Malnutrition Assessment in Hemodialysis Patients: Role of Bioelectrical Impedance Analysis Phase Angle

Laurynas Rimsevicius, MD, PhD,*† Alvita Gincaitė, MD,* Vaidas Vicka, MD,*
Diana Sukackienė, MD,† Jelena Pavinic, MD,† and Marius Miglinas, MD, PhD*†

Objective: To determine the most potent bioelectrical impedance analysis (BIA) marker of malnutrition and to adjust its application to hemodialysis (HD) patients.

Design: An observational study.

Subjects: A total of 99 patients on maintenance HD were enrolled in the study.

Intervention: The nutritional state of the patients was examined before and after the HD procedure using Subjective Global Assessment Scale (SGA), serum albumin, body mass index and BIA-derived fat-free mass index, reactance, resistance, and phase angle (PA). Malnutrition defined by the SGA questionnaire was used to detect the most potent marker of malnutrition. This marker was further analyzed and corrected for the excess fluid, age, and gender producing the nutritional state-specific cutoffs.

Results: The SGA rates of nutritional state were as follows: 57.6% (57) well nourished, 28.3% (28) moderately malnourished, and 14.1% (14) severely malnourished. Multivariate forward logistic regression analysis of the nutrition markers revealed PA as the most potent malnutrition predictor (odds ratio $3.69; 95\%$ confidence interval [CI]: $1.59-8.62; P = .002$). PA was adjusted for the excess fluid ($5.00 \pm 0.97$ vs $4.87 \pm 1.08 P < .001$). Patients were assigned into groups with adjusted PA values below the 5th through the 50th percentile of the mean PA reference value. The moderately malnourished patients were most accurately identified by the percentile group of $25\%$ (area under the curve $= 0.70; 95\%$ CI: $0.60-0.81; P = .001$), and the severely malnourished patients were most accurately identified by the percentile group of $15\%$ (area under the curve $= 0.74; 95\%$ CI: $0.62-0.85; P = .005$).

Conclusion: Malnutrition is present almost in a half of the HD patients. BIA-provided PA is the most potent predictor of malnutrition. PA can be adjusted for the excess fluid after HD, age, and gender and used accordingly.

Introduction

MALNUTRITION IS A prevalent condition in patients experiencing various chronic diseases.1 From 20% to 70% of the maintenance hemodialysis (HD) patients are found to be malnourished depending on the method used to evaluate the nutritional status.2-4 This complex state is caused by factors comprising of uremia, persistent inflammation, physical disability, dietary restrictions, gastrointestinal tract disturbances, metabolic acidosis, or HD by itself.5 Malnutrition is independently responsible for a decreased quality of life and a greater risk of mortality.4 Therefore, early recognition and diagnosis of malnutrition are some of the key points in HD patients’ management.

Bioelectrical impedance analysis (BIA) is widely recognized as a method for evaluating body composition, which contributes information about the nutritional status of the patient. BIA provides various nutritional markers, such as fat-free mass index, reactance, resistance, and phase angle (PA).6 These markers are commonly studied, and their application is well established in cardiology,7 cardiac surgery,8 oncology,9 pulmonology, and geriatrics.10,11 BIA-derived nutritional markers are used to identify the malnourished patients and, therefore, to evaluate the risk of the deleterious clinical outcomes and provide a basis for the nutritional therapy.

In HD patients, BIA is mostly used for the evaluation of fluid balance. Application of BIA to diagnose malnutrition is challenging, and hence, criticized a lot.12 The alterations in fluid and electrolyte balance distort the electric measurements and fault the results of BIA.13 Overhydration,14 age, and gender tend to decrease the bioelectrical impedance and thus cause false results leading to inaccurate diagnosis of malnutrition.15 However, various BIA indices of
nutrition are still named as potent predictors of prolonged hospitalization, complications, and mortality in current research of HD patients. Therefore, the aim of this study is to determine the most potent BIA marker of malnutrition and to adjust its application to HD patients.

Methods

Patients

An observational study was conducted in a tertiary referral university hospital between September 2015 and December 2015. This study was approved by the research ethics committee of the hospital, and informed consent was obtained from the patients prior the study. The enrollment of the patients was performed by implementing the selection criteria. All the patients were on maintenance HD and had no contraindications for BIA, that is, they were not limbless and had no pacemaker. The only patients who were not included in the study were those who did not agree to participate or had impaired mental function and could not give an informed consent.

Evaluation of the Nutritional Status

The nutritional status of the patients was examined after the HD procedure. American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.)–recommended Subjective Global Assessment Scale (SGA) was used to identify well-nourished, malnourished, and severely malnourished patients. BIA was performed using InBody S10® (Biospace, Seoul, Korea) body composition analyzer. The device was calibrated before the study and set to use a Caucasian population reference equation for the analysis. The analysis was conducted for patients in lying posture, 20 minutes before and after HD procedure and according to all recommendations from ESPEN and the manufacturers.

BIA-derived fat-free mass index, reactance, resistance, and PA were calculated. These nutritional markers were tested for their potency to predict SGA-defined malnutrition in a logistic regression model. The most potent marker was selected for further analysis.

Adjustment of the Most Potent Marker

The most potent BIA-derived marker of malnutrition was corrected for fluid overload. Linear regression coefficient was produced by calculating a mean change in a marker per mean volume of filtered water during the HD procedure. The excess fluid of the patient was calculated by adopting the equation provided by manufacturers: extracellular water minus intracellular water times 0.61. Volume of the excess fluid was converted to the marker units using the regression coefficient and added to the original post-HD value of the marker.

Furthermore, measurements of the selected marker were adjusted by age and gender reference values of healthy subjects. This step allowed us to account for the physiological changes of the body composition occurring in women and elderly patients. Subjects were assigned into groups with values below the 5th through the 50th percentile of the mean reference value.

Validation of the Selected Marker

The relationship between the selected marker groups and SGA-defined moderate malnutrition and severe malnutrition was evaluated using receiver operating characteristic area under the curve. The most accurate percentile for each malnutrition group was detected providing the cutoff values.

Statistical Analysis

Descriptive statistics were used to describe baseline characteristics of the patients. The normality of the distribution was assessed using Kolmogorov–Smirnov test, and the data are presented accordingly.

Univariate and multivariate logistic regression model was used to evaluate potency of BIA-provided nutrition markers to predict SGA-defined malnutrition. The BIA-provided markers found to be significant in univariate logistic regression analysis were entered into the multivariate logistic regression model with forward selection process. The most potent predictor of the SGA malnutrition was selected and further adjusted for fluid overload by applying the linear regression coefficient, which was produced by calculating a change in marker per volume of filtered water during the HD procedure.

The relationship between the selected marker groups and SGA-defined moderate malnutrition and severe malnutrition were evaluated using receiver operating characteristic area under the curve.

A 2-tailed P value of less than .05 was considered to be significant. Statistical analysis was performed using statistical tools package IBM SPSS Statistics V21® (IBM Corporation, New York).

Results

Baseline Characteristics of the Patients

During the study period, 99 patients were enrolled. Most of them were men, with mean age of 58.7 years. The most common comorbidities in the study group included hypertension, anemia, secondary hyperparathyroidism, and coronary artery disease compiling to the mean Charlson Comorbidity Index of 5.77. These baseline characteristics of the patients are presented in Table 1.

Evaluation of the Nutritional Status

SGA-defined moderate malnutrition was present in almost half of the patients. Severe malnutrition was detected in a proportionally lesser part of the cohort. These results and the raw measurements of BIA are presented in Table 1.

Multivariate forward logistic regression of the nutrition markers revealed that PA was the most potent predictor of
the SGA-defined malnutrition (Table 2). This marker was selected for the further analysis.

Adjustment of the PA

Linear regression analysis revealed the change of the PA of 0.144°/C14 per 1 liter of filtered water during the HD procedure (B = 0.14 95% CI: 0.05-0.18; P = .001). Volume of the excess fluid after HD was converted to marker units using the regression coefficient and when added to the original value of the PA. The fluid excess adjusted PA value was increased by a mean of 0.13° compared with its original value (5.00 ± 0.97 vs 4.87 ± 1.08; P < .001).

Moreover, measurements of the PA were further adjusted by age and gender reference values of the healthy subjects. Patients were assigned into groups with values below the 5th through the 50th percentile of the mean reference value. Rates of subjects in the different percentile cutoff groups were as follows:

- <5th: 27.3% (27)
- 5th to 10th: 46.5% (46)
- 10th to 15th: 52.5% (52)
- 15th to 20th: 60.6% (60)
- 20th to 25th: 64.6% (64)
- 25th to 30th: 71.7% (71)
- 30th to 35th: 74.7% (74)
- 35th to 40th: 76.9% (76)
- 40th to 45th: 82.8% (82)
- >45th: 85.9% (85)

Feasibility of the Adjusted PA

The most accurate PA percentile cutoff groups for SGA-defined moderate and severe malnutrition were different. The moderately malnourished patients were most accurately identified by the percentile group of 25th (AUC = 0.70; 95% CI: 0.60-0.81; P = .01), and the severely malnourished patients were most accurately identified by the percentile group of <15th (AUC = 0.74; 95% CI: 0.62-0.85; P = .005). The cutoff percentiles of the PA for each nutritional state group of the SGA are presented in Figure 1 for men and in Figure 2 for women.

Discussion

In our study, PA is revealed to be the most potent BIA-provided marker of malnutrition in HD patients. These results are concordant with other findings in malnutrition-related research of end-stage renal disease patients. In all these studies, PA is concluded to be an early indicator of malnutrition and correlates well with other standard methods of nutrition evaluation including underwater weighing, isotope dilution, and total body potassium. It is postulated that PA value is readily affected by the subtle alterations of integrity of cell membrane and may reflect even the earliest changes of the nutrition patterns. Therefore, our study adds to the pool of evidence directed to the further research and clinical implementation of malnutrition diagnostics using BIA in HD patients.

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**Table 1. Baseline Characteristics of the Patients**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean ± SD or Median (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (male), n (%)</td>
<td>51 (51.5)</td>
</tr>
<tr>
<td>Age (y)</td>
<td>58.7 ± 14.38</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
</tr>
<tr>
<td>Time on HD (y)</td>
<td>6.07 ± 5.61</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>17 (25)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>88 (88.9)</td>
</tr>
<tr>
<td>Anemia, n (%)</td>
<td>60 (88.2)</td>
</tr>
<tr>
<td>CAD, n (%)</td>
<td>26 (38.2)</td>
</tr>
<tr>
<td>SHPT, n (%)</td>
<td>35 (51.5)</td>
</tr>
<tr>
<td>CCI</td>
<td>5.77 ± 2.23</td>
</tr>
<tr>
<td>Nutrition markers</td>
<td></td>
</tr>
<tr>
<td>FFMI (kg/m²)</td>
<td>17.43 ± 2.31</td>
</tr>
<tr>
<td>Reactance (Ω)</td>
<td>19.22 ± 5.35</td>
</tr>
<tr>
<td>Resistance (Ω)</td>
<td>231.08 ± 44.91</td>
</tr>
<tr>
<td>PA (degrees)</td>
<td>4.88 ± 1.08</td>
</tr>
<tr>
<td>SGA A, n (%)</td>
<td>57 (57.6)</td>
</tr>
<tr>
<td>SGA B, n (%)</td>
<td>28 (28.3)</td>
</tr>
<tr>
<td>SGA C, n (%)</td>
<td>14 (14.1)</td>
</tr>
<tr>
<td>Serum albumin (g/dL)</td>
<td>4.02 ± 0.49</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.93 ± 5.59</td>
</tr>
<tr>
<td>Hydration state</td>
<td></td>
</tr>
<tr>
<td>ICW after HD (L)</td>
<td>22.5 ± 4.95</td>
</tr>
<tr>
<td>ECW after HD (L)</td>
<td>14.62 ± 3.24</td>
</tr>
<tr>
<td>TBW after HD (L)</td>
<td>37.12 ± 8.09</td>
</tr>
<tr>
<td>Excess water after HD (L)</td>
<td>0.81 [0.30 – 1.46]</td>
</tr>
</tbody>
</table>

**Table 2. Multivariate Regression Analysis of the Malnutrition Predictors**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Estimate Univariate</th>
<th>95% CI</th>
<th>P value</th>
<th>Estimate Multivariate</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PA</td>
<td>3.70</td>
<td>1.79-7.69</td>
<td>&lt;.001</td>
<td>3.69</td>
<td>1.59-8.62</td>
<td>.002</td>
</tr>
<tr>
<td>FFMI</td>
<td>1.28</td>
<td>0.96-1.69</td>
<td>.086</td>
<td>n.i.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reactance</td>
<td>1.16</td>
<td>1.03-1.32</td>
<td>.014</td>
<td>n.s.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resistance</td>
<td>1.00</td>
<td>0.98-1.01</td>
<td>.637</td>
<td>n.i.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>1.09</td>
<td>0.96-1.22</td>
<td>.195</td>
<td>n.i.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum albumin</td>
<td>1.22</td>
<td>1.04-1.42</td>
<td>.013</td>
<td>n.s.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BMI, body mass index; CI, confidence interval; FFMI, fat-free mass index; n.i., not included; n.s., not significant with P value >.05; PA, phase angle.
The adjustment of the PA measurement has been proven to be necessary for the implementation of the PA into clinical practice. The adjustment of raw BIA output of the PA we perform in our study lets us clarify and account for the effect of the excess fluid in HD patients and provides us with the specific cutoffs for malnutrition. First of all, there is a significant difference between values of the PA measured before and after HD, depending on the amount of water removed. Furthermore, there is a significant amount of excess fluid after the HD. In this case, application of an unadjusted PA for excess fluid would be a poor decision. Moreover, there is a distinct effect of age and gender toward the lower measurements of the PA. Therefore, it is crucial to account for these factors and to use different and specific cutoffs for the HD patients, which are presented in our study.

In our study, we provide the cutoffs of the PA, which best discriminate the well-nourished, moderately malnourished, and severely malnourished HD patients. These malnutrition cutoffs are based on a notion that the PA is able to differentiate the severity of the malnutrition, and thus, the value of it drops proportionally to the intake of food. After adopting the age and gender reference values of the healthy subjects, we are able to assign the patients into the standardized groups of the reduced PA. These groups represent the gradual decrease of the PA and, hence, a worse nutritional state of the patient. The standardization process of the PA has been proven to be successful in other fields of medicine including cardiac surgery, geriatrics, and oncology. These studies provide the disease-specific cutoffs of malnutrition: 15th percentile in the cardiac surgery patients and 5th percentile in the oncology patients.

Possible limitations of our study include general limitations of BIA and the specific nature of the HD patients. The regression equations used in BIA devices are based on measurements of the healthy population. HD patients suffer from misbalanced electrolytes and fluid shifting between the intracellular and extracellular spaces, lowered...
levels of albumin, and increased levels of urea in blood serum, all these factors contributing to the altered impedance of the body. These disturbances may question the nutritional nature of the low PA in our study and limit the application of it.

Conclusion
Malnutrition is present in almost a half of the HD patients. We found that BIA-provided PA is an accurate and appropriate method of nutritional state evaluation. Furthermore, despite excess fluid, age and gender being important limitations in the application of BIA, PA can be adjusted for these factors and used accordingly. The malnutrition cutoff percentiles of the PA we report in our study must be further evaluated in upcoming research.

Practical Application
In our study, we present a way to use BIA both for evaluation of the fluid balance and for the nutritional state examination of the HD patients. We provide BIA-derived and HD-adjusted PA cutoff values of the well-nourished, moderately malnourished, and severely malnourished patients in user-friendly diagrams.

Acknowledgments
The authors are indebted to all patients who participated in the study.

References