Original Article

Assessment of a predictive score for pulmonary complications in cancer patients after esophagectomy

Xue-zhong Xing, Yong Gao, Hai-jun Wang, Shi-ning Qu, Chu-lin Huang, Hao Zhang, Hao Wang, Quan-hui Yang

Department of Intensive Care Unit, Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100021, China

Corresponding Author: Xue-zhong Xing, Email: xingxzh2000@aliyun.com

BACKGROUND: Esophagectomy is a very important method for the treatment of resectable esophageal cancer, which carries a high rate of morbidity and mortality. This study was undertaken to assess the predictive score proposed by Ferguson et al for pulmonary complications after esophagectomy for patients with cancer.

METHODS: The data of patients who admitted to the intensive care unit after transthoracic esophagectomy at Cancer Hospital of Chinese Academy of Medical Sciences and Peking Union Medical College between September 2008 and October 2010 were retrospectively reviewed.

RESULTS: Two hundred and seventeen patients were analyzed and 129 (59.4%) of them had postoperative pulmonary complications. Risk scores varied from 0 to 12 in all patients. The risk scores of patients with postoperative pulmonary complications were higher than those of patients without postoperative pulmonary complications (7.27 ± 2.50 vs. 6.82 ± 2.67 ; $P=0.203$). There was no significant difference in the incidence of postoperative pulmonary complications as well as in the increase of risk scores ($\chi^2=5.477$, $P=0.242$). The area under the curve of predictive score was 0.539 ± 0.040 (95%CI 0.461 to 0.618; $P=0.324$) in predicting the risk of pulmonary complications in patients after esophagectomy.

CONCLUSION: In this study, the predictive power of the risk score proposed by Ferguson et al was poor in discriminating whether there were postoperative pulmonary complications after esophagectomy for cancer patients.

KEY WORDS: Respiratory insufficiency; Esophagectomy; Predictive

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INTRODUCTION

Esophagectomy is a very important method for the treatment of resectable esophageal cancer, which carries a high rate of morbidity and mortality.^[1–2] Postoperative pulmonary complications (PCs) are reported to occur in 15.9% to almost 40% of patients who have undergone esophagectomy,^[3–8] and are associated with increased in-hospital death rate and decreased 3- and 5-year survival rates.^[7]

Several risk factors are reported to be associated with increased postoperative PCs, such as increased age, operation duration, decreased forced expiratory

volume in 1 second (FEV₁%), decreased diffusion capacity of the lung for carbon monoxide (D_{LCO}%), poor performance status (PS), salvage esophagectomy after definitive chemoradiotherapy, and the amount of blood loss.^[3,5,8] In 2011, Ferguson et al^[3] developed a predictive pulmonary risk score using the data of 516 patients after esophagectomy. The scoring system including four preoperative variables as age, performance status, FEV₁% and D_{LCO}% predicted the occurrence of postoperative major PCs with an area under the curve of 70.8%. In a subsequent external validation study with 136 patients, Reinersman et al^[9] found good accuracy

of the risk score system for predicting major pulmonary complications with a sensitivity of 76%. However, the scoring system was developed and validated from the patients of similar characteristics, and it has not been validated outside the United States of America. Therefore, the aim of this study was to assess the pulmonary risk score in a high volume hospital in China.

METHODS

Patients

Patients who admitted to the intensive care unit (ICU) after esophagectomy at Cancer Hospital of Chinese Academy of Medical Sciences (CAMS) and Peking Union Medical College (PUMC) between September 2008 and October 2010 were enrolled in the study. Exclusion criteria included patients who underwent exploratory thoracotomy and induction therapy, and those who had incomplete data. This study was approved by the Institutional Review Board of Cancer Hospital of CAMS and PUMC and performed in accordance with the ethical standards of the 1964 *Declaration of Helsinki* and its later amendments. And patients' consents were waived because of the observational nature of this study.

To determine the sample size of the study, we defined the confidence level as 95%, and the confidence interval as 34% to 42% (major PCs rate was 38% in Ferguson et al study). Therefore, the sample size was 150, which was needed to validate the predictive score.

Preoperative staging and physiologic assessments

Preoperative staging was carried out according to the guidelines of the Department of Thoracic Surgery of Cancer Hospital of CAMS and PUMC, which included whole blood test, biochemical test, chest CT, abdomen ultrasound, barium contrast study, endoscopy, pulmonary function test, and electrocardiography.^[10] Preoperative physiologic assessments were based on age older than 70 or less, results of pulmonary function tests including forced expiratory volume at 1 second (FEV_1) ≥ 1.20 L, $FEV_1\%$ $\geq 40.0\%$, and $D_{LCO}\%$ $\geq 40.0\%$. Patients were advised to stop smoking one week before surgery. And they received antibiotic therapy for at least 3–5 days if pulmonary infection existed, and the therapy continued until disappearance of symptoms of inflammation shown by chest imaging.

Surgical approaches

Surgical approaches included transthoracic approach,

either one incision (left transthoracic) or two incisions (Ivor-Lewis approach), or Mckeown approach (three stage esophagectomy and cervical anastomosis). The selection of which approach was based on the location of the lesions, the results of pulmonary function test, and the general status of the patients. None of patients with minimally invasive esophagectomy (MIE) was admitted to the ICU in the study period although MIE was introduced to our hospital in 2009.^[11]

Postoperative respiratory tract management

Postoperative management of the respiratory tract included chest physiotherapy and early ambulation. And patient-controlled analgesia was given to every patient to control postoperative pain. Simple goal directed fluid therapy was used for postoperative fluid management, and the following four goals were considered: level of blood pressure, central venous pressure, urine output, and circulation of skin.^[12] First, blood pressure (BP) was kept at normal level individually, i.e. at 100–110/60–70 mmHg for patients without a history of hypertension and at preoperative level for patients with a history of hypertension. Second, CVP level was kept at 8–12 cmH₂O in our practice, which resembles conservative therapy in acute respiratory distress syndrome (ARDS).^[13] Third, fluid volume was adjusted according to whether there is edema of skin. Finally, urine output was kept at more than 0.5 mL/(kg•hour). To achieve these goals, diuretic agents, fluid supplements or vasopressors were used to keep these four variables in the ranges mentioned above.

Groups

The patients were divided into two groups: postoperative major PCs group and no major PCs group. Postoperative major PCs were defined as respiratory insufficiency in need of ventilation, and pneumonia requiring antibiotic therapy. Pneumonia was defined according to the definition of Centers for Disease Control and Prevention (CDC) and National Healthcare Safety Network (NHSN) surveillance definition.^[14] Pathological staging was performed using the American Joint Committee on Cancer (AJCC) Cancer Staging Handbook (7th edition).^[15] The operative mortality of the patients was defined as death within 30 days of esophagectomy.

Statistical analyses

Statistical analyses were carried out using SPSS software for Windows, version 16.0 (SPSS Inc., Chicago, IL, USA). Continuous variables were presented as mean

±standard deviation and compared respectively using Student's *t* test. Categorical variables were reported as absolute numbers (frequency percentages) and analyzed using the Chi-square test. The area under the receiver operating characteristic curve (AUROC) was used to evaluate the ability of the model to discriminate between patients who developed postoperative PCs or not (discrimination). A two-tailed *P* value < 0.05 was considered statistically significant.

RESULTS

A total of 245 patients were admitted to the ICU during the study period. Twenty-eight patients were excluded including 4 patients who underwent exploratory thoracotomy, 9 patients who received induction therapy, and 15 patients with incomplete data. Thus, 217

Figure 1. Flowchart of the study.

Table 1. Preoperative characteristics of patients who underwent esophagectomy

Variables	Pulmonary complications		<i>t/χ</i> ²	<i>P</i>
	No (n=88)	Yes (n=129)		
Age (years)	65.05±9.71	64.27±9.38	0.589	0.557
Male, n (%)	105 (85.4)	77 (81.9)	0.469	0.493
BMI (kg/m ²)	24.00±3.78	23.75±3.95	0.463	0.644
Current cigarette use, n (%)	56 (63.6)	79 (61.2)	0.128	0.721
Alcohol use, n (%)	50 (56.8)	59 (45.7)	2.570	0.109
Hypertension, n (%)	41 (46.6)	45 (34.9)	2.997	0.083
Coronary artery disease, n (%)	9 (10.2)	16 (12.5)	0.263	0.608
Diabetes mellitus, n (%)	13 (14.8)	13 (9.3)	1.536	0.215
COPD, n (%)	2 (2.3)	2 (1.6)	0.151	0.698
Performance status	0.58±0.52	0.58±0.50	-0.026	0.979
Hemoglobin (g/dL)	13.97±1.78	13.47±2.18	1.751	0.081
Albumin (g/L)	41.53±5.10	40.54±4.40	1.515	0.131
FEV ₁ (L)	2.33±0.67	2.29±0.62	0.472	0.638
FEV ₁ %	78.87±9.80	76.53±10.69	1.590	0.113
D _{LCO} %	79.41±18.51	76.90±18.02	0.914	0.362
Risk scores	6.82±2.67	7.27±2.50	-1.276	0.203

BMI: body mass index; COPD: Chronic obstructive pulmonary disease; FEV₁%, forced expiratory volume in 1 second; D_{LCO}%, diffusion capacity of the lung for carbon monoxide.

patients were enrolled for the final analysis (Figure 1). Demographic and clinical characteristics of the patients are listed in Tables 1 and 2. No significant differences were seen in co-morbidities including hypertension, coronary heart diseases, diabetic mellitus, and chronic obstructive pulmonary diseases in patients with or without major PCs. Other preoperative variables including age, performance status, FEV₁% and D_{LCO}% were also not significantly different between the two groups. Overall, 129 (59.4%) patients had postoperative major PCs and 13 (6.0%) patients died during the operation. Of the 129 patients, 106 were subjected to mechanical ventilation for more than 24 hours because of respiratory insufficiency, and 23 were given antibiotics because of pulmonary infection. Of the 13 patients, 7 died of septic shock caused by gastrointestinal fistula, 1 died of myocardial infarction, 1 died of cardiac arrest during intubation due to respiratory insufficiency, and 4 died of respiratory insufficiency induced by pulmonary infection.

The risk score of patients with major PCs was 7.27±2.50, which was higher than 6.82±2.67 of patients without postoperative PCs. However, there was no significant difference between the two groups (*P*=0.203). Patients with postoperative intrathoracic anastomotic leak had more major PCs than did those without anastomotic leak (18.6% vs. 3.4%; *P*=0.001).

Risk scores varied from 0 to 12 in all patients (Figure 2). There was no significant difference in the incidence

Table 2. Operative and postoperative characteristics of patients who underwent esophagectomy

Variables	Pulmonary complications		<i>t/χ</i> ²	<i>P</i>
	No (n=88)	Yes (n=129)		
Surgical approach, n (%)			1.749	0.417
Left transthoracic	70 (79.5)	94 (72.9)		
Ivor-Lewis approach	8 (9.1)	12 (9.3)		
Mckeown	10 (11.4)	23 (17.8)		
Histology, n (%)			0.922	0.631
Adenocarcinoma	21 (23.9)	29 (22.5)		
Squamous cell	66 (75.0)	96 (74.4)		
Others	1 (1.1)	4 (3.1)		
Pathological stage, n (%)			2.351	0.671
Tis	0 (0)	1 (0.8)		
I	9 (10.2)	11 (8.5)		
II	30 (34.1)	44 (34.1)		
III	48 (54.5)	73 (56.6)		
IV	1 (1.1)	0 (0)		
Intraoperative transfusion (mL)	307±523	425±763	-1.262	0.208
Anastomotic leak, n (%)				
Cervical leak	4 (4.5)	8 (6.2)	0.275	0.600
Intrathoracic leak	3 (3.4)	24 (18.6)	11.088	0.001
Length of operation (minute)	244±79	247±84	-0.203	0.839
ICU mortality, n (%)	0 (0)	4 (3.1)	2.780	0.095
Operative mortality, n (%)	2 (2.3)	11 (8.5)	3.634	0.057

ICU: intensive care unit.

Figure 2. Distribution of risk scores in patients who underwent esophagectomy.

Figure 3. The incidence of pulmonary complications calculated according to risk scores grouped in quintiles. PC: pulmonary complications.

Figure 4. Receiver operator characteristic curve for risk score and pulmonary complications. Area under the curve=0.539±0.040 ($P=0.324$; 95%CI 0.461 to 0.618).

of postoperative major PCs but there was an increment of risk scores ($\chi^2=5.477$, $P=0.242$; Figure 3). AUROC of the predictive score was 0.539 ± 0.040 ($P=0.324$; 95% confidential interval 0.461 to 0.618) in predicting the occurrence of postoperative major PCs (Figure 4).

DISCUSSION

Our study demonstrated that the predictive risk score proposed by Ferguson et al^[3] was poor in predicting

the occurrence of postoperative PCs in patients after esophagectomy for cancer.

The predictive score should be validated before clinical application. Ferguson et al^[3] developed a predictive risk score in 2011 using the data of 516 patients who underwent esophagectomy. The scoring system based on four preoperative variables including age, FEV₁%, D_{LCO}% and PSScore predicted the occurrence of postoperative major PCs with an area under the curve of 70.8%. Postoperative major PCs in our study were defined as respiratory insufficiency in need of ventilation, pneumonia requiring antibiotic therapy, similar to the definition proposed by Ferguson et al,^[3] which included respiratory insufficiency and pulmonary infiltrate requiring antibiotic therapy. Therefore, the method of our study was comparable to that of Ferguson et al's study. In the present study, however, the area under the curve of this predictive score was only 53.9%. We did not find its sensitivity in predicting the risk of postoperative major PCs in our cohort.

In our study, age was not significantly different in univariate analysis of patients with or without postoperative PCs. Some studies^[3,7,8] found that age was an independent predictor for postoperative PC, but others found different results.^[5,16,17] Zingg et al^[16] reported that unlike age, preoperative co-morbidities were associated with increased pulmonary morbidity. Therefore, advanced age alone may not exclude esophagectomy for patients with esophageal cancer.^[18]

Impaired preoperative pulmonary function has long been considered as an important tool for the evaluation of the risk of PCs after esophagectomy.^[3,19,20] Avendano et al^[19] and Shiozaki et al^[20] reported that preoperative FEV₁% less than 65% and 60% were associated with increased PCs after esophagectomy. But Ferguson et al^[3] found that FEV₁% and D_{LCO}% could be used as independent predictors for postoperative PCs. In our study, however, both FEV₁% and D_{LCO}% were not significantly different in patients with or without postoperative PCs. In a study from our center,^[21] 69.3% of the patients with normal pulmonary function defined as FEV₁% larger than that in 70% of the patients with postoperative respiratory insufficiency. Surgery-related complications such as anastomotic fistula played an important role in the development of postoperative respiratory insufficiency. Another study^[22] revealed that postoperative anastomotic fistula was an independent risk factor for acute respiratory distress syndrome, a serious pulmonary complication after esophagectomy with a mortality rate of 50%. In our study, postoperative

anastomotic intrathoracic leak was found to be associated with an increased rate of postoperative PCs, which was consistent with the result of previous studies.^[21–22]

Almost 1 500 esophagectomies were performed in our hospital annually and less than 50 patients who were admitted to the ICU directly from operation room were subjected to ventilation, other patients were transferred to wards after direct extubation. About 50 patients in the wards were admitted to the ICU mainly because of respiratory insufficiency after esophagectomy. Thus, the proportion of PCs was over 50% in the ICU, which was higher than 10%–20% reported in the literature.^[2–3,5,8]

Currently, many studies have investigated the risk factors of esophagectomy.^[2,5,8] But only Ferguson et al developed a scoring system for predicting the risk of complication after esophagectomy and validated it in patients.^[3,9]

There are some limitations to this study. First, we excluded the patients who received induction therapy such as chemotherapy and/or radiotherapy. Induction therapy may decrease FEV₁% and D_{LCO}%, thereby increasing the risk of postoperative PCs. However, a recent study^[23] did not find an increased rate of PCs in patients who received neoadjuvant chemoradiotherapy compared with those who did not receive neoadjuvant chemoradiotherapy. Therefore, exclusion of patients who received induction may not influence the result of this study. Second, only 217 patients were enrolled in the study, so it is difficult to draw a conclusion. However, the number of patients in our study was more than 150, which made the result of this study credible. Third, the retrospective nature of this study may be related to the completeness of data. However, we excluded the patients who had incomplete data making the results of this study believable.

In summary, in this cohort the predictive risk score for postoperative PCs was not accurate in discriminating patients with or without postoperative PCs after esophagectomy for cancer. Other factors such as anastomotic leak were associated with an increased rate of major PCs.

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Ethical approval: This study was approved by the Institutional Review Board of Cancer Hospital of CAMS and PUMC. It was therefore performed in accordance with the ethical standards of the 1964 *Declaration of Helsinki* and its amendments. Patients' consents were waived because of the observational nature of this study.

Conflicts of interest: The authors declare that there are no conflicts of interest related to the publication of this paper.

Contributors: Xing XZ proposed the study, analyzed the data

and wrote the first draft. All authors contributed to the design and interpretation of the study and to further drafts.

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