Clinical Nutrition xxx (xxxx) xxx

Contents lists available at ScienceDirect

Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

Meta-analyses

Bioelectrical impedance analysis (BIA) -derived phase angle in sarcopenia: A systematic review

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ARTICLE INFO

Article history:
Received 25 June 2020
Accepted 23 October 2020

Keywords:
Bioimpedance analysis
Phase angle
Sarcopenia
Muscle mass
Muscle strength
Survival

SUMMARY

Background & aims: Bioelectrical impedance analysis-derived phase angle (PhA) has been gaining attention in the clinical evaluation of nutritional status because it is thought to be a proxy of water distribution and body cell mass; it is also associated to muscle strength and is an effective predictor of different clinical outcomes. Since an association may be expected between PhA and sarcopenia (defined by low skeletal muscle mass and impaired muscle function), the aim of this systematic review was to evaluate: a) changes in PhA due to sarcopenia; b) prevalence of sarcopenia according to PhA values; c) derivation of phase angle cut-offs for detecting sarcopenia; d) sarcopenia and PhA as predictors of clinical outcomes.

Methods: A systematic research on electronic databases (PubMed, Embase, Scopus and Web of Science) from inception to January 31st, 2020 was performed according to PRISMA checklist. Using PICOS strategy, "P" corresponded to participants of any age, gender or ethnicity, "I" designated diagnosis of sarcopenia, "C" indicated subjects without sarcopenia, "O" corresponded to PhA, and "S" selected all study types. Methodological quality was assessed using the National Institute of Health (NIH) quality assessment tool.

Results: Through the initial literature search and after removing duplicates and excluding papers by screening titles and abstracts, 79 potentially relevant studies were examined. Thirteen studies (7668 subjects) met the inclusion criteria. The overall risk of bias was low. Sarcopenia was associated with a significant lower PhA in seven studies out of eight, while five studies out of six reported a high prevalence of sarcopenia was in patients with low PhA. Different cut-off point values from 4.05 to 5.05° have been derived for the identification of sarcopenia. PhA and sarcopenia were independent predictors of survival in cancer patients and geriatric hospitalized patients.

Conclusions: Data from the selected papers demonstrate that PhA is decreased in sarcopenic subjects and the prevalence of sarcopenia is higher in subjects with low PhA. Further studies are needed to determine to what extent PhA may be valuable in detecting low muscle quality and/or identifying sarcopenia.
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1. Introduction

The evaluation of nutritional status and physical fitness plays an important role in performing a multidimensional, interdisciplinary assessment and in preventing malnutrition or sarcopenia in the elderly, as well as in rehabilitation programmes and nutrition care process [1–3]. In the clinical setting, the use of simple and reliable markers of nutritional status and muscle function may be helpful in detecting different nutritional phenotypes in both community-dwelling elderly individuals and in those suffering from acute/chronic diseases [3–5].

Bioelectrical impedance analysis (BIA) is a widely used, simple and non-invasive field method [6] for assessing body composition, which evaluates the electrical characteristics (i.e. impedance = Z and phase angle = PhA) of human body. Regarding body compartments, fat-free mass (FFM), skeletal muscle mass (SM) or appendicular skeletal mass (ASM) can be estimated by means of predictive equations including BIA variables and almost always age, stature and weight [7,8]. Such estimates of body composition are used for the diagnosis of sarcopenia [9–11] and/or malnutrition [12]. Indeed, it has been suggested that equations and cut-off values should be selected taking into consideration that BIA equations and cut-off values may be population and device-specific [11,13,14].

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https://doi.org/10.1016/j.clnu.2020.10.048
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Please cite this article as: O. Di Vincenzo, M. Marra, A. Di Gregorio *et al.*, Bioelectrical impedance analysis (BIA) -derived phase angle in sarcopenia: A systematic review, Clinical Nutrition, https://doi.org/10.1016/j.clnu.2020.10.048

Alternatively, nutritional status may be assessed by measuring raw BIA variables; in particular, PhA describes the angular shift (phase difference) between voltage and current sinusoidal waveforms; in the human body the current reaches its maximum/minimum peaks after the voltage (positive values), likely because of the presence of cell membranes and tissue interfaces [4,15]. PhA has been gaining attention because it is thought to be a proxy of water distribution (ratio between extracellular water-ECW and intracellular water-ICW) and body cell mass (BCM) [4]. Thus, high PhA suggests greater cellularity (e.g. more BCM relative to FFM), cellular integrity and cell functions [4]. The variability in PhA values may be ascribed to factors such as age [7,8], gender [7,8], race [16], body composition [16], level of physical activity [17], and adiposity [7].

PhA has been directly related to muscle strength [6,18], for instance being higher in athletes [19], and declines with aging [20] in line with that is known about physiological changes of BCM and ECW/ICW ratio with aging [16]. PhA decreases with disease, inflammation, malnutrition, and prolonged physical inactivity [15], and is associated with impaired quality of life [21] and poor prognosis in various chronic diseases [22–24]. In the elderly, it is also an independent predictor of clinical adverse outcomes such as frailty [25], falls [26], incident disability [27] and mortality [4,28]. Interestingly, from a practical standpoint, the EWGSOP 2019 consensus on sarcopenia suggested that PhA could be regarded as an index of overall muscle quality [9].

Thus, the current body of evidence encourages research on the use of PhA in the nutrition care process and diagnosis [4,6]. In particular, an association may be expected between PhA and sarcopenia [9] as defined by low skeletal muscle mass (SMM) and loss of muscle function, i.e. low muscle strength (dynapenia) and physical performance [10].

Facing this background, we aimed to evaluate whether and to which extent PhA and sarcopenia (as identified using standard reference criteria) are related to each other. We focused on: a) changes in PhA due to sarcopenia; b) prevalence of sarcopenia according to PhA values; c) derivation of phase angle cut-offs for detecting sarcopenia; d) assessment of sarcopenia and PhA as predictors of clinical outcomes.

2. Materials and methods

2.1. Search strategy

Two authors (ODV and MM) independently performed a literature search until January 2020 of the electronic databases PubMed, Embase, Scopus, and Web of Science. The following terms were used as search strategy string: “PHASE ANGLE” AND (IMPEDANCE OR BIOELECTRICAL OR BIA) AND SARCOPENIA.

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [29] were followed for performing the present review. Due to the study type (systematic review), ethical approval was not required.

2.2. Eligibility criteria

The PICOS strategy was defined as follows: “P” (patients) corresponded to participants of any age, gender or ethnicity, “I” (intervention) designated diagnosis of sarcopenia, “C” (comparison) indicated subjects without sarcopenia, “O” (outcome) corresponded to PhA, and “S” (study design) selected all study types.

Eligibility criteria were: a) both genders; b) well-defined assessment of sarcopenia and use of BIA phase-sensitive devices to ensure data on PhA; c) full papers published in peer-reviewed journals; d) studies published from inception to January 2020; e) papers written in English. No restriction was applied in relation to sample size.

Studies were excluded according to the following criteria: a) inadequate definition of sarcopenia; b) insufficient description of methods used to measure PhA and different components of sarcopenia; c) absence of data on the relationships between PhA and sarcopenia; c) articles without full-text availability, opinion pieces, review articles and editorials.

Overall, the selected studies focused on: a) changes in PhA due to sarcopenia; b) prevalence of sarcopenia related to PhA; c) derivation of phase angle cut-offs for sarcopenia; d) assessment of sarcopenia and PhA as predictors of clinical outcomes.

2.3. Study selection and data extraction

Titles and abstracts from the electronic searches were screened independently by two authors (ODV and MM). The full texts of selected articles were then checked by the same two authors to consider the fit with eligibility criteria. A third reviewer (LS) revised any differences in opinion to make a final decision. An electronic database was designed to store all relevant data. Data were extracted separately by two investigators (ODV and MM). In the case of disagreement, LS, FP and ADG cross-examined doubtful data. The following data were extracted: authors, year of publication, country of origin, study population (sample size, gender and age), subjects’ characteristics, diagnostic criteria for sarcopenia, cut-off points for sarcopenia components, and nutritional phenotypes (sarcopenic, pre-sarcopenic, etc.).

2.4. Risk of bias

Methodological quality was assessed using the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies, as recommended by the National Institute of Health, U.S. Department of Health and Human Services [30], which was based on Evidence-based Practice Centers (AHRQ) criteria (Supplementary Table 1). The tool consists of 14 criteria used to assess quality, including whether the objective of the study was clearly stated, the population studied was clearly specified and defined, and the outcome assessors were blinded. For each criterion a rating was given as “yes”, “no”, “cannot be determined”, “not reported”, or “not applicable”.

Quality rates were good, fair, or poor as judged by two independent observers (ODV and MM) following the instructions given by the National Institute of Health and taking into consideration the number of positive responses [30]. High risk of bias translates to a rating of poor quality and vice versa.

3. Results

3.1. Study selection

A total of 226 articles were identified through the initial literature search. After removing duplicates (n = 54), 93 studies were then excluded by screening titles and abstracts because they did not fulfil the inclusion criteria. The full text of the remaining 79 potentially relevant studies was examined; 13 studies were considered appropriate and suitable for the systematic review. The selection process is shown in Fig. 1.

3.2. Study characteristics

The main characteristics of selected studies (n = 13) are summarized in Table 1. The articles were published from 2012 to 2020. Overall, data on 7668 subjects were taken into consideration, with more women (n = 4028) than men (n = 3640) included. Five

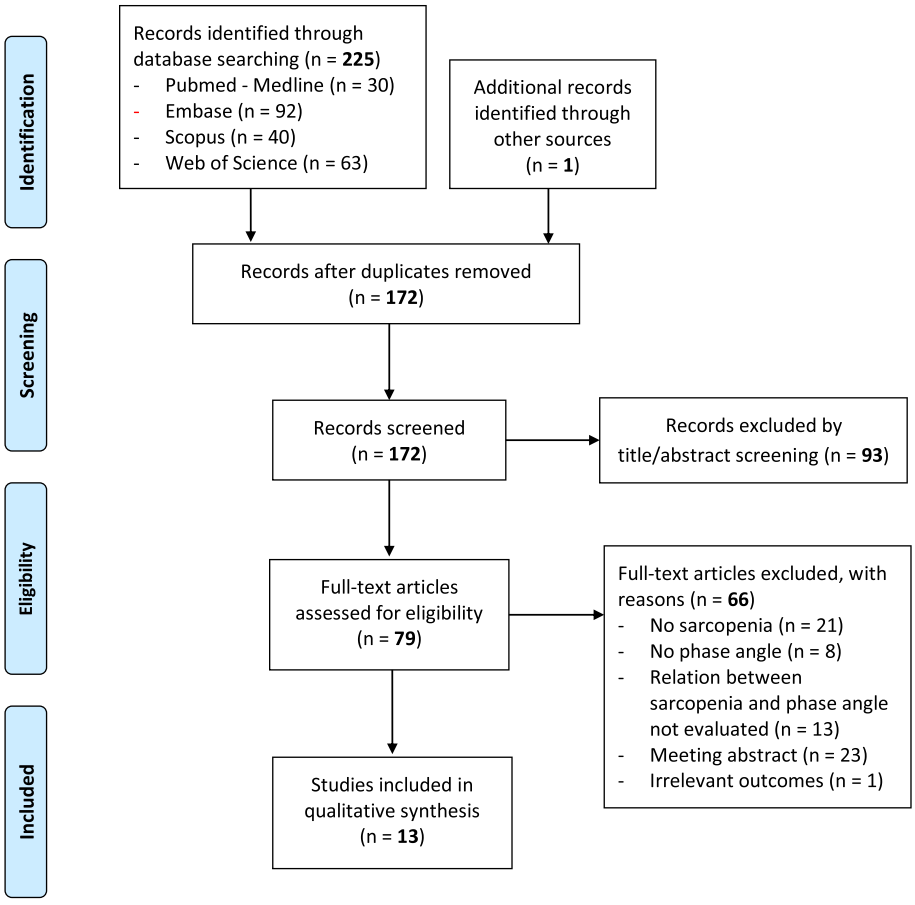

Fig. 1. Flowchart on the search and selection of articles to be included in the systematic review.

studies were carried out in Central and South America, four in Europe and four in Asia.

Five studies evaluated community-dwelling (free living) elderly subjects, two hospitalized elderly patients and one community-dwelling plus hospitalized patients. The other five studies included also younger patients: two involved kidney transplant recipients, the other three, one each, patients with cancer, cirrhosis or chronic obstructive pulmonary disease (COPD).

In all studies BIA-derived PhA was measured at the frequency of 50 kHz. Muscle mass was assessed as (Table 1): 1) appendicular skeletal muscle mass (ASM) in two studies using DXA [31,32]; 2) skeletal muscle mass (SM) in six studies using BIA [23,32–36] and the Janssen equation [37]; 3) appendicular muscle mass (AMM) in four studies [26,27,38,39] using BIA and manufacturer's equations [40]. No information was given in one study [39]. The cut-off points for low muscle mass are shown in Table 1 with respect to: ASM index (ASMI) = ASM/height^2, SM index (SMI) = SM/height^2, AMM index (AMI) = AMM/height^2, and relative muscle mass (RMM) = SM/weight.

Eleven studies assessed muscular strength measuring handgrip strength (HGS). For detecting low values, six studies [23,25,34–36,41] used the EWGSOP 2010 criteria ([10] based on Lauretani et al. [42]), four [26,27,38,39] the AWSG criteria [43], and only one [32] the EWGSOP 2019 criteria ([9] based on Dodds et al. [44]). Cut-off values are showed in Table 1. The same eleven studies assessed physical performance with the gait speed test (GS) performed on 4 (n = 8), 5 (n = 2) or 6 m (n = 1). In all cases, with the exception of Sipers et al. [41] (IWGS criteria), the cut-off point was set at 0.8 m/s (Table 1).

Sarcopenia was identified in five studies [23,25,34–36] with the EWGSOP 2010 criteria (slightly modified in ref. [10]), in one [32] with the EWGSOP 2019 criteria [9], and in four [26,27,38,39] according to the AWGS criteria [43]. Sipers et al. [41] applied four different criteria sets: EWGSOP 2010 [10], IWGS [45], FNIH [46] and SIG [47]. In the remaining two studies [31,33] only muscle mass was considered for diagnosis (Table 1) according to the criteria proposed by the EWGSOP 2010 consensus [10] and Baumgartner et al. [48], respectively. According to the sarcopenia staging proposed by the EWGSOP 2010 Consensus [10], five studies identified pre-sarcopenic individuals and six evaluated separately sarcopenia (in the following mentioned as “non-severe sarcopenia”) and severe sarcopenia.

3.3. Risk of bias

Sample size was below 200 subjects in five [32,34–36,41], between 200 and 500 in other five [23,25,26,31,39] and above 500 subjects in three studies [27,33,38]. All the studies were carried out in a single centre, with the exception of the multicentre study by Kilic et al. [25]. BIA measurement conditions and procedures were described in detail in eight out of thirteen studies [23,25,32–36,38]. Other information on the risk of bias is summarized in Supplementary Table 1. Overall, according to the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies [30], the risk of bias was low: as a matter of fact, eleven studies had

Table 1
Descriptive characteristics of the studies included in the systematic review.

Authors (Year)	Country, sample and age[a]	Subjects	Diagnostic criteria of sarcopenia	Method for assessing muscle mass and cut-off points for sarcopenia	Nutritional phenotypes evaluated
Marini et al. (2012) [31]	Italy n = 207 M 75 (75.8±6.9) F 132 (70.8±4.0)	Community-dwelling elderly individuals (convenience group)	Baumgartner et al.	Muscle mass from DEXA ASM/h^2 M < 7.26 kg/m^2, F < 5.45 kg/m^2	Sarcopenic Non-sarcopenic
Kilic et al. (2017) [25]	Turkey n = 263 M 110, F 153 > 65 yrs	Community-dwelling and hospitalised elderly patients	EWGSOP 2010 modified	Muscle mass from BIA SMI M < 8.72 kg/m^2, F < 7.34 kg/m^2 HGS M < 30 kg, F < 20 kg GS (6 m) < 0.8 m/s	Severe sarcopenic Non severe sarcopenic Pre-sarcopenic Non-sarcopenic
Perez Camargo et al. (2017) [33]	Mexico n = 628 M 257, F 371 median and range 57 yrs (19-89)	Cancer patients	EWGSOP 2010 modified	Muscle mass from BIA SMI M < 8.87 kg/m^2, F < 6.42 kg/m^2	Severe sarcopenic Non severe sarcopenic Non-sarcopenic
de Blasio et al. (2018) [23]	Italy n = 263 M 185, F 78 69.8±8.0	Patients with chronic obstructive pulmonary disease (COPD)	EWGSOP 2010	Muscle mass from BIA SMI M < 8.50 kg/m^2, F < 5.75 kg/m^2 HGS M < 30 kg, F < 20 kg GS (4 m) < 0.8 m/s	Severe sarcopenic Non severe sarcopenic Non-sarcopenic
Dos Reis et al. (2018) [34]	Brasil n = 129 M 88, F 41 47.8±11.8	Kidney transplant recipients	EWGSOP 2010	Muscle mass from BIA SMI M < 10.76 kg/m^2, F < 6.76 kg/m^2 HGS M < 30 kg, F < 20 kg GS (4 m) < 0.8 m/s	Severe sarcopenic Non severe sarcopenic Pre-sarcopenic
Santana et al. (2018) [35]	Brazil n = 148 M 76 (70.6±7.1) F 72 (72.6±7.9)	Hospitalised elderly patients	EWGSOP 2010	Muscle mass from BIA SMI M < 8.50 kg/m^2, F < 5.75 kg/m^2 HGS M < 30 kg, F < 20 kg GS (4 m) < 0.8 m/s	Severe sarcopenic Non severe sarcopenic Pre-sarcopenic Non-sarcopenic
Yamada et al. (2018) [38]	Japan n = 1009 M 285 (81.1±7.1) F 724 (80.4±6.8)	Community-dwelling elderly individuals (convenience group)	AWGS	Muscle mass from BIA SMI M < 7.0 kg/m^2, F < 5.8 kg/m^2 HGS M < 26 kg, F < 18 kg GS (5 m) < 0.8 m/s	Sarcopenic Pre-sarcopenic Non-sarcopenic
Espirito Santo Silva et al. (2019) [32]	Brazil n = 119 M 54.4±10.2	Cirrhotic patients	EWGSOP 2019	Muscle mass from DEXA ASM/h^2 M < 7.0 kg/m^2, F < 5.5 kg/m^2 HGS M < 27 kg, F < 16 kg GS (4 m) < 0.8 m/s	Sarcopenic Non-sarcopenic
Pessoa et al. (2019) [36]	Brazil n = 94 F > 60	Community-dwelling elderly individuals (convenience group)	EWGSOP 2010	Muscle mass from BIA SMI M < 8.50 kg/m^2, F < 5.75 kg/m^2 HGS M < 30 kg, F < 20 kg GS (4 m) < 0.8 m/s	Severe sarcopenic Non severe sarcopenic Pre-sarcopenic
Sipers et al. (2019) [41]	The Netherlands n = 81 M 22, F 59 84±5	Hospitalized elderly patients	EWGSOP 2010 IWGS SIG FNIH	Muscle mass from BIA SMI M < 8.87 kg/m^2, F < 6.42 kg/m^2 HGS M < 30 kg, F < 20 kg GS (4 m) < 0.8 m/s SMI M < 10.76 kg/m^2, F < 6.76 kg/m^2 GS < 1 m/s low low RMM Class 1 M < 37% Class 1 F < 28%, Class 2 M < 31% Class 2 F < 22% GS < 0.8 m/s Weakness + SMI M < 8.87 kg/m^2, F < 6.42 kg/m^2 HGS M < 26 kg, F < 16 kg	Sarcopenic Non-sarcopenic
Uemura et al. (2019) [27]	Japan n = 4312 M 2228 (71.9±5.4) F 2084 (71.6±5.3)	Community-dwelling elderly individuals (convenience group)	AWGS	Muscle mass from BIA SMI M < 7.0 kg/m^2, F < 5.8 kg/m^2 HGS M < 26 kg, F < 18 kg GS (4 m) < 0.8 m/s	Sarcopenic Non-sarcopenic
Uemura et al. (2019) [26]	Japan n = 205 M 73, F 132 72.6±4.8	Community-dwelling elderly individuals (convenience group)	AWGS	Muscle mass from BIA SMI M < 7.0 kg/m^2, F < 5.8 kg/m^2 HGS M < 26 kg, F < 18 kg GS (4 m) < 0.8 m/s	Sarcopenic Non-sarcopenic

Table 1 (*continued*)

Authors (Year)	Country, sample and age[a]	Subjects	Diagnostic criteria of sarcopenia	Method for assessing muscle mass and cut-off points for sarcopenia	Nutritional phenotypes evaluated
Kosoku et al. (2020) [39]	Japan n = 210 M 122, F 88 median and range 55 yrs (45-66)	Kidney transplant recipients	AWGS	Muscle mass from BIA SMI M < 7.0 kg/m^2, F < 5.8 kg/m^2 HGS M < 26 kg, F < 18 kg GS (5 m) < 0.8 m/s	Sarcopenic Non-sarcopenic

SD = standard deviation; M = males; F = females.
EWGSOP = European Working Group on Sarcopenia in Older People; IWGS = International Working Group on Sarcopenia; SIG = Special Interest Group of Sarcopenia, Cachexia and Wasting Disorders; FNIH = Foundation for the National Institutes of Health; AWGS = Asian Working Group for Sarcopenia; for EWGSOP 2010; ASM = appendicular skeletal muscle mass; SMI = appendicular skeletal muscle mass/height^2 while SMI = skeletal muscle mass/height^2 only for AWGS; RMM = skeletal muscle mass/weight; HGS = handgrip strength; GS = gait speed; BIA = bioelectrical impedance analysis; DEXA = dual X-ray absorptiometry.
Severe, non severe and pre-sarcopenic phenotypes defined according to EWGSOP 2010.
[a] mean ± standard deviation if not otherwise indicated.

an overall good rating in terms of quality, while two were rated as fair and none as poor.

3.4. From sarcopenia to phase angle

Eight studies evaluated whether PhA changed depending on the presence of sarcopenia: two on community-dwelling elderly individuals, two on hospitalised elderly patients, and four on adult/elderly patients with specific diseases. All studies assessed the difference between sarcopenic and non-sarcopenic individuals/patients, four papers considered non-severe and severe sarcopenia, and three evaluated pre-sarcopenia (see Tables 1 and 2 for details).

In 2012, Marini et al. [31] studied 207 free-living elderly individuals. Based on ASMI, sarcopenia was identified in 24.3% of men and only 3.9% of women. PhA was markedly lower in sarcopenic than non-sarcopenic subjects (−18.0% in men and −14.8% in women). More recently, in 1009 community-dwelling older Japanese subjects (>65 yrs, 12.6% pre-sarcopenia and 16.4% sarcopenia), PhA was lower in pre-sarcopenic and sarcopenic vs. non-sarcopenic men (−8.4% and −24.4%, respectively), and in sarcopenic vs. non sarcopenic women (−20.0%) [38].

As far community-dwelling and hospitalized elderly patients (overall prevalence of sarcopenia 15.2%) were concerned, Kilic et al. (2017) indicated that there was a declining trend of PhA as follows (median values): 4.97° in non-sarcopenic, 4.60 in pre-sarcopenic, 4.45 in non-severe sarcopenic and 3.75 in severe sarcopenic patients [25]. In another study (148 hospitalized elderly patients) mean PhA was lower in sarcopenic than non-sarcopenic male patients (−17.6%), whereas no significant difference was found in females (−4.9%) [35] PhA was decreased in severe sarcopenia in both men (−25.7%) and women (−11.4%), but not in pre-sarcopenic patients.

Looking at specific diseases, in patients with advanced cancer (median age 57 years, 28% non-severe and 18% severe sarcopenia), the prevalence of low PhA values differed between no sarcopenia (45%), non-severe sarcopenia (48%) and severe sarcopenia (56%) [33]. PhA was slightly lower in patients with severe sarcopenia than in the non-sarcopenic ones (median values, 3,9 vs 4.1°, p = 0.018). In patients with stable COPD aged 69.8 ± 8.0 yrs, de Blasio et al. [23] found a significant reduction in PhA values in those with non-severe and severe sarcopenia (−4.9% and −12.5%, respectively) compared to the non-sarcopenic ones. In male patients with cirrhosis (54.4 ± 10.2 yrs), Espirito Santo Silva et al. [32] showed that those with sarcopenia (12.6% of total sample) had lower PhA values (−22.4%) than the non-sarcopenic ones. Low PhA values (≤4.9°) was observed in 66.6% of sarcopenic vs. 38.5% of non-sarcopenic patients, while patients with sarcopenia were 5.6 times more likely to have PhA values ≤ 5.05° (OR 5.6; 95% CI: 1.19−19.54, p < 0.01). Finally, in a very recent paper Kosoku et al. [39] examined kidney transplant recipients (median age 55 yrs). The prevalence of sarcopenia was 11.4% of the total sample with a median PhA lower in sarcopenic than non-sarcopenic patients (−10.4%, p < 0.001).

3.5. From phase angle to sarcopenia

Six studies have evaluated whether and to what extent the prevalence of sarcopenia varies depending on PhA (Fig. 2). Cut-off values of low PhA were derived using ROC analysis [25,39] or taking as reference the first tertile of the group of interest [26,27,34,36]. Previous reference values were used in one paper [32]. Table 2 gives more detailed results on statistical analysis.

Two studies took into consideration community-dwelling individuals. Pessoa et al. [36] evaluated 94 women aged >60 years enrolled in a physical and recreational program. The subjects in the first tertile of PhA exhibited higher prevalence of non-severe sarcopenia (41.9% vs 27.0%) and severe sarcopenia (9.7% vs 1.6%) compared to second and third tertiles. Multivariate logistic regression analysis showed that women with low PhA did not present higher odds to have sarcopenia. More recently, Uemura et al. [26] analysed 205 community-dwelling older adults (72.6 ± 4.8 yrs). The overall prevalence of sarcopenia was low, but indeed higher in the first tertile of PhA (10% vs. 2.1% in the other subjects). Similarly, in a study on geriatric patients [25], low PhA was associated with a higher prevalence of sarcopenia (26.9% in low vs 7.5% in normal PhA group, p < 0.001), with PhA being a significant predictor for sarcopenia in a multivariate logistic regression analysis.

Three studies focused on specific diseases. Dos Reis et al. [34] compared kidney transplant recipients in the first tertile of PhA vs. other tertiles, showing no differences with regard to the prevalence of non-severe sarcopenia (41.9 vs 46.5%) or severe sarcopenia (6.9 vs 4.6%). In addition, in a multivariate logistic regression analysis low PhA was not associated with a higher prevalence of sarcopenia after adjustment for potential confounders. Espirito Santo Silva et al. [32] found that cirrhotic patients with PhA≤4.9° had a higher prevalence of sarcopenia than those with PhA>4.9° (20% vs 7.2%; p = 0.037). Finally, in 210 kidney transplant recipients Kosoku et al. [39] showed that PhA was significantly associated with sarcopenia even after adjustment for potential confounders (age, sex, C-reactive protein, dialysis vintage, time after transplant, diabetes, etc.).

3.6. Derivation of phase angle cut-offs for detecting sarcopenia

Four studies have performed ROC analysis to identify cut-off values of PhA that may be used to detect sarcopenia. Further details on statistical analysis can be found in Table 2.

In community-dwelling individuals. Yamada et al. [38], reported that the best cut-off values were 4.05° in men (sensitivity 82%, specificity 52.2%) and 3.55° in women (sensitivity 71.4%, specificity 65.8%). In geriatric patients, a value ≤ 4.55° was indicated (sensitivity 70% and specificity 65.9%) [25].

In cirrhosis, Espirito Santo Silva et al. [32] identified a PhA ≤5.05° as a cut-off value for sarcopenia (sensitivity 73.3%, specificity 61.5%). Positive likelihood ratio was 1.9 (95% CI 1.29−2.81), a

Table 2
Main results of the studies included in the systematic review.

Authors (Year)	From sarcopenia to PhA (degrees, mean value±SD or median)	From PhA to sarcopenia	PhA as predictor of sarcopenia	PhA cut-off points for detecting sarcopenia	Correlation coefficients between PhA and different components of sarcopenia	PhA and sarcopenia as predictors of survival
Marini et al. (2012) [31]	Sarcopenia: M 5.0±1.0, F 5.2±0.5 No sarcopenia: M 6.1±1.1, F 6.1±0.8 (M $p < 0.001$, F $p = 0.015$)				ASM: M $r = 0.51$ $p < 0.01$ F $r = 0.38$ $p < 0.05$ ASM/h^2: M $r = 0.52$ $p < 0.01$ F $r = 0.31$ $p < 0.01$	
Kilic et al. (2017) [25]	Severe sarcopenia: 3.75 Non severe sarcopenia: 4.45 Pre-sarcopenia: 4.60 No sarcopenia: 4.97 ($p < 0.001$)	Prevalence of sarcopenia ($p < 0.001$) PhA≤4.55 degrees: 26.9% PhA > 4.55 degrees: 7.5%	PhA (as continuous variable) significant predictor of sarcopenia: OR 0.59, 95% CI 0.40-0.87, $p = 0.008$	≤4.55 degrees (sensitivity 70%, specificity 65.9%) AUC 0.703, 95% CI = 0.644-0.758	SM: r = NR $p < 0.00$ SMI: r = NR $p < 0.001$ HGS: r = NR $p < 0.001$	
Perez Camargo et al. (2017) [33]	Sarcopenia: 3.9 No sarcopenia: 4.1 ($p = 0.018$)					For time until death: PhA: HR 1.9, 95%CI = 1.6 −2.4, $p = 0.001$ Sarcopenia: HR 1.2, 95% CI = 0.9 −1.5, $p = 0.008$
de Blasio et al. (2018) [23]	Severe sarcopenia: 4.29±0.89 Non severe sarcopenia: 4.66±0.88 No sarcopenia: 4.90±0.87 ($p < 0.05$)					
Dos Reis et al. (2018) [34]		Prevalence of sarcopenia (p = NS) PhA M < 6.2 or F < 5.8 degrees: 41.9% (non severe) 6.9% (severe) PhA M > 6.2 or F > 5.8 degrees: 46.5% (non severe) 4.6% (severe)	Low PhA (M < 6.2 and F < 5.8 degrees) not significantly associated with the prevalence of sarcopenia. First vs third quartile: OR 1.95, 95% CI 0.71-5.39, p = NS		SM: $r = 0.27$ $p = 0.004$ SMI: $r = 0.28$ $p = 0.003$ HGS: $r = 0.34$ $p < 0.001$	
Santana et al. (2018) [35]	Sarcopenia: M 5.6±2.3, F 5.8±2.0 No sarcopenia: M 6.8±1.9, F 6.1±1.6 (M $p = 0.033$, F $p = 0.013$)				ASM/h^2: M $r = 0.238$ $p = 0.038$ F $r = 0.137$ $p = 0.251$ HGS: M $r = 0.326$ $p = 0.004$ F $r = 0.366$ $p = 0.002$ GS: M $r = 0.315$ $p = 0.008$ F $r = 0.285$ $p = 0.026$	
Yamada et al. (2018) [38]	Sarcopenia: M 3.40±0.74, F 3.31±0.66 Pre-sarcopenia: M 4.12±0.85, F 4.07±0.51 No sarcopenia: M 4.50±0.86, F 4.14±0.71 ($p < 0.05$ between the three groups)			M ≤4.05 degrees (sensitivity 82%, specificity 52.2%) AUC 0.718, 95% CI = 0.652-0.784; F≤3.55 degrees (sensitivity 71.4%, specificity 65.8%) AUC 0.721, 95% CI = 0.669-0.773	HGS: M $r = 0.567$ $p < 0.001$ F $r = 0.554$ $p < 0.001$ GS: M $r = 0.415$ $p < 0.001$ F $r = 0.445$ $p < 0.001$	
Espirito Santo Silva et al. (2019) [32]	Sarcopenia: 4.18±1.41 No sarcopenia: 5.39±1.18 ($p = 0.005$)	Prevalence of sarcopenia ($p = 0.037$) PhA≤4.9 degrees: 20% PhA > 4.9 degrees: 7.2%		≤5.05 degrees (sensitivity 73.3%, specificity 61.5%) AUC 0.730, 95% CI = 0.598 0.872	SM: $r = 0.198$ $p = 0.031$ HGS: $r = 0.469$ $p <$ 0.001	
Pessoa et al. (2019) [36]		Prevalence of sarcopenia (p = NR) PhA < 5.7 vs. > 5.7 degrees: 41.9 vs. 27% (non	Low PhA < 5.7 degrees not significantly associated with the prevalence of sarcopenia.		GS: $r = 0.24$, $p = 0.023$	

Table 2 (*continued*)

Authors (Year)	From sarcopenia to PhA (degrees, mean value±SD or median)	From PhA to sarcopenia	PhA as predictor of sarcopenia	PhA cut-off points for detecting sarcopenia	Correlation coefficients between PhA and different components of sarcopenia	PhA and sarcopenia as predictors of survival
		severe) 9.7% vs. 1.6% (severe)	First tertile vs others: OR = 1.50, 95% CI 0.520 −4.319, p = NS			
Sipers et al.(2019) [41]						For 2-years survival: HR 0.679, 95% CI = 0.527 −0.874; p = 0.003 vs HR 3.433 95% CI = 1.822−6.506; p < 0.001
Uemura et al. (2019) [27]		Prevalence of sarcopenia (p = 0.01) PhA M < 5.2 or F < 4.5 degrees: 10% PhA M > 5.2 or F > 4.5 degrees: 2.1%			SMI: M r = 0.44 p < 0.001 F r = 0.30 p < 0.001 HGS: M r = 0.40 p < 0.001 F r = 0.24 p = 0.005	
Uemura et al. (2019) [26]						
Kosoku et al. (2020) [39]	Sarcopenia: 4.3 (IQR 3.9-4.6) No sarcopenia: 4.8 (IQR 4.4-5.4) (p < 0.001)		PhA (as continuous variable) significant predictor for sarcopenia: OR 0.36, 95% CI 0.16−0.82, p = 0.015	4.46 degrees (sensitivity 74%, specificity 70%) AUC 0.73, 95% CI = NR		

M = males; F = females; SD = standard deviation; IQR = interquartile range; PhA = phase angle; For EWGSOP 2010: ASM = appendicular skeletal muscle mass; SM = skeletal muscle mass; SMI = skeletal muscle mass/height^2; for AWGS: SMI = appendicular skeletal muscle mass/height^2; HGS = handgrip strength; GS = gait speed; NS = not significative; NR = not reported; AUC = area under the curve; OR = odds ratio; HR = hazard ratio; CI = confidence interval.

negative likelihood ratio of 0.43 (95% CI 0.189−1.01). Lastly, in the recent study by Kosoku et al. [39] the authors found that the optimal PhA cut-off value for sarcopenia in kidney transplant recipients was 4.46°, with sensitivity 74% and specificity 70%.

3.7. Relationships between PhA and different components of sarcopenia

Eight of the studies included in this systematic review also provided results on the relationships between PhA and different components of sarcopenia (Table 2).

Four studies included community-dwelling individuals. In the less recent studies Marini et al. [31] showed that PhA positively correlated with ASM and ASM/h^2 in both men and women, while Yamada et al. [38] observed a moderate association of PhA with HGS and GS. In another study [36] PhA was not associated with SM, SMI and HGS in elderly women, whereas a weak correlation emerged between PhA and GS after adjustment for confounding parameters. Additionally, a logistic regression analysis showed that low PhA was not associated with low SMI, low HGS or low GS. Finally, PhA was found by Uemura et al. [26] to be positively correlated with SMI and HGS in both genders, but not with GS.

In the first study on elderly patients, those with low PhA had lower SM, SMI and HGS [25], while in the second one there was a weak/moderate correlation of PhA with ASM/h^2, HGS and GS in both genders [35].

In kidney transplant recipients [34] patients with lower PhA presented a decreased HGS when compared with those with higher PhA, whereas no difference was observed for SM, SMI and GS. PhA was positively associated with SM, SMI and HGS, but not with GS. In cirrhotic patients, found that male patients with low PhA had decreased HGS; in addition, PhA was directly associated with HGS and SM [32].

3.8. Phase angle and sarcopenia as predictors of clinical outcomes

Two studies have examined PhA and sarcopenia (or its components) as concurrent predictors of survival (Table 2). Pérez Camargo et al. [33] showed that in cancer patients PhA (p = 0.003) and sarcopenia (p = 0.001) were associated with survival in univariate analysis. In the multivariate Cox-regression analysis, PhA emerged as a more significant predictive factor (p = 0.001) than sarcopenia (p = 0.08). Later, Sipers et al. [41] studied 81 geriatric hospitalized patients, using four different criteria sets for sarcopenia. Patients who deceased within two years after hospitalization had a significantly lower PhA at baseline than patients who were still alive (6.0 ± 1.6 vs 7.4 ± 1.7° in men and 6.2 ± 1.3 vs 7.0 ± 1.4° in women). In a Cox proportional hazard ratio model, patients with sarcopenia (EWGSOP or FNIH criteria), lower PhA or lower GS had a significantly lower 2-y survival. When a multivariate Cox regression was carried out, sarcopenia (FNIH criteria) and PhA were both predictors of mortality.

Two other studies deserve to be mentioned, which evaluated PhA and some components of sarcopenia as risk factors for incident disability and falls. Uemura et al. [26] found that the lower tertile of PhA was associated with an increased risk for incident falls relative to tertiles 2 and 3 (univariate Cox regression analysis: HR 2.51, 95% CI 1.13−5.60). Subsequent multivariate Cox regression analysis confirmed that PhA, but not components of sarcopenia such as low muscle mass or low muscle function, was a significant risk factor for incident falls (HR 2.32, 95% CI 1.03−5.21). Surprisingly, sarcopenia as such was not considered as a potential predictor of falls. The same authors, in a

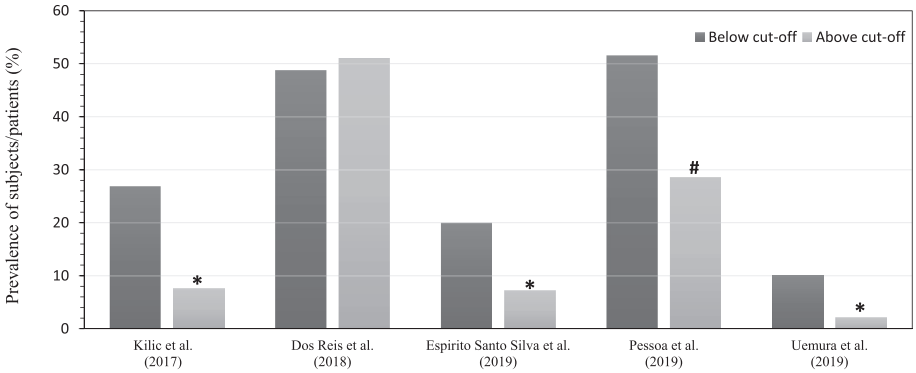

Fig. 2. Prevalence of sarcopenia depending on phase angle. For study characteristics see Table1; for cut-offs see Table 2. * $p < 0.05$; #significance not reported.

larger study [27], assessed 4312 community-dwelling elderly subjects without disability at baseline (4.2% sarcopenia). Univariate Cox regression analysis revealed that PhA was a significant predictor for incident disability (in men HR = 0.37, 95% CI = 0.30–0.46 and in women HR = 0.46, 95% CI = 0.38–0.56, $p < 0.001$ in both cases). After adjustment for confounders, multivariate Cox regression analysis identified PhA, but not ASM/BMI, as an independent predictor for incident disability (in men HR 0.73, 95% CI 0.53–0.99 and in women HR 0.80, 95% CI 0.64–0.99. $p < 0.05$ in both cases).

4. Discussion

This study aimed to evaluate the relations between BIA-derived PhA and sarcopenia. Overall, evidence of the literature reasonably supports the view that PhA is decreased in sarcopenic subjects/patients and that the prevalence of sarcopenia increases when PhA is low.

The use of raw BIA variables for evaluating nutritional status has increasingly gained attention, in particular with respect to PhA, high values suggesting greater cellularity, lower ratio between ECW and ICW and cell membrane integrity [4]. In the elderly PhA is an independent predictor of clinical adverse outcomes such as frailty [25], falls [26], incident disability [27] and mortality [4]. Furthermore, it has been associated with impaired quality of life [21] and poor prognosis in various chronic diseases [22–24], as well as with muscle strength [6,18]. Finally, the EWGSOP 2019 consensus on sarcopenia suggested that PhA could be regarded as an index of overall muscle quality [9]. In view of these considerations, research is encouraged regarding the use of PhA as nutritional marker in the clinical setting, thus, we have tried to assess PhA in relation to sarcopenia as identified by reference criteria [9,10,43,45–47] using different angles of view.

First ("from sarcopenia to PhA"), we evaluated whether and to what extent PhA differed in sarcopenic compared to non-sarcopenic subjects/patients (Table 2). With respect to severe sarcopenia or "overall" sarcopenia, two studies [31,38] showed a substantially lower PhA in community dwelling elderly subjects with sarcopenia (recalculated for the entire sample, −16.0% and −21.2%, respectively). Similar results were also obtained in patients with COPD (−12.5%) or cirrhosis (−22.4%), hospitalized patients (−25.7%), free living/hospitalized patients (−24.5%) and kidney transplant recipients (−10.4%), whereas only a small difference was observed in cancer patients (−4.9%). On the other hand, difference was smaller for non-severe sarcopenic [23,25] and negligible for pre-sarcopenic subjects/patients, the latter being those with just a reduced muscle mass and no muscle impairment [25,35,38]. In addition, using logistic regression analysis, another study [32] showed that sarcopenic patients were 5.6 times more likely to have low PhA values. Thus, available results strongly support the idea that sarcopenia is associated with a reduced PhA, with this difference possibly being affected by age, disease or other confounding factors.

Secondly, we changed our perspective (new issue "from PhA to sarcopenia") and evaluated the prevalence of sarcopenia in subjects/patients stratified according to low or high PhAs [25,26,32,34,36]. Among different studies, cut-off values of PhA varied from 4.4 to 6.2°, possibly because of the methods used for their identification. Cut-offs were derived using ROC analysis [25,39] or taking the first tertile of the group of interest as reference [26,27,34,36], whereas previous reference values were used only in one paper [32].

As shown in Table 2, sarcopenia was more prevalent in subjects/patients with low PhA in four out of five studies [25,26,32,36], the difference being almost two times higher. The only exception was the study by Dos Reis et al. [34] on kidney transplant recipients, possibly because of confounders such as type and dialysis time, transplant time, donor type, and drug use. In addition, the relationships of PhA with the different components of sarcopenia were assessed in eight papers [25,26,31,32,34–36,38] by linear correlation analysis. On the whole, a weak/moderate association was found with SM in six studies [25,27,31,32,34,35], with HGS in six studies [25,27,32,34,35,38] and with GS in three studies [35,36,38]. Thus, low PhA was a marker for both sarcopenia and impairment of its components.

Along the same lines, logistic analysis was employed in four studies [25,34,36,39] for evaluating PhA as a possible predictor of sarcopenia (Table 2). In all cases HRs indicated an increased risk for sarcopenia in those subjects/patients who had a lower PhA. Indeed, in two studies [34,36] this finding was not significant, possibly due to low sample size and/or low prevalence of sarcopenic subjects.

In the clinical setting, it is crucial to identify the best criteria for detecting sarcopenic patients. By performing ROC analysis, cut-off values of PhA were derived varying from a minimum of 3.55° in community-dwelling elderly women to a maximum of 5.05 in cirrhotic patients [25,32,38,39]. Difference may be due to individuals' characteristics as well as the use of different devices. It should be noted that sensitivity tended to be around 70% and specificity varied from 52 to 70%. Although there are no agreed criteria for judging sensitivity and specificity, in our opinion these cut-offs appear to be not sufficiently reliable because a substantial proportion of subjects was misclassified. On the other hand, sensitivity and specificity may be also affected by the uncertainties on the diagnosis of sarcopenia, in other words by the inherent problems in identifying true sarcopenic subjects/patients.

Additionally, in defining cut-offs it should be considered that a high variability in PhA values could be influenced by several factors such as age [7,8], gender [7,8], race [16], body composition [16], level of physical activity [17], and adiposity [7].

Finally, sarcopenia and PhA were evaluated as prognostic factors related to survival in hospitalized elderly patients or cancer patients [33,41] (Table 2). In both cases, PhA and sarcopenia were independent predictors of survival in univariate and multivariate Cox analysis. Indeed, in the paper by Sipers et al. [41] sarcopenia was predictive only when the EWGSOP 2010 or FNIH criteria were used. Of note, in two different studies, Uemura et al. [26,27] also showed that a low PhA was a risk factor for incident falls and disability whereas low muscle mass and low muscle function (both components of sarcopenia) were not. Once more, these findings suggest that PhA could be used along with other components of sarcopenia for better assessing muscle quality.

Some limitations are to be acknowledged. According to inclusion criteria, a relatively small number of studies was selected (only one multicentre study), which in some cases had a small sample size. Additionally, there are no definite data for certain types of patients who are expected to suffer from sarcopenia, i.e. those with heart failure, diabetes, etc. A single study is available for cancer, COPD and cirrhosis, making difficult to draw any specific conclusion.

Furthermore, the evaluation of sarcopenia was a secondary aim in many of the studies. In addition, comparisons between studies may be hampered by discrepancies in the characteristics of study groups and by using different definitions of sarcopenia; only one study used the recent EWGSOP 2019 criteria. Moreover, there was a certain degree of uncertainty due to considering overall sarcopenia or severe vs. non severe sarcopenia. Muscle mass was determined using a criterion method (DXA) just in two studies. Also, the definition of cut-off values has been based on relatively small samples, and no validation studies have been so far carried out in other independent groups of patients. Finally, there is only few data available on PhA and sarcopenia as possible concurrent predictors of hard clinical outcomes.

In conclusion, a number of papers have evaluated the relationship between PhA and sarcopenia using different approaches. The results of the selected studies strongly suggest that PhA is decreased in sarcopenic subjects/patients and that the prevalence of sarcopenia is higher in subjects/patients with low PhA. Of note, quite different cut-off PhA values have been derived for identifying sarcopenia. From a methodological point of view, more information should be obtained on PhA and the derivation of diagnostic cut-offs with respect to both differences between populations and diseases, and standardization of measuring conditions and devices. BIA is a simple and reproducible technique for assessing the electrical characteristics of the human body, which may be applied in the different phases of nutrition care process, for instance in diagnosis and clinical management. In this respect, further studies are needed to determine whether PhA may or should be used as an additional parameter for detecting low muscle quality and identifying sarcopenia.

Funding

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

Conflict of interest

None declared.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2020.10.048.

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