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# Cutoff percentiles of bioelectrical phase angle predict functionality, quality of life, and mortality in patients with cancer[1,2]

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**ABSTRACT**

**Background:** The bioelectrical phase angle has shown predictive potential in various diseases, but general cutoffs are lacking in the clinical setting.

**Objectives:** This study evaluated the prognostic value of the fifth percentile of sex-, age-, and body mass index–stratified phase angle reference values in patients with cancer with respect to nutritional and functional status, quality of life, and 6-mo mortality. In a second step, we also studied the effect of the standardized phase angle (with a $z$ score to determine individual deviations from the population average) on these variables.

**Design:** A total of 399 patients with cancer were studied. Phase angle was obtained with bioelectrical impedance analysis; muscle function was assessed by handgrip strength and peak expiratory flow. Quality of life was determined by the European Organization for Research and Treatment of Cancer questionnaire. Nutritional status was assessed by using Subjective Global Assessment. Survival of patients was documented after 6 mo.

**Results:** Patients with a phase angle of less than the fifth reference percentile had significantly lower nutritional and functional status, impaired quality of life ($P < 0.0001$), and increased mortality ($P < 0.001$). The standardized phase angle emerged as a significant predictor for malnutrition and impaired functional status in generalized linear model regression analyses. It was also a stronger indicator of 6-mo survival than were malnutrition and disease severity in the Cox regression model ($P < 0.0001$) and according to the receiver operating characteristic curve.

**Conclusions:** The standardized phase angle is an independent predictor for impaired nutritional and functional status and survival. The fifth phase angle reference percentile is a simple and prognostically relevant cutoff for detection of patients with cancer at risk for these factors. *Am J Clin Nutr* doi: 10.3945/ajcn.2010.29215.

## INTRODUCTION

The bioelectrical phase angle has consistently been shown to have great prognostic relevance with regard to morbidity and mortality in disease (1–4). As a raw variable derived from bioelectrical impedance analysis, the phase angle reflects the contributions between resistance—the pure opposition of a biological conductor to the flow of an alternating electric current—and reactance—the resistive effect produced by tissue interfaces and cell membranes (5, 6). Over the past years, the use of raw variables from bioelectrical impedance instead of the calculation of body compartments has gained popularity in the clinical setting (3, 7–11). Impedance variables provide information on hydration status and cellular membrane integrity without algorithm-inherent errors or requiring assumptions such as constant tissue hydration (7).

Disease, inflammation, malnutrition, or prolonged physical inactivity can result in disturbed electric tissue properties that directly affect the phase angle. In sepsis, for instance, fluid shifts from intracellular to extracellular water occur at an early stage (12) and are accompanied by alterations of phase angle. Not surprisingly, a low phase angle has therefore been associated with an impaired outcome in tumor disease such as pancreatic cancer, colorectal cancer, breast cancer, and lung cancer as well as in HIV/AIDS, liver cirrhosis, dialysis, pulmonary disease, bacteremia, and sepsis (1–4, 8, 9, 12–19). However, most authors generated phase angle cutoffs within their study population by using primarily the median or the lowest quartile or created cutoffs in comparison with a healthy control group. A major drawback of this method is that these cutoffs are not necessarily transferable to other populations and might thus not be applicable in the general clinical setting. By contrast, reference values from a healthy population offer the possibility of assessing individual deviations of a patient in relation to the population average and percentiles that might be used as cutoffs in the general clinical setting for the early identification of patients at risk of impaired functional and nutritional status and increased mortality. Whereas several reference values have been published, only the reference values generated in a healthy German population ($n$ = 214,732 adults) (20) were stratified according to sex, age, and body mass index (BMI), which are established major determinants of the phase angle.

It is known that ≤50% of patients with tumor disease experience cancer cachexia with loss of adipose and skeletal muscle

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tissue, resulting in weight loss, decreased muscle strength, reduced quality of life, and decreased survival (21). This prospective study therefore aimed to investigate the prognostic value of the fifth percentile of sex-, age-, and BMI-stratified phase angle reference values in cancer patients with respect to nutritional status, muscle function, quality of life, and 6-mo mortality. In a second step, to obtain standardized continuous data for patients in addition to the dichotomous variable (below or above the fifth reference percentile), we also studied the effect of the standardized phase angle (with a $z$ score to determine individual deviations from sex-, age-, and BMI-stratified phase angle reference values) on nutritional status, muscle function, quality of life, and 6-mo mortality.

## SUBJECTS AND METHODS

A total of 399 consecutively admitted patients (191 women and 208 men) to the Charité University Hospital (Department of Gastroenterology, Hepatology, and Endocrinology; the Department of Oncology and Hematology; or the Department of Radiotherapy) or the Helios Klinikum Bad Saarow were included between December 2006 and June 2007 in the study. Patients were considered for the study if they were older than 18 y with solid or hematologic tumor disease and gave written informed consent. Patients with implanted pacemakers or defibrillators were excluded because of the theoretical possibility of interference with the device activity due to the field of current induced by the impedance measurements; patients with neuromuscular disease, hemiplegia, or arthritis located in the hands were excluded to avoid potential confounders on muscle strength.

Measurements were made within 48 h of admission to hospital by 2 nutrition scientists. The Ethics Committee of the Charité-Universitätsmedizin Berlin approved the study. Demographic characteristics, such as age and sex, and clinical variables such as Karnofsky Performance Scale, duration of disease (defined as length of time in days since diagnosis), cancer location, and UICC (Union contre le Cancer) stage classification were documented. Moreover, number of drugs per day, number of comorbidities, type of treatment, and length of hospital stay were recorded. Patients were contacted via telephone 6 mo after the first assessment; if patients could not be reached, the local death register was consulted.

### Bioelectrical impedance measurements

Bioelectrical impedance analysis was performed by using a Nutriguard M (Data Input GmbH, Darmstadt, Germany) applying alternating electric currents of 800 microamperes ($\mu$A) at 50 kHz, and resistance (R) and reactance (Xc) were measured. The phase angle was calculated by using the following equation: phase angle (degrees) = arctan (Xc/R) $\times$ (180/$\pi$). The percentage of patients with a phase angle below the fifth percentile of sex-, age-, and BMI-stratified reference values was determined and compared with the percentage of patients with a phase angle above the fifth reference percentile. Values for the single fifth reference percentiles can be found in the article by Bosy-Westphal et al (20). Individual phase angle values were also standardized according to the reference values as follows: standardized phase angle = (observed phase angle − mean phase angle)/SD of the phase angle, where the mean and SD are from sex-, age-, and BMI-stratified reference values.

Measurements were made according to a standardized protocol as described in detail elsewhere (20). In brief, patients were measured in the morning after an overnight fast, in the supine position with arms and legs abducted from the body. Source and sensor electrodes (Ag/AgCl, Bianostic Classic Electrodes; Data Input GmbH) were placed on the dorsum of both the hand and foot of the dominant side of the body. The CV of repeated measurements of R and Xc at 50 kHz was assessed in 5 patients by the 2 observers: CVs were 2.8% and 3.1% for R and 2.6% and 2.9% for Xc.

### Anthropometric measurements

Body weight was measured while subjects were wearing light clothes with a portable electronic scale (Seca 910; Seca, Hamburg, Germany) to the nearest 0.1 kg, and height was measured with a portable stadiometer (Seca 220 telescopic measuring rod) to the nearest 0.1 cm. Weight and height were used to calculate BMI (weight in kilograms divided by height in meters squared).

Further anthropometric measurements were taken to describe nutritional status. Mid-upper arm circumference was determined, and triceps skinfold thickness was measured with a Holtain caliper (Crymych, United Kingdom) on the nondominant arm. Arm muscle area (AMA) and arm fat area (AFA) were calculated by applying the formula by Gurney and Jelliffe (22).

### Assessment of malnutrition: Subjective Global Assessment

The Subjective Global Assessment (SGA) was carried out by using the protocol developed by Detsky et al (23) to determine nutritional status. This assessment relies on the patient's history regarding weight loss, dietary intake, gastrointestinal symptoms, functional capacity, and physical signs of malnutrition (loss of subcutaneous fat or muscle mass, edema, ascites). Patients were classified as well nourished (A), moderately malnourished or suspected of being malnourished (B), or severely malnourished (C). The examiners were trained together and reached an interrater agreement of 90% in the test trial.

### Muscle function

#### *Handgrip strength*

Handgrip strength was measured in the nondominant hand with a Jamar dynamometer (Sammons Preston Rolyan, Chicago, IL). Patients performed the test while sitting comfortably with their shoulder adducted and forearm neutrally rotated, elbow flexed to 90°, and forearm and wrist in a neutral position. Patients were instructed to perform a maximal isometric contraction. The test was repeated within 30 s, and the highest value of 3 tests was used for the analysis.

#### *Expiratory peak flow*

Expiratory peak flow was assessed with the ASSESS Peak Flow Meter (Respironics HealthScan Inc, Cedar Grove, NJ). Patients were told to exhale as fast and forcefully as possible. The test was carried out 3 times, and the highest reading was recorded.

**TABLE 1**
Tumor type (*n* = subjects with tumors) and disease severity stage (% with this stage) in patients with cancer (*n* = 399)[1]

| | UICC stage 1 | UICC stage 2 | UICC stage 3 | UICC stage 4 |
|---|---|---|---|---|
| Gastrointestinal tumors (*n* = 149) | 13.4 | 10.7 | 14.8 | 61.1 |
| Head and neck or lung tumors (*n* = 71) | 3.3 | 1.4 | 18.3 | 76.1 |
| Urogenital tumors (*n* = 23) | 26.4 | 0 | 0 | 73.7 |
| Gynecologic tumors (*n* = 35) | 14.3 | 8.6 | 5.7 | 71.4 |
| Neuroendocrine, adrenal, and thyroid tumors (*n* = 30) | 30 | 3.3 | 6.7 | 60 |
| Others (*n* = 20) | 10.6 | 5.3 | 21.1 | 63.2 |

[1] UICC, Union contre le Cancer. Hematologic disease (*n* = 71): stage 1, 9.6%; stage 2, 19.2%; stage 3, 44.2%; stage 4, 26.9%.

## Health-related quality of life and depression

Quality of life was determined with the validated core questionnaire QLQ-30 of the European Organization for Research and Treatment of Cancer (EORTC). The questionnaire assesses quality of life in 9 domains. It includes 30 questions exploring 5 functional scales (physical, role, emotional, cognitive, and social functioning), 9 symptom scales (fatigue, nausea/vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial effect of disease), and one global scale (general health status).

Risk of depression was assessed by using the validated German version of the Center for Epidemiologic Studies–Depression Scale (24).

## Statistics

Statistical analysis was carried out by using the software package SPSS version 16 (SPSS Inc, Chicago, IL). All data are given as means and SDs. Pearson's correlation was calculated to assess the relation between variables.

Comparison between patients with a phase angle below or above the fifth reference percentile was performed with Student's *t* test or Mann-Whitney-Wilcoxon's test where indicated. The odds ratios (OR) and the positive predictive value for 6-mo mortality were calculated for patients with a phase angle below the fifth reference percentile. The standardized phase angle—as a measure of the individual deviation from the population average—was introduced as a risk factor together with disease severity according to UICC stage, tumor type, type of treatment, age, sex, BMI, and handgrip strength in all regression models. We used the standardized phase angle because the absolute phase angle was no longer significant when the standardized phase angle was introduced into the regression models.

A generalized linear model (GLM) univariate regression analysis was used to investigate the effect of standardized phase angle, disease severity according to UICC stage, tumor type, type of treatment, age, sex, and BMI on handgrip strength as an objective indicator of muscle function and on the global function score of the EORTC quality-of-life questionnaire. Backward stepwise multinomial logistic regression was used to define risk factors for malnutrition defined by SGA.

Survival time in days from the starting point of the study baseline was examined. A stepwise Cox proportional hazards regression model was used to calculate hazard ratios and 95% CIs and to identify predictors for enhanced 6-mo mortality. A receiver operating characteristic (ROC) curve analysis was then performed to compare these risk indicators with regard to survival prediction

**TABLE 2**
Nutritional functional and clinical variables in all patients (*n* = 399) and stratified according to the fifth percentile of the phase angle[1]

| | All (*n* = 399) | Below fifth percentile (*n* = 191) | Above fifth percentile (*n* = 208) | *P* |
|---|---|---|---|---|
| Age (y) | 63.0 ± 11.8 | 64.0 ± 11.8 | 62.1 ± 11.8 | NS |
| Sex (M/F) | 208/191 | 96/95 | 112/96 | NS |
| Nutritional variables | | | | |
| Malnourished according to SGA (B or C) (%) | 58.1 | 78.0 | 39.1 | <0.0001 |
| BMI (kg/m$^2$) | 24.9 ± 4.8 | 23.9 ± 4.6 | 25.8 ± 4.8 | <0.0001 |
| AMA (mm$^2$) | 4863.3 ± 1402.5 | 4379.2 ± 1243.6 | 5318.3 ± 1388.0 | <0.0001 |
| AFA (mm$^2$) | 2013.0 ± 1174.4 | 1737.6 ± 1023.3 | 2264.1 ± 1250.4 | <0.0001 |
| Protein intake (g/kg body weight) | 0.80 ± 0.43 | 0.76 ± 0.45 | 0.83 ± 0.41 | NS |
| Energy intake (g/kg body weight) | 23.6 ± 11.2 | 23.6 ± 11.8 | 23.6 ± 10.7 | NS |
| Functional variables | | | | |
| Handgrip strength (kg) | 27.2 ± 10.7 | 24.1 ± 9.749 | 30.1 ± 10.8 | <0.0001 |
| Peak expiratory flow (L/min) | 339.2 ± 135.7 | 302.9 ± 123.7 | 374.3 ± 136.7 | <0.0001 |
| Karnofsky Performance Scale (points) | 73.3 ± 13.72 | 69.0 ± 13.9 | 77.3 ± 11.2 | <0.0001 |
| Clinical variables | | | | |
| Advanced disease stage (%)[2] | 60.8 | 71.9 | 50.8 | <0.0001 |
| Length of stay (d) | 11.8 ± 11.2 | 12.7 ± 1.0 | 9.5 ± 0.7 | <0.001 |

[1] SGA, Subjective Global Assessment (B = moderately malnourished or suspected of being malnourished, C = severely malnourished); AMA, arm muscle area; AFA, arm fat area. Student's *t* test was used to compare the groups.

[2] Patients with solid tumor disease and hematologic disease were both included in this variable.

capacity, and the area under the curve (AUC) was calculated. Kaplan-Meier 6-mo survival curves were generated for patients with a phase angle below and above the fifth reference percentile.

## RESULTS

A total of 399 patients were included in the study. Tumor type and disease stages are given in **Table 1**. The majority of patients had tumor disease of the gastrointestinal tract. UICC stage 4 disease was most prevalent in patients with solid tumors. According to SGA, 132 patients (66 men) were classified as moderately malnourished and 100 as severely malnourished (52 men). Demographic, nutritional, and functional characteristics are given in **Table 2**; 47.2% of patients were not receiving active cancer treatment (not yet or no longer), 31.7% were receiving chemotherapy, 7.1% were receiving radiotherapy, 10.4% were receiving combined radio- and chemotherapy, and 3.6% were receiving other treatment.

### Fifth percentile of sex-, age-, and BMI-stratified reference values as a cutoff

The mean phase angle was 4.59° ± 1.12° and ranged from 2.04° to 8.30°. As expected, phase angle was slightly higher in men than in women (4.70° ± 1.17° in men compared with 4.47° ± 1.04° in women, $P = 0.043$) and correlated weakly with BMI ($r = 0.245$, $P < 0.000$) and inversely with age ($r = -0.362$, $P < 0.000$).

One hundred ninety-one patients (47.9%) had a phase angle below the fifth percentile of sex-, age-, and BMI-specific reference values. Age and sex distribution did not differ between groups above and below the fifth percentile of phase angle.

Seventy-eight percent of patients who had a phase angle below the fifth reference percentile were moderately or severely malnourished in contrast to 39.1% of patients with a phase angle above the fifth reference percentile (Table 2). Moreover, patients with a phase angle below the fifth reference percentile also had significantly lower handgrip strength, peak expiratory flow, and Karnofsky Performance Scale (Table 2). The close correlation between phase angle and handgrip strength is shown in **Figure 1**. Significantly reduced handgrip strength in both male and female patients with a phase angle below the fifth reference percentile is shown in **Figure 2**. Moreover, all function scales of the EORTC quality-of-life questionnaire apart from emotional function were significantly impaired in patients with a phase angle below the fifth reference percentile, and among the symptom scales fatigue, nausea and vomiting, pain, dyspnea, appetite loss, and constipation increased. The risk of depression as assessed by the Center for Epidemiologic Studies–Depression Scale was also higher in patients with a phase angle below the fifth reference percentile (**Table 3**). Although the reference values are stratified according to BMI, patients with a phase angle below the fifth reference percentile still had significantly lower BMI, AMA, and AFA values (Table 2).

When compared with patients with a higher phase angle, patients with a phase angle below the fifth reference percentile had more comorbidities (4.2 ± 2.3 compared with 3.5 ± 2.2, $P < 0.001$) and consumed more drugs per day (7.7 ± 3.8 compared with 5.4 ± 3.6, $P < 0.0001$) but did not have a longer duration of disease (28.4 ± 49.8 compared with 27.5 ± 46.9 mo, NS).

The use of the standardized phase angle (with a $z$ score to determine the individual deviations of the population average) showed that 64.4% of patients had phase angle values $< -1$ SD, 23.8% had values between $-1$ and 0 SD, and 11.8% had values $>0$ SD from the population average (**Figure 3**).

### Standardized phase angle as an independent risk factor for reduced functional status and malnutrition

The standardized phase angle was an independent predictor of muscle function as were sex, age, and SGA in a GLM regression model and an independent predictor for EORTC global function score next to SGA, BMI, handgrip strength, and age (*see* **Table 4**). In contrast, disease severity, tumor entity, and type of treatment had no significant effect on either subjective or objective functional variables.

Multinomial logistic regression showed that a high standardized phase angle had the strongest positive effect on both

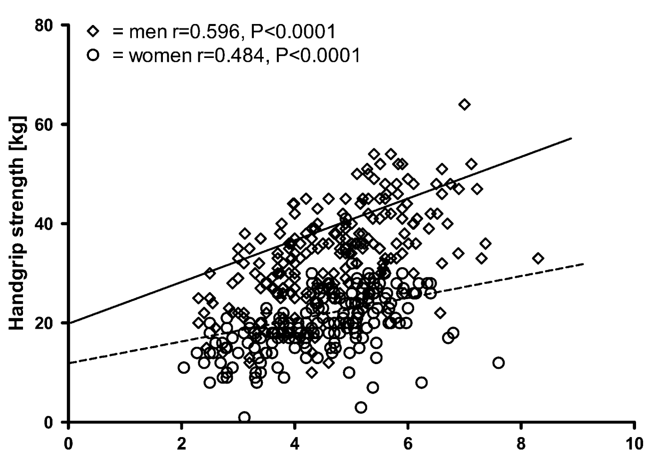


**FIGURE 1.** Pearson's correlation between phase angle and handgrip strength in men ($n = 208$, solid line) and women ($n = 191$, dotted line).

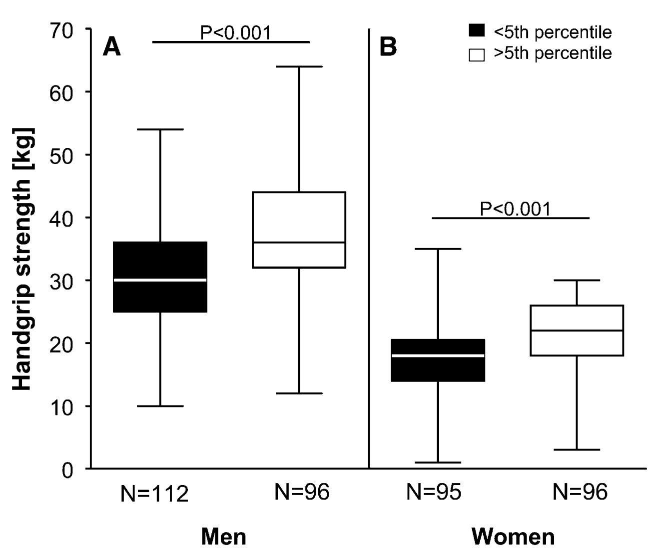


**FIGURE 2.** Box and whiskers plots comparing handgrip strength in men ($n = 208$) and women ($n = 191$) with a phase angle below or above the 5th reference percentile. Mann-Whitney-Wilcoxon's test was used to compare the median handgrip strength.

**TABLE 3**
Quality of life and risk of depression in all patients ($n$ = 399) and stratified according to the fifth percentile of the phase angle[1]

| | All ($n$ = 399) | Below fifth percentile ($n$ = 191) | Above fifth percentile ($n$ = 208) | $P$ |
|---|---|---|---|---|
| Global health status | 42.9 ± 24.8 | 35.5 ± 21.9 | 49.4 ± 25.4 | <0.0001 |
| Quality-of-life total score | 46.6 ± 7.4 | 45.7 ± 7.3 | 47.7 ± 6.5 | <0.0001 |
| Functional scales | | | | |
| Physical function | 61.6 ± 27.8 | 51.2 ± 27.4 | 70.7 ± 24.9 | <0.0001 |
| Role function | 48.1 ± 36.7 | 36.1 ± 32.7 | 58.8 ± 36.9 | <0.0001 |
| Emotional function | 60.1 ± 25.9 | 59.6 ± 27.0 | 60.6 ± 24.9 | NS |
| Cognitive function | 74.9 ± 26.2 | 70.1 ± 28.1 | 79.2 ± 23.6 | <0.001 |
| Social function | 59.2 ± 35.9 | 55.1 ± 36.8 | 62.9 ± 34.7 | 0.039 |
| Symptom scales | | | | |
| Fatigue | 52.7 ± 30.1 | 61.3 ± 28.4 | 45.0 ± 29.5 | <0.0001 |
| Nausea and vomiting | 18.4 ± 28.5 | 22.2 ± 30.3 | 15.1 ± 26.3 | 0.018 |
| Pain | 40.8 ± 35.7 | 45.6 ± 35.5 | 36.6 ± 35.5 | 0.016 |
| Dyspnea | 35.4 ± 34.97 | 43.6 ± 35.6 | 27.9 ± 32.8 | <0.0001 |
| Insomnia | 42.9 ± 37.5 | 45.5 ± 36.7 | 40.8 ± 38.1 | NS |
| Appetite loss | 39.3 ± 40.3 | 49.5 ± 40.6 | 30.1 ± 37.8 | <0.0001 |
| Constipation | 22.6 ± 33.9 | 26.4 ± 34.7 | 19.2 ± 32.9 | 0.042 |
| Diarrhea | 15.7 ± 29.2 | 16.8 ± 29.3 | 14.7 ± 29.0 | NS |
| Financial difficulties | 29.7 ± 36.3 | 28.7 ± 34.5 | 30.6 ± 37.9 | NS |
| CES-D | 19.8 ± 10.1 | 21.3 ± 10.4 | 18.7 ± 9.8 | 0.027 |

[1] CES-D, Center for Epidemiologic Studies–Depression Scale. Student's $t$ test was used to compare the groups.

moderate (SGA B) and severe malnutrition (SGA C) next to the BMI, whereas higher age and UICC stage 4 had a negative effect on malnutrition (*see* **Table 5**).

Patients with a phase angle below the fifth reference percentile also exhibited a significantly higher 6-mo mortality risk (OR: 4.0; 95% CI: 2.4, 6.8; $P < 0.001$) (*see* **Figure 4**) and a 37.4% probability of death (positive predictive value). Survival was particularly impaired within the first 30 d after assessment in these patients as shown in Figure 4.

### Standardized phase angle for prediction of outcome and 6-mo mortality

Length of hospitalization was considerably higher in patients with a phase angle below the fifth reference percentile (*see* Table 1). Six-month mortality data were obtained in 362 patients (90.7%). Ninety-one patients died within 6 mo (median follow-up: 180 d; range: 2–405 d), whereas most patients (68, 74.7%) had a phase angle below the fifth reference percentile.

Age, sex, disease severity according to UICC stage (or the respective hematologic score), SGA, handgrip strength, and standardized phase angle were entered in a stepwise Cox proportional hazards regression model in which standardized phase angle, disease severity, and malnutrition defined by SGA emerged as significant independent predictors (*see* **Table 6**) for 6-mo mortality.

ROC analysis revealed that the standardized phase angle with an AUC of 0.734 performed better than both SGA (AUC: 0.697) and disease severity (AUC: 0.622) with regard to survival prediction (*see* **Figure 5**).

## DISCUSSION

With this prospective study in 399 patients with cancer, we showed that the fifth percentile of sex-, age-, and BMI-stratified reference values (20) is a suitable and clinically relevant indicator of cancer cachexia–related symptoms and decreased survival. Patients with a phase angle below the fifth reference percentile had a significantly impaired nutritional and functional status, decreased quality of life, and increased morbidity and shortened survival. The use of the fifth reference percentile allows identification of patients at risk who are in particular need of intensified medical and nutritional attention. Moreover,

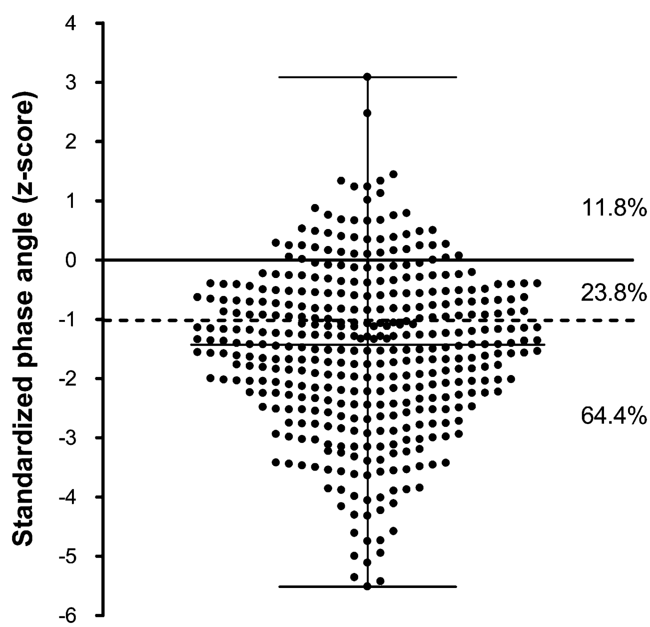


**FIGURE 3.** Distribution of the standardized phase angle [with a $z$ score to determine the individual deviations from the reference values; standardized phase angle = (observed phase angle − mean phase angle)/SD of the phase angle] showing median and range (minimum–maximum: −5.52–3.09). The dotted line indicates values < −1 SD. $n$ = 399

**TABLE 4**
Significant risk factors for objective and subjective functional status identified by a generalized linear model univariate regression analysis[1]

| | Coefficient B | 95% CI | *P* |
|---|---|---|---|
| Global function score (EORTC) | | | |
| Standardized phase angle | 4.121 | 2.126, 6.115 | <0.0001 |
| SGA | −5.069 | −8.354, −1.783 | 0.003 |
| BMI | −0.611 | −1.096, −0.126 | 0.014 |
| Handgrip strength | 0.307 | 0.081, 0.532 | 0.008 |
| Age | 0.203 | 0.004, 0.402 | 0.045 |
| Handgrip strength | | | |
| Sex | −14.796 | −16.202, −13.390 | <0.0001 |
| Age | −0.229 | −0.289, −0.169 | <0.0001 |
| Standardized phase angle | 1.902 | 1.321, 2.483 | <0.0001 |
| SGA | −1.239 | −2.212, −0.266 | <0.0001 |

[1] *n* = 399. Age, sex, standardized phase angle, Subjective Global Assessment (SGA), BMI, handgrip strength [on the European Organization for Research and Treatment of Cancer (EORTC) scale only], tumor type, disease severity, and type of treatment were introduced into the generalized linear model univariate regression model.

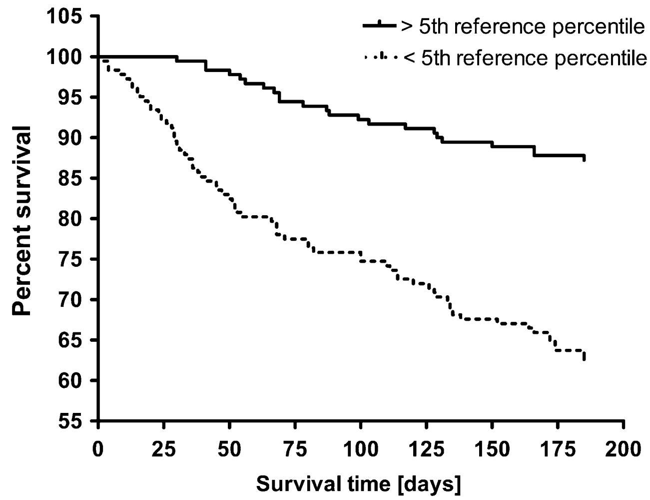


**FIGURE 4.** Kaplan-Meier 6-mo survival curves in patients below (*n* = 183, dotted line) and above (*n* = 179, solid line) the fifth percentile of phase angle reference values.

transforming phase angle values into a *z* score allows the assessment and quantification of individual deviation of patients from sex-, age-, and BMI-specific population averages, which clearly enhances its predictive power. The standardized phase angle emerged as an independent predictor for impaired muscle function and global function score (EORTC), malnutrition, and increased 6-mo mortality, where it was shown to perform better than malnutrition as assessed by SGA and disease severity.

Although our findings are consistent with the results of other studies that have shown the prognostic potential of the phase angle (13), the suitability of a phase angle reference percentile as a simple, clinically relevant cutoff has, to our knowledge, not been previously published. A generally applicable prognostic cutoff for clinical practice has been lacking because most studies have generated cutoffs within their study population, which questions their adequacy in other disease settings. Generating cutoffs within a very sick population with an overall reduced prognosis might also limit their general applicability.

**TABLE 5**
Risk factors for malnutrition assessed by Subjective Global Assessment (SGA) identified by backward stepwise multinomial logistic regression[1]

| | Odds ratio | 95% CI | *P* |
|---|---|---|---|
| Moderate malnutrition (SGA B) | | | |
| Standardized phase angle | 0.633 | 0.504, 0.794 | <0.0001 |
| BMI | 0.917 | 0.866, 0.972 | 0.004 |
| Age | 1.036 | 1.013, 1.060 | 0.002 |
| UICC stage 4[2] | 4.344 | 1.721, 10.966 | 0.002 |
| Severe malnutrition (SGA C) | | | |
| Standardized phase angle | 0.449 | 0.337, 0.597 | <0.0001 |
| BMI | 0.879 | 0.815, 0.948 | 0.001 |
| Age | 1.051 | 1.021, 1.082 | 0.001 |
| UICC stage 4[2] | 4.071 | 1.62, 12.164 | 0.012 |

[1] *n* = 399. SGA B, moderately malnourished or suspected of being malnourished; SGA C, severely malnourished; UICC, Union contre le Cancer. Age, sex, standardized phase angle, SGA, BMI, handgrip strength, tumor type, disease severity, and type of treatment were introduced into the backward stepwise multinomial logistic regression model.
[2] Reference variable: UICC stage 1.

Furthermore, standardizing the phase angle according to sex-, age-, and BMI-stratified reference values enhances the prognostic relevance of the phase angle, because individual deviations from population norms provide better information than absolute values.

A limitation of the study is the use of 2 examiners, which might introduce interrater variability bias, even though they were trained together by one person. Also, the study population was heterogeneous with regard to tumor entity, type of treatment, and disease duration and severity, which weakens the results. A more homogeneous study population would have allowed more robust conclusions.

Many studies have emphasized the close correlation between nutritional status and phase angle. Because there is a great body of evidence that malnutrition is a predictor of shortened survival in cancer, the association between phase angle and survival is not surprising. However, although the phase angle has been proposed as a marker of clinically relevant malnutrition in patients with liver cirrhosis (characterized by decreased body cell mass, increased extracellular mass, and low skeletal muscle mass) (18), it failed to reliably detect clinically relevant malnutrition in other populations, such as hemodialysis patients with severe malnutrition identified by SGA (25). Similarly, Gupta et al (26) observed only modest sensitivities and specificities for different cutoffs of the

**TABLE 6**
Predictors for 6-mo mortality from a stepwise Cox proportional hazards regression model[1]

| | HR | 95% CI | *P* |
|---|---|---|---|
| Standardized phase angle | 0.567 | 0.470, 0.683 | <0.0001 |
| SGA | 1.617 | 1.218, 2.148 | 0.001 |
| UICC stage 3[2] | 10.812 | 1.495, 77.960 | 0.018 |
| UICC stage 4[2] | 10.455 | 1.377, 79.352 | 0.023 |

[1] *n* = 362. UICC, Union contre le Cancer; HR, hazard ratio; SGA, Subjective Global Assessment. Age, sex, standardized phase angle, SGA, handgrip strength, tumor type, disease severity, and type of treatment were introduced into the Cox proportional hazards regression model.
[2] Reference variable: UICC stage 1.

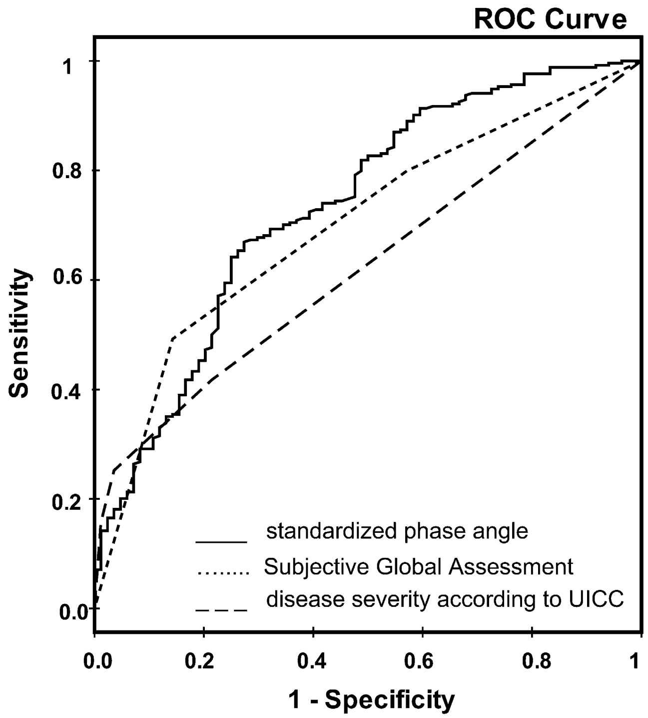


**FIGURE 5.** Receiver operating characteristic (ROC) curve analysis comparing standardized phase angle, malnutrition (Subjective Global Assessment), and disease severity [Union contre le Cancer (UICC)] for prediction of survival. The calculated area under the curve (AUC) for the standardized phase angle was 0.734, the AUC for Subjective Global Assessment was 0.697, and the AUC for disease severity was 0.622; $n$ = 362. Subjective Global Assessment and UICC stage were inversely coded to be portrayed in the analysis together with the standardized phase angle.

phase angle when comparing it with the SGA in patients with advanced colorectal cancer. Nevertheless, malnutrition has a strong effect on electric tissue properties and thus on the phase angle (ie, reduced reactance with maintained resistance, indicating comparable hydration but loss of cell mass in malnutrition) (27).

In this study, malnutrition as assessed by SGA and phase angle both emerged as independent risk factors for impaired 6-mo mortality, which suggests that the phase angle is more than an indicator of nutritional status.

Phase angle has also been associated with function (18). In agreement with this finding, we showed earlier that both resistance and reactance are predictors of muscle strength (28), and in this study population phase angle correlated with handgrip strength (Figure 1) and peak expiratory flow, functional components of the EORTC quality-of-life questionnaire and the Karnofsky Performance Scale (data not shown).

Interestingly, the standardized phase angle performed better than did handgrip strength as a risk indicator with regard to 6-mo mortality. Handgrip strength has been shown repeatedly to be an excellent indicator of short- and long-term outcome (29–32), but in this setting handgrip strength lost its prognostic significance when the standardized phase angle was included in the regression models for survival analysis.

Our focus was to study the clinical relevance of the fifth phase angle reference percentile with regard to a multivariable profile including muscle function, nutritional status, and quality of life (which are frequently impaired in cancer cachexia); risk of depression; and 6-mo survival. Fearon et al (33) used a similar symptom complex with decreased lean body mass and handgrip strength, Karnofsky Performance Scale, and components of the EORTC questionnaire to describe the adverse functional aspects of cachexia in pancreatic cancer. They observed that a 3-factor profile including only weight loss, reduced nutritional intake, and increased inflammation was associated with the effect of cachexia on physical function, but they did not evaluate the phase angle in their study.

In conclusion, standardizing the phase angle with regard to sex-, age-, and BMI-stratified reference values enhances its predictive power. The standardized phase angle is an independent predictor for impaired functional and nutritional status and a better indicator of 6-mo mortality than are malnutrition and disease severity in cancer. In the clinical setting, the fifth phase angle reference percentile appears to be a simple and prognostically relevant cutoff for detection of patients with cancer at risk of these factors.

The authors' responsibilities were as follows—KN and MP: study concept; KN, NS, and MP: writing of the manuscript; RS and KN: statistical analysis; NS, DZ, AS, and CS: data collection and management; and AB-W: critical input and revision of the manuscript. The authors declared that they had no financial conflicts of interest.

## REFERENCES

1. Gupta D, Lis CG, Dahlk SL, Vashi PG, Grutsch JF, Lammersfeld CA. Bioelectrical impedance phase angle as a prognostic indicator in advanced pancreatic cancer. Br J Nutr 2004;92:957–62.
2. Gupta D, Lammersfeld CA, Vashi PG, et al. Bioelectrical impedance phase angle as a prognostic indicator in breast cancer. BMC Cancer 2008;8:249.
3. Gupta D, Lammersfeld CA, Vashi PG, et al. Bioelectrical impedance phase angle in clinical practice: Implications for prognosis in stage IIIB and IV non-small cell lung cancer. BMC Cancer 2009;9:37.
4. Ott M, Fischer H, Polat H, et al. Bioelectrical impedance analysis as a predictor of survival in patients with human immunodeficiency virus infection. J Acquir Immune Defic Syndr Hum Retrovirol 1995;9:20–5.
5. Baumgartner RN, Chumlea WC, Roche AF. Bioelectric impedance phase angle and body composition. Am J Clin Nutr 1988;48:16–23.
6. Nyboer J, Bagno S, Nims LF. The electrical impedance plethysmograph an electrical volume recorder. Washington, DC: National Research Council, Committee on Aviation, 1943. (Report 143.)
7. Barbosa-Silva MC, Barros AJ. Bioelectrical impedance analysis in clinical practice: A new perspective on its use beyond body composition equations. Curr Opin Clin Nutr Metab Care 2005;8:311–7.
8. Gupta D, Lammersfeld CA, Burrows JL, et al. Bioelectrical impedance phase angle in clinical practice: Implications for prognosis in advanced colorectal cancer. Am J Clin Nutr 2004;80:1634–8.
9. Nescolarde L, Piccoli A, Roman A, et al. Bioelectrical impedance vector analysis in haemodialysis patients: Relation between oedema and mortality. Physiol Meas 2004;25:1271–80.
10. Piccoli A, Brunani A, Savia G, et al. Discriminating between body fat and fluid changes in the obese adult using bioimpedance vector analysis. Int J Obes Relat Metab Disord 1998;22:97–104.
11. Piccoli A, Pittoni G, Facco E, Favaro E, Pillon L. Relationship between central venous pressure and bioimpedance vector analysis in critically ill patients. Crit Care Med 2000;28:132–7.
12. Schwenk A, Ward LC, Elia M, Scott GM. Bioelectrical impedance analysis predicts outcome in patients with suspected bacteremia. Infection 1998;26:277–82.
13. Toso S, Piccoli A, Gusella M, et al. Altered tissue electric properties in lung cancer patients as detected by bioelectric impedance vector analysis. Nutrition 2000;16:120–4.
14. Barbosa-Silva MC, Barros AJ. Bioelectric impedance and individual characteristics as prognostic factors for post-operative complications. Clin Nutr 2005;24:830–8.
15. Ikizler TA, Wingard RL, Harvell J, Shyr Y, Hakim RM. Association of morbidity with markers of nutrition and inflammation in chronic hemodialysis patients: A prospective study. Kidney Int 1999;55:1945–51.

16. Mushnick R, Fein PA, Mittman N, Goel N, Chattopadhyay J, Avram MM. Relationship of bioelectrical impedance parameters to nutrition and survival in peritoneal dialysis patients. Kidney Int Suppl 2003;87:S53–6.
17. Schwenk A, Beisenherz A, Romer K, Kremer G, Salzberger B, Elia M. Phase angle from bioelectrical impedance analysis remains an independent predictive marker in HIV-infected patients in the era of highly active antiretroviral treatment. Am J Clin Nutr 2000;72:496–501.
18. Selberg O, Selberg D. Norms and correlates of bioimpedance phase angle in healthy human subjects, hospitalized patients, and patients with liver cirrhosis. Eur J Appl Physiol 2002;86:509–16.
19. Shime N, Ashida H, Chihara E, et al. Bioelectrical impedance analysis for assessment of severity of illness in pediatric patients after heart surgery. Crit Care Med 2002;30:518–20.
20. Bosy-Westphal A, Danielzik S, Dorhofer RP, Later W, Wiese S, Muller MJ. Phase angle from bioelectrical impedance analysis: Population reference values by age, sex, and body mass index. JPEN J Parenter Enteral Nutr 2006;30:309–16.
21. Tisdale MJ. Cancer cachexia. Curr Opin Gastroenterol 2010;26: 146–51.
22. Gurney JM, Jelliffe DB. Arm anthropometry in nutritional assessment: Nomogram for rapid calculation of muscle circumference and cross-sectional muscle and fat areas. Am J Clin Nutr 1973;26:912–5.
23. Detsky AS, McLaughlin JR, Baker JP, et al. What is subjective global assessment of nutritional status? JPEN J Parenter Enteral Nutr 1987;11: 8–13.
24. Radloff LS. The CES-D scale: A self report depression scale for research in the general population. Appl Psychol Meas 1977;1:385–401.
25. Maggiore Q, Nigrelli S, Ciccarelli C, Grimaldi C, Rossi GA, Michelassi C. Nutritional and prognostic correlates of bioimpedance indexes in hemodialysis patients. Kidney Int 1996;50:2103–8.
26. Gupta D, Lis CG, Dahlk SL, et al. The relationship between bioelectrical impedance phase angle and subjective global assessment in advanced colorectal cancer. Nutr J 2008;7:19.
27. Norman K, Smoliner C, Kilbert A, Valentini L, Lochs H, Pirlich M. Disease-related malnutrition but not underweight by BMI is reflected by disturbed electric tissue properties in the bioelectrical impedance vector analysis. Br J Nutr 2008;100:590–5.
28. Norman K, Pirlich M, Sorensen J, et al. Bioimpedance vector analysis as a measure of muscle function. Clin Nutr 2009;28:78–82.
29. Bohannon RW. Dynamometer measurements of hand-grip strength predict multiple outcomes. Percept Mot Skills 2001;93:323–8.
30. Rantanen T, Harris T, Leveille SG, et al. Muscle strength and body mass index as long-term predictors of mortality in initially healthy men. J Gerontol A Biol Sci Med Sci 2000;55:M168–73.
31. Sasaki H, Kasagi F, Yamada M, Fujita S. Grip strength predicts cause-specificmortality in middle-aged and elderly persons. Am J Med 2007; 120:337–42.
32. Vecchiarino P, Bohannon RW, Ferullo J, Maljanian R. Short-term outcomes and their predictors for patients hospitalized with community-acquired pneumonia. Heart Lung 2004;33:301–7.
33. Fearon KC, Voss AC, Hustead DS. Definition of cancer cachexia: Effect of weight loss, reduced food intake, and systemic inflammation on functional status and prognosis. Am J Clin Nutr 2006; 83:1345–50.