Original Article

Analysis of the risk factors of postoperative cardiopulmonary complications and ability to predicate the risk in patients after lung cancer surgery

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Background: Postoperative cardiopulmonary complications might be fatal for patients with lung cancer after surgery. The aim of this study was to identify the risk factors of postoperative cardiopulmonary complications in lung cancer patients and get a fitting formula for predicting incidences of cardiopulmonary complications.

Methods: We conducted a retrospective analysis of 653 patients with a diagnosis of lung cancer who underwent a surgery in the Tianjin Medical University Cancer Institute and Hospital (Tianjin, China) from January to December 2014. All patients received lung cancer surgeries. Clinical data was collected for the analysis of the influence factors of cardiopulmonary complication after lung cancer surgeries. The medical statistical analysis program R was used to calculate cardiopulmonary complication probability of classification of quantitative results.

Results: Our work showed that ages, lymphocyte count, smoking history, chronic bronchitis history, operation mode and extubation time were significantly associated with lung infection both in univariate and multivariate survival analysis. And ages, smoking history, arrhythmia of electrocardiogram and operation mode were significantly associated with postoperative arrhythmia both in univariate and multivariate survival analysis. Multiple linear regressions were generated with risk factors by program R software. Finally, we got a fitting formula for predicting cardiopulmonary complications. Risk score for each patient could be obtained by this formula.

Conclusions: The incidences of pulmonary infection and arrhythmia were high for patients who underwent lung cancer surgery. It is important to discriminate risk factors for each patient for reducing the risk of heart and lung complications. Preoperative quantitative evaluation of cardiopulmonary complication after operation is beneficial to the risk control.

Keywords: Lung cancer; surgery; lung infection; arrhythmia; risk score

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Introduction

Lung cancer is one of the most commonly diagnosed cancers all over the world and remains the leading cause of cancer-related deaths in China (1). Surgery was one of the most sufficient treatments for patients with lung cancer. However, with optimal surgical treatment, more than 20% of patients designated as early stages by conventional criteria would recur, and several eventually died of recurrent lung cancer (2,3). Because of the lung loss, functions of respiratory system and circulation system might be badly influenced. Complications might be developed for many patients after pulmonectomy and these complications could even be fatal. The lung infection, cardiac functional insufficiency and arrhythmia after pulmonectomy were the most common difficult problems perplexing surgeons with a high rate of fatality (4,5). This study was to investigate the causes of pulmonectomy complications by collecting clinical information of 653 patients underwent lung cancer surgery.

Material and methods

We conducted a retrospective study of 653 patients with lung cancer who underwent lung cancer surgery at Tianjin Cancer Institute and Hospital from January to December 2014. Data were collected for ages, genders, smoking status, medical histories of respiratory and circulation systems, blood responding quotas, forced expiratory volume in one second (FEV1)% Forced vital capacity (FVC)%, surgical approaches, extent of resections and pathological stages. Complete resection was defined as cancer-free surgical margins, both grossly and histologically. In addition, preoperative evaluation included medical histories, physical and laboratory examinations.

Of the 653 surgical lung cancer patients, 186 patients were aged 65 years or older. 386 patients were males. In our study, 584 patients underwent complete pulmonary resection and systematic node dissection, among these patients, 510 patients were performed lobectomy with lymph node dissection, 38 patients were performed pneumonectomy with lymph node dissection, 36 were performed segmentectomy with lymph node dissection and 69 patients underwent pallitalive pulmonary resection.

In this study, cases were excluded in patients who had lung infection or other infective diseases before surgeries, used antibiotic before surgeries, were given tracheotomy and other traumatic operations or those with long time of mechanical ventilation, who were liable to get secondary infection. Lung infection was diagnosed based on the following evidences: the main evidences include coughing, expectorating, bilateral or unilateral lung with wet rales or percussion dullness, chest CT or chest X-ray showed new or progressive exudative lesions; Secondary evidences include fever with body temperature ≥38 ℃, peripheral blood white cells being equal to or more than 10×10^9 /L, secretion and lavage fluid culture positive by deep sputum bacterial culture and fiber optic bronchoscopy. Arrhythmia was recorded only when patients with arrhythmia needed to be treated. Cases with postoperative sinus tachycardia were not recorded as arrhythmia when induced by fever or pain.

The study was approved by institutional ethics committee of Tianjin Medical University Cancer Institute and Hospital (No. Ek2017088).

Statistical analysis

Related factors of pulmonary infection and arrhythmia after lung cancer surgery were estimated using Univariate Analysis of Chi-square test table. For multivariate analysis, non-conditional logistic regression analysis was applied. We determined the variables for multivariate analysis that showed a statistical significance in Univariate analysis for pulmonary infection and arrhythmia after lung cancer surgery. All statistical analysis above was carried out using the statistical package SPSS for windows 22.0 (Chicago, USA). P values <0.05 were considered statistically significant. All tests were two-sided. The factors, which were proved to be statistical significance, such as history of smoking, history of chronic bronchitis (binary variables) and actual clinical data such as ages, mode of operations, lymphocyte counts (continuous variables), were selected for calculating a predicting formula of complications incidences using R program. According to analysis by R program, age, lymphocyte count, surgical methods had a strong correlation to postoperative pulmonary infection which was a kind of generalized multiple linear regression. We adopted $y=a+bx+cx^2$, quadratic curve fitting, and used linear regression to fit the factors of smoking history, history of chronic bronchitis.

Results

Lung infection

A total of 653 patients after surgery of lung cancer in our hospital were analyzed. *Table 1* summarized the population

Table 1 Univariate analysis of Chi-square test table and related factors of pulmonary infection after lung cancer surgery

Relative factors	N	Infection number	Percentage	Chi-square	P value
Age					
<65	432	296	68.52	13.298	0.000
≥65	221	181	81.90		
Gender					
Male	386	268	69.43	6.275	0.012
Female	267	209	78.28		
Lymphocyte count					
$\geq 1.1\times10^9$/L	611	440	72.01	5.190	0.023
$<1.1\times10^9$/L	42	37	88.10		
Smoking history					
Yes	358	239	66.76	15.913	0.000
No	295	238	80.68		
Chronic bronchitis history					
Yes	164	131	79.88	5.190	0.023
No	489	346	70.76		
FEV1/FVC					
≥80%	331	230	69.49	4.324	0.042
<80%	322	247	76.71		
Extubation time					
≥7days	273	212	77.66	5.060	0.024
<7days	380	265	69.74		
Family history					
Yes	108	81	75.00	0.251	0.617
No	545	396	72.66		
COPD					
Yes	4	2	50.00	1.086	0.297
No	649	475	73.19		
History of asthma					
Yes	6	5	83.33	0.325	0.568
No	647	472	72.95		
BMI					
≥25	278	208	74.82	0.773	0.379
<25	375	269	71.73		

Table 1 *(continued)*

Table 1 *(continued)*

Relative factors	N	Infection number	Percentage	Chi-square	P value
History of diabetes					
Yes	66	48	72.73	0.004	0.951
No	587	429	73.08		
Operation mode					
Lobectomy with lymph node dissection	510	416	81.57	113.680	0.000
Pneumonectomy with lymph node dissection	38	18	47.37		
Segmentectomy with lymph node dissection	36	26	72.22		
Pallitalive pulmonary resection	69	17	24.64		

COPD, chronic obstructive pulmonary disease; BMI, body mass index.

characteristics of our study accompanied with lung infection. The relevant data of single factor Chi-square test analysis revealed that pulmonary infection after operation of lung cancer occurrence showed significant difference with ages (P<0.001), genders (P=0.012), lymphocyte counts (P=0.023), smoking histories (P<0.001), chronic respiratory diseases (P=0.023), FEV1/FVC (P=0.042), patients after drainage tube in dwelling time (P=0.024) and operation modes (P<0.001). Through logistic regression multivariate analysis, it was found that ages (P=0.022, 95% CI: 1.077–2.540), lymphocyte counts (P=0.017, 95% CI: 1.248–9.304), smoking histories (P<0.001, 95% CI: 1.665–3.691), histories of chronic bronchitis (P=0.007, 95% CI: 1.194–3.013), exudation time (P=0.011, 95% CI: 1.124–2.519) and operation modes (P<0.001, 95% CI: 1.836–3.078) remained significantly independent. Other factors were confirmed as false correlation (*Table 2*).

Arrhythmia

Table 3 summarized the population characteristics of our study accompanied with arrhythmia after lung cancer surgery. The relevant data of single factor χ^2 test analysis revealed that pulmonary infection after operation of lung cancer occurrence showed significant difference with ages (P<0.001), histories of coronary heart disease (P<0.001), histories of myocardial infarction (P=0.001), hypertension histories (P<0.001), drinking histories (P=0.011), ST-T of electrocardiogram (ECG) (P<0.001), arrhythmia of ECG (P<0.001) and operation modes (P=0.001). Through logistic regression multivariate analysis, it was found that ages (P<0.001, 95% CI: 5.852–20.223), histories of coronary heart disease (P<0.001, 95% CI: 1.735–6.204), hypertension histories (P=0.004, 95% CI 1.284-3.865), smoking histories (P=0.030, 95% CI: 1.069–3.766), arrhythmia of ECG (P=0.001, 95% CI: 1.482–5.035) and operation modes (P=0.001, 95% CI: 1.485–4.934) remained significantly independent. Other factors were confirmed as false correlation (*Table 4*).

Predicting formula

Infection Rate= $-0.4238687 - 0.0137439 \times A + 0.0001784 \times A^2 + 0.0956266 \times B + 0.1435408 \times S - 0.0361227 \times L + 0.0011634 \times L^2 + 1.0366447 \times O - 0.1924415 \times O^2$

Arrhythmia Rate= $-1.0859 + 0.0156 \times A + 0.1147 \times C + 0.0485 \times H + 0.1027 \times S + 0.1593 \times AC + 0.0635 \times O$

By this formula, where A was age, B was chronic bronchitis history, S was smoking history, L was Lymphocyte count, O was Operation mode, C was history of coronary heart disease, H was hypertension. and AC was arrhythmia of ECG, we could obtain the risk score for each patient. Then we calculated the occurrence probability of each patient to compared with the actual results. *Table 5* summarized the data analysis of lung infection after lung surgery. *Table 6* summarized the data analysis of arrhythmia. It was found that higher the risk scores, higher the complications incidence rates. We could observe that in *Table 5* that scores more than 0.5 of the patients had a significantly higher risk. The lung infection

Table 2 Postoperative pulmonary infection related factors Logistic regression multivariate analysis

Relative factors	B	S.E.	Wald	P-value	OR	OR 95% CI	
						Lower limit	Upper limit
Age	0.503	0.219	5.278	0.022	1.654	1.077	2.540
Lymphocyte count	1.226	0.513	5.721	0.017	3.407	1.248	9.304
Smoking history	0.908	0.203	19.967	0.000	2.479	1.665	3.691
chronic bronchitis history	0.640	0.236	7.338	0.007	1.896	1.194	3.013
Operation mode	0.866	0.132	43.134	0.000	2.377	1.836	3.078
Extubation time	0.520	0.206	6.389	0.011	1.683	1.124	2.519

risk rate of patients after surgery with scores more than 0.9 was 87%. The risk rate with scores 0.8–0.9 was 89%. On the other hand, the risk rate with scores less than 0.1 was 0. The similarly result could be obtained in patients with arrhythmia. The risk rate with scores more than 0.9 was 71%. The risk rate with scores 0.8-0.9 was 100%.

Discussion

Lung cancer is a common solid tumor of respiratory system. It is the most common cause of cancer death in men in the world, and is the second most common cause of death in women (6). Besides tumor recurrence and metastasis, postoperative complication was also a fatal factor for lung cancer patients. It is observed that lung cancer could be accompanied by immune abnormalities because of surgery and chemotherapy. And thoracic surgical trauma, long operative time and surgical resection of lung tissue may also lead to respiratory function insufficiency and caused complications related to heart and lung. It was reported that the incidence rate of pulmonary infections was 2.5%–25% (7-9). It is important to investigate the risk factors of postoperative complications for patient management. A systematic evaluation to predict the risk rate for patient before surgery is needed (10).

Our work showed that ages, lymphocyte counts, smoking histories, histories of chronic bronchitis, operation modes and postoperative extubation time were significantly associated with pulmonary infection. Schussler (9) determined that postoperative pneumonia after lung resection developed in 25% of patients, and others also have demonstrated that elderly patients tend to develop respiratory infections after thoracic surgery (11,12). It was demonstrated, by multivariate analysis, that lung cancer patients of advanced ages, in particular those 75 years of age and older, was a high-risk group for postoperative pneumonia (12). It might be related to the decline of body's function and immune function of elder patients (13). The growth of beta-lactamase producing bacteria is particularly favoured in elderly people (14). Elder patients would be prone to get postoperative secondary infection.

Long-term history of smoking could impair the barrier function of respiratory epithelium and alveolar macrophages (15,16). Smoking could suppress the cilia activity, stimulate the glands secretion and tracheal spasm, and seriously destroy the ventilator function (17,18). Furthermore, the chest tube drainage was routinely placed after pulmonary resection for lung cancer. Patients with long time of indwelling pipe was prone to get retrograde infection. It was reported by Pimentel that S. agalactiae infections were mostly detected among patients who have used indwelling medical devices (77.2%) (19). Operation mode also would be an important factor of lung infection after surgery. Okada (20) reported that selective lymphadenectomy may be considered in elderly lung cancer patients. Our study also proved this viewpoint that larger wound of surgery would be easier to be infected.

Arrhythmia was also one of the main causes of death in patients with lung cancer during postoperative period, and it directly affected the postoperative recovery (21,22). It could be seen that the occurrence of arrhythmia after lung cancer surgery was influenced by a variety of factors, such as preoperative ECG abnormalities, advanced ages, and hypertension, operation modes. A report revealed age to be an independent risk factor for postoperative arrhythmia (23). In elderly lung cancer patients with postoperative complications, the incidence of arrhythmia was high (24,25). Our study confirmed that age was an

Table 3 Univariate analysis of Chi-square test table and related factors of arrhythmia after lung cancer surgery

Relative factors	N	Incidence number	Percentage	Chi-square	P value
Age					
<65	432	15	3.5	142.918	0.000
≥65	221	87	39.37		
Gender					
Male	386	55	14.25	1.347	0.246
Female	267	47	17.60		
History of coronary heart disease					
Yes	214	68	31.78	63.034	0.000
No	439	34	7.75		
History of myocardial infarction					
Yes	9	5	55.56	11.042	0.001
No	644	97	15.06		
Hypertension history					
Yes	212	53	25.00	20.954	0.000
No	441	49	11.11		
Smoking history					
Yes	296	44	14.87	6.489	0.011
No	357	58	16.25		
Arrhythmia history					
Yes	15	4	26.67	1.225	0.271
No	638	98	15.36		
Drinking history					
Yes	140	13	9.29	5.425	0.018
No	513	89	17.35		
ST-T of ECG					
Yes	281	66	23.49	23.164	0.000
No	372	36	9.68		
Arrhythmia of ECG (before surgery)					
Yes	113	43	38.05	52.173	0.000
No	540	59	10.93		
Triglyceride					
≤1.7	530	86	16.23	0.784	0.376
>1.7	123	16	13.01		
Cholesterol					
≤5.17	447	74	16.55	0.939	0.333
>5.17	206	28	13.59		
Operation mode					
Lobectomy with lymph node dissection	510	88	17.25	15.571	0.001
Pneumonectomy with lymph node dissection	38	10	26.32		
Segmentectomy with lymph node dissection	36	2	5.56		
Pallitalive pulmonary resection	69	2	2.90		

Table 4 Postoperative arrhythmia incidence related factors Logistic regression multivariate analysis

Relative factors	B	S.E.	Wald	P value	OR	OR 95% CI	
						Lower limit	Upper limit
Age	2.387	0.316	56.923	0.000	10.878	5.852	20.223
History of coronary heart disease	1.188	0.325	13.355	0.000	3.281	1.735	6.204
Hypertension	0.801	0.281	8.123	0.004	2.228	1.284	3.865
Smoking history	0.696	0.321	4.694	0.030	2.006	1.069	3.766
arrhythmia of ECG	1.005	0.312	10.574	0.001	2.731	1.482	5.035
Operation mode	0.996	0.306	10.574	0.001	2.707	1.485	4.934

Table 5 Incidence rate of postoperative pulmonary infection in 653 patients with lung cancer through predictive formula

Risk score grading	Cases with pulmonary infection	Total cases	Incidence rate (%)
<0.1	0	3	0
≥0.1 and <0.2	3	26	12
≥0.2 and <0.3	7	22	32
≥0.3 and <0.4	5	20	25
≥0.4 and <0.5	6	19	32
≥0.5 and <0.6	12	15	80
≥0.6 and <0.7	54	86	63
≥0.7 and <0.8	142	180	79
≥0.8 and <0.9	164	185	89
≥0.9	84	97	87

Table 6 Incidence rate of postoperative arrhythmia in 653 patients with lung cancer through predictive formula

Risk score grading	Cases with arrhythmia	Total cases	Incidence rate (%)
<0.1	3	320	1
≥0.1 and <0.2	4	114	4
≥0.2 and <0.3	6	67	9
≥0.3 and <0.4	16	56	29
≥0.4 and <0.5	28	38	74
≥0.5 and <0.6	13	20	65
≥0.6 and <0.7	14	16	88
≥0.7 and <0.8	6	8	75
≥0.8 and <0.9	7	7	100
≥0.9	5	7	71

independent risk factor. Cardiovascular disease history was also considered to be a high-risk factor for lung cancer surgery in postoperative correlation factors (26). The results of our study suggested that patients with a history of cardiovascular disease before surgery had a high rate of postoperative arrhythmia. Moreover, patients who had a long history of smoking might accompanied with a decreased pulmonary function, and smoking history would reduce the compensatory ability of cardiac pulmonary function after surgery and further increase the risk of arrhythmia (27). Also, pulmonary capillary bed reduction and insufficiency of pulmonary ventilation function after lung resection would result in decreasing of lung ventilation/perfusion ratio and increasing of pulmonary capillary blood flow (28). Cardiac function would also significantly be reduced (29). The above factors played important roles in the induction of arrhythmia. Heart and lung comorbidities treatments, heart function improvement, well-controlling of hypertension before operations would reduce the occurrence of heart complication. Respiratory tract cleaning during and after the procedure of surgery would be important for lung infection prevention. In addition, ECG monitoring and preventive treatment for arrhythmia would be helpful to reduce the risk of arrhythmia (30-32).

Our study finally obtained a formula to calculate the probability of complications occurrence for each patient after the operation, so that the risk quantization could be achieved. The formulas seemed to perform well for predicting the complications. The ability to predict which

patient is at high risk for the cardiopulmonary complications may help to select patients who are appropriate for surgeries, advise preoperative interventions to decrease operative risks, and provide increased therapeutic measures to decrease the incidence of complications (4). Other scoring systems specific for lung resection have been reported, including the CPRI, the PRQ, and the PPP (33-35). Despite their potential utility, other scoring systems required the collection of large amounts of data and time-consuming calculations in order to generate a risk score for an individual patient. In our study, we investigated 653 cases and generated stratification of the scores, indicating that with increasing the score the likelihood of adverse outcome increases. It is beneficial to predict the risk of postoperative complications by collecting relevant medical histories. The practicality of the formula also needs to be further verified by prospective researches of patients.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The study was approved by institutional ethics committee of Tianjin Medical University Cancer Institute and Hospital (No. Ek2017088) and written informed consent was obtained from all patients.

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