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Risk factors and measures of pulmonary complications after thoracoscopic esophagectomy for esophageal cancer

Masaki Ohi[1] · Yuji Toiyama[1] · Yusuke Omura[1] · Takashi Ichikawa[1] · Hiromi Yasuda[1] · Yoshinaga Okugawa[1] ·
Hiroyuki Fujikawa[1] · Yoshiki Okita[2] · Shigeyuki Yoshiyama[1] · Junichiro Hiro[1] · Toshimitsu Araki[1] · Masato Kusunoki[1,2]

Abstract

Purpose Postoperative pulmonary complications (PCs) after thoracoscopic esophagectomy for esophageal cancer (EC) still occur too frequently. We conducted this study to identify the risk factors for PCs developing in EC patients who undergo thoracoscopic esophagectomy.

Methods The subjects of this retrospective study were 89 patients with EC who underwent thoracoscopic esophagectomy in our department between January 2010 and December 2015. Univariate and multivariate logistic regression analyses were used to evaluate the association between the incidence of PC and clinical factors. In January 2016, we introduced a new prophylactic intervention for reducing the incidence of delirium and assessed its significance for PCs.

Results PCs developed in 19 patients (21.3%). Univariate analysis revealed the following risk factors: age (> 69 years), ratio of the forced expiratory volume in 1 s to forced vital capacity ($< 70\%$), chronic obstructive pulmonary disease (COPD), and postoperative delirium. Multivariate analysis found that COPD and postoperative delirium were independent risk factors for PCs. Our new intervention for delirium significantly reduced its occurrence ($p = 0.00004$) and also the frequency of PCs ($p = 0.04148$).

Conclusions Postoperative delirium and COPD were risk factors for PCs in patients who underwent thoracoscopic esophagectomy. Our intervention study showed clearly that reducing the occurrence of postoperative delirium could decrease the incidence of PCs.

Keywords Esophageal cancer · Thoracoscopic esophagectomy · Pulmonary complications · Delirium

Introduction

Esophageal cancer (EC) is the sixth leading cause of cancer-related death worldwide because of its high malignant potential and poor prognosis [1]. Although esophagectomy with lymphadenectomy is a highly invasive surgical procedure, postoperative outcomes have improved with recent advances in surgical techniques and perioperative management [2]. Pulmonary complications (PCs) following esophagectomy are a major cause of in-hospital morbidity and mortality, as well as prolonged hospitalization, increased costs, and compromised quality of life [3–6]. Furthermore, PCs impact long-term survival [7–9]. The increasing use of minimally invasive esophagectomy via thoracoscopy and laparoscopy or mediastinoscopy has reduced the postoperative PC rate from that following conventional open thoracotomy [10–12]. Osugi et al. reported on the superiority of the thoracoscopic approach for reducing PCs [13].

PCs occur after esophagectomy in 13–38% of patients [3–6, 14–18]. Several preoperative and perioperative risk factors have been associated with PCs, including older age, history of heavy smoking, reduced forced expiratory volume, diabetes, chronic renal dysfunction, preoperative definitive chemoradiotherapy, large volume of blood loss during surgery, and operative time [15–21]. However, the risk factors for PCs in EC patients undergoing thoracoscopic esophagectomy have not been fully investigated.

✉ Masaki Ohi
mohi1012@clin.medic.mie-u.ac.jp

1 Department of Gastrointestinal and Pediatric Surgery, Mie University Graduate School of Medicine, Edobashi 2-174, Tsu, Mie 514-8507, Japan

2 Department of Innovative Surgery, Mie University Graduate School of Medicine, Edobashi 2-174, Tsu, Mie 514-8507, Japan

We conducted this study, first to identify the risk factors associated with the occurrence of PCs following thoracoscopic esophagectomy, and then to investigate if reducing the incidence of these identified risk factors could reduce the incidence of PCs.

Methods

Patients

Between January 2010 and December 2015, 91 patients underwent thoracoscopic esophagectomy with lymphadenectomy for EC at the Department of Gastrointestinal and Pediatric Surgery of Mie University Graduate School of Medicine. After the exclusion of two patients who underwent two-stage surgery, 89 patients were enrolled in this study. We recorded patient characteristics, including demographic data [gender, age, body mass index (BMI), and American Society of Anesthesiologists (ASA) classification], tumor-specific data (T classification, lymph node metastasis, pathological type, and lymphatic and venous invasion) according to the Japanese classification of EC (11th Ed.) [22], preoperative biochemical variables (tumor markers, and systemic inflammatory markers), surgery-related factors [estimated blood loss, duration of surgery, presence or absence of artificial pneumothorax, anastomotic location, approach used for abdominal surgery (laparoscopic or open laparotomy), preservation or resection of right bronchial artery], and postoperative complications [surgical site infection (SSI), anastomotic leak, recurrent laryngeal nerve paralysis, delirium]. In addition, we recorded the smoking history of every patient undergoing surgery and calculated the Brinkman index.

All patients underwent pulmonary function testing, which included measuring forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV1), and echocardiography to calculate the ejection fraction (EF) before thoracoscopic esophagectomy. Peripheral blood samples were also collected prior to surgery. Neutrophil and lymphocyte counts were used to calculate the neutrophil-to-lymphocyte ratio (NLR), and albumin (Alb) and C-reactive protein (CRP) levels were used to calculate the modified Glasgow prognosis score (mGPS).

Definitions of preoperative risks

Pulmonary dysfunction was defined as %FVC < 80% the predicted normal value, FEV1/FVC < 70% the predicted normal value, and a history of COPD. Cardiac dysfunction was defined as EF < 55% of the predicted normal value.

The cut-off values for carcinoembryonic antigen (CEA) and squamous cell carcinoma (SCC) antigen were 5 and 1.5 ng/mL, respectively, based on the normal ranges at our institution. The cut-off values for Alb and CRP were 3.5 g/dL and 0.5 mg/dL, respectively, based on the reference values for mGPS [23]. Patients were categorized according to mGPS scores of 0, 1, or 2. The cut-off value for the NLR was 2.5 and the cut-off value for the BMI was 18.5 kg/m^2, based on the definition for "underweight" according to the World Health Organization [24].

Treatment strategy

For EC patients who were lymph node positive, except for those older than 75 years old or those with creatinine clearance of less than 30 mL/min in, we performed esophagectomy with neoadjuvant chemotherapy using FP regimens, including fluorouracil and cisplatin, which has become the standard choice in Japan [25]. FP regimens do not affect the occurrence of PC after esophagectomy [26]. For EC patients who were lymph node negative, we performed esophagectomy without neoadjuvant chemotherapy. When lymph node metastases were confirmed pathologically after the operation, adjuvant chemotherapy was commenced.

Procedure of video-assisted thoracoscopic esophagectomy

We introduced video-assisted thoracoscopic esophagectomy for EC in January 2010. Thoracoscopic esophagectomy and dissection of the thoracic lymph nodes were performed with the patient in the prone position with artificial pneumothorax but while maintaining respiratory function whenever possible. Three-field lymphadenectomy was performed in all except those patients with early EC located in the lower or abdominal esophagus. The degree of mediastinal lymph node dissection was the same in patients with superficial and those with advanced cancer. The thoracic duct and right and left bronchial artery were preserved as much as possible, except if there was suspected direct invasion. The proximal esophagus was divided using a linear stapling device in the upper mediastinum. Then, the perigastric lymph nodes were dissected by laparotomy or laparoscopy. The right gastric artery, right gastroepiploic artery, and branches of the left gastroepiploic arteries were preserved and provided vascular supply to the gastric wall through an arcade of peripheral vessels. The omentum was freed from the transverse colon and divided at the edge adherent to the colon so vessel communications and a sufficient amount of omentum were fully preserved. A collar incision was then made 2 cm above the sternum, and the bilateral clavicles and paraesophageal lymph nodes of the neck were dissected. A gastric conduit, 4 cm wide, was made extra-abdominally by stapling the lesser curvature of the stomach. This was usually elevated to the neck via the retrosternal route. Finally, we performed

cervical esophagogastric end-to-side anastomoses using a circular stapler, or end-to-end anastomoses using a hand-sewn technique. If the gastric conduit was not considered appropriate, we applied the reconstructive organ with colon or jejunum through the pericardial subcutaneous layer. Patients were transferred to the intensive care unit (ICU) after surgery and returned to the ward on the basis of extubation the next morning. A feeding jejunostomy was placed routinely and enteral feeding was started from postoperative day (POD) 1. Antibiotics were administered 30 min before the operation and then every 3 h during the operation.

Definitions of postoperative complications

PCs were defined as the development of one or more of the following: bronchial circulatory disturbance, ventilatory disorder, atelectasis requiring antibiotics or bronchoscopy, pneumonia, mediastinitis, empyema, respiratory failure, and acute respiratory distress syndrome (ARDS), of Clavien–Dindo [27] Grade 2 or higher, respectively. Pneumonia was defined as the presence of pulmonary infiltrates on a chest radiograph or computed tomography scan with positive bacterial culture from a bronchoalveolar lavage specimen. Acute respiratory distress syndrome (ARDS) was defined as a ratio of partial pressure of oxygen in arterial blood (PO_2)/fractional inspired oxygen (FiO_2) < 200 with positive end expiratory pressure > 5 cm H_2O for > 24 h, and bilateral pulmonary opacities without clinical suspicion of cardiac failure or fluid overload [28]. SSI was defined as superficial pus expressed from the abdominal, thoracic, or drain incision sites, requiring surgical debridement and antibiotic treatment (Clavien–Dindo Grade 2 or more). Anastomotic leak was defined as anastomotic dehiscence that was clinically symptomatic (abscess, mediastinitis, externalized drainage of digestive fluid), or clinically asymptomatic but detected by contrast study within 30 days after esophagectomy. Anastomotic leak was assessed by a water-soluble,

monomeric, ionic X-ray contrast medium (Gastrografin; Schering AG, Berlin, Germany) or an upper gastrointestinal endoscopy (Clavien–Dindo Grade 2 or more). Recurrent laryngeal nerve paralysis was defined as disturbance of vocal cord mobility with insufficient glottic closure observed via flexible laryngoscopy and was recorded according to the affected side (Clavien–Dindo Grade 1 or more). Delirium was diagnosed according to the criteria of the Fourth Edition of the Diagnostic and Statistical Manual of Mental Disorders [29]. Each patient's chart was reviewed independently by two psychiatrists. The diagnosis of delirium was based on agreement according to methodology used in previous delirium studies [30]. Patients' charts were reviewed daily for key words derived from previous studies and included the following terms: "delirious," "agitated," "confused," and "disoriented." Data were collected from POD 1–14.

Prophylactic intervention for delirium

We introduced an intervention for preventing the development of postoperative delirium in patients with EC who underwent thoracoscopic esophagectomy after January 2016 (Table 1). The alternative intervention was composed of several factors selected by recent accumulating evidence to prevent postoperative delirium. The following steps were undertaken.

1) Before esophagectomy, patients were given the Japanese herbal drug, yokukansan (TJ-54) 7.5 g three times a day from 7 days before surgery until POD 14. Some reports have shown that TJ-54 effectively controls aggressive and impulsive behavior, thereby improving postoperative delirium in patients with traumatic brain injury [31]. Before oral intake was resumed after surgery, each patient was given TJ-54, dissolved in warm water, through a jejunal feeding tube, as described previously [32].

Table 1 Prophylactic interventions for postoperative delirium before and after January 2016

	Conventional intervention (~ 2015.12)	Alternative intervention (2016.1~)
Preoperative preparation	Prohibition of drinking and smoking	–
1	–	Yokukansan (TJ-54)
2	–	Psychiatry consultation (high risk)
Perioperative care		
3: SIRS	Corticosteroid 3 days	Corticosteroid 1 day
4: pain relief	Fentanyl continuous IV	Acetaminophen
5: anti-ulcer	H2-blocker	Proton pump inhibitor
6: sleep agent	H1-blocker	Haloperidol
7: duration of ICU stay	2 days	1 day
8: early postoperative ambulation	Nurse or doctor	Physical therapist

SIRS Systemic inflammatory response syndrome, *ICU* intensive care unit

2) A psychiatric consultation was ordered for each patient at high risk of the development of delirium. Because complex neuropsychiatric syndrome with generalized cognitive impairment causes delirium, it is necessary to address the sleep–wake cycle and motor-activity disturbances through psychiatry consultation [33].

3) The duration of postoperative steroid therapy was changed from 3 days to 1 day after surgery because it induces neuropsychiatric disorders [34].

4) Postoperative pain control was changed from continuous intravenous fentanyl to acetaminophen, if possible because narcotic analgesics can trigger mental status changes [35].

5) Perioperative antiulcer medication was changed from an H2-blocker to a proton pump inhibitor as H2-blockers have been reported to be responsible for drug-induced delirium and switching the antiulcer drug from an H2-blocker to a proton pump inhibitor has been found to reduce delirium [36].

6) Perioperative sleep medication for patients with insomnia was changed from an H1-blocker to haloperidol. Fukata et al. reported that the prophylactic administration of haloperidol at the early stage of delirium significantly reduced the incidence of severe postoperative delirium in elderly patients [37].

7) The stay in the intensive care unit was defined as 1 day, to be as short as possible.

8) Early physical therapy was introduced to encourage the postoperative ambulation of all patients, because shortening the ICU stay and early physical mobility have been shown to decrease the risk of delirium [38]. Between January 2016 and December 2017, 34 patients with EC underwent thoracoscopic esophagectomy with intervention to prevent the development of postoperative delirium.

Statistical analysis

Continuous variables are shown as means with standard deviation (SD). Comparisons were made using the Mann–Whitney or Kruskal–Wallis test, as appropriate. Univariate and multivariate logistic regression analyses were performed to identify risk factors affecting PCs. The association between prophylactic intervention and postoperative PC or postoperative delirium was analyzed by the chi-squared test. Parameters with $p < 0.05$ by univariate analysis where considered significant were tested by multivariate analysis. JMP software, version 10 (SAS Institute, Cary, NC, USA) was used for statistical analysis.

Results

Patients and pulmonary complications

The study group comprised 72 men and 17 women, with a mean age of 69 years (range 41–90 years). Table 2 summarizes the clinical characteristics of the study population. According to the Japanese classification of EC (11th Ed.) [22], there were 11 patients (12.4%) with pathological stage 0, 32 (36.0%) with stage I, 22 (24.7%) with stage II, 17 (19.1%) with stage III, and 7 (7.9%) with stage VI disease. The median estimated blood loss was 480 mL (range 102–4450 mL) and the median estimated blood loss in the thoracic phase was 60 mL (range 12–203 mL). The median duration of surgery was 584 min (range 323–900 min), and the median thoracic procedure time was 250 min (range 41–425 min). Thirty-one of the 89 patients (34.8%) received neoadjuvant chemotherapy. Table 2 shows the efficacy of chemotherapy. The clinical response rate was 38.7% (complete response, $n = 1$; partial response, $n = 11$; stable disease, $n = 16$; progression of disease, $n = 3$). The pathological therapeutic effect rate was achieved in 25.8% of patients (Grade 3, $n = 3$; Grade 2, $n = 1$; Grade 1b, $n = 4$; Grade 1a, $n = 22$; Grade 0, $n = 1$).

PCs developed in 19 (21.3%) of the 89 study patients; as pneumonia in 14 (73.7%), atelectasis in 2 (10.5%), ARDS in 2 (10.5%), and empyema in 1 (5.3%). The first episode of the PC occurred between POD 5 and 14. Moreover, 20 (22.5%), 8 (9.0%), 8 (9.0%), 1 (1.1%), 1 (1.1%), and 50 (56.2%) patients suffered SSI, anastomotic leak, recurrent laryngeal nerve paralysis, necrosis of the gastric conduit anastomotic bronchial fistula, or delirium, respectively (Table 2).

Univariate analysis of risk factors for postoperative pulmonary complications

Patients older than 69 years [HR 4.875, 95% confidence interval (CI) 0.0541–0.6318; $p = 0.0049$], those with a high Brinkman index (> 800) (HR 3.1726, 95% CI 0.1004–0.8975; $p = 0.0302$), low FEV1/FVC (< 70%) (HR 10.1142, 95% CI 0.0297–0.3016; $p = 0.0001$), and COPD (HR 14.2222, 95% CI 0.0180–0.2414; $p = 0.0001$) had a significantly higher incidence of postoperative PCs (Table 3). In contrast, gender, BMI, ASA classification, preoperative treatment, and clinicopathological factors were not significantly associated with PCs (Table 3). Preoperative tumor markers, mGPS, and NLR were also not associated with PCs. Surgery-related factors, namely, estimated blood loss, duration of surgery, artificial pneumothorax, abdominal approach, isolation of the right

Table 2 Clinical characteristics of the study population ($N = 89$)

Variables	Number (%)	Median ± SD
Gender		
Male	72 (80.9%)	
Female	17 (19.1%)	
Age (years)		69 ± 9.5
ASA classification		
≦ 2	82 (92.1%)	
≧ 3	7 (7.9%)	
Tumor location		
Upper	14 (15.7%)	
Middle	38 (42.7%)	
Lower	37 (41.6%)	
Pathological T		
T1a, T1b, T2	65 (73.0%)	
T3, T4	24 (27.0%)	
Pathological N		
Absent	46 (51.7%)	
Present	43 (48.3%)	
Lymphatic invasion		
Absent	52 (58.4%)	
Present	37 (41.6%)	
Venous invasion		
Absent	62 (69.7%)	
Present	27 (30.3%)	
Pathology		
SCC	80 (89.9%)	
Others	9 (10.1%)	
Pathological stage		
0	11 (12.4%)	
I	32 (36.0%)	
II	22 (24.7%)	
III	17 (19.1%)	
IV	7 (7.9%)	
Preoperative treatment		
Absent	58 (65.2%)	
Present	31 (34.8%)	
Clinical response		
CR, PR	12 (38.7%)	
SD, PD	19 (61.3%)	
Pathological therapeutic effect		
Grade 3, 2, 1b	8 (25.8%)	
Grade 1a, 0	23 (74.2%)	
Estimated blood loss (g)		480 ± 643
Estimated blood loss in thoracic phase (g)		60 ± 46
Duration of operation (min)		584 ± 142
Duration of thoracic procedure (min)		250 ± 75
Artificial pneumothorax		
Absent	15 (16.9%)	
Present	74 (83.1%)	

Table 2 (continued)

Variables	Number (%)	Median ± SD
Abdominal approach		
Open laparotomy	85 (95.5%)	
Laparoscopic	4 (4.5%)	
Right bronchial artery		
Preserve	71 (79.8%)	
Resection	18 (20.2%)	
Lymphadenectomy		
Three field	63 (70.8%)	
Two field	26 (29.2%)	
Location of anastomosis		
Cervical	72 (80.9%)	
Intrathoracic	17 (19.1%)	
Route		
Retrosternal	63 (70.8%)	
Posterior mediastinal	26 (29.2%)	
Pericardial subcutaneous layer	8 (9.0%)	
Complications		
Surgical site infection	20 (22.5%)	
Anastomotic leakage	8 (9.0%)	
Necrosis of gastric conduit	1 (1.1%)	
Anastomotic bronchial fistula	1 (1.1%)	
Respiratory complication	19 (21.3%)	
Recurrent laryngeal nerve paralysis	8 (9.0%)	
Delirium	50 (56.2%)	

ASA American society of anesthesiologists, *SCC* squamous cell carcinoma, *CR* complete response, *PR* partial response, *SD* stable disease, *PD* progression disease

bronchial artery and location of the anastomosis were not significantly associated with PC. Postoperative complications such as SSI, anastomotic leak, and recurrent laryngeal nerve paralysis were not associated with the development of PCs. Patients with postoperative delirium had a significantly higher incidence of postoperative PCs (HR 5.4898, 95% CI 0.0398–0.6074; $p = 0.0043$) (Table 3).

Chronic obstructive pulmonary disease and delirium as independent risk factors for postoperative pulmonary complications

Table 4 shows the results of a multivariate analysis of factors found to be significant by univariate analysis. COPD (HR 13.3113, 95% CI 0.0064–0.5952; $p = 0.0132$) and postoperative delirium (HR 8.3086, 95% CI 0.01422–0.5991; $p = 0.0077$) were identified as independent risk factors for PCs following surgery for EC.

Table 3 Factors associated with postoperative pulmonary complications in patients undergoing thoracoscopic esophagectomy: univariate logistic regression analysis

Variables	Univariate analysis		
	HR	95% CI	*p* value
Gender (male vs. female)	2.3611	0.0627–1.7106	0.5128
Age (> 69 vs. ≤ 69 years)	**4.875**	**0.0541–0.6318**	**0.0049**
BMI (≥ 18.5 vs. < 18.5 kg/m^2)	2.7000	0.0194–2.1733	0.3073
ASA classification (≥ 2 vs. 1)	1.9861	0.1610–1.4309	0.2014
Preoperative therapy (present vs. absent)	1.4545	0.2439–1.9944	0.4824
Smoking	2.3611	0.0627–1.7106	0.2471
Brinkmann index (> 800)	**3.1726**	**0.1004–0.8975**	**0.0302**
EF(< 55)	0.00013	0–0	0.2225
%VC (< 80)	1.2500	0.2094–3.9142	0.5085
%EFV1 (< 70)	**10.1142**	**0.0297–0.3016**	**0.0001**
Chronic obstructive pulmonary disease	**14.2222**	**0.0180–0.2414**	**0.0001**
T classification (T3, 4 vs. T0, 1, 2)	1.3077	0.2591–2.4461	0.6378
Lymphatic node metastasis (present vs. absent)	1.2121	0.2934–2.2920	0.7106
Pathology (SCC vs. others)	2.3606	0.3939–45.2695	0.3883
Lymphatic invasion (present vs. absent)	0.7848	0.4459–3.8398	0.6535
Venous invasion (present vs. absent)	1.4955	0.2285–2.0460	0.4702
CEA (> 5 vs. ≤ 5 ng/μl)	2.1250	0.1381–1.7366	0.2463
SCC (> 1.5 vs. ≦ 1.5 ng/dl)	0.2031	0.8915–92.2407	0.0709
mGPS (1–2 vs. 0)	1.4117	0.2386–2.2747	0.5478
NLR (> 2.5 vs. ≤ 2.5)	2.1739	0.7737–6.2146	0.1398
Estimated blood loss (> 480 vs. ≦ 480 g)	2.1014	0.1599–1.3288	0.1576
Estimated blood loss in thoracic phase (> 60 vs. ≦ 60 g)	2.6559	0.1202–1.0698	0.0671
Duration of operation (> 584 vs. ≦ 584 min)	2.5052	0.8819–7.8405	0.0855
Duration of thoracic procedure (> 250 vs. ≦ 250 min)	1.3357	0.4818–3.8363	0.5787
Artificial pneumothorax (present vs. absent)	4.5806	0.0116–1.2074	0.0874
Abdominal approach (laparoscopic or open laparotomy)	0.00013	0–0	0.1576
Right bronchial artery (preserve or resection)	1.7436	0.1229–1.9911	0.4005
Location of anastomosis (cervical vs. intrathoracic)	0.5895	0.4772–5.4422	0.6678
Surgical site infection	0.3599	0.6968–18.6559	0.1593
Anastomotic leak	0.00004	0–0	0.0589
Recurrent laryngeal nerve paralysis	0.4921	0.3299–39.2694	0.4878
Delirium	**5.4898**	**0.0398–0.6074**	**0.0043**

Significant associations are shown in bold (*p* < 0.05)

HR Hazard ratio, *CI* confidence interval, *BMI* body mass index, *ASA* American society of anesthesiologists, *SCC* squamous cell carcinoma, *CEA* carcinoembryonic antigen, *SCC* squamous cell carcinoma antigen, *Alb* albumin, *CRP* C-reactive protein, *mGPS* modified Glasgow prognosis score, *NLR* neutrophil-to-lymphocyte ratio, *%VC* vital capacity, *%EFV1* forced expiratory volume in 1 s, *EF* ejection fraction

Prophylactic intervention for delirium could be an option for reducing the risk of PC

Until the end of December 2015, a conservative intervention had been performed to reduce the risk of postoperative delirium. In January 2016, a new intervention was implemented, which provided a significant reduction in the development of postoperative delirium, down to 5 of 34 [14.7%] patients affected; *p* = 0.00004. Table 5 summarizes the characteristics of this study population. No significant differences were observed in the backgrounds, clinicopathological factors,

surgical procedures, or postoperative care between the conventional intervention group and the new intervention group (Table 5). Moreover, there were significantly fewer PCs in the EC patients receiving the new intervention than in those who received the conventional intervention [2/34 (5.9%) versus 19/89 (21.3%), respectively; *p* = 0.04148; Table 6].

Table 4 Independent risk factors for postoperative pulmonary complications in patients undergoing thoracoscopic esophagectomy: multivariate logistic regression analysis

Variables	Multivariate analysis		
	HR	95% CI	*p* value
Age (> 69 vs. ≤ 69 years)	2.8586	0.0710–1.4366	0.1473
Brinkmann index (> 800)	1.6133	0.1492–2.5627	0.5019
%EFV1 (< 70)	1.5467	0.1007–4.9648	0.6568
Chronic obstructive pulmonary disease	**13.3113**	**0.0064–0.5952**	**0.0132**
Delirium	**8.3086**	**0.0142–0.5991**	**0.0077**

Significant associations are shown in bold ($p < 0.05$)

HR Hazard ratio, *CI* confidence interval, *%EFV1* forced expiratory volume at 1 s

Discussion

Despite recent progress in surgical techniques and perioperative management, PCs still occur too frequently following esophagectomy. However, a recent randomized controlled trial comparing minimally invasive esophagectomy with open esophagectomy found that the frequency of pulmonary infections within the first 2 weeks postoperatively was lower for patients who underwent minimally invasive surgery than for those who underwent an open procedure [39]. Moreover, using propensity score methods, Iwahashi et al. reported that minimally invasive esophagectomy performed with the patient in the prone position was associated with less impairment of pulmonary function including FVC, earlier recovery of activity, and lower subsequent morbidity, than open esophagectomy [40]. Conversely, a systematic review did not find a strong tendency toward decreased PC incidence after minimally invasive esophagectomy [41, 42]. Therefore, whether or not minimally invasive esophagectomy does reduce the occurrence of postoperative PC remains controversial. It is known that the incidence of PCs has decreased since minimally invasive esophagectomy became popular, but other factors are necessary to prevent PCs. Although several risk factors, including patient age, preoperative definitive chemoradiotherapy, increased blood loss, and comorbidities such as diabetes, postoperative pain, aspiration, postoperative atelectasis, and recurrent laryngeal nerve injury, have already been reported to be associated with PCs, most previous studies have shown that age, smoking, and/or impaired pulmonary function are independent risk factors [15–21]. However, most of these studies were from western countries, where patients generally undergo either the Ivor-Lewis procedure or transhiatal esophagectomy. Very few specific studies have been published on postoperative PCs in patients who have undergone minimally invasive esophagectomy. Uchihara et al. recently reported that a history of heavy smoking and advanced clinical stage were risk factors for PCs after minimally invasive esophagectomy [43].

In the current study focusing on minimally invasive esophagectomy, the prevalence of PCs is as high as 17.6%, which cannot be ignored. According to our univariate analysis, patients older than 69 years, those with a high Brinkman index (> 800), low FEV1/FVC (< 70%), or COPD had a significantly higher risk of postoperative PCs. To our knowledge, this is the first study to identify preoperative COPD and postoperative delirium as independent risk factors of postoperative PCs in patients with EC who underwent thoracoscopic esophagectomy.

Elderly patients who require esophagectomy should always be monitored carefully because of their high risk of age-related organ dysfunction and comorbid illness after major surgery [44, 45]. In addition, most patients with EC are current or former smokers. In this study, 84% (100/119) of the patients had a history of smoking, and 41% (49/119) had a Brinkman index > 800, while 12.6% (15/119) had COPD. A Brinkman index > 800 relates to the risk of COPD. Although tobacco cessation and preoperative respiratory rehabilitation has been reported to reduce the occurrence of PCs [46, 47], the mean FEV1 of patients with COPD was 57%. In fact, smoking cessation and respiratory rehabilitation did not reduce the occurrence of postoperative PC. According to a recent report, preoperative training of the inspiratory muscles increased the function of preoperative inspiratory muscles, but did not result in a decreased incidence of pneumonia after esophagectomy [48]. Since a conclusive history of the patients, including COPD, had been taken preoperatively, the prevention of postoperative PCs in COPD patients might be difficult.

In our study, 30.9% of patients with delirium suffered a PC, in contrast to 6.3% of those without delirium. Moreover, the first episode of delirium manifested on POD 2–5, before the PC developed. Taken together, the results suggest that PCs might result from delirium. We think the following mechanisms account for the association of delirium with PC. First, patients with delirium could not obey the instructions of the physical therapists or nurses, making physical therapy, abdominal breathing, and active coughing for drainage of respiratory secretions obsolete. This hypothesis is supported by a previous study showing that early rehabilitation decreases postoperative complications and reduces hospitalization after esophagectomy [47]. Second, patients with delirium often become somnolent because of the various drugs they are given, which leads to a delay in the implementation of physical therapy and respiratory rehabilitation. Therefore, because rehabilitation is delayed in patients with cognitive and physical impairments due to the condition itself and the side effects of sedation, delirium might be a marker for the subsequent development of PCs.

Table 5 Characteristics of the two delirium management cohorts within the study population

Variables	2010–2015 ($n=89$)	2016–2017 ($n=34$)	p value
Gender			
Male	72 (80.9%)	29 (80.9%)	0.5695
Female	17 (19.1%)	5 (19.1%)	
Age (years)			
> 69	46 (51.7%)	21 (61.8%)	0.3154
≦ 69	43 (48.3%)	13 (38.2%)	
ASA classification			
≦ 2	82 (92.1%)	34 (100%)	0.092
≧ 3	7 (7.9%)	0 (0%)	
Brinkmann index			
≦ 800	47 (52.8%)	24 (70.6%)	0.0742
> 800	42 (47.2%)	10 (29.4%)	
%VC			
≧ 80	79 (88.8%)	32 (94.1%)	0.3708
< 80	10 (11.2%)	2 (5.9%)	
%EFV1			
≧ 70	67 (75.3%)	29 (85.3%)	0.2312
< 70	22 (24.7%)	5 (14.7%)	
Chronic obstructive pulmonary disease			
Absent	77 (86.5%)	33 (97.1%)	0.0890
Present	12 (13.5%)	1 (2.9%)	
Preoperative therapy			
Absent	58 (65.2%)	26 (76.5%)	0.228
Present	31 (34.8%)	8 (23.5%)	
T classification			
T0, T1a, T1b, T2	65 (73.0%)	21 (61.8%)	0.223
T3, T4	24 (27.0%)	13 (38.2%)	
Lymphatic node metastasis			
Absent	46 (51.7%)	19 (55.9%)	0.6767
Present	43 (48.3%)	15 (44.1%)	
Pathology			
SCC	80 (89.9%)	29 (85.3%)	0.4731
Others	9 (10.1%)	5 (14.7%)	
Lymphatic invasion			
Absent	52 (58.4%)	18 (52.9%)	0.5827
Present	37 (41.6%)	16 (47.1%)	
Venous invasion			
Absent	62 (69.7%)	26 (76.5%)	0.4542
Present	27 (30.3%)	8 (23.5%)	
Estimated blood loss (mL)			
≦ 480	46 (51.7%)	22 (76.5%)	0.1940
> 480	43 (48.3%)	12 (23.5%)	
Estimated blood loss of thoracic phase (mL)			
≦ 60	46 (51.7%)	16 (47.1%)	0.6463
> 60	43 (48.3%)	18 (52.9%)	
Duration of operation (min)			
≦ 584	45 (50.6%)	15 (44.1%)	0.5225
> 584	44 (49.4%)	19 (55.9%)	
Duration of thoracic phase (min)			
≦ 220	37 (41.6%)	15 (44.1%)	0.7983
> 220	52 (58.4%)	19 (55.9%)	

Table 5 (continued)

Variables	2010–2015 ($n=89$)	2016–2017 ($n=34$)	p value
Artificial pneumothorax			
Absent	15 (16.9%)	3 (8.8%)	0.2598
Present	74 (83.1%)	31 (91.2%)	
Abdominal approach			
Open laparotomy	85 (95.5%)	29 (85.3%)	0.0518
Laparoscopy	4 (4.5%)	5 (14.7%)	
Right bronchial artery			
Preserve	71 (79.8%)	22 (64.7%)	0.0818
Resection	18 (20.2%)	12 (35.3%)	
Lymphadenectomy			
Three field	63 (70.8%)	26 (76.5%)	0.5284
Two field	26 (29.2%)	8 (13.5%)	
Location of anastomosis			
Cervical	72 (80.9%)	26 (76.5%)	0.5852
Intrathoracic	17 (19.1%)	8 (23.5%)	
Route			
Retrosternal	63 (70.8%)	25 (73.5%)	0.945
Posterior mediastinal	26 (29.2%)	9 (26.5%)	
Pericardial subcutaneous layer	8 (9.0%)	2 (5.9%)	
Method of anastomosis			
End-to-side	82 (92.1%)	28 (82.4%)	0.1145
End-to-end	7 (7.9%)	6 (17.6%)	

Table 6 Results of prophylactic intervention to prevent postoperative delirium in patients undergoing thoracoscopic esophagectomy

Variables	Conventional intervention group ($N=89$)	Alternative intervention group ($N=34$)	p value
Delirium			
Present	50	5	0.00004
Absent	39	29	
Pulmonary complications			
Present	19	2	0.04148
Absent	70	32	

Significant associations are shown in bold ($p < 0.05$)

According to previous studies, older age, preoperative impairment of cognition, depressive symptoms, psychotropic drug use, intraoperative blood transfusions, and previous amputation are well-known risk factors for postoperative delirium [49–51]. These risk factors are especially relevant for patients undergoing complicated and prolonged cardiovascular surgery [39]. Few studies have focused on postoperative delirium in patients who have undergone esophagectomy for EC. Takeuchi et al. reported that the risk of delirium is associated with older age, administration of flunitrazepam in the ICU, and postoperative complications after either conventional esophagectomy or minimally invasive esophagectomy [52].

We introduced a new prophylactic intervention for delirium after January 2016, based on the results of our study on the risk factors for PCs. The intervention reduced the incidence of delirium from 56.2 to 14.7% and the incidence of PCs from 21.3 to 5.9%. Thus, it was found to contribute to the decreased incidence of PCs after thoracoscopic esophagectomy, suggesting that it would also contribute to reducing hospitalization time and medical costs and, ultimately, better surgical outcomes for patients with EC. On the other hand, two of our patients suffered PCs after this prophylactic intervention, although they had other strong risk factors for PC. One was older than 69 years, with a Brinkman index > 800 and COPD, and the other had a Brinkman index > 800 and low FEV1/FVC (< 70%). Postoperative delirium also developed in both patients, delaying physical therapy and respiratory rehabilitation and making the prevention of PCs difficult.

This study has some limitations. First, it was an observational study based on reviews of medical records; not a randomized control study. Second, since our study population was small, a larger study is required to validate the results. Third, the intervention in this study included various elements and we could not establish which specific element of the intervention contributed most to the reduced incidence of delirium.

We implemented a multi-factorial intervention to prevent postoperative delirium. By evaluating the results

retrospectively, we were able to prevent not only postoperative delirium, but also PCs. However, we think that shortening the ICU stay and promoting early postoperative ambulation with a physical therapist contribute strongly to the prevention of PCs, based on the mechanism of the association between delirium and PCs. We also believe that drugs such as Yokukansan, an analgesic, an anti-ulcer drug, and sleep support this through their pharmacological actions [32–37].

In conclusion, we found that preoperative COPD and postoperative delirium are independent predictors of PCs after surgery for EC. Moreover, the prophylactic measures introduced to decrease the incidence of delirium might contribute to reducing the incidence of PC following EC surgery.

Compliance with ethical standards

Conflict of interest We have no conflicts of interest and received no financial support for this study.

Ethical statement All procedures and subsequent analyses were performed with the approval of the Institutional Review Boards of Mie University Hospital in Japan (no. 2017-3203). The study was conducted in accordance with the guidelines of the 1975 Declaration of Helsinki. Written informed consent was obtained from all study participants.

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