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ORIGINAL PAPER

Bioimpedance analysis versus lung ultrasonography for optimal risk prediction in hemodialysis patients

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Abstract Fluid overload is associated with adverse outcomes in hemodialysis (HD) patients. Two bedside methods are increasingly utilized to evaluate objectively fluid status—bioimpedance and lung ultrasonography, but there is no available direct, head-to-head comparison of their prognostic significance. Importantly, their predictive abilities have never been tested in a HD population, alongside those of a classic model that also incorporates established echocardiographic parameters of increased mortality risk. Between 26 May 2011 and 26 October 2012, we included in the study 173 patients undergoing chronic HD treatment for at least 3 months in a single dialysis unit. Relative fluid overload (RFO) and B-lines score (BLS) were used as candidate predictors. From Cox survival analysis we evaluated the increase in the predictive abilities for all-cause mortality of adding continuous RFO or BLS to a model including conventional predictors. 31 patients (17.9 %) died during a median follow-up of 21.3 (interquartile range 19.9–30.3) months. All Cox models showed good calibration. The C statistic for the all-cause mortality prediction increased significantly when the RFO was included into the baseline model (ΔC statistics 0.058 95 %CI = 0.003–0.114), but not when the BLS was included into the baseline model. Only the model that incorporated RFO showed significantly better risk reclassification abilities than the baseline model (IDI = 3.6 % and continuous NRI = 24.8 %). Fluid overload, as assessed by bioimpedance, and not by lung ultrasonography, improves risk prediction for death, beyond classical and echocardiographic-based risk prediction scores/parameters.

Keywords Lung ultrasonography · Bioimpedance · Fluid status · Echocardiography · Hemodialysis · Survival

Introduction

End-stage renal disease (ESRD) has an unacceptably high mortality rate [1]. The yearly mortality rate in dialysis patients, mostly related to cardiovascular causes, is between 5 and 27 % [2] and although it has decreased in recent years [1], it still remains higher than that of many cancers or heart failure. Numerous risk factors—both common and ESRD specific—contribute to this high risk of death. Among ESRD-specific contributors, fluid overload is now receiving growing attention, as it is one of the modifiable risk factors that could improve patients' outcomes. It is pathophysiologically related to hypertension, increased arterial stiffness, left ventricular hypertrophy or heart failure, ultimately leading to a higher mortality rate [3]. In making an accurate assessment of fluid overload, two simple, bedside methods that evaluate more objectively the fluid status show promise in clinical research in recent years: bioimpedance and lung ultrasonography.

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Bioimpedance spectroscopy, defines the individual fluid status/overload on the basis of an individual's normal extracellular volume, taking into account the individual's body composition. Recent studies indicate that the fluid overload indices derived from bioimpedance measurement are independent predictors of mortality in prevalent hemodialysis (HD) patients [4], and importantly, using this method to actively guide HD patients toward normohydration, blood pressure, arterial stiffness [5, 6] and even survival [6] may be improved.

The second bedside evaluation—lung echography, through B-lines score (BLS) evaluation, detects extravascular lung water. Although this represents a relatively small component of total body water (TBW), it is fundamental as the water content of the lung interstitium is strictly dependent on the filling pressure of the left ventricle. BLS have been shown to be associated with N-terminal pro-brain natriuretic peptide (NT-proBNP) [7] and diastolic function in patients with acute dyspnea [8] and after a stress test; in addition, this method also predicts all-cause mortality and cardiac events in HD patients [9].

HD patients represent a selected population with a unique risk factor profile so that predictive models developed in the general population may not be appropriate for individuals with ESRD [10]. In addition, there is no available direct, head-to-head comparison of the predictive capabilities for death, between bioimpedance and lung ultrasonography. Most importantly, their predictive abilities have never been tested in a HD population, alongside those of a classic model that also incorporates established echocardiographic parameters of increased mortality risk.

Methods

Patients

Between 26 May 2011 and 26 October 2012, we invited all patients undergoing chronic HD treatment for at least 3 months in a single dialysis unit, to take part in this study. We excluded patients under 18 years old, with systemic infections and terminal neoplasia; subjects with metallic joint prostheses, cardiac pacemakers or stents, decompensated cirrhosis and limb amputations were also excluded, since accurate bioimpedance assessment cannot be performed in patients with these conditions.

From an overall eligible 215 HD patients we excluded 42 patients because of limb amputation (N = 8), decompensated cirrhosis (N = 4) or presence of a cardiac pacemaker or stent (N = 10). Twenty additional patients did not provide informed consent and were not included in the study. Details of the final patient population (N = 173) are presented in Tables 1, 2, 3 and 4. All included patients performed 4 h HD session × three times per week, using high-flux Fresenius Polysulfone® membrane dialyzers. Biochemical parameters were determined pre-dialysis, at the beginning of each month. The study protocol was approved by the Ethics Committee of University Hospital "Dr C.I. Parhon" (Iasi, Romania).

All included patients were followed-up for time-to-event analysis until occurrence of death. Patients were censored at the last follow-up (31 May 2014) or if they moved to another dialysis unit, switch to peritoneal dialysis or received a kidney transplant.

B-lines score

Lung ultrasonography examinations were performed before dialysis, with patients in the near-to-supine or supine positions. Ultrasound scanning was performed for a total of 28 positions per complete examination, as previously described [11]. At every scanning site, B-lines could be counted from 0 to 10. Zero was defined as a complete absence of B-lines in the investigated area, while the full white screen is considered, when using a cardiac probe, as corresponding to 10 lung comets. The sum of the B-lines yielded a score denoting the extent of extravascular fluid in the lung [12]—see the Supplementary Fig. 1 with two measurements performed in two different areas in one patient from our study.

Bioimpedance spectroscopy

The hydration state and the body composition were assessed using a portable whole body bioimpedance spectroscopy device (BCM—Fresenius Medical Care D GmbH). This device measures the impedance spectroscopy at 50 frequencies. Measurements were performed before dialysis.

Two trained physicians blinded to patients' daily management performed all measurements. The extracellular water (ECW), intracellular water (ICW) and TBW were determined as previously described [13]. 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).

Echocardiography

Echocardiographic measurements were performed on an interdialytic day (second interdialytic interval) by two trained echocardiographers that were unaware of lung ultrasonography and bioimpedance results. All echocardiographic evaluations were made according to the

Table 1 Demographic and clinical parameters of the study population

	All (N = 173)	Survivors (N = 142)	Deceased (N = 31)	*p**
Age (years)	57.9 ± 14.0	57.1 ± 13.8	61.8 ± 14.9	0.05
Dialysis vintage (months)	48.9 (17.5–96.1)	50.6 (20.2–95.1)	44.5 (14.3–97.9)	0.46
Weight (Kg)	69.5 (58.5–81.9)	69.7 (58.5–81.9)	66.6 (58.6–78.6)	0.70
Anuric [N (%)]	74 (42.8)	62 (43.7)	12 (38.7)	0.61
Male [N (%)]	85 (49.1)	69 (48.6)	16 (51.6)	0.76
Smoking [N (%)]	56 (32.4)	43 (30.3)	13 (41.9)	0.21
Diabetes [N (%)]	36 (20.8)	25 (17.6)	11 (35.5)	**0.03**
Hypertension [N (%)]	134 (77.5)	112 (78.9)	22 (71.0)	0.35
SBP (mmHg)	143.3 ± 22.9	144.0 ± 23.2	139.9 ± 21.9	0.37
DBP (mmHg)	74.8 ± 15.0	76.2 ± 15.1	68.5 ± 13.3	**0.01**
Heart rate (beats/min)	74.0 (67.0–82.0)	74.0 (67.0–81.0)	76.0 (69.0–85.0)	0.27
NYHA class [N (%)]	1–2: 133 (76.9)	1–2: 116 (81.7)	1–2: 17 (54.8)	**0.001**
	3–4: 40 (23.1)	3–4: 26 (18.3)	3–4: 14 (45.2)	
HCV [N (%)]	43 (24.9)	36 (25.4)	7 (22.6)	0.75
HBV [N (%)]	14 (8.1)	10 (7.0)	4 (12.9)	0.28
BLS	9.0 (3.0–14.0)	8.0 (3.0–13.0)	11.0 (3.0–29.0)	0.12

Significant values are indicated in bold

BLS B-lines score, *DBP* diastolic blood pressure, *HBV* hepatitis B virus, *HCV* hepatitis C virus, *NYHA* New York Heart Association, *SBP* systolic blood pressure

* Comparison between survivors and deceased

Table 2 Biological parameters of the entire study population

	All (N = 173)	Survivors (N = 142)	Deceased (N = 31)	*p**
Hemoglobin (g/dl)	11.5 ± 1.6	11.5 ± 1.5	11.6 ± 1.9	0.76
WBC ($\times 10^3$/mmc)	6.2 (5.2–7.7)	6.2 (5.1–7.7)	6.9 (5.5–7.9)	0.30
Albumin (g/dl)	3.9 (3.7–4.1)	3.9 (3.7–4.1)	3.8 (3.5–3.9)	0.06
hsCRP (mg/l)	0.4 (0.2–1.0)	0.4 (0.2–1.0)	0.8 (0.3–1.2)	**0.02**
Calcium (mg/dl)	8.5 (8.1–8.8)	8.5 (8.2–8.8)	8.5 (8.1–8.9)	0.86
Phosphorus (mg/dl)	5.2 (4.2–6.6)	5.2 (4.3–6.7)	5.1 (3.7–5.9)	0.15
iPTH (ng/l)	306.2 (163.1–482.8)	319.4 (184.2–473.6)	197.0 (93.9–632.9)	0.13
Cholesterol (mg/dl)	171.0 (146.5–212.0)	170.5 (147.0–210.5)	173.0 (141.0–217.0)	0.86
Triglycerides (mg/dl	131.6 (93.9–189.5)	132.1 (91.7–195.4)	130.8 (96.3–158.1)	0.60
eKt/V	1.5 (1.3–1.7)	1.5 (1.4–1.7)	1.5 (1.2–1.7)	0.46

Significant values are indicated in bold

hsCRP high-sensitivity C-reactive protein, *iPTH* intact parathyroid hormone, *WBC* white blood cells

* Comparison between survivors and deceased

Table 3 Bioimpedance analysis of the entire study population

	All (N = 173)	Survivors (N = 142)	Deceased (N = 31)	*p**
TBW (L)	32.0 (27.8–36.6)	32.1 (27.9–36.8)	30.6 (26.8–33.8)	0.14
ECW (l)	15.2 (13.5–17.9)	15.2 (13.5–18.0)	15.0 (13.0–17.0)	0.63
ICW (l)	16.4(14.3–18.8)	16.6 (14.6–19.1)	15.7 (13.0–17.0)	**0.03**
AFO (l)	1.2 ± 1.3	1.1 ± 1.4	1.7 ± 1.1	**0.03**
RFO (%)	7.4 ± 7.9	6.7 ± 8.1	10.7 ± 6.1	**0.01**

Significant values are indicated in bold

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

* Comparison between survivors and deceased

Table 4 Echocardiographic parameters of the entire study population

	All (N = 173)	Survivors (N = 142)	Deceased (N = 31)	p*
LVMI (g/m^2)	155.4 ± 39.6	152.7 ± 36.6	167.9 ± 42.2	0.05
LAVI (ml/m^2)	38.2 ± 6.6	37.5 ± 5.9	40.9 ± 8.8	0.05
E/E′	15.6 ± 6.3	15.4 ± 6.3	16.8 ± 6.3	0.35
IVST (mm)	12.0 (10.6–13.0)	12.0 (10.6–13.0)	12.4 (11.0–14.5)	0.22
LVPWT (mm)	11.6 (10.3–13.0)	11.6 (10.3–12.9)	11.9 (10.9–14.0)	0.09
LVEF (%)	60.0 (57.0–65.0)	60.0 (56.8–65.0)	60.0 (57.0–65.0)	0.72

IVS interventricular septum thickness, *LAVI* left atrial volume index, *LVMI* left ventricular mass index, *LVPWT* left ventricular posterior wall thickness, *LVEF* left ventricular ejection fraction

* Comparison between survivors and deceased

recommendations of the American Society of Echocardiography [14].

Statistical analysis

All calculations were made using SPSS for Windows, version 19.0.1, Chicago, IL and R (version 3.1.2)—package for statistical analysis (Foundation for Statistical Computing, Vienna, Austria).

Data are expressed as mean ± SD, median and interquartile range or as percent frequency, as appropriate. Between-group comparisons were performed for the categorical variables with the χ^2 test, 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 and logarithmic conversion was performed for non-normally distributed variables.

To determine the optimal cut-off points for the RFO or BLS as predictors of all-cause mortality we used the method described by Contal and O'Quigley [15]. From this analysis, we found a cut-off of 6.88 % for RFO and of 22 for BLS, respectively.

Time-to-event analysis of death was performed using Kaplan–Meier and Cox analyses, including adjustment for potential confounding factors. The Kaplan–Meier curves were compared using the log-rank test. In the multivariate Cox models, we adjusted for all variables that correlated to the study outcomes with $p < 0.05$ at univariate Cox analyses [the presence of NYHA class 3 or 4, diabetes, high-sensitivity C-reactive protein (hs-CRP) levels and left ventricular mass index (LVMI)].

From Cox proportional hazards models including conventional predictors (the presence of NYHA class 3 or 4, diabetes, hs-CRP levels and LVMI) with and without continuous RFO or BLS, we evaluated the C statistic difference, continuous NRIs, and IDI using methods accounting for censoring [16, 17]. We used the Hosmer and Lemeshow test to evaluate the calibration of the models. Additionally, we calculated the Bayesian information criterion (BIC) and the Akaike information criterion (AIC) for each Cox model; there is no statistical test that compares different BIC or AIC estimations, and a lower value indicates a better fitted model.

To avoid the problem of overfitting due to the low number of incident outcomes, we performed bootstrapping validation, in order to determine the confidence intervals for estimating β in the Cox proportional hazard regression.

Results

One hundred and seventy-three patients were included in this analysis. Overall demographic, biological, bioimpedance and echocardiographic parameters of the study population are presented in Tables 1, 2, 3 and 4. The most frequent cause of ESRD was chronic glomerulonephritis (33.4 %), followed by diabetic nephropathy (16.2 %).

During the follow-up 31 patients (17.9 %) died. The deceased patients had a higher prevalence of diabetes and a more severe baseline NYHA class. They also had significantly lower diastolic blood pressure, higher hs-CRP levels, and increased left atrium volume and fluid overload (both in absolute and relative values). However, there was no difference in regard to the BLS between these two groups ($p = 0.12$).

Survival and prognostic analysis

The median time of observation was 21.3 (interquartile range 19.9–30.3) months. The RFO cut-off had better sensitivity, but lower specificity for the outcome than the BLS cut-off (74.2 %, 95 % CI 55.4–88.1 % vs. 32.3 %, 95 % CI 16.7–51.4 % and 52.1 %, 95 % CI 43.6–60.6 % vs. 87.3 % 95 % CI 80.7–92.3 %, respectively). Using these cut-offs, patients who had more than 22 BLS or a RFO greater than 6.88 % had an increased risk for death in the univariate Cox survival analysis (see Table 5 and Fig. 1). These results were maintained, even after adjustments for the severity of NYHA class, diabetes, hs-CRP levels or LVMI (Table 5).

Table 5 Lung congestion and relative fluid overload association with all-cause mortality

	ULC		RFO	
	HR[a]	95 % CI	HR[b]	95 % CI
Unadjusted	3.08	1.45–6.54	2.68	1.20–6.03
Adjusted	2.72	1.19–6.16	2.93	1.30–6.58

Adjusted for: severity of NYHA class (0—NYHA class 1, 2; 1—NYHA class 3, 4), diabetes, hs-CRP, and left ventricular mass index

[a] The group with ≤22 ULC was used as reference

[b] The group with ≤6.88 RFO was used as reference

A crucial point of our analysis was to determine if pulmonary ultrasonography (the BLS) or bioimpedance (the RFO value) are able to improve the risk prediction for death, beyond that of classical clinical, biological and most importantly, echocardiographic parameters. We tested the potential incremental prognostic value of individually adding BLS or RFO value to commonly used risk factors (the severity of NYHA class, diabetes, hs-CRP levels or LVMI), using three measurements of performance: calibration, discrimination and reclassification.

All models used in the prognostic analysis showed good calibration ($p > 0.05$ for the Hosmer–Lemeshow test for all three models—Table 6). However, the model that included RFO had the lowest AIC and BIC, showing better global goodness-of-fit than the other two models (Table 6). When analyzing the discrimination abilities of the models, the C statistic for the all-cause mortality prediction increased significantly when the RFO was included into the baseline model (ΔC statistics 0.058 95 % CI = 0.003–0.114), but not when the BLS was included into the same model (Table 6). Similarly, only the model that incorporated RFO showed significantly better risk reclassification abilities than the baseline model (IDI = 3.6 % and continuous NRI = 24.8 %—Table 6).

Discussion

This study confirms that both BLS and RFO are independently associated with all-cause mortality in a HD population. However, we show for the first time, that overhydration, as assessed by bioimpedance, and not by lung ultrasonography, improves risk prediction for death, beyond classical and echocardiographic-based risk prediction scores/parameters.

Adequate fluid assessment in HD patients has been an important challenge for nephrologists in the last decades. Several methods were proposed and evaluated to properly assess and manage fluid overload (inferior vena cava diameter, blood volume monitoring, or different plasma volume markers), but until now, only two have been prospectively associated with mortality risk in dialysis populations: bioimpedance analysis and lung ultrasonography.

Several prospective observational studies have shown that using bioimpedance analysis for assessing and correction of fluid overload improves cardiac function [18, 19] and control of blood pressure [18, 20], with fewer intradialytic adverse events [18]. In a seminal paper, Wizemann et al. [4] demonstrated in a prevalent HD population that overhydration is associated with mortality. Recently, our group confirmed these findings in a similar HD population, and further showed that the bioimpedance assessed overhydration is associated with survival independently of echocardiographic parameters [21], known determinants of worse outcomes in these patients [22, 23]. In line with

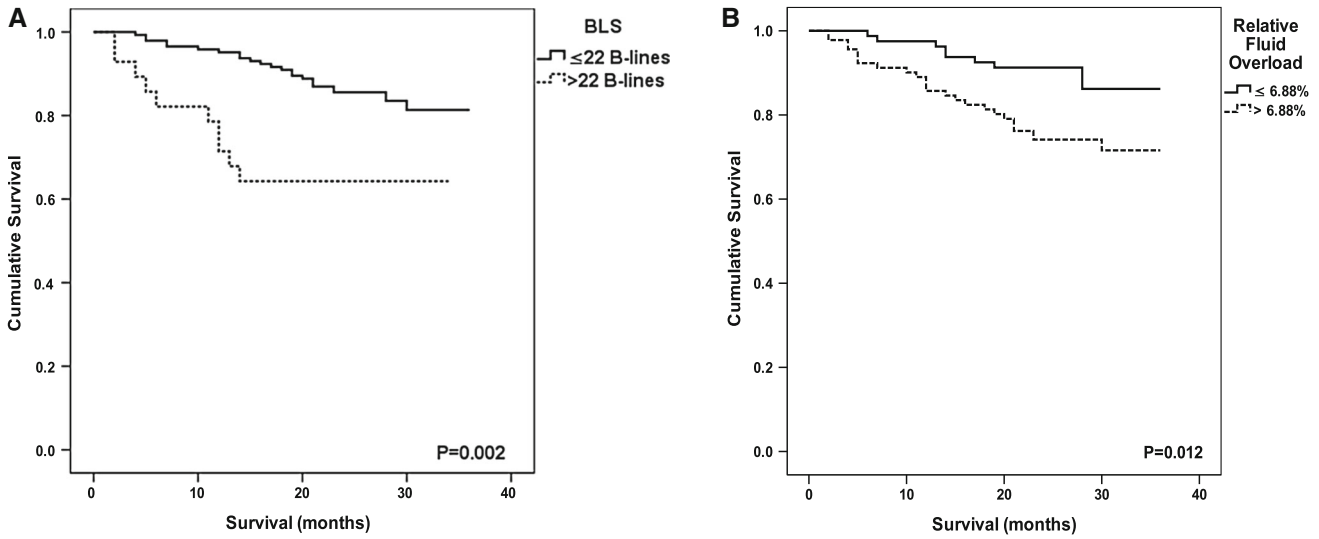

Fig. 1 Kaplan–Meier analysis for all-cause mortality according to B-lines score (**a**) and relative fluid overload (**b**) cut-offs

Table 6 Performance of the models

	Model 1	Model 2	Model 3
Discrimination[a]			
ΔC statistics, 95 % CI	Reference	0.017 (−0.060–0.094)	0.058 (0.003–0.114)
Calibration			
AIC	299.69	299.53	293.88
BIC	305.42	306.71	301.05
H–L	$\chi^2 = 8.25$	$\chi^2 = 13.91$	$\chi^2 = 13.61$
	$p = 0.41$	$p = 0.08$	$p = 0.09$
Reclasification[a]			
IDI, 95 % CI	Reference	0.036 (−0.005–0.141)	0.036 (0.000–0.096)
NRI, 95 % CI	Reference	0.125 (−0.188–0.350)	0.248 (0.021–0.112)

C statistic with only conventional predictors was 0.728

Model 1—severity of NYHA class, diabetes, hs-CRP, and left ventricular mass index

Model 2—Model 1 + LogULC score

Model 3—Model 1 + RFO

[a] Comparison with model 1

these observational findings, two randomized controlled trials showed that using bioimpedance analysis for dry weight estimation led to a significant reduction in blood pressure, arterial stiffness [5, 6], LVMI [5] and to a better survival [6].

Lung ultrasonography can detect pulmonary congestion at a pre-clinical stage in dialysis patients [24], and is associated with cardiac functional [24] and bioimpedance parameters [25] or NT-proBNP [26]. Importantly, the extravascular lung water is associated with CVE [9] and mortality [9, 25] in HD populations. Zoccali et al. [9] demonstrated that patients with very severe congestion (BLS > 60) had a 4.2-fold risk of death and a 3.2-fold risk of CVE (adjusted for NYHA class and other risk factors), when compared with patients having mild or no congestion. In addition, we subsequently reported that this BLS is associated with survival, even after adjustments for echocardiographic or bioimpedance-derived parameters [25].

Although in their seminal papers, the group of Zoccali et al. [9] has shown that lung ultrasonography can improve risk prediction for CVE and mortality in HD patients, this ability was tested only against clinical and biological parameters. Our study now shows that including the BLS into a baseline model that also incorporated LVMI does not significantly improve the predictive abilities of the model. In contrast, including RFO into the same model led to an improvement of both discrimination and reclassification abilities for prediction of all-cause mortality. The populations analyzed in these two studies were fairly similar in regard to age, nutrition parameters, and observational period. However, our patients had a lower dialysis vintage, diabetes prevalence and a less severe cardiac failure and these aspects could have led to the lower mortality incidence observed in our study.

We confirm the independent associations between fluid overload indices, as assessed by both methods (bioimpedance and pulmonary ultrasonography), and mortality. However, our results could also imply that in the complex relationship between cardiac function, fluid overload and mortality, the pulmonary ultrasonography evaluation only provides similar information to echocardiography. Nevertheless, this is important since this method would still improve patients' management and outcomes, as it is easier (bedside, technician operated) to be performed, cheaper and more available than echocardiography [27]. However, if the patient has already an echocardiographic assessment, adding pulmonary echocardiography to his evaluation wouldn't improve the risk prediction for mortality. In contrast, using bioimpedance and obtaining an overall fluid assessment could provide information complementary to echocardiography, and as such improve patients' risk prediction irrespective of the echocardiographic assessment.

Although not the principal aim of the study, we identified two cut-offs for defining fluid overload (as evaluated by pulmonary ultrasonography and bioimpedance) association with mortality in HD patients. The 22 BLS cut-off for defining pulmonary congestion's risk for mortality is new and should be tested for accuracy in other HD population, but the 6.88 % cut-off for RFO is very similar to the upper-limit of normohydration status—7 % as previously described [4, 28]. The fact that in our analysis the RFO cut-off showed better sensitivity, but a lower specificity for mortality than the BLS cut-off could imply that the bioimpedance analysis could be used as a better screening tool, identifying high-risk patients in which additional investigations should be performed.

Limitations

Firstly, we included patients from a single dialysis center from a country with one of the best survival rates in the world [29] and our cohort may not represent the average US HD patient; ideally, these results should be validated in other HD cohorts. Secondly, our sample size and number of outcome events are relatively modest, but we used different statistical approaches to overcome these shortcomings. Thirdly, we weren't able to precisely identify the specific cause of death.

Conclusions

This study is the first one that compares the prognostic abilities for death, above and beyond echocardiographic parameters, of the two most important methods for fluid status assessment in HD patients. Although bioimpedance appears to have more prognostic capabilities, in specific patients a dry weight reduction based on pulmonary ultrasonography could be tested. Two randomized controlled trials regarding this approach are currently ongoing (ClinicalTrials.gov Identifiers: NCT01815762 and NCT02310061). The results of these trials are expected to bring final proves about the usefulness of pulmonary congestion assessment in HD patients.

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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. The other authors have nothing to declare.

Ethical standard 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.

Informed consent Informed consent was obtained from all individual participants included in the study.

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