



# Early postoperative pulmonary complications after minimally invasive esophagectomy in the prone position: incidence and perioperative risk factors from the perspective of anesthetic management

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## Abstract

**Objectives** To investigate the incidence of and the risk factors for early postoperative pulmonary complications (PPC) after minimally invasive esophagectomy (MIE) in the prone position from the perspective of anesthetic management.

**Methods** We conducted a historical cohort study of patients who underwent MIE in the prone position between September 2010 and August 2018. PPC was defined as pneumonia, atelectasis, acute respiratory distress syndrome (ARDS), respiratory failure, and pulmonary embolism (Clavien–Dindo Classification Grade II or higher) that occurred within 7 days after MIE.

**Results** Out of 489 patients, there were 90 patients (18.4%) with PPC: 75 patients with pneumonia, 24 patients with atelectasis, 13 patients with respiratory failure, 6 patients with ARDS, and 2 patients with pulmonary embolism. Twenty-eight patients suffered from 2 or more components of PPC. PPC patients were older (66.6 vs. 63.6 year,  $P=0.038$ ) and had higher amount of crystalloid (4200 vs. 3550 mL,  $P<0.0001$ ), and longer duration of anesthesia (670 vs. 625 min,  $P=0.0062$ ) than non-PPC patients. PPC patients were more likely to have had chronic obstructive pulmonary disease (COPD) (26.7 vs. 7.8%,  $P<0.001$ ). Incidence of PPC was significantly higher in patients with one-lung ventilation than with two-lung ventilation (37.1 vs. 15.3%,  $P<0.001$ ). Multivariable logistic regression analysis showed that PPC was associated with age (per 10 years, odds ratio (OR) = 1.41), COPD (OR = 3.43), one-lung ventilation (OR = 1.94), and volume of crystalloid (per 500 mL, OR = 1.22).

**Conclusions** Two-lung rather than one-lung ventilation should be chosen and fluid overload should be avoided in patients undergoing MIE in the prone position.

**Keywords** Postoperative pulmonary complication · Minimally invasive esophagectomy · Prone position · One-lung ventilation · Risk factors

## Introduction

Treatment for esophageal cancer has made major progress in the last three decades. Although esophagectomy was traditionally performed with the combination of thoracotomy and laparotomy, minimally invasive esophagectomy (MIE), which includes thoracoscopic, laparoscopic, mediastinoscopic, and robotic surgery, for esophageal cancer seems to have been spreading around the world [1] since the introduction of the right thoracoscopic approach by Dallemagne et al. in 1991 [2]. The thoracoscopic approach in esophagectomy may be performed in the prone position [3]. One of the advantages of MIE in the prone position is that a total lung collapse by the use of one-lung ventilation may not be necessary for dissecting the esophagus [4]. One-lung

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ventilation, especially with traditional high tidal volume, has been shown to be associated with systemic inflammation after esophagectomy [5].

At the Cancer Institute Hospital, MIE for esophageal cancer in the prone position was introduced in 2010. Although one-lung ventilation with a double-lumen tube or a bronchial blocker was used when it was first implemented, two-lung ventilation is now used and partial lung collapse is achieved with the use of carbon dioxide insufflation. This thoracoscopic approach in the prone position can be less invasive and associated with a lower incidence and less severity of postoperative pulmonary complications (PPCs) compared with the traditional open esophagectomy [6, 7]. However, we still may have postoperative adverse events including PPCs although their incidence and severity may be low. PPCs remain the major cause of postoperative mortality after esophagectomy [8].

As anesthesiologists, our goal is to improve patients' outcomes by providing the best possible anesthetic management in patients undergoing esophagectomy. To achieve this goal, we focused on PPCs in the early stage of postoperative period and attempted to find factors that may help us improve anesthetic management. The objectives of the present study were threefold: (1) to calculate the incidence of PPCs within 7 days after esophagectomy; (2) to identify risk factors for PPCs; and (3) to investigate the effects of PPCs on outcomes. Since two different ventilatory settings (one-lung or two-lung ventilation) were used during the thoracic part of MIE over the past years, we especially focused on their effects on PPCs after MIE. Because the left lung presumably receives higher tidal volume in one-lung ventilation compared with two-lung ventilation, we assumed that patients with one-lung ventilation may be at higher risk for PPCs than those with two-lung ventilation.

## Methods

This study was approved by the Institutional Review Board of The Cancer Institute Hospital of Japanese Foundation for Cancer Research (No. 2018-1131, September 20, 2018), and the need for informed consent was waived. The protocol summary was publicized on the institutional website ([https://www.jfcr.or.jp/up\\_pdf/20190117142031\\_1.pdf](https://www.jfcr.or.jp/up_pdf/20190117142031_1.pdf)) clearly informing the patients of their right to refuse to participate. This report is based on our single-center historical cohort study of patients who underwent MIE and is in keeping with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [9].

## Patient inclusion and data collection

A historical cohort study of patients who underwent MIE for esophageal cancer between September 2010 and August 2018 was conducted. Patients who underwent combined surgery, open thoracotomy, two-stage surgery, surgery without the use of carbon dioxide pneumothorax, and who were planned to undergo tracheostomy or to be transported to the intensive care unit intubated were excluded. Patient data, surgical data, and anesthetic data, as well as laboratory data, were manually abstracted from the patients' electronic charts. Data collected included: age, gender, height, body weight, body mass index, American Society of Anesthesiologists physical status (ASA-PS), history of cigarette smoking (e.g., Brinkman index) and alcohol dependence, history of asthma, chronic obstructive pulmonary disease (COPD), diabetes mellitus, and hypertension, preoperative use of bronchodilators, history of chemotherapy and radiotherapy, cancer histology, tumor location and preoperative cancer stage. The Union for International Cancer Control (UICC) Tumor Node Metastasis (TNM) Classification of Malignant Tumors, 7th edition, was used for staging esophageal cancer. Preoperative laboratory values including hemoglobin, albumin, aspartate aminotransferase, alanine aminotransferase (ALT), serum creatinine concentration, estimated glomerular filtration rate (eGFR), arterial blood gases, and respiratory function test were obtained from the electronic charts. Surgical and anesthetic factors recorded were: surgical procedure, organ used for reconstruction, route of reconstruction, emergency or elective surgery, maintenance anesthetic agent, thoracic epidural anesthesia, ventilatory management (one-lung or two-lung ventilation), duration of anesthesia, surgery, prone position and carbon dioxide pneumothorax, volume and type of intraoperative fluids (crystalloid or colloid) and albumin administered, and intraoperative steroid use. Intraoperative transfusions of red blood cells, fresh frozen plasma or platelets, urine output, and estimated blood loss were recorded. One unit of each blood component was derived from 200 mL of whole blood. Because ventilatory settings were changed during anesthesia depending on the patients' condition, tidal volume with the longest duration of each case during the thoracic part of the procedure was sampled. The pressure of the carbon dioxide pneumothorax to improve the surgical field during the thoracic part of esophagectomy was left to the discretion of the surgeons. The highest pressure of pneumothorax was sampled in the present study.

## Management of anesthesia

Patients were anesthetized with general anesthesia combined with epidural anesthesia unless contraindicated. Choice of maintenance anesthetic agent and analgesic drugs was left to the discretion of the anesthesiologists. Patient controlled analgesia was routinely used epidurally for postoperative analgesia. If epidural anesthesia was not used for some reason, intravenous patient controlled analgesia was used instead. Ventilatory management was shifted from one-lung ventilation to two-lung ventilation in 2013. When one-lung ventilation was used for MIE in our institute, protective one-lung ventilation strategy including low tidal volume ( $< 6$  mL/kg (predicted body weight)) had not been implemented. The level of PEEP was at the anesthesiologists' discretion. During thoracoscopy with two-lung ventilation in the prone position, PEEP was requested not to be applied by the surgeons to improve the surgical field. At the end of the surgery, patients were routinely extubated in the operating room; however, if the risks for respiratory complications or reintubation were considered high, they were transferred to the intensive care unit without extubation.

## Definitions and outcomes

This study investigated the incidence of and risk factors for PPCs after MIE. PPCs were defined as pneumonia, atelectasis, ARDS, respiratory failure, and pulmonary embolism that occurred within 7 days after MIE. We focused on PPCs in the early stage of postoperative period (e.g., 7 days) because we considered that they may be related to the anesthetic management including ventilatory management (one-lung vs. two-lung ventilation) and that clarifying risk factors for PPCs after MIE may help us improve anesthetic management. PPCs that occur in the later stage of postoperative period were excluded because they may not be related to anesthetic management including ventilatory management (one-lung vs. two-lung ventilation). Each component of PPCs (pneumonia, atelectasis, ARDS, respiratory failure, and pulmonary embolism) was defined according to the Clavien-Dindo Classification (CDC) [10] Grade II or higher. Other outcome variables included mortality, duration of hospital stay, and reintubation.

## Statistical analysis

Continuous variables are summarized as median (25th, 75th percentiles) or mean (standard deviation) values. Categorical variables are summarized as frequencies (percentages). Normally and non-normally distributed continuous data were

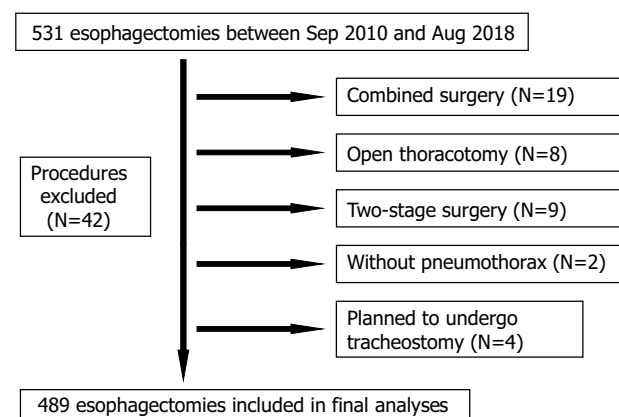
analyzed using Student's two-sample *t*-test or the Wilcoxon rank-sum test, respectively. Categorical data were analyzed using Fisher's exact test.

Multivariable logistic regression was used to model the relationship between postoperative PPCs developing within 7 days and perioperative risk factors. To identify perioperative risk factors, exploratory data analysis was first performed using univariate comparisons. Then, the model included all covariates of clinical importance regardless of statistical significance (age, gender, COPD, Brinkman index, and ventilatory management (one-lung or two-lung ventilation)) and all covariates with associations on exploratory analysis ( $P < 0.10$ ). To avoid multicollinearity, two or more predictor variables that were highly correlated ( $r > 0.8$ ) were not included, and the analyses were performed by backward stepwise selection methods. Data are presented as odds ratios with 95% confidence intervals.

All tests were two-sided, and a *P*-value  $< 0.05$  was considered significant. Statistical analyses were conducted using STATA version 13 (StataCorp, College Station, TX).

## Results

In total, 531 patients who underwent esophagectomy between September 2010 and August 2018 were identified for this study. After excluding 42 patients, 489 patients were included in the final analysis (Fig. 1). There were 90 patients (18.4%) with PPCs: 75 with pneumonia (CDC Grade II: 67 patients, IIIa: 5 patients, IVa: 2 patients, V: 1 patient), 24 with atelectasis (Grade II: 11 patients, IIIa: 7 patients, IIIb: 1 patient, IVa: 5 patients), 13 with respiratory failure (Grade II: 1 patient, IIIb: 1 patient, IVa: 11 patients), 6 with ARDS (Grade II: 1 patient, IVa: 5 patients), and 2 with pulmonary



**Fig. 1** Flow chart outlining the inclusion and exclusion criteria used in the study. From 531 patients who underwent esophagectomy, 42 patients were excluded leaving 489 patients included in the final analysis

embolism (Grade IVa: 2 patients). Twenty-eight patients suffered from 2 or more components of PPCs.

Patients who developed PPCs were significantly older and had higher ASA-PS and lower ALT than non-PPC patients. PPC patients were more likely than non-PPC patients to have a history of COPD. No significant differences were observed in arterial blood gases or respiratory function tests between PPC and non-PPC patients (Table 1). Among ex-smokers, there was no significant difference in the duration of smoking cessation between PPC (4 (0–17) years,  $P=0.56$ ) and non-PPC patients (5 (0–16) years).

Incidence of PPC was significantly higher in patients with one-lung ventilation than those with two-lung ventilation (37.1% vs. 15.3%,  $P<0.001$ ). PPC patients received a significantly higher amount of crystalloid and albumin than non-PPC patients. There were significant differences in duration of pneumothorax, prone position, surgery and anesthesia between PPC and non-PPC patients. The retrosternal route was more likely to be chosen for reconstruction in non-PPC patients (Table 2). No patients received fresh frozen plasma during anesthesia. There was no significant difference in tidal volume during the thoracic part of esophagectomy between PPC ( $8.9 \pm 1.4$  mL/kg (predicted body weight),  $P=0.27$ ) and non-PPC patients ( $8.7 \pm 1.3$  mL/kg) who received two-lung ventilation, although the data were available only in 41 patients with PPC (64.0%) and 235 patients without PPC (66.2%). The data of tidal volume were available only in 4 patients (6.2–8.0 mL/kg (predicted body weight)) who received one-lung ventilation.

The multivariable model for developing PPCs was adjusted for age, gender, COPD, Brinkman index, ventilatory management (one-lung or two-lung ventilation), chemotherapy, hypertension, ALT, eGFR, forced expiratory volume in one second (FEV1), volume of crystalloid, volume of albumin, urine volume, duration of anesthesia, duration of pneumothorax, and reconstruction route. Duration of surgery and prone position were not included in the model since they were highly correlated with the duration of anesthesia and pneumothorax, respectively ( $r=0.95$  and  $0.90$ ). ASA-PS was not included in the multivariable model because it is related to other variables such as hypertension, COPD, and eGFR. Since antethoracic or other routes were selected only in a small number of patients, posterior mediastinum, antethoracic and other routes were combined in the multivariable logistic regression analysis. Multivariable logistic regression analysis showed that age, COPD, one-lung ventilation, and volume of crystalloid were significantly associated with PPCs (Table 3). During the process of backward stepwise selection, Brinkman index, eGFR, duration of anesthesia, duration of pneumothorax, urine volume, volume of albumin, hypertension, FEV1, gender, reconstruction route, and chemotherapy were eliminated from the multivariable regression analysis model.

There were significant differences in in-hospital mortality, length of hospital stay and incidence of reintubation between PPC and non-PPC patients (Table 4). One of 3 patients who died during hospitalization was reintubated and received mechanical ventilation on postoperative day (POD) 3 because of aspiration pneumonia. This patient suffered from repetitive pneumonia even after weaning from the ventilator and finally passed away on POD 453 because of respiratory failure and pneumonia. Although the remaining 2 patients suffered from PPC within 7 days, their causes of deaths were not related to PPC within 7 days. One of them passed away because of sepsis and ARDS and the other passed away because of anastomotic leakage and tracheogastric tube fistula.

## Discussion

The incidence of and the risk factors for early PPCs in patients undergoing MIE in the prone position were examined from the perspective of anesthetic management. PPCs, which were defined as pneumonia, atelectasis, ARDS, respiratory failure, and pulmonary embolism that occurred within 7 days after MIE, were found in 90 patients (18.4%). A multivariable logistic regression analysis showed that one-lung ventilation and volume of crystalloid were modifiable risk factors for early PPCs. In-hospital mortality was significantly higher in PPC patients than non-PPC patients.

MIE has been shown to be associated with a lower incidence rate of PPCs compared with traditional esophagectomy with right thoracotomy. Biere et al. demonstrated in their randomized study [6] that the incidence of postoperative pulmonary infection was significantly lower in patients undergoing MIE (9%) than open right thoracotomy (29%). Furthermore, in the study by Kanekiyo et al. [7] using propensity score matching, patients who underwent thoracoscopic esophagectomy in the prone position had a lower incidence of PPCs (16.9%) than those who underwent right thoracotomy (33.9%). Although it may not be possible to compare PPC incidence rates among studies because of the difference in the definitions of PPCs, the incidences of pneumonia (pulmonary infection) (15.3%) and PPCs (18.4%) observed in the present study may be lower than those found in patients undergoing esophagectomy with right thoracotomy in those studies [6, 7].

As far as we are aware, this is the first study that investigated risk factors for PPCs exclusively in patients who underwent MIE in the prone position and addressed the effects of different ventilatory management on PPCs; however, there are several studies that investigated pulmonary complications after other types of esophagectomy. Zingg et al. included both patients with esophageal cancer undergoing right thoracotomy and those undergoing MIE in the

**Table 1** Preoperative patient characteristics

	PPC (+) ( <i>n</i> = 90)	PPC (–) ( <i>n</i> = 399)	P value
<b>Demographic factors</b>			
Age, years (SD)	66.6 (9.1)	63.6 (8.7)	0.038
Female, <i>N</i> (%)	15 (16.7)	91 (22.8)	0.26
Height, cm (SD)	163.8 (7.9)	164.7 (8.0)	0.32
Weight, kg (SD)	59.8 (11.1)	58.9 (10.8)	0.49
BMI, kg/m <sup>2</sup> (SD)	22.2 (3.2)	21.6 (3.0)	0.12
ASA classification, <i>N</i> (%)			0.001
1	15 (16.7)	141 (35.4)	
2	74 (82.2)	251 (62.9)	
3	1 (1.1)	7 (1.7)	
4	0 (0.0)	0 (0.0)	
5	0 (0.0)	0 (0.0)	
Never smoker, <i>N</i> (%)	15 (16.7)	78 (19.6)	0.66
Brinkman index (IQR)	590 (250–980)	500 (200–800)	0.13
Alcohol dependence, <i>N</i> (%)	3 (3.3)	9 (2.3)	0.47
Chemotherapy, <i>N</i> (%)	42 (46.7)	228 (57.1)	0.079
Radiotherapy, <i>N</i> (%)	1 (1.1)	17 (4.3)	0.22
<b>Esophageal cancer</b>			
Cancer histology, <i>N</i> (%)			0.93
Squamous cell, <i>N</i> (%)	78 (86.7)	338 (84.7)	
Adenocarcinoma, <i>N</i> (%)	10 (11.1)	47 (11.8)	
Other, <i>N</i> (%)	2 (2.2)	14 (3.5)	
Tumor location			0.69
Upper, <i>N</i> (%)	16 (17.8)	59 (14.8)	
Middle, <i>N</i> (%)	36 (40.0)	175 (43.9)	
Lower, <i>N</i> (%)	38 (42.2)	165 (41.4)	
Preoperative cancer stage, <i>N</i> (%) <sup>a</sup>			0.50
0	0 (0.0)	2 (0.5)	
I	43 (47.8)	187 (46.9)	
II	31 (34.4)	108 (27.1)	
III	13 (14.4)	83 (20.8)	
IV	3 (3.3)	19 (4.8)	
Comorbidity, <i>N</i> (%)			
Asthma	4 (4.4)	27 (6.8)	0.63
COPD	24 (26.7)	31 (7.8)	<0.001
Diabetes	12 (13.3)	48 (12.0)	0.72
Hypertension	41 (45.6)	137 (34.3)	0.052
Perioperative medication, <i>N</i> (%)			
Bronchodilator	4 (4.4)	15 (3.8)	0.48
Laboratory test			
Hemoglobin, g/dL (SD)	12.8 (1.5)	12.7 (1.4)	0.60
Albumin, g/dL (SD)	4.0 (0.3)	4.1 (0.4)	0.26
AST, IU/L (IQR)	20 (18–23)	21 (17–25)	0.48
ALT, IU/L (IQR)	14 (11–21)	16 (12–22)	0.048
Creatinine, mg/dL (SD)	0.81 (0.19)	0.78 (0.19)	0.16
eGFR, mL/min/1.73 m <sup>2</sup> (SD)	73.5 (14.9)	76.8 (17.0)	0.090
Arterial blood gas			
pH (SD)	7.41 (0.03)	7.41 (0.03)	0.30
PaO <sub>2</sub> , mmHg (SD)	88.9 (13.1)	88.8 (11.4)	0.93
PaCO <sub>2</sub> , mmHg (SD)	40.2 (3.9)	40.4 (3.9)	0.68

**Table 1** (continued)

	PPC (+) (n = 90)	PPC (–) (n = 399)	P value
Respiratory function test			
Vital capacity, L (SD)	3.67 (0.80)	3.75 (0.83)	0.38
%VC, % (SD)	114.0 (18.5)	116.4 (16.1)	0.21
FEV1, L (SD)	2.65 (0.64)	2.79 (0.67)	0.067
FEV1%, % (SD)	73.2 (10.3)	74.4 (8.1)	0.21

PPC postoperative pulmonary complication; SD standard deviation; BMI body mass index; ASA American Society for Anesthesiologists; IQR interquartile range; COPD chronic obstructive pulmonary disease; AST aspartate aminotransferase; ALT alanine aminotransferase; eGFR estimated glomerular filtration rate; %VC vital capacity as percent of predicted; FEV1 forced expiratory volume in one second; FEV1% forced expiratory volume in one second as percent of forced vital capacity

<sup>a</sup>The Union for International Cancer Control (UICC) Tumor Node Metastasis (TNM) Classification of Malignant Tumors, 7th edition, was used for staging esophageal cancer

**Table 2** Perioperative variables

	PPC (+) (n = 90)	PPC (–) (n = 399)	P value
Surgery			
Reconstruction organs, N (%)			0.54
Stomach	86 (95.6)	387 (97.0)	
Colon	4 (4.4)	10 (2.5)	
Others	0 (0.0)	2 (0.5)	
Reconstruction route, N (%)			0.001
Retrosternal	42 (46.7)	262 (65.7)	
Posterior mediastinum	43 (47.8)	117 (29.3)	
Antethoracic	3 (3.3)	8 (2.0)	
Others	2 (2.2)	12 (3.0)	
Highest pressure of pneumothorax, mmHg (IQR)	6 (6–8)	6 (6–8)	0.33
Duration of pneumothorax, min (IQR)	245 (195–297)	224 (180–272)	0.026
Duration of prone position, min (IQR)	294 (245–340)	270 (225–310)	0.0043
Duration of surgery, min (IQR)	598 (518–646)	553 (486–624)	0.0060
Anesthesia			
Anesthetic agent, N (%)			0.40
TIVA	9 (23.1)	30 (76.9)	
Inhalational	81 (18.0)	369 (82.0)	
Epidural, N (%)	85 (94.4)	379 (95.0)	0.79
Ventilatory management			<0.001
One-lung ventilation	26 (37.1)	44 (62.9)	
Two-lung ventilation	64 (15.3)	355 (84.7)	
Steroids, N (%)	68 (75.6)	314 (78.7)	0.57
Crystalloid, mL (IQR)	4200 (3350–5140)	3550 (2950–4350)	<0.0001
Colloid, mL (IQR)	1000 (700–1400)	1000 (500–1350)	0.41
Albumin, mL (IQR)	0 (0–500)	0 (0–100)	0.0001
Estimated blood loss, mL (IQR)	160 (90–270)	130 (80–260)	0.24
Urine volume, mL (IQR)	945 (590–1550)	720 (450–1080)	0.0012
Transfusion of RBC, N (%)	2 (2.2)	3 (0.8)	0.23
Duration of anesthesia, min (IQR)	670 (593–728)	625 (562–697)	0.0062

PPC postoperative pulmonary complication; SD standard deviation; IQR interquartile range; TIVA total intravenous anesthesia; RBC red blood cell



**Table 3** Multivariable logistic regression analysis for postoperative pulmonary complications

Variables	OR unadj	OR adj	95% CI	P-value
Age (per 10 years)	1.48	1.41	1.05–1.91	0.023
Gender (female)	0.68	–		
COPD	4.32	3.43	1.83–6.44	<0.001
Brinkman index (per 100 unit)	1.05	–		
Ventilatory management				
Two-lung ventilation	1 (reference)	1 (reference)		
One-lung ventilation	3.28	1.94	1.03–3.65	0.039
Chemotherapy	0.66	–		
Hypertension	1.60	–		
Alanine aminotransferase	0.98	0.98	0.96–1.00	0.15
eGFR (per 10 mL/min/1.73 m <sup>2</sup> )	0.89	–		
FEV1	0.72	–		
Crystalloid (per 500 mL)	1.27	1.22	1.10–1.37	<0.001
Albumin (per 500 mL)	1.80	–		
Urine (per 100 mL)	1.30	–		
Duration of anesthesia (per 100 min)	1.33	–		
Duration of pneumothorax (per 100 min)	1.21	–		
Reconstruction route				
Retrosternal	1 (reference)	–		
Else than retrosternal	2.19	–		

*ORunadj* odds ratio unadjusted; *ORadj* odds ratio adjusted; *CI* confidence interval; *COPD* chronic obstructive pulmonary disease; *eGFR* estimated glomerular filtration rate; *FEV1* forced expiratory volume in 1 sec

**Table 4** Outcomes

	PPC (+) (n=90)	PPC (–) (n=399)	P value	OR	95% CI
In-hospital mortality (n (%))	3 (3.3)	0 (0.0)	0.006	Infinite <sup>a</sup>	
Hospital stay (day, IQR)	23 (19–35)	19 (17–24)	<0.001		
Hospital stay > 20 days (n (%))	57 (63.3)	162 (40.6)	<0.001	2.5 <sup>b</sup>	1.6–4.1
Reintubation (n (%))	12 (13.3)	4 (1.0)	<0.001	15.2	4.8–48.3

*PPC* postoperative pulmonary complication; *OR* odds ratio; *CI* confidence interval; *IQR* interquartile range

<sup>a</sup>Since no patient in the non-PPC group died, the OR was infinite

<sup>b</sup>Since the median hospital stay was 20 days, a measure of the odds of hospital stay exceeding 20 days in the PPC group compared to the odds of the same event happening in the non-PPC group was calculated

prone position and found that the number of preoperative comorbidities and smoking were risk factors for PPCs [11]. Molena et al. included nearly 3000 patients with esophageal cancer or gastric cancer who underwent esophagectomy (e.g., transhiatal, Ivor Lewis, McKeown) and found that numerous factors including advanced age, smoking, alcohol use, dyspnea, history of COPD, and prolonged operative time were risk factors for PPCs [8]. Smoking has been shown to be one of the commonest risk factors for PPC in patients undergoing esophagectomy [8, 11]. Although it is difficult to explain why smoking was not a risk factor for PPCs in the present study, it may be related to the policy of the Cancer Institute Hospital that candidates for esophagectomy are strictly prohibited from smoking from the date they

first see an esophageal cancer specialist. According to the study by Yoshida et al. [12], esophagectomy patients with a preoperative smoking cessation period longer than 30 days were at lower risk for postoperative pneumonia than those with a smoking cessation period of 30 days or shorter. Since patients who undergo neoadjuvant chemotherapy followed by esophagectomy generally need to wait for a couple of months until surgery, during which time they were required not to smoke, the effects of smoking habit on PPCs may have been small in the present study.

Multivariable logistic regression analysis in the present study showed that one-lung ventilation was one of the modifiable risk factors for PPCs after MIE (Table 3). Since protective one-lung ventilation strategy including low tidal

volume (< 6 mL/kg (predicted body weight)) had not been implemented before 2013 in our institution, our results may suggest that patients with conventional one-lung ventilation were at higher risk for PPC. Shen et al. [13] demonstrated that low tidal volume (5 mL/kg) combined with 5 cmH<sub>2</sub>O of PEEP decreased ventilation-associated lung inflammation compared with a conventional tidal volume (8 mL/kg), thereby minimizing PPC after MIE. From the standpoint of minimizing the risk for PPC, protective lung strategy with low tidal volume may need to be chosen during the thoracic part of MIE when surgeons and/or anesthesiologists prefer one-lung ventilation rather than two-lung ventilation. Although protective one-lung ventilation seems safer than conventional one-lung ventilation, since there has been no study that compared safety and usefulness between protective one-lung ventilation and two-lung ventilation, further studies may be required to compare the effects of protective one-lung and two-lung ventilation on PPCs in a prospective and randomized fashion.

Intraoperative crystalloid volume seemed to be the other modifiable risk factors for PPCs in the present study, which was in line with the study by Casado et al. [14]. Although the precise mechanisms are not clear, excess fluid administration may have led to lung edema and interstitial water retention. There is also a possibility that patients with poor preoperative conditions (e.g., hypovolemia), who may have been more likely to develop PPC, required more crystalloid intraoperatively. For example, patients with obstruction to the passage of food and water due to cancer may likely suffer from hypovolemia preoperatively. Further studies may be needed to investigate the best way to monitor circulating blood volume and to maintain appropriate fluid balance in patients undergoing esophagectomy. Goal-directed fluid therapy might be helpful to guide fluid administration and prevent PPCs [15], although it has not yet been proven in patients undergoing esophagectomy.

The cause of death was related to PPCs in only one of 3 patients. Thus, we presume that PPCs within 7 days may not be necessarily related to the patients' in-hospital mortality even though mortality was higher in PPC patients.

Several limitations of the present study need to be addressed. First, as with all observational research, residual or unmeasured confounders may be an alternative explanation for the results. Generalizability is limited to centers with patient and surgical profiles similar to our own. Second, data on the tidal volume during the thoracic part of esophagectomy was available for only 276 patients (66%) with two-lung ventilation and 4 patients with one-lung ventilation, although a high tidal volume during one-lung ventilation has been suggested to be one of the risk factors for PPCs after esophagectomy [5]. Lastly, PPCs that occurred in the later stage of postoperative period were not included in this

study since we assume that they may not be related to the anesthetic management.

## Conclusions

The incidence of early PPCs was 18.4% in patients who underwent MIE in the prone position. One-lung ventilation and volume of crystalloid seem to be modifiable risk factors for early PPCs from the perspective of anesthetic management. In patients undergoing MIE in the prone position, two-lung ventilation rather than conventional one-lung ventilation should be chosen and fluid overload should be avoided. PPCs resulted in higher mortality, longer hospital stays, and higher incidence of reintubation.

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## Declarations

**Conflict of interest** The authors declare no conflict of interest associated with this manuscript.

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