiovascular complications and prognosis in patients with ESRD undergoing hemodialysis.

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INTRODUCTION Despite advances in medical technology and pharmacology, morbidity and mortality rates in patients with end-stage renal disease (ESRD) remain high.[1] Cardiovascular events are the leading cause of death in this population, accounting for up to 50% of fatal cases. Cardiovascular risk is elevated even in the early stages of chronic kidney disease (CKD). Thus, CKD was identified as an independent risk factor for cardiovascular disease by the American Heart Association.[2-5] High cardiovascular mortality in patients with ESRD may be linked to several pathological processes, including endothelial damage, myocardial dysfunction, valvular abnormalities, and arrhythmias. However, coronary artery disease secondary to atherosclerosis remains the leading cause of cardiovascular events in this population.[6] In addition to classic risk factors, patients with ESRD are burdened with some specific conditions related to the presence of uremic toxemia. These nontraditional risk factors are almost exclusive to this population and include chronic low-grade inflammation, malnutrition, kidney-related anemia, oxidative stress, soft tissue calcifications, and overhydration.[7,8] They can affect prognosis to a greater extent than traditional risk factors.

Overhydration is a common finding in patients with ESRD. It is defined as an excess of water in the body. Available data suggest that

WHAT'S NEW?

Mortality in patients with end-stage renal disease (ESRD) is considerably higher than in age- and sex-matched general population with cardiovascular events as the leading cause of death. Chronic fluid overload, a nontraditional cardiovascular risk factor, seems to have a critical contribution to this fatal outcome. We aimed to provide statistical evidence for the relation between overhydration and high cardiovascular mortality in patients with ESRD. We confirmed that fluid overload is an independent risk factor for death in this population. We also identified other interesting factors associated with poor prognosis, including male sex, diabetes, cardiac insufficiency, smoking, and cerebrovascular events. Finally, we provided additional evidence supporting the use of bioimpedance for proper fluid balance in ESRD. We believe that by highlighting some of the less known issues, our study will help improve the medical care of patients undergoing hemodialysis.

overhydration negatively affects the cardiovascular system by increasing blood pressure as well as inducing cardiac preload, cardiac remodeling, and collagen gene activation leading to fibrosis and arterial stiffness. All these effects are considered to be cardiotoxic and are linked with high mortality.[9,10] Overhydration as a component of cardiorenal syndrome may also be present in the earlier stages of kidney disease (CKD stages G3–G4 based on estimated glomerular filtration rate). Uncontrolled fluid overload can even accelerate CKD progression and prompt initiation of hemodialysis.[11] Therefore, chronic volume overload may seem to be one of the most important cardiovascular risk factors. Studies conducted in the past 15 years have provided clear evidence for the association between abnormal hydration status and poor prognosis in patients with ESRD, with overhydration reported as one of the most powerful independent predictors of mortality.[12-16] Since the restoration of fluid balance is considered to be the cornerstone of effective hemodialysis, fluid overload seems to be a promising therapeutic target.

A recent surge of studies describing the connection between overhydration and cardiovascular mortality can be attributed to the introduction of new standardized methods for hydration assessment in dialysis centers. Routine clinical and laboratory techniques are often irreproducible and unable to describe fluid overload in a quantifiable manner.[17] Whole-body bioimpedance spectroscopy (BIS), which allows for an easy, quick, and low-cost assessment of hydration, seems to be a reasonable alternative.[18] It has been validated (according to dilution techniques) for use in patients with ESRD and is considered to be an adequate, objective, and reproducible method of hydration assessment.[19,20] However, it remains debatable which bioimpedance parameter is the best marker of fluid overload. It is believed that since some overhydration parameters are a result of mathematical estimation, they may be sensitive to measurement errors. It was postulated that using parameters that have been adjusted to body weight or total body water (TBW) is a much safer approach.[21] Nevertheless, several studies provided evidence that overhydration assessed on the basis of bioimpedance measurement is strongly connected with mortality in patients with ESRD.[13-16] Therefore, the popularization of whole-body BIS for hydration assessment in hemodialysis patients may play a key role in the improvement of medical care.

The aim of this study was to assess the effect of chronic overhydration as well as changes in the degree of overhydration over time (ie, decrease and increase) on the serum levels of selected cardiac biomarkers, incidence of atherosclerosis-related comorbidities and cardiovascular events, as well as all-cause and cardiovascular mortality rates in ESRD patients undergoing hemodialysis.

PATIENTS AND METHODS

Study design

This multicenter prospective observational study included 511 patients (201 women, 310 men) with ESRD treated with prevalent hemodialysis. The median (first quartile [Q1]; third quartile [Q3]) age of the study group was 67.4 (57.1; 77.5) years. The study protocol is compliant with the Declaration of Helsinki and was approved by the local ethics committee. Before obtaining written consent, all patients were informed about the risks and benefits involved in study participation. Patients aged 18 years or older with a hemodialysis vintage of more than 4 weeks were eligible for the study. The exclusion criteria were as follows: implantation of an implantable cardioverter defibrillator or other subcutaneous devices, history of prosthetic joint replacement or amputation, poor short-term prognosis, and the use of a temporary hemodialysis catheter. At baseline (visit 1), each patient underwent medical history taking, physical examination, hydration status assessment, and blood sampling. During follow-up, cardiovascular events (ie, myocardial infarction and cerebrovascular events) as well as mortality rates were recorded. Some patients (n = 277) underwent additional follow-up visits (visits 2–4) using the same protocol. The median (Q1; Q3) follow-up duration was 21.8 (15.3; 39.0) months. The follow-up was terminated in the event of death or kidney transplant, or if patients were considered ineligible for hemodialysis.

Hydration status assessment

Hydration status was assessed with whole-body BIS using Body Composition Monitor (Fresenius Medical Care Deutschland GmbH; Bad Homburg, Germany). The measurements were performed shortly before a mid-week hemodialysis session in the supine position, using 4 disposable electrodes attached to the patient's hand and foot contralateral to the arteriovenous shunt (when present), as per the device manual. The parameters describing fluid status included absolute overhydration (expressed in liters), relative overhydration (= absolute overhydration / body weight; expressed in percentage), TBW (expressed in liters),

as well as extracellular and intracellular water compartment volume (ECW and ICW, respectively, expressed in liters).

Laboratory tests Blood samples were collected before a mid-week hemodialysis session at the time of whole-body BIS. The blood work panel included complete blood count with hemoglobin, albumin, and total cholesterol. Cardiovascular status was evaluated using serum N-terminal pro-B-type natriuretic peptide (NT-proBNP; Elecsys assay, Roche Diagnostics, Basel, Switzerland) and cardiac troponin T (cTnT; Elecsys Troponin T fourth generation assay, Roche Diagnostics). Hemodialysis efficacy was assessed with Kt/V, ultrafiltration volume, and weekly hemodialysis dose expressed as a total weekly time span of hemodialysis. Residual diuresis recorded on a non-dialysis day was used for the assessment of residual kidney function.

Subgroups The whole study cohort (n = 511) was divided into 4 subgroups according to the hydration status at baseline: normal (<1.0 l, n = 126), mild overhydration (≥1.0 and <2.0 l, n = 127), moderate overhydration (≥2.0 and <3.0 l, n = 108), and severe overhydration (≥3.0 l, n = 150). Additionally, patients with at least 2 follow-up visits (n = 277) were assigned to the following 4 subgroups according to the pattern of changes in the degree of overhydration over time: stable low (n = 125), stable high (n = 54), ascending (n = 40), and descending (n = 58). The cutoff value for discriminating patients with a stable high and stable low degree of overhydration was set at 2.5 l. Patients with overhydration levels below the threshold of 2.5 l both at baseline and during follow-up were assigned to the stable-low subgroup, while those with overhydration levels above that threshold were assigned to the stable-high subgroup. Finally, patients with 2 different values at 2 different time points were assigned either to the ascending subgroup (low overhydration level at baseline and high level during follow-up) or the descending subgroup (high level at baseline and low level during follow-up).

Statistical analysis Initially, the data were tested for normal distribution using the Shapiro–Wilk test. Since few parameters met the normality criteria, subsequent analysis was conducted using nonparametric tests only. Significant differences between 2 unpaired and multiple unpaired groups were determined with the Mann–Whitney and Kruskal–Wallis tests, respectively. For paired parameters, the Wilcoxon signed-rank test and Friedman analysis of variance were used, respectively. The χ^2 test was used to analyze qualitative data, whereas the significance of correlations was assessed with the Spearman test. Survival analysis was conducted using the Kaplan–Meier curves. Finally, factors influencing mortality were determined using the Cox proportional hazards method. A P value lower than 0.05 was considered significant. The values were presented as medians (Q1; Q3), unless indicated otherwise. Statistical analysis was performed using StatSoft, Inc. (2014) STATISTICA (data analysis software system) version 12 (www.statsoft.com).

RESULTS

Characteristics of the study groups

The most common cause for ESRD in the studied cohort was diabetic kidney disease (n = 126, 24.7%), followed by chronic glomerulonephritis (n = 75, 14.7%), hypertensive nephropathy (n = 57, 11.2%), and ischemic nephropathy (n = 51, 10.0%). The demographic and clinical characteristics of patients are presented in TABLE 1. The median (Q1; Q3) follow-up was 21.8 (15.3; 39.0) months, with a median (Q1; Q3) hemodialysis vintage of 47.1 (32.0; 76.2) months. During the study, patients underwent a total of 1016 follow-up visits (visit 1 [baseline], 511 patients; visit 2, 277 patients; visit 3, 148 patients; and visit 4, 80 patients). A total of 237 patients (46.4%) were lost to follow-up: 187 patients (36.6%) died, 46 patients underwent a kidney transplant (9.0%), 4 patients (0.8%) were considered ineligible for hemodialysis, and the remaining 14 patients (2.7%) were either transferred to another dialysis center or were switched to peritoneal dialysis. The remaining 260 patients (50.9%) completed the follow-up. The mortality rate was 13.5% in the first year, 14.9% in the second year, 12.6% in the third year, and 14.9% in the fourth year of follow-up. In most cases, death was secondary to cardiovascular events (57.1%). Detailed data on the causes of death are presented in TABLE 2. In the entire cohort, overhydration was not correlated with patient age (R = 0.0138, P = 0.76). On the other hand, the presence of diabetes (median [Q1; Q3] absolute overhydration, 2.2 [1.3; 4.3] vs 1.8 [0.7; 2.8] l in patients without diabetes, P <0.001), heart failure (2.3 [1.3; 4.2] vs 1.6 [0.7; 2.6] l in patients without heart failure, P <0.001), and male sex (2.2 [1.2; 3.9] vs 1.7 [0.7; 2.6] l in women, P <0.001) were significant risk factors for higher fluid overload.

Analysis of subgroups classified according to the degree of overhydration at baseline The clinical characteristics of patients with normal hydration status as well as mild, moderate, and severe overhydration are presented in TABLE 1. There were no significant differences between the subgroups in terms of age. However, male sex was more prevalent in the subgroups with higher fluid overload (moderate and severe overhydration, P <0.001). In terms of comorbidities, higher degrees of overhydration were related to increased prevalence of diabetes and heart failure (both P <0.001). The prevalence of smoking and cerebrovascular events differed between patients with normal hydration status and those with severe overhydration (P = 0.049 and P = 0.007, respectively). Fluid distribution in the body compartments also differed between the subgroups. The ECW expansion was observed in the subgroups with more

TABLE 1 Demographic and clinical characteristics of the whole cohort and subgroups divided according to the hydration status at baseline

Parameter		Cohort (n = 511)	Hydration status				*P* value
			Normal (n = 126)	Mild overhydration (n = 127)	Moderate overhydration (n = 108)	Severe overhydration (n = 150)	
Male-to-female ratio		310:201	67:59	68:59	63:45	112:38	<0.001
Age, y		67.4 (57.1; 77.5)	64.8 (57.0; 76.9)	66.8 (53.7; 78.0)	68.3 (58.5; 78.6)	67.3 (58.4; 76.8)	0.59
Smoking, %		31.9	28.0	30.9	25.6	40.3	0.08
CAD, %		52.1	49.1	51.7	45.9	59.1	0.32
MI, %		26.0	25.8	22.4	21.4	32.4	0.31
Cerebrovascular events, %		11.2	4.8	11.1	13.5	14.9	0.05
Arrhythmia, %		29.8	28.6	26.3	27.8	35.3	0.41
HF, %		53.1	42.9	41.2	55.7	69.6	<0.001
Diabetes mellitus, %		38.5	23.4	38.9	37.9	51.4	<0.001
TBW, l		34.6 (30.4; 40.0)	33.2 (29.2; 40.3)	33.0 (29.4; 38.1)	34.6 (29.5; 38.6)	36.6 (32.6; 41.5)	<0.001
ECW, l		17.6 (15.2; 19.9)	15.8 (13.9; 18.8)	16.8 (14.6; 18.7)	17.2 (15.5; 19.6)	19.7 (17.5; 21.9)	<0.001
ICW, l		17.1 (14.7; 20.1)	17.6 (14.8; 21.8)	16.4 (14.4; 19.9)	16.6 (14.3; 19.2)	17.1 (14.8; 19.6)	0.09
ECW/ICW ratio		1.02 (0.92; 1.13)	0.91 (0.81; 0.99)	0.97 (0.90; 1.07)	1.05 (0.97; 1.12)	1.16 (1.05; 1.25)	<0.001
Absolute overhydration, l		2.0 (1.0; 3.3)	0.1 (-0.4; 0.6)	1.5 (1.3; 1.8)	2.4 (2.2; 2.6)	4.5 (3.7; 5.8)	<0.001
Relative overhydration, %		2.68 (1.24; 4.77)	0.14 (-0.45; 0.74)	2.07 (1.65; 2.50)	3.27 (2.71; 4.07)	6.24 (4.95; 8.29)	<0.001
Albumin, g/dl		4.02 (3.70; 4.30)	4.20 (3.93; 4.44)	4.09 (3.87; 4.30)	4.09 (3.77; 4.30)	3.87 (3.41; 4.14)	<0.001
Total cholesterol, mg/dl		169 (140; 199)	181 (153; 217)	183 (153; 204)	173 (136; 199)	149 (125; 177)	<0.001
NT-proBNP, pg/ml		5949 (1886; 21058)	2435 (989; 6834)	5070 (1888; 9549)	6957 (2169; 20921)	18585 (5571; 35000)	<0.001
cTnT, ng/l		49 (31; 88)	36 (24; 56)	48 (28; 73)	49 (29; 81)	84 (48; 143)	<0.001
Hemoglobin, g/dl		11.1 (10.1; 12.0)	11.6 (10.7; 12.5)	11.2 (10.3; 12.2)	11.0 (10.1; 11.8)	10.7 (9.5; 11.5)	<0.001
CRP, mg/l		5.6 (1.9; 13.0)	6.7 (1.7; 15.0)	3.7 (1.1; 8.6)	8.3 (3.3; 16.1)	5.1 (2.1; 13.9)	0.06
Kt/V		1.25 (1.05; 1.41)	1.30 (1.08; 1.44)	1.30 (1.12; 1.45)	1.15 (0.97; 1.4)	1.21 (1.04; 1.37)	0.02
Hemodialysis dose, h/wk		12.00 (12.00; 12.25)	12.00 (12.00; 12.50)	12.00 (12.00; 12.25)	12.0 (10.5; 12.0)	12.00 (12.00; 12.50)	0.25
Ultrafiltration volume, ml		2100 (1400; 3200)	2000 (1200; 3000)	2300 (1300; 3100)	2000 (1500; 3000)	2250 (1660; 3500)	0.14
Residual diuresis, ml		700 (100; 1250)	1000 (300; 1500)	650 (100; 1300)	700 (100; 1000)	500 (100; 1000)	0.03
MAP, mm Hg	Before dialysis	93 (86; 103)	90 (82; 98)	97 (87; 103)	97 (83; 107)	100 (91; 107)	<0.001
	After dialysis	90 (83; 96)	87 (77; 93)	90 (83; 97)	90 (80; 100)	95 (87; 100)	<0.001

Data are expressed as median (first and third quartile).

SI conversion factors: to convert albumin to g/l, multiply by 10; total cholesterol to mmol/l, by 0.0259; NT-proBNP to ng/l, by 1.0; cTnT to µg/l, by 0.001; hemoglobin to g/l, by 10.0.

Abbreviations: CAD, coronary artery disease; CRP, C-reactive protein; cTnT, cardiac troponin T; ECW, extracellular water; HF, heart failure; ICW, intracellular water; MAP, mean arterial pressure; MI, myocardial infarction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; TBW, total body water

severe fluid overload (ECW / TBW%; *P* <0.001) than in those with less severe fluid overload. On the other hand, the intracellular compartment was smaller in these patients (ICW / TBW%; *P* <0.001). The same association was also reflected by the differences in the ECW / ICW ratio (P <0.001). The cardiovascular toxicity of increasing fluid overload was reflected by elevated levels of NT-proBNP (*P* <0.001) and cTnT (*P* <0.001) as well as an increase in blood pressure levels measured before and after hemodialysis. Albumin and total cholesterol levels were the lowest in patients with severe overhydration (both *P* <0.001). There were no differences between patients with the normal hydration status as well as mild, moderate, and severe overhydration in terms of the follow-up duration (21.9 [17.4; 39.5], 21.8 [16.9; 40.8], 21.9 [16.0; 42.9], 21.6 [12.1; 31.8] months, respectively; *P* = 0.15) and hemodialysis vintage (43.4 [32.7; 63.6], 47.9 [32.3; 73.8], 47.6 [29.6; 84.6], and 47.4 [32.4; 78.3] months, respectively; *P* = 0.75).

Analysis of subgroups classified according to changes in the degree of overhydration over time The demographic characteristics and changes in the analyzed parameters in the subgroups with descending, stable low, stable high, and ascending pattern of changes in overhydration are summarized in TABLE 3. Age did not differ between the subgroups. However, male sex was more prevalent in the stable-high and ascending

TABLE 2 Distribution of the causes of death in the studied cohort

Cause of death		Number (%) of cases
Cardiovascular	Cardiac arrest	27 (14.4)
	Heart failure	26 (13.9)
	Acute coronary syndrome	21 (11.2)
	Stroke	16 (8.6)
	Nonspecific	15 (8.0)
	Aortic aneurysm	2 (1.1)
	Subtotal	107 (57.2)
Noncardiovascular	Infections	26 (13.9)
	Neoplasm	25 (13.4)
	Hemorrhage	8 (4.3)
	Cachexia	4 (2.2)
	Trauma	3 (1.6)
	Other	4 (2.2)
	Subtotal	70 (37.4)
Unknown		10 (5.3)

TABLE 3 Demographic and clinical data of patients divided according to the pattern of changes in overhydration during follow-up

Parameter	Pattern of changes in overhydration			
	Descending (n = 58)	Stable low (n = 125)	Stable high (n = 54)	Ascending (n = 40)
Male-to-female ratio	37:21	64:61	41:13	28:12[b]
Age, y	67.5 (57.6; 77.3)	68.0 (57.0; 76.9)	66.7 (57.5; 75.6)	67.7 (53.6; 76.3)
Smoking, %	38.9	29.2	34.1	40.5
CAD, %	54.7	49.6	62.0	65.8
MI, %	28.1	24.0	27.8	25.0
Cerebrovascular events, %	10.5	6.4	16.7	12.5
HF, %	71.7	47.0	72.0	68.4**
Diabetes mellitus, %	36.8	34.4	38.9	45.0
Absolute overhydration, l	–1.8 (-3.3; –1.1)[c]	0.1 (–0.6; 0.7)	–0.7 (–1.7; 0.2)[b]	2.1 (0.4; 2.9)[c]
Relative overhydration, %	–2.8 (–5; –1.51)[c]	0.24 (–0.74; 1.07)	–0.76 (–2.18; 0.49)[a]	2.40 (0.37; 3.87)[c]
ECW/TBW ratio, %	–2.66 (–4.5; –0.03)[c]	0.53 (–0.94; 1.55)	–0.38 (–1.75; 1.33)	2.56 (0.55; 4.69)[c]
ICW/TBW ratio, %	2.73 (0; 4.48)[c]	–0.54 (–1.61; 0.85)[a]	0.51 (–1.33; 1.83)	–2.56 (–4.6; –0.55)[c]
ECW/ICW ratio	–0.10 (–0.02; 0)[c]	0.02 (–0.03; 0.06)	–0.02 (–0.08; 0.05)	0.12 (0.02; 0.2)[c]
Albumin, g/dl	0.20 (0.10; 0.50)	0.00 (–0.16; 0.2)	0.10 (–0.17; 0.3)	–0.1 (–0.3; 0.1)
NT-proBNP, pg/ml	0 (–10 688; 2476)	–28 (–1325; 700)	366 (–1787; 8084)	2068 (–35; 17 656)[b]
cTnT, ng/l	–9 (–43; 26)	2 (–6; 8)	–2 (–21; 16)	4 (–14; 15)
Residual diuresis, ml	0 (–500; 0)[b]	0 (–200; 0)	0 (–125; 100)	0 (–500; 0)[a]

Data are expressed as median (first quartile; third quartile).

SI conversion factors: see TABLE 1

a $P < 0.05$; b $P < 0.01$; c $P < 0.001$

Abbreviations: see TABLE 1

subgroups than in the remaining subgroups ($P = 0.009$). Heart failure was less prevalent in the stable-low subgroup than in the other subgroups ($P = 0.002$). A separate analysis was performed for the combined subgroups of similar character (descending + stable low and ascending + stable high). The group including patients with descending and stable-low pattern of changes in overhydration had a lower prevalence of heart failure (54.8% vs 70.5%; $P = 0.01$) and coronary artery disease (52.9% vs 66.3%; $P = 0.04$) than the group with ascending and stable-high pattern. Changes in TBW volume in the ascending and descending subgroups were also associated with corresponding adjustments within the body water compartments (ie, ECW and ICW; TABLE 3).

TABLE 4 Mortality in the study subgroups

Baseline overhydration subgroups		Normal hydration status (n = 126)	Mild overhydration (n = 127)	Moderate overhydration (n = 108)	Severe overhydration (n = 150)	*P* value
All-cause mortality	Deaths	30	35	44	78	<0.001
	%	23.8	27.6	40.7	52.0%	
Cardiovascular mortality	Deaths	15	17	22	53	<0.001
	%	13.5	15.6	25.6	42.4	
Dynamic overhydration subgroups		**Descending overhydration (n = 58)**	**Stable low overhydration (n = 125)**	**Stable high overhydration (n = 54)**	**Ascending overhydration (n = 40)**	***P* value**
All-cause mortality	Deaths	15	37	26	22	0.002
	%	25.9	29.6	48.2	55.0	
Cardiovascular mortality	Deaths	10	20	20	10	0.007
	%	18.9	18.5	41.7	35.7	

Data are expressed as absolute number of cases and percentage of subgroups.

TABLE 5 Number of patients at risk with a total number of censored observations and cumulative survival during follow-up

Mortality	Overhydration subgroup	Time, mo								
		0	12	24	36	48	12	24	36	48
		Patients at risk (censored)					Cumulative survival, %			
All-cause	Normal hydration status	126	104 (12)	57 (47)	39 (61)	19 (78)	91.7	80.0	72.9	66.6
	Mild	127	104 (12)	51 (51)	39 (59)	26 (68)	90.9	76.7	70.0	61.5
	Moderate	108	87 (4)	51 (29)	36 (37)	18 (48)	84.0	73.0	61.7	48.1
	Severe	150	113 (4)	55 (39)	34 (49)	20 (55)	77.7	60.3	46.6	34.1
	Descending + stable low	183	131 (28)	93 (54)	61 (75)	0 (131)[a]	85.8	76.4	65.8	59.2
	Ascending + stable high	94	68 (7)	53 (10)	32 (18)	0 (46)[a]	78.5	64.7	47.1	40.0
Cardiovascular	Normal hydration status	111	94 (12)	52 (47)	37 (61)	19 (78)	95.2	87.6	85.0	82.5
	Mild	109	90 (12)	46 (51)	34 (59)	25 (68)	93.3	87.2	78.5	78.5
	Moderate	86	73 (4)	43 (29)	32 (37)	16 (48)	89.3	83.1	76.5	62.7
	Severe	125	101 (4)	48 (39)	30 (49)	19 (55)	83.7	67.0	53.3	43.1
	Descending + stable low	161	117 (28)	84 (54)	58 (75)	0 (131)[a]	88.4	82.5	76.8	73.6
	Ascending + stable high	76	57 (7)	47 (10)	31 (18)	0 (46)[a]	83.6	72.9	59.0	52.3

a For subgroups divided according to changes in overhydration over time, the longest follow-up duration was 47.9 months.

Interestingly, alterations in fluid overload were associated with similar changes in median NT-proBNP levels. However, no similar trend was observed for cTnT. Residual diuresis decline was observed both in patients with ascending and descending overhydration. In terms of nutrition, a significant increase in serum albumin levels was noted in the descending overhydration subgroup (TABLE 3).

Correlations The analysis for the entire cohort (n = 511) revealed that relative overhydration was correlated with ECW/TBW (R = 0.561; P <0.001), ICW/TBW (R = –0.565; P <0.001), and ECW/ICW ratios (R = 0.567; P <0.001). In addition, relative overhydration was correlated with NT-proBNP (R = 0.468, P <0.001), cTnT (R = 0.394; P <0.001), albumin (R = –0.342; P <0.001), and hemoglobin (R = –0.282; P <0.001) levels. The degree of overhydration was also correlated with the mean arterial pressure measured before (R = 0.193; P <0.001) and after (R = 0.189; P <0.001) dialysis. However, no correlations were observed between overhydration and basic dialysis parameters including Kt/V (R= –0.046; P = 0.46) and ultrafiltration volume (R = 0.063; P = 0.32).

Survival analysis Mortality rates in the subgroups classified according to the hydration status at baseline as well as changes in fluid overload during follow-up are presented in TABLE 4. In the Kaplan–Meier analysis, the subgroups with the normal hydration status and mild overhydration (FIGURE 1A and 1B) as well as the ascending and stable-low overhydration subgroups (FIGURE 2A and 2B) showed better survival than the remaining subgroups. The results of survival analysis are presented in TABLE 5. The multivariable Cox proportional hazards analysis revealed the following risk factors for all-cause mortality: relative overhydration (hazard ratio [HR], 1.13; 95% CI, 1.05–1.22; P <0.001), NT-proBNP quartile

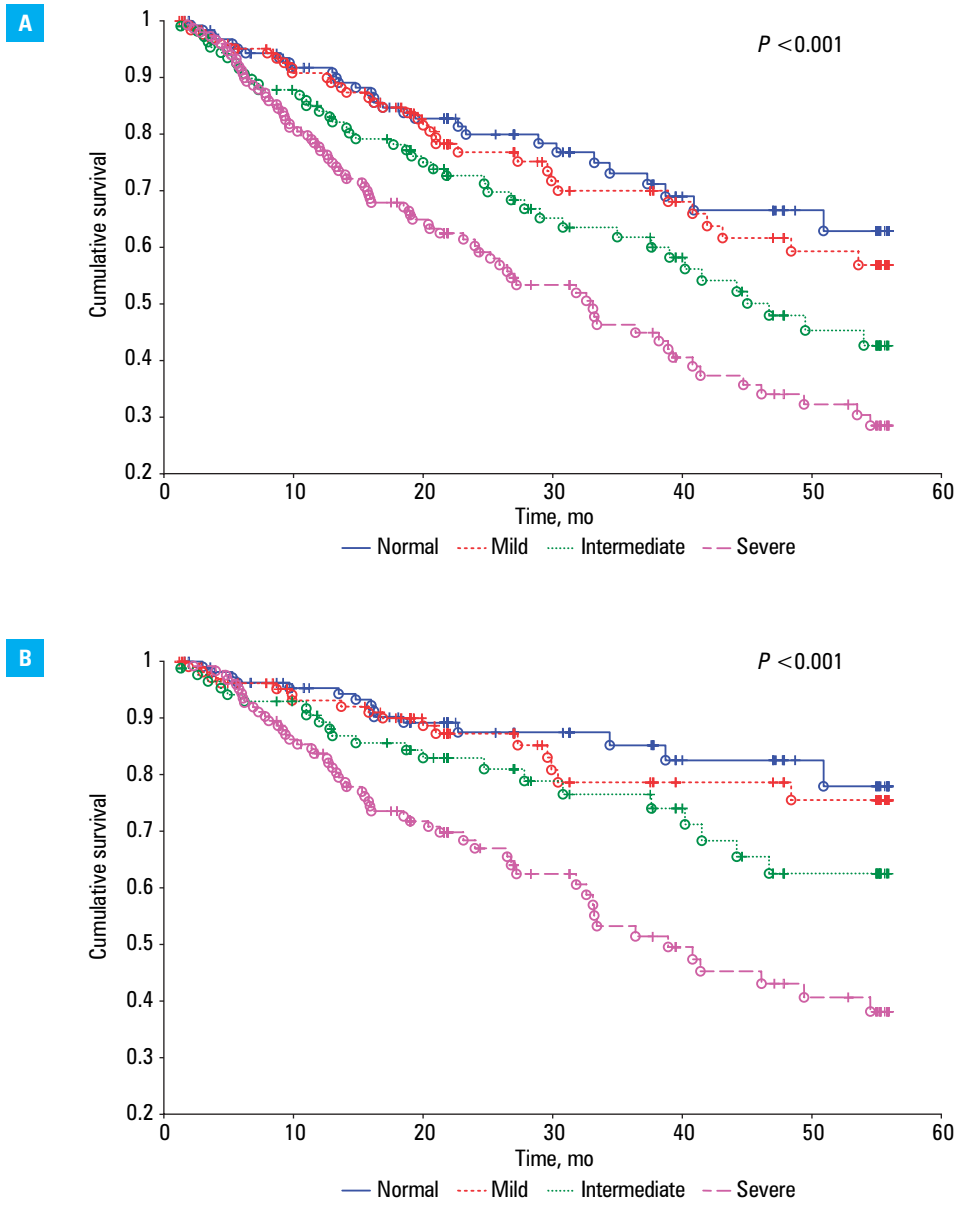

FIGURE 1 Kaplan–Meier curves for all-cause (**A**) and cardiovascular (**B**) mortality in the subgroups divided according to the degree of overhydration at baseline

(HR, 1.23; 95% CI, 1.03–1.48; P = 0.02), history of myocardial infarction (HR, 1.48; 95% CI, 1.02–2.15; P = 0.04), smoking (HR, 1.52; 95% CI, 1.04–2.23; P = 0.03), age (expressed in decades, HR, 1.55; 95% CI, 1.32–1.82; P <0.001), and residual diuresis lower than 100 ml (HR, 1.91; 95% CI, 1.26–2.91; P = 0.002).

DISCUSSION Chronic asymptomatic overhydration is a typical finding in patients with ESRD undergoing standard hemodialysis (three 4-hour sessions per week).[22] Overhydration is associated with several clinical sequelae, including elevated blood pressure, peripheral swelling, incidental pulmonary edema, increased arterial stiffness, left ventricular hyperplasia, and congestive heart failure. Fluid overload was reported as an independent risk factor for mortality in this population.[22,23] In our study, fluid overload greater than 1 l was detected in over 75% of patients (n = 385). In nearly 30% of patients (n = 150), the fluid volume was 3 l or greater. Similar findings were reported by other authors.[13,22,24]

The analysis of changes in fluid overload over time showed 4 distinctive patterns. In some cases, hydration parameters remained stable, while in others, we observed dynamic changes during follow-up. The cutoff value of 2.5 l for differentiating between patients with high and low level of fluid overload was selected based on the study by Wizemann et al.[13] Patients with the descending pattern showed a mean reduction in fluid overload of 2 l, an increase in the ICW compartment volume, as well as higher albumin levels and adipose tissue mass (data not shown). In contrast, the ascending pattern was associated with a decline in the ICW / TBW ratio, lower median hemoglobin levels, and increased NT-proBNP levels. Both these subgroups showed a decline in residual diuresis with no change in blood pressure.

Other investigators also used whole-body BIS to assess the impact of overhydration. Hur et al[25] applied bioimpedance to study the effect of fluid overload in 156 hemodialysis patients during a 12-month follow-up. The study group showed a significant improvement in left ventricular

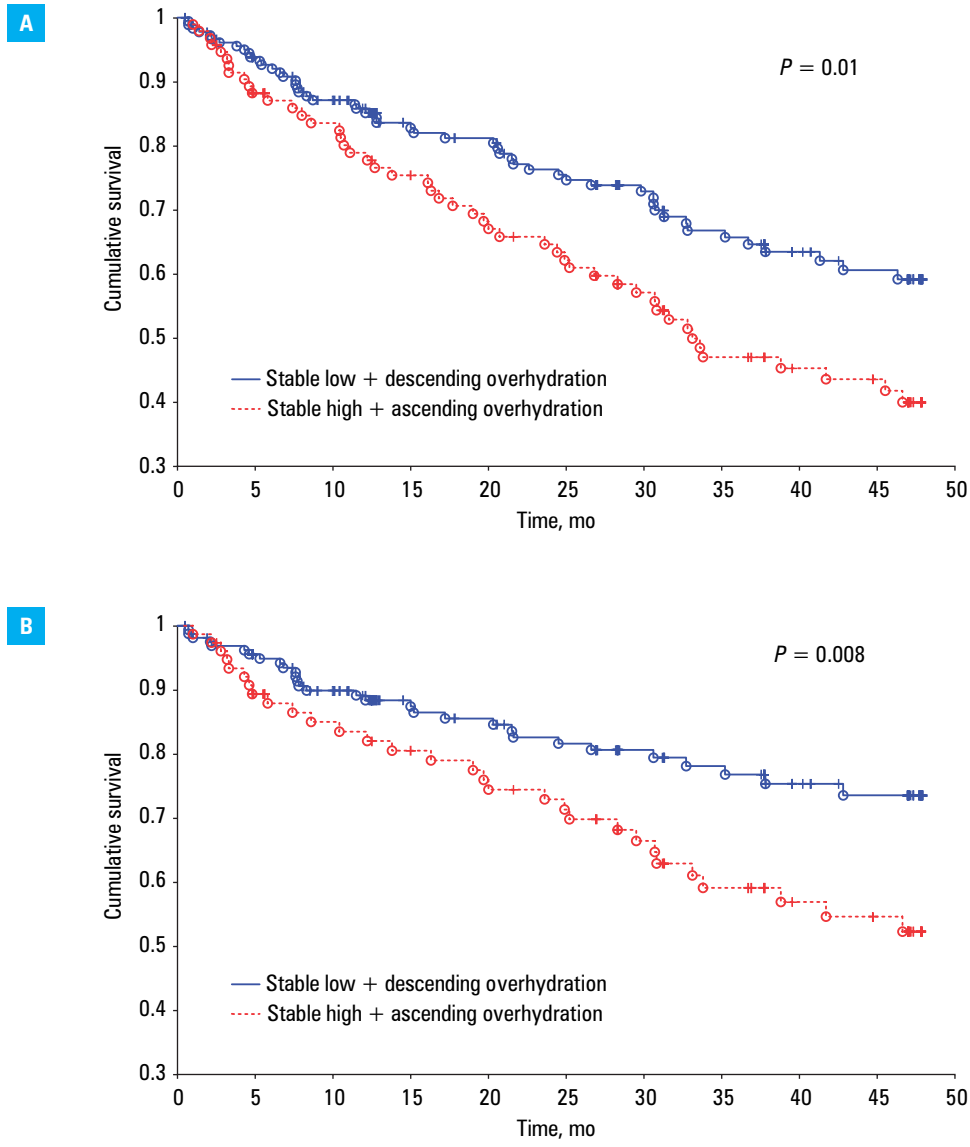

FIGURE 2 Kaplan–Meier curves for all-cause (**A**) and cardiovascular (**B**) mortality in the subgroups divided according to changes in overhydration during follow-up. For the purpose of the analysis, the subgroups with a similar degree of changes in overhydration were combined.

mass index, atrial volumes, blood pressure, and arterial stiffness parameters, along with an increase in albumin, hemoglobin, triglyceride, and total cholesterol levels. The hydration status improved significantly despite a decline in residual diuresis. These findings are also in line with an interventional study by Onofriescu et al.[16] The authors showed that a reduction in fluid overload was associated with lower arterial stiffness and blood pressure in patients assessed with whole-body BIS over a 3-year follow-up. The benefits of lower fluid volume in patients with ESRD were also confirmed by other studies. Moissl et al[26] reported that a reduction in fluid overload is associated with a decrease in mean arterial pressure (by 9.9 mm Hg per each liter change in fluid overload). Machek et al[27] demonstrated that a reduction in fluid overload, as measured by whole-body BIS, is associated with lower blood pressure and a reduction in antihypertensive medication, without increasing the rate of intradialytic adverse events. Han et al[28] studied a total of 135 predialysis patients with ESRD. The authors reported that fluid overload was a considerable risk factor for functional and structural alterations of the left ventricle. Czyżewski et al[29] demonstrated that overhydration is an independent risk factor in arterial distension, while Mitsides et al[30] reported that extracellular fluid overload was significantly associated with microinflammation and endothelial dysfunction markers, which might reflect an interaction between ECW volume expansion and vascular damage at the endothelial level. In a study on 285 hemodialysis patients, Siriopol et al[31] showed that the use of 2 complementary methods for fluid status assessment (BIS and NT-proBNP measurement) could enhance the diagnosis of fluid overload and thus improve patient outcome. The above findings, along with our current study, seem to support the usefulness of whole-body BIS for fluid overload assessment in patients with ESRD.

Interestingly, the degree of overhydration at baseline and during follow-up was not associated with patient age or hemodialysis vintage. We hypothesized that fluid overload would be higher in elderly patients and in those with longer dialysis vintage. This could result from difficulties in adherence to an appropriate fluid regimen as well as progressive loss of residual kidney

function. However, this was not supported by our results, which is also in line with a number of other studies.[23,24,32,33] On the contrary, some authors linked overhydration with hemodialysis vintage[13,22,34] and age.[18,22,33,35] Based on available literature and our own results, we may hypothesize that hemodialysis vintage has a greater effect on fluid overload–related complications and mortality in patients with ESRD than patient age.

Other significant factors associated with overhydration were male sex, diabetes, and heart failure. Male sex was more prevalent among patients with a tendency for fluid overload. At the same time, the Kaplan–Meier analysis did not show any association between male sex and cardiovascular or all-cause mortality (data not shown). Available literature data are conflicting. Some authors did not find any significant differences in sex distribution depending on fluid overload.[15,23,24] However, in most studies, increased fluid overload was associated with male sex.[22,26,33,36-38] The reason for this is unclear, and the results of studies published in the last 15 years are inconclusive. It may be hypothesized that higher fluid overload in men is related to greater appetite, lack of adherence to fluid and salt intake regimen, different fat distribution, and hormonal disorders, among other factors.

Our study also revealed that diabetes, heart failure, smoking, and cerebrovascular events are risk factors for overhydration. This finding is in line with studies by other authors, who also reported that the risk of overhydration increases with a more severe depletion of the lean or fat tissue compartment, which is further aggravated by the presence of inflammation and the use of multiple antihypertensive medications.[39,40] In a large international study by Hecking et al,[41] fluid overload before and after dialysis was associated with increasing patient age, lower body mass index, and multiple comorbidities. Additionally, fluid overload after dialysis was strongly associated with mortality risk.

In our cohort, a higher degree of fluid overload was linked to a gradual increase in NT-proBNP levels as well as cardiotoxicity reflected by elevated cTnT levels. In the analysis of patients with the descending, stable-low, stable-high, and ascending pattern of changes in fluid overload, the NT-proBNP level was a sensitive marker of the hydration status. The median NT-proBNP levels reflected changes both in relative overhydration and the ECW / TBW ratio. However, changes in the median cTnT levels were negligible, suggesting that other factors are also responsible for the observed cardiotoxicity. These results are in line with the available literature mostly confirming a linear relationship between overhydration and increasing NT-proBNP levels.[24,28,42-45] However, other studies did not report such a relationship, perhaps due to differences in patient selection algorithms or applied methodology.[46,47]

The population of hemodialysis patients is characterized by high mortality rates, comparable to some aggressive forms of cancer. In over 50% of cases, death is caused by cardiovascular complications. Our study proved that overhydration is a significant prognostic factor in these patients. Cardiovascular mortality gradually increased with an increasing degree of overhydration, and this finding was also supported by the Kaplan–Meier analysis. Other unfavorable prognostic factors were relative overhydration, history of myocardial infarction, smoking, advanced age, and anuria. Available literature confirms a strong relationship between overhydration and mortality in hemodialysis patients. In a retrospective study, Kalantar-Zadeh et al[36] assessed mortality in a group of 34,107 hemodialysis patients with respect to interdialytic weight gain. Despite using a fairly imprecise hydration marker, a multivariable analysis showed that significant interdialytic weight gain was associated with high all-cause and cardiovascular mortality rates. In another study, Wizemann et al[13] reported that overhydration is an independent predictor of mortality in hemodialysis patients. Interestingly, it was second in order of importance after diabetes. In survival analysis, factors such as overhydration, age, high systolic blood pressure, diabetes, and peripheral vascular disease significantly affected the prognosis. Some of the above links were also supported by our study. Dekker et al[40] assessed the association of malnutrition, fluid overload, and inflammation with survival and showed that the presence of more than 1 of those risk factors was associated with an increased risk of mortality. Siriopol et al[48] reported higher mortality risk in patients with the most dynamic fluctuations in the fluid volume status. Moreover, in their analysis, predialysis fluid depletion was associated with intradialytic hypotension, myocardial stunning, arrhythmias, myocardial fibrosis, and increased risk of sudden cardiac death.[48] In another interesting study by Chazot et al,[14] the authors investigated the relationship between blood pressure, fluid overload, and mortality by dividing the cohort of patients into 4 subgroups, with the hydration status cutoff set at an ECW / body weight of more than 15% and the blood pressure cutoff set at a systolic blood pressure of 140 mm Hg. Patients with fluid overload were characterized by increased mortality. The mortality rate was particularly high in individuals with normal blood pressure. The authors concluded that overhydration may have a greater impact on mortality than hypertension itself and that the use of antihypertensive drugs without an effective hydration assessment can lead to numerous adverse events. Another interesting contribution to the discussion was made by Kim et al,[23] who reported higher mortality in the group with overhydration than in the group without overhydration (26.9% and 8.8%, respectively). Surprisingly, the most common cause of death in this

Korean cohort was infection. Logistic regression and Cox proportional hazards analysis revealed that overhydration and advanced age significantly affected prognosis. Moreover, Onofriescu et al[22] confirmed that patients with fluid overload (defined as overhydration / ECW >15%) were characterized by a 2.12- and 2.46-fold increase in the risk of all-cause mortality and cardiovascular events, respectively. Age, sex, hemodialysis vintage, overhydration, hypertension, and other cardiovascular disorders were significantly associated with the above endpoints. Interestingly, overhydration in this study was also linked with higher hospitalization rates. In our research, the analysis of changes in the hydration status showed that patients with stable-high and ascending patterns had a significantly worse survival prognosis. The mortality rate in this subgroup was almost 2-fold higher than in the remaining patients. The association of changes in fluid overload with mortality risk was also assessed by Onofriescu et al.[16] Patients were randomly assigned to a group with strict volume control using whole-body BIS to guide ultrafiltration or a group in which the management was guided by clinical judgement without BIS for 2.5 years. In the bioimpedance group, a decline in fluid overload (and improvement in several secondary endpoints such as arterial stiffness parameters and blood pressure profile) was associated with better prognosis. The Kaplan–Meier cumulative survival rate was 96% (HR, 0.112; 95% CI, 0.014–0.918).

In summary, numerous available publications and our current results indicate a significant relationship between fluid overload and poor prognosis in patients with ESRD. It was postulated that permanent fluid accumulation interspersed with short hemodialysis sessions mimics repeated episodes of acute decompensated heart failure, which triggers fluctuations in compensatory mechanisms, such as an increase in sympathetic activity or changes in the rennin-angiotensin-aldosterone system.[10] It was proved that overhydration affects the cardiovascular system at a cellular level regardless of other factors, leading to increased vascular stiffness, atherosclerosis, and left ventricular hypertrophy and dysfunction.[10] Literature data show that a reduction in fluid overload through appropriate regimens, low sodium diet, and improved blood pressure control may lead to a decrease in left ventricular mass index and other echocardiographic markers of left ventricular hypertrophy, which lowers the incidence of cardiovascular complications and improves prognosis.[49] The results of this study, supported by observations of other investigators, corroborate the hypothesis that overhydration is an important modifiable cardiovascular risk factor for mortality in patients with ESRD.

Study limitations The main fluid overload parameter used in the study, that is, absolute overhydration, is a result derived from bioimpedance parameters using a mathematical model. This might have a significant impact on the quality of the obtained results and the significance of differences between the subgroups. Moreover, the study included a relatively homogenous population of white patients. In addition, both patients and clinicians involved in the study were not blinded to the results of the bioimpedance analysis and laboratory tests. This might have significantly affected the extent of the described phenomena, in particular, the degree of overhydration recorded during follow-up visits. Finally, we did not use any imaging methods to assess myocardial damage (eg, echocardiography), which could have supported the significance of the presented results.

Conclusions The degree of overhydration in hemodialysis patients is significantly associated with the incidence of cardiovascular complications such as heart failure, myocardial infarction, and cerebrovascular events. Fluid overload has a significant negative impact both on cardiovascular and all-cause mortality. Overhydration is more common in patients with concomitant diabetes, heart failure, history of cerebrovascular events, and ischemic heart disease.

ARTICLE INFORMATION

CONTRIBUTION STATEMENT Conceptualization: KS, KH, and KP; data curation: KS, KH, MK, MD, and AŁ; formal analysis: KS, KH, MO, JN, and KP; investigation: KS, KH, MK, MO, JN, AŁ, and KP; methodology: KS and KP; project administration: KS; resources: KS and KP; software: KS and MD; supervision: AO and KP; visualization: KS, MK, MD, and KP; writing – original draft: KS, KH, MD, MO, JN, and AŁ; writing – review and editing: AO and KP.

CONFLICT OF INTEREST None declared.

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