

# Analysis of risk factors for pulmonary infection in patients with minimally invasive esophagectomy

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**Abstract.** Clinical manifestations of patients with pulmonary infection after minimally invasive esophagectomy were analyzed. A total of 500 patients undergoing minimally invasive esophagectomy in Sichuan Cancer Hospital and Institute from January 2015 to December 2016 were consecutively selected, among which 124 patients with pulmonary infection after surgery were taken as the infection group, and the remaining 376 patients were taken as the control group. The clinical data of all patients were collected. The pulmonary infection rate after minimally invasive esophagectomy was calculated, and clinical factors with difference were analyzed using the multivariate logistic regression analysis. There were significant differences in age, long-term smoking history, presence or absence of concurrent basic diseases and vital capacity ( $P<0.01$ ). The application time of antibiotics and antacids and hospitalization duration in the infection group were obviously longer than those in the control group ( $P<0.01$ ). Age, long-term smoking history, vital capacity, application time of antibiotics and antacids, hospitalization duration and concurrent diabetes mellitus/coronary heart disease/diseases of respiratory system increase the risk of postoperative pulmonary infection in patients with esophageal cancer, and age, long-term smoking history, diabetes mellitus, diseases of respiratory system and hospitalization duration are independent risk factors for pulmonary infection in patients after minimally invasive esophagectomy.

## Introduction

Esophageal cancer refers to the malignant tumor of epithelial tissues derived from the esophagus. The number of deaths

due to esophageal cancer is approximately 500,000 every year worldwide (1). The pathogenesis of esophageal cancer is related to a variety of factors, such as chemical factors (nitrosamine), biological factors (fungus), deficiency of vitamins and trace elements and dietary habits. People with different genetic backgrounds have different susceptibility to esophageal cancer (2,3). Therefore, the epidemiological characteristics of esophageal cancer have certain regional features. The incidence and mortality rate of esophageal cancer vary from country to country, and its distribution in population is related to age, sex, occupation and race (4). The symptoms occur with varying degrees, and are slow to develop, and most patients are diagnosed at the advanced stage, with poor prognosis and a 5-year survival rate of up to 20% (5,6).

Currently, surgical resection is a preferred therapeutic method for esophageal cancer when the patient's physical capacity allows (7). However, even after resection, the prognosis and quality of life of patients will be severely affected by complications, metastasis, recurrence and progression of esophageal cancer. The 5-year survival rate is only ~25% (8,9). As a new surgical method, minimally invasive esophagectomy is performed for patients through thoracoscope and laparoscope, which reduces the patient's trauma, alleviates the patient's pain and accelerates the recovery of the patient compared with conventional thoracotomy (10). However, pulmonary infection is still the first postoperative complication, as well as one of the main causes of postoperative death except the quality of surgery itself, seriously harming surgical quality and prognosis of patients (11). In the present study, relative factors to pulmonary infection in patients after minimally invasive esophagectomy were analyzed, so as to provide a theoretical basis for the prevention and treatment of pulmonary infection after radical surgery for esophageal cancer, and reduce the incidence and mortality rate of postoperative complications.

## Patients and methods

**Subjects of study and grouping.** General clinical data of 500 patients undergoing minimally invasive esophagectomy in Sichuan Cancer Hospital and Institute (Chengdu, China) from January 2015 to December 2016 were collected, and patients were grouped, among which 124 patients with pulmonary infection after surgery were taken as the infection group with

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Table I. Comparison of the basic clinical data between the two groups of patients.

Factors	Infection group (n=124)	Control group (n=376)	$\chi^2/t$	P-value
Age (years)			55.47	0.001
$\geq 60$	84 (67.74)	113 (30.05)		
<60	40 (32.26)	263 (69.05)		
Sex [n (%)]			0.22	0.64
Male	89 (71.77)	278 (73.94)		
Female	35 (28.23)	98 (26.06)		
BMI (kg/m <sup>2</sup> )	24.11 $\pm$ 5.86	25.32 $\pm$ 6.32	1.95	0.06
Marital status [n (%)]			0.66	0.72
Single	5 (4.03)	16 (4.26)		
Married	80 (64.52)	256 (68.09)		
Divorced	39 (31.45)	104 (27.66)		
Educational level			2.20	0.33
Junior high school and below	42 (33.87)	125 (33.24)		
Senior high school and junior college	54 (43.55)	142 (37.77)		
Undergraduate and above	28 (22.58)	109 (28.99)		
Long-term smoking history [n (%)]			49.98	0.001
Yes	66 (53.23)	76 (20.21)		
No	58 (46.77)	300 (79.79)		
Drinking history [n (%)]			0.00	0.96
Yes	37 (29.84)	113 (30.05)		
No	87 (70.16)	263 (69.95)		
Basic diseases [n (%)]			12.39	0.001
Yes	78 (62.90)	168 (44.68)		
No	46 (37.10)	208 (55.32)		
Chemoradiotherapy [n (%)]			0.04	0.84
Yes	111 (89.52)	339 (90.16)		
No	13 (10.48)	37 (9.84)		
Vital capacity (ml)	870.12 $\pm$ 139.22	1287.31 $\pm$ 110.34	30.37	0.001
Pathological type				
I-II	108 (87.10)	338 (89.89)	0.76	0.38
III-IV	16 (12.90)	38 (10.11)		

an incidence rate of pulmonary infection of 24.8%, and the remaining 376 patients without pulmonary infection were taken as the control group. Among the 500 patients, there were 367 males and 133 females aged 60.13 $\pm$ 10.83 years, and 60 years was the cut-off value of the patient's age. The vital capacity was 1101.83 $\pm$ 124.73 ml, and 1100 ml was the cut-off value of the patients' vital capacity. The inclusion criteria were the following: i) patients meeting the diagnostic criteria for esophageal cancer (12); ii) patients receiving esophageal cancer staging according to the UICC-AJCC TNM staging criteria (13); iii) patients undergoing minimally invasive esophagectomy; iv) patients in the infection group meeting the diagnostic criteria for pulmonary infection (14); and v) patients who had signed the informed consent and willing to cooperate in the study. The exclusion criteria were the following: i) patients with incomplete clinical data; ii) patients complicated with other serious basic organ diseases in the liver or kidney; iii) patients complicated with mental disease

or mental disorder; or v) patients with primary immune system diseases and immunocompromised.

The present study was approved by the Ethics Committee of Sichuan Cancer Hospital and Institute.

*Method.* After clinical data of all patients were collected, whether there were significant differences in the sex, age, vital capacity, history of disease and operation time were compared and analyzed between the two groups of patients. The pulmonary infection rate after minimally invasive esophagectomy was calculated, and the clinical factors with difference were analyzed using the multivariate logistic regression analysis.

*Statistical analysis.* Statistical Product and Service Solutions (SPSS) 19.0 software package (IBM Corp., Armonk, NY, USA) was used for data analysis and processing. Measurement data were expressed as mean  $\pm$  SD and significant differences were compared using t-test. Enumeration data were

Table II. Comparison of type and proportion of main diseases in basic diseases.

Factors	Infection group (n=124)	Control group (n=376)	$\chi^2$	P-value
Hypertension			0.00	0.94
Yes	49 (39.52)	150 (39.89)		
No	75 (60.48)	226 (60.11)		
Coronary heart disease			5.32	0.001
Yes	20 (16.13)	33 (8.78)		
No	104 (83.87)	343 (91.22)		
Diabetes mellitus			13.37	0.001
Yes	25 (20.16)	37 (9.84)		
No	99 (79.84)	339 (90.16)		
Diseases of respiratory system			38.40	0.001
Yes	37 (29.84)	30 (7.98)		
No	87 (70.16)	346 (92.02)		

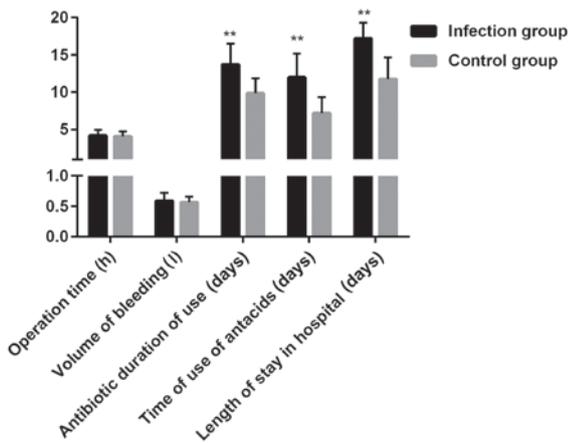


Figure 1. Comparison of treatment conditions between the two groups of patients. The operation time and amount of intraoperative bleeding were not significantly different between the two groups ( $P>0.05$ ), but the application time of antibiotics and antacids and hospitalization duration in the infection group were obviously longer than those in the control group.  $**P<0.01$ .

analyzed using the Chi-square test. After univariate analysis, multivariate logistic regression analysis was performed, and factors ( $P<0.05$ ) that were independent risk factors for pulmonary infection in patients after minimally invasive esophagectomy. The significance level was set as  $\alpha=0.05$ .

**Results**

*Comparison of basic clinical data between the two groups of patients.* There were no differences in sex, body mass index (BMI), marital status, educational level, drinking history, chemoradiotherapy and pathological type between the two groups ( $P>0.05$ ), but there were significant differences in age, long-term smoking history, presence or absence of concurrent basic diseases and vital capacity ( $P<0.001$ ). The age in the infection group was significantly higher than that in the control group, the number of patients with long-term smoking history and basic diseases in the infection group were

significantly larger than that in the control group, and the vital capacity in the infection group was significantly lower than that in the control group (Table I). The main concurrent basic diseases in both groups included hypertension, coronary heart disease, diabetes mellitus and diseases of respiratory system. There was no difference in the proportion of patients complicated with hypertension between the groups ( $P>0.05$ ), but there were differences in the proportion of patients complicated with coronary heart disease, diabetes mellitus and diseases of respiratory system ( $P<0.001$ ) (Table II).

*Comparison of treatment conditions between the two groups of patients.* The operation time was  $4.21\pm0.75$  h in the infection group and  $4.09\pm0.66$  h in the control group, the amount of intraoperative bleeding was  $0.59\pm0.13$  ml in the infection group and  $0.57\pm0.09$  ml in the control group, the application time of antibiotics was  $13.72\pm2.76$  days in the infection group and  $9.87\pm1.98$  days in the control group, the application time of antacids was  $11.98\pm3.21$  days in the infection group and  $7.21\pm2.11$  days in the control group, and the hospitalization duration was  $17.21\pm2.11$  days in the infection group and  $11.76\pm2.92$  days in the control group. The operation time and amount of intraoperative bleeding were not significantly different between the two groups ( $P>0.05$ ), but the application time of antibiotics and antacids and hospitalization duration in the infection group were obviously longer than those in the control group ( $P<0.05$ ) (Fig. 1).

*Comparison of infection rate under difference factors.* The incidence rate of pulmonary infection in 500 patients after minimally invasive esophagectomy was 24.80%. According to the stratification analysis based on difference factors, it was found that the pulmonary infection rate after minimally invasive esophagectomy was obviously higher in patients aged  $\geq 60$  years, with a long-term smoking history and vital capacity  $<1100$  ml, and complicated with coronary heart disease/diabetes mellitus/diseases of respiratory system than that in patients aged  $<60$  years, without a long-term smoking history, with vital capacity  $\geq 1100$  ml, and without coronary

Table III. Comparison of postoperative pulmonary infection rate under difference factors.

Difference factor	Total case (n=500)	Case of infection (n=124)	Infection rate (%)	$\chi^2$	P-value
Age (years)				55.47	0.001
$\geq 60$	197	84	42.64		
$< 60$	303	40	13.20		
Long-term smoking history				49.98	0.001
Yes	142	66	46.48		
No	358	58	16.20		
Vital capacity (ml)				24.09	0.001
$\geq 1100$	212	76	16.67		
$< 1100$	288	48	35.85		
Coronary heart disease				5.319	0.02
Yes	53	20	37.74		
No	447	104	23.27		
Diabetes mellitus				9.14	0.02
Yes	62	25	40.32		
No	438	99	22.60		
Diseases of respiratory system				38.40	0.001
Yes	67	37	55.22		
No	433	87	20.09		

Table IV. Multivariate logistic regression analysis.

Difference factor	B	Wald	OR	95% CI	P-value
Age	0.19	5.204	1.28	1.08-1.56	0.02
Long-term smoking history	0.62	15.41	11.80	8.83-24.32	0.001
Diabetes mellitus	0.42	1.43	1.32	0.32-4.32	0.13
Coronary heart disease	0.12	2.98	3.46	1.76-9.533	0.07
Diabetes mellitus	0.24	7.45	4.78	1.33-7.43	0.01
Diseases of respiratory system	1.23	16.56	5.53	2.43-11.34	0.001
Application time of antibiotics	0.32	2.21	3.42	1.43-7.43	0.22
Application time of antacids	0.91	2.54	4.32	0.98-8.54	0.49
Hospitalization duration	1.72	9.23	3.52	1.21-7.43	0.001

OR, odds ratio; CI, confidence interval.

heart disease/diabetes mellitus/diseases of respiratory system ( $P < 0.05$ ) (Table III).

*Multivariate logistic regression analysis of difference factor.* Multivariate logistic regression analysis was performed for difference factor screened with pulmonary infection after minimally invasive esophagectomy as the dependent variable, and results demonstrated that age (OR=1.28,  $P=0.02$ ), long-term smoking history (OR=11.80,  $P < 0.001$ ), diabetes mellitus (OR=4.78,  $P=0.01$ ), diseases of respiratory system (OR=5.53,  $P < 0.001$ ) and hospitalization duration (OR=3.52,  $P < 0.001$ ) were independent risk factors for pulmonary infection in patients after minimally invasive esophagectomy (Table IV).

## Discussion

The incidence rate of esophageal cancer, a common malignant tumor in the digestive system, is among the top 10 in the world, which is second only to gastric cancer in China. The number of patients with esophageal cancer in China accounts for half of the total worldwide. The elderly patients are in the majority, and its incidence rate in male is about three times that in female (15,16). The prognosis of esophageal cancer is poor, and its mortality rate is high in China. The preferred therapeutic method is surgical resection supplemented by chemoradiotherapy (17). Pulmonary infection is one of the major complications of minimally invasive esophagectomy (18). To reduce the incidence rate of complications

after surgery for esophageal cancer and the mortality rate of patients, relative factors to pulmonary infection after minimally invasive esophagectomy were investigated in the present study, so as to provide a theoretical basis for the prevention and treatment of pulmonary infection after radical surgery for esophageal cancer.

Patients in the infection group had pulmonary infection after surgery for esophageal cancer, but no pulmonary infection occurred in the control group after surgery. There were no differences in the sex, BMI, marital status and educational level between the two groups of patients, but there were significant differences in the age, vital capacity, long-term smoking history and presence or absence of concurrent basic diseases. When stratifying the infection rate for these different factors, we found that the high age, long-term smoking history and concurrent diabetes mellitus, coronary heart disease and diseases of respiratory system may increase the probability of pulmonary infection in patients after minimally invasive esophagectomy. The comparison of treatment factors between the two groups of patients revealed that there were no significant differences in the operation time and amount of intraoperative bleeding between the two groups, and the application time of antibiotics and antacids and hospitalization duration in the infection group were significantly longer than those in the control group, suggesting that the application time of antibiotics and antacids and hospitalization duration may affect the incidence rate of pulmonary infection in patients after minimally invasive esophagectomy. It was found in the multivariate logistic regression analysis that the age, long-term smoking history, diabetes mellitus, diseases of respiratory system and hospitalization duration were independent risk factors for pulmonary infection in patients after minimally invasive esophagectomy. Wang *et al* (10) studied the risk factors for pneumonia in patients with esophageal cancer after transthoracic esophagectomy and found that BMI, age and concurrent diabetes mellitus were major influencing factors. In our study, however, BMI did not affect the incidence rate of postoperative pulmonary infection in patients with esophageal cancer. The possible reason is that open surgery was adopted in the study of Wang *et al* (10), while the minimally-invasive surgery was adopted in this study. Wang *et al* (10) studied the relative factors to pulmonary infection after surgery for esophageal cancer and found that the age, operation time, other concurrent basic diseases and recurrent laryngeal nerve injury are risk factors for postoperative infection, which, except the operation time, are consistent with results in the present study. The possible reason is that the study of Wang *et al* (10) was a comprehensive study containing various surgical methods, while only risk factors for minimally invasive esophagectomy were explored in this study, thus, leading to different results. According to the study of Saito *et al* (19), the cellular immunodeficiency after surgery for esophageal cancer can promote the occurrence of infection. Besides, Saito *et al* (20) found that the increase in superoxide anion production (SOP) of polymorphonuclear neutrophil can predict the postoperative infection of esophageal cancer. Therefore, some indexes reflecting cellular immunodeficiency, such as T cells, B cells and phytohaemagglutinin (PHA)-induced transformation, and SOP can be added to future research, so as to investigate the postoperative cellular immunodeficiency and SOP in patients

after minimally invasive esophagectomy and their correlations with pulmonary infection.

It was found in the comparison of the type and proportion of basic diseases between the two groups that the proportions of coronary heart disease and diabetes mellitus were not high in either group (only approximately 20-30 cases), which may affect the results of the analysis. Therefore, the sample size needs to be increased for repeated verification. Moreover, several basic diseases could occur simultaneously in patients, such as hypertension and diabetes mellitus. To improve the efficiency, however, such a situation was not considered in the analysis of the type and proportion of basic diseases in this study, but the focus was placed on one variable. Multiple variables were considered in the multivariate logistic regression analysis, and it was found that the history of diabetes mellitus and diseases of respiratory system were independent risk factors for pulmonary infection in patients after minimally invasive esophagectomy. Thus, the history of diabetes mellitus and/or diseases of respiratory system increase the risk of pulmonary infection after minimally invasive esophagectomy, regardless of the type and number of other concurrent diseases. However, whether the rate of pulmonary infection after minimally invasive esophagectomy is associated with the types and numbers of concurrent several basic diseases, needs larger-sample studies for verification.

Due to the limitations of the retrospective study, we did not collect all the immune indicators data of patients to judge the immune function, and the judgement of immune function is complex. At present, we need to combine multiple indicators and make a comprehensive judgement (21). Also, the factors affecting immunity are also complex and varied (22). In this study, all the subjects were middle-aged and elderly individuals, with an average age of  $60.13 \pm 10.83$  years, and their immunity gradually declined with age. In addition, all the subjects were suffering from esophageal cancer, and esophageal cancer itself can affect the immunity of patients (23). Therefore, considering that patients' own immunity may affect the probability of pulmonary infection after minimally invasive surgery (24), we excluded patients with primary immune system diseases and those immunocompromised. For those with secondary immune dysfunction or immunocompromise, we summarized the effect of secondary immunity on pulmonary infection after surgery into their primary diseases, such as diabetes mellitus patients with secondary immunocompromise, which affects the probability of pulmonary infection after surgery (25). This effect is thought to be caused by diabetes, not by low immunity, because low immunity here is only a secondary effect of diabetes. Since we excluded the patients with primary immune dysfunction or immunocompromise, the age of the two groups was not different, and minimally invasive esophagectomy was also performed. Thus, although immune dysfunction or immunocompromise may have an impact on the incidence of postoperative pulmonary infection, it is not the main factor in the present study.

In conclusion, age, long-term smoking history, vital capacity, application time of antibiotics and antacids, hospitalization duration and concurrent diabetes mellitus/coronary heart disease/diseases of respiratory system increase the risk of postoperative pulmonary infection in patients with esophageal cancer, and age, long-term smoking history, diabetes mellitus,

diseases of respiratory system and hospitalization duration are independent risk factors for pulmonary infection in patients after minimally invasive esophagectomy.

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### Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

### Authors' contributions

GL drafted the manuscript. GL and LP were mainly involved in collecting and interpreting the general data of patients. BL and KW analyzed the pulmonary infection. GL, BL and YH were responsible for the analysis of clinical factors. All authors read and approved the final manuscript.

### Ethics approval and consent to participate

The present study was approved by the Ethics Committee of Sichuan Cancer Hospital and Institute (Chengdu, China). Signed informed consents were obtained from the patients and/or guardians.

### Patient consent for publication

Not applicable.

### Competing interests

The authors declare that they have no competing interests.

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