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ORIGINAL ARTICLE

Hand grip strength as a predictor of postoperative complications in esophageal cancer patients undergoing esophagectomy

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Abstract
Background Radical esophagectomy remains the primary treatment option for resectable esophageal cancer. However, it sometimes induces postoperative complications due to its invasive nature. Recently, the impact of loss of muscle mass on postoperative complications and survival among cancer patients has been highlighted. This study aimed to identify the impact of low hand grip strength (HGS) on postoperative complications after esophagectomy.
Methods A total of 188 patients (male: 166, female: 22) who underwent radical esophagectomy with gastric tube reconstruction between 2008 and 2014 were included. The correlation between HGS and age was analyzed using Pearson's correlation coefficient. Due to the small patient numbers, only male patients were stratified into two groups according to age (<70 years: non-elderly group, ≥70 years: elderly group). Receiver operating characteristic curve analysis was performed for each group using postoperative complication occurrence as the endpoint to determine an optimal HGS cutoff value.
Results Postoperative complications occurred in 60.9% of the elderly group and 47.4% of the non-elderly group. When the cutoff values were set at 30.5 and 37 kg for the elderly and non-elderly group, respectively, low HGS was an independent predictive factor of postoperative complications on multivariate analysis only in the elderly group ($p = 0.008$). In the elderly group, the incidence of postoperative pneumonia was 39.5% among patients with low HGS vs. 3.8% among patients with high HGS.
Conclusion Preoperative HGS is an independent predictive factor of postoperative complications, especially postoperative pneumonia, for elderly male patients with esophageal cancer treated with radical esophagectomy.

Keywords Handgrip strength · Postoperative complications · Esophageal cancer

Introduction

Esophageal cancer is the ninth most common cancer worldwide, with 442,000 new cases annually, and the sixth most common cause of cancer death, with 440,000 deaths in 2013 [1]. Although advances in multimodality therapy, such as surgery, chemotherapy, and radiotherapy, have improved survival, the prognosis remains poor [2]. Esophagectomy remains a mainstay treatment for potentially curable esophageal cancer [3, 4]. Due to extensive nodal involvement, extended radical esophagectomy with two- or three-field lymph node dissection is performed in Japan [5]. This highly invasive procedure is associated with severe postoperative complications, such as pneumonia, anastomotic leakage, and recurrent laryngeal nerve paralysis. Therefore, preoperative evaluation to predict postoperative complications and prognostic outcome is important.

Sarcopenia is defined as the age-related loss of muscle mass, muscle strength, and performance [6]. Cancer patients often have age-related sarcopenia (primary sarcopenia) plus disease-related and nutrition-related sarcopenia (secondary sarcopenia). Sarcopenia arising from comorbidities also often occurs in elderly cancer patients [7].

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Low muscle strength is one criterion to define sarcopenia. The European Working Group for Sarcopenia in Older People (EWGSOP) proposed that sarcopenia be diagnosed using the criteria of loss of muscle mass with either muscle weakness or poor physical performance. Concerning muscle strength, hand grip strength (HGS) is widely used [8]. Low HGS alone is reportedly a predictor of postoperative complications [9, 10], worse outcomes [11, 12], and longer hospital stay [13] in patients with cancer. However, there have been only a few studies evaluating the impact of preoperative HGS on morbidity following esophagectomy [12, 14]. This study aimed to investigate the impact of low HGS on postoperative complications.

Materials and methods

Patients and data collection

We performed a retrospective analysis of 337 consecutive patients with esophageal cancer who underwent radical esophagectomy with thoracotomy or thoracoscopy from January 2007 to December 2014 at Shizuoka General Hospital. HGS was measured within 30 days before surgery in 207 patients (61.4%). Patients with simultaneous other advanced cancers ($n = 3$), treated with esophagectomy and laryngopharyngectomy ($n = 5$), treated with pull-through esophagectomy ($n = 3$), and those treated with colonic interposition after esophagectomy ($n = 8$) were excluded. Thus, 188 patients were eligible for this study. Patients' background information, laboratory data including predicted vital capacity (VC) and predicted forced expiratory volume in 1 s ($FEV_{1.0}$), clinical stage (TMN classification 7th edition) [15], treatment information, and prognosis were obtained from medical records. Postoperative complications were classified according to the Clavien–Dindo classification [16] with complications being defined as Grade II or above. The study protocol was approved by the ethics committee of Shizuoka General Hospital (SGHIRB#2016014). Patient consent was waived due to the retrospective nature.

Hand grip strength measurement

HGS was measured in kilograms (kg) by a digital handgrip dynamometer (T.K.K.5401, Takei Scientific Instruments Co. LTD, Niigata, Japan) in the dominant and non-dominant hands within 30 days preoperatively. Patients performed the measurements while standing comfortably with forearm, wrist, and elbow in neutral position. Patients were asked to maintain maximum grip strength and measurements were repeated three times. The average of maximum measured values of the dominant and non-dominant hands was registered.

Statistical analysis

Fisher's exact test, Chi-squared test, and Mann–Whitney *U* test were used to compare the characteristics and outcomes of patients. The correlation between HGS and age was analyzed using Pearson's correlation coefficient. A receiver operating characteristic (ROC) curve was plotted and analyzed to predict the incidence of postoperative complications. Univariate logistic regression analyses were performed to assess the association between various predictors and postoperative complications. Factors on univariate analysis showing values of $p < 0.25$ were entered into multivariate logistic regression analyses. All statistical analyses were performed using SPSS version 22.0 (IBM Corporation, Armonk, NY, USA), with p values <0.05 considered statistically significant.

Results

Patient characteristics

Median age was 67 years (range 40–89 years), and all patients had undergone esophagectomy for curative intent with reconstruction by gastric tube. Histological tumor types were squamous cell carcinoma (90.4%, 170 of 188), adenocarcinoma (5.3%, 10 of 188), basaloid carcinoma (1.8%, 3 of 188), spindle cell carcinoma (1.1%, 2 of 188), malignant melanoma (1.1%, 2 of 188), and mucoepidermoid carcinoma (0.5%, 1 of 188). Median HGS of male patients was 32.1 kg (range 20–51.6 kg) and median HGS of female patients was 23.6 kg (range 17.9–31.9 kg). Median follow-up period was 30.75 months (range 0.23–110 months).

Correlation between HGS and age

The correlation between HGS and age was analyzed using Pearson's correlation coefficient. HGS showed a significant inverse association with age in both males and females (Pearson's correlation coefficient, male: −0.492, $p < 0.001$; female: −0.539, $p = 0.01$) (Fig. 1a, b). We stratified all male patients according to age (<70 years, ≥70 years) and then assessed if HGS could be a predictor of postoperative complications. We excluded female patients for further investigation because the number ($n = 22$) was too small to assess the impact of low HGS.

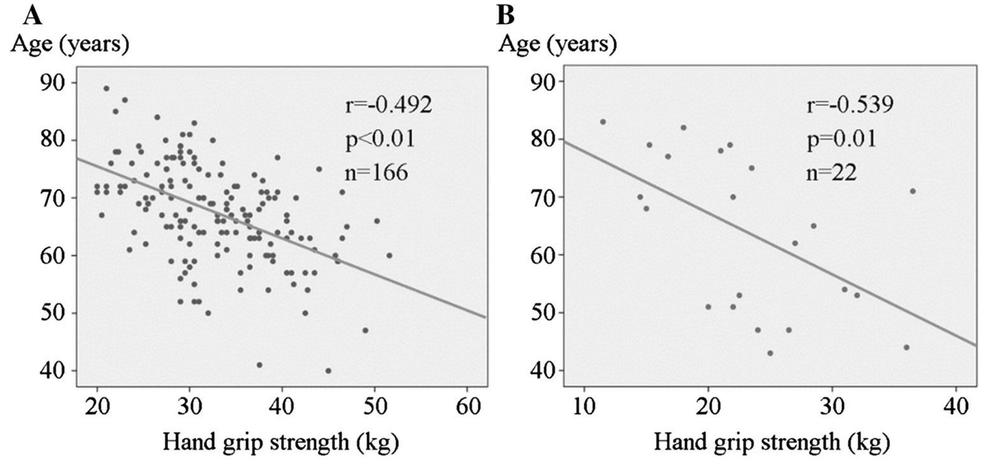

Fig. 1 Correlation between hand grip strength and age. **a** Male, **b** female

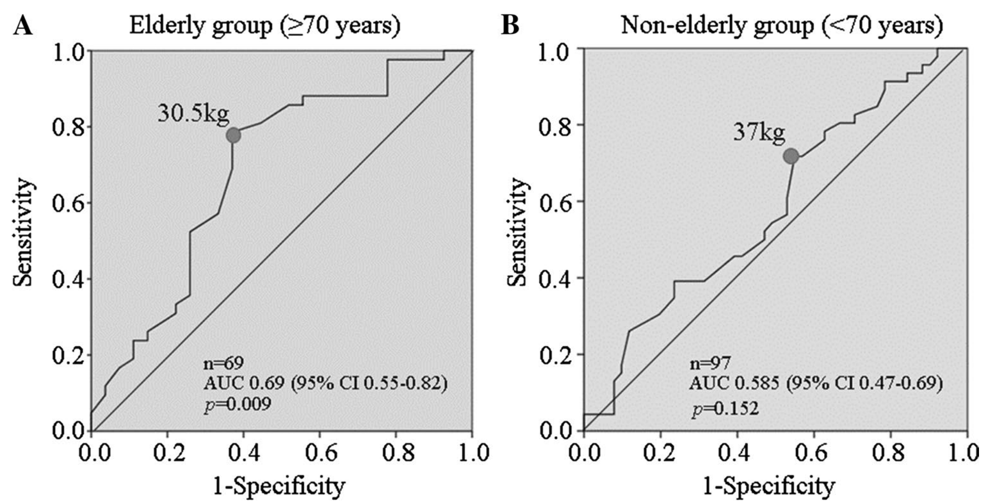

Fig. 2 Receiver-operating characteristics (ROC) curve for predicting postoperative complications. **a** Elderly patients (≥70 years), **b** non-elderly patients (<70 years). *AUC* area under the curve, *n* number, *CI* confidence interval

Evaluation of the HGS cutoff value

ROC analysis was performed to define the cutoff value to determine whether HGS could predict postoperative complications. The ROC curves identified an optimal HGS cutoff value of 30.5 kg predicting postoperative complications in the elderly group (≥70 years) [area under the curve (AUC) = 0.69, p = 0.009], and 37 kg in the non-elderly group (<70 years) (AUC = 0.585, p = 0.162) (Fig. 2a, b). We divided the patients into two categories (high-HGS patients and low-HGS patients) based on the HGS cutoff value of 30.5 kg for the elderly group and 37 kg for the non-elderly group. Table 1 summarizes the characteristics of the high- and low-HGS patients in the two groups. The low-HGS patients in the elderly group were significantly older and had lower body mass index. In the non-elderly group, the low-HGS patients were also significantly older. Moreover, the proportion of patients with more advanced cancer stage at the time of diagnosis was significantly higher among low-HGS patients (p = 0.043).

HGS and postoperative complications

Potential predictive factors for postoperative complication were evaluated in univariate and multivariate analyses in both groups (Table 2). In the multivariate analyses, low HGS was an independent predictive factor of postoperative complications in the elderly group (odds ratio = 4.893, 95% confidence interval 1.528–15.671, p = 0.008), but not in the non-elderly group (p = 0.198). There was no independent predictive factor for postoperative complications on multivariate analysis in the non-elderly group, while a borderline significant trend (p = 0.053) was observed for longer operation time (≥7 h). We compared the incidence of postoperative complications between the low-HGS and high-HGS patients using Fisher's exact test in both groups (Table 3). In the elderly group, the incidence of pneumonia was significantly higher among low-HGS patients compared to high-HGS patients (p = 0.001), and the incidence of recurrent laryngeal nerve paralysis tended to be higher in low-HGS patients. On the other hand, complications did

Table 1 Hand grip strength and patient characteristics

	Elderly group			Non-elderly group		
	Low HGS ($n = 43$)	High HGS ($n = 26$)	p value	Low HGS ($n = 61$)	High HGS ($n = 36$)	p value
Age, median (range)	76 (70–89)	72 (70–83)	0.005	65 (50–69)	60 (40–69)	0.002
BMI (kg/m^2)						
<25	39	17	0.013	57	31	0.285
≥25	4	9		4	5	
Preoperative treatment						
No	16	14	0.177	20	18	0.093
Yes	27	12		41	18	
cStage						
IA–IIB	23	14	0.977	26	23	0.043
IIIA–IV	20	12		35	13	
Serum Alb (mg/dL)						
<4.0	29	21	0.276	35	32	<0.001
≥4.0	14	5		26	4	
VC (%)						
≥80	39	24	1.000	54	35	0.144
<80	4	2		6	0	
				1	1	
FEV1.0 (%)						
≥70	27	18	0.586	45	30	0.434
<70	16	8		15	5	
				1	1	

HGS hand grip strength, *BMI* body mass index, *cStage* clinical stage, *Alb* albumin, *VC* vital capacity, *FEV* forced expiratory volume

not differ significantly between low- and high-HGS patients in the non-elderly group.

HGS and short-term surgical outcome

The median length of hospital stay tended to be longer in patients with low HGS than patients with high HGS both in the elderly group (33 vs. 23.5 days, $p = 0.087$) and the non-elderly group (23 vs. 20 days, $p = 0.100$). Hospital mortality occurred in four patients (2.4%), and all of them were patients with low HGS in the elderly group (Table 3).

Discussion

In this study, low HGS was associated with postoperative complications, especially pneumonia, after radical esophagectomy among male elderly patients with esophageal cancer. Sarcopenia is associated with postoperative complications [14, 17–20] and long-term outcomes [17, 21–23] in several cancers. However, sarcopenia was diagnosed based on the depletion of skeletal mass alone in many studies. Makiura et al. reported that sarcopenia and high Brinkman index were independent risk factors for the development of pulmonary complications in esophageal cancer following esophagectomy. In this study, sarcopenia was defined as low muscle mass plus low muscle strength and/or low physical performance [14]. These definitions and practical criteria for the diagnosis of sarcopenia were proposed by EWGSOP in 2010 [8]. Loss of skeletal muscle mass is an essential and important criterion for the diagnosis of sarcopenia. Body imaging techniques [e.g., computed tomography, magnetic resonance imaging, and dual-energy X-ray absorptiometry (DXA)] or bioelectrical impedance analysis is used to estimate muscle mass. Esophageal cancer patients usually undergo computed tomography to confirm cancer staging, and this technique can be used to estimate muscle mass. However, these methods are not easily used for routine investigation because of limited access to software and complexity of measurement.

Some reports indicate that muscle mass has a positive correlation with HGS [24, 25]. Lee et al. reported that HGS was associated with skeletal muscle index in elderly Chinese people [24]. Maximum HGS was also reported to correlate with total skeletal muscle mass measured using DXA [25], suggesting that HGS could be a surrogate marker of muscle mass. HGS offers the benefits of being relatively simple and inexpensive to be performed at any institution. EWGSOP suggested using <30 kg for males and <20 kg for females as the cutoff values for low HGS to diagnose

Table 2 Analysis of risk factors for postoperative complications

Variable	Complications+ ($n = 42$)	Complications− ($n = 27$)	Univariate			Multivariate		
			OR	95% CI	*p* value	OR	95% CI	*p* value
Elderly group								
Age, median (range)	74.5 (70–89)	74 (70–85)	1.051	0.936–1.179	0.400			
BMI								
<25 kg/m^2 (ref)	36	20	1			1		
≥25 kg/m^2	6	7	0.476	0.141–1.613	0.233	0.638	0.142–2.859	0.638
Handgrip strength								
≥30.5 kg (ref)	9	17	1			1		
<30.5 kg	33	10	6.233	2.130–18.244	<0.001	4.893	1.528–15.671	0.008
VC								
≥80% (ref)	38	25	1					
<80%	4	2	1.316	0.224–7.731	0.761			
FEV1.0								
≥70% (ref)	25	20	1			1		
<70%	17	7	1.943	0.674–5.600	0.219	2.068	0.607–7.048	0.246
Alb								
<4.0 mg/dL (ref)	30	20	1					
≥4.0 mg/dL	12	7	0.875	0.294–2.604	0.810			
Comorbidity								
Hypertension								
No (ref)	13	13	1			1		
Yes	29	14	2.071	0.763–5.625	0.153	1.423	0.455–4.450	0.545
Diabetes mellitus								
No (ref)	36	26	1			1		
Yes	6	1	4.333	0.492–38.191	0.187	3.776	0.338–42.177	0.280
Surgical approach								
Thoracotomy (ref)	29	16	1					
Thoracoscopy	13	11	0.652	0.238–1.788	0.406			
Preoperative treatment								
No (ref)	19	11	1					
Yes	23	16	0.832	0.313–2.215	0.713			
cStage								
IA–IIB (ref)	22	15	1					
IIIA–IV	20	12	1.136	0.430–3.001	0.796			
Histological type								
Squamous cell carcinoma (ref)	38	24	1					
Others	4	3	0.842	0.173–4.096	0.831			
Operation time								
<7 h (ref)	32	18	1					
≥7 h	10	9	0.625	0.214–1.822	0.389			
Intraoperative blood loss								
<500 mL (ref)	18	10	1					
≥500 mL	24	17	0.784	0.291–2.114	0.631			
Variable	**Complications + ($n = 46$)**	**Complications − ($n = 51$)**	**Univariate**			**Multivariate**		
			OR	**95% CI**	***p* value**	**OR**	**95% CI**	***p* value**
Non-elderly group								
Age, median (range)	63.5 (40–69)	62 (41–69)	1.035	0.965–1.110	0.336			

Table 2 (continued)

Variable	Complications + ($n = 46$)	Complications − ($n = 51$)	Univariate			Multivariate		
			OR	95% CI	*p* value	OR	95% CI	*p* value
Body mass index								
<25 kg/m^2 (ref)	40	48	1			1		
≥25 kg/m^2	6	3	2.400	0.564–10.211	0.236	1.825	0.381–8.744	0.452
Hand grip strength								
≥37 kg (ref)	13	23	1			1		
<37 kg	33	28	2.085	0.895–4.860	0.089	1.884	0.718–4.944	0.198
VC								
≥80% (ref)	42	49	1					
<80%	4	2	2.333	0.407–13.383	0.342			
FEV1.0								
≥70% (ref)	38	39	1					
<70%	8	12	0.684	0.252–1.860	0.457			
Alb								
<4.0 mg/dL (ref)	33	34	1					
≥4.0 mg/dL	13	17	0.788	0.331–1.874	0.590			
Comorbidity								
Hypertension								
No (ref)	27	39	1			1		
Yes	19	12	2.287	0.955–5.478	0.063	2.292	0.872–6.023	0.092
Diabetes mellitus								
No (ref)	35	46	1			1		
Yes	11	5	2.891	0.920–9.085	0.069	2.326	0.666–8.126	0.186
Surgical approach								
Thoracotomy (ref)	28	39	1			1		
Thoracoscopy	18	12	2.089	0.869–5.022	0.100	1.792	0.683–4.702	0.236
Preoperative treatment								
No (ref)	19	19	1					
Yes	27	32	0.844	0.373–1.909	0.683			
cStage								
IA–IIB (ref)	23	26	1					
IIIA–IV	23	25	1.040	0.469–2.380	0.923			
Histological type								
Squamous cell carcinoma (ref)	42	46	1					
Others	4	5	0.876	0.220–3.482	0.851			
Operation time								
<7 h (ref)	27	41	1			1		
≥7 h	19	10	2.885	1.165–7.145	0.022	2.669	0.987–7.222	0.053
Intraoperative blood loss								
<500 mL (ref)	23	31	1					
≥500 mL	23	20	1.550	0.692–3.471	0.287			

BMI body mass index, *VC* vital capacity, *FEV1.0* forced expiratory volume in 1 s, *Alb* albumin, *OD* odds ratio, *ref* reference, *cStage* clinical stage, *CI* confidence interval

sarcopenia [8]; however, the cutoff value should be modified based on race, age, and purpose of the study. Wu et al. reported a difference between Caucasians and Taiwan Chinese grip strength [26] and the Asian Working Group for Sarcopenia recommends different cutoff values from EWGSOP for hand grip strength (<26 kg for males and <18 kg for females) [27]. Furthermore, it has been reported that reference values of HGS in healthy populations decline with aging both in Japan and other countries [28–30]. Our data showed that there is a significant inverse

Table 3 Incidence of each postoperative complication in each HGS group, and correlations between HGS and short-term surgical outcomes

	Total	Low HGS (*n* = 43)	High HGS (*n* = 26)	*p* value
Elderly group				
Complications				
Anastomotic leakage	11 (15.9%)	6 (14.0%)	5 (15.3%)	0.736
Recurrent laryngeal nerve paralysis	9 (13.0%)	8 (18.6%)	1 (3.8%)	0.138
Pneumonia	18 (26.1%)	17 (39.5%)	1 (3.8%)	0.001
Lymphorrhea	5 (7.2%)	3 (7.0%)	2 (7.7%)	1.000
Cardiovascular complications (ischemic heart disease, acute dysrhythmias)	8(11.6%)	6 (14.0%)	2 (7.7%)	0.701
Superficial SSI	4 (5.8%)	3 (7.0%)	1 (3.8%)	1.000
Others	9 (13.0%)	7 (16.3%)	2 (7.7%)	0.466
Short-term surgical outcomes				
Hospital stay (days), median (range)	29 (10–116)	33 (10–108)	23.5 (16–116)	0.087
Hospital mortality	4 (5.8%)	4 (9.3%)	0 (0%)	0.289
	Total	Low HGS (*n* = 61)	High HGS (*n* = 36)	*p* value
Non-elderly group				
Complications				
Anastomotic leakage	11 (11.3%)	6 (9.8%)	5 (13.9%)	0.530
Recurrent laryngeal nerve paralysis	4 (4.1%)	3 (3.9%)	1 (2.8%)	1.000
Pneumonia	7 (7.2%)	5 (8.2%)	2 (5.6%)	1.000
Lymphorrhea	6 (6.2%)	4 (6.6%)	2 (5.6%)	1.000
Cardiovascular complications (ischemic heart disease, acute dysrhythmias)	6 (6.2%)	5 (8.2%)	1 (2.8%)	0.407
Superficial SSI	3 (3.1%)	2 (3.3%)	1 (2.8%)	1.000
Others	23 (23.7%)	17 (27.9%)	6 (16.7%)	0.230
Short-term surgical outcomes				
Hospital stay (days), median (range)	21 (15–97)	23 (16–97)	20 (15–85)	0.100
Hospital mortality	0 (0%)	0 (0%)	0 (0%)	1.000

HGS hand grip strength, *SSI* surgical site infection

association between age and HGS in patients with esophageal cancer. In several reports on the correlation between HGS and postoperative complications including young patients, gender-specific single cutoff values of HGS were determined without distinction by age [9, 10, 12]. However, in general, young patients represent a certain proportion of patients with cancer. Therefore, it would be appropriate to determine stratified cutoff values according to age, as we did, rather than a single cutoff value, as is used to diagnose sarcopenia for elderly people. Webb et al. reported that age-standardized grip strengths can predict postoperative complications [31]. Although we determined stratified cutoff values according to age, cutoff value of HGS in the non-elderly group had low accuracy and low predictive value (AUC = 0.58, $p = 0.162$), and low HGS was not an independent predictive factor of postoperative complications on multivariate analysis in the non-elderly group. There was an important difference in patient characteristics between the elderly and the non-elderly groups. The non-elderly group with low HGS included considerably more patients with advanced tumor stage, and it seems that HGS strongly reflected cancer-related and/or nutrition-related sarcopenia in the non-elderly group. On the other hand, there was no difference in tumor stage at diagnosis between low- and high-HGS patients in the elderly group, and it seems that HGS more strongly reflected age-related sarcopenia in the elderly group. This could in part explain the high predictive value of HGS for postoperative complications obtained only in the elderly group. Thus, HGS might be an effective measurement only for elderly patients with esophageal cancer.

Chen et al. reported age-standardized grip strength to be an adequate indicator of mortality in patients from 51 to 70 years of age after esophagectomy [12]. We found hospital mortality only in elderly patients with low HGS, indicating that HGS might be useful to predict short-term mortality.

There are various definitions of elderly people. Many countries accept the age of 65 years and older as a definition of elderly. However, currently, many Japanese people older than 65 years remain active. It is reported that healthy life expectancy, which is calculated by subtracting the time expected to suffer from an illness from the predicted average life expectancy, at birth in 2015 was 71.54 for men in Japan [32]. Therefore, in Japan, there is debate as to whether the elderly definition should be raised above 70 years old or over 75 years old. Based on these facts, we defined people over the age of 70 as elderly in this study.

Further investigation to further reduce postoperative complications when performing radical esophagectomy for sarcopenic patients is warranted. Yamamoto et al. reported the effect of a preoperative exercise and nutritional support program for sarcopenic patients with gastric cancer aged 65 years or older. Twenty-two sarcopenic patients received a preoperative program for a median of 16 days. After the program, HGS significantly increased, and postoperative severe complications of Clavien–Dindo classification Grade III or higher were not observed [33]. Further similar research will clarify appropriate timing and regimens of intervention to reduce postoperative complications and improve outcomes after esophagectomy.

Our study has some limitations. This was a retrospective study at a single institution. HGS was measured in only 61.4% of patients before radical esophagectomy, and females were excluded due to the small patient numbers. Protocols for measuring HGS (e.g., posture, number of measurement, arm side, and handle position) differ among previous studies, though HGS is a well-established indicator of muscle status. It might be necessary to evaluate whether our protocol is appropriate, and consensus is needed concerning the measuring protocol of HGS. In the present study, patients were divided into two groups based on age. Both in the elderly and non-elderly groups, the low-HGS patients were significantly older. It would be better to set cutoff values stratified finely by age groups to minimize the influence of age. However, because the number of patients was small in the current analysis, we could not divide patients into more detailed age groups. Finally, no data were available regarding physical performance and nutritional intake.

Preoperative risk assessment is increasingly important with aging of the Japanese population. Further study is required to develop simple and useful preoperative risk assessment methods for patients with esophageal cancer.

Conclusion

Preoperative HGS has the potential to predict postoperative complications, especially pneumonia, for elderly male patients with esophageal cancer after radical esophagectomy. We should recognize the possibility of postoperative pneumonia in elderly patients with low HGS, and provide careful postoperative management.

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Compliance with ethical standards

Ethical Statement All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions. Informed consent was waived due to the retrospective nature of the study.

Conflict of interest All authors have no conflict of interest.

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