Impact of Low Pharyngeal/Esophageal Pressure Associated with Sarcopenia on Post-Endoscopic Submucosal Dissection Pneumonia in Patients with Superficial Esophageal Cancer

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Authors' contributions

Study concept and design: Y.T, J.O, and M.H; Acquisition of data: Y.T, J.O, M.T, N.H, H.T, and N.Y; Analysis and interpretation of data: Y.T, J.O, M.H, and H.K; Drafting of the manuscript: Y.T, J.O, and M.H; Critical revision of the manuscript for important intellectual content: all authors; Study supervision: H.T, Y.K, and K.N.

Abstract

Objectives:

The aging population, including patients with superficial esophageal cancer, encounters critical dysphagia- and postoperative pneumonia-related issues. Although endoscopic submucosal dissection (ESD) provides advantages over other modalities, older patients are at higher risk of postoperative pneumonia. Furthermore, the etiologies of pneumonia are complex and include patient- (such as sarcopenia) and treatment- (including ESD) related factors. Therefore, this study evaluated swallowing function in patients with superficial esophageal cancer and identified post-ESD pneumonia-associated factors.

Methods:

Comprehensive swallowing function and sarcopenia were evaluated in patients pre-ESD and 2 months post-ESD using high-resolution manometry and several swallowing studies by multiple experts. The effects of mucosal resection and sarcopenia on swallowing function changes post-ESD, the relationship between preoperative swallowing function and sarcopenia, and the factors influencing postoperative pneumonia were investigated.

Results:

Twenty patients were included in the study. Patients with preoperative sarcopenia had significantly lower pharyngeal/upper esophageal sphincter and tongue pressures than those without sarcopenia. However, ESD did not worsen pharyngeal or upper esophageal pressure. Post-ESD pneumonia incidence tended to be higher in patients with sarcopenia than in those without sarcopenia. The lower upper esophageal sphincter-integrated relaxation pressure (UES-IRP) was a significant factor in pneumonia development. Furthermore, the receiver operating characteristic curve for UES-IRP in pneumonia yielded an area under the curve of 0.82.

Conclusions:

Sarcopenia is associated with preoperative dysphagia, which increases post-ESD pneumonia risk. Therefore, postoperative pneumonia incidence is expected to increase with an aging population, making preoperative sarcopenia and swallowing function evaluation crucial.

Keywords: Aspiration pneumonia, dysphagia, endoscopic submucosal dissection, esophageal cancer, manometry.

Introduction

Dysphagia and aspiration pneumonia are critical issues in the older population, considering the rapid aging of the world's population. In Japan, where over 25% of the population is aged ≥65 years [1], aspiration pneumonia incidence is increasing [2, 3]. Additionally, postoperative aspiration pneumonia or chemoradiotherapy is a major concern with the aging of patients with esophageal cancer [4]. Interestingly, endoscopic submucosal dissection (ESD) is an effective treatment option for superficial esophageal cancers. It provides several advantages, including a lower incidence of adverse events, shorter hospital stays, and improved quality of life compared with other treatment modalities [5-7]. Despite its benefits, post-ESD pneumonia risk is higher in older patients with esophageal cancer, with aspiration pneumonia reported in approximately 30% of patients in a computed tomography-based evaluation study [8]. Therefore, post-ESD aspiration pneumonia treatment is crucial.

The mechanisms of dysphagia and aspiration pneumonia in patients with cancer are complex and involve treatment- (including surgery and radiotherapy) [9, 10] and patient- (including sarcopenia and malnutrition) [11-13] related factors. Regarding esophageal cancer, ESD can cause an increase in esophageal

pressure and dysphagia [10, 14]. Sarcopenia- and malnutrition-associated dysphagia contribute to respiratory adverse events after esophageal surgery [15]. However, the association between these factors and post-ESD pneumonia in patients with superficial esophageal cancer has not been comprehensively studied. Furthermore, swallowing function assessment is complex and requires multidisciplinary partnership and comprehensive examination [16, 17].

Therefore, this study comprehensively evaluated swallowing function in patients with superficial esophageal cancer and identified post-ESD pneumonia-associated factors.

Methods

Patients

Overall, 20 patients diagnosed with superficial esophageal squamous cell carcinoma (SCC) who underwent their first ESD at the Department of Gastroenterology and Hepatology, Nagasaki University Hospital, between January 2022 and September 2022 were included in this study (Supplementary Fig. 1). We excluded patients with a history of esophageal or pharyngeal cancer treatment with ESD, surgery, or chemoradiotherapy; those with stroke or dementia; and those with non-SCC tumors. After enrollment, patients were followed up at three different time points as follows: pre-ESD, 2 weeks post-ESD, and 2 months post-ESD as a prospective cohort study.

Written informed consent was obtained from all patients before enrollment. The study protocol adhered to the tenets of the Declaration of Helsinki and was approved by the Nagasaki University Ethics Committee (approval number: 21062101).

Evaluation of high-resolution manometry

Pharyngeal and esophageal pressures were assessed using high-resolution manometry (HRM) (Starlet ST4000/36K12, Star Medical, Tokyo, Japan), a valuable indicator of swallowing function [18]. HRM is categorized into high-resolution esophageal manometry (HREM) and high-resolution pharyngeal manometry (HRPM). Each protocol included inserting an internal pressure sensor catheter into the esophagus, followed by 10 water swallows for esophageal pressure measurement (Supplementary Fig. 2). Subsequently, the catheter was repositioned in the pharynx to measure the pressure during the three water swallows. The following parameters were measured: (i) velopharyngeal contractile integral (VPCI), (ii) meso-hypopharyngeal contractile integral (MHPCI), (iii) upper esophageal sphincter basal pressure (UES-BP), (iv) upper esophageal sphincter integrated relaxing pressure (UES-IRP), (v) proximal contractile integral (PCI) in HRPM, (vi) distal contractile integral (DCI), and (vii) lower esophageal sphincter integrated relaxation pressure (LES-IRP). HRM assessments were performed pre- and 2 months post-ESD, with the patient seated and ingesting 2–3 cc of room-temperature water at 30-s intervals. However, three patients withdrew consent for HRM measurements after undergoing ESD.

Evaluation of swallowing function using the fiberoptic endoscopic evaluation of swallowing and videofluoroscopic swallowing study

Fiberoptic endoscopic evaluation of swallowing (FEES) was performed using the Hyodo rating scale. Briefly, 3 cc of blue-dyed water was initially administered in a neutral position to identify the presence of laryngeal penetration and/or tracheal aspiration and swallowing efficiency, including bolus retention after swallowing [19]. Hyodo et al. proposed a simple 4-point scoring system (0, normal; 1, mildly impaired; 2, moderately impaired; and 3, severely impaired) for FEES, evaluating four parameters [20], which were used in this study.

A videofluoroscopic swallowing study (VFSS) was comprehensively performed using the penetration aspiration scale (PAS). The PAS, an 8-point ordinal scale, was employed to accurately quantify specific facets of penetration and aspiration, including the degree of airway invasion and whether any material entering the airway was expelled [21]. Here, we performed PAS to grade the severity of any observed penetration or aspiration incident during the VFSS.

Evaluation of swallowing function using a self-administered questionnaire

or tongue pressure

Swallowing function was assessed using the Eating Assessment Tool-10 (EAT-10) or the tongue pressure test. The EAT-10, a self-administered questionnaire, was used to assess swallowing function with a score of >3, signifying swallowing function impairments [22]. Tongue pressure was measured using a tongue pressure meter (JMS, TPM-02E) at the Eating and Swallowing Rehabilitation Center of Nagasaki University Hospital. Measurements were conducted five times, and the average of the three highest readings was determined as the maximum tongue pressure (MTP). MTP is reportedly a valuable indicator of swallowing function [23, 24]. Evaluations of the EAT-10 and tongue pressure were conducted three times as follows: pre-ESD, 2 weeks post-ESD, and 2 months post-ESD.

Evaluation of skeletal muscle, muscle strength, and sarcopenia

Sarcopenia was diagnosed according to the criteria outlined by the 2019 Asian Working Group for Sarcopenia (AWGS) [25]. The diagnostic criteria for sarcopenia comprised low handgrip strength and skeletal mass index (SMI). Handgrip strength was assessed upright using a Smedley handgrip

dynamometer (TTM; Tokyo, Japan). Two trials were performed for the right and left hands, and the average of the two highest values was used for statistical analysis. The cut-off values for sarcopenia diagnosis were 28 and 18 kg for males and females, respectively. SMI was calculated using bioelectrical impedance analysis with InBody 770 (InBody Japan, Tokyo, Japan) by dividing the sum of the skeletal muscle mass of the arms and legs by the square of the individual's height (kg/m^2). The cut-off values for sarcopenia diagnosis were 7.0 and 5.7 kg/m^2 for males and females, respectively. SMI was measured pre-ESD alone, whereas handgrip strengths were measured pre-ESD, 2 weeks post-ESD, and 2 months post-ESD.

Evaluation of nutritional status

Blood tests were performed pre- and 2 months post-ESD. Nutritional assessment was performed using the Geriatric Nutritional Risk Index (GNRI) and the neutrophil-to-lymphocyte ratio (NLR). The GNRI was assessed once pre-ESD, and NLR assessments were performed pre-ESD and 2 months post-ESD. The GNRI was calculated using serum albumin level and body mass index (BMI): GNRI = 14.89 × serum albumin (g/dL) + 41.7 × BMI/22. The NLR was calculated

by dividing the total neutrophil count by the total lymphocyte count.

Evaluation of pulmonary function

Pulmonary function was assessed using a CHESTAC-8900 spirometer (Chest MI, Tokyo, Japan). We recorded vital capacity (VC), forced VC (FVC), and forced expiratory volume in 1 s (FEV1.0). Furthermore, we diagnosed chronic obstructive pulmonary disease (COPD) in patients with FEV1.0 of <70% and pulmonary function tests were performed once pre-ESD.

ESD procedure and post-ESD aspiration pneumonia evaluation

ESD was performed under intravenous anesthesia using midazolam and pethidine without general anesthesia cases. Esophageal ESD was conducted as previously described [26]. We defined pneumonia as the presence of fever and pneumonia on imaging based on a previous report [27]. Here, post-ESD pneumonia was defined as a fever of ≥37°C and the presence of infiltrates or ground-glass opacities on post-ESD radiographs that were not observed preoperatively. Chest radiography was performed post-ESD day 1 in all patients, and subsequent chest radiographs were evaluated as appropriate in cases of elevated temperature,

cough, decreased saturation of percutaneous oxygen, or elevated inflammatory response indicated by blood analysis.

Sample size

The sample size was set to examine the association between sarcopenia and post-ESD pneumonia using logistic regression. The number of post-ESD pneumonia cases required for logistic regression was 10. Assuming post-ESD pneumonia incidence to be 0.25 according to the previous study [8], the sample size required to obtain 10 pneumonia cases was 40. Here, we enrolled 37 cases with a target of 40 cases. However, since 17 dropouts were recorded, 20 cases were used in this study.

Statistical analysis

Data are presented as the mean ± standard deviation (SD). Categorical and continuous data were compared using Fisher's exact and Mann–Whitney U tests, respectively, between the groups. Additionally, multiple comparisons and multivariate analysis were performed using Šídák's multiple comparison test and multiple logistic regression, respectively. The diagnostic performance of post-

ESD pneumonia was assessed using receiver operating characteristic (ROC) curve analysis. Statistical significance was considered at $p<0.05$. All statistical analyses were performed using GraphPad Prism 9 (GraphPad Software, San Diego, CA, USA) and JMP, version 16 (SAS Institute, Cary, NC, USA).

Results

Association between sarcopenia and swallowing function

We first evaluated the association between sarcopenia and swallowing function. We categorized patients into non-sarcopenia and sarcopenia groups to examine (i) the association between sarcopenia and preoperative swallowing function and (ii) between sarcopenia and the degree of swallowing function change pre- and post-ESD. Five patients (25%) had sarcopenia (Table 1). The sarcopenia group was older, with significantly lower SMI and handgrip strength than the non-sarcopenia group; however, no differences were found in other factors. The sarcopenia group had lower preoperative pharyngeal and upper esophageal pressure than the non-sarcopenia group (Fig. 1A-E). However, no significant differences were observed in middle to lower esophageal pressures (Fig. 1F-H). Swallowing indices, such as VFSS and EAT-10, were mostly worse in the sarcopenia group than in the non-sarcopenia group (Fig. 1J, K). We compared the degree of swallowing function change between the groups and found no significant differences (Supplementary Fig. 3). We also examined the association between sex and swallowing function. Grip strength differed between the sexes, whereas pharyngeal and esophageal pressure did not differ

(Supplementary Fig. 4).

Association between the extent of esophageal mucosal resection and swallowing function

We subsequently investigated the association between ESD-based mucosal resection, a possible risk factor for aspiration pneumonia, and swallowing function, including tongue pressure, HRM, FEES, VFSS, and EAT-10 scores. ESD had minimal effect on most swallowing test results (Supplementary Fig. 5A-J). The EAT-10 score increased after 2 weeks but returned to pre-treatment levels after 2 months (Supplementary Fig. 5K). Pre- and post-ESD swallowing function changes were compared between the small- and large-resection groups. Patients in whom more than and less than three-quarters of the esophageal circumference was resected were allocated to the large- (14 patients, 70%) and small- (6 patients, 30%) resection groups, respectively (Supplementary Table 1). No severe adverse events, including bleeding or perforation, occurred. Furthermore, no major between-group differences in patient background, nutrition, or sarcopenia were discovered.

Characteristics of post-ESD pneumonia-related preoperative factors

Post-ESD pneumonia was observed in three (60%) and three (20%) patients in the sarcopenia and non-sarcopenia groups, respectively, indicating that the sarcopenia group had a higher rate of pneumonia than the non-sarcopenia group (p=0.11) (Table 1). We categorized patients into non-pneumonia and post-ESD pneumonia groups and compared their backgrounds and treatment- and patient-related factors. All patients with post-ESD pneumonia developed it within 24 h post-ESD. The post-ESD pneumonia group comprised six (30%) patients (Table 2). Univariate analysis revealed lower UES-IRP in the post-ESD pneumonia group than in the non-pneumonia group (Table 2). The ROC curve revealed that UES-IRP had a high diagnostic performance for post-ESD pneumonia (area under the curve: 0.82, cut-off: 10.8 mmHg) (Fig. 2). Moreover, preoperative HREM and HRPM images revealed lower pharyngeal and upper esophageal sphincter pressures in the post-ESD pneumonia group than in the non-pneumonia group (Fig. 3).

Effects of post-ESD pneumonia on patients' nutritional status and swallowing function

We investigated the impact of post-ESD pneumonia on postoperative nutritional status and swallowing function. Accordingly, we compared the postoperative NLR, a biomarker for nutritional status indices, and the EAT-10 score between the two pneumonia groups 2 months post-ESD. Notably, the post-ESD pneumonia group tended towards a higher NLR and worse EAT-10 scores than the non-pneumonia group (Supplementary Fig. 6).

Association between the HRM results and EAT-10 score

We investigated the association between the HRM and EAT-10 score results as a complementary analysis. Next, we classified the patients into no score (n=17) and the score of 1 or 2 (n=3) groups and investigated the difference in the HRM results between the groups. The VPCI, MHPCI, UES BP, UES IRP, and PCI tended to be lower, although not significantly different in the score of 1 or 2 group (Supplementary Table 2).

Discussion

This study examined the swallowing function and post-ESD pneumonia in patients with superficial esophageal cancer. Esophageal pressure, tongue pressure, velopharyngeal closure, and vocal fold movements were comprehensively evaluated by multiple experts, giving reliability to the swallowing assessments. We hypothesized that sarcopenia and ESD would influence swallowing function and postoperative pneumonia in patients with superficial esophageal cancer [28, 29]. Our study revealed that sarcopenia may contribute to impaired preoperative swallowing. Notably, sarcopenia strongly correlated with tongue pressure and pharyngeal and upper esophageal pressures but not mid-to-lower esophageal pressures. This may be because voluntary muscles control tongue pressure and swallowing in the pharynx and upper esophagus, whereas involuntary smooth muscles are mainly involved in the lower esophagus, which is less affected by sarcopenia [30].

Additionally, we conducted a prospective cohort study to compare swallowing function pre- and post-ESD, but no significant differences were observed, suggesting that ESD is minimally invasive and has less impact on swallowing than surgery or other treatments [31, 32]. Therefore, further case

accumulation or long-term observation may help identify factors that affect swallowing post-ESD and provide new insights into preventing pneumonia. However, this is the first prospective study using comprehensive assessment to compare swallowing pre- and post-ESD since most studies on swallowing in patients with gastrointestinal cancer are retrospective or focused on local regions, including the mid-to-lower esophagus.

Consistent with previous reports [8], approximately 30% of our study's patients developed post-ESD pneumonia despite ESD being minimally invasive. Our patients' mean age was 70 years, reflecting Japan's aging population, possibly leading to a higher invasiveness and pneumonia incidence. Therefore, investigating risk factors for post-ESD pneumonia is important, considering its expected increase in the aging population. Our study indicates the possibility of an association between sarcopenia and post-ESD pneumonia. Additionally, our study revealed that a low UES-IRP was a risk factor for post-ESD pneumonia with high diagnostic performance. These results convinced us that preoperative swallowing function is associated with post-ESD pneumonia. Previous studies linked high UES-IRPs to dysphagia in patients with stroke and Parkinson's disease [33, 34], rather than in those with cancer. However, the relationship between

UES-IRP and postoperative pneumonia has not yet been reported. Post-ESD pneumonia is believed to be affected by the patient's intraoperative lateral decubitus position and sedation, and a previous report linked it to esophagopharyngeal reflux [8, 35]. HRM examination of patients with post-ESD pneumonia showed decreased pressure from the pharynx to the upper esophagus pre-ESD, suggesting that reflux was more likely to occur. Therefore, post-ESD pneumonia may have a different cause than regular aspiration pneumonia, and identifying a low UES-IRP as a risk factor for ESD pneumonia is reasonable.

Furthermore, post-ESD pneumonia may lead to nutritional deficiency and impaired swallowing. Chronic inflammation from pneumonia can cause muscle wasting in the respiratory, skeletal, and swallowing systems, resulting in sarcopenia and decreased swallowing [36]. Patients with superficial esophageal cancer are prone to recurrence and frequently need multiple treatments over a long period [37]. Therefore, postoperative pneumonia-induced secondary sarcopenia and swallowing impairment may raise the risk of future complications. Our study demonstrated that preoperative sarcopenia and dysphagia are risk factors for post-ESD pneumonia, and they worsened postoperative nutrition and

swallowing. This indicates a vicious cycle where preoperative sarcopenia can cause postoperative pneumonia, and the pneumonia-induced loss of fitness increases the risk of future postoperative complications. However, this study partly explored postoperative nutritional status; therefore, further study should elucidate the full connection between post-ESD pneumonia, nutrition, and swallowing.

This study had some limitations. First, the number of patients was small; therefore, further cases should be accumulated through collaborative research because of the limited facilities available for performing esophageal ESD. Second, the 2-month observation period was relatively short to evaluate nutritional status post-ESD; therefore, the observation period should be extended, and nutritional indices should be evaluated. Lastly, we could not assess reflux in patients with low UES-IRPs since fluid backflow from the esophagus to the pharynx was not measured, although accurately measuring fluid reflux during ESD is difficult.

Our study also has strengths. This is the first study to investigate the correlation between sarcopenia and/or poor swallowing function and post-ESD pneumonia in patients with superficial esophageal cancer. Preoperative sarcopenia and swallowing assessments can forecast post-ESD pneumonia,

which will likely rise in an aging population. Preoperative nutritional intervention and swallowing therapy may improve swallowing function and reduce the post-ESD pneumonia risk.

In conclusion, this study highlights the increased risk of post-ESD pneumonia in patients with esophageal cancer with sarcopenia and associated dysphagia. Moreover, post-ESD pneumonia incidence is expected to rise in the aging population, increasing the need to evaluate preoperative sarcopenia and swallowing function in these patients. Therefore, physicians should be aware of this potential complication and act appropriately to minimize its occurrence in high-risk patients.

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Conflicts of interest

The authors declare that they have no conflict of interest.

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Figure legends

Figure 1. Association between sarcopenia and preoperative swallowing function. The preoperative swallowing function was compared between the non-sarcopenia and sarcopenia groups. The sarcopenia group had significantly lower pharyngeal and upper esophageal sphincter pressures than the non-sarcopenia group (A-D); however, no significant differences were found in the mid-to-lower esophageal pressures (F-H). Regarding other swallowing tests, the sarcopenia group had worse scores than the non-sarcopenia group (I-K).

Figure 2. Receiver operating characteristic curve of UES-IRP or SMI in predicting the development of post-ESD pneumonia. The UES-IRP showed high diagnostic performance, with an area under the ROC curve. SMI, skeletal muscle index; ROC, Receiver Operating Characteristic; UES-IRP, upper esophageal sphincter integrated relaxation pressure.

Figure 3. HREM and HRPM images of patients in the non-pneumonia and post-endoscopic submucosal dissection (ESD) pneumonia groups. This figure compares the pharyngeal and esophageal pressures in a patient without post-

ESD pneumonia (A) and one with post-ESD pneumonia (B). Patients in the post-ESD pneumonia group had lower pharyngeal and upper esophageal sphincter pressures than those in the non-pneumonia group. HREM, high-resolution esophageal manometry; HRPM, high-resolution pharyngeal manometry.

Supplementary figure 1. Diagram of the study participants. CRT, chemoradiotherapy; SCC, squamous cell carcinoma.

Supplementary figure 2. Order and method of swallowing function examination. First, the tongue pressure test was performed (A). Second, the DCI and LES-IRP were measured using high-resolution esophageal manometry (B). Finally, the VPCI, MHPCI, UES-BP, UES-IRP, and PCI were measured using high-resolution pharyngeal manometry (C). DCI, distal contractile integral; LES-IRP, lower esophageal sphincter-integrated relaxation pressure; MHPCI, meso-hypopharyngeal contractile integral; PCI, proximal contractile integral; UES-BP, upper esophageal sphincter-basal pressure; UES-IRP, upper esophageal sphincter-integrated relaxation pressure; VPCI, velopharyngeal contractile integral.

Supplementary figure 3. Association between sarcopenia and degree swallowing function change. Sarcopenia did not contribute to the degree of swallowing function change pre- and post-endoscopic submucosal dissection (ESD) (A-K).

Supplementary figure 4. Association between sex and preoperative swallowing function. Sex contributed to handgrip strength (A) rather than swallowing function (B-I).

Supplementary figure 5. Association between the extent of esophageal mucosal resection and the degree of swallowing function changes. A comparison of swallowing function pre- and post-endoscopic submucosal dissection (ESD) is shown in each figure. The extent of resection did not contribute to the degree of swallowing function change pre- and post-ESD (A-K). (A) Maximum tongue pressure (MTP); (B) Velopharyngeal contractile integral (VPCI); (C) Meso-hypopharyngeal contractile integral (MHPCI); (D) Upper esophageal sphincter basal pressure (UES BP); (E) Upper esophageal sphincter integrated relaxation

pressure (UES IRP); (F) Proximal contractile integral (PCI); (G) Distal contractile integral (DCI); (H) Lower esophageal sphincter integrated relaxation pressure (LES IRP); (I) Fiberoptic endoscopic evaluation of swallowing (FEES); (J) Videofluoroscopic swallowing study (VFSS); (K) Eating Assessment Tool-10.

Supplementary figure 6. Impact of post-endoscopic submucosal dissection (ESD) pneumonia on postoperative nutritional status and swallowing function 2 months post-ESD. The post-ESD pneumonia group tended towards a higher neutrophil-to-lymphocyte ratio (NLR) (A) and worse Eating Assessment Tool-10 (EAT-10) (B) scores than the non-pneumonia group.

Table 1. Characteristics of the patients in the non-sarcopenia and sarcopenia groups

	Non-sarcopenia (n=15)	Sarcopenia (n=5)	*p*-value
Age, years	68.9 (7.5)	77.6 (4.6)	0.02*
Sex, male/female	12/3	3/2	0.56
BMI, kg/m^2	22.7 (2.4)	20.9 (2.5)	0.17
Drinking (%)	15 (100)	5 (100)	-
Brinkmann index	673 (613)	1064 (888)	0.38
COPD (%)	4 (27)	3 (60)	0.29
VC, L	3.7 (0.7)	2.6 (0.7)	0.04
FVC, L	3.4 (0.6)	2.5 (0.7)	0.03
FEV 1.0, L	2.5 (0.5)	1.8 (0.4)	0.01
NLR	2.3 (1.0)	1.9 (0.4)	0.63
ALB, g/dL	4.3 (0.3)	4.1 (0.2)	0.18
GNRI	106.9 (7.5)	100.6 (7.6)	0.13

Tumor location, Ce~Ut/Mt~Abd	1/14	1/4	0.45
Tumor size, mm	15.9 (9.8)	17.6 (6.9)	0.46
Resection size, mm	41.0 (7.9)	41.0 (13.7)	0.76
Resection time, min	42.9 (25.5)	64.2 (54.0)	0.57
More than three-quarters of MDC (%)	10 (67)	4 (80)	1.00
Post-ESD breeding or perforation	0 (0)	0 (0)	-
Post-ESD stricture (%)	1 (6.7)	1 (20)	0.45
Post-ESD pneumonia (%)	3 (20)	3 (60)	0.11
SMI, kg/m^2	7.1 (0.9)	5.4 (0.5)	0.007
Handgrip strength, kg	34.0 (10.8)	20.1 (4.6)	0.01

Data are presented as the mean (SD). Abd, abdominal esophagus; ALB, albumin; BMI, body mass index; Ce, cervical esophagus; COPD, chronic obstructive pulmonary disease; ESD, endoscopic submucosal dissection; FEV 1.0, forced expiratory volume in one second, FVC, forced vital capacity; GNRI, geriatric nutritional risk index; MDC, mucosal defect circumference; Mt, middle thoracic

esophagus; NLR, neutrophil-to-lymphocyte ratio; SMI, skeletal mass index; Ut, upper thoracic esophagus, VC, vital capacity.

Table 2. Characteristics of the preoperative factors related to post-ESD pneumonia

Preoperative factor	Non-pneumonia (n=14)	Post-ESD Pneumonia (n=6)	Univariate OR (95%CI)	Univariate *p*-value
Age, years	70.2 (7.9)	73.0 (7.9)	1.05 (0.93–1.24)	0.4522
Sex, male/female	11/3	4/2	1.83 (0.21–15.3)	0.6126
BMI, kg/m^2	22.6 (2.4)	21.4 (2.6)	0.80 (0.49–1.19)	0.2840
Drinking (%)	14 (100)	6 (100)	-	-
Brinkman index	784 (675)	740 (780)	0.99 (0.99–1.00)	0.8909
COPD (%)	4 (29)	3 (50)	2.50 (0.34–18.0)	0.3627
VC, L	3.4 (0.8)	2.9 (0.6)	0.42 (0.10–1.74)	0.1605

FVC, L	3.3 (0.8)	2.9 (0.5)	0.43 (0.10–1.82)	0.1360
FEV 1.0, L	2.4 (0.6)	2.1 (0.4)	0.35 (0.05–2.50)	0.1603
NLR	2.1 (1.0)	2.4 (0.7)	1.37 (0.47–3.92)	0.4095
ALB, g/dL	4.2 (0.32)	4.3 (0.26)	2.14 (0.07–83.0)	0.6573
GNRI	105.8 (7.8)	104.3 (8.6)	0.97 (0.86–1.10)	0.7415
Tumor location, Ce~Ut/Mt~Abd	0/14	2/4	-	0.0729
Tumor size, mm	17.5 (9.6)	13.6 (7.6)	0.94 (0.82–1.07)	0.3520
Resection size, mm	42.4 (8.2)	37.8 (11.4)	0.94 (0.81–1.05)	0.2876
Resection time, min	44.6 (24.5)	56.7 (52.9)	1.01 (0.98–1.04)	0.4742
More than three-quarters of	11 (79)	3 (50)	0.27 (0.04–2.11)	0.3027

MDC (%)				
SMI, kg/m^2	7.0 (1.1)	6.1 (1.1)	0.46 (0.15–1.13)	0.0902
Handgrip strength, kg	32.8 (11.8)	25.2 (8.8)	0.92 (0.81–1.02)	0.1270
Sarcopenia (%)	2 (14.3)	3 (50)	6.00 (0.67–53.6)	0.1090
EAT-10	0.1 (0.3)	0.5 (0.8)	5.25 (0.54–51.3)	0.1267
MTP, mmHg	34.1 (8.1)	37.8 (13.2)	1.04 (0.94–1.17)	0.4062
VPCI, mmHg-cm-s	164.9 (64.5)	123.8 (66.9)	0.99 (0.97–1.00)	0.1853
MHPCI, mmHg-cm-s	237.1 (83.4)	178.5 (77.8)	0.99 (0.97–1.00)	0.1308
UES-BP, mmHg	102.6 (96.5)	69.2 (42.43)	0.99 (0.97–1.01)	0.3531
UES-IRP, mmHg	30.3 (25.2)	8.9 (11.1)	0.92 (0.83–0.99)	0.0221
PCI, mmHg-cm-s	251.9 (214.8)	272.7 (104.4)	1.00 (0.99–1.01)	0.8162

DCI, mmHg-cm-s	2096.7 (3689.2)	1169.5 (1300.9)	0.99 (0.99–1.00)	0.4814
LES-IRP, mmHg	10.3 (5.5)	14.7 (3.7)	1.25 (0.99–1.77)	0.0584
Penetrate Aspiration Scale	2.0 (2.2)	1.7 (1.6)	0.91 (0.42–1.48)	0.7178
Hyodo score	1.8 (2.0)	2.2 (3.1)	1.07 (0.68–1.66)	0.7266

Data are presented as the mean (SD). Abd, abdominal esophagus; ALB, albumin; BMI, body mass index; BP; basal pressure, Ce, cervical esophagus; COPD, chronic obstructive pulmonary disease; DCI; distal contractile integral, EAT-10; eating assessment tool-10, ESD, endoscopic submucosal dissection; FEV 1.0, forced expiratory volume in one second, FVC, forced vital capacity; GNRI, geriatric nutritional risk index; IRP; integrated relaxation pressure, LES, lower esophageal sphincter; MDC, mucosal defect circumference; MHPCI, meso-hypopharyngeal contractile integral, Mt, middle thoracic esophagus; MTP, maximum tongue pressure; NLR, neutrophil-to-lymphocyte ratio; PCI, proximal contractile integral; SMI, skeletal mass index; UES, upper esophageal sphincter; Ut, upper thoracic esophagus; VC, vital capacity; VPCI, velopharyngeal contractile integral.

Supplementary Table 1. Characteristics of the patients in the small- and large-resection groups

	Small (n=6)	Large (n=14)	*p*-value
Age, years	74.8 (3.1)	69.5 (8.7)	0.15
Sex, male/female	5/1	10/4	1.0
BMI, kg/m^2	22.1 (3.0)	22.3 (2.4)	0.87
Drinking (%)	6 (100)	14 (100)	-
Brinkmann index	720 (505)	793 (769)	0.84
COPD (%)	3 (50)	1 (28)	0.61
VC, L	3.3 (0.6)	3.2 (0.9)	0.86
FVC, L	3.3 (0.5)	3.1 (0.9)	0.93
FEV 1.0, L	2.4 (0.4)	2.3 (0.6)	0.86
NLR	2.7 (1.2)	2.0 (0.7)	0.14
ALB, g/dL	4.4 (0.3)	4.2 (0.3)	0.28
GNRI	106.7 (9.9)	104.7 (7.1)	0.56

Tumor location, Ce~Ut/Mt~Abd	1/5	1/13	0.52
Tumor size, mm	10.3 (5.5)	18.9 (9.1)	0.03
Resection size, mm	35.0 (8.4)	43.6 (8.6)	0.11
Resection time, min	32.0 (21.7)	55.3 (37.0)	0.09
Post-ESD breeding or perforation	0	0	-
Post-ESD stricture (%)	0	2 (14.3)	1.0
Post-ESD pneumonia (%)	3 (50)	3 (21)	0.30
SMI, kg/m^2	6.7 (1.0)	6.7 (1.2)	0.93
Handgrip strength, kg	29.6 (8.0)	30.9 (12.7)	0.93
Sarcopenia (%)	1 (17)	4 (29)	1.0

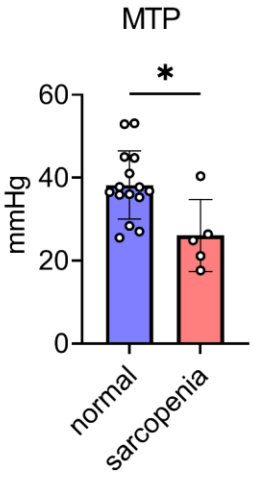
Data are presented as the mean (SD). Abd, abdominal esophagus; ALB, albumin; BMI, body mass index; Ce, cervical esophagus; COPD, chronic obstructive pulmonary disease; ESD, endoscopic submucosal dissection; FEV 1.0, forced expiratory volume in one second, FVC, forced vital capacity; GNRI, geriatric nutritional risk index; Mt, middle thoracic esophagus; NLR, neutrophil-to-

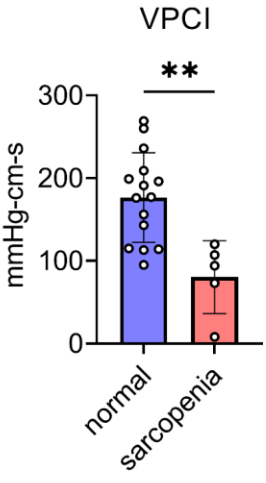
lymphocyte ratio; SMI, skeletal mass index; Ut, upper thoracic esophagus; VC, vital capacity.

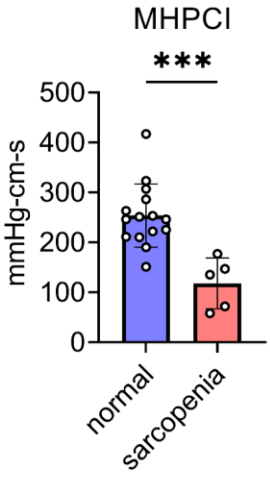
Supplementary Table 2. Association between the EAT-10 score and HRM

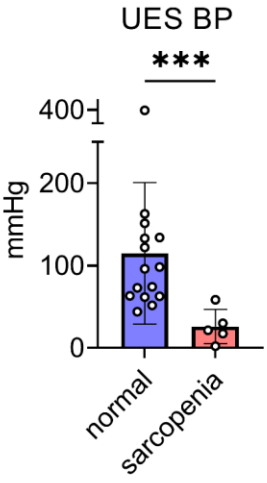
	No score (n=17)	Score 1 or 2 (n=3)	*p*-value
VPCI, mmHg-cm-s	161.2 (59.9)	103.6 (93.0)	0.26
MHPCI, mmHg-cm-s	227.8 (74.9)	172.0 (136.3)	0.36
UES BP, mmHg	96.9 (87.3)	67.6 (72.6)	0.49
UES IRP, mmHg	26.1 (24.8)	10.9 (13.2)	0.31
PCI, mmHg-cm-s	280 (189.1)	130.3 (114.1)	0.18
DCI, mmHg-cm-s	1859.6 (1187.3)	2320.3 (1339.6)	0.73
LES IRP, mmHg	11.9 (4.96)	9.66 (8.30)	0.56

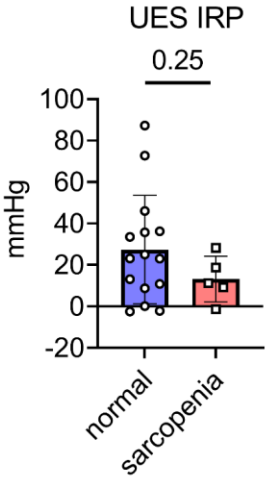
Data are presented as the mean (SD). DCI, distal contractile integral; EAT-10, eating assessment tool-10; HRM, high-resolution manometry; LES IRP, lower esophageal sphincter integrated relaxation pressure; MHPCI, meso-hypopharyngeal contractile integral; PCI, proximal contractile integral UES BP, upper esophageal sphincter basal pressure; UES IRP, upper esophageal sphincter integrated relaxation pressure; VPCI, velopharyngeal contractile integral.

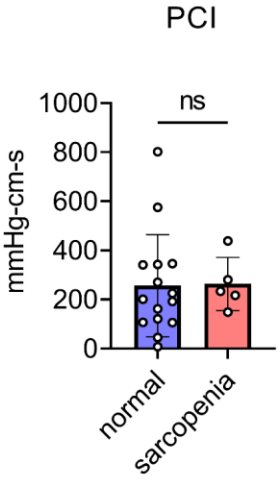

MTP
*
mmHg
60
40
20
0
normal
sarcopenia

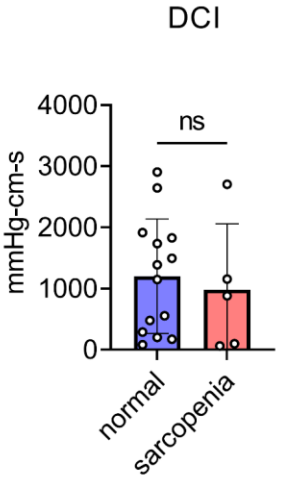

VPCI
**
mmHg-cm-s
300
200
100
0
normal
sarcopenia

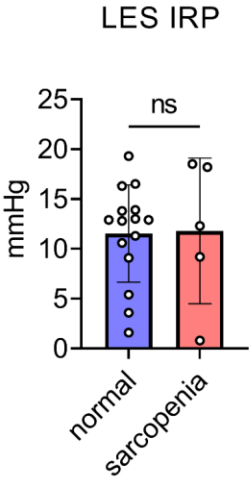

MHPCI
***
mmHg-cm-s
500
400
300
200
100
0
normal
sarcopenia

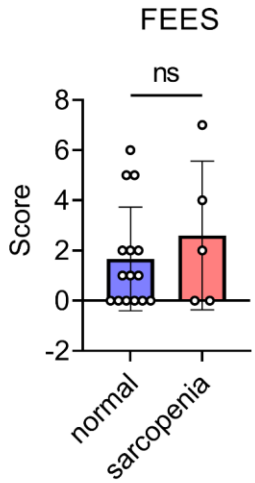

UES BP
***
mmHg
400
200
100
0
normal
sarcopenia

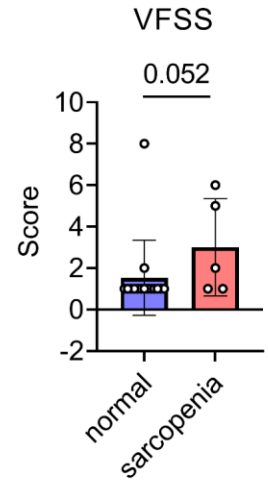

UES IRP
0.25
mmHg
100
80
60
40
20
0
-20
normal
sarcopenia

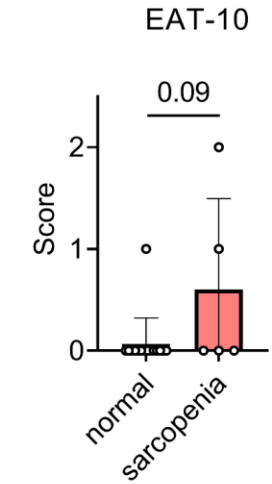

PCI
ns
mmHg-cm-s
1000
800
600
400
200
0
normal
sarcopenia

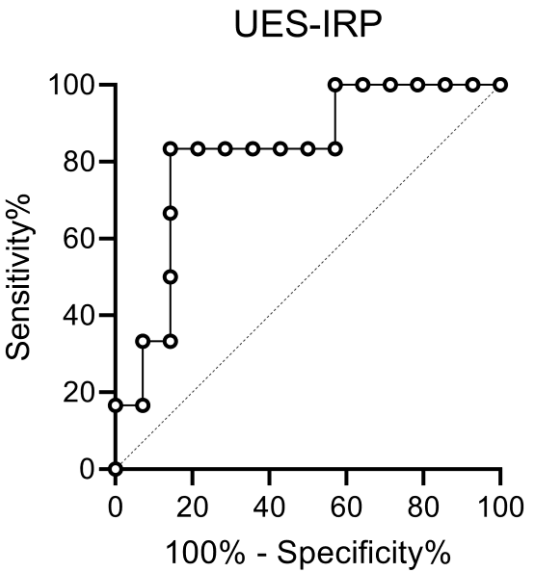

DCI
ns
mmHg-cm-s
4000
3000
2000
1000
0
normal
sarcopenia


LES IRP
ns
mmHg
25
20
15
10
5
0
normal
sarcopenia

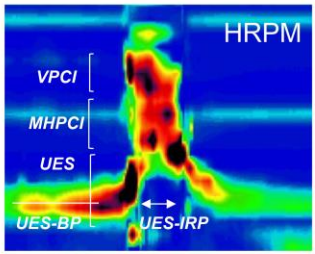

FEES
ns
Score
8
6
4
2
0
-2
normal
sarcopenia

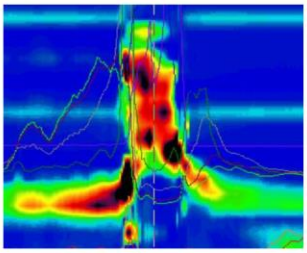

VFSS
0.052
Score
10
8
6
4
2
0
-2
normal
sarcopenia

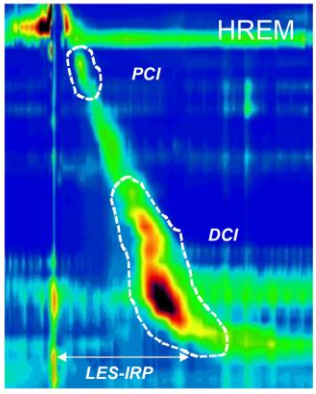

EAT-10
0.09
Score
2
1
0
normal
sarcopenia


UES-IRP
Sensitivity%
100
80
60
40
20
0
0
20
40
60
80
100
100% - Specificity%

The 73-year-old patient who did not develop post-ESD pneumonia

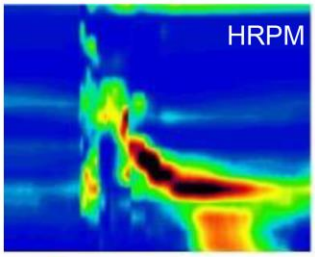


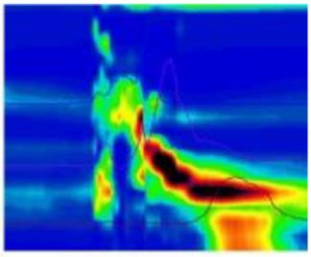


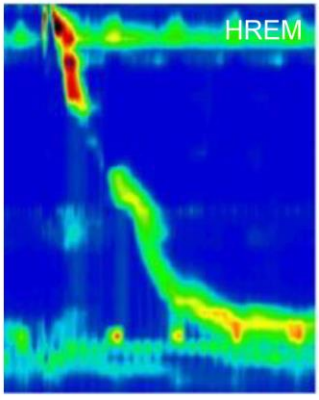


VPCI: 196 (mmHg-cm-s)
MHPCI: 323 (mmHg-cm-s)
UES-BP: 151 (mmHg)
UES-IRP: 8.7 (mmHg)
PCI: 8 (mmHg)
DCI: 1493 (mmHg)
LES IRP: 1.6 (mmHg)
VE: 1 score, normal
VF: 1 score, normal
EAT-10: 1 score, normal

The 79-year-old patient who developed post-ESD pneumonia







VPCI: 8 (mmHg-cm-s)
MHPCI: 58 (mmHg-cm-s)
UES BP: 21.5 (mmHg)
UES IRP: -1.4 (mmHg)
PCI: 234 (mmHg)
DCI: 60.4 (mmHg)
LES IRP: 9.2 (mmHg)
VE: 7 score, dysphagia
VF: 5 score, dysphagia
EAT-10: 2 score, normal

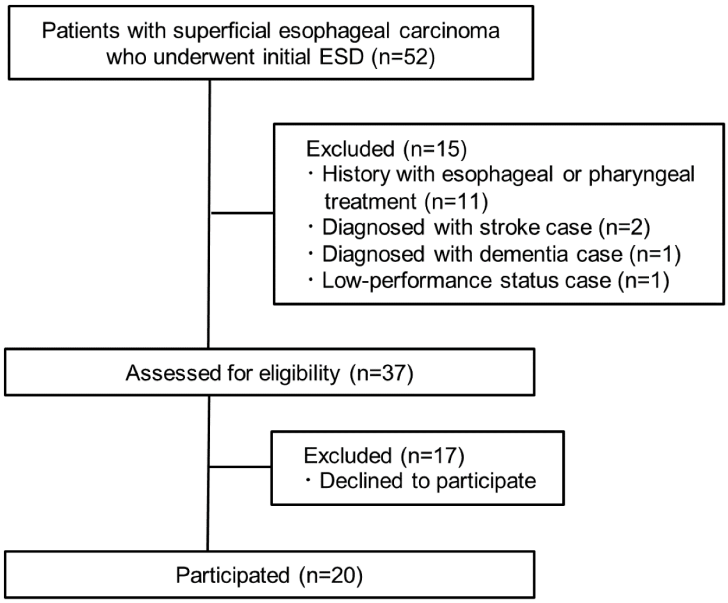
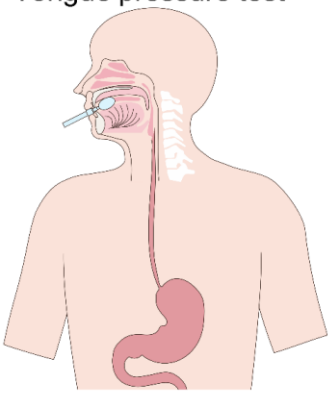


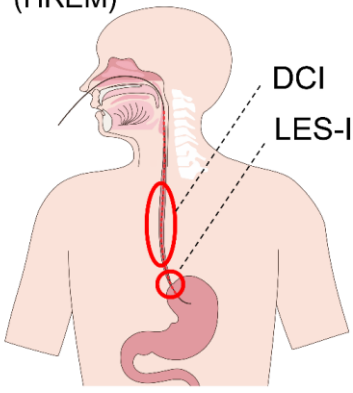
Figure 1. Flowchart of the study design.
ESD; endoscopic submucosal dissection; CRT; chemoradiotherapy; SCC, squamous cell carcinoma.

Tongue pressure test



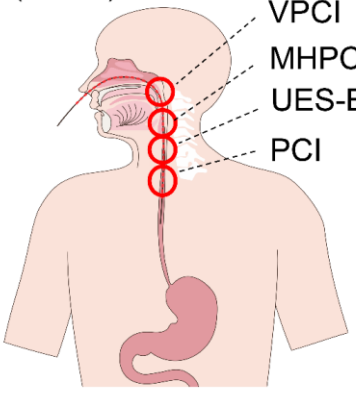
5 times

High resolution
esophageal manometry
(HREM)

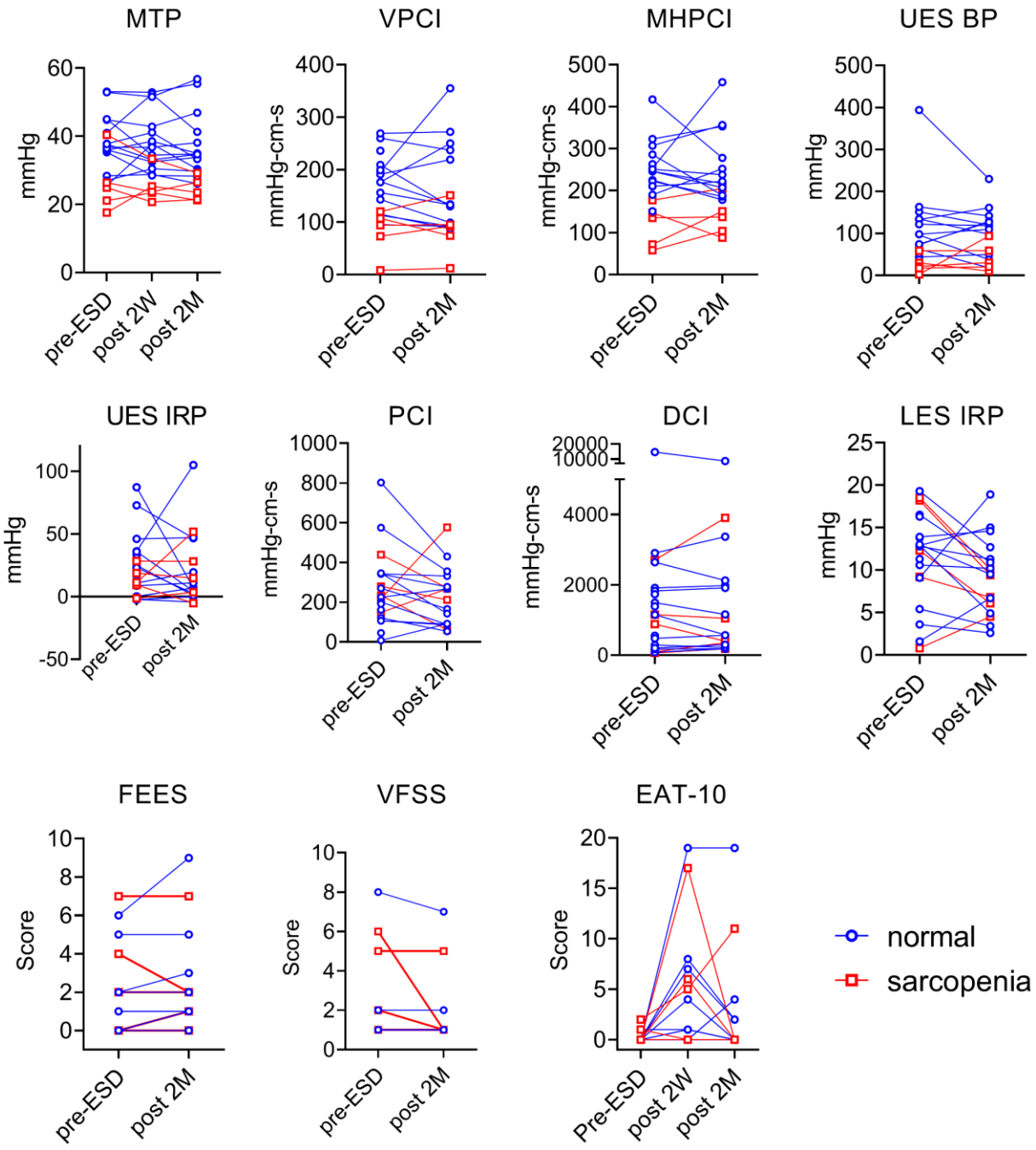


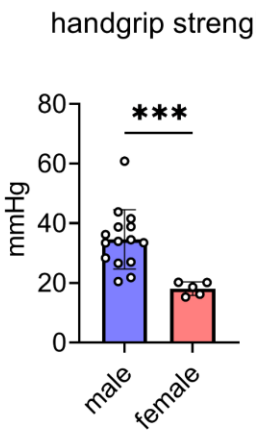
10 water swallows

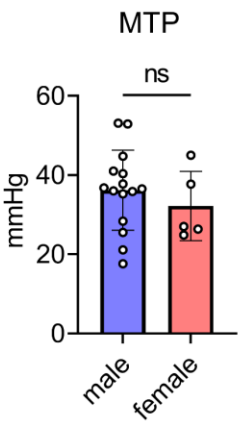
High resolution
pharyngeal manometry
(HRPM)

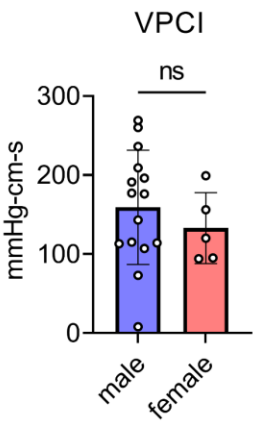


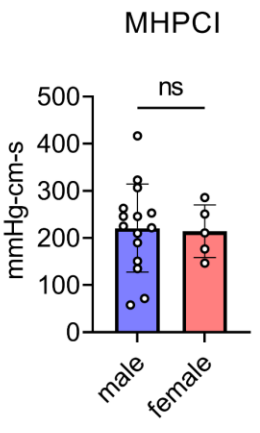
3 water swallows

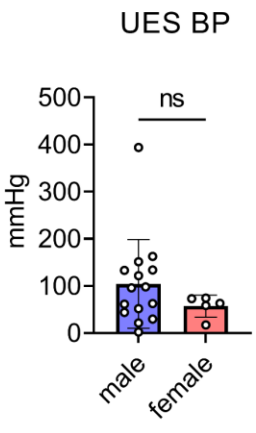

MTP
mmHg
60
40
20
0
pre-ESD
post 2W
post 2M
VPCI
mmHg-cm-s
400
300
200
100
0
pre-ESD
post 2M
MHPCI
mmHg-cm-s
500
400
300
200
100
0
pre-ESD
post 2M
UES BP
mmHg
500
400
300
200
100
0
pre-ESD
post 2M
UES IRP
mmHg
100
50
0
-50
pre-ESD
post 2M
PCI
mmHg-cm-s
1000
800
600
400
200
0
pre-ESD
post 2M
DCI
mmHg-cm-s
20000
10000
4000
2000
0
pre-ESD
post 2M
LES IRP
mmHg
25
20
15
10
5
0
pre-ESD
post 2M
FEES
Score
10
8
6
4
2
0
pre-ESD
post 2M
VFSS
Score
10
8
6
4
2
0
pre-ESD
post 2M
EAT-10
Score
20
15
10
5
0
Pre-ESD
post 2W
post 2M
normal
sarcopenia

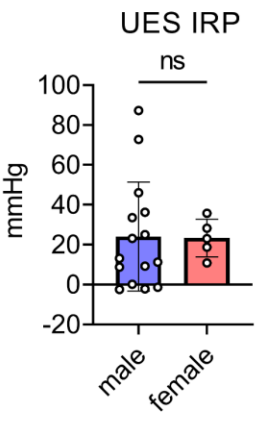

handgrip strengh
***
mmHg
80
60
40
20
0
male
female

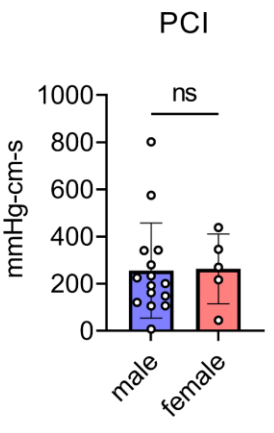

MTP
ns
mmHg
60
40
20
0
male
female

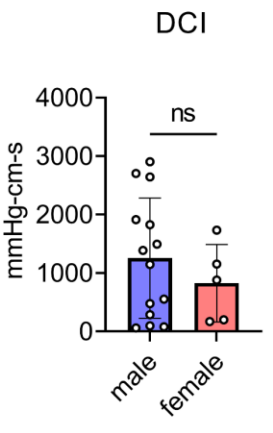

VPCI
ns
mmHg-cm-s
300
200
100
0
male
female

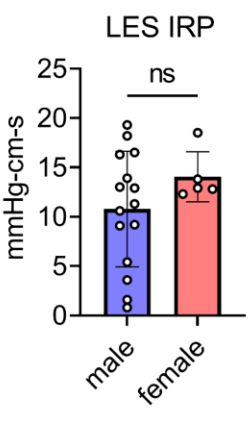

MHPCI
ns
mmHg-cm-s
500
400
300
200
100
0
male
female

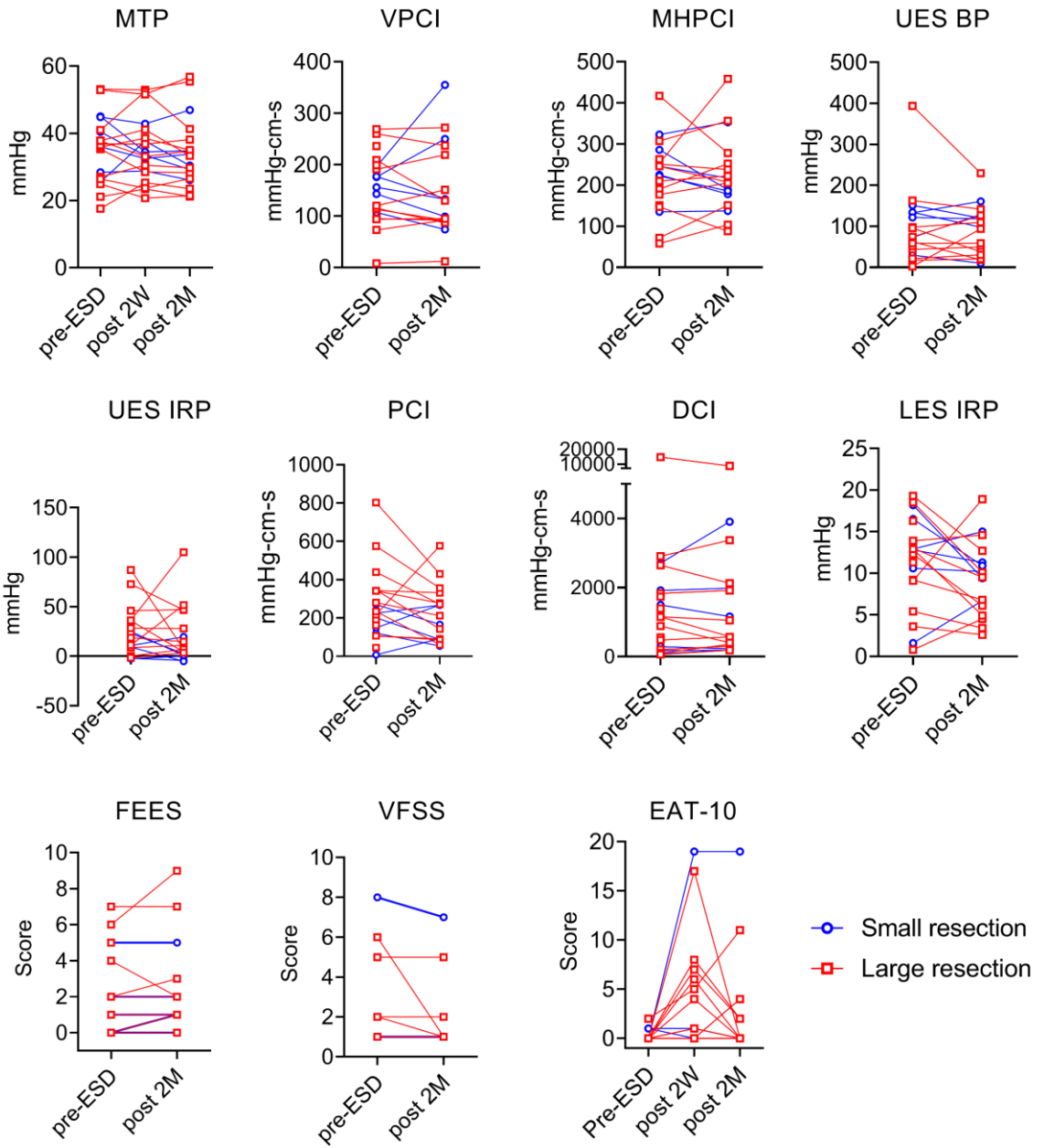

UES BP
ns
mmHg
500
400
300
200
100
0
male
female

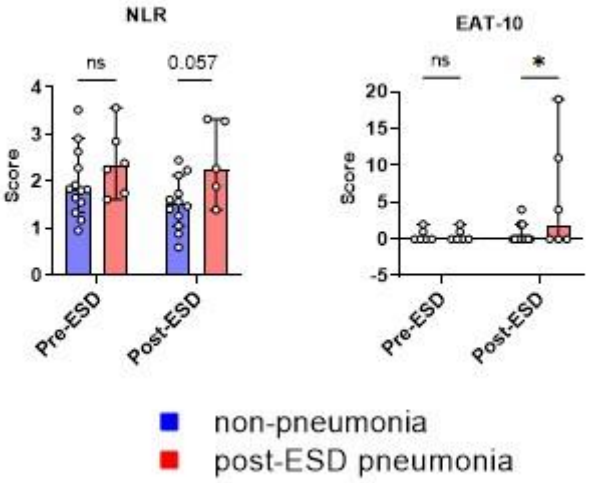

UES IRP
ns
mmHg
100
80
60
40
20
0
-20
male
female


PCI
ns
mmHg-cm-s
1000
800
600
400
200
0
male
female


DCI
ns
mmHg-cm-s
4000
3000
2000
1000
0
male
female


LES IRP
ns
mmHg-cm-s
25
20
15
10
5
0
male
female


MTP
mmHg
60
40
20
0
pre-ESD
post 2W
post 2M
VPCI
mmHg-cm-s
400
300
200
100
0
pre-ESD
post 2M
MHPCI
mmHg-cm-s
500
400
300
200
100
0
pre-ESD
post 2M
UES BP
mmHg
500
400
300
200
100
0
pre-ESD
post 2M
UES IRP
mmHg
150
100
50
0
-50
pre-ESD
post 2M
PCI
mmHg-cm-s
1000
800
600
400
200
0
pre-ESD
post 2M
DCI
mmHg-cm-s
20000
10000
4000
2000
0
pre-ESD
post 2M
LES IRP
mmHg
25
20
15
10
5
0
pre-ESD
post 2M
FEES
Score
10
8
6
4
2
0
pre-ESD
post 2M
VFSS
Score
10
8
6
4
2
0
pre-ESD
post 2M
EAT-10
Score
20
15
10
5
0
Pre-ESD
post 2W
post 2M
Small resection
Large resection


NLR
ns
0.057
Score
4
3
2
1
0
Pre-ESD
Post-ESD
EAT-10
ns
*
Score
20
15
10
5
0
-5
Pre-ESD
Post-ESD
non-pneumonia
post-ESD pneumonia