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Revisión

Phase angle as a prognostic factor in patients with cancer: a systematic review of the existing evidence via a meta-analysis

El ángulo de fase como factor pronóstico en pacientes con cáncer: una revisión sistemática de la evidencia disponible a través de un metaanálisis

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Abstract

Background: the phase angle (PA) is expressed via bioelectrical impedance and an indicator of cell membrane health, integrity, hydration, and nutritional status. The associations between PA and cancer survival are inconsistent and unclear. This study aimed to assess PA's role as a prognostic marker of cancer survival.

Methods: we searched PubMed and EMBASE to identify all relevant studies up to December 2023. A meta-analysis was performed to clarify PA's prognostic role for cancer patients.

Results: a total of 30 studies covering 6587 participants were included in this study. There was a significant prognostic role for PA in the context of cancer patients' survival (HR = 0.73; 95 % CI, 0.66-0.81, $p < 0.0001$, $I^2 = 0.0$ %). Patients with low PA values were 27 % less likely to survive than patients with high values. Our subgroup analyses showed that geographical population (American: HR = 0.66, 95 % CI: 0.55-0.79, $I^2 = 0.0$ %; European: HR = 0.63, 95 % CI: 0.47-0.84, $I^2 = 23.2$ %; Asian: HR = 0.48, 95 % CI: 0.31-0.74), the type of cancer (head and neck, colorectal, lung, or pancreatic cancer), and type of therapy (palliative vs. non-palliative treatment) did not change the prognostic value.

Conclusions: the findings highlight the potential of PA to be a non-invasive, cost-effective prognostic tool in oncological care.

Keywords:

Phase angle. Cancer. Survival. Prognosis. Meta-analysis.

Resumen

Antecedentes: el ángulo de fase (PA) se expresa a través de la impedancia bioeléctrica y es un indicador de la salud, la integridad, la hidratación y el estado nutricional de la membrana celular. El vínculo entre el PA y la supervivencia del cáncer es inconsistente y poco claro. El objetivo de este estudio fue evaluar el papel del PA como indicador pronóstico de supervivencia del cáncer.

Métodos: se realizaron búsquedas en PubMed y EMBASE para identificar todos los estudios relevantes hasta diciembre de 2023. Se realizaron metaanálisis para aclarar el efecto pronóstico del PA en los pacientes con cáncer.

Resultados: se incluyeron 30 estudios con 6587 participantes. El PA tuvo un efecto pronóstico significativo en la supervivencia de los pacientes con cáncer (HR = 0,73, IC del 95 %: 0,66-0,81, $p < 0,0001$, $I^2 = 0,0$ %). Los pacientes con bajos niveles de PA tenían un 27 % menos de probabilidades de sobrevivir que los pacientes con altos niveles de PA. Nuestro análisis de subgrupos mostró que la población geográfica (americanos: HR = 0,66, 95 % CI: 0,55-0,79, $I^2 = 0,0$ %; europeos: HR = 0,63, 95 % CI: 0,47-0,84, $I^2 = 23,2$ %; asiáticos: HR = 0,48, 95 % CI: 0,31-0,74); el tipo de cáncer (cáncer de cabeza y cuello, colorrectal, pulmón o páncreas) y el tipo de tratamiento (tratamientos paliativos y no paliativos) no alteraron el pronóstico.

Conclusiones: la medición del PA puede ser un factor pronóstico importante para la supervivencia en pacientes con cáncer.

Palabras clave:

Ángulo de fase. Cáncer. Supervivencia. Pronóstico. Metaanálisis.

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INTRODUCTION

Cancer is recognized as a leading cause of morbidity and mortality worldwide. According to statistics from the Global Cancer Observatory (GLOBOCAN), there was an estimated incidence of 19.3 million new cases and 10 million cancer deaths in the year 2020, and it is projected that by 2040, this number will be 28.4 million, making it one of the important barriers to increasing life expectancy in every country of the world (1). Malnutrition has been identified as a negative prognostic factor for the overall survival of cancer patients, and negative prognostic factors can lead to a reduced response to cancer treatment, serious postoperative complications, increased treatment-related adverse effects, poorer quality of life, and cancer mortality (2). The early identification, monitoring, prevention, and treatment of these nutritional deficiencies could improve the cancer patients' physical performance, outcomes in terms of quality of life, and chances of survival (3).

There are many methods for the subjective and objective assessment of patients' nutritional status, including basic anthropometric parameters (e.g., weight change, triceps skinfold thickness, arm and wrist circumference, body mass index), laboratory measurements (serum albumin, prealbumin, and transferrin assays), and nutritional screening questionnaires (the Nutrition Risk Screening 2002, Mini Nutrition Assessment, and Patient-generated Subjective Global Assessment) (4). In practical work, anthropometric and nutritional screening procedures are not ideal because they require well-trained staff to carry out, which is difficult to implement in insufficiently staffed institutions (5). Laboratory indicators have long half-lives, meaning that it is challenging to evaluate changes in nutritional status over a short period, and these factors may be affected by many non-nutritional factors such as hepatic and renal failure, hormone infusion, and infection (6).

In recent years, the role of bioelectrical impedance analysis (BIA) has been examined because it is an easy-to-use and non-invasive technique for evaluating changes in body composition and nutritional status. Moreover, whether it is hospitalization or only outpatient treatment will not have an impact on our acquisition of the above indicators. The portability and low cost of BIA allow for routine, bedside, single or repeated measurements (7,8). The phase angle (PA), a parameter that can be obtained using the ratio between resistance (R) and reactance (Xc) (PA = tangent arc Xc / R), is one of the important parameters of BIA (9). Higher PA values represent large quantities of intact cell membranes, greater membrane integrity, and better cell function, whereas low PA values indicate a poorer status of cell membranes, impaired muscle function, and cell death (10). Thus, PA may be seen as a measure of tissue damage. Recently, a growing body of evidence has demonstrated a relationship between PA and malnutrition. The PA is increasingly used to evaluate nutritional status, treatment complications, and overall survival in patients with heart failure, kidney diseases, human immunodeficiency virus, and other chronic diseases (11-16).

The evaluation of the PA in patients with cancers is a promising tool for predicting patient survival and formulating therapeutic strategies. Some systematic reviews have shown that PA has a significant correlation with the overall survival of cancer patients (2,17,18), while some authors believe that PA has nothing to do with the prognosis of breast cancer (19). As the literature is still heterogeneous in this regard, the present meta-analysis was conducted to investigate the relationship between PA and survival among adult patients diagnosed with cancer. Clarifying this relationship provides information to assess the usability of the PA as a potential tool for cancer prognosis and survival.

MATERIALS AND METHODS

The present study was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (20). All the steps, including the online database searches, study selection, data extraction, and critical appraisal, were followed separately by two authors (QR Kong and LJ Tian). Any disagreements in either title/abstract or in the full-text paper review phases were resolved by discussing with a third investigator (M Yu). The finding has registered in INPLASY (registration number 202410002; DOI: 10.37766/inplasy2024.10.0025).

IDENTIFICATION AND ELIGIBILITY CRITERIA OF RELEVANT STUDIES

Searches were performed until the 20th of December 2023 using the following electronic databases: PubMed and EMBASE. Both medical words and free-text search terms were adopted. The reference lists of related and included studies were also screened to identify any additional articles. Our database searches were conducted using the following keywords: (phase angle or bioelectrical impedance or electric impedance or bioelectric impedance) and (cancer survival or prognosis or cancer mortality). No filters were applied for language, study design, or publication date during our database searches.

STUDY SELECTION AND ELIGIBILITY CRITERIA

The study selection was defined by the following components identified using the PICOS (Population, Intervention, Comparison, Outcome, and Study design) rubric: P (adult patients with any type of cancer), I (the use of BIA for evaluating PA), C (differences in PA), O (cancer survival), S (all types of cohort studies). The inclusion criteria were as follows: (1) original human cohort studies; (2) studies published in English; (3) studies evaluating the PA in relation to survival among patients with any type of cancer. We excluded articles that were non-human studies, case reports, review articles, any studies without original data, or articles without any related outcome measures. After being read by two independent reviewers (QR Kong and LJ Tian), the candidate articles were screened for inclusion in our meta-analysis based

on their titles and abstracts. If a study could not be categorized by its abstract, a full-text review was carried out. The reported data required for our meta-analysis were then extracted (YH Wang).

DATA EXTRACTION

The following information was extracted from each of the included studies: the general characteristics of the studies (first author, year of publication, country of origin, study design, follow-up time), participant characteristics (sample size, sex, age, body mass index, type of cancer, and therapy), and information about the PA (assay method, cut-off value, statistical method).

The PA cut-off values vary significantly according to study and patient population, including lower quartile, the sample mean, median, or critical value established from earlier evidence, and there is no uniform standard at present. Based on the above reasons, our study did not establish consistent PA cut-offs. However, we have meticulously recorded the cut-offs of each study for the reference of subsequent researchers.

The included studies were categorized based on how the relationship between the PA and the survival of cancer patients was assessed and reported. The studies that reported relative risks (RRs) or hazard ratios (HRs) as an effect size for the correlation between PA and cancer patient survival were included. To ascertain the validity of the eligible studies, pairs of reviewers working independently determined the adequacy of randomization and concealment of allocation, data collectors, and outcome assessors. Any disagreements were resolved through discussion and, if necessary, consultation with a third investigator (M Yu).

QUALITY ASSESSMENT

We assessed the quality of the included studies by using the Newcastle-Ottawa Quality Assessment Scale (NOS), which consists of three domains: selection, comparability, and outcome. The maximum score is 9 points. Studies with scores ≥ 7, scores of 4-6, and scores ≤ 3 points were considered as high-, moderate-, and low-quality studies, respectively (21).

DATA SYNTHESIS AND STATISTICAL ANALYSIS

A meta-analysis was conducted to evaluate quantitative summary estimates of the relationship between PA and cancer survival. STATA 14 (STATA Corporation, College Station, TX, USA) was used for our analysis. Two reviewers independently conducted the data synthesis, considering the meta-bias of the data extracted from all the primary studies. All participants were divided into two groups according to cut-off value. A study was considered statistically significant when at p-value < 0.05. RRs or HRs were used to measure the relationship between PA and cancer survival and converted by using their natural logarithms. Heterogeneity was assessed for all endpoints using the I^2 statistic. In the presence of significant heterogeneity, a random effects model was used; otherwise, a fixed effects model was implemented (22). Publication bias was assessed using Begg's statistics, and it was considered that there is no publication bias when the p-value was more than 0.05 (23). When publication bias was found, trim and fill analysis was implemented to adjust for the effects of potential publication bias on overall effect size.

ETHICAL APPROVAL

All data included in the meta-analysis were based on previously published studies. Therefore, ethical approval was not required.

RESULTS

STUDY SELECTION

Our electronic search algorithm retrieved a total of 359 initial citations. Following screening, 206 studies were identified for potential inclusion. After assessing the titles and abstracts of the studies, 108 articles met the inclusion criteria for the present systematic review. After reading the full texts of the articles, 78 studies were excluded (laboratory research [n = 2], no related data of PA and survival [n = 39], lacking exploitable data [n = 21], duplicate data [n = 2], review articles [n = 14]). Finally, 30 studies (n = 6587 participants) were found to be eligible for the meta-analysis and subsequently included in the meta-analysis (Fig. 1).

STUDY CHARACTERISTICS

The characteristics of the included studies are listed in table I (5,24-50,58,59). A total of 30 studies involving 6587 participants were included in this study, and these studies had sample sizes ranging from 28 to 1814 participants. The mean ages of the study participants varied between 40 and 74 years, the study participants' BMI values ranged from 18.6 to 25.5 kg/m^2, and the PA cut-offs ranged from 3.0 to 5.95°. The included studies were conducted between 2004 and 2023. Regarding the countries of origin of the 30 studies included in our meta-analysis, 8 were from America (5,24-27,41,58,59), 7 were from Germany (28,31,32,36,39,44,45), 3 were from Brazil (33,35,40), 3 were from Mexico (29,37,46), 2 were from Japan (43,47), 1 was from China (50), 1 was from Egypt (42), 1 was from Italy (49), 1 was from Korea (30), 1 was from Poland (34), 1 was from Spain (48), and 1 was from Sweden (38). Of the 30 studies, 22 studies were cohort studies, and 8 studies had a cross-sectional design. The follow-up durations of the studies ranged from 60 days to 11.6 years from baseline. Based on the NOS, 25 studies were ranked as high-quality studies, 5 were considered to be of moderate quality, and none were considered low-quality studies.

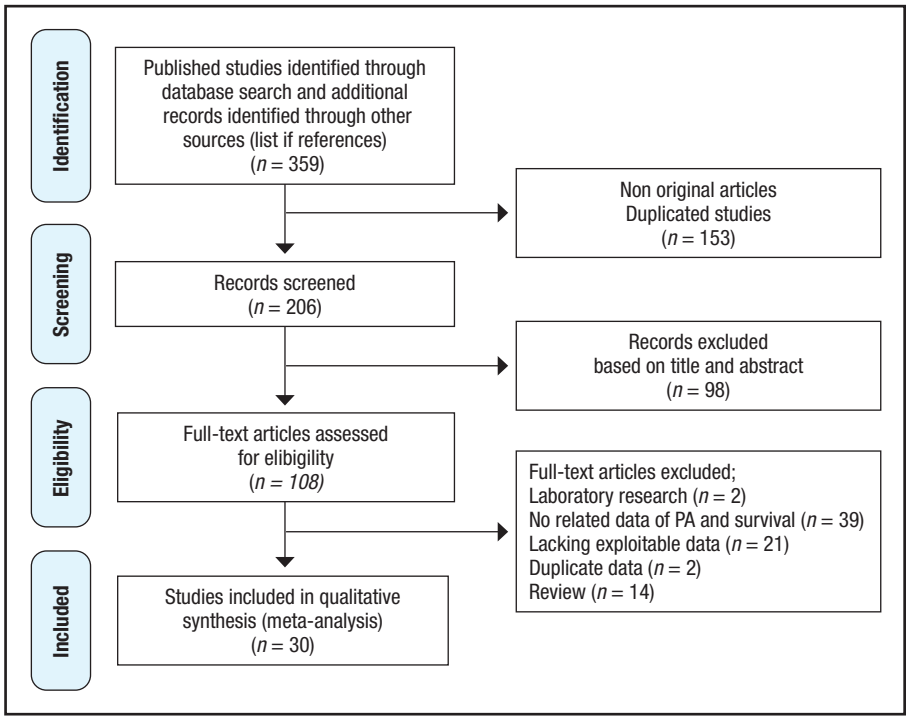

Figure 1.
PRISMA flow diagram of the literature search process.

RESULTS AND RISK OF BIAS

All of the studies evaluated the impact of PA on survival in cancer patients using HR. PA has a significant prognostic effect on patients' survival (HR = 0.73, 95 % CI: 0.66-0.81, $p < 0.0001$) (Fig. 2). In other words, patients with low PA values were 27 % less likely to survive than patients with high PA values. No significant heterogeneity was found among the effect size of the included studies ($I^2 = 0.0$ %, $p = 0.471$).

Our subgroup analysis based on geographical population did not change the overall findings in the America (HR = 0.66, 95 % CI: 0.55-0.79, $I^2 = 0.0$ %) (Fig. 3A), Europe (HR = 0.63, 95 % CI: 0.47-0.84, $I^2 = 23.2$ %) (Fig. 3B), or Asia subgroups (HR = 0.48, 95 % CI: 0.31-0.74, $I^2 = 0.0$ %) (Fig. 3C).

Our subgroup analysis based on cancer types also confirmed this conclusion in patients with head and neck cancer (HR = 0.53, 95 % CI: 0.34-0.81, $I^2 = 17.6$ %) (Fig. 4A), colorectal cancer (HR = 0.47, 95 % CI: 0.24-0.92, $I^2 = 0.0$ %) (Fig. 4B), lung cancer (HR = 0.65, 95 % CI: 0.36-1.19, $I^2 = 0.0$ %) (Fig. 4C), and pancreatic cancer (HR = 0.84, 95 % CI: 0.73-0.97, $I^2 = 0.0$ %) (Fig. 4D).

In addition, our subgroup analysis based on the type of therapy utilized (palliative vs. non-palliative treatment) also proved the prognostic effect of PA on survival for non-palliative treatment (HR = 0.66, 95 % CI: 0.56-0.77, $I^2 = 5.5$ %) (Fig. 5A) and palliative treatment (HR = 0.69, 95 % CI: 0.57-0.85, $I^2 = 0.0$ %) (Fig. 5B).

No significant publication biases were found in any of the meta-analyses, as determined using Begg's test ($p > 0.05$) (Fig. 6).

DISCUSSION

This meta-analysis was performed to systematically evaluate the association between PA and survival among patients with cancers. Our findings indicated that patients with low PA values were 27 % less likely to survive than patients with high PA values. Our subgroup analyses results also confirmed the prognostic role PA can play in the context of survival among cancer patients. These results suggest that PA could be a useful predictor of adverse outcomes in cancer patients.

Survival prognostication is a challenging task, particularly in patients with advanced cancer. Approximately 80 % of patients with advanced cancer want to be informed of their prognosis, especially their treatment outcomes, adverse effects, and body changes in their last months and days of life (51). Considering the complexity and time-consuming nature of anthropometry and nutrition screening methods, as well as the delays associated with laboratory indicators, a more portable and low-cost method of evaluating cancer survival is needed. In recent years, the scientific community's interest in the effectiveness of PA as an indicator has been increasing, as a strong correlation between prognosis and diagnostic factors has been observed. According to statistics, more than 350 articles have been published since 2004, and 20 % of these articles were published in 2022 alone (52). The published systematic reviews on this topic have covered sarcopenia (11), obesity (12), metabolic diseases (13), surgery (18), critical illnesses (14), heart failure, chronic kidney disease (15), coronavirus disease-2019 (COVID-19) (16), and other diseases and conditions (53).

Table I. Characteristics of the included studies

Author, year	Country	Study design	Follow up time	Sample size (F/M)	Age (mean)	BMI (mean)	Patients selection information	Current treatment	PA assay method	PA cut-off	Statistical method	Results	Quality score
Gupta et al. 2004 (1) (5)	US	Cross-sectional	NM	22/30	55.8	NM	Colorectal cancer	NM	BIA-101Q	5.57	Multivariate analysis adjusted for age, weight, serum albumin, etc.	Poor survival with PA ≤ 5.57°	High
Gupta et al. 2004 (2) (24)	US	Cross-sectional	NM	23/35	56.2	NM	Pancreatic cancer	NM	BIA-101Q	5.0	Multivariate analysis adjusted for albumin and treatment history	Poor survival with PA ≤ 5.0°	High
Gupta et al. 2008 (25)	US	Cross-sectional	NM	259/-	median 49	NM	Breast cancer	NM	BIA-101Q	5.6	Multivariate analysis adjusted for stage and treatment history	Poor survival with PA ≤ 5.6°	High
Davis et al. 2009 (26)	US	Cohort	60 days	20/30	63	NM	Pancreatic, lung, breast, etc.	Palliation therapy	RJL BIA apparatus	NM	Multivariate analysis adjusted for resistance, body water, and sodium	Poor survival with low PA	Moderate
Gupta et al. 2009 (27)	US	Cross-sectional	NM	72/93	median 56	NM	Lung cancer	NM	BIA-101Q	5.3	Multivariate analysis adjusted for age, stage and treatment history	Poor survival with PA ≤ 5.3°	High
Norman et al.2010 (28)	Germany	Cohort	6 months	191/208	63	24.9	Gastrointestinal, head and neck, lung, etc.	Chemotherapy, radiotherapy, other treatment	Nutriguard-M	5th percentile of study population	Multivariate analysis adjusted for sex, age, SGA, etc.l	Poor survival with PA < 5th percentile	High
Sánchez-Lara et al. 2012 (29)	Mexico	Cohort	Median 6 ± 5 months	64/55	60.5	24.8	Lung cancer	Chemotherapy	Bodystat Quadscan 4000	5.8	Multivariate analysis adjusted for sex, age, ECOG, etc.	Poor survival with PA ≤ 5.8°	High
Hui et al. 2014 (59)	US	Cohort	Median 118 days	131/91	55	18.6	Breast, gastrointestinal, urinary, etc.	Palliation therapy	RJL Systems Quantum IV	4.4	Multivariate analysis adjusted for prognostic score, albumin, and fat free mass	Poor survival with PA ≤ 4.4°	High
Lee et al. 2014 (30)	Korea	Cohort	NM	15/13	NM	19.8	Digestive tract, hematologic, lung, etc.	Palliation therapy	Biodynamics model 450	4.4	Multivariate analysis adjusted for age, PPI, and BMI	Poor survival with PA ≤ 4.4°	High
Maasberg et al.2015 (36)	Germany	Cross-sectional	Median 44 months	105/98	63.4	24.7	Neuroendocrine neoplasia	Surgery, chemotherapy, interferon, etc.	Nutriguard-M	5th percentile of study population	Multivariate analysis adjusted for sex, age, Ki-67 grade, etc.	Poor survival with PA < 5th percentile	Moderate
Norman et al. 2015 (31)	Germany	Cohort	12 months	190/243	69.7	24.9	Gastrointestinal, hematologic, urogenital, etc.	Chemo-radiotherapy, and other treatment	Nutriguard-M	5th percentile of study population	Multivariate analysis adjusted for age, sex, BMI, etc.	Poor survival with PA < 5th percentile	High
Schütte et al. 2015 (32)	Germany	Cohort	Median 218 days	7/44	66.18	27.48	Hepatocellular carcinoma	NM	BIACORPUS RX 4000	4.8	Multivariate analysis adjusted for stage and NA score	Poor survival with PA≤4.8°	High

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Table I (cont.). Characteristics of the included studies

Author, year	Country	Study design	Follow up time	Sample size (F/M)	Age (mean)	BMI (mean)	Patients selection information	Current treatment	PA assay method	PA cut-off	Statistical method	Results	Quality score
Mauricio et al. 2016 (33)	Brazil	Cohort	4 years	127/101	62.1	NM	Colon, rectum, esophagus, etc.	Adjuvant chemo-radio therapy	Quantum X model	5th percentile of study population	Multivariate analysis adjusted for sex, age, diagnosis, etc.	Poor survival with PA < 5th percentile	High
Władysiuk et al. 2016 (34)	Poland	Cohort	5.5 years	8/67	56.88	NM	Head and neck cancer	NM	SFB7 BioImp v1.55	4.733	Multivariate analysis adjusted for sex, age, SGA, etc.	Poor survival with PA ≤ 4.733°	High
Barao et al. 2017 (35)	Brazil	Cohort	NM	121/129	70.9	25.5	Colorectal cancer	Chemotherapy, surgery, and palliation therapy	Bodystat Quadscan 4000	5	Multivariate analysis adjusted for stage, ECOG, and PG-SGA	Poor survival with PA ≤ 5°	High
Hui et al. 2017 (58)	US	Cross-sectional	Median 924 days	168/198	58	NM	Breast, gastrointestinal, urinary, etc.	Palliation therapy	InBody 720	4.5	Multivariate analysis adjusted for ECOG, hypoalbuminemia, dehydrogenase, etc.	Poor survival with PA ≤ 4.5°	Moderate
Pérez Camargo et al. 2017 (37)	Mexico	Cohort	NM	255/197	57.56	22.84	Gastric, lung, gynecological cancer, etc.	Palliation therapy	InBody 720	4	Multivariate analysis adjusted for sex, age, diagnosis, and BMI	Poor survival with PA ≤ 4°	High
Axelsson et al. 2018 (38)	Sweden	Cohort	Median 11.6 years	41/87	61.4	24.9	Head and neck cancer	Surgery, chemo-radiotherapy	BIA-101S Akern	5.95	Multivariate analysis adjusted for age, performance status, tumor site, etc.	Poor survival with PA ≤ 5.95°	High
Buentzel et al. 2019 (39)	Germany	Cross-sectional	> 2 years	22/20	67.29	23.69	Head and neck cancer	Surgery and radio-chemotherapy	Biocorpus 4000	5	NM	Poor survival with PA ≤ 5°	Moderate
Cavagnari et al. 2019 (40)	Brazil	Cohort	NM	34/12	62.8	NM	Colorectal cancer	Surgery and neo-adjuvant radiotherapy	QuadScan 4000	5	NM	Survival was marginally correlated with PA	High
Hui et al. 2019 (41)	US	Cohort	NM	110/94	61.8	NM	Breast, gastrointestinal, urinary, etc.	Palliation therapy	RJL Systems Quantum IV	3	Multivariate analysis adjusted for age, sex, race, etc.	Poor survival with PA ≤ 3°	High
Mohamed Sad et al. 2020 (42)	Egypt	Cohort	> 5 years	43/46	median 40	NM	Colorectal cancer	Chemotherapy and target therapy	TANITA MC-780U	4.1	Multivariate analysis adjusted for age, performance status, BMI, etc.	Poor survival with PA ≤ 4.1°	High

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Table I (cont.). Characteristics of the included studies

Author, year	Country	Study design	Follow up time	Sample size (F/M)	Age (mean)	BMI (mean)	Patients selection information	Current treatment	PA assay method	PA cut-off	Statistical method	Results	Quality score
Katsura et al. 2021 (43)	Japan	Cross-sectional	NM	44/70	74	19.2	Cancer cachexia	NM	InBody S10	5.3	Multivariate analysis adjusted for age, sex	Poor survival with PA≤5.3°	Moderate
Löser et al. 2021 (44)	Germany	Cohort	Median 15 months	17/44	median 63	24.4	Head and neck cancer	Chemo-radiotherapy	Biacorpus RX4004M	4.7	NM	Poor survival with PA≤4.7°	High
Sehoul et al. 2021 (45)	Germany	Cohort	59 months	226/-	median 59	25	Gynecologic cancer	Surgery and chemotherapy	Biacorpus RX4004M	4.5	Multivariate analysis adjusted for ECOG, FIGO stage, and BMI	Poor survival with PA≤4.5°	High
Sat-Muñoz et al. 2022 (46)	Mexico	Cohort	> 2 years	32/107	63.5	NM	Head and neck cancer	NM	mBCA SECA514	4.42	NM	Poor survival with PA ≤ 4.42°	High
Yamanaka et al. 2022 (47)	Japan	Cohort	> 3 years	18/78	median 67	median 21.2	Head and neck cancer	Radiation therapy	InBody S10	25th percentile of study population	Multivariate analysis adjusted for cancer site and cancer stage	Poor survival with PA < 25th percentile	High
García-García et al. 2023 (48)	Spain	Cohort	1 year	22/35	median 62	median 23	Lung, hepatobiliary, pancreatic,etc.	Chemotherapy, radiotherapy, surgery, et al	Single-frequency analyzer	men < 5.9 women < 5.3	Multivariate analysis adjusted for sex, age, BMI, RFCSA and CRP	Poor survival with low PA	High
Sandini et al. 2023 (49)	Italy	Cohort	Median 27 months	71/90	median 66	median 23.7	Pancreatic cancer	Surgery	Single-frequency analyzer	NM	Multivariate analysis adjusted for age, fat-free mass, CCI, etc..	Decreased value of PA is related to unfavorable prognosis	High
Zou et al. 2023 (50)	China	Cohort	Median 19.6 months	821/993	median 59	NM	Lung, gastric, breast, etc.	NM	InBody S10	Adjust for age	Multivariate analysis adjusted for sex, age, BMI, etc.	Poor survival with low PA	High

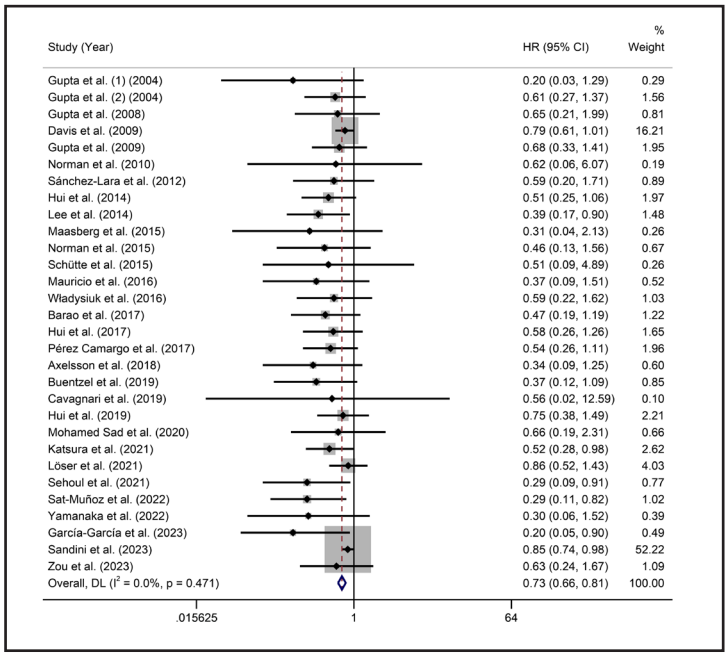

Figure 2.

Forest plot of the meta-analysis of phase angle and survival in cancer patients as assessed by hazard ratios.

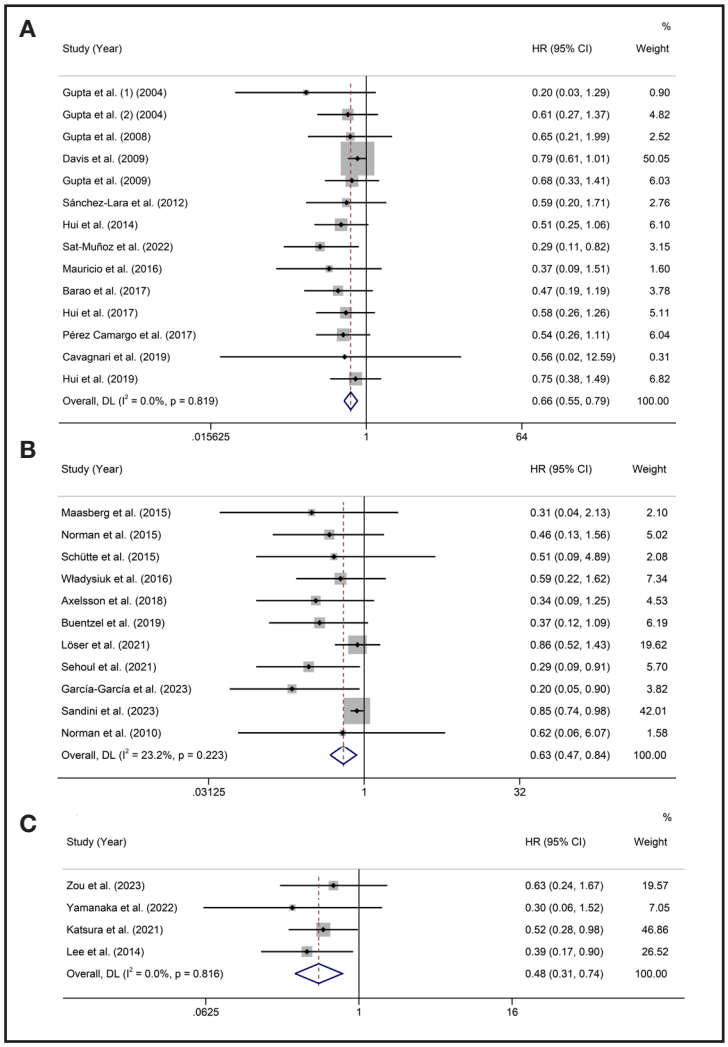

Figure 3.

Forest plot of the meta-analysis of phase angle and survival based on geographical population. America (A); Europe (B); Asia (C).

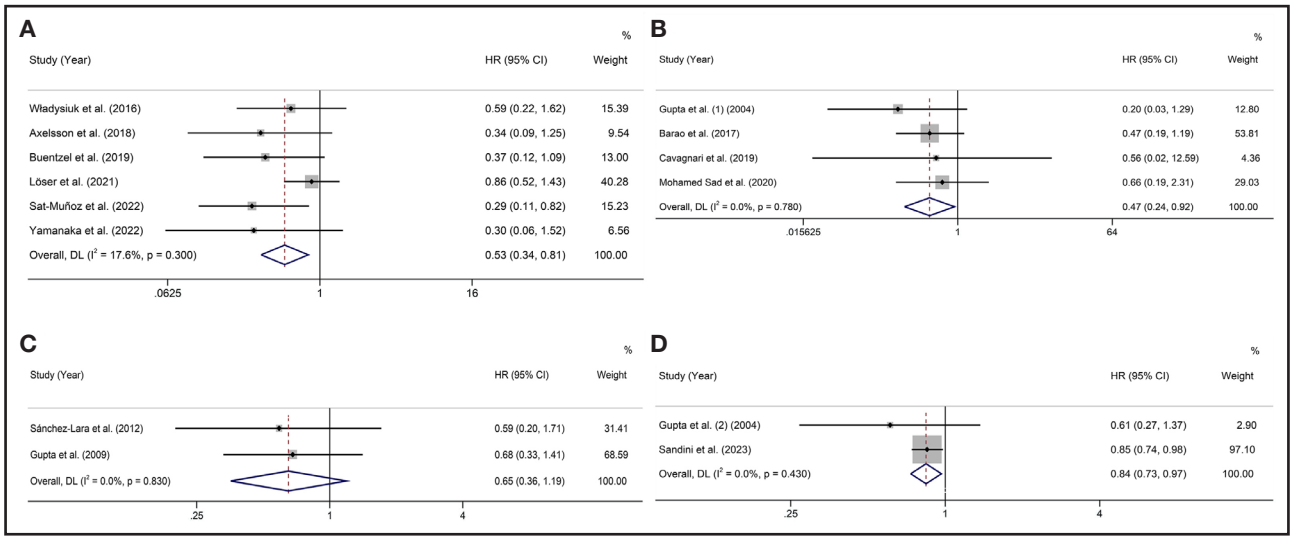

Figure 4.

Forest plot of the meta-analysis of phase angle and survival based on cancer types. Head and neck cancer (A); colorectal cancer (B); lung cancer (C); pancreatic cancer (D).

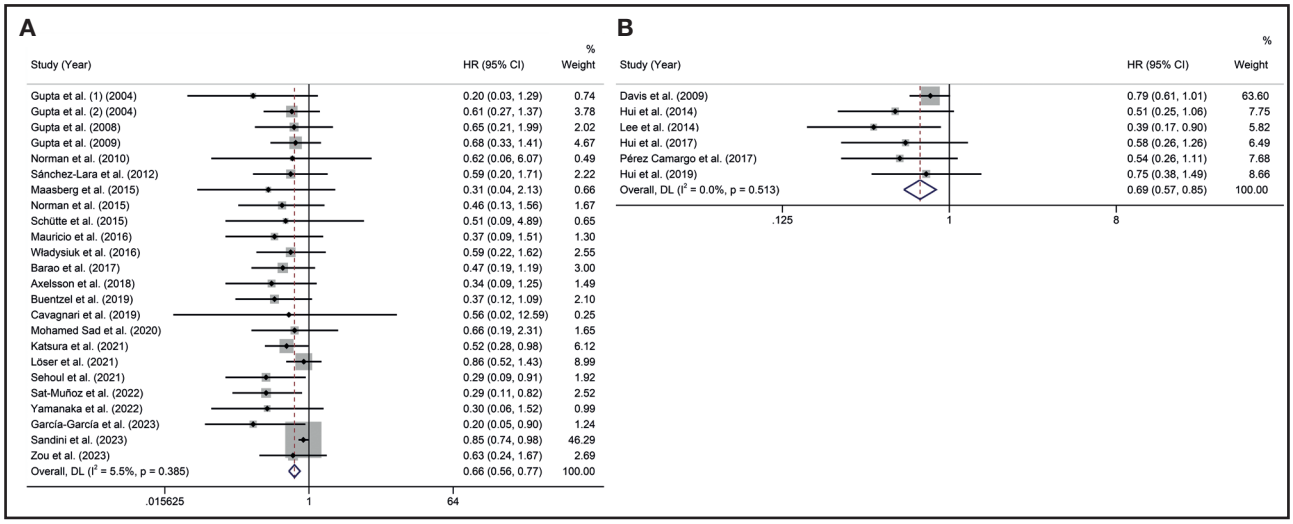

Figure 5.

Forest plot of the meta-analysis of phase angle and survival based on the type of therapy utilized. Non-palliative treatment (A); palliative treatment (B).

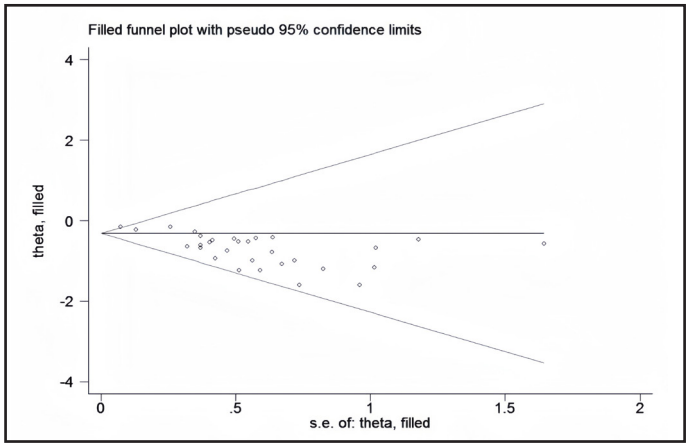

Figure 6.

Funnel plot with pseudo 95 % confidence intervals of the relationship between phase angle and survival in cancer patients as assessed by hazard ratios.

Initially, many researchers focused on exploring PA changes and the utility of considering the PA in cancer patients receiving anti-tumour treatments such as chemotherapy, radiotherapy, surgery, or other forms of treatment. Morlino et al. found that the value of PA decreased significantly by 5-15 % after chemotherapy in patients with breast cancer, and such an effect may last for more than 2 years, which indicates that chemotherapy may change the balance of body fluids and deprive lean body mass, thus affecting cancer prognosis (19). Ramos da Silva et al. also proved that chemotherapy leads to worsened PA values and nutritional risk index (NRI) scores, suggesting that PA may be a predictive factor for cancer survival (54). The prognostic value of PA has also been observed in radiotherapy. A study that included a total of 53 patients showed that PA can be used as a standard for malnutrition detection and a predictor of survival in head and neck cancer patients receiving radiotherapy, with a cut-off point of 5.65. This method can prevent the interruption of treatment due to malnutrition and provide personalized nutrition consultation during radiotherapy (55). A systematic review evaluated the feasibility of using PA measured by BIA as a marker of perioperative risk in adult patients undergoing elective surgery for cancer (18). Four studies found that postoperative complications were more common in patients with low PA values. In another retrospective study on gastrointestinal tumours, Yasui-Yamada et al. demonstrated that the incidence of severe postoperative complications, assessed using the Clavien-Dindo classification, increased significantly with a decrease in PA value (56). The authors believe that PA is a useful short-term and long-term postoperative prognostic marker for patients with gastrointestinal (GI) and hepatobiliary and pancreatic (HBP) cancers.

Subsequent studies have paid attention to using PA as a predictor of nutritional status and survival prognosis in tumour patients. In a systematic review that included a total of 1238 patients with head and neck, oesophageal, gastric, pancreatic, or colorectal cancer or neuroendocrine tumours in 11 studies (53), the author found that there was a considerable difference in the PA values between well-nourished and malnourished patients, and PA decreased significantly with the deterioration of malnutrition. Pereira et al. (17) reviewed five prospective cohort studies and four retrospective cohort studies using data on 1496 patients with various cancers. PA data were analysed as continuous variables or according to different cut-offs under a frequency of 50 kHz. They demonstrated that low PA was associated with worse nutrition status and indicated worse overall survival. Arab et al. (2) also suggested that there was a significant prognostic role for PA in predicting patients' survival (HR = 0.77), indicating that patients with low PA values were 23% less likely to survive than patients with high PA values.

In conclusion, the current literature suggests that PA is related to the cancer patients' nutritional status, cancer treatment complications, and overall survival rates. The insufficiency is that these studies include subjects with different geographical populations, cancer types, and therapy types, and no statistical control of cancer types has been observed.

Our study involved subgroup analyses performed according to geographical population, cancer type, and treatment type. The results of our subgroup analyses emphasized the prognostic value of PA in the context of patients' survival. Considering the severe inflammation, intracellular dehydration, and other factors that can result in disturbances in the electrical properties of tissues, one study was excluded because all the cancer patients in it were admitted to intensive care units and had been diagnosed with systemic inflammatory response syndrome or sepsis (57).

In addition, lots of the studies involved in this meta-analysis used a multivariate cox regression analysis and adjusted for a variety of possible confounding factors, including age, sex, stage, Eastern Cooperative Oncology Group (ECOG) score, body mass index (BMI), weight loss, laboratory measurements, mini nutritional assessment, NRI score, sarcopenia, and cachexia. This shows that PA could be an independent prognostic factor for the survival of patients with advanced cancer.

It is notable that multifrequency BIA has been reported to improve the accuracy of body composition analysis. Hui et al. (58) retrospectively examined the relationship between PA values obtained from multifrequency BIA and overall survival in patients with advanced cancer. Their multifrequency bioelectric impedance analysis assessed the PA values of 366 patients at three different frequencies (5/50/250 kHz) on each hemibody (right/left). The mean PA for the frequencies of 5, 50, and 250 kHz were 2.2°, 4.4°, and 4.2° on the right and 2.0°, 4.2°, and 4.1° on the left, respectively. All six PAs remained independently associated with overall survival after adjusting for cancer type, performance status, weight loss, and inflammatory markers. This study confirmed the physiological value of 50 kHz bioelectrical impedance by showing no difference in PA at frequencies above 50 kHz and demonstrated that PA represents a novel objective prognostic factor in outpatient palliative cancer care settings, regardless of frequency and body sides. Therefore, all the studies included in our meta-analysis considered PA values at a bioelectrical impedance of 50 kHz.

Compared to the delay of laboratory indicators (serum albumin, prealbumin, and transferrin assays), anthropometric (triceps skinfold thickness, body mass index) and nutritional screening procedures are difficult to carry out in insufficiently staffed institutions. The portability and low cost of PA permit routine, bedside, single or repeated measurements. So far, PA has shown the potential to serve as a prognostic factor for cancer patients which can be used not only as an independent prognostic factor in clinical environments but also to reflect various nutritional measurements, and PA could become part of regular patient assessments alongside other nutritional evaluations (59). One systematic review proposed that nutritional interventions or supplementation (oral nutritional supplements, eicosapentaenoic acid, high-protein diets, and personalized diets) can improve PA in cancer patients, highlighting its potential as an indicator of nutritional and functional status (60). Therefore, PA could be incorporated into routine clinical practice, and we hypothesize that the survival of patients may be improved by monitoring PA and nutritional interventions. Of course, more research is needed to confirm this conclusion.

This study has some limitations that need to be acknowledged. Firstly, body composition was not evaluated in most of the eligible studies. Assuming that body composition can affect the survival rate, it is suggested to control this potential confounding factor in future research. Secondly, the use of different types of equipment and the lack of detailed descriptions of measurement conditions may have led to the differences between the various studies, affecting the results. It seems that different types of apparatus cannot be interchanged with each other, as the setting and mathematical formulas programmed vary. Thirdly, only 8 studies mentioned the tumour stage, and they simply defined it as early tumours and advanced tumours. Moreover, TNM staging was not conducted according to AJCC standards. It's difficult to perform subgroup analysis based on the tumour stage. In future work, we will pay more attention to the influence of tumour staging on PA. In addition, the follow-up times adopted in the studies were different. More studies, especially large-sample studies with adequate follow-up times, are needed.

Though ultimately not significant, it is also worth noting the statistical and clinical heterogeneity of the included studies. We attempted to minimize publication bias by making our searches as robust as possible, but unavoidably, some data were missing for various reasons. The heterogeneity of the included studies could be attributed to their differences in sample size, BIA equipment and performance, PA cut-off values, statistical adjustments, and follow-up times.

CONCLUSIONS

Survival prognostication remains a challenge in patients with advanced cancer. This meta-analysis indicated that PA may be an important prognostic factor for survival among this population. Further studies with high-quality designs are required to verify PAs sensitivity and specificity in clinical practice. Furthermore, PA values could be used to design personalized nutritional interventions to assess the effectiveness of treatment strategies in a timely manner, and possibly improve the prognosis of cancers patients.

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