Is the Phase Angle, a Prognostic Indicator for Nutritional Status in Cirrhotic Patients?

Sabrina Alves Fernandes*, Maria Cristina Gonzalez, Lilian Bassani, Daniella Miranda, Bianca Pivatto, Daniele Lazzarotto Harter and Cláudio Augusto Marroni

1PPG Medicina Hepatologia, Universidade Federal de Ciências da Saúde de Porto Alegre (UFCSPA), Porto Alegre, Rio Grande do Sul, Brazil
2PPG Saúde e Comportamento Universidade Católica de Pelotas (UCPEL), Pelotas, Rio Grande do Sul, Brazil

Abstract

Background & Aim: The phase angle value, obtained by bioelectrical impedance analysis, is an important prognostic indicator in several clinical conditions. This study aimed to compare the performance of the standardized phase angle with that of Child-Pugh score, a well-known prognostic indicator of chronic liver disease.

Methods: A cross-sectional study was conducted with cirrhotic patients. Bioelectrical impedance analysis was performed, and the standardized phase angle was calculated. Low standardized phase angle was defined as a value below -1.65. The significance level was set at 5%.

Results: Of 195 participants, 59% were male. Mean age was 55.9 ± 10.8 years; 59% of patients were classified as Child-Pugh class A, 22.6% as class B, and 18.5% as class C. The Phase Angle average was 5.79 (±1.20) with z score average -0.75 (±1, 61). 76.4% of the population studied showed Phase Angle indicative of good prognosis.

Conclusions: The standardized phase angle was correlated with the Child-Pugh score and can therefore be considered a reliable prognostic indicator of nutritional status in cirrhotic patients.

Keywords: Liver cirrhosis; Nutritional assessment; Bioelectrical impedance; Phase angle

Abbreviations: BIA: Bioelectrical Impedance Analysis; PA: Phase Angle; PCM: Protein-Calorie Malnutrition; SPA: Standardized Phase Angle; HBP: High Blood Pressure; T1D: Type 1 Diabetes; T2D: Type 2 Diabetes

Introduction

Protein-Calorie Malnutrition (PCM) is a frequent complication in cirrhotic patients, with a prevalence ranging from 25 to 80%, depending on the method used [1,2]. PCM is characterized by changes in cell membrane integrity and alterations in fluid balance [3] and it results in higher prevalence of morbidity and mortality [1,4,5].

The assessment of nutritional status of cirrhotic patients is quite complex when body conditions such as edema of the limbs and ascites are present. The phase angle (PA), which has helped a lot in this matter of body asymmetry which can be determined by the bioelectrical impedance analysis (BIA) has proven to be an effective, safe, fast and inexpensive method to assess the prognosis of these patients [6]. The PA contains is based two parameters Resistance (R) and Reactance (Xc). Resistance, which is the opposition of the body to the flow of an electrical current, is inversely related to the presence of water and electrolytes in the body. Resistance is related to the capacitance properties of the cell membranes and varies with their integrity, function and composition [7]. Phase Angle, which is an indicator of cell membrane integrity, is calculated from Resistance and Reactance expressed in degrees [6,8]; PA values range from 3 to 15° [9]. Low Phase Angle values are indicative of impaired cell membrane integrity or death, whereas high values are indicative of intact cell membranes [10].

Studies have shown that PA is a good prognostic indicator in several clinical situations [11-16]. Different cut-off values are used based on reference values for age and gender. Standardized PA (SPA) values exist for the Swiss, German, American and Brazilian populations. The SPA can be used to compare results among different populations and to correlate an SPA with a particular disease, as reported by Barbosa-Silva et al. [17] in 2008 with the Brazilian population. The results of this study allow us to use the SPA values as parameters for other several diseases.

The objective of this study is to compare the performance of the SPA with that of the Child-Pugh score, etiology of the disease and co morbidities which is a well-known prognostic indicator of chronic liver disease.

Materials and Methods

A cross-sectional study was performed with patients who were diagnosed with cirrhosis after clinical and/or histological tests. All patients were adults over 18 years who met the inclusion criteria were classified based on disease severity by the Child-Pugh score (albumin, prothrombin time, ascites, bilirubin encephalopathy). The patients enrolled were treated at the ambulatory service and hospitalized. The study was approved by the Research Ethics Committee of Universidade Federal de Ciências da Saúde de Porto Alegre, Brazil, and was conducted in accordance with the provisions of the Declaration of Helsinki. Written informed consent was obtained from all participants.

Resistance and Reactance was obtained using a bioimpedance device (Biodynamics, model 450, Seattle, WA) with an electrical
current of 800 A and 50 kHz. The Resistance and Reactance values were used to calculate PA. Patients were evaluated under standard position and conditions. PA was calculated using the following equation 3:

$$PA = \arctan\left(\frac{Xc}{R}\right) \times \left(\frac{180}{\pi}\right)$$

The SPA was estimated from the reference values for the Brazilian population, according to the equation: subtracting the reference PA value according to sex and age from the observed PA and then, dividing the result by the respective age and sex reference standard deviation $SPA = \frac{PA - PA_{ref}}{SD_{PA}}$. A SPA cutoff value of $-1.65$ was chosen to classify the patients in two groups: low PA or not. This should be understood in the same way as $Z$ score (as used for weight and height in children). The SPA cutoff values of $-1.65$ stands for the fifth percentile of normal population, therefore, it can be considered as the lower limit accepted in a healthier population. Comparisons among groups with different mean ages and sex distribution can be done using the same SPA cutoff ($-1.65$), as SPA was obtained from an already adjusted age and sex reference values.

### Statistical analysis

The results were expressed as the mean and standard deviation. ANOVA and the Tukey test were used to compare the SPA values and disease severity (classified by the Child-Pugh score). Pearson’s chi-squared test was applied to evaluate the association between the SPA and the Child-Pugh score, sex, etiology, comorbidities and ascites. The t-student test was used to compare averages of age between subjects with good and poor prognosis. The variables which have a $p$-value $<0.20$ in the bivariate analysis were entered into a Multiple Poisson Regression model to evaluate factors independently associated with poor prognosis. The significance level was set at 5%. All analyses were performed using SPSS version 18.0.

### Results

In the total population of 195 cirrhotic allocated for this study, 59% were male with a mean age of 54.5 ($\pm$ 10.6), females had a mean age of 57.9 ($\pm$ 10.9). The prevalent etiology in the population studied is C virus (79%), where 62% are women. The second prevalence etiology is alcohol (25.1%), with the prevalence of 93.9% of men. The observed distribution according to the severity of disease was 59% Child-Pugh A, 22.6% B and 18.5% C. All characteristics of the sample are presented in table 1. Regarding the selected comorbidities, 52% of the population has High Blood Pressure (HBP). Only 1% of the sample diagnosed with Type 1 Diabetes (T1D). Moreover, 54% of patients had Type 2 Diabetes (T2D). With decomposition of disease and changes in body symmetry 67% of the patients evaluated had ascites.

As we observed in table 2 among all variables analyzed, the only ones that showed a statistically significant relationship with prognosis was gender, disease classification (Child Pugh), HBP and ascites.

The factors that remained associated with poor prognosis after adjustment by Multiple Poisson Regression model were: gender, Child-Pugh and ascites. Men had a 71% higher prevalence of poor prognosis when compared with women ($PR=1.71$, $95\% CI$: 1.01-2.88, $p=0.044$). Concerning the Child Pugh score, patients rated B had 1.3 times higher prevalence compared with Child-Pugh A, not being significant. However, patients with Child Pugh C had a 2.6 times higher prevalence of poor prognosis compared with patients with Child-Pugh A ($PR=2.60$, $95\% CI$: 1.32 to 5.11, $p=0.006$). Patients with ascites had a prevalence 2.16 times more chances of having a poor prognosis ($PR=2.16$, $95\% CI$: 1.14 to 4.12, $p=0.019$), all independently associated with the outcome (Table 3).

According to the isolated analysis of phase angle (Table 4) we observed that 46% of cirrhotic patients have poor prognosis indicator, not belonging mostly to averages of Resistance, reactance and PA z-score.

As we observed in figure 1, there was difference in PA z score according to severity of cirrhosis ($p<0.001$), and the Child C had significantly lower values than those of Child A and B, which did not differ significantly. For the difference identified between Child Pugh A, B and C, the SPA cutoff of $-1.65$ was chosen as the lower limit in the healthy population, according to the equation: subtracting the reference SPA and then, dividing the result by the respective age and sex reference standard deviation $SPA = \frac{PA - PA_{ref}}{SD_{SPA}}$. A SPA cutoff value of $-1.65$ was chosen to classify the patients in two groups: low SPA or not. This should be understood in the same way as $Z$ score (as used for weight and height in children). The SPA cutoff values of $-1.65$ stands for the fifth percentile of normal population, therefore, it can be considered as the lower limit accepted in a healthier population. Comparisons among groups with different mean ages and sex distribution can be done using the same SPA cutoff ($-1.65$), as SPA was obtained from an already adjusted age and sex reference values.
B and C in relation to poor prognosis the power is estimated at 99.5%.

**Discussion**

There is a progressive increase in cases of cirrhosis with the majority being diagnosed late and this involves complications, one of which is the protein calorie malnutrition. Until now there was not an instrument capable of attach nutritional conditions to the standard score Child-Pugh clinic classification of cirrhotic, offering a prognostic overview of survival. D’Amico et al. [18] in 2006 in the review of 118 studies of survival of cirrhotic patients found that the greater validity score in clinical classification of liver disease is the Child-Pugh.

Alberino et al. [19] show that malnutrition can be directly related to poorer survival of patients with cirrhosis and its correction is a strong indicator of improvement in quality of life, especially those who are on the waiting list for liver transplantation. Early detection of malnutrition of cirrhotic is an aspect of great clinical relevance and interferes positively in patient recovery [7,20].

![Table 3: Multiple Poisson Regression for evaluating factors associated with a poor prognosis.](image)

**Table 3:** Multiple Poisson Regression for evaluating factors associated with a poor prognosis.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>PR (CF 95%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td>1.71 (1.01-2.88)</td>
<td>0.044</td>
</tr>
<tr>
<td>HBP</td>
<td>0.74 (0.37-1.48)</td>
<td>0.392</td>
</tr>
<tr>
<td>Child Pugh A</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>1.30 (0.64-2.65)</td>
<td>0.474</td>
</tr>
<tr>
<td>C</td>
<td>2.60 (1.32-5.11)</td>
<td>0.006</td>
</tr>
<tr>
<td>Ascites</td>
<td>2.16 (1.14-4.12)</td>
<td>0.019</td>
</tr>
</tbody>
</table>

PR=Prevalence Ratio; CF 95%=95% of confidence level

**Table 4:** Phase Angle and prognosis.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>n=195, Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resistance</td>
<td>504.8 ± 96.7</td>
</tr>
<tr>
<td>Reactance</td>
<td>51.0 ± 12.9</td>
</tr>
<tr>
<td>PA</td>
<td>5.79 ± 1.20</td>
</tr>
<tr>
<td>PA z-score</td>
<td>-0.75 ± 1.61</td>
</tr>
<tr>
<td>PA Classification - n (%)</td>
<td></td>
</tr>
<tr>
<td>Poor Prognosis</td>
<td>46 (23.6)</td>
</tr>
<tr>
<td>Good Prognosis</td>
<td>149 (76.4)</td>
</tr>
</tbody>
</table>

**Figure 1:** Association of PA z-score with CHILD PUGH.

Faced with this information is that we aimed the study and we corroborate with several findings in the literature. The sample analyzed in this study showed a predominance of males which is in agreement with findings in the literature [21,22]. The etiology of cirrhosis was predominantly in patients with C virus hepatitis, followed by alcohol, demonstrating that the poor prognosis is not directly related to nutritional status caused the alcohol, but it is a characteristic of cirrhotic "per se".

With the Phase Angle (PA) by bioelectrical impedance, it becomes possible to measure integrity of membranes, Selberg and Selberg [6] using PA in a population of hospitalized cirrhotics demonstrated that those who were below the PA 5.4° should be considered at nutritional risk, correlating with disease severity by Child Pugh score.

Fernandes et al. [23], showed that of the different methods analyzed for nutritional assessment in cirrhotic the only one nutritional change that correlated with disease classification by Child Pugh score was the PA by electrical bioimpedance with the finding of PA 5.4° reinforcing the data found by Selberg and Selberg in 2002 [6].

In a study with cirrhotic patients, divided into patients with and without ascites, Pirlich et al. [24] reported that ascites is not a clinical sign of greater negative impact on the determination of body composition. The authors also suggest that values and specific equations for cirrhotic patients should be created as a benchmark for evaluation use with bioelectrical impedance.

Corroborating with the findings of this study, where we observed that ascites is not a limitation for realization of bioelectrical impedance. Furthermore, this study showed that ascites is an isolated indicator of poor prognosis, being linked to worsening of clinical status and depletion of lean body mass and protein reserves with significant metabolic alteration, ranking cirrhotic as sarcopenic. In the present study, not only ascites is showing up as a single indicator of poor prognosis, but the male gender also, not being described comparative data for this finding in the literature until now.

Not only cirrhotic patients are those that present changes in the distribution of extracellular and intracellular fluids, but patients with renal or heart failure or chronic obstructive pulmonary disease or obese patients also have body asymmetry [14,25-27].

Thus, it is difficult to describe the real nutritional status of these populations, Norman et al. [28] in their publication of 2012 reinforce that the value of the phase angle, being a variable cellular integrity, is not linked to algorithmic equations, which may suffer errors by alterations of hydro electrolytic disorders, as happens with other parameters offered by bioimpedance device. The PA can be used to measure metabolic disorders in any kind of disease and be used as a prognostic marker associated with specific markers in clinical practice.

As an example of such use, Schwenk et al. [12] suggest that PA can be used as a prognostic indicator in several diseases, after evaluating HIV-infected patients, identifying early changes in the body through the PA.

Similarly, Gupta et al. [14] showed that PA is a strong predictor of survival in patients with advanced pancreatic cancer, comparing the method with the traditional parameters of nutritional assessment, such as albumin, prealbumin and transferrin. Still in oncology, a recent study by Paiva et al. [29] evaluated survival rates among cancer patients submitted to chemotherapy, and reinforces the assessment of PA as an excellent prognostic marker.
In conclusion, this study reinforces the association of PA with Child-Pugh score as a strong prognostic indicator. The findings of this study call attention to future studies in the area of survival in order to identify predictors of poor prognosis of cirrhosis.

Acknowledgements
The authors would like to thank Prof. Dra Cristiane Valle Tovo for facilitating the allocation of patients.

Statement of Authorship
Daniella Miranda, Bianca Coccaro Pivatto, Daniele Harter e Lilian Bassani carried out the studies. Sabrina Fernandes data analyses, drafted the manuscript. Maria Cristina Gonzalez carried out the samples analyses. Sabrina Fernandes and Maria Cristina Gonzalez participated in the design of the study and performed the statistical analysis. Claudio Augusto Morrani conceived of the study, and participated in its design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

Conflict of Interest Statement
The authors declare that they have no competing financial, personal or other interests that might be perceived to influence the results and/or discussion reported in this paper.

Funding Sources
This study received no funding from any source.

References