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Original Article

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New Method to Predict Survival in Hemodialysis Patients Using the Impedance Ratio

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Abstract

Objective: Bioimpedance spectroscopy (BIS) can be used to determine hypervolemia and malnutrition in chronic hemodialysis (HD) patients. In this prospective observational study, we investigated the survival predictability of impedance ratio (IR) calculated by BIS in HD patients (Clinical Trials Gov Identifier: NCT01468363).
Materials and Methods: A total of 430 chronic HD patients, out of 500 prevalent chronic HD patients from the city of Zonguldak who met the inclusion criteria, were included in the study. With a mean follow-up of 32.2±14.4 months, BIS was performed in all patients. The IR percentage (IR%) was calculated by dividing the resistance values using the 200 kHz and 5 kHz impulses. Student's t-test, Cox regression analysis, and Kaplan–Meier survival analysis were performed, and a p<0.05 was accepted as statistically significant.
Results: The mean age of 430 patients was 59±15 (10-92) years, and 54% of patients were male. By the end of the study, 125 (29%) patients died. Diabetes mellitus was observed in 46% of patients. Sixty-seven percent of patients used erythropoietin, and 41% used diuretics. The mean systolic blood pressure of patients before the dyalisis was 133±26 mmHg, and diastolic blood pressure was 79±12 mmHg. The IR values ranged between 73.2% and 94.1%. A multi-regression analysis that used the IR and included diabetes mellitus, age, gender, and albumin and hemoglobin levels showed that the mortality risk increased 16% (p<0.001). Evaluation using the quartiles showed decreased survival. Survival in the first quartile group was 42.8 months compared to 30.6 months in the last quartile group.
Conclusion: The IR calculated using BIS data is a useful tool that can be employed to predict the survival in chronic HD patients. An early awareness of this increased mortality risk is important in terms of a close follow-up and appropriate treatment of these patients.
Keywords: Bioimpedance, impedance ratio, survival, hemodialysis

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INTRODUCTION

Hemodialysis (HD) is the most frequently used renal replacement therapy overall in the world. The survival rates are increasing, and they greatly depend on the early diagnosis of cardiac and non-cardiac risk factors. Inflammation, abnormal volume, and nutritional status are well-known factors (1-3). Biochemical, radiological, and bioimpedance methods are used to explore the patient status. Bioimpedance spectroscopy (BIS) could be used to determine hypervolemia and malnutrition in chronic HD patients (4).

The impedance ratio (IR) is derived from a non-invasive BIS technique and calculated as the ratio between impedance measurements at high and low frequencies (200/5 kHz). It is practical, inexpensive, directly derived from impedance values, and it has been found to be associated with volume and nutritional status in recent studies (5-8).

To date, there have been a limited nomber of studies on HD mortality data according to the IR calculated using the BIS method involving Turkish patients. In the present study, we used the body composition monitor (BCM; Fresenius Medical Care, Bad Homburg, Germany) in all the dialysis centers in Zonguldak.

In this prospective observational study, we investigated the survival predictability of IR calculated by BIS in HD patients (Clinical Trials Gov Identifier: NCT01468363).

MATERIALS AND METHODS

Patient Selection

Study participants were recruited from the patients undergoing maintenance HD from all the dialysis centers in Zonguldak (11 HD centers), Turkey, where 430 out of 550 patients were treated, after an approval of the Ethics Committee of Zonguldak Karaelmas University in November 2011 (ZKÜ 2011-77-21/06), and they were followed for an average of 32.2±14.4 months.

Patients older than 18 years who were willing to participate in the study and signed a written informed consent, and who were on maintenance HD therapy scheduled thrice weekly (12 hours weekly) for 3 months or longer, were included in the study. Exclusion criteria were the following: 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 co-morbid conditions (e.g., malignancy, uncontrollable infection, and end-stage cardiac, pulmonary, or hepatic disease), and being pregnant, or lactating. After the enrollment, 430 individuals who met the study criteria were 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

The following patient characteristics were recorded: age (years), gender, height (cm), initial body weight (kg), overhydration (L), dry body weight (kg), initial systolic/diastolic blood pressure (mmHg), initial co-morbidities (presence of diabetes), and initial laboratory data (hemoglobin, blood urea nitrogen, creatinine, albumin, alanine aminotransferase, sodium, potassium,

Table 1. Baseline laboratory findings of impedance ratio groups

	1st IR group (79.8±1.73)	2nd IR group (83.1±0.86)	3rd IR group (85.5±0.70)	4th IR group (88.7±1.73)
Age (years)	50.1±13.5	55.6±12.9[a]	63.8±13.2[ab]	68.5±11.2[abc]
Sex (%F)	31	41	55 ab	59[ab]
Height (m)	163.2±8.86	162.1±9.05	159.5±9.35[ab]	159±10.1[ab]
Weight (kg)	73.7±18.82	69.4±14.43	70±12.53	66.8±15[a]
BMI (kg/m²)	27.6±6.88	26.4±5.04	27.6±5.17	26.3±5.14
DM (%)	29	20	40[b]	46[ab]
SBP (mmHg)	133.5±26.30	133.7±24.82	133.9±25.45	137.1±23.61
DBP (mmHg)	80.5±14.17	79.2±11.93	79.1±11.54	79.8±10.20
Ultrafiltration (L)	3.08±1.35	3.14±1.01	3.08±1.04	2.99±1.08
Hemoglobin (g/dL)	11.3±1.22	11.3±1.23	11.3±1.36	11±1.31
Albumin (g/dL)	4.02±0.40	3.93±0.38	3.83±0.39[a]	3.67±0.43[abc]
Sodium (meq/L)	137.8±5.76	136.8±3.21	136.9±4.09	136.8±3.67
Potassium (meq/L)	5.44±0.83	5.25±0.79	5.16±0.77[a]	5.12±0.78[a]
Calcium (mg/dL)	8.7±0.86	8.86±0.76	8.66±0.82	8.69±0.66
Phosphorus (mg/dL)	5.4±1.44	5.05±1.41	5.05±1.23	4.6±1.29[abc]
TBW (L)	37.4±6.38	34.1±6.3[a]	31.6±5.13[ab]	30.3±7.55[ab]
ECW (L)	16.8±3.18	16.1±3.04	15.9±2.73[ab]	15.4±3.17[a]
ICW (L)	20.6±3.47	18±3.49[a]	15.7±2.54[a]	14.9±5.41[ab]

IR: impedance ratio; BMI: body mass index; DM: diabetes mellitus; SBP: systolic blood pressure; DBP: diastolic blood pressure; UF: ultrafiltration; TBW: total body water; ECW: extracellular water; ICW: intracellular water.
[a]Group vs. 1; [b]Group vs. 2; [c]Group vs. 3; ($p<0.05$).

Table 2. Laboratory findings of non-survivor and survivors

	Non-survivors	Survivors	p
Hemoglobin (g/dL)	11.2±1.3	11.6±1.3	NS
Hematocrit (%)	36.3±3.7	37.2±4.3	NS
Leukocyte (1000/mm^3)	7.3±2.1	7.0±2.8	NS
Platelet (1000/mm^3)	219±90	196±71	NS
Urea pre-dialysis (mg/dL)	84±36	117±46	<0.01
Urea post-dialysis (mg/dL)	24.1±12.7	32.6±16.3	NS
UF	43.4±32.2	26.7±32.3	NS
Wpost	64.6±12.1	65.8±14.6	NS
Kt/V daugirdas2	1.6±0.3	1.6±0.3	NS
URR	72.4±7.3	73±6.0	NS
Creatinine pre-dialysis (mg/dL)	6.1±1.2	8.1±2.2	<0.01
Creatinine post-dialysis (mg/dL)	2.2±0.7	3.1±1.7	<0.05
Serum iron	51.1±22.6	71.3±31.5	<0.05
Total protein (g/dL)	6.7±0.7	6.7±0.5	NS
Albumin (g/dL)	3.7±0.5	3.9±0.4	<0.05
ALT (IU/L)	13.8±6.5	11.1±6.4	NS
Sodium (meq/L)	138±3.7	138±3.2	NS
Potassium (meq/L)	5.0±0.8	5.4±0.7	NS
Calcium (mg/dL)	8.9±0.6	8.9±0.8	NS
Phosphorus (mg/dL)	4.6±0.8	5.0±1.2	NS
Iron saturation (%)	58.7±66.9	47.6±37.9	NS
Ferritin (ng/mL)	788±400	1042±510	NS
PTH (pg/dL)	458±294	467±345	NS
Uric acid (mg/dL)	5.8±1.5	6.1±1.3	NS
Alkaline phosphatase (mg/dL)	161±82.3	134±92.8	NS
Glucose (mg/dL)	166±81.9	131±71.1	NS
Sensitive CRP (mg/L)	14.2±28.0	12.2±31.7	NS
T. cholesterol (mg/dL)	165±28.5	161±39.5	NS
LDL-cholesterol (mg/dL)	93.2±23.9	86.6±27.3	NS
HDL-cholesterol (mg/dL)	35.9±13.4	31.9±9.5	NS
Triglyceride (mg/dL)	167±114	205±161	NS

UF: ultrafiltration; URR: urea reduction rate; ALT: alanine aminotransferase; PTH: parathyroid hormone; CRP: C-reactive protein; LDL: Low density lipoprotein

calcium, phosphorus, iron saturation, ferritin, intact parathyroid hormone, uric acid, alkalen phosphatase, glucose, sensitive C-reactive protein, total cholesterol, antriglyceride) evaluated at baseline, second-year of the study. Hospitalizations and complications in HD sessions were also recorded.

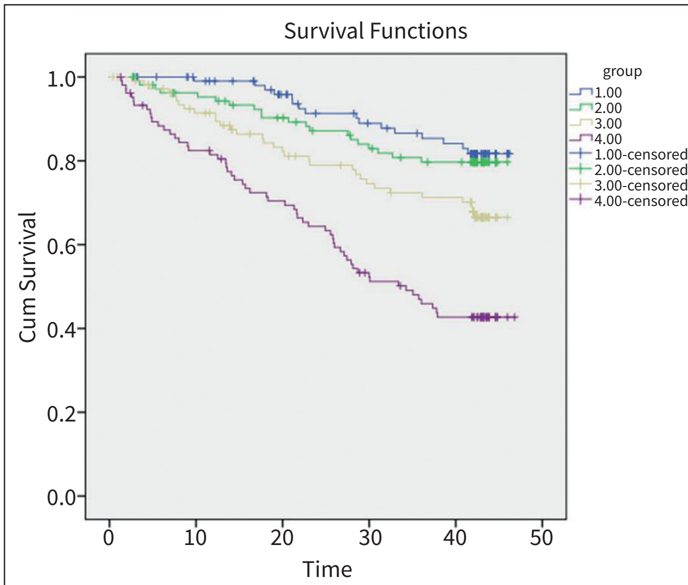

Figure 1. Kaplan Meier survival curve of two groups for all-cause mortality

Fluid Overload Assessment

Measurements were performed in the supine position in all patients. The BCM 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 were determined by the BCM using a previously described approach (9), which was validated against bromide and deuterium dilution in patients and healthy individuals (10). The difference between the fluid overload measured before and after HD sessions was also validated against the intradialytic weight loss (mean, 0.015±0.8 [SD] L) (7). The fluid overload is calculated by the BCM based on a physiologic tissue model (11). This model separates the body into three compartments: extracellular fluid overload, normohydrated lean tissue, and normohydrated adipose tissue. Tissue properties of the normohydrated lean and adipose tissue are assumed to be consistent (12). Therefore, no adjustments for gender or ethnic origin were applied. This method calculates the normal hydration status, in other words, the expected normal values for ECW and ICW that would result from a healthy kidney function (normohydrated lean and adipose tissue). Because normal ECW or ICW can be determined for a given weight and body composition (11), the fluid overload can be calculated from the difference between the normal ECW expected and measured ECW. ICW and ECW parts of the tissue use the ratio of impedance detected at low and high frequencies. Over time, if differences between these two values come close, this may show that the cell is becoming unhealthy. The resistance of the cell membrane at 5 kHz is significantly reduced in the case of critical illness, and the difference between the impedance values at 5 and 200 kHz is markedly closer to each other, indicating cellular deterioration; the 5-200 kHz impedance rate was defined as the IR and given as percentage.

Outcomes

The primary outcome was the survival of patients on maintenance HD treated in all the dialysis centers in Zonguldak (11 HD centers), Turkey, where 430 out of 550 patients were treated.

RESULTS

The mean age of 430 patients was 59±15 (10-92) years, and 54% of patients were male. Before the end of the study, 125 (29%) patients died. Diabetes mellitus was found in 46% of patients. Sixty-seven percent of patients used erythropoietin, and 41% used diuretics. The mean pre-dialysis systolic blood pressure was 133±26 mmHg, and diastolic blood pressure was 79±12 mmHg.

Baseline demographic and laboratory findings were grouped into impedance ratio quartiles. Older patients, shorter in stature, and mostly females with decreased albumin, potassium, and phosphours TBW and ICW were found in advanced IR quartiles (Table 1).

There were significant anemia and hypoalbuminemia found in the non-survivor group at the beginning. The second-year laboratory tests also revealed that the non-survivor group had nutritional problems. Pre-dialysis urea (84±36 vs. 116±46 mg/dL), creatinine (6.1±1.2 vs. 8.1±1.2), post-dialysis creatinine (2.2±0.7 vs. 3.1±1.7 mg/dL), serum iron (51.1±22.6 vs. 92±71.3), and serum albumin levels (3.7±0.5 vs. 3.9±0.4) were significantly lower in the non-survivor group than in survivors (Table 2).

The impedance ratio values ranged between 73.2% and 94.1%. IR values in the non-survivor group were higher than in the survivor group (86±3.52 vs. 83.5±3.5, respectively; $p<0.001$). Multi-regression analysis using diabetes mellitus, age, gender, and albumin and hemoglobin values showed an increased mortality risk using IR (Hazard Ratio, 1.16; 95% confidence interval, 1.091-1.242; $p<0.001$). The quartiles evaluation showed decreased survival. Survival in the first quartile group was 42.8 months compared to 30.6 months in the last quartile group (Figure 1).

DISCUSSION

Increased mortality among HD patients can be attributed to cardiovascular events (13). Chronic fluids overload, in other words unadjusted dry weight in these patients, generally leads to cardiac hypertrophy and eventually to heart failure and death (14, 15). For this reason, the volume status is the key point to predict the mortality risk. Up to now, the biochemical, radiological, and bioelectric methods have been used to diagnose the fluid status.

Recently, devices to measure dry weight by BIS have become available. This non-invasive, cheap, and easily repeatable method has the potential to improve dialysis outcomes in the majority of patients all over the world. The analysis of body composition gained much more interest with the use of the non-invasive practical method of bioimpedance. We have previously published studies about this method (16-20).

In present observational study, we showed that the IR is an independent predictor of all-cause mortality in a large cohort of HD patients in a follow-up that lasted over 3 years.

The ideal hemoglobin level for patients with end-stage renal disease remains obscure. Ofsthun et al. analyzed HD patients to determine whether increasing the hemoglobin level above the current Kidney Dialysis Outcomes Quality Initiative recommendations was associated with an increased risk of mortality and hospitalization. They concluded that both the number of hospitalizations and the length of stay decreased as the level of hemoglobin increased, and they said that the relative risk of death and hospitalization was inversely associated with hemoglobin levels. Anemia is also associated with increased hospitalization and mortality rates in patients with CKD (21, 22). Most recently, a single-center retrospective study conducted by Kim et al. reported that overhydrated patients had significantly lower hemoglobin serum levels. 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 of overhydration rather than malnutrition or decrease in the red blood cell number (23). In our study, there was significant anemia in the non-survivor group.

Inflammation and malnutrition may be related to overhydration (24, 25). It is not clear whether malnutrition or inflammation is a cause or a consequence of it. 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 HD. Conditions such as malnutrition, chronic inflammation (26, 27), atherosclerosis (28, 29), and hypervolemia (30) all contribute to hypoalbuminemia in chronic HD patients. In our study, there was significant hypoalbuminemia at the baseline and second-year low urea, creatinine, serum iron, and albumin levels as indicating the malnutrition process in the non-survivor group.

In typical HD patients, volume changes were seen pre- and post-dialysis, and also at the beginning or during the midweek periods. The IR is also influenced by volume changes (31). In this study, we measured BIS at midweek pre-HD sessions for standardization.

In the literature, the IR was proposed as a volume marker. The authors proposed local BIS measurement to determine the body weight in incident HD patients (32). In another study from Chine calf, the IR was used for dry weight estimation, and the authors showed that the IR was correlated with age (33). In another study from the same authors, an improvement in the blood pressure control, left ventricular hypertrophy, and arterial stiffness were shown at the 1-year follow-up (34). Gangji et al. (35) showed the IR correlation with fibrosis inflammation and nutrition markers such as serum albumin, peritoneal effluent interleukin-6, and transforming growth factor-ß1 in PD patients. Demirci et al. (36) conducted a study that included prevalent HD patients and found that IR predicts overall mortality as well as CV mortality. The risk of all-cause mortality was 3.4 times higher in patients with an IR above 83.5% compared to those with an IR lower than 78.8%. With regard to CV mortality, each 1% increase in the IR was associated with a 15% higher risk of CV mortality.

In present study involving 430 prevalent HD patients prospective observational study for 32 moths follow-up; in addition to well-known albumin and hemoglobin levels, BIS-derived IR was also shown to be a reliable mortality predictor. A multi-regression analysis that used the IR and included diabetes mellitus, age, gender, and albumin and hemoglobin levels showed that the mortality risk increased 16%. Evaluation with the quartiles showed decreased survival. Survival in the first quartile group was 42.8 months compared to 30.6 months in the last quartile group.

Study Limitations

Our study has several limitations:

1. The bioimpedance assessment was conducted in all patients, but echocardiography was not performed.
2. The residual renal function was not assessed as a parameter, which could have influenced the body fluid composition, although most of the patients were anuric.
3. The study population comes from the western Black Sea region of Zonguldak, which has a humid climate that may affect diet and drinking habits, and further studies are required to confirm our results.

CONCLUSION

The IR calculated using BIS data is a useful tool that can be employed to predict survival in chronic HD patients. Early awareness of this increased mortality risk is important in terms of a close follow-up and an appropriate treatment of these patients.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Zonguldak Karaelmas University (ZKÜ 2011-77-21/06).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – E.H., C.G., Ş.K.; Design - E.H., C.G., Ş.K.; Supervision - E.H., C.G., Ş.K.; Resources - E.D., K.M., G.Y.; Materials - E.D., K.M., G.Y.; Data Collection and/or Processing - E.D., K.M., G.Y.; Analysis and/or Interpretation - E.D., K.M., G.Y.; Literature Search – B.T., S.S., S.D.; Writing Manuscript - B.T., S.S., S.D.; Critical Review - B.T., S.S., S.D.; Other - B.T., S.S., S.D.

Conflict of Interest: The authors have no conflicts of interest to declare.

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