Clinical Nutrition ESPEN 29 (2019) 65–71

Contents lists available at ScienceDirect

Clinical Nutrition ESPEN

journal homepage: http://www.clinicalnutritionespen.com

Original article

Phase angle as a screening tool for mortality risk among hematopoietic stem cell transplanted adult patients

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ARTICLE INFO

Article history:
Received 22 June 2018
Accepted 7 December 2018

Keywords:
Phase angle
Arm muscle area
Fat mass
Prognostic factors
Hematopoietic stem cell transplantation

SUMMARY

Background: Mortality among adult patients undergoing hematopoietic stem cell transplantation (HSCT) is high, especially within the first 100 days after the event. Therefore, identifying prognostic factors would be useful as screening tools to protect patients at risk throughout early intervention. In our previous work, the standardized phase angle (SPA) was explored as a useful indicator of survival and nutritional status among children and adolescent within the first 180 days after HSCT. The aim of this study was to evaluate the SPA and the arm muscle area (AMA) as prognostic indicators of mortality and nutritional status among adults in the same population.

Methods: This study was conducted with 29 adult patients undergoing allogeneic HSCT and 28 controls. Anthropometric assessment as well as body composition and laboratory data were analyzed. The phase angle was standardized according to reference values for healthy population. The correlation of SPA and AMA with other variables was verified and sensibility and specificity were tested by constructing ROC curves considering mortality and nutritional status as outcomes. Kaplan–Meier analysis was applied to calculate survival considering the cut-off points found in ROC curves. Chi-squared test and Kappa coefficient were used for evaluate the agreement among methods of nutritional assessment.

Results: SPA presented a predictive value for mortality and nutritional status considering the cut-off point at −0.19. In fact, the mortality incidence was higher among patients with values below the cut-off point for SPA as compared to the ones with SPA above this value up to 90 days after the HSCT. Regarding to AMA, mortality was higher using the values bellow P15 (percentile 15) as reference. The average SPA decreased after the beginning of conditioning and after the HSCT, while the decrease of AMA was observed only 90 days after the transplant.

Conclusions: In this study SPA was confirmed as a prognostic tool for adult HSCT patients. In addition, it seems that SPA is more sensitive to detect structural body changes among the transplanted patients as compared to AMA. More studies are needed to confirm it as a tool to screen patients at risk of mortality for early intervention.

Abbreviations: AC, Arm circumference; AMA, Arm muscle area; BEE, Baseline energy expenditure; BIA, Bioelectrical impedance analysis; BMI, body mass index; CRP, C-reactive protein; FFM, Fat free mass; FM, Fat mass; GVHD, Graft-versus-host disease; HSCT, Hematopoietic stem cell transplantation; IBGE, Brazilian Institute of Geography and Statistics; PA, Phase angle; %WL, Percentage weight loss; Xc, Reactance; R, Resistance; ROC, Receiver Operator Characteristic Curves; SPA, Standardized phase angle; TSF, Triceps skinfold; WHO, World Health Organization.

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https://doi.org/10.1016/j.clnesp.2018.12.004
2405-4577/

1. Introduction

The HSCT is used to treat diseases that cause disorders in the bone marrow [1]. In the last decades, there has been an expansion of its use due to the chances of cure or increase of survival of large number of patients receiving hematopoietic stem cells; however, the incidence of morbimortality is still significant.

The nutritional status is directly related to the success of the transplantation, thus the assessment of nutritional status should be performed during the early stages of the treatment, in the pre-transplant period, to identify malnourished patients or those at nutritional risk; however, classic parameters may not detect early body changes and compromising the adequate intervention [2,3].

The phase angle (PA), obtained from bioelectrical impedance analysis (BIA), has been used in clinical practice to detect cellular modifications that may reflect cellular health in such a way that it has been considered as a possible indicator of nutritional status [4,5] and prognostic in several types of diseases [6,7]. In 2013, our previous retrospective work suggested that the SPA could be utilized as a prognostic and nutritional status tool considering mortality within 180 days in children and adolescents submitted to allogeneic HSCT [8]. In another retrospective study, we verified that the arm muscle area (AMA) of adults submitted to allogenic HSCT, obtained in the pre-transplant period, could also indicate graft-versus-host disease (GVHD) and mortality within 180 days after transplantation [9].

The PA and AMA seems to be relevant methods for this population, considering that they are sensitive as predictors of nutritional status and mortality as indicated previously [8,9]; however, it is important to perform prospective studies to understand better the prognostic value of PA and AMA in adults undergoing HSCT, seeking for reduction of morbidity and mortality. Thus, the objective of this study was to evaluate, prospectively, the SPA and AMA as prognostic indicators of mortality and nutritional status in patients submitted to allogeneic HSCT.

2. Methods

2.1. Design and setting

This study, characterized as observational controlled clinical study, was approved by the Human Research Ethics Committee of the Clinical Hospital Complex (Federal University of Paraná). Both patients and healthy volunteers signed the informed consent form.

2.2. Population study

Between February 2015 and January 2016, 81 patients underwent HSCT at the Bone Marrow Transplantation Service of the Clinical Hospital Complex in Curitiba, Paraná, Brazil. Of these, 29 met the inclusion criteria with age between 18 and 59 years before hospitalization for submission to allogeneic HSCT and accepted to participate in the study. The exclusion criteria were: submission to autologous HSCT and submission to a second HSCT.

Twenty-eight controls were matched with patients by gender, age and body mass index (BMI). Their data served as control for nutritional status and measurement of PA to identify the behavior of the variables analyzed among patients during treatment.

2.3. Data collect

The variables were evaluated in four different periods: five days before patients started conditioning with chemotherapy or chemotherapy and radiotherapy (D − 5), and 14 (D + 14), 30 (D + 30) and 90 days (D + 90) after HSCT.

2.4. Anthropometric assessment

The anthropometric assessment was performed by the same qualified technician (Nutritionist) in all periods. To minimize technical errors during the anthropometric measurements, as well as to calibrate de caliper utilized to measure triceps skinfold (TSF), the accuracy and precision of the evaluator and the equipment was performed before the beginning of the data collection. Anthropometric measurements were weight, height, arm circumference (AC) TSF. In addition, BMI, AMA and percentage of weight loss (%WL) were calculated.

The weight was measured using the Toledo® brand digital scale and a stadiometer with scale in centimeter was used to obtain the height. The AC was measured with the inelastic Shakir's tape with 0.1 cm precision and the TSF with a scientific adipometer Lange® (Cambridge Instrument, Cambridge, MA) [10]. Both TSF and AC measurements were taken three times, and the mean was used for the analysis. The Arm Muscular Area was calculated by using the following equation: AMA (cm^2) = [AC (cm) − π × TSF (mm)]^2/4π [11].

Nutritional status was identified by using AC, TSF and AMA measurements and the 15th percentile was chosen as the cut-off point for malnutrition [10], having. The BMI assessment was based on the cut-off points proposed by the World Health Organization (WHO) for adults [12].

The difference between the weight at 14, 30 and 90 days post-HSCT in relation to the pre-transplant weight in percentage was used to calculate %WL, and the classification of weight loss was determined following Blackburn and Thornton (1979) [13] criteria. The time interval between the date of the first evaluation and the date of discharge or death of the patient in a period of 90 days was considered as the time of survival.

For the control group weight, height, AC and TSF, were measured in one-time point and BMI and AMA were calculated following the same criteria used for the patients.

2.5. Bioelectric impedance and phase angle

The BIA analysis was performed by using a tetrapolar BIA Quantum 101 (RJL Systems ®, Inc. USA), with frequency of 50 Khz and 800 μA. The participants were assessed lying in a supine position, with legs and arms apart, as well as fasting for 4 h, with the bladder empty and, in the case of the control group, 8 h without intense physical activity before the test was performed. The electrodes were placed on specific parts of the ankle, foot, wrist and hand as previously described [14,15].

After obtaining resistance (R) and reactance (Xc), fat free mass (FFM) was calculated by the equation of Kyle et al. (2001) [16] and AF was calculated using the equation PA: [Arc tangent (Xc/R)]/(180/π) [17]. The standardization of PA according to gender, age and BMI was based on the reference values for the German population, since there is not a reference available for Brazilians, as follow: SPA = observed PA (°)−PA medium for gender, age and BMI (°)/standard deviation of the PA for gender, age and BMI [18].

The fat mass (FM) was obtained discounting de value of FFM from total body weight. It was also estimated the percentage of FFM and FM.

2.6. Laboratory analysis

The laboratory analysis of serum albumin and C-reactive protein (CPR) is part of the weekly routine at the Clinical Laboratory of the Hospital. Blood tests were carried out along the week before the transplant and in the week of D+14. The values obtained from the CPR/Albumin ratio were classified according to Corrêa et al. (2011)

[24] to analyze risk of complications derived from metabolic stress as follow: no risk: <0.4, low risk: 0.4–1.2, moderate risk: 1.2–2.0, and high risk: >2.0.

2.7. Clinical data

The following clinical data were obtained from the medical charts: medical diagnosis, conditioning regimen, type of transplantation, chemotherapy not related to transplantation, presence of GVHD, infection, vomiting, mucositis, diarrhea and emesis for three or more consecutive days, use of corticosteroids, date of discharge and death along 90 days after transplantation.

2.8. Statistical analysis

The SPSS 20 software (SPSS Inc., Chicago, IL, USA) was used to analyze the data. The data distribution was analyzed by the Shapiro–Wilk test. Demographic and anthropometric variables were described using frequencies, percentages, means, and standard deviations.

Initially the correlation of SPA and AMA with the other variables was verified by Pearson or Spearman's coefficients for parametric and non-parametric data respectively. The sensitivity and specificity of SPA and AMA were tested through the construction of Receiver Operator Characteristic Curves (ROC) curves, considering mortality and nutritional status as outcomes, with expectation of area under the curve greater than 0.5.

The Kaplan–Meier was used to evaluate survival difference between patients, considering the cut-off point established for SPA and for AMA. The Kappa coefficient for quantitative data and Chi-square test for qualitative data were used to evaluate the agreement between methods of nutritional status assessment.

A variance analysis with repeated measurements was applied to analyze the SPA, AMA, reactance and resistance in different time periods (D − 5; D + 14, D + 30, D + 90). The Tuckey's test was employed to identify minimal significant differences among the means across time. An alternative test was utilized for non-parametric data analysis (Kruskal–Wallis followed by Bonferroni).

To compare control group versus patients group regarding to anthropometric and body composition data, test-t for independent groups was performed or the alternative Wilcoxon test for non-parametric data. For both variance and test-t tests a confidence interval of 95% was considered.

3. Results

In the pre-transplant period, patients presented anthropometric, SPA e body composition characteristics that were similar to the healthy group (Table 1). According to BMI, most patients were overweight or obese (17 individuals), 11 patients were eutrophic and only one was undernourished.

Most patients were male, young and submitted to a related HSCT. The main causes for transplantation were malignant diseases and the most used conditioning regimens were those composed by Busulfan and Cyclophosphamide, combined with Fludarabine. Only 8 patients underwent radiotherapy in association with chemotherapy. The mean time of hospitalization was 35 ± 4.5 days, and the follow-up period consisted of 95 days (D-5 up to D + 90). Six patients had GVHD and 3 patients died within the study period (Table 2).

3.1. Prognostic value of the standard phase angle and AMA

When the patients were admitted (D-5), SPA, anthropometric (BMI, TSH, AC, CPR/Albumin) and body composition (percentage of FFM and percentage of FM) data were measured as predictors of mortality (up to 90 days after HSCT). After constructing a ROC curve, the SPA cut-off point with 66.7% sensitivity and 16.7% specificity was −0.19 (Fig. 1).

Table 1
Anthropometric and body composition data at the pre-transplant analysis: comparison between patients and control participants.

Variable	Patients (n 29)	Control (n 28)	*P*
Weight (Kg)	73.7 ± 18.1	72.7 ± 14.5	0.813
BMI (Kg/m^2)	26.6 ± 5.0	25.9 ± 4.9	0.588
Resistance (Ω)	526.6 ± 73.8	552.1 ± 77.6	0.209
Reactance (Ω)	63.6 ± 10.5	68.6 ± 9.6	0.069
PA (°)	6.9 ± 0.9	7.1 ± 0.6	0.333
SPA (°)	0.7 ± 1.0	1.1 ± 0.6	0.122
AC (cm)	31.2 ± 4.1	30.8 ± 4.0	0.675
TSF (mm)	19.5 (5.6–29)*	19.9 (4.3–29.6)*	0.971
AMA (mm^2)	51.9 (30.1–83.6)*	49.2 (29.6–81.6)*	0.355
%FFM	71.2 ± 10.9	71 ± 9.9	0.952
%FM	28.8 ± 10.9	28.97 ± 9.9	0.960

BMI: body mass index; AC: arm circumference; TSF: triceps skin fold; AMA: arm muscle area; PA: phase angle; SPA: standardized phase angle; %FFM: percentage of fat free mass, %FM: percentage of fat mass. *Values presented in medians. Test-t for independent groups or the alternative Wilcoxon test for non-parametric data were performed to compare patients and control groups. Confidence interval of 95% was considered.

Patients with SPA below −0.19 before HSCT had a shorter survival time than those with SPA above the cut-off point as shown in Fig. 2.

All the other parameters did not reach an acceptable are under the curve (>0.5), except percentage of FM (0.692) with cut-off point at 36.8%, 66.7% of sensitivity and 70.8% of specificity (Fig. 3).

Patients with percentage of FM above of 36.8 had shorter survival than those with percentage of FM below of this cut-off point (Fig. 4).

Using a cut-off point with the same sensitivity and specificity as the one used for percentage of FM, it was noticed that patients with SPA below of the 1.06 had shorter survival (Fig. 5).

Factors that could interfere with SPA such as previous chemotherapy (prior to conditioning), medical diagnosis, type of HSCT, use of corticoid, conditioning regimen, infection, mucositis, diarrhea, vomiting, cumulative energy deficit, and cumulative protein deficit did not correlate with SPA. However, infection was associated with SPA ($p = 0.010$; R^2 0.21).

When SPA was used as predictor of undernourishment (up to 90 days after HSCT), the AMA was used to classify the nutritional. The AMA values were dichotomized as above or below P15, based on the results of our previous study [9] and the data were obtained in D + 14, D + 30 and D + 90. The same SPA cut-off point found for mortality was found for nutritional status in the three assessment periods (D + 14, D + 30 and D + 90).

However, when the potential of AMA as predictor of mortality was studied it was not possible to determine a cut-off point according to ROC curve and there was no association between decrease in AMA and mortality risk adjusting AMA to age and gender and using P15.

3.2. Effect of HSCT on nutritional status and SPA

Throughout the treatment, the SPA decreased right after the beginning of the conditioning treatment (D − 5) and immediately after the HSCT, remaining low until D + 90. Similarly, weight, BMI, AC, decreased in this period. %WL increased post transplantation, being that the highest increased occurring within the first 30 days (D + 30) and remaining low until D + 90. It was possible to detect reduction of AMA only between the first and fourth evaluation (D − 5 – D + 90). On the other hand, the values of TSF, percentage of

Table 2
Clinical data from patients undergoing HSCT.

Variable	N (%)	Median (CI)	*p* values
Gender			
Male	16 (55.2%)		
Female	13 (44.8%)		0,000
Age (years)		30 (18–52)[a]	0.015
Diagnosis			
Non malignant diseases			
Severe aplastic anemia	10 (34.5%)		
Fanconi anemia	2 (6.9%)		
Immunodeficiency	1 (3.4%)		
Malignant diseases			
Acute myeloid leucemia	6 (20.7%)		
Chronic myeloid leukemia	3 (10.3%)		
Acute Lymphoblastic Leukemia	6 (20.7%)		
Acute myelofibrosis	1 (3.4%)		
Conditioning regimen			
Busulphan + Cyclophosphamide	11(34.4%)		
Busulphan + Cyclophosphamide + ATG	4 (13.8%)		
Busulphan + Cyclophosphamide + TBI	1 (2.9%)		
Busulphan + Fludarabine	1 (2.9%)		
Busulphan + Fludarabine + ATG	2 (6.8%)		
Cyclophosphamide	2(6.8%)		
Cyclophosphamide + Fludarabine	1 (2.9)		
Cyclophosphamide + TBI	4 (13.8)		
Cyclophosphamide + Fludarabine + TBI	2(6.8%)		
Cyclophosphamide + Fludarabine + Thymoglobulin + TBI	1 (2.9%)		
Type of HSCT			
Allogeneic related	18 (62.1%)		
Allogeneic not-related	11 (37.9%)		
Chemotherapy not related to transplantation			
Yes	15 (51.7%)		
No	14 (48.3%)		
Presence of mucositis			
Yes	29 (100%)		
No	0		
Presence of infections			
Yes	14 (48.3%)		
No	15 (51.7%)		
Presence of GVHD			
Yes	6 (20.6%)		
No	23 (79.4%)		
Episodes of vomiting			
Yes	11 (37.9%)		
No	18 (62.1%)		
Episodes of diarrhea			
Yes	14 (48.3%)		
No	15 (51.7%)		
Use of steroids			
Yes	9 (31.1%)		
No	20 (68.9%)		

HSCT: hematopoietic stem cell transplantation, ATG: antithymocyte globulin, TBI: total body irradiation, GVHD: graft versus host disease, CI: confidence interval. Infections: acinobacter, extended-spectrum beta-lactamase (ESBL), *Aspergillus* sp., *Staphylococcus epidermidis*, *Candida* sp., *Klebsiella pneumoniae Carbapenemase* (KPC), *Escherichia coli*. Presence of mucositis: along the entire follow-up period; Episodes of vomiting: at least 1 event; Diarrhea (more than 3 events in 24h over three consecutive.days). Clinical data are presented in number of cases and percentage.

[a] Results are shown as median and maximum and minimum values. To compare gender and age homogeneity was performed Test-t. Confidence interval of 95% was considered.

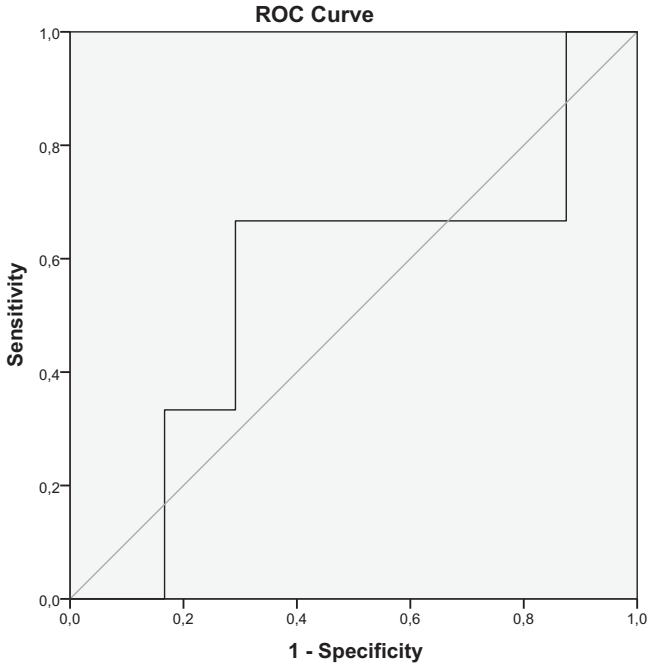

Fig. 1. ROC curve to identify a cutoff point for the standardized phase angle as a prognostic factor for mortality after a follow-up of 90 days after transplant. Area under the curve: 0.556. The cutoff point −0.19 showed sensitivity of 66.7% and specificity of 16.7%.

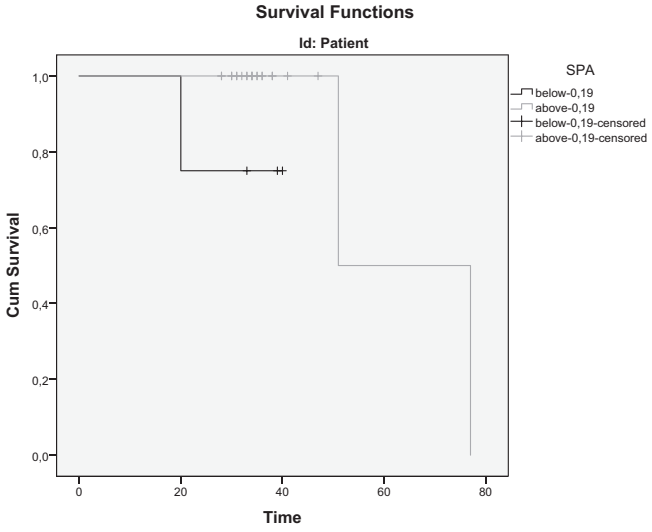

Fig. 2. Survival curve of patients categorized above or below the standardized phase angle cut-off point of −0.19. SPA: standardized phase angle. Line black indicates patients with SPA below the −0.19 cut-off point and gray line indicates patients with SPA above −0.19 cut-off point. Survival time was shorter among patients with SPA below the −0.19 cut-off point.

FFM and percentage of FM had not significant differences along the four evaluations (Table 3).

No correlation was found between SPA and nutritional assessment methods. In the case of AMA, correlation with weight (R^2 0.782), BMI (R^2 0.782) and AC (R^2 0.782) was found, as expected (Table 4). There was no agreement for undernourishment diagnosis between SPA (cut-off point −0.19), TSF, AMA, AC (P15h) and BMI (<18.5 kg/m^2).

4. Discussion

Our results indicate that SPA and percentage of FM measured before the conditioning for bone marrow transplant could be useful as predictors of mortality along 90 days after transplant, differently from other parameters such as anthropometric data. It makes sense considering that body composition measures from BIA are more accurate than anthropometric measures. Moreover, in this group,

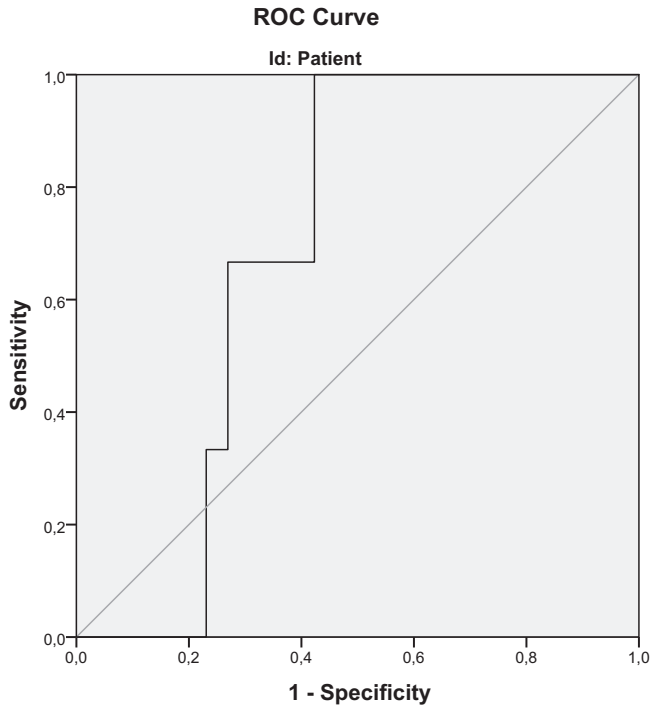

Fig. 3. ROC curve to identify a cut-off point for percentage of fat mass as a prognostic factor for mortality. Area under the curve: 0.692. The cut-off point of 36.8% showed a sensitivity of 66.7% and 70.8% of specificity.

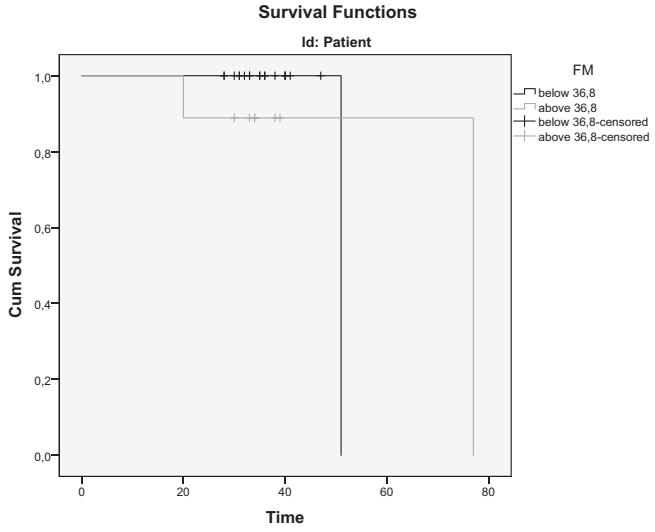

Fig. 4. Survival curve of patients categorized above or below the percentage of fat mass 36.8 cut-off point. %FM: percentage of fat mass. Line black indicates patients with %FM below the 36.8% cut-off point and gray line indicates patients with %FM above the 36.8% cut-off point. Survival time was shorter among patients with %FM above the 36.8 cut-off point.

patients at risk would not be detected only using classical body composition changes along the treatment as observed by the maintenance of percentage of FFM or percentage of FM until 90 days after transplant. Interestingly, SPA seems to be appropriate for screening patients at risk and percentage of FM seems to be more specific considering the ROC curve for mortality. Although it is expected that muscle mass would be associated to higher mortality risk among cancer patients [25], this parameter did not

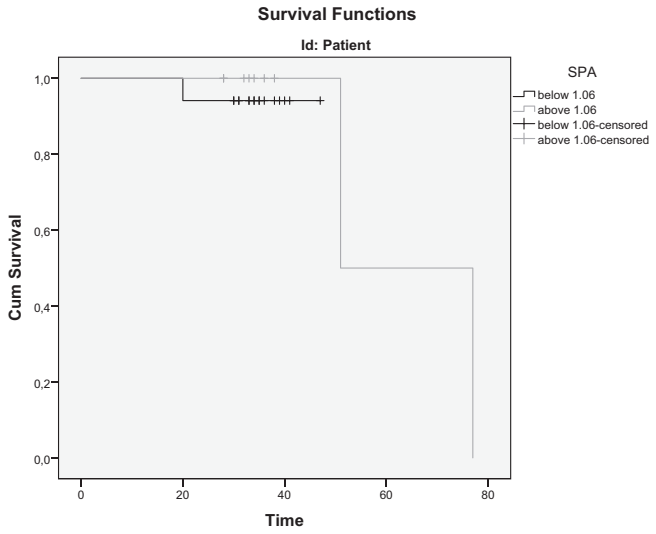

Fig. 5. Survival curve of patients categorized above or below the standardized phase angle. SPA: the standardized phase angle. Line black is SPA below cut -off point and gray line is SPA above cut -off point. Survival time was shorter among patients with AFP below the cutoff point 1.06.

discriminate patients at risk in our study. It seems that the swift observed between fat and muscle mass as result of nutrition transition phenomenon [26,27] plays a role in this case. Although there was no decrease in FM% along the 90 days follow-up, the average of percentage of FM is above the expected levels among the patients assessed.

Taking the cut-off point used for survival analysis, the fact of SPA better discriminate the patients as compared to percentage of FM, indicate that changes in cell membrane electric potential promoted by chemotherapy [28,29] might be the factor that differentiates these two parameters. We have been consistently demonstrating that changes SPA values can detect earlier than any variation in anthropometric and laboratory measures (CPR and albumin). This finding could be explained by the fact that PA reflects the electrical properties of biological tissues [30], that could be detected directly by BIA, different from weight, BMI, skinfolds and body circumferences, which indicate changes in body composition through indirect measures [31]. In several clinical situations, PA is considered a promising prognostic indicator, and the explanation for this function is the association of low PA values with cell death or loss of cellular integrity, changes in membrane selective permeability and fluid balance [32,33].This situation was found in the study with presurgical hospitalized patients, when SPA indicated impaired nutritional status; however, was poorly correlated with other methods such as with BMI, TSF and AMA [34].

The identification of the factors that contributed to the reduction of SPA is beyond the scope of this work, however, it seems that infection affects the SPA as demonstrated by the association between SPA and incidence of infection. Otherwise, medical diagnosis, transplant type, use of corticoids, energy and protein deficit, and diarrhea did not correlate with SPA. It seems that chemotherapy plays a role on the decrease of SPA. In fact, has long been pointed that the chemotherapy causes effects on cell membrane functions, calcium channels, growth receptors, among others [28,29].

In the scientific milieu, it is still controversial whether PA can be considered a marker of nutritional status, especially malnutrition, by the ability to reflect changes in body cell mass and fluid balance [35–37]. In fact, we also could not correlate SPA with classical methods of nutritional assessment in the adult patients

Table 3
Nutritional assessment measures along the follow-up period.

Variable	Before conditioning	D+14	D+30	D+90
Weight (Kg)	72.1 ± 17.6[a]	69.5 ± 16.9[bd]	66.4 ± 15.2[cd]	66.6 ± 17.1[bcd]
BMI (Kg/m^2)	26.4 ± 5.2[a]	25.5 ± 5.1[bd]	24.4 ± 4.6[cd]	24.2[bcd]
%WL	–	3.4 ± 3.9[a]	7.4 ± 4.3[b]	7.29 ± 7.9[ab]
AC (cm)	30.8 ± 4.04[a]	29.8 ± 3.9[bd]	29.01 ± 3.8[cd]	28.7 ± 3.9[bcd]
TSF (mm)	15.6 (5.6–29)[a]	14 (4.30–29.,3)[a]	15.7 (5–28.3)[a]	19.2 (4.3–28)[a]
PA (°)	6.9 ± 0.9[a]	5.9 ± 1.1 [bd]	5.5 ± 1.0 [cd]	5.5 ± 1.1 [bcd]
SPA (°)	0.7 ± 1.07[a]	−0.5 ± 1.2[b,c]	−1.2 ± 1.3[c,d]	−1.3 ± 1.5[b,c,d]
AMA (mm^2)	51.5 (34.3–83.6)[a]	46.8 (29,6–76.03)[ab]	42.3 (32.6–67.04)[ab]	42.7 (32.4–69.1)[b]
%FFM	72.4 ± 11.4[a]	74.2 ± 12.3[a]	74.2 ± 12.7[a]	71.7 ± 11.9[a]
%FM	27.5 ± 11.4[a]	25.9 ± 12.3[a]	25.7 ± 12.7[a]	28.2 ± 11.9[a]
Albumin (g/dL)	3.6 ± 0.39[a]	3.2±(0.42)[a]	–	–
CPR (mg/dL)	1.1 (0.03–14.1)[a]	6.5 (0.4–29.2)[b]	–	–
CPR/Alb	0.3 (0.01–5)[a]	2.05 (0.1–10.4)[b]	–	–

AC: arm circumference, AMA: Arm muscle area, BMI: body mass index, CPR: C-reactive protein, PA: phase angle, SPA: standardized phase angle TSF: Triceps skinfold, %FFM: percentage of fat free mass, %FM: percentage of fat mass, CPR: C-reactive protein, Alb: albumin, %WL: percentage of weight loss. The assessment was performed in four moments: before conditioning, 14 days after HSCT (D+14), 30 days after HSCT (D+30) and 90 days after HSCT (D+90). Albumin and CPR were evaluated before the beginning of conditioning and in D+14. Repeated measures variance analysis was performed to compare means within and between groups along the follow-up period. Post hoc Tukey's test was performed to identify significant minimal difference between averages. In the case of non-parametric data, Kruskal Wallis was performed to compare means within and between groups along the follow-up period. Different letters mean statistical difference. Confidence interval of 95% was considered.

Table 4
Association of SPA and AMA with nutritional assessment parameters.

Variable	*P*	R^2	Variable	*P*	R^2
SPA			AMA		
Weight (Kg)	0.340	–	Weight (Kg)	0.000	0.782
BMI (Kg/m^2)	0.631	–	BMI (Kg/m^2)	0.001	0.782
Resistance (Ω)	0.735	–	Resistance (Ω)	0.061	–
Reactance (Ω)	0.000	–	Reactance (Ω)	0.651	–
PA (°)	0.000	0.804	PA (°)	0.005	–
SPA (°)	–	–	SPA(°)	0.135	–
AC (cm)	0.708	–	AC (cm)	0.000	0.782
TSF (mm)	0.065	–	TSF(mm)	0.683	–
AMA (mm^2)	0.135	–	AMA (mm^2)	–	–
%FFM	0.144	–	%FFM	0.457	–
%FM	0.144	–	%FM	0.467	–
Albumin (g/dL)	0.286	–	Albumin (g/dL)	0.153	–
CPR (mg/dL)	0.104	–	CPR (mg/dL)	0.908	–
CPR/Alb	0.131	–	CPR/Alb	0.931	–

AC: arm circumference, AMA: arm muscle area, BMI: body mass index, CPR: C-reactive protein, PA: phase angle, SPA: standardized phase angle, TSF: triceps skinfold, %FFM: percentage of fat free mass, %FM: percentage of fat mass, CPR: C-reactive protein, Alb: albumin. The Statistical analysis was performed using Spearman's correlation, followed by Multiple Linear Regression. Confidence interval of 95% was considered. Only the statistic significant R squares are shown.

submitted to allogeneic HSCT. In addition; it was also not possible to correlate low values of SPA with malnutrition, even with reduction of Xc. It's important to highlight that, few patients were classified as malnourished with the nutritional assessment parameters used, for example, the majority was classified as overweight when considering BMI. Thus, these classical parameters of nutritional evaluation could underestimate the risk of mortality from the metabolic alterations suffered by the transplant patient.

During the period of follow-up, the patient had a significant weight loss before starting the conditioning regimen until 90 days after HSCT, but other parameters as TSF, percentage of FFM and percentage of FM, remained without significant difference along the 4 evaluations. On the other hand, PA values decreased after the beginning of the conditioning regime and after submission to the transplant, indicating that, in this period, there was a change in the physiology of the cells and that, consequently, resulted in modifications in the electrical properties of the tissues changing the ionic conduction, represented by low PA [38].

It should be noted that biological processes depend of the continuous passage of ions between the intra and extracellular media through the ion channels, present in the plasma membrane. Some ion channels, such as voltage-dependent ones, may undergo conformational modifications due to changes in membrane potential caused, for example, by the immune response [39].

SPA and AMA did not show similar behavior during treatment. The AMA haven't a prognostic value of mortality up to 90 days after transplant, different from our previous study in which we found that AMA below the 15th percentile in the pre-transplantation period was a predictor of mortality 180 days after transplantation [9]. This analysis was probably affected by the low incidence of mortality by 90 days after HSCT in the present study.

Similar to our study, in 2013, a study was carried out with 105 adult patients submitted to allogeneic HSCT, and those with SPA below the cut-off point −1.31 in the pre-transplant period, had less survival time up to two years after submission to treatment [7].

Previously, we also performed a study with children and adolescents who underwent to the same transplant treatment and, in that case, SPA correlated with nutritional assessment parameters, and patients with SPA less than the established reference value had a shorter survival time, suggesting the possible use of SPA as an indicator of nutritional status and mortality in the case of infants [8]. This study was performed with children whose PA had different behavior as compared to adults given the growth process. In fact, Farias et al. (2013) [8] demonstrated that SPA correlated positively with age. In the present study, we could not establish a correlation between SPA and nutritional status parameters considering classic anthropometric methods for adults, which are diverse from the ones used for children.

Some limitations should be pointed in this study such as the sample size and the lack of PA reference values for the Brazilian population, which led us to use Germany reference. Moreover, the comparison of our results was also limited by the scarce of prognostic studies in this area.

5. Conclusion

Our results indicate that SPA and percentage of FM measured before the conditioning for bone marrow transplant could be useful as predictors of mortality along 90 days after transplant, differently from other parameters such as anthropometric and biochemical data.

More studies are necessary to explore the biological functioning of SPA and AMA as prognostic indicators in patients submitted allogeneic HSCT. In addition, nutrition transition and the resultant

increase in percentage of FM should be also more explored to better understand the impact of this phenomenon on survival of patients undergone HSCT.

Ethics approval and consent to participate

This study was approved by the Human Research Ethics Committee of the Clinical Hospital Complex of the Federal University of Paraná. Both patients and participants in the control group signed the informed consent form.

Statement of authorship

We hereby certify that this is an original publication and the manuscript has not been previously submitted or published elsewhere. The authors' responsibilities were as follows: AS and RV were responsible for the study design, statistical and data analyses, and manuscript writing. AS performed the nutritional assessment and collected the data. MS, DC and VF performed a critical analysis of the manuscript. All authors read and approved the final manuscript.

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Acknowledgements

We thank the patients and volunteers that agreed to participate in this study. We also thank the Bone Marrow Transplant Unit of Clinical Hospital Complex of Federal University of Paraná, the Postgraduate Program in Food and Nutrition at the Nutrition Department of Federal University of Paraná, the Program of Scientific Initiation in Research (PIBIC). We also thank the student of scientific initiation, Giovana Regina Ferreira, for her technical support on calculating the food intake of the research participants. The first author was sponsored scholarships by the CAPES.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnesp.2018.12.004.

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