Factors Affecting Pulmonary Complications after Combined Thoracolaparoscopic Radical Esophagectomy for Esophageal Cancer in Elderly Patients

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ABSTRACT

Objective: To determine the frequency and risk factors for pulmonary complications in elderly patients undergoing combined thoracolaparoscopic radical esophageal cancer surgery, and to develop a predictive model for pulmonary complications occurrence.

Study Design: Observational study.

Place and Duration of the Study: Department of Thoracic Surgery, Lujiang County People's Hospital, Anhui Province, China, from January 2017 to August 2022.

Methodology: Two hundred and sixty elderly patients who underwent combined thoracic and laparoscopic radical esophagectomy were included. Univariate and multifactorial analyses were performed to identify risk factors for pulmonary complications, and a predictive model was developed using significant factors.

Results: Pulmonary complications occurred in 27.69% of patients. Advanced age, smoking index, diabetes mellitus, tumour location, advanced clinical stage, intraoperative bleeding, duration of operation, and postoperative mechanical ventilation time were significantly associated with pulmonary complications ($p<0.05$). Multifactorial analysis identified advanced age, diabetes, smoking index, advanced clinical stage, and time of surgery as independent risk factors for pulmonary complications. The prediction model had good predictive efficacy with an area under the ROC curve of 0.857, sensitivity of 83.3%, and specificity of 71.1%.

Conclusion: Combined thoracolaparoscopic radical esophageal cancer surgery has a high incidence of pulmonary complications in elderly patients. Advanced age, diabetes, smoking index, advanced clinical stage, and time of surgery are independent risk factors for pulmonary complications, and the developed predictive model will be contributing to identify high-risk patients.

Key Words: *Esophageal cancer, Elderly patients, Pulmonary complications, Risk factors*.

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INTRODUCTION

Esophageal cancer (EC) is the eighth most common cancer in the world and the sixth leading cause of cancer-related deaths worldwide.[1] Patients diagnosed with EC often exhibit limited early symptoms and present with a high degree of malignancy, ultimately leading to an unfavourable prognosis. Despite recent advances in neoadjuvant radiotherapy and targeted therapy, surgical intervention remains the primary approach for managing EC, with radical esophageal cancer resection being considered the standard of care.[2] Esophageal cancer resection is one of the most complex and invasive gastrointestinal surgery, and although the surgical approach has improved, the incidence of postoperative complications morbidity and mortality are still high.[3-5]

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Current literature suggests that 8 to 13% of patients with esophageal cancer develop pulmonary complication (PC) after radical surgery.[6,7] This is a major cause of postoperative prognosis for patients with esophageal cancer, and a primary contributing factor to the escalation of treatment expenses and hospitalisation duration for these patients. For elderly patients, it is poorly tolerated and the development of complications may increase the morbidity and mortality of patients. In recent years, thoracoscopic technology has been extensively applied to the radical resection of esophageal cancer and has demonstrated favourable outcomes. Its unique minimally invasive nature has substantially reduced patient trauma.

The rationale of this study was to investigate perioperative factors that may influence the occurrence of PC following combined thoracolaparoscopic radical esophageal cancer surgery in elderly patients. The study aimed to identify independent risk factors for PC and to provide a basis for prognostic assessment of patients.

METHODOLOGY

Retrospective analysis of 260 patients with EC treated surgically in the Lujiang County People's Hospital, Anhui Province,

China, Hospital, from January 2017 to August 2022 in thoracic surgery. Inclusion criteria were all patients aged 60 years or older, who had diagnosed and continued EC and those undergoing combined thoracolaparoscopic surgical treatment. No other tumour-specific treatment modalities, such as radiotherapy and chemotherapy, were administered prior to surgery, for resectable that did not invade other tissues. Exclusion criteria were pre-operative pulmonary infection, a previous history of thoracoabdominal surgery or esophageal surgery, the combination of other serious underlying diseases, incomplete information such as clinical data, pathological results, and follow-up; those who did not consent or did not agree to participate in this study. The methodology of this retrospective study was approved by the Hospital's Ethics Committee.

Anaesthesia was administered using general anaesthesia with bronchial intubation. The operation was performed in three main steps. Firstly, thoracoscopic mobilisation of the thoracic esophagus was carried out, followed by the removal of mediastinal lymph nodes. Secondly, laparoscopic assistance was used to mobilise the stomach and create a gastric tube, resulting in the formation of a tubular stomach. Lastly, a gastro-oesophageal anastomosis was performed.

The patient was placed in the left lateral position, and one-lung ventilation was initiated for the left lung. A 1-cm incision was made in the 7^{th} intercostal space at the mid-axillary line and a Trocar was inserted for the thoracoscopic camera. A 3-cm incision was made in the 4^{th} intercostal space at the anterior axillary line as the primary operating port, and the secondary port was in the 7^{th} intercostal space at the posterior axillary line. The thoracic cavity was dissected to expose the esophageal bed, and a lung clamp was inserted through the posterior axillary line incision. The pleura was lifted and cut longitudinally along the esophageal bed to explore the esophageal lesion. The tissue surrounding the azygos vein was freed, and the two ends of the azygos vein were clamped with Hem-en-lok forceps and dissected with an ultrasonic knife. The esophagus was freed along the lateral side of the spine, and the lymph nodes were cleared sequentially.

The patient underwent laparoscopic total gastrectomy. The procedure involved creating a 1 cm transverse subumbilical arc incision and establishing a pneumoperitoneum with an intra-abdominal pressure of 12 mmHg. Laparoscopic instruments were inserted through small incisions at various locations. The greater and lesser curvature of the stomach were dissected, and the left gastroepiploic artery, left gastric artery, short gastric artery, and their branches were severed while preserving the right gastroepiploic artery and right gastric artery. The entire stomach was removed and fashioned into a tube shape outside the body, then connected to the esophageal ligature *via* a 5 cm epigastric incision.

An incision was made at the inner edge of the left sternocleidomastoid muscle to reveal the cervical segment of the esophagus, and the intrathoracic esophagus was pulled out through the incision and the tubular stomach was lifted up to the neck. The esophagus was cut at the preformed anastomosis, and the 23 mm tubular anastomosis was used to complete the esophage-gastric anastomosis, after which the gastric stump was intermittently sutured with a No. 1 silk suture and checked for bleeding points. A fine latex tube was placed and the neck incision was closed. Finally, a nutrition tube and a gastric tube were placed, fixed in place, and the abdominal incision was closed layer by layer.

Postoperative PC was defined as thoracic or lung-related complications such as pneumonia, lung abscess, respiratory failure, pulmonary oedema, and respiratory failure within one month after surgery. Patient-related clinical data were accessed through the inpatient electronic case system, and the results of patient age, gender, smoking index, combined underlying diseases, tumour location, clinical stage, operative time, intraoperative bleeding, and postoperative mechanical ventilation time were entered into an excel sheet and double-entry error correction was performed. Patients were divided into PC and non-PC groups according to the presence or absence of PC. There were 72 patients in the PC group and 188 patients in the non-PC group, and the differences in relevant factors between the two groups were compared, and those with statistical significant differences were further analysed by unconditional dichotomous logistic regression.

Data were analysed using the IBM-SPSS 26.0 software package, with measures expressed as ($X\pm s$) and statistically analysed using the student's-t test for two independent samples; count data were statistically described using composition ratios or rates and statistically analysed using the $\chi 2$ test. Multifactorial analyses were performed using unconditional dichotomous logistic regression models, and the ratio (OR) and its 95% confidence interval (CI) were calculated. Diagnostic efficacy prediction was analysed using subject operating characteristic curves (ROC curves), and the area under the curve (AUC), sensitivity, and specificity were calculated. Differences were considered statistically significant at $p<0.05$.

RESULTS

A total of 260 elderly patients with CE underwent combined thoracolaparoscopic radical surgery, with ages ranging from 60 to 85 years and a mean age of 68.85±6.05 years. Of these patients, 153(58.8%) were males and 107(41.2%) were females. Postoperative complications occurred in 72 patients, resulting in a morbidity rate of 27.69% (72/260). Out of 72 cases, 50 were diagnosed with pneumonia, representing 69.44% (50/72) of the total cases. Nine cases of pleural effusion, accounting for 12.50% (9/72); 8 cases of respiratory failure, accounting for 11.11% (8/72); 3 cases of empyema, accounting for 4.17% (3/72); 2 cases of pulmonary oedema, accounting for 2.78% (2/72).

The general clinical data and intraoperative observations of patients in the PC and non-PC groups were compared, and the results showed that advanced age, smoking index, diabetes mellitus, tumour location, advanced tumour stage (stage III and IV), operative time, and intraoperative bleeding were closely related to the occurrence of PC (all $p<0.05$, Table I).

Table I: Univariate analysis affecting the occurrence of PC [(X±s), cases (%)].

Parameter	PC group (n=72)	Non-PC group (n=188)	t/χ^2 value	p-value
Gender (male / female) n (%)	45 (62.5) / 27 (37.5)	108 (57.4) / 80 (42.6)	0.549	0.459
Age (years)			8.962	0.003
60~70	30 (41.7)	117 (62.2)		
>70	42 (58.3)	71 (37.8)		
Underlying disease n (%)				
Diabetes	34 (47.2)	37 (19.7)	19.894	<0.001
Hypertension	40 (55.6)	93 (49.5)	0.772	0.380
Smoking index n (%)			20.398	<0.001
<400	30 (41.7)	135 (71.8)		
≥400	42 (58.3)	53 (28.2)		
Tumor location n (%)			6.828	0.009
Upper thoracic segment	43 (59.7)	143 (76.1)		
Middle and lower thoracic segment	29 (40.3)	45 (23.9)		
Clinical stages n (%)			9.530	0.002
Phase I and II	46 (63.9)	154 (81.9)		
Phase III and IV	26 (36.1)	34 (18.1)		
Duration of operation (min)	212.72±17.83	193.51±17.15	7.997	<0.001
Intraoperative bleeding (ml)	195.74±23.57	189.17±22.86	2.054	0.041
Postoperative mechanical ventilation time (h)	11.24±1.76	10.48±1.91	2.933	0.004

p-value: t-test was used for the duration of operation, intraoperative bleeding and postoperative mechanical ventilation time, and the chi-square test was used for other parameters.

Table II: Multivariate logistic regression analysis of postoperative PC in patients with CE.

Parameter	B value	SE	Wald	OR value	95% CI	p-value
X_1 Age >70	0.906	0.357	6.438	2.475	1.229~4.984	0.011
X_2 Diabetes	1.118	0.378	8.762	3.057	1.459~6.408	0.003
X_3 Smoking index ≥400	1.157	0.353	10.739	3.179	1.592~6.349	0.001
X_4 Clinical stages (III, IV)	0.890	0.397	5.030	2.435	1.119~5.300	0.025
X_5 Duration of operation	0.065	0.011	33.802	1.067	1.044~1.091	<0.001

The variables that were significant in the univariate analysis described above (advanced age, diabetes, smoking index, tumour location, clinical stage, time of surgery, and intraoperative bleeding) were used as independent variables, and then the presence or absence of PC events (1 for presence and 0 for absence) were used as dependent variables in an unconditional dichotomous logistic regression analysis, and the optimisation model was fitted using the stepwise backward method. The results showed that advanced age (OR = 2.475, 95% CI:1.229 ~ 4.984, p = 0.011), diabetes (OR = 3.057, 95% CI:1.459 ~ 6.408, p = 0.003), smoking index ≥400 (OR = 3.179, 95% CI:1.592 ~ 6.349, p=0.001), and advanced clinical stage (stage III and IV) (OR = 2.435, 95% CI:1.119 ~ 5.300, p = 0.025) and duration of operation (OR = 1.067, 95% CI:1.044 ~ 1.091, p<0.001) were independent risk factors for the development of PC after combined thoracolaparoscopic radical esophageal cancer surgery in elderly patients (OR all >1, p-value all <0.05, Table II).

The variables with positive results in the multifactorial analysis (X1 advanced age, X2 diabetes, X3 smoking index, X4 clinical stage, and X5 duration of operation) were included in the prediction model equation, resulting in Y = -15.507 + 0.893X1 + 1.079X2 + 1.169X3 + 0.855X4 + 0.064X5. ROC curve was plotted, showing an AUC of 0.857 (95% CI: 0.804 ~ 0.909), the sensitivity was 83.3%, and the specificity was 71.1% (Figure 1).

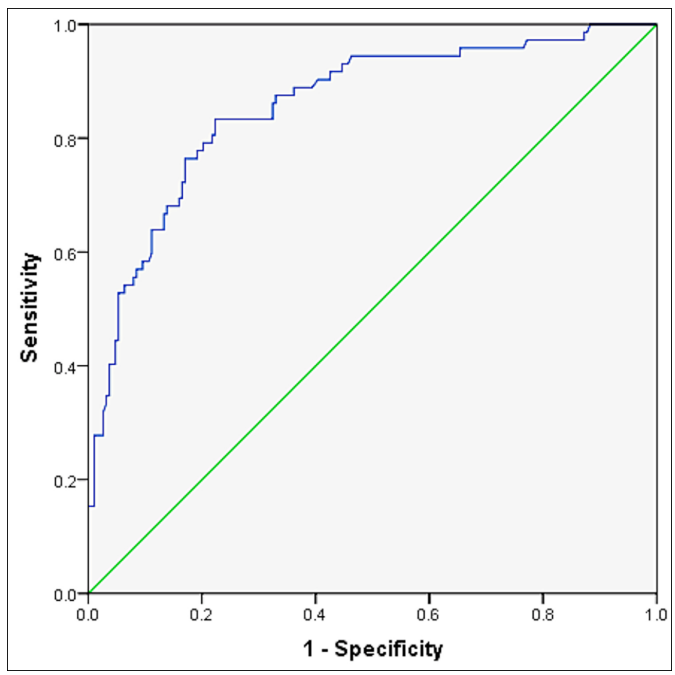

Figure 1: Diagnostic efficacy of predictive models for the occurrence of postoperative PC in multiple elderly patients with esophageal cancer.

DISCUSSION

In recent years, minimally invasive surgery has become one of the major surgical procedures for patients with esophageal cancer.[8,9] However, PC such as lung inflamma-

tion, lung abscess, and other respiratory diseases have surpassed anastomotic leakage as the most frequent complication following thoracoscopic minimally invasive resection of esophageal cancer.[10-12] These complications significantly reduce the prognosis of patients, emphasising the need for effective management strategies.

Limited research has been conducted on the factors that contribute to the development of PC following esophageal cancer surgery. Li *et al.* reported that patients' serum albumin level, duration of surgery, perioperative blood transfusion, and length of hospital stay were independent predictors of postoperative pulmonary infection in esophageal cancer.[13] In contrast, a meta-analysis including 2822 esophageal cancer cases concluded that preoperative impaired lung function was a risk factor for postoperative respiratory failure, and the degree of preoperative impaired lung function and postoperative respiratory failure were typically positively correlated.[14] Some investigators have attempted to predict and assess the occurrence of postoperative pneumonia in esophageal cancer by developing clinical prediction models.[15] This study adopts a comprehensive approach to investigating pulmonary complications as a collective research object following surgical intervention for esophageal cancer, which shows that the incidence of PC in elderly patients with esophageal cancer after radical surgery is 27.69%. The elderly, smoking index, late clinical stage (III, IV) and operation time are independent risk factors for the occurrence of PC. This study also uses the above-related risk factors to establish a clinical prediction model. It is also confirmed that the model has good diagnostic efficacy in the occurrence of PC after esophageal cancer surgery (AUC is 0.857, sensitivity is 83.3%, specificity is 71.1%).

Radical esophageal cancer surgery requires combined thoracoscopic and laparoscopic procedures, which are complex and invasive, and elderly patients may be less tolerant of surgery, spend more time in bed, and have slower absorption of exudate from the wound surface, leading to the occurrence of PC. Diabetes mellitus is a wasting disease and patients with hyperglycemia are prone to pulmonary infections.[16] Previous studies have confirmed that advanced age and diabetes mellitus are independent risk factors for PC after minimally invasive esophagectomy.[17] In the present study, smoking index ≥400 was shown to be an independent risk factor for the development of PC. Previous studies have also shown that smoking-related factors are associated with pulmonary disease after esophageal cancer surgery.[18] Among patients with a current smoking index ≥400, the proportion of chronic obstructive pulmonary disease was significantly higher. In addition, patients had significantly lower FEV1.0% values. These adverse clinical features appear to contribute to the increased pulmonary morbidity. Some studies have reported that smoking cessation for more than one month prior to esophagectomy significantly reduces the incidence of PC.[19] Studies reporting clinical stage and postoperative pulmonary complications in esophageal cancer are currently controversial. A study by Uchihara *et al.* concluded that there was no significant correlation between the clinical stage of the patient and postoperative pulmonary complications in esophageal cancer.[18] Mantziari *et al.* concluded that stage III to IV clinical stage was independent risk factor for the occurrence of PC after esophageal cancer surgery.[20] The results of the present study are consistent with the latter and also suggest that late clinical-stage (stages III and IV) can independently influence the occurrence of PC, because the later clinical stage often predicts a combination of poorer nutritional levels, lower haemoglobin, and other clinical status. This study also confirmed that prolonged operative time is an independent risk factor for the development of PC after esophageal cancer surgery. Tong *et al.* study also used the ROC curve to determine the threshold of operative time (240 min),[21] which is important for adjusting risk factors.

However, this study has some limitations. First, this is a retrospective and non-randomised study for a single institution, and selection bias in the sample is difficult to avoid. Second, the combined thoracolaparoscopic minimally invasive treatment of EC, especially in elderly patients, has been performed at the authors' institution for a relatively short period of time, and patients with early-stage esophageal cancer were selected as candidates for minimally invasive treatment in the early stages of performing this procedure. In the later stages, as the surgical technique became more sophisticated, patients with more advanced diseases were also included as indications for minimally invasive treatment, and the different stages of EC patients likewise led to the different incidences of PC.

CONCLUSION

Advanced age, combined diabetes, smoking index, late clinical-stage (stage III and IV), and time of surgery are independent risk factors for PC after esophagectomy. Appropriate interventions should be made early to diagnose the risk factors to reduce the occurrence of PC and improve the prognosis of patients.

ETHICAL APPROVAL:
This study was approved by the ethics committee of the People's Hospital of Lujiang County, Anhui Province, China, before the start of this study.

PATIENTS' CONSENT:
All patients in this study signed a written informed consent form prior to surgery.

COMPETING INTEREST:
The authors declared no competing interest.

AUTHORS' CONTRIBUTION:
HC: Research design, treatment, postoperative follow-up, statistical analysis, and manuscript writing.

MD, YX: Treatment, personnel coordination, and postoperative follow-up.
DM: Funds management, research design, surgical instructions, personnel coordination, and manuscript writing.
All the authors have approved the final version of the manuscript to be published.

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