Pre-dialysis and post-dialysis hydration status and N-terminal pro-brain natriuretic peptide and survival in haemodialysis patents

[1]Kamonwan Tangvoraphonkchai MD, [2]Andrew Davenport FRCP

[1]Faculty of Medicine, Mahasarakham University, Mahasarakham, Thailand
[2]UCL Centre for Nephrology, Royal Free Hospital, University College London Medical School, London NW3 2PF, UK

Kamonwan Tangvoraphonkchai kamonwan.tangvoraphonkchai@nhs.net
Andrew Davenport andrewdavenport@nhs.uk

Address for correspondence
Andrew Davenport andrewdavenport@nhs.net

contact andrewdavenport@nhs.net
UCL Centre for Nephrology, Royal Free Hospital, University College London Medical School, Rowland Hill Street, London NW3 2PF
tel 44-2074726457 fax 44-2073178591

short title change in bioimpedance hydration index following haemodialysis

key words bioimpedance haemodialysis over hydration extracellular water intracellular water brain natriuretic peptide

word count

abstract	237
body	2338
figures	2
tables	4
references	34

Funding Royal Free Hospital

Neither author has any conflict of interest

Abstract

Background

Many dialysis centres have no formal program for assessing and adjusting post-haemodialysis (HD) target weight. Apart from clinical assessment, there are bioimpedance devices and natriuretic peptides which could potentially aid clinical management. We wished to determine whether pre or post HD bioimpedance assessment of extracellular water ECW), or N terminal probrain natriuretic peptide (NT-proBNP) affected patient outcomes.

Methods

Multi-frequency bioimpedance assessments (MFBIA) were made pre and post the midweek dialysis session along with post dialysis NT-proBNP measurement.

Results

Data from 362 patients, median age of 63 (50-76) years, 59.7% male, 41.2% Caucasoid, with a median dialysis vintage of 31.4 (13.5-61.7) months were available for review. During a median follow up of 49.6(21.9-50.2) months there were 110 (30.4%) deaths. Patients who died had significant increased ECW, as % overhydrated both pre 6.6 (5.8-7.6)% vs survivors 5.1 (4-6.6)%, and post HD 5.1 (4-6.6)% vs 0.5 (-1-2.2.0, $p<0.001$, respectively, and higher NT-proBNP (325 (122-791) vs 102 (48-342) pmol/l, $p=0.002$. Using an adjusted Cox model only pre-HD ECW over-hydration remained an independent factor associated with mortality (% over hydration: hazard ratio 1.15, 95% limits 1.03-1.28, $p=0.013$), with a receiver operator curve (ROC) value of 0.7.

Summary

ECW excess is associated with increased mortality for HD patients, with the strongest association being with ECW excess pre dialysis, although these patients also had increased ECW post-dialysis. Future trials are required to determine whether achieving euvolaemia as determined by bioimpedance improves patient survival.

Introduction

Despite the advances in haemodialysis technology over the last 50 years [1], and widespread use with more than 2 million patients now receiving treatment world-wide, survival has not equally improved. In the UK, the expected lifespan for patients starting dialysis aged 40 to 49 years of age is approximately 10 years and 5 years for those aged 60 to 69 years of age [2] Not only are these substantially worse than those for the general population [3], but also worse than for some of the more common solid organ malignancies [4].

Prospective multicentre randomised controlled trials have failed to demonstrate that increasing small solute clearances (urea) [5], or increasing membrane flux have improved survival [6]. Solute clearance is only one part of the dialysis prescription, as dialysis should also restore hydration status and sodium balance. Patients who are consistently more than 2 kg above their post-dialysis target weight are at increased risk for mortality [7]. In most centres determining volume status and the post dialysis target weight depends upon physical examination and blood pressure review [8]. More recently the introduction of bioimpedance techniques [9] as established that many haemodialysis patients are chronically volume overloaded, and that volume overload is an independent risk factor for mortality [10]. Volume overload also increases the release of natriuretic peptides from the heart, such as N terminal probrain natriuretic peptide (NT-proBNP) [11]. Both bioimpedance measurements of volume overload and plasma NT-proBNP have been reported to be associated with increased risk of mortality for haemodialysis patients [10,12].

As it is unclear as to whether the association between increased mortality risk and volume overload is related to increased hydration status pre-dialysis [10] or those who remain overhydrated post-dialysis [7], we reviewed the outcomes of patients who had corresponding pre- and post-dialysis bioimpedance measurements along with post dialysis NT-proBNP measurements.

Methods

We included all established adult dialysis outpatients who had corresponding pre and post mid-week dialysis session bioimpedance measurements recorded along with a post session NT-proBNP measurement dialysing in our kidney dialysis centres January 2011-December 2011. Patients who did not have an established target were excluded; including those who had been discharged from hospital within the previous 90 days and patients who had been established on dialysis for < 90 days. Patients who could not stand to be weighed, and those with pacemakers were also excluded.

Patients used either Fresenius 4008H/5008 or BBraun Dialogue+® dialysis machines with integrated blood pressure monitors (Fresenius Bad Homburg, Germany and BBraun, Melsungen, Germany), polysulfone dialyzers (Nipro Corporation, Osaka, Japan)[13], with ultrapure quality dialysis water and we used single bolus low molecular weight heparin anticoagulation (Tinzaparin, Leo Laboratories, Princes Risborough, UK) [14].

Blood pressure and dialysis session parameters were recorded in the renal department password protected electronic data base, along with patient

demographics and medical records. Patient co-morbidity was graded according to the Stoke-Davies co-morbidity score [15].

Multi-frequency bio-electrical impedance assessments (MF-BIA) were standardized by taking measurements pre and 20-30 minutes post-dialysis session, using an eight-electrode MF-BIA device (Biospace In body 720, Seoul, South Korea)[16,17]. Patients with pacemakers or implantable defibrillators and amputees were excluded from study. Relative extracellular water volume (ECW) excess termed extracellular water over hydration was estimated according to the method recommended by the European Society for Parenteral and Enteral Nutrition (ESPN) [18].

Serum biochemistry samples were analysed with a standard multi-channel biochemical analyzer (Roche Integra, Roche diagnostics, Lewes, UK), using the bromocresol green method for albumin determination, NT-proBNP was measured by immunoassay (ECLIA Roche Diagnostics, GMBH, Mannhein, Germany), with an inter assay coefficient of variation 1.3% [19], and a sensitive C reactive protein assay (<0.5 mg/L) as used by the UK National Amyloid service[20], and β2 microglobulin measured by rate nephelometry (Image 800 analyser, Beckman Coulter, High Wycombe, UK) [21]. Standard blood tests were taken after the pre-dialysis bioimpedance measurement and prior to starting the midweek dialysis session and NT-proBNP measured post dialysis prior to the post-dialysis bioimpedance measurement.

158 Statistical analysis

159 Data with a normal distribution was presented as mean ±SD, while non-
160 normally distributed data was presented as median and interquartile range.
161 Student's t test and the Mann Whitney U test were used for intergroup
162 comparisons respectively, with correction for multiple testing as appropriate by
163 Bonferroni or Dunn's correction respectively. For further analysis data which
164 was not normally distributed was log transformed as appropriate. Pearson's rank
165 correlation was performed for univariate analysis to select significant variables
166 and those with $p<0.1$ which were then entered into a multivariate Cox
167 proportional hazard model to examine hazard function of each variable. Pre and
168 post dialysis extracellular to total body water and percent over-hydration were
169 analysed in separate model due to high correlation among variables. The
170 predictive values of all significant variables were then compared by ROC curves
171 with AUC calculation. SPSS Statistics version 23 (University of Chicago, Illinois,
172 USA) was used for statistical analysis. A p-value <0.05 was taken as achieving
173 statistical significance.

174

175 Ethics

176 We audited the results of pre and post haemodialysis bioimpedance
177 measurements obtained during routine clinical practice to determine whether
178 bioimpedance derived hydration status was associated with an increased
179 mortality. Patient specific data was anonymised. Ethical approval fulfilled UK
180 NHS clinical service development and audit (UK NHS guidelines for clinical audit

and service development (http://www.hra.nhs.uk/documents /2013/09/ defining-research.pdf)).

Results

Records of 362 patients were available for review with a median age of 63 (50-76) years, with 59.7% being male, 41.2% Caucasoid, and a median dialysis vintage of 31.4 (13.5-61.7) months. In terms of co-morbidity 36.7% had diabetes, 81.5% hypertension, 25.7% had cardiac disease and 27.3% were Davies co-morbidity grade 0, 58.6% grade 1 and 14.1% grade 2.The majority of patients dialysed with an arterio-venous fistula (71.3%), and 37.6% of patients were treated by haemodiafiltration and 63.4% by high flux haemodialysis. The median follow-up time was 49.6 (21.9-50.2) months during which there were 110 (30.4%) deaths. The total number of patients scheduled for dialysis was 465; 103 patients were excluded from analysis due to inability to stand to be weighed (14 due to amputations, 4 severe stroke and 4 stretcher cases), pacemakers (12), recent starters on the haemodialysis program (31), recent discharge from hospital (15) and non-attendance for dialysis due to holiday and hospital in-patient admission (13), missing post dialysis bioimpedance results (7), and no NT-proBNP measurement (3).

We compared the demographics of patients who died during follow up with those who survived, as expected survivors were younger, weighed more, with less co-morbidity, lower CRP, and higher serum albumin and haemoglobin

(table 1). Survivors also had lower extracellular water (ECW) to total body water (TBW) ratios both re and post-dialysis (Figure 1), and also less ECW for their intracellular water (ICW), expressed as percentage, termed over hydration, and lower NT-proBNP values (table 1). We used β2 microglobulin as a surrogate for residual renal function, and found no difference between groups.

We found no difference in mortality between those treated by haemodialysis compared to haemodiafiltration. Similarly there was no difference in hydration status, either pre-dialysis (haemodialysis 5.8(4.3-6.7) vs haemodiafiltration 5.8(4.2-7.1) % over hydration) or post dialysis (1.1 (-0.5 -2.8) vs 1.3 (-06-3.1) % over hydration), respectively. However the haemodiafiltration group had a higher haemoglobin (11.8(11.0-12.5) vs 11.2(10.1-12.3) g/dL),p=0.02; serum albumin 41.0 (40-44) vs 41.0 (38-43) g/l, p=0.034, and lower CRP (4(2-8) vs 5(2-14.3)mg/L),p=0.013, and NT-proBNP pmol/L (106(48-321) vs 200 (71-538)),p=0.012, respectively .

Univariate analysis was then undertaken to determine which factors were associated with mortality (table 2). A Cox model showed that Davies co-morbidity grade, log CRP, and pre-dialysis ECW excess, either as pre dialysis ECW/TBW or as percentage over hydration, were independently predictive of mortality. Whilst greater pre dialysis weight and serum albumin were found to be significantly protective factors (tables 3 and 4). However ECW excess post-dialysis, was not associated with mortality, whether assessed by ECW/TBW ratio or percentage over hydration (p = 0.424 and 0.383 respectively).

Receiver operating curves (ROC) for mortality were plotted (figure 2), showing in descending order the area under the curve (AUC) was greatest for pre dialysis ECW/TBW, 0.70 ($p < 0.001$), percentage over hydration pre-dialysis 0.697 ($p < 0.001$), Davies co-morbidity grade 0.689 ($p < 0.001$); post dialysis Log NT-proBNP 0.616 ($p = 0.001$), and Log CRP 0.607 ($p = 0.002$), respectively.

Discussion

Mortality for kidney dialysis patients remains high [2]. Studies have failed to show that increasing urea clearance (Kt/V) increases survival [5]. Similarly simply increasing dialyzer pore size to increase middle molecular weight toxin clearance with high flux dialysis failed to demonstrate any significant survival advantage [6], although achieving high volume on-line haemodiafiltration exchanges has recently been suggested to potentially improve patient survival [22]. On the other hand there are several observational studies showing a strong association between increased inter-dialytic weight gains [23], and ECW overload and mortality [10,24]. Despite the clear association between ECW excess and mortality, most dialysis centres rely on clinical assessment of patients and have no formalised policy of how to address achieving post-dialysis target weights [8]. As not all haemodialysis patients with an expanded ECW are hypertensive, and similarly pre-dialysis blood pressures may equally not be lower in those who are dehydrated with a contracted ECW [25,26], there is a clinical need to develop biomarkers and other measurements to aid clinical decision making in determining post-dialysis target weight.

Bioimpedance devices have developed over the last twenty years from simple frequency devices to multi-frequency and spectroscopy devices [6] capable of measuring ECW and ICW. As there is no simple relationship between patient anthropomorphometry and ECW, there have been debates as how best to express ECW excess, so allowing interpatient comparisons [27], with some authors simply expressing the ratio of ECW/TBW [28], whereas others have estimated the amount of ECW to be expected from the measured ICW, and then expressed the difference in ECW measured and that expected as a measure of, or percentage over hydration [29].

Natriuretic peptides are increased in patients with heart failure, and some reports have suggested an association with ECW excess and increasing concentrations in dialysis patients [11], although others have reported no association [30]. BNP is produced from a pre-prohormone precursor which is cleaved to form N-terminal pro B-type natriuretic peptide, which is then split into BNP 1-32 and NT-proBNP 1-76. Normally there are only small amounts of intact BNP 1-32 in blood, and the major circulating forms of BNP are degradation products which can be detected by different BNP assays to a varying extent. To exclude any possible cross reactivity, and technical problems due to the instability of BNP, we elected to measure the more stable NT-proBNP. We also chose to measure NT-proBNP post the midweek dialysis session, as previous reports have suggested that BNP values are relatively stable during the latter half of the dialysis weekly schedule [31]. We did observe that NT-proBNP values were lower in the haemo-diafiltration group, raising the

possibility that there may have been some removal during treatment, as it has a molecular weight of 8.5 kD. However NT-proBNP is also influenced by inflammation [32], and the haemodiafiltration group had higher haemoglobin and albumin concentrations and lower CRP values. Although we found that the AUC on ROC for NT-proBNP was similar to that of CRP in terms of association with mortality, this was not as high as for pre-dialysis over hydration. Although NT-proBNP is increased by ECW expansion, NT-proBNP may also be influenced by cardiovascular co-morbidity counted as part of the Davies co-morbidity grade [15], and systemic inflammation linked to CRP [33].

We did observe that pre-dialysis ECW excess, whether measured by ECW/TBW ratio or percentage over hydration was independently associated with mortality in our cohort of patients, whereas there was no such association with post-dialysis ECW excess. However those patients who died did have higher levels of ECW than those who survived. This may suggest that patients with greater ECW excess are volume overloaded all through the dialysis week and that they are even more volume overloaded prior to dialysis, or that being more volume overloaded leads to higher ultrafiltration rates, which patients can not readily tolerate, so that patients achieve similar net ultrafiltration during the dialysis session, but then leave more volume overloaded. Several studies have suggest that patients requiring higher ultrafiltration rates, a surrogate for greater ECW overload are at increased risk of death [7].

As many dialysis centres do not have formal protocols or algorithms to assess and change patients' target weights we audited our own results of

measuring pre and post-dialysis bioimpedance measurements along with NT-proBNP, to help decide which if any of these could be a useful biomarker to help in clinical decision making. We found that the pre dialysis ECW/TBW ratio and percentage ECW over hydration measured by bio-impedance had the greatest association with subsequent patient mortality compared to either post dialysis NT-proBNP or hydration status assessed by the ECW/TBW ratio or percentage ECW over hydration. The association between pre dialysis ECW/TBW ratio and percentage ECW over hydration and mortality remained after adjusting for known risk factors including comorbidity index, serum albumin and CRP. Whereas after adjustment, NT-proBNP was longer an independent factor associated with mortality. From our study it would appear that volume assessment would best be served by a pre-dialysis bioimpedance measurement, dispensing with post-dialysis bioimpedance and NT-proBNP measurements.

Many studies have shown an association between volume status and mortality for haemodialysis patients. However these have variously reported an association between either pre-dialysis over hydration [23], or post dialysis over hydration [7]. In the new era of bio-impedance measurements, studies have only reported on pre-dialysis bioimpedance measurements [10, 12,24]. Our study is the first to compare the effect of over hydration measured both pre and post-dialysis. On multivariate analyses we noted an association between pre-dialysis ECW excess and mortality, and although there was no statistical association with either post-dialysis ECW excess or NT-proBNP, both were increased in those who died. However our report is a retrospective observational study from

a single centre, which requires confirmation by other centres in prospective trials to determine whether patient mortality is reduced by targeting a reduction in pre-dialysis ECW expansion by adding bioimpedance measurements to clinical assessments of volume status in haemodialysis patients.

Neither author has any conflict of interest

Funding Royal Free Hospital, KT was awarded an ISN scholarship

References

1. Davenport A. Can advances in haemodialysis machine technology prevent intradialytic hypotension? Semin Dial. 2009;22(3):231-6
2. Steenkamp R, Rao A, Roderick P. UK Renal Registry 17th Annual Report: Chapter 5 Survival and Cause of Death in UK Adult Patients on Renal Replacement Therapy in 2013: National and Centre-specific Analyses. Nephron. 2015;129 Suppl 1:99-129.
3. Arias E. United States Life Tables, 2011. National vital statistics reports : from the Centers for Disease Control and Prevention, National Center for Health Statistics, National Vital Statistics System. 2015;64(11):1-63
4. GBD 2013 Mortality and Causes of Death Collaborators. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2015;385(9963):117-71
5. Eknoyan G, Beck GJ, Cheung AK, Daugirdas JT, Greene T, Kusek JW, Allon M, Bailey J, Delmez JA, Depner TA, Dwyer JT, Levey AS, Levin NW, Milford E, Ornt DB, Rocco MV, Schulman G, Schwab SJ, Teehan BP, Toto R; Haemodialysis (HEMO) Study Group. Effect of dialysis dose and membrane flux in maintenance haemodialysis. N Engl J Med. 2002;347:2010-2019.
6. Locatelli F, Martin-Malo A, Hannedouche T, Loureiro A, Papadimitriou M, Wizemann V, Jacobson SH, Czekalski S, Ronco C, Vanholder R; Membrane Permeability Outcome (MPO) Study Group. Effect of membrane permeability on survival of haemodialysis patients. J Am Soc Nephrol. 2009;20(3):645-54
7. Flythe JE, Kshirsagar AV, Falk RJ, Brunelli SM. Associations of Post haemodialysis Weights above and below Target Weight with All-Cause and Cardiovascular Mortality. Clin J Am Soc Nephrol 2015;10(5):808-16
8. Dasgupta I, Farrington K, Davies SJ, Davenport A, Mitra S. UK National Survey of Practice Patterns of Fluid Volume Management in Haemodialysis Patients: A Need for Evidence. Blood Purif. 2016; 41(4):324-331
9. Davies S, Davenport A. The role of bioimpedance and biomarkers in helping to aid clinical decision-making of volume assessments in dialysis patients. Kidney Int. 2014;86(3):489-96.
10. Wizemann V, Wabel P, Chamney P, Zaluska W, Moissl U, Rode C, et al. The mortality risk of overhydration in haemodialysis patients. Nephrol Dial Transplant.2009;24(5):1574-9.
11. Nongnuch A, Panorchan K, Davenport A. Predialysis NTproBNP predicts magnitude of extracellular volume overload in haemodialysis patients. Am J Nehrol. 2014;40(3):251-7
12. Paniagua R, Ventura MD, Avila-Diaz M, Hinojosa-Heredia H, Mendez-Duran A, Cueto-Manzano A, et al. NT-proBNP, fluid volume overload

and dialysis modality are independent predictors of mortality in ESRD patients. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association. 2010;25(2):551-7.

13. Vernon K, Peasegood J, Riddell A, Davenport A. Dialyzers designed to increase internal filtration do not result in significantly increased platelet activation and thrombin generation. Nephron Clin Pract. 2011;117(4):c403-408
14. Davenport A. Low-molecular-weight heparin as an alternative anticoagulant to unfractionated heparin for routine outpatient haemodialysis treatments. Nephrology (Carlton). 2009;14(5):455-461
15. Davies SJ, Phillips L, Naish PF, Russell GI. Quantifying comorbidity in peritoneal dialysis patients and its relationship to other predictors of survival. Nephrol Dial Transplant 2002; 17: 1085-1092
16. Fürstenberg A, Davenport A. Comparison of multi-frequency bioelectrical impedance analysis and dual-energy X-ray absorptiometry assessments in outpatient haemodialysis patients. Am J Kidney Dis. 2011;57(1):123-129
17. Kumar S, Khosravi M, Massart A, Potluri M, Davenport A. Changes in upper limb extracellular water content during haemodialysis measured by multi-frequency bioimpedance. Int J Artif Organs. 2013;36(3):203-7
18. Kyle UG, Bosaeus I, De Lorenzo AD, Deurenberg P, Elia M, Gómez JM, Heitmann BL, Kent-Smith L, Melchior JC, Pirlich M, Scharfetter H, Schols AM, Pichard C; Composition of the ESPEN Working Group. Bioelectrical impedance analysis--part I: review of principles and methods. Clin Nutr. 2004;23(5):1226-43
19. Davenport A. Changes in N-terminal pro-brain natriuretic peptide correlate with fluid volume changes assessed by bioimpedance in peritoneal dialysis patients. Am J Nephrol. 2012;36(4):371-6
20. Booth J, Pinney J, Davenport A. N-terminal proBNP--marker of cardiac dysfunction, fluid overload, or malnutrition in hemodialysis patients? Clin J Am Soc Nephrol 2010;5(6):1036-40
21. Oates T, Pinney JH, Davenport A. Haemodiafiltration versus high-flux haemodialysis: Effects on phosphate control and erythropoietin response. Am J Nephrol. 2011;33(1):70-5
22. Davenport A, Peters SA, Bots ML, Canaud B, Grooteman MP, Asci G, Locatelli F, Maduell F, Morena M, Nubé MJ, Ok E, Torres F, Woodward M, Blankestijn PJ. Higher convection volume exchange with online hemodiafiltration is associated with survival advantage for dialysis patients: the effect of adjustment for body size. Kidney Int. 2015 Sep 9. doi: 10.1038/ki.2015.264. PMID: 26352299
23. Kalantar-Zadeh K, Regidor DL, Kovesdy CP, Van Wyck D, Bunnapradist S, Horwich TB, Fonarow GC. Fluid retention is associated with

cardiovascular mortality in patients undergoing long-term haemodialysis. Circulation. 2009;119(5):671-9

24. Chazot C, Wabel P, Chamney P, Moissl U, Wieskotten S, Wizemann V. Importance of normohydration for the long-term survival of haemodialysis patients. Nephrol Dial Transplant. 2012;27(6):2404-10
25. Nongnuch A, Campbell N, Stern E, El-Kateb S, Fuentes L, Davenport A. Increased postdialysis systolic blood pressure is associated with extracellular overhydration in haemodialysis outpatients. Kidney Int. 2015;87(2):452-7.
26. Kumar S, Khosravi M, Massart A, Potluri M, Davenport A. Are serum to dialysate sodium gradient and segmental bioimpedance volumes associated with the fall in blood pressure with haemodialysis? Int J Artif Organs. 2014;37(1):21-8.
27. Konings CJ, Kooman JP, Schonck M, van Kreel B, Heidendal GA, Cheriex EC, van der Sande FM, Leunissen KM Influence of fluid status on techniques used to assess body composition in peritoneal dialysis patients. Perit Dial Int. 2003 ;23(2):184-190
28. Konings CJ, Kooman JP, Schonck M, Cox-Reijven PL, van Kreel B, Gladziwa U, Wirtz J, Gerlag PG, Hoorntje SJ, Wolters J, Heidendal GA, van der Sande FM, Leunissen KM. Assessment of fluid status in peritoneal dialysis patients. Perit Dial Int. 2002;22(6):683-692
29. Chamney PW, Wabel P, Moissl UM, Müller MJ, Bosy-Westphal A, Korth O, Fuller NJ. A whole-body model to distinguish excess fluid from the hydration of major body tissues. Am J Clin Nutr. 2007;85(1):80-9
30. Argarwal R. B-type natriuretic peptide is not a volume marker among patients on haemodialysis. Nephrol Dial Transplant. 2013;28(12):3082-9
31. Sheen V, Bhalla V, Tulua-Tata A, Bhalla MA, Weiss D, Chiu A, Abdeen O, Mullaney S, Maisel A. The use of B-type natriuretic peptide to assess volume status in patients with end-stage renal disease. Am Heart J. 2007; 153: 244. e1-5
32. Kumar S, Khosravi M, Massart A, Davenport A. Is there a role for N-terminal probrain-type natriuretic peptide in determining volume status in haemodialysis patients? Nephron Clin Pract. 2012;122(1-2):33-7
33. Jacobs LH, van der Kerkhof JJ, Mingels AM, Passos VL, Kleijnen VW, Mazairac AH, van der Sande FM, Wodzig WK, Konings VW, Leunissen KM, van Dieijen-Visser MP, Kooman JP. Inflammation over hydration and cardiac biomarkers in haemodialysis patients: a longitudinal study. Nephrol Dial Transplant 2010;25(1):243-8
34. Raimann JG, Zhu F, Wang J, Thijssen S, Kuhlmann MK, Kotanko P, et al. Comparison of fluid volume estimates in chronic hemodialysis patients by bioimpedance, direct isotopic, and dilution methods. Kidney international. 2014;85(4):898-908

Figure 1. Extracellular water (ECW) to total body water (TBW) ratios measured by multi-frequency bioimpedance pre and post the md week dialysis session. Values expressed as median (interquartile range). ***p<0.001

Figure 2. Receiver operating curve (ROC) for variables in Cox models. The area under the curve (AUC) for the individual variables were in descending order: pre dialysis extracellular to total body (ECW/TBW) 0.700 (p <0.001), percentage over hydration pre-dialysis 0.697 (p <0.001), Davies co-morbidity grade 0.689 (p <0.001); post dialysis Log NT-proBNP 0.616 (p = 0.001), and Log CRP 0.607 (p = 0.002), respectively.

519 Table 1. Baseline demographics of survivors and those who died during follow up.
520 Davies co-morbidity grade(Davies), Mean arterial blood pressure (MAP), pre-
521 dialysis (pre) and post-dialysis (post), C reactive protein (CRP), N terminal pro-
522 brain natriuretic peptide (NT-proBNP), single pool Kt/V (spKt/V). Data
523 expressed as mean ±SD, median (inter-quartile range) or percentage. P value
524 compared to deceased group.
525

Variable	Deceased	Survivors	P-Value
Patient number	110	252	
Age years	69.5 (59.3-77)	58.5 (46-71)	<0.001
Male (%)	62 (56.4%)	154 (61.1%)	0.416
Caucasoid (%)	51 (46.4%)	98 (38.9%)	0.202
Diabetic (%)	49 (44.5%)	84 (33.3%)	0.045
Vintage months	29 (12.4-72.7)	33.1 (14.3-58.8)	0.870
haemodiafiltration (%)	40 (36.4%)	96 (38.1%)	0.814
Hypertension (%)	88 (80%)	207 (82.1%)	0.660
Heart disease (%)	47 (42.7%)	46 (18.3%)	<0.001
Davies grade 0 (%)	12 (10.9%)	87 (34.5%)	
Davies grade 1 (%)	67 (60.9%)	145 (57.5%)	
Davies grade 2 (%)	31 (28.2%)	20 (7.9%)	<0.001
Arteriovenous fistula (%)	68 (61.8%)	190 (75.4%)	0.011
MAP pre mmHg	90.5 (81.9-107.2)	97.7 (85.6-108.8)	0.109
MAP post mmHg	87.3 (76.6-99.8)	89.5 (80-100.7)	0.317
Weight pre kg	65.1 (57.4-80)	72.3 (62.9-82.5)	0.005
Weight post kg	64.4 (56.4-78.6)	71 (61.2-81)	0.007
Ultrafiltration litres	1.6 (1-2.1)	1.7 (1.1-2.2)	0.160
Over hydration pre %	6.6 (5.8-7.6)	5.1 (4-6.6)	<0.001
Over hydration post %	2.4 (1.2-3.6)	0.5 (-1-2.2)	<0.001
NT-proBNP pmol/l	324.5 (121.5-790.5)	102 (47.8-341.5)	0.002
CRP, mg/L	7 (2-18.9)	4 (2-10)	0.003
Albumin, g/L	40 (38-42)	42 (40-44)	<0.001
Haemoglobin, g/dL	11.1 (10-12.1)	11.6 (10.6-12.5)	0.033
Serum urea pre, mmol/l	19.5 (16.2-22.4)	18.9 (15.8-22.9)	0.788
spKt/V	1.53 (1.22-1.81)	1.52 (1.29-1.79)	0.554
β2 microglobulin ug/l	32.9 (32.1-33.7)	28.9 (23.7-31.4)	0.165

526

527

528

529

Table 2. Univariate analysis of factors associated with mortality. Davies co-morbidity grade (Davies), Mean arterial blood pressure (MAP), pre-dialysis (pre) and post-dialysis (post), C reactive protein (CRP), N terminal pro- brain natriuretic peptide (NT-proBNP), single pool Kt/V (spKt/V).

Variable	R	*P*-value	Variable	R	*P*-value
Age	0.234	<0.001	%Over hydration pre	0.317	<0.001
Davies score	0.318	<0.001	%Over hydration post	0.330	<0.001
MAP pre	-0.086	0.104	Log NT-proBNP	0.166	0.002
MAP post	-0.041	0.434	Log CRP	0.157	0.003
Weight pre	-0.149	0.005	Haemoglobin	-0.090	0.089
Weight post	-0.142	0.007	Serum albumin	-0.211	<0.001
ECW/TBW pre	0.322	<0.001	spKt/V	-0.033	0.555
ECW/TBW post	0.332	<0.001	Ultrafiltration	-0.060	0.256

Table 3 Cox regression model for all-cause mortality, using pre-dialysis ratio of extracellular water (ECW) to total body water (TBW) as measurement of fluid status. Davies co-morbidity grade (Davies), pre-dialysis (pre) and post-dialysis (post), C reactive protein (CRP), N terminal pro- brain natriuretic peptide (NT-proBNP). Hazard ratio (HR)

Variable	HR	Lower 95% CI	Upper 95% CI	*P*-value
Age	1.007	0.992	1.022	0.372
Davies grade	1.582	1.288	1.942	<0.001
Weight pre	0.982	0.968	0.997	0.016
ECW/TBW pre	2.7×10^{9}	123	6.0×10^{15}	0.012
Serum Albumin	0.935	0.885	0.988	0.017
Log CRP	1.974	1.974	2.894	<0.001
Log NT-proBNP	1.050	0.740	1.489	0.784

553 Table 4. Cox regression model for all-cause mortality, using pre-dialysis over
554 hydration % as measurement of fluid status. Davies co-morbidity grade(Davies),
555 pre-dialysis (pre) and post-dialysis (post), C reactive protein (CRP), N terminal
556 pro- brain natriuretic peptide (NT-proBNP). Hazard ratio (HR)

557

Variable	HR	Lower 95% CI	Upper 95% CI	*P*-value
Age	1.007	0.992	1.022	0.370
Davies grade	1.582	1.288	1.943	<0.001
Weight pre	0.982	0.968	0.997	0.016
% Over hydration pre	1.148	1.029	1.279	0.013
Serum Albumin	0.935	0.885	0.988	0.017
Log CRP	1.974	1.347	2.895	<0.001
Log NT-proBNP	1.050	0.740	1.489	0.786

559