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NEPHROLOGY - ORIGINAL PAPER

Dry weight assessment by combined ultrasound and bioimpedance monitoring in low cardiovascular risk hemodialysis patients: a randomized controlled trial

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Abstract
Purpose Fluid overload is associated with adverse outcomes in hemodialysis (HD) patients. The precise assessment of hydration status in HD patients remains a major challenge for nephrologists. Our study aimed to explore whether combining two bedside methods, lung ultrasonography (LUS) and bioimpedance, may provide complementary information to guide treatment in specific HD patients.
Methods In total, 250 HD patients from two dialysis units were included in this randomized clinical trial. Patients were randomized 1:1 to have a dry weight assessment based on clinical (control) or LUS with bioimpedance in case of clinical hypovolemia (active)-guided protocol. The primary outcome was to assess the difference between the two groups on a composite of all-cause mortality and first cardiovascular event (CVE)—including death, stroke, and myocardial infarction.
Results During a mean follow-up period was 21.3 ± 5.6 months, there were 54 (21.6%) composite events in the entire population. There was a nonsignificant 9% increase in the risk of this outcome in the active arm (HR = 1.09, 95% CI 0.64–1.86, $p = 0.75$). Similarly, there were no differences between the two groups when analyzing separately the all-cause mortality and CVE outcomes. However, patients in the active arm had a 19% lower relative risk of pre-dialytic dyspnea (rate ratio—0.81, 95% CI 0.68–0.96), but a 26% higher relative risk of intradialytic cramps (rate ratio—1.26, 95% CI 1.16–1.37).
Conclusions This study shows that a LUS–bioimpedance-guided dry weight adjustment protocol, as compared to clinical evaluation, does not reduce all-cause mortality and/or CVE in HD patients. A fluid management protocol based on bioimpedance with LUS on indication might be a better strategy.

Keywords Hemodialysis · Fluid status · Bioimpedance · Lung ultrasonography · Cardiovascular events

Introduction

Fluid overload is one of the most common modifiable risk factors associated with the increased mortality risk observed in hemodialysis (HD) patients [1]. However, precise assessment of hydration status in these patients remains a major challenge for nephrologists. Clinical signs such as hypertension or edema do not correlate well with the degree of fluid overload, and newer, bedside methods, such as lung ultrasound (LUS) or bioimpedance spectroscopy, have entered into clinical practice.

Bioimpedance describes the individual fluid status/overload on the basis of an individual's normal extracellular

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volume, taking into account the body composition. This technique has been validated against solid gold standard methods [2]. Fluid overload, as assessed by bioimpedance, predicts mortality in observational studies [3–6]. Furthermore, this method may help to guide ultrafiltration prescription and therefore to improve hypertension control and arterial stiffness in HD patients [7, 8]. In addition, in a randomized trial we showed that a dry weight assessment based on bioimpedance, as compared to only clinical evaluation, was associated with reduced mortality risk [8].

Extravascular lung water is related to the ventricular filling pressure of the left ventricle, an established biomarker for risk assessment and for fluid therapy prescription in critical care units [9]. LUS is a new and simple method to appropriately evaluate extravascular lung water. The ultrasound beam is reflected by the subpleural interstitial edema, generating hyperechoic reverberation artifacts between the thickened interlobular septa and the overlying pleura, which are called B-lines. The presence of these B-lines is evaluated by scanning the anterior and lateral chest, on both sides [10]; the total sum yields a score [B-lines score (BLS)] that can objectively assess the degree of lung congestion. The use of LUS has received increasing consideration in different clinical settings, such as heart failure [10, 11] or in intensive care unit [12] patients. More recently, lung congestion, as assessed by this LUS, has been independently associated with mortality and cardiovascular events (CVE) in HD patients [13, 14], being able to improve the risk prediction for these outcomes beyond and above traditional and peculiar to end-stage renal disease (ESRD) risk factors [14].

In severe cardiovascularly compromised patients (a history of myocardial infarction with or without ST elevation or unstable angina, acute coronary syndrome or stable angina pectoris or dyspnea class III–IV NYHA) at high risk of lung congestion, the ERA-EDTA EURECA-m working group (EUropeanREnal and CArdiovascular Medicine) initiated the LUST Study (Lung Water by Ultrasound Guided Treatment in Hemodialysis Patients, Clinical Trials ID: NCT02310061) to test the utility of dry weight management guided uniquely by LUS. Our study was designed as complementary to the ongoing LUST trial, aiming to explore whether *combining LUS with BIS* may provide valid information to guide treatment in patients with *less severe* cardiovascular involvement (i.e., those who did not qualify for enrollment into the LUST). Based on the findings of the CLIMB trial [15], we hypothesized that concomitant measurement of lung congestion (as assessed by LUS) and fluid overload (as assessed by bioimpedance) might be useful (in this type of patients) to treat less severe degrees of lung congestion, while at the same time avoiding the risk of hypovolemia and clinically unapparent underperfusion for sensitive vascular beds (such as coronaries and cerebrovascular system) [15]. Herein we describe the results of this trial.

Methods

Study design

The BUST Study (Extravascular Lung Water Monitoring by Combined Bioimpedance and Ultrasonography as a Guide for Treatment in Hemodialysis Patients) was a prospective, randomized, open-label clinical trial in patients performing HD in Iasi, Romania (Clinical Trials ID – NCT 01,815,762). We included in this study all eligible patients from two HD centers.

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. All patients signed informed consent forms, and the study was approved by the 'Grigore T. Popa' University of Medicine and Pharmacy Ethics Committee.

Study population

The inclusion criteria were patients aged >18 years receiving thrice-weekly HD for more than 3 months. Being the trial complementary to LUST, the main exclusion criteria were the presence of severe cardiac failure (NYHA class III–IV), past myocardial infarction, stable or unstable angina, and acute coronary syndrome. Due to bioimpedance assessment limitation, we excluded patients with metallic joint prostheses, cardiac stent or pacemakers, decompensated cirrhosis, pregnancy, and limb amputations, as bioimpedance cannot be accurately performed in such cases. Due to LUS measurement limitation, we also excluded patients with known persistent pleurisy, pulmonary fibrosis or pneumectomy. Other exclusion criteria were malignancy, active infections, temporary or permanent catheter as a vascular access, mental incompetence, and unwillingness to participate in the study (Fig. 1).

The BUST-guided intervention

The intervention in the BUST was different from that of the LUST study. Patients were randomized 1:1 to have a dry weight assessment based on clinical (control) or LUS–bioimpedance (active)-guided protocol. In the control group, post-dialysis dry weight was adjusted based on clinical criteria only (blood pressure, presence of edema, intradialytic hypotension, cramps, etc.) and in the active group the target weight was prescribed using LUS and bioimpedance evaluation (Fig. 2).

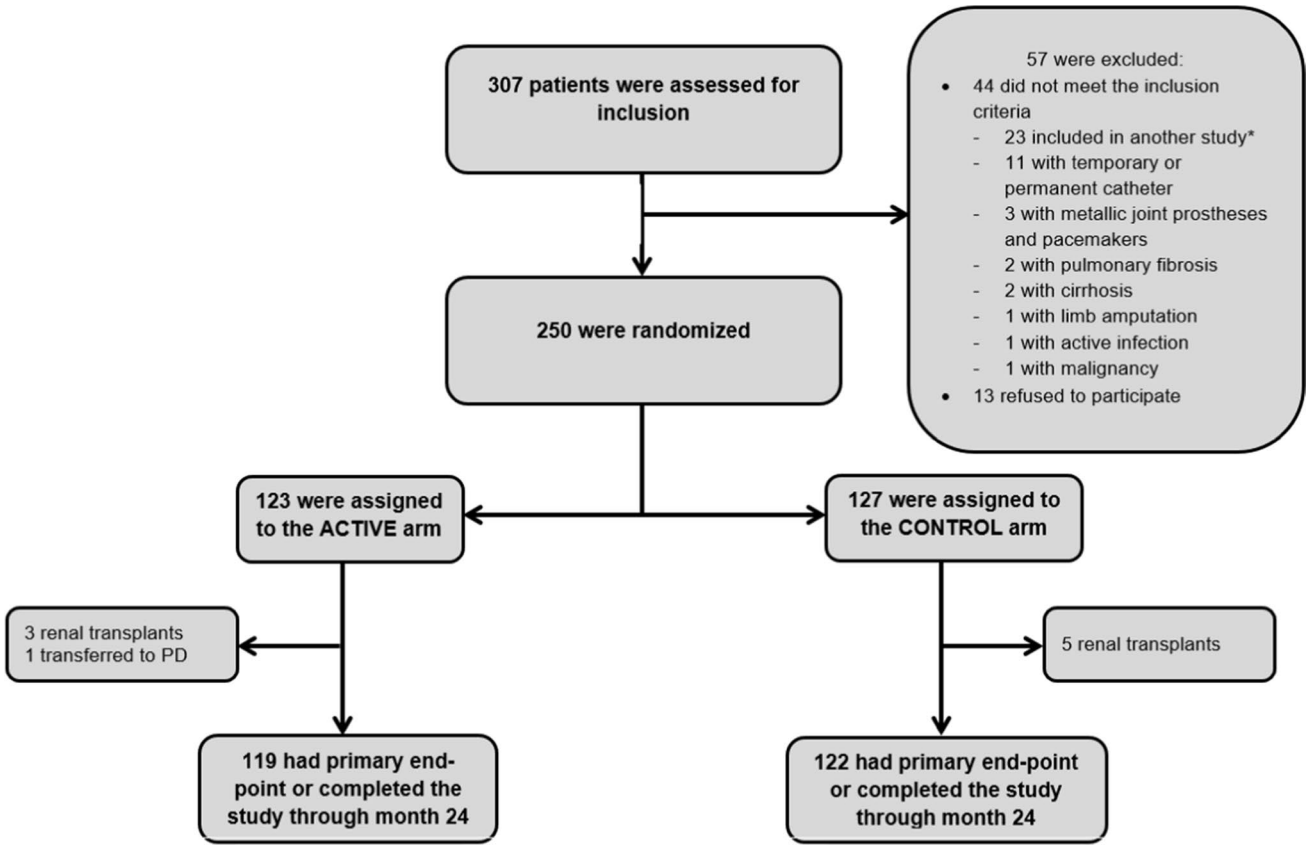

Fig. 1 Consolidated standards of reporting trials (CONSORT) flow diagram. *These patients had atleast one of the following: severe cardiac failure (NHYA class III–IV), past myocardial infarction, stable or unstable angina and acute coronary syndrome and were included in the LUST study.

In patients randomized to the active arm of the study, the ultrasound BLS was measured before dialysis by three trained physicians (DS, LV, and MA) and these measurements were used to titrate ultrafiltration prescription. In patients presenting moderate to severe lung congestion (≥15 BLS pre-dialysis), LUS measurements were repeated once a week until the treatment goal was achieved (<15 BLS pre-dialysis) and once a month thereafter. The same (monthly) monitoring frequency was adopted also in patients without pulmonary congestion at pre-dialysis baseline (<15 BLS). Furthermore, the use of the technique was allowed whenever its application was deemed useful to assume clinical decisions by attending physicians. Patients in the active arm of the study without evidence of lung congestion at baseline who developed pulmonary congestion (≥15 BLS) during the trial received the same treatment contemplated for those with lung congestion at baseline during the trial. The treatment goal was pursued by ultrafiltration intensification realized within the same HD schedule (3 sessions × 4 h/week) or, if not tolerated, by extra-dialyses, according to individual tolerance and feasibility. In case of clinical hypovolemia (persistent cramps, hypotension, etc.), *additional* dry weight adjustments were performed according to the bioimpedance measurement, provided that the patients are below 15 BLS. We considered this addition necessary in order to be able to increase the dry weight in patients with a persistent BLS < 15 and avoid underperfusion.

Patients in the control arm of the study were followed up and managed strictly with standard criteria according to current recommendations; the use of LUS/bioimpedance assistance was not allowed in these patients.

A computerized random-generator method was used to allocate patients to each group. The length of the recruitment period was one month, and the study was completed when all surviving patients had a follow-up of 24 months.

Primary and secondary outcomes

The primary outcome in BUST differed from that of the LUST study and was to assess the effect of a LUS–bioimpedance-guided dry weight adjustment protocol on a composite of all-cause mortality and first CVE (including

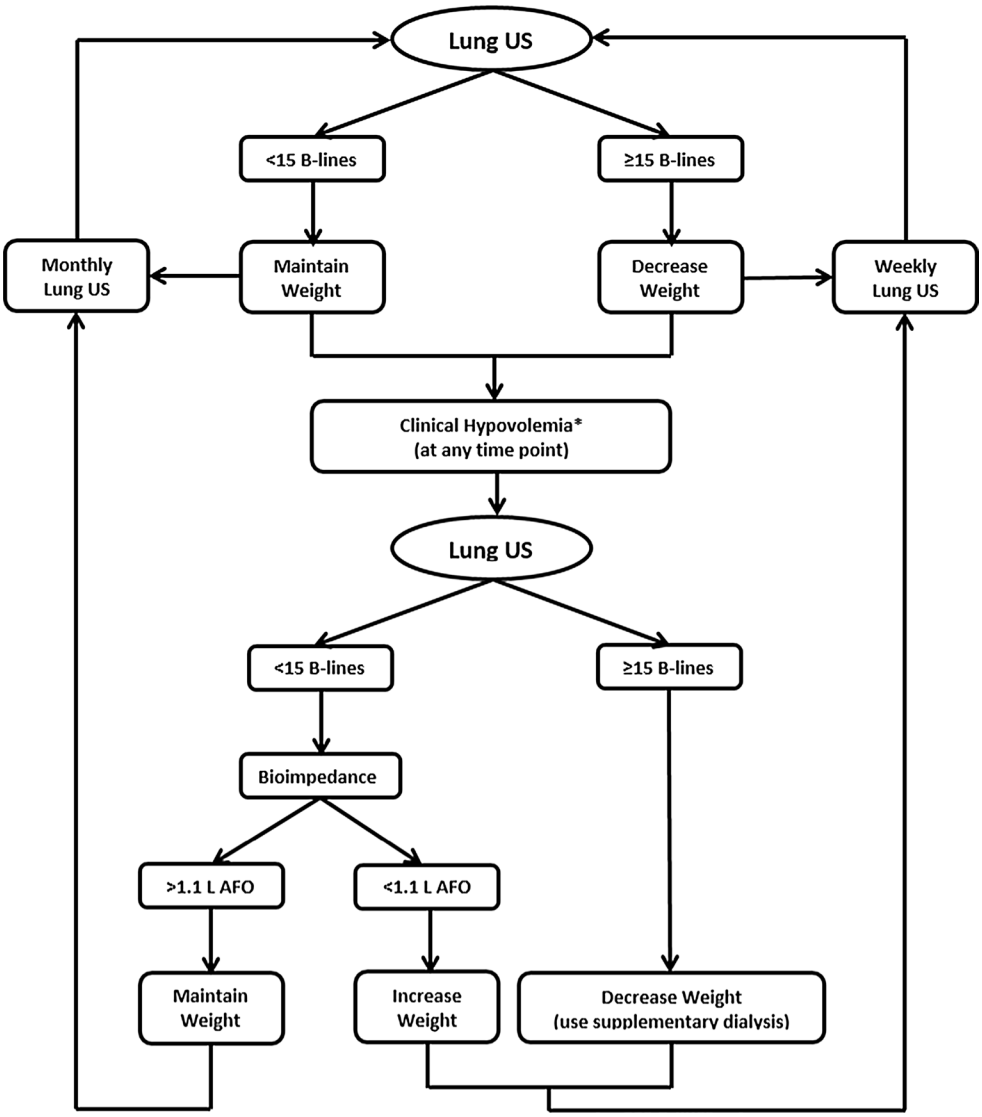

Fig. 2 BUST operating protocol. *AFO* absolute fluid overload, *US* ultrasound. *Persistent cramps, post-dialysis hypotension

death, stroke, and myocardial infarction). A cardiovascular death is counted once in the primary and as both a death and a CVE in the secondary analysis (see below). Information on these outcomes was obtained by independent investigators unaware of the baseline parameters and group randomization.

The secondary objectives were all-cause mortality, CVE, all-cause hospitalization, dialysis-related adverse events (intradialytic symptomatic hypotension and cramps episodes, pre-dialytic dyspnea episodes—present/absent, vascular access thrombosis), changes in N-terminal pro-brain natriuretic peptide (NT-proBNP) and high sensitivity cardiac troponin T (hs-cTnT), hemoglobin, C-reactive protein (CRP), calcium, phosphorus, and impact on arterial stiffness (PWV), and on fluid compartments, as assessed by bioimpedance, during the study follow-up (24 months). All patients underwent serial bioimpedance assessments, but the results were disclosed to clinicians only for the interventional arm in case of clinical hypovolemia.

Due to logistic issues, we were not able to perform echocardiographic measurements and apply health-related quality of life questionnaires.

Treatment characteristics

Synthetic high-flux dialyzers were used for all patients included in the study (FX60 and FX80—Fresenius Medical Care, Bad Homburg, Germany), and all dialysis sessions were performed with ultrapure dialysis fluids, defined as <0.1 CFU/ml and <0.03 EU/ml. The composition of dialysate was the same in both groups—sodium 138 mmol/L, potassium 2.0 mmol/L, calcium 1.50 mmol/L, magnesium 0.5 mmol/L, chloride 106 mmol/L, bicarbonate 32 mmol/L, acetate 6 mmol/L, and glucose 1.0 g/L.

Study variables

The information on vascular access and comorbidities at baseline was obtained from the electronic database of the dialysis provider and from the patients' charts. We have also calculated the Charlson Comorbidity Index and then categorized it into 2 groups: 2 (severe renal disease only) or more [16].

The following *laboratory data* were recorded at baseline and every 3 months: hemoglobin, CRP, calcium, phosphorus. All these laboratory determinations were performed locally by standard procedures in certified laboratories.

Fluid status estimations were also recorded at baseline and at every 3 months using the BIS device (BCM®—Fresenius Medical Care, Bad Homburg, Germany). Trained nurses blinded to patients' group allocation performed all measurements. The extracellular water (ECW), intracellular water (ICW) and TBW were determined as previously described [2]. Absolute fluid overload (AFO) was defined as the difference between the expected patient's ECW under normal physiological conditions and the actual ECW, whereas the relative fluid overload (RFO), used to facilitate comparison between patients, was defined as the absolute fluid overload to extracellular water ratio (AFO/ECW). All measurements were performed before the midweek dialysis session.

The PWV was performed by two trained physicians (SH and IN) using the SphygmoCor® device (AtCor Medical, Westmead, Sydney, Australia) and was computed from carotid and femoral artery waveforms recorded consecutively, using an electrocardiogram-gated signal and anthropometric distances. All PWV measurements were done twice in a row on each occasion, and the results were averaged.

Serum NT-proBNP and hs-cTnT levels were evaluated at baseline, at 12 months and at the study end, before a midweek dialysis session. The hs–cTnT determination was made using a fifth-generation electrochemiluminescence assay (Elecsys, Cobas e411 analyzer, Roche Diagnostics). NT-proBNP was analyzed centrally using the Roche Elecsys® kit, an electrochemiluminescence 'sandwich' immunoassay based on polyclonal antibodies against NT-proBNP.

Clinical monitoring included intradialysis symptoms, hospital admissions for any reasons, and withdrawals from the study and their causes.

Sample size calculation

For sample size estimation, we followed the subsequent assumptions: 2 year patient incidence in the primary outcome of 20%, and a two-sided type I error of 5%, an 80% power to detect a decrease of 40% in the annual rate of the primary endpoint in the patients with the dry weight assessment on the basis of the BLS protocol. The assumption for the 40% risk reduction was based on previous studies [14, 17]. We estimated the 20% rate for the primary endpoint on the basis of a 14% annual combined mortality and CVE rate reported in the units included in the study. Thus, we estimated that the required sample size would be of 480 patients.

Based on the work by Onofriescu et al. [5], the final study population fulfilled initial power calculations for detecting a significant difference between groups in PWV of 2 m/s. Such a change in PWV was computed in regard to mean baseline values of 9.7 m/s [5] and would require 80 patients in each group for 95% power at a 2-tailed alpha of 0.05.

Statistical analyses

Data are presented as mean ± standard deviation, median with interquartile range or number and percent frequency, as appropriate. Between-groups comparison was performed using the Chi-square test for categorical variables and by Mann–Whitney test or independent *t* test for the remaining variables, as appropriate. The normality of the distribution was assessed by the Shapiro–Wilk test.

All-cause mortality and CVE were compared between the study groups using the Kaplan–Meier method. We used the log-rank test for comparison, and the HR and the respective 95% CI were estimated from the unadjusted Cox model.

Time repeated measurements were analyzed using linear mixed models including treatment, time, and the treatment by time interaction term. Normally distributed continuous variables were assessed through mixed models for repeated measurements, adjusting by the baseline value, and for non-normally distributed data by penalized quasi-likelihood under restricted maximum likelihood models. Treatment inferences, effect estimates, and 95% CIs were taken from these models. The incidence rate and rate ratio and 95% CI were estimated by Poisson regression models.

We considered a *P* value of less than 0.05 to be significant. All statistical analyses were performed using the SPSS for Windows, version 19.0.1 (SPSS Inc., Chicago, IL, USA), and MedCalc, version 16.4.3.

Results

Baseline characteristics

During the enrollment period, we screened for eligibility all available patients that were performing HD in our dialysis units. From the 284 available patients were,

Table 1 Demographic and clinical characteristics of the study population

	All ($N = 250$)	Active ($N = 123$)	Control ($N = 127$)	P*
Age (years)	59.2 ± 14.1	59.0 ± 14.9	59.4 ± 13.3	0.73
Male, *N* (%)	116 (46.4)	58 (47.2)	58 (45.7)	0.89
Weight (kg)	71.9 ± 15.4	72.1 ± 14.7	71.6 ± 16.1	0.74
Dialysis vintage (months)	43.4 (15.3–87.1)	47.8 (15.7–87.5)	41.1 (14.7–86.0)	0.33
Diabetes, *N* (%)	48 (19.2)	27 (22.0)	21 (16.5)	0.34
Hypertensive, *N* (%)	190 (76.0)	92 (74.8)	98 (77.2)	0.77
CAD, *N* (%)	39 (15.6)	24 (19.5)	15 (11.8)	0.12
PAD, *N* (%)	39 (15.6)	18 (14.6)	21 (16.5)	0.73
Stroke, *N* (%)	23 (9.2)	14 (11.4)	9 (7.1)	0.28
CCI > 2, *N* (%)	96 (38.4)	54 (43.9)	42 (33.1)	0.08
AVF, *N* (%)	243 (97.2)	118 (95.9)	125 (98.4)	0.28
Anuric, *N* (%)	141 (53.6)	76 (61.8)	65 (51.2)	0.09

Data are expressed as mean ± SD, median with IQR or number and percent frequency

AVF arteriovenous fistula, *CAD* coronary artery disease, *CCI* Charlson comorbidity index, *PAD* peripheral artery disease

* Comparison between groups

Table 2 Biological and arterial stiffness characteristics of the study population

	All ($N = 250$)	Active ($N = 123$)	Control ($N = 127$)	P*
NT-proBNP (pg/ml)	4396.0 (1615.0–10,744.8)	4505 (1897–11,487)	4166 (1486.6–10,118)	0.41
hs-cTnT (ng/l)	36.9 (24.9–51.7)	38.1 (23.7–55.7)	35.9 (25.5–48.4)	0.74
PWV (m/s)	9.9 (7.8–11.4)	9.4 (6.7–12.0)	10.2 (9.0–11.1)	
Hemoglobin (g/dl)	11.4 ± 1.4	11.6 ± 1.5	11.3 ± 1.4	0.23
Albumin (g/dl)	3.9 ± 0.3	3.8 ± 0.4	3.9 ± 0.3	0.24
Calcium (mg/dl)	8.3 ± 0.6	8.3 ± 0.6	8.4 ± 0.7	0.13
Phosphorus (mg/dl)	5.2 (3.9–6.2)	5.1 (3.5–6.1)	5. (4.3–6.3)	0.10

Data are expressed as mean ± SD

hs-cTnT high sensitivity cardiac troponin T, *NT-proBNP* N-terminal pro-brain natriuretic peptide

* Comparison between groups

thirty-four patients were excluded before randomization because they did not meet the inclusion criteria (21 patients) or refused to participate (13 patients).The total number of included patients was 250, with 123 patients included in the active group and 127 patients in the control group (Fig. 1). Baseline demographic, clinical, biological and vascular characteristics of the entire population and in both groups are presented in Tables 1, 2 and 3. At baseline, in the active group the median BLS 7 [interquartile range (IQR) 3–12] and only 19 (15.4%) patients had a BLS higher than 15.

Table 3 Bioimpedance characteristics of the study population

	All ($N = 250$)	Active ($N = 123$)	Control ($N = 127$)	P*
AFO, L	1.2 ± 2.2	1.2 ± 1.3	1.3 ± 2.9	0.32
RFO, %	7.1 ± 10.8	7.0 ± 7.2	7.2 ± 13.4	0.30
TBW, L	33.9 ± 6.4	33.9 ± 6.2	33.8 ± 6.5	0.96
ECW, L	16.1 ± 2.9	16.2 ± 2.9	16.1 ± 3.0	0.94
ICW, L	17.7 ± 3.7	17.7 ± 3.7	17.7 ± 3.8	0.97

Data are expressed as mean ± SD

AFO absolute fluid overload, *ECW* extracellular water, *ICW* intracellular water, *RFO* relative fluid overload, *TBW* total body water

* Comparison between groups

Primary outcome

During a mean follow-up period of 21.3 ± 5.6 months, there were 54 (21.6%) composite events (all-cause mortality and CVE) in the entire population, with a 2 year rate of 22.8 and 20.5% in the active and control groups, respectively. These results are translated into a nonsignificant 9% increase in the risk of this outcome in the active arm (HR = 1.09, 95% CI 0.64–1.86, $p = 0.75$) (Fig. 3a). Furthermore, in the active group, baseline BLS was not significantly associated with the primary outcome in the survival analysis.

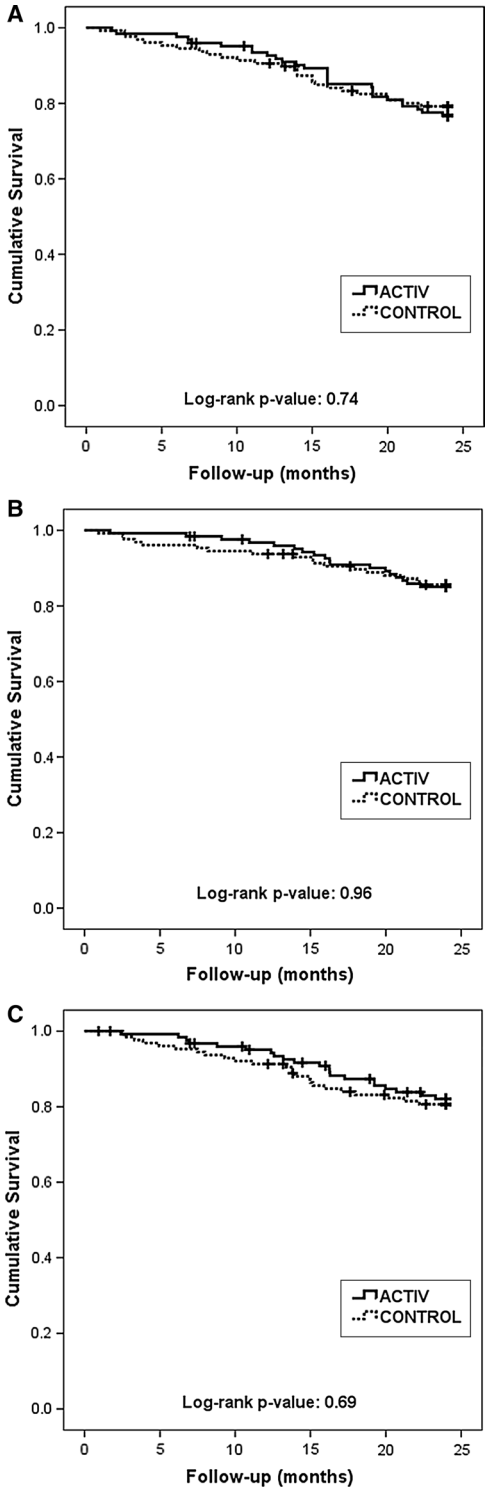

Fig. 3 Kaplan–Meier curves comparing the two groups for the time to the first primary composite outcome (Panel **a**), all-cause mortality (Panel **b**), and cardiovascular events (Panel **c**)

Secondary outcomes

All-cause mortality and cardiovascular events

When analyzing separately the all-cause mortality outcome, during a mean follow-up period of 22.2 ± 4.7 months, there were registered 36 (14.4%) deaths. The 2 year all-cause mortality rates in the active and control group were 14.6 and 14.2%, respectively, implying a nonsignificant 2% increase in the risk of this outcome (HR = 1.02, 95% CI 0.53–1.96, $p = 0.96$) (Fig. 3b). In regard to the CVE outcome, the mean follow-up period was 21.4 ± 5.5 months. During this period, there were 45 (18%) events in the entire study population, with 2 year CVE rates of 17.1 and 18.9% in the active and control group, respectively. Similarly, these results are translated into a nonsignificant 11% reduction in the risk of CVE (HR = 0.89, 95% CI 0.49–1.59, $p = 0.69$) (Fig. 3c). Similar to the primary outcome, in the active group, the baseline BLS was not associated with any of these secondary outcomes in the Cox survival analysis.

Hospitalizations and dialytic events

During the follow-up, there were 193.3 (95% CI 175.8–212.0) episodes per 100 patient-years of dry weight adjustment according to BLS in the active group. There were only 20 (16.3%) patients in the active arm that had a BLS ≤ 15 during the *entire* follow-up. In regard to the bioimpedance post-dialysis weight adjustment, there were 620.7 (95% CI 588.9–653.9) episodes per 100 patient-years of *increase* in the dry weight, as guided by bioimpedance-derived ideal dry weight and BLS < 15. The rate of intradialytic hypotension, all-cause hospital admissions, and vascular access thrombosis was nonsignificantly different between the two arms (Table 4). However, patients in the active arm had a 19% lower relative risk of pre-dialytic dyspnea (rate ratio—0.81, 95% CI 0.68–0.96), but a 26% higher relative risk of intradialytic cramps (rate ratio—1.26, 95% CI 1.16–1.37) (Table 4).

Biochemical parameters and arterial stiffness

Serum NT-proBNP and hs-cTnT levels did not significantly change during the follow-up and did not differ between the study arms (Table 5). However, pulse wave velocity (PWV) significantly increased during the study period, irrespective of treatment group allocation (Table 5). There were no significant changes in regard to hemoglobin, CRP, calcium or phosphorus levels during the 2 years of follow-up (Supplementary Table 1).

Table 4 Secondary outcome data for the entire cohort

	Control group ($N = 127$) (236.3 Patient-years at risk)		Active group ($N = 123$) (232.3 Patient-years at risk)		Rate ratio (95% CI)
	No. of events	No. of events/100 patient-years	No. of events	No. of events/100 patient-years	
Intradialytic hypotension	1035	438.1	1104	475.3	1.08 (0.99–1.18)
Intradialytic cramps	1056	446.9	1313	565.2	1.26 (1.16–1.37)
Pre-dialytic dyspnea	302	127.8	240	103.3	0.81 (0.68–0.96)
Hospitalizations	89	37.7	103	44.3	1.18 (0.88–1.58)
Vascular access thrombosis	13	5.5	20	8.6	1.56 (0.74–3.42)

Table 5 Biomarker levels and arterial stiffness outcomes

	Length of follow-up			p*	$p^{\dagger}$
	Baseline	12 months	24 months		
NT-proBNP (pg/ml)					
Control	8722.2 (6478.5–10,965.8)	9123.6 (6387.6–11,859.6)	12,186.4 (9256.6–15,115.6)	0.09	0.72
Active	8896.3 (6944.8–10,847.8)	9428.4 (6642.8–12,213.9)	10,728.6 (7775.4–13,680.7)		
$p^{\ddagger}$	–	0.88	0.49		
Hs-cTnT (ng/l)					
Control	42.9 (37.9–47.8)	45.4 (40.1–50.7)	44.6 (38.9–50.2)	0.14	0.65
Active	44.0 (38.7–49.3)	49.4 (43.9–54.7)	45.0 (39.4–50.7)		
$p^{\ddagger}$	–	0.30	0.91		
PWV (m/s)					
Control	10.3 (9.8–10.9)	11.0 (10.0–12.1)	12.3 (11.1–13.6)	<0.001	0.32
Active	9.7 (9.1–10.4)	11.5 (10.8–12.3)	12.6 (11.7–13.5)		
$p^{\ddagger}$	–	0.45	0.77		

Data are presented as mean (95% CI) at baseline, and least-squares mean (95% CI) at 12 months and 24 months. Analysis was conducted using a mixed model for repeated measures

* p value for time effect—trend over time in both arms

† p value for treatment × time interaction—evaluates if changes in one arm are different from the changes in the other arm

‡ p value for comparison between arms at each moment

Dry weight and bioimpedance parameters

Dry body weight did not change during the study (Supplementary Table 2). However, when analyzing the hydration status, ICW decreased from month 0 to month 24 in both arms, while AFO and RFO increased during the same period. TBW also increased in both groups, but to a lesser extent in the control group (Supplementary Table 2).

When analyzing only the patients from the active arm, we observed that those patients that did not require a change in the dry weight during the study ($N = 45$), according to the BLS, had lower RFO values than those patients in which dry weight was reduced ($N = 73$), both at baseline, but also during the follow-up ($p = 0.003$, Supplementary Table 3). As shown above, RFO increased in the active arm, irrespective of the dry weight adjustments made according to the BLS (Supplementary Table 3).

Discussion

In this prospective, randomized control study, we found that in HD patients a combined LUS–bioimpedance-guided dry weight adjustment protocol was not associated with a reduction in all-cause mortality and/or CVE compared to the standard clinical approach. To our knowledge, this is the first randomized trial that evaluated LUS use for volume control in this population.

LUS recently emerged as an important tool that could be added/replace the clinical evaluation, to improve

hemodynamic profiling and treatment optimization. BLS has been shown to correlate to cardiac function or NT-proBNP in patients with acute dyspnea [18] or heart failure [11] and can also help differentiate cardiogenic versus non-cardiogenic dyspnea [19–21]. In patients with heart failure and coronary artery disease, the use of LUS predicted death and CVE [22, 23], and this ability was superior to that of standard echocardiographic parameters, diabetes or NYHA score [22].

In HD patients, BLS is characterized by good interobserver and interprobe agreement [24] and has been correlated with physical performance [25], left ventricular ejection fraction [24] or bioimpedance-derived parameters [13]. Similar to studies performed in patients with cardiac disease, BLS was associated in ESRD patients with all-cause mortality and CVE [13, 14], independently of clinical and biological parameters [14] or echocardiographic and bioimpedance-derived characteristics [13]. Although the addition of BLS to traditional and CKD-related risk factors offered limited discrimination gain, it improved the reclassification abilities of the baseline model for death and CVE [14], suggesting that this method may add important data for the risk quantification in ESRD patients.

The fact that in our study a primarily BLS-guided protocol did not result in a lower all-cause mortality or CVE could have several explanations. As compared to the seminal study by Zoccali et al. [14], our patients were younger (59 vs. 65 years), with a lower dialysis vintage and prevalence of diabetes (19.2 vs. 29%) and without any severe heart failure (our study included only patients with NYHA classes I and II). These characteristics form a particular population, and although we did not evaluate cardiac function directly, it is plausible that our patients had better cardiac function, with a subsequent lower risk of volume-dependent clinical outcomes. In line with this ascertainment, baseline NT-proBNP and hs-cTnT levels observed in our patients were similar to other HD populations without significant cardiac disease [26]. In HD patients, both NT-proBNP and hs-cTnT are associated with echocardiographic parameters [26–29] and are able to properly identify patients at an increased risk of adverse events [30–32]. The baseline BLS score was low (median 7) and the vast majority of patients had less than 15 B-lines, further supporting this hypothesis. The usefulness of BLS in HD patients with myocardial ischemia or severe heart failure, a population at a higher risk of hemodynamic or pulmonary congestion, is currently tested in the ongoing LUST study.

The neutral results of BLS-derived adjustments in dry weight on study outcomes could also be explained by the insufficient impact of this strategy on total body water/body water components. During the follow-up, despite maintaining patients below 15 BLS score in the intervention group, we observed a similar increase between the two study arms in AFO or RFO—two important parameters of fluid overload that were shown to be associated with mortality. Onofriescu et al. [8] previously demonstrated that a bioimpedance-derived dry weight adjustment, leading to a significant decrease in fluid overload estimates in the active arm, was associated with a reduction in arterial stiffness and even death. Corroborating these findings would suggest that in the absence of an adequate control for overall fluid overload (as assessed by bioimpedance), there are no beneficial effects of maintaining a normal BLS in HD patients. To further strengthen this hypothesis, in the study by Onofriescu et al. [8], an increase in PWV in both groups has been observed after the end of the intervention period and a similar pattern was observed during the 2 years of follow-up in our study, irrespective of treatment allocation. In addition, our group recently showed that LUS has lower sensitivity despite better specificity for all-cause mortality compared to bioimpedance spectroscopy [6], suggesting that BIS could be used as a better routine screening tool, identifying high-risk patients in which additional investigations (like LUS) should be performed.

Limitations

Our study has limitations and strengths. Firstly, our study was underpowered for the primary endpoint. Due to technical and logistical issues, we were able to include only patients from two dialysis units. However, the results clearly show that using this protocol does not change the risk of any of the outcomes under investigation. Secondly, our study population comes from only one part of Romania and has included selected patients (without severe cardiac failure, inappropriate vascular access) and as such our results cannot be inferred to other HD populations. In line with this assumption, the baseline BLS was low, with a minority of patients having an increased baseline score, implying that tracking modest degrees of water accumulation in the lung could be immaterial to clinical outcomes. Thirdly, we did not perform an echocardiographic evaluation, as this would have added important information in the relationship between fluid status—cardiac function. However, we have investigated the effect on NT-proBNP levels, a known biomarker strongly associated with cardiac structure and function in HD patients [27, 33]. Fourthly, we did not assess the exact number of dry weight changes in the control group.

Conclusions

In conclusion, the BUST study shows that a LUS-guided dry weight adjustment protocol, as compared with clinical

evaluation, does not reduce all-cause mortality and/or CVE in HD patients. In addition, this intervention does not have any positive influence on bioimpedance-assessed fluid status, PWV, or NT-proBNP and cTnT levels. If the effect of such an intervention is beneficial in higher-risk HD patients, it will be established in the ongoing LUST trial.

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Compliance with ethical standards

Conflict of interest Prof. Dr. Adrian Covic is an honorary speaker for Fresenius Medical Care. Fresenius Medical Care is the manufacturer of the BCM® device and was not involved in any way in the study.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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