

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

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4 Running head: Impact of phase angle on postoperative prognosis

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6 Sonoko Yasui-Yamada^{a,b,*}, Yu Oiwa^a, Yu Saito^{a,c}, Nozomi Aotani^a, Atsumi Matsubara^a, Sayaka

7 Matsuura^a, Mayu Tanimura^a, Yoshiko Tani-Suzuki^{a,b}, Hideya Kashiwara^{b,c}, Masaaki Nishi^c, Mitsuo

8 Shimada^c, Yasuhiro Hamada^{a,b}.

9 ^aDepartment of Therapeutic Nutrition, Institute of Biomedical Sciences, Tokushima University

10 Graduate School, Japan

11 ^bDepartment of Nutrition, Tokushima University Hospital, Japan

12 ^cDepartment of Digestive Surgery and Transplantation, Institute of Biomedical Sciences, Tokushima

13 University Graduate School, Japan

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19 *Corresponding author

20 Department of Therapeutic Nutrition, Institute of Biomedical Sciences, Tokushima University

21 Graduate School, 3-18-15 Kuramoto-Cho, Tokushima 770-8503, Japan

22 Tel.: +81-88-633-9124

23 Fax: +81-88-633-9574.

24 E-mail: yamada.sonoko@tokushima-u.ac.jp (S. Yasui-Yamada).

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26 Author contributions

27 S.Y-Y. designed the research; S.Y-Y., Y.O., N.A., A.M., S.M., M.T., and Y.T-S. conducted the
28 nutritional assessment and collected the data; Y.S., H.K., and M.N. performed the medical data
29 collection; S.Y-Y. and Y.O interpreted the results and analyzed the data; S.Y-Y. drafted the
30 manuscript; M.S. and Y.H. critically revised the manuscript. All authors read and approved the final
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32

33 Declarations of Interest

34 None.

35

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42

43

44 Objective

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

49 Research Methods & Procedures

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

57 Results

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

64 and 2% in high-PhA ($P < 0.001$)]. The 5-year survival rate was 74% in all patients [68% in low-PhA,
65 74% in normal-PhA, and 79% in high-PhA ($P < 0.001$)]. The multivariate analysis demonstrated
66 that a low-PhA group was an independent risk factor for mortality (hazard ratio, 1.99; 95%
67 confidence interval 1.05–3.90; $P = 0.034$).

68 Conclusion

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

71

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

74

75 ¹Abbreviations

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

97 [21].

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

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

109

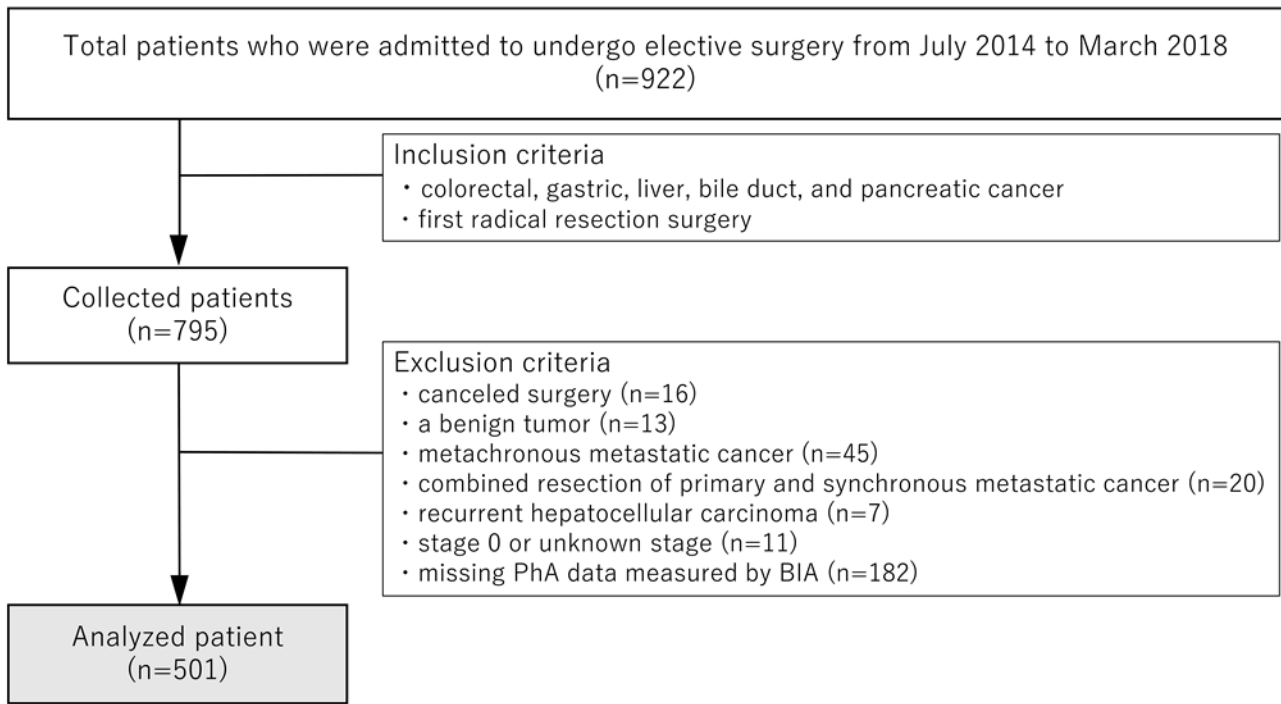
Materials and Methods

110

111 Patients

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

124



126 **Figure 1.** Selection of patients analyzed in this study

127 PhA, phase angle; BIA, bioelectrical impedance analysis

128

129 **Data collection**

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

133

134 **Nutritional assessment**

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

139 skinfold thickness (TSF), mid-upper arm muscle area (AMA), and handgrip strength], BIA, and
140 serum biochemical tests [albumin, hemoglobin, total lymphocyte, and C-reactive protein (CRP)].
141 The dietitians performed SGA and classified the patients as A (well-nourished) and B or C (with
142 moderate or severe malnutrition), as defined previously [22]. Body mass index (BMI) was
143 calculated as weight/height² (kg/m²). Five well-trained dietitians measured AC and TSF at the
144 midpoint of the triceps of the non-dominant arm with adipometer calipers (Abbot Laboratories,
145 Tokyo, Japan). AMA was calculated using the following equation: $AMA (cm^2) = [AC (cm) - \{\pi \times$
146 $TSF (cm)\}]^2/4\pi$ [23]. Grip strength of both hands was measured in a standing position using a
147 dynamometer (Takei Scientific Instruments, Niigata, Japan). These tests were repeated twice for
148 each hand, and the highest value for each hand was included in the overall mean. Biochemical tests
149 were conducted at the Department of Clinical Laboratory in the Tokushima University Hospital, and
150 these data were collected from electronic medical records. Serum albumin concentrations were
151 measured by the modified bromocresol purple method, serum CRP concentrations were measured
152 by the latex agglutination method, hemoglobin was measured by the colorimetric method, and total
153 lymphocyte counts were determined by flow cytometry. We calculated prognostic nutritional index
154 (PNI)—a nutritional and immunological parameter—as follows: $10 \times$ serum albumin concentration
155 $(g/dL) + 0.005 \times$ lymphocyte count (number/mm²) in the peripheral blood as described by Onodera
156 et al [24]. The cut-off value of PNI was determined to be 40 based on an original investigation [24].
157 Sarcopenia was diagnosed by the cut-off points of low handgrip strength and low skeletal muscle
158 index suggested by the Asian Working Group of Sarcopenia. [25]. The cut-off values of handgrip
159 strength were 26 kg in men and 18 kg in women, and the cut-off values of low skeletal muscle mass

160 were 7.0 kg/m² in men and 5.7 kg/m² in women. We assessed cancer cachexia as described by
161 Fearon et al [26].

162

163 BIA

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

174

175 Outcomes

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

181 discharge and were classified from grades 1 to 5 according to the Clavien–Dindo classification [27].
182 We defined complications of grade ≥ 3 as severe. The long-term outcome was defined as the 5-year
183 survival rate. Survival time was calculated from the time of surgery to the last follow-up date (June
184 30, 2019) or death.

185

186 Statistical analysis

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

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

210

211

Results

212

213

214 Patient characteristics

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

220

221 **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%)	
II	150 (30%)	40 (32%)	75 (30%)	35 (28%)	0.186
III	116 (23%)	30 (24%)	61 (24%)	25 (20%)	
IV	59 (12%)	21 (17%)	26 (10%)	12 (10%)	
	160.0	157.0	160.8	162.0	
Height (cm)	(152.0–167.0)	(149.3–166.0)	(153.0–167.0)	(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

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

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

225

226 Correlation of phase angle to clinical parameters and nutritional markers

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

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

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

243

244 **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%)	

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

246 Statistical analysis; chi-squared test

247

248 Association between PhA and postoperative short-term outcomes

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

252 of stage IV disease, and belonging to the normal- and low-PhA groups (as a categorical variables)
 253 were significant risk factors for postoperative complications (Table 4). In the multivariate analysis,
 254 there is a trend that PhA (as a continuous variable) can predict complications in postoperative
 255 period, but does not show a significant P-value [odds ratio (OR) = 0.68; 95% CI 0.44–1.06; P =
 256 0.088, shown in Table 4, multivariate 1]. Furthermore, there is a trend that belonging to the
 257 low-PhA group aids in predicting complications in postoperative period, although no significant
 258 P-value is observed (OR = 3.00; 95% CI 0.98–9.20; P = 0.055, shown in Table 4, multivariate 2).
 259 The incidence of prolonged postoperative HCU or/and ICU stays was 8% in all patients [16% in
 260 low-PhA group, 8% in normal-PhA group, and 2% in high-PhA group (P < 0.001)]. In the univariate
 261 analysis, age, presence of bile duct and pancreatic cancers, presence of stage IV disease, low PhA
 262 (as a continuous variable), and belonging to the low-PhA group (as a categorical variable) were
 263 significant risk factors for longer HCU or/and ICU stays (Table 5). In the multivariate analysis, PhA
 264 (as a continuous variable) remained an independent risk factor for longer HCU or/and ICU stays
 265 (OR = 0.54; 95% CI 0.31–0.92; P = 0.024, shown in Table 5, multivariate 1). Furthermore,
 266 belonging to the low-PhA group was an independent risk factor for longer HCU or/and ICU stays
 267 (OR = 5.69; 95% CI 1.38–23.39; P = 0.016, shown in Table 5, multivariate 2).

268

269 **Table 4.** Univariate and multivariate analyses of risk factors associated with postoperative
 270 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

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

272 Multivariate 1: using PhA as a continuous variable

273 Multivariate 2: using PhA as a categorical variable

274 Statistical analysis; univariate and multivariate logistic regression analyses

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**

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

279 Multivariate 1: using PhA as a continuous variable

280 Multivariate 2: using PhA as a categorical variable

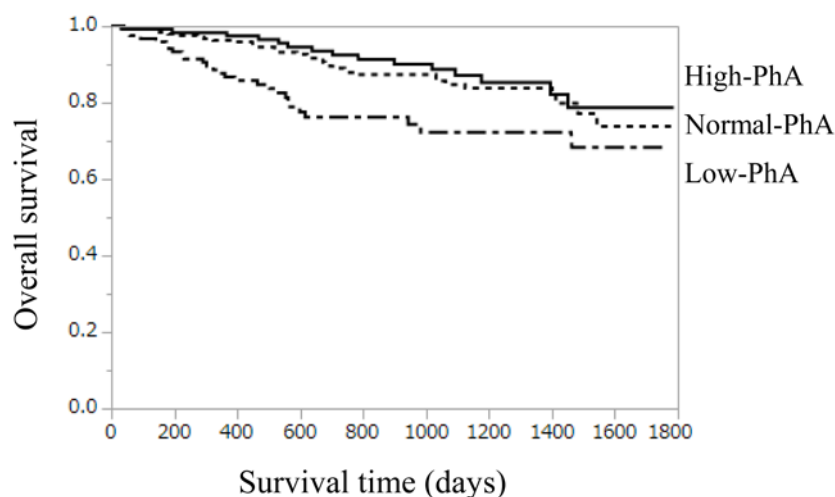
281 Statistical analysis; univariate and multivariate logistic regression analyses

282

283 Survival outcome

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

288



289

290 **Figure 2.** Kaplan–Meier survival curves by phase angle

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

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

297

298 Table 6 shows the HR and 95% CI. In the univariate analysis, cancer site, cancer stage, and
 299 PhA (as both continuous and categorical variables) were significant risk factors for mortality,
 300 whereas age and sex were not. In the multivariate analysis, low PhA (as a continuous variable) was
 301 an independent risk factor for mortality (HR = 0.56; 95% CI 0.40–0.79; P < 0.001, shown in
 302 multivariate 1). Similarly, belonging to the low-PhA group (as a categorical variable) was a
 303 significant risk factor for mortality (HR = 1.99; 95% CI 1.05–3.90; P = 0.034, shown in multivariate
 304 2).

305

306 **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

311

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

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

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

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

344 In the present study, we observed a correlation between PhA and various nutritional or clinical
345 variables. Consistent with other reports [5], PhA was higher in men than in women and was
346 positively correlated with BMI and negatively correlated with age. Interestingly, PhA showed a
347 positive correlation with AMA (muscle mass index) but not with TSF (fat mass index). PhA
348 positively correlated with handgrip strength (muscle function index). In addition, the ratio of
349 sarcopenia was higher in the low-PhA group than in the other groups. These findings suggest that
350 PhA reflects the nutritional status of patients, particularly their muscle volume and function. On
351 analyzing PhA by cancer stage, we observed that PhA is significantly higher in patients with stage I
352 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

353 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
354 negative correlation with CRP level. These results suggest that PhA presents both nutritional
355 information and disease severity.

356 Preoperative low PhA has been associated with postoperative length of stay or complications in
357 cardiac patients undergoing surgery [31], in patients with advanced ovarian cancer [32], in patients
358 with head and neck cancer [33], and in patients with gastric cancer [34]. In our study, there was a
359 trend toward low PhA predicting complications in the postoperative period, this did not reach
360 significance. One recent report showed that standardized PhA had no association with postoperative
361 complications (P = 0.199) in patients undergoing resection of colorectal cancer [35]. The authors of
362 this report discussed the merit of assessing PhA, namely that it is non-invasive and of low cost, and
363 argued that further research with a larger sample size was needed to demonstrate the usefulness of
364 standardized PhA in predicting clinical outcomes [35]. Malnutrition has been reported to be
365 associated with reduced immune competence and more infections [36]. Preoperative malnutrition is
366 well recognized as a risk factor for increased morbidity in patients undergoing major surgery [37,
367 38]. Low PhA is a marker of depletion of muscular mass and of resources in general [32]. Thus, low
368 PhA may be associated with the reduced immune response to cancer and may influence
369 postoperative recovery. We observed that low PhA was a risk factor for prolonged postoperative
370 HCU or/and ICU stays. Typically, patients stay in the HCU or/and ICU for only up to 2 days
371 postoperatively in our center according to the clinical path; however, patients with low PhA exhibit
372 a high incidence of postoperative complications, and their length of stay exceeded 3 days. Our
373 results suggest that PhA is a useful postoperative short-term prognostic indicator.

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

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

394 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.

406

407

- 409 1. Bozzetti F. Rationale and indications for preoperative feeding of malnourished surgical
410 cancer patients. *Nutrition* 2002;18:953–9. [https://doi.org/10.1016/s0899-9007\(02\)00988-7](https://doi.org/10.1016/s0899-9007(02)00988-7).
- 411 2. Argiles JM. Cancer-associated malnutrition. *Eur J Oncol Nurs* 2005;9:S39–50.
412 <https://doi.org/10.1016/j.ejon.2005.09.006>.
- 413 3. Heymsfield SB, Matthews D. Body composition: research and clinical advances--1993
414 A.S.P.E.N. research workshop. *JPEN J Parenter Enteral Nutr* 1994;18:91–103.
415 <https://doi.org/10.1177/014860719401800291>.
- 416 4. Norman K, Wirth R, Neubauer M, Eckardt R, Stobaus N. The bioimpedance phase angle
417 predicts low muscle strength, impaired quality of life, and increased mortality in old patients with
418 cancer. *J Am Med Dir Assoc* 2015;16:173.e117–22. <https://doi.org/10.1016/j.jamda.2014.10.024>.
- 419 5. Barbosa-Silva MC, Barros AJ, Wang J, Heymsfield SB, Pierson RN Jr. Bioelectrical
420 impedance analysis: population reference values for phase angle by age and sex. *Am J Clin Nutr*
421 2005;82:49–52. <https://doi.org/10.1093/ajcn.82.1.49>.
- 422 6. Schwenk A, Beisenherz A, Romer K, Kremer G, Salzberger B, Elia M. Phase angle from
423 bioelectrical impedance analysis remains an independent predictive marker in HIV-infected patients
424 in the era of highly active antiretroviral treatment. *Am J Clin Nutr* 2000;72:496–501.
425 <https://doi.org/10.1093/ajcn/72.2.496>.
- 426 7. Maggiore Q, Nigrelli S, Ciccarelli C, Grimaldi C, Rossi GA, Michelassi C. Nutritional and
427 prognostic correlates of bioimpedance indexes in hemodialysis patients. *Kidney Int* 1996;50:2103–8.
428 <https://doi.org/10.1038/ki.1996.535>.

- 429 8. Selberg O, Selberg D. Norms and correlates of bioimpedance phase angle in healthy human
430 subjects, hospitalized patients, and patients with liver cirrhosis. *Eur J Appl Physiol* 2002;86:509–16.
431 <https://doi.org/10.1007/s00421-001-0570-4>.
- 432 9. Gupta D, Lis CG, Dahlk SL, Vashi PG, Grutsch JF, Lammersfeld CA. Bioelectrical
433 impedance phase angle as a prognostic indicator in advanced pancreatic cancer. *Br J Nutr*
434 2004;92:957–62. <https://doi.org/10.1079/bjn20041292>.
- 435 10. Gupta D, Lammersfeld CA, Burrows JL, Dahlk SL, Vashi PG, Grutsch JF, et al.
436 Bioelectrical impedance phase angle in clinical practice: implications for prognosis in advanced
437 colorectal cancer. *Am J Clin Nutr* 2004;80:1634–8. <https://doi.org/10.1093/ajcn/80.6.1634>.
- 438 11. Schutte K, Tippelt B, Schulz C, Rohl FW, Feneberg A, Seidensticker R, et al. Malnutrition
439 is a prognostic factor in patients with hepatocellular carcinoma (HCC). *Clin Nutr* 2015;34:1122–7.
440 <https://doi.org/10.1016/j.clnu.2014.11.007>.
- 441 12. Axelsson L, Silander E, Bosaeus I, Hammerlid E. Bioelectrical phase angle at diagnosis as
442 a prognostic factor for survival in advanced head and neck cancer. *Eur Arch Otorhinolaryngol*
443 2018;275:2379–86. <https://doi.org/10.1007/s00405-018-5069-2>.
- 444 13. Władysiuk MS, Mlak R, Morshed K, Surtel W, Brzozowska A, Małeczka-Massalska T.
445 Bioelectrical impedance phase angle as a prognostic indicator of survival in head-and-neck cancer.
446 *Curr Oncol* 2016;23:e481–7. <https://doi.org/10.3747/co.23.3181>.
- 447 14. Gupta D, Lammersfeld CA, Vashi PG, King J, Dahlk SL, Grutsch JF, et al. Bioelectrical
448 impedance phase angle as a prognostic indicator in breast cancer. *BMC Cancer* 2008;8:249.
449 <https://doi.org/10.1186/1471-2407-8-249>.

- 450 15. Gupta D, Lammersfeld CA, Vashi PG, King J, Dahlk SL, Grutsch JF, et al. Bioelectrical
451 impedance phase angle in clinical practice: implications for prognosis in stage IIIB and IV
452 non-small cell lung cancer. *BMC Cancer* 2009;9:37. <https://doi.org/10.1186/1471-2407-9-37>.
- 453 16. Toso S, Piccoli A, Gusella M, Menon D, Bononi A, Crepaldi G, et al. Altered tissue electric
454 properties in lung cancer patients as detected by bioelectric impedance vector analysis. *Nutrition*
455 2000;16:120–4. [https://doi.org/10.1016/s0899-9007\(99\)00230-0](https://doi.org/10.1016/s0899-9007(99)00230-0).
- 456 17. Norman K, Stobaus N, Zocher D, Bosy-Westphal A, Szramek A, Scheufele R, et al. Cutoff
457 percentiles of bioelectrical phase angle predict functionality, quality of life, and mortality in patients
458 with cancer. *Am J Clin Nutr* 2010;92:612–9. <https://doi.org/10.3945/ajcn.2010.29215>.
- 459 18. Hui D, Bansal S, Morgado M, Dev R, Chisholm G, Bruera E. Phase angle for
460 prognostication of survival in patients with advanced cancer: preliminary findings. *Cancer*
461 2014;120:2207–14. <https://doi.org/10.1002/cncr.28624>.
- 462 19. Paiva SI, Borges LR, Halpern-Silveira D, Assunção MC, Barros AJ, Gonzalez MC.
463 Standardized phase angle from bioelectrical impedance analysis as prognostic factor for survival in
464 patients with cancer. *Support Care Cancer* 2010;19:187–92.
465 <https://doi.org/10.1007/s00520-009-0798-9>.
- 466 20. do Amaral Paes TC, de Oliveira KCC, de Carvalho Padilha P, Peres WAF. Phase angle
467 assessment in critically ill cancer patients: Relationship with the nutritional status, prognostic
468 factors and death. *J Crit Care* 2018;44:430–5. <https://doi.org/10.1016/j.jcrc.2018.01.006>.
- 469 21. Hui D, Moore J, Park M, Liu D, Bruera E. Phase angle and the diagnosis of impending
470 death in patients with advanced cancer: Preliminary findings. *Oncologist* 2019;24:e365–73.

471 <https://doi.org/10.1634/theoncologist.2018-0288>.

472 22. Baker JP, Detsky AS, Wesson DE, Wolman SL, Stewart S, Whitewell J, et al. Nutritional
473 assessment: a comparison of clinical judgement and objective measurements. *N Engl J Med*
474 1982;306:969–72. <https://doi.org/10.1056/nejm198204223061606>.

475 23. Boye KR, Dimitriou T, Manz F, Schoenau E, Neu C, Wudy S, et al. Anthropometric
476 assessment of muscularity during growth: estimating fat-free mass with 2 skinfold-thickness
477 measurements is superior to measuring midupper arm muscle area in healthy prepubertal children.
478 *Am J Clin Nutr* 2002;76:628–32. <https://doi.org/10.1093/ajcn/76.3.628>.

479 24. Onodera T, Goseki N, Kosaki G. [Prognostic nutritional index in gastrointestinal surgery of
480 malnourished cancer patients]. *Nihon Geka Gakkai Zasshi* 1984;85:1001–5.

481 25. Chen LK, Liu LK, Woo J, Assantachai P, Auyeung TW, Bahyah KS, et al. Sarcopenia in
482 Asia: consensus report of the Asian Working Group for Sarcopenia. *J Am Med Dir Assoc*
483 2014;15:95–101. <https://doi.org/10.1016/j.jamda.2013.11.025>.

484 26. Fearon K, Strasser F, Anker SD, Bosaeus I, Bruera E, Fainsinger RL, et al. Definition and
485 classification of cancer cachexia: an international consensus. *Lancet Oncol* 2011;12:489–95.
486 [https://doi.org/10.1016/s1470-2045\(10\)70218-7](https://doi.org/10.1016/s1470-2045(10)70218-7).

487 27. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new
488 proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg*
489 2004;240:205–13. <https://doi.org/10.1097/01.sla.0000133083.54934.ae>.

490 28. Barbosa-Silva MC, Barros AJ, Post CL, Waitzberg DL, Heymsfield SB. Can bioelectrical
491 impedance analysis identify malnutrition in preoperative nutrition assessment? *Nutrition*

- 492 2003;19:422–6. [https://doi.org/10.1016/s0899-9007\(02\)00932-2](https://doi.org/10.1016/s0899-9007(02)00932-2).
- 493 29. Barbosa-Silva MC, Barros AJ. Bioelectrical impedance analysis in clinical practice: a new
494 perspective on its use beyond body composition equations. *Curr Opin Clin Nutr Metab Care*
495 2005;8:311–7. <https://doi.org/10.1097/01.mco.0000165011.69943.39>.
- 496 30. Gonzalez MC, Barbosa-Silva TG, Bielemann RM, Gallagher D, Heymsfield SB. Phase
497 angle and its determinants in healthy subjects: influence of body composition. *Am J Clin Nutr*
498 2016;103:712–6. <https://doi.org/10.3945/ajcn.115.116772>.
- 499 31. Ringaitiene D, Gineityte D, Vicka V, Zvirblis T, Norkiene I, Sipylaite J, et al. Malnutrition
500 assessed by phase angle determines outcomes in low-risk cardiac surgery patients. *Clin Nutr*
501 2016;35:1328–32. <https://doi.org/10.1016/j.clnu.2016.02.010>.
- 502 32. Uccella S, Mele MC, Quagliozzi L, Rinninella E, Nero C, Cappuccio S, et al. Assessment
503 of preoperative nutritional status using BIA-derived phase angle (PhA) in patients with advanced
504 ovarian cancer: correlation with the extent of cytoreduction and complications. *Gynecol Oncol*
505 2018;149:263–9. <https://doi.org/10.1016/j.ygyno.2018.03.044>.
- 506 33. Lundberg M, Dickinson A, Nikander P, Orell H, Makitie A. Low-phase angle in body
507 composition measurements correlates with prolonged hospital stay in head and neck cancer patients.
508 *Acta Otolaryngol* 2019;139:383–7. <https://doi.org/10.1080/00016489.2019.1566779>.
- 509 34. Yu B, Park KB, Park JY, Lee SS, Kwon OK, Chung HY. Bioelectrical impedance analysis
510 for prediction of early complications after gastrectomy in elderly patients with gastric cancer: the
511 phase angle measured using bioelectrical impedance analysis. *J Gastric Cancer* 2019;19:278–289.
512 <https://doi.org/10.5230/jgc.2019.19.e22>.

- 513 35. Maurício SF, Xiao J, Prado CM, Gonzalez MC, Correia MITD. Different nutritional
514 assessment tools as predictors of postoperative complications in patients undergoing colorectal
515 cancer resection. Clin Nutr 2018;37:1505–11. <https://doi.org/10.1016/j.clnu.2017.08.026>.
- 516 36. Arends J, Baracos V, Bertz H, Bozzetti F, Calder PC, Deutz NEP, et al. ESPEN expert
517 group recommendations for action against cancer-related malnutrition. Clin Nutr 2017;36:1187–
518 1196. <https://doi.org/10.1016/j.clnu.2017.06.017>.
- 519 37. Schiesser M, Müller S, Kirchhoff P, Breitenstein S, Schäfer M, Clavien PA. Assessment of
520 a novel screening score for nutritional risk in predicting complications in gastro-intestinal surgery.
521 Clin Nutr 2008;27:565–70. <https://doi.org/10.1016/j.clnu.2008.01.010>.
- 522 38. Fukuda Y, Yamamoto K, Hirao M, Nishikawa K, Maeda S, Haraguchi N, et al. Prevalence
523 of malnutrition among gastric cancer patients undergoing gastrectomy and optimal preoperative
524 nutritional support for preventing surgical site infections. Ann Surg Oncol 2015;22:S778–85.
525 <https://doi.org/10.1245/s10434-015-4820-9>.

526