The Relationship Between Bioimpedance-Measured Volume and Nutritional Parameters and Mortality in Hemodialysis Patients

Hemodiyaliz Hastalarında Biyoempedansla Değerlendirilen Volüm ve Beslenme Belirteçleri ile Mortalite İlişkisi

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ABSTRACT

OBJECTIVE: Hypervolemia and malnutrition are often undiagnosed risk factors for hemodialysis (HD). Our aim was to investigate the long-term effects of hypervolemia and malnutrition evaluated by bioimpedance spectroscopy (BIS) on survival. (Clinical Trials. Gov Identifier: NCT01468363).

MATERIAL and METHODS: A total of 431 Prevalent HD patients were followed for 32.2±14.4 months. The patients underwent BIS measurement, a medical history was obtained, and routine tests were analyzed at the baseline and at the end of the study. Hospitalizations and complications of HD were recorded.

RESULTS: The mean age was 59.4±14.6 (10-92) years with a total of 431 (53.6% males) patients of which 125 died. The percentage of diabetics was 47%, erythropoietin use 67%, and diuretic use 40%. Predialysis systolic blood pressure (BP) was 133.4±25.8 and diastolic BP 79.2±12.4 mm Hg.

The rate of diabetes, and the number of hospitalizations and blood transfusions were higher in the patients who died. Diastolic BP as a clinical hypervolemia finding, BIS hypervolemia indicator of over hydration (OH), and extracellular water (ECW) were all increased, and fat tissue index as a malnutrition finding was decreased in patients who died. There were significant rates of anemia and hypoalbuminemia in this group as well.

The cumulative survival was lower in hypervolemic patients as assessed by relative hydration status OH/ECW.

CONCLUSION: Hypervolemia and malnutrition are the long-term mortality indicators in hemodialysis. Early diagnosis and treatment is important. Clinical findings may not be sufficient and laboratory and BIS methods can be used for diagnosis.

KEY WORDS: Overhydration, Bioimpedance, Malnutrition, Fat tissue index, Mortality

ÖZ

AMAÇ: Hemodiyalizde hipervolemi ve malnütrisyon çoğu kez gözden kaçan risk faktörleridir. Çalışmamızda amaç, biyoempedans sektroskopi (BİS) ile gösterilen hipervolemi ve malnütrisyonun uzun dönem sağkalım üzerine etkisini araştırmaktır (Clinical Trials. gov Identifier:NCT01468363).

GEREÇ ve YÖNTEMLER: Çalışmaya 431 prevalan HD hastası alınarak 32,2±14,4 ay takip edilmiştir. Hastalara BIS ölçümü yapılmış, ilaç kullanımları, bazal ve çalışma sonundaki rutin tetkikleri değerlendirilmiştir. Çalışma süresince hastane yatışları, seanslar sırasında yaşanan komplikasyonlar değerlendirilmiştir.

BULGULAR: Yaş ortalaması 59,4±14,6 (10-92) yıl olan toplam 431 (%53,6'sı erkek) hastadan 125'i çalışma sonunda exitus olmuştur. Diyabet oranı %47, eritropoietin %67, diüretik kullanımı %40, prediyaliz sistolik kan basıncı 133,4±25,8 diyastolik kan basıncı 79,2±12,4 mm Hg dir.

Ölen hastaların diyabet oranı, hastaneye yatışları ve kan transfüzyon sayıları daha fazla idi. Ölen hastalarda: klinik hipervolemi bulgularından diyastolik kan basıncı, BİS hipervolemi göstergesi olan aşırıhidrasyon (OH), Hücredışı su (ECW), artmış, malnütrisyon bulgusu olarak yağ kitle endeksi azalmıştı. Bu grupta anlamlı anemi ve hipoalbuminemi mevcuttu.

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Biyoempedans verilerine göre göreceli hidrasyon durumu OH/ECW değerlendirildiğinde, kümülatif sağkalım, hipervolemik olanlarda daha düşük olarak bulundu.

SONUÇ: Hemodiyaliz hastalarında hipervolemi ve malnütrisyon uzun dönem mortalite göstergesidir, erken tanı ve zamanında müdahale çok önemlidir. Klinik bulgular tanıda yeterli olmayabilir laboratuvar verileri ve BİS yöntemi hipervolemi ve malnütrisyon tanısında kullanılabilir.

ANAHTAR SÖZCÜKLER: Aşırı hidrasyon, Biyoempedans, Malnütrisyon, Yağ kitle endeksi, Mortalite

INTRODUCTION

Hypervolemia and malnutrition are devastating problems for patients with chronic kidney disease (CKD). Although clinical findings are enough for the detection of volume and nutritional status, underdiagnosis is common due to nonsignificant clinical findings.

Increased mortality among hemodialysis (HD) patients might be attributed to cardiac disease that is directly related to insufficient fluid control. There has been no practical method to detect excess extracellular water and consequently assess dry weight (1). Thus, it has been necessary to clinically define dry weight by trial and error and several indirect methods. In addition to poor control of hypertension, intradialytic hypotension has continued to be a problem (2), particularly in elderly and cardiovascularly compromised patients (3).

Recently we have investigated efficiency of bioimpedance spectroscopy (BIS) for detection of hypervolemia and it was found as a reliable method to evaluate volume status in end-stage renal disease patients. OH/ECW measured by BIS is a major determinant of left atrial diameter, left ventricular mass and ejection fraction (4, 5).

To date, there has been no study of HD patients' mortality data for Turkish patients according to the fluid status measured by the BIS method. For present study we have used the body composition monitor (BCM; Fresenius Medical Care, Bad Homburg, Germany) in all the dialysis centers in Zonguldak since 2011, and the hydration and nutritional status measured by BCM.

The aim of this prospective observational study was to investigate the long-term effects of hypervolemia and malnutrition evaluated by BIS on HD patients. (Clinical Trials Gov Identifier: NCT01468363).

MATERIALS and METHODS

Patient Selection

Study participants were recruited from patients on maintenance HD treated in all the dialysis centers in Zonguldak (11 HD centers), Turkey, where 550 patients were being treated. After approval of the Ethics Committee of Karaelmas University in November 2011 and followed for an average of 32.2 ± 14.4 months.

Patients who were willing to participate in the study with written informed consent, older than 18 years, and on maintenance HD therapy scheduled thrice weekly (12 hours weekly) for 3 months or longer were included. Exclusion criteria were the presence of a pacemaker or defibrillator, artificial joints or pins, amputation, permanent or temporary catheters, being scheduled for living donor kidney transplantation, presence of serious life-limiting comorbid situations (eg, malignancy, uncontrollable infection, and end-stage cardiac, pulmonary, or hepatic disease), being pregnant, or lactating. After enrollment of 431 individuals who met the study criteria assigned to the intervention

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and in compliance with the Good Clinical Practice Guidelines. All patients were seen by their physician every month.

Clinical Parameters

Patients characteristics medical history; age at start of study (years), sex, height (cm), initial body weight (kg), overhydration (L), dry body weight (kg), initial systolic/diastolic BP (mm Hg), initial comorbidities (presence of diabetes) and initial laboratory data (hemoglobin, blood urea nitrogen, creatinine (Cr), albumin, alanine aminotransferase (ALT), sodium, potassium, calcium, phosphorus, iron saturation, ferritin, intact parathyroid hormone (PTH), uric acid, aspartate aminotransferase (AST), Alkaline phosphatase, Glucose, sensitive C-reactive protein, total cholesterol, Triglyceride, gamma glutamine transferase (GGT), thyroid stimulating hormone (TSH), HbAlC were evaluated at baseline and at the end of the study. Hospitalizations and complications in HD sessions were recorded.

Fluid Overload Assessment

Measurements were performed in the supine position in all patients. The Body Composition Monitor analyzes total-body electrical impedance to an alternating current at 50 different frequencies (5-1000 kHz). Extracellular water (ECW), intracellular water (ICW), and total body water are determined by the BCM using the approach described previously (6) has been validated against bromide and deuterium dilution in patients and healthy individuals (7). The difference between fluid overload measured before and after HD sessions was also validated against intradialytic weight loss (mean, 0.015±0.8 (SD) L) (7). Fluid

overload is calculated by the BCM based on a physiological tissue model (8). This model separates the body into three compartments: Extracellular fluid overload, normohydrated lean tissue, and normohydrated adipose tissue. Tissue properties of normohydrated lean and adipose tissue are assumed to be constant (9). Therefore, no adjustments for sex or ethnic origin were applied. This method calculates normal hydration status, in other words, the expected normal values for ECW and ICW that would result in healthy kidney function (normohydrated lean and adipose tissue). Because normal ECW or ICW can be determined for a given weight and body composition (8), fluid overload can be calculated from the difference between the normal ECW expected and measured ECW.

Outcomes

A primary outcome was survival of patients on maintenance HD treated in all the dialysis centers in Zonguldak (11 HD centers), Turkey, where 550 patients were being treated.

RESULTS

The mean age 59.4 ± 14.6 (18-92) years with a total of 431 (53.6% males) were followed, among them 125 patients were died. Diabetic group 47%, patients on erythropoietin treatment were 67%, diuretics 40%, predialysis mean systolic blood pressure 133.4 ± 25.8 and diastolic blood pressure were 79.2 ± 12.4 mm Hg.

The proportion of diabetes (63 vs. 40%), the number of hospitalizations except vascular access problems (3.16 vs. 1.43) and the blood transfusions (3 vs. 1), parenteral iron treatment (73 vs. 49%) were more in patients who died but anti potassium drug usage (6 vs. 20%) less in this group compared to the live patients.

There were no differences in patients using anti hypertensives, erythropoietin, vitamin D, phosphorus binders and essential amino acids either in the dead or alive groups (Table I).

Diastolic blood pressure (82.4 ± 12.1 vs. 78.6 ± 11.7 mm Hg), as a clinical hypervolemia finding, BIS hypervolemia indicator of over hydration (OH) (1.79 ± 1.50 vs. 1.12 ± 2.00 L), and extracellular water (ECW) (16.58 ± 3.27 vs. 15.83 ± 2.94 L) were all increased. Nutritional status evaluated by BCM and as a malnutrition findings, fat tissue index (FTI) (12.26 ± 6.80 vs. 13.86 ± 6.50 kg/m^2), relative Fat (32.20 ± 12.93 vs. 35.76 ± 11.33%) were decreased in patients who died compared to the alive group.

There was significant anemia and hypoalbuminemia in the dead group. Hemoglobin (11.0 ± 1.33 vs. 11.3 ± 1.25 g/dl), albumin (3.77 ± 0.42 vs. 3.90 ± 0.42 g/dl), creatinine (post-dialysis) (2.66 ± 0.97 vs. 3.00 ± 1.02 mg/dl), serum iron (63.1 ± 26.1 vs. 75.6 ± 34.6), iron saturation (31.3 ± 15.2 vs. 46.2 ± 46.7%), uric acid (6.12 ± 1.43 vs. 6.42 ± 1.31 mg/dl), glucose (121.8 ± 63.8 vs. 139.3 ± 70.3 mg/dl), GGT (22.9 ± 17.1 vs. 39.7 ± 51.1), AST (11.4 ± 6.5 vs. 94.5 ± 237.2), ALT (12.2 ± 6.6 vs. 16.4 ± 15.2 IU/L) were all decreased in the dead group (Table II).

Urea reduction rate (71.4 ± 6.19 vs. 69.9 ± 5.94%) and Kt/V (1.54 ± 0.22 vs. 1.47 ± 0.22) were increased in the dead group (Table III).

The differences in systolic blood pressure and body mass index between the dead and living groups were not statistically significant (Table II).

The cumulative survival was found to be lower in patients with hypervolemia according to the relative hydration status of overhydration / extracellular water (OH / ECW) measured by bioimpedance (Figure 1). In addition to age and diabetes, hypervolemia was found to be an independent risk factor for the mortality of these hemodialysis patients.

Table I: Clinical findings of dead and alive patients.

	Dead	Alive	p
Age (10-92) years	60.2±13.8	59.2 ± 14.9	NS
Sex (M/F)	70/55	161/145	NS
Diabetes (%)	63	40	<0.01
SBP (mm Hg)	136.3±23.0	133.9 ± 25.6	NS
DBP (mm Hg)	82.4±12.1	78.6 ± 11.7	<0.01
Diuretics (%)	37	42	NS
Beta blockers (%)	38	32	NS
CCB (%)	26	25	NS
ACE-i/ARBs (%)	12	9	NS
Alpha blockers (%)	10	15	NS
EPO (%)	63	69	NS
Vitamin D (%)	22	24	NS
Vitamine D analogues (%)	11	13	NS
Phosphorus binders (calcium based) (%)	73	75	NS
Sevalamer (%)	22	27	NS
Iron parenteral (%)	73	49	<0.01
Anti-potassium (%)	6	20	<0.01
Essential amino acids (%)	26	34	NS
Blood transfusion (%)	3	1	<0.05
Number of hospitalizations (Except vascular access problems)	3.16±2.48	1.43 ± 1.79	<0.01

SBP: Systolic blood pressure, **DBP:** Diastolic blood pressure, **CCB:** Calcium channel blockers, **ACEi/ARB:** Angiotensin converting enzyme inhibitors / Angiotensin receptor blockers, **EPO:** Erythropoietin

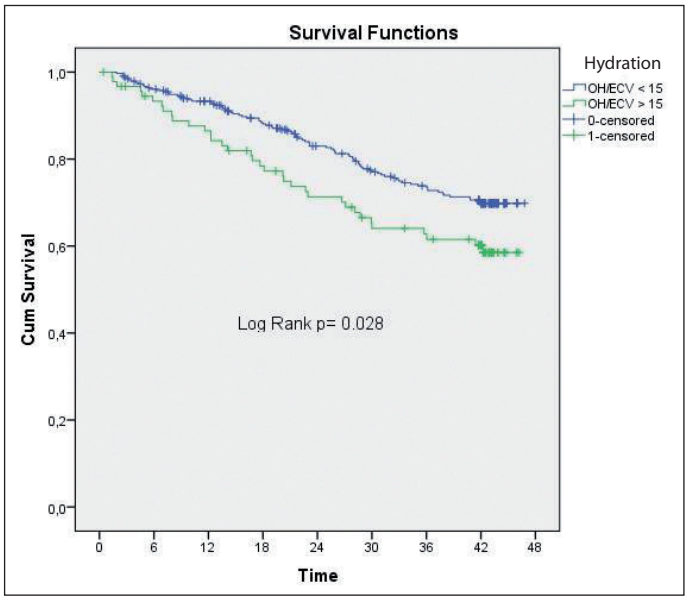

Figure 1: *Kaplan-Meier survival curve of two groups for all-cause mortality. Follow up: 32.2±14.4 months.*

DISCUSSION

Chronic kidney disease is one of the major health problems affecting a considerable percentage of the population (10). Hypervolemia is commonly seen as major mortality and morbidity risk factor especially for advanced renal diseases (11). Volume excess may present clinically as arterial hypertension, pretibial edema, dyspnea, jugular venous congestion and increased cardiothoracic index, ascites as radiologically and exantric left ventricular hypertrophy and diastolic dysfunction as cardiac findings (12). It may be best if we all accept the majority of end-stage renal disease patients as hypervolemic until proven otherwise.

Cardiovascular causes of the mortality of dialysis patients are mostly related to a large part to hypertension and cardiac damage (13). In dialysis patients, hypertension persists despite antihypertensive medication while cardiac hypertrophy does not decrease or even increases. In the past, some authors have accepted heart disease as a usual process for these patients, suggesting that deterioration is inevitably linked to that procedure (14). On the contrary, Charra and Özkahya (15,16) have proven that a precise volume control of HD patients decreases arterial blood pressure, causes regression of cardiac hypertrophy and prolongs survival. This suggests that volume control is not enough in most patents, despite the fact that treating physicians may consider that ''Dry Weight'' (DW) of their patients has been reached. In reality, an easily applicable method is needed to determine extra cellular volume and consequently estimate DW. Thus DW has to be clinically defined by "trial and error" and several indirect methods.

Table II: Bioimpedance measurements of dead and alive patients.

	Dead	Alive	p
Height (cm)	162.0 ± 9.2	160.5 ± 9.6	NS
Body weight (kg)	69.6 ± 14.8	70.2 ± 15.8	NS
BMI (kg/m^2)	26.6 ± 5.6	27.2 ± 5.6	NS
OH (L)	1.79 ± 1.50	1.12 ± 2.00	<0.01
SBP (mm Hg)	136.3 ± 23.0	133.9 ± 25.6	NS
DBP (mm Hg)	82.4 ± 12.1	78.6 ± 11.7	<0.01
TBW (L)	34.30 ± 7.34	32.99 ± 6.66	NS
ECW (L)	16.58 ± 3.27	15.83 ± 2.94	<0.05
ICW (L)	17.72 ± 4.49	17.15 ± 4.38	NS
E/I	0.96 ± 0.14	0.95 ± 0.15	NS
LTI (kg/m^2)	13.35 ± 3.29	12.85 ± 3.20	NS
FTI (kg/m^2)	12.26 ± 6.80	13.86 ± 6.50	<0.05
LTM (kg)	35.57 ± 11.00	33.51 ± 9.81	NS
rel LTM (%)	52.78 ± 17.19	48.91 ± 15.36	<0.05
Fat (kg)	23.17 ± 12.06	26.08 ± 12.08	<0.05
rel Fat (%)	32.20 ± 12.93	35.76 ± 11.33	<0.01
ATM (kg)	31.5 ± 16.4	35.5 ± 16.4	<0.05
BCM (kg)	19.7 ± 7.4	18.3 ± 6.6	NS
Re (Ohm)	553.3 ± 88.3	585.3 ± 97.2	<0.01
Ri (Ohm)	1608.1 ± 430.6	1648.0 ± 456.1	NS
Cm (nF)	1.29 ± 0.63	1.28 ± 0.66	NS
Td (ns)	0.90 ± 3.81	0.31 ± 3.64	NS
Alpha	0.63 ± 0.06	0.61 ± 0.08	<0.01
Quality	93.8 ± 5.2	92.7 ± 7.2	NS
Phi 50 kHz (°)	4.65 ± 1.09	4.57 ± 1.07	NS

BMI: Body mass index, **OH:** Overhydration, **SBP:** Systolic blood pressure, **DBP:** Diastolic blood pressure, **TBW:** Total body water, **ECW:** Extracellular water, **E:** Extracellular, **I:** Intracellular, **LTI:** Lean tissue index, **FTI:** Fat tissue index, **LTM:** Lean tissue mass, **ATM:** Adipose tissue mass, **BCM:** Body cell mass, **Phi**: Phase angle.

Recently, devices to measure DW by Bioimpedance spectroscopy (BIS) have become available. This non-invasive, inexpensive and easily repeatable method has the potential to improve dialysis outcome in the majority of patients all over the world. The analysis of body composition has attracted much more interest with the use of the non-invasive practical method of bioimpedance. We have previously published studies about this method (5,17-20).

Table III: Laboratory findings of dead and alive patients.

	Dead	Alive	p
Hemoglobin (g/dl)	11.0 ± 1.33	11.3 ± 1.25	<0.05
Hematocrit (%)	32.7 ± 4.08	34.2 ± 3.72	<0.01
Leukocyte (1000/mm^3)	7.5 ± 2.31	7.2 ± 2.27	NS
Platelet (1000/mm^3)	197.4 ± 60.78	195.5 ± 71.68	NS
Urea pre-dialysis (mg/dl)	133.9 ± 39.64	138.3 ± 40.29	NS
Urea post-dialysis (mg/dl)	38.5 ± 15.35	41.0 ± 13.97	NS
UF	2.92 ± 1.17	3.12 ± 1.07	NS
Kt/V daugirdas2	1.54 ± 0.22	1.47 ± 0.22	<0.01
URR (%)	71.4 ± 6.19	69.9 ± 5.94	<0.05
Creatinine pre-dialysis (mg/dl)	7.58 ± 2.29	7.85 ± 2.32	NS
Creatinine post-dialysis (mg/dl)	2.66 ± 0.97	3.00 ± 1.02	<0.01
Serum iron	63.1 ± 26.1	75.6 ± 34.6	<0.01
Total protein (g/dl)	6.63 ± 0.46	6.82 ± 0.61	<0.01
Albumin (g/dl)	3.77 ± 0.42	3.90 ± 0.42	<0.01
ALT (IU/L)	12.2 ± 6.6	16.4 ± 15.2	<0.01
Sodium (meq/L)	137.3 ± 5.89	137.0 ± 3.50	NS
Potassium (meq/L)	5.13 ± 0.76	5.29 ± 0.81	NS
Calcium (mg/dl)	8.33 ± 0.65	8.89 ± 0.78	<0.01
Phosphorus (mg/dl)	4.98 ± 1.45	5.06 ± 1.34	NS
Iron saturation (%)	31.3 ± 15.2	46.2 ± 46.7	<0.01
Ferritin (ng/ml)	672.2 ± 550.0	725.5 ± 430.4	NS
PTH (pg/dl)	369.4 ± 341.4	373.0 ± 312.2	NS
Uric acid (mg/dl)	6.12 ± 1.43	6.42 ± 1.31	<0.05
AST (IU/L)	11.4 ± 6.5	94.5 ± 237.2	<0.01
Alkaline phosphatase (mg/dl)	141.4 ± 176.9	133.3 ± 116.5	NS
Glucose (mg/dl)	121.8 ± 63.8	139.3 ± 70.3	<0.05
Sensitive CRP (mg/L)	8.67 ± 19.06	16.49 ± 59.44	NS
T.cholesterol (mg/dl)	160.0 ± 44.1	152.5 ± 46.8	NS
Triglyceride (mg/dl)	178.3 ± 104.2	176.5 ± 144.0	NS
GGT (IU/L)	22.9 ± 17.1	39.7 ± 51.1	<0.05
TSH (μIU/ml)	3.20 ± 11.20	1.98 ± 1.53	NS
HbA1C (%)	7.06 ± 1.21	7.44 ± 1.61	NS

UF: Ultrafiltration, **URR:** Urea reduction rate, **ALT:** Alanine aminotransferase, **PTH:** Parathyroid hormone, **AST:** Aspartate aminotransferase, **CRP:** C reactive protein, **GGT:** Gamma glutamyl transferase, **TSH:** Thyroid stimulating hormone

Wizemann et al. measured the hydration status in 269 prevalent HD patients (28% diabetics, dialysis vintage = 41.2 ± 70 months) in three European centres with a body composition monitor (BCM) for the quantitative assessment of hydration status and body composition. In that study they found the hydration state was an important and independent predictor of mortality in chronic HD patients secondary only to the presence of diabetes (21). In our study, the proportion of diabetes, the number of hospitalizations and the blood transfusions were also higher in the patient group who died.

The optimal target hemoglobin for patients with end-stage renal disease (ESRD) remains controversial. Ofsthun et al. analyzed a large database of hemodialysis patients to determine whether increasing hemoglobin level above the current Kidney Dialysis Outcomes Quality Initiative (K/DOQI) recommendations was associated with increased risk of mortality and hospitalization. They found that both number of hospitalizations and length of stay decreased as hemoglobin increased and concluded the relative risk of death and hospitalization were inversely associated with hemoglobin levels. Anemia is also associated with increased rates of hospitalization and mortality in patients with CKD (22,23). Most recently a single-center retrospective study conducted by Kim YJ et al. reported that overhydrated patients had significantly lower serum levels of hemoglobin. They concluded that anemia might have contributed to the increase of overall mortality, though the Odds ratio was not increased to a statistically significant degree. Anemia may be a secondary effect by overhydration rather than malnutrition or decrease in red blood cells (24). In our study there was significant anemia in the mortality group.

Malnutrition and inflammation are closely related to fluid overload (25,26). It is not clear that malnutrition or inflammation is a cause or consequence of fluid overload. Initial levels of hemoglobin and albumin were significantly lower in the overhydtration group, but the level of C-reactive protein was not in that study. Hypoalbuminemia is a well-known risk factor for increased morbidity and mortality in patients on hemodialysis. Chronic dialysis patients having malnutrition, chronic inflammation (27, 28), atherosclerosis (29, 30), the concentration of free toxins such as p-cresol (31), and overhydration (32) all contribute to hypoalbuminemia. In our study, there was also significant hypoalbuminemia in this group.

In summary, overhydration has been defined as a mortality risk factor in dialysis patients. Evaluation of dry weight is difficult. There is no easily applicable method to determine extra cellular volume and consequently estimate dry weight (1). Bioimpedance spectroscopy represents a different approach to the assessment of fluid status and this analytic technique mainly uses the electrical properties of biological cells and fluids (33-35). The Body Composition Monitor is a bioimpedance spectroscopy device for clinical use, validated by isotope dilution methods (6), and reference body composition methods (7), and has been used in hemodialysis patients (21, 36-38).

Moving patients into the normohydration target range leads to a better control of hypertension (38, 39), fewer intradialytic adverse events and improved cardiac function (38, 40). Recently Onofriescu et al. prospectively conducted a study to investigate the impact of hydration status measured by BCM to all cause mortality and found that the hydration status was associated with the mortality risk in a HD population, independently of cardiac morphology and function (41). In the present study, we found that the proportion of hypervolemic patients evaluated by either clinical, laboratory or bioimpedance methods was significantly higher in the dead group and hypervolemia was an independent risk factor for mortality.

CONCLUSION

Bioimpedance analysis is an easily applicable method for detection of hypervolemia as well as nutritional status of HD patients. In the present study, 431 prevalent HD patients were prospectively followed up for 3 years on average and 125 died. Hypervolemia and malnutrition diagnosed by clinical, laboratory and bioimpedance measurements were more prevalent in the patients who died. The cumulative survival was found to be lower in patients with hypervolemia according to the relative hydration status of overhydration / extracellular water (OH / ECW) measured by bioimpedance. In the future, prospective randomized interventional studies are needed for this issue.

LIMITATIONS

Our study has several limitations.

1. All patients were measured with the use of the bioimpedance assessment but echocardiography was not performed in these patients
2. Residual renal function was not assesed as a parameter that could have influenced body fluid composition, although most of the patients were anuric.
3. The study population was from a western black sea region of Zonguldak having a humid climate that could affect the diet and drinking habits and our results would be better to be supported by further studies.

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