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Impact of Preoperative Skeletal Muscle Mass and Nutritional Status on Short-and Long-Term Outcomes After Esophagectomy for Esophageal Cancer: A Retrospective Observational Study

Impact of Psoas Muscle Mass and Body Mass on Esophagectomy

Toshiaki Shichinohe, MD, PhD[1,2], Shion Uemura, MD[1,2], Satoshi Hirano, MD, PhD[1], and Masao Hosokawa, MD, PhD[2]

[1]Department of Gastroenterological Surgery II, Hokkaido University Faculty of Medicine, Sapporo, Hokkaido, Japan; [2]Keiyukai Sapporo Hospital, Sapporo, Hokkaido, Japan

ABSTRACT

Background. Preoperative muscle volume and body mass index (BMI) are associated with postoperative outcomes. Because esophagectomy for esophageal cancer (EC) is associated with high morbidity and because EC has a poor prognosis, this study investigated the association of preoperative skeletal muscle mass and nutritional status with postoperative outcomes.

Methods. The study analyzed 483 patients who underwent esophagectomy from 2009 to 2012. The cross-sectional area of the psoas muscle index (PMI) was measured at the third lumbar vertebral level using computed tomography. Clavien–Dindo classifications were used to analyze postoperative complications. Because skeletal muscle mass varies according to sex, all analyses were performed accordingly (390 males, 93 females).

Results. For male patients, BMI was a significant multivariate factor, and PMI, a univariate factor, predicted postoperative complications and overall survival (OS). Using a preoperative nutritional and muscular (PNM) score derived from BMI and PMI results (patients were allocated 1 point if their BMI was < 18.5 kg/m^2 and 1 point if their PMI was < 600 mm^2/m^2, for a possible maximum total of 2 points), male patients were categorized as high risk (score 2), moderate risk (score 1), or low risk (score 0). In the low-risk group, anastomotic leakage was significantly less ($p = 0.01$), and the 3-year OS was significantly better ($p < 0.01$). On the other hand, in female patients, neither BMI nor PMI was a significant factor for postoperative outcomes.

Conclusions. For male patients, the PNM score is a promising tool for predicting postoperative outcomes and identifying patients requiring preoperative nutritional intervention and rehabilitation.

Esophageal cancer (EC) is the ninth most common cancer and the sixth most common cause of cancer death worldwide, accounting for 440,000 deaths in 2013.[1] Men are approximately three times more likely than women to experience EC.[1] This is believed to be due to the higher rates of alcohol consumption and smoking among men than among women.

Despite the advances in multimodality therapies such as surgery, chemotherapy, and radiotherapy, the prognosis for EC remains poor.[2] Although esophagectomy remains the main treatment for curable EC, it is a highly invasive procedure and associated with postoperative complications.[3] Therefore, preoperative risk assessment of patients is necessary to predict postoperative outcomes.

Whole skeletal muscle mass is known to correlate with the psoas muscle index (PMI) or the skeletal muscle index (SMI).[4–6] Recent studies have shown that low preoperative skeletal muscle mass is associated with poor short- and long-term outcomes in several types of cancers.[4,7–18] Skeletal muscle mass is known to decrease with age and progression of cancer. Loss of muscle mass related to aging is defined as

Shion Uemura and Toshiaki Shichinohe have equally contributed to this work.

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T. Shichinohe, MD, PhD
e-mail: shichino@med.hokudai.ac.jp

primary sarcopenia, and muscle mass related to diseases (e.g., cancer, inflammation, and infection), undernutrition, and hypoactivity is defined as secondary sarcopenia.

Because skeletal muscle mass differs significantly according to sex,[19,20] the criteria of the European Working Group for Sarcopenia in Older People (EWGSOP)[19] and the Asian Working Group for Sarcopenia (AWGS)[20] define sarcopenia according to sex. It also is known that the prognosis for EC is better for women than for men.[21–23] However, to the best of our knowledge, there are no studies in the literature on the influence of sex on patients with sarcopenia and EC. We believe this is the first report evaluating the associations of skeletal muscle mass with short- and long-term outcomes after esophagectomy based on sex.

METHODS

Patients

From January 2009 to December 2012, 527 consecutive patients underwent radical esophagectomy at Keiyukai Sapporo Hospital. Patients with a diagnosis of definitive cT4b, distant metastasis, or severe organ failure and those showing a score of 3 or 4 on the Eastern Cooperative Oncology Group (ECOG) Score of Performance Status[24] were not suitable for radical esophagectomy and thus were excluded from this study. Therefore, we performed a retrospective analysis of 483 patients using preoperative cross-sectional proximate computed tomography (CT) images of the psoas muscle and skeletal muscle at the third lumbar vertebral level.

The study included 390 men and 93 women (Table 1). The operative procedures included subtotal esophagectomy with cervical anastomosis (n = 386), Ivor-Lewis esophagectomy (n = 74), and other operative procedures (n = 23). Conduits were the gastric tube (n = 438), ileocolic (n = 24), and jejunum (n = 21). The characteristics of these patients were obtained retrospectively from medical records. This study was approved by the institutional review board (authorization number: H29-7) of the institution. Information about the aim of the study was posted on the Keiyukai Sapporo Hospital website, and potential participants could decline to participate or opt out at any time.

Pre- and Intraoperative Investigations

The following background information was collected for each patient. Body weight and height were measured for all the patients before surgery, and BMI was calculated as weight (kg)/height (m^2). The prognostic nutritional index (PNI) was defined as per the following definition by Onodera et al.:[25] (10 × Alb) + (0.005 × total lymphocyte count). The modified Glasgow prognostic scale (mGPS) was defined as per the definition by Miki and Kusunoki[26] and classified into four categories according to serum albumin (Alb: cutoff value, 3.5 g/dL) and C-reactive protein (CRP: cutoff value, 0.5 mg/dL).

Postoperative complications were classified by Clavien–Dindo classification (CD)[27] and defined as lower than or equal to grade 3a (reoperation unnecessary) and higher than or equal to grade 3b (reoperation necessary). Survival analyses were performed for overall survival (OS) and recurrence-free survival (RFS).

Image Analysis

The cross-sectional area of the psoas muscle and skeletal muscle tissue at the level of the third lumbar vertebra (L3), obtained using the HOPE EGMAIN-GX electronic medical record system (Fujitsu, Tokyo Japan), was measured by manual tracing on computed tomography (CT) scans imaged just before operations and used for clinical staging. The psoas muscle area and the skeletal muscle area normalized by the square of the height (m^2) were the PMI (mm^2/m^2) and the SMI (cm^2/m^2), respectively.

Statistical Analysis

Continuous variables were expressed as median (range) and analyzed using the Mann–Whitney U test to compare two groups without setting a cutoff value. Categorical variables were analyzed using the Chi square test. Multivariate analyses of postoperative complications were performed using a logistic regression model with backward stepwise selection. Survival curves were estimated using the Kaplan–Meier method and compared using the log-rank test. Survival analyses were performed using a Cox proportional hazard model with backward stepwise selection.

To evaluate preoperative skeletal muscle loss or low nutritional status, we analyzed the association of PMI and BMI with short- and long-term outcomes after esophagectomy, and the cutoff values were set by classification and regression tree (CART)[28] for OS.

Correlative analyses of PMI, SMI, and BMI were performed using Pearson's correlation coefficient (R). Differences were defined as statistically significant if p was lower than 0.05, and an R higher than 0.7 was defined as a strong correlation. All statistical analyses were performed using EZR version 1.35 software[29] (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of R commander designed to add statistical functions frequently used in biostatistics. CART was performed by the rpart package in R 3.4.1 software.

TABLE 1 Patient background, postoperative complications, and survival by sex

Variable	Category	Male (n = 390) n (%)	Female (n = 93) n (%)	p values
Age: years (range)		65.5 (39–83)	64 (41–81)	0.79
Alcohol	+	331 (85)	49 (53)	< 0.01[a]
Smoking	+	356 (91)	58 (62)	< 0.01[a]
Diabetes mellitus	+	49 (13)	9 (10)	0.44
Hypertension	+	141 (36)	19 (20)	< 0.01[a]
BMI: kg/m^2 (range)		22.7 (13.3–33.1)	20.4 (14.4–29.3)	< 0.01[a]
PMI: mm^2/m^2 (range)		530.0 (222.3–1008)	364.1 (203.1–602.3)	< 0.01[a]
SMI: cm^2/m^2 (range)		41.2 (23.7–63.2)	32.3 (22.2–44.6)	< 0.01[a]
Albumin: g/dL (range)		4.3 (3.1–5.4)	4.2 (3.5–5.3)	0.58
CRP: mg/dL (range)		0.12 (0–6.9)	0.1 (0–1.79)	0.02[a]
PNI: n (range)		51.4 (37.2–65.8)	51.4 (38.8–62.0)	0.65
mGPS	A	289 (78)	74 (84)	0.21
Preoperative therapy	None	355 (91)	83 (89)	0.60
Bleeding: g (range)		410 (50–39,280)	260 (50–1629)	< 0.01[a]
Operative time: min (range)		275 (135–535)	240 (115–410)	< 0.01[a]
cT factor	2,3,4	257 (66)	73 (78)	0.02[a]
cN factor	1	240 (61)	49 (53)	0.12
cStage	2,3,4	298 (76)	75 (81)	0.38
pT	2,3,4	235 (60)	65 (70)	0.09
pN	+	240 (62)	55 (60)	0.71
pStage	2,3,4	286 (73)	73 (78)	0.31
ly	+	190 (49.6)	47 (51)	0.87
v	+	154 (40)	36 (39)	0.76
Histopathology	Scc	332 (85)	84 (90)	0.19
Anastomotic leakage	+	48 (12)	6 (6)	0.11
Pulmonary complications	+	59 (15)	6 (6)	0.03[a]
Empyema	+	9 (2)	2 (2)	0.93
Abdominal abscess	+	10 (3)	1 (1)	0.39
Recurrent nerve palsy	+	55 (14)	21 (22)	0.13
CD $\geq$ 3b		36 (9)	10 (11)	0.65
3-year OS		68.7	76.5	0.02[a]
3-year RFS		61.4	71.4	0.02[a]

BMI body mass index, *PMI* psoas muscle index, *SMI* skeletal muscle index, *CRP* C-reactive protein, *PNI* prognostic nutritional index, *mGPS* modified Glasgow prognostic scale, *ly* lymph-vessel invasion, *v* venous invasion, *CD* Clavien–Dindo classification, *OS* overall survival rate, *RFS* recurrence-free survival rate

[a]Statistically significant

RESULTS

Patient Characteristics

Table 1 shows that the rates of alcohol drinking and smoking were significantly higher among male patients than among female patients (both $p < 0.01$). In female patients, BMI, PMI, and SMI were significantly lower than in male patients (all $p < 0.01$).

Both OS and RFS tended to be better in female patients than in male patients (male vs. female: 3-year OS: 68.7% vs. 76.5%, $p = 0.02$; 3-year RFS: 61.4% vs. 71.4%, $p = 0.02$) (Table 1). We analyzed postoperative complications and survival by sex because of the difference in BMI, skeletal muscle mass, OS, and RFS.

Muscle Indexes

Pearson's correlative analyses were performed for PMI, SMI, and BMI. In male patients, PMI and SMI were correlated (correlation coefficient [R] = 0.70; $p < 0.01$), as were BMI and SMI ($R = 0.74$; $p < 0.01$), but not BMI and PMI ($R = 0.49$; $p < 0.01$).

In female patients, PMI and SMI were correlated ($R = 0.69$; $p < 0.01$). On the other hand, BMI and SMI ($R = 0.62$; $p < 0.01$) and BMI and PMI ($R = 0.38$; $p < 0.01$) were not correlated. Therefore, we adopted PMI for the multivariate analyses in this study because PMI is easily measured.

Analyses of Postoperative Complications

The number and percentage of the patients who had postoperative complications categorized by CD classification were as follows; no complications ($n = 194$, 40%), CD1 ($n = 67$, 14%), CD2 ($n = 66$, 14%), CD3a ($n = 110$, 23%), CD3b ($n = 25$, 5%), CD4a ($n = 5$, 1%), CD4b ($n = 8$, 2%), and CD5 ($n = 8$, 2%). The main postoperative complications were pulmonary complications ($n = 65$, 13%), anastomotic leakage ($n = 54$, 11%), empyema ($n = 11$, 2%), abdominal abscess ($n = 11$, 2%), and recurrent nerve palsy ($n = 76$, 15%).

The postoperative complications according to sex are shown in Table 2. The analyses of male patients showed that BMI and PMI were significantly lower for CD3b or higher ($p < 0.01$ and $p = 0.03$, respectively). The multivariate analysis showed that age (odds ratio [OR], 1.15; 95% CI, 1.03–1.29; $p = 0.01$) and BMI (OR, 0.66, 95% confidence interval [CI], 0.47–0.91; $p = 0.01$) were independent factors. On the other hand, no factor was associated with postoperative complications in female patients.

Analyses of Overall and Recurrence-Free Survival

The results of the survival analyses according to sex are shown in Table 3. The univariate analysis of male OS showed that age ($p = 0.04$), BMI ($p < 0.01$), PMI ($p = 0.03$), preoperative therapy (+) ($p < 0.01$), operative time ($p < 0.01$), pT(2,3,4) ($p < 0.01$), pN(+) ($p = 0.01$), pStage (2,3,4) ($p < 0.01$), and ly(+) ($p < 0.01$) were significantly different for the male patients. The multivariate analysis showed that the independent prognostic factors were age (hazard ratio [HR], 1.04; 95% CI, 1.01–1.06; $p < 0.01$), BMI (HR, 0.93; 95% CI, 0.88–0.99; $p = 0.02$), preoperative therapy(+) (HR, 3.12; 95% CI, 1.89–5.13; $p < 0.01$), operative time (HR, 1.004; 95% CI, 1.001–1.006; $p < 0.01$), pT(2,3,4) (HR, 1.63; 95% CI, 1.10–2.42; $p = 0.01$), and ly(+) (HR, 1.52; 95% CI, 1.06–2.18; $p = 0.02$). On the other hand, in the univariate analysis of RFS for male patients, BMI was one of the significant factors, whereas PMI was not.

As for the female patients, the univariate analyses of OS and RFS showed no significant differences according to BMI or PMI.

The multivariate analyses of female OS and RFS showed that mGPS and pathologic N status were independent prognostic factors.

Proposed Cutoff Values for PMI and the Preoperative Nutritional and Muscular Score

The findings showed PMI and BMI to be the factors that could possibly improve with preoperative interventions, so a definitive cutoff value set by the data from the patients with EC was required. Because OS is the most important postoperative outcome for patients, we analyzed the cutoff values of BMI and PMI for male patients using CART[28] for OS. The calculated cutoffs were 18.9 kg/m^2 for BMI and 599 mm^2/m^2 for PMI. Therefore, we set the cutoff value for BMI at 18.5 kg/m^2, which is lower than normal,[30] and the cutoff value for PMI at 600 mm^2/m^2. The percentages of male patients with a PMI lower than 600 mm^2/m^2 or a BMI lower than 18.5 kg/m^2 were respectively 66% and 12%.

We then categorized the male patients into three groups using preoperative BMI and PMI values. A Preoperative Nutritional and Muscular (PNM) risk score was derived as follows. The patients were allocated 1 point if their BMI was lower than 18.5 kg/m^2 and 1 point if their PMI was below 600 mm^2/m^2 (for a possible maximum total of 2 points). According to the PNM score, the patients were categorized into the following three groups: score 2 (high risk), score 1 (moderate risk), and score 0 (low risk). In the score 0 group, anastomotic leakage was significantly lower ($p = 0.01$) (Table 4) and OS was significantly better (3-year OS: score 0 [78%], score 1 [70%], score 2 [47%]; score 0 vs. score 1: [$p = 0.01$], score 0 vs. score 2 [$p < 0.01$]) (Fig. 1). Moreover, the multivariate analyses, including the PNM score instead of PMI and BMI, showed that score 0 was a significant prognostic factor with respect to OS and RFS for male patients (OS: HR, 0.57; 95% CI, 0.38–0.85; $p < 0.01$; RFS: HR, 0.63; 95% CI, 0.44–0.91; $p < 0.01$).

DISCUSSION

This study showed that sex and nutritional status influence short- and long-term outcomes after esophagectomy for EC and that skeletal muscle mass status might also affect these outcomes. We proposed that a PMI cutoff value of 600 mm^2/m^2 and a BMI cutoff value of 18.5 kg/m^2 were useful for identification of male patients with preoperative risks. We also proposed that it was useful to predict postoperative prognosis by PNM score, which was made by those cutoff values and could classify male

TABLE 2 Postoperative complications by sex

Variable	Category	Male						Female		
		Univariate			Multivariate			Univariate		
		CD $\leq$ 3a (n = 354) n (%)	CD $\geq$ 3b (n = 36) n (%)	p values	OR	95% CI	p values	CD $\leq$ 3a (n = 83) n (%)	CD $\geq$ 3b (n = 10) n (%)	p values
Age: years (range)		65 (39–83)	70 (41–83)	0.04[a]	1.15	1.03–1.29	0.01	64 (47–81)	71 (41–79)	0.32
Alcohol	+	300 (85)	31 (86)	0.83				44 (53)	5 (50)	0.86
Smoking	+	324 (92)	32 (89)	0.59				51 (61)	7 (70)	0.6
Diabetes mellitus	+	45 (13)	4 (11)	0.78				8 (10)	1 (10)	0.97
Hypertension	+	126 (36)	15 (42)	0.47				16 (19)	3 (30)	0.43
BMI: kg/m^2 (range)		22.3 (13.3–33.1)	20.4 (16.1–25.7)	< 0.01[a]	0.66	0.47–0.91	0.01	20.4	19.6	0.48
PMI: mm^2/m^2 (range)		533 (222–1008)	492 (317–769)	0.03[a]				362.4	378.9	0.99
Albumin: g/dL (range)		4.3 (3.1–5.4)	4.2 (3.2–5.1)	0.17				4.245	4.2	0.83
CRP: mg/dL (range)		0.11 (0–6.91)	0.23 (0.01–5.2)	0.26				0.09	0.065	0.95
PNI: n (range)		51.4 (37.2–65.2)	50.6 (37.5–65.8)	0.17				51.5	51.1	0.69
mGPS	A	260 (78)	29 (81)	0.71				66 (83)	8 (89)	0.68
Preoperative therapy	None	325 (92)	30 (83)	0.09				73 (88)	10 (100)	0.25
Bleeding: g (range)		405 (50–3780)	555 (70–39,280)	< 0.01[a]				260 (50–1629)	235 (110–950)	0.65
Operative time: min (range)		270 (135–530)	309.5 (155–535)	< 0.01[a]				240 (115–410)	227 (155–350)	0.82
cT factor	2,3,4	236 (67)	21 (58)	0.32				66 (80)	7 (70)	0.49
cN factor	1	224 (63)	16 (44)	0.03[a]				43 (52)	6 (60)	0.62
cStage	2,3,4	273 (77)	25 (69)	0.3				68 (82)	7 (70)	0.37

CD Clavien–Dindo classification, *OR* odds ratio, *CI* confidence interval, *BMI* body mass index, *PMI* psoas muscle index, *CRP* C-reactive protein, *PNI* prognostic nutritional index, *mGPS* modified Glasgow prognostic scale

[a]Statistically significant

TABLE 3 Analyses of survival in male and female patients

Male	OS						RFS					
Factor	Univariate			Multivariate			Univariate			Multivariate		
	HR	95% CI	*p* values	HR	95% CI	*p* values	HR	95% CI	*p* values	HR	95% CI	*p* values
Age (years)	1.02	1.001–1.046	0.04[a]	1.04	1.013–1.06	< 0.01[a]	1.01	0.99–1.03	0.19			
Alcohol (+)	1.1	0.68–1.79	0.69				1.16	0.74–1.82	0.51			
Smoking (+)	1.01	0.56–1.83	0.97				1.02	0.6–1.74	0.94			
Diabetes mellitus (+)	1.2	0.74–1.95	0.46				0.88	0.55–1.42	0.6			
Hypertension (+)	1.11	0.79–1.57	0.55				1.2	0.88–1.64	0.24			
BMI (kg/m^2)	0.92	0.87–0.98	< 0.01[a]	0.93	0.88–0.99	0.02[a]	0.94	0.89–0.99	0.02[a]			
PMI (mm^2/m^2)	0.998	0.997–0.999	0.03[a]				1	1.00–1.00	0.07			
Albumin (g/dL)	0.7	0.44–1.12	0.13				0.7	0.46–1.06	0.09			
CRP (mg/dL)	1.02	0.84–1.22	0.87				1	0.84–1.19	1			
PNI	0.97	0.94–1.002	0.07				0.97	0.94–1	0.02[a]			
mGPS (B, C, D)	1.23	0.82–1.84	0.32				1.24	0.86–1.78	0.25			
Preoperative therapy (+)	2.66	1.67–4.24	< 0.01[a]	3.12	1.89–5.13	< 0.01[a]	2.11	1.34–3.3	< 0.01[a]	2.27	1.41–3.65	< 0.01[a]
Bleeding (g)	1	1.00–1.00	0.02[a]				1	1.00–1.00	0.01[a]			
Operative time (min)	1.004	1.002–1.007	< 0.01[a]	1.004	1.001–1.006	< 0.01[a]	1	1–1.01	< 0.01[a]	1	1.001–1.006	< 0.01[a]
pT (2,3,4)	1.89	1.31–2.74	< 0.01[a]	1.63	1.10–2.42	0.01[a]	2.12	1.5–2.98	< 0.01[a]	2.21	1.39–2.95	< 0.01[a]
pN (+)	1.57	1.1–2.25	0.01[a]				1.82	1.3–2.55	< 0.01[a]			
pStage (2,3,4)	1.9	1.23–2.93	< 0.01[a]				2.34	1.55–3.54	< 0.01[a]			
ly (+)	1.59	1.13–2.24	< 0.01[a]	1.52	1.06–2.18	0.02[a]	1.78	1.3–2.43	< 0.01[a]	1.54	1.09–2.17	0.01[a]
v (+)	1.12	0.8–1.58	0.51				1.36	1–1.84	0.05			
Histopathology (scc)	1.74	0.98–3.09	0.06				1.45	0.9–2.34	0.13			
Female	OS						RFS					
Factor	Univariate			Multivariate			Univariate			Multivariate		
	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
Age	0.97	0.92–1.01	0.17				0.98	0.93–1.02	0.27			
Alcohol (+)	1.26	0.54–2.95	0.59				1.29	0.60–2.78	0.52			
Smoking (+)	0.7	0.30–1.62	0.41				0.84	0.39–1.82	0.66			
Diabetes mellitus (+)	0.44	0.06–3.28	0.42				0.31	0.04–2.32	0.26			
Hypertension (+)	0.9	0.31–2.68	0.86				0.65	0.22–1.88	0.42			
BMI (kg/m^2)	1.04	0.92–1.18	0.51				1.01	0.90–1.14	0.84			
PMI (mm^2/m^2)	1	1.00–1.01	0.1				1	1.00–1.01	0.52			
Albumin	0.62	0.18–2.14	0.45				0.41	0.13–1.29	0.13			

TABLE 3 continued

Female	OS						RFS					
Factor	Univariate			Multivariate			Univariate			Multivariate		
	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
CRP	1.95	0.76–4.99	0.16				2.3	1.06–4.98	0.03			
PNI	0.95	0.86–1.04	0.26				0.93	0.86–1.01	0.1			
mGPS (B, C, D)	2.79	1.08–7.19	0.03[a]	2.71	1.04–7.03	0.04[a]	3.41	1.48–7.87	< 0.01[a]	3.27	1.41–7.54	< 0.01[a]
Preoperative therapy (+)	2.09	0.71–6.19	0.18				1.65	0.57–4.76	0.36			
Bleeding (g)	1	1.00–1.00	0.42				1	1.00–1.00	0.43			
Operative time (m)	1	0.99–1.01	0.83				1	1.00–1.01	0.5			
pT (2,3,4)	5.33	1.24–22.82	0.02[a]				4.43	1.33–14.72	0.02[a]			
pN (+)	8.2	1.92–35.11	< 0.01[a]	7.74	1.80–33.3	< 0.01	4.65	1.61–13.47	< 0.01[a]	4.38	1.51–12.73	< 0.01[a]
pStage (2,3,4)	3.2	0.75–13.71	0.12				4.17	0.99–17.63	0.05			
ly (+)	1.81	0.76–4.32	0.18				1.76	0.81–3.86	0.16			
v (+)	1.51	0.65–3.51	0.34				2.06	0.96–4.41	0.06			
Histopathology (scc)	2.12	0.29–15.77	0.46				1.35	0.32–5.70	0.68			

OS overall survival, *RFS* recurrence-free survival, *HR* hazard ratio, *CI* confidence interval, *BMI* body mass index, *PMI* psoas muscle index, *CRP* C-reactive protein, *PNI* prognostic nutritional index, *mGPS* modified Glasgow prognostic scale, *ly* lymph-vessel invasion, *v* venous invasion

[a]Statistically significant

TABLE 4 Comparison of postoperative complications by preoperative nutritional and muscular score

Variable	Score 0 (n = 129) n (%)	Score 1 (n = 219) n (%)	Score 2 (n = 42) n (%)	p values
Anastomotic leakage (+)	9 (7)	29 (13)	10 (24)	0.01[a]
Pulmonary complications (+)	18 (14)	33 (15)	8 (19)	0.73
Empyema (+)	6 (4.7)	3 (1.4)	0	0.08
Abdominal abscess (+)	4 (3.1)	4 (1.8)	2 (4.8)	0.49
Recurrent nerve palsy (+)	16 (12)	34 (16)	5 (12)	0.66
CD ≥ 3b	7 (5.4)	22 (10)	7 (17)	0.08
CD ≥ 3a	37 (29)	77 (35)	18 (43)	0.2
Complication (+)	71 (55)	135 (62)	29 (69)	0.22

CD Clavien–Dindo classification

[a]Statistically significant

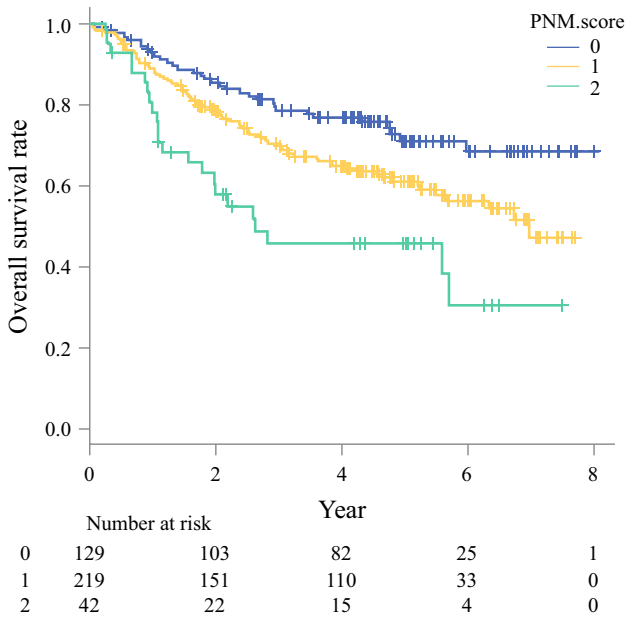

FIG. 1 Comparison of overall survival rate according to preoperative nutritional and muscular score

patients with risks into three groups. The 3-year OS of the low-risk group (PNM score 0) was 78.7%, and it was significantly the best compared with the other groups.

In this study, we also evaluated nutritional prognostic scores such as PNI and mGPS. For the male patients, the low-risk group (PNM score 0) was a multivariate factor in both the short-term (Table 4) and long-term analyses (HR, 0.63; 95% CI, 0.44–0.91; p = 0.01). However, PNI and mGPS were not significant factors. For the female patients, mGPS was the only multivariate factor among those three factors.

Sarcopenia is defined by low muscle mass, low muscle strength, and low physical performance according to the EWGSOP[19] or AWGS[20] criteria. Aging and cancer-bearing are risk factors for sarcopenia, and elderly patients or patients with advanced EC requiring preoperative therapy may carry a risk of decreasing skeletal muscle. Because the physical status of the "real" sarcopenia patients is poor, they usually are precluded from major surgery. Therefore, the criteria for "surgical sarcopenia" in patients who receive surgery should be defined according to their postoperative risks.

Previous studies have shown that the preoperative skeletal muscle volume of patients with EC is associated with poor short- and long-term outcomes after esophagectomy. Sheetz et al.[31] demonstrated the relationship between the psoas muscle cross-sectional area and long-term survival after esophagectomy for EC. In their study, although the psoas muscle area of the fourth lumbar vertebra on CT was associated with OS, they did not analyze it by gender or by normalizing the psoas muscle area by height.

No previous report has defined cutoff values of the muscle indexes for patients who undergo esophagectomy. This is the first large-scale study to report radical esophagectomy for EC at a single institution that proposes a cutoff value of PMI associated with postoperative complications and long-term prognosis.

We set the cutoff value of "surgical sarcopenia" for male patients to be a PMI lower than 600 mm^2/m^2 based on 3-year OS and evaluated the usefulness of predicting postoperative risks with a combination of the BMI score.

Most studies in the past have analyzed PMI or SMI by categorizing the patients into two groups using cutoff values that had been applied to other etiologies or statistical values such as the median and the lower quartile. For example, Nakashima et al.[13] used a median SMI cutoff value because it was near the cutoff values reported for other cancers, such as colorectal, respiratory, and gastrointestinal tract cancers. However, a median cutoff value

might not be appropriate for high-risk patients who require preoperative intervention. As another example, surgical sarcopenia cutoff values using PMI (male, 636 mm^2/m^2; female, 392 mm^2/m^2) have been proposed by Hamaguchi et al.[32] These values originated from the evaluation of postoperative risks after live donor liver transplantation, and the data were obtained from young healthy liver donors (median age, 39 years; range, 22–66 years). Therefore, these values may not be applicable for older patients with EC. In fact, most of the patients (male, 75.6%; female, 60.2%) in our study would receive a diagnosis of surgical sarcopenia using these cutoff values.

In this study, we proposed a PMI cutoff value of 600 mm^2/m^2 for male patients according to a risk analysis of 3-year OS. By applying this cutoff value, 66% of the patients had a PMI lower than that, and the rate increased with age (62% for men younger than 65 years; 69% for men older than 65-years; 79% for men older than 75-years).

We set the BMI cutoff value at 18.5 kg/m^2 for men, which is lower than the normal range of BMIs by world standards. Then, we proposed a PNM score for male patients using a combination of BMI at 18.5 kg/m^2 and PMI at 600 mm^2/m^2. This score might be useful not only to predict postoperative complications, for example anastomotic leakage and long-term survival, but also as a useful index to indicate the need for preoperative nutritional interventions and rehabilitation.

This study showed that skeletal muscle mass was not associated with short- and long-term outcomes after esophagectomy for female patients. For male patients, skeletal muscle mass may depend on male sex hormones that decrease with age. Therefore, depletion of skeletal muscle mass in women may not correlate with aging as it does in men. Moreover, in women, sarcopenia tends to be more prominent in decreasing muscle strength and physical performance than in skeletal muscle mass.[33–35] Therefore, we conclude that analyses of skeletal muscle mass may not be useful for predicting postoperative risks for female patients who undergo esophagectomy.

Our study had several limitations. First, the diagnosis of sarcopenia requires assessment of physical performance (walking), muscle strength (grip), and muscle mass by bioelectrical analysis or dual-energy X-ray absorptiometry. In this study, we investigated only skeletal muscle mass at the third lumbar area using CT, and due to the retrospective nature of the study, we did not investigate physical performance or muscle strength, which might be important for predicting sarcopenia in female patients.

Second, the cutoff point for BMI was lower than the international average. Although this cutoff point was useful for our male patients, it is unknown whether the cutoff point may be useful for other populations.

Third, this study did not demonstrate the risk of high BMI or obesity. Because we did not measure the visceral fat volume, the relationships between fat volume and prognoses were not evaluated. For male patients, the average BMI was 22.2 ± 3.0 kg/m^2. The number of patients with a BMI higher than 25 kg/m^2 (higher than normal)[31] was 65 (17%). No statistical differences of complications or OS were observed between high BMI group and others.

Finally, this was a retrospective study at a single institution. Therefore, our proposed BMI and PMI cutoff values should be validated by other institutions. Moreover, prospective studies on the short- and long-term effectiveness of preoperative interventions to increase skeletal muscle mass and to improve the nutritional status of male patients are needed.

In conclusion, this study is the first to demonstrate that sex, skeletal muscle mass, and nutritional status influence short- and long-term outcomes after esophagectomy for EC. To predict long-term outcomes for male patients, we propose the cutoff values of 600 mm^2/m^2 for PMI and 18.5 kg/m^2 for BMI. The PNM score using the combination of PMI and BMI cutoff values shows promise as a useful tool for predicting postoperative outcomes and selecting patients who require preoperative nutritional intervention and physical rehabilitation.

DISCLOSURE There are no conflicts of interest.

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