Journal of Critical Care 44 (2018) 430–435

Contents lists available at ScienceDirect

Journal of Critical Care

journal homepage: www.jccjournal.org

Outcomes/Predictions

Phase angle assessment in critically ill cancer patients: Relationship with the nutritional status, prognostic factors and death☆

Tatiana Cathoud do Amaral Paes [a], Kátia Cansanção Correa de Oliveira [b], Patrícia de Carvalho Padilha [b], Wilza Arantes Ferreira Peres [b,*]

[a] Serviço de Nutrição e Dietética, Hospital de Câncer I, Instituto Nacional de Câncer José Alencar Gomes da Silva, Rio de Janeiro, Brazil
[b] Instituto de Nutrição Josué de Castro, Centro de Ciências da Saúde, Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil

ARTICLE INFO

Keywords:
Cancer
Critically ill patients
Bioelectrical impedance analysis
Phase angle
Prognostic factors
Survival

ABSTRACT

Purpose: To evaluate the relationship between phase angle (PA) and nutritional status and the prognostic significance of PA in critically ill cancer patients.
Methods: 31 patients that had been admitted to the intensive care unit (ICU) of a center on oncology were evaluated. Their PA was obtained from their bioelectrical impedance within 48 h of the ICU admission. The logistic regression analysis of Cox was used in order to identify the independent predictors of the outcomes.
Results: Negative and significant correlations were observed between the PA and the following variables: the length of hospital ward stay, the length of ICU stay, the total time of hospital stay, the mechanical ventilation time, and the acute physiology and chronic health evaluation II (APACHE II) scores. A positive correlation was ascertained between the PA and albumin. PA was significantly associated with death. Patients with a PA ≤3.8° presented a significantly shorter survival time than those with a PA >3.8°.
Conclusion: PA was a prognostic marker in this population, independently of previously established prognostic factors. PA can represent a clinically feasible approach for the initial identification of critically ill cancer patients who require an early and specialized nutritional intervention.

1. Introduction

Cancer is a world public health problem, occupying the second place as the cause of death in Brazil [1,2]. The complications related to the tumor itself and to the antineoplastic treatment can cause hospitalization in an intensive care unit (ICU) [2]. Of those patients that require hospitalization in an ICU, the prevalence of malnutrition is approximately 50%, which may reach 100%. This contributes to an increase in their hospitalization time, morbidity, and mortality [3,4,5]. Malnutrition in a critical illness is associated with metabolic changes, with an emphasis on an increased basal metabolic rate, protein catabolism, and insulin resistance [3]. Therefore, the nutritional status deficit and the depletion of lean mass that are present in critically ill cancer patients are closely related to a decrement in the response to chemotherapeutic, radiotherapeutic or surgical therapy, their quality of life and functional capacity, increasing their risk of infections, postoperative complications, the length of hospital stay, and the occurrence of death [6,7]. In view of these scenarios, the use of classical measurements for an nutritional status assessment may be limited, since metabolic and hydration alterations, difficulties in patient mobilization, bed restrictions, alterations of physiological homeostasis, mechanical ventilations and sedation, are all common in an intensive care setting [8,9]. As a result, bioelectrical impedance analysis (BIA) has been widely used, as it is a simple non-invasive method and because it provides a phase angle (PA) measurement. PA is considered to be an indicator of nutritional status, for it reflects the changes in intracellular and extracellular fluids. Additionally, it can be interpreted as an indicator of cell membrane integrity and a predictor of total body cell mass [10-16]. Currently, there are studies using PA as a tool, in order to assess the nutritional status of cancer patients and other chronic diseases [8,14,15,17-27]. However, as far as we know, there are no studies evaluating its applicability in critical

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

* Corresponding author at: Universidade Federal do Rio de Janeiro, Instituto de Nutrição Josué de Castro, Av. Carlos Chagas Filho, 373, Edifício do Centro de Ciências da Saúde, Bloco J, 2 andar, sala 07, CEP: 21941-902, Ilha do Fundão, Cidade Universitária, Rio de Janeiro, Brazil.
E-mail address: wilza@nutricao.ufrj.br (W.A.F. Peres).

https://doi.org/10.1016/j.jcrc.2018.01.006
0883-9441/

oncology patients when they are admitted to an ICU. Thus, the objective of the present study has been to evaluate the relationship between PA and nutritional status and the prognostic significance of PA in critically ill cancer patients.

2. Materials and methods

2.1. Study design

This was a longitudinal prospective study, which was held between April 2014 and May 2015. It included critically ill cancer patients, aged 19 years and older, who had been diagnosed with systemic inflammatory response syndrome (SIRS) or sepsis and that had been admitted into the ICU at the Cancer Hospital of the National Cancer Institute (INCA) in Rio de Janeiro, Brazil. The protocol for this study was approved by the Research Ethics Committee at the Hospital Universitário Clementino Fraga Filho, Rio de Janeiro, Brazil and the aforesaid Cancer Hospital of the National Cancer Institute. Informed written consent was obtained from the patients or their legal guardians. The exclusion criteria were as follows: patients with any amputation; patients with a pacemaker or with a metal prosthesis; and patients with skin problems that were susceptible of changing the conduction of the electrode-skin.

2.2. Demographic and clinical data

The sociodemographical information, as well as the clinical data regarding the location and the type of neoplasia, the staging evaluated by the classification system of malignant tumors TNM [28], the performance status (PS) using the Eastern Cooperative Oncology Group (ECOG) scale [29], the comorbidities, and the treatment that was used, were all obtained from the medical records. The usage and the duration of the mechanical ventilation were followed up during their hospitalization in the units. In order to calculate the length of hospital stay, the difference between the date of the hospital stay and the date of discharge or death were considered. The specific length of the ICU stay was obtained from the difference between the date of admission hospital and the date of discharge/death dates in the referred units. The time of the hospitalization until the admission to the ICU was also counted. The estimated morbidity and mortality risk, together with the severity and the prognosis of the disease, were calculated for each patient by using the acute physiology and chronic health evaluation II (APACHE II) [30] and sequential organ failure assessment I (SOFA I) [31] scores, performed within 24 h of their ICU admission.

2.3. Phase angle

In order to obtain their PA, a BIA was performed by using a BIA-450 impedance analyzer (Biodynamics Corporation, Washington, USA), at a current of 800 μA, with 50 kHz frequency, resistance range: 200–1500 Ohms, resolution: 1 Ohm and with an accuracy of 1%, within 48 h of their ICU admission. The examinations were performed according to the standardization of the technique [32]. All of the evaluations were conducted on the right-hand side of the patients, with the subjects in a supine position, with their legs apart and with their arms not touching their torso. Four electrodes were then positioned on the skin after cleansing, between the prominences of the radius and the ulna; on the posterior surface of the right wrist and between the malleolus of the tibia and the fibula; and on the anterior surface of the right ankle. All of the measurements were performed in duplicate, without the removal of the electrodes, by the same examiner, within a maximum period of 15 min. Their PA was calculated by using the following equation: Phase angle = (resistance (R) / capacitance (Xc)) × (180° / π).

2.4. Nutritional risk in the critically ill: the (NUTRIC) score instrument

The nutritional risk in the critically ill (NUTRIC) score instrument [33] was applied within 24 h of the date of their ICU admission. Those patients with scores above 5 were classified as high risk and according to the information from the tool, they were associated with worse clinical outcomes (mortality, mechanical ventilation).

2.5. Anthropometrical evaluations

For the anthropometrical evaluations, their current weight was obtained by a bed-scale and their height was assessed from their recumbent length. Their body mass index (BMI) was calculated by using the formula: weight(kg)/height(m^2). The evaluations were carried out up to the 48th hour after their hospital internment.

2.6. Serum albumin

The serum albumin was quantified by the bromocressol green method, the values were collected from their medical records, being those that were used from the first examination after their admission to the ICU. The hypoalbuminemia values were considered when they registered <3.5 g/dl [34].

2.7. Diagnosis of cachexia

The diagnosis of cachexia were made based upon the recommendations of the International Consensus on Cachexia of Cancer [35] and according to the following criteria: weight loss >5% or body mass index (BMI) <20 and weight loss >2% or sarcopenia and weight loss >2%. Sarcopenia was evaluated by mid upper-arm muscle area below the 5th percentile by anthropometry.

2.8. Occurrence of death

The data on their deaths was obtained from the electronic medical records and it was followed up for a period of 1 year after the date of their admission. The following items were considered for an association of PA and death: (i) those that occurred as a result of the anticancer treatment; (ii) postoperative complications; and (iii) disease progression.

2.9. Statistical analyzes

The distribution of the referred values was identified as not normal. Statistical comparisons for significance were made using the Kruskal–Wallis non-parametric test as appropriate and multiple comparisons of Dunn's test were used in order to compare the three subgroups. The Mann–Whitney test was used to compare the numeric variables between the two groups. Associations between the categorical variables were performed by ×2 test. The relationship between the phase angle and the clinical and severity variables was analyzed by using Spearman's Correlation Coefficient. A receiver operating characteristic (ROC) analysis was used to determine the PA threshold with the best death predictive value. For the Kaplan–Meier survival analysis, PA measurements were categorizes into two equal and mutually exclusive groups with a PA score of 3.8° as the cut-off, obtained by the ROC analysis. The influence of possible risk factors on patient survival was analyzed by Cox multivariate regression. The determination for the significance of the level was adopted at 5%. All statistical analyzes were performed by using the statistical software SAS® Version 6.11 (SAS Institute, Inc., Cary, North Carolina, USA).

Table 1
General characteristics of the critical cancer patients.

Variables	Median	IQR	*n* (%)
Age (years)	61.0	47.0–68.0	31 (100%)
Gender	–	–	
Female	–	–	16 (51.6%)
Male			15 (48.4%)
Phase angle (°)	4.0	3.2–5.2	31 (100%)
Site of tumor	–	–	
Digestive tract	–	–	11 (35.5%)
Lymphomas	–	–	4 (12.9%)
Respiratory system	–	–	3 (9.7%)
Oral cavity and larynx	–	–	2 (6.5%)
Brain and nervous system	–	–	2 (6.5%)
Urinary system	–	–	2 (6.5%)
Other	–	–	7 (22.4%)
Stages	–	–	
I/II	–	–	14 (45.2%)
III/IV	–	–	17 (54.8%)
Performance status			
≥2	–	–	12 (38.7%)
<2	–	–	19 (61.3%)
APACHE II score	14.5	9.0–23.0	31 (100%)
SOFA 1 score	3.0	1.8–6.3	31 (100%)
Weight (kg)	65.7	57.0–84.5	31 (100%)
BMI (kg/m2)	25.1	21.7–30.1	31 (100%)
Cachexia			
Yes	–	–	20 (64.5%)
No	–	–	11 (35.5%)
NUTRIC scores			
High risk	–	–	5 (16.1%)
Low risk	–	–	26 (83.9%)
Albumin (mg/dl)	2.60	2.10–3.10	27 (87%)
Length of hospital ward stay (days)	19.0	13.0–40.0	31 (100%)
Length of ICU stay (days)	8.0	4.0–18.0	31 (100%)
Total time of hospital stay (days)	5.0	2.0–11.0	31 (100%)
MV			
Yes	–	–	18 (58.1%)
No	–	–	13 (41.9%)
Time of MV (days)	4.0	0–13.0	18 (58.1%)

Results are reported as median - IQR: Interquartile Range (Q1–Q3).
APACHE, acute physiology and chronic health evaluation; BMI, body mass index; ICU, intensive care unit; MV, mechanical ventilation; SOFA, sequential organ failure assessment.

3. Results

A total of 31 critical cancer patients who met the inclusion criteria participated in this study. The characteristics of the patients are described in Table 1. The median age was 61 years (19–82), with a total of 51.6% female patients ($n = 15$). The most prevalent tumor sites were: digestive system 35.5%, lymphomas 12.9%, respiratory system 9.7%, as well as an oral cavity, pharynx, brain, nervous system, and urinary system, with 6.5% each, representing a total of 77.6% of the sample. Regarding the severity of the disease, 54.8% had clinical stage III and IV and 38.7% had PS ≥ 2. The median length of the hospital stay was 19 days, ranging from 2 to 70 days, while the median length of stay in the ICU was 8 days (1–39). According to the NUTRIC scores, 16.1% were considered to be high risk. 64.5% ($n = 20$) of the patients had diagnosis of cachexia. At the time of hospitalization in the intensive care unit, the APACHE II scores of the patients presented a median of 14.5 (IQR 9.0–23.3) points. 58.1% of the patients required invasive mechanical ventilation and they remained for an average time of 8 (0–36) days. The ICU death rate was 29% ($n = 9$), while 38.7% ($n = 12$) of the patients had died by the end of the study period. We found significant positive correlations between the PA and albumin ($r = 0.565$; $p = .002$). Additionally, a significant reverse correlation was observed between the PA and the length of hospital ward stay ($r = -0.495$; $p = .004$); the length of stay in the ICU ($r = -0.463$; $p = .008$); the total time of the hospital stay ($r = -0.496$; $p = .004$); the time of mechanical ventilation ($r = -0.428$; $p = .016$); and the APACHE II scores ($r = -0.579$; $p = .008$) (Table 2).

Table 2
Correlation between the phase angle (°) and the clinical variables and the disease severity.

Variables	*n*	r_s	*p* value
Age (years)	31	−0.460	0.009
APACHE II	30	−0.579	0.0008
SOFA1	30	−0.277	0.14
Length of hospital ward stay (days)	31	−0.496	0.004
Length of ICU stay (days)	31	−0.463	0.008
Total time of hospital stay (days)	31	−0.495	0.004
Time of MV(days)	31	−0.428	0.016
Albumin (g/dl)	27	0.565	0.002

r Spearman's rank correlation coefficient.
APACHE, acute physiology and chronic health evaluation; ICU, intensive care unit; MV, mechanical ventilation; SOFA, sequential organ failure assessment.

The data presented in Table 3 shows the variations of the PA according to the clinical variables. It was observed that the median PA was significantly lower in patients with high nutritional risk assessed by the NUTRIC scores, as well as in individuals with PS ≥ 2 and in patients with cachexia diagnosis.

Table 4 presents the results of the comparisons between the medians of the clinical and severity variables, among those patients who evolved, or not, into death in the ICU. Those who resulted in death presented significantly higher values of hospital stay prior to the ICU ($p = .016$), the length of stay in the ICU ($p = .035$), the time of mechanical ventilation ($p = .002$), and the severity indexes of APACHE II and SOFA 1. Those patients who progressed into death had significantly lower values of PA ($p = .002$) and albumin ($p = .021$).

Fig. 1 shows the ROC curve for the PA as a predictor of death in the ICU. According to the ROC curve, it was identified that the best cut-off point for predicting death was ≤3.8°, with a sensitivity of 88.9% and a specificity of 77.3%. The arean under the curve was 0.86 (95% CI: 0.73 to 0.99; $p = .002$).

During the study period, 12 (38.7%) patients died and 19 were censored (i.e., they reached the end of the follow-up period without dying). Those patients with a PA ≤3.8° had an average survival time of 130 days (95% CI: 47–213), while those with a PA >3.8° lived on average for 329 days (95% CI: 294–364). PA was significantly associated with death ($p < .0001$). The Kaplan–Meier survival curve that was stratified by the phase angle cut-off point is shown in Fig. 2. Those patients with a PA ≤3.8° had a significantly shorter survival time than those with a PA >3.8°.

Table 5 shows the results of the Cox regression analyzes for the death outcomes, including the following variables: male gender, age (in years), APACHE (scores), SOFA1 (scores), staging III/IV, BMI (kg/

Table 3
Phase angle variation (°) according to the clinical and severity variables.

Patient subgroup	*n*	Median	IQR	*p* value
Gender				
Male	15	4.6	3.5–5.5	0.15
Female	16	3.7	3.1–4.5	
NUTRIC scores				
High risk	5	2.7	2.1–3.9	0.018
Low risk	26	4.3	3.5–5.4	
Albumin				
<3,5 g/dl	22	3.8	3.1–4.7	0.052
≥3,5 g/dl	5	4.7	4.5–5.8	
Cachexia				
Yes	20	3.5	2.9–4.7	0.021
No	11	4.7	4.0–5.6	
Performance status				
≥2	12	3.5	2.7–3.9	0.009
<2	19	4.7	3.7–5.6	
Stages				
I/II	14	4.3	3.5–5.4	0.25
III/IV	17	3.7	2.9–4.7	

Results are reported as median - IQR: Interquartile Range (Q1–Q3). Comparison was conducted by using the one way Mann–Whitney U test. $p < .05$ was considered to be statistically significant.

Table 4
Comparison between death and survival in the ICU.

Variables	Death in the ICU					Survival in the ICU					*p* value
	n	Median	IQR			*n*	Median	IQR			
Age (years)	9	66.0	55.5	–	68.5	22	56.5	45.3	–	67.3	0.24
APACHE II	8	22.0	15.5	–	29.5	22	11.5	8.0	–	21.3	0.034
SOFA1	8	6.5	4.5	–	12.5	22	2.0	1.0	–	5.3	0.005
Weight (kg)	9	58.6	56.5	–	69.8	22	67.9	57.0	–	85.5	0.34
Length of hospital ward stay (days)	9	27.0	16.5	–	45.0	22	18.5	12.0	–	36.5	0.27
Length of ICU stay (days)	9	18.0	7.5	–	30.0	22	6.0	4.0	–	15.0	0.035
Total time of hospital stay (days)	9	10.0	7.5	–	17.5	22	4.0	1.8	–	9.3	0.016
Time of MV (days)	9	11.0	9.5	–	23.0	22	0.0	0.0	–	11.3	0.002
Phase angle (°)	9	3.0	2.4	–	3.7	22	4.7	3.8	–	5.5	0.002
Albumin (g/dl)	7	2.20	1.90	–	2.50	20	2.85	2.25	–	3.60	0.021

Results are reported as median - IQR: Interquartile Range (Q1–Q3). Comparison was conducted by using the one way Mann–Whitney U test. $p < .05$ was considered to be statistically significant.
APACHE, acute physiology and chronic health evaluation; ICU, intensive care unit; MV, mechanical ventilation; SOFA, sequential organ failure assessment.

m^2), albumin <3.5 g/dl, NUTRIC scores (high risk), symptomatic PS/bed (≥2) and cachexia. The multivariate Cox regression analyzes showed that a PA ≤3.8° ($p = .008$, 95% CI: 2.37–363) and stage III/IV ($p = .050$, 95% CI: 1.0–175) were independent predictors for death in the ICU.

4. Discussion

This study has allowed us to evaluate PA behavior in cancer patients in the ICU and its association with nutritional status, clinical outcomes, and prognoses. We have observed that those patients with lower PA values had longer hospital and ICU stays, longer mechanical ventilation times, and higher clinical severity scores. PA readings ≤3.8° were a predictor of mortality, independently of other factors, such as staging. These findings may be considered a relevant indicator for unfavorable clinical and worse outcomes, with a decrement in the survival rate. PA correlated with the nutritional status of these patients, which was observed through the NUTRIC scores and cachexia diagnosis. Additionally, those patients with a lower PA had a relative risk of death in the ICU of 29.9%. In a previous study, the PA ≤4.4° in the patients with advanced cancer was a predictor of mortality, independently of the other factors, such as hypoalbuminemia, malnutrition and a palliative prognostic (PaP) score [12], in our research PA values were lower, probably due to the influence of inflammation and its metabolic repercussion on critical cancer patients. Although the biological significance of PA has not yet been fully elucidated, it has been considered a good indicator of nutritional status as it reflects total cell mass. Thus, inflammation, malnutrition as well as other factors can result in disturbances in the electrical properties of tissues, altering PA since catabolic diseases are associated with intracellular dehydration [24,36].

In the present study, the PA values were significantly lower among the group that died (3.0°) than in those who survived (4.7°). Similarly to our findings a study that was conducted in critical but non-cancer patients that were hospitalized in a general ICU, the PA values were 2.89° in the patients who died and 4.11° in the patients who survived [37]. However, they were lower than those that were found by Peres et al. [7] who when evaluating patients with a chronic liver disease, observed a PA median of 4.55° in the patients who died versus a PA median of 5.28° in the survivors. These findings reinforce the postulation that low PA levels are associated with decreased cell membrane integrity and increased mortality.

Our findings have indicated a better sensitivity and a specific cut-off point of PA ≤3,8° (IC5%: 0,73–0,99), in order to predict the death of cancer patients in the ICU, which is below that which has been previously described in the literature. Gupta et al. [17] observed that a PA value of 5.3° was the best predictor of survival in patients with lung cancer. In a study of patients with terminal cancer, it was demonstrated that patients with a PA >4.4° presented a longer survival time [4]. In lung cancer and in advanced cancer, patients with a PA >4.5° presented a higher

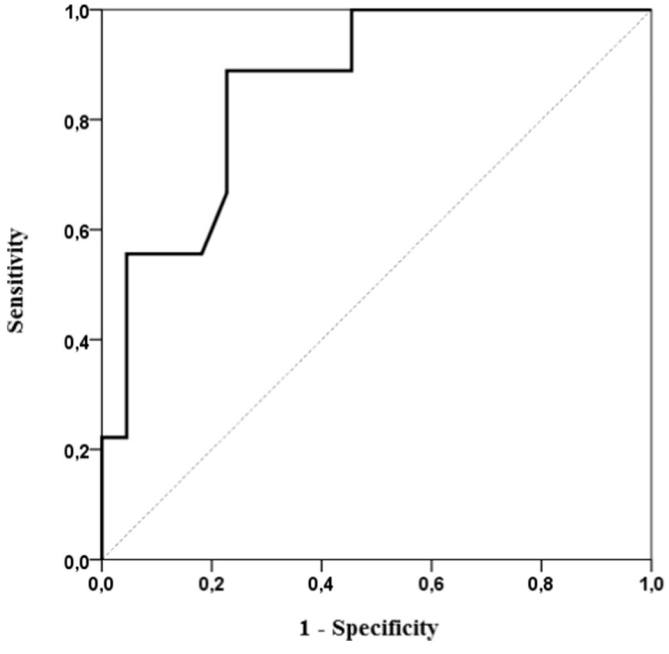

Fig. 1. Receiver operating characteristic (ROC) curve analysis: phase angle for death in the ICU.

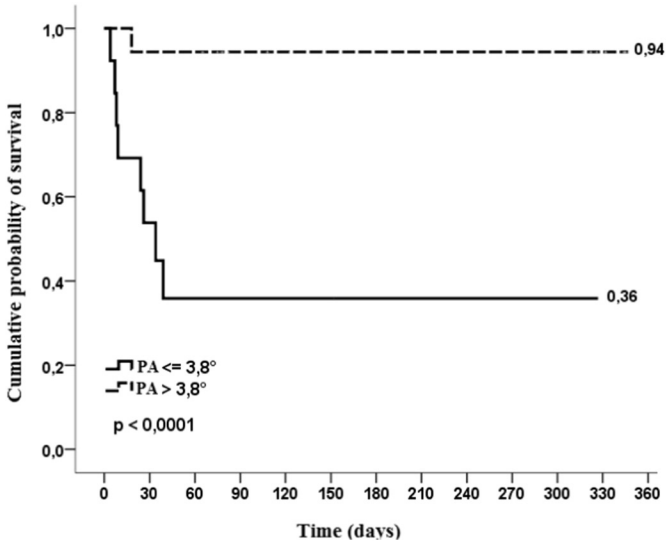

Fig. 2. Kaplan–Meier cumulative survival for death when stratified by a PA ≤ 3.8°.

Table 5
Multivariate cox regression analyzes for death in the UCI.

Significant variable	Coefficient	SE	*p* value	RR	95% CI
Phase angle ≤3.8°	3.380	1.283	0.008	29.4	2.37–363
Stages III/IV	2.551	1.332	0.050	12.8	1.0–175

SE: Standard Error; RR: relative risk; 95% CI: Confidence Interval 95% for the relative risk.

survival [12,18]. The difficulty in defining a cut-off point lies in the fact that each study has consisted of a different disease and the data can not be extrapolated to different groups. However, it is important to note that although these studies were performed in different populations, they provided consistent results, associating low PA values with lower survival.

In the present study, the correlation between PA and the APACHE II prognostic index, that is widely used in the ICU, has been highlighted. The inverse correlation that was found between PA and the APACHE II scores and between PA and the length of stay in the ICU and the mechanical ventilation time, has shown that a reduction in PA values was associated with worse clinical and prognostic indicators, since these conditions are associated with a worsening of the nutritional status and the loss of lean mass. However, a study by Berbigier et al. [38] with septic patients did not find a relationship between PA and the prognostic indexes of APACHE II and SOFA and the time of hospitalization, which was attributed to the homogeneity of their sample. In this study, the PA correlated positively with nutritional status assessed by the NUTRIC scores tool. Many groups have been dedicated to studying the relation between PA and nutritional status [14,39]. A recent study performed with patients who were diagnosed with head and neck cancer showed that the individuals that were classified as moderately or severely malnourished by SGA (SGA-B and SGA-C), had lower values of PA ($4.73° \pm 0{,}96°$), while those that were defined as well-nourished, had higher PA values ($5.25° \pm 0.76°$), corroborating our findings [39].

Although the total number of the sample was small, it represents the number of eligible patients attended at the time of this study's collection at the national reference center for cancer treatment in Brazil.

5. Conclusions

To our knowledge, this is the first study to evaluate PA as a predictor of death and its relationship with nutritional status, in patients with cancer who were admitted to an ICU. Our results have been consistent with the hypothesis of the present study, in identifying PA as an important prognostic marker in critically ill cancer patients, independently of previously established prognostic factors, such as staging, PS, APACHE II and SOFA. It is now possible to suggest that the best cut-off point for a PA to predict an ICU death is ≤3.8°. PA has been shown to be a clinically viable tool for the initial use and the identification of critical cancer patients who require an early nutritional intervention and specialized treatment.

Conflicts of interest: None.

Acknowledgements

The authors would like to thank the Nutrition Service of National Cancer Institute (INCA).

References

[1] World Health Organization. National cancer control program: policies and managerial guidelines. , 180pGeneva (SZ): World Health Organization; 2002.
[2] Instituto Nacional de Câncer. Estimate 2014: cancer incidence in Brazil. Rio de Janeiro, Brazil: Instituto Nacional de Câncer; 2013.
[3] Raslan M, Gonzalez MC, Torrinhas RSMM, Ravacci GR, Pereira JCR, Waitzberg DL. Complementarity of Subjective Global Assessment (SGA) and Nutritional Risk Screening 2002 (NRS 2002) for predicting poor clinical outcomes in hospitalized patients. Clin Nutr 2011;30:49–53. https://doi.org/10.1016/j.clnu.2010.07.002.
[4] Lee SY, Lee YJ, Yang JH, Kim CM, Choi WS. The association between phase angle of bioelectrical impedance analysis and survival time in advanced cancer patients: preliminary study. Korean J Fam Med 2014;35:251–6. https://doi.org/10.4082/kjfm.2014.35.5.251.
[5] Lukaski HC, Bolonchuk WW, Hall CB, Siders WA. Validation of tetrapolar bioelectrical impedance method to assess human body composition. J Appl Physiol 1986;60:1327–32.
[6] Kyle UG, Piccoli A, Pichard C. Body composition measurements: interpretation finally made easy for clinical use. Curr Opin Clin Nutr Metab Care 2003;6:387–93.
[7] Peres WA, Lento DF, Baluz K, Ramalho A. Phase angle as a nutritional evaluation tool in all stages of chronic liver disease. Nutr Hosp 2012;27:2072–8. https://doi.org/10.3305/nh.2012.27.6.6015.
[8] Norman K, Stobäus N, Zocher D, Bosy-Westphal A, Szramek A, Scheufele R, et al. Cut-off percentiles of bioelectrical phase angle predict functionality, quality of life, and mortality in patients with cancer. Am J Clin Nutr 2010;92:612–9. https://doi.org/10.3945/ajcn.2010.29215.
[9] Norman K, Stobäus N, Pirlich M, Bosy-Westphal A. Bioelectrical phase angle and impedance vector analysis – clinical relevance and applicability of impedance parameters. Clin Nutr 2012;31:854–61. https://doi.org/10.1016/j.clnu.2012.05.008.
[10] Stobäus N, Pirlich M, Valentini L, Schulzke JD, Norman K. Determinants of bioelectrical phase angle in disease. Br J Nutr 2012;107:1217–20. https://doi.org/10.1017/S0007114511004028.
[11] Norman K, Wirth R, Neubauer M, Eckardt R, Stobäus N. The bioimpedance phase angle predicts low muscle strength, impaired quality of life, and increased mortality in old patients with cancer. J Am Med Dir Assoc 2015;173:e17–173. https://doi.org/10.1016/j.jamda.2014.10.024 e22.
[12] Hui D, Bansal S, Morgado M, Dev R, Chisholm G, Bruera E. Phase angle for prognostication of survival in patients with advanced cancer: preliminary findings: phase angle for survival prognostication. Cancer 2014;120(14):2207. https://doi.org/10.1002/cncr.28624.
[13] Gupta D, Vashi PG, Lammersfeld CA, Braun DP. Role of nutritional status in predicting the length of stay in cancer: a systematic review of the epidemiological literature. Ann Nutr Metab 2011;59:96–106. https://doi.org/10.1159/000332914.
[14] Gupta D, Lis CG, Dahlk SL, King J, Vashi PG, Grutsch JF, et al. The relationship between bioelectrical impedance phase angle and subjective global assessment in advanced colorectal cancer. Nutr J 2008;7(19). https://doi.org/10.1186/1475-2891-7-19.
[15] Gupta D, Lis CG, Dahlk SL, Vashi PG, Grutsch JF, Lammersfeld CA. Bioelectrical impedance phase angle as a prognostic indicator in advanced pancreatic cancer. Br J Nutr 2004;92:957–62. https://doi.org/10.1079/BJN20041292.
[16] Toso S, Piccoli A, Gusella M, Menon D, Crepaldi G, Bononi A, et al. Bioimpedance vector pattern in cancer patients without disease versus locally advanced or disseminated disease. Nutrition 2003;19:510–4. https://doi.org/10.1016/S0899-9007(02)01084-5.
[17] Gupta D, Lammersfeld CA, Vashi PG, King J, Dahlk SL, Grutsch JF, et al. Bioelectrical impedance phase angle in clinical practice: implications for prognosis in stage IIIB and IV non-small cell lung cancer. BMC Cancer 2009;9(37). https://doi.org/10.1186/1471-2407-9-37.
[18] Toso S, Piccoli A, Gusella M, Menon D, Bononi A, Crepaldi G, et al. Altered tissue electric properties in lung cancer patients as detected by bioelectric impedance vector analysis. Nutrition 2000;16:120–4. https://doi.org/10.1016/S0899-9007(99)00230-0.
[19] Scheunemann L, Wazlawik E, Bastos JL, Ristow Cardinal T, Mayumi Nakazora L. Agreement and association between the phase angle and parameters of nutritional status assessment in surgical patients. Nutr Hosp 2011;26:480–7. https://doi.org/10.1590/S0212-16112011000300008.
[20] Fearon K, Strasser F, Anker SD, Bosaeus I, Bruera E, Fainsinger RL, et al. Definition and classification of cancer cachexia: an international consensus. Lancet Oncol 2011;12:489–95. https://doi.org/10.1016/S1470-2045(10)70218-7.
[21] Azoulay E. A new standard of care for critically ill patients with cancer. Chest 2014;146:241–4. https://doi.org/10.1378/chest.14-0620.
[22] Máttar JA. Application of total body bioimpedance to the critically ill patient. Brazilian group for bioimpedance study. New Horiz 1996;4:493–503.
[23] Lima e Silva RR, CPS Pinho, Rodrigues IG, JGM Jr Monteiro. Phase angle as an indicator of nutritional status and prognosis in critically ill patients. Nutr Hosp 2014;31:1278–85. https://doi.org/10.3305/nh.2015.31.3.8014.
[24] Llames L, Baldomero V, Iglesias ML, Rodota LP. Valores del ángulo de fase por bioimpedancia eléctrica: estado nutricional y valor pronóstico. Nutr Hosp 2013;28:286–95. https://doi.org/10.3305/nh.2013.28.2.6306.
[25] Finn PJ, Plank LD, Clark MA, Connolly AB, Hill GL. Progressive cellular dehydration and proteolysis in critically ill patients. Lancet 1996;347:654–6.
[26] Haussinger D, Reinehr R, Schliess F. The hepatocyte integrin system and cell volume sensing. Acta Physiol 2006;187:249–55. https://doi.org/10.1111/j.1748-1716.2006.01542.x.
[27] Schwenk A, Schlottmann S, Kremer G, Diehl V, Salzberger B, Ward L. Fever and sepsis during neutropenia are associated with expansion of extracellular and loss of intracellular water. Clin Nutr 2000;19:35–41. https://doi.org/10.1054/clnu.1999.0070.
[28] TNM Classification of Malignant Tumours. UICChttp://www.uicc.org/tnm-classification-malignant-tumours-6th-edition/6th edition. ; 2015[Accessed 13 Out 2015].
[29] Buccheri G, Ferrigno D, Tamburini M. Karnofsky and ECOG performance status scoring in lung cancer: a prospective, longitudinal study of 536 patients from a single institution. Eur J Cancer 1996;32A:1135–41.
[30] Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Crit Care Med 1985;13:818–29.
[31] Vincent JL, Moreno R, Takala J, Willatts S, De Mendonça A, Bruining H, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/

failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. Intensive Care Med 1996;22:707–10.
[32] Kyle UG, Bosaeus I, De Lorenzo AD, Deurenberg P, Elia M, Gómez JM, et al. Bioelectrical impedance analysis—part I: review of principles and methods. Clin Nutr 2004;23:1226–43. https://doi.org/10.1016/j.clnu.2004.06.004.
[33] Heyland DK, Dhaliwal R, Jiang X, Day AG. Identifying critically ill patients who benefit the most from nutrition therapy: the development and initial validation of a novel risk assessment tool. Crit Care 2011;15:R268. https://doi.org/10.1186/cc10546.
[34] Garth AK, Newsome CM, Simmance N, Crowe TC. Nutritional status, nutrition practices and post-operative complications in patients with gastrointestinal cancer. J Hum Nutr Diet 2010;23:393–401. https://doi.org/10.1111/j.1365-277X.2010.01058.x.
[35] Fearon K, Strasser F, Anker SD, Bosaeus I, Bruera E, Fainsinger RL, et al. Definition and classification of cancer cachexia: an international consensus. Lancet Oncol 2011;12:489–95. https://doi.org/10.1016/S1470-2045(10)70218-7.
[36] Barbosa-Silva MCG, Barros AJ. Bioelectrical impedance analysis in clinical practice: a new perspective on its use beyond body composition equations. Curr Opin Clin Nutr Metab Care 2005;8:311–7.
[37] Lee Y, Kwon O, Shin CS, Lee SM. Use of bioelectrical impedance analysis for the assessment of nutritional status in critically ill patients. Clin Nutr Res 2015;4:32–40. https://doi.org/10.7762/cnr.2015.4.1.32.
[38] Berbigier MC, Fernandes V, Moraes B, Schweigert ID. Ângulo de fase derivado de bioimpedância elétrica em pacientes sépticos internados em unidades de terapia intensiva. Rev Bras Ter Intensiva 2013;25:25–31. https://doi.org/10.1590/S0103-507X2013000100006.
[39] Małecka-Massalska T, Mlak R, Smolen A, Morshed K. Bioelectrical impedance phase angle and subjective global assessment in detecting malnutrition among newly diagnosed head and neck cancer patients. Eur Arch Otorhinolaryngol 2016;273:1299–305. https://doi.org/10.1007/s00405-015-3626-5.