# The Prognostic Role of Phase Angle in Advanced Cancer Patients: A Systematic Review

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## Abstract

Phase angle (PA) is a ratio between the reactance and resistance obtained by bioelectric impedance analysis and has been interpreted as a cell membrane integrity indicator and a predictor of total body cell mass. A low PA may suggest deterioration of the cell membrane, which in advanced cancer patients may result in a reduced overall survival (OS). This systematic review sought to investigate the current evidence regarding whether there is an association between PA and OS in patients with advanced cancer (ie, metastatic disease). The search was conducted on electronic databases in August 2017. A total of 34 articles were identified in the initial literature search. Nine studies reporting on 1496 patients were deemed eligible according to our inclusion criteria. PA data were analyzed as continuous variables or according to different cutoffs, under a frequency of 50 Khz. Low PA was associated with worse nutrition status evaluated by body mass index, serum albumin level, transferrin, and fat-free mass. The median OS of the included papers varied from 25.5–330 days, and all studies analyzed showed a significant association between PA and OS, in that patients with low PA had worse OS. Future studies are necessary to justify the use of PA in therapeutic decisions for this population and to evaluate whether nutrition status can influence the association between PA and survival. (*Nutr Clin Pract.* 2018;33:813–824)

## Keywords

bioelectric impedance; cancer; neoplasms; nutrition assessment; phase angle; survival

## Introduction

Cancer is recognized as a global public health problem. In developing countries, at the time of diagnosis, the majority of patients with cancer have late-stage disease.[1] Malnutrition is a frequent manifestation in patients with advanced cancer and is correlated with poor prognosis and high mortality.[2-5]

Bioelectrical impedance analysis (BIA) has been increasingly used to assess nutrition status.[6,7] BIA consists of a rapid, relatively inexpensive, non-invasive, and reproducible method for providing indirect estimates of the body's compositional compartments, as well as the distribution of fluids in the intracellular and extracellular spaces.[6,8] In this context, BIA can be useful in clinical practice to assess changes in body composition.[9] BIA measures the parameters of body resistance (opposition offered by the body to the flow of an alternate electrical current) and reactance (resistive effect produced by the tissue interfaces and cell membranes).[10]

The phase angle (PA) is a ratio between reactance and resistance, and it has been suggested as a marker of cellular function and, consequently, of nutrition status.[11] By definition, PA is positively associated with capacitance and negatively associated with resistance.[11] Lower PA suggests cell death or decreased cell integrity, while higher PA suggests large quantities of intact cell membranes. Current evidence presents PA as an indicator of nutrition status, a predictive factor for risk of complications and death in patients suffering from different clinical conditions[8] and an independent prognostic factor in advanced cancer patients.[7,12-14] In the present study, we conducted a systematic review of the literature (SRL) to investigate the evidence regarding whether there is an association between PA and overall survival (OS) in patients with advanced cancer (ie, metastatic disease).

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**Table 1.** Keywords Used in Search Strategy in Electronic Databases.

| Electronic Databases | Keywords |
|---|---|
| MEDLINE/PubMed (https://www.ncbi.nlm.nih.gov/pubmed) | ("advanced cancer") AND ("electric impedance" OR "phase angle") AND ("survival" OR "outcomes" OR "mortality" OR "prognosis") |
| Scopus (https://www.scopus.com) | (advanced cancer) AND (electric impedance) AND (survival OR outcomes OR mortality OR prognosis) |
| LILACS (http://lilacs.bvsalud.org/) | (advanced cancer) AND (electric impedance OR phase angle) AND (survival OR outcomes OR mortality OR prognosis) |
| Cochrane Library (http://onlinelibrary.wiley.com/cochranelibrary/search) | (advanced cancer) AND (electric impedance OR phase angle) AND (survival OR outcomes OR mortality OR prognosis) |

## Methods

### Literature Search and Study Selection

A comprehensive search of the literature was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria[15] using well-known indexed databases, including MEDLINE/PubMed, Scopus, LILACS, and the Cochrane Library in August 2017; a combination of search terms is described in Table 1. No restrictions were made regarding language or publication date. We selected the studies by the following inclusion criteria: 1) abstract available on-line, 2) original articles, 3) cohort or case-control design, 4) performed in humans, 5) participants aged ≥18 years, and 6) presented the relationship between PA and OS. The reference lists of related and included papers were also screened to search for additional potential studies.

Two authors independently reviewed search results. Reviewers assessed each title and abstract and considered each study for a full-text review. Any disagreements in either title/abstract or in the full-text paper review phases were resolved by consensus. The opinion of a third reviewer was sought when necessary.

### Data Extraction

Data extraction tables were specifically developed for this SRL, and the following information was selected independently by 2 reviewers: the general characteristics of the studies (first author, year of publication, study design, sample size, country, study aims, and statistical test), participant characteristics (age and cancer population), information about the BIA measurements (model, current frequency, and PA thresholds) and main results about associations between PA and nutrition status and OS rates.

### Quality Assessment

The quality assessment was performed by 2 independent reviewers using the Newcastle-Ottawa Scale (NOS)[16] (Appendix 1). The scale consists of 3 quality criteria: selection, comparability, and outcome. The maximum score is 9 points (4 for selection, 2 for comparability, and 3 for outcome). Study quality was defined as poor when the score was 1–3, fair when the score was 4–6, and good when the score was 7–9 points.

Regarding the comparability domain, in addition to age and sex, other confounding factors considered for the statistical analysis controls were prognostic evaluation through the Palliative Prognostic Index (PPI) or Palliative Prognostic (PAP) Score, Karnofsky Performance Score (KPS), and the Eastern Cooperative Oncology Group (ECOG) Scale of Performance Status. The score assigned for each paper is described in Figure 1.

Inter-reviewer reliability was determined using Cohen's $\kappa$ statistics. The interpretation of the coefficient was based on the proposal of Shrout.[17] The inter-reviewer reliability presented an optimal accuracy ($\kappa = 0.89$), representing an agreement of 92.5%.

## Results

### Literature Search and Characteristics of the Included Studies

The search resulted in a total of 34 papers. After the exclusion for study design, 27 papers were selected for title and abstract review. Subsequently, 18 papers were selected for full-text review (Figure 2). Papers were excluded by the careful reading of titles and abstracts, with reasons for exclusion listed in Table S1. In addition, the examination of the reference lists of the papers did not recover any further studies. Finally, 9 studies reporting on 1496 patients were deemed eligible for this SRL.

The selected papers were all published within the last 14 years,[7,12,14,18-23] and most were performed on outpatients[14,19,21-23] and conducted in the United States,[12,14,20-23] Mexico,[18,19] and South Korea.[7] Five studies were prospective,[7,12,18-20] and the others were
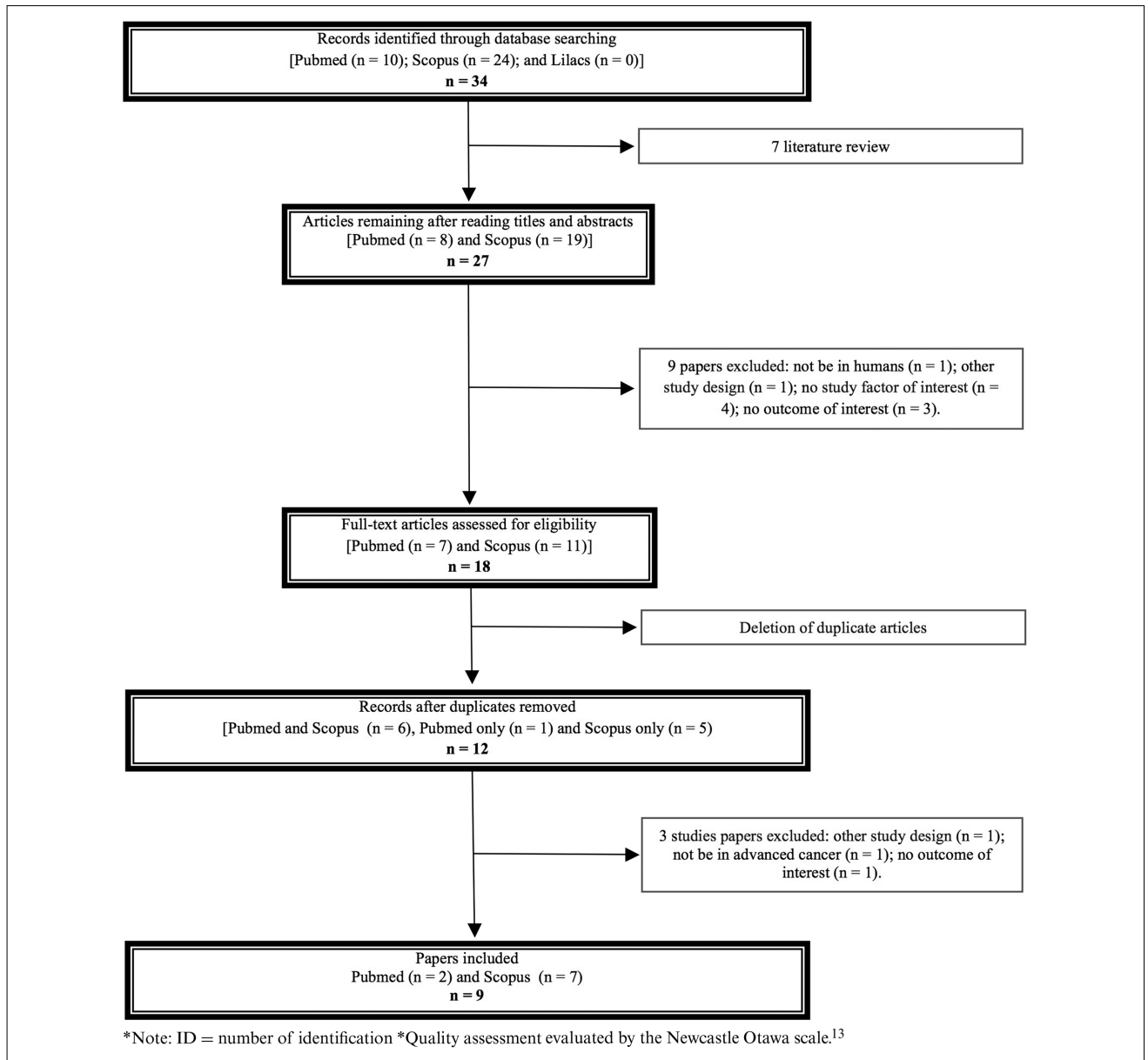
Records identified through database searching
[Pubmed (n = 10); Scopus (n = 24); and Lilacs (n = 0)]
**n = 34**

7 literature review

Articles remaining after reading titles and abstracts
[Pubmed (n = 8) and Scopus (n = 19)]
**n = 27**

9 papers excluded: not be in humans (n = 1); other study design (n = 1); no study factor of interest (n = 4); no outcome of interest (n = 3).

Full-text articles assessed for eligibility
[Pubmed (n = 7) and Scopus (n = 11)]
**n = 18**

Deletion of duplicate articles

Records after duplicates removed
[Pubmed and Scopus (n = 6), Pubmed only (n = 1) and Scopus only (n = 5)
**n = 12**

3 studies papers excluded: other study design (n = 1); not be in advanced cancer (n = 1); no outcome of interest (n = 1).

Papers included
Pubmed (n = 2) and Scopus (n = 7)
**n = 9**

*Note: ID = number of identification *Quality assessment evaluated by the Newcastle Otawa scale.[13]

**Figure 1.** Evaluation of the methodological quality of selected papers.

| | Selection | | | | Comparability | Outcome | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Study** | **1** | **2** | **3** | **4** | **1** | **1** | **2** | **3** | **Total** | **Classification** |
| Lee *et al.*, 2014[7] | – | * | * | * | ** | * | * | * | 8* | High quality |
| Hui *et al.*, 2014[9] | * | * | * | * | ** | * | * | * | 9* | High quality |
| Hui *et al.*, 2017[11] | * | * | * | * | ** | * | * | * | 9* | High quality |
| Camargo *et.al.*, 2017[15] | * | * | * | * | * | * | * | * | 8* | High quality |
| Sánchez-Lara *et al.*, 2012[16] | * | * | * | * | ** | * | * | * | 9* | High quality |
| Davis *et al.*, 2009[17] | * | * | * | * | * | * | – | * | 8* | High quality |
| Gupta *et al.*, 2009[18] | * | * | * | * | * | * | * | * | 8* | High quality |
| Gupta *et al.*, 2004[19] | * | * | * | * | * | * | * | * | 8* | High quality |
| Gupta *et al.*, 2004[20] | * | * | * | * | * | * | * | * | 8* | High quality |

*Note: n = number of observation *Designed in accordance with PRISMA Group, 2009.[12]

**Figure 2.** Flow chart of studies selection.

**Table 2.** Description of Studies Regarding Authors, Year of Publication, Origin, Age of Participants, Study Design, Sample Size, Cancer Type, Objectives, and Type of Bioelectrical Impedance Analysis.

| Author/Year | Origin | Study Design | Sample Size | Cancer Population | Age | Objectives | BIA |
|---|---|---|---|---|---|---|---|
| Gupta et al., 2004[22] | USA | Retrospective cohort | 52 | Outpatients, stage IV colorectal cancer | $55.8 \pm 10.8$ years[a] | Investigate prognostic role of PA in advanced colorectal cancer. | BIA-101Q analyzer (RJL Systems, Clinton Township, MI, USA), single frequency (50 kHz) |
| Gupta et al., 2004[23] | USA | Retrospective cohort | 42 | Outpatients, stage IV pancreatic cancer | $56.2 \pm 10.7$ years[a] | Investigate prognostic role of PA in advanced pancreatic cancer. | BIA-101Q analyzer (RJL Systems, Clinton Township, MI, USA), single frequency (50 kHz) |
| Davis et al., 2009[20] | USA | Prospective cohort | 50 | Inpatients, without defining advanced cancer. Cancer type: pancreatic (12.0%), lung (12.0%), breast (12.0%), myeloma (6.0%), renal (6.0%), colon (6.0%), gastric (6.0%). | $63.0 \pm 12.0$ years[a] | Determine if BIA correlates before hydration or changes during hydration and determine if these changes were prognostically important. | (RJL Systems, Clinton Township, MI, USA), single frequency (50 kHz) |
| Gupta et al., 2009[21] | USA | Retrospective cohort | 165 | Outpatients, stages IIIB and IV with non-small-cell lung cancer, treated at Cancer Treatment Centers of America. | $56.0 \pm 9.1$ years[a] | Investigate prognostic role of BIA-derived PA in patients with advanced non-small-cell lung cancer. | SFB7 BioImp v1.55 analyzer (ImpediMed, Brisbane, Australia), single frequency (50 kHz) |
| Sánchez-Lara et al., 2012[19] | Mexico | Prospective cohort | 119 | Outpatients, diagnosis of histopathologic-confirmed or cytologic-confirmed stage III or IV non-small-cell lung cancer. | $60.5 \pm 12.5$ years[a] | Evaluate association of nutrition parameters in health-related quality of life and OS in patients with advanced non-small-cell lung cancer. | Bodystat Quadscan 4000, multi-frequency |
| Lee et al., 2014[7] | South Korea | Prospective cohort | 28 | Inpatients, without defining advanced cancer. Cancer type: digestive tract (39.2%), lung (10.7%), hematology (10.7%), bladder/renal (10.7%), and other (28.5%). | >70 years = 53.6% 50–70 years = 35.7% 30–50 years = 10.7% | Investigate BIA-derived PA as prognostic indicator for survival in advanced cancer patients. | Biodynamics model 450 (Biodynamics Co., Seattle, WA, USA), single frequency (50 kHz) |

(*continued*)

**Table 2. (continued)**

| Author/Year | Origin | Study Design | Sample Size | Cancer Population | Age | Objectives | BIA |
|---|---|---|---|---|---|---|---|
| Hui et al., 2014[12] | USA | Prospective cohort | 222 | Inpatients, without defining advanced cancer. Cancer type: digestive tract most common (33.0%), respiratory (16.0%), breast (13.0%), gynecologic (11.0%), genitourinary (9.0%), head and neck (5.0%), hematologic (5.0%), and other (9.0%). | 55.0 (22.0–79.0) years[b] | Determine association of PA, hand grip strength, and maximal inspiratory pressure with OS in patients with advanced cancer. | Quantum IV (RJL Systems, Clinton Township, MI, USA), single frequency (50 kHz) |
| Hui et al., 2017[14] | USA | Retrospective cohort | 366 | Outpatients with advanced cancer defined as locally advanced, recurrent or metastatic disease for solid tumors, or progressive/refractory/incurable disease for hematologic tumors. Cancer type: gastrointestinal (30.0%), breast (14.0%), head and neck (13.0%), respiratory (11.0%), gynecologic (9.0%), and other (15.0%). | 58.0 (21.0–90.0) years[b] | Determine association of PA obtained from multi-frequency BIA with OS in patients with advanced cancer. | Inbody 720 (Inbody, Cerritos, CA, USA), multi-frequency (5, 50, and 250 kHz) |
| Camargo et al., 2017[18] | Mexico | Prospective cohort | 452 | Inpatients, without defining advanced cancer. Cancer type: gastric (39.2%), lung (18.8%), gynecologic (16.6%), and other (25.4%). | 57.6 ± 14.6 years[a] | Associate PA and OS in palliative patients at National Cancer Institute of Mexico. | Inbody 720 (Inbody, Cerritos, CA, USA), single frequency (50 kHz) |

BIA, bioelectrical impedance analysis; OS, overall survival; PA, phase angle.
[a] Mean (± standard deviation).
[b] Median (interquartile range).

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retrospective.[11,18-20] The age of the population included in the studies varied between the fifth and sixth decade of life. Four studies included a population with specific types of cancer. One study was exclusively with colorectal cancer patients,[22] 1 with pancreatic cancer patients,[23] and 2 studies with lung cancer patients.[19,21] For studies that included different cancer types,[7,12,14,18,20] digestive tract cancer was the most common type (Table 2).

### Type of BIA Used to Assess PA

Regarding the BIA equipment, different models (Biodynamics 450, Inbody 720, Bodystat quadscan 400, SFB7 Bioimp v1.55 analyzer, and RJL systems) were used to assess PA; most were manufactured in the U.S. Only 2 studies used a multi-frequency BIA,[14,20] but only 1 study presented PA data using these different frequencies (5, 50, and 250 kHz).[14] Further studies were conducted at a single frequency of 50 kHz (Table 2).[7,12,18-23]

### PA Association With Nutrition Status

The association between PA and nutrition status or body composition was included only in 3 of the selected papers and evaluated by pre–serum albumin level[23]: 1 for body mass index (BMI),[18] 1 for subjective global assessment (SGA),[23] and 1 for fat-free mass.[12] With the exception of SGA, these nutrition markers showed a negative and significant association with PA, indicating that subjects with worse nutrition status had lower values of PA (Table 3).

### PA Association With OS

Survival analyses were performed using Cox proportional hazards models with bivariate and multivariate logistic regression in all the studies. Kaplan-Meier curves were constructed to analyze the probability of OS according to PA,[12,14,18-23] and the log-rank test was used[7,12,14,18,20-23] to verify survival differences between the groups.

Regarding the confounder variables used for controls in Cox regression analyses, a high variability among the studies was observed: 6 studies controlled for age,[7,14,18-21] 3 controlled for gender,[14,18,20] and only 1 controlled for race.[17] None of the studies controlled for physical activity. The nutrition status of patients was not considered in 3 of the 9 papers.[11,20,21] Some studies controlled for different markers, such as BMI,[7,15,19] SGA,[19,22] pre–serum albumin level,[23] and transferrin,[23] and only 2 of these studies adjusted for body composition, such as fat-free mass.[12,22] Four studies included information about useful tools for predicting survival; 3 publications[11,19,20] included the ECOG scale, and 1[7] included the KPS and PPI (Table 3).

Different PA cutoffs were used varying from 4.0°→6.0°, and in 3 of the studies, no cutoffs were used for the Cox analysis; the PA was used as a continuous variable.[7,12,20] In general, patients with a PA ≤5.6° presented a significantly shorter survival time than those with a PA >5.6°.

The median OS of the included papers varied from 25.5–330 days, and the papers that compared the median OS among those with low and high PA showed decreased values in OS for those with low PA (Table 3).[12,18-23]

It was observed that patients with colorectal cancer presented a median OS of 8.6 months when the PA was ≤5.6°,[22] lung cancer patients presented a median OS of 7.6 months when PA was ≤5.4°,[16] and in pancreatic cancer patients, the median OS was 6.3 months among those with PA ≤5.0°.[20] For studies that included a population with different types of cancer, median OS varied from 35–162 days with the previously mentioned cutoffs (Table 3).[7,12,14,18]

In the Cox analyses, the hazard ratio was approximately 20% higher for each unit increase of PA.[7,12,14,20-23] When different cutoffs were tested, the hazard ratio for mortality varied between 1.8-fold–10.7-fold risk for death.[18,19,22] In addition, it was observed that all the studies included in this SRL showed a significant association between PA and OS (Table 3).

## Discussion

This is the first SRL that evaluated the association between PA and OS in advanced cancer patients. Our results confirmed that a lower PA value was associated with OS in advanced cancer patients. These findings suggest PA as a relevant indicator for unfavorable outcomes, with a decrement in the survival rate. To determine reliable and useful prognostic factors that can be used in clinical practice, the improvement of therapeutic approaches for this type of population is necessary.[24,25] In this context, PA is an objective and non-invasive method that can be used for prognosis.

Patients with advanced cancer may present a PA lower than those observed in a healthy population.[26] This reduced PA may be related to the metabolic disarrangement that this population experiences, such as malnutrition and cancer cachexia.[27] In fact, a poor nutrition status can result in a body fluid imbalance and cell membrane changes.[12,27,28] Thus, the relationship of PA with body composition and nutrition status makes it an indicator for the predictive risk of morbidity and mortality.[12]

In this context, a significant association was found between PA and the nutrition markers such as pre–serum albumin level, BMI, and fat-free mass. Pre–serum albumin level is a reliable indicator of acute changes in nutrition status, and it is unaffected by hydration status. On the other hand, the use of BMI has been vastly discussed in the literature as a nutrition marker that does not take into account the evaluation of fat-free mass and body fat. Hui et al. tested the association between PA and fat-free mass, and found a positive and significant association, emphasizing the idea

**Table 3.** Description of Statistical Tests, Cutoffs for Phase Angle, Survival, Potential Confounding, and Main Findings Applied in Studies.

| Author/Year | Statistical Test | Cutoff for PA (50 kHz) | Potential Confounding | Association Between PA and Nutrition Status | Association Between PA and OS | Main Findings |
|---|---|---|---|---|---|---|
| Gupta et al., 2004[22] | Cox regression; Kaplan-Meier; log-rank test. | 5.57° | Diagnostic time; body weight; lean mass; serum albumin level; pre–serum albumin level; transferrin; SGA; stage of tumor; prior treatment. | — | Patients with PA ≤5.6° had median survival of 8.6 months, while others presented median OS of 40.4 months. In multivariate analysis, PA (≤5.6°) was a prognostic indicator in patients with advanced colorectal cancer (HR = 10.7; 95% CI: 1.9–60.2; P-value = 0.007). | PA and age at diagnosis presented positive correlation with OS. Furthermore, SGA was not associated with OS. PA was prognostic indicator in patients with advanced colorectal cancer. The risk was approximately 11-fold higher for those with PA ≤5.6°. |
| Gupta et al., 2004[23] | Spearman correlation; Pearson correlation; Cox regression; Kaplan-Meier; log-rank test. | 5.0° | Pre–serum albumin level; serum albumin level; prior treatment. | PA was associated with pre–serum albumin level (r = 0.32; P = 0.04), transferrin (r = 0.19; P = 0.25) and SGA (r = -0.26; P = 0.10). | Patients with PA ≤5.0° had median OS of 6.3 months, while others presented a median OS of 10.2 months (P-value = 0.02). Multivariate analysis after adjusting for pre–serum albumin level demonstrated relative risk reduction (= 0.69; 95% CI: 0.49; 0.97) that was associated with each unit increase in PA. PA continued to be statistically significant (P-value = 0.02) after jointly controlling for serum albumin level, pre–serum albumin level, and previous treatment history. | PA associated positively with OS. Pre–serum albumin level (<150mg/L) was also associated with OS. PA was strong prognostic indicator in advanced pancreatic cancer patients. Therefore, each unit increase on PA showed reduction of mortality of 31%. |

*(continued)*

**Table 3. (continued)**

| Author/Year | Statistical Test | Cutoff for PA (50 kHz) | Potential Confounding | Association Between PA and Nutrition Status | Association Between PA and OS | Main Findings |
|---|---|---|---|---|---|---|
| Davis et al., 2009[20] | Spearman correlation; Pearson correlation; Cox regression; Kaplan-Meier; log-rank test. | Survival curves: Decreased or not altered vs increased PA Regression: Continuous variable | Resistance; total body fluid; sodium; gender; age; skin color; ECOG. | — | Higher PA before hydration predicted a borderline and significantly lower OS (HR = 0.8; 95% CI: 0.6–1.0; $P$-value = 0.057); paradoxically, an increase in PA during hydration predicted lower OS (HR = 1.2; 95% CI: 1.1–1.4; $P$-value = 0.007). | Weight loss was associated with shorter OS. PA positively predicted borderline and significantly lower OS in advanced cancer patients on first day of their hospital stay, indicating that each unit increase on PA presented reduction of 20% in mortality. |
| Gupta et al., 2009[21] | Cox regression; Kaplan-Meier; log-rank test. | 5.3° | Age; stage of tumor; prior treatment. | — | Patients with PA ≤5.3 had median OS of 7.6 months, while those >5.3 had 12.4 months ($P$ = 0.02). In multivariate analysis, each degree of increase in PA, adjusted for age, stage at diagnosis, and prior treatment, history was associated with OS (HR = 0.8; 95% CI: 0.6–1.0; $P$-value = 0.020). | Stage at diagnosis and treatment history was associated with OS. BIA-derived PA was positive and independently prognostic indicator of OS in patients with stage IIIB and IV non-small-cell lung cancer. Nutrition interventions targeted at improving PA could potentially lead to improved OS in patients with advanced non-small-cell lung cancer. Therefore, each unit increase on PA presented reduction of 20% in mortality. |
| Sánchez-Lara et al., 2012[19] | Mann-Whitney U test; Cox regression; Kaplan-Meier. | 5.8° | Gender; age; ECOG; stage of tumor; weight loss; BMI; SGA; serum albumin level; PLR; NLR; CRP; IL-6; TNF-$\alpha$. | — | Median follow-up was 6 (± 5) months. In multivariate analysis, patients with ECOG = 2 (HR = 2.7; 95% CI: 1.5–4.7; $P$-value = 0.001), PA ≤5.8° (HR = 3.0; 95% CI: 1.2–7.1; $P$-value = 0.011) and malnutrition (HR = 2.7; 95% CI: 1.3–5.5; $P$-value = 0.005) had worse OS. | Malnutrition measured by SGA, weight loss >10%, and BMI >20 was associated with lower related quality of life. Patients with ECOG = 2, high content serum IL-6, and lower PA showed lower OS. PA was presented to be an independent prognostic factor in advanced non-small-cell lung cancer, where those with PA ≤5.8° presented risk 3-fold higher than those with higher values. |

*(continued)*

**Table 3. (continued)**

| Author/Year | Statistical Test | Cutoff for PA (50 kHz) | Potential Confounding | Association Between PA and Nutrition Status | Association Between PA and OS | Main Findings |
|---|---|---|---|---|---|---|
| Lee et al., 2014[7] | Spearman correlation; Cox regression; log-rank test. | Survival curves: 4.4° Regression: Continuous variable | Age; BMI; PPI; KPS. | — | Median OS time was 25.5 days. PA ≥4.4° showed a longer survival time compared with PA <4.4° (100 vs 125 days, respectively; $P$-value = 0.01). In multivariate analysis, each degree of increase in PA, adjusted for age, PPI, BMI, and PA was associated with OS (HR = 0.64; 95% CI: 0.42–0.95; $P$-value = 0.028). | PA showed positive and significant association with OS, where each unit increase on PA presented a reduction of 36% in mortality. However, age, PPS, and BMI did not show significant relationship with OS. BIA-derived PA may serve as independent prognostic indicator in advanced cancer patients. |
| Hui et al., 2014[12] | Spearman correlation; Cox regression; Kaplan-Meier; log-rank test. | Survival curves: 4.4° vs >4.4° 2.0–2.9° vs 3.0–3.9° vs 4.0–4.9° vs 5.0–5.9° vs ≥6.0° <P5 vs >P95 Regression: Continuous variable | PAP Score; serum albumin level; fat-free mass. | PA was associated with fat free mass (r = 0.29; $P$ <0.001) and the fat free mass index (r = 0.33; $P$ <0.001). | Median OS was 106 days (95% CI: 71–128 days). Patients with lower PA (<3°) had lower survival (35 vs 220 days) when compared with those with higher values (PA ≥6.0°). In multivariate analysis, each degree of increase in PA was associated with OS (HR = 0.86; 95% CI: 0.74–0.99; $P$-value = 0.04). | PA was positively associated with OS, where each unit increase on PA presented a reduction of 14% in mortality. Furthermore, patients with lower KPS, PPS, hypoalbuminemia (<3.0 g/dL), and lower fat-free mass (≤51.6 kg) had poor survival. PA was shown to be an independently established prognostic factor for advanced cancer setting during hospital stay. |
| Hui et al., 2017[11] | Spearman correlation; Contal & O'Quigley; Cox regression; Kaplan-Meier; log-rank test. | Survival curves: Right side of body: 4.5° Left side of body: 4.3° Regression: Right side of body: 4.4° Left side of body: 4.2° | Gender; age; race; tumor type; ECOG; weight loss in 6 months; serum albumin level; calcium; hemoglobin; leukocytes; lactate; lymphocytes; neutrophils. | — | Median OS was 250 days. Patients with PA ≤4.5° showed a significant lower median of OS (162 days) when compared with those with higher (>4.5°) values (403 days). In multivariate analysis, each degree increase in PA was associated with OS (HR = 0.85; 95% CI: 0.72–0.99; $P$-value = 0.048). | PA was positively associated with OS, where each unit increase on PA presented a reduction of 15% in mortality. In addition, hypoalbuminemia (<4.0g/dL) elevated lactate dehydrogenase (>618 unit), serum albumin levels, and neutrophil-lymphocyte ratio (>3) were correlated with poor survival. PA represented novel objective prognostic factor in an outpatient palliative cancer-care setting, regardless of frequency and body sides. |

**Table 3. (continued)**

| Author/Year | Statistical Test | Cutoff for PA (50 kHz) | Potential Confounding | Association Between PA and Nutrition Status | Association Between PA and OS | Main Findings |
|---|---|---|---|---|---|---|
| Camargo et al., 2017[15] | Spearman correlation; Cox regression; Kaplan-Meier; log-rank test. | 4.0° | Gender; age; diagnose; BMI. | Patients with BMI <24.9kg/m² had significantly lower mean PA (3.73° ±0.92) than those with BMI ≥ 25 kg/m² (4.37° ±0.98; $P$ = 0.011). | Average survival was 86 vs 163 days for patients with PA ≤4.0° and >4.0°, respectively ($P$ >0.0001). In the multivariate analysis, patients with PA ≤4.0° had HR = 1.8; 95% CI: 1.4–2.3; $P$-value >0.0001. | PA and BMI were positively correlated with OS. Therefore, risk for mortality was approximately 2-fold higher for those with PA ≤4.0°. |

BIA, bioelectrical impedance analysis; BMI, body mass index; CI, confidence interval; CRP, C-reactive protein; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; IL-6, interleukin 6; KPS, Karnofsky Performance Status; NLR, neutrophils/lymphocytes ratio; OS, overall survival; PA, phase angle; PAP Score, Palliative Prognostic Score; PLR, platelets/lymphocytes ratio; PPI, Palliative Prognostic Index; PPS, Palliative Performance Scale; SGA, subjective global assessment; TNF-α, tumor necrosis factor-α; vs, versus.

that body composition has an important influence on PA values.[12]

It is worth noting that despite all the papers included in this SRL that assessed PA by using the BIA, most studies did not evaluate body composition in their study population. Based on the assumption that body composition may influence OS, it is reasonable to say that controlling for this potential confounder in these analyses is necessary. However, most of the studies controlled for at least 1 marker of nutrition status in the Cox regression.

Other potential confounders used in the Cox analyses in these studies should be discussed. The first is performance status (KPS) or prognostics scales (PPI and PAP score), which are useful tools for predicting survival of palliative subjects.[13] Only 4 studies, however, included this information. Nevertheless, these confounders were considered in the evaluation of quality assessment in this SRL. Other confounders that should be included in analyses that are influences on PA values are ethnicity/race, gender, age, weight and height.[12,29,30] Therefore, these aspects should be considered in the study design when involving measurements of PA because these confounders may lead to a prejudice in the associations between PA and OS.

Another factor that may also play a role in these statistical analyses could be the population included in the studies; some studies included subjects with different cancer types, and no statistic control was observed for cancer type. The lack of control for this variable might influence the PA analysis and its association with OS. Thus, further investigation regarding this issue is necessary.

Another important issue is related to the different PA cutoffs in the analyses of the studies. Currently, there is no known precise PA value capable to identify the length of survival in individuals with advanced cancer. In general, the mean, median, or lower PA quartiles found in the groups studied were used as a parameter. However, it can be affirmed that sick individuals present lower values of PA, which correlates with the severity of the disease.[7,12,14,18-23]

In all the studies, the data were collected in a single care center and were related to inpatient and/or outpatient follow-ups.[7,12,14,18-23] It is worth mentioning that survival may differ substantially between inpatients and outpatients.[14] Inpatients present specific features that demand specialized treatment, including better symptom control, which could limit the generalization of these findings.

The use of different methods to evaluate PA was influenced by the BIA frequency that was used to evaluate it, i.e., single-frequency or multi-frequency.[31,32] In this SRL, different methods of BIA were used in the included studies, while only 2 studies used a multi-frequency BIA.[14,19] However, only 1 of these studies showed results that were related to different frequencies in patients with advanced cancer in palliative care; this study was the first with differential analyses relating PA and OS.[14] Lower frequencies of PA

(<50 kHz) are associated with a flow through the extracellular compartment, whereas higher frequency currents (>200 kHz) penetrate the cell membranes and pass through thin tissues.[33] This differential tissue penetration at a higher frequency current allows for better accuracy in assessing the body's composition in healthy individuals.[34] Still, more studies are needed to evaluate the usefulness of different frequencies in the evaluation of PA in advanced cancer patients.

With regard to strengths, the SRL methodology was consistent with the PRISMA statement.[15] The search was conducted in different databases and in the reference lists of the included papers; there were also no restrictions made for language, the year of publication, or the place of execution.

## Conclusions

Considering that survival prediction remains a challenge in individuals with advanced cancer, the results of this SRL show that PA, derived from BIA, is an important objective predictive factor of OS for this population. Nonetheless, there is still a lack of information regarding the use of thresholds in this population. Future studies are necessary to identify cutoffs of PA to guide therapeutic decisions and to evaluate whether nutrition status can influence the association between PA and survival. While no specific threshold can be used as a prognostic factor in this population, the reduction in values of PA, evaluated routinely, could indicate a worse OS.

## Statement of Authorship

L. Calixto-Lima and L.C. Oliveira equally contributed to the conception and design of the research; L.C. Oliveira, M.M.E. Pereira, M.S.C. Queiroz, E.M. Wiegert, and J. Rodrigues contributed to the acquisition, analysis, and interpretation of the data; L.C. Oliveira and L. Calixto-Lima drafted the manuscript; M.M.E. Pereira, M.S.C. Queiroz, N.M.C. de Albuquerque, J. Rodrigues, E.M. Wiegert, L. Calixto-Lima, and L.C. Oliveira critically revised the manuscript; M.M.E. Pereira, M.S.C. Queiroz, N.M.C. de Albuquerque, J. Rodrigues, E.M. Wiegert, L. Calixto-Lima, and L.C Oliveira agree to be fully accountable for ensuring the integrity and accuracy of the work. All authors read and approved the final manuscript.

## Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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