Constructing a risk prediction model for anastomotic leakage after esophageal cancer resection

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Abstract

Objective: The purpose of this study was to investigate a newly constructed risk prediction model for anastomotic leakage after esophageal cancer resection.

Methods: A retrospective survey of 205 patients who underwent esophageal cancer resection was conducted using a self-designed questionnaire. The influencing factors were explored by single factor analysis, and a logistic regression analysis was performed to construct the prediction equation. A receiver operating characteristic curve was used to evaluate the model.

Results: The incidence of anastomotic leakage after esophageal cancer resection was 11.73%. There were five independent risk factors entered into the regression equation. The risk prediction equation was $Z = 0.108 \times \text{age} + 2.011 \times \text{preoperative chemotherapy history} + 3.007 \times \text{incision redness/exudation} + 2.632 \times \text{pleural effusion} + 1.934 \times \text{increased white blood cell count} - 12.304$. According to the receiver operating characteristic curve test, the area under the curve was 0.946, the sensitivity was 0.833, the specificity was 0.912, and the Youden index was 0.745.

Conclusion: The risk model of anastomotic leakage after esophageal cancer resection had a good predictive effect that was of significance for guiding clinical observation and early-screening.

Keywords

Esophageal cancer resection, anastomotic leakage, risk prediction model, early diagnosis, pleural effusion, exudation

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Introduction

Esophageal cancer is a common malignant tumor of the digestive tract that occurs in the esophageal epithelium. In 2018, there were 572,000 new esophageal cancer cases worldwide, including 258,000 new esophageal cancer patients in China, ranking seventh and sixth among all new malignant tumor diagnoses, respectively.[1] Surgery is a main treatment option for esophageal cancer, and anastomotic leakage is one of the most serious complications after esophageal cancer resection.

Currently, owing to differences in patient conditions and inconsistent diagnostic criteria, the incidence of anastomotic leakage following esophageal cancer resection has been reported to be quite different domestically and abroad, with rates ranging from 2% to 20%.[2,3] The occurrence of anastomotic leakage can lead to increased mortality, increased hospitalization costs, prolonged hospitalization, and causes serious threats to the health of patients as well as pain to the patients and their families. Therefore, early observation and early identification of anastomotic leakage is a priority of nursing staff. The aim of this study was to establish a risk prediction model that analyzes clinical indicators to suggest when anastomotic leakage may occur. This model will help clinical nursing staff identify the high-risk population for anastomotic leakage earlier so that they can perform the necessary interventions.

Methods

Study subjects

This study retrospectively investigated 205 patients who underwent esophageal cancer resection in a tertiary hospital in Guangzhou from January 2017 to March 2018. The inclusion criteria were: (1) age 18 years and older; (2) pathological diagnosis of primary esophageal cancer; and (3) those who underwent esophageal cancer resection for the first time. The exclusion criteria were: (1) those who had a previous history of other serious underlying diseases and malignant tumors; (2) those who could not continue to undergo observation after hospital transfer for various reasons; and (3) those with incomplete medical records. Because the retrospective nature of this study, patient consent for inclusion was waived.

Study design and data collection

A self-designed questionnaire was used that included general information of the patients, perioperative signs and examinations, examination results, and patient complaints. The bad habits mentioned were long-term addiction to alcohol and tobacco, solid and overheating foods, and eating too fast, which may cause chronic irritation or inflammation of the esophagus, contributing to the occurrence of esophageal cancer.[4] Data were collected through electronic medical records. This study was approved by the ethics committee of Sun Yat-sen University Cancer Center. Neck and chest anastomotic leakage were both diagnosed as anastomotic leakage based on the clinical manifestations combined with auxiliary examinations, including swallowing methylthionine chloride, taking esophageal barium meals, and esophagoscopy. In the medical records, it was confirmed that the diagnosis was postoperative anastomotic leakage.

Statistical analysis

Statistical analysis was performed on the data using IBM SPSS Statistics for Windows, version 21.0 (IBM Corp., Armonk, NY, USA). Data are described using the mean and standard deviation, or frequency and percentage. Univariate

analysis was performed by t test, rank sum test, or chi-square test. Multivariate logistic regression analysis was used to calculate the risk prediction equation for anastomotic leakage, and the receiver operating characteristic (ROC) curve was used to test the effect of the risk prediction equation. Statistical significance level was set at $\alpha = 0.05$. All data in this study have been recorded at Sun Yat-sen University Cancer Center for further reference (number RDDA2019001350).

Results

Patient characteristics

We initially filtered out 48 patients who did not meet the inclusion criteria; thus, 205 patients were included in this study. The general information of these patients is shown in Table 1.

Table 1. Patient characteristics.

Variables	Cases (n)	Percentage (%)
Gender		
Female	43	20.98
Male	162	79.02
Lesion position		
Upper section	13	6.34
Middle section	112	54.63
Lower section	65	31.71
Junction	15	7.32
Pathology		
Squamous cell carcinoma	188	91.71
Non-squamous cell carcinoma	17	8.29
Staging		
1st stage	47	22.93
2nd stage	58	28.29
3rd stage	88	42.93
4th stage	12	5.85
Anastomotic position		
Neck	126	61.46
Chest	79	38.54

Single factor analysis of postoperative anastomotic leakage

From a chi-square analysis, the incidence of patients who had a history of preoperative chemotherapy, chest tightness/chest pain, incision redness/exudation, pleural effusion, pneumonia/lung atelectasis, postoperative fever, and increased drainage fluid (drainage fluid after 4 days of surgery $>400\,\mathrm{mL/}$ day) were statistically significant ($P < 0.05$). From a t-test, patient age and postoperative oxygenation index were statistically significant ($P < 0.05$). See Table 2 for details.

Multivariate analysis of postoperative anastomotic leakage

Statistically significant risk factors in single factor analysis were used as independent variables. Logistic regression analysis was performed using the stepwise regression method. The relevant assignments are shown in Table 3. The logistic analysis results are shown in Table 4.

The risk prediction model was $Z = 0.108 \times \mathrm{age} + 2.011 \times \mathrm{preoperative}$ chemotherapy history $+ 3.007 \times \mathrm{incision}$ redness/ exudation $+ 2.632 \times \mathrm{pleural}$ effusion $+ 1.934 \times \mathrm{increased}$ white blood cell count $- 12.304$.

ROC curve analysis

The predictive equation was used to calculate and evaluate the risk score for postoperative anastomotic leakage in patients with esophageal cancer. The ROC curve was used to test the fitting effect of the score on the patient's postoperative anastomotic leakage. See Figure 1 for details. The maximum value of the Youden index was used as the optimal threshold for the prediction model. The area under the curve was 0.946, the sensitivity was 0.833, the specificity was 0.912, and the Youden index was 0.745.

Table 2. Single factor analysis of influencing factors for anastomotic leakage [n (%)].

Risk factors	Anastomotic leakage		χ^2/t	p
	No ($n_1 = 181$)	Yes ($n_2 = 24$)		
Gender				
Female	39 (21.55)	4 (16.67)	0.304	0.790
Male	142 (78.45)	20 (83.33)		
Underlying disease				
No	133 (73.48)	18 (75.00)	0.025	1.000
Yes	48 (26.52)	6 (25.00)		
Bad habits				
No	68 (37.57)	6 (25.00)	1.451	0.265
Yes	113 (62.43)	18 (75.00)		
Preoperative chemotherapy history				
No	152 (83.98)	16 (66.67)	4.293	0.049*
Yes	29 (16.02)	8 (33.33)		
Preoperative radiotherapy history				
No	164 (90.61)	21 (87.50)	0.232	0.711
Yes	17 (9.39)	3 (12.50)		
Anastomotic position				
Neck	111 (61.33)	15 (62.50)	0.012	1.000
Inside the chest	70 (38.67)	9 (37.50)		
Shortness of breath				
No	161 (88.95)	18 (75.00)	3.724	0.093
Yes	20 (11.05)	6 (25.00)		
Chest tightness/chest pain				
No	168 (92.82)	19 (79.17)	4.930	0.043*
Yes	13 (7.18)	5 (20.83)		
Lower breathing sound				
No	151 (83.43)	16 (66.67)	3.941	3.941
Yes	30 (16.57)	8 (33.33)		
Rale				
No	148 (81.77)	16 (66.67)	3.020	0.102
Yes	33 (18.23)	8 (33.33)		
Incision redness/exudation				
No	178 (98.34)	15 (62.50)	49.397	<0.001**
Yes	3 (1.66)	9 (37.50)		
Pleural effusion				
No	158 (87.29)	7 (29.17)	45.587	<0.001**
Yes	23 (12.71)	17 (70.83)		
Pneumonia/lung atelectasis				
No	131 (72.38)	12 (50.00)	5.029	0.033
Yes	50 (27.62)	12 (50.00)		
Anemia				
No	161 (88.95)	18 (75.00)	3.724	0.093
Yes	20 (11.05)	6 (25.00)		
Increased white blood cells				
No	95 (52.49)	4 (16.67)	10.888	0.001*

Table 2. Continued.

Risk factors	Anastomotic leakage		χ^2/t	p
	No ($n_1 = 181$)	Yes ($n_2 = 24$)		
Yes	86 (47.51)	20 (83.33)		
Increased proportion of neutrophils				
No	63 (34.81)	0 (0.00)	12.060	<0.001**
Yes	118 (65.19)	24 (100.00)		
BMI grouping				
Thinning	23 (12.71)	7 (29.17)	4.993	0.082
Normal	106 (58.56)	10 (41.67)		
Overweight	52 (28.73)	7 (29.17)		
Postoperative fever				
No	154 (85.08)	15 (62.50)	7.465	0.018*
Yes	27 (14.92)	9 (37.50)		
Increased drainage fluid				
No	104 (57.46)	7 (29.17)	6.832	0.015*
Yes	77 (42.54)	17 (70.83)		
Age (years)	61.14 ± 7.55	66.79 ± 7.16	−3.466	0.001*
Postoperative oxygenation index	302.08 ± 72.63	229.74 ± 72.89	4.584	<0.001**
BMI	22.28 ± 3.22	21.43 ± 3.67	1.202	0.231

Note: *$P < 0.05$, differences were statistically significant; **$P < 0.001$, differences were statistically significant.

Table 3. Variable assignment table.

| Variables	Assignment
Anastomotic leakage	0 = no, 1 = yes
Age	Analysis by actual age
Preoperative chemotherapy history	0 = no, 1 = yes
Incision redness/exudation	0 = no, 1 = yes
Pleural effusion	0 = no, 1 = yes
Increased white blood cells	0 = no, 1 = yes

Discussion

Significance of the predictive model of anastomotic leakage risk in patients with esophageal cancer after surgery

Anastomotic leakage is one of the most serious complications after esophageal cancer surgery because it affects prognosis and increases mortality. Studies have shown that early detection of anastomotic leakage and the formation of a multidisciplinary collaborative group to make treatment decisions reduces the patient mortality rate.[5,6] Therefore, the early identification of anastomotic leakage is of great significance to patient prognosis. Currently, the clinical diagnosis of anastomotic leakage in esophageal cancer primarily includes esophageal endoscopy, barium meal angiography, and staining (methylthionine chloride) swallowing. These diagnostic methods are highly specific, but the diagnosis time is relatively lagging.[7,8] Until now, there has been no protocol for managing and identifying anastomotic fistula after esophageal cancer. The possibility of anastomotic leakage should be considered, and further diagnosis should be made in combination with an imaging examination when the following symptoms appear. For patients who have undergone neck anastomosis, the appearance of neck incision swelling, scleromas, and

Table 4. Multivariate logistic regression analysis of anastomotic leakage.

	β	S_E	Wald χ^2	OR	P
Incision redness/exudation	3.007	0.863	12.152	20.222	0.000
Pleural effusion	2.632	0.645	16.639	13.908	0.000
Preoperative chemotherapy history	2.011	0.689	8.506	7.468	0.004
Increased white blood cells	1.934	0.796	5.908	6.916	0.015
Age	0.108	0.045	5.796	1.114	0.016
Constant	−12.304	3.247	14.357	0.000	0.000
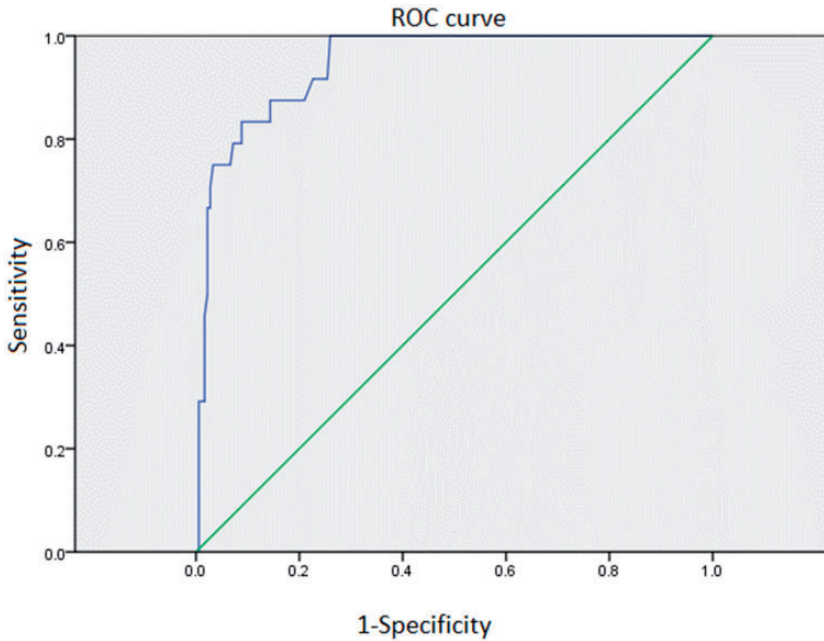
Figure 1. Prediction score for the equation using the ROC curve test.

subcutaneous fluctuations indicate anastomotic leakage; for the patients who have undergone intrathoracic anastomosis or anastomosis in the neck but the anastomotic fell into the chest cavity, the occurrence of digestive juice or continuous gas extraction in the chest drainage tube indicate the same problem. In this study, the diagnostic method for anastomotic fistula after surgery for esophageal cancer was based on its clinical manifestations, and the final diagnosis was confirmed by the results of gastrointestinal angiography, esophageal endoscopy, CT, or other imaging examinations. Currently, there are still some difficulties to the early identification of anastomotic leakage, as early symptoms are only shortness of breath, chest tightness, and chest pain with deep inhalation of the lungs or movement of the muscles in the chest wall[9] along with other symptoms. These are easily confused with postoperative pain, pneumonia, and other complications, as they lack specificity, which is not conducive to early identification and intervention.[10]

In this study, an effective risk assessment model for anastomotic leakage was established by comprehensively evaluating risk factors, clinical symptoms, and signs of perioperative anastomotic leakage in patients. The prediction time of the model started from the fourth day, and the risk assessment was managed until the seventh day or the day of discharge. Nurses were "sentinel" for observing patients' conditions, and the model can provide a basis for the medical staff to identify the occurrence of anastomotic leakage early and reduce the influence of anastomotic leakage on the prognosis of patients through early treatment.

Analysis of related factors in the occurrence of anastomotic leakage

Age. In previous studies, it was uncertain whether age was a risk factor for anastomotic leakage.[11] The results of this study suggested that increased patient age was an independent risk factor for anastomotic leakage. With increased age, the incidence of vascular lesions in the body was significantly increased, which in turn affects the blood supply around the anastomotic stoma after resection of esophageal cancer lesions, increasing the risk of anastomotic leakage.[12] Another study has shown that postoperative cardiopulmonary complications and anastomotic leakage had a higher mortality rate in elderly patients with esophageal cancer.[13]

Preoperative chemotherapy history. The guideline for the standardization of esophageal cancer in China suggest that untreated patients with advanced thoracic esophageal squamous cell carcinoma should undergo preoperative radiotherapy and chemotherapy. Patients with advanced esophageal cancer show improved tumor resection rates and local tumor control rates by preoperative adjuvant chemotherapy.[14] The results of this study showed that preoperative chemotherapy increases the risk of postoperative

anastomotic leakage. The chemotherapy drugs used for esophageal cancer were mainly cisplatin and fluorouracil. While inhibiting the growth of tumor cells, the growth and repair ability of normal cells is also affected, and the healing ability of the tissue is decreased, thereby increasing the occurrence of postoperative anastomotic leakage.[15]

Incision redness/exudation. The results of this study showed that postoperative incision redness/exudation suggested that anastomotic leakage may occur. When the anastomotic stoma is not well healed, a small fistula is formed early, saliva and digestive juice are further stimulated, inflammatory factors are released, and the incision is corroded, resulting in an anastomotic and wound and inflammatory reaction, which further leads to insufficient blood supply, aggravation of healing, and redness/ exudate. Clinically, the incision redness/ exudation is accompanied by changes in traits. The exudate is saliva-like, purulent, and odorous. It is an important diagnostic criterion for postoperative anastomotic leakage, especially for anastomotic leakage in the neck. Therefore, nurses should pay attention to wound healing when changing the dressing for wounds and daily body examinations, as well as determining whether wounds are red and swollen, have exudate or increased exudate when pressing around the wounds. When the wounds are not well healed, it is important to remind the doctors in a timely manner, and if necessary, conduct wound incision exploration.

Pleural effusion. This study found that postoperative chest X-ray examinations showed moderate to large effusion, which suggested that anastomotic leakage may occur. A previous study proved that when there was disappearance of the costophrenic angle along with 500–800 mL pleural effusion, it is appropriate to consider it as moderate

effusion, and when the chest was filled with over 800 mL of pleural effusion, the intercostal space is widened, the diaphragm is lowered and the trachea, mediastinum, and heart are shifted to the healthy side.[16] Because the time of anastomotic leakage appeared sooner or later, the imaging performance also differed. Owing to the absence of extensive adhesions in the thoracic cavity, early onset fistula may appear as a free pneumothorax or liquid pneumothorax. In the middle and late stage, due to adhesion, it can form a packaged effusion.[17] Therefore, nurses should pay attention to the non-specific clinical manifestations of postoperative chest radiographs, especially as time progresses. Imaging could suggest that pleural effusion should be considered, so that the risk of anastomotic leakage can be more comprehensively evaluated.

Increased white blood cell count. Because of the influence of surgery, early postoperative inflammatory reactions can cause the patient's white blood cell counts and other inflammatory factors to transiently increase. These inflammatory factors generally began to rise at 24 hours after surgery, and began to fall after peaking at 72 hours.[18] Studies have shown that patients with anastomotic leakage have no statistically significant difference in white blood cell counts within 3 days or between the fourth and fifth day after surgery compared with patients who do not have fistula.[19] Therefore, this study selected leukocyte levels on the sixth and seventh day after surgery as an observational index. The results showed that the continuous increase of white blood cells after surgery was an independent risk factor for anastomotic leakage, which was consistent with the findings of Noble et al.[20] The continuous increase of inflammatory factors such as leukocytes suggests postoperative infectious inflammatory reactions, which lead to difficulty in healing of anastomotic stoma. Tsujimoto et al. and other studies have shown that patients with

systemic inflammatory response syndrome on the fourth day after surgery have a significantly increased risk of anastomotic leakage.[19] Therefore, postoperative monitoring of changes in inflammatory factors such as white blood cell counts, early detection of the presence of infection, and interventions may help reduce the risk of anastomotic leakage.

Establishment of the risk prediction model and effect evaluation. In this study, the risk prediction model was obtained by logistic regression analysis, and the ROC curve was used to test and evaluate the prediction effect of the risk prediction model. The area under the curve was 0.912, which indicated that the model predicts better results. The sensitivity was 0.833, the specificity was 0.912, and the best diagnostic value was 0.745. Thus, when the risk prediction equation calculated a score of $Z \geq 0.745$, the patients were in a high-risk group with anastomotic leakage. When scores reached or approached 0.745, the patient should be paid close attention by medical staff, and the occurrence of anastomotic leakage should be identified as early as possible.

Conclusion

In this study, a retrospective analysis was conducted to establish a predictive model for the risk of anastomotic leakage after esophageal cancer surgery, and it had a good predictive effect. This model suggested the nursing observation points of patients with postoperative anastomotic leakage after esophageal cancer surgery. The prediction of risk degree provided a reference for doctors to diagnose anastomotic leakage in patients following surgery for esophageal cancer by paying close attention to incision redness/exudation, pleural effusion, and increased white blood cell counts, combined with age and preoperative chemotherapy history. Using this risk

assessment model may prevent severe outcomes of anastomotic leakage. This study was conducted in only one hospital, the sample source was limited, and the prediction effect of the risk model need to be further verified by large samples.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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