Muscle strength is a stronger prognostic factor than muscle mass in patients with gastrointestinal and hepatobiliary-pancreatic cancers

Running head: Muscle strength is a stronger prognostic factor than mass

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Conflicts of Interest

The authors declare no conflict of interest.

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Abstract

Objective: Sarcopenia have been reported as a prognostic risk factor in patients with gastrointestinal (GI) and hepatobiliary-pancreatic (HBP) cancers. This study aimed to investigate whether the loss of muscle mass or strength is a stronger prognostic factor and explore the cutoff values of skeletal muscle mass index (SMI) and handgrip strength (HGS) based on the survival outcome in patients with GI and HBP cancers.

Methods: A total of 480 elderly patients with primary GI and HBP cancers who underwent their first resection surgery were analyzed retrospectively. The patients were divided into four groups: appropriate SMI and HGS, low SMI alone, low HGS alone, and low SMI and HGS. Low SMI derived from a bioelectrical impedance analysis and low HGS were defined according to the Asian Working Group for Sarcopenia 2019 criteria.

Results: Multivariate analysis showed that the low SMI was a significant risk factor for mortality only in men, while the low HGS was significant in both sexes. From the multivariate analysis of the four groups, the low HGS alone and low SMI and HGS showed a significantly higher hazard ratio than appropriate SMI and HGS in both sexes. SMI 7.21 kg/m^2 and HGS 28 kg were obtained as cutoff values based on the 3-year survival outcomes in men.

Conclusion: Low muscle strength was a stronger prognostic factor than low muscle mass. Therefore, it is essential to measure muscle strength in all the patients.

Keywords: skeletal muscle mass; handgrip strength; sarcopenia; dynapenia; survival; gastrointestinal and hepatobiliary-pancreatic cancer

[1]Abbreviations

[1] ASM, appendicular skeletal muscle mass; AUC, area under the curve; AWGS, Asian Working Group for Sarcopenia; BIA, bioelectrical impedance analysis; BMI, body mass index; CI, confidence interval; ECW/TBW, extracellular water/ total body water; EWGSOP, European Working Group on Sarcopenia in Older People; GI, gastrointestinal; HBP, hepatobiliary-pancreatic; HGS, handgrip strength; HR, hazard ratio; OS, overall survival; PhA, phase angle; ROC, receiver operating characteristic; SMI, skeletal muscle mass index; VFA, visceral fat area.

Introduction

The prevalence of preoperative sarcopenia in patients with gastrointestinal (GI) and hepatobiliary-pancreatic (HBP) cancers is high. In fact, it has been reported to be 12%–49%. Studies have also reported that sarcopenia is associated with worse outcomes, such as increased postoperative complications and poor survival [1–6]. However, the definitions of sarcopenia in these reports differ. While some defined it as low muscle mass alone, others defined it as low muscle mass and strength or physical function.

The original definition of sarcopenia is the age-related loss of skeletal muscle mass proposed by Rosenberg (1989) [7]. However, over the decade definition of sarcopenia has become the age-related loss of skeletal muscle mass and strength [8]. Clark *et al*. (2008) proposed the term dynapenia defined as the age-related loss of strength, and they argued that the term of sarcopenia should be limited to its original definition [9].

Recently, global interest in sarcopenia has increased. In 2010, the European Working Group on Sarcopenia in Older People (EWGSOP), and in 2014, the Asian Working Group for Sarcopenia (AWGS) published definition and criteria for diagnosing the sarcopenia [10,11]. Both groups' criteria involved three factors: muscle mass, muscle strength, and the physical performance. However, the relationship between the mass and strength is not linear [12], and it has been recognized that the strength is better than mass in predicting the adverse outcomes [13–15].

Therefore, the revised version of EWGSOP in 2018 defined the low muscle strength as a primary parameter of sarcopenia with a loss of muscle quantity or quality as determinants [16]. On the other hand, for diagnosing sarcopenia, low muscle mass is an essential parameter in AWGS 2019 [17]. According to this algorithm, people who retained muscle mass, but lost muscle strength will be classified in non-sarcopenia. It is less known about whether the patients who have appropriate muscle mass but low muscle strength (i.e., non-sarcopenia but dynapenia) is associated with a poor prognosis.

Furthermore, there is one more issue that needs to be clarified. Although EWGSOP and AWGS have suggested the need for the outcome-based cutoff values as a diagnosis of sarcopenia, there is still insufficient evidence. Hence, they recommended standardized approaches (use of healthy young people with the cutoff values at two standard deviations below the mean or the lower 20^{th} percentile) [10,11,16,17]. Indeed, there are few studies that investigating the cutoff values of a skeletal muscle mass index (SMI) or handgrip strength (HGS) based on the survival outcome.

The purpose of the present study was to ascertain whether the loss of muscle mass or strength is a stronger prognostic factor and whether the prognosis of the patients who have appropriate muscle mass but low muscle strength is associated with a poor outcome in patients with GI and HBP cancers. Secondary purpose was to investigate the cutoff values of SMI and HGS based on survival outcome.

Materials and Methods

Patients

This retrospective observational study was performed at the Department of Digestive Surgery and Transplantation in Tokushima University Hospital from July 2014−March 2021. The inclusion criteria were patients who were admitted to undergo first elective radical resection surgery for primary GI and HBP cancers and were aged ≥65 years. The exclusion criteria were patients who were at stage 0 or an unknown stage and without any data for SMI or HGS. This study was conducted in accordance with the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of Tokushima University Hospital (No. 3157-2), and all the patients agreed to participate in this study.

Data Collection

The preoperative data including age, sex, height, cancer site, and cancer stage were collected from electronic medical records.

Measurement of Muscle Mass

Body weight and muscle mass were measured by multi-frequency bioelectrical impedance analysis (BIA) using InBody 770 (InBody Japan, Tokyo, Japan). BIA was conducted with patients in a standing position and was not conducted in patients who found it hard to stand or with

pacemakers. Patients fasted for ≥4 h before the measurement. The InBody 770 automatically estimates appendicular skeletal muscle mass (ASM), visceral fat area (VFA), and extracellular water/total body water (ECW/TBW). We defined VFA more than 100 cm^2 as high VFA according to the Japanese visceral obesity criteria [18]. Body mass index (BMI) was calculated as weight/height^2 (kg/m^2). SMI was calculated as ASM/height^2 (kg/m^2). Phase angle (PhA) value at 50 kHz was calculated as follows:

PhA (degrees) = arctan (Xc/R) × (180/π).

Xc is reactance in ohms and R is resistance in ohms.

Measurement of Muscle Strength

HGS was measured using a dynamometer (Takei Scientific Instruments, Niigata, Japan) while in a standing position, with patients' arms facing downwards and ensuring that the second joint of their finger is almost at a right angle. This test was repeated twice for each hand, and we used the maximum value of either hand.

Definitions of Low Muscle Mass and Low Muscle Strength

We defined low muscle mass and low muscle strength according to the cutoff values of AWGS 2019. Low muscle mass was defined as SMI <7.0 kg/m^2 for men and <5.7 kg/m^2 for women. Low muscle strength was defined as HGS <28 kg for men and <18 kg for women. To investigate the

difference of impact between the muscle mass and strength on mortality, we divided them into four groups: appropriate SMI and HGS, low SMI alone, low HGS alone, and low SMI and HGS.

Outcome

We set an overall survival (OS) as an end point. OS was followed for up to 5 years and defined as the duration from the day of surgery to patient's death or last follow-up date (July 31, 2021).

Statistical Analysis

Continuous variables were expressed as a median with interquartile range, and categorical variables as numbers and percentages. Comparisons of continuous variables were performed by the Wilcoxon's rank sum test and statistically significant differences among four groups were calculated using the Steel–Dwass test. Categorical variables were compared using Pearson's chi-square test. Multivariate cox proportional hazard regression analysis was used to calculate the hazard ratios (HRs) and 95% confidence intervals (CIs), and to identify the predictors for mortality. Multivariate analysis was adjusted by the clinically important parameters (cancer site and the cancer stage). Receiver operating characteristics (ROC) curve analysis was used to develop the SMI and HGS cutoff values associated with 3-year survival. We defined the point on curve closest to the upper left corner of the graphs as cutoff values. All the statistical analyses were performed using JMP ver. 13.0 (SAS Institute Inc., Cary, NC, USA). Differences with a $P < 0.05$ were statistically

significant. We used standard methods to estimate the appropriate sample size for multivariate Cox proportional hazards regression models, with at least 10 outcomes required for each independent variable included. The sample size was calculated using data from our preliminary study. With an expected mortality rate of 17%, we required 176 (3 × 10 / 0.17) patients (30 incidents) to appropriately perform multivariate Cox proportional hazards regression analysis with three variables. Patients were recruited to include at least 176 women, which was the smaller group.

Results

Patient Characteristics

Overall, 757 elderly patients with GI and HBP cancers were included. A total of 277 patients were excluded; 14 with stage 0 or an unknown stage and 263 missing data on SMI or HGS. Finally, data of 480 (293 men and 187 women) elderly patients were analyzed. **Tables 1** and **2** show patient characteristics for men and women, respectively. In both sexes, although age, height, weight, BMI, SMI, HGS, ECW/TBW, and PhA were significantly different among the four groups, cancer site and stage were not. Furthermore, the proportion of high VFA was significantly different among the four groups only in women.

Table 1. Patient characteristics for men.

	All (n = 293)	Appropriate SMI and HGS (n = 124)	Low SMI alone (n = 69)	Low HGS alone (n = 21)	Low SMI and HGS (n = 79)	*P*-value	Steel–Dwass test*
Age (years)	73 (69–78)	71 (68–74)	74 (70–77)	71 (69–76)	78 (74–83)	**<0.001**	1, 3, 5, 6
Cancer site (n, %)						0.094	
Colorectal	97 (33.1)	42 (33.9)	22 (31.9)	4 (19.1)	29 (36.7)		
Stomach	89 (30.4)	45 (36.3)	23 (33.3)	7 (33.3)	14 (17.7)		
Liver	56 (19.1)	21 (16.9)	10 (14.5)	7 (33.3)	18 (22.8)		

Bile duct	31 (10.6)	10 (8.1)	9 (13.0)	0 (0)	12 (15.2)		
Pancreas	20 (6.8)	6 (4.8)	5 (7.3)	3 (14.3)	6 (7.6)		
Cancer stage (n, %)						0.067	
I	89 (30.4)	39 (31.5)	26 (37.7)	9 (42.9)	15 (19.0)		
II	103 (35.2)	41 (33.1)	20 (29.0)	7 (33.3)	35 (44.3)		
III	64 (21.8)	31 (25.0)	17 (24.6)	3 (14.3)	13 (16.5)		
IV	37 (12.6)	13 (10.5)	6 (8.7)	2 (9.5)	16 (20.3)		
Height (cm)	163.0 (158.5–168.0)	166.0 (161.7–169.5)	162.0 (158.1–168.0)	164.4 (160.5–172.2)	159.0 (153.2–162.1)	**<0.001**	1, 3, 5, 6
Body weight (kg)	59.7 (53.3–66.1)	64.2 (60.4–70.6)	55.3 (51.9–60.8)	66.1 (58.8–75.4)	52.6 (47.4–57.8)	**<0.001**	1, 3, 4, 5, 6
BMI (kg/m²)	22.4 (20.6–24.5)	24.0 (22.2–26.0)	20.9 (19.6–22.6)	24.0 (22.3–25.9)	20.9 (19.5–22.7)	**<0.001**	1, 3, 4, 6
BMI (n, %)						**<0.001**	
Under weight	23 (7.9)	2 (1.6)	8 (11.6)	0 (0)	13 (16.5)		
Normal	206 (70.3)	75 (60.5)	58 (84.1)	13 (61.9)	60 (76.0)		
Obese	64 (21.8)	47 (37.9)	3 (4.4)	8 (38.1)	6 (7.6)		
SMI (kg/m²)	6.99 (6.43–	7.48 (7.19–	6.59 (6.32–	7.25 (7.15–	6.20 (5.83–	**<0.001**	1, 3, 4, 5, 6

	7.45)	7.95)	6.86)	7.96)	6.57)		
HGS (kg/m²)	30.4 (26.0–35.3)	35.0 (30.9–39.3)	32.2 (29.9–34.8)	24.9 (22.5–26.6)	24.2 (20.4–25.9)	**<0.001**	1, 2, 3, 4, 5
ECW/TBW	0.391 (0.384–0.398)	0.388 (0.383–0.394)	0.389 (0.383–0.395)	0.398 (0.392–0.409)	0.396 (0.391–0.402)	**<0.001**	2, 3, 4, 5
PhA (°)	4.7 (4.2–5.3)	5.2 (4.7–5.6)	4.8 (4.3–5.3)	4.5 (3.8–5.0)	4.2 (3.8–4.7)	**<0.001**	1, 2, 3, 5
High VFA (≥100 cm^2)	39 (13.3)	18 (14.5)	5 (7.3)	5 (23.8)	11 (13.9)	0.223	

BMI, body mass index; ECW/TBW, extracellular water/total body water; HGS, handgrip strength; PhA, phase angle; SMI, skeletal muscle mass index; VFA, visceral fat area.

* Numbers indicate significant differences in the Steel–Dwass test: 1, appropriate SMI and HGS *vs.* low SMI alone; 2, appropriate SMI and HGS *vs.* low HGS alone; 3, appropriate SMI and HGS *vs*. low SMI and HGS; 4, low SMI alone *vs.* low HGS alone; 5, low SMI alone *vs.* low SMI and HGS; 6, low HGS alone *vs.* low SMI and HGS.

$P < 0.05$ is represented in bold.

Table 2. Patient characteristics for women.

	All	Appropriate SMI	Low SMI	Low HGS	Low SMI and	*P*-value	Steel–Dwass

		and HGS	alone	alone	HGS		test*
	(n = 187)	(n = 51)	(n = 64)	(n = 18)	(n = 54)		
Age (years)	75 (69–80)	72 (68–77)	71 (68–78)	78 (74–86)	78 (75–83)	**<0.001**	2, 3, 4, 5
Cancer site (n, %)						0.545	
Colorectal	72 (38.5)	18 (35.3)	24 (37.5)	10 (55.6)	20 (37.0)		
Stomach	39 (20.9)	13 (25.5)	13 (20.3)	4 (22.2)	9 (16.7)		
Liver	15 (8.0)	4 (7.8)	5 (7.8)	1 (5.6)	5 (9.3)		
Bile duct	25 (13.4)	7 (13.7)	5 (7.8)	3 (16.7)	10 (18.5)		
Pancreas	36 (19.3)	9 (17.7)	17 (26.6)	0 (0)	10 (18.5)		
Cancer stage (n, %)						0.367	
I	51 (27.3)	17 (33.3)	17 (26.6)	5 (27.8)	12 (22.2)		
II	86 (46.0)	21 (41.2)	27 (42.2)	12 (66.7)	26 (48.2)		
III	42 (22.5)	11 (21.6)	15 (23.4)	1 (5.6)	15 (27.8)		
IV	8 (4.3)	2 (3.9)	5 (7.8)	0 (0)	1 (1.9)		
Height (cm)	149.0 (145.7–153.0)	151.5 (147.5–156.0)	149.3 (146.1–152.9)	146.8 (145.9–152.5)	147.3 (141.3–150.6)	**<0.001**	3, 5
Body weight (kg)	48.0 (43.2–53.2)	54.9 (49.7–58.6)	46.9 (42.7–49.9)	50.4 (46.6–60.1)	43.7 (39.3–47.2)	**<0.001**	1, 3, 6
BMI (kg/m²)	21.7 (20.0–	23.3 (21.5–	21.0 (19.2–	23.4 (21.0–	20.4 (18.9–	**<0.001**	1, 3, 4, 6

	23.3)	25.7)	22.4)	26.8)	22.1)		
BMI (n, %)						**<0.001**	
Under weight	23 (12.3)	1 (2.0)	12 (18.8)	0 (0)	10 (18.5)		
Normal	137 (73.3)	35 (68.6)	49 (76.6)	11 (61.1)	42 (77.8)		
Obese	27 (14.4)	15 (29.4)	3 (4.7)	7 (38.9)	2 (3.7)		
SMI (kg/m²)	5.49 (5.05–5.98)	6.06 (5.83–6.43)	5.28 (5.00–5.53)	6.15 (5.90–6.40)	5.05 (4.67–5.40)	**<0.001**	1, 3, 4, 6
HGS (kg/m²)	19.6 (16.6–22.2)	22.8 (21.0–25.3)	21.0 (19.6–22.7)	16.4 (12.6–17.0)	15.3 (13.2–17.0)	**<0.001**	1, 2, 3, 4, 5
ECW/TBW	0.396 (0.392–0.401)	0.394 (0.391–0.397)	0.394 (0.390–0.400)	0.407 (0.397–0.415)	0.399 (0.394–0.403)	**<0.001**	2, 3, 4, 5, 6
PhA (°)	4.1 (3.8–4.6)	4.5 (4.2–4.8)	4.1 (3.9–4.5)	3.9 (3.2–4.1)	3.9 (3.5–4.2)	**<0.001**	1, 2, 3, 5
High VFA (≥100 cm^2)	42 (22.5)	16 (31.4)	14 (21.9)	7 (38.9)	5 (9.3)	**0.015**	

BMI, body mass index; ECW/TBW, extracellular water/total body water; HGS, handgrip strength; PhA, phase angle; SMI, skeletal muscle mass index; VFA, visceral fat area.

* Numbers indicate significant differences in the Steel–Dwass test: 1, appropriate SMI and HGS *vs.* low SMI alone; 2, appropriate SMI and HGS *vs.* low HGS alone; 3, appropriate SMI and HGS *vs.*

low SMI and HGS; 4, low SMI alone *vs.* low HGS alone; 5, low SMI alone *vs.* low SMI and HGS; 6, low HGS alone *vs.* low SMI and HGS.

$P < 0.05$ is represented in bold.

Associations between SMI or HGS and Survival

During the follow-up period, 48 (16.4%) out of 293 male patients and 31 (16.6%) out of 187 female patients died. Table 3 shows the association between SMI or HGS and survival. In multivariate analysis in men, both low SMI and low HGS (both continuous and categorical variables) were significant independent risk factors for mortality. On the other hand, in women, only low HGS (both continuous and categorical variables) but not low SMI was significant independent risk factor for mortality.

Table 3. Multivariate cox proportional hazard ratio in men and women.

	Multivariate		
	HR	95% CI	*P*-value
Men			
SMI as continuous	0.41	0.28–0.60	**<0.001**
SMI as category			
Appropriate	1.00	-	-
Low	2.41	1.31–4.60	**0.004**
HGS as continuous	0.93	0.89–0.97	**0.001**

HGS as category			
Appropriate	1.00	-	-
Low	3.43	1.90–6.31	**<0.001**
Women			
SMI as continuous	0.75	0.40–1.37	0.347
SMI as category			
Appropriate	1.00	-	-
Low	1.26	0.60–2.82	0.545
HGS as continuous	0.89	0.82–0.97	**0.010**
HGS as category			
Appropriate	1.00	-	-
Low	2.84	1.30–6.29	**0.009**

CI, confidence interval; HGS, handgrip strength; HR, hazard ratio; SMI, skeletal muscle mass index.

$P < 0.05$ is represented in bold.

Table 4 shows the association between the four groups and survival. In the multivariate analysis of both men and women, the patients with low SMI and HGS and the patients with low HGS alone were independent risk factors for poor OS compared with the patients with appropriate SMI and HGS. In contrast, the patients with low SMI alone were not.

Table 4. Multivariate cox proportional hazard ratio in men and women.

	Multivariate		
	HR	95% CI	*P*-value
Men			
Appropriate SMI and HGS	1.00	-	-
Low SMI alone	1.69	0.65–4.21	0.272
Low HGS alone	3.28	1.03–9.07	**0.046**
Low SMI and HGS	4.45	2.16–9.65	**<0.001**
Women			
Appropriate SMI and HGS	1.00	-	-
Low SMI alone	1.20	0.45–3.38	0.716
Low HGS alone	7.57	1.41–34.20	**0.021**
Low SMI and HGS	2.75	1.04–7.90	**0.042**

CI, confidence interval; HGS, handgrip strength; HR, hazard ratio; SMI, skeletal muscle mass index.

$P < 0.05$ is represented in bold.

ROC Analysis

Among all the patients, the 257 patients who could follow up 3-year were analyzed for ROC analysis. The 3-year mortality rate was 18.6 % (30 out of 161) in men and 13.5 % (13 out of 96) in women. **Table 5** shows the results of ROC analysis. Significant cutoff values were obtained for predicting 3-year survival in men (SMI < 7.21 kg/m^2 and HGS < 28.0 kg) but not in women.

Table 5. ROC curve analysis.

	AUC	Cutoff value	Sensitivity (%)	Specificity (%)	*P*-value
Men					
SMI (kg/m^2)	0.69	7.21	0.87	0.44	**<0.001**
HGS (kg)	0.68	28.0	0.60	0.77	**0.001**
Women					
SMI (kg/m^2)	0.54	4.93	0.38	0.88	0.434
HGS (kg)	0.63	23.9	1.00	0.28	0.117

AUC, area under the curve; HGS, handgrip strength; ROC, receiver operating characteristic curve; SMI, skeletal muscle mass index.

$P < 0.05$ are represented in bold.

Discussion

In this study, we found that low HGS was an independent risk factor for mortality in both sexes, whereas low SMI was independent risk factor for mortality only in men. Not only patients with low SMI and HGS (i.e., sarcopenia) but also patients with low HGS alone (i.e., non-sarcopenia but dynapenia) were the significant risk factors for mortality in both sexes. Moreover, we provide cutoff values of SMI and HGS based on the survival outcome in men.

Preoperative low muscle mass and/or strength were reported to be a risk factor for poor outcomes [1–6,13–15,19]. Studies on healthy individuals have shown that the loss of muscle

strength is a more reliable predictor of adverse outcomes, such as functional decline and mortality than mass [13–15]. A recent study on 63 patients with the unresectable hepatocellular carcinoma also showed that patients with low HGS were associated with poor OS and post-progression survival unlike patients with low SMI [19]. Consistent with these reports, this study showed that low muscle strength was more associated with the mortality in both sexes than low muscle mass. Furthermore, we found that low HGS alone was an independent risk factor for mortality in both sexes compared with appropriate SMI and HGS, but low SMI alone was not. Similar results were reported in two studies, which assessed the muscle mass using dual-energy X-ray absorptiometry [20,21]. One study based on a national representative sample of 4,449 older adults has shown that mortality among individuals with low muscle strength was higher, whether they had low muscle mass (adjusted odds ratio [aOR], 2.03; 95% CI, 1.27–3.24) or not (aOR, 2.66; 95% CI, 1.53–4.62), compared with those with normal muscle mass and strength [20]. They also showed that a combination of low muscle mass with normal muscle strength was not significantly associated with all-cause mortality. Another study involving 330 dialysis patients also reported that those with low muscle strength had an increased risk of mortality, whether their muscle mass was appropriate (aHR, 1.98; 95% CI, 1.01–3.87) or not (aHR, 1.93; 95% CI, 1.01–3.71), when compared with those having appropriate muscle mass and strength [21]. Moreover, patients with low muscle mass alone did not exhibit a higher risk of mortality. We speculated that these results, wherein low muscle strength was associated with poor prognosis regardless of muscle mass, are partly attributable to the poor muscle

quality in the low-strength group. A cross-sectional study comparing muscle quality among the four groups has been reported [22]. They assessed muscle quality using echo intensity measured by ultrasonography, muscle density index, and muscle quality index. Their results showed that muscle quality indicators were lower in the group with low muscle strength, regardless of muscle mass. Our results also showed that patients with low HGS had lower PhA, reflecting muscle quality [17]. These results suggested that even though muscle mass was maintained, low muscle quality leads to lower muscle strength, associated with poor prognosis. However, the data derived from BIA interpretation requires careful consideration in cases of abnormal body water balance like edema [23–25] because these data are estimated values calculated from an estimation formula that assumes certain body water equilibrium. Our results for both men and women showed that ECW/TBW was higher in patients with low HGS alone. Thus, a possibility exists that muscle mass might have been overestimated in this group. Taken together, we confirmed again that the muscle strength is a stronger prognostic factor than mass even in patients with GI and HBP cancers. It became clear that measuring muscle strength for all the patients is important to identify patients at risk in the clinical settings.

Interestingly, we observed the sex differences in SMI as a risk factor, with SMI not being a significant risk factor for mortality in women. Although the reasons for the sex differences are unclear, we considered the differences in the VFA. A previous study has positively and significantly associated visceral fat with a higher mortality rate, independent of overall adiposity

[26]. In our study, the prevalence of high VFA was significantly higher in the patients with appropriate SMI than in those with low SMI, only in women. Thus, it may be possible that the unfavorable effects of adipose counteracted the beneficial effect of a maintained muscle mass. These differences in VFA may explain our unexpected result that low HGS alone had a 2.8-fold higher risk of mortality than low SMI and HGS in women. Although data were not shown, the prevalence of high VFA was significantly higher in the patients with low HGS alone (39%) than in low SMI and HGS (9%) in our study ($P < 0.01$). There are no such characteristics in men. These results may lead to the interpretation that the group of low HGS alone in women may be included patients like dynapenic abdominal obesity in this study. A 10-year prospective study of Italy adults aged 66–78 years demonstrated dynapenic abdominal obesity subjects were higher at a risk of mortality than the subjects with dynapenia or abdominal obesity only [27], which partially supported our finding.

In the present study, we identified a population-specific SMI and HGS thresholds of 7.21 kg/m^2 and 28 kg, respectively, for men to predict 3-year survival outcome. These cutoffs are similar to AWGS criteria (7.00 kg/m^2 for SMI and 28 kg for HGS) [17]. However, we could not identify the significant cutoff values in women. It is quite likely that small number of events. Therefore, large studies are needed to determine these cutoff values for women.

The strength of this study is, to our best knowledge, this is the first study that revealed the muscle strength is more predictable for mortality than the muscle mass, and that patients with not

only sarcopenia, but also patients with non-sarcopenia but dynapenia were at risk condition in patients with GI and HBP cancers. We also found the outcome-based cutoff value of SMI and HGS in men. However, this study had some limitations. First, this study includes several cancer sites. It would have been better if we could have analyzed each cancer type separately; however, we could not do this because of the sample size. Therefore, we performed a multivariate analysis to adjust for the cancer site. Another limitation was large number of missing SMI or HGS data. However, mortality of patients with the missing data was comparable to analyzed patients in the present study. Moreover, although we determined cutoff values in men, whether it could be acceptable to the other population is unknown. Further studies are needed to be done for the clarity.

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Conclusions

Our results showed low HGS appears to be a significant risk factor rather than low SMI. Additionally, not only subjects with low SMI and HGS (sarcopenia) but also subjects with low HGS alone (non-sarcopenia but dynapenia) was at a higher risk of mortality when compared to the subjects with appropriate SMI and HGS. Further studies are required to confirm our findings and develop the outcome-based cutoff values.

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