

Predictivity of bioimpedance phase angle for incident disability in older adults

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Abstract

Background Bioelectrical impedance analysis (BIA)-derived phase angle is expected to be an efficient prognostic marker of health adverse events with aging as an alternative of muscle mass. We aimed to examine the predictive ability of phase angle for incident disability in community-dwelling elderly and determine the optimal cut-off values.

Methods Community-dwelling elderly aged ≥ 65 years ($n = 4452$; mean age = 71.8 ± 5.3 years, 48.3% women) without disability at baseline participated in this prospective cohort study. Phase angle and appendicular skeletal muscle mass (ASM) were examined using a multi-frequency BIA at baseline. Other potential confounding factors (demographics, cognitive function, depressive symptoms, medications, and physical performance) were also assessed. Incident disability was monitored on the basis of long-term care insurance certification.

Results Over a follow-up of 24 months, 4.0% ($n = 174$) experienced disability, with an overall incidence rate of 20.6 per 1000 person-years. The Cox hazard regression analysis showed that phase angle, as a continuous variable, was independently associated with incident disability after adjusting the covariates [male: hazard ratios (HRs) = 0.61, 95% confidence interval (CI) = 0.37–0.98; female: HR = 0.58, 95% CI = 0.37–0.90], although body mass index adjusted ASM was not. Receiver operating characteristic analysis indicated moderate predictive abilities of phase angle for incident disability [male: area under the receiver operating characteristic curve (AUC) = 0.76, 95% CI = 0.70–0.83; female: AUC = 0.71, 95% CI = 0.65–0.76], while those of body mass index adjusted ASM were low (male: AUC = 0.59, 95% CI = 0.521–0.66; female: AUC = 0.58, 95% CI = 0.52–0.63). Multivariate Cox regression analysis showed that low phase angle categorized by cut-off value (male, $\leq 4.95^\circ$; female, $\leq 4.35^\circ$) was independently related to increased risk of incident disability (HR = 1.95, 95% CI = 1.37–2.78).

Conclusions Lower phase angle independently predicts the incident disability separately from known risk factors. BIA-derived phase angle can be used as a valuable and simple prognostic tool to identify the elderly at risk of disability as targets of preventive treatment.

Keywords Body composition; Cellular health; Muscle mass; Nutrition; Aging

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Introduction

It is an essential goal for clinical medicine and public health to prevent disability and maintain functional independence, particularly in the elderly. Healthcare cost for the elderly is

reported to be more strongly related to the presence of disability than to remaining life expectancy.¹ Therefore, in order to take measures before the onset of physical weakening, the efficient prognostic indicator is necessary to identify the elderly who are most likely to develop incident disability. Low

muscle mass becomes more common with increased age² and has been thought as a potential contributor to disability³ and thus is used for the diagnostic criteria of sarcopenia. Although sarcopenia is considered to be a major cause of disabilities, used clinical definitions of sarcopenia were varied.⁴ The associations between sarcopenia and clinical adverse outcomes (i.e. disability, fracture, and mortality) were also varied, depending on the definition of sarcopenia and the formula for calculating muscle mass.⁴⁻⁶

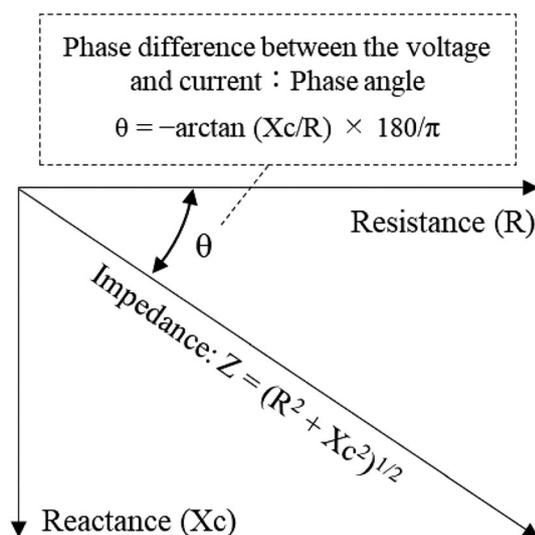
Bioelectrical impedance analysis (BIA) has become a popular non-invasive, inexpensive, and quick method to estimate body composition across different populations, particularly to assess sarcopenia in geriatrics. BIA measures whole-body impedance (Z), which is the opposition of the body to alternating current consisting of the following two components: resistance (R) and reactance (X_C), $Z^2 = R^2 + X_C^2$. BIA is therefore not a direct method for the assessment of body composition. Conventional BIA parameters, including total body water and muscle mass, are calculated using regression equations for each population studied and must be interpreted cautiously in some clinical situations, as the BIA algorithm is shown to be inaccurate in participants with very low or very high body mass index (BMI) values or abnormal hydration levels.⁷ On the other hand, phase angle has emerged as a sensitive indicator of cellular health, with higher values reflecting cell membrane integrity or vitality of living tissue.⁸ Healthy cell membranes behave like good capacitors, which store the current and consequently cause a delay in its flow. The phase difference between the voltage and current, caused by the lag of the current penetrating the cell membranes and tissue interfaces, is expressed as phase angle. Phase angle is calculated using the arc tangent value of the directly measured ratio of X_C to R (Figure 1) and does not depend on

conventional regression equations of body composition, which could be error prone in a disease. Because of this advantage, BIA-derived phase angle is considered to be a practical alternative to using muscle mass for monitoring physical health status and the risk of adverse events. Phase angle usually ranges between 5° and 7° in healthy adults and is usually lower in women than men.^{9,10}

Recently, there is a growing body of evidence indicating that phase angle could be used as a notable prognostic marker to predict impaired nutritional status,¹¹ disease prognosis,¹² and mortality risk¹³ in patient populations. In community-dwelling general populations, phase angle has been shown to decrease with aging and correlates positively with muscle strength.¹⁴ It is also reported that the elderly with lower phase angles are at a higher risk for major hallmarks of unhealthy aging, including sarcopenia,¹⁵ frailty, and mortality.¹⁶ Thus, phase angle is expected to be increasingly used as a simple indicator of physical health in the elderly. However, despite the previously mentioned prognostic potentials of phase angles, the predictive ability of phase angles for incident disability has not been studied.

We suppose that phase angle can be a novel and useful tool to assess the risk of subsequent disability among the elderly, which enables safe measurement in a limited space and time, without the need for professionals. This prospective cohort study aimed to investigate the clinical relevance of phase angle in predicting incident disability in community-dwelling elderly. We examined if phase angle is independently associated with an increased risk of disability after adjusting the confounding factors and compared predictive ability with skeletal muscle mass as a conventional BIA parameter using receiver operating characteristic (ROC) analysis. We also attempted to determine the optimal cut-off values of phase angle in detecting individuals at higher risk of incident disability to apply it in clinical and community setting.

Figure 1 Diagram of the graphical derivation of the phase angle and its relationship with resistance (R), reactance (X_C), and impedance (Z).



Methods

Participants

The participants were from the Obu Study of Health Promotion for the Elderly, which is part of the National Center for Geriatrics and Gerontology—Study of Geriatric Syndromes.¹⁷ Participants aged ≥ 65 years at examination in 2011 or 2012, who lived in Obu City, who had not participated in another study, and who had not been certified as needing support or care by the Japanese public long-term care insurance (LTCI) system (care level $\geq 3/5$) were included in the study. Recruitment was conducted through letters mailed to 14 313 elderly, and only 5104 elderly underwent a baseline assessment, including a face-to-face interview and measurement of physical and cognitive function. In the current study,

only participants who independently performed basic activities of daily living at baseline were included. This was confirmed through interviews or on no LTCI certification at any level. We excluded participants based on the following criteria: (i) having a disability based on the LTCI system at baseline; (ii) history of Parkinson's disease, Alzheimer's disease, or stroke; (iii) unable to undergo BIA (i.e. heart pacer); or (iv) died or moved to another city during the follow-up. All participants signed the informed consent before their enrolment in the study in accordance with the Declaration of Human Rights, Helsinki, 1975. The study was approved by the ethics committee of the National Center for Geriatrics and Gerontology.

Disability data

We monitored the Japanese public LTCI certification for all participants during 24 month follow-up. Under the Japanese public LTCI system, the elderly, who are certified as requiring support or care according to physical and/or mental disability, are eligible for benefits (institutional-based and community-based services but not cash). The LTCI system certifies a person in 'Support Level 1 or 2' due to a need for support for daily activities or 'Care Level 1, 2, 3, 4, or 5' due to a need for continuous care. In this study, we defined incident disability as a new certification of LTCI service at any level, with data updated monthly, among participants without LTCI certification at baseline assessment. The detailed process of LTCI certification has already been introduced elsewhere.^{18,19} In short, a trained local government official visits the home to evaluate support and care needs using a questionnaire on current physical and mental status (73 items) and use of medical procedures (12 items). Based on the results, standardized scores are calculated for seven dimensions of physical and mental status, and the time required to perform nine categories of care (grooming/bathing, eating, toileting, transferring, eating, assistance with instrumental activities of daily living, behavioural problems, rehabilitation, and medical services) is evaluated. The assigned care needs level is based on the total estimated care minutes. A Nursing Care Needs Certification Board, consisting of experts in health and social services appointed by a mayor, determines whether the initial assessment is appropriate, based on the applicant's primary care physician's statement and notes written by the assessor during the home visit. The board makes the final decision on LTCI certification.

Body composition measurements

Body composition parameters, including phase angle, appendicular skeletal muscle mass (ASM), and BMI, were obtained using a multi-frequency bioelectrical impedance analyzer

(MC-980A, Tanita, Tokyo, Japan), a tool used to assess whole-body and segmental body compositions.²⁰ The BIA instrument used six electrical frequencies (1, 5, 50, 250, 500, and 1000 kHz). The surface of the hand electrode was placed in contact with each of the participant's five fingers, while the participant's heels and forefeet were placed on the circular-shaped foot electrodes. The participants held out their arms and legs to avoid contact with any other body segments during the procedure. Measurements were obtained by well-trained staff and completed within 30 s. According to the recommendations for clinical application of BIA,⁷ phase angle at 50 kHz was used for analysis. Using segmental body compositions, the ASM was determined²¹ and adjusted by BMI (ASM/BMI).²² An estimation equation for ASM using a multi-frequency bioelectrical impedance analyzer has previously been validated via comparison with a dual-energy X-ray absorptiometry-measured ASM among a Japanese population.²¹

Covariates

We recorded the demographic characteristics of the participants, including age, sex, and years of education. Licensed nurses interviewed the participants regarding their medical condition, including the total number of prescribed medication doses taken regularly (every day or every week). Global cognitive function was assessed using the Mini-Mental State Examination (MMSE).²³ Depressive symptoms were measured using the 15-item Geriatric Depression Scale (GDS).²⁴ Gait speed was assessed at the usual pace using a stopwatch and was expressed in metres per second. The grip strength of the participant's dominant hand was measured using a portable grip strength dynamometer (Takei Ltd., Niigata, Japan).

Sarcopenia

We defined sarcopenia based on the diagnostic algorithm recommended by the Asian Working Group for Sarcopenia. As per the algorithm, the diagnosis of sarcopenia requires the presence of both low muscle mass and muscle function (low physical performance or muscle strength).²⁵ Low physical performance was defined as a gait speed of <0.8 m/s, whereas low muscle strength was defined as a handgrip strength of <26 kg for men and <18 kg for women.

Statistical analysis

Demographics and clinical characteristics at baseline were summarized using either means and standard deviations or frequencies and percentages, as appropriate. Age-dependent changes in phase angle were analysed among five age groups (65–69, 70–74, 75–79, 80–84, and 85+ years) using one-way analysis of variance in both sexes. Independent sample *t*-test

was used to compare the phase angle between male and female participants. Using the Cox proportional hazards regression analyses, we initially estimated the hazard ratios (HRs) and 95% confidence intervals (CIs) of phase angle and ASM/BMI as continuous variables for incident disability. The separate analysis was performed on each sex. The multivariate model was adjusted for age, BMI, years of education, number of medications, MMSE score, GDS, grip strength, gait speed, hypertension, heart disease, diabetes mellitus, and hyperlipidaemia. We used the area under the ROC curve (AUC) to assess the discriminatory ability of body composition parameters for incident disability as the outcome variable. The significance of the difference in AUCs between phase angle and ASM/BMI was assessed by means of DeLong’s test.²⁶ The optimal cut-off values were obtained from the maximal Youden’s index, calculated as (sensitivity + specificity – 1), and the best combination of sensitivity and specificity. To test the sensitivity of the results, we also performed ROC curve analysis among a sample of older adults including individuals excluded from primary analysis because of missing baseline value. Then, the Cox regression analysis was performed to calculate HRs of low phase angle based on the cut-off values in crude and multivariate models. Cumulative incidence function curves were generated to illustrate the incident disability. We also used the AUC to assess the relationship between phase angle and sarcopenia status at baseline. The level of significance was 0.05. IBM SPSS version 25 (IBM Corp., Chicago, IL) was used to perform all statistical analyses.

Results

Out of the 5104 participants who completed the baseline assessment, 742 were excluded because of disability based on the LTCI system ($n = 160$), Parkinson’s disease ($n = 14$), Alzheimer’s disease ($n = 5$), stroke ($n = 255$), unable to undergo BIA ($n = 32$), and missing baseline data ($n = 276$). Additionally, participants with an event, who moved to another city ($n = 16$), or died ($n = 34$) during follow-up period were excluded. Finally, 4312 elderly were included in the analyses. Demographics and clinical characteristics are presented in Table 1. Figure 2 shows the mean phase angle values for different age groups and sex with standard deviation. Phase angle values showed age-related gradual decline in both sexes ($F = 185.8, P < 0.001$). Male participants showed significantly higher phase angle than female participants ($P < 0.001$).

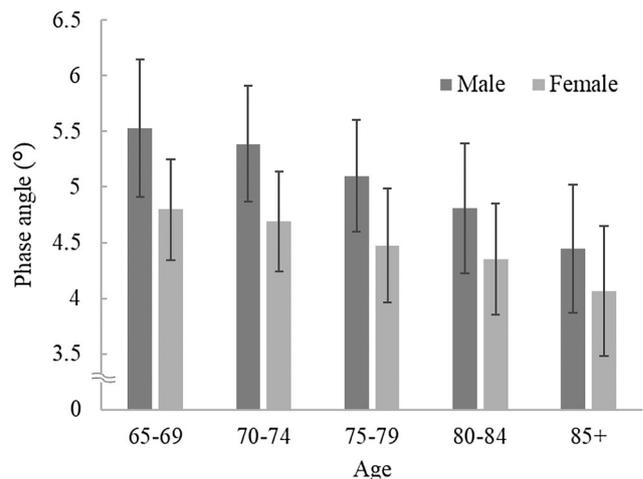
Over a follow-up of 24 months, 4.0% ($n = 174$) experienced disability, with an overall incidence rate of 20.6 per 1000 person-years (male, $n = 69, 16.8$ per 1000 person-years; female, $n = 105, 24.1$ per 1000 person-years). Table 2 reports the Cox proportional hazards models for the main outcome, incident disability, for phase angle, and ASM/BMI as continuous variables. Univariate Cox regression analysis revealed that both

Table 1 Demographics and clinical characteristics of participants at baseline

Variable	All ($n = 4312$)		Male ($n = 2228$)		Female ($n = 2084$)	
	Mean	SD	Mean	SD	Mean	SD
Age (years)	71.8	(5.3)	71.9	(5.4)	71.6	(5.3)
Education (years)	11.4	(2.5)	11.9	(2.8)	10.9	(2.2)
BMI (kg/m^2)	23.4	(3.1)	23.7	(2.8)	23.1	(3.3)
MMSE (points)	26.3	(2.7)	25.9	(2.7)	26.6	(2.7)
GDS (points)	2.8	(2.8)	2.7	(2.6)	2.8	(2.5)
Grip strength (kg)	26.9	(7.9)	33.2	(6.1)	21.1	(4.0)
Gait speed (m/s)	1.28	(0.21)	1.27	(0.21)	1.28	(0.22)
Medications (n)	1.91	(2.0)	1.9	(2.1)	1.9	(2.0)
Chronic disease						
Hypertension	1913	(44.4)	966	(46.4)	947	(42.5)
Heart disease	673	(15.6)	373	(17.9)	300	(13.5)
Diabetes mellitus	554	(12.8)	325	(15.6)	229	(10.3)
Hyperlipidaemia	1760	(40.8)	687	(33.0)	1073	(48.2)
Body composition						
Phase angle ($^\circ$)	4.98	(0.65)	5.32	(0.62)	4.66	(0.50)
ASM/BMI	0.74	(0.13)	0.87	(0.07)	0.64	(0.06)
Sarcopenia	180	(4.2)	97	(4.7)	83	(3.7)

BMI, body mass index; MMSE, Mini-Mental State Examination; GDS, Geriatric Depression Scale; ASM/BMI, body mass index adjusted appendicular skeletal muscle mass. Values are mean (standard deviation) or n (%).

Figure 2 Bar chart showing mean phase angle values for different age groups and both sexes with standard deviation.



phase angle and ASM/BMI were potential predictor variables for incident disability for each sex. However, subsequent multivariate Cox regression analysis identified only phase angle (male: HR = 0.73, 95% CI = 0.53–0.99; female: HR = 0.80, 95% CI = 0.64–0.99) as an independent predictor for incident disability. HRs of ASM/BMI were not significant in multivariate model for both sexes (male: HR = 1.19, 95% CI = 0.93–1.53; female: HR = 1.19, 95% CI = 0.94–1.52).

The AUC and cut-off values of phase angle and ASM/BMI for incident disability are presented in Table 3 and Figure 3.

Table 2 Cox proportional hazards regression analysis of relationship between body composition parameters as continuous variables and incident disability

	Sex	Univariate analysis			Multivariate analysis		
		HR	95% CI	P-value	HR	95% CI	P-value
Phase angle (per 1 SD)	Male	0.37	0.30–0.46	<0.001	0.73	0.53–0.99	0.043
	Female	0.46	0.38–0.56	<0.001	0.80	0.64–0.99	0.049
ASM/BMI (per 1 SD)	Male	0.76	0.61–0.95	0.017	1.19	0.93–1.53	0.18
	Female	0.73	0.60–0.89	0.002	1.19	0.94–1.52	0.14

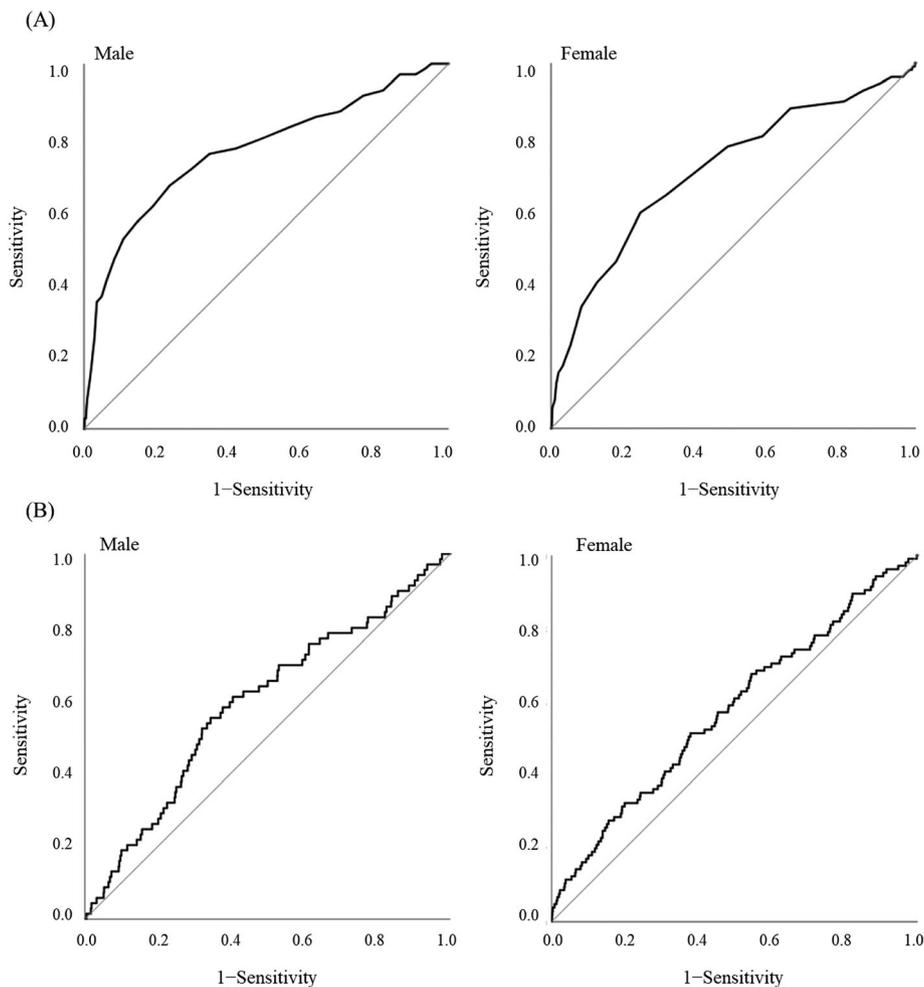
ASM/BMI: body mass index adjusted appendicular skeletal muscle mass; CI, confidence interval; HR, hazard ratio.

Multivariate analysis: adjusted for age, body mass index, years of education, number of medications, Mini-Mental State Examination score, Geriatric Depression Scale, grip strength, gait speed, hypertension, heart disease, diabetes mellitus, and hyperlipidaemia.

Table 3 Predictive ability of body composition parameters and cut-off values for incident disability

	Sex	AUC	95% CI	P-value	Cut-off	Sensitivity (%)	Specificity (%)
Phase angle	Male	0.762	0.696–0.829	<0.001	4.95	66.7	76.4
	Female	0.706	0.651–0.762	<0.001	4.35	59.0	75.5
ASM/BMI	Male	0.591	0.521–0.661	0.01	0.84	55.1	65.7
	Female	0.576	0.518–0.634	0.008	0.62	51.4	62.1

ASM/BMI, body mass index adjusted appendicular skeletal muscle mass; AUC, area under the receiver operating characteristic curve; CI, confidence interval.

Figure 3 Receiver operating characteristic curves for the (A) phase angle and (B) body mass index adjusted appendicular skeletal muscle mass (ASM/BMI) to detect the risk of incident disability during the 24 month follow-up period.

Results showed moderate predictive abilities of phase angle for incident disability (male: AUC = 0.76, 95% CI = 0.70–0.83; female: AUC = 0.71, 95% CI = 0.65–0.76). Meanwhile, those of ASM/BMI were low (male: AUC = 0.59, 95% CI = 0.52–0.66; female: AUC = 0.58, 95% CI = 0.52–0.63). There were significant differences between the AUCs of phase angle and ASM/BMI in both men and women ($P < 0.01$). The cut-off values of phase angle were 4.95° in male participants and 4.35° in female participants. Sensitivity analysis, among a sample of older adults including individuals excluded because of missing baseline value ($n = 4578$), found consistent findings with the primary analysis, as presented in Supporting Information, *Table S1*.

Incident disability rates of the two groups categorized by the cut-off values of phase angle were 51.3 per 1000 person-years ($n = 66$) in participants with low phase angle (male, $\leq 4.95^\circ$; female, $\leq 4.35^\circ$) and 10.4 per 1000 person-years ($n = 108$) in participants without low phase angle (male, $> 4.95^\circ$; female, $> 4.35^\circ$), respectively (*Figure 4*). Cox regression analysis among all participants showed that low phase angle categorized by cut-off value was associated with increased risk of incident disability (HR = 4.95, 95% CI = 3.65–6.71) in crude model. In the multivariate model, low phase angle was independently related to incident disability, after adjusting for age, sex, BMI, years of education, number of medications, MMSE score, GDS, grip strength, gait speed, hypertension, heart disease, diabetes mellitus, and hyperlipidaemia (HR = 1.84, 95% CI = 1.29–2.62). Furthermore, the

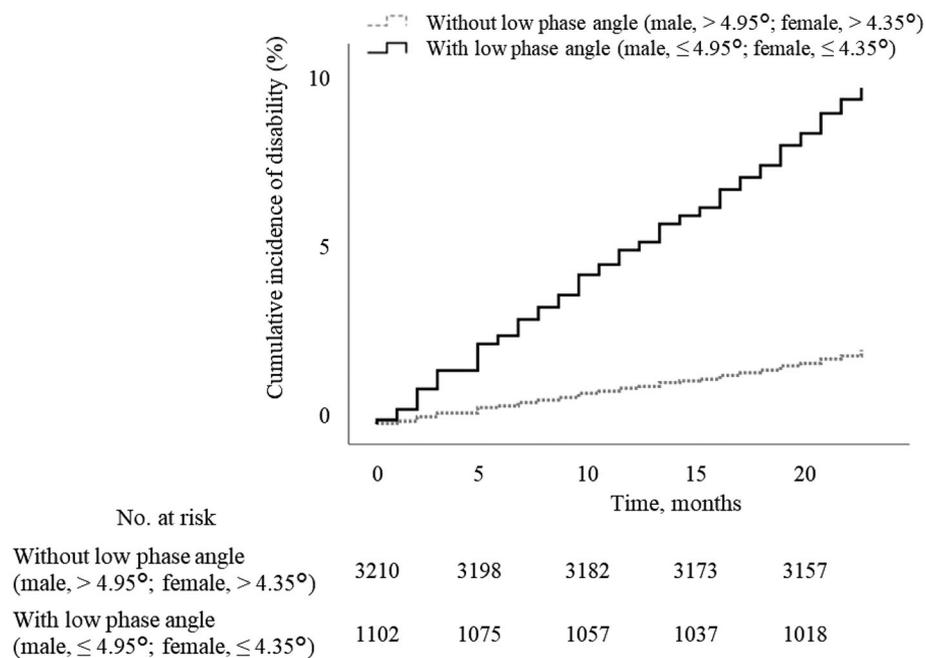
AUCs also showed moderate predictive ability of phase angle for detecting the presence of sarcopenia (male: AUC = 0.79, 95% CI = 0.75–0.84; female: AUC = 0.76, 95% CI = 0.71–0.82).

Discussion

We demonstrated the independent association of lower bioimpedance phase angle with higher risk of incident disability separately from age, grip strength, gait speed, depressive symptoms, and global cognitive function known as major risk factors.^{27–29} HRs of multivariate Cox regression indicated that the risk of incident disability increased by 1.6 in men and 1.7 in women per 1° decrease in phase angle. This is the first longitudinal study to clarify the clinical relevance of bioimpedance phase angle in predicting incident disability in community-dwelling elderly. The ROC analysis showed that phase angle was much superior to ASM/BMI in distinguishing individuals likely to experience incident disability during 24 month follow-up period. The predictive ability of phase angle (male, AUC = 0.76; female, AUC = 0.71) was comparable with physical performance tests, including gait speed (AUC = 0.69–0.72)²⁷ and timed up and go test (AUC = 0.74),³⁰ which have been validated in the existing literature.

Aside from the effectiveness as a prognostic indicator of survival, as previously reported,¹⁶ our results support the predictive ability of phase angle for health adverse events among

Figure 4 Cumulative incidence function curve for participants with vs. without low phase angle based on the cut-off values (male: $\leq 4.95^\circ$, female: $\leq 4.35^\circ$). The number of participants at risk at a time point is the number of participants who stay in the study at that time point, that is, those who have not had events.



community-dwelling elderly. Largely, phase angle has been validated among patient populations, such as cancer and haemodialysis patients, as predictors of disease prognosis,¹² impaired quality of life,¹³ malnutrition,³¹ and increased mortality.³² Findings of the present study suggested the usefulness of phase angle as a routine assessment in community-based health screening and indicated simple and highly prognostic cut-off values for the detection of older individuals at high risk of disability in the near future. Risk of incident disability for older adults with low phase angle based on the cut-off values (male, ≤ 4.95 ; female, ≤ 4.35) was approximately double after adjusting the confounding factors compared with the rest of the participants. Interestingly, the cut-off values of phase angle, determined by the present study, were similar to the cut-off values for nutritional risk (male, ≤ 5.0 ; female, ≤ 4.6) among hospital patients.¹¹

Although the mechanism for these findings is not yet completely understood, phase angle might be a global marker of age-related physiological changes, which also reflects physical performance,¹⁴ physical activity level,³³ and nutritional status.³⁴ Previously, Basile and colleagues³⁵ reported the existence of an independent linear relationship between phase angle and muscle mass and strength reduction. They further argued that phase angle could be a good bioelectrical marker for identifying elderly patients at high risk of sarcopenia. Our study results support their hypothesis particularly as phase angle efficiently identified subjects with sarcopenia (loss of muscle mass and function), an observation that has been reported in previous studies as well.³⁶ Healthy cell membranes act as good capacitors that store current and cause a delay in its flow, which is expressed as the phase angle. Theoretically, X_C is an index of the volume of cell membrane capacitance and an indirect measure of the intracellular volume or body cell mass. Lower phase angle is considered to be consistent with low X_C ³⁷ and equals either cell death or a breakdown in the selective permeability of the cell membrane.³⁸ Decreased cell membrane integrity and function might cause lower capacity to produce force and functional decline.

Predictive abilities of muscle mass measures (ASM/BMI) were low (male, AUC = 0.591; female, AUC = 0.576), and association with incident disability was not significant independently. It is in line with the existing literature reporting poor association between muscle mass-based measures of sarcopenia and functional outcomes (i.e. mobility and disability) in the elderly.^{4,39} The present study utilized phase angle, an inspection technique of BIA, which is calculated directly without regression equation. Phase angle can be a valuable alternative to muscle mass in predicting disability, as it overcomes the limitation of conventional BIA parameter precision of indirect estimation through regression equation.

The major strengths of this study include the large sample size, comprehensive nature of assessment, longitudinal study design, and an objective and mandatory assessment of incident disability based on the Japanese public LTCI certification.

This universal LTCI system was introduced by the government and uses a systematic methodology in evaluating an individual's status. Thus, disability assessment is reliable and commonly performed. However, as this system and its process are unique to Japan, the current findings should be interpreted with caution and cannot be generalized to other countries. This is one of the limitations of our study. Secondly, we included relatively healthy participants because the baseline assessment was conducted in a community setting, which might be a constraint on the generalizability and applications to practice. Additionally, as the 24 month follow-up period was relatively shorter than those in the previous studies,^{6,40} future studies should provide a longer follow-up period for incident disability to clarify how the incidence of disability increases with advancing age.

In conclusion, we revealed that bioimpedance phase angle predicts incident disability during the 24 month follow-up independently of known risk factors including age, physical performance, and mental status among community-dwelling elderly. The major finding of the study is that phase angle was much more efficient than ASM/BMI in detecting the risk of incident disability in the near future. Lastly, we proposed the optimal cut-off values of phase angle (male, ≤ 4.95 ; female, ≤ 4.35) to identify the targets for preventive treatment in community-based health screening. These findings of BIA-derived phase angle contribute to the development of a practical alternative to using muscle mass in assessing the risk of health adverse events and measuring effectiveness of interventions in the elderly.

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Conflict of interest

None declared.

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Online supplementary material

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Predictive ability of body composition parameters and cutoff values for incident disability (results of sensitivity analysis)

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