Impact of phase angle on postoperative prognosis in patients with gastrointestinal and hepatobiliary–pancreatic cancer

Running head: Impact of phase angle on postoperative prognosis

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Word count: 6690

Number of figure: 2

Number of tables: 6

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Declarations of Interest

None.

Acknowledgments

We thank the medical staff of the Digestive Surgery and Transplantation and the dieticians at the Department of Nutrition in Tokushima University Hospital for their cooperation.

Funding

This work was partially supported by JSPS KAKENHI [grant number 16H05897].

Abstract

Objective

Phase angle (PhA), by bioelectrical impedance analysis, has been used in patients with several diseases; however, its prognostic value in patients with gastrointestinal and hepatobiliary–pancreatic (HBP) cancer is unclear. The present study aimed to investigate the impact of PhA on postoperative short-term outcomes and long-term survival in these patients.

Research Methods & Procedures

This retrospective study reviewed data of 501 patients with gastrointestinal and HBP cancers who underwent first resection surgery and divided the data into the following groups according to the preoperative PhA quartile values by sex: high-PhA group with the highest quartile (Q4), normal-PhA group with middle quartiles (Q3 and Q2), and low-PhA group with the lowest quartile (Q1). Preoperative nutritional statuses, postoperative short-term outcomes during hospitalization, and 5-year survival between three groups were compared. Cox proportional hazard models were used to evaluate the prognostic effect of PhA.

Results

PhA positively correlated with body weight, skeletal muscle mass, and handgrip strength, and negatively correlated with age and C-reactive protein levels. The low-PhA group showed a high prevalence of malnutrition (48%) than normal-PhA (25%), and high-PhA (9%) ($P < 0.001$). The incidence of postoperative severe complications was 10% in all patients [14% in low-PhA, 12% in normal-PhA, and 4% in high-PhA ($P = 0.018$)]. The incidence of prolonged postoperative high care unit or/and intensive care unit stays was 8% in all patients [16% in low-PhA, 8% in normal-PhA,

and 2% in high-PhA (P < 0.001)]. The 5-year survival rate was 74% in all patients [68% in low-PhA, 74% in normal-PhA, and 79% in high-PhA (P < 0.001)]. The multivariate analysis demonstrated that a low-PhA group was an independent risk factor for mortality (hazard ratio, 1.99; 95% confidence interval 1.05–3.90; P = 0.034).

Conclusion

PhA is a useful short-term and long-term postoperative prognostic marker for patients with gastrointestinal and HBP cancers.

Keywords: Phase angle, Bioelectrical impedance analysis, Nutritional status, Gastrointestinal cancer, Postoperative, Prognosis

[1]Abbreviations

[1] PhA, phase angle; HBP, hepatobiliary–pancreatic; BIA, bioelectrical impedance analysis; HCU, high care unit; ICU, intensive care unit; SGA, subjective global assessment; PNI, prognostic nutritional index; AC, arm circumference; TSF, triceps skinfold thickness; AMA, mid-upper arm muscle area; CRP, C-reactive protein; BMI, body mass index; HR, hazard ratio; CI, confidence interval; BW, body weight; FFM, fat free mass; OR, odds ratio

Introduction

Malnutrition is highly prevalent among patients with pancreatic (83%), gastric (83%), and colorectal (60%) cancers [1]. Preoperative malnutrition is associated with an increase in postoperative complications, prolonged length of hospital stay, and increased mortality [1, 2]. Therefore, it is crucial to precisely assess the nutritional status of patients.

Bioelectrical impedance analysis (BIA) has widely been used for measuring body composition in clinical settings because it is easy, inexpensive, and noninvasive [3]. Phase angle (PhA) is a parameter of BIA that is derived from resistance (R) and reactance (Xc) measurements. R is the pure resistance of the alternating electric current flowing throughout the body, and Xc is the resistance of the double-layered cell membrane [4]. PhA is considered as an indicator of cell membrane integrity [5]. PhA is higher in men than in women, decreases with aging, and varies among races in healthy individuals [5]. PhA has been reported as a nutritional and prognostic indicator in non-oncologic and oncologic patients. There have been reports that low PhA is a marker of poor prognosis in patients who have human immunodeficiency virus [6], are on hemodialysis [7], or have liver cirrhosis [8]. In oncologic patients, there have been reports that low PhA is a marker of poor prognosis in patients with advanced pancreatic cancer [9], advanced colorectal cancer [10], hepatocellular carcinoma [11], head and neck cancer [12, 13], breast cancer [14], lung cancer [15, 16]. Further studies showed similar finding in more diverse oncologic populations: a group with various types of cancers (including gastrointestinal, head and neck, gynecologic, and others) [17, 18, 19], critically ill cancer patients admitted to an intensive care unit (ICU) [20], and patients with advanced cancer admitted to an acute palliative care unit

[21].

Although PhA has been associated with survival in patients with pancreatic cancer [9], colorectal cancer [10], and hepatocellular carcinoma [11], the association of PhA with postoperative short-term outcomes such as postoperative complications and hospital length of stay is unknown. Moreover, the nutritional and clinical significances of PhA in patients with cancer remain ambiguous.

In the present study, we assessed the usefulness of preoperative PhA assessment for providing nutritional or prognostic information in patients with gastrointestinal and HBP cancers scheduled for elective surgery. Our primary objective was to assess associations between preoperative PhA values and postoperative short-term outcomes or long-term survival. The secondary objective was to consider the nutritional and clinical significances of PhA by evaluating possible associations between PhA and other clinical parameters.

Materials and Methods

Patients

This retrospective, observational study included data from 922 patients admitted for elective gastrointestinal and HBP cancer surgery at the Digestive Surgery and Transplantation center in the Tokushima University Hospital between July 2014 and March 2018. After applying the inclusion criteria (patients with gastric, colorectal, liver, bile duct, or pancreatic cancers and those who underwent first radical resection surgery), we collected records of 795 patients. We excluded 16 patients who canceled surgery, 13 with benign tumors, 45 with metachronous metastatic cancer, 20 with combined resection of primary and synchronous metastatic cancer, 7 with recurrent hepatocellular carcinoma, 11 with stage 0 or unknown stage, and 182 missing PhA data measured via BIA. Finally, we analyzed data of 501 patients (Figure 1). This study was conducted in accordance with the tenets of the Declaration of Helsinki, and the ethical committee of the Tokushima University Hospital approved the protocol (No. 3157), and all patients agreed to participate in the study.

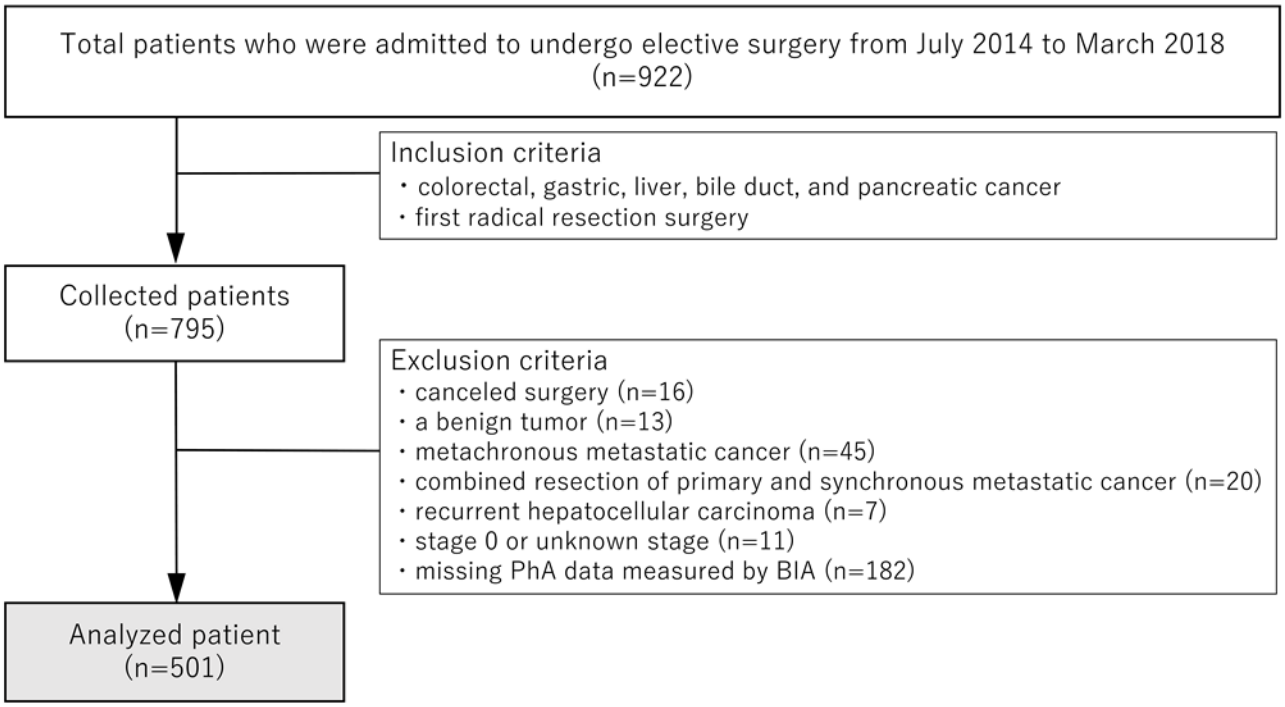

Figure 1. Selection of patients analyzed in this study

PhA, phase angle; BIA, bioelectrical impedance analysis

Data collection

We collected data on age, sex, height, weight, cancer site, cancer stage, serum biochemical data, postoperative complications, postoperative length of high care unit (HCU) or/and ICU stay, date of operation, and date of death from electronic medical records.

Nutritional assessment

All preoperative nutritional assessments were performed routinely during the period between admission and surgery by well-trained registered dieticians. All patients were assessed at least within 1 week before the surgery to 1 day before the surgery. Baseline nutritional assessments included subjective global assessment (SGA), anthropometries [arm circumference (AC), triceps

skinfold thickness (TSF), mid-upper arm muscle area (AMA), and handgrip strength], BIA, and serum biochemical tests [albumin, hemoglobin, total lymphocyte, and C-reactive protein (CRP)]. The dieticians performed SGA and classified the patients as A (well-nourished) and B or C (with moderate or severe malnutrition), as defined previously [22]. Body mass index (BMI) was calculated as weight/height^2 (kg/m^2). Five well-trained dietitians measured AC and TSF at the midpoint of the triceps of the non-dominant arm with adipometer calipers (Abbot Laboratories, Tokyo, Japan). AMA was calculated using the following equation: AMA (cm^2) = [AC (cm) − {π × TSF (cm)}]^2/4π [23]. Grip strength of both hands was measured in a standing position using a dynamometer (Takei Scientific Instruments, Niigata, Japan). These tests were repeated twice for each hand, and the highest value for each hand was included in the overall mean. Biochemical tests were conducted at the Department of Clinical Laboratory in the Tokushima University Hospital, and these data were collected from electronic medical records. Serum albumin concentrations were measured by the modified bromocresol purple method, serum CRP concentrations were measured by the latex agglutination method, hemoglobin was measured by the colorimetric method, and total lymphocyte counts were determined by flow cytometry. We calculated prognostic nutritional index (PNI)—a nutritional and immunological parameter—as follows: 10 × serum albumin concentration (g/dL) + 0.005 × lymphocyte count (number/mm^2) in the peripheral blood as described by Onodera et al [24]. The cut-off value of PNI was determined to be 40 based on an original investigation [24]. Sarcopenia was diagnosed by the cut-off points of low handgrip strength and low skeletal muscle index suggested by the Asian Working Group of Sarcopenia. [25]. The cut-off values of handgrip strength were 26 kg in men and 18 kg in women, and the cut-off values of low skeletal muscle mass

were 7.0 kg/m^2 in men and 5.7 kg/m^2 in women. We assessed cancer cachexia as described by Fearon et al [26].

BIA

BIA was performed using Inbody770 (InBody, Tokyo, Japan), and R and Xc were measured using an eight-point tactile electrode and multi-frequency current. BIA was conducted in a standing position and was not conducted in patients with pacemakers or those who had difficulty standing. Patients fasted for at least 4 h before the measurement. PhA values at 50 kHz were calculated as follows: PhA (degrees) = arctan (Xc/R) × (180/π). In order to investigate the characteristics of patients with particularly high and low PhA, we divided patients into three groups according to the PhA quartile values by sex. The high-PhA group was PhA > 75th percentile (Q4), the low-PhA group was PhA ≦ 25th percentile (Q1), and the normal-PhA group was between 25th and 75th percentile (Q3 and Q2). The cut-off value of the 25th and 75th percentile was 4.4° and 5.5° in men, and 4.0° and 4.8° in women.

Outcomes

The short-term outcomes were defined as the incidence of prolonged postoperative length of stay (≥ 3 days) in HCU or/and ICU or the incidence of severe postoperative complications. This was based on the usual clinical path of the Digestive Surgery and Transplantation Center in the Tokushima University Hospital, which is that patients stay in the HCU or/and ICU for up to 2 days postoperatively. Postoperative complications were assessed from the first day post-surgery until

discharge and were classified from grades 1 to 5 according to the Clavien–Dindo classification [27]. We defined complications of grade ≥3 as severe. The long-term outcome was defined as the 5-year survival rate. Survival time was calculated from the time of surgery to the last follow-up date (June 30, 2019) or death.

Statistical analysis

We expressed non-normally distributed continuous variables as medians and interquartile ranges. We performed comparisons among three groups (high-, normal-, and low-PhA groups) and continuous variables using the Kruskal–Wallis analysis. We calculated statistical differences among the three groups using the Steel–Dwass test. We performed comparisons among three groups and categorical variables using the chi-squared test. We applied the Spearman correlation coefficient test to determine correlations between PhA and other nutritional indexes such as BMI, AC, AMA, TSF, handgrip strength, and serum biochemical data. The associations between PhA and postoperative short-term outcomes were performed using univariate and multivariate logistic regression analyses. Baseline variables with $P < 0.1$ in the univariate analysis were included in the multivariate models. We applied the Kaplan–Meier analysis to calculate survival time and the log-rank test to evaluate significant differences. For multiple comparisons, we used the Bonferroni correction. We used univariate and multivariate Cox proportional hazards regression models to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) and to identify predictors for mortality. Any variables with $P < 0.1$ in univariate analysis were included in the multivariate Cox proportional hazard model. All statistical analyses were performed using the JMP version 13.0 software (SAS Institute, Cary,

NC, USA). We considered all values of $P < 0.05$ as statistically significant. We followed standard methods to estimate the appropriate sample size for multivariate logistic regression analyses and multivariate Cox proportional hazards regression models, with at least 10 outcomes required for each included independent variable. The sample size was calculated using data from our preliminary study, with an expected incidence of postoperative severe complications and prolonged postoperative HCU or/and ICU stays, and mortality rate of 10%, we required 400 (4×10/0.1) patients (40 incidents) to appropriately perform multivariate logistic regression analyses and multivariate Cox proportional hazards regression models with four variables.

Results

Patient characteristics

Table 1 presents the characteristics of the 501 patients included in the study. Median (interquartile ranges) of PhA values was 5.0° (4.4°–5.5°) in men and 4.4° (4.0°–4.8°) in women. We divided the patients into low-, normal-, and high-PhA groups according to the quartile PhA values by sex. Age, height, body weight, BMI, PhA, and fat free mas (FFM) were significantly different among the three groups.

Table 1. Patient characteristics

	All n = 501	Low-PhA n = 125	Normal-PhA n = 251	High-PhA n = 125	P-value
Age (years)	70 (63–76)	77 (70–83)	69 (64–69)	65 (56–72)	<**0.001**
Sex					
Men	316 (63%)	79 (63%)	158 (63%)	79 (63%)	1.000
Women	185 (37%)	46 (37%)	93 (37%)	46 (37%)	
Cancer site					
Gastric	155 (31%)	33 (26%)	77 (31%)	45 (36%)	0.459
Colorectal	201 (40%)	52 (42%)	98 (39%)	51 (41%)	
Liver	75 (15%)	19 (15%)	36 (14%)	20 (16%)	
Bile duct	38 (8%)	11 (9%)	22 (9%)	5 (4%)	
Pancreas	32 (6%)	10 (8%)	18 (7%)	4 (3%)	

Stage					
I	176 (35%)	34 (27%)	89 (35%)	53 (42%)	0.186
II	150 (30%)	40 (32%)	75 (30%)	35 (28%)	
III	116 (23%)	30 (24%)	61 (24%)	25 (20%)	
IV	59 (12%)	21 (17%)	26 (10%)	12 (10%)	
Height (cm)	160.0 (152.0–167.0)	157.0 (149.3–166.0)	160.8 (153.0–167.0)	162.0 (154.0–167.2)	**0.015**
BW (kg)	57.2 (49.9–65.3)	52.5 (44.4–59.8)	58.2 (51.2–65.1)	61.3 (53.4–69.1)	**<0.001**
BMI (kg/m^2)	22.4 (20.6–24.5)	20.9 (19.0–23.0)	22.5 (20.7–24.4)	23.4 (21.8–25.4)	**<0.001**
PhA(°)	4.7 (4.2–5.3)	3.8 (3.5–4.1)	4.7 (4.5–5.1)	5.6 (5.1–6.0)	**<0.001**
FFM (kg)	42.5 (35.6-49.2)	38.4 (32.3-44.8)	43.2 (36.1-49.7)	46.0 (37.8-52.8)	**<0.001**
Surgery time (min)	288 (240-348)	286 (229-350)	289 (240-347)	294 (246-339)	0.780

BW, body weight; BMI, body mass index; PhA, phase angle; FFM, fat free mass

Statistical analysis; Kruskal–Wallis analysis for continuous variables, chi-squared test for categorical variables.

Correlation of phase angle to clinical parameters and nutritional markers

Table 2 shows the correlation of PhA to clinical parameters and nutritional markers. We observed significant negative correlations between PhA and age and between PhA and serum CRP levels. Further, we observed positive correlations between PhA and height, body weight, BMI, AC, AMA, skeletal muscle mass, handgrip strength, albumin level, hemoglobin level, total lymphocyte count, and PNI. TSF and body fat mass showed no correlation with PhA.

232

233 **Table 2.** Spearman correlation coefficients between phase angle and clinical or nutritional

234 markers

	Spearman correlation coefficient	P-value
Age (years)	−0.47	**<0.001**
Height (cm)	0.39	**<0.001**
Body weight (kg)	0.48	**<0.001**
Body mass index (kg/m^2)	0.31	**<0.001**
Arm circumference (cm)	0.41	**<0.001**
Mid-upper arm muscle area (cm^2)	0.48	**<0.001**
Triceps skinfold thickness (mm)	0.00	0.935
Skeletal muscle mass (kg)	0.60	**<0.001**
Body fat mass (kg)	0.09	0.052
Handgrip strength (kg)	0.68	**<0.001**
Albumin (g/dL)	0.44	**<0.001**
Hemoglobin (g/dL)	0.48	**<0.001**
Total lymphocyte (/mm^3)	0.17	**<0.001**
C-reactive protein (mg/dL)	−0.14	**0.001**
PNI	0.43	**<0.001**

235 PNI, prognostic nutritional index

236 Statistical analysis; Spearman correlation coefficient test

237

238 Comparison of the nutritional status in three groups

Table 3 shows the prevalence of malnutrition, sarcopenia, and cachexia in the low-, normal-, and high-PhA groups. According to the SGA, the rates of moderate or severe malnutrition were higher in the low-PhA group. The number of patients with low PNI, sarcopenia, and cachexia were significantly higher in the low-PhA group.

Table 3. Prevalence of malnutrition, sarcopenia, and cachexia by phase angle

		Low-PhA	Normal-PhA	High-PhA	P-value
SGA	A	65 (52%)	187 (75%)	113 (91%)	**<0.001**
	B or C	60 (48%)	63 (25%)	11 (9%)	
PNI	High	73 (59%)	196 (79%)	118 (95%)	**<0.001**
	Low	51 (41%)	52 (21%)	6 (5%)	
Non-sarcopenia		60 (57%)	175 (87%)	104 (94%)	**<0.001**
Sarcopenia		45 (43%)	26 (13%)	7 (6%)	
Non-cachexia		53 (44%)	150 (64%)	88 (73%)	**<0.001**
Cachexia		67 (56%)	86 (36%)	33 (27%)	

PhA, phase angle; SGA, subjective global assessment; PNI, prognostic nutritional index

Statistical analysis; chi-squared test

Association between PhA and postoperative short-term outcomes

The incidence of postoperative severe complications (Clavien–Dindo classification grade ≥ 3) was 10% in all patients [14% in low-PhA group, 12% in normal-PhA group, and 4% in high-PhA group (P = 0.018)]. In the univariate analysis, presence of bile duct and pancreatic cancers, presence

of stage IV disease, and belonging to the normal- and low-PhA groups (as a categorical variables) were significant risk factors for postoperative complications (Table 4). In the multivariate analysis, there is a trend that PhA (as a continuous variable) can predict complications in postoperative period, but does not show a significant P-value [odds ratio (OR) = 0.68; 95% CI 0.44–1.06; P = 0.088, shown in Table 4, multivariate 1]. Furthermore, there is a trend that belonging to the low-PhA group aids in predicting complications in postoperative period, although no significant P-value is observed (OR = 3.00; 95% CI 0.98–9.20; P = 0.055, shown in Table 4, multivariate 2). The incidence of prolonged postoperative HCU or/and ICU stays was 8% in all patients [16% in low-PhA group, 8% in normal-PhA group, and 2% in high-PhA group (P < 0.001)]. In the univariate analysis, age, presence of bile duct and pancreatic cancers, presence of stage IV disease, low PhA (as a continuous variable), and belonging to the low-PhA group (as a categorical variable) were significant risk factors for longer HCU or/and ICU stays (Table 5). In the multivariate analysis, PhA (as a continuous variable) remained an independent risk factor for longer HCU or/and ICU stays (OR = 0.54; 95% CI 0.31–0.92; P = 0.024, shown in Table 5, multivariate 1). Furthermore, belonging to the low-PhA group was an independent risk factor for longer HCU or/and ICU stays (OR = 5.69; 95% CI 1.38–23.39; P = 0.016, shown in Table 5, multivariate 2).

Table 4. Univariate and multivariate analyses of risk factors associated with postoperative complications

	Univariate			Multivariate 1			Multivariate 2		
	OR	95% CI	P-value	OR	95% CI	P-value	OR	95% CI	P-value

Age (years)	1.02	0.99–1.05	0.194	-	-	-	-	-	-
Sex									
Men	1.00	-	-	1.00	-	-	1.00	-	-
Women	0.54	0.28–1.03	0.053	0.29	0.13–0.63	**0.002**	0.36	0.17–0.76	**0.008**
Cancer site									
Colorectal	1.00	-	-	1.00	-	-	1.00	-	-
Gastric	0.68	0.27–1.76	0.430	0.65	0.24–1.72	0.382	0.64	0.24–1.72	0.377
Liver	0.81	0.26–2.58	0.728	0.69	0.21–2.23	0.533	0.69	0.21–2.26	0.543
Bile duct	9.43	3.99–22.28	**<0.001**	12.83	4.95–33.26	**<0.001**	12.59	4.83–32.81	**<0.001**
Pancreas	9.89	4.01–24.39	**<0.001**	10.35	3.77–28.41	**<0.001**	9.79	3.57–26.88	**<0.001**
Stage									
I	1.00	-	-	1.00	-	-	1.00	-	-
II	1.19	0.52–2.73	0.684	0.50	0.18–1.38	0.182	0.50	0.18–1.38	0.184
III	1.88	0.83–4.22	0.128	1.21	0.48–3.06	0.687	1.19	0.47–3.01	0.714
IV	4.25	1.84–9.84	**<0.001**	1.45	0.52–4.04	0.475	1.54	0.56–4.24	0.402
PhA (°)	0.73	0.51–1.05	0.088	0.68	0.44–1.06	0.088	-	-	-
PhA									
High	1.00	-	-	-	-	-	1.00	-	-
Normal	3.14	1.18–8.31	**0.022**	-	-	-	2.60	0.91–7.41	0.075
Low	4.04	1.45–11.25	**0.008**	-	-	-	3.00	0.98–9.20	0.055

PhA, phase angle; OR, odds ratio; CI, confidence interval

Multivariate 1: using PhA as a continuous variable

Multivariate 2: using PhA as a categorical variable

Statistical analysis; univariate and multivariate logistic regression analyses

275

276 **Table 5.** Univariate and multivariate analyses of risk factors associated with postoperative length
277 of HCU or/and ICU stay for ≥ 3 days

	Univariate			Multivariate 1			Multivariate 2		
	OR	95% CI	P-value	OR	95% CI	P-value	OR	95% CI	P-value
Age (years)	1.04	1.00–1.07	**0.038**	1.01	0.97–1.06	0.556	1.01	0.97–1.06	0.629
Sex									
Men	1.00	-	-	-	-	-	-	-	-
Women	0.75	0.38–1.48	0.397	-	-	-	-	-	-
Cancer site									
Colorectal	1.00	-	-	1.00	-	-	1.00	-	-
Gastric	1.12	0.37–3.39	0.847	1.19	0.38–3.76	0.770	1.21	0.39–3.82	0.741
Liver	1.15	0.29–4.59	0.838	1.21	0.30–4.95	0.791	1.12	0.28–4.59	0.870
Bile duct	16.17	5.94–44.01	**<0.001**	15.57	5.35–45.29	**<0.001**	16.46	5.61–48.29	**<0.001**
Pancreas	16.63	5.88–47.03	**<0.001**	14.73	4.78–45.34	**<0.001**	15.03	4.78–47.21	**<0.001**
Stage									
I	1.00	-	-	1.00	-	-	1.00	-	-
II	2.16	0.88–5.30	0.092	0.80	0.27–2.35	0.682	0.89	0.31–2.58	0.828
III	1.77	0.66–4.72	0.257	0.94	0.30–2.94	0.913	0.94	0.30–2.92	0.910
IV	4.81	1.83–12.64	**0.001**	1.41	0.43–4.63	0.569	1.42	0.43–4.64	0.566
PhA (°)	0.47	0.31–0.71	**<0.001**	0.54	0.31–0.92	**0.024**	-	-	-
PhA									
High	1.00	-	-	-	-	-	1.00	-	-
Normal	3.33	0.97–11.48	0.057	-	-	-	2.25	0.59–8.50	0.232

Low	7.75	2.24–26.80	**0.001**	-	-	-	5.69	1.38–23.39	**0.016**

PhA, phase angle; OR, odds ratio; CI, confidence interval

Multivariate 1: using PhA as a continuous variable

Multivariate 2: using PhA as a categorical variable

Statistical analysis; univariate and multivariate logistic regression analyses

Survival outcome

Figure 2 shows the survival curves of the low-, normal-, and high-PhA groups. The 5-year survival rate was 74% in all patients (68% in low-PhA group, 74% in normal-PhA group, and 79% in high-PhA group). Overall mortality was significantly higher in the low-PhA group than in the normal-PhA (P = 0.008) and high-PhA (P = 0.007) group.

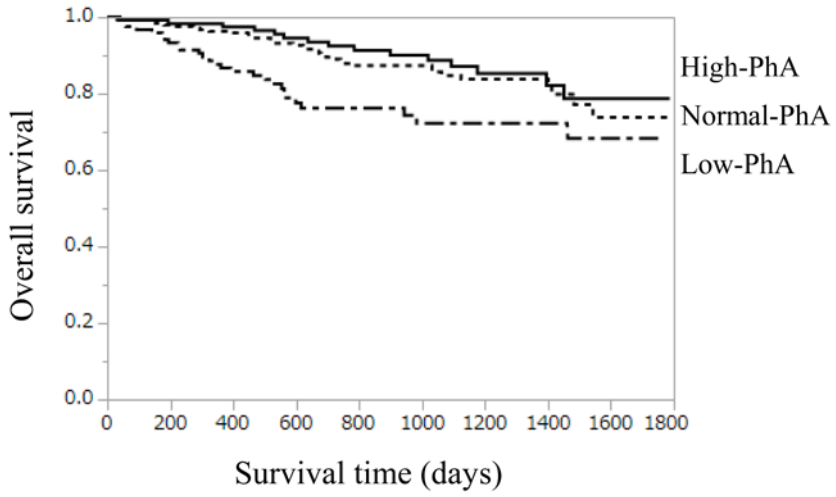

Figure 2. Kaplan–Meier survival curves by phase angle

We calculated the overall survival from the time of surgery to the last follow-up date or death. The solid line represents the high-PhA group; the dotted line, the normal-PhA group; and the dashed line, the low-PhA group. PhA, phase angle.

Statistical analysis; Kaplan–Meier analysis was used to calculate survival time and the log-rank test used to evaluate significant differences. For multiple comparisons, we used the Bonferroni correction.

Table 6 shows the HR and 95% CI. In the univariate analysis, cancer site, cancer stage, and PhA (as both continuous and categorical variables) were significant risk factors for mortality, whereas age and sex were not. In the multivariate analysis, low PhA (as a continuous variable) was an independent risk factor for mortality (HR = 0.56; 95% CI 0.40–0.79; P < 0.001, shown in multivariate 1). Similarly, belonging to the low-PhA group (as a categorical variable) was a significant risk factor for mortality (HR = 1.99; 95% CI 1.05–3.90; P = 0.034, shown in multivariate 2).

Table 6. Univariate and multivariate Cox proportional hazard ratio

	Univariate			Multivariate 1			Multivariate 2		
	HR	95% CI	P-value	HR	95% CI	P-value	HR	95% CI	P-value
Age (years)	1.00	0.98–1.03	0.850	-	-	-	-	-	-
Sex									
Men	1.00			-	-	-	-	-	-
Women	0.70	0.42–1.12	0.142	-	-	-	-	-	-
Cancer site									
Colorectal	1.00			1.00			1.00		
Gastric	1.11	0.56–2.19	0.763	1.91	0.95–3.81	0.074	1.89	0.93–3.83	0.138

Liver	2.62	1.36–5.04	**0.005**	2.51	1.30–4.88	**0.008**	2.31	1.19–4.52	**0.017**
Bile duct	3.89	1.85–8.18	**0.001**	0.53	0.24–1.18	**0.017**	3.12	1.45–6.70	**0.013**
Pancreas	7.69	3.89–15.20	**<0.001**	4.96	2.44–10.09	**<0.001**	4.47	2.13–9.36	**<0.001**
Stage									
I	1.00			1.00			1.00		
II	3.67	1.45–11.18	**0.005**	3.04	1.17–9.42	**0.022**	3.48	1.34–10.75	**0.010**
III	7.15	2.94–21.28	**<0.001**	6.46	2.58–19.62	**<0.001**	6.41	2.56–19.48	**<0.001**
IV	24.68	10.51–72.26	**<0.001**	18.25	7.35–55.47	**<0.001**	17.71	7.14–53.75	**<0.001**
PhA (°)	0.56	0.42–0.76	**<0.001**	0.56	0.40–0.79	**<0.001**	-	-	-
PhA									
High	1.00			-	-	-	1.00		
Normal	1.21	0.67–2.28	0.530	-	-	-	1.04	0.57–1.98	0.910
Low	2.38	1.28–4.59	**0.006**	-	-	-	1.99	1.05–3.90	**0.034**

307 PhA, phase angle; HR, hazard ratio; CI, confidence interval

308 Multivariate 1: using PhA as a continuous variable

309 Multivariate 2: using PhA as a categorical variable

310 Statistical analysis; Cox proportional hazards regression models

Discussion

We assessed the possible association between PhA and postoperative short- or long-term prognosis in patients with gastrointestinal and HBP cancers scheduled for resection surgeries and analyzed the association between PhA and nutritional or clinical variables. PhA positively correlated with skeletal muscle mass, biochemical nutritional or immunological markers, and handgrip strength, and negatively correlated with age and CRP. Low PhA was associated with a longer HCU or/and ICU stay. Low PhA was independently associated with poor survival.

In the present study, we used the BIA method because it is easy to use, inexpensive, and non-invasive, and it requires no training. Although BIA-derived variables, such as skeletal muscle mass, have widely been used, measurement data on abnormal fluid balance, such as edema or ascites, should be carefully interpreted [5, 28]. BIA does not directly measure body composition; its accuracy depends on regression equations [5, 28, 29]. This is one of the limitations of BIA for assessing the muscle mass. In an edematous state, resistance is reduced, and cellular function may also be negatively affected, leading to decreased reactance [21]. This results in decreased impedance and thus a higher lean body mass is calculated by regression equations via BIA. By contrast, PhA is a raw data that describes the relation between two vector components of impedance (R and Xc) of the human body to an alternating electric current [6]. Reactance reflects “the ability of cell membranes to act as imperfect capacitors” [6]. Therefore, PhA has been considered as an indicator of cell membrane integrity [6]. In an edematous state, resistance is reduced, and cellular function may also be negatively affected, leading to decreased reactance and thus a lower PhA [21]. Therefore, PhA is different from the other BIA parameters such as lean body mass [19] and has the

advantage of being more useful in predicting prognosis than other BIA parameters. However, its biological and clinical interpretations remain unclear.

Studies on healthy individuals have shown that PhA is significantly higher in men and that racial differences exist [5]. PhA values have been reported at 6.55° ± 1.10° for Asians, 6.82° ± 1.13° for Caucasians, 7.21° ± 1.19° for African-Americans, and 7.33° ± 1.13°for Hispanics. Another study involving healthy individuals showed that age, race, height, FFM were PhA determinants in both men and women [30]. They suggested the need for specific reference values for each population. Indeed, in studies conducted in the American population [9, 10], the median PhA value of patients with pancreatic and colorectal cancers were 5.0° and 5.57°, respectively; however, the median PhA values of Japanese patients in the present study were lower with 4.6° and 4.7° in cases of pancreatic and colorectal cancers, respectively. Our results indicate the racial differences of PhA, and the reference value suggested in this study may be useful for Asian populations.

In the present study, we observed a correlation between PhA and various nutritional or clinical variables. Consistent with other reports [5], PhA was higher in men than in women and was positively correlated with BMI and negatively correlated with age. Interestingly, PhA showed a positive correlation with AMA (muscle mass index) but not with TSF (fat mass index). PhA positively correlated with handgrip strength (muscle function index). In addition, the ratio of sarcopenia was higher in the low-PhA group than in the other groups. These findings suggest that PhA reflects the nutritional status of patients, particularly their muscle volume and function. On analyzing PhA by cancer stage, we observed that PhA is significantly higher in patients with stage I disease than in others ($P < 0.05$); the PhA values were 4.9° (4.3°–5.5°) in stage I, 4.6° (4.1°–5.1°) in

stage II, 4.7° (4.1°–5.2°) in stage III, and 4.6° (4.1°–5.0°) in stage IV. Moreover, PhA showed a negative correlation with CRP level. These results suggest that PhA presents both nutritional information and disease severity.

Preoperative low PhA has been associated with postoperative length of stay or complications in cardiac patients undergoing surgery [31], in patients with advanced ovarian cancer [32], in patients with head and neck cancer [33], and in patients with gastric cancer [34]. In our study, there was a trend toward low PhA predicting complications in the postoperative period, this did not reach significance. One recent report showed that standardized PhA had no association with postoperative complications (P = 0.199) in patients undergoing resection of colorectal cancer [35]. The authors of this report discussed the merit of assessing PhA, namely that it is non-invasive and of low cost, and argued that further research with a larger sample size was needed to demonstrate the usefulness of standardized PhA in predicting clinical outcomes [35]. Malnutrition has been reported to be associated with reduced immune competence and more infections [36]. Preoperative malnutrition is well recognized as a risk factor for increased morbidity in patients undergoing major surgery [37, 38]. Low PhA is a marker of depletion of muscular mass and of resources in general [32]. Thus, low PhA may be associated with the reduced immune response to cancer and may influence postoperative recovery. We observed that low PhA was a risk factor for prolonged postoperative HCU or/and ICU stays. Typically, patients stay in the HCU or/and ICU for only up to 2 days postoperatively in our center according to the clinical path; however, patients with low PhA exhibit a high incidence of postoperative complications, and their length of stay exceeded 3 days. Our results suggest that PhA is a useful postoperative short-term prognostic indicator.

In the present study, we observed that PhA was an independent risk factor for mortality, despite adjusting for other factors (such as cancer site and cancer stage). In a study conducted on patients with cancer, a standardized PhA according to age, sex, and BMI was an independent 6-month survival prognostic factor [17]. However, the report included various types of cancer such as gastrointestinal, head and neck, and urogenital cancers; therefore, their results do not necessarily apply to patients with gastrointestinal and HBP cancers. Studies on patients with gastrointestinal cancer have also been reported [9, 10, 11]. Studies on patients with pancreatic [9] and colon [10] cancers and on patients with hepatocellular carcinoma [11] have demonstrated that low PhA is a poor prognosis factor. However, these reports do not provide data regarding the association between PhA and postoperative short-term outcomes, and the analysis of survival outcomes in these studies were not adjusted by sex and cancer stage, which was one of the limitations of these studies.

This study has several key strengths. The first is the use of BIA which is an easy, noninvasive, and inexpensive tool to predict short-term and long-term prognosis. The second strength is that, to the best of our knowledge, this is the first report indicating that PhA can predict both short- and long-term prognosis in patients with gastrointestinal and HBP cancers. The third strength is that our results provide the reference values in patients with gastrointestinal and HBP cancer by sex in Asians for the first time. Most studies of PhA have been conducted in Western or American populations, and data for Asian populations are scarce. Our results indicate that the lowest quartile value (4.4° in men and 4.0° in women) can be useful as a prognostic cut-off value in patients with gastrointestinal and HBP cancers.

The limitations of this study must be acknowledged. The study has a retrospective design and

395 further prospective intervention studies are warranted to elucidate whether the improvement of
396 preoperative PhA leads to better prognoses. There were many missing data of BIA measurements. It
397 would be best if we could analyze each cancer type separately; however, we could not analyze each
398 cancer type separately because of the sample size. To adjust the effect of cancer types on prognosis,
399 we conducted multivariate analysis. Although the results of PhA as a continuous variable showed
400 that low PhA was a poor prognostic risk factor, the reference values we used may be applicable to
401 the Asian population but not to individuals in other countries because PhA values differ according
402 to the population.

403 In conclusion, our analysis suggests that PhA is short- and long-term prognosis marker for
404 patients with gastrointestinal and HBP cancers. Further studies are required to elucidate whether
405 nutritional interventions can improve PhA and, consequently, the prognoses in these patients.

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