Risk factors and survival analysis of arrhythmia following lung cancer surgery: a retrospective study

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Background: Surgical treatment of lung cancer is one of the important treatments for early-stage non-small cell lung cancer (NSCLC). However, arrhythmia, especially atrial fibrillation (AF) and supraventricular arrhythmia, are quite common among patients after surgical treatment of lung cancer. The impact of postoperative arrhythmia (PA) on survival is rarely reported. Our aim was to evaluate the risk factors of PA and its impact on overall survival (OS) after lung cancer surgery.

Methods: A total of 344 patients diagnosed with NSCLC who underwent lung cancer surgery were enrolled in this study. These patients were divided into two groups based on the occurrence of PA. Univariate and multivariate logistic regression analyses were conducted to identify the risk factors of PA. The Kaplan-Meier method was applied to show the OS differences between the two groups.

Results: The incidence of PA was 16% (55/344). Among these 55 patients, 20 had AF, 30 had sinus tachycardia, and 5 had premature beats. A total of 332 patients underwent lung cancer radical resection. Operation type ($P<0.001$), preoperative abnormal ECG ($P=0.032$), transfusion ($P=0.016$), postoperative serum potassium concentration ($P=0.001$) and clinical stage ($P<0.05$) were risk factors for PA. PA (HR 2.083, 95% CI, 1.334–3.253; $P=0.001$), age (HR 1.543, 95% CI, 1.063–2.239; $P=0.025$) and mediastinal lymph node metastasis (HR 2.655, 95% CI, 1.809–3.897; $P<0.001$) were independent prognostic risk factors for OS by multivariate cox analysis.

Conclusions: We identified PA as an independent prognostic risk factor to predict poor OS in patients who underwent lung cancer surgery and had risk factors for PA. We therefore provides guidance for PA in improving the prognosis of lung cancer patients.

Keywords: Lung cancer; surgery; postoperative arrhythmia (PA); prognosis

Introduction

Surgery is one of the most important treatments for early-stage non-small cell lung cancer (NSCLC). The procedure often leads to the removal of functional lung tissue, which may lead to hypoxemia and impair heart function. Most patients with lung cancer have a long history of smoking, which tends to damage the cardiopulmonary functions (1).

Therefore, arrhythmias commonly occur in patients after lung cancer surgery.

Postoperative arrhythmia (PA), especially postoperative atrial fibrillation (PAF), is a common postoperative complication in lung cancer patients. The prevalence of PAF is 10–15% after lobectomy and 20–30% after pneumonectomy (2). Although the PAF is usually transient, it is sometimes associated with other severe complications,

848

Gong et al. Postoperative arrhythmia is a risk factor for poor prognosis

including thromboembolic events, hemodynamic deterioration and heart failure (3). It has been reported that PAF could also extend the length of hospital stay and increase perioperative mortality (4). However, there have been few studies on whether arrhythmia has an influence on postoperative survival among patients with lung cancer.

Therefore, this study aimed to assess the impact of PA on the overall survival (OS) of patients after lung cancer resection and to identify risk factors associated with PA. We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/jtd-20-2740).

Methods

Population and study design

Between January 2007 and January 2008, we retrospectively reviewed 362 patients undergoing lung cancer surgery at Tianjin Medical University Cancer Hospital. Patients with complete preoperative examination information were included: a pulmonary function test, electrocardiogram (ECG), venous color Doppler ultrasound of the lower limbs, emission computed tomography, chest computed tomography and head computed tomography or magnetic resonance imaging; undergoing lung cancer surgery via thoracotomy or thoracoscope; and receiving a continuous telemetry strip after surgery. The following patients were excluded: patients with pace-maker devices, permanent AF and incomplete records. Finally, 344 patients were enrolled in this study. According to the occurrence of PA, these patients were divided into two groups: PA (n=55), and non-PA (n=289). The baseline data of these patients are shown in *Table 1*. The data were collected from the hospital medical records. The study has conformed to the provisions of the Declaration of Helsinki (as revised in 2013). This study was approved by the ethics committee of Tianjin Medical University Cancer Hospital (bc2020193) and individual consent was waived because of the retrospective nature of this study.

The detection and definition of PA

After surgery, all patients were given continuous ECG monitoring for at least 48 hours postoperatively. Once the telemetry showed arrhythmia disturbances or the patients had obvious symptoms such as palpitation and suffocation, a 12-lead ECG recording was obtained. The definition of AF was that the ECG recordings demonstrated the presence of characteristic ECG features of AF lasting for at least 30 seconds. Sinus tachycardia was defined as the ECG showing a sinus rhythm greater than 100 beats per minute and lasting more than 3 seconds, and premature beats were defined as more than 100 beats in 24 hours (both ventricular and atrial).

Patient management and follow up

After discharge, routine examinations such as a computed tomography scan of the chest, head, and abdomen and an ultrasound of the neck and abdomen were generally taken every 3 months for the first 2 years postoperatively and every 6 months for the next 5 years. Afterward, the patients were assessed annually. Follow-up data were collected by contacting the patients or their relatives via telephone or obtaining them from the hospital records. Eight patients were lost to contact after discharge in the PA group and six patients in the non-PA group. We compared the 14 patients with lost contact and the 330 patients who had follow-up information, and there was no statistically significant difference between the two groups (P>0.05, Table S1). The end-point of the study was OS, which was defined as the interval between the date of the operation and the date of death or censoring. The follow-up information and OS were both calculated in months. The follow-up was completed in December 2019 or to the date of the death of the patients.

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences version24.0 (SPSS Inc, Chicago). Categorical variables were compared using chi-square test or Fisher's exact test expressed as frequency and percentage. Continuous variables were tested for normal distribution by the Kolmogorov Smirnov test, then compared between groups with a t-test among the normal distribution variables and expressed as the mean ± standard deviation. Those with skewed distributions were compared with the Mann-Whitney test and expressed as medians and interquartile range. Three groups of continuous variables in accordance with the normal distribution were compared by ANOVA test, and variables with skewed distributions were compared by the Kruskal-Wallis H test.

Univariate and multivariate logistic analyses were performed to predict the risk factors for PA. Survival was

Table 1 Basic clinicopathologic features and perioperative data of patients

Variables	PA (n=55)	Non-PA (n=289)	P value
Gender, n (%)			0.441
Male	38 (69.1)	184 (63.7)	
Female	17 (30.9)	105 (36.3)	
Smoking history, n (%)			0.600
Yes	32 (58.2)	179 (61.9)	
No	23 (41.8)	110 (38.1)	
Age, n (%)			0.126
<65	31 (56.4)	189 (65.4)	
≥65	24 (43.6)	100 (34.6)	
Previous history, n (%)			0.039
CVD	17 (30.9)	51 (17.6)	
Others	16 (29.1)	76 (26.3)	
Healthy	22 (40.0)	162 (56.1)	
Preoperative biochemical data, mean ± SD			
Hg (g/L)	136.0±17.5	37.8±14.92	0.483
WBC (10^9/L)	6.83±2.44	7.09±2.34	0.452
LDH (U/L)	176.49±43.10	176.15±38.02	0.953
ALP (U/L)	72.67±22.30	76.32±22.52	0.271
Preoperative respiratory data, mean ± SD			
FEV1, L	75.60±18.22	75.91±17.64	0.905
FEV1/FVC, %	94.69±15.44	94.33±12.83	0.583
Preoperative ECG, n (%)			0.003
Normal ECG	26 (47.3)	189 (65.4)	
Sinus arrhythmia	9 (16.4)	35 (12.1)	
Atrial arrhythmia	6 (10.9)	4 (1.4)	
A-V junction arrhythmia	0 (0.0)	1 (0.3)	
Ventricular arrhythmia	7 (12.7)	13 (4.5)	
Myocardial ischemia	5 (9.1)	32 (11.1)	
Conduction block	2 (3.6)	11 (3.8)	
Others	0 (0.0)	4 (1.4)	
Tumor side, n (%)			0.771
Left	24 (43.6)	120 (41.5)	
Right	31 (56.4)	169 (58.5)	

Table 1 (*continued*)

850

Gong et al. Postoperative arrhythmia is a risk factor for poor prognosis

Table 1 (*continued*)

Variables	PA (n=55)	Non-PA (n=289)	P value
Pathological, n (%)			0.512
ADC	19 (34.5)	120 (41.5)	
SCC	22 (40)	115 (39.8)	
ASC	8 (14.5)	19 (6.6)	
SCLC	2 (3.6)	8 (2.8)	
LCLC	0 (0.0)	4 (1.4)	
Others	4 (7.3)	23 (7.9)	
Surgical time, min, median [IQR]	105 [150–90]	120 [162.5–90]	0.062
Surgical blood loss, mL, median [IQR]	100 [150–80]	150 [200–100]	<0.001
Transfusion, n (%)	9 (16.4)	120 (41.5)	<0.001
Previous heart disease, n (%)	7 (12.7)	14 (4.8)	
Postoperative data			
WBC, 10^9/L, mean ± SD	11.79±7.84	12.23±3.47	0.401
NEUT, %, median [IQR]	85 [87–80]	83 [87–78]	0.207
Serum potassium concentration, mmol/L, mean ± SD	4.26±0.60	3.95±0.55	<0.001
Operation type, n (%)			<0.001
Lobectomy	39 (70.9)	251 (86.9)	
Pneumonectomy	7 (12.7)	30 (10.4)	
Sleeve lobectomy	0	5 (1.7)	
Wedge lobectomy	9 (16.4)	3 (1.0)	
Surgical approach, n (%)			0.144
Thoracotomy	47 (85.5)	265 (91.7)	
Thoracoscope	8 (14.5)	24 (8.3)	
Number of dissected LN, median [IQR]	19 [28–13]	18 [27–11]	0.698
Station number of dissected LN, median [IQR]	6 [7–4]	5 [7–4]	0.091
Station number of positive LN, median [IQR]	2 [2–0]	3 [3–0]	0.120
Metastatic LN station number, median [IQR]	2 [2–0]	2 [2–0]	0.161
Mediastinal LN metastasis, n (%)	14 (25.5)	115 (39.8)	0.044
Clinical stage, n (%)			0.001
IA$_1$/IA$_2$/IA$_3$/IB	14 (25.5)	96 (33.2)	
IIA/IIB	25 (45.5)	64 (22.1)	
IIIA/IIIB	16 (29.1)	129 (44.6)	

PA, postoperative arrhythmia; CVD, cardiovascular disease; SD, standard deviation; Hg, hemoglobin; WBC, white blood cell; LDH, lactate dehydrogenase; ALP, alkaline phosphatase; FEV1, forced expiratory ventilation in 1 second; FVC, forced vital capacity; ECG, electrocardiograph; A-V, atrioventricular; ADC, adenocarcinoma; SCC, squamous cell carcinoma; ASC, adenosquamous carcinoma; SCLC, small cell lung cancer; LCLC, large cell lung cancer; IQR, interquartile range; NEUT, neutrophil; LN, lymph node.
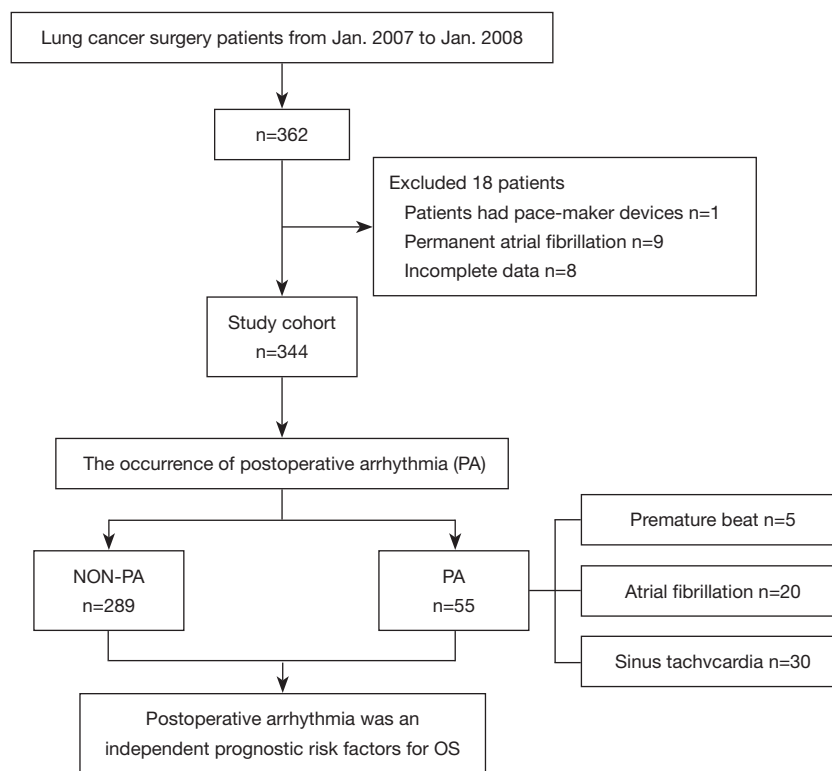
Figure 1 The flow chart.

estimated by the Kaplan-Meier method and compared using log-rank tests. Multivariate Cox proportional hazards regression analysis was used to calculate the hazard ratio (HR) and 95% CI. In all analyses, a two-tailed P<0.05 was considered statistically significant.

Results

Baseline data and operative characteristics

With reference to the analysis of risk factors of PA in the previous literature (4-8), we collected the basic clinicopathologic features and perioperative data of these 344 patients as shown in *Table 1*, and the study process as shown in *Figure 1*. The results of the preoperative ECG showed significant difference between the patients in the PA and non-PA groups. Among the 55 patients, 26 (47.3%) patients had normal ECG, 9 patients (16.4%) had sinus arrhythmia, 6 patients (10.9%) had an atrial arrhythmia, 7 patients (12.7%) had ventricular arrhythmia, 5 patients (9.1%) had myocardial ischemia and 2 patients (3.6%) showed a conduction block. The results for their previous history was significantly different between two groups (all P<0.05).

Among the 344 patients who underwent lung cancer surgery (thoracotomy and thoracoscopic surgery), the majority (n=332, 96.5%) underwent radical resection, including sleeve lobectomy (n=5, 1.5%), lobectomy (n=290, 84.3%) and pneumonectomy (n=37, 10.5%), while nonradical resection consisted of a wedge lobectomy (n=12, 3.5%). Significant differences were seen between the patients with or without PA (P<0.001). Moreover, different clinical stages also had significant differences in the PA group compared to the non-PA group, and 41 patients (74.5%) were at least clinical stage II in the PA group. The median amount of blood loss of the PA group was 100 mL, and that of the other group was 150 mL. There was a statistically significant difference in blood loss amount between two groups (P<0.001).

Characterization of PA

Table 2 shows that the overall incidence of arrhythmia after lung cancer surgery was 16% (55/344), among which the most common arrhythmia type was sinus tachycardia (n=30), more common than AF (n=20) and a premature beat

Table 2 Baseline data of three postoperative arrythmias groups

Variables	Atrial fibrillation (n=20)	Sinus tachycardia (n=30)	Premature beat (n=5)	P value
Age, n (%)				0.783
<65	10 (50.0)	17 (56.7)	2 (40.0)	
≥65	10 (50.0)	13 (43.3)	3 (60.0)	
Gender, n (%)				0.325
Male	14 (70.0)	19 (63.3)	5 (100.0)	
Female	6 (30.0)	11 (36.7)	0 (0.0)	
Smoking history, n (%)				0.183
Yes	11 (55.0)	16 (53.3)	5 (100.0)	
No	9 (45.0)	14 (46.7)	0 (0.0)	
FEV1, L, mean ± SD	76.15±21.38	78.13±14.23	58.20±20.28	0.073
FEV1/FVC, mean ± SD	91.40±21.99	97.30±11.03	92.20±29.18	0.395
Preoperative ECG, n (%)				0.243
Normal	8 (40.0)	17 (56.7)	1 (20.0)	
Abnormal	12 (60.0)	13 (43.3)	4 (80.0)	
Previous history, n (%)				0.882
Healthy	8 (40.0)	12 (40.0)	2 (40.0)	
Diabetes/hypertension	3 (15.0)	7 (23.3)	1 (20.0)	
Heart disease	5 (25.0)	3 (10.0)	1 (20.0)	
Others	4 (20.0)	8 (26.7)	1 (20.0)	
Tumor location, n (%)				0.199
Left	9 (45.0)	11 (36.7)	4 (80.0)	
Right	11 (55.0)	19 (63.3)	1 (20.0)	
Surgical approach, n (%)				0.680
Thoracotomy	17 (85.0)	25 (83.3)	5 (100.0)	
Thoracoscope	3 (15.0)	5 (16.7)	0 (0.0)	
Surgical time, min, median [IQR]	112.5 [147.5–90]	112.5 [146.25–90]	100 [165–75]	0.905
Surgical Blood loss, mL, median [IQR]	100 [115–100]	100 [185–50]	100 [100–65]	0.440
Operation type, n (%)				0.553
Radical resection	18 (90.0)	24 (80.0)	4 (80.0)	
Non-radical resection	2 (10.0)	6 (20.0)	1 (20.0)	
Transfusion, n (%)	2 (10.0)	5 (16.7)	2 (40.0)	0.238
Serum potassium concentration, mmol/L, mean ± SD	4.28±0.78	4.23±0.49	4.40±0.50	0.849
Postoperative NEUT, %, median [IQR]	77.5 [85–70]	85 [90–82]	87 [90.5–86]	0.003

Table 2 (*continued*)

Table 2 (*continued*)

Variables	Atrial fibrillation (n=20)	Sinus tachycardia (n=30)	Premature beat (n=5)	P value
Pathological type, n (%)				0.062
SCC	7 (35.0)	12 (40.0)	3 (60.0)	
ADC	11 (55.0)	8 (26.7)	0 (0.0)	
Others	2 (10.0)	10 (33.3)	2 (40.0)	
Number of dissected LN, median [IQR]	20 [29.75–17.25]	18 [28–9.75]	13 [26.5–8]	0.357
Station number of dissected LN, median [IQR]	7 [8–5]	6 [7–3.75]	5 [8–3]	0.295
Number of positive LN, median [IQR]	0 [0.75–0]	0 [4–0]	0 [2–0]	0.333
Station number of positive LN, median [IQR]	0 [0.75–0]	0 [2–0]	0 [0.5–0]	0.141
Mediastinal LN metastasis, n (%)	3 (15.0)	10 (33.3)	1 (20.0)	0.379
Duration time, min, median [IQR]	19.5 [33.75–10.5]	11 [21–5.75]	11 [25–4]	0.061
Occurrence time of postoperative hours, median [IQR]	2 [2.75–1]	2 [3–1]	1 [3.5–1]	0.970
Drug treatment, n (%)	20 (100.0)	16 (53.3)	3 (60.0)	<0.001

FEV1, forced expiratory ventilation in 1 second; FVC, forced vital capacity; ECG, electrocardiograph; SD, standard deviation; IRQ, interquartile range; NEUT, neutrophil; SCC, squamous cell carcinoma; ADC, adenocarcinoma; LN, lymph node.

(n=5). Among the 5 patients with premature beats, two patients were diagnosed with atrial premature beats and the other 3 patients were diagnosed with ventricular premature beats. These two patients with atrial premature beats and the two patients with ventricular premature beats were all bigeminy beats, while the one patient with ventricular premature beats had trigeminy beats. Among these patients, 16 had a transient arrhythmia and converted to a sinus rhythm without the need for medication, and the other 39 were given drugs to treat their arrhythmias (P<0.001, *Figure 2A*). Thirty-nine patients were prescribed medications, and 11 were treated with digoxin (20%), 9 were treated with digoxin combined with verapamil (16.4%), 6 were treated with digoxin plus metoprolol (10.9%) and 3 were treat with furosemide (5.5%). Three patients with premature beats were treated with lidocaine and moricizine to control their ventricular rate. PA usually occurred on the first day after surgery, and it peaked in the first hours after surgery. It lasted from 1 to 72 hours, and the average duration of each type of arrhythmia is shown in *Figure 2B*.

Univariate and multivariate logistic analyses to identify risk factors of PA

The results of the univariate and multivariate logistic analyses are shown in *Table 3*. Univariate regression revealed that a history of heart disease (coronary heart disease, arrhythmia, etc.), preoperative abnormal ECG performance, transfusion, mediastinal lymph node metastasis, postoperative serum potassium concentration, operation type and the clinical stage were significant factors to predict PA. The blood loss amount was also statistically significant.

The variables with P<0.05 in univariate analysis were included in the multivariate analysis using a forward method. The results of the multivariate logistic regression showed that preoperative abnormal ECG, postoperative serum potassium concentration, transfusion, operation type and clinical stage were independent factors for the development of PA. The OR for preoperative abnormal ECG was 2.167 (P=0.032, 95% CI, 1.070–4.390) compared with patients with a preoperative normal ECG. The ORs for postoperative serum potassium concentration and transfusion were 2.706 (P=0.001, 95% CI, 1.467–4.991) and 2.798 (P=0.016, 95% CI, 1.208–6.480) respectively. The OR of patients undergoing lung cancer radical dissection was 15.687 (P<0.001, 95% CI, 3.665–67.136) compared with patients undergoing wedge lobectomy (nonradical dissection). The ORs of stage II patients were 3.060 (P=0.015, 95% CI, 1.247–7.507) compared with
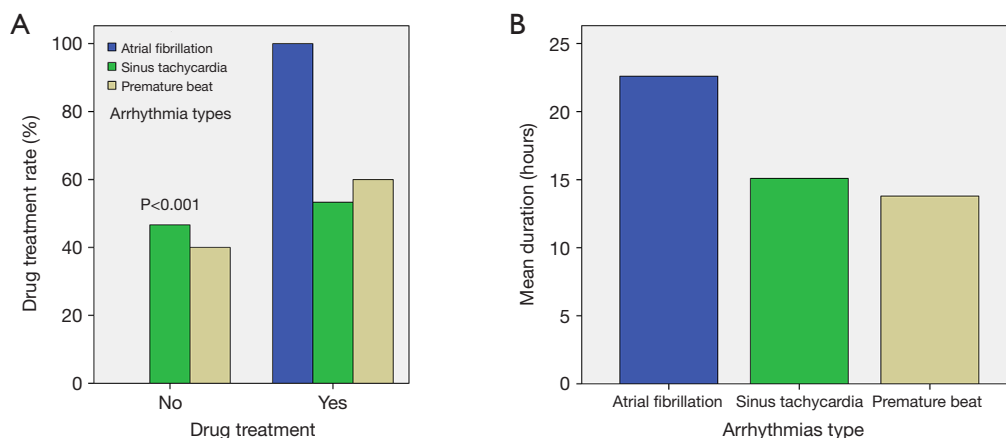
Figure 2 The drug treatment rate of each kind of postoperative arrhythmia (A) and the mean duration of each type of arrhythmia (B).

stage I or III.

Long term survival and analysis of survival factors

As *Figure 3* shows, the five-year and ten-year survival rates in patients with PA were 39.7% and 33.6% respectively and that in patients without PA were 57.1% and 56.5% respectively. Log rank test showed that PA (P=0.006), clinical stage (P<0.001), TNM classification (P=0.002), the number of dissected lymph node (P<0.001), the number of metastatic lymph node stations (P<0.001), mediastinal lymph node metastasis (P<0.001) and the number of N2 metastatic stations (P<0.001) were associated with a poor OS.

The duration of follow-up after surgery was 155 months in the study population. The median follow-up duration was 26 months in the PA group and it was 41 months in the other group. The cause of death was lung cancer in most cases. A total of 135 patients died during the follow-up period. Twenty-six patients died in the PA group and 106 patients without PA died. Among these 106 patients who died without PA, one patient died due to a pulmonary infection in the hospital and the other 105 patients died due to lung cancer recurrence or metastasis. Among these 26 patients who died with PA, 2 patients died after surgery in the hospital and 4 patients died of heart disease in the follow-up period, while the rest died of cancer recurrence or metastasis.

The results of the Cox proportional hazards analyses are shown in *Table 4*. Age, clinical stage, mediastinal lymph node metastasis, the number of positive lymph nodes, the station number of the positive lymph nodes, the station number of the positive N2 lymph nodes and PA were all significant factors by univariate analysis (all P<0.05). PA

(HR 1.995, 95% CI, 1.261–3.157; P=0.003), age (HR 1.543, 95% CI, 1.063–2.239; P=0.023) and mediastinal lymph node metastasis (HR 2.657, 95% CI, 1.802–3.918; P<0.001) were identified as independent prognostic risk factors by multivariate analysis.

Discussion

Arrythmia, especially AF, is the most common cardiac complication following lung cancer surgery. According to a previous review (9), its incidence ranges from10% to 20% after lobectomy and up to 40% after pneumonectomy (more common in the right side). Our study revealed similar observations: patients who had right-sided surgery were more likely to experience PA (n=31) than patients who had left-sided surgery (n=24).

New-onset AF usually occurs within a week after the lung cancer surgery, and peaks in 2 to 4 days (10). Ivanovic *et al.* (6) reported that AF always occurred in the first 24 hours after the operation, while the average time of arrhythmia appearing in our study was earlier than in these previously reported data. The shorter time before the appearance of an arrhythmia after surgery may be related to the fact that the patients were admitted directly to the thoracic intensive care unit after surgery and received continuous ECG monitoring.

The reasons for PA are complex and not fully understood. There is evidence showing a strong correlation between PA and pulmonary vein as well as other atrial sites (11), but a specific mechanism has yet to be found. For instance, inappropriate intraoperative management of the pulmonary vein may trigger PA (12), while postoperative

Table 3 Results of univariate and multivariate analyses to identify risk factors of postoperative arrhythmia

Factors	Univariate analysis			Multivariate analysis		
	OR	95% CI	P value	OR	95% CI	P value
Gender	0.784	0.422–1.457	0.442			
Age	1.571	0.879–2.809	0.128			
Previous history						
Healthy		Reference				
Diabetes/hypertension	1.723	0.780–3.810	0.179			
CHD/ arrhythmia/other heart disease	3.898	1.550–9.807	0.004			
Others	1.519	0.721–3.200	0.271			
Preoperative abnormal ECG	2.108	1.178–3.773	0.012	2.167	1.070–4.390	0.032
Tumor side	0.917	0.512–1.641	0.771			
Transfusion	3.629	1.711–7.696	0.001	2.798	1.208–6.480	0.016
Surgical blood loss	0.995	0.991–0.999	0.011			
Surgical time	0.993	0.985–1.000	0.060			
Postoperative WBC	0.965	0.889–1.048	0.400			
Postoperative NEUT	1.012	0.978–1.047	0.483			
Postoperative serum potassium concentration	2.615	1.557–4.392	0.000	2.706	1.467–4.991	0.001
Thoracotomy/ thoracoscope	0.532	0.226–1.255	0.150			
Operation type	18.652	4.868–71.464	<0.001	15.687	3.665–67.136	<0.001
Pathological type						
SCC		Reference				
ADC	0.828	0.426–1.609	0.577			
Others	1.355	0.644–2.852	0.423			
Mediastinal LN metastasis	1.936	1.010–3.711	0.047			
Number of dissected LN	1.002	0.978–1.027	0.860			
Station number of dissected LN	1.116	0.963–1.292	0.145			
Number of positive LN	0.958	0.889–1.032	0.257			
Station number of positive LN	0.871	0.705–1.077	0.202			
Clinical stage						
IA$_1$/IA$_2$/IA$_3$/IB		Reference			Reference	
IIA/IIB	2.679	1.295–5.540	0.008	3.060	1.247–7.507	0.015
IIIA/IIIB	0.850	0.396–1.827	0.678	0.863	0.351–2.117	0.747

CHD, coronary heart disease; ECG, electrocardiogram; WBC, white blood cell; NEUT, neutrophil; SCC, squamous cell carcinoma; ADC, adenocarcinoma; LN, lymph node.
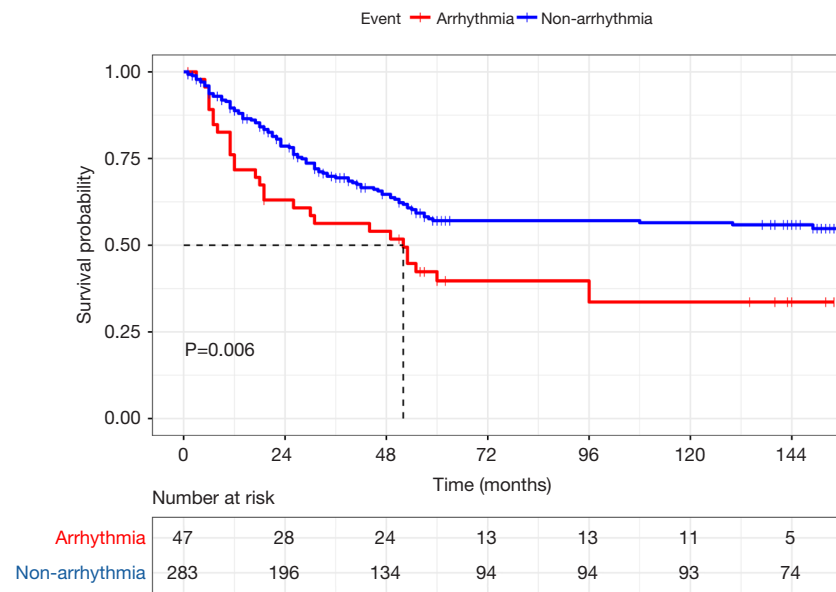
Figure 3 Kaplan-Meier curves for patients with postoperative arrhythmia and patients without postoperative arrhythmia.

pain could trigger a sympathetic response that contributes to the PA (13). Pain-induced sympathetic outflow and the imbalance between the sympathetic and parasympathetic activity could produce atrial ectopic beats and, in susceptible patients, trigger PAF (14).

The 2012 National Comprehensive Cancer Network (NCCN) Lung Cancer Guidelines recommended thoracoscopic lobectomy as a radical surgical procedure for early NSCLC (15). A recent guideline divided the surgical procedure into three different risk levels based on the likelihood of PAF, with lobectomy and pneumonectomy placed in the high risk group (>15% incidence) (16). Radical resection, especially pneumonectomy (4,9), is a strong independent risk factor for PA. The operation process decreases the pulmonary tissue and capillary bed. Pulmonary capillary bed reduction and insufficiency of pulmonary ventilation function after lung resection would result in a decline of the lung ventilation/perfusion ratio and an increase in the pulmonary capillary blood flow (1). During the surgery process, mechanical manipulation of the heart and pericardium leads to local tissue trauma and local inflammatory responses which may both lead to PAF (17-19). An analysis of the Society of Thoracic Surgeons database also demonstrated that increasing the extent of the operations was another risk factor for postoperative AF (20), and De Decker *et al.* (9) reported that the volume of pulmonary resection was a critical risk factor for the

development of PAF.

The identified risk factors for the development of sustained postoperative AF are almost identical to those known to make the atrium vulnerable to the development of AF in the nonsurgical setting (16). Several risk factors have been identified for the development of PAF, such as age, male gender, heart disease history and higher clinical stages (4-8,20). In the current study, a preoperative abnormal ECG, operation type, higher clinical stages, postoperative serum potassium concentration and the need for transfusion were independently associated with PA development in multivariate analysis.

A Japanese group has reported that the surgical approach itself is another risk factor for PA (8). However, their results contradict the findings of the current study, and one possible explanation could be that the sample size of the thoracotomy surgery patients (n=312) was much larger than that of the thoracoscopy patients (n=32). Previous studies reported that mediastinal lymph node dissection was considered to be a risk factor for postoperative AF (8,21). The reason for mediastinal lymph node metastasis being correlated with PA may be surgical management during mediastinal lymph node dissection, which is carried out near the vagal nerve and its branches, especially the cardiac plexus and pulmonary veins (22). This fits into the purported origin of paroxysmal AF in the pulmonary veins (11).

In the current study, the postoperative serum potassium

Table 4 Univariate and multivariate cox predictors to postoperative arrythmia mortality

Predictors	Univariate analysis			Multivariate analysis		
	OS			OS		
	HR	95% CI	P value	HR	95% CI	P value
Gender	0.943	0.665–1338	0.742			
Age	1.610	1.146–2.263	0.006	1.543	1.063–2.239	0.023
Smoking history	0.838	0.595–1.179	0.310			
Preoperative ECG	0.834	0.584–1.190	0.317			
Transfusion	0.903	0.640–1.275	0.564			
Surgical approach	1.147	0.634–2.076	0.649			
Operation type	1.007	0.372–2.723	0.990			
Tumor side	1.092	0.775–1.537	0.616			
Pathological type						
SCC		Reference				
ADC	1.219	0.830–1.791	0.313			
Others	1.507	0.953–2.383	0.079			
Clinical stage						
$IA_1/IA_2/IA_3/IB$		Reference				
IIA/IIB	1.578	0.962–2.590	0.071			
IIIA/IIIB	2.377	1.542–3.662	<0.001			
Mediastinal LN metastasis	2.423	1.661–3.533	<0.001	2.657	1.802–3.918	<0.001
Postoperative arrythmia	1.766	1.171–2.664	0.007	1.995	1.261–3.157	0.003
Number of positive LN	1.038	1.012–1.065	0.005			
Station number of positive LN	1.193	1.099–1.295	<0.001			
Station number of positive N2 LN	1.252	1.119–1.401	<0.001			

ECG, electrocardiograph; SCC, squamous cell carcinoma; ADC, adenocarcinoma; LN, lymph node.

concentration (OR 2.706, 95% CI, 1.467–4.991, P=0.001) and the need for a transfusion after surgery (OR 2.798, 95% CI, 1.208–6.480, P=0.016) were statistically significant in multivariate analysis to predict PA. Electrolyte disturbance has been proven to cause postoperative supraventricular arrhythmias (23). A tight preoperative control of electrolytes is recommended to decrease the incidence of PAF (24). Walsh *et al.* (25) reported that in a prospective study, an arrhythmia after colorectal surgery may be caused by a low intracellular potassium concentration. Potassium deficiency may precipitate arrhythmias (13). The need for a transfusion usually means hypovolemia and it is likely that transfusion acts as a marker of a more complex or difficult

dissection (21). It has been demonstrated that intraoperative hypovolemia, together with hypoxia and anemia, may lead to ischemia of atrial cells and myocardial conduction tissue, altering the cell's electric properties and leading to arrhythmias, both ventricular and supraventricular (26-28).

One of the major findings of the current study was that patients with PA had a poor prognosis compared to patients without it. The Cox proportional hazards regression analysis showed that PA was an independent risk factor for the prognosis after lung cancer surgery. However, the effects of PA on survival after lung cancer surgery are controversial. Cardinale *et al.* (29) reported that postoperative AF did not have any negative impact on

858

Gong et al. Postoperative arrhythmia is a risk factor for poor prognosis

short- and long-term mortality or on the recurrence rate in a prospective study of 233 people with 3-year follow-up. Amar *et al.* (30) reported that supraventricular tachycardia dysrhythmias occurrence after resection of NSCLC is associated with OS, while Imperatori *et al.* (5) reported that AF after pulmonary lobectomy for lung cancer, in addition to causing higher hospital morbidity and mortality, predicted a worse outcome in 5-year survivors. With a median follow-up period of 6 months, the recorded 1-, 5-, 10-year OS rate were 98%, 42%, and 31% respectively among patients with PAF. This result indicated that PA was an independent risk factor for OS, but no significant factor was found in the arrhythmia subgroup.

The risk factors of PA are complex and diverse and are closely related to the operation type, preoperative ECG, clinical stage, transfusion and postoperative potassium concentration. The occurrence of PA is associated with a poor prognosis, and therefore, it is necessary to actively treat basic heart diseases preoperatively and detect electrolyte concentrations. The selection of surgical treatment options should be individualized to reduce the surgical trauma, and postoperative management should be strengthened, such as a prolonged ECG monitoring time and reducing postoperative pain and other stimuli. It should be timely corrected to shorten the duration of arrhythmia and to reduce the adverse consequences caused by arrhythmias.

This study has several limitations. First, B-type natriuretic peptide (BNP) is an effective risk predictor for new-onset AF after lung cancer surgery (31), as well as the ultrasonic cardiogram results (32). However, these factors were not included in the current study, and the results suggest that patients with abnormal perioperative ECG should be tested for BNP and undergo echocardiography. Second, this is a single-center retrospective study, and the sample size is limited. Moreover, the follow-up information does not include the recurrence AF and other arrythmias, and the relationship among these variables and recurrent arrythmia have also has not been evaluated. Finally, there were many patients who lost contact with the research team after surgery. Those patients also ceased to participate in regular examinations at the clinic. Therefore, there is a need for prospective, multicenter and larger-scale trials in order to study the effects of arrhythmias on OS after lung cancer surgery.

Conclusions

In conclusion, we found that a preoperative abnormal ECG,

transfusion, postoperative serum potassium, clinical stage and operation type were independent risk factors of PA. We identified PA as an independent prognostic risk factor to predict a poor OS in patients who underwent lung cancer surgery. This, therefore, provides guidance for evaluating PA to improv the prognosis of lung cancer patients.

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at http://dx.doi.org/10.21037/jtd-20-2740

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/jtd-20-2740). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study has conformed to the provisions of the Declaration of Helsinki (as revised in 2013). This study was approved by the ethics committee of Tianjin Medical University Cancer Hospital (bc2020193) and individual consent was waived because of the retrospective nature of this study.

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Table S1 Basic data of lost contact patients and not lost contact patients

Characteristic	Lost contact, N=14	Not lost contact, N=330	P value
Gender, n (%)			0.262
Male	11 (78.6)	211 (63.9)	
Female	3 (21.4)	119 (36.1)	
Age, n (%)			0.588
<65	8 (57.1)	212 (64.2)	
≥65	6 (42.9)	118 (35.8)	
Smoking history, n (%)			0.817
Yes	9 (64.3)	202 (61.2)	
No	5 (35.7)	128 (38.8)	
Perioperative ECG, n (%)			0.398
Normal ECG	7 (50)	208 (63.0)	
Sinus arrhythmia	3 (21.4)	41 (12.4)	
Atrial arrhythmia	1 (7.1)	9 (2.7)	
A-V junction arrhythmia	0 (0.0)	1 (0.3)	
Ventricular arrhythmia	2 (14.3)	18 (5.5)	
Myocardial ischemia	1 (7.1)	36 (10.9)	
Conduction block	0 (0.0)	13 (3.9)	
Others	0 (0.0)	4 (1.2)	
Respiratory data, mean ± SD			
FEV1, L	78.43±18.83	75.76±17.68	0.580
FEV1/FVC, %	91.43±15.18	94.52±13.18	0.394
Biochemical data, mean ± SD			
Hg, g/L	135.29±12.03	137.61±15.48	0.580
WBC, 10^9/L	6.90±1.95	7.06±2.38	0.810
LDH, u/L	173.5±49.31	176.32±38.39	0.790
ALP, u/L	74.57±18.73	75.79±22.66	0.843
Tumor side, n (%)			0.961
Left	5 (35.7)	139 (42.1)	
Right	9 (64.3)	191 (57.9)	
Clinical stage, n (%)			0.833
IA_1/IA_2/IA_3/IB	5 (35.7)	105 (31.8)	
IIA/IIB	4 (28.6)	85 (25.8)	
IIIA/IIIB	5 (35.7)	140 (42.4)	
Pathological, n (%)			0.505
ADC	5 (35.7)	134 (40.6)	
SCC	6 (42.9)	131 (39.7)	
ASC	2 (14.3)	25 (7.6)	
SCLC	1 (7.1)	9 (2.7)	
LCLC	0 (0.0)	4 (1.2)	
Others	0 (0.0)	27 (8.2)	

ECG, electrocardiograph; A-V, atrioventricular; SD, standard deviation; FEV1, forced expiratory ventilation in 1 second; FVC, forced vital capacity; Hg, hemoglobin; WBC, white blood cell; LDH, lactate dehydrogenase; ALP, alkaline phosphatase; ADC, adenocarcinoma; SCC, squamous cell carcinoma; ASC, adenosquamous carcinoma; SCLC, small cell lung cancer; LCLC, large cell lung cancer.