BMC Sports Science, Medicine and Rehabilitation

RESEARCH **Open Access**

# Physical fitness predicts post-esophagectomy complications after chemoradiotherapy: a pilot study

Chien-Hung Chiu[1], Wei-Yang Chang[2], Lan-Yan Yang[3], Yin-Kai Chao[1], Wei-Hsun Chen[1], Yun-Hen Liu[1], Ya-Tzu Tsao[4], Yu-Ling Chang[5] and Shu-Chun Huang[6,7,8*]

## Abstract

**Background** Esophagectomy following neoadjuvant chemoradiotherapy or definitive chemoradiotherapy has been shown to yield favorable oncological outcomes in patients with locally advanced esophageal squamous cell carcinoma. However, postoperative complications are frequent and can adversely affect patient survival. This study aimed to identify physical fitness factors across multiple domains associated with major postoperative complications.

**Methods** This study enrolled patients with esophageal squamous cell carcinoma who were treated with neoadjuvant chemoradiotherapy or definitive chemoradiotherapy and underwent esophagectomy between 2020 and 2022. Multivariate logistic regression analysis was conducted to identify the factors associated with major postoperative complications. Additionally, a tree-based learning process was employed to assess all the variables influencing major complications.

**Results** A total of 142 esophageal cancer patients who underwent esophagectomy were screened. Of these, 72 eligible patients were included in the study, and 29 (40.2%) experienced major postoperative complications. In the full model, factors such as low body weight, low body mass index, low peak oxygen consumption ($\dot{V}O_{2peak}$), low $\dot{V}O_{2peak}$/skeletal muscle mass (SMM), low appendicular skeletal muscle index (ASMI), and low ASMI–$\dot{V}O_{2peak}$/SMM product (A$\dot{V}$P) were found to be significantly associated with major postoperative complications. However, in the parsimonious model, only low A$\dot{V}$P ($P < 0.01$) was associated with major complications. Additionally, A$\dot{V}$P, $EqO_2$nadir, and hand grip strength emerged as the key predictors of major post-esophagectomy complications in the tree-based learning analysis, which showed a sensitivity of 0.448, specificity of 0.977, and accuracy of 76.4%, with false negative and false positive rates of 55.2% and 2.3%. A$\dot{V}$P alone yielded similar results.

**Conclusions** Patients with low A$\dot{V}$P, high $EqO_2$nadir, and low HGS are at a very high risk of experiencing major postoperative complications, with low A$\dot{V}$P showing the strongest correlation. Preoperative physical fitness screening can help identify high-risk patients and guide appropriate perioperative management.

**Keywords** Physical fitness, Esophageal cancer, Chemoradiotherapy, Esophagectomy, Complications

*Correspondence:
Shu-Chun Huang
h0711@ms13.hinet.net

Full list of author information is available at the end of the article

## Background

Esophageal cancer, particularly esophageal squamous cell carcinoma (ESCC), presents as an aggressive disease with a poor prognosis [1]. Studies indicate that individuals with ESCC who did not undergo surgery experienced worse outcomes [1]. For locally advanced esophageal cancer, planned esophagectomy following neoadjuvant chemoradiotherapy (nCRT) has become widely accepted, offering a survival benefit [2]. Salvage esophagectomy is also recognized as a viable option for residual or recurrent disease after definitive chemoradiotherapy (dCRT), leading to improved long-term outcomes [3]. Despite advancements in surgical techniques and anesthesia, post-esophagectomy complications remain relatively common [4–9]. Moreover, individuals experiencing postoperative complications tend to exhibit inferior long-term survival rates [8, 9].

Physical fitness comprises diverse elements including body composition, muscle strength, cardiorespiratory fitness, etc [10, 11]. Prior investigations have correlated factors such as low skeletal muscle mass (SMM) or diminished hand grip strength (HGS) with heightened post-esophagectomy complication rates [12, 13]. Similarly, inadequate preoperative cardiorespiratory fitness levels, commonly assessed using cardiopulmonary exercise testing (CPET), have been associated with an increased risk of postoperative complications [4, 5, 14–16]. Nonetheless, existing literature has predominantly focused on individual aspects of physical fitness—namely body composition, muscle strength, or cardiorespiratory fitness—without providing a comprehensive assessment that integrates these domains [4, 5, 12–16] Consequently, the predictive accuracy remains suboptimal. For example, the areas under the receiver operating characteristic curves (AUCs) for peak oxygen consumption ($VO_2$peak) or the ventilatory anaerobic threshold (AT) range from 0.60 to 0.62 [5, 15]. Therefore, it is essential to explore multiple dimensions of physical fitness and consider composite indicators that may better predict surgical risk.

$VO_{2peak}$ is closely associated with oxygen-consuming exercising muscles. In this study, $VO_{2peak}$ normalized by skeletal muscle mass (SMM), in addition to the commonly used normalization by body weight, was utilized to quantify oxygen consumption per unit of oxygen-consuming tissue [17, 18]. Furthermore, to integrate muscle mass and cardiorespiratory fitness, we proposed a novel index—appendicular skeletal muscle mass index (ASMI)–$VO_{2peak}$/SMM product (AVP)—calculated by multiplying ASMI and $VO_{2peak}$ normalized by SMM.

A comprehensive preoperative evaluation is essential for patients undergoing surgery for esophageal cancer, especially those undergoing nCRT or dCRT. This prospective exploratory study aimed to investigate the predictive value of different domains of physical fitness for major postoperative complications in patients with ESCC who underwent esophagectomy after completing chemoradiotherapy.

## Methods

### Patients

This prospective observational study was approved by the Chang Gung Medical Foundation Institutional Review Board (IRB No. 201802337A3). All participants provided informed consent prior to the administration of the physical fitness evaluation. Between April 2020 and August 2023, 142 patients diagnosed with esophageal cancer underwent esophagectomy at the Chang Gung Memorial Hospital in Linkou, Taiwan. After excluding patients who underwent upfront esophagectomy, had incomplete physical fitness evaluations, or were diagnosed with pathologies other than squamous cell carcinoma, 72 eligible patients were analyzed. We then assessed predictors by comparing patients with and without postoperative complications.

### Neoadjuvant chemoradiotherapy

Two chemotherapeutic regimens were administered throughout the study period. The first regimen consisted of 5-fluorouracil and cisplatin. The second regimen involved the weekly administration of carboplatin and paclitaxel. Radiation therapy was administered between days 8 and 29, with a total dose of 45 Gy delivered in daily fractions of 200 cGy. The radiation field encompassed the primary tumor, regional lymph nodes, and involved lymph nodes.

### Definitive chemoradiotherapy

The chemotherapy regimens used in dCRT were similar to those used in nCRT, involving 5-fluorouracil plus cisplatin or carboplatin plus paclitaxel. In dCRT, the total radiation dose amounted to 50.4 Gy, delivered in daily fractions of 180 or 200 cGy.

### Surgery

For patients who underwent nCRT, planned esophagectomy was done 6–8 wk after the completion of nCRT. Salvage esophagectomy was defined as surgical resection in patients who received dCRT but showed persistent disease or locoregional recurrence.

The McKeown procedure was performed for lesions located in the upper or middle third of the esophagus. The Ivor–Lewis procedure was performed for esophageal cancer involving the lower third of the esophagus or the esophagogastric junction. All patients underwent at least a two-field lymph node dissection.

Post-esophagectomy complications were recorded in accordance with the guidelines established by the

Esophageal Complications Consensus Group [7]. The severity of postoperative complications was assessed using the Clavien–Dindo Classification, which ranges from grade I to grade V [19]. Major complications were defined as those above grade III.

## Physical fitness

Once patients completed nCRT or dCRT, their physical fitness was evaluated within four weeks before surgery.

### *Body composition*

Whole-body composition was assessed using InBody s10 (Seoul, Korea), which measures electrical resistance at four different frequencies (5, 50, 250, and 500 kHz). Prior to the test, participants were instructed to fast for 2 hr. Each participant remained seated upright on a nonconductive chair throughout the approximately 10-minute testing procedure. The sensors for measuring the electrical resistance were positioned at the level of each body segment according to the manufacturer's instructions. Parameters including appendicular skeletal muscle index (ASMI), fat-free mass (FFM), lean body mass (LBM), skeletal muscle mass (SMM) [20], and phase angle (PA) were recorded. ASMI was calculated as the sum of SMM for the four limbs divided by body height (BH) [21]. The $FFM/BH^2$, $SMM/BH^2$, and $LBM/BH^2$ were used for inter-individual body composition comparisons.

### *Cardiopulmonary exercise testing (CPET)*

A symptom-limited incremental exercise test was conducted in the upright position by using a calibrated bicycle ergometer (Ergoselect 150P, Germany) to evaluate aerobic fitness and hemodynamic function. The CPET was performed 2–4 h after a light meal, starting with 2 min of rest, followed by a 1-min warm-up at 10 W, followed by a ramp increase of 10 W/min until exhaustion. Minute ventilation (V̇E), oxygen consumption ($\dot{V}O_2$), and carbon dioxide production ($\dot{V}CO_2$) were measured breath-by-breath using a computer-based system (MasterScreen CPX, Cardinal Health, Germany), with data averaged every 15 s. Resting and exercise 12-lead ECG were monitored via a stress ECG recorder (CardioSoft, GE, Milwaukee, WI, USA), arterial blood pressure was measured using an automated device (Tango, SunTech Medical, UK), and arterial oxygen saturation was tracked using a pulse oximeter (model 9500, Nonin Onyx, Plymouth, MS, USA). The rate of perceived exertion was assessed every 2 min. Participants were instructed to maintain a cadence of $60 \pm 3$ revolutions per minute (RPM) until symptoms became limited (pedaling cadence $< 50$ RPM). Termination criteria included: (1) inability to sustain pedaling frequency above 50 RPM; (2) reaching volitional fatigue; (3) peak $VO_2$ plateau or decline despite continued exercise; or (4) occurrence of adverse cardiovascular events [22] Peak oxygen consumption ($\dot{V}O_{2peak}$) was defined as the highest rate of oxygen consumption achieved by an individual during exercise testing. Ventilation efficiency was evaluated using three parameters: (i) $EqO_2$nadir, representing the lowest value of ventilatory equivalent for oxygen ($\dot{V}E/\dot{V}O_2$); (ii) $EqCO_2$nadir, indicating the lowest value of ventilatory equivalent for carbon dioxide ($\dot{V}E/\dot{V}CO_2$)[23]; and (iii) oxygen uptake efficiency slope (OUES), derived from the slope of $\dot{V}O_2$ versus the logarithm of V̇E ((L/min)/log(L/min)), which signifies higher oxygen uptake efficiency with a steeper slope [24]. Ventilatory anaerobic threshold (AT) was primarily determined using the V-slope method and confirmed based on ventilatory criteria, such as departure from linearity for $\dot{V}CO_2$ against $\dot{V}O_2$, an increase in the $\dot{V}E/\dot{V}O_2$ ratio without a corresponding rise in the $\dot{V}E/\dot{V}CO_2$ ratio, and an increase in end-tidal tensions of oxygen ($PETO_2$) without a corresponding decrease in end-tidal tensions of carbon dioxide ($PETCO_2$) [25]. AT identification was performed by two independent reviewers. In this study, we introduced a novel marker, AVP, calculated as the product of ASMI and $\dot{V}O_{2peak}$/SMM, for a composite evaluation of muscle mass and cardiorespiratory fitness.

### *Muscular strength*

Hand grip strength (HGS) was measured using a dynamometer (TTM, Tokyo) with the participants standing and their hands hanging naturally. The grip distance was adjusted according to the optimal force. The participants exerted a maximum force for approximately 3 s. Two trials were conducted on alternating sides for each hand. The average of the highest values of each hand was calculated.

## Statistical analysis

Summary statistics employed counts and percentages for categorical variables, and means and standard deviations for continuous variables. An independent samples t-test was used to determine the differences between patients with and without major postoperative complications. For binary variables, the chi-squared test or Fisher's exact test was used.

To explore associations between clinical variables and major postoperative complications, both univariate and multivariate logistic regression analyses were performed. Given the exploratory nature of the study and the relatively limited sample size, a forward selection procedure was applied [26, 27].

Receiver operating characteristic curve analysis was used to determine the specificity and sensitivity of the optimal physical fitness variables for predicting major postoperative complications. To enhance clinical applicability, a tree-based learning process was performed using the R package rpart to explore and estimate all variables influencing major complications. All statistical analyses were performed using the SPSS version 22 (SPSS, Armonk, NY, US) or R software (version 4.1.3). Statistical significance was determined using a two-tailed $P<0.05$.

## Results

The clinical characteristics of the patients are summarized in Table 1. The cohort comprised 95.8% (69/72) male patients. The mean age, body mass index, and albumin levels of the 72 patients were 57.7 year, 22.5 kg/m², and 4.1 g/dL, respectively. All patients received chemoradiotherapy before the operation, and nCRT was performed in 75% of the patients. The mean $VO_{2peak}$/BW is 18.0 mL/min/kg.

Most patients (88.9%) underwent minimally invasive surgery, with the McKeown esophagectomy being the predominant procedure (98.6%). The mean duration of intensive care unit stay and hospital stay was 2.5 and 18 days, respectively.

Among the patients, 40.2% (29/72) experienced major postoperative complications, predominantly grade IIIa (75.9%). The most common major postoperative complications were neurological (58.6%), gastrointestinal (37.9%), and pulmonary (31%) (Table 2).

Patients with major postoperative complications were characterized by older age ($P=0.037$), lower body weight (BW) ($P=0.033$), lower body mass index ($P=0.039$), reduced $VO_{2peak}$ ($P=0.008$), diminished $VO_{2peak}$/SMM ($43.6\pm6.3$ vs. $40.0\pm7.0$, $P=0.033$), decreased ASMI ($7.6\pm1.2$ vs. $6.9\pm0.7$, $P=0.011$), and lower AVP ($329.1\pm68.8$ vs. $278.2\pm57.9$, $P=0.003$). Moreover, the duration of intensive care unit and hospital stay was longer in patients with major postoperative complications ($P=0.039$ and $P<0.001$, respectively) (Table 1).

### Multivariate logistic regression analysis of major complications

Taking all the clinical and physical fitness variables into consideration, old age ($P=0.042$), low BW ($P=0.039$), low body mass index ($P=0.044$), low $VO_{2peak}$ ($P=0.011$), low $VO_{2peak}$/SMM ($P=0.039$), low ASMI ($P=0.026$) and low AVP ($P=0.005$) were found to be associated with major complications. After stepwise variable selection, only AVP ($P=0.005$) remained significantly correlated with major complications (Table 3). Receiver operating characteristic analysis indicated an optimal AVP threshold level of 260.717 mL/min/m$^2$ for predicting major complications (area under the curve = 0.717; sensitivity = 0.5 and specificity = 0.889; $P=0.003$) (Fig. 1). The corresponding predictive accuracy, false negative rate and false positive rate were 73.2%, 50.0% and 11.1% in the current cohort.

### Tree-based learning analysis

A tree-based method was employed to identify the algorithms of clinical variables associated with major post-esophagectomy complications (Fig. 2). AVP, $EqO_2$nadir, and HGS were found to be statistically significant and were grouped to construct a prediction model for major complications following esophagectomy. The model demonstrated a sensitivity of 0.448 and a specificity of 0.977. The predictive accuracy, false negative rate, and false positive rate were 76.4%, 55.2%, and 2.3% in the present cohort.

## Discussion

For resectable esophageal cancer, esophagectomy has been shown to offer improved long-term survival [1–3]. Major postoperative complications occurred in 31.3–48.9% of patients following esophagectomy [6, 7]. In this study, 40.2% of patients experienced major complications after esophagectomy subsequent to chemoradiotherapy. Patients who experienced major complications also had extended intensive care unit and hospital stays. Our analysis revealed that a lower preoperative AVP was associated with an increased likelihood of major postoperative complications. Additionally, AVP, $EqO_2$nadir, and HGS emerged as key variables in the predictive model for major post-esophagectomy complications. The tree analysis model demonstrated a modest improvement in predictive performance over AVP alone. To the best of our knowledge, this study is the first to use multiple domains of physical fitness, including body composition, muscle strength, and cardiopulmonary fitness, to predict surgical outcomes after esophagectomy.

Declining cardiopulmonary reserve and low muscle mass are prevalent among patients with esophageal cancer undergoing chemotherapy or chemoradiotherapy [12, 28–30]. A European multicenter cohort study demonstrated that cardiopulmonary comorbidity was correlated with postoperative complications following esophagectomy [6]. Preoperative low muscle mass or strength served as a predictor of postoperative complications in esophageal cancer surgery [12, 13]. Our investigation revealed that complications after esophagectomy could extend hospital stay. Additionally, individuals experiencing postoperative complications exhibited poorer overall survival rates [8, 9]. In this study, we observed a relatively high rate of major complications following esophagectomy, which we attribute to suboptimal physical fitness after chemoradiotherapy. Therefore, comprehensive assessment before esophagectomy is crucial for these patients.

Sarcopenia is a muscular disorder characterized by adverse changes in muscle composition. It is characterized by low muscle strength, reduced muscle quantity/quality, or diminished physical performance [31]. A

**Table 1** Characteristics of the participants

| Variables | Major complications | | | *p* value |
|---|---|---|---|---|
| | All ($N=72$) | No ($N=43$) | Yes ($N=29$) | |
| | *N* (%) | *N* (%) | *N* (%) | |
| ***Clinical information*** | | | | |
| Age, year | 57.7 ± 7.4 | 56.2 ± 7.4 | 59.9 ± 6.9 | 0.037 |
| Gender | | | | 0.268 |
| Female | 3 (4.2) | 3 (7.0) | 0 (0) | |
| Male | 69 (95.8) | 40 (93.0) | 29 (100) | |
| BW, kg | 63.2 ± 11.8 | 65.6 ± 13.1 | 59.6 ± 8.6 | 0.033 |
| Body mass index, kg/m$^2$ | 22.5 ± 3.3 | 23.2 ± 3.5 | 21.5 ± 2.8 | 0.039 |
| Albumin, g/dL | 4.1 ± 0.3 | 4.2 ± 0.3 | 4.1 ± 0.3 | 0.595 |
| Charlson comorbidity index | | | | 0.571 |
| 0 | 52 (72.2) | 30 (69.8) | 22 (75.9) | |
| >1 | 20 (27.8) | 13 (30.2) | 7 (24.1) | |
| Indication | | | | 0.488 |
| Planned esophagectomy | 54 (75.0) | 31 (72.1) | 23 (79.3) | |
| Salvage esophagectomy | 18 (25.0) | 12 (27.9) | 6 (20.7) | |
| Type of surgery | | | | 0.706 |
| Minimally invasive | 64 (88.9) | 39 (90.7) | 25 (86.2) | |
| Non-minimal invasive | 8 (11.1) | 4 (9.3) | 4 (13.8) | |
| Surgery procedure | | | | 1.000 |
| McKeown | 71 (98.6) | 42 (97.7) | 29 (100) | |
| Ivor-Lewis | 1 (1.4) | 1 (2.3) | 0 (0) | |
| Quality of resection | | | | 1.000 |
| R0 | 63 (87.5) | 38 (88.4) | 25 (86.2) | |
| Non-R0 | 9 (12.5) | 5 (11.6) | 4 (13.8) | |
| ypStage | | | | 0.470 |
| Early (0 + I + II) | 63 (87.5) | 39 (90.7) | 24 (82.8) | |
| Late (III + IV) | 9 (12.5) | 4 (9.3) | 5 (17.2) | |
| Blood loss, ml | 121.1 ± 85.4 | 114.1 ± 88.8 | 131.6 ± 80.6 | 0.398 |
| ICU stay, days | 2.5 ± 2.7 | 1.8 ± 1.0 | 3.4 ± 3.9 | 0.039 |
| Hospital stay, days | 18.0 ± 10.5 | 14.0 ± 5.7 | 24.0 ± 13.0 | < 0.001 |
| ***Cardiopulmonary fitness*** | | | | |
| $\dot{V}O_{2peak}$, mL/min | 1102.5 ± 253.3 | 1168.0 ± 259.5 | 1007.7 ± 214.5 | 0.008 |
| $\dot{V}O_{2peak}$/BW, mL/min/kg | 18.0 ± 3.2 | 18.4 ± 3.1 | 17.3 ± 3.2 | 0.150 |
| $\dot{V}O_{2peak}$/SMM, mL/min/kg | 42.0 ± 6.8 | 43.6 ± 6.3 | 40.0 ± 7.0 | 0.033 |
| AT, mL/min | 642.4 ± 132.9 | 665.8 ± 149.2 | 610.2 ± 100.2 | 0.068 |
| AT/BW, mL/min/kg | 10.5 ± 2.0 | 10.5 ± 2.1 | 10.5 ± 1.8 | 0.958 |
| AT/SMM, mL/min/kg | 24.6 ± 3.9 | 24.6 ± 3.8 | 24.6 ± 4.2 | 0.983 |
| $EqO_2$nadir | 30.3 ± 4.6 | 29.8 ± 4.3 | 31.0 ± 5.0 | 0.281 |
| $EqCO_2$nadir | 31.8 ± 4.6 | 31.3 ± 4.6 | 32.5 ± 4.6 | 0.275 |
| OUES, (L/min)/log(L/min) | 1.25 ± 0.28 | 1.26 ± 0.30 | 1.23 ± 0.26 | 0.696 |
| ***Body composition*** | | | | |
| FFM, kg | 47.5 ± 7.8 | 49.0 ± 8.9 | 45.5 ± 5.6 | 0.055 |
| FFM/BH$^2$, kg/m$^2$ | 16.9 ± 1.9 | 17.3 ± 2.1 | 16.5 ± 1.6 | 0.087 |
| LBM, kg | 45.2 ± 7.7 | 46.5 ± 8.4 | 43.5 ± 6.2 | 0.115 |
| LBM/BH$^2$, kg/m$^2$ | 9.3 ± 1. | 9.6 ± 1.3 | 9.1 ± 1.3 | 0.14 |
| SMM, kg | 26.5 ± 2.5 | 26.7 ± 2.4 | 26.2 ± 2.7 | 0.409 |
| SMM/BH$^2$, kg/m$^2$ | 16.1 ± 2.0 | 16.4 ± 2.0 | 15.7 ± 2.0 | 0.18 |
| ASMI, kg/m$^2$ | 7.3 ± 1.1 | 7.6 ± 1.2 | 6.9 ± 0.7 | 0.011 |
| PARA | 5.5 ± 0.8 | 5.6 ± 0.9 | 5.3 ± 0.6 | 0.116 |
| PALA | 5.4 ± 0.7 | 5.5 ± 0.8 | 5.2 ± 0.6 | 0.171 |
| PATR | 7.7 ± 1.4 | 7.8 ± 1.4 | 7.7 ± 1.4 | 0.747 |
| PARL | 5.5 ± 1.1 | 5.5 ± 1.1 | 5.4 ± 1.1 | 0.722 |

**Table 1** (continued)

| Variables | Major complications | | | p value |
|---|---|---|---|---|
| | All (N=72) | No (N=43) | Yes (N=29) | |
| | N (%) | N (%) | N (%) | |
| PALL | 5.2±1.1 | 5.2±1.1 | 5.3±1.1 | 0.817 |
| AVP, mL/min/m$^2$ | 306.8±68.7 | 329.1±68.8 | 278.2±57.9 | 0.003 |
| ***Muscle strength*** | | | | |
| HGS, kg | 36.9±7.9 | 38.0±8.5 | 35.3±7.0 | 0.168 |

Categorical data shown as N (%). Continuous data expressed as mean±standard deviation

Intergroup comparisons between major complication groups were performed with Student's t-tests or Mann Whitney U test for continuous variables and Pearson X2 or Fisher exact tests for categorical variables as appropriate

ASMI = appendicular skeletal muscle index; AT = ventilatory anaerobic threshold; AV P = ASMI-V$O_{2peak}$/SMM product; BH = body height; BW = body weight; Eq$O_2$nadir = ventilatory equivalent for $O_2$; Eq$CO_2$nadir = ventilatory equivalent for $CO_2$; FFM = fat free mass; HGS = hand grip strength; ICU = intensive care unit; LA = left arm; LBM = lean body mass; LL = left leg; OUES = oxygen uptake efficiency slope; PA = phase angle; RA = right arm; RL = right leg; SMM = skeletal muscle mass; TR = trunk; V$O_{2peak}$ = peak oxygen consumption

**Table 2** Postoperative major complication feature (N=29)

| Variables | N (%) |
|---|---|
| Complication Severity* | |
| Grade IIIa | 22 (75.9) |
| Grade IIIb | 5 (17.2) |
| Grade IVa | 2 (6.9) |
| Grade IVb | 0 (0) |
| Grade V | 0 (0) |
| Complication Groups** | |
| Pulmonary | 9 (31) |
| Gastrointestinal | 11 (37.9) |
| Thromboembolic | 1 (3.4) |
| Cardiac | 2 (6.9) |
| Urologic | 0 (0) |
| Infection | 4 (13.8) |
| Neurologic/Psychiatric | 17 (58.6) |
| Wound/Diaphragm | 0 (0) |
| Other complications | 4 (13.8) |

*Clavien-Dindo Classification was used for complication severity

**Complication groups were recorded according to guideline of Esophageal Complications Consensus Group

Pulmonary: pneumonia, pleural effusion, pneumothorax, atelectasis, respiratory failure, acute respiratory distress syndrome, acute aspiration, tracheobronchial injury

Gastrointestinal: esophagoenteric leak, conduit necrosis, ileus, small bowel obstruction, feeding tube complications, GI bleeding, delayed conduit emptying

Thromboembolic: DVT, PE, stroke

Cardiac: cardiac arrest, myocardial infarction, atrial dysrhythmia, ventricular dysrhythmia, congestive heart failure, pericarditis

Infection: wound infection, central IV line infection, intrathoracic/intra-abdominal abscess, generalized sepsis, other infections

Neurologic/Psychiatric: recurrent nerve injury, other neurologic injury, acute delirium, delirium tremens

Other complications: chyle leak, reoperation for reasons other than anastomotic leak or conduit necrosis, multiple organ dysfunction syndrome

meta-analysis involving 2,387 patients revealed that sarcopenic individuals had a higher risk of postoperative pneumonia and overall complications following esophagectomy [12]. In the current study, we found no statistically significant association between HGS and major complications, although there was a trend suggesting that patients with lower HGS tended to experience higher rates of major complications. Furthermore, although we observed a higher incidence of major postoperative complications in patients with lower ASMI and body mass index, this trend was evident in the univariate analysis but did not persist in the multivariate regression analysis. These findings suggest that sarcopenia alone may not be a robust predictor of postoperative complications in patients undergoing esophagectomy after chemoradiotherapy.

Suboptimal cardiopulmonary fitness have been also linked to adverse surgical outcomes [4, 5, 15, 16, 32, 33]. In major elective intra-abdominal surgeries, AT and VE/V$CO_2$ have been shown to predict postoperative complications, length of hospital stay, and mortality [32, 33]. Regarding esophagogastric cancer surgery, patients with low AT face a higher risk of developing postoperative cardiopulmonary complications [5, 15]. Nagamatsu et al. demonstrated that the rate of postoperative cardiopulmonary complications was 86% in ESCC patients with preoperative V$O_{2peak}$ levels < 699 mL/min/m² [4]. In our study, although patients with lower V$O_{2peak}$ levels showed a higher tendency to experience major postoperative complications. However, V$O_{2peak}$ did not emerge as significant in multivariate regression analysis. Thus, these conventional CPET variables, including V$O_{2peak}$ and AT, were not utilized as predictors of postoperative complications in our study.

Conventional CPET variables, such as V$O_{2peak}$/BW and AT/BW, are widely used. However, the interpretation of these results is influenced by body composition [34]. Given that SMM is the actual oxygen-consuming exercising tissues, SMM-normalized V$O_{2peak}$ is supposed to be a more accurate parameter for reflecting aerobic capacity [18]. To go further, we integrated markers from CPET and body composition to establish a novel marker: AVP. We found that major postoperative complications were more common in patients with lower V$O_{2peak}$/SMM and AVP. Furthermore, suboptimal AVP demonstrated

**Table 3** Full logistic regression model and parsimonious model after forward variable selection for major complications

| Variables | Univariable | | | Multivariable | | |
|---|---|---|---|---|---|---|
| | OR | 95% CI | *p* | OR | 95% CI | *p* |
| **Clinical information** | | | | | | |
| Age, year | 1.08 | (1.00, 1.16) | 0.042 | | | |
| BW, kg | 0.95 | (0.91, 1.00) | 0.039 | | | |
| Body mass index, kg/m$^2$ | 0.85 | (0.72, 1.00) | 0.044 | | | |
| Albumin, g/dL | 0.67 | (0.16, 2.86) | 0.589 | | | |
| Charlson comorbidity index | | | | | | |
| 0 | 1.36 | (0.47, 3.97) | 0.572 | | | |
| >1 | Ref. | | | | | |
| Indication | | | | | | |
| Planned esophagectomy | 1.48 | (0.48, 4.54) | 0.489 | | | |
| Salvage esophagectomy | Ref. | | | | | |
| Type of surgery | | | | | | |
| Minimally invasive | 0.64 | (0.15, 2.80) | 0.554 | | | |
| Non-minimal invasive | Ref. | | | | | |
| Surgery procedure | | | | | | |
| McKeown | NA | | | | | |
| Ivor-Lewis | Ref. | | | | | |
| Quality of resection | | | | | | |
| R0 | 0.82 | (0.20, 3.36) | 0.785 | | | |
| Non-R0 | Ref. | | | | | |
| ypStage | | | | | | |
| Early (0 + I + II) | 0.49 | (0.12, 2.02) | 0.324 | | | |
| Late (III + IV) | Ref. | | | | | |
| Blood loss, ml | 1.00 | (1.00, 1.01) | 0.404 | | | |
| ***Cardiopulmonary fitness*** | | | | | | |
| $\dot{V}O_{2peak}$, mL/min | 1.00 | (1.00, 1.00) | 0.011 | | | |
| $\dot{V}O_{2peak}$/BW, mL/min/kg | 0.89 | (0.76, 1.04) | 0.152 | | | |
| $\dot{V}O_{2peak}$/SMM, mL/min/kg | 0.92 | (0.84, 1.00) | 0.039 | | | |
| AT, ml/min | 1.00 | (0.99, 1.00) | 0.090 | | | |
| AT/BW, mL/min/kg | 1.01 | (0.79, 1.29) | 0.957 | | | |
| AT/SMM, mL/min/kg | 1.00 | (0.88, 1.14) | 0.983 | | | |
| $EqO_2$nadir | 1.06 | (0.95, 1.18) | 0.280 | | | |
| $EqCO_2$nadir | 1.06 | (0.95, 1.18) | 0.278 | | | |
| OUES | 1.00 | (1.00, 1.00) | 0.691 | | | |
| ***Body composition*** | | | | | | |
| FFM, kg | 0.94 | (0.88, 1.01) | 0.078 | | | |
| FFM/BH$^2$, kg/m$^2$ | 0.91 | (0.81, 1.02) | 0.092 | | | |
| LBM, kg | 0.95 | (0.88, 1.01) | 0.120 | | | |
| LBM/BH$^2$, kg/m$^2$ | 0.87 | (0.69, 1.08) | 0.201 | | | |
| SMM, kg | 0.92 | (0.74, 1.13) | 0.405 | | | |
| SMM/BH$^2$, kg/m$^2$ | 0.85 | (0.62, 1.15) | 0.291 | | | |
| ASMI, kg/m$^2$ | 0.52 | (0.30, 0.93) | 0.026 | | | |
| PARA | 0.59 | (0.30, 1.15) | 0.120 | | | |
| PALA | 0.60 | (0.28, 1.25) | 0.172 | | | |
| PATR | 0.94 | (0.65, 1.36) | 0.742 | | | |
| PARL | 0.92 | (0.57, 1.47) | 0.717 | | | |
| PALL | 1.06 | (0.67, 1.66) | 0.813 | | | |
| A$\dot{V}$P, mL/min/m$^2$ | 0.99 | (0.98, 1.00) | 0.005 | 0.99 | (0.98, 1.00) | 0.005 |
| ***Muscle strength*** | | | | | | |
| HGS, kg | 0.96 | (0.90, 1.02) | 0.168 | | | |

ASMI = appendicular skeletal muscle index; AT = ventilatory anaerobic threshold; AV *P* = ASMI-V$O_{2peak}$/SMM product; BH = body height; BW = body weight; $EqO_2$nadir = ventilatory equivalent for $O_2$; $EqCO_2$nadir = ventilatory equivalent for $CO_2$; FFM = fat free mass; HGS = hand grip strength; LA = left arm; LBM = lean body mass; LL = left leg; OUES = oxygen uptake efficiency slope; PA = phase angle; RA = right arm; RL = right leg; SMM = skeletal muscle mass; TR = trunk; V$O_{2peak}$ = peak oxygen consumption

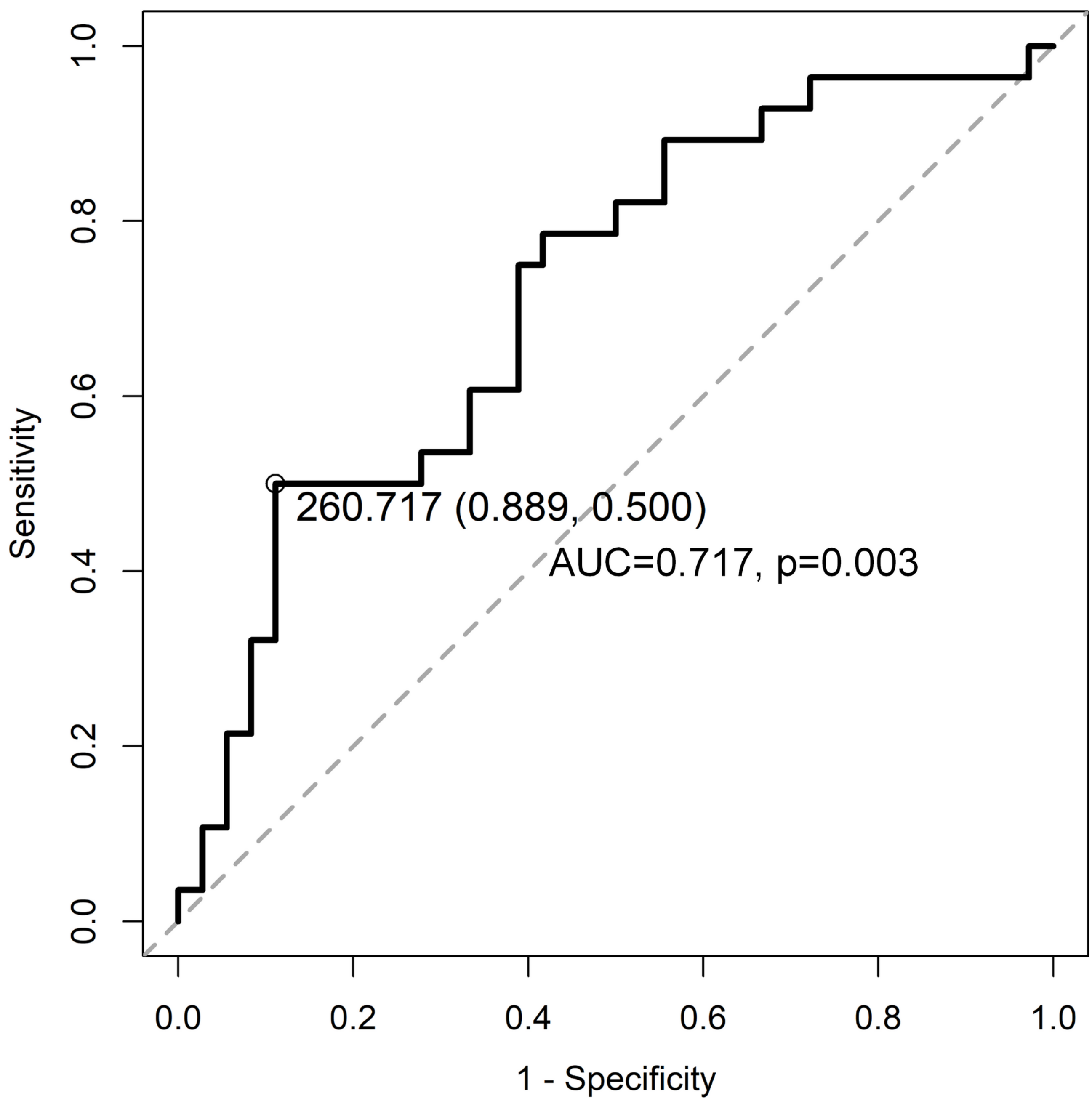


**Fig. 1** Receiver operator characteristic (ROC) curve to predict major complications from AV̇P, calculated as the product of appendicular skeletal muscle index (ASMI) and peak oxygen consumption ($\dot{V}O_{2peak}$) divided by the skeletal muscle mass (SMM). The area under the ROC curves was 0.717 (sensitivity = 0.5 and specificity = 0.889; *P* = 0.003)

a significant independent predictive value in identifying patients at risk for major post-esophagectomy complications. An AVP of 260.717 mL/min/m² was determined by receiver operative characteristics curve analysis as the optimal value for predicting major complications.

Previous studies have shown that individual predictors for post-esophagectomy complications were suboptimal, with an AUC of 0.62 for $VO_{2peak}$ and 0.60 for AT [5, 15]. In our study, we introduced AVP as a novel marker that integrates muscle mass and cardiorespiratory fitness, and demonstrated improved predictive performance with an AUC of 0.717. The high specificity and low false positive rate of AVP indicate that patients with low AVP are very likely to have major surgical complications. The relatively low sensitivity and high false negative rate of AVP suggest that the causes of surgical complications are multifactorial, with physical fitness being only one major contributing factor. Similarly, the predictive accuracy of the

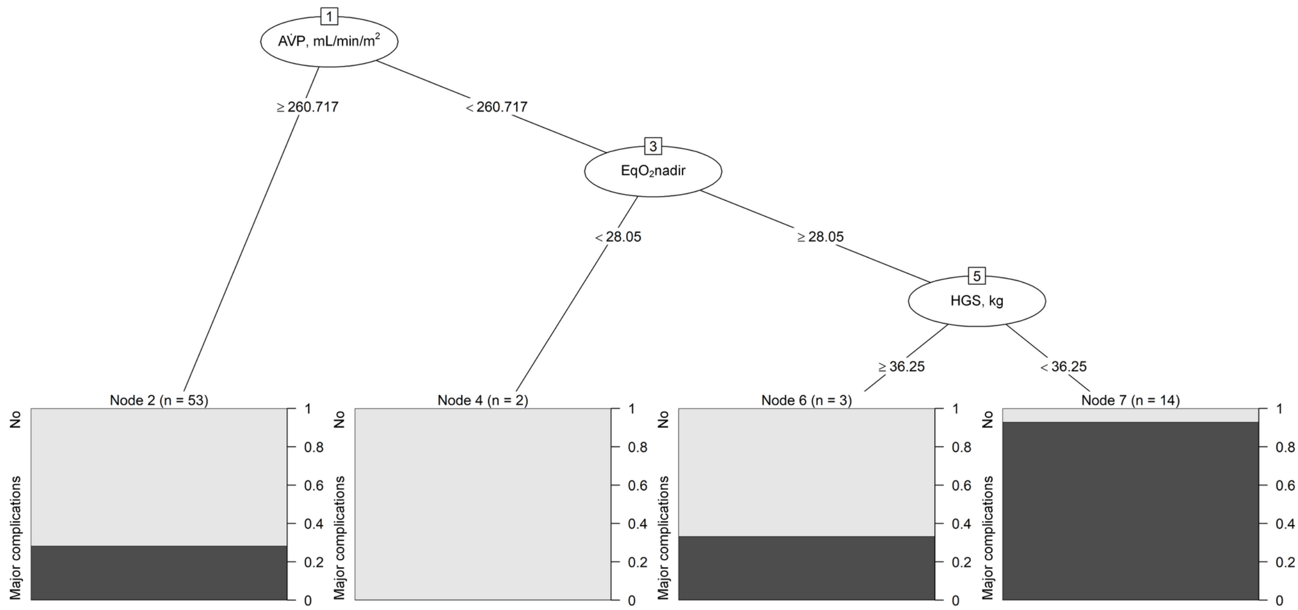


**Fig. 2** Decision-tree analysis for major complications post-esophagectomy

decision tree analysis demonstrated a comparable pattern. To the best of our knowledge, this is the first study to conduct a comprehensive assessment of physical fitness across multiple domains and to incorporate these parameters in predicting post-esophagectomy outcomes.

Prehabilitation before esophagectomy improved perioperative functional capacity and decreases respiratory complications [35, 36]. In the current study, the tree-based method identified that patients with AV̇P < 260.717 mL/min/m$^2$, $EqO_2$nadir > 28.05 and HGS < 36.25 kg were more likely to have major postoperative complications. Exercise training induces systemic adaptation of the oxygen transport chain, primarily within the skeletal muscle, which may result in an increase in $\dot{V}O_{2peak}$/SMM ratio [37] Therefore, enhanced exercise training for those with inadequate physical fitness is likely to decrease overall postoperative complications.

A comprehensive preoperative physical fitness assessment can identify individuals at risk of major complications following esophagectomy. In the current era of promoting Enhanced Recovery After Surgery and amidst limited medical resources, we believe prehabilitation should be targeted at a sub-population of patients with high operative risk, rather than providing preoperative exercise training universally.

This study has limitations. First, as squamous cell carcinoma is the predominant esophageal pathology in our country, we included only patients with ESCC, limiting the applicability of our results to other pathologies, particularly in regions where adenocarcinoma is more common. Second, although the sample size of this study is relatively small, we employed three distinct statistical approaches—multivariate regression, ROC curve analysis, and tree-based learning methods—to confirm the association between physical fitness and surgical complications, demonstrating a consistent trend and acceptable predictive accuracy. Further prospective validation studies with larger patient cohorts are necessary to strengthen these findings.

## Conclusions

Complications after esophagectomy are common in patients who undergo chemoradiotherapy. Preoperative assessment of AV̇P, a composite indicator that simultaneously reflects muscle mass and cardiorespiratory fitness, help identify individuals at risk for major postoperative complications. Additionally, patients with low AV̇P, high $EqO_2$nadir, and low HGS are at a very high risk of experiencing postoperative complications.

**Abbreviations**

| | |
|---|---|
| ASMI | Appendicular skeletal muscle index |
| AT | Anaerobic threshold |
| AV̇P | ASMI–$\dot{V}O_{2peak}$/SMM product |
| BH | Bbody height |
| BW | Body weight |
| CPET | Cardiopulmonary exercise testing |
| dCRT | Definitive chemoradiotherapy |
| ESCC | Esophageal squamous cell carcinoma |
| FFM | Fat-free mass |
| HGS | Hand grip strength |
| LBM | Lean body mass |
| nCRT | Neoadjuvant chemoradiotherapy |
| OUES | Oxygen uptake efficiency slope |
| PA | Phase angle |
| $PETCO_2$ | end-tidal tensions of carbon dioxide |
| $PETO_2$ | End-tidal tensions of oxygen |
| RPM | Revolutions per minute |
| SMM | Skeletal muscle mass |
| V̇E | Minute ventilation |
| $\dot{V}CO_2$ | Carbon dioxide production |

| | |
|---|---|
| $\dot{V}O_2$ | Oxygen consumption |
| $\dot{V}O_{2peak}$ | Peak oxygen consumption |
| $\dot{V}E/\dot{V}O_2$ | Ventilatory equivalent for oxygen |
| $\dot{V}E/\dot{V}CO_2$ | Ventilatory equivalent for carbon dioxide |

## Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13102-025-01158-7.

Supplementary Material 1

**Acknowledgements**

The authors acknowledge the statistical assistance provided by the Clinical Trial Center, Chang Gung Memorial Hospital, Taoyuan.

**Author contributions**

Study conception and design: Chien-Hung Chiu, Yin-Kai Chao, Wei-Hsun Chen, Yun-Hen Liu, Ya-Tzu Tsao, Yu-Ling Chang, and Shu-Chun Huang; data collection: Chien-Hung Chiu, Yin-Kai Chao and Shu-Chun Huang; analysis and interpretation of results: Chien-Hung Chiu, Wei-Yang Chang, Lan-Yan Yang and Shu-Chun Huang; draft manuscript preparation: all authors. All authors reviewed the results and approved the final version of the manuscript.

**Funding**

This work was supported by Chang Gung Memorial Hospital (CORPG3J0621, CMRPVVK0111-3 and CMRPVVL0121-3), National Science and Technology Council, Taiwan (MOST 109-2314-B-182 A-074-MY3, 113-2314-B-182A-094-) and Ministry of Health and Welfare of Taiwan (MOST 108-2314-B-182 A-061 and MOHW113-TDU-B-212-114010).

**Data availability**

The datasets generated andanalysedduring the current study are available from the corresponding author on reasonable request.

## Declarations

**Ethics approval and consent to participate**

All procedures involving human participants were carried out in compliance with the Declaration of Helsinki. This study was approved by the Chang Gung Medical Foundation Institutional Review Board (IRB No. 201802337A3). The informed consent of the participants was obtained prior to the physical fitness evaluation.

**Consent for publication**

Not applicable.

**Competing interests**

The authors declare no competing interests.

**Author details**

[1]Division of Thoracic Surgery, Chang Gung Memorial Hospital at Linkou, Taoyuan, Taiwan
[2]Clinical Trial Center, Chang Gung Memorial Hospital at Linkou, Taoyuan, Taiwan
[3]Division of Clinical Trial, Department of Medical Research, Taichung Veterans General Hospital, Taichung, Taiwan
[4]Department of Medical Nutrition Therapy, Chang Gung Memorial Hospital at Linkou, Taoyuan, Taiwan
[5]Chang Gung University, Taoyuan, Taiwan
[6]Department of Physical Medicine and Rehabilitation, New Taipei Municipal Tucheng Hospital, Chang Gung Memorial Hospital, New Taipei City 333423, Taiwan
[7]Department of Physical Medicine & Rehabilitation, Chang Gung Memorial Hospital at Linkou, Taoyuan, Taiwan
[8]College of Medicine, Chang Gung University, Taoyuan, Taiwan

Received: 5 November 2024 / Accepted: 15 April 2025
Published online: 30 April 2025

**References**

1. Then EO, Lopez M, Saleem S, et al. Esophageal cancer: an updated surveillance epidemiology and end results database analysis. World J Oncol. 2020;11(2):55–64.
2. van Hagen P, Hulshof MC, van Lanschot JJ, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med. 2012;366(22):2074–84.
3. Swisher SG, Moughan J, Komaki RU, et al. Final results of NRG oncology RTOG 0246: an Organ-Preserving selective resection strategy in esophageal Cancer patients treated with definitive chemoradiation. J Thorac Oncology: Official Publication Int Association Study Lung Cancer. 2017;12(2):368–74.
4. Nagamatsu Y, Shima I, Yamana H, et al. Preoperative evaluation of cardiopulmonary reserve with the use of expired gas analysis during exercise testing in patients with squamous cell carcinoma of the thoracic esophagus. J Thorac Cardiovasc Surg. 2001;121(6):1064–8.
5. Yanni F, Moyes LH, McCaffer CJ, et al. Cardiopulmonary exercise testing as a predictor of complications. Ann R Coll Surg Engl. 2014;96(1):86.
6. Klevebro F, Elliott JA, Slaman A, et al. Cardiorespiratory comorbidity and postoperative complications following esophagectomy: a European multicenter cohort study. Ann Surg Oncol. 2019;26(9):2864–73.
7. Low DE, Kuppusamy MK, Alderson D, et al. Benchmarking complications associated with esophagectomy. Ann Surg. 2019;269(2):291–8.
8. Sesti J, Almaz B, Bell J, et al. Impact of postoperative complications on long-term survival after esophagectomy in older adults: A SEER-Medicare analysis. J Surg Oncol. 2021;124(5):751–66.
9. Fransen LFC, Verhoeven RHA, Janssen T et al. The association between postoperative complications and long-term survival after esophagectomy: a multicenter cohort study. Dis Esophagus: Official J Int Soc Dis Esophagus / ISDE. 2023;36(6).
10. Caspersen CJ, Powell KE, Christenson GM. Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research. Public Health Rep (Washington DC: 1974). 1985;100(2):126–31.
11. Wilder RP, Greene JA, Winters KL, et al. Physical fitness assessment: an update. J long Term Eff Med Implants. 2006;16(2):193–204.
12. Wang PY, Xu LD, Chen XK, et al. Sarcopenia and Short-Term outcomes after esophagectomy: A Meta-analysis. Ann Surg Oncol. 2020;27(8):3041–51.
13. Colcord ME, Benbow JH, Trufan S, et al. Preoperative muscle strength is a predictor of outcomes after esophagectomy. J Gastrointest Surg. 2021;25(12):3040–8.
14. Feeney C, Reynolds JV, Hussey J. Preoperative physical activity levels and postoperative pulmonary complications post-esophagectomy. Dis Esophagus: Official J Int Soc Dis Esophagus / ISDE. 2011;24(7):489–94.
15. Forshaw MJ, Strauss DC, Davies AR, et al. Is cardiopulmonary exercise testing a useful test before esophagectomy? Ann Thorac Surg. 2008;85(1):294–9.
16. Benington S, Bryan A, Milne O, et al. CPET and cardioesophagectomy: A single centre 10-year experience. Eur J Surg Oncol. 2019;45(12):2451–6.
17. Sanada K, Kearns CF, Kojima K, et al. Peak oxygen uptake during running and arm cranking normalized to total and regional skeletal muscle mass measured by magnetic resonance imaging. Eur J Appl Physiol. 2005;93(5–6):687–93.
18. Beekley MD, Abe T, Kondo M, et al. Comparison of normalized maximum aerobic capacity and body composition of sumo wrestlers to athletes in combat and other sports. J Sports Sci Med. 2006;5(Cssi):13–20.
19. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg. 2004;240(2):205–13.
20. Janssen I, Heymsfield SB, Baumgartner RN, et al. Estimation of skeletal muscle mass by bioelectrical impedance analysis. J Appl Physiol (Bethesda Md: 1985). 2000;89(2):465–71.
21. Ohmae N, Yasui-Yamada S, Furumoto T, et al. Muscle mass, quality, and strength; physical function and activity; and metabolic status in cachectic patients with head and neck cancer. Clin Nutr ESPEN. 2023;53:113–9.
22. Huang SC, Lee CH, Hsu CC, et al. Prediction for blood lactate during exercise using an artificial intelligence-Enabled electrocardiogram: a feasibility study. Front Physiol. 2023;14:1253598.
23. Huang SC, Hsu CC, Fu TC, et al. Application of stepper in cardiopulmonary exercise test for patients with hemiplegia. Med (Baltim). 2020;99(28):e21058.
24. Huang SC, Hsu CC, Fu TC, et al. Stepper-Based training improves Monocyte-Platelet aggregation and thrombin generation in nonambulatory hemiplegic patients. Med Sci Sports Exerc. 2022;54(5):821–9.

25. Huang SC, Yeh CH, Hsu CC et al. Trainability for cardiopulmonary fitness is low in patients with peripheral artery disease. Eur J Cardiovasc Nurs. 2023;23(2):127-136.
26. Sauerbrei W, Schumacher M. A bootstrap resampling procedure for model building: application to the Cox regression model. Stat Med. 1992;11(16):2093–109.
27. Zhang Z. Variable selection with Stepwise and best subset approaches. Annals Translational Med. 2016;4(7):136.
28. Sinclair R, Navidi M, Griffin SM, et al. The impact of neoadjuvant chemotherapy on cardiopulmonary physical fitness in gastro-oesophageal adenocarcinoma. Ann R Coll Surg Engl. 2016;98(6):396–400.
29. Chen X, Du M, Tang H, et al. Comparison of pulmonary function changes between patients receiving neoadjuvant chemotherapy and chemoradiotherapy prior to minimally invasive esophagectomy: a randomized and controlled trial. Langenbeck's archives of surgery /. Dtsch Gesellschaft fur Chirurgie. 2022;407(7):2673–80.
30. Hagens ERC, Feenstra ML, van Egmond MA, et al. Influence of body composition and muscle strength on outcomes after multimodal oesophageal cancer treatment. J Cachexia Sarcopenia Muscle. 2020;11(3):756–67.
31. Cruz-Jentoft AJ, Bahat G, Bauer J, et al. Sarcopenia: revised European consensus on definition and diagnosis. Age Ageing. 2019;48(1):16–31.
32. Snowden CP, Prentis JM, Anderson HL, et al. Submaximal cardiopulmonary exercise testing predicts complications and hospital length of stay in patients undergoing major elective surgery. Ann Surg. 2010;251(3):535–41.
33. Wilson RJ, Davies S, Yates D, et al. Impaired functional capacity is associated with all-cause mortality after major elective intra-abdominal surgery. Br J Anaesth. 2010;105(3):297–303.
34. Heileson JL, Papadakis Z, Ismaeel A et al. The benefits of utilizing total body composition as a predictor of cardiorespiratory fitness based on age: A pilot study. Int J Environ Res Public Health. 2022;19(9).
35. Minnella EM, Awasthi R, Loiselle SE, et al. Effect of exercise and nutrition prehabilitation on functional capacity in esophagogastric Cancer surgery: A randomized clinical trial. JAMA Surg. 2018;153(12):1081–9.
36. Akiyama Y, Sasaki A, Fujii Y, et al. Efficacy of enhanced prehabilitation for patients with esophageal cancer undergoing esophagectomy. Esophagus: Official J Japan Esophageal Soc. 2021;18(1):56–64.
37. LeMaitre JP, Harris S, Hannan J, et al. Maximum oxygen uptake corrected for skeletal muscle mass accurately predicts functional improvements following exercise training in chronic heart failure. Eur J Heart Fail. 2006;8(3):243–8.

## Publisher's note