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Original article

Phase angle as a marker for sarcopenia in cirrhosis

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SUMMARY

Background: In patients with cirrhosis nutritional disturbances can progress to sarcopenia, worsening the disease prognosis. Phase angle (PA) may be a useful marker for sarcopenia in this clinical population reflecting the cellular integrity level. This cross-sectional and prospective study evaluated the association between low PA values and clinical/nutritional variables in cirrhosis with emphasis on sarcopenia.

Methods: Male patients with cirrhosis (n = 122) were grouped according their PA values (>4.9° or ≤ 4.9°) after performing electrical bioimpedance. Sarcopenia diagnosis was assessed by considering appendicular skeletal muscle mass indexes <7.0 kg/m2 (dual-energy X-ray absorptiometry) and non-dominant handgrip strength (HGS) < 27 kg (dynamometry). Logistic regression model was used to examine the correlation between clinical/nutritional variables and PA values and the ROC curve area was calculated to identify the power of PA values in predicting sarcopenia.

Results: Sarcopenic patients presented lower HGS (19.57 *vs.* 30.55, p = 0.000), PA value (4.18 vs. 5.39, p = 0.005), SM (17.17 vs. 22.00 (p = 0.05), reactance (36.76 *vs.* 51.11, p = 0.023), and albumin (3.10 *vs.* 3.75, p = 0.037), as well as higher resistance values (512.56 *vs.* 457.01, p = 0.021) and CRP levels (7.89 *vs.* 3.53, p = 0.040) than non-sarcopenic patients. Furthermore, the PA values ≤ 5.05° were able to predict with high sensitivity the diagnosis of sarcopenia in the studied population.

Conclusion: In male patients with cirrhosis, low PA values may reflect disease prognosis by correlating to sarcopenia among other clinical/nutritional changes and performed as a good marker for this main nutritional complication when ≤5.05°.

1. Introduction

Sarcopenia is a malnutrition-associated syndrome characterized by the progressive and generalized loss of skeletal muscle (SM) mass and strength that comprises a risk factor for several adverse outcomes, including death [1]. Reduced food intake, slow oro-cecal transit, hypermetabolism, macro and micronutrient malabsorption, among other nutritional and metabolic alterations, make malnutrition a prevalent complication in advanced liver disease regardless its etiology [2,3]. Malnutrition is associated with poor prognosis and accompanied by SM mass depletion in patients with liver cirrhosis suggesting sarcopenia as its potential consequence [4].

Electrical bioimpedance analysis (BIA) is one of the most simple, easy and clinically accessible method applied to assess malnutrition by estimating body composition based on the tissue conductivity [5]. The method also generates the phase angle (PA) value, that has been shown to reflect cellular vitality and integrity [5–8]. In patients with cirrhosis, fluid imbalances (ascites or edema) can limit the performance of BIA in estimating SM mass for sarcopenia diagnosis, but a ≤4.9° PA value obtained by the method was recently proposed as the best reference value for malnutrition associated with the severity of the disease [7].

Low PA values have been correlated to reduced SM mass and low handgrip strength (HGS) [9,10] in some clinical populations, both markers of sarcopenia [1]. Nevertheless, the association between low PA values and sarcopenia in cirrhosis remains to be tested. Here it assessed the correlation of low PA values obtained

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from patients with cirrhosis with clinical/nutritional depletions that can reflect the disease prognosis and its potential in diagnosing sarcopenia.

2. Methods

2.1. Subjects

After the study protocol approval by the local Ethical Committee (0646/11) and its register at www.clinicaltrials.gov (NCT02421848), 119 male patients with cirrhosis (aging 22–76) were prospectively recruited from the Serviço de Cirurgia do Aparelho Digestivo do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (HC-FMUSP) between January 2012 and December 2014. Exclusion criteria were alcohol abuse, human immunodeficiency virus positivity, cancer diagnosis, chronic or acute lung, liver, kidney failures, heart disease, use of orthopedic prosthesis and dementia. All patients provided written informed consent prior to participating in the study.

2.2. Demographic and clinical/nutritional data

Age, Child-Pugh and Model for Terminal Liver Disease (MELD), presence of encephalopathy, levels of inflammatory markers (interleukins [IL-) 6, 10, 1A, and 1B; tumor necrosis factor alpha [TNFα], C-reactive protein [CRP]) and albumin, body weight and height, and body mass index (BMI) were demographic and clinical/nutritional data collected. Levels of inflammatory markers and albumin were measured by standard biochemical tests at the Central Laboratory of the HC-FMUSP. Body weight was measured with the participant standing in the center of a single electronic weighing platform (PDA; BOD POD TM BC system; Life Measurement Instruments, Concord, CA, USA), barefoot and wearing only light clothing. Body height was measured by a single stadiometer (Sanny, São Paulo, SP, Brazil) with the individual standing barefoot, heels together, straight back and arms extended at the side of the body. BMI was calculated as the weight divided by the squared height (kg/m^2) [11].

2.3. Phase angle measuring

PA was assessed by 50 kHz full body bioimpedance (Bodystat 4000, Bodystat Ltd., Douglas, Isle of Man, British Isles) with APEX software (version 4.02; Hologic Inc., Bedford, MA, United States). The 4-hour fasting subjects removed all metal objects and other items that could interfere with the scan and they were instructed to empty the bladder. Each subject was placed in the supine position at the sweeping table center with palms down and arms at the side of the body [12]. Their age, height, weight, gender, and ethnicity were registered in the system. PA values were calculated as PA = tangent arc $Xc/R \times 180/\pi$. Patients were grouped according to the value of PA (high PA: > 4,9° or low PA: ≤ 4,9°) [13].

2.4. Sarcopenia diagnosis

Diagnosis of sarcopenia was based on the simultaneous presence of low appendix SM index and low muscle strength using the reference values of the European Consensus for the definition and diagnosis of sarcopenia [1]: dual energy X -ray absorptiometry (DXA) < 7.0 kg/m ^{2} and handgrip strength (HGS) estimated by dynamometry < 27 kg. It was applied a specific device (Discovery model; Hologic Inc., Bedford, MA) for the appendicular SM assessment by DXA, which was calibrated at baseline according to the manufacturer's recommendation and coupled to the APEX software (version 4.02; Hologic, Inc., Bedford, MA). Participants removed all metal objects and were instructed to empty their bladders before to be placed in the supine position at the scanning table center, with palms down and arms at the side of the body. Data related to age, height, weight, gender and ethnicity were recorded and full-body DXA exams measured the regional lean mass (all four limbs). The appendicular skeletal muscle mass index was calculated by dividing the sum of the lean mass in all four limbs by body height squared (kg/m^2) [4]. For the HGS assessment by dynamometry it was applied a specific digital device (Charder Co Ltda®, Taichung City 41262, Taiwan) to examine the non-dominant hand. The Individuals were verbally encouraged to produce their maximum grip strength [14] and the best result in three attempts in a one-minute pause between the was recorded in kilograms (kg). During the analysis, the subjects remained seated in an adjustable height chair, with their legs upright and feet resting on the floor in order to obtain the right hip, knee and joint angles.

2.5. Statistical analysis

Data were expressed as mean, standard deviation, median, interquartile ranges (IQRs, 25°–75° percentiles) or percentages depending on the normality of its distribution and the type of variable analyzed. Differences in the studied variables were tested using the Student t or Chi-square tests as appropriate. Pearson's correlation test was applied to access the correlation of PA values with demographic and clinical/nutritional markers. The ROC curve area was calculated to identify a cutoff value of PA for the sarcopenia diagnosis and test its power by sensitivity and specificity ratio analyzes. Analysis of the likelihood ratio (RV) was performed to obtain positive likelihood ratio and negative likelihood ratio for the diagnosis of sarcopenia by phase angle. Kappa concordance analysis was performed between the diagnosis of sarcopenia provided by phase angle and that provided by DXA associated with HGS. Logistic regression model was created to examine factors related to low PA values, where demographic and clinical/nutritional variables were considered dependent. All analyzes were performed with the SPSS software version 20.0 (SPSS Inc, Chicago, IL, USA) under the significance level of 5%.

3. Results

3.1. Subjects

Patients (mean age = 54.4 ± 10.2 years) were mainly white (71%), and almost half of them (42%) were at the liver transplantation list. Alcohol was the prevalent disease etiology (48%), followed by C viruses (12%). From the total patients, 15 were diagnosed as sarcopenic and 50 presented PA values ≤ 4,9° (mean = 5.30° ± 1.27°). Sarcopenic patients presented lower HGS (19.57 vs. 30.55, p = 0.000), PA value (4.18 vs. 5.39, p = 0.005), SM (17.17 vs. 22.00 (p = 0.05), reactance (36.76 vs. 51.11, p = 0.023), and albumin (3.10 vs. 3.75, p = 0.037), higher resistance values (512.56 vs. 457.01, p = 0.021) and CRP levels (7.89 vs. 3.53, p = 0.040) when compared to non-sarcopenic patients (Table 1). Patients with PA values ≤ 4.9° had lower albumin levels (3.6 *vs*. 3.9; p = 0.040) and HGS (25.0 *vs*. 32.2; p = 0.000) and higher age (0.57.9 *vs*. 51.9; p = 0.001), episode of hepatic encephalopathy (30 *vs*. 26, p = 0.016), Child-pugh score B (32 *vs*. 28; p = 0.030), and sarcopenia (10 *vs*. 5; p = 0.030) than patients with PA values > 4.9° (Table 1).

3.2. PA values in predicting disease prognosis and sarcopenia

PA values were inversely correlated to age (r −0.379; p = 0.000) and those ≤ 4.9° were directly correlated to hepatic encephalopathy (r 0.216; p = 0.018), HGS (r 0.469; p = 0,000), SM (r 0.198; p = 0.031) and albumin (r 0.232; p = 0.012), but not to any

Table 1
Clinical and nutritional data associated with phase angle and sarcopenia in patients with hepatic cirrhosis.

Characteristics	Phase angle		P value	Sarcopenia		P value
	≤ 4,9° (n = 50)	> 4,9° (n = 69)		Yes (n = 15)	No (n = 104)	
Age (years)	57,92 (9,49)	51,95 (10,06)	0,001[a]	59,40 (10,28)	53,75 (10,06)	0,061
MELD score	14,36 (4,26)	13,86 (6,31)	0,614	15,00 (7,06)	13,94 (5,30)	0,584
Child-Pugh						
A	6 (25)	18 (75)		1 (0,8)	23 (19,3)	
B	32 (53,3)	28 (46,7)	0,030[c]	7 (5,9)	53 (44,5)	0,189
C	12 (34,5)	23 (65,7)		7 (5,9)	28 (23,5)	
With ascites	37 (43,5)	48 (56,5)	0,596	13 (10,9)	72 (60,5)	0,136
With HE	30 (53,6)	26 (46,4)	0,016[c]	5 (4,2)	51 (42,9)	0,195
BMI (kg/m^2)	26,18 (5,05)	26,36 (3,97)	0,836	24,54 (4,32)	26,53 (4,42)	0,113
HGS (Kg)	25,0 (9,07)	32,19 (7,32)	0,000[a]	19,57 (4,65)	30,55 (8,37)	0,000[a]
Phase angle	–	–	–	4,18 (1,41)	5,39 (1,18)	0,005[c]
Sarcopenia	10 (66,66)	5 (33,3)	0,037[c]	–	–	–
Muscle mass DXA	21,80 (4,05)	22,45 (3,52)	0,368	17,17 (2,49)	22,00 (3,38)	0,000[a]
Muscle mass BIA	57,59 (11,48)	58,06 (9,30)	0,666	51,12 (9,96)	58,83 (9,94)	0,063
Resistance	473,1 (94,17)	457,42 (97,62)	0,378	512,56 (77,87)	457,01 (96,76)	0,021[a]
Reactance	33,24 (9,01)	60,94 (66,37)	0,001[a]	36,76 (11,43)	51,11 (55,84)	0,023[a]
IL-10	2,05 (0,41–35,78)	2,05 (0,50–56,26)	0,662	2,74 (0,50–7,05)	1,92 (0,41–56,26)	0,650
IL-1A	0,25 (0,07–219)	0,33 (0,02–88,47)	0,394	0,49 (0,14–2,51)	0,28 (0,02–219)	0,971
IL-1B	0,64 (0,44–90,72)	0,73 (0,44–56,97)	0,214	0,64 (0,50–1,18)	0,71 (0,44–90,72)	0,280
IL-6	2,74 (0,43–90,72)	2,30 (0,55–53,50)	0,144	5,48 (1,16–90,72)	2,59 (0,43–53,50)	0,145
TNF	11,16 (1,32–70,55)	10,76 (2,78–50,88)	0,463	13,3 (7,47–70,55)	10,61 (1,32–68,8)	0,116
PCRu	4,30 (0,24–120)	3,46 (0,17–41,44)	0,419	7,89 (0,35–120)	3,53 (0,17–41,4)	0,004[b]
Albumin	3,60 (1,80–5,0)	3,90 (1,80–5,0)	0,044[b]	3,10 (1,80–4,70)	3,75 (1,80–5,0)	0,037[b]

MELD: The Model for End Stage Liver Disease; HE: Hepatic encephalopathy; BMI: Body mass index; HGS: Handgrip strength; DXA: Dual Energy X -Ray Absorptiometry; BIA: Electrical Bioimpedance; IL10: Interleukin-10; IL-1A: Interleukin-1A; IL-1B: Interleukin-1B; IL-6: Interleukin-6; TNF: Tumor Necrosis Factor; PCRu: Ultra-sensitive C Reactive Protein.
[a] Test t-student.
[b] Mann-Whitney.
[c] Chi-Square.

Table 2
Pearson's correlation coefficient between phase angle and clinical and nutritional data in patients with hepatic cirrhosis.

Characteristics	Phase angle	
	r	p
Age (years)	−0,379	0,000
MELD	−0,162	0,079
HE	0,216	0,018
HGS	0,469	0,000
Muscle mass DXA	0,198	0,031
BMI	0,127	0,170
Albumin	0,232	0,012
IL10	0,042	0,659
IL1A	0,107	0,259
IL1B	0,121	0,204
IL6	−0,128	0,177
TNF	0,072	0,449
PCRu	−0,074	0,441

MELD: The Model for End Stage Liver Disease; HE: Hepatic encephalopathy BMI: Body mass index; IL: Interleukin; TNF: Tumor Necrosis Factor; PCR: Ultra-sensitive C Reactive Protein.

inflammatory marker or MELD score (Table 2). The ROC curve area (0.73; Fig. 1) identified PA ≤ 5.05° as a cutoff value with 73.3% sensitivity, 61.5% specificity to diagnose sarcopenia (p = 0.000, 95% CI 0.598–0.872). RV analysis found that the positive likelihood ratio was 1.9 (CI 1.29–2.81), a negative likelihood ratio of 0.43 (CI 0.189–1.01). Furthermore, the concavities between phase angle and DXA showed a high agreement of this cutoff for the diagnosis of sarcopenia (Kappa 0.172, p = 0.011). When testing the correlation between PA values and sarcopenia by logistic regression, patients presenting sarcopenia were 5,6 times more likely to have PA values ≤ 5,05° (OR: 5,6; 95% CI: 1.19–19.54) when adjusted for hepatic encephalopathy (Table 3).

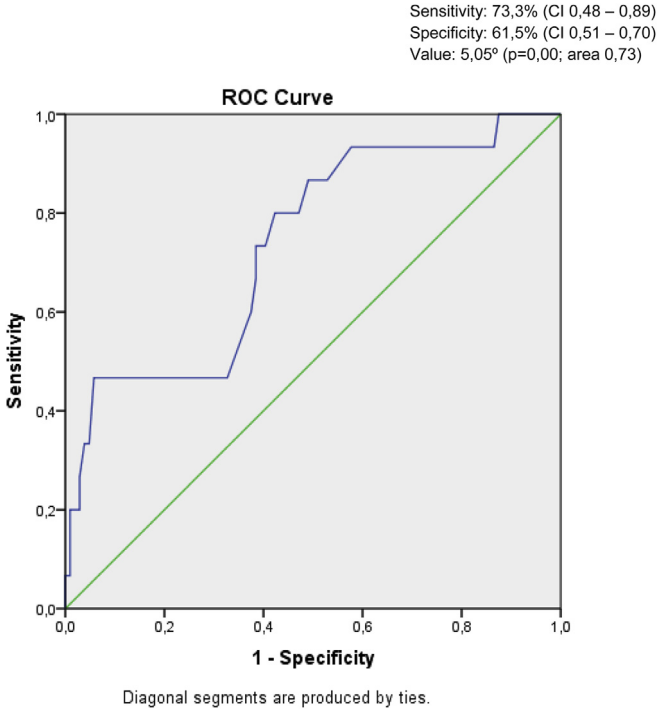

Fig. 1. ROC curve for assessing the power of the phase angle to diagnose sarcopenia in patients with hepatic cirrhosis.

4. Discussion

PA values have been shown to be highly predictive for clinical progression in various diseases, including a prognostic value for

Table 3
Logistic regression model with predictive factors for lower phase angle value (≤5,05) in patients with hepatic cirrhosis.

Variables	Beta Coefficient Regression	p	OR	IC 95%
With HE	1019	0,011	2,77	1,26–6,07
Sarcopenia	1727	0,007	5,62	1,59–19,54

OR: Odds Ratio adjusted for hepatic encephalopathy; HE: Hepatic encephalopathy.

mortality associated with malnutrition in cirrhosis [5–8]. This study confirmed a correlation of low PA values (≤4.9) with clinical/nutritional depletions in patients with cirrhosis. Furthermore, this study showed for the first time that this correlation also occurs to sarcopenia and highlighted a PA ≤ 5.05° value as a potential cutoff for the diagnosis of this nutritional complication in cirrhosis.

The relationship between PA values and diseases prognosis can be understood by the picture of inflammation and prolonged malnutrition that negatively affect the electrical properties of tissues, resulting in cell death [5,8]. In this scenario, the cirrhosis's physiopathology may explain the prognostic value of PA on the disease. Inflammation is an important trigger for liver cirrhosis decompensation and malnutrition is the most prevalent complication in this clinical setting [15].

Disease prognosis in liver cirrhosis has been widely assessed by applying the Child–Pugh and MELD scores, which consider a set of clinical variables (including some inflammatory and nutritional) for this purpose [16]. In patients with chronic liver disease at different stages, PA values did not correlate to Child-Pugh [16]. This previous find differs from the data here obtained in a more homogenous population with cirrhosis, where low PA values correlated to Child-Pugh score B. In the other hand, this investigation did not find correlations between PA values and MELD score, suggesting that Child-Pugh may better reflect cellular integrity in cirrhosis than MELD [16].

Among the individual clinical variables assessed in this study, hepatic encephalopathy is associated with hyperammonemia, oxidative stress and inflammation, which can impair cellular integrity [6]. The natural physiopathology of hepatic encephalopathy makes it a good target for risk detection by PA measuring. Accordingly, more than a half (53.6%) of studied patients with hepatic encephalopathy presented ≤ 4.9 PA and significantly complication correlated to this low PA value. This finding is in line with the study by Ruiz-Margáin et al. (2016) that reported a higher proportion of hepatic encephalopathy in patients with cirrhosis and low PA values, from a prospective cohort of 220 subjects [6].

In the other hand, several cytokines are involved in inflammation that triggers liver fibrogenesis [17] and this study did not find a significant correlation among low PA values and cytokine levels. This finding differs from this study previous report in 134 patients with liver cirrhosis, where those presented ≤4.9° PA value had higher IL-6/IL-10 ratio and CRP levels than those presented >4.9° PA [13]. This variation of data can be explained by the sample homogeneity. Maybe, PA values are more sensitive to reflect the effects of malnutrition on cellular depletion in cirrhosis, mainly in SM and in those patients with non-decompensated disease (42% of this study sample with PA ≤ 4.9°).

Indeed, in this study low PA values correlated to sarcopenia among central markers of malnutrition with SM mass depletion (lower albumin and HGS). Studies have now showed that mechanisms contributing to the development of sarcopenia in patients with cirrhosis include a reduction in serum testosterone and elevation of serum IGF-1 levels, contributing to increase the myostatin levels [18]. These alterations may induce muscle catabolism and loss of lean mass by proteolysis and cell apoptosis, which can be potentially reflected by low PA values [6,17].

Studies in different clinical populations have analyzed the association between PA and sarcopenia. Blasio et al. (2018) reported that PA is significantly lower in patients with chronic obstructive pulmonary disease presenting severe sarcopenia and cachexia [19]. Similarly, Basile et al. (2014) demonstrated that PA can be considered a good marker to identify elderly patients at risk for sarcopenia [20]. Studies of this nature in patients with cirrhosis are lacking, but here it showed that patients with cirrhosis and encephalopathy presenting PA ≤ 5.05° had 5.6 times more chance to be sarcopenic.

Accordingly, in addition to a significant correlation between low PA values and low HGS (a main sarcopenia predictor), this study showed that almost 70% patients presenting sarcopenia (12.6% sample) exhibited a PA value ≤ 4.9° and this measuring was significantly correlated to the syndrome. Furthermore, 42,9% patients with sarcopenia presented ≤5.05° PA values and this cutoff was able to predict the syndrome with good specificity and high sensitivity. These findings suggested a potential value in using PA to diagnose sarcopenia in cirrhosis.

This study has some limitations that deserve to be highlighted. There are several definitions for diagnosis of sarcopenia, but all of them include low SM, alone or combined to low muscle strength and/or performance [1]. Here it combined values for DXA-measured appendicular SM and dynamometry-measured HGS proposed by the European criteria for this purpose because it has a good performance in diagnosing sarcopenia in patients with cirrhosis, previously showed [13]. Nevertheless, complementary data on muscle performance are lacking. This study has chosen to examine exclusively male subjects because in this institution most patients with cirrhosis are men and the disease incidence also is higher in that gender than in females worldwide, as well as the prognostic value of the sarcopenia [21,22]. Therefore, only men composed the sample in this investigation, which is clinically representative and uniform, once avoid potential bias inherent to differences between genders.

Based on this data, this study concludes that low PA values can be a good cirrhosis prognosis predictor and suggest its use as a viable marker for sarcopenia in this clinical setting. Currently, accurate sarcopenia diagnosis requires the use of imaging methods that are highly sensitive, but also present a high cost [23,24]. In the other hand, PA is considered a method of easy access, good reproducibility and relatively low cost.

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Appendix A. Supplementary data

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