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REVIEW ARTICLE

Phase angle and mortality: a systematic review

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Abstract

Background/objectives The phase angle, expressed through bioelectrical impedance, has been studied as a prognostic marker in several health conditions. As this issue is still conflicting, the question whether this parameter correlates with mortality in the most diverse clinical situations remains. Therefore, this study aimed to evaluate the relationship between phase angle and mortality through a systematic review of the literature.

Subjects/methods This research was conducted in electronic databases (Pubmed, Embase, Cochrane, Lilacs, Scielo, e Scopus), and included studies that had phase angle as a variable of interest and mortality/survival as an outcome. Data were extracted independently by two reviewers and disagreements were assessed by a third reviewer.

Results Forty-eight of 455 papers were assessed and an amount of 42 showed a correlation between phase angle and mortality.

Conclusions Phase angle seems to be a good indicator for mortality in many clinical situations and can be used in screening individuals prone to this outcome.

Introduction

The bioelectrical impedance analysis (BIA) is an indirect method to assess body composition, and was established through the correlation between impedance and body water content [1, 2]. As it is a fast, safe, non-invasive, and relatively cheap method, BIA has been used to estimate body composition and nutritional state of healthy and ill individuals [1, 3, 4].

The correlation between the resistance (R) and reactance (Xc) vectors given by BIA creates the phase angle (PA), whose degrees vary depending on the cell composition and water volume of the tissues, in addition to its membrane potential [5]. Low PA values indicate low Xc and high R, showing reduction of the cell integrity [5, 6]. Contrarily, high PA values present high Xc and low R, which is associated to a higher amount of intact cell membranes, suggesting an adequate health state [5]. As opposed to other BIA measurements, the PA is obtained by these secondary analyses of BIA, without the use of anthropometric parameters. This could be useful in the clinical setting as anthropometry, especially height measurement, is difficult to perform accurately in some patients [7, 8].

As PA displays the electrical integrity of body membranes, and it is well known that disease, inflammation, malnutrition, and functional disabilities can result in disturbed electric tissue properties that directly affect the PA [8–10], its role has been investigated as a prognostic marker for mortality in many clinical conditions, such as cancer, kidney and cardiac diseases, people with human

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immunodeficiency virus (HIV), amyotrophic lateral sclerosis, and others [11–16].

In these contexts, Hui et al. [17] investigated the association between PA and survival in individuals with terminal cancer, where the increment of 1 degree in PA was associated with higher survival rates. Although PA has been found to be a predictor of survival in other several clinical conditions [10, 11], the literature is still heterogeneous in this regard. For instance, values below the cutoff point established by the authors in surgical heart patients (5.38°) were not considered as predictors for risk of mortality [18].

Therefore, this systematic review of the role of the PA in prognosis and his cutoffs in different clinical situations would provide an excellent tool for clinicians to assess and monitor patients' risk.

Methods

Search and selection strategy of the studies

The research was conducted between April 2016 and May 2017, using electronic databases (Pubmed, Embase, Cochrane, Lilacs, Scielo, and Scopus), with results limited to original research, with no publishing date or language restrictions. In order to do the search, a combination of the following descriptors was used in Medline: "Phase angle and (bioelectrical impedance [Mesh] or bioelectrical impedance or electric impedance [Mesh] or electric impedance or bioelectric impedance) AND (mortality [Mesh] or mortality OR death [Mesh] or death OR prognosis [Mesh] or prognosis)". Similar combinations of terms were used in the search platforms Embase and Scopus, excluding the "Mesh" terms. In the Cochrane platform, the terms used were as follows: "phase angle", "prognostic", "mortality", and "bioelectrical impedance".

The authors of studies that were only available as abstracts or that had missing information were contacted in an attempt to obtain the data.

In the first phase of the study, the papers were selected based on their titles and abstracts. The references of review papers were also analyzed in order to minimize the chances of missing studies of interest. Disagreements were assessed by a third reviewer (G.C.S.), and the Kappa index was calculated to assess the degree of agreement between both independent reviewers/researchers (L.M.G. and F.D.A.).

Eligibility criteria

The papers that were eligible included individuals with age >18 years, who presented a pathology, and that had the PA as a variable of interest, as well as a mortality/survival outcome. Studies with healthy individuals, or with no report of illness, were excluded.

Data extraction and quality assessment of the studies

The information was extracted independently by two reviewers through a pre-built spreadsheet. The extracted data included the following: references, delimitation, country of origin, study population (clinical situation, number of participants, sex, and age), total PA of the sample, follow-up time, BIA protocol used, cutoff point for the established PA, outcome analysis, number of events, and presence or absence of association with mortality. Abstracts whose relevant data quantity were available were included.

The review was conducted following the Meta-analysis of Observational Studies in Epidemiology (MOOSE) [19] directives. The quality of the papers was assessed by the Newcastle Quality Assessment Scale [20], which evaluates three cohort study domains, where a total score of 5 or less was considered of low quality; 6–7 of moderate quality, and 8–9 of high quality (see Supplementary Material).

This paper was also protocoled at the International Prospective Register of Systematic Reviews (PROSPERO), entitled as "Phase angle and prognosis in different diseases", registered under the number CRD42016039998.

Results

From the database search, a total of 455 references were identified and 94 were selected for assessment. Only one study was written exclusively in another language than English, and was appropriately translated. Besides studies written in English, articles written in two languages were also detected, one of them being English. For the extraction of data, only the English version was used. Ten were excluded because of duplicated data publishing, and 36 did not fill the eligibility criteria (Fig. 1). Nine out of the 48 observational studies were retrospectives [6, 21–28] (Table 1). There was high degree of agreement between the reviewers: $\kappa = 0.98$ ($p < 0.001$).

According to the Newcastle Quality Assessment Scale [20] for cohort studies, the majority of the papers were classified as high-quality publications, with a score above 8, indicating a low bias risk (Table 1). Two papers could not be assessed on their quality [29, 30] because of the fact that they were abstracts with scarce information for a critical analysis on sample selection, comparability, and results.

The research's result covered the following clinical situations: kidney disease [13, 21, 31–40], heart disease [14, 18, 22, 41], critically ill patient [23, 42–45], cancer [6, 12,

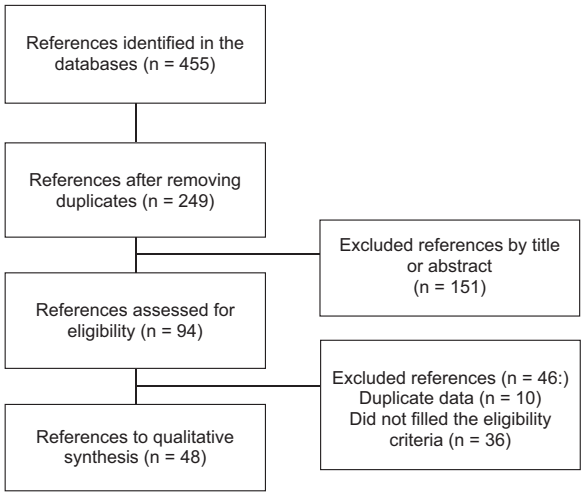

Fig. 1 Data extraction flowchart

17, 24–30, 46–51], sclerosis [16, 52–54], liver disease [5, 55–57], pulmonary disease [58], and HIV [15, 59]. The publication dates indicated that the correlation between PA and mortality has been studied for ~20 years.

A total of 11,534 individuals were included in the study. Cancer was the chronic disease that presented the highest amount of publications, totalizing 2249 participants [6, 12, 17, 24–30, 46–51] in 16 studies. Kidney disease was the second most published chronical disease, with 12 papers and 5210 individuals included in the researches [13, 21, 31–40]. Sixteen countries, the majority located on the European continent, published papers relating PA with mortality. The USA presented the highest amount of published papers: 12 publications, the majority regarding cancer (Table 1).

A lower mean of PA values (3.2 ± 1.1) [52] was found in French patients with amyotrophic lateral sclerosis, with a mean age of 63.4 ± 12 years.

The highest PA mean was observed in Abad et al. [31] (7.8° ± 1.2°) in Spanish individuals submitted to hemodialysis and peritoneal dialysis, with an average age of 61.1 ± 14.5 years. The minimum and maximum ages in the studies varied from 38.9 (HIV patients) [59] to 71 (64–77) years (chronic obstructive pulmonary disease) [58] (Table 1).

There was a higher number of male participants in 86% of the studies, especially with HIV (90.7% were male), while the female gender presented a higher prevalence in the sclerosis studies (60%; Table 1).

Regarding the BIA and PA characteristics, nine of the studies did not describe how BIA was utilized [6, 21, 29, 30, 36, 38, 53, 54, 59]. Only four studies obtained the PA value expressed by the BIA [14, 17, 31, 46], and nine did not expose the PA extraction method [15, 29, 30, 35, 37, 38, 44, 50, 57]. All other researches obtained the value through calculation involving R and Xc.

The most used brand was RJL Systems, tetrapolar model with 50 kHz frequency, and 800 mA, as seen in 20 papers [5, 17, 21, 22, 25–27, 33–35, 37–41, 46, 51, 56, 57, 59]. There were four studies, two abstracts [29, 30], and two full papers [6, 48] that did not mention the BIA brand used (Table 1).

The majority of the papers established PA cutoff points, in order to relate it to mortality through the analysis of survival, receiver operating curve (ROC), or multivariate regression, with the exception of 13 studies [12, 16, 23, 24, 29, 34, 36, 37, 46, 48, 49, 54, 58]. The highest variation observed on the PA cutoff points established for mortality was regarding kidney disease: 3.6° to ≤8° [31, 35]. The category that presented less variation in the cutoff point was HIV: <5.3° to <5.6° [15, 59]. There was a variation of < 4.2° to < 5.5° [22, 41] in heart disease, 4.1° to <6° [44, 45] in critically ill patient, <4.4° to <5.8° [47, 50] in cancer, <2.5° to ≤3.9° [52, 53] in sclerosis, and <4.4° to ≤5.2° [5, 56] in liver disease. The PA cutoff point was not determined for chronic obstructive pulmonary disease [58] (Table 2).

The most used measures of association to determine the correlation between PA and mortality were relative risk (RR) and hazard ratio (HR). In kidney disease, the increment of 1 degree in PA showed an association with survival in four studies with kidney disease patients [13, 21, 32, 36], whose HR varied from HR 0.390 (95% CI 0.267–0.570) [36] to HR 0.737 (0.557–0.975) [21]. The highest RR registered was 20 in individuals in chronic hemodialysis with PA≤4.8°, when compared to a PA of 6.5° [39] (Table 2).

In cardiopathic patients, the study performed on acute decompensated heart failure showed a risk of mortality associated with PA < 4.8° of RR 2.67 (95% CI 1.21–5.89, $p = 0.015$) [14]. The RR observed in heart failure was 3.08 (95% CI 1.06–8.99, $p < 0.0001$) for individuals whose PA was lower than 4.2° in comparison to PA higher than 5.7° [22]. There was another research with congestive heart failure individuals, but it did not evidence differences in survival rates among the ones whose PA was lower than 5.5°, compared to those who had higher values through the Kaplan–Meier analysis ($p = 0.13$) [41]. In cardiac surgical patients, a PA lower than 5.38° was not associated with a higher chance of mortality (OR 2.49, 95% CI 0.45–13.67, $p = 0.294$) [18] (Table 2).

In critically ill patients, differences were found between the PA of living and deceased in one of the studies performed with septic shock patients ($p = 0.01$) [44] and individuals admitted to the ICU ($p < 0.01$) [23]. Another study [45] showed that the increment in 1 degree in PA was associated with protection against mortality (OR 0.86, 95% CI 0.78–0.96) [45]. The rest of the papers did not present any difference between PA of living and deceased [42, 43] (Table 2).

Table 1 Characteristics of the studies included in the systematic review

Reference	Delimitation	Country	Population/*n*	BIA brand	PA (degrees)	Age (years)	Gender (male)	Follow-up time	Peculiarity/	Publication quality scores[a]
Kidney disease										
Abad et al., 2011[31][b]	Observational prospective	Spain	HD: 127 PD: 37	Bioscan	7.8 ± 1.2	61.1 ± 14.5	60.3%	37 ± 24 months	54 Patients with previous kidney Tx	8
Beberashvili et al., 2014 [13]	Observational prospective	Israel	Maintenance HD: 250	Nutriguard-M	4.7 ± 1.3	68.7 ± 14	58.4%	17 (9–24) months	6 Tx kidney TX occurred during the study	8
Caravaca et al., 2011[32][b]	Prospective	Spain	Advanced CKD: 175	Fresenius	5.4 ± 1	66 ± 14	56%	16 (14–17) months		7
Chertow et al., 1997 [33]	Analytical cohort	USA	HD: 2990	RJL Systems	4.8 ± 1.8	60.5 ± 15.5	52.8%	2 Days–18 months		8
Di Iorio et al., 2004 [34]	Observational prospective	Italy	HD: 515	RJL Systems	NR	63.6 ± 15.3	61.3%	15 Months		8
Dumler et al., 2010 [35]	Observational prospective	USA	HD: 205 PD: 80	RJL Systems	NR	62 ± 14	59%	18 Months		7
Koh et al., 2011 [36]	Prospective	Malaysia	PD: 128	Bioscan	4.7	48 ± 1.2	47%	26–27 Months	322 Healthy controls	8
Maggiore et al., 1996 [37]	Prospective	Italy	HD: 131	RJL Systems	4.2 ± 1 (pre-HD)	62.5 ± 13.6	49.6%	27 ± 9 Months	272 Healthy controls	8
Mushnick et al., 2003 [38]	Prospective	USA	PD: 48	RJL Systems	6.2 ± 1.6	51 ± 15	42%	51 ± 44 Months		8
Pupim et al., 2004 [39]	Prospective cohort	USA	Chronic HD: 194	RJL Systems	5.4 ± 1.7 (basal)	56 ± 15	53.1%	36 (3–57) Months	Cardiac arrest	8
Rodrigues et al., 2014 [21]	Retrospective	Portugal	HD: 181	RJL Systems	5.6 ± 1.2	65.8 ± 12	54.7%	57 ± 29 Months		8
Segall et al., 2009 [40]	Cohort	Romania	HD: 149	RJL Systems	6.7 ± 4.8	54 ± 14	55%	13 ± 1.5 months		8
Heart disease										
Alves et al., 2016 [14]	Cohort	Brazil	ADHF: 59	Biodynamics	5.6 ± 2	61 ± 12	63%	24 Months	Hospitalized patients	8
Colín-Ramírez et al., 2012 [22]	Retrospective	USA	HF: 389	RJL Systems	NR	NR	54%	36 Months	Outpatients	8
Doesch et al., 2010 [41]	Prospective	Germany	CHF: 41	RJL Systems	5.5	63 ± 12	88%	60 Months	16 Healthy controls; cardiac arrest	7
Visser et al., 2012 [18]	Prospective cohort	Netherlands	Surgical heart patients: 325	Fresenius	5.9 ± 1	66.2 ± 10	72.3%	NR	Admitted patients for myocardial revascularization and/or extracorporeal circulation; phase angle measurement prior to surgery	7

Table 1 (continued)

Reference	Delimitation	Country	Population/*n*	BIA brand	PA (degrees)	Age (years)	Gender (male)	Follow-up time	Peculiarity/	Publication quality scores[a]
Critically ill patient										
Berbigier et al., 2013 [42][b]	Cohort	Brazil	Septic patients: 50	Biodynamics	5.4 ± 2.6	65.6 ± 16.5	58%	28 Days	Admitted to the ICU for at least 72 h	7
Da Silva et al., 2015 [43]	Cohort	Brazil	Admitted to the ICU: 95	Biodynamics	4.9 ± 1.4	63.7 ± 14.6	63.1%	28 Days	45 Septic patients	7
Díaz-De Los Santos et al., 2010 [44][c]	Longitudinal analytical	Peru	Septic shock: 30	Body Stat	5.3 ± 1.8	60 ± 21	60%	8 ± 6 Days (time at ICU)		7
Lee et al., 2015 [23]	Retrospective	Korea	Admitted to the ICU: 66	Inbody	NR	63.1 ± 15.7	63.6%	NR	Multicentric; 10 involved centers	7
Thibault et al., 2016 [45]	Prospective	France	Admitted to the ICU: 931	Nutriguard-M	4.5° ± 1.9°	61 ± 16	60%	28 Days		8
Cancer										
Büntzel et al., 2012 [24]	Retrospective	Germany	Head and neck radiotherapy: 66	Biacorpus	NR	67.7 (49–89)	75.7%	NR	Oropharyngeal ca (18), hypopharyngeal ca (13), others (35)	7
Davis et al., 2009 [46]	Observational prospective	USA	Advanced Ca: 50	RJL Systems	NR	63 ± 12	80%	2 Months	During hydration in pancreatic ca (6), lung ca (6), breast ca (6), myeloma (4), kidney ca (3), colon ca (3), and gastric ca (3)	7
Generoso et al., 2014 [29]	Observational	Brazil	Surgical ca patients: 77	NR	NR	61.1 ± 11.7	53.2%	NR	Hn and GIT ca	—
Gupta et al., 2004 [25]	Retrospective	USA	Advanced colorectal ca: 52	RJL Systems	5.6 ± 1.5	55.8 ± 10.8	57.7%	50 Months		7
Gupta et al., 2004 [26]	Retrospective	USA	Advanced pancreatic ca: 58	RJL Systems	5.3 ± 1.5	56.2 ± 10.7	60.3%	50 Months		7
Gupta et al., 2008 [27]	Retrospective	USA	Breast ca: 259	RJL Systems	5.6– (1.5–8.9)	49 (27–74)	0%	70 Months		7
Gupta et al., 2009 [6]	Retrospective	USA	Lung ca: 165	NR	5.3 (2.9–8)	56 ± 9	56%	70 Months	Small cell ca stages IIIB (61) and IV (104)	7
Hui et al., 2014 [17]	Prospective	USA	Terminal ca: 222	RJL Systems	4.4 (3.5–5.3)	55 (22–79)	41%	4 (1–8) months	Hospitalized patients. Breast ca (28), GIT ca (73), genitourinary ca (19), gynecological ca (24), hn ca (11), hematological ca (12), respiratory ca (36), and others (19)	8
Hui et al., 2017 [28]	Retrospective	USA	Terminal ca: 366	Inbody	4.4 ± 1	58 (21–90)	54%	50 Months	Outpatients Breast ca (50), GIT ca (111), genitourinary ca (20), gynecological ca (34), hn ca (48), hematological ca (8), respiratory ca (40), and others (55)	8

Table 1 (continued)

Reference	Delimitation	Country	Population/*n*	BIA brand	PA (degrees)	Age (years)	Gender (male)	Follow-up time	Peculiarity/	Publication quality scores[a]
Lee et al., 2014 [47]	Observational prospective	Korea	Advanced ca: 28	Byodinamics	4.5 (1.8–6.5)	54% > 70 Years	46.4%	4 Months	GIT ca (11), lung ca (3), hematological ca (3), kidney ca (3), and others (8)	8
Santarpia et al., 2009 [48]	Cohort	Italy	Advanced ca: 13	NR	4.84 (2.86–5.91)	58.4 ± 7.5	46.1%		Colorectal ca (3), gastric ca (5), esophageal ca (2), pancreatic ca (2), and pulmonary ca (1)	6
Martin et al., 2016 [49]	Prospective	Sweden	PEG: 131	BodyScout	4.8	NR	65%	60 Days	83% Individuals with ca	—
Norman et al., 2015 [12]	Prospective	Germany	Elderly with ca: 428	Nutriguard-M	4.4 ± 1	69.7 ± 6.1	56.1%	12 Months		8
Sánchez-Lara et al., 2012 [50]	Prospective	Mexico	Lung ca: 119	Bodystat	5.8 ± 1.8	60.5 ± 12.5	46.2%	6 ± 5 months	Non-small cell ca	8
Skowronek et al., 2014 [30]	Prospective	Germany	Ovarian ca patients and peritoneum surgery: 152	NR	NR	56 (19–84)	NR	NR		—
Toso et al., 2000 [51]	Observational	Italy	Lung ca: 63	RJL Systems	IIIB: 4.7 ± 1.5 IV: 4.4 ± 1.3	NR	100%	18 Months	Ca stages IIIB (33) and IV (30); 56 healthy controls	8
Sclerosis										
Desport et al., 2008 [52]	Prospective	France	ALS: 168	Analycor	3.2 ± 1	63.4 ± 12	NR	23 ± 17 Months		8
Krause et al., 2010 [53]	Prospective	Germany	Systemic: 124	BIA 2000-M	4.7 ± 0.9	54.3 ± 13.2	16%	35 ± 7 Months	2295 Healthy controls	8
Marin et al., 2011 [54]	Prospective	France	ALS: 92	Analycor	3.4 (2.6–4.3) On the day of diagnosis	66 (56.5–73)	46%	18 Months		7
Robeau et al., 2015 [16]	Prospective	France	ALS: 117	Bodystat	4 ± 1.8	64 ± 11	57%	16 ± 18 Months		8
Liver disease										
Belarmino et al., 2017 [55]	Prospective	Brazil	Cirrhosis: 134	Bodystat	NR	54.3 ± 10.1	100%	25 Months		8
Peres et al., 2012 [56][b]	Transversal	Brazil	Patients with liver disease: 66	RJL Systems	5.2 (1.9–8.4)	59 (41–79)	58%	17 Months	Individuals with chronic hepatitis, cirrhosis, and hepatocellular carcinoma	8
Ruiz- Margáin et al., 2015 [57]	Cohort	Mexico	Cirrhosis: 249	RJL Systems	5 ± 1.1	NR	NR	33.5 (8–48) Months	Divided between well-nourished and malnourished	8

Table 1 (continued)

Reference	Delimitation	Country	Population/*n*	BIA brand	PA (degrees)	Age (years)	Gender (male)	Follow-up time	Peculiarity/	Publication quality scores[a]
Selberg et al., 2002 [5]	Prospective	Germany	Cirrhosis: 305	RJL Systems	NR	NR	53%	24 Months		7
Pulmonary disease										
Maddocks et al., 2015 [58]	Prospective	England	DPOC: 502	Bodystat	NR	71 (64–77)	58.7%	16 (4–23) months		8
HIV										
Ott et al., 1995 [59]	Prospective	Germany	HIV: 75	RJL Systems	5.8 ± 0.6	38.9	100%	33 Months		8
Schwenk et al., 2000 [15]	Cohort	England	HIV: 257	BIA 2000-M	NR	40 ± 10	85%	20 Months		8

Data described as mean and s.d. or median and interquartile range

PA phase angle, *HD* hemodialysis, *PD* peritoneal dialysis, *Tx* transplant, *CKD* chronic kidney disease, *ADHF* acute decompensated heart failure, *HF* heart failure, *CHF* congestive heart failure, *ICU* intensive care unit, *Ca* cancer, *hn* head and neck, *GIT* gastrointestinal tract, *PEG* percutaneous endoscopic gastrostomy, *ALS* amyotrophic lateral sclerosis, *COPD* chronic obstructive pulmonary disease, *HIV* human immunodeficiency virus, *NR* not reported

[a]Publication quality for cohort studies: Newcastle Quality Assessment Scale [20]

[b]Article available in two languages, one of them being English. The data were extracted from the articles in the English version

[c]Article available in Spanish, appropriately translated

For patients with cancer, the most expressive RR value was 10.75 (95% CI 1.92–60.24, $p = 0.007$) in individuals with PA lower or equal to 5.57° with advanced colorectal cancer. Those individuals presented an average survival of 8.6 months, while in those with PA above 5.57° the average survival was 40.4 months [25]. In a study whose subjects were composed predominantly by cancer patients submitted to percutaneous endoscopic gastrostomy, the authors did not observe associations between mortality and PA (OR 0.93, 95% CI 0.37–2.37) [49] (Table 2).

On the studies performed with individuals with amyotrophic lateral sclerosis, only one paper did not find any correlation to the outcome (HR 1.27, 95% CI 0.92–1.75) [54]. In systemic sclerosis, the difference between PA values lower or equal to 3.9° and higher or equal to 5° was significant ($p < 0.001$) [53] (Table 2).

In patients with liver disease, the measure of association used among the studies was HR, with similar values that indicate the correlation between PA and mortality [5, 55–57]. In the research performed with chronic obstructive pulmonary disease patients, the highest number of deaths occurred in individuals with low PA (8.2% vs. 3.6%, $p = 0.02$) [58]. One study on HIV found differences between PA from dead and alive ($p < 0.0001$) [59], and another indicated that the increment of one degree in PA might be a protection factor (HR 0.33, 95% CI 0.18–0.61) [15] (Table 2).

There were 42 studies that verified the existence of a correlation between PA and mortality: in all researches performed on kidney disease [13, 21, 31–40], liver disease [5, 55–57], chronic obstructive pulmonary disease [58], and HIV [15, 59], low PA values showed a correlation with mortality, and high values with survival. An amount of 2100 death were reported (27.4%) among the 7651 individuals. Eight papers did not mention their number of events [16, 17, 30, 33, 46, 48, 50, 51]. Sclerosis was the disease with the highest percentage of deaths (54%), although one study did not present their numbers [16]. Cancer was also a disease that evidenced a high number of deaths (43.7%) reported in 10 papers [6, 12, 24–29, 47, 49].

Discussion

This review was conducted with the goal to assess, systematically, the correlation between PA and mortality, as most of the studies showed such association. PA reflects the electrical unit of the tissues, where a lower value would be associated with the reduction of the cell integrity or even to cell death, while higher values would correspond to whole cell membranes, indicating an adequate health state [1, 5, 6].

In kidney disease [13, 21, 31–40], liver disease [5, 55–57], chronic obstructive pulmonary disease [58], and HIV patients [15, 59], 100% of the studies showed an association between PA and mortality. The findings on patients with kidney disease, liver disease, and HIV seropositive indicates that PA can be useful to predict mortality and were consistent with the findings exposed by Kyle et al. [3]. Specifically, in renal hemodialysis patients, the study of Beberashvili et al. [10] identified inverse longitudinal changes in PA and IL-6, showing that changes in PA have independent associations with changes in inflammatory parameters over time and consequently with long-term survival in these patients. Author's concluded that PA appears to be reliable in detecting changes in nutritional and inflammatory parameters over time, which, in turn, could contribute to the understanding of its prognostic utility. Besides that, our review includes a higher number of clinical situations, revealing potential associations between PA and mortality.

The studies performed on cardiopathic patients [14, 18, 22, 41], critically ill patients [42, 45], cancer [6, 12, 17, 24–30, 46–51], and sclerosis [16, 52–54] obtained discordant results. In the study with decompensated heart failure patients, the authors did not find any association between PA values and mortality, pointing out the small sample size [41] as a limitation factor, which might have interfered on the Kaplan–Meier analysis. Visser et al. [18] performed a study with a considerable big sample of surgical heart patients, but only 2.7% of the individuals died. The mentioned limitations are due to the fact that elderly individuals who had a higher risk of surgical complications were less willing to participate on the research, and 8% of the sample presented hydroelectrolytic disorders, which could overestimate the PA value, since it reflects the reason between membrane capacity (Xc) and tissue water amounts (R) [60].

On the other hand, the studies on individuals with compensated heart failure and acute decompensated heart failure found association with mortality with similar cutoff points, 4.2° (RR 3.08; 95% CI 1.06–8.99, $p < 0.0001$) [22] and 4.8° (HR 2.67; 95% CI 1.21–5.89, $p = 0.015$) [14], respectively. Nevertheless, the authors warn for the limitations of the study, such as the lack of hemodynamic assessments, and sample size, which might interfere in the results, making it impossible to extrapolate for other individuals with that condition.

The critical illness covers a series of clinical or surgical features with different metabolic responses, which might be fatal in intensive care units (ICUs) [61]. In a sample composed exclusively of septic individuals [42] and another of severe patients admitted to the ICU [43], the authors did not find any difference between the PA of deceased and survivals. Still, Díaz-De Los Santos et al. [44] observed a correlation between PA < 6° and mortality in individuals with septic shock, as well as Lee et al. [23], who observed a significant difference between the PA from individuals

Table 2 Risk of mortality associated with phase angle in different clinical situations

Author, year	Population	Outcome analysis	# Of events/total participants	Association with the outcome
Kidney disease				
Abad et al., 2011 [31]	HD, DP	PA >8° vs. PA 5-6°—Kaplan–Meier, $p < 0.00$; cutoff point: ≤8°	100/164	Yes
Beberashvili et al., 2014 [13]	Maintenance HD	↑ 1° In baseline PA HR 0.63 (CI 95% 0.48–0.81), $p < 0.001$; cutoff point: ≤4° (lowest tercile)	64/250	Yes
Caravaca et al., 2011 [32]	Advanced KCD	↑ 1° In PA HR: 0.491 (CI 95% 0.263–0.917), p 0.026; cutoff point: <5.3°	16/175	Yes
Chertow et al., 1997 [33]	HD	PA < 3°, RR = 2.2 (CI 95% 1.6–3.1) (compared to PA ≥4°); cutoff point: <4°	NR	Yes
Di Iorio et al., 2004 [34]	HD	↓ 1° PA RR = 2.5, $p = 0.043$; cutoff point: NR	75/515	Yes
Dumler et al., 2010 [35]	HD, PD	Mortality rate of the lowest tercile significantly differed of the highest $p <$ 0.05; cutoff point: 3.6° (lowest tercile)	104/285	Yes
Koh et al., 2011 [36]	PD	↑ 1°PA HR 0.390 (CI 95% 0.267–0.570), $p < 0.001$; cutoff point: NR	35/128	Yes
Maggiore et al., 1996 [37]	HD	Lowest quartile vs. highest quartile, RR = 2.6 (CI 95% 1.6–4.2); cutoff point: NR	23/131	Yes
Mushnick et al., 2003 [38]	PD	PA > 6°, RR = 0.39, $p = 0.027$; cutoff point: < 6°	8/48	Yes
Pupim et al., 2004 [39]	Chronic HD	PA ≤ 4.8°, RR = 20, $p < 0.001$ (compared to PA ≥ 6.5°); cutoff point: ≤4.8°	50/194	Yes (cardiovascular death)
Rodrigues et al., 2014 [21]	HD	↑ 1° in PA HR 0.737 (CI 95% 0.557–0.975), $p < 0.05$; cutoff point: <4.9°	96/181	Yes
Segall et al., 2009 [40]	HD	PA < 6°, RR 4.12 (CI 95% 1.09–15.53), $p = 0.036$; cutoff point: 6°	11/149	Yes
Heart disease				
Alves et al., 2016 [14]	ADHF	PA < 4.8°, HR = 2.67 (CI 95% 1.21–5.89), p 0.015; cutoff point: <4.8°	29/59	Yes
Colín-Ramírez et al., 2012 [22]	HF	PA < 4.2°, RR = 3.08 (IC 95% 1.06–8.99), $p < 0.0001$ (compared to PA > 5.7°); cutoff point: < 4.2°	66/389	Yes
Doesch et al., 2010 [41]	CHF	Kaplan–Meier (cutoff point < 5.5°), $p = 0.13$; cutoff point: <5.5°	8/41	No (cardiac arrest)
Visser et al., 2012 [18]	Surgical heart patients	PA < 5.38°, OR = 2.49 (CI 95% 0.45–13.67), $p = 0.294$; cutoff point: <5.4°	9/325	No
Critically ill patient				
Berbigier et al., 2013 [42]	Septic patients	There was no difference between the PA of diseased and survivors, $p =$ 0.76; cutoff point: 5°	15/50	No
Da Silva et al., 2015 [43]	Admitted to the ICU	There was no difference between the PA of diseased and survivors, $p =$ 0.508; cutoff point: <5.1°	15/95	No
Díaz-De Los Santos et al., 2010 [44]	Septic shock	There was correlation between PA < 6° and mortality, $p = 0.01$; cutoff point: <6°	15/30	Yes
Lee et al., 2015 [23]	Admitted to the ICU	Significant difference between PA of diseased and survivors, $p < 0.01$; cutoff point: NR	8/66	Yes
Thibault et al., 2016 [45]	Admitted to the ICU	↑ 1° in PA OR = 0.86 (CI 95% 0.78–0.96), p 0.008; cutoff point: 4.1°	180/931	Yes
Cancer				
Büntzel et al., 2012 [24]	Head and neck radiotherapy		39/66	Yes

Table 2 (continued)

Author, year	Population	Outcome analysis	# Of events/total participants	Association with the outcome
		Survivors showed PA stabilization (4.7°–5.2°) compared to diseased ones (4.6°–3.7°), $p < 0.05$; cutoff point: NR		
Davis et al., 2009 [46]	Advanced ca	PA changes during hydration HR: 1.2 (CI 95% 1.06–1.4), $p = 0.007$; cutoff point: NR	NR	Yes
Generoso et al., 2014 [29]	Surgical ca patients	Significant difference between PA of diseased and survivors, $p = 0.001$; cutoff point: NR	2/77	Yes
Gupta et al., 2004 [25]	Advanced colorectal ca	PA ≤ 5.57°, RR = 10.75 (CI 95% 1.92–60.24) $p = 0.007$; cutoff point: ≤5.6°	24/52	Yes
Gupta et al., 2004 [26]	Advanced pancreatic ca	↑ 1° PA, RR = 0.69 (CI 95% 0.49–0.97), $p = 0.03$; cutoff point: 5°	42/58	Yes
Gupta et al., 2008 [27]	Breast ca	↑ 1° PA, RR = 0.82 (CI 95% 0.68–0.99), $p = 0.041$; cutoff point: ≤ 5.6°	85/259	Yes
Gupta et al., 2009 [6]	Lung ca	↑ 1° PA, RR = 0.79 (CI 95% 0.64–0.97), $p = 0.02$; cutoff point: ≤ 5.3°	111/165	Yes
Hui et al., 2014 [28]	Advanced ca	↑ 1° PA, RR = 0.86 (CI 95% 0.74–0.99), $p = 0.04$; cutoff point: ≤ 4.4°	142/222	Yes
Hui et al., 2017 [17]	Advanced ca	↑ 1° PA, RR = 0.85 (CI 95% 0.72–0.99), $p = 0.048$; cutoff point: ≤ 4.5°	NR	Yes
Lee et al., 2014 [47]	Advanced ca	↑ 1° PA, RR = 0.64 (CI 95% 0.42–0.95), $p = 0.028$; cutoff point: < 4.4°	22/28	Yes
Santarpia et al., 2009 [48]	Advanced ca	PA strictly related to survival time ($R^2 = 0.384$, $p = 0.024$); cutoff point: NR	NR	Yes
Martin et al., 2016 [49]	PEG	Decrease in PA was not associated to risk of mortality (OR 0.93, CI 95% 0.37–2.37); cutoff point: NR	7/131	No
Norman et al., 2015 [12]	Elderly with ca	PA below the reference percentile HR = 2.1 (CI 95% 1.4–3.09), $p <$ 0.0001; cutoff point: NR	175/428	Yes
Sánchez-Lara et al., 2012 [50]	Lung ca	PA ≤ 5.8°, RR = 3.02 (CI 95% 1.2–7.11), $p = 0.011$; cutoff point: <5.8°	NR	Yes
Skowronek et al., 2014 [30]	Ovarian ca and peritoneum surgery patients	PA ≤ 4.5°, HR = 2.88 (CI 95% 1.60–5.19), $p < 0.001$; cutoff point: ≤4.5°	NR	Yes
Toso et al., 2000 [51]	Lung ca	PA ≤ 4.5°, OR = 1.25 (CI 95% 1.01–1.55), $p = 0.04$; cutoff point: ≤ 4.5°	NR	Yes
Sclerosis				
Desport et al., 2008 [52]	ALS	↑ 1°PA HR = 0.80 (CI 95% 0.65–0.98), $p = 0.03$; cutoff point: < 2.5°	115/168	Yes
Krause et al., 2010 [53]	Systemic sclerosis	PA ≤ 3.9° and PA ≥ 5 °—Kaplan–Meier, $p < 0.001$; cutoff point: <3.9° (lowest tertile)	11/111	Yes
Marin et al., 2011 [54]	ALS	↓ 1°PA HR = 1.27 (CI 95% 0.92–1.75), $p = 0.15$; cutoff point: NR	74/92	No
Robeau et al., 2015 [16]	ALS	↓ 1°PA HR = 2.39 (CI 95% 1.12–5.13), $p = 0.022$; cutoff point: NR	NR	Yes
Liver disease				
Belarmino et al., 2017 [55]	Cirrhosis	PA <4.9°, HR = 2.05 (CI 95% 1.11–3.77), $p = 0.021$; cutoff point: ≤4.9°	48/134	Yes
Peres et al., 2012 [56]	Patients with liver disease	PA ≤ 5.18°, HR = 2.5 (CI 95% 1.85–6.01), $p = 0.032$; cutoff point: ≤ 5.2°	37/66	Yes
Ruiz- Margáin et al., 2015 [57]	Chronic cirrhosis	PA ≤ 4.9°, HR = 2.15 (CI 95% 1.18–3.92), $p = 0.024$; cutoff point: ≤ 4.9°	62/249	Yes

Table 2 (continued)

Author, year	Population	Outcome analysis	# Of events/total participants	Association with the outcome
Selberg et al., 2002 [5]	Cirrhosis	PA 5.4° vs. 6.6°, Kaplan–Meier, $p < 0.001$; cutoff point: <4.4°	113/305	Yes
Pulmonary disease				
Maddocks et al., 2015 [58]	COPD	The proportion of individuals who died was significantly higher among those with ↓ PA, comparing to normal PA (8.2% vs. 3.6%), $p = 0.02$; cutoff point: NR	25/502	Yes
HIV				
Ott et al., 1995 [59]	HIV	Significant difference between PA of diseased and survivors, $p = 0.0001$; cutoff point: <5.6°	29/75	Yes
Schwenk et al., 2000 [15]	HIV	↑ 1° PA, HR = 0.33 (CI 95% 0.18–0.61); cutoff point: <5.3°	10/257	Yes

PA phase angle, *HR* hazard ratio, *RR* relative risk, *OR* odds ratio, *CI* confidence interval, *HD* hemodialysis, *PD* peritoneal dialysis, *CKD* chronic kidney disease, *ADHF* acute decompensated heart failure, *HF* heart failure, *CHF* congestive heart failure, *ICU* intensive care unit, *Ca* cancer, *ALS* amyotrophic lateral sclerosis, *COPD* chronic obstructive pulmonary disease, *PEG* percutaneous endoscopic gastrostomy, *HIV* human immunodeficiency virus, *NR* not reported

admitted to the ICU who died and those who survived. In addition, Thibault et al. [45] found that the increment of one degree in PA is associated with a higher survival rate. It was observed that, in both studies performed with septic patients and the ones admitted to the ICU, those who did not demonstrate correlation between the outcome had higher average age. Furthermore, it is important to emphasize that critically ill individuals have a wide diversity regarding clinical condition [62].

The studies on cancer, however, covered different types of the disease, such as breast [27], lung [6, 50, 51], and pancreatic cancer [26]. Although the majority of those researches (94%) were indicating association between the lower PA values and mortality, Martin et al. [49], who assessed PA as a prognostic marker for mortality on patients submitted to percutaneous endoscopic gastrostomy, did not find an association between low PA values and mortality. They did find it in inflammatory markers and low albumin levels. The authors discuss a possible selection bias due to the fact that it was a convenience sample, with a tendency to include individuals with better health conditions. It should also be noted that, although this study had been included in such category, 17% of the sample did not suffer from cancer, and the period of the following was short (60 days), with only 5% of death during the study.

In this review, we noticed that only one paper did not favor PA as a prognostic marker for amyotrophic lateral sclerosis (HR 1.27; 95% CI 0.92–1.75, $p = 0.15$) [54]. Since it is a severe disease, which progressively degenerates the upper and lower motor neurons, there is a variability of period in survival of those individuals related to clinical phenotypes. However, the average survival period is of ~35 months [63]. It is necessary to consider that, during the following of the aforementioned study, 80% of the sample died, with an average PA of 3.4° (2.6–4.3°) [54]. Furthermore, it is known that factors such as advanced age at the beginning of the disease, early respiratory failure, malnutrition, and bulbar-onset disease are associated with a reduction on survival [63], which can interfere on the results, since this study had the highest average age sample. Regarding systemic sclerosis, a severe condition characterized by inflammation and fibrosis [64], only one paper verified the relation between PA and mortality, finding association with the outcome [53].

The studies on kidney disease patients presented the highest numerical variation on cutoff points established for PA (3.6°–8°) [31, 35], and the lowest variation between cutoff points were proposed for HIV (5.3°–5.6°) [15, 59]. According to Bosy-Westphal et al. [65], the prognostic values for PA in distinct clinical conditions are not possible, because of different implications of specific diseases over the cell mass, cell membrane integrity, and hydration. For instance, there can be a major correlation between PA and liver disease, while the

same will not occur in patients with metabolic syndrome when compared to a healthy control group.

Factors such as age, gender, and ethnicity are used as determinants for PA and might have implications in divergences of the observed results. Advanced age, as well as female gender, are related to a lower PA [1, 3, 66, 67]. The safety of the results also depends on previous care, as directed by the European Society for Clinical Nutrition and Metabolism (ESPEN). These previous cares include the performance of the BIA examination with the individual in decubitus position and with no contact with any metallic surface; fasting (no liquid or food ingestion between 4 and 6 h prior to the examination); no physical activities 8 h prior to the examination; and the analysis performed at the same daytime in longitudinal studies, among other recomendations [3, 68].

In the studies included in this review, the majority described the position of the individual and the electrodes during the test, and only five papers reported preparatory fasting for the participants' examination [14, 39, 56–58]. In order to optimize the results of the BIA analysis, it is necessary to use a method standardized by universal protocols, since conditions such as food and liquid ingestion, position of the subject, and physical exercise prior to the examination can alter the examined parameters [3].

In our review, we sought to assess the correlation between PA and mortality, synthetizing the results and features found on those papers, in order to aid for a better comprehension about what is available nowadays regarding the subject. In accordance to Norman et al. [11], our results indicate that PA is a raw measurement with good prognostic capability, and can be considered a tool for tracking individuals in nutritional and functional risk.

As PA is influenced by gender and age [1, 67], more studies establishing cutoff points associated with mortality, stratified for those variables, are necessary. The strengths of this review that should be taken into account are the number of included papers, as well as the number of participants and the diversity of the database where the search for the studies took place, encompassing what is presented in the literature regarding this subject.

The limitations of the review include clinical and statistical heterogeneity of the studies, most of them constrained by a small sample size, without a description of withdrawal of patients. Methodological differences, such as the heterogenicity of BIA equipment and performance, suggest that the results must be interpreted within the context of these limitations. On the other hand, the heterogeneity of those papers allowed a study such as ours to have a wider scope on the use of PA.

Still, it does not seem viable, until this moment, to extrapolate the cutoff points verified among the studies to the clinical practice, since the papers differ in sample characteristics, geographical location, and the BIA equipment used. Thus, there is a necessity for other well-designed studies involving big cohorts, in order to establish a specific cutoff point for each type of condition.

Conclusion

On the basis of the information gathered from the analyzed studies in this review, the evidence on the correlation between PA and mortality are substantial, especially regarding kidney disease and cancer. Although the HIV and liver disease papers appeared in smaller quantities, they are equally conclusive about this association. Even in clinical situations where there is a certain discordance, there are strong indications of association between the decreased values of PA and mortality. In order to use PA as a prognostic indicator in the aforementioned clinical situations, it is necessary to expand those studies, seeking also associations with other parameters over time and which could contribute to the understanding of the use of PA as a prognosis in the most diverse clinical situation. PA seems to be a good prognostic marker for mortality, offering an option for tracking individuals more susceptible to such outcome.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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