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Phase Angle and Bioelectrical Impedance Vector Analysis (BIVA) in Amyotrophic Lateral Sclerosis (ALS) Patients

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Featured Application: Body composition and bioelectrical parameters are useful in nutritional assessment and monitoring of ALS patients.

Abstract: Phase angle (PhA) and bioelectrical impedance vector analysis (BIVA) have emerged as valuable tools for assessing nutritional status and prognosis in various patient populations, but there is a lack of studies in rare neurodegenerative diseases. The purpose of this cross-sectional study was to investigate these bioelectrical parameters in patients with amyotrophic lateral sclerosis (ALS), compared with healthy peers. The tetrapolar impedance method was applied and bioimpedance analysis (BIA) was performed. Bioelectrical parameters were obtained (Resistance—R; Reactance—Xc) or calculated (PhA; BIVA). For BIVA, bivariate vectors and confidence ellipses were graphically represented. In addition, R and Xc were used to determine body composition (BC) (Fat Mass—FM; Fat-Free Mass—FFM; and Total Body Water—TBW). In this study, 40 participants were divided into two groups: case group (n = 20, ALS patients) and control group (n = 20, healthy subjects. Our main results showed that ALS patients presented low levels of BMI, FFM, R, and Xc adjusted by height (R/H, Xc/H), hydration, and cellularity, compared to the healthy subjects. Our findings highlight BC and bioelectrical parameters, including PhA and BIVA, as valuable indicators of nutrition status, which should be implemented in the nutrition care process of ALS patients during the disease course.

Keywords: amyotrophic lateral sclerosis; body composition; electric impedance

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1. Introduction

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease characterized by the progressive degeneration of both upper and lower motor neurons [1,2]. Currently, ALS is considered a multisystemic disease [3] that primarily affects motor neurons and has great genetic, clinical, and neuropathological heterogeneity [4]. The age group most at risk for developing this disease is 45 to 75 years old. Its most common form is sporadic (90% of cases), in which its pathogenesis is related to complex interactions between genetic and environmental factors. The remainder of the cases (10%) are of the familial type, where there is the presence of an autosomal dominant inheritance pattern proven by the occurrence of a family history of the disease [4].

The etiology of ALS is not yet fully understood, but it is known that there are interactions between genetic and environmental factors, in addition to aging-related dysfunctions [4]. The pathophysiology of ALS is marked by neuronal dysfunction with eventual cell death (neuronal apoptosis). Hypotheses guiding its pathophysiology include glutamate toxicity, oxidative stress, neuroinflammation, protein aggregation (e.g. TDP-43 protein),

defects in RNA processing, mitochondrial dysfunction, axonal transport dysfunction, toxin exposure, and viral infections [5,6].

In ALS, the first observation of symptoms usually occurs between the ages of 51 and 66 [7]. As the disease affects motor neurons, the most characteristic symptoms are muscle atrophy and weakness. The affected muscles are skeletal and those involved in breathing, speaking, and swallowing. In this way, a range of signs and symptoms can be observed, such as dysarthria, dysphonia, dysphagia, atrophy, and muscle weakness [4,5]. Other signs and symptoms include drooling, fasciculations, hyperreflexia, sensory impairment, cramps, and emotional liability. Around 50% of patients will present other non-motor symptoms, related to cognitive and behavioral changes. One example is frontotemporal dementia in 10–15% of cases, clinically characterized by behavioral changes, impairment of executive functions, and/or language impairment [4].

The diagnosis of ALS is based on clinical history and physical examination, which shows signs of progressive dysfunction of the upper and lower motor neurons. It is usually supported by electrophysiological and neuroimaging studies, as well as laboratory tests, especially in cases of familial ALS. Exclusionary diagnoses should be considered [8]. The El Escorial criteria were developed to standardize ALS diagnosis for clinical research [9]. Early diagnosis can contribute to better clinical management of the disease. However, incorrect diagnoses early in the disease can delay the diagnosis of ALS. Studies show that the delay in diagnosing ALS can range from 9 to 24 months [7].

Currently, some guidelines address the treatment of ALS [5,10,11] and all recommendations support a multidisciplinary approach. Regarding drug treatment, although several clinical trials are underway, there are two drugs approved by the Food and Drug Administration (FDA): Riluzole and Edaravone. Riluzole acts as a glutamate antagonist and reduces its excitotoxicity, increasing survival by only about 3 to 6 months [12]. On the other hand, Edaravone acts to reduce oxidative stress and has been shown to improve the functional status and increase the survival of patients with ALS [13].

As a limitation, the treatment of the disease is focused on managing the symptoms that occur throughout the disease. Authors demonstrate that multidisciplinary care in ALS is capable of significantly increasing survival [14].

The prognosis for patients with ALS is unfavorable, but survival time after diagnosis varies greatly. The factors that lead to shorter survival of patients with ALS are bulbar onset, delay in diagnosis, rapid functional decline, pronounced loss of weight or body mass index (BMI), advanced age at the onset of symptoms, presence of frontotemporal dementia, and low forced vital capacity. In general, the average survival of patients with ALS is 3 to 5 years, but about 5% to 10% of patients live longer than 10 years [5,7].

The ALS hallmark features encompass the gradual weakening of limb and respiratory muscles, with the common co-occurrence of dysarthria and dysphagia. In most cases, respiratory failure and malnutrition are the primary factors leading to mortality [1,15,16], typically occurring approximately 3 to 5 years after the onset of symptoms [17].

Denervation and malnutrition bring changes in body composition (BC) and result in a gradual decline in weight, muscle mass, and fat stores in ALS patients [1]. Research indicates that the reduction in muscle mass is linked to a poor prognosis, while an increase in fat content may be associated with better survival among individuals with ALS [15]. For this reason, BC is an important component of the nutrition evaluation and monitoring in ALS [18].

There are many methods to evaluate BC. Among them, bioelectrical impedance analysis (BIA) has been validated and used in ALS [18,19] and has advantages because it is fast, safe, inexpensive, accurate, and non-invasive [20]. BIA measures the impedance (Z), comprised of resistance (R) and reactance (Xc), of a small alternating current applied to the body [20]. R and Xc values are used in predictive equations to calculate fat-free mass (FFM), fat mass (FM), total body water (TBW), and phase angle (PhA), the latter used as an indicator of health, cellular quality, function, and membrane integrity [20,21]. BIA is based on the premise that FM offers greater resistance to the electrical current flow, while

FFM provides less resistance. Additionally, body fluids and cell membranes contribute to conductivity and low impedance. In contrast, bone, fat, and triglycerides lack conductivity and have high impedance [22]. Many factors can influence the BIA results such as hydration status, ascites, edema, electrolyte balance, use of a pacemaker, body position, prior physical activity, body temperature, and dietary intake. Thus, an adequate standardization of BIA is required to achieve dependable measurements [18].

BIA can be complemented by the BIVA, developed by Piccoli et al. [23]. In BIVA, R and Xc, adjusted for height, are represented as points on a graph. These points can be compared to tolerance ellipses set at 50%, 75%, and 95% based on a healthy population of the same gender and race. The size and shape of the ellipse change with age and body size [22]. This semi-quantitative method allows the determination of changes in body fluids, hydration status, and body cell mass [24]. The main advantage of BIA is that it can be used to evaluate patients directly using bioelectrical parameters, without relying on predictive equations or body weight [22].

BIVA tolerance ellipses interpretation stands that an abnormal situation is indicated when the experimental data falls outside the 95th percentile ellipsis; a high body cell mass is suggested when the data are positioned above the long axis of the ellipsis; and hypohydration is inferred when the data appears to the right of the short axis of the ellipsis. The TBW shows an inverse relationship with the length of the impedance vector, and the combination of this vector's length and direction is referred to as the PhA [25].

BIVA has been used in the evaluation of BC and as a predictor of mortality in several neurological diseases, such as Duchenne muscular dystrophy (DMD) [26], Alzheimer's [27], Parkinson's [28], and systemic sclerosis [29]. BIVA may be an interesting approach to consider in ALS for a number of reasons. First, BIVA does not depend on error-prone predictive equations such as those used for BIA. Secondly, BIVA does not require weight, a parameter not always available, especially for patients in wheelchairs. Thirdly, BIVA is sensitive to identifying early and minimal changes in BC.

Considering that nutritional status directly influences prognosis and survival in ALS, and that there is no gold standard method to assess the nutritional status, it is of the utmost importance to connect complementary data about nutritional status in ALS patients, especially those related to BC.

We believe that taking PhA and BIVA into account, since the early stages of ALS, is critical in guiding nutrition interventions for maintaining proper nutritional status and avoiding malnutrition, factors that can improve the prognosis in ALS. We hypothesized that BIVA could bring new insights for nutrition evaluation and monitoring in ALS patients. Therefore, the aim of this study was to investigate the BC in ALS patients, including the BIVA approach, compared with matched healthy individuals.

2. Materials and Methods

2.1. Ethical Aspects and Sample Characterization

A cross-sectional observational study was performed with ALS patients treated at a multidisciplinary outpatient facility of the Onofre Lopes University Hospital (HUOL) in Natal, Brazil.

This study was approved by the Research Ethics Committee of the Federal University of Rio Grande do Norte (UFRN), Brazil (CAAE: 40467214.0.0000.5292). Data were collected between March 2016 and December 2016. All patients provided written informed consent before enrolling in the study.

Considering the low cost and the time frame, the subjects were selected by convenience sampling based on their accessibility and proximity to the research [30]. At the time of the study, only 24 patients were being followed up in our facility. Thus, the sample size of 20 patients was representative of the target population. In addition, because ALS is a rare disease, non-multicentric studies with a small sample size have been published [19,31–33]. Following the El Escorial criteria for ALS diagnosis [9] patients with probable and definite ALS were included in our study. Patients with respiratory insufficiency, edema, or using a

pacemaker were excluded due to the difficulty in performing BIA or possible interference with BIA [34]. The control group was comprised of healthy individuals from the same community. A matching system based on age and sex was adopted to improve the quality of the data.

2.2. Functional Status and Anthropometry

In order to characterize the patients regarding the severity of the disease, their functional status was evaluated by the Revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R) that scores the functional status of the patients from 48 (maximum score = normal) to 0 (minimum score = no ability) [35].

Bodyweight (kg) and height (cm) were measured using an electronic ramp scale (KN R 500/50, KN Waagen, São Paulo, Brazil) and a stadiometer (Professional Sanny, American Medical do Brazil, São Paulo, Brazil), respectively. BMI was calculated as the ratio between body weight and height squared (kg/m^2).

2.3. Bioelectrical Impedance Analysis

The bioimpedance parameters R (Ω) and Xc (Ω) were obtained using the Quantum II® body composition analyzer (RJL Systems, Clinton Township, MI, USA) obtained as described by Lukaski et al. (1986) [24,36]. The tetrapolar approach was applied for BIA, with the patient lying supine and four self-adhesive point electrodes placed on the dorsal surfaces of the right hand and foot, respectively, according to the literature [26,36]. Bioimpedance analysis was used to determine BC (FM, FFM, and TBW) as well as other bioelectrical parameters (PhA, R/H, and Xc/H) [24,36,37].

2.4. Phase Angle and Bioelectrical Impedance Vector Analysis

Protocols and considerations for the assessment of the PhA and BIVA are described in the literature [23,36–38]. Briefly, R and Xc data were subsequently used to determine the PhA and BIVA. The PhA was calculated using the following formula: PhA = tangent arc (Xc/R)*180/π [37]. The BIVA results were based on the analysis of normalized R and Xc values for the patients' height (H) measurements (R/H and Xc/H in Ω/m), as a single vector measured in an individual at a single time [39].

Confidence intervals established for the healthy population were compared to specific metrics [38]. The vector shift over the ellipse is a semiquantitative method for assessing BC, whereas the shortening or lengthening of the vector suggests changes in body hydration [26]. Vector shifts parallel to the minor axis of the ellipses indicate changes in cell mass [24].

To plot the bivariate 50th, 75th, and 95th percentiles of the population by age group, the values of resistance and reactance adjusted by height were utilized. Values that are outside of the ellipse at 75% were deemed abnormal [23]. Mean impedance vectors were compared with Hotelling's T^2 test for vector analysis. Hotelling's T2 test is a multivariate extension of Student's *t*-test for unpaired data used for the comparison of mean vectors from two groups. Two mean vectors are significantly different in the R-Xc graph if their 95% confidence ellipses did not overlap according to Hotelling's T2 test ($p < 0.05$). On the contrary, if the vectors are overlapping, they are not significantly different ($p > 0.05$) [40]. Bivariate vectors and confidence ellipses of participants were plotted in graphs.

2.5. Statistical Analysis

Statistical analysis was performed using GraphPad Software, LLC. (Boston, MA, USA, Version 9.5.1), observing the distribution of the data in a normal curve using the Shapiro–Wilk test. Quantitative variables with a normal distribution were expressed as the means and standard deviations. Anthropometric and BC data were compared between groups using the student's *t*-test. All analyses for BIVA were performed using the BIVA 2002 software [39]. A value of $p < 0.05$ indicated statistical significance.

3. Results

In this study, 40 participants were divided into two groups: case group (n = 20, ALS patients) and control group (n = 20, healthy subjects. The mean ages for the case and control groups were 52.7 and 50.6 years, respectively. Among ALS patients, 45% were female, and 30% had bulbar onset ALS. Additionally, the average disease duration was 44 (20–55) months, and the ALSFRS-R score was 22.6 (8.8). In comparison to the control group, the case group exhibited significantly lower values in BMI (p = 0.0002), FFM, TBW, PhA, and R/H (all $p < 0.0001$), and Xc/H (p = 0.0017) (Table 1).

Table 1. Anthropometric data, body composition, and bioelectrical parameters of participants.

Variable	Cases (n = 20)	Controls (n = 20)	p
Sex, Male/Female	11/9	11/9	-
Age, years	52.7 (11.6)	50.3 (10.0)	-
Body Mass Index, kg/m^2	21.9 (2.9)	27.2 (5.1)	**0.0002**
Fat Mass, Kg	19.2 (5.8)	22.1 (9.6)	0.2616
Fat Free Mass, Kg	37.9 (6.0)	51.7 (11.0)	**<0.0001**
Total Body Water, Kg	27.1 (4.3)	37.4 (8.3)	**<0.0001**
Phase Angle, °	3.4 (0.9)	6.2 (1.0)	**<0.0001**
R/H, Ohm/m	455.2 (76.4)	322.4 (73.6)	**<0.0001**
Xc/H, Ohm/m	26.7 (6.6)	34.2 (7.3)	**0.0017**

Values expressed as mean (standard deviation). R/H, Resistance/Height. Xc/H, Reactance/Height.

The evaluation of tolerance ellipses shows that the vectors of ALS patients are shifted to the right, and all patients are placed out of ellipses at 95% for both men and women, which means lower PhA and cell mass (Figure 1). The mean impedance vector was statistically different between cases and controls ($p < 0.0001$), with case vectors shifting significatively to the right (Figure 2).

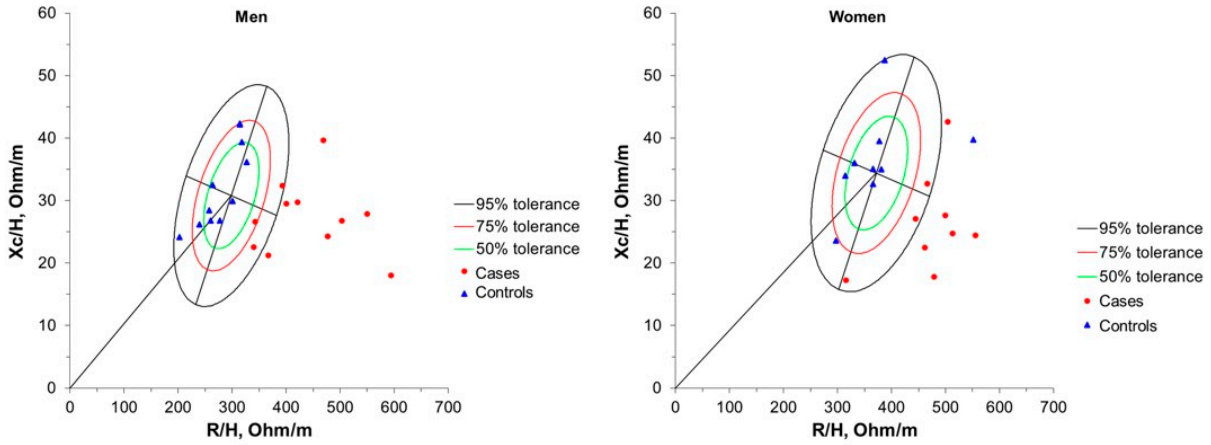

Figure 1. Bivariate vector positioning and tolerance ellipses of ALS patients (cases) and healthy subjects (controls). Impedance vectors plotted in the tolerance ellipses of 50%, 75%, and 95%, according to the reference population. R/H, Resistance/Height. Xc/H, Reactance/Height.

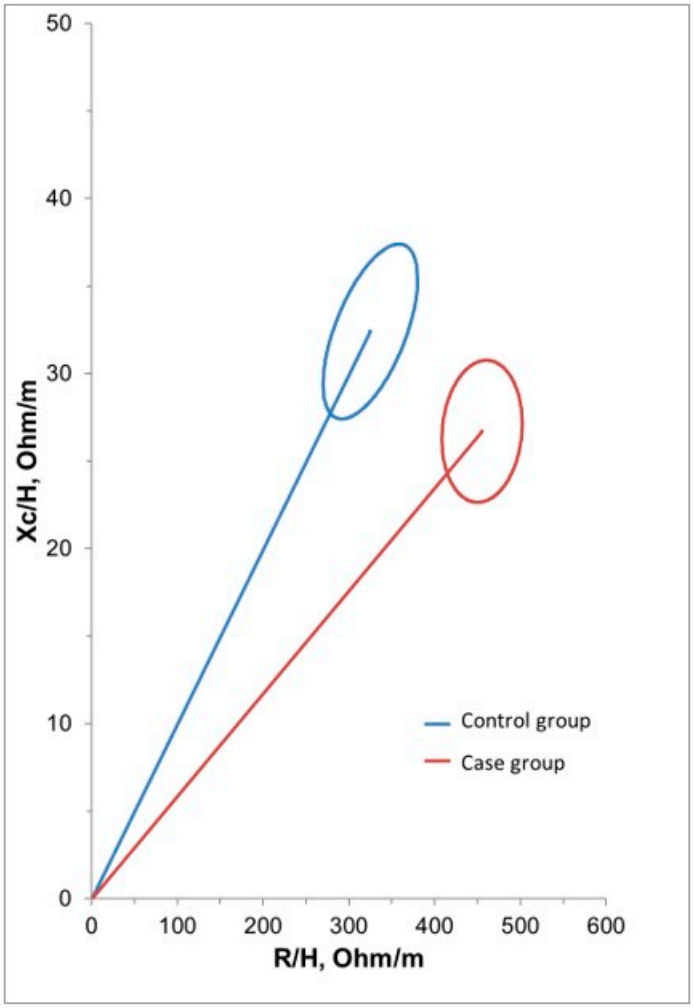

Figure 2. Confidence ellipses of ALS patients (cases) (in red) and healthy subjects (controls) (in blue). The statistical analysis was performed by Hotelling's T2 test. R/H, Resistance/Height. Xc/H, Reactance/Height.

4. Discussion

In this study, we evaluated BC and bioelectrical parameters in Brazilian ALS patients compared to healthy peers. Our main results showed that ALS patients presented low levels of BMI, FFM, R/H, Xc/H, hydration, and cellularity, compared to the control group.

Malnutrition is frequent in ALS patients [2,17], affecting 9 to 55% of them [41]. Authors have shown that patients with a weight loss of 5% or more at the time of diagnosis experience a twofold increase in the risk of death [42]. Also, weight loss is associated with a poor prognosis in different periods of the disease, even before its onset [1,15,18,33,43]. Overweight or additional feeding to maintain BMI is advantageous and prolongs survival in ALS [1]. A high BMI can positively influence the survival of ALS patients [44]. The main causes of malnutrition in ALS include dysphagia, poor oral intake, progressive muscle degeneration, and potential hypermetabolism. Therefore, it is crucial to conduct nutrition evaluations and regularly monitor these patients [2].

In individuals with ALS, the catabolism (breakdown of FM and FFM) is well documented, and it is usually a consequence of reduced food consumption, increased metabolic rate, and denervation of skeletal muscle [41,42,45,46]. Hypermetabolism in ALS is contradictory, and its origin remains unknown. Theoretically, catabolism, especially marked by muscle atrophy in ALS patients, should be followed by a decreased metabolic rate since the muscle is the most metabolically active tissue in the body [47]. However, the common hypermetabolism in ALS patients might occur as a consequence of a set of factors,

including denervation of skeletal muscle, mitochondrial dysfunction, increased respiratory muscle expenditure, and hypothalamic atrophy [48,49]. Muscle denervation can elevate the oxygen utilization rate, mitochondrial dysfunction impairs oxygen use and energy production, heightened respiratory effort adds more energy demand and hypothalamic atrophy can influence food intake and energy expenditure, changing neuroendocrine mechanisms related to the overall metabolism [48].

Studies have confirmed that hypermetabolism [50–55] affects not only body composition but the prognosis, especially in those ALS patients with low BMI at the time of diagnosis [56]. Also, hypermetabolism is an independent risk factor for death and tracheostomy in ALS [55].

In our study, we identified significantly lower BMI and FFM values in ALS patients when compared to healthy controls. In addition, no difference was found in FM between the groups. Interestingly, Li et al. (2022) observed no significant difference in BC between ALS patients and controls, except BMI [15]. On the other hand, Marin et al. (2011) identified significantly lower BMI and FFM values in ALS patients, comparing at diagnosis and before death [42].

Although BMI is a common indicator for evaluating the nutritional status of people and is even recommended by guidelines for the nutritional assessment of patients with ALS [5,11], this parameter does not differentiate between body composition compartments, such as FM and FFM. Thus, an exploration of BC, rather than solely relying on BMI, could be beneficial in guiding nutritional interventions, as well as in evaluating disease progression and survival.

Investigating BC and prognosis in ALS patients, a study has revealed that men experience more pronounced deterioration in their BC than women, leading to a swifter disease progression and reduced lifespan. This accelerated decline may be explained by men having less FM and more metabolically active FFM, resulting in lower energy storage [1]. Loss of FFM can also be considered a risk factor, accelerating progression, and causing early death [57]. Thus, FFM is another important parameter to consider for the nutritional monitoring of ALS patients.

Hydration plays a crucial role in maintaining good health and preventing diseases [58]. Compared to healthy controls, we observed dehydration in ALS patients, according to low levels of TBW and the placements of the vectors. In agreement, Marin et al. (2011) identified significantly lower TBW values in ALS patients [42]. Risk factors for dehydration in ALS include bulbar-onset, dysphagia, old age, and advanced disease. These authors have found that water intake and hydration status are prognostic indicators of survival in ALS, independent of age, site of onset, BMI, body size, or disease severity [59]. Water intake and TBW parameters should stand out in monitoring and guiding nutrition intervention in ALS patients.

Regarding the PhA, our study observed an average value of 3.4, indicating low cellularity. In agreement, Roubeau et al. (2015) found means of 3.8 and 4.5 for women and men with ALS, respectively [18]. Desport et al. (2008) demonstrated that the PhA was greatly reduced in ALS patients, with a mean value of 3.2. Moreover, a PhA below 2.5 was associated with a significantly poor survival rate [60].

PhA values ranging from 5 to 7 signify healthy cellular structure and robust membrane integrity, typically observed in a good population. Conversely, lower PhA values are associated with alterations in fluid balance and compromised membrane integrity [21,61]. A large body of evidence confirms that PhA is related to cellular health and hydration, muscle mass [62,63], muscle strength [64], and quality of soft tissues [20,61], reflecting cellular integrity [18]. Also, PhA has been useful as an indicator of muscle strength and muscle quality [64].

Low PhA in ALS can be a reflex of malnutrition and alterations in cell membrane integrity [60], loss of muscle strength [65], inflammation, and oxidative stress [66]. This can compromise cell functions and increase the risk of cell apoptosis [67].

PhA relates to metabolically active tissue such as FFM. In a representative study with healthy subjects, FFM emerged as one of the key determinants of PhA [66]. PhA has a relevant role in ALS because it is an independent prognostic factor [18,68]. The decrease in PhA during ALS reflects changes in BC, overall health, and functional status [42], and is associated with shorter survival [18].

PhA has been used as a prognostic factor not only in ALS [41,60] but in many clinical conditions such as DMD [26], systemic sclerosis [29], Alzheimer's [27,69], Parkinson [28], and psychogeriatric patients [70]. PhA has a good correlation with other nutritional assessment methods [60]. Thus, the use of the PhA should be encouraged in the nutrition care of ALS patients.

Regarding the BIVA, we observed that most patients, regardless of sex, were outside the 95% tolerance ellipse. ALS patients had lower R/H and Xc/H values when compared to the controls, which can be seen by the case group vector shift to the right. This confirms lower PhA and less soft tissue in ALS patients. Because of the lack of studies relating to BIVA and ALS patients, we discussed this point considering other neurological conditions.

In systemic sclerosis patients, authors observed significant differences in several BIVA variables when compared to the control group. In addition, BIVA had a predictive association with mortality in these patients [29]. In another study comparing BIVA between healthy individuals and patients with Parkinson's disease (PD), the authors found a significant displacement of the average impedance vector in PD male patients aged 60 to 79 years, compared with healthy controls. Also, BIVA was useful in detecting cachexia and dehydration in individual patients with PD [71]. The literature points to BIVA as a useful measure for detecting changes in muscle mass and sarcopenia in elderly people [64]. In a study performed with Alzheimer's patients, authors point to BIVA as a potential tool to identify initial shifts in body BC that might mirror the early symptoms of the disease process [27].

These examples provide insights into the contribution of BIVA as an assessment and monitoring tool in ALS patients. Again, BIVA does not present limitations such as errors derived from predictive equations for BC assessment [20]. Therefore, BIVA is useful in periodical nutritional status evaluation in ALS patients, in order to monitor the disease progression and guide the nutritional intervention.

This study has some limitations. First, the cross-sectional design of this study cannot infer cause and effect related to the differences in BC found between ALS patients and health controls. Second, the small sample size, as it is a rare disease, and a single-center study shows the sample size limitation. Another limitation is the lack of comparison of BC with a gold standard such as dual emission X-ray densitometry (DXA). More studies minimizing these limitations are needed. We also encourage new studies and designs investigating BIVA in ALS patients, unveiling its potential as a prognostic indicator in ALS patients.

5. Conclusions

The BC of ALS patients and healthy subjects differ significantly. ALS patients presented a significantly lower PhA and low levels of hydration, cellularity, and muscle mass, even with a mean eutrophic BMI. Our findings highlight BC and bioelectrical parameters, including PhA and BIVA, as valuable indicators of nutrition status, which should be implemented in the nutrition care process of ALS patients during the disease course.

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