Analysis of the associated factors for severe weight loss after minimally invasive McKeown esophagectomy

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Keywords
Esophageal neoplasm; esophagectomy; risk factor; weight loss.

Abstract
Background: This study investigated the risk factors for severe weight loss (SWL) within one year after minimally invasive McKeown esophagectomy.

Methods: Esophageal cancer patients who underwent McKeown esophagectomy between January and July 2017 were prospectively enrolled. Preoperative body weight (PBW) was chosen as the initial body weight.

Results: Forty-four patients were enrolled and successfully followed up for one year. Median weight loss was 7.4% (quartile: 5.3–8.1%) and 12.6% (quartile: 8.8–17.7%) four weeks and one year after surgery, respectively. Accelerated weight loss occurred during the first two weeks after discharge, with median weight loss of 5.6% (quartile: 4.2–7.1%). Multivariable analysis showed that age ≥ 70 years (odds ratio [OR] 7.65; P = 0.030), preoperative sarcopenia (OR 7.18; P = 0.030), the first surgery in the daily schedule (OR 6.87; P = 0.032) and vocal cord paralysis (OR 12.30; P = 0.046) were independent risk factors for short-term (4 weeks) SWL (> 7.5% PBW), while an American Society of Anesthesiologists score of 3–4 (OR 7.65; P = 0.030), preoperative sarcopenia (OR 7.18; P = 0.030), the first surgery in the daily schedule (OR 6.87; P = 0.032) and vocal cord paralysis (OR 12.30; P = 0.046) were independent risk factors for long-term (1 year) SWL (> 13.0% PBW) after esophagectomy. Postoperative symptoms of insomnia, appetite loss, dysphagia, eating difficulties, and taste issues were also related to SWL.

Conclusions: In esophageal cancer patients who have undergone esophagectomy, the first two weeks after hospital discharge is a key period for nutrition intervention. Patients with associated factors for SWL require postoperative nutrition support.

Introduction
Esophageal cancer is the 11th most common cancer and the sixth most common cause of perioperative mortality worldwide.1 Esophagectomy or neoadjuvant therapy followed by esophagectomy is the critical therapy for this malignant tumor.2 Postoperative weight loss is a common problem in patients with esophageal cancer, and severe weight loss (SWL) is closely related to poor prognosis.3,4 However, the degrees of postoperative body weight changes and the risk factors for SWL have not been identified.5,6 The purpose of this study was to prospectively observe body weight changes in patients who underwent minimally invasive McKeown esophagectomy (McKeown-MIE) to explore the regularity of body weight changes and to analyze the risk factors leading to SWL.

Methods
Study design and patients
Patients who underwent McKeown-MIE as initial treatment from January to July 2017 at the Department of...
Thoracic Surgery, Affiliated Cancer Hospital of Zhengzhou University were prospectively included. The inclusion criteria were: (i) age 18–80 years, (ii) preoperative diagnosis of esophageal cancer, and (iii) good cardiopulmonary function that was evaluated to tolerate surgery. The exclusion criteria were: (i) a preoperative examination that showed that the tumor had invaded into surrounding tissues, lymph nodes, and important organ metastases; (ii) esophagectomy after neoadjuvant therapy; and (iii) a history of previous gastrointestinal malignancies, rheumatic immune disease, or inflammatory bowel disease.

This study met the ethical standards of the Affiliated Cancer Hospital of Zhengzhou University Ethics Committee. All patients signed informed consent prior to their inclusion in the study.

Data collection

Patients’ body composition was assessed at 7:00 a.m. on the operation day using multifrequency bioelectrical impedance with eight tactile electrodes (BCA-IB Body Component Analyzer, Tsinghua Tongfang Co. Ltd., Beijing, China). Various parameters, including the fat-free mass (FFM), skeletal muscle, and fat mass were automatically measured. Preoperative sarcopenia (depletion of skeletal muscle mass) was diagnosed as skeletal muscle below the normal range of the Chinese population provided by the BCA-IB Body Component Analyzer. Body mass index (BMI) was calculated as the weight in kilograms divided by the height in square meters (kg/m²), and was classified according to the Asian-specific BMI cut-off. Preoperative performance status was assessed using Eastern Cooperative Oncology Group performance status (ECOG-PS) and Karnofsky Performance Status (KPS).

For clinical data collection, the included patients were staged before and after surgery according to the eighth edition American Joint Committee on Cancer/Union for International Cancer Control Tumor Node Metastasis (TNM) Classification. Preoperative clinical staging was based on esophagography, endoscopy, endoscopic ultrasonography (EUS), and computed tomography (CT) of the chest and upper abdomen. A biopsy of the cervical lymph nodes and positron emission tomography were used to determine the clinical stage if needed. Postoperative complications were defined according to the international consensus on the standardization of data collection for complications associated with esophagectomy produced by the Esophagectomy Complications Consensus Group, and graded according to the Clavien–Dindo classification.

To measure and follow-up body weight, weight was measured in the morning after defecation on an empty stomach with a single layer of clothes. The figures were accurate to 0.1 kg, and the average of three consecutive measurements was used as the final measurement. The preoperative body weight (PBW) was measured on the morning of the operation day. Patients’ body weight was measured every three to four days over four weeks, every week from 5 to 12 weeks, and every two weeks from 13 to 56 weeks after surgery. Follow-up was arranged by telephone, and details were explained to patients ahead of time to ensure the accuracy of weight measurement. Data were collected by email.

Surgery and recovery

All patients underwent McKeown-MIE with a two-field lymph node dissection, and anastomosis was performed to sew up the gastric conduit to the distal esophagus, as previously described. All operations were performed by one surgical team led by one author. The “non-tube no fasting” fast-track program was the first choice for all patients, except when symptoms of aspiration or the appearance of serious complications arose, at which time oral feeding was delayed or ceased. Normally the nutrition provided by intravenous approach decreases with the increase in oral feeding, and is removed on the fourth day after surgery. The need for adjuvant therapy after surgery is determined by the pathology stage and the patients’ aspiration and nutrition status.

Quality of life

The European Organization for Research and Treatment of Cancer questionnaires C30 and OES18 were used to assess quality of life (QOL) at baseline (1 week before surgery) and 2, 4, 8, 12, and 24 weeks after surgery. Questionnaire scales related to intake and body weight recovery were analyzed to investigate the association between QOL and postoperative weight loss. Baseline data were collected in the hospital and follow-up assessments were arranged by telephone and performed by mail, with one telephone reminder if required.

Statistical analysis

The categorical data are presented as the frequency (percentage), and the continuous data are presented as the mean ± standard deviation or the medians and interquartile ranges according to the results of the Shapiro–Wilk test. QOL data are presented as mean ± standard deviation. Comparisons between the groups were performed using the t-test for independent samples in cases of normal data distribution and the Mann–Whitney U test in cases of non-normal data distribution. Univariate and multivariate logistic regression models were used to analyze the risk factors. The continuous variables were grouped according to the mean, median, and practical significance to be included in risk.
factor analysis. A two-tailed \( P \) value of < 0.05 was considered statistically significant. All analyses were conducted using SPSS version 17.0 (SPSS Inc., Chicago, IL, USA).

**Results**

A total of 45 patients met the study criteria during the study period. All of the patients were included in the study after signing informed consent, and the baseline data collection rate was 100%. One patient dropped out of the study three weeks after surgery, and 44 patients were followed up for one year. No perioperative or follow-up death occurred and no tumor recurrence or metastasis.

**Table 1 Basic patient characteristics and clinical data**

| Variables                              | Values                           |
|----------------------------------------|----------------------------------|
| Demographic data, N (%)                |                                 |
| Age (years), mean ± SD                 | 65.7 ± 7.7                       |
| Gender (male)                          | 26 (59.1)                        |
| Brinkman index (≥ 100)                 | 18 (40.9)                        |
| Alcohol index (≥ 2000)                 | 7 (15.9)                         |
| Preoperative morbidity, N (%)          |                                 |
| Diabetes                               | 3 (6.8)                          |
| Cardiovascular disease                 | 11 (25.0)                        |
| COPD                                   | 4 (9.1)                          |
| Cerebral vascular disease              | 6 (13.6)                         |
| ASA score 3–4                          | 19 (43.2)                        |
| ECOG PS score > 1 point                | 11 (25)                          |
| KPS score < 90%                        | 13 (29.5)                        |
| Preoperative nutrition, mean ± SD      |                                 |
| Body weight (kg)                       | 66.1 ± 7.8 (male); 54.9 ± 5.7 (female) |
| FFM (kg)                               | 49.9 ± 6.2 (male); 37.7 ± 3.4 (female) |
| Fat mass (kg)                          | 16.3 ± 4.2 (male); 17.3 ± 3.5 (female) |
| Weight loss in last 3 months (%)       | 4.3 ± 0.5                        |
| BMI (kg/m²)                            | 23.1 ± 2.3                       |
| Preoperative sarcopenia, N (%)         | 18 (40.9)                        |
| Tumor characteristics, N (%)          |                                 |
| Location (upper/middle/lower)          | 2 (4.5)/29 (65.9)/13 (29.5)       |
| cTNM (0–II–III)                        | 19 (43.2)/25 (56.8)              |
| pTNM (0–III)                           | 34 (77.3)/10 (22.7)              |
| Histological type (SCC/AC)             | 19 (43.2)/25 (56.8)              |
| Differentiation (well/moderately/poorly)| 2 (2.3%)§                      |
| Tumor length (mm), mean ± SD           | 47.5 ± 19.3                      |
| Adjuvant therapy, N (%)                | 1 (2.3%)§                       |

†Brinkman index = daily count of cigarettes × smoking years. ‡Alcohol index = daily alcohol consumption (g) × drinking years. §One patient underwent postoperative chemotherapy. AC, adenocarcinoma; ASA, American Society of Anesthesiologists; BMI, body mass index; COPD, chronic obstructive pulmonary disease; ECOG PS, Eastern Cooperative Oncology Group performance status; FFM, fat-free mass; KPS, Karnofsky Performance Status; pTNM, pathological tumor node metastasis; SCC, squamous cell carcinoma; SD, standard deviation.

**Data characteristics**

The patient characteristics are shown in Table 1. There were 26 (59.1%) men and 18 (40.9%) women at an average age of 65.7 ± 7.7. Squamous cell carcinoma (SCC) dominated the pathological types, with 43 (97.7%) patients. The perioperative parameters and postoperative complications are shown in Table 2. In total, 31 (70.5%) patients successfully completed the fast-track program, oral feeding was delayed to the fourth day after surgery in 9 (20.5%) patients because of aspiration, 3 (6.8%) patients did not complete the fast-track program and underwent gastrointestinal decompression because of severe stomach distention, and 1 (2.3%) patient returned to the intensive care unit and oral feeding was stopped because of acute respiratory distress syndrome. Among the 9 (20.5%) patients with symptoms of aspiration, 7 (15.9%) patients developed vocal cord paralysis (VCP) because of the operation, 1 (2.3%) patient developed VCP because of

**Table 2 Perioperative parameters and postoperative complications**

| Variables                              | Values                           |
|----------------------------------------|----------------------------------|
| Operative parameters                   |                                 |
| Operation order (first/others), N (%)   | 21 (47.7)/23 (52.3)              |
| Operative time (minutes), mean ± SD    | 185.0 ± 38.0                     |
| Blood loss (mL), mean ± SD             | 97.5 ± 30.2                      |
| Curability (R0/R1-2), N (%)            | 44 (100)/0                      |
| Postoperative complications, N (%)     |                                 |
| Cardiac dysrhythmia                    | 5 (11.4)                        |
| Pneumonia                              | 4 (9.1)                          |
| Pleural effusion                       | 4 (9.1)                          |
| ARDS                                   | 1 (2.3)                          |
| VCP                                    | 7 (15.9)                         |
| Wound infection                        | 2 (4.5)                          |
| Pulmonary embolus                      | 1 (2.3)                          |
| Anastomotic leakage                    | 0 (0)                            |
| Other complications                    | 2 (4.5)                          |
| Overall complications†                 | 13 (29.5)                        |
| Recurrent need of ICU treatment        | 2 (4.5)                          |
| In-hospital mortality                  | 0 (0)                            |
| Clavien–Dindo classification           | 9 (20.5)/4 (9.1)                 |
| Fast track program, N (%)              | 31 (70.5)                        |
| Length of postoperative stay, mean ± SD| 9.0 ± 3.2                        |
| Perioperative serum parameters, mean ± SD|                                 |
| Preoperative serum prealbumin (mg/L)   | 203.3 ± 63.6                     |
| Preoperative serum albumin (g/L)       | 43.7 ± 3.9                       |
| POD1 serum prealbumin (mg/L)           | 148.0 ± 33.2                     |
| POD1 serum albumin (g/L)               | 33.2 ± 3.8                       |
| POD7 serum prealbumin (mg/L)†          | 109.3 ± 27.2                     |
| POD7 serum albumin (g/L)†              | 36.6 ± 3.8                       |

†Defined as the presence of one or more of the complications listed above in a single patient. ‡Data was missing for three patients. ARDS, acute respiratory distress syndrome; ICU, intensive care unit; POD, postoperative day; SD, standard deviation; VCP, vocal cord paralysis.
Weight loss after esophagectomy

The preoperative average weight of the 44 patients was 61.5 ± 8.9 kg, and this value decreased to 55.1 ± 8.8 kg one year after surgery. Using the PBW as a reference, the changes in the body weight in each period after surgery are presented in Table 3. The median and quartile weight loss rates at one year were 12.6% (8.8–17.7%), and the maximum weight loss rate within the first year was 13% (9.5–17.7%). We also drew a line chart to describe patient’s weekly body weight changes after surgery (Fig. 1). We noticed that the patients’ weight loss was concentrated within four weeks after surgery, while the change in body weight in the first week was minor. Considering that the length of the hospitalization was 9.0 ± 3.2 days, we speculated that the patients underwent accelerated weight loss in the short term after discharge. Subsequently, we analyzed the changes in body weight in and out of the hospital, with the discharge time as the observation point (Table 3). We observed that accelerated weight loss occurred in the first two weeks after discharge, with a weight loss rate of 5.6% (4.2–7.1%), contributing to 46.4% ± 16.7% of the maximum weight loss within one year after surgery.

**Risk factors for short-term (4 weeks) severe weight loss after esophagectomy**

The patients’ average weight loss rate at four weeks after surgery was 7.6% ± 3.8%, with a median weight loss rate of 7.4% (quartile: 5.3–8.1%). Therefore, a weight loss rate > 7.5% was chosen as the criteria to recognize SWL at four weeks after surgery. Twenty (45.5%) patients were assigned to the SWL group and 24 (54.5%) to a normal weight loss (NWL) group. The outcomes of the univariate logistic regression models are presented in Table 4. Age ≥ 70 years (odds ratio [OR] 4.50; *P* = 0.022), ECOG PS > 1 (OR 9.00; *P* = 0.011), KPS < 90% (OR 5.73; *P* = 0.022), preoperative sarcopenia (OR 7.06; *P* = 0.004), a poorly differentiated tumor (OR 15.33; *P* = 0.047), the first surgery in the daily schedule (OR 3.71; *P* = 0.040), VCP (OR 15.33; *P* = 0.022), and a previous recurrent nerve injury caused by preoperative cervical lymph node biopsy, and 1 (2.3%) patient developed VCP as a result of a previous recurrent nerve injury caused by thyroidectomy.

| Time          | Weight loss (%) | Contributing to 1-year MWL (%) |
|---------------|----------------|-------------------------------|
| 1st week AO   | 0.2 (0.7, 0)   | 2.6 ± 4.7                     |
| 2nd week AO   | 3.4 (5.2, 2.4) | 29.1 ± 13.4                   |
| 3rd week AO   | 2.2 (3.2, 1.3) | 17.5 ± 9.7                    |
| 4th week AO   | 0.6 (1.4, 0.3) | 7.0 ± 7.7                     |
| 1–4 weeks AO  | 7.4 (1.1, 0.3) | 56.3 ± 18.0                   |
| 1–12 weeks AO | 9.8 (1.1, 5.9) | 68.9 ± 18.3                   |
| 1–24 weeks AO | 10.6 (1.4, 9.1)| 81.0 ± 24.6                   |
| 1 year AO     | 12.6 (17.7, 8.8)| 100                          |
| In-hospital   | 0.3 (0.8, 0.1) | 2.5 ± 5.7                     |
| 1st week AD   | 3.6 (5.5, 2.5) | 34.3 ± 15.9                   |
| 2nd week AD   | 1.3 (2.6, 1.0) | 14.7 ± 9.5                    |
| 3rd week AD   | 0.5 (1.2, 0.3) | 6.7 ± 7.9                     |
| 4th week AD   | 0.2 (6.0, 0.0) | 2.9 ± 4.4                     |
| 1–2 weeks AD  | 5.6 (7.1, 4.2) | 46.4 ± 16.7                   |
| 1–4 weeks AD  | 7.1 (7.9, 5.4) | 55.8 ± 17.8                   |

†Preoperative body weight was chosen as initial body weight. †Negative values (−) mean weight loss; positive values (+) mean weight gain. §Calculated as the weight loss during the corresponding period divided by the maximum weight loss (MWL) within the first year after surgery; weight gain was noted as 0%. AD, after discharge; AO, after operation; SD, standard deviation.
Table 4 Outcomes of univariate analysis of the risk factors for SWL

| Variables                              | 4W SWL (n = 20)† | 1-year SWL (n = 21)‡ |
|----------------------------------------|------------------|---------------------|
|                                        | OR (95% CI)      | P                   | OR (95% CI)     | P                   |
| Demographic data                       |                  |                     |                  |                     |
| Age ≥ 70 years                         | 4.50 (1.24–16.28)| 0.022               | 1.71 (0.51–5.73)| 0.389               |
| Gender (male)                          | 0.73 (0.22–2.45) | 0.615               | 1.25 (0.37–4.17)| 0.717               |
| Body mass index ≥ 100                  | 0.43 (0.12–1.49) | 0.183               | 0.80 (0.24–2.67)| 0.717               |
| Alcohol index ≥ 2000                   | 0.42 (0.07–2.46) | 0.338               | 0.79 (0.16–4.04)| 0.779               |
| Preoperative morbidity                 |                  |                     |                  |                     |
| Diabetic                               | 3 (17): (0.22)   | 0.300               | 0.53 (0.04–6.25)| 0.610               |
| Cardiovascular disease                 | 2.49 (0.66–11.06)| 0.170               | 2.38 (0.58–9.72)| 0.229               |
| COPD                                   | 4.06 (0.39–42.49)| 0.242               | 3.67 (0.35–38.35)| 0.278               |
| Cerebral vascular disease              | 2.75 (0.45–16.90)| 0.275               | 6 (15): (0.23)* | 0.020               |
| ASA score 3–4                          | 2.44 (0.72–8.31) | 0.153               | 4.60 (1.28–16.58)| 0.020               |
| ECOG-PS score > 1 point                | 9.00 (1.65–49.00)| 0.011               | 2.38 (0.58–9.72)| 0.229               |
| KPS score < 90%                        | 5.73 (1.28–25.58)| 0.022               | 0.18 (0.47–6.90)| 0.391               |
| Preoperative nutrition                 |                  |                     |                  |                     |
| High body weight                       | 1.40 (0.42–6.42) | 0.581               | 3.72 (1.06–12.98)| 0.040               |
| High FFM†                              | 1.71 (0.52–5.67) | 0.379               | 7.08 (1.88–26.72)| 0.004               |
| High fat mass                          | 0.82 (0.25–2.69) | 0.741               | 1.43 (0.44–4.69)| 0.555               |
| Weight loss in last 3 months ≥ 5%      | 1.62 (0.46–5.68) | 0.452               | 2.13 (0.60–7.57) | 0.245               |
| BMI ≥ 23 (kg/m²)                       | 0.87 (0.26–2.89) | 0.824               | 2.18 (0.64–7.40) | 0.211               |
| Preoperative sarcopenia                | 7.06 (1.84–27.14)| 0.004               | 2.51 (0.73–8.64)| 0.143               |
| Tumor characteristics                  |                  |                     |                  |                     |
| Location (lower vs. upper/middle)      | 0.67 (0.18–2.50) | 0.547               | 2.22 (0.59–8.34)| 0.240               |
| Differentiation                        |                  |                     |                  |                     |
| Moderate (vs. well)                    | 8.80 (0.93–83.35)| 0.058               | 13.00 (1.36–124.30)| 0.026               |
| Poorly (vs. well)                      | 10.67 (1.04–109.94)| 0.047               | 8.00 (0.78–82.05)| 0.080               |
| pTNM                                   |                  |                     |                  |                     |
| Stage II (vs. 0–I)                     | 1.03 (0.26–4.17) | 0.966               | 1.03 (0.26–4.17)| 0.966               |
| Stage III (vs. 0–I)                    | 1.65 (0.37–7.37) | 0.512               | 2.41 (0.52–11.10)| 0.260               |
| Positive lymph nodes status            | 1.62 (0.44–5.96) | 0.471               | 2.22 (0.59–8.34)| 0.240               |
| Tumor length ≥ 50 mm                   | 0.79 (0.24–2.62) | 0.697               | 0.97 (0.30–3.23)| 0.967               |
| Perioperative parameters               |                  |                     |                  |                     |
| The first operation (vs. others)       | 3.71 (1.06–12.98)| 0.040               | 2.07 (0.62–6.91)| 0.235               |
| Operation time ≥ 190 minutes           | 1.71 (0.52–5.67) | 0.379               | 2.07 (0.62–6.91)| 0.235               |
| Blood loss ≥ 100 mL                    | 1.64 (0.48–5.56) | 0.430               | 1.41 (0.42–4.75)| 0.583               |
| Cardiac dysrhythmia                   | 1.94 (0.29–12.95)| 0.493               | 0.70 (0.11–4.67)| 0.714               |
| Pulmonary complication†|| 3.67 (0.63–21.45)| 0.149               | 0.79 (0.16–4.04)| 0.779               |
| VCP                                    | 15.33 (1.71–137.40)| 0.015               | 13.54 (1.52–120.85)| 0.020               |
| Overall complications                  | 7.00 (1.57–31.18)| 0.011               | 2.22 (0.59–8.34)| 0.240               |
| Clavien–Dindo grade 3–4 (vs. 0–2)      | 1.22 (0.16–9.56) | 0.848               | 1.11 (0.14–8.64)| 0.924               |
| Fast track program                    | 0.40 (0.10–1.49) | 0.171               | 0.45 (0.12–1.70)| 0.240               |
| Length of postoperative stay > 8 days  | 1.40 (0.42–6.42) | 0.581               | 3.71 (1.06–12.98)| 0.040               |
| Perioperative serum parameters        |                  |                     |                  |                     |
| Preoperative serum PA < 200 mg/L       | 0.69 (0.21–2.28) | 0.545               | 0.58 (0.18–1.91)| 0.367               |
| Preoperative serum A < 43.5 g/L        | 1.00 (0.31–3.28) | 1.000               | 0.58 (0.18–1.91)| 0.367               |
| POD1 serum PA < 150 mg/L               | 1.00 (0.31–3.28) | 1.000               | 0.83 (0.26–2.72)| 0.763               |
| POD1 serum A < 33.0 g/L                | 1.33 (0.39–4.57) | 0.647               | 0.61 (0.18–2.09)| 0.428               |
| POD7 serum PA < 110 mg/L†              | 5.67 (1.55–20.79)| 0.009               | 1.43 (0.44–4.69)| 0.555               |
| POD7 serum A < 36.5 g/L††             | 3.00 (0.87–10.30)| 0.081               | 0.82 (0.25–2.69)| 0.741               |

‡The former is the number and rate of the severe weight loss (SWL) group, and the latter is the number and rate of the normal weight change group. †Defined as weight loss > 7.5% of preoperative body weight four weeks after surgery. ††Defined as weight loss > 13.0% of preoperative body weight one year after surgery. †High fat-free mass (FFM) was defined as >50.0 kg for men and >38.0 kg for women. †Pulmonary complication was defined as pneumonia, pleural effusion, or acute respiratory distress syndrome (ARDS). ††Data were missing for three patients. A albumin; ASA American Society of Anesthesiologists; BMI, body mass index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; ECOG-PS, Eastern Cooperative Oncology Group performance status; KPS, Karnofsky Performance Status; OR, odds ratio; PA, pre-albumin; POD, postoperative day; pTNM, pathological tumor node metastasis; SWL, serious weight loss; VCP, vocal cord paralysis.
Weight loss after esophagectomy

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The multivariate logistic regression model demonstrated that an postoperative stay (LOS) > 8 days (OR 3.71; \( P = 0.004 \)), a moderately differentiated tumor (OR 13.00; \( P = 0.040 \)), high FFM (> 50.0 kg for men or >38.0 kg for women, OR 7.08; \( P = 0.040 \)) and VCP (OR 12.30; \( P = 0.046 \)) were independent risk factors for short-term SWL after esophagectomy (Table 5).

Risk factors for long-term (1 year) severe weight loss after esophagectomy

The average and median of the body weight loss rate one year after surgery were 13.1% ± 6.5% and 12.6% (8.8–17.7%), respectively. Thus, we defined long-term SWL as a body weight loss > 13%. Ultimately, 21 (47.7%) patients belonged to the SWL group and 23 (52.3%) to the NWL group. According to the outcomes of univariate analysis shown in Table 4, cerebral vascular disease (\( P = 0.020 \)), an American Society of Anesthesiologists (ASA) score of 3–4 (OR 4.60; \( P = 0.020 \)), a high PBW (> 66.0 kg for men or > 55.0 kg for women, OR 3.72; \( P = 0.040 \)), high FFM (> 50.0 kg for men or > 38.0 kg for women, OR 7.08; \( P = 0.004 \)), a moderately differentiated tumor (OR 13.00; \( P = 0.026 \)), VCP (OR 13.54; \( P = 0.020 \)), and the length of postoperative stay (LOS) > 8 days (OR 3.71; \( P = 0.040 \)) were associated with SWL one year after surgery. The multivariate logistic regression model demonstrated that an ASA score of 3–4 (OR 6.58; \( P = 0.047 \)), high FFM (OR 21.91; \( P = 0.003 \)), and VCP (OR 25.83; \( P = 0.017 \)) were independent risk factors leading to long-term SWL after esophagectomy (Table 5).

Quality of life and weight loss

We studied the impact of postoperative intake-related QOL on short-term and long-term weight loss, respectively (Table 6). No significant difference in baseline QOL was observed between the groups in regard to short-term weight loss, except for a higher prevalence of insomnia (\( P = 0.001 \)) and reflux (\( P = 0.017 \)) in the SWL group. Two weeks after the operation, patients in the SWL group reported statistically significantly more problems with insomnia (\( P = 0.032 \)), appetite loss (\( P = 0.006 \)), dysphagia (\( P = 0.001 \)), eating difficulties (\( P = 0.040 \)), taste issues (\( P = 0.016 \)), coughing (\( P = 0.040 \)), and difficulty talking (\( P = 0.002 \)) with a lower score of emotional functioning (\( P = 0.021 \)) than patients in the NWL group. A significant difference was still observed four weeks after surgery.

In the long-term weight loss analysis, emotional functioning (\( P = 0.002 \)) was significantly lower in patients in the SWL group four weeks after surgery, and they reported more serious symptoms of insomnia (\( P = 0.010 \)), appetite loss (\( P = 0.017 \)), dysphagia (\( P = 0.045 \)), eating difficulties (\( P = 0.031 \)), esophageal pain (\( P = 0.043 \)), taste issues (\( P = 0.028 \)), coughing (\( P = 0.002 \)), and difficulty talking (\( P = 0.048 \)) at that time. While the difference in esophageal pain, coughing, and difficulty talking decreased with time, the differences in other symptoms remained significant within one year after surgery.

Discussion

Previous studies have reported different degrees of postoperative weight loss in esophageal cancer patients. A prospective study including 226 patients showed that 63.7% of patients suffered from weight loss > 10% of the PBW six months after surgery, and 20.4% patients showed weight loss of > 20% of the PBW.6 Recently, two retrospective studies conducted in Asian countries showed weight loss rates of 10.95% ± 7.50% and 12.9% ± 9.08% of the PBW one year after esophagectomy.5,18 The results of our prospective study, which included Chinese patients who underwent McKeown-MIE, also demonstrated obvious weight loss one year after surgery, at a rate of 13.1% ± 6.5%. Additionally, consecutive follow-up over a year showed that the first two weeks after discharge represented an accelerated weight loss period. According to our experience and the results of previous studies, at least three factors contributed to this particular term:

1. Poor eating function. Both our patient sample and previous studies reported adverse postoperative eating

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Table 5: Outcomes of multivariate analysis of the risk factors for SWL.

| Risk factors | OR    | 95% CI          | \( P \) |
|-------------|-------|-----------------|--------|
| Short-term (4 weeks) SWL (\( n = 20 \))† |       |                 |        |
| Age ≥ 70 years | 7.65  | 1.22–48.13      | 0.030  |
| Preoperative sarcopenia | 7.18  | 1.22–42.38      | 0.030  |
| The first surgery in the daily schedule | 6.87  | 1.18–40.14      | 0.032  |
| VCP          | 12.30 | 1.04–144.96     | 0.046  |
| Long-term (1 year) SWL (\( n = 21 \))‡ |       |                 |        |
| ASA score 3–4 | 5.68  | 1.03–42.26      | 0.047  |
| High FFM§     | 21.91 | 2.93–163.81     | 0.003  |
| VCP          | 25.83 | 1.80–371.28     | 0.017  |

†Defined as weight loss > 7.5% of preoperative body weight four weeks after surgery. ‡Defined as weight loss >13.0% of preoperative body weight one year after surgery. §High fat-free mass (FFM) was defined as >50.0 kg for men and >38.0 kg for women. ASA, American Society of Anesthesiologists; CI, confidence interval; OR, odds ratio; SWL, severe weight loss; VCP, vocal cord paralysis.
# Table 6: Patients' SWL and related QOL

| Questionnaire and items | Pre 2W, 4W, and QOL | Long-term (1Y) SWL and QOL |
|-------------------------|----------------------|--------------------------|
|                         | SWL (n = 20) | NWL (n = 24) | P | SWL (n = 20) | NWL (n = 24) | P | SWL (n = 21) | NWL (n = 23) | P | SWL (n = 21) | NWL (n = 23) | P | SWL (n = 21) | NWL (n = 23) | P |
| EORTC QLQC-30 function scales | | | | | | | | | | | | | | |
| Emotional               | 87.9 ± 11.3 | 90.6 ± 10.2 | 0.427 | 79.0 ± 9.7 | 85.4 ± 7.9 | 0.021 | 79.1 ± 11.6 | 87.1 ± 9.2 | 0.022 | 88.1 ± 11.4 | 90.6 ± 10.1 | 0.481 | 80.0 ± 87.7 | 87.7 ± 8.7 | 0.002 |
| Nausea and vomiting     | 7.5 ± 8.5 | 7.0 ± 8.4 | 0.826 | 14.2 ± 15.5 | 6.3 ± 9.6 | 0.076 | 15.8 ± 15.7 | 7.6 ± 9.8 | 0.077 | 8.0 ± 8.5 | 6.5 ± 8.3 | 0.575 | 13.5 ± 15.5 | 9.4 ± 11.0 | 0.466 |
| Insomnia                | 26.7 ± 23.2 | 5.6 ± 12.7 | 0.001 | 26.7 ± 23.2 | 12.5 ± 19.2 | 0.032 | 20.0 ± 20.0 | 8.3 ± 17.7 | 0.027 | 25.4 ± 23.3 | 5.8 ± 12.9 | 0.002 | 20.6 ± 19.6 | 7.2 ± 17.3 | 0.010 |
| Appetite loss           | 16.7 ± 17.1 | 11.1 ± 16.0 | 0.268 | 28.3 ± 27.1 | 8.3 ± 17.7 | 0.006 | 36.7 ± 24.0 | 15.3 ± 24.0 | 0.004 | 17.4 ± 17.0 | 10.1 ± 15.6 | 0.144 | 34.9 ± 26.8 | 15.9 ± 22.2 | 0.017 |
| Constipation            | 3.3 ± 10.2 | 4.2 ± 11.2 | 0.797 | 3.3 ± 10.2 | 9.7 ± 15.5 | 0.121 | 5.0 ± 12.2 | 12.5 ± 16.5 | 0.099 | 6.3 ± 13.4 | 1.4 ± 6.9 | 0.129 | 7.9 ± 14.5 | 10.1 ± 15.7 | 0.626 |
| Diarrhea                | 1.7 ± 7.4 | 2.8 ± 9.4 | 0.666 | 5.0 ± 12.2 | 5.6 ± 12.7 | 0.882 | 15.0 ± 20.2 | 13.9 ± 19.4 | 0.858 | 16.7 ± 7.3 | 2.9 ± 9.6 | 0.609 | 11.1 ± 19.2 | 17.4 ± 19.8 | 0.195 |
| Dysphagia               | 13.9 ± 7.1 | 12.0 ± 8.0 | 0.443 | 31.6 ± 6.5 | 23.1 ± 8.6 | 0.001 | 30.0 ± 21.3 | 10.3 ± 10.8 | 0.008 | 14.4 ± 8.0 | 11.6 ± 7.1 | 0.213 | 28.5 ± 11.9 | 22.2 ± 11.1 | 0.045 |
| Eating difficulties     | 16.7 ± 13.0 | 12.5 ± 9.2 | 0.355 | 26.3 ± 12.2 | 18.1 ± 11.9 | 0.040 | 27.5 ± 14.6 | 18.1 ± 14.2 | 0.039 | 17.8 ± 13.0 | 11.2 ± 8.2 | 0.094 | 27.0 ± 14.9 | 18.1 ± 14.1 | 0.031 |
| Reflux                  | 19.2 ± 16.5 | 9.7 ± 14.7 | 0.017 | 2.5 ± 6.1 | 6.3 ± 8.3 | 0.099 | 11.7 ± 11.0 | 13.2 ± 12.0 | 0.698 | 18.3 ± 10.4 | 10.2 ± 19.3 | 0.002 | 13.5 ± 11.3 | 11.6 ± 11.7 | 0.533 |
| Esophageal pain         | 8.3 ± 8.7 | 6.5 ± 8.6 | 0.436 | 11.7 ± 8.4 | 11.1 ± 8.0 | 0.819 | 11.1 ± 8.1 | 13.9 ± 8.2 | 0.259 | 7.9 ± 7.9 | 6.8 ± 9.3 | 0.485 | 10.0 ± 7.8 | 15.0 ± 7.9 | 0.043 |
| Difficulty swallowing   | 10.0 ± 15.7 | 9.7 ± 15.5 | 0.952 | 18.3 ± 20.2 | 9.7 ± 15.5 | 0.138 | 13.3 ± 16.7 | 5.6 ± 12.7 | 0.087 | 9.5 ± 15.4 | 10.1 ± 15.7 | 0.894 | 12.7 ± 16.6 | 5.8 ± 12.9 | 0.128 |
| Choke when swallowing   | 16.7 ± 20.2 | 16.7 ± 17.0 | 0.871 | 23.3 ± 15.7 | 13.9 ± 16.8 | 0.063 | 16.7 ± 17.1 | 11.1 ± 16.0 | 0.268 | 15.9 ± 17.0 | 17.4 ± 19.8 | 0.882 | 17.4 ± 17.0 | 10.1 ± 15.7 | 0.144 |
| Dry mouth               | 18.3 ± 20.2 | 15.3 ± 16.9 | 0.676 | 26.3 ± 13.9 | 20.3 ± 19.4 | 0.209 | 13.3 ± 16.7 | 19.7 ± 9.6 | 0.624 | 22.2 ± 19.2 | 11.6 ± 16.2 | 0.062 | 14.3 ± 16.9 | 15.9 ± 19.8 | 0.871 |
| Taste issue             | 11.7 ± 16.3 | 8.7 ± 15.0 | 0.530 | 43.3 ± 24.4 | 26.9 ± 19.6 | 0.016 | 42.1 ± 26.9 | 20.2 ± 24.1 | 0.011 | 12.7 ± 16.6 | 7.6 ± 14.3 | 0.278 | 40.0 ± 27.8 | 21.2 ± 24.2 | 0.028 |
| Coughing                | 6.7 ± 13.7 | 2.8 ± 9.4 | 0.267 | 36.7 ± 21.4 | 23.3 ± 18.3 | 0.040 | 25.0 ± 21.3 | 11.1 ± 18.8 | 0.021 | 6.3 ± 13.4 | 2.9 ± 9.6 | 0.323 | 27.0 ± 20.1 | 8.7 ± 18.0 | 0.002 |
| Difficulty talking      | 3.3 ± 10.2 | 2.8 ± 9.4 | 0.850 | 31.7 ± 27.5 | 8.3 ± 14.7 | 0.002 | 21.7 ± 24.8 | 6.9 ± 13.8 | 0.028 | 16.7 ± 7.3 | 4.3 ± 11.5 | 0.345 | 20.6 ± 24.7 | 7.2 ± 14.0 | 0.048 |

The scores are presented as mean ± standard deviation. EORTC, European Organization for Research and Treatment of Cancer; NWL, normal weight loss; QOL, quality of life; SWL, severe weight loss.
Weight loss after esophagectomy

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symptoms, including dysphagia, eating difficulties, trouble swallowing saliva, and choking when swallowing within a short time after esophagectomy. These symptoms worsened in the short term after discharge because of the lack of medical guidance but relieved gradually with time.

2 Stress response. Surgical damage, incision scar, new lifestyle after discharge, and residual symptoms (coughing, dysphagia, cracked voice) can cause significant stress responses after discharge, which lead to greater catabolism and energy consumption, severe sleep disorders, and decreased digestive function.

3 Gut hormone secretion disorder. Previous studies have shown that patients with esophageal cancer experience a severe decrease in ghrelin secretion and a significant increase in postprandial plasma glucagon-like peptide 1 (GLP-1) and peptide YY (PYY), contributing to severe appetite loss and decreased food intake after esophagectomy.

Short-term SWL after esophagectomy has not been extensively studied worldwide. The results of our study show significant differences in risk factors for postoperative short-term and long-term SWL in patients with esophageal cancer, while VCP was the only common independent risk factor. Patients suffering from VCP are reported to experience symptoms of aspiration, which result in eating difficulties and a serious postoperative stress response. The impact of this adverse factor may continue for a number of months to several years. Damage to macromolecules in human cells accumulates with age, resulting in the gradual decline of cell function. Older patients are more likely to experience SWL in the short term after surgery because of decreased anabolism and physical dysfunction. Sarcopenia, related to advanced age and malignant tumors, results in weakness and decreased resistance and tolerance. Previous studies have shown that preoperative sarcopenia is a risk factor for mortality, postoperative complications, and poor survival. Our results show that this factor also leads to postoperative short-term SWL. Additionally, the first surgery in the daily schedule was associated with short-term SWL, but no significant difference in patient characteristics and perioperative data was observed between the first and following surgery groups (data not shown). Patients in our center who underwent the first surgery in the daily schedule usually entered the preoperative area an hour earlier, and thus may have experienced more serious preoperative anxiety than patients that underwent following surgeries with a shorter wait in the preoperative area. The rate of delay to the start of the scheduled first operation is higher than for the following surgeries, which may influence short-term weight loss. Further studies are warranted to confirm the effect of operation order on patients’ postoperative body weight recovery.

The FFM is defined as the main factor determining resting energy expenditure (REE), and allows a person to maintain biological function during resting. Patients with a high FFM experience a higher energy requirement during the postoperative chronic recovery term, during which the REE is the main energy expenditure. However, patients are reported to experience hypermetabolism caused by multiple factors in the acute stage after esophagectomy. Our results also showed no association between FFM and short-term SWL. Patients with an ASA score of 3–4 always suffer from severe systemic diseases and dysfunction before surgery, which appear to affect not only perioperative complications and mortality but also postoperative weight recovery. Previous studies have also investigated the risk factors for SWL after esophagectomy. Park et al. reported that preoperative weight and postoperative VCP were independent risk factors for weight loss > 10% of PWL one year after esophagectomy. Harada et al. reported that the absence of pyloroplasty was the sole risk factor for > 10% weight loss of PWL one year after esophagectomy. A retrospective study with six months follow-up after esophagectomy showed that preoperative BMI and a shorter LOS resulted in > 10% weight loss. In this study, however, except for VCP, we found no definitive association between the PBW, BMI, and LOS with long-term SWL.

Patients’ body weight is always associated with food intake and energy expenditure. Previous studies have reported the detrimental effect of esophagectomy on patients’ short-term QOL, particularly in regard to eating. But few studies have focused on the impact of eating symptoms on body weight loss. Martin et al. reported that eating difficulties, pain, fatigue, nausea and vomiting, and appetite loss were clinically relevant and statistically significantly worse among patients with weight loss of ≥ 15% five years after esophageal cancer surgery. Our results indicate that postoperative esophageal symptoms, including appetite loss, dysphagia, eating difficulties, and taste issues are related to both short-term and long-term SWL, mainly because of their detrimental effect on food intake. Patients suffering from insomnia are not likely to get proper rest, which contributes to SWL. Additionally, patients that experienced SWL reported worse emotional functioning, indicating tension, anxiety and depression, which were related to stress response and energy expenditure. There is surely complex interaction among eating symptoms, insomnia, emotional functioning, and weight loss, revealing the need for postoperative life guidance and nutrition intervention for esophageal cancer patients.

In this study, we prospectively observed changes in the body weight of 44 patients with esophageal cancer one year after surgery and propose the existence of an accelerated weight loss period in the first two weeks after discharge.
We also investigated the risk factors for SWL at four weeks and one year after surgery. However, there were limitations to this study. Only a small sample of Asian patients during the short term was analyzed, and the pathological type of the tumor was mainly SCC. Patients who underwent neoadjuvant therapy followed by esophagectomy were excluded, and all of the patients in this study underwent McKeown MIE. Thus, the effects of multi-treatment and surgical methods on weight recovery require further exploration.

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Disclosure

No authors report any conflict of interest.

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