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ORIGINAL ARTICLE

The diagnostic value of phase angle, an integrative bioelectrical marker, for identifying individuals with dysmobility syndrome: the Korean Urban-Rural Elderly study

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Abstract

Summary Low phase angle, a non-invasive bioimpedance marker, is associated with elevated odds of dysmobility syndrome and its components. Phase angle (estimated cutoffs: < 4.8° in men; < 4.5° in women) can be used to detect dysmobility syndrome in community-dwelling older adults as a simple, integrative screening tool.

Introduction Dysmobility syndrome uses a score-based approach to predict fracture risk that incorporates the concepts of osteoporosis, sarcopenia, and obesity. Low phase angle (PhA), a simple, non-invasive bioelectrical impedance marker, was associated with low lean mass, high fat mass, and poor muscle function. We aimed to investigate the association between PhA and dysmobility syndrome, with the exploration of the diagnostic cutoffs.

Methods In a community-dwelling Korean older adult cohort, dysmobility syndrome was defined as the presence of ≥ 3 of the following components: osteoporosis, low lean mass, falls in the preceding year, low grip strength, high fat mass, and poor timed up and go performance.

Results Among the 1825 participants (mean age 71.6, women 66.7%), subjects were classified into sex-stratified PhA tertiles. The prevalence of dysmobility syndrome increased from the highest PhA tertile group to the lowest (15.50 to 2.45% in men; 33.41 to 12.25% in women, *P* for trend < 0.001). The mean PhA values decreased as the dysmobility score increased (5.33° to 4.65° in men; 4.76° to 4.39° in women, *P* for trend < 0.001). Low PhA (cutoff: < 4.8° in men; < 4.5° in women) was associated with twofold elevated odds of dysmobility syndrome after adjusting for age, sex, and conventional risk factors. Low PhA improved the identification of individuals with dysmobility syndrome when added to the conventional risk model (area under the curve, 0.73 to 0.75, $P = 0.002$).

Conclusion Low PhA was associated with dysmobility syndrome and its components, independent of age, sex, body mass index, nutritional status, and inflammation.

Keywords Aging · Bioelectric impedance analysis · Falls · Obesity · Osteoporosis · Sarcopenia

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Introduction

Osteoporosis, sarcopenia, obesity, and mobility limitation are important determinants of the musculoskeletal health status of the elderly individuals. These conditions contribute to the risk of adverse consequences such as falls, fractures, disability, and mortality [1–6]. The concept of dysmobility syndrome has been developed to predict the risk of fractures using a score-based approach, similar to the concept of metabolic syndrome. The components of dysmobility syndrome include osteoporosis, low lean mass, a history of falls in the preceding year, low grip strength, high fat mass, and low gait speed [7]. Binkley et al. equally weighted the abovementioned factors (1 point each) and defined dysmobility syndrome as having a score of ≥ 3. Identifying individuals with dysmobility syndrome could identify persons at a high risk of fall and fracture events [7]. In Asian and Caucasian cohorts of community-dwelling older adults, dysmobility syndrome showed a stronger association with the prevalence of the fracture when added to a conventional fracture prediction model using the Fracture Risk Assessment Tool (FRAX) score [8, 9]. Dysmobility syndrome also predicted the prospective risk of fracture in the osteoporotic fractures in men cohort [10]. Furthermore, dysmobility syndrome was associated with higher mortality in the National Health and Nutrition Examination Survey cohort [11]. Given the potential of dysmobility syndrome testing to improve prediction of musculoskeletal adverse events including fractures in older adults, a simple, non-invasive, integrative screening tool for dysmobility syndrome would be helpful to facilitate the clinical application of this novel concept.

Bioelectrical impedance analysis (BIA) is a technique that measures the impedance of the body by introducing a small current into the body and is based on the principle that biological tissues act as conductors, semiconductors, or insulators [12]. Phase angle (PhA) is a raw variable derived from BIA that is estimated based on the ratio of reactance (Xc) to resistance (R) as follows: PhA (°) = arctangent (Xc/R) × (180°/π) [13]. Resistance is the degree of the obstruction of current flow by the non-conductive (low levels of fluid content) tissue components, such as fat mass in the body. Reactance is an additional conduction delay, derived from the capacitance of the cell membrane and tissue interfaces, and is correlated with the impaired integrity of the cell membrane and lower body cell mass [13]. In prior studies, low PhA was associated with low lean mass, high fat mass, high extracellular-to-intracellular-fluid ratio (increased resistance), and impaired cellular integrity (decreased reactance) [13–15]. In another study based on a large healthy population, even in individuals with a similar BMI, PhA decreased when fat mass dominated over lean mass, indicating the potential of PhA to reflect the relative contribution of fat and lean mass to overall body mass [14]. PhA has also been shown to reflect the decreased capacitance of body cell mass under circumstances that disrupt cellular membranes, such as malnutrition, inflammation, and cachexia [16]. This notion has been further supported by the findings from several studies showing that low PhA predicts poor survival outcomes in patients with colorectal, lung, breast, or pancreatic cancers [17–19].

There is a large body of evidence showing the association between PhA and each component of the dysmobility syndrome. By definition, low PhA reflects a low body cell mass, low proportion of lean mass, and high proportion of fat mass. Several studies have reported that low PhA correlates with poor muscle function (grip strength and functional performance testing) and a high prevalence of falls and osteoporosis, all of which are incorporated in the components that define dysmobility syndrome [16, 20–22]. Thus, PhA could be used as a simple, integrative, and non-invasive biomarker for identifying individuals at high risk for dysmobility syndrome. However, data regarding the association between PhA and dysmobility syndrome are limited. In this study, we aimed to determine whether PhA is associated with dysmobility syndrome and its components in Korean community-dwelling older adults and explore the optimal cutoff values of PhA that would indicate the presence of dysmobility syndrome.

Methods

Subjects

Our subjects were participants in the Korean Urban-Rural Elderly (KURE) study, a prospective cohort study on health, aging, and common geriatric disorders of Korean elderly persons [23]. During the baseline study between 2012 and 2015, 3517 community-dwelling older adults aged ≥ 65 years were recruited from 4 districts in Korea—3 urban areas in Seoul (Mapo-gu, Seodaemun-gu, and Eunpyeong-gu) and 1 rural area in Incheon (Ganghwa). Participants aged < 65 years, who lived in their current residence for < 8 months, or who were planning to move from their current residence in 2 years were not enrolled. Among the initial 3517 participants, all the individuals enrolled in 2013 were excluded due to missing data on BIA results (n = 1098). Participants who had any contraindication for BIA measurement (having cardiac devices or metal implants) were not included in the study (n = 567). Since altered fluid distribution can be a potential confounder in the interpretations of PhA, we excluded patients with end-stage renal disease (diagnosed with a glomerular filtration rate [GFR] < 15 mL/min/1.73m^2) (n = 4) [16]. Participants with missing data on dual-energy X-ray absorptiometry (DXA) (n = 6), grip strength (n = 8), timed up and go (TUG) test (n = 7), and hemoglobin A1c (HbA1c) levels (n = 2) were excluded. Finally, 1825 participants were included in the final analyses (Fig. 1).

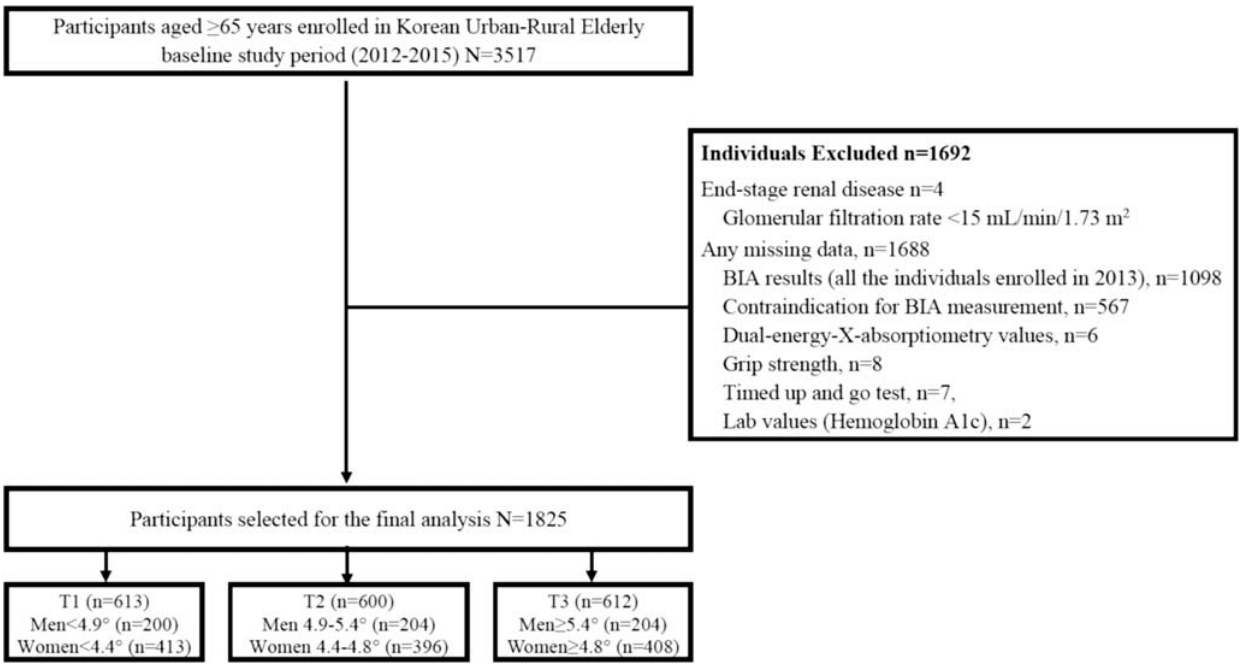

Fig. 1 Flow chart of the study. A total of 3517 participants aged ≥ 65 years were enrolled in KURE baseline survey (2012–2015). Among the initial 3517 participants, 1825 participants were selected for the final analysis. Participants were classified into sex-stratified phase angle tertiles (lowest [T1], n = 613; middle [T2], n = 600; highest [T3], n = 612) with the following cutoff values: 4.9° and 5.4° in men, 4.4°and 4.8° in women). BIA, bioelectrical impedance analysis

Dysmobility syndrome

In the present study, dysmobility syndrome was defined as the presence of ≥ 3 of the following components: osteoporosis, low lean mass, a history of falls in the preceding year, low grip strength, high fat mass, and poor TUG performance according to the modified definition published previously [8]. Osteoporosis was defined as a T-score of ≤ − 2.5 at the lumbar spine, femoral neck, or hip by DXA measurement. Falling history was defined as ≥ 1 self-reported falls in the last year [7]. Low lean mass was defined as appendicular skeletal muscle mass (ASM)/height^2 < 7.0 kg/m^2 in men and < 5.7 kg/m^2 in women estimated by BIA, in accordance with the Asian Working Group for Sarcopenia (AWGS) guideline [24]. High fat mass was defined as > 30% in men and > 40% in women measured by BIA. The cutoff values for low grip strength were < 26 kg in men and < 18 kg in women, in accordance with the AWGS guideline (in the original definition, the cutoff was < 30 kg in men and < 20 kg in women per the Caucasian reference) [24, 25]. Since we did not measure the gait speed, low gait speed (< 1.0 m/s) was replaced by poor TUG performance (≥ 12 s) [26].

Measurements

All subjects underwent a comprehensive health evaluation. General medical information including current and past medical history of medication, falling, and fracture was collected by questionnaires and interviews. Anthropometric indices were assessed by a stadiometer (DS-102, JENIX, Korea), and blood pressures were measured using an electronic manometer (HEM-7111, Omron Healthcare Co., Ltd., Kyoto, Japan). Laboratory tests for HbA1c, albumin, creatinine, white blood cells, and high-sensitivity C-reactive protein (hsCRP) were performed using fasting morning blood samples according to specified protocols [23, 27]. Hypertension was defined as a history of using an antihypertensive medication or mean blood pressure > 120/90 mmHg. Diabetes was also defined as a history of using an antidiabetic drug, HbAlc levels > 6.5%, or fasting glucose > 126 mg/dL. Atherosclerotic cardiovascular disease (ASCVD) and cancer were defined as a previous diagnosis by physician noted in the self-reported questionnaire. Anemia was defined according to the definition of the World Health Organization (hemoglobin level < 13 g/dL in men and < 12 g/dL in women) [28]. The GFR was estimated using the following Chronic Kidney Disease-Epidemiology equation: GFR = $141\times \min(\mathrm{Scr}/\kappa, 1)^{\alpha}\times \max(\mathrm{Scr}/\kappa, 1)^{-1.209}\times 0.993^{\mathrm{Age}}\times 1.018$, where Scr is serum creatinine, κ is 0.7 for females and 0.9 for males, α is − 0.329 for females and − 0.41 for males, min indicates the minimum of Scr/κ, 1, and max indicates the maximum of Scr/κ, 1 [29].

Whole-body BIA measurement was performed using the Inbody 720 (Biospace Co., Ltd., Seoul, Korea). This system uses a multifrequency BIA approach, measuring the impedance

with frequencies of 1, 5, 50, 250, 500 kHz, and 1 MHz at 5 locations—the right arm, left arm, trunk, right leg, and left leg [23]. Following the standardized protocol, subjects with light clothing were instructed to stand barefoot on two metallic electrodes and hold metallic grip electrodes, keeping their arms and legs extended. Fat mass was calculated by subtracting total lean mass (estimated using height [Ht] and the segmental resistances of right arm [R_{RA}], right leg [R_{RL}], and trunk [R_T]: total lean mass = 0.236× Ht^2 / R_{RA} + 0.0109× Ht^2 / R_T + 0.121× Ht^2/R_{RL} + 1.554) from total body weight [30, 31]. Using resistance (R) and reactance (Xc) obtained from BIA measurement, PhA was calculated as follows: PhA (°) = arctangent (Xc/R)× (180°/π) [13]. PhA was calculated using the reactance and resistance dataset obtained at 50 Hz in the right hemibody (the right arm, trunk, and right leg).

Statistical analysis

The characteristics of the study participants were described according to the PhA tertiles. Variables were presented as mean ± SD, as median with interquartile range, or as numbers (percentages). Differences were assessed using one-way analysis of variance (or Fisher's exact test) with Bonferroni postestimation and chi-square test for continuous and categorical variables, respectively. The linear trend of the prevalence of dysmobility syndrome across PhA tertiles was analyzed using the Cochran–Armitage trend test. The trend between the number of dysmobility components and the mean PhA values was assessed using Cuzick's test. Multiple logistic regression analyses were performed to identify whether PhA was associated with dysmobility syndrome or its components, either as a categorical variable of the tertile group or as a continuous variable. The multivariable logistic models were adjusted for age, sex, BMI, serum albumin level, anemia, and log-transformed hsCRP level. The log-transformed hsCRP level was used in the analysis due to a right-skewed distribution. To find clinical cutoffs of PhA for detecting dysmobility syndrome, study participants were randomly stratified into two groups (70% as a train set and 30% as a test set; prevalence of dysmobility syndrome in the train set: 17.2%; in the test set: 17.3%). Sex-stratified receiver operating characteristics (ROC) curve analyses were used to determine the optimal PhA cutoff values to predict the presence of dysmobility syndrome among men and women in the train set. The points with the maximum Youden index (J) on the ROC curve (J = sensitivity + specificity − 1) were determined to find the optimal cutoff values. The performance of estimated cutoff values was evaluated in the test set, then applied to the entire cohort. To compare the additive discriminatory value of low PhA to conventional risk factors (such as age, sex, BMI, serum albumin level, anemia, and log-transformed hsCRP level), the area under the curve (AUC) of the final model (low PhA and conventional risk factors) was compared to that of the model including conventional risk factors using the DeLong method [32]. A two-sided $P < 0.05$ level was considered statistically significant. All statistical analyses were conducted using R software version 3.6.2.

Results

Characteristics of study population

A total of 1825 participants were included in the final analysis, of whom 66.7% were women (n = 1217). The mean participant age was 71.6 ± 4.4 years (Table 1). Women had lower mean PhA values than men (4.6° ± 0.5° vs. 5.1° ± 0.6°, $P <$ 0.001). Participants were classified into sex-stratified PhA tertiles (lowest, n = 613; middle, n = 600; highest, n = 612) with the following cutoff values: 4.9° and 5.4° in men; 4.4°and 4.8° in women. Participants in the lowest PhA tertiles were older and had lower BMI and appendicular lean mass index than those in the highest tertile. The prevalence of dysmobility syndrome in our cohort was 17.3% (n = 315). The prevalence of anemia increased with the decreasing PhA values. No significant differences in kidney function and inflammatory markers, including white blood cell count and hsCRP level, were observed among the PhA tertile groups.

Phase angle and dysmobility components

The prevalence of dysmobility syndrome significantly increased from the highest PhA tertile group (T3) to the lowest (T1) (T1, 15.50%; T2, 5.88%; T3, 2.45%, P for trend < 0.001 in men and T1, 33.41%, T2, 19.95%, T3, 12.25%, P for trend < 0.001 in women) (Fig. 2a). Similarly, the prevalence of each dysmobility component tended to increase from the highest PhA tertile toward the lowest (Table 1). When the dysmobility score was defined as the number of coexisting components that agreed with the cutoff values, the mean PhA values decreased in a stepwise manner with the increasing dysmobility score (5.33° to 4.65°, P for trend < 0.001 in men and 4.76° to 4.39°, P for trend < 0.001 in women) (Fig. 2b).

Association of phase angle and dysmobility syndrome

PhA was associated with dysmobility syndrome and its components in the univariable logistic regression models (Table 2). Even after adjusting for conventional risk factors including age, sex, BMI, serum albumin level, anemia, and log-transformed hsCRP level, PhA showed a robust inverse association with elevated odds of dysmobility syndrome and its components; however, the association with osteoporosis was attenuated. Compared to the highest PhA tertile group (T3), the lowest (T1) and middle tertile group (T2) had elevated odds of dysmobility syndrome (adjusted odds ratio

Table 1 Baseline characteristics of study participants according to phase angle sex-stratified tertile groups

Variables	Overall (n = 1825)	T1 (n = 613) Men < 4.9° (n = 200) Women < 4.4° (n = 413)	T2 (n = 600) Men 4.9–5.4° (n = 204) Women 4.4–4.8° (n = 396)	T3 (n = 612) Men > 5.4° (n = 204) Women > 4.8° (n = 408)	P
Age (years)	71.6 ± 4.4	73.3 ± 4.7	71.5 ± 4.1*	69.9 ± 3.8*†	< 0.001
Women, n (%)	1217 (66.7)	413 (67.4)	396 (66.0)	408 (66.7)	0.879
Body mass index (kg/m^2)	24.3 ± 3.1	23.7 ± 3.2	24.3 ± 3.0*	24.8 ± 2.8*	< 0.001
Phase angle (°)					
Men	5.1 ± 0.6	4.5 ± 0.4	5.2 ± 0.1*	5.8 ± 0.3*†	< 0.001
Women	4.6 ± 0.5	4.1 ± 0.2	4.6 ± 0.1*	5.1 ± 0.3*†	< 0.001
Appendicular lean mass (kg)					
Men	20.7 ± 2.7	20.2 ± 2.9	20.6 ± 2.6	21.2 ± 2.4*†	< 0.001
Women	14.5 ± 2.0	14.1 ± 2.1	14.3 ± 1.8	15.1 ± 1.9*†	< 0.001
Appendicular lean mass index (kg/m^2)					
Men	7.5 ± 0.7	7.2 ± 0.7	7.5 ± 0.6*	7.8 ± 0.6*†	< 0.001
Women	6.2 ± 0.6	6.0 ± 0.6	6.1 ± 0.5*	6.5 ± 0.6*†	< 0.001
Dysmobility syndrome	315 (17.3)	169 (27.6)	91 (15.2)*	55 (9.0)*†	< 0.001
Osteoporosis	695 (38.1)	275 (44.9)	222 (37.0)*	198 (32.4)*	< 0.001
Low lean mass	385 (21.1)	222 (36.2)	111 (18.5)*	52 (8.5)*†	< 0.001
History of falls within the past year	435 (23.8)	182 (29.7)	145 (24.2)	108 (17.6)*†	< 0.001
Poor timed up and go performance	325 (17.8)	142 (23.2)	90 (15.0)*	93 (15.2)*	< 0.001
Low grip strength	255 (14.0)	114 (18.6)	80 (13.3)*	61 (10.0)*	< 0.001
High fat mass	326 (17.9)	133 (21.7)	122 (20.3)	71 (11.6)*†	< 0.001
Diabetes	421 (23.1)	156 (25.4)	129 (21.5)	136 (22.2)	0.219
Hypertension	1113 (61.0)	392 (63.9)	360 (60.0)	361 (59.0)	0.171
Atherosclerotic cardiovascular disease	208 (12.6)	85 (14.8)	71 (13.2)	52 (9.6)*	0.028
Cancer	40 (2.4)	18 (3.1)	9 (1.7)	13 (2.4)	0.280
Anemia	187 (10.2)	108 (17.6)	52 (8.7)*	27 (4.4)*†	< 0.001
Albumin (g/dL)	4.4 ± 0.2	4.3 ± 0.2	4.4 ± 0.2*	4.4 ± 0.2*†	< 0.001
Glomerular filtration rate (mL/min/1.73 m^2)	67.5 ± 11.8	66.8 ± 11.9	68.1 ± 11.7	67.5 ± 11.8	0.299
White blood cell count (10^3/L)	5.7 ± 1.7	5.7 ± 1.8	5.7 ± 1.6	5.7 ± 1.7	0.751
High sensitivity C-reactive protein (mg/L)	0.7 [0.40–1.33]	0.7 [0.38–1.33]	0.7 [0.41–1.29]	0.7 [0.41–1.36]	0.601

T1 the lowest phase angle tertile group, *T2* middle phase angle tertile group, *T3* the highest phase angle tertile group. *: P<0.05 vs. T1; †: P<0.05 vs. T2. Values were presented as mean ± standard deviation, median [interquartile range], or number (%) as appropriate.

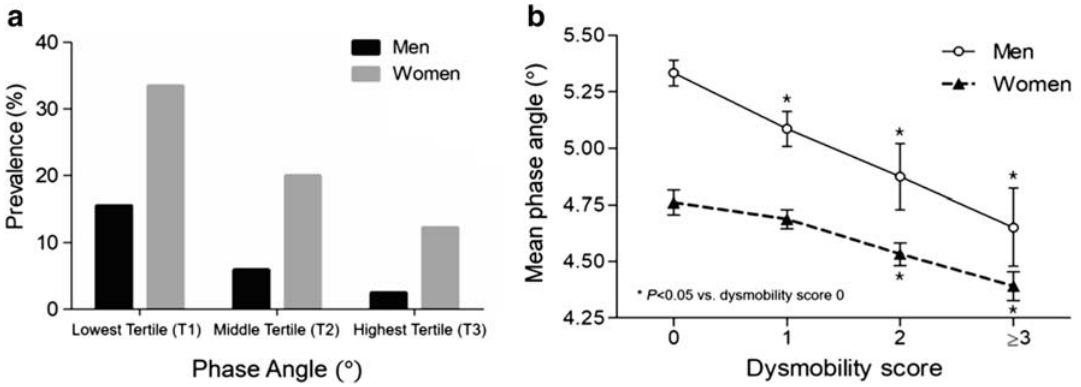

Fig. 2 **a** Increase in prevalence of dysmobility syndrome from the highest phase angle tertile group (T3) to the lowest (T1) (in men, T1, 15.50%; T2, 5.88%; T3, 2.45%, *P* for trend < 0.001; in women, T1, 33.41%, T2, 19.95%, T3, 12.25%, *P* for trend < 0.001). **b** Decrease in mean phase angle with the increasing dysmobility score. Dysmobility score was defined as the number of coexisting components which met the cut points. Mean phase angle values decreased in a stepwise manner with the increasing dysmobility score (in men, 5.33° to 4.65°, *P* for trend < 0.001; in women, 4.76° to 4.39°, *P* for trend < 0.001). Error bars represent ± 95% confidence interval of the mean. Significant difference ($P < 0.05$) with Bonferroni correction in analysis of variance post hoc test) compared with individuals without any component of dysmobility syndrome within each sex stratum (asterisk)

[aOR], 2.66 and 1.56, respectively; $P < 0.05$), high fat mass (aOR, 6.84 and 3.93, respectively; $P < 0.001$), low lean mass (aOR, 4.40 and 2.04, respectively; $P < 0.001$), and history of falls (aOR, 1.95 and 1.49, respectively; $P < 0.01$) in a stepwise manner after adjusting for conventional risk factors (Fig. 3). Among the various components, high fat mass showed the strongest association with the tertiles of PhA (the highest odds ratio), followed by low lean mass, and history of falls. Compared to the highest PhA tertile group (T3), the lowest tertile group (T1) was associated with an elevated odds of low grip strength and poor TUG performance (OR, 2.06 and 1.68, respectively; $P < 0.001$) in the univariable models; however, the associations were attenuated after adjustment for conventional risk factors in multiple variable models.

Improved ability of phase angle to predict the dysmobility syndrome

In our cohort, the diagnostic performance of PhA for the presence of dysmobility syndrome was equivalent to that of the model composed of conventional risk factors including age, sex, BMI, serum albumin level, anemia, and log-transformed hsCRP level (AUC, 0.72 vs. 0.73, $P = 0.592$) (Fig. 4). According to the sex-stratified ROC curve analysis, estimated

Table 2 Association of phase angle with dysmobility syndrome and its components

Variable	Univariable model			Multivariable model 1			Multivariable model 2		
	OR*	95% CI	*P*	OR*	95% CI	*P*	OR*	95% CI	*P*
Dysmobility syndrome	1.19	(1.16–1.23)	< 0.001	1.14	(1.10–1.18)	< 0.001	1.14	(1.10–118)	< 0.001
Dysmobility components									
Osteoporosis	1.11	(1.09–1.14)	< 0.001	1.01	(0.98–1.04)	0.646	1.00	(0.97–1.03)	0.876
Low lean mass	1.16	(1.13–1.20)	< 0.001	1.17	(1.12–1.21)	< 0.001	1.17	(1.12–1.22)	< 0.001
History of falls in last year	1.07	(1.04–1.09)	0.001	1.06	(1.03–1.09)	< 0.001	1.06	(1.03–1.09)	< 0.001
Poor timed up and go performance	1.07	(1.04–1.10)	< 0.001	1.04	(1.01–1.08)	0.012	1.04	(1.01–1.08)	0.012
Low grip strength	1.13	(1.11–1.16)	< 0.001	1.10	(1.07–1.13)	< 0.001	1.10	(1.07–1.13)	< 0.001
High fat mass	1.05	(1.03–1.08)	< 0.001	1.20	(1.15–1.26)	< 0.001	1.22	(1.16–1.28)	< 0.001

Multivariable model 1: adjusted for age, sex and body mass index. Multivariable model 2: adjusted for age, sex, body mass index, albumin, anemia, and log-transformed high-sensitivity C-reactive protein

OR odds ratio, *CI* confidence interval

*Odds ratio (OR) per 0.1 unit (degree) reduction of phase angle

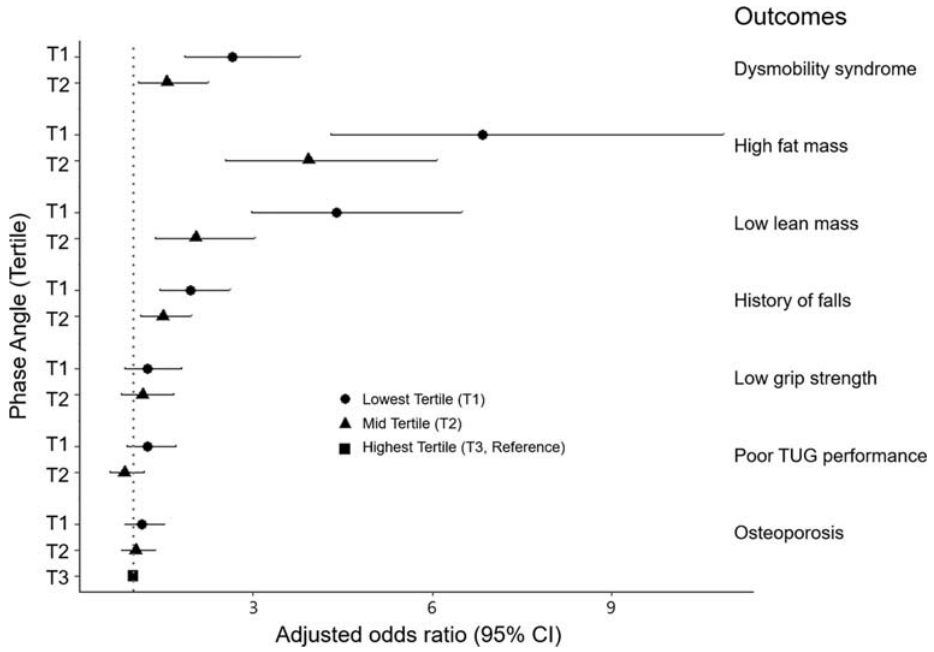

Fig. 3 The odds of dysmobility components and its component according to the tertiles for phase angle after adjustment for risk factors (such as age, sex, body mass index, serum albumin level, anemia, and log-transformed high-sensitivity C-reactive protein). Compared to the highest phase angle tertile group (T3), the lowest (T1) and middle tertile group (T2) had elevated odds of dysmobility syndrome (adjusted odds ratio [aOR], 2.66 and 1.56, $P < 0.05$), high fat mass (aOR, 6.84 and 3.93, $P < 0.001$), low lean mass (aOR, 4.40 and 2.04, $P < 0.001$), and history of falls (aOR, 1.95 and 1.49, $P < 0.01$) in a stepwise manner after adjusting for the conventional risk factors. Circle = the lowest phase angle tertile group (T1); triangle = middle phase angle tertile group (T2); square = the highest phase angle tertile group (T3, the reference)

cutoffs of low PhA to detect the dysmobility syndrome was < 4.8° and < 4.5° in men and women, respectively (sensitivity 53.7%, specificity 69.3% in the test set [hold-out set]; Supplementary Table 1). In the entire cohort, low PhA was associated with a twofold elevated odds for dysmobility syndrome (aOR, 2.13; 95% confidence interval, 1.62 to 2.81; $P < 0.001$) in the multiple logistic regression model (sensitivity 57.1% and specificity 71.4%). When low PhA was defined based on the identified cutoffs above, low PhA modestly improved discriminatory performance for dysmobility syndrome when added to the model with conventional risk factors (AUC, 0.73 and 0.75, $P = 0.002$) (Fig. 4). PhA alone was not superior to ALM or ALM/Ht^2 (AUC: PhA 0.72 vs. ALM 0.77 or ALM/Ht^2 0.76; $P < 0.05$ for all). However, PhA enhanced discriminatory performance for dysmobility syndrome when added to ALM (AUC: PhA 0.72, ALM 0.77, PhA + ALM 0.78; ALM vs ALM + PhA, $P < 0.01$) (Supplementary Fig. 1).

Discussion

In this study, we found that low PhA was associated with an elevated odds of dysmobility syndrome and its components, independent of age, sex, BMI, nutritional status, and inflammatory markers in community-dwelling Korean older adults. Sex-specific dichotomized cutoffs of PhA values were proposed using the ROC analysis to diagnose the dysmobility syndrome (4.8° and 4.5° in men and women, respectively). Low PhA, defined by the proposed cutoffs, improved the identification of individuals with dysmobility syndrome when added to the model with the conventional risk factors such as age, sex, BMI, serum albumin level, anemia, and log-transformed hsCRP level.

BIA is a technology to measure the electrical impedance of the body on the basis of the principle that all the biological tissues act as conductors or insulators [12]. Historically, BIA was established to measure the body water content, but the scope of its use has expanded to measure body compartments such as lean mass, fat mass, extracellular and intracellular water, and body cell mass using general prediction equations. These equations, however, are derived from the statistical relationships within a particular calibration population [33, 34]. The results based on the regression equations were often population specific; hence, they were not ideal for estimating body composition in other populations. Recently, the use of measurements directly obtained from BIA has been gaining popularity as it can avoid the error introduced by indirect estimation techniques [13]. PhA is a directly measured parameter in BIA and is defined as the angular transformation of the reactance-to-resistance ratio [13]. By definition, PhA is positively associated with reactance and inversely proportional to resistance. Resistance is related to the level of fluid content in the body; hence, it indicates the volume status and the body

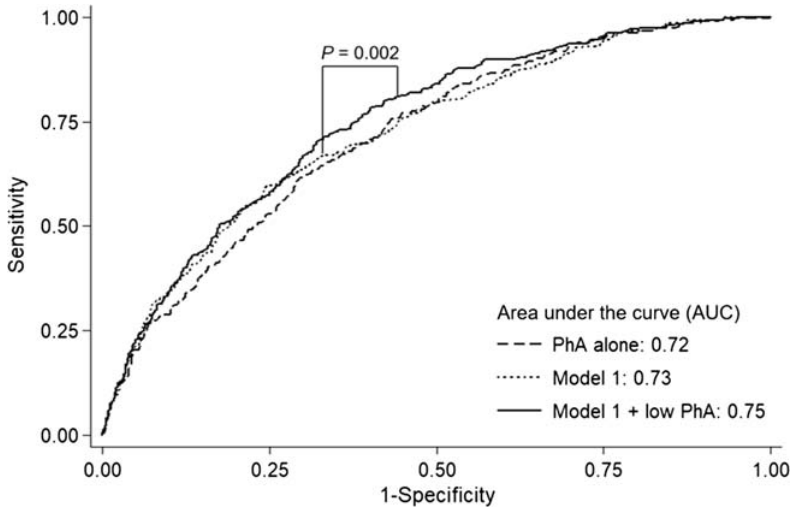

Fig. 4 Improved ability of phase angle to predict the dysmobility syndrome. The diagnostic performance of phase angle for the presence of dysmobility syndrome was equivalent to that of the model composed of conventional risk factors (expressed as "Model 1" in the figure) including age, sex, BMI, serum albumin level, anemia, and log-transformed high-sensitivity C-reactive protein (area under the curve [AUC], 0.72 vs. 0.73, $P = 0.592$). Low phase angle was defined as < 4.8° and < 4.5 in men and women, based on the sex-stratified receiver operating characteristics curve analysis. Low phase angle modestly improved discriminatory performance for dysmobility syndrome, when added to Model 1 (AUC, 0.73 to 0.75, $P = 0.003$). PhA, phase angle; Model 1, model using the conventional risk factors

composition (lean mass and fat mass). Reactance implies the integrity of cell membranes and body cell mass. Several studies have reported that low PhA is associated with low lean mass, high fat mass, and low bone density [20, 22]. Low PhA has been highly predictive of poor clinical outcomes for mortality in patients with HIV infection, cancer, end-stage kidney disease, liver cirrhosis, and chronic obstructive pulmonary disease [35]. In line with these findings, we found that low PhA was associated with dysmobility syndrome and its components. The association remained robust after adjusting for potential confounders, including age, nutritional status, and inflammation markers. In addition, to the best of our knowledge, this study is the first to propose diagnostic cutoffs for dysmobility syndrome in community-dwelling older adults; however, further validation studies are needed.

In this study, low lean mass and high fat mass showed strong associations with lower PhA values. Several studies in large healthy individual cohorts have revealed that fat mass and lean mass are significant PhA determinants, which is consistent with our findings [14, 36]. A previous study in a Japanese community-dwelling elderly cohort has reported an association between PhA and incident falls [21]. Similarly, we found a correlation between low PhA and the prevalence of falls, which comprehensively implied an elevated risk of fracture. Norman K. et al. have demonstrated a significant correlation between PhA and the muscle function parameters (handgrip and knee extension strength) in a cohort of nursing home residents [37]. According to a study with 215 ambulatory rehabilitation patients, when the study participants were divided into quartiles based on functional measurements, including the TUG test, the fourth quartile (i.e., highest value) showed a significantly lower PhA than the first quartile ($P < 0.001$) for TUG performance [38]. Consistent with those findings, low grip strength and poor TUG performance were found to be associated with low PhA values in our study, indicating the potential clinical value of PhA in predicting muscle function and performance status. In a study by Tanaka et al., there was a significant association between PhA and osteoporosis (aOR 0.576, $P = 0.012$) in a multiple logistic regression analysis adjusted by age, sex, and osteoporosis-related factors, such as serum protein level, mineral concentration, and appendicular skeletal muscle index [22]. In our study, although low PhA was also associated with an elevated odds of low bone mass in the univariable model, the association between osteoporosis and PhA was attenuated after adjusting for age, sex, BMI, nutritional factors, and inflammation. Our finding suggests that the association between low bone mass and low PhA largely depends on BMI, particularly the contribution of fat mass, considering the strong influence of fat mass, rather than lean mass, on bone density [39]. Taken together, our findings suggest the potential clinical utility of PhA for early detection of dysmobility syndrome as a simple, non-invasive marker that can easily be measured in various clinical settings. As ALM was used to define low lean mass as one of the components constituting dysmobility syndrome, PhA alone did not show a superior diagnostic value for dysmobility syndrome compared with ALM in this study. However, PhA improved

discriminatory performance for dysmobility syndrome when added to ALM alone or along with clinical risk factors, which suggest independent and additive diagnostic value of PhA for dysmobility syndrome.

We estimated the sex-stratified PhA cutoff values at 4.8° for men and 4.5° for women to identify individuals with dysmobility syndrome based on ROC analysis. In a previous study using a Japanese elderly cohort, low PhA was defined as the first tertile for incident fall, with a slightly higher cutoff for men (≤ 5.2°) and identical cutoff for women (≤ 4.5°) compared to our study cutoffs [21]. Another study evaluated cutoff values of PhA (≤ 5.0° in men and ≤ 4.6°in women) to identify the presence of nutritional risk in a cohort of healthy and hospitalized subjects [40]. The diagnostic cutoffs proposed in our study were similar to those reported in previous studies, even though the ethnicity was not identical to that of our cohort [21, 40]. Several studies have suggested potential ethnic differences in PhA [14, 36]. In the cohort composed of healthy adults aged 18–94 years, PhA was the highest in Hispanics, followed by African Americans, Caucasians, and Asians, possibly reflecting that body size is similar to the ethnic variation shown in previous bone density studies [41]. Further studies are needed to validate whether the cutoff values identified in this study, based on the Korean older adult cohort, could be applicable to other races.

This study had several limitations. This study was based on a cross-sectional analysis; hence, we could not infer causality. One of the potential limitations related to a BIA approach was the potential variability of measurement depending on BIA devices from different manufacturers. However, this did not affect the study results because we used BIA parameters measured by a single machine throughout the study. Cross-calibration for PhA values might be required if multiple machines from different manufacturers are used in a multicenter study [13, 34]. The conventional method for estimating body composition in BIA depends on the statistical regression model derived from a specific population, which limits the usefulness of BIA in other populations. However, in our study, we used PhA values, which did not rely on calculating the regression equations and, therefore, might have a better chance of harmonization among races and manufacturers, thus meriting further investigation. It should be noted that PhA is just one of the markers of electrical properties of the body via multi-frequency BIA, including characteristic frequency, membrane capacitance, and low- to high-frequency impedance ratio [42–44]. However, PhA is a marker supported by numerous studies investigating its population reference values and clinical utilities among the BIA-derived measures [14, 16, 20–22, 35, 37–39]. Although we sought arbitrary cutoffs of PhA for clinical use, the false-negative rate and false-positive rate of the sex-specific cutoffs were 46.3% and 30.6% in test set (hold-out set), respectively (Supplementary Table 1). Seven among ten test-positive (low PhA) subjects actually had dysmobility syndrome, whereas four to five among ten test-negative (normal to high PhA) subjects also had dysmobility syndrome, which limit the utility of the proposed single cutoff for ruling out the disease in individuals with PhA value above the cutoffs. Dysmobility syndrome is still an evolving concept, and there is a need for clear conceptualization and standardization of the components and cutoff values. Nonetheless, an increasing number of studies have been investigating the association between dysmobility syndrome and other indicators of poor health outcomes [8–11]. Although DXA is the gold standard for soft tissue estimation, we used BIA instead of DXA for assessing body composition. This might cause some bias in the study result; however, BIA results have been shown to have a strong correlation with DXA results [45]. DXA is certainly one of the best reference methods to measure body composition, but it is often inaccessible to the public. BIA is much simpler to implement and is cost-effective with no risk of radiation exposure; hence, it is widely used in field studies and for public use [45].

In summary, low PhA was associated with the dysmobility syndrome and its components, independent of age, sex, BMI, nutritional status, and inflammation. Even though PhA alone was not superior to ALM in the detection of dysmobility syndrome, PhA improved diagnostic performance for dysmobility syndrome when added to ALM or clinical risk factors. Our findings indicate that PhA can serve as a simple, non-invasive integrative marker of dysmobility syndrome, which merits further investigation.

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Data availability The survey dataset of the KURE cohort are not available for sharing at this point and further directions regarding sharing archived dataset will be announced by the National Biobank of Korea.

Compliance with ethical standards

Conflict of interest None.

Ethics approval The study protocol was approved by the International Review Board of Yonsei University Health System, Severance Hospital (IRB No. 4-2012-0172). All participants provided written informed consent prior to study participation. All procedures performed in the studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments.

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