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Bioimpedance-derived phase angle and mortality among older people

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Abbreviations: BMI: body mass index; BIA: bioelectrical impedance analysis, FFMI: fat-free mass index; CIRS: Cumulative Illness Rating Score; ROC: receiver operating characteristic.

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ABSTRACT

Background: Phase angle measured by bioelectrical impedance analysis (BIA) may be a marker of health state.

Objective: This historical cohort study of prospectively collected BIA measurements aims to investigate the link between phase angle and mortality in older people and evaluate whether a phase angle cut-off can be defined.

Design: We included all adults aged ≥65 years who underwent a BIA measurement by the Nutriguard® device at the Geneva University Hospitals. We retrieved retrospectively the phase angle and co-morbidities at the last BIA measurement and the mortality until December 2012. We calculated phase angle standardized for sex, age, and body mass index, using reference values determined with the same brand of BIA device. Sex-specific and standardized phase angle were categorized into quartiles. The association of mortality with sex-specific or standardized phase angle was evaluated through univariate and multivariate Cox regression models, Kaplan-Meier curves, and ROC curves.

Results: We included 1307 (38% women) participants, among whom 628 (44% women) died. In a multivariate Cox regression model adjusted for co-morbidities and setting of measurement (ambulatory vs. hospitalized), the protective effect against mortality increased progressively as the standardized phase angle quartile increased (HR 0.71 (95% CI 0.58, 0.86), 0.53 (95% CI 0.42, 0.67), 0.32 (95% CI 0.23, 0.43)). The discriminative value of continuous standardized phase angle, assessed as the area under the ROC curve, was 0.72 (95%CI 0.70, 0.75). We could not define an acceptable phase angle cut-off for individual prediction of mortality (LK), based on sensibility and specificity values.

Conclusions: This study shows the association of phase angle and mortality in older patients, independently of age, sex, comorbidities, BMI categories, and setting of measurement.

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INTRODUCTION

Bioelectrical impedance (BIA) is widely used to assess body composition in clinical practice. BIA-derived fat free mass index has been related to mortality (1). However, it requires the use of validated population-specific equations and is inaccurate in the case of altered fluid balance, as often found in older people, body shape asymmetries, and extreme body mass indices (2).

In view of these limitations, an increasing number of studies have focused on raw BIA-derived electrical parameters, such as phase angle, whose accuracy does not rely on equations or anthropometrical characteristics. In BIA measurements, a generator applies an alternating electrical current to the human body. The human body presents an overall opposition to this current, termed bioelectrical impedance, consisting of two elements: the reactance which is due to the capacitance (electrostatic storage) of cellular membranes, tissue interfaces and nonionic tissues, and the resistance which refers to the pure resistive behavior of tissues due to extra- and intracellular water. In response to an alternating electrical current, the capacitance causes a time delay between the voltage waveform and the current waveform which lags behind (3,4). This time delay can be expressed in units of time, i.e., phase shift, or as a percent of the entire wave period consisting of 360 degrees, i.e., phase angle. Mathematically, the phase angle can be calculated from the arctangent of the measured reactance to resistance ratio (3). Although its metabolic significance is not yet clear, the phase angle has been reported to reflect cell membrane integrity, cell size and/or the distribution of intra- vs. extracellular water (5).

A low phase angle has been shown to predict mortality in patients with critically illness (6) (7) or specific chronic diseases such as cancer (8), chronic heart failure (9), liver cirrhosis (10), HIV infection (11), amyotrophic lateral sclerosis (12), and hemodialysis (13). Thus, the phase angle may be viewed as a prognostic marker in specific diseases. However, only a few large cohort studies have evaluated the link between phase angle and mortality in polymorbid older people (14,15). These studies have found a fourfold increase in in-hospital mortality with a phase angle below 3.5° (vs. 5.0-5.5°) (14) or a twofold higher risk of 12-year mortality with a

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phase angle below 5.4° in women (vs. >6.02°) and 5.6° in men (vs. >6.34°) (15). These studies confirm the association of low phase angle and high mortality, but they have found variable cut-offs, likely due to the type of BIA device used, the characteristics of the study populations and their co-morbidities, and the length of considered follow-up.

We hypothesized that a low phase angle is associated with an increased mortality risk, independently of the co-morbidities and the setting of measurement, i.e. ambulatory or hospitalized. If this hypothesis was confirmed, it would suggest that phase angle could be used as a monitoring tool to evaluate the impact of therapeutic strategies, as drugs or lifestyle changes. This study aims to 1) investigate the link between phase angle and mortality in older hospitalized and ambulatory people, 2) compare the impact of phase angle vs. fat-free mass index (FFMI) on mortality, and 3) evaluate whether a phase angle cut-off value can be defined with respect to mortality.

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SUBJECTS AND METHODS

This retrospective study includes all BIA measurements performed in people aged ≥65 years between 1990 and 2011 at the Geneva University Hospitals, either for research or clinical purpose. The indications for BIA measurements in the clinical and research settings at our hospital, the data retrieval from our hospital and research computer database, and the data merging has been detailed elsewhere (1). We included only the last available BIA measurement of each person, as it was the closest to death and thus the most likely to be associated with mortality. This protocol was accepted by the Ethical Committee of the HUG, who waived the need to obtain informed consent, and was registered under clinicaltrials.gov (NCT01472679).

We chose to use phase angles measured by a single device as the values may differ between devices, precluding their use in the same database. We focused on the measurements performed with the Nutriguard® (Data Input, Pöcking, Germany) because 1) this device is being used since 2001 until now, in contrast to other devices that were used from 1990 to 2001; and 2) we could calculate a sex-, age- and body mass index (BMI)-standardized phase angle (Z-score) using the German phase angle reference values, which were measured with the same brand of BIA device (16). The following formula was used for the calculation of the Z-score: Standardized phase angle = (observed phase angle - mean reference phase angle)/SD of reference phase angle.

We excluded subjects with missing height (n=4), weight (n=3), and residency abroad (n=14), as we could not retrieve their mortality data, and those who died on the day of measurement (n=143) as they are not considered in Cox regression models, and those with BIA measurements performed with another device than the Nutriguard ® (n=1878).

All the BIA measurements were performed while the person was lying in the supine position. Four electrodes were placed on the right hand, wrist, foot, and ankle and were connected to a generator applying an alternating electrical current of 0.8 mA and 50 kHz. We reported the

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phase angle, impedance, resistance, and reactance and calculated the fat-free mass by our BIA formula, developed in the population of the Geneva area (17) and validated in older people against dual energy x-ray absorptiometry (18). In our routine procedure, the weight and height of the patients are measured on the same day as BIA assessments. FFMI was calculated as fat-free mass (kg)/height $(m)^2$ and BMI as weight (kg)/height $(m)^2$.

Co-morbidities and medication were retrieved, whenever available, from the computerized medical records of the Geneva University Hospitals at the time of BIA measurements and reported in the form of the Cumulative Illness Rating Scale (CIRS). This comorbidity index rates 14 organs and systems from 0 (healthy) to 4 (severe disease) by taking into account the symptoms, laboratory findings, medical history, lifestyle factors, and medications. In total, it ranges from 0 to 56 points (19,20).

The date and cause of death were obtained from the computer database of the Geneva University Hospitals, the Geneva population register of deaths (21), and the Swiss National Cohort (22). The latter is a Swiss data platform linking anonymously national censuses with all-cause and cause-specific mortality coded through the International Statistical Classification of Diseases and Related Health Problems (10th revision).

Statistics

The normality of distribution for continuous data was checked with Shapiro-Wilk tests. As it was not verified for age, BMI, CIRS-score, phase angle, and standardized phase angle at the time of the last BIA measurement, the data were categorized into the followings: age as 65-74 yrs, 75-84 yrs and ≥85 yrs; BMI as <18.5, 18.5-24.9, 25-29.9 and ≥30 kg/m^2; CIRS score and standardized phase angle as quartiles; and phase angle as sex-specific quartiles. Quartile 1 corresponded to the lowest phase angle values and was used as a reference category in subsequent analyses. Continuous data were compared between men and women or hospitalized and ambulatory people with Wilcoxon ran-sum u test, and ordinal data with Mann-Whitney U

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tests.

Using univariate Cox regressions, we first evaluated the association of raw BIA-derived electrical parameters, such as quartiles, with mortality to verify whether phase angle is the best predictor of mortality among the measured electrical parameters. The multivariate included three Cox regressions models: the first two models used sex-specific phase angle quartiles (women: model 1; men: model 2) and were adjusted for age category, BMI category, CIRS quartile, and hospitalized vs. ambulatory state. The third Cox regression model used standardized phase angle quartiles adjusted only for CIRS quartiles and hospitalized vs. ambulatory state (model 3). To evaluate whether phase angle better predicts mortality than FFMI alone, we replaced the sex-specific phase angle quartiles in model 1 and 2 by sex-specific FFMI quartiles or added sex-specific FFMI quartiles. For each Cox regression model, we calculated hazards ratio (HRs) and their 95% CI, the adjusted R-squared (R^2), and 95% CI with 5000 bootstrap replications. R^2 corresponds to the variance of mortality explained by each model and allows comparisons between the different Cox regression models. We tested the collinearity between predictor variables by calculating their variance inflation factor. The latter values were all below 10, indicating the absence of collinearity. We performed Kaplan-Meier analysis and calculated mortality trends according to sex-specific and standardized phase angle quartiles.

To determine the discriminative ability of the phase angle, we computed receiver operating characteristic (ROC) curves predicting mortality from logistic models. These models included phase angle in women, phase angle in men or standardized phase angle as the only dependent continuous variable.

Statistical analyses were run with Stata software version 13.1 (TX, USA). The limit of significance was set at $p<0.05$.

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RESULTS

We included 1307 people (38% women) whose characteristics at the last BIA measurement are shown in **Table 1**. The standardized phase angle was below -1SD in 919 (70%) people and below -2SD in 523 (40%) people. The cut-offs for the sex-specific phase angle quartiles, the standardized phase angle quartiles and the CIRS quartiles are shown in **Table 2**. Among the included people, 49% were measured in the hospital setting. Compared to ambulatory people, hospitalized women and men had a lower phase angle, were older and had more co-morbidities (**Supplemental Table 1**).

Univariate Cox regression analyses showed that, on the basis of R^2 (95%CI), phase angle was a better predictor of mortality than resistance, reactance, and impedance (**Supplemental Table 2**). The risk of mortality decreases as the phase angle or standardized phase angle quartiles increase in univariate (**Table 3**) and multivariate **(Table 4)** Cox regression models. When replacing sex-specific phase angle quartiles by sex-specific FFMI quartiles in models 1 and 2, the R^2 (95% CI) decreased from 15.6 (11.4, 27.2) to 8.6 (3.8, 16.5) in women and from 21.5 (17.1, 29.2) to 14.2 (9.4, 20.2) in men. The addition of sex-specific FFMI quartiles to models 1 and 2 led to an R^2 (95%CI) of 15.1 (11.7, 28.0) in women and 21.3 (17.4, 29.7) in men. Thus, the phase angle better predicts mortality than BIA-derived FFMI, and the addition of FFMI to phase angle does not improve the Cox regression models. Kaplan-Meier analyses showed the higher risk of mortality with lower phase angle (**Supplemental figure 1**) or standardized phase angle quartiles (**Figure 1**). Mortality trends are shown in **Supplemental Table 3.**

The discriminative value of continuous phase angle, as assessed by the area under the ROC curve, was 0.72 (95% CI 0.67, 0.76) in women and 0.76 (95% CI 0.73, 0.79) in men while the discriminative value of continuous standardized phase angle amounted to 0.72 (95%CI 0.70, 0.75). The best thresholds were 3.97 in women (sensibility and specificity 66%) and 4.38 in men (sensibility and specificity 68%) for continuous phase angle, and -1.41 for standardized

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166 phase angle (sensibility and specificity 67%).

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DISCUSSION

This study shows that phase angle or standardized phase angle quartiles predict mortality in older people, even when adjusted for co-morbidities or setting of measurement. Phase angle is a stronger predictor of mortality than other BIA-derived electrical parameters and BIA-derived FFMI. However, the discriminative ability of continuous phase angle or standardized phase angle is not good enough to perform individual predictions. This is supported by the fact that the dichotomization of phase angle or standardized phase angle by thresholds leads to a significant loss of predictive capacity.

Few other articles have linked phase angle with mortality in older people unselected for their primary disease. Wirth et al. included 1071 patients aged >60 yrs who were admitted to an acute German geriatric hospital unit, mainly for heart failure, dementia or acute stroke (14). All BIA measurements were performed with a device of the same brand as in our study within 3 days of admission, and mortality was considered until the end of the hospital stay. They found a significantly lower phase angle in women than men (4.1±1.1° vs. 4.4±1.2°), but this gender difference disappeared after correction for age. The mortality risk was increased fourfold in patients with an age-corrected phase angle <3.5° vs. all other patients, although it was not adjusted for co-morbidities or BMI. No Cox regressions were performed. In our study, a value <3.5° corresponds to phase angle values of quartile 1. The mortality trends show that the risk of mortality decreases progressively with higher phase angle quartiles and is over 4 times higher in quartile 1 than in quartile 4.

In another study, 4667 US ambulatory frail people aged >60 yrs underwent a phase angle measurement by a Valhalla device and were followed over 12 years (15). Cox regressions were performed for men and women separately and adjusted for age, ethnicity and five self-reported physician diagnosis (diabetes, chronic lung disease, chronic kidney disease, cardiovascular disease and arthritis). The mean phase angle was 6.3° in women and 6.7° in men. A phase angle value in the lowest quintile (2.7-5.4° in women, 3.1-5.6° in men) more than doubled the risk of

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mortality compared to higher phase angle values. The association between phase angle and mortality was also found in people with limited or no co-morbidities at the time of BIA measurement. Thus, our study confirms that phase angle can be considered as a prognostic marker in a population of older people, as in both studies detailed above.

The mean phase angle in our study was similar to the values of the aforementioned German study but was lower than in the American study. These differences may be related to the considered BIA device and the study population. Indeed, in people aged >70 yrs, the American reference values of phase angle measured by an RJL device were 5.6±1.0° in women and 6.2±1.0° in men (23) while the German reference values, measured by a Data Input device, were 5.1±0.8° and 5.1±0.9° in normal-weight women and men, respectively (16). In order to overcome the problematic issue of device-dependent phase angles and in the absence of a gold standard method, we suggest that the phase angle values should preferentially be compared with the measurements performed with BIA devices of the same brand or cross-validated for phase angle. Comparisons of the phase angle between studies using different BIA devices require the calculation of a standardized phase angle (Z-score) through device-specific reference values.

In view of this association between phase angle and mortality, the question arises whether there is a device-specific phase angle cut-off associated with an increased risk of mortality. In our study, the cut-offs maximizing sensitivity and sensibility was 3.97° in women and 4.38° in men or -1.41, when using standardized phase angle, but they were not good enough to perform individual predictions. Other studies using the same brand of BIA device as in our study evaluated this issue in specific diseases, such as cancer, HIV, and hemodialysis. In cancer patients, Norman et al. have suggested the use of a phase angle value corresponding to values below percentile 5 of the German sex-, age- and BMI-specific reference values as cut-offs (16). These values corresponded to a phase angle <3.9° and <3.8° in normal-weight women and men aged ≥70 yrs, respectively. They were related to a worse nutritional state, lower handgrip strength, peak expiratory flow and physical ability, more co-morbidities, and a higher risk of

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mortality (8) (24). An increased mortality risk has also been demonstrated with a phase angle ≤3.9° in systemic sclerosis patients (25) and a phase angle <5.3° in HIV patients (11), but the cut-offs were arbitrarily determined. These results show that cut-offs relating absolute phase angle values with mortality have not yet been clearly defined, even when using a similar BIA device. Thus, it may be more useful to rely on the evolution of phase angle for prognosis assessment than on a single measurement. Interestingly, cross-sectional studies have shown that the mortality risk decreases by 36% and by over 50% for every 1° increase in phase angle in hemodialysis (13) and HIV patients (11), respectively.

Whether using a standardized phase angle improves the predictive power of mortality remains questionable. In our study, we could not highlight any improvement as compared to the use of sex-specific absolute phase angle values. This may be related to the fact that we have considered sex- specific absolute phase angle in a population ≥ 65 years. Standardized phase angle may be a better predictor of mortality in study populations combining both sexes and of a larger age range. In cancer patients, a standardized phase angle below -1.65, corresponding to values below percentile 5 of Brazilian Reference values, was associated with a higher weight loss (26) and mortality (27). Furthermore, a standardized phase angle below percentile 5 of German Reference values was reported to have a higher predictive power of mortality than malnutrition and disease severity (8).

The originality of this study relies on the large sample of both hospitalized and ambulatory older people. Phase angle was associated with mortality even when taking into account many co-morbidities and subsequent treatments through the CIRS score. We could show that phase angle is a better predictor of mortality than BIA-derived FFMI, even though FFMI was measured by a locally validated BIA formula. As we focused on phase angle measurements performed with a BIA device for which reference values have been published, we could calculate the standardized phase angles. This allows comparisons with other studies that have standardized their phase angle through device-specific reference values.

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This study has several limitations. It is a retrospective and not a population-based study. We could not retrieve the co-morbidities for all patients. However, for patients with existing data, the information was based on medical discharge letters, which is likely more reliable than patient reports. We used the phase angle measurements performed with a single BIA device as this device was used to publish phase angle reference values in people living in Central Europe. Finally, despite the fact the phase angle is a strong predictor of mortality, we do not know yet how to influence it clinically in an older community-dwelling people.

CONCLUSION

This study confirms the association of phase angle and mortality in older patients unselected for their primary disease, although we could not define a cut-off useful for individual predictions. This result suggests the potential use of phase angle as a prognostic marker and as a tool for monitoring of therapeutic strategies. Future studies should cross-validate the phase angle values between devices of different brands or standardize their phase angle values through device-specific reference values, in order to allow comparisons of outcome between studies using different BIA devices.

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Role of funder

The funding source had no role in the design and conduct of the study, acquisition analysis and interpretation of data, preparation of the manuscript and decision to submit the manuscript for publication.

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Author Disclosure Statement

None of the authors have any conflict of interest.

Authors' contributions

LG, LK, FRH and CG designed research; LG, AS, CP, LK and CG conducted research; LG, KN, FRH and CG analyzed data or performed statistical analysis; LG and CG wrote the paper; LG has the primary responsibility for final content.

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Table 1: Characteristics of the included people at the time of the last BIA measurement (n=1307)

	Women			Men			
	n	**%**	**Median (Interquartile range)**	**n**	**%**	**Median (Interquartile range)**	**P[1]**
Continuous							
Age at measurement, y	491	100	72.8 (10.0)	816	100	72.0 (9.2)	0.228
Age at death, y	215	43.8	77.0 (10.7)	413	50.6	75.5 (10.6)	0.012
Length of follow-up, y	491	100	2.2 (3.7)	816	100	1.7 (2.9)	<0.001
Body mass index, kg/m^2	491	100	22.6 (7.0)	816	100	23.7 (5.9)	0.004
Cumulative Illness Rating Scale	438	89.2	14.0 (9.0)	743	91.1	16.0 (9.0)	<0.001
Resistance, Ω	491	100	589.0 (148.0)	816	100	517.5 (119.0)	<0.001
Reactance , Ω	491	100	43.0 (17.0)	816	100	40.0 (16.0)	<0.001
Impedance , Ω	491	100	591.7 (147.4)	816	100	518.1 (118.6)	<0.001
Phase angle, degrees	491	100	4.1 (1.6)	816	100	4.4 (1.8)	<0.001
Standardized phase angle[2] , degrees	491	100	-1.5 (1.7)	816	100	-1.3 (-2.0)	0.001
Categorical							
Age, y							0.177
65-74	297	60.5		523	64.1		
75-84	159	32.4		244	29.9		
≥85	35	7.1		49	6.0		
Body mass index, kg/m^2							0.038
<18.5	94	19.1		86	10.5		
18.5-24.9	223	45.4		416	51.0		
25.0-29.9	113	23.0		242	29.7		
≥30	61	12.4		72	8.8		

[1] P: comparisons of continuous data were performed with Wilcoxon rank-sum test and of ordinal data with Mann-Whitney U-tests.
[2] Standardized phase angle = (observed phase angle-mean reference phase angle)/ SD of reference phase angle

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Table 2: Quartiles for phase angle, standardized phase angle and Cumulative Illness Rating Scale at the time of the last BIA measurement

	n	(%)	Degrees
Phase angle in women (n=491)			
Quartile 1	123	25.1	1.10, 3.33
Quartile 2	123	25.1	3.34, 4.06
Quartile 3	123	25.1	4.07, 4.89
Quartile 4	122	24.9	4.90, 11.20
Phase angle in men (n=816)			
Quartile 1	204	25.0	0.93, 3.53
Quartile 2	204	25.0	3.54, 4.38
Quartile 3	204	25.0	4.39, 5.33
Quartile 4	204	25.0	5.34, 8.23
Standardized phase angle[1] (n=1307)			
Quartile 1	327	25.0	-5.54, -2.28
Quartile 2	327	25.0	-2.27, -1.39
Quartile 3	327	25.0	-1.38, -0.35
Quartile 4	326	25.0	-0.34, 7.30
Cumulative Illness Rating Scale (n=1181)			
Quartile 1	298	25.2	0, 10
Quartile 2	326	27.6	11, 15
Quartile 3	300	25.4	16, 20
Quartile 4	257	21.8	21, 39

[1] Standardized phase angle = (observed phase angle-mean reference phase angle)/ SD of reference phase angle

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Table 3: Univariate Cox regressions for phase angle and standardized phase angle quartiles

	HR (95%CI)	**P**	**R^2 (95%CI)**
Phase angle in women (n=491)			21.6 (14.6, 30.9)
Quartile 1	1.00		
Quartile 2	0.63 (0.45, 0.87)	0.005	
Quartile 3	0.41 (0.29, 0.59)	<0.001	
Quartile 4	0.14 (0.08, 0.23)	<0.001	
Phase angle in men (n=816)			24.4 (18.5, 31.1)
Quartile 1	1.00		
Quartile 2	0.67 (0.53, 0.85)	0.001	
Quartile 3	0.42 (0.33, 0.55)	<0.001	
Quartile 4	0.13 (0.08, 0.18)	<0.001	
Standardized phase angle[1] (n=1307)			20.6 (16.1, 25.9)
Quartile 1	1.00		
Quartile 2	0.67 (0.56, 0.82)	<0.001	
Quartile 3	0.40 (0.33, 0.50)	<0.001	
Quartile 4	0.16 (0.12, 0.22)	<0.001	

[1] Standardized phase angle = (observed phase angle-mean reference phase angle)/ SD of reference phase angle

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Table 4: Multivariate Cox regression analyses (n=1181)

	HR (95%CI)	**P**	**R^2 (95%CI)**	**p**
Model 1[1] (n=438 women)			15.6 (11.4, 27.2)	<0.001
Phase angle quartile 1	1.00			
Phase angle quartile 2	0.69 (0.49, 0.97)	0.031		
Phase angle quartile 3	0.56 (0.37, 0.85)	0.006		
Phase angle quartile 4	0.30 (0.17, 0.53)	<0.001		
Model 2[1] (n=743 men)			21.5 (17.1, 29.2)	<0.001
Phase angle quartile 1	1.00			
Phase angle quartile 2	0.81 (0.63, 1.04)	0.104		
Phase angle quartile 3	0.62 (0.47, 0.83)	0.001		
Phase angle quartile 4	0.37 (0.23, 0.57)	<0.001		
Model 3[2] (n=1181)			17.0 (13.4, 22.3)	<0.001
Standardized phase angle[3] quartile 1	1.00			
Standardized phase angle[3] quartile 2	0.71 (0.58, 0.86)	0.001		
Standardized phase angle[3] quartile 3	0.53 (0.42, 0.67)	<0.001		
Standardized phase angle[3] quartile 4	0.32 (0.23, 0.43)	<0.001		

[1]Adjusted for age category, BMI category, Cumulative Illness Rating Scale quartile, hospitalized vs. ambulatory state

[2] Adjusted for Cumulative Illness Rating Scale quartiles, hospitalized vs. ambulatory state

[3] Standardized phase angle = (observed phase angle-mean reference phase angle)/ SD of reference phase angle

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FIGURE

Figure 1: This figure shows the Kaplan-Meier analysis for standardized phase angle (sPA) quartiles. The curves are significantly different between phase angle quartiles (logrank test $p<0.001$).