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Original Articles

Predicting mortality in haemodialysis patients: a comparison between lung ultrasonography, bioimpedance data and echocardiography parameters

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ABSTRACT

Background. The use of lung ultrasonography to evaluate extravascular lung water and its consequences has received growing attention in different clinical areas, including, in recent years, end-stage renal disease patients treated by haemodialysis (HD). Lung congestion is a direct consequence of either overall overhydration and/or cardiac dysfunction, but the exact contribution of each of these tests to mortality is unknown.
Methods. In this prospective observational study, we enrolled 96 patients from a single HD unit undergoing thrice weekly HD. We used three different methods of evaluation: lung ultrasonography (pre- and post-dialysis), bioimpedance spectroscopy (pre- and post-dialysis) and echocardiography (pre-dialysis). The objective of the study was to test for the first time the prognostic value of ultrasound lung comets (ULC) combined with bioimpedance-derived data [total body water (TBW), extravascular water, hydration status—ΔHS] and several echocardiographic parameters. Mortality was analysed after a median of 405.5-day follow-up.
Results. Pre-dialysis lung congestion was classified as moderate (ULC = 16–30) in 19.8% of the patients and severe in 12.5% of patients (ULC > 30), while only 19.8% appear to be hyperhydrated (ΔHS > 15%). The pre-dialysis ultrasound lung congestion score correlated significantly with all of the bioimpedance-derived parameters. In a multivariate Cox model that included ULC score, demographic, ecocardiographic and bioimpedance parameters, the factors that remained significantly associated with survival time were the pre-dialysis ULC score and left ventricular mass index. The pre-HD ULC score has a significant discriminating power for survival, while the bioimpedance-derived hydration status has no discriminatory abilities in terms of survival.
Conclusions. To our knowledge, this study is the first one that compares three different strategies to predict mortality in haemodialysed patients. The lung comet score emerged as the best predictor for the relationship hydration status—mortality,

independently of bioimpedance-derived parameters in this population.

INTRODUCTION

End-stage renal disease patients treated by chronic dialysis have a worryingly high mortality rate, comparable with aggressive forms of cancer [1]. Chronic fluid overload is very frequent in haemodialysis (HD) patients treated by a standard duration treatment (three times per week), so one of the major targets of HD therapy is to maintain a normal extracellular volume status. Preventing volume overload is a central recommendation when it comes to nephrology best practice guidelines for dialysis patients [2], as it is directly associated with hypertension, increased arterial stiffness, left ventricular hypertrophy, heart failure and ultimately higher mortality and morbidity [3].

To determine the hydration state, clinical (pedal oedema, interdialytic weight gain, ultrafiltration rate or blood pressure) [4, 5] or paraclinical (inferior vena cava diameter and its collapsibility index, relative plasma volume monitoring) [6, 7] surrogate parameters are used.

Multifrequency bioimpedance spectroscopy is a promising method that objectively defines the individual (over)hydration status, taking into account the individual's body composition. Most importantly, this technique is validated by isotope dilution methods, by accepted reference body composition methods and by techniques that measure relative changes in fluid volumes [8]. Recent studies indicate that the hydration status, evaluated using the bioimpedance spectroscopy method, is an important and independent predictor of mortality in chronic HD patients secondary only to the presence of diabetes [9], but stronger than blood pressure [10].

Extravascular lung water (ELW) is a relatively small, but fundamental component of body fluid volumes [11] and represents the water content of the lung interstitium that is strictly dependent on the filling pressure of the left ventricle, an established haemodynamic parameter for risk stratification and monitoring of fluid therapy in critical care [12]. In recent years, the use of lung ultrasonography to detect ELW has received growing attention in clinical research in patients with heart failure [13], intensive care [14] and chronic kidney disease undergoing HD [15, 16]. Recently, it has been shown that this method can predict the all-cause mortality and cardiac events in HD patients [17].

The aim of this present study was to test the prognostic value of ELW combined with bioimpedance spectroscopy-derived data and echocardiographic parameters, in a cohort from a single HD unit.

METHODS

Patients

The protocol of this study was approved by the Ethics Committee of University Hospital 'Dr C.I.Parhon' (Iasi, Romania). Between 26 May 2011 and 3 July 2012, we invited all patients undergoing chronic HD treatment for at least 3 months in a single unit to take part in this study. Exclusion criteria were age under 18 years; systemic infections and terminal neoplasia; metallic joint prostheses, cardiac pacemakers or stents; decompensated cirrhosis and limb amputations—since accurate bioimpedance evaluation cannot be performed in patients with these conditions.

There were 122 patients who fulfilled the pre-specified inclusion criteria; 12 patients were excluded because of limb amputation ($N = 6$), decompensated cirrhosis ($N = 2$) or presence of a cardiac pacemaker or stent ($N = 4$). Fourteen additional patients did not accept to be included in the study. Details of the final patient population ($N = 96$) are presented in Table 1. HD therapy was performed 4 h × three times per week, using high-flux Fresenius Polysulfone® membrane dialyzers (FX60). Biochemical parameters were determined on the first Monday (or Tuesday) of each month, pre-dialysis, after the long interval of dialysis.

Lung comets

Echographic examinations were performed after a short dialysis period, with patients in the near-to-supine or supine positions. Measurements were performed starting 15–20 min before dialysis, and 35 min after dialysis. Ultrasound scanning of the anterior and lateral chest was obtained on the right and left haemithorax, from the second to the fifth (on the left side to the fourth) intercostal spaces and from the parasternal to the midaxillary line for a total of 28 positions per examination, as was previously described [14].

The comet-tail sign was defined as an echogenic, coherent, wedge-shaped signal with a narrow origin in the near field of the image. In each intercostal space, the number of comet-tail signs was recorded at the parasternal, midclavear, anterior axillary and midaxillary sites. At every scanning site, ultrasound lung comets (ULC) could be counted from 0 to 10. Zero is defined as a complete absence of ULC 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 comet-tail signs yielded a score denoting the extent of extravascular fluid in the lung [18].

On the basis of this score [19], we grouped the patients into three categories of increasingly severe pulmonary congestion (none or mild: <16 comets, moderate: 16–30 comets and severe: >30 comets).

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 the start and 30 min after the end of the HD treatment. This technique involves attaching electrodes to the patient's non-fistula forearm and ipsilateral ankle, with the patient in a supine position. All measurements were performed by two trained physicians.

Table 1. Main demographic, clinical, somatometric and pre-dialysis haemodynamic data of the study population						
	All	<16 ($N = 65$)	16–30 ($N = 19$)	>30 ($N = 12$)	P for trend	r (P)
Age, years	59.1 ± 14.2	58.7 ± 14.0	58.5 ± 15.8	62.2 ± 14.0	0.72	0.05 (0.60)
Dialysis vintage, months	64.3 ± 59.2	59.6 ± 54.7	73.6 ± 66.8	75.1 ± 71.5	0.53	0.05 (0.61)
BMI, kg/m^2	25.9 ± 6.1	26.8 ± 6.1	23.2 ± 4.8	25.6 ± 7.4	0.08	**−0.24 (0.018)**
Male sex, %	51	52.3	36.8	66.7	0.96	
Diabetes, %	24	26.2	15.8	25.0	0.54	
Systolic pressure, mmHg	147.6 ± 24.6	145.6 ± 22.8	150.4 ± 27.4	153.8 ± 30.2	0.50	0.18 (0.08)
Diastolic pressure, mmHg	74.9 ± 15.3	75.3 ± 14.6	70.8 ± 17	79.5 ± 15.7	0.29	0.06 (0.54)
Heart rate, beats/min	76.6 ± 16.0	75.0 ± 12.8	78.2 ± 24.2	82.3 ± 15.6	0.32	0.04 (0.67)
Haemoglobin, g/dL	11.2 ± 1.5	11.4 ± 1.5	10.9 ± 1.5	10.9 ± 1.5	0.34	−0.16 (0.12)
Albumin, g/dL	3.9 ± 0.3	3.9 ± 0.3	3.9 ± 0.4	3.7 ± 0.4	0.14	−0.03 (0.76)
Calcium, mg/dL	8.4 ± 0.7	8.5 ± 0.7	8.0 ± 0.8	8.7 ± 0.7	**0.01**	0.002 (0.99)
Phosphate, mg/dL	5.6 ± 2	5.7 ± 2.1	5.4 ± 1.8	5.5 ± 1.9	0.88	0.04 (0.70)
eK_t/V	1.5 ± 0.3	1.4 ± 0.2	1.6 ± 0.3	1.5 ± 0.4	0.15	0.16 (0.12)
Cholesterol, mg/dL	171.9 ± 42.2	173.5 ± 40.2	163.8 ± 34	175.9 ± 62.7	0.64	0.08 (0.43)
Lung disease, %	6.3	1.5	15.8	25.0	**0.034**	
CRP	12.0 ± 22.8	11.7 ± 23.3	8.2 ± 9.6	14.8 ± 17.5	0.38	**0.21 (0.04)**
NYHA class, %	I (34.4)	I (40.0)	I (36.8)	I (0)	**0.014**	
	II (33.3)	II (32.3)	II (42.1)	II (25.0)		
	III (30.2)	III (27.7)	III (21.1)	III (58.3)		
	IV (2.1)	IV (0)	IV (0)	IV (16.7)		

Data are expressed as mean ± SD or percent frequency, as appropriate. Bold values are statistically significant.
r, Spearman rank correlation coefficient between lung comets score and variables; BMI, body mass index; NYHA, New York Heart Association.

The extracellular water (ECW), intracellular water (ICW) and TBW were determined as previously described [19]. To facilitate the comparison between patients, the hydration state was normalized to the ECW (ΔHS = HS/ECW). The patient population was divided into a hyperhydrated, normohydrated and hypohydrated groups using a cut-off of 15% for the relative hydration status. The definition of hyperhydration for ΔHS >15% is based on the work described by Wabel *et al.* [20] and Wizemann *et al.* [9].

Echocardiography

Echocardiographic evaluations were made in each patient after a short dialysis period, starting 40 min before dialysis. All echocardiographic measurements were carried out according to the recommendations of the American Society of Echocardiography [21] by an observer unaware of the lung ultrasound and bioimpedance results.

Statistical analysis

Data are expressed as mean ± SD, median and inter-quartile range or as percent frequency, as appropriate. Comparisons among groups were made by P-value for linear trend (one-way analysis of variance or χ^2 test). Among patients, comparisons were made by the paired t-test (normally distributed data) or by the Wilcoxon signed-rank test (non-normally distributed data). Correlations between the variables were investigated by the Pearson product moment correlation coefficient or by the Spearman rank correlation coefficient, as appropriate. Kaplan–Meier and Cox regression analysis were used to investigate the prognostic value of the lung comets score for predicting mortality. In this analysis, the backward stepwise (Wald) method was applied to phase out factors that did not have a significant influence on survival. We obtained the best multivariate model [Hosmer–Lemeshow tests —$\chi^2 = 6.51$, df = 8, P = 0.59, 95% confidence interval (95% CI)]. The contribution of covariates explaining the dependent variable was assessed by the Wald test, with a P-value of <0.05 considered as significant. 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. After resampling, the Hosmer–Lemeshow analysis demonstrated that the model obtained using the backward stepwise (Wald) method was correctly selected ($\chi^2 = 9.06$, df = 8, P = 0.34, 95% CI). All calculations were made using a standard statistical package (SPSS for Windows, version 19.0.1, Chicago, IL).

RESULTS

Ninety-six (51% males) patients were enrolled. The demographic and clinical characteristics of the study population are reported in Table 1. Twenty-three (24.0%) patients had diabetic nephropathy and 6 (6.3%) had chronic obstructive pulmonary disease. Patients with lung disease had a higher ULC score (median: 30, inter-quartile range 15.6–101.5) than those without (median: 9, inter-quartile range 3–17, P = 0.003). Thirty-one (32.3%) patients had a New York Heart Association (NYHA) score of at least 3. All patients had residual diuresis of <500 mL per day (median 200 mL per day).

Pre-dialysis

The mean pre-dialysis arterial pressure and heart rate were 147.6 ± 24.6/74.9 ± 15.3 mmHg and 76.6 ± 16 beats/min, respectively. The median number of pre-dialysis ULC was 11 (inter-quartile range 4–19).

Lung congestion was classified as absent to mild (≤15 lung comets) in 67 patients (67.7%), moderate (16–30 lung comets) in 19 patients (19.8%) and severe (>30 lung comets) in the remaining 12 patients (12.5%). There was no difference between these three groups in gender distribution, diabetes prevalence, systolic and diastolic blood pressure and different biochemical parameters. A significant difference between these groups was observed when we analysed the distribution of the NYHA functional class: patients with moderate or severe lung congestion had a higher NYHA functional class (Figure 1 and Table 1).

On the basis of ΔHS, 77 (80.2%) patients were classified as being normohydrated and 19 (19.8%) as hyperhydrated. The hyperhydrated patients were younger (49.4 ± 16.9 versus 61.5 ± 12.5 years, P < 0.01) and had significantly more ULC (a median of 12, inter-quartile range 8–22 versus a median of 9, interquartile range 3–16.5, P = 0.048) than the normohydrated ones. We found no difference in regard to gender distribution, diabetes prevalence, systolic and diastolic blood pressure and NYHA class between the normohydrated and hyperhydrated patients. Among the hyperhydrated patients, 14 (73.7%)

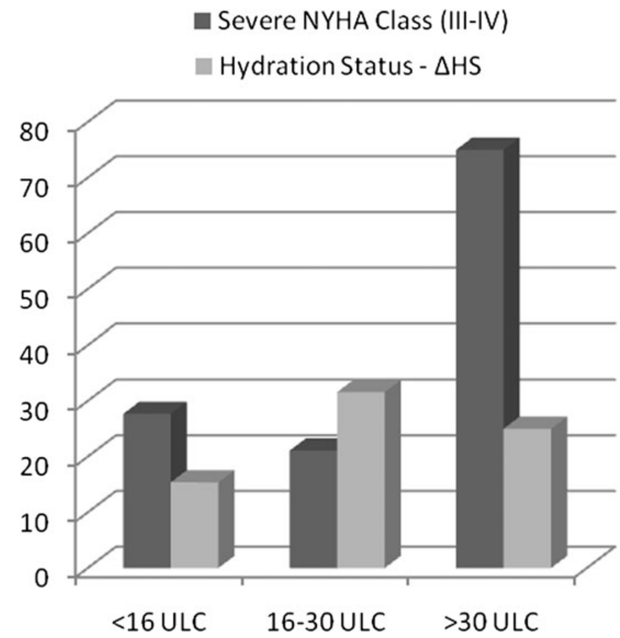

FIGURE 1: NYHA class and hydration status across the groups of lung congestion.

were asymptomatic (NYHA Class I and II, see Figure 1). Also, no differences were also found when we compared the ecocardiographic parameters between the normohydrated and hyperhydrated patients (as defined by ΔHS).

Tables 2 and 3 show the bioimpedance (BCM derived) data (ΔHS, TBW, ECW and ICW) and echocardiographic parameters, respectively, as well as their distribution across the three ULC-derived categories of lung congestion. There was a significant difference in the ΔHS and left atrial diameter among the three groups of lung congestion (P < 0.05 for both).

The pre-dialysis ULC score significantly correlated with all the BCM-derived parameters (ΔHS, TBW, ECW and ICW), but this was not related to any of the anatomical and functional echocardiographic parameters evaluated in the study.

Post-dialysis

The mean post-dialysis arterial pressure and heart rate were 134.0 ± 20.2/70.0 ± 11.7 mmHg and 77.0 ± 11.7 beats/min, respectively. The median number of post-dialysis ULC was 4.5 (inter-quartile range 2–9).

After dialysis, there were 87 (90.6%) patients with absent or mild lung congestion, 4 (4.2%) with moderate and 5 (5.2%) with severe lung congestion. Using the post-dialysis ΔHS, 11 (11.5%) patients were hypohydrated, 84 (87.5%) were normohydrated and only 1 (1%) remained hyperhydrated.

Seven of the patients with >30 lung comets before dialysis changed their class of lung congestion post-dialysis (four moved to the absent or mild, while three to the moderate lung congestion class). There were no significant (demographic, clinical, biochemical, bioimpedance and ecocardiographic parameters) differences between the three ULC groups of lung congestion. The observed difference in NYHA functional class prevalence between the ULC categories was also maintained after dialysis ($r = 0.548$, P < 0.001). Similar to the pre-dialysis

Table 2. Bioimpedance spectroscopy data of the study population						
	All	<16 ($N = 65$)	16–30 ($N = 19$)	>30 ($N = 12$)	P for trend	r (P)
TBW, l	31.7 ± 6.3	32.6 ± 6.4	28.7 ± 5.1	31.7 ± 6.1	0.06	**−0.22 (0.034)**
ECW, l	15.6 ± 3.7	16.1 ± 3.8	14 ± 2.7	15.8 ± 3.7	0.08	**−0.21 (0.042)**
ICW, l	16.2 ± 3.4	16.7 ± 3.5	14.7 ± 2.7	15.9 ± 2.9	0.07	**−0.24 (0.021)**
ΔHS, %	7.9 ± 7.5	6.5 ± 7.2	10.1 ± 8.1	11.6 ± 6.6	**0.03**	**0.29 (0.004)**

Data are expressed as mean ± SD. Bold values are statistically significant.
r, Spearman rank correlation coefficient between lung comets score and variables; TBW, total body water; ECW, extracellular water; ICW, intracellular water.

Table 3. Echocardiographic Parameters of the Study Population						
	All	<16 ($N = 65$)	16–30 ($N = 19$)	>30 ($N = 12$)	P for trend	r (P)
LVMI, g/m^2	153.0 ± 44.8	150.0 ± 42.7	150.8 ± 28.8	172.2 ± 70.5	0.35	0.18 (0.12)
Left atrial diameter, mm	46.3 ± 7.6	45.6 ± 7.4	45.1 ± 6.6	51.8 ± 8.5	**0.04**	0.20 (0.08)
Interventricular septum, mm	12.4 ± 2.4	12.3 ± 2.6	12.7 ± 2.1	12.7 ± 2.1	0.78	0.10 (0.40)
LVPWT, mm	12.0 ± 2.3	11.9 ± 2.4	12.5 ± 2.0	12.1 ± 1.9	0.68	0.13 (0.25)
End-diastolic left ventricular diameter, mm	48.4 ± 7.5	49 ± 7.4	45 ± 6.5	50.8 ± 8.3	0.10	−0.07 (0.53)
End-systolic left ventricular diameter, mm	32.2 ± 6.8	32.2 ± 6.9	30.3 ± 4.7	34.9 ± 8.5	0.25	0.13 (0.91)
LVEF, %	61.5 ± 7.7	61.8 ± 7.7	62.6 ± 4.5	58.2 ± 10.7	0.69	−0.75 (0.51)

Data are expressed as mean ± SD. Bold values are statistically significant.
r, Spearman rank correlation coefficient between lung comets score and variables; LVMI, left ventricular mass index; LVPWT, left ventricular posterior wall thickness; LVEF, left ventricular ejection fraction.

results, a weak correlation between the ULC score and some of the BCM parameters was observed (ΔHS: $r = 0.30$, P = 0.003; TBW: $r = -0.24$, P = 0.018; ICW: $r = -0.27$, P = 0.009).

The ULC score after dialysis correlated weakly with the left atrial diameter and the left ventricular ejection fraction (LVEF; $r = 0.28$, P = 0.013 and $r = -0.28$, P = 0.013, respectively).

Pre- and post-dialysis

The body weight decreased from 70.2 ± 17.3 pre-dialysis to 68.4 ± 17.1 kg post-dialysis (P < 0.001). The mean arterial pressure and the ULC score were also significantly lower compared with the start of dialysis (P ≤ 0.001 for all).

The proportion of patients who were hyperhydrated fell significantly after dialysis (P < 0.001). The reduction in the ULC score was correlated with the pre-dialysis ULC score ($r = 0.83$, P < 0.001), but not with the ultrafiltration volume or any of the BCM or echocardiographic parameters.

Survival

The median time of observation was 405.5 (interquartile range 234.8–518.0) days. During the follow-up, 13 (13.5%) patients died: 6 (9.2%) in the group with absent or mild lung congestion and 2 (10.5%) and 5 (41.7%) in the group with moderate and severe lung congestion, respectively.

In the survival analysis (Figure 2 and Table 4), the hazard ratio (HR) for mortality was higher in the group with pre-dialysis severe lung congestion (ULC >30 comets) compared with the other two groups (HR = 5.03, 95% CI = 1.5–16.5).

Taking into account that the ULC score can be theoretically influenced by either the left ventricular function and/or the body water content, we analysed the true impact of lung water on survival in a multivariate Cox model that included demographic, ecocardiographic and bioimpedance parameters (Table 5). Factors that remained significantly associated with survival time were the pre-dialysis ULC score and the left ventricular mass index (LVMI). These survival predictors (LVMI and pre-dialysis ULC) maintained their statistical significance after bootstrapping analysis. The appropriate (for overfitting predicting models) Cox regression model is presented in Supplementary Table S1 and Supplementary Figure S1.

The post-dialysis ULC score also had a significant (albeit low) impact on survival in the crude Cox analysis (P = 0.003, HR = 1.021, 95% CI = 1.007–1.036). However, after adjusting for different confounders (LVMI, ejection fraction, post-dialysis hydration status, albumin, age and dialysis vintage), the score lost its statistical significance (see Supplementary Table S2).

Finally, we compared the discriminative power for predicting survival (the area under the curve—AUC) for: pre-dialysis ULC (AUC − ULC = 0.791, P = 0.008), NYHA class (AUC − NYHA = 0.785, P = 0.014) and LVMI (AUC − LVMI = 0.762, P = 0.004). The hydration status had no discriminatory abilities in terms of survival (AUC − ΔHS = 0.612, P = 0.197).

DISCUSSION

Our study demonstrates that the ELW measured by lung ultrasonography is an important tool to assess and predict the potential deleterious impact of occult overhydration in HD patients. This is the first study that investigates holistically the hydration status and its cardiovascular consequences, by combining pre-/post-dialysis lung ultrasound and total body impedance, with contemporary echocardiographic imaging, in a survival analysis. The ULC score emerged as the best predictor for the relationship hydration status—mortality, independently of bioimpedance-derived parameters, thus opening promising avenues for future interventional trials.

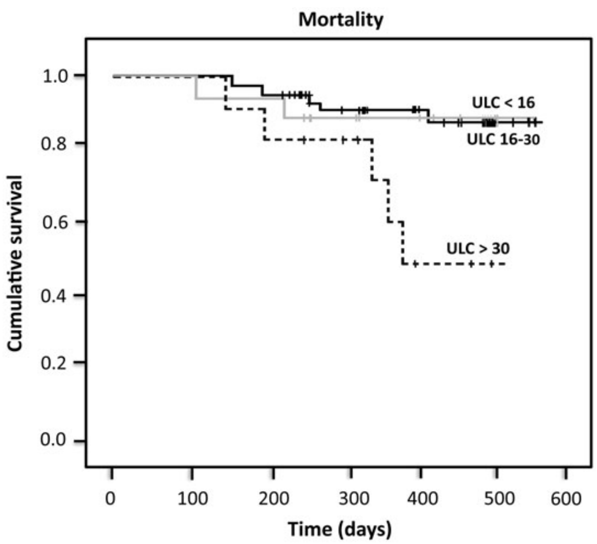

FIGURE 2: Kaplan–Meier survival analysis according to the ULC score.

The bioimpedance analysis has been used in clinical studies for >20 years, but only recently has this method shown an impact of hyperhydration on survival [9, 10]. In a prospective study, Wizemann *et al.* [9] measured baseline overhydration in 269 HD patients who were followed for a period of 3.5 years. The ΔHS >15% (as a marker of overhydration) was found to be an independent predictor of mortality (HR for all-cause mortality = 2.1). Chazot *et al.* [10] compared 158 patients selected from Giessen (Germany) with 50 patients selected from Tassin (France) who were considered as a reference population. The relative expansion of the extracellular compartment (ΔHS >15%) was used as a cutt-off to stratify the 158 patients into non-hyperhydrated and hyperhydrated. After a follow-up of 6.5 years, there was no difference in mortality between the Tassin group and the non-hyperhydrated group from Giessen, while the multivariate adjusted all-cause mortality was significantly increased in the hyperhydrated Giessen patient group (HR = 3.41).

By comparison, our study included fewer patients and the follow-up period was shorter, but the proportion of patients who were hyperhydrated was similar (∼20% in all three studies). There was a significant difference in age between the normohydrated and hyperhydrated patients in our study (the hyperhydrated patients were younger), but including age into the Cox regression model did not alter the results of the survival analysis. A serious limitation of the two previous studies is the lack of echocardiographic measurements. Although these are associated with the high intra- and interobserver variability [22], the prognostic value of different echocardiographic parameters in haemodialysed patients has been clearly demonstrated [23, 24].

Quite recently, the group of Zoccali *et al.* suggested that the lung compartment of the total extracellular body water might be the most prognostically relevant and therefore amenable to intervention (http://www.era-edta.org/privata/images/LUST_%28Zoccali%29_final_application.pdf). The usefulness of the

Table 4. Survival of the study population

	Hazard ratio (95% CI and P-value)	Adjusted hazard ratio (95% CI and P-value)
Lung comets score		
<16	1	1
16–30	1.11 (0.22–5.48), P = 0.90	1.21 (0.24–6.12), P = 0.82
>30	5.03 (1.53–16.53), P < **0.01**	3.63 (1.03–12.74), P < **0.05**
NYHA class (0 = I–II, 1 = III–IV)		2.59 (0.77–8.70), P = 0.12
Hydration status (0 = normohydrated, 1 = hyperhydrated)		1.22 (0.26–5.74), P = 0.80

Bold values are statistically significant.
CI, confidence interval; NYHA, New York Heart Association.

Table 5. Adjusted Cox regression for mortality

Pre-dialysis variables	β	SE	Wald	Significant P-value	Exp (β) HR	95% CI for Exp (β)	
						Lower	Upper
ULC score, pre-dialysis	0.975	0.049	4.939	**0.026**	2.651	1.122	6.262
LVMI, g/m^2	0.020	0.008	5.889	**0.015**	1.320	1.004	1.437
Age, years	0.048	0.035	1.949	0.163	1.049	0.981	1.123
CRP, mg/L	0.018	0.019	0.897	0.344	1.018	0.981	1.058
Hydration status—pre-ΔHS	0.051	0.059	0.739	0.390	1.052	0.937	1.182
Albumin, g/dL	−1.047	0.091	0.630	0.427	0.351	0.026	4.657
LVEF, %	−0.017	0.046	0.135	0.713	0.983	0.899	1.076
Dialysis vintage, months	0.002	0.007	0.099	0.754	1.002	0.989	1.015

Bold values are statistically significant.
CI, confidence interval; HR, hazard ratio; SE, standard error; ULC, ultrasound lung comets; LVMI, left ventricular mass index; CRP, C-reactive protein; LVEF, left ventricular ejection fraction.

lung ultrasound examination has only been recently established in HD patients. Mallamaci *et al.* [16] used this technique in a population of 75 HD patients to cross-sectionally estimate the prevalence of pulmonary congestion and its reversibility after dialysis. The high prevalence of pulmonary congestion in both symptomatic and asymptomatic patients was unrelated to the hydration status, but was strongly associated with an LVEF. A recent study done by the same group [17] tested the prognostic value of ELW measured by lung ultrasound in a multicentre study that enrolled 392 HD patients. Patients with very severe pulmonary congestion (>60 ULC) had an HR = 4.2 for death and HR = 3.2 for cardiac events, compared with those having mild or no pulmonary congestion (<15 ULC), even after multiple adjustments for NYHA functional class and other risk factors.

It is, however, evident that lung congestion is a direct consequence of either overall (total body) overhydration and/or cardiac dysfunction. At the same time, there is a direct pathophysiological link between overall hydration and left ventricular (LV) structure and function. Additional confounding layers are represented by the nutritional and inflammatory status—involved in cardiovascular outcomes and hydration mechanics, through the malnutrition-inflammation-atherosclerosis syndrome. Therefore, it was still uncertain which of these three inter-related factors is most relevant for diagnostic and therapeutic purposes. Only a study combining all three angles could further dissect this intricate pathophysologic al puzzle and shed additional light. The Cox model (see Table 5) that included demographic parameters (with albumin as a proxy for nutritional status and C-reactive protein as a proxy for inflammation), ULC score, bioimpedance-determined ECW and ICW, as well as LV mass/LV systolic function showed that the ULC score remains the best overall independent predictor for mortality.

The differences between findings in our study (regarding the relation between ULC, bioimpedance parameters and LVEF) and that of Mallamaci *et al.* are most certainly the result of differences in study populations: our patients (being younger and possibly with less comorbidities) had better volaemic control (only 19.8% were hyperhydrated at the beginning of dialysis) and a preserved left ventricular systolic function (only 6.3% of our patients had an LVEF of <50%). Such differences are in fact rather a strength, since they independently confirm and complement the findings from previous reports, in a different dialysis setting.

Our study strongly supports the impact of the ULC score on survival and brings new 'players' into this relationship. Although the prospective observational study performed by Zoccali *et al.* is a path breaker, its main limitation is the lack of data regarding the overall hydration status and cardiac performance. We evaluated survival in a more complex pattern, and our results clearly indicate that estimating lung water is most probably the best predictor of mortality, surpassing the overall hydration status and cardiac parameters.

LIMITATIONS

The follow-up period was relatively short, and we included a relatively small number of patients from a single dialysis centre. However, we performed additional statistical techniques that allow for adjustment when it comes to 'optimism', and the results were similar. Although the investigators who measured the ULC score were blinded to ecocardiographic and bioimpedance evaluations, they were not blinded to the moment of measurement (pre- or post-dialysis). Finally, we could not specify the cause of death and the data about non-fatal events were not collected.

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CONCLUSIONS

This study is the first one that compares three different strategies to predict mortality in HD patients. The ULC score emerged as the best predictor for the relationship hydration status—mortality, independently of bioimpedance-derived parameters. Taken together with recent evidence, this clearly opens the path for a large multicentric interventional trial. Such a trial centred on manipulation of the ULC score has been designed and initiated by the European Renal Association–European Dialysis Transplantation Association and will bring definitive proof to one of the most promising avenues in current dialysis practice.

SUPPLEMENTARY DATA

Supplementary data are available online at http://ndt.oxfordjournals.org.

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CONFLICT OF INTEREST STATEMENT

The results presented in this paper have not been published previously in whole or part. A.C. is in the speaker bureau and advisory board for Fresenius Medical Care, Amgen and Abbot. A.C., D.S., M.O., and R.S. are members of the EURECAM LUST study.

(See related article by Zoccali *et al.* Lung congestion as a hidden threat in end-stage kidney disease: a call to action. *Nephrol Dial Transplant* 2013; 28: 2657–2660.)

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ORIGINAL ARTICLE

Convective therapies *versus* low-flux hemodialysis for chronic kidney failure: a meta-analysis of randomized controlled trials

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ABSTRACT

Background. Although convective therapies have gained popularity for the optimal removal of uremic solutes, their benefits and potential risks have not been fully elucidated. We conducted a meta-analysis of all randomized controlled trials comparing convective therapies with low-flux hemodialysis in patients with chronic kidney failure.
Methods. We performed a literature search using MEDLINE (inception-December 2012), Cochrane Central Register of Controlled Trials, ClinicalTrials.gov, scientific abstracts from meetings and bibliographies of retrieved articles. Randomized controlled trials comparing the effect of convective therapies including high-flux hemodialysis, hemofiltration or hemodiafiltration versus low-flux hemodialysis were included. Random-effects model meta-analyses were used to examine continuous and binary outcomes.
Results. Sixty-five (29 crossover and 36 parallel-arm) trials were identified (n = 12 182). Convective therapies resulted in a decrease in all-cause mortality [relative risk (RR) 0.88; 95% confidence interval (CI) 0.76, 1.02, P = 0.09], cardiovascular mortality (RR 0.84; 95% CI 0.71, 0.98, P = 0.03), all-cause hospitalization (RR 0.91; 95% CI 0.82, 1.01; P = 0.08) and therapy-related hypotension (RR 0.55, 95% CI 0.35, 0.87, P = 0.01). Convective therapies also resulted in an increase in the clearance of several low-molecular-weight (urea, creatinine and phosphate), middle-sized (β-2 microglobulin and leptin) and protein-bound (homocysteine, advanced glycation end-products and pentosidine) solutes and a decrease in inflammatory markers (interleukin-6). There was no impact of