



ORIGINAL ARTICLE

Any grade of relative overhydration is associated with long-term mortality in patients with Stages 4 and 5 non-dialysis chronic kidney disease

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ABSTRACT

Background: Overhydration (OH) is associated with mortality in chronic kidney disease (CKD). A relative overhydration adjusted for extracellular water (OH/ECW) measured by bioimpedance >15% has shown an increased mortality risk in haemodialysis but few studies have been developed in advanced CKD. Our objective was to evaluate the effect of OH on mortality in patients with Stage 4 or 5 non-dialysis CKD.

Methods: We performed a prospective study of 356 patients enrolled in 2011 and followed up until 2016. At baseline we collected general characteristics, serum inflammatory and nutrition markers, cardiovascular events (CVEs) and body composition using bioimpedance spectroscopy. During a median follow-up of 50 (24–66) months we collected mortality data.

Results: The mean creatinine was 3.5 ± 1.3 mg/dL, median proteinuria was 0.5 [interquartile range (IQR) 0.2–1.5] g/24 h, median OH was 0.6 (IQR –0.4–1.5) L and mean relative OH (OH/ECW) was $2.3 \pm 0.8\%$. We found that 32% of patients died. The univariate Cox analysis showed an association between mortality and age, diabetes, previous CVEs, Charlson comorbidity index, low albumin and pre-albumin, high C-reactive protein (CRP), low lean tissue and high OH/ECW. Multivariate Cox analysis confirmed an association between mortality and age [exp(B) 1.1 [95% confidence interval (CI) 1.0–1.3]; $P = 0.001$], Charlson comorbidity index [exp(B) 1.1 (95% CI 1.0–1.2); $P = 0.01$], CRP [exp(B) 1.1 (95% CI 1.0–1.2); $P = 0.04$], OH/ECW [exp(B) 3.18 (95% CI 2.09–4.97); $P = 0.031$] and low lean tissue [exp(B) 0.82 (95% CI 0.69–0.98); $P = 0.002$]. Kaplan–Meier analysis confirmed higher mortality in patients with OH/ECW >0% (log rank 11.1; $P = 0.001$).

Conclusion: Any grade of relative OH measured by OH/ECW >0% is associated with long-term mortality in patients with Stage 4 or 5 non-dialysis CKD.

Keywords: bioimpedance, cardiovascular events, chronic kidney disease, mortality, overhydration

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INTRODUCTION

Patients with advanced chronic kidney disease (CKD) have an increased risk of developing cardiovascular events (CVEs) and mortality [1, 2]. Chronic fluid overload has been shown to be a mortality and morbidity risk factor in patients undergoing haemodialysis [3, 4]. An association between fluid overload and morbidity in CKD has also been reported [5–7]. However, hydration status may be difficult to assess due to the imprecision of clinical findings such as arterial hypertension, pulmonary and peripheral oedema and heart failure, which is not always present on examination. Therefore, objective tools to estimate hydration status and body composition are needed. Bioimpedance spectroscopy (BIS) is a simple and non-invasive technique based on tissue resistance to the flow of an alternating current ranging from 5 to 1000 kHz in frequency [8–11]. It has been validated using reference methods. BIS is therefore a useful and reliable tool for assessing body composition and hydration status [12–14].

BIS allows one to estimate overhydration adjusted for extracellular water (OH/ECW). Values >15% have been shown to be a risk factor for mortality and morbidity in patients on haemodialysis [3]. A study demonstrated an association between fluid overload and traditional and novel risk factors for CV disease such as inflammation, proteinuria, male sex, age or diabetes in the CKD population [15]. Another study showed an association between relative overhydration >7% and mortality in patients with advanced CKD [7].

The objective of this study was to evaluate the effect of OH on mortality in patients with Stage 4 or 5 non-dialysis CKD.

MATERIALS AND METHODS

Design of the study

This is a prospective study that started in January 2011 and patients were followed up until December 2016. Variables were collected at the beginning of the study and at the end of the study we collected mortality data. Patients who started renal replacement therapy during follow-up were excluded.

Study population

A total of 370 Stage 4 or 5 non-dialysis CKD patients were enrolled in this study at a single centre in Madrid, Spain. CKD was defined and staged according to Kidney Disease Outcomes Quality Initiative guidelines using the Modification of Diet in Renal Disease four-variable equation (MDRD4) [16]. Inclusion criteria were clinical stability with no recent hospitalization in the past 3 months, outpatient follow-up for >3 months, age >18 years and informed consent obtained. Exclusion criteria were an inability to understand the study, contraindication to BIS (patients with pacemakers or limb amputation), loss of laboratory parameters or loss to follow-up. Of these, 17 patients were finally excluded.

Baseline variables

At baseline, demographic and clinical data were collected, including age, sex, CKD aetiology, presence of diabetes mellitus, hypertension (defined using the Eighth Report of the Joint National Committee) [17], dyslipidaemia (defined using Adult Treatment Panel III guidelines) [18], Charlson comorbidity index [19] and a history of prior heart disease including congestive heart failure (CHF) and myocardial infarction, peripheral vascular disease (PVD) and stroke.

Fluid status was assessed at baseline using BIS (body composition monitor, Fresenius Medical Care, Bad Homburg, Germany). Measurements were taken after a 10-min resting period in the supine position. Hydration parameters were total body water [TBW (in litres)], ECW (in litres), intracellular water [ICW (in litres)] and fluid overload [OH (in litres)], defined as water not included in extracellular and intracellular spaces and considered as excess water. We estimated relative OH by dividing OH by ECW (OH/ECW) [6]. We also collected lean tissue index [LTI (in kg/m²)] and fat tissue index [FTI (in kg/m²)] data.

Laboratory variables recorded included creatinine and glomerular filtration rate (MDRD4 equation), proteinuria, N-terminal prohormone of brain natriuretic peptide (NT-proBNP), nutritional and inflammatory parameters (pre-albumin and albumin), and C-reactive protein (CRP).

Follow-up

During follow-up {50 [interquartile range (IQR) 24–66] months}, new CVEs and mortality were recorded. CVEs were defined as ischaemic or haemorrhagic cerebrovascular accident (diagnosed by computed tomography), myocardial infarction (diagnosed by cardiac marker elevation and electrocardiography and confirmed by coronary angiography), CHF (diagnosed by the presence of acute pulmonary oedema and an echocardiogram with ventricular systolic dysfunction and left ventricular ejection fraction <45%) and peripheral vascular events (diagnosed by stenosis of major arteries or lower limbs confirmed by arteriography and/or the need for amputation).

Mortality aetiology was classified as CV, tumoural, infection, rejection to start renal replacement therapy and other.

Statistical analysis

All variables were analysed using a Kolmogorov–Smirnov test to classify them as normally or non-normally distributed. Values are given as mean ± SD or median (IQR). Univariate analysis was performed using logistic regression to assess factors associated with mortality and CVEs. A multivariate Cox regression analysis was performed in order to establish independent predictors of mortality and CVEs. The models included factors that showed a significant association or those considered confounding factors. Outcomes were analysed using Kaplan–Meier plots and survival curves were compared using a log-rank test. All statistical analyses were performed with SPSS 18.0 software (SPSS, Chicago, IL, USA). P-values <0.05 were considered statistically significant.

RESULTS

Baseline characteristics

We included 356 patients; 64% were male with a mean age of 67 ± 13 years. Baseline characteristics are shown in Table 1. The mean creatinine was 3.5 ± 1.3 mg/dL, mean glomerular filtration rate (MDRD equation) was 16 mL/min/1.73 m² and median proteinuria was 0.5 (IQR 0.2–1.5) g/24 h. Forty-three percent of patients were receiving diuretics. The median OH was 0.6 (IQR –0.4–1.5) L and mean relative OH (OH/ECW) was 2.3 ± 0.8%. The percentage of patients with a lower mean relative OH (OH/ECW <2.3 ± 0.8%) was 44% and the percentage with a higher mean relative OH (OH/ECW >2.3 ± 0.8%) was 56%.

A total of 236 patients (66%) had relative OH (OH/ECW) >0% and 120 patients (34%) had a relative OH (OH/ECW) <0%.

Table 1. Baseline characteristics of the study population (n = 356)

Characteristics	Value
General characteristics (%)	
Sex (male)	64
Age (years), mean \pm SD	67 \pm 13
Charlson comorbidity index, mean \pm SD	7.2 \pm 2.7
Diabetes	36
Hypertension	87
Dyslipidaemia	72
CKD aetiology (%)	
Glomerular	23
Diabetes	19
Vascular	28
Interstitial	13
Polycystic	10
Other	7
Previous CVE (%)	
Myocardial Infarction	28
CHF	27
Stroke	15
Peripheral vascular disease (%)	12
Laboratory parameters	
Creatinine (mg/dL), mean \pm SD	3.5 \pm 1.5
MDRD (mL/min/1.73 m ²), mean \pm SD	16.0 \pm 5.5
Proteinuria (g/24 h), median (IQR)	0.5 (0.2–1.5)
Albumin (g/dL), mean \pm SD	4.1 \pm 0.4
NT-proBNP (ng/dL), median (IQR)	84 (37–181)
CRP (mg/dL), median (IQR)	0.3 (0.1–0.7)
Pre-albumin (mg/dL), median (IQR)	32 (27–38)
Hydration statement and corporal composition	
BMI (kg/m ²), mean \pm SD	28.0 \pm 5.2
FTI (kg/m ²), mean \pm SD	12.3 \pm 5.6
LTI (kg/m ²), mean \pm SD	15.7 \pm 3.4
OH (L), median (IQR)	0.6 (–0.4–1.5)
ECW (L), mean \pm SD	17.0 \pm 3.5
ICW (L), mean \pm SD	19.7 \pm 4.7
ECW/ICW, mean \pm SD	0.8 \pm 0.1
OH/ECW (%), mean \pm SD	2.3 \pm 0.8

BMI, body mass index; CHF, congestive heart failure; CKD, chronic kidney disease; CRP, C-reactive protein; ECW, extracellular water; FTI, fat tissue index; ICW, intracellular water; LTI, lean tissue index; MDRD, MDRD equation to estimate glomerular filtration rate; NT-ProBNP, N-terminal prohormone of brain natriuretic peptide; OH, overhydration; PVD, Peripheral vascular disease.

CVEs at the end of follow-up

A total of 150 patients (42%) experienced a CVE during follow-up. The most common CVE was CHF (47%), as well as myocardial infarction (28%), peripheral vascular disease (13%) and cerebrovascular accident (12%).

Univariate analysis showed that older age, diabetes, hypertension, dyslipidaemia, previous CVE, higher Charlson comorbidity index, proteinuria, CRP, NT-proBNP levels, lower albumin levels and impaired kidney function were associated with CVEs. Multivariate analysis confirmed an independent association between proteinuria [exp(B) 1.1; P = 0.001], CRP [exp(B) 1.2; P = 0.02], NT-proBNP [exp(B) 1.2; P = 0.01], impaired kidney function [exp(B) 0.7; P = 0.03] and previous CVEs [exp(B) 2.7; P = 0.001] and development of CVEs during follow-up.

Mortality

We found that 113 patients (32%) died during follow-up. Mortality causes were CV, 19%; tumoural, 7%; infections, 3%; conservative treatment, 1% and other, 2%.

The univariate Cox analysis showed an association between mortality and age, diabetes, Charlson comorbidity index, previous CVE, low albumin level, low pre-albumin, high levels of CRP, high OH, low LTI and high OH/ECW (Table 2). Multivariate Cox analysis showed an independent association with mortality and age, Charlson comorbidity index, higher CRP levels, low LTI and relative OH (OH/ECW) as seen in Table 2. We divided patients into two groups (OH/ECW <0% and OH/ECW >0%). Kaplan–Meier analysis confirmed higher mortality in patients with OH/ECW >0% (log rank 11.1; P = 0.001) as seen in Figure 1.

Start of renal replacement therapy

A total of 125 patients (35%) needed dialysis during follow-up.

DISCUSSION

This study shows that any grade of relative OH in patients with advanced CKD is a long-term independent mortality risk factor. Thus minimal OH, even difficult to detect on examination, is related to mortality. The majority of studies related to OH and mortality have been performed in patients receiving renal replacement therapy. Wizemann *et al.* [9] studied the relation between relative OH and mortality in patients receiving chronic haemodialysis and established a cut-off of relative overhydration >15%. We found in a transverse study in haemodialysis patients an association between CVEs and relative OH. This association was maintained even when we decreased the cut-off to 10% [20]. In patients receiving peritoneal dialysis, the same association between mortality and relative OH >15% has been found, so this association could not be dependent on the type of renal replacement therapy chosen by patients [21]. Tsai *et al.* [7] studied relative OH in advanced CKD non-dialysis patients and found a significant cut-off for mortality of 7%. Based on our results, we propose to decrease the cut-off to as low as possible, because any degree of relative OH in CKD is harmful and, if possible, should be avoided.

The most common mortality cause in advanced CKD, as in our group of patients, is CV. Some known CV factors (traditional and novel ones), such as male sex, age and diabetes, are associated and increase in prevalence with overhydration. All of these, including inflammatory and cardiac biomarkers and a history of CV disease have been demonstrated as independent risk factors for CVEs and mortality in the CKD population [22–24]. The main finding of this study is that OH by itself is also an independent long-term mortality risk factor. Therefore BIS can help detect high-risk patients, as it is an easy and useful tool [17]. Probably, and although our study lacks serial measurements, performing BIS more frequently, for example, at each clinical visit, could improve patient survival [25]. Those patients with OH could then receive closer follow-up, adjusting diuretics if necessary and receiving more frequent visits to the nephrologist.

Body composition may influence mortality in advanced CKD as we previously described [26]. Low LTI is associated with mortality. Lean tissue is related to physical activity, so we encourage our patients to practice exercise regularly. Other significant factors such as age, Charlson comorbidity index and high levels of CRP are frequent variables related to mortality in the general population and in CKD [27, 28]. Another interesting finding is that the association between mortality and other risk factor such as previous CVEs, diabetes and low pre-albumin level were not significant in our study and relative OH and low lean tissue had an independent association.

CVEs were recorded in 150 patients. Nearly half of these patients had CHF, and this frequent association contributes

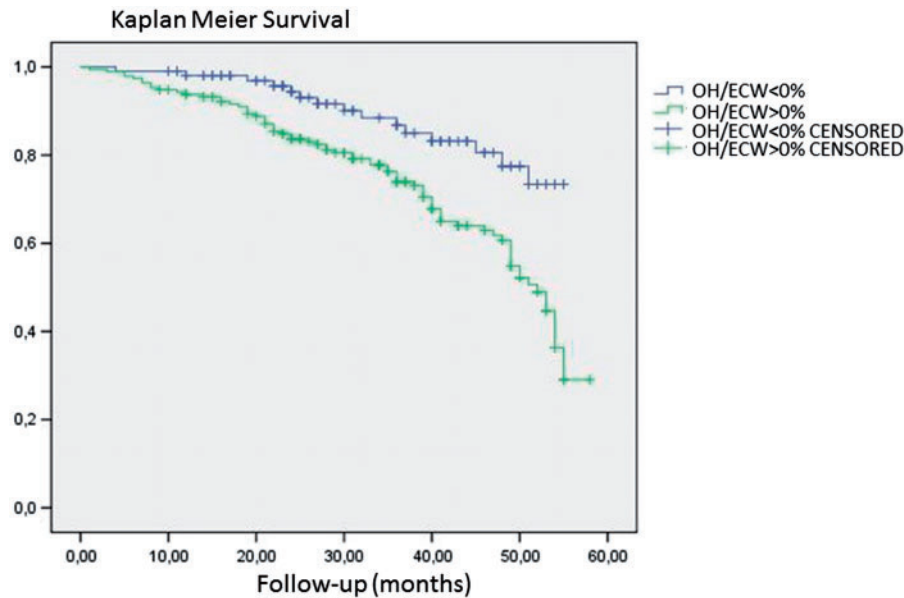


FIGURE 1: Kaplan–Meier analysis for mortality and relative OH. Log rank 11.1; $P = 0.001$.

Table 2. Cox proportional hazards regression analysis for mortality

Baseline characteristics	Univariate		Multivariate	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Sex (male, %)	1.35 (0.76–1.79)	0.34		
Age (years)	1.08 (1.01–1.20)	0.001	1.1 (1.0–1.3)	0.001
Diabetes (%)	1.50 (1.20–1.98)	0.024	1.30 (0.62–1.87)	0.32
Hypertension (%)	1.65 (0.33–1.98)	0.76		
Dyslipidaemia (%)	1.43 (0.54–1.87)	0.45		
Charlson comorbidity index	1.27 (1.03–1.74)	0.02	1.1 (1.0–1.2)	0.01
Previous global CVEs	1.50 (1.19–1.99)	0.001	1.59 (0.89–3.30)	0.26
Creatinine (mg/dL)	1.02 (0.89–1.18)	0.34		
Proteinuria (g/24 h)	1.001 (0.99–1.01)	0.69		
Albumin (g/dL)	0.38 (0.12–0.79)	0.001	0.84 (0.68–1.12)	0.54
Prealbumin (mg/dL)	0.94 (0.56–0.99)	0.001	0.99 (0.89–1.23)	0.31
CRP (mg/dL)	1.20 (1.03–1.78)	0.01	1.3 (1.1–1.9)	0.04
NT-proBNP (ng/dL)	1.00 (0.99–1.01)	0.677		
Cholesterol	0.99 (0.98–1.01)	0.07		
OH (L)	1.1 (1.02–1.19)	0.01	1.10 (0.99–1.20)	0.08
ECW (L)	0.96 (0.88–1.05)	0.640		
ICW (L)	0.88 (0.81–1.04)	0.12		
OH/ECW (%)	3.10 (1.88–5.01)	0.001	3.18 (2.09–4.97)	0.031
BMI (kg/m^2)	0.98 (0.93–1.04)	0.650		
FTI (kg/m^2)	1.04 (0.89–1.08)	0.124		
LTI (kg/m^2)	0.85 (0.33–0.97)	0.001	0.82 (0.69–0.98)	0.002

Bold significance is for P-values <0.05.

BMI, body mass index; CRP, C-reactive protein; CVEs, cardiovascular events; ECW, extracellular water; FTI, fat tissue index; ICW, intracellular water; LTI, lean tissue index; Nt-ProBNP, N-terminal prohormone of brain natriuretic peptide; OH, overhydration; OH/ECW, Relation between overhydration and extracellular water.

to the development of cardiorenal syndrome, which explains the morbidity of this association [29]. A significant number of patients suffered from myocardial infarction. Chronic disease has been shown to increase mortality in patients with ischaemic heart disease [30]. Monitoring of serum cardiac biomarkers may therefore be helpful to detect these conditions, as NT-proBNP was associated to the development of CVEs in our

study. As regards mortality, CVEs were also the most important cause of death. For these reasons, we suggest that new strategies to detect early CVEs should be developed to improve the survival of our CKD patients. Meanwhile, the use of BIS to monitor fluid overload may be helpful.

Our study has some limitations. Only one BIS measurement was available for each patient and no additional BIS

measurements could be done to evaluate their changes and consequences. We did not measure urine sodium and sodium intake, which could be involved in oedema formation.

In conclusion, any grade of relative OH measured by OH/ECW >0% is associated with long-term mortality in patients with Stages 4 and 5 CKD.

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AUTHORS' CONTRIBUTIONS

A.V., S.A., I.A., N.M. and J.L. designed the study. A.G-P., T.L., E.T. and A.H. performed BIS. N.M. gave informed consent. A.V., S.A. and I.A. collected data. A.V. wrote the manuscript.

CONFLICT OF INTEREST STATEMENT

None declared. The authors alone are responsible for the content and writing of this paper.

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