ORIGINAL

Phase angle is a predictor of functional outcomes at discharge in patients with acute ischemic stroke

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Abstract : The aim of this study was to investigate the association between phase angle (PhA) at admission and functional outcomes at discharge in patients with acute ischemic stroke. This single-center, prospective cohort study measured PhA and skeletal muscle index (SMI) in patients with acute ischemic stroke using bioelectrical impedance analysis (BIA). Functional outcomes were assessed using the modified Rankin Scale (mRS) at discharge, with mRS scores of 3–5 difined as poor functional outcomes. The association between PhA or SMI and poor functional outcomes was analyzed for male and female patients. This study included 287 patients (195 males, 92 females). Logistic regression indicated that PhA, but not SMI, was independently correlated with poor functional outcomes at discharge (males : OR : 0.58, 95% confidence interval [CI] : 0.34–0.98, p = 0.041, females : OR : 0.31, 95% CI : 0.12–0.80, p = 0.015). Receiver operating characteristic curve analysis determined PhA cutoff values for poor functional outcomes : 4.70 in males (sensitivity : 0.627, specificity : 0.680, area under curve [AUC] : 0.674) and 3.70 in females (sensitivity : 0.467, specificity : 0.830, AUC : 0.712). PhA was identified an independent predictor of poor functional outcomes at discharge in patients with acute ischemic stroke, and it was superior to SMI in this regard. J. Med. Invest. 72 : 148-155, February, 2025

Keywords **:** *phase angle, skeletal muscle index, acute, ischemic stroke*

INTRODUCTION

The global burden of stroke is increasing, with more than 80 million stroke survivors reported in 2016 (1-3). While most patients with stroke undergo rehabilitation during hospitalization (4), approximately 40% experience severe disabilities in activities of daily living (ADLs) at discharge from acute care hospitals (5). In rehabilitation medicine, accurate prognostication is necessary for establishing appropriate treatment goals and programs (6). Therefore, there is a need for early indicators that can predict stroke prognosis more accurately and conveniently, from the onset of stroke.

Recent research has reported the relationship between skeletal muscle mass and functional outcomes in stroke, including sarcopenia (7-9). These reports used bioelectrical impedance analysis (BIA) to noninvasively measure skeletal muscle mass (9) and identified the skeletal muscle index (SMI) as a predictor of physical function, length of stay, and poor outcomes at discharge from acute and post-acute care hospitals (10-12). However, the estimation of skeletal muscle mass using the BIA method includes prediction equations based on age, height, and weight, which may be influenced by body composition and body edema (13, 14). In the acute phase, infusion-induced body edema occurs, necessitating an index that is less affected by fluid retention (13).

Phase angle (PhA) is less affected by fluid retention because it is calculated from the reactance and resistance of the cell membrane (14). PhA, which indicates cell membrane resistance and is calculated using BIA (15, 16), has been associated with muscle quality, nutritional status, and the functional independence measure motor score (16-19). However, these studies examined different subtypes of strokes but did not clearly establish their association with prognosis based on subtype (20, 21). Furthermore, the comparison of accuracy between PhA and SMI regarding functional outcomes remains unclear.

This study aimed to investigate the association between PhA and functional outcomes in patients with acute stroke, focusing on those with ischemic stroke, the most prevalent stroke subtype. In addition, we aimed to determine cutoff values for PhA and SMI in predicting poor functional outcome and compare their accuracy.

MATERIALS AND METHODS

Patients

This single-center, prospective cohort study was conducted at a 692-bed acute care hospital in Japan. We included consecutive patients with acute ischemic stroke admitted to the stroke care unit of our university hospital from September 2019 to January 2023. The exclusion criteria were as follows : (1) a pre-stroke modified Rankin Scale (mRS) score of 3–5, (2) presence of implants or pacemakers, (3) inability to measure PhA due to poor general condition, (4) ischemic stroke resulting from Trousseau syndrome, (5) discharge due to death, and (6) missing data.

Rehabilitation started within 3 days of admission, with a maximum duration of 3 hours per day, 5 days per week. The program included a range of motion exercises, muscle strengthening,

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basic movement training, walking, ADL training, aerobic exercises, dysphagia rehabilitation, language training, and cognitive function training. The program was tailored to each patient's functional level and needs, following the recommendations of the rehabilitation doctor.

Nutritional requirements during hospitalization were individually calculated by dietitians. This included oral and tube feeding, targeting 25–30 kcal/kg of ideal body weight per day, and protein intake of 1.0–1.2 g/kg of ideal body weight per day. Nutritional supplements were provided to patients with inadequate oral intake.

The study was reviewed and approved by the Ethics Committee of our institution (Approval No. 3703-2) and was conducted in accordance with the principles of the Declaration of Helsinki.

Data collection

We collected the following data : age, sex, body mass index, comorbidities before onset, premorbid mRS score, the National Institutes of Health Stroke Scale (NIHSS) at onset, stroke classification (TOAST classification), treatment for stroke (rt-PA, mechanical thrombectomy (MT)), length of hospital stay, serum data (albumin, hemoglobin, CRP), and nutritional status (Geriatric Nutritional Risk Index [GNRI]). GNRI was calculated as follows : GNRI = 14.89 × albumin (g/dL)] + 41.7 × (weight / ideal body weight). All data were extracted from patient medical records.

Measurement of phase angle and skeletal muscle mass

Phase angle and skeletal muscle mass were assessed using the BIA method. Measurements were conducted within 14 days of admission, at least 3 hours after meal, using a portable noninvasive multi-frequency bioimpedance device (InBody S10 ; InBody, Tokyo, Japan). Measurements were acquired with patients in the supine position, with electrodes placed on the thumb and middle finger of both hands and both ankle joints. PhA was calculated from cell membrane resistance (R) and reactance (Xc) using the formula arc tangent (Xc/R) × 180°/π at a frequency of 50 kHz. SMI was calculated as the limb skeletal muscle mass divided by height squared (kg/m²).

Outcome

The primary outcome was defined as poor functional outcomes at discharge from the acute care hospital (22). Functional outcomes were measured using the modified Rankin Scale (mRS). Social disadvantage and behavioral limitations were assessed using an ordinal scale ranging from grade 0 (asymptomatic) to grade 6 (death). In this study, an mRS score of 3–5 indicated poor functional outcomes (23).

The secondary outcome was the mRS score of patients who were available for follow-up 1 year post-discharge from the acute care hospital. The long-term prognosis was confirmed through correspondence via mail and follow-up communication by telephone. Similarly, this holds true, with a mRS score of 3–5 denoting poor functional outcomes (23).

Statistical analysis

PhA is influenced by sex (24) ; therefore, the participants were divided into male and female groups for statistical analyses (25). Regarding participant characteristics, continuous variables are expressed as mean ± standard deviation for parametric data and median (interquartile range : IQR) for nonparametric data. Categorical variables are denoted as n (%).

Comparisons between males and females were performed using the chi-squared test for categorical variables and the Mann–Whitney U test or t-test, depending on the normality of continuous variables.

The relationship between the PhA assessment from onset and the PhA value was examined using Spearman's rank correlation coefficient.

Next, Logistic regression analysis was performed to assess the impact of PhA at admission on mRS scores of 3–5 at discharge, analyzed separately for males and females. The impact of SMI on mRS scores of 3–5 at discharge was similarly analyzed. Multivariate analysis was adjusted for age, initial NIHSS score, GNRI, presence of MT, and presence of cognitive decline as covariates (25-27). Furthermore, PhA at admission, was analyzed in an identical manner to assess its impact on the mRS score participants who were available for follow-up after 1 year.

Optimal cutoff values for PhA and SMI predicting poor functional outcome were determined using receiver operating characteristic (ROC) curves. These cutoff values were then calculated using the Youden index. The discriminatory ability of each cutoff value was assessed by calculating the area under the curve (AUC) of the ROC curve.

All P-values were two sided, and P-values of ≤ 0.05 were considered statistically significant. All statistical analyses were performed with EZR (Saitama Medical Centre, Jichi Medical University ; http://www.jichi.ac.jp/saitama-sct/SaitamaHP.files/statmedEN.html ; Kanda, 2012), which is a graphical user inter-face for R (The R Foundation for Statistical Computing, Vienna, Austria, version 2.13.0) (28). More precisely, it is a modified version of R commander (version 1.6-3) specifically designed to include statistical functions frequently used in biostatistics.

RESULTS

Overall, 537 consecutive stroke patients were admitted to the stroke center during the study period. Patients were excluded owing to a premorbid mRS score of 3–5 (n = 55), presence of pacemakers (n = 7), ischemic stroke attributed to Trousseau syndrome (n = 36), inability to measure PhA due to poor general condition (n = 62), discharge due to death (n = 8), and missing data (n = 82). Finally, we included 287 patients (195 males and 92 females) in the analysis.

Patients discharged from an acute care hospital with mRS scores of 3–5 accounted for 67 (34.4%) males and 45 (48.9%) females. The prevalence of mRS scores of 3–5 at discharge was higher in females than in males. The distribution of mRS scores at discharge by sex is shown in Table 1.

Patient characteristics, categorized by sex, are detailed in Table 2. Male patients were younger (mean age : males 72.0 years vs. females 78.0 years, $p < 0.001$) and had lower prevalence of musculoskeletal diseases ($p = 0.036$) and dementia ($p = 0.032$) than female patients. Males were also found to be more independent in premorbid mRS ($p = 0.025$), whereas females had significantly higher initial NIHSS scores ($p = 0.048$).

Table 1. Distribution of mRS scores at discharge by sex

	Male (n = 195)	Female (n = 92)
mRS score at discharge, n (%)		
0	31 (15.9)	13 (14.1)
1	49 (25.1)	18 (19.6)
2	48 (24.6)	16 (17.4)
3	28 (14.4)	21 (22.8)
4	30 (15.4)	18 (19.6)
5	9 (4.6)	6 (6.5)

mRS, modified Rankin Scale

No significant correlation was identified between PhA assessment from onset and PhA values (males : r = -0.012, p = 0.089, females : r = -0.016, p = 0.882). The scatter plots are shown in supplementary Figure.1.

Sex-specific logistic regression analysis was conducted to evaluate the impact of PhA and SMI on mRS scores of 3–5 at discharge (Tables 3 and 4). Multiple logistic regression analysis revealed PhA as an independent predictor of mRS scores of 3–5 in both males (odds ratio [OR] : 0.58, 95% confidence interval [CI] : 0.34–0.98, p = 0.041) and females (OR : 0.31, 95% CI : 0.12–0.80, p = 0.015). However, SMI did not independently predict mRS scores of 3–5 in males (OR : 0.63, 95% CI : 0.37–1.06, p = 0.080) or females (OR : 0.70, 95% CI : 0.39–1.27, p = 0.244). The optimal cutoff values (sensitivity and specificity) for PhA, derived from ROC curves, were 4.70 (sensitivity : 0.627, specificity : 0.680, AUC : 0.674) for males and 3.70 (sensitivity : 0.467, specificity : 0.830, AUC : 0.712) for females (Figure 1). Regarding SMI, the cutoff values were 6.86 (sensitivity : 0.642, specificity : 0.711, AUC : 0.640) for males and 5.02 (sensitivity : 0.467, specificity : 0.830, AUC : 0.669) for females (Figure 2).

Additionally, A comparable analysis was conducted on a cohort of 245 patients (167 males and 78 females) who were enrolled in the follow-up study after 1-year post-discharge. Multiple logistic regression analysis showed that PhA independently predicted long-term prognosis mRS scores of 3-5 in males (Table 5).

DISCUSSION

This study investigated the association between PhA and functional outcomes at discharge in patients with acute ischemic stroke. Multivariate analysis revealed that PhA was negatively correlated with functional outcomes (males : [OR : 0.58, 95% CI : 0.34–0.98, p = 0.041], females : [OR : 0.31, 95%CI : 0.12–0.80, p = 0.015]). The cutoff values for PhA predicting poor functional outcomes were 4.70 (sensitivity : 0.627,

Table 2. Comparison of baseline characteristics by sex

	Male n = 195	Female n = 92	p-value
Age (years), median (IQR)	72.0 (65.0–78.5)	78.0 (72.8–85.0)	<0.001
BMI, mean (SD)	23.7 (3.3)	23.2 (4.2)	0.271
Previous history, n (%)			
Hypertension	121 (62.4)	54 (59.3)	0.696
Diabetes	56 (28.7)	19 (20.9)	0.194
Atrial fibrillation	35 (17.9)	18 (19.6)	0.746
Stroke	38 (19.5)	17 (18.5)	0.874
Cancer	22 (11.3)	11 (12.0)	0.845
Musculoskeletal disease	30 (15.4)	24 (26.1)	0.036
Dementia	0 (0.0)	3 (3.3)	0.032
Premorbid mRS, n (%)			0.025
0	159 (81.5)	62 (67.4)	
1	25 (12.8)	19 (20.7)	
2	11 (5.6)	11 (12.0)	
Initial NIHSS, median (IQR)	4 (2–10)	6 (2–14)	0.048
TOAST subtype, n (%)			0.207
Large artery atherosclerosis	90 (46.2)	39 (42.4)	
Small-vessel occlusion	25 (12.8)	10 (10.9)	
Cardioembolism	43 (22.1)	25 (27.2)	
ESUS	13 (6.7)	12 (13.0)	
Other	24 (12.3)	6 (6.5)	
Treatment, n (%)			
rt-PA	42 (21.5)	22 (23.9)	0.651
MT	42 (21.5)	27 (29.3)	0.183
Post-stroke presence of cognitive impairment, n (%)	66 (33.8)	33 (33.7)	1.000
Phase angle assessment from onset, days, median (IQR)	8.0 (3.0–10.0)	8.5 (4.0–11.0)	0.304
Length of stay, days, median (IQR)	15.0 (11.0–21.5)	16.0 (11.0–20.0)	0.630
GNRI at discharge	98.7 (91.6–106.0)	96.2 (87.8–103.2)	0.075
Phase angle (SD)	4.9 (0.9)	4.2 (0.8)	<0.001

IQR, interquartile range ; *SD*, standard deviation ; *mRS*, modified Rankin Scale ; *NIHSS*, National Institutes of Health Stroke Scale ; *TOAST*, Trial of Org 10172 in Acute Stroke Treatment ; *ESUS*, embolic stroke of undetermined source ; *rt-PA*, recombinant tissue plasminogen activator ; *MT*, mechanical thrombectomy ; *GNRI*, geriatric nutritional risk index

Table 3. Multiple logistic regression analysis of factors for an mRS score of 3–5 at discharge (phase angle)

	Males			Females		
Variable	OR	95% CI	p-value	OR	95% CI	p-value
Phase angle	0.58	0.34–0.98	0.041	0.31	0.12-0.80	0.015
Age	1.02	0.98–1.05	0.371	1.00	0.95–1.05	0.853
Initial NIHSS	1.16	1.08–1.25	<0.001	1.05	0.96–1.15	0.327
GNRI at discharge	1.00	0.97–1.03	0.863	1.01	0.97–1.05	0.717
Treatment (MT)	1.24	0.47–3.28	0.658	0.92	0.23–3.65	0.902
Post-stroke cognitive impairment (yes)	0.87	0.40–1.88	0.723	4.48	1.29–15.50	0.018

mRS, modified Rankin Scale ; *NIHSS*, National Institutes of Health Stroke Scale ; *GNRI*, geriatric nutritional risk index ; *MT*, mechanical thrombectomy ; *CI*, confidence interval

Table 4. Multiple logistic regression analysis of factors for an mRS score of 3–5 at discharge (skeletal muscle index)

	Males			Females		
Variable	OR	95% CI	p-value	OR	95% CI	p-value
Skeletal muscle index	0.63	0.37–1.06	0.080	0.70	0.39–1.27	0.244
Age	1.02	0.99–1.06	0.199	1.03	0.98–1.07	0.241
Initial NIHSS	1.17	1.09–1.26	0.327	1.05	0.96–1.15	0.270
GNRI at discharge	1.00	0.97–1.04	0.790	1.00	0.96–1.03	0.838
Treatment (MT)	1.35	0.51–3.58	0.552	0.84	0.21–3.36	0.808
Post-stroke cognitive impairment (yes)	0.88	0.41–1.90	0.740	3.75	1.14–12.40	0.030

mRS, modified Rankin Scale ; *NIHSS*, National Institutes of Health Stroke Scale ; *GNRI*, geriatric nutritional risk index ; *MT*, mechanical thrombectomy ; *CI*, confidence interval

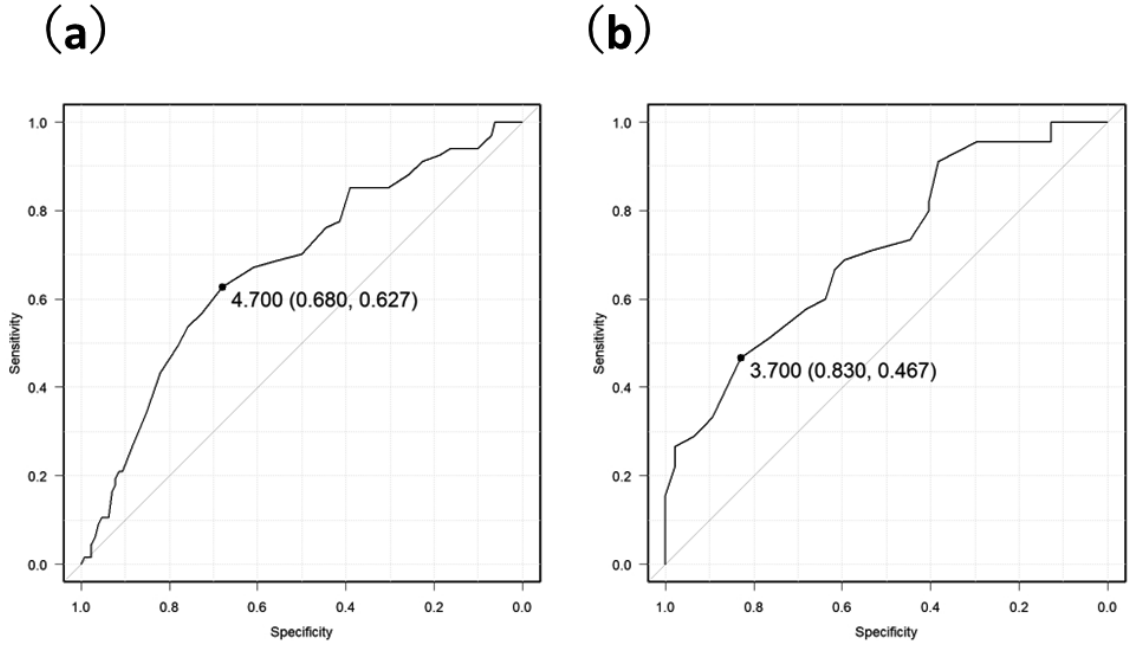

Figure 1. ROC curves to identify the optimal phase angle cutoff for detecting mRS scores of 3–5 in males (a) and females (b). In males, the optimal SMI cutoff value for predicting poor functional outcomes was 4.70 (sensitivity 0.627, specificity 0.680, AUC 0.674). In females, the optimal cutoff was 3.70 (sensitivity 0.467, specificity 0.830, AUC 0.712). AUC, area under the curve ; ROC, receiver operating characteristic ; SMI, skeletal muscle index.

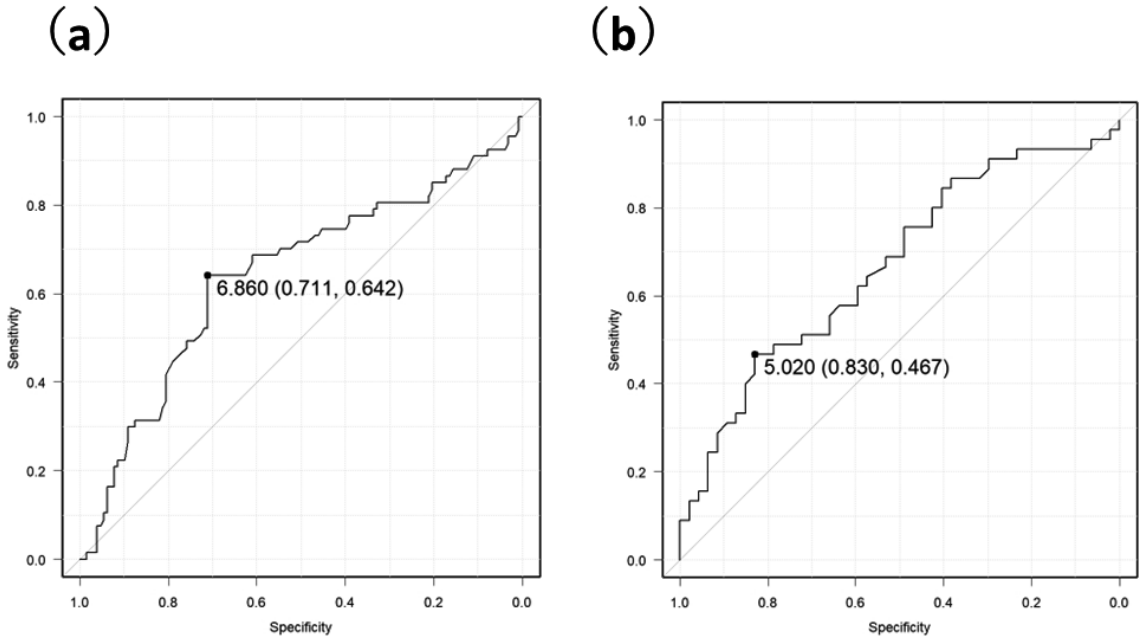

Figure 2. ROC curves to identify the optimal SMI cutoff for detecting mRS scores of 3–5 in males (a) and females (b). In males, the optimal SMI cutoff value for predicting poor functional outcomes was 6.86 (sensitivity 0.642, specificity 0.711, AUC 0.640). In females, the optimal cutoff was 5.02 (sensitivity 0.467, specificity 0.830, AUC 0.669). AUC, area under the curve ; mRS, modified Rankin Scale ; SMI, skeletal muscle index.

Table 5. Multiple logistic regression analysis of factors for an mRS score of 3–5 at 1 year (phase angle)

	Males			Females		
Variable	OR	95% CI	p-value	OR	95% CI	p-value
Phase angle	0.31	0.15–0.65	0.002	0.27	0.06–1.21	0.087
Age	1.08	1.02–1.13	0.005	1.20	1.06–1.37	0.005
Initial NIHSS	1.12	1.02–1.22	0.012	0.95	0.84–1.07	0.381
GNRI at discharge	1.03	0.98–1.09	0.207	1.04	0.97–1.11	0.248
Treatment (MT)	0.75	0.23–2.45	0.638	2.05	0.37–11.20	0.409
Post-stroke cognitive impairment (yes)	0.64	0.25–1.66	0.363	0.06	0.01–0.40	0.004

mRS, modified Rankin Scale ; *NIHSS*, National Institutes of Health Stroke Scale ; *GNRI*, geriatric nutritional risk index ; *MT*, mechanical thrombectomy ; *CI*, confidence interval

specificity : 0.680, AUC : 0.674) for males and 3.70 (sensitivity : 0.467, specificity : 0.830, AUC : 0.712) for females.

PhA was an independent predictor of mRS at discharge in both male and female patients with acute ischemic stroke. Ischemic stroke is the most prevalent stroke subtype globally (29), leaving approximately 30% of its patients severely disabled (29). Additionally, compared to patients with intracerebral hemorrhage, those with ischemic stroke tend to have delayed functional recovery (20, 21, 30). Therefore, it is essential to consider each disease when predicting functional outcomes. While previous research has associated PhA with functional outcomes (16, 25, 31) at discharge from acute and post-acute care hospitals, these studies included a variety of stroke types. To the best of our knowledge, this is the first report to investigate the association between PhA and functional outcomes, focusing exclusively on patients with ischemic stroke.

PhA indicates muscle quality and nutritional status (29, 31, 32), which could affect mRS scores. Functional outcomes in ischemic stroke may be influenced by both the condition of the paralyzed side and muscle quality of the nonparalyzed side (33, 34). In cases of severe hemiplegia, the function of the nonparalytic side notably contributes to walking ability (33). Therefore, PhA, which reflects muscle quality on the nonparalyzed side, might be useful in predicting ADL. Malnutrition in stroke patients in acute care hospitals has also been linked to both functional outcomes and mortality (35-37). Research on rats has demonstrated that malnutrition can decrease astrogliosis and microglial activity, which are involved in neural repair in the infarcted and penumbra areas (38). This can potentially affect neurological recovery after ischemic stroke. Therefore, delayed nerve recovery caused by malnutrition may also impact the recovery of ADLs.

The study results showed that PhA was an independent

predictor of poor functional outcomes, whereas SMI was not significant. Additionally, the AUC of PhA (males : 0.674, females : 0.712) was a more accurate predictor of mRS scores at discharge than SMI (males : 0.640, females : 0.669). The advantage of using PhA as a prognostic indicator for acute ischemic stroke is to avoid the effects of edema. PhA is a variable derived from directly measured reactance (Xc) and resistance (R), independent of the regression equation for body composition (39) and less influenced by water content (14). Therefore, in settings where infusion management is frequent, such as in patients with acute ischemic stroke, prediction using PhA might be an objective clinical index that can be easily and accurately implemented. In the future, it will be necessary to conduct a composite evaluation with other indicators to improve prediction accuracy.

This study has some limitations. First, it was conducted in a single acute care hospital in Japan, which may have affected the generalizability of the results. Further multicenter studies are needed to validate these findings in different clinical settings. Second, the measurement of the days to phase angle may be susceptible to bias, influenced by muscle atrophy and nutritional intake associated with the period of rest following hospitalization. However, in the current study, the BIA measurement period spanned 14 days from onset, yet no significant correlation was observed between the duration and PhA levels. Future measurements should be conducted at an earlier time point to mitigate these effects.

In conclusion, our findings demonstrated that PhA was independently correlated with ADL at discharge in patients with acute ischemic stroke. It demonstrated better predictive accuracy than SMI, with cutoff values of 4.70 in males and 3.70 in females indicating favorable functional outcomes. PhA could serve as a valuable tool in predicting prognosis for patients with acute ischemic stroke.

CONFLICTS OF INTEREST

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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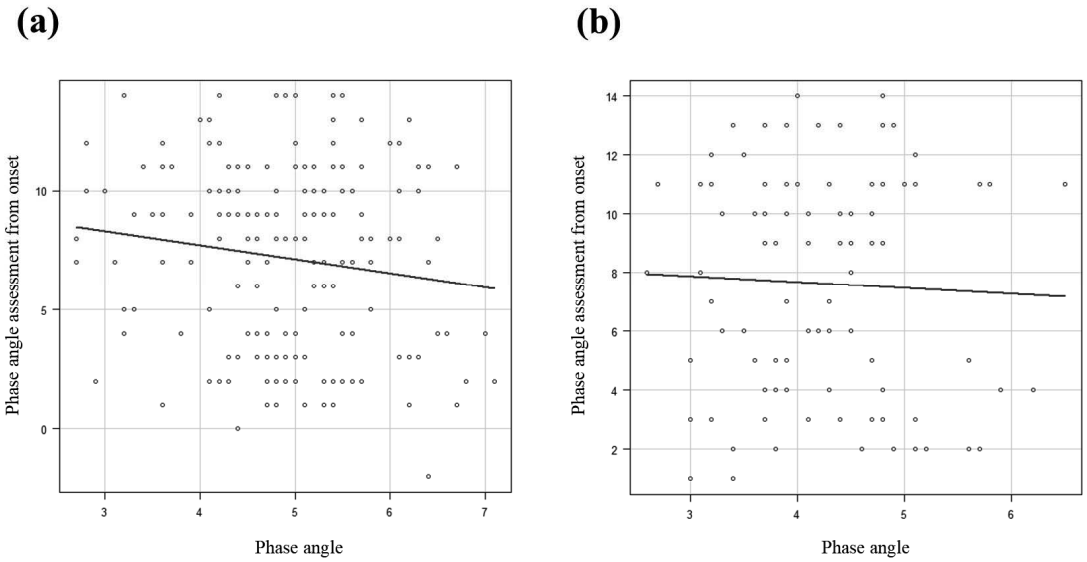

Supplementary Figure 1. Scatter plots showing correlation between PhA assessment from onset and PhA values in males (a) and females (b). No correlation was found between days to measurement and PhA values for both males ($r = -0.012$, $p = 0.089$) and females ($r = -0.016$, $p = 0.882$).