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Clinical significance of multi-frequency bioimpedance spectroscopy in peritoneal dialysis patients: independent predictor of patient survival

Emma L. O'Lone[1], Annemarie Visser[2], Hazel Finney[3] and Stanley L. Fan[1]

[1]Department of Renal Medicine and Transplantation, The Royal London Hospital, Barts Health NHS Trust, London, UK, [2]Department of Nutrition and Dietetics, Barts Health NHS Trust, London, UK and [3]Department of Clinical Biochemistry, Barts Health NHS Trust, London, UK

Correspondence and offprint requests to: Stanley L. Fan; E-mail: s.fan@qmul.ac.uk

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ABSTRACT

Background. It is becoming increasingly evident that the accurate assessment of hydration status is critical to care of a dialysis patient. Using the Body Composition Monitor, different parameters (overhydration (OH), extra-cellular water/total body water (ECW/TBW) or OH/ECW) have been proposed to indicate hydration status. We wished to determine which parameter (if any) was most predictive of all-cause mortality, and if this was independent of nutritional indices.

Methods. We performed a single-centre retrospective analysis of prospectively collected data of all peritoneal dialysis (PD) patients between 1 January 2008 and 30 March 2012. Record review was undertaken to establish patient survival, clinical and demographic data. Follow-up was continued even after PD technique failure (transfer to haemodialysis) and transplantation.

Results. The study included 529 patients. OH index (OH and OH/ECW) was the independent predictor of mortality in multi-variate analysis. ECW/TBW as a continuous variable was not associated with increased risk of death. In contrast, patients that were severely overhydrated (highest 33%) had hazard ratios (HRs) that were statistically significant irrespective of the parameter used to define hydration. Using OH, severely overhydrated patients had an HR of 1.83 [95% confidence interval (CI) 1.19–2.82, P < 0.01], OH/ECW: 2.09 (95% CI 1.36–3.20, P < 0.001) and ECW/TBW: 2.05 (95% CI 1.31–3.22, P < 0.005).

Conclusions. Our results also indicated that there was no influence of body mass index (BMI) on the hydration parameter OH/ECW. OH/ECW remained an independent predictor of mortality when the BMI and lean tissue index were included in multivariate model. However, it remains to be determined if correcting the OH status of a patient will lead to improvement in mortality.

Keywords: bioimpedance, fluid status, mortality, overhydration, peritoneal dialysis

INTRODUCTION

It is becoming increasingly evident that the accurate assessment of hydration status (normally hydrated volume of distribution, V_d) is critical to the care of a dialysis patient. V_d is an important and independent predictor of mortality in chronic haemodialysis (HD) patients secondary only to the presence of diabetes [1]. Over-hydration (the amount by which V_d is expanded, OH) contributes to this risk of death as it is associated with hypertension, increased left ventricular mass [2–6] and reduced arterial distensibility [7]. In addition, a study has shown in peritoneal dialysis (PD) patients that a high level of pro-BNP, likely driven by volume overload, is an important predictor of survival [8]. However, avoidance of hypovolaemia to prevent reduction in residual renal function (RRF) is equally important; a decrement of RRF by 1 mL/min was associated with a 50% increase in the risk of death [9]. Unfortunately, physician assessment of V_d and OH is often inaccurate and alternative methods such as tracer-dilution techniques are laborious, time consuming and is not widely available for clinical use.

Bioimpedance analysis (BIA) measures conductance and reactance, and has been used to evaluate nutrition status, which has been shown to predict survival [10, 11]. This technology is also proposed to accurately determine V_d [12]. The Body Composition Monitor (BCM, Fresenius Medical Care, Germany) is a bioimpedance spectroscopy (BIS) device, and validated by isotope dilution methods [13] and reference body-composition methods [14]. Extra-cellular water (ECW), intra-cellular water (ICW) and total body water (TBW) are determined from measured impedance data following the model of Moissl *et al.* [15], using normal population data as reference. Different indices of hydration are provided by the machine. ECW/TBW is most widely accepted to be an index of hydration, but it does not inform the clinician of the degree of OH and obesity can confound this parameter [16] (fat cells have proportionally lower ICW so an euvolaemic obese patient will have higher ECW/TBW that a euvolaemic muscular lean patient of the same weight). Using population data, the BCM machine also provides an estimate of OH measured in litres. The accuracy of OH depends on the physiological hydration properties of body tissues which are considered to be independent of the population measured. These hydration properties were derived by dilution methods [15, 16]. The same amount of OH can be of different clinical relevance depending on the size of the patient; an OH of 2 L in a small female may be clinically more significant than in a muscular large male. Thus, studies using this machine have normalized the OH value to OH/ECW.

If the BCM readings are precise, accurately reflect hydration status and have clinical relevance, we hypothesized that OH defined that use of the BCM should be an independent predictor of mortality. We also determined which (if any) parameter of hydration (ECW/TBW versus OH versus OH/ECW) was a better predictor of mortality. We also confirmed that the predictive value of OH/ECW remains independent of nutritional status as the latter is known to influence mortality.

MATERIALS AND METHODS

Patients

The study was conducted in accordance with the principles set out by the local ethical committee according to the UK National Health Service audit and clinical service development. We studied a cohort of patients from a single PD unit. All patients with amputations, cardiac pacemakers or defibrillators were excluded as we were unable to perform BIS measurements. The cohort of patients consists of all continuous ambulatory PD (CAPD) and automated PD (APD) patients between 1 January 2008 and 30 March 2012, who had at least one BCM reading. The first BCM reading performed on the patient was used in this study to determine its predictive value (with death as the end point). For incident patients, BCM measurements were usually performed during their PD training, but if this was not possible (e.g. patients were trained at home) and for prevalent patients, BCM measurements were performed routinely during clinical appointments (quarterly for stable patients but more frequently as clinically dictated). All results were available to the clinician to manage patients' dialysis care.

Patients were followed up until 15 September 2012, regardless of whether they were transplanted or switched to HD beforehand. Only patients that recovered renal function or who were transferred to another dialysis unit for geographic relocation reasons were excluded (their survival follow-up could not be accurately determined). In all cases, baseline characteristics were collated through review of case notes and included primary cause of renal failure, dialysis vintage, presence or absence of diabetes mellitus and biochemical parameters (almost invariably performed on the day of the BCM or within a few days). RRF (protocolized every 3 months) was assessed through 24-h urine collections by determining urine volume and creatinine clearance [arithmetic mean of creatinine and urea clearances normalized to 1.73 m^2 body surface area (BSA)].

The multi-frequency bio-impedance spectroscopy monitors

The Fresenius Body Composition Monitor (BCM—Fresenius Medical Care, Bad Homburg, Germany) was used to measuring bioimpedance at 50 frequencies between 5 and 1000 kHz. The measurement is performed by placing electrodes on one hand and one foot in the BCM and entering current height and weight data into the machine. Readings including the weight of the patient were performed with the peritoneal dialysate *in situ*.

Statistical analysis

Categorical variables have been expressed as a number and a percentage. Continuous variables are expressed as means and standard error of the means (SEM) or median with quartile ranges depending on whether the results of the parameters were normally distributed (determined by the D'Agostino–Pearson omnibus normality test). If not normally distributed these parameters were analysed on a logarithmic scale. Correlation coefficients then multivariate logistical regression analyses were undertaken with SPSS software for Windows version 20.0 (SPSS, Inc., Chicago, IL). The regression model was created based on those clinical variables known to effect survival on PD.

RESULTS

Demographics

There were 529 APD and CAPD patients who had at least one BCM reading during the study period. The median (quartile range) age of patients was 57.0 (46.7–68.8) years with a median dialysis vintage of 5.1 (0.8–32.1) months, 62% were male and 33% had diabetes mellitus (Table 1). The mean (SEM) values of the hydration parameters are OH 1.28 (0.11) L, OH/ECW 0.06 (0.05) and ECW/TBW 0.48 (0.00). Over the follow-up period, 18% of the cohort died.

Correlation between hydration parameters

As might be expected, there were statistically significant correlations between the OH value and the other two parameters of hydration ($P < 0.0001$ for both OH/ECW and ECW/TBW) although the correlation with OH/ECW was better; $r^2 = 0.91$ versus 0.31 for ECW/TBW (Figure 1). Patients were considered severely over hydrated if their OH value was ≥1.9 L, OH/ECW of >0.10 or ECW/TBW of >0.50 (i.e. were in the top 30% of that parameter). Of the 175 patients defined as severely over hydrated by OH value, 10 (5.6%) were not severely overhydrated by OH/ECW and 52 (30%) were considered not severely overhydrated by the ECW/TBW threshold.

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Table 1. **Baseline demographic and biochemical details of patients included in study (including sub-division between prevalent versus incident patients)**

	All (*n* = 529)	Incident (*n* = 225)	Prevalent (*n* = 304)	P-value*
Age[a] (years)	57.0 (46.7–68.8)	53.7 (42.9–66.9	58.6 (48.4–69.8)	<0.01
Male, *n* (%)	329 (62)	131 (60)	198 (65)	
Diabetic mellitus, *n* (%)	173 (33)	78 (35)	95 (28)	
Assessed as suitable for transplantation, *n* (%)	253 (48)	95 (42)	158 (52)	
Dialysis vintage[a] (months)	5.1 (0.8–32.1)	0.7 (0.4–1.3)	27.4 (10.0–56.8)	<0.001
BMI				
Body composition measurements: mean (SEM)				
OH (L)	1.28 (0.11)	1.84 (0.17)	0.86 (0.13)	<0.001
OH/ECW	0.06 (0.01)	0.06 (0.01)	0.04 (0.01)	<0.001
ECW/TBW	0.48 (0.00)	0.48 (0.00)	0.47 (0.00)	ns
Biochemical values: mean (SEM)				
Serum sodium (mmol/L)	139.62 (0.15)	140 (0.2)	139.1 (0.2)	<0.001
Serum albumin (g/L)	39.34 (0.26)	39.6 (0.4)	39.1 (0.3)	ns
Log (CRP)	0.93 (0.02)	0.89 (0.23)	0.95 (0.02)	<0.05
RRF: mean (SEM)				
CrCl resid norm (L/week/1.73 m^2 BSA)	52.2 (7.9)	53.7 (7.1)	51.0 (12.2)	ns
Urine volume (mL)	789 (31)	886 (46)	724 (40.0)	<0.01
Peritoneal membrane function: mean (SEM)				
Dialysate/plasma creatinine at 4 h	0.64 (0.01)	0.63 (0.01)	0.65 (0.01)	ns
Ethnicity, *n* (%)				
Whites	197 (37)	73 (32)	124 (41)	
Blacks	105 (20)	42 (19)	63 (21)	
Asians	196 (37)	88 (39)	108 (36)	
Others	31 (6)	22 (10)	9 (3)	
Cause of renal failure, *n* (%)				
Unknown	134 (25)	66 (30)	68 (22)	
GN	87 (16)	26 (12)	61 (20)	
Cancer/trauma	4 (1)	3 (1)	1 (0)	
Congenital/familial	12 (2)	5 (2)	7 (23)	
Diabetes	145 (27)	69 (31)	76 (25)	
Hypertension	43 (8)	16 (7)	27 (9)	
APKD	32 (6)	11 (5)	21 (7)	
TIN/chr pyelo	14 (8)	29 (13)	43 (14)	

Incident PD patients were defined if enrolment into study was within 90 days of PD initiation.
OH denotes the over-hydration reading from the BCM. ECW denotes the derived extra-cellular water volume.
CRP, C-reactive protein; CrCl resid norm, estimated glomerular filtration rate derived from 24-h urine collection (mean of the creatinine and urea clearance, normalized to 1.73 m^2 BSA). GN, glomerulonephritis; APKD, adult polycystic kidney disease; TIN, tubular-interstitial nephritis.
Values represent mean (SEM) or number (%) unless denoted by [a](values shown are median, interquartile ranges).
*P-value comparing incident versus prevalent patient characteristics.

Univariate analysis for predictors of patient survival

On separate univariate analyses, we found that a younger age, absence of diabetes, shorter dialysis vintage, females, not being of Asian ethnicity, lower baseline C-reactive protein (CRP) and assessed as being suitable for kidney transplantation were factors associated with improved patient survival (Table 2). All three hydration parameters predicted death on univariate analyses. The median time difference between the BCM and RRF/peritoneal equilibration test result was 71 days. However, RRF expressed as 24-h urinary volume or creatinine clearance, serum albumin and peritoneal membrane function defined by dialysate/plasma creatinine ratio on peritoneal equilibration test were not predictors of survival.

Multivariate analysis for predictors of patient survival

Three multivariate Cox regression models were created using the variables that were shown on univariate analysis to be predictive of death (each with a different parameter of hydration). In addition, because serum albumin has been shown to be associated with BIS readings, we included this parameter in our model even though it was not statistically predictive of survival in our univariate analysis.

Consistently, increasing age and dialysis vintage, male, ethnicity and high CRP remained independent predictors of death in our cohort. Interestingly, suitability for transplantation, diabetes status and serum albumin was not found to be independent predictors in the multivariate Cox regression models irrespective of which BCM hydration parameter was included.

Both the OH and OH/ECW values were statistically significant independent predictors of survival. However, ECW/TBW as a continuous variable was not an independent predictor of death (Table 3).

Severe OH defined as the highest 30% of OH, OH/ECW or ECW/TBW were all independent predictors of death (Table 4). The 30% of patients most severely overhydrated as defined by ECW/TBW had the highest increased adjusted risk of death of 2.05 [95% confidence interval (CI) 1.31–3.22, P < 0.005], even though as a continuous variable it was not a predictor. In contrast, the severely overhydrated patients defined

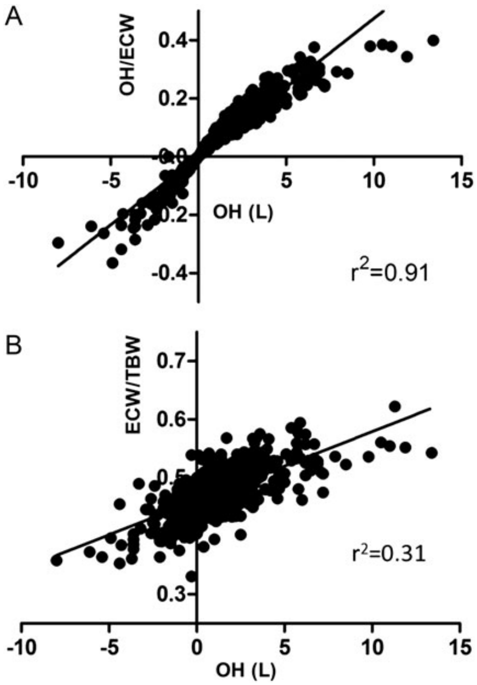

FIGURE 1: Comparing the BCM readings of hydration: correlation between OH and (**A**) OH/ECW, (**B**) ECW/TBW.

Table 2. Univariate Cox regression analysis for different factors as risk for death

	HR	95% CI	P-value
Parameter of hydration			
OH (per L)	1.13	1.05–1.22	<0.001
OH/ECW (per %)	1.04	1.02–1.05	<0.001
ECW/TBW (per 0.1)	1.47	1.22–1.76	<0.001
Age (per year)	1.07	1.05–1.09	<0.001
Diabetes mellitus	1.96	1.31–2.94	<0.001
Dialysis vintage (per month)	1.004	1.00–1.01	<0.01
Gender (men versus females)	2.04	1.27–3.29	<0.005
Suitability for transplantation	0.30	0.19–0.47	<0.001
RRF			
Urine output (mL/day)	1.00	1.00–1.00	0.28
RRF CrCl (L/week/1.73 m^2 BSA)	1.00	0.99–1.00	0.32
Dialysate/plasma creatinine ratio	6.95	0.97–49.58	0.05
Serum albumin (per g/L)	0.98	0.95–1.02	0.35
Serum CRP (per mg/L)	0.01	1.00–1.01	<0.005
Ethnicity			
White versus non-W	0.86	0.56–1.31	0.47
Black versus non-B	0.62	0.35–1.10	0.10
Asian versus non-A	1.54	1.03–2.30	<0.05

OH, overhydration measurement; ECW, extra-cellular water volume; TBW, total body water volume; RRF, residual renal function estimated as the mean of urea and creatinine clearance (measured from 24-h urine collections) that is normalized to 1.72 m^2 BSA. CRP, C-reactive protein; CrCl, creatinine clearance.
P-values of <0.05 were considered statistically significant.

by OH had an increased adjusted risk of death of 1.83 (95% CI 1.19–2.82, P < 0.01), Figure 2.

Comparing the predictive values of different thresholds of OH

Using the pre-defined threshold of 30% to classify OH, OH was able to predict death in the patients with a sensitivity of 47% and a specificity of 49%. OH/ECW had a near identical level of sensitivity and specificity (48 and 49%, respectively) while ECW/TBW showed a marginally better level of sensitivity and specificity (53 and 48%). We repeated the sensitivity and specificity analysis of each parameter to predict death when the threshold was raised to the highest 25, 20, 15, 10 and 5%. The receiver operating characteristic for the three parameters to predict death was similar (Figure 3).

Influence of nutrition parameters on BIA and its predictive value

Patients were divided into tertiles according to their body mass index (BMI). The derived OH/ECW values were not statistically different in the different BMI groups (Figure 4) confirming that BCM was designed to take into account the underlying body composition when calculating ECW and OH. The BCM also calculates the lean tissue index (LTI) of the individual. Separately, BMI and LTI were included in the Cox proportion hazard model but neither was predictive of mortality. The patients with the lowest 1/3 LTI had a hazard ratio (HR) of death of 1.52 (95% CI 0.88–2.63, P = 0.13). Interestingly, after OH/ECW was included in the model, the predictive value of low LTI improved although it remained non-statistically significant: 1.63 (95% CI 0.94–2.83, P = 0.08). OH/ECW remained a statistically significant independent predictor of mortality even after inclusion of either BMI or LTI (data not shown).

Effect of gender on survival

In our current study, the effect of gender on mortality was marked (Table 2: univariate HR 2.04, 95% CI 1.27–3.29), and this was also significant on multivariate analysis (Table 3). The literature on the effect of gender on survival in dialysis patients is somewhat conflicting. In a 1999 systematic review of 24 publications that studied risk factors for dialysis mortality, gender was found to be poorly reported and no analysis could be made [17]. US renal data system (USRDS) data from 1999 found that males had higher mortality. Although there appeared to be an era-dependent effect, the prevalent male dialysis patients still had a higher adjusted mortality rate in the 2013 report [18]. Nevertheless, our finding that men doubled the risk of death is much higher than that found in both the USRDS and the French Association Régionale des Néphrologues de Rhône–Alpes Registry [19]. Thus, although not prespecified at the outset of the study, we felt it necessary to perform further analysis. The marked difference in survival may reflect selection bias of the study population (this was essentially a prevalent PD study and differential PD take on technique survival and transplantation rates prior to patient enrolment into the study may be important confounders). Using the parameters of OH and OH/ECW, males were significantly more over-hydrated than females. Although there was no difference in the mean ECW/TBW between males and females, this is clinically very significant; the normal range of ECW/TBW is age–gender dependent. Thus, in the Supplementary data, we transformed the raw ECW/TBW data and expressed the value as the number of deviations from the

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Table 3. Multivariate analyses using different hydration parameters in each model

	OH value (per L)				OH/ECW (%)				ECW/TBW (per increment of 0.1)			
	P-value	HR	95% CI		P-value	HR	95% CI		P-value	HR	95% CI	
			Lower	Upper			Lower	Upper			Lower	Upper
BCM parameter	0.025	1.10	1.01	1.20	0.00	1.03	1.01	1.05	0.12	1.21	0.95	1.54
Diabetes mellitus (versus non-diabetes mellitus)	0.12	1.43	0.91	2.25	0.14	1.41	0.89	2.22	0.22	1.34	0.84	2.14
M gender (versus F)	0.01	2.08	1.22	3.57	0.01	2.08	1.22	3.57	0.00	2.22	1.28	3.84
Age (per year)	0.00	1.07	1.04	1.10	0.00	1.07	1.04	1.10	0.00	1.06	1.04	1.09
Dialysis vintage (per month)	0.00	1.01	1.00	1.01	0.00	1.01	1.00	1.01	0.00	1.01	1.00	1.01
Unsuitable for transplantation	0.32	1.37	0.73	2.57	0.35	1.34	0.72	2.50	0.17	1.54	0.83	2.86
Ethnicity (non-W versus W as reference)	0.00	2.02	1.25	3.24	0.00	2.03	1.27	3.26	0.01	1.92	1.20	3.08
Serum albumin (per g/L)	0.28	0.98	0.94	1.02	0.27	0.98	0.94	1.02	0.27	0.98	0.94	1.02
Log(CRP)	0.00	2.21	1.40	3.50	0.00	2.22	1.41	3.49	0.00	2.37	1.50	3.77

HR, hazard ratio; BCM, Body Composition Monitor parameters; M, male; F, females; W, whites; CRP, C-reactive protein, measured in mg/L.

Table 4. Multivariate analyses using different hydration parameters to determine if severe overhydration (highest 30%) predicts death

	OH value				OH/ECW				ECW/TBW			
	P-value	HR	95% CI		P-value	HR	95% CI		P-value	HR	95% CI	
			Lower	Upper			Lower	Upper			Lower	Upper
BCM parameter	0.01	1.83	1.19	2.82	0.00	2.09	1.36	3.20	0.00	2.05	1.31	3.22
Diabetes mellitus	0.12	1.44	0.91	2.26	0.12	1.43	0.91	2.26	0.43	1.21	0.75	1.93
M gender (versus F)	0.01	2.02	1.17	3.50	0.01	2.07	1.20	3.57	0.00	2.36	1.38	4.07
Age (per year)	0.00	1.07	1.05	1.10	0.00	1.07	1.05	1.10	0.00	1.06	1.04	1.09
Dialysis vintage (per month)	0.00	1.01	1.00	1.01	0.00	1.01	1.00	1.01	0.00	1.01	1.00	1.01
Suitable for transplantation	0.45	0.78	0.42	1.47	0.48	0.80	0.43	1.50	0.21	0.67	0.36	1.25
Ethnicity (W versus non-W)	0.01	0.51	0.32	0.82	0.01	0.52	0.32	0.83	0.00	0.45	0.28	0.74
Serum albumin	0.18	0.97	0.93	1.01	0.20	0.97	0.94	1.01	0.30	0.98	0.94	1.02
Log(CRP)	0.00	2.30	1.45	3.63	0.00	2.26	1.43	3.57	0.00	2.37	1.49	3.76

Serum albumin measured in g/L. For the categorical values, the reference points are: not diabetic, females, not suitable for transplant and white.
HR, hazard ratio; BCM, Body Composition Monitor parameters; M, male; F, females; W, whites; CRP, C-reactive protein (g/L).

age- and gender-adjusted mean. The transformed data also suggested (consistent with OH and OH/ECW data) that males in our cohort were more overhydrated than females (Supplementary data Figure S3). The differences in demographics and clinical characteristics of the male and female patients included in the study have been described in more details in the Supplementary data. There was no difference in the mean BMI of males (26.8 ± 0.3) versus females (26.9 ± 0.4, P = ns).

Prevalent versus incident patients in the study

The design of the study included prevalent and incident patients. The median time between the patient starting PD and having their BCM measurement was 5.10 months. Using the 90-day threshold, there were 225 incident versus 304 prevalent patients. The differences in the incident versus prevalent cohorts are provided in Table 1. Using the OH and OH/ECW parameters, incident patients were significantly more overhydrated than prevalent patients, but there was no statistically significant difference in their ECW/TBW values.

We performed multi-variate analysis and determined that OH/ECW and ECW/TBW remained significant predictors of death for the prevalent cohorts (incorporating the factors: age, gender, diabetes mellitus status, dialysis vintage, ethnicity, serum albumin and CRP) although statistical significance was not reached for ECW/TBW in the incident patients (further details available in the Supplementary data). The lack of statistical significance for ECW/TBW in the incident cohort may be due to the smaller number of patients and the lower rate of mortality (Type II statistical error).

Males and females have different proportions of lean and fat tissue mass, and it was, therefore, particularly important that we tried to dissociate the nutritional status from the hydration effects on the bioimpedance readings repeating the mortality HR within different BMI tertiles.

DISCUSSION

Our study showed that different parameters to quantify hydration by bioimpedance technology were all independent predictors of death in PD patients. Wizemann *et al.* [1] also used the BCM machine and showed that hydration state defined by OH/ECW was an important and independent predictor of mortality in chronic HD patients secondary only to the presence of diabetes. Paniagua *et al.* [8] similarly showed in a

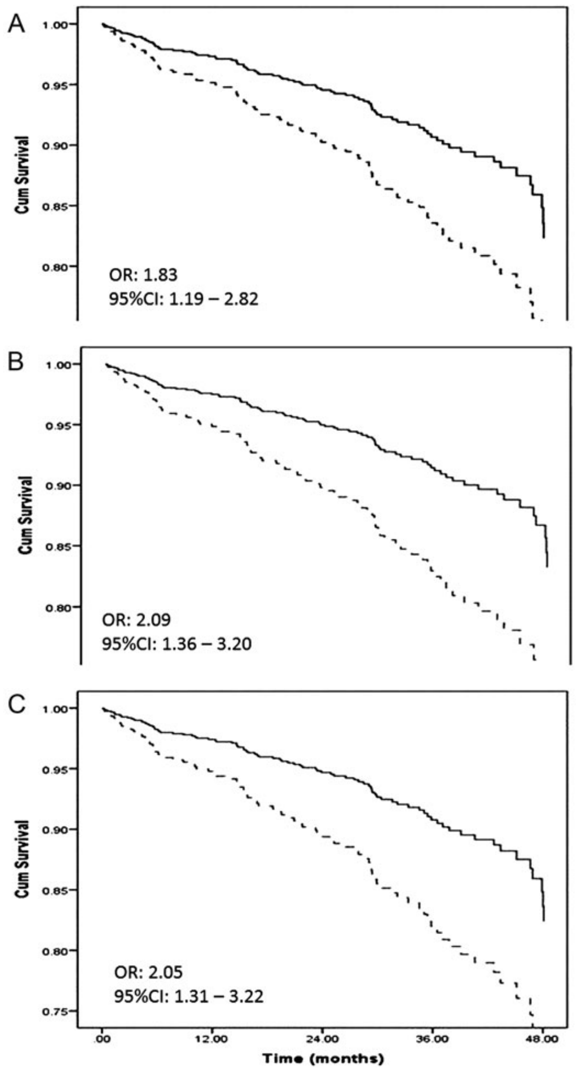

FIGURE 2: Adjusted (using factors included in Table 4) survival curve according to patients' hydration status. 'Severely overhydrated' (broken line) and the 'not severely overhydrated' (solid line) were defined according to the BCM using (**A**) OH values, (**B**) OH/ECW and (**C**) ECW/TBW. Threshold was set at highest 30%.

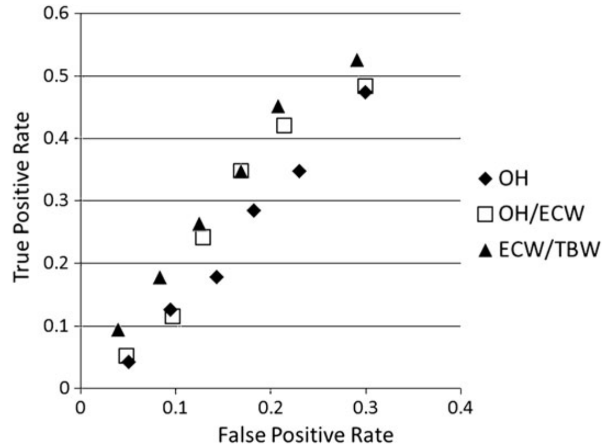

FIGURE 3: Comparing the different BCM parameters. Positive and negative predictive values for death using OH, OH/ECW or ECW/TBW. OH, diamonds; OH/ECW, open boxes and ECW/TBW, triangles.

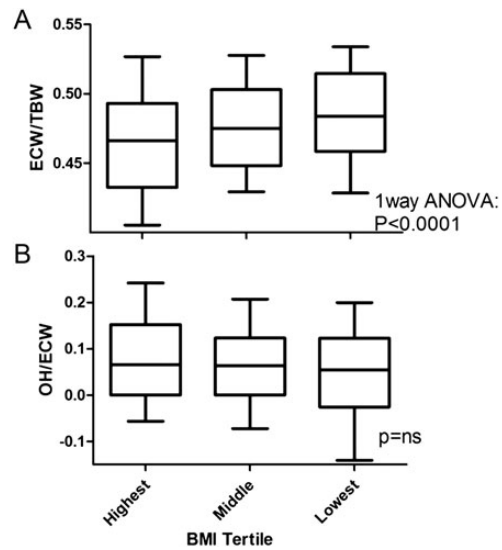

FIGURE 4: Effect of obesity (BMI) and its effect on hydration parameters: (**A**) ECW/TBW, (**B**) OH/ECW. Box plots representing median, quartiles, 10th and 90th centile ranges.

mixed cohort of PD and HD patients that hydration defined by BIS was also a predictor of mortality. We believe these studies demonstrate that the BCM and bioimpedance technology provides useful and important information for managing patients with end-stage renal failure.

We found that the OH value or the normalized OH value (OH/ECW) outputted by the BCM machine were independent predictors of death, whereas the continuous variable ECW/TBW was not an independent predictor. There are many possible reasons for this. In particular, the 'normal value' for ECW/TBW will be dependent on age and gender. Deviations of this value from the norm can be due to both hydration and the nutritional status of the patient (a known important determinant of mortality as shown elsewhere using independent reference methods [16]). Our data confirmed that OH/ECW was unchanged in different BMI tertiles, suggesting that this parameter was not confounded by nutritional status of the patient. Moreover, including BMI into the Cox proportional-hazard models did not affect the predictive value of OH/ECW for mortality. Thus, the BCM would appear to be able to predict mortality based on its algorithm to estimate hydration status, and this was independent of the nutritional status of the patient.

When we set thresholds to define severe OH (highest 30%), paradoxically, ECW/TBW predicted death slightly better than OH or OH/ECW. This is graphically illustrated by the receiver operator curve (Figure 3), although differences in predictive values were marginal. It is also important to note that the positive predictive values of BCM for death were poor (sensitivity using a threshold of the highest 30% was ∼50%). However, this was expected as outcome was all-cause mortality, and the study design meant some patients were only followed up for 6 months (although the median follow-up was 27 months).

We believe that our study supports the use of the BCM 'OH' value to determine hydration status. This parameter is particularly useful as this is directly outputted from the machine allowing point of care result without the clinician having to calculate an index. Secondly, the OH value provides an estimate of how much the patient is overhydrated and allows the clinician to set a new target/euvolaemic weight for the patient to achieve. In contrast, ECW/TBW readings are confounded by nutritional status and cannot estimate the exact degree of OH. Moreover, this 'raw' value should be interpreted cautiously; the 'normal' value will vary according to the patient's age and gender [20]. A further complicating factor is that the calculation used to determine the normal value of ECW/TBW was based on a normal population that was 98% Caucasian.

In the re-analysis of the CANUSA study [9], each 250 mL of daily urine output conferred a 36% reduction in mortality. The importance of preserving RRF has, therefore, played a large part in the treatment of CAPD patients. Gunal *et al.* [21] reported that strict salt and water restriction and/or increased ultrafiltration (without using bioimpedance technology) led to a 28% reduction in urine output and a 10% reduction in weekly *Kt*/*V* urea. This has led to proposals that PD patients should be kept 'mildly overhydrated' to preserve RRF. Interestingly, we did not find that RRF was an independent predictor of death (likely to be a Type II statistical error related to sample size). In contrast, OH was a predictor of death, suggesting that we should not trade OH for preservation of RRF. Moreover, in a previous cross-sectional survey, we have shown that greater ECW content was not associated with higher RRF [22]. We also showed in a small cohort study that correcting severe OH was possible and did not lead to significant loss of RRF over a 6-month period [23]. It is, therefore, a concern that in a large multi-centre European study of 639 patients, 53% of PD patients were overhydrated and 25% had an OH status equivalent to >2 [24].

We also showed in a previous study that patients of Asian ethnicity demonstrated a discrepancy between BIS-determined TBW compared with anthropomorphic-based equations [25]. In the Supplementary data, we have compared the BCM readings of our cohort according to ethnicity. We found that whites were more 'overhydrated' than Asians and blacks (Supplementary data Figure S6). But, it is not possible from our data to determine if there were true differences in hydration status or if the apparent OH is misinterpretation of bio-impedance given that body composition may be different between whites, asians and blacks. It was therefore important that we included ethnicity in our multivariate analysis and still found that the OH/TBW remained an independent predictor.

Limitations of this study include the retrospective nature of the data collection and the fact that we included both incident and prevalent patients (who had very different hydration characteristics although dialysis vintage was included in the multivariate analysis). To address this issue, we performed separate analyses on prevalent and incident patients (Supplementary data) and found consistent results (Supplementary data Figure S5). Measuring BIA with dialysate *in situ* may have reduced the precision of the measurements [26]. We only studied a single BCM reading; even in healthy individuals, variations in hydration can be detected [27]. Nevertheless, it is important to note that, despite these limitations, the BCM hydration value continued to be significantly correlated with mortality suggesting that the BCM may have a role in clinical practice.

Our study demonstrated (as we expected) that age, dialysis vintage, diabetes and serum CRP were independent predictors of death, suggesting that our data collection was accurate. There were four factors that we initially expected, but were not shown, to be independent predictors: diabetes mellitus status, RRF, serum albumin and physician assessment for suitability for transplant. Although the first and last of these factors were predictive in unadjusted analyses, perhaps it is not surprising that after including confounders such as age and CRP, suitability for transplantation was no longer an independent predictor. Moreover, large registry databases have also shown that once age is included, diabetes status is no longer an independent predictor of mortality in dialysis patients. We would, however, emphasize caution when interpreting our data; the high mortality of men compared with women would suggest some degree of selection and treatment bias; Supplementary data shows that if follow-up is censored for transplantation and PD technique failure, there is no difference in mortality between the genders (Supplementary data Table S2, although mortality falls from 18 to 10% so the probability of a Type II statistical error increases). Therefore, our results should be confirmed in further studies.

It has been demonstrated in a randomized, controlled and blinded study that the BCM can aid the physician in achieving better volume control [28]. Our study does not prove that achieving better volume control leads to improved survival but suggests that further randomized, controlled trails designed to address hydration status would be worthwhile. Therefore, we await with great interest the results of two randomized studies on the impact BIA might have on left ventricular mass [29] and survival [30].

SUPPLEMENTARY DATA

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

CONFLICT OF INTEREST STATEMENT

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