



Postoperative atrial fibrillation in pneumonectomy for primary lung cancer

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Background: This study assessed the incidence and risk factors (RFs) of postoperative atrial fibrillation (POAF) and its impact on clinical outcomes in patients undergoing pneumonectomy for lung cancer.

Methods: Between 2013 and 2018, this monocentric retrospective study enrolled 324 consecutive pneumonectomy patients for primary lung cancer from our institution and 350 lobectomy and 349 segmentectomy cases matched by age, sex and body mass index (BMI). RF for POAF and postoperative death in pneumonectomy patients were assessed by logistic regression, and long-term outcomes after a median follow-up of 30 (range, 2–61) months by Cox proportional hazard model. Electrophysiology study (EPS) files of 30 AF patients with lung resection history were reviewed.

Results: POAF developed more often after pneumonectomy than lobectomy and segmentectomy (23.2% *vs.* 6.6% *vs.* 1.4%, respectively; $P < 0.001$). Among 75 pneumonectomy patients with POAF, POAF was solitary in 55 patients (73.3%) and concurrent with other complications in 3 patients (4%). POAF risk after pneumonectomy was 4 and 22 times that after lobectomy and segmentectomy, respectively, with age > 60 years and left atrial diameter (LAd) ≥ 35 mm as independent predictors. POAF, infection and hemorrhage were independent RFs for perioperative death after pneumonectomy; however, POAF was not RF for long-term death. Pulmonary vein (PV) trigger was identified in 60% (18/30) of AF patients with lung resection history, with stump PVs being more active than non-stump PVs (38.2% *vs.* 10.5%, $P < 0.001$).

Conclusions: Post-pneumonectomy AF, with remarkable incidence, risk and independent predictors including age > 60 years and LAd ≥ 35 mm, was mostly solitary and possibly secondary to stump and non-stump PV triggers. POAF, along with infection and hemorrhage, was a RF for perioperative death.

Keywords: Postoperative atrial fibrillation (POAF); primary lung cancer; pneumonectomy; lobectomy; segmentectomy

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Introduction

Lung cancer is the most frequent cause of death from cancer worldwide (1), and surgical resection remains the preferred

treatment, especially for early-stage lung cancer (2). Postoperative atrial fibrillation (POAF) is the most common arrhythmia after thoracic surgery, especially after lung

resection, with reported overall incidence ranging from 6.4% to 19%, increasing morbidity, mortality, hospital stay and cost (3-5). And identified risk factors (RFs) after lung section included advanced age, blood transfusion, pneumonectomy, cardiac dysfunction, diabetes mellitus and so on (6-9). Most studies about POAF focused on lobectomy and segmentectomy, some of which tended to consider POAF as generally benign and temporary (10). Although a higher risk of POAF in pneumonectomy patients was observed, our knowledge about POAF after pneumonectomy remains quite limited, and currently, it was speculated that a large extent of surgical resection may be the cause (9). One important characteristic of pneumonectomy is that pulmonary circulation is forced to flow through the remaining side of pulmonary vessels, consequently raising vascular wall tension and possibly increasing POAF incidence. However, this has been rarely mentioned before. In addition, previous studies on POAF after pneumonectomy were limited by small sample size (5,11). Therefore, with relatively large sample size, this study was conducted to assess incidence and RFs of POAF and its impact on clinical outcomes in patients undergoing pneumonectomy for primary lung cancer. We present the following article in accordance with The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting checklist (available at <http://dx.doi.org/10.21037/jtd-20-1717>).

Methods

The study population of this retrospective observational monocentric study was enrolled from the database of our institution. The study protocol was approved by the Shanghai Chest Hospital Ethics Committee (ID: KS1846) and individual consent for this retrospective analysis was waived. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Study population

Settings

Medical records of patients undergoing lung resection at our center for primary lung cancer between January 2013 and May 2018 were reviewed. Pneumonectomy patients were enrolled if eligibility criteria were met. The selection process has been summarized in a flow diagram (Figure S1). Lobectomy and segmentectomy patients with matched sex,

age and body mass index (BMI) were selected randomly.

Clinical variables and outcome data

The preoperative variables included age, gender, BMI, smoking history, coronary artery disease, diabetes mellitus, hypertension, symptomatic heart failure, chronic obstructive pulmonary disease (COPD), preoperative chemotherapy history and echocardiography parameters. Intraoperative variables included tumor laterality, surgical approach and pericardial incision. Pathological variables included TNM stage and pathological pattern. The primary outcome was the occurrence of POAF, and secondary outcomes were other postoperative complications. Perioperative mortality was defined as death within 30 days after surgery or later during the same hospitalization.

Eligibility criteria

Firstly, every enrolled patient underwent surgery for primary lung cancer without metastasis. Secondly, in lobectomy and segmentectomy group, only single lobectomy and single segmentectomy cases were enrolled, and other anatomical resections such as bi-lobectomy and bi-segmentectomy were excluded. Thirdly, patients were excluded if atrial fibrillation (AF) history, severe lung disease, or incomplete medical records were present.

Follow-up

After surgery, all pneumonectomy patients along with 17 lobectomy patients were transferred to the intensive care unit (ICU), and the other patients were transferred to hospital wards. Continuous ECG monitoring with rhythm-analysis function was used in all patients to assess arrhythmia occurrence. The identified AF episodes were reviewed by cardiologists to avoid misinterpretation, and divergence of opinion was solved by discussion. AF burden was defined as the proportion of AF duration recorded by ECG monitoring during the period from after surgery to discharge (12). Relevant data such as onset, frequency and duration of POAF were recorded automatically and reviewed by cardiologists. Postoperative complications other than POAF were also documented. And according to occurrence timing, POAF were categorized into solitary (without other complications), concurrent with other complications (i.e., occurring within 24 h) and non-concurrent with other complications (i.e., either >24 h before or >24 h after other complications).

Electrophysiology study (EPS)

Institutional EPS files of AF patients with lung resection history due to primary lung cancer were reviewed. Briefly, a decapolar diagnostic catheter was placed in the coronary sinus and a circular mapping catheter was placed in the left atrium (LA) via transseptal puncture. The LA electroanatomic shell was then constructed and each pulmonary vein (PV) was carefully mapped successively, including remnant PV stumps. Electrograms at or within each PV were documented with a mapping catheter and compared with intracardiac electrograms obtained from the coronary sinus catheter to identify PV triggers. PV trigger was defined as an atrial ectopic focus localized in stump or non-stump PV according to the earliest atrial activity relative to the reference electrogram or the onset of the ectopic P wave. The role of ectopic beats in initiation of AF was confirmed by on-site recording (13). Circumferential PV ablation was then performed, and AF was considered originating from PV if AF converted to sinus rhythm or other types of atrial tachycardia upon achieving isolation of remaining PVs or stumps. EPS was then repeated to confirm PV isolation.

Statistical analysis

Data are expressed as mean \pm standard deviation for normally distributed continuous variables, median (range) for abnormally distributed continuous variables, and percentage for discrete variables. Comparisons between variables were conducted by χ^2 test for categorical variables; independent-sample *t*-test or one-way ANOVA plus LSD *t*-test for continuous variables with normal distribution; and Mann-Whitney U test or Kruskal-Wallis H test for continuous variables with non-normal distribution. Logistic regression was performed to assess the relationship between baseline or perioperative characteristics and POAF occurrence. In order to exclude confounding effect of non-significant variables, multivariate regression only included significant univariate RFs. Event-free survival was estimated by the Kaplan-Meier method and compared by the log-rank test. Cox proportional hazard model was used to determine the relationship between patients' characteristics and long-term outcomes. A P value <0.05 was considered statistically significant. Statistical analysis was performed using SPSS version 22.0 (IBM Corp., Armonk, NY, USA) and Stata 14.0 (Stata Corp., TX, USA).

Results

Baseline and perioperative characteristics

Baseline characteristics (Table 1) were generally similar among the three groups. A total of 1,023 patients, including 324 pneumonectomy patients, 350 lobectomy patients and 349 segmentectomy patients were enrolled. Most pneumonectomies were performed via open thoracotomy and were left-sided. All other procedures were performed via VATS except for one lobectomy; 31.1% lobectomies and 58.5% segmentectomies were left-sided. TNM \geq IIa were more prevalent in pneumonectomy group than lobectomy group and segmentectomy group (99.4% vs. 36.9% vs. 3.4%, respectively; $P<0.001$). And squamous carcinoma was the major pathological type in pneumonectomy group, while adenocarcinoma predominated in other groups. Notably, intraoperative AF occurred in 8.33% (27/324) pneumonectomy patients after the pulmonary artery was clamped. Pneumonectomy patients had longer postoperative stay.

POAF and non-POAF complications

POAF incidence was 23.2% (75/324) for pneumonectomy, 6.6% (23/350) for lobectomy and 1.4% (5/349) for segmentectomy. As shown in Table 2, most patients with POAF restored sinus rhythm pharmacologically, including 56 pneumonectomy patients and 22 non-pneumonectomy patients. Because pneumonectomy patients had remarkably longer hospitalization and most POAF episodes occurred within the first 7 postoperative days (pneumonectomy, 94.7%, 71/75; non-pneumonectomy, 100%, 28/28), we focused on AF burden within this period. And pneumonectomy group had higher AF burden than non-pneumonectomy group (median, 3.0% vs. 1.8%; $P=0.011$). In pneumonectomy group, patients with POAF had longer postoperative (median, 13 vs. 10 days; $P<0.001$) and ICU (median, 4 vs. 2 days; $P<0.001$) stays than those without POAF.

Briefly, non-POAF complications were more varied and occurred more frequently after pneumonectomy (Table 3). Yet POAF was concurrent with other complications in only 4% (3/75) patients after pneumonectomy and 7.1% (2/28) patients after non-pneumonectomy. In univariate logistic regression, POAF developed independently from other complications in pneumonectomy; however, POAF might

Table 1 Baseline and perioperative characteristics of the patients studied

Variables	Pneumonectomy (n=324)	Lobectomy (n=350)	Segmentectomy (n=349)	Statistical value	P value
Age	58.4±7.9	59.0±7.3	58.4±7.2	F=7.00	0.497
Male sex	291 (88.7)	312 (89.1)	317 (90.8)	$\chi^2=0.56$	0.757
BMI	23.4±2.6	23.7±2.8	23.7±2.5	F=1.25	0.288
Smoking history	180 (55.6)	105 (30.0) ^a	63 (18.1) ^{a,b}	$\chi^2=109.11$	<0.001
Coronary artery disease	9 (2.8)	5 (1.4)	8 (2.3)	$\chi^2=1.51$	0.471
Diabetes mellitus	9 (2.8)	25 (7.1) ^a	6 (1.7) ^b	$\chi^2=15.30$	<0.001
Hypertension	42 (13.0)	43 (12.3)	32 (9.2)	$\chi^2=2.77$	0.251
Symptomatic heart failure	17 (5.3)	7 (2.0) ^a	9 (2.6) ^a	$\chi^2=9.74$	0.008
COPD	14 (4.3)	5 (1.4) ^a	4 (1.2) ^a	$\chi^2=9.33$	0.009
Echocardiography					
LVDs (mm)	28.0±2.7	28.1±2.9	28.3±2.8	F=0.53	0.59
LVDd (mm)	47.4±3.1	47.1±3.3	47.0±3.0	F=1.36	0.258
LAd (mm)	33.7±3.2	34.1± 3.3	33.8±3.3	F=1.69	0.181
PAd (mm)	23.5±1.4	22.9±1.3 ^a	22.6±1.4 ^{a,b}	F=36.11	<0.001
LVEF (%)	63.4±2.4	63.5±2.6	63.6±3.0	F=0.90	0.407
MR	12 (3.7)	15 (4.3)	13 (3.7)	$\chi^2=0.20$	0.905
TR	23 (7.1)	22 (6.3)	18 (5.5)	$\chi^2=1.11$	0.574
AR	13 (4.0)	19 (5.4)	16 (4.6)	$\chi^2=0.77$	0.681
Preoperative chemotherapy	33 (9.3)	0	0		
Laterality (left)	270 (83.3)	109 (31.1)	204 (58.5)	$\chi^2=187.43$	<0.001
Approach (VATS)	34 (10.5)	349 (99.7) ^a	349 (100.0) ^a	$\chi^2=868.59$	<0.001
Pericardial incision	64 (19.8)	1 (0.3) ^a	0		
Cancer stage					
Tis	0	17 (4.9)	62 (17.8) ^b		
Ia	11 (3.3)	180 (51.4) ^a	267 (76.5) ^{a,b}	$\chi^2=372.73$	<0.001
Ib	7 (2.2)	24 (6.9) ^a	8 (2.3) ^b	$\chi^2=13.46$	0.001
IIa	12 (3.8)	17 (4.9)	3 (0.9) ^{a,b}	$\chi^2=9.73$	0.008
IIb	76 (23.5)	63 (18.0)	7 (2.0) ^{a,b}	$\chi^2=69.24$	<0.001
IIIa	124 (38.3)	43 (12.3) ^a	2 (0.6) ^{a,b}	$\chi^2=180.06$	<0.001
IIIb	73 (22.5)	6 (1.7) ^a	0		
IIIc	21 (6.5)	0	0		
Pathology					
Squamous carcinoma	228 (70.4)	109 (31.1) ^a	17 (4.9) ^{a,b}	$\chi^2=321.35$	<0.001
Adenocarcinoma	58 (17.9)	212 (60.6) ^a	321 (92.0) ^{a,b}	$\chi^2=381.87$	<0.001

Table 1 (continued)

Table 1 (continued)

Variables	Pneumonectomy (n=324)	Lobectomy (n=350)	Segmentectomy (n=349)	Statistical value	P value
LCLC	9 (2.8)	6 (1.7)	2 (0.6) ^a	$\chi^2=5.01$	0.082
SCLC	15 (4.6)	6 (1.7) ^a	1 (0.3) ^a	$\chi^2=6.84$	0.033
Other	14 (4.3)	17 (4.9)	8 (2.3)	$\chi^2=3.47$	0.176
Blood transfusion	61 (18.8)	14 (4) ^a	5 (1.4) ^{a,b}	$\chi^2=81.29$	<0.001
POAF	75 (23.2)	23 (6.6) ^a	5 (1.4) ^{a,b}	$\chi^2=94.69$	<0.001
Postoperative stay	10 [3–79]	6 [2–145] ^a	5 [2–101] ^a	H=497.42	<0.001

Values are expressed as mean \pm standard deviation, n (%) or median [range]. ^a, vs. pneumonectomy, P<0.05; ^b, vs. lobectomy, P<0.05. BMI, body mass index; COPD, chronic obstructive pulmonary disease; LVDs, left ventricular end-systolic diameter; LVDd, left ventricular end-diastolic diameter; LAd, left atrial diameter; PAd, pulmonary artery diameter; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; TR, tricuspid regurgitation; AR, aortic regurgitation; VATS, video-assisted thoracoscopic surgery; LCLC, large cell lung cancer; SCLC, small cell lung cancer; POAF, postoperative atrial fibrillation.

possibly be associated with fistula in lobectomy patients (P<0.001).

Most (10/11) perioperative mortality occurred after pneumonectomy, and notably, POAF occurred in 9 of these 10 pneumonectomy mortalities. After pneumonectomy, AF burden (median, 7.7% vs. 2.4%; P=0.006) and total AF duration (median, 13.0 vs. 4.0 h; P=0.035) were higher in perioperative death cases than other patients. In pneumonectomy group, all patients with intraoperative AF had POAF occurrence, yet no significant difference was observed in perioperative mortality between patients with and without intraoperative AF (17.4% vs. 9.6%; P=0.443).

Multivariate analysis

Receiver operating characteristic (ROC) curve was employed to identify optimal cut-off value for continuous variables, and cut-off value for age, left atrial diameter (LAd), left ventricular end-systolic diameter (LVDs) and BMI were 60 y, 35 mm, 29 mm and 23.6 kg/m², respectively. In univariate analysis, POAF risk after pneumonectomy was almost 4 times that after lobectomy [hazard ratio (HR): 4.3; 95% confidence interval (CI): 2.6–7.0; P<0.001] and 20 times that after segmentectomy (Figure 1); moreover, POAF risk after lobectomy was 4.8 times that after segmentectomy. Other univariate RFs for POAF included pericardial incision, male sex, age >60 y, symptomatic heart failure, diabetes mellitus, postoperative transfusion, open thoracotomy, left-sided resection, smoking history,

LAd \geq 35 mm, squamous carcinoma, fistula, infection and hemorrhage. In multivariate analysis (Figure 2), independent RFs for POAF included pneumonectomy, lobectomy, age >60 years, diabetes mellitus, LAd \geq 35 mm, fistula and hemorrhage.

In pneumonectomy patients, univariate RFs for POAF (Figure 1) included age >60 years, LAd \geq 35 mm and LVDs >29 mm. In multivariate analysis (Figure 2), independent RFs for POAF included age >60 years and LAd \geq 35 mm. In univariate analysis, RFs for POAF after lobectomy included symptomatic heart failure and fistula (Figure 1); fistula was also an independent RF.

Ten perioperative deaths occurred among the 324 pneumonectomy patients (3.1%), 9 of which had POAF occurrence. And univariate RFs included age >60 y, symptomatic heart failure, postoperative transfusion, POAF, fistula, infection and hemorrhage. In multivariate analysis, POAF (HR: 16.9; 95% CI: 1.8–159.7; P=0.014), infection (HR, 8.8; 95% CI: 1.4–55.9; P=0.021) and hemorrhage (HR: 16.7; 95% CI: 1.8–159.1; P=0.014) were independent RFs for perioperative death.

Electrophysiological study

EPS files of 30 patients with AF (19 paroxysmal and 11 persistent) who underwent radiofrequency catheter ablation at our institution between January 2012 and December 2018 were selected. Among the 19 patients with paroxysmal AF, 17 had lobectomy history, and 2 had left pneumonectomy history; while among the 11 patients with persistent AF,

Table 2 POAF characteristics

Variables	Pneumonectomy (n=75)	Non-pneumonectomy (n=28)	Statistical value	P value
Onset (day)	2 [0–10]	2 [0–7]	U=858.00	0.144
Patients with multiple POAF episodes, number of episodes (median; range)	35 (2; 1–6)	12 (2; 2–4)	$\chi^2=0.12$	0.73
POAF episodes within first 7 days	91.3% (126/138 episodes)	93.3% (42/45)	$\chi^2=0.19$	0.667
Total POAF duration (hour)	5 [1–71]	3 [1–10]	U=680.50	0.006
POAF duration within first 7 days	5 [1–54]	3 [1–10]	U=662.00	0.004
AF burden	3.0% (0–32.1%)	1.8% (0.6–6.0%)	U=707.00	0.011
SR restoration methods				
No medication	19	6		
Amiodarone	39	18		
Propafenone	17	4		
AAD duration (hour)				
No AAD (observation)	3 [1–23]	3 [1–7]	U=41.00	0.302
With AAD	2 [1–15]	2 [1–5]	U=470.00	0.095
AAD dose (mg)				
Amiodarone	300 [150–1,500], 5 [1–32]	300 [150–900], 3.5 [2–7]	U=261.00	0.119
Propafenone	140 [70–420], 2 [1–6]	140 [70–210], 2 [1–3]		
POAF and other complications				
Solitary	55 (73.3)	20 (71.4)	$\chi^2=0.04$	0.847
Concurrent with others	3 (4.0)	2 (7.1)	(Fisher probabilities)	0.611
Fistula	0	2		
Hemorrhage	2	0		
Pleural effusion	1	0		
Non-concurrent with others	17 (22.7)	6 (21.5)	$\chi^2=0.02$	0.893
Fistula	2	4		
Infection	4	2		
Hemorrhage	6	0		
Pleural effusion	1	0		
Others	7	0		

Data are expressed as n (%) or median [range]. POAF, postoperative atrial fibrillation; AF, atrial fibrillation; SR, sinus rhythm; AAD, anti-arrhythmic drug.

9 had lobectomy and 2 had left pneumonectomy. Lung resection and AF trigger details are summarized in *Table 4*. Overall, among a total of 120 PVs, there were 34 stumps and 86 remaining PVs. PV trigger was identified in 14

stumps of 12 patients and 9 non-stump PVs of 6 patients (examples in *Figure 3*); and non-PV trigger was identified in the other 12. PV trigger was more active in stump PVs than in non-stump PVs (13/34 vs. 9/86, $P<0.001$).

Table 3 Non-POAF complication characteristics

Variables	Pneumonectomy (n=75)	Non-pneumonectomy (n=28)
Non-POAF complications		
Fistula	6	19
Infection	23	17
Hemorrhage	6	3
Pleural effusion	5	3
Death	10	1
Others	12	0
ARDS	3	0
Hepatic dysfunction	3	0
Pulmonary thromboembolism	1	0
Intestinal obstruction	1	0
Respiratory failure	2	0
Secondary hyperthyroidism	1	0
Deep vein thrombosis	1	0
Cause of death		
Gastrointestinal hemorrhage	3	0
Fistula	2	1
Severe infection	2	0
Pulmonary thromboembolism	1	0
Intestinal obstruction	1	0
Sudden cardiac arrest	1	0

POAF, postoperative atrial fibrillation; ARDS, acute respiratory distress syndrome.

Long-term outcomes

At median 30 (range, 2–61) months follow-up, 143 of 1,012 patients died after discharge, including 116 pneumonectomy patients, 24 lobectomy patients and 3 segmentectomy patients, with causes including tumor metastasis (n=113), respiratory failure (n=15), stroke (n=13), and intracranial hemorrhage (n=2). The cumulative survival rate was 79.1%, 95.6%, and 98.2% for pneumonectomy, lobectomy and segmentectomy groups, respectively ($P<0.001$, *Figure 4*). In pneumonectomy patients, univariate RFs for post-discharge death included age >60 years (HR: 2.0; 95% CI: 2.0–2.9; $P<0.001$); TNM \geq IIIa (HR: 1.6; 95% CI: 1.1–2.4; $P=0.025$); smoking history (HR: 1.4; 95% CI: 1.0–2.0; $P=0.096$); squamous carcinoma (HR: 1.8; 95% CI: 1.1–2.8; $P=0.013$); and POAF (HR: 1.5; 95% CI: 1.0–2.2; $P=0.058$);

in multivariate analysis, independent RFs were age >60 years (HR: 1.9; 95% CI: 1.3–2.7; $P=0.001$) and TNM \geq IIIa (HR: 1.8; 95% CI: 1.2–2.8; $P=0.003$).

Discussion

Little is known about POAF after lung resection, while most studies have focused on POAF after cardiac surgery. The present study on POAF after lung resection yielded the following major findings: (I) POAF occurred in 23.2% of pneumonectomy patients, more often than in lobectomy (6.6%) and segmentectomy (1.4%) patients, and mostly as the sole complication; (II) POAF risk after pneumonectomy was almost 4 times that after lobectomy and 22 times that after segmentectomy, with pneumonectomy patients aged >60 years or LAd \geq 35 mm

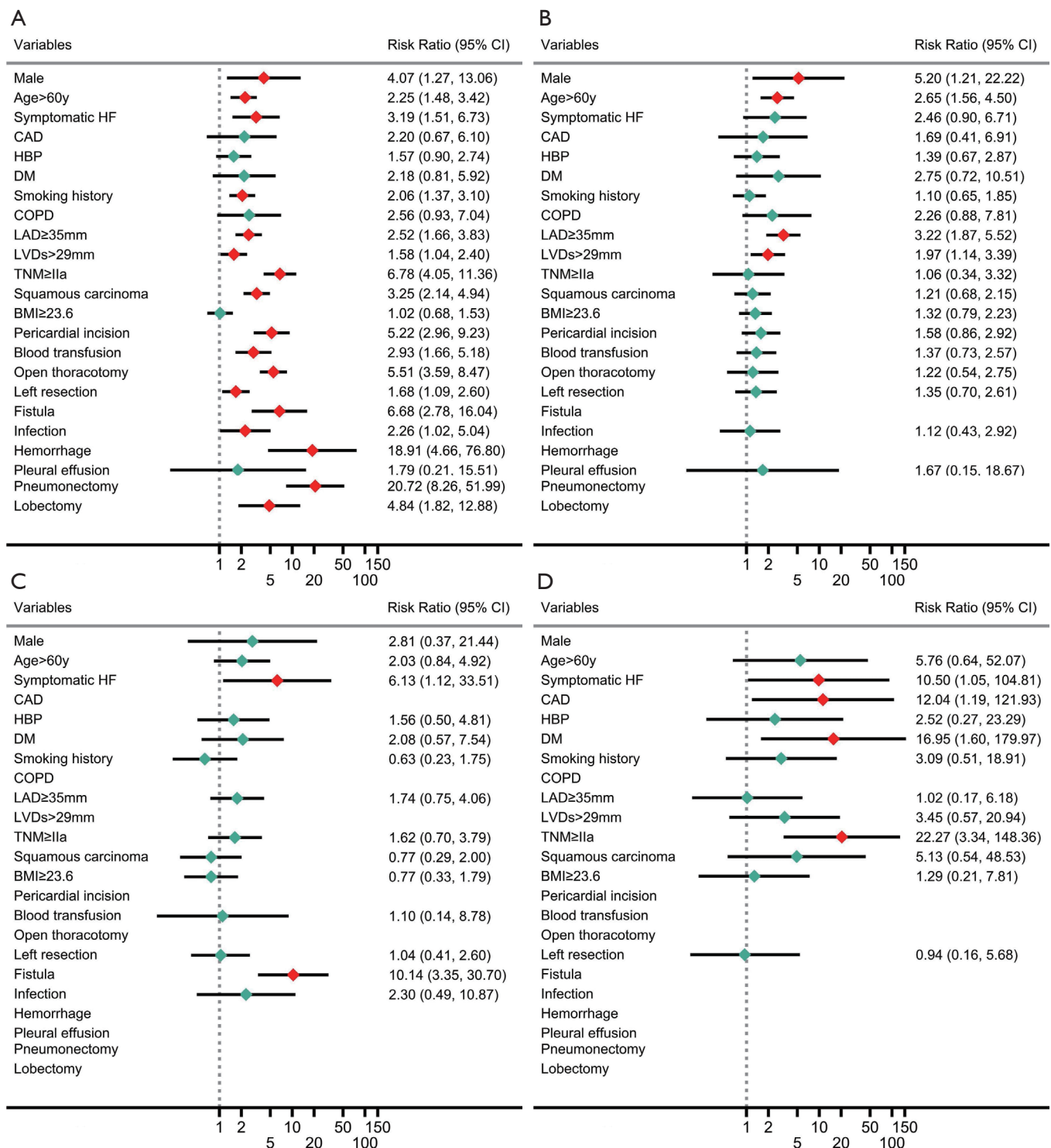


Figure 1 Risk ratio of POAF after lung resection according to variables in univariate logistic regression model. A $P < 0.05$ was considered significant, which was indicated by red diamonds, otherwise turquoise diamonds. (A) All patients, (B) pneumonectomy group, (C) lobectomy group, (D) segmentectomy group. POAF, postoperative atrial fibrillation; CI, confidence interval; HF, heart failure; CAD, coronary artery disease; HBP, high blood pressure; DM, diabetes mellitus; COPD, chronic obstructive pulmonary disease; LAD, left atrial diameter; LVD, left ventricular diameter; BMI, body mass index.

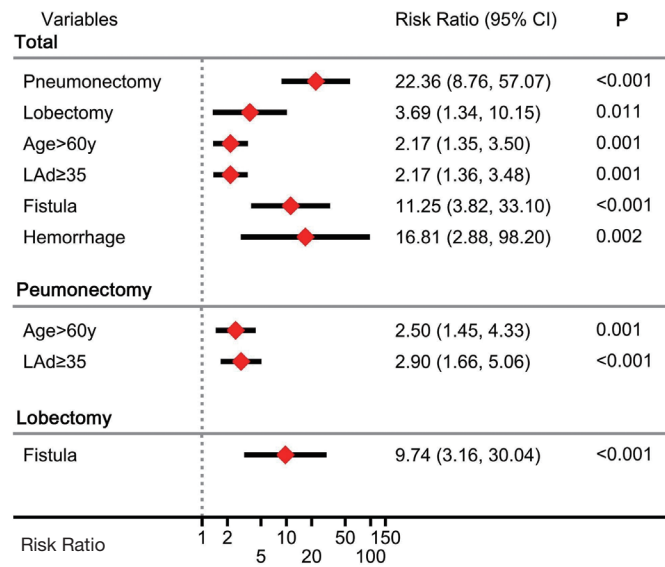


Figure 2 Risk ratio of POAF after lung resection in patients overall and pneumonectomy group according to variables in multivariate logistic regression model. A P<0.05 was considered significant, which was indicated by red diamonds, otherwise turquoise diamonds. POAF, postoperative atrial fibrillation; CI, confidence interval; LAd, left atrial diameter.

Table 4 Trigger and PV characteristics of AF patients with history of lung resection

Lung resection	N	Patients with AF mechanisms			Active PVs		Total PVs		
		Stump	Non-stump	Non-PV trigger	Stump	Non-stump	Stump	Non-stump	All PVs
PAF (n=19)									
Left upper lobectomy	3	2	1 (right upper PV)	0	2	1	3	9	12
Left lower lobectomy	6	3	1 (right upper + lower PVs)	2 (SVC)	3	2	6	18	24
Right upper lobectomy	3	1	1 (left lower PV)	1 (CS)	1	1	3	9	12
Right lower lobectomy	5	4	1 (left lower PV)	0	4	2	5	15	20
Left pneumonectomy	2	1	1 (right upper + lower PVs)	0	2	2	4	4	8
Summary	19	11	5	3	12	8	21	55	76
PerAF (n=11)									
Left upper lobectomy	2	0	0	2 SVC	0	0	2	6	8
Left lower lobectomy	2	1	0	1 TC	1	0	2	6	8
Right upper lobectomy	1	0	0	1 LAA	0	0	1	3	4
Right lower lobectomy	4	0	1 (left-upper PV)	3 (2 SVC, 1 LAR)	0	1	4	12	16
Left pneumonectomy	2	0	0	2 unidentified	0	0	4	4	8
Summary	11	1	1	9	1	1	13	31	44
Total	30	12	6	12	14	9	34	86	120

PV, pulmonary vein; AF, atrial fibrillation; PAF, paroxysmal atrial fibrillation; PerAF, persistent atrial fibrillation; SVC, superior vena cava; CS, coronary sinus; TC, terminal crest; LAA, left atrial appendage; LAR, left atrial roof.

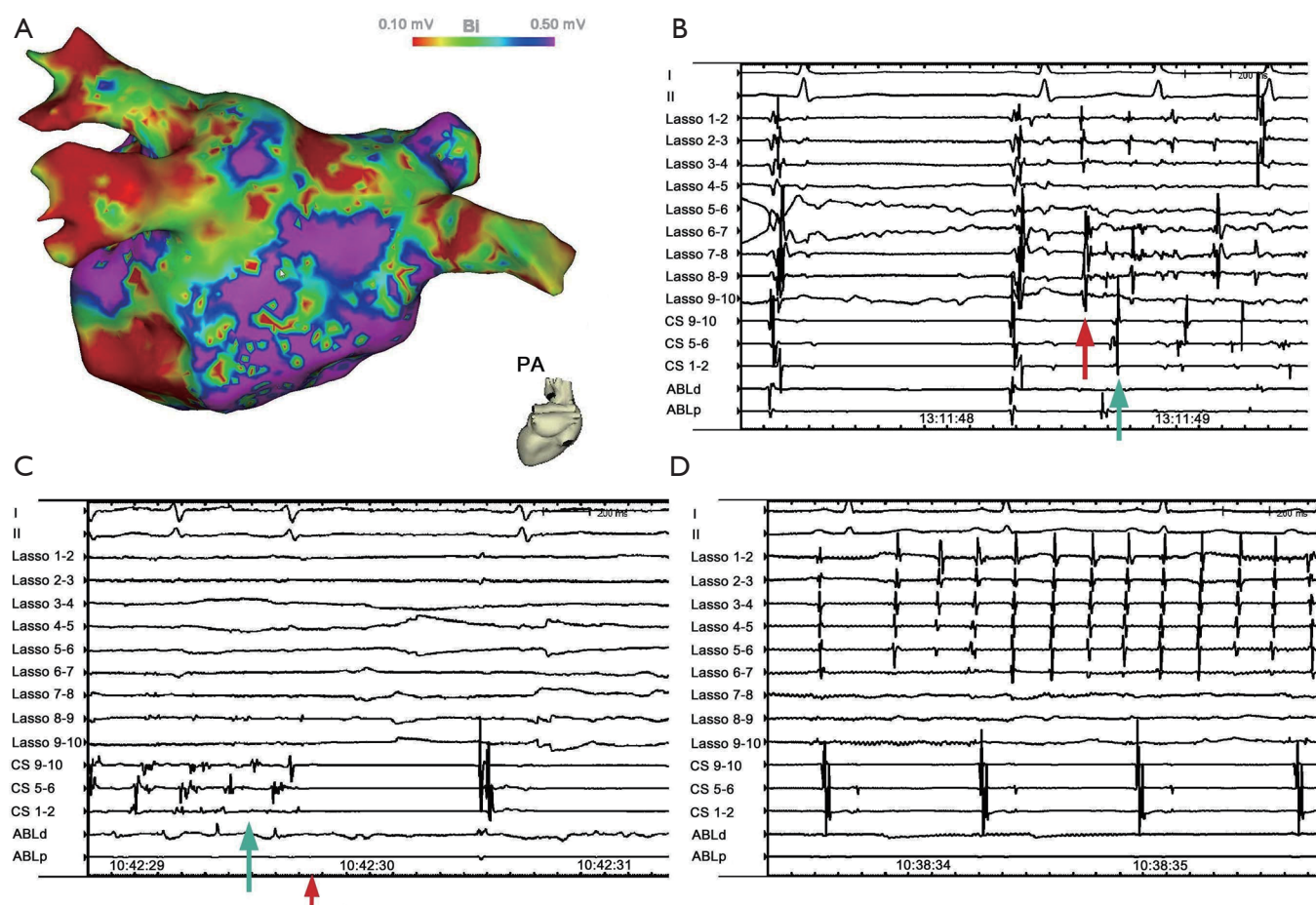


Figure 3 Examples of electrophysiological study files of AF patients with lung resection history. (A) Three-dimensional electroanatomic map of a patient with right-superior lobectomy history in CARTO system of left atria in the posterior-anterior view; (B) AF onset set off by PV trigger from stump PV (right-inferior PV), recorded by a circular mapping catheter (Lasso) in the stump, which was indicated by PV potential (red arrow) preceding atrial potential (turquoise arrow) at AF onset; (C) sinus rhythm was restored right after left PV (non-stump PV) isolation in a patient with left-superior lobectomy history. Turquoise arrow indicated atrial fibrillation recorded by CS catheter; red arrow indicated PV isolation completion; (D) after right PV isolation (non-stump PV), active PV potential recorded by a circular mapping catheter placed within right-superior PV and simultaneous sinus rhythm recorded by CS catheter, indicating that AF originated from right-superior PV. Lasso indicates PV potential recorded by a circular mapping catheter. AF, atrial fibrillation; PV, pulmonary vein; CS, coronary sinus; ABLd, distal ablation catheter potential; ABLp, proximal ablation catheter potential.

being at higher risk for POAF; (III) POAF, along with infection and hemorrhage, may be independent predictors of perioperative death after pneumonectomy; and, (IV) active PV potentials originating from stump and non-stump PVs might be a potential mechanism for POAF in pneumonectomy.

Independence of POAF

Regardless of the surgical target organ, one can posit that

the occurrence of POAF results from superimposition of acute surgery-related factors on pre-existing atrial substrate which is vulnerable to AF initiation and maintenance (14), and for POAF to occur independently of other postoperative complications. In our study, most POAF in pneumonectomy occurred as the sole postoperative complication, which is consistent with a previous study (3) indicating that mechanism underlying POAF in pneumonectomy possibly involved more than inflammation and autonomous nerve system activation.

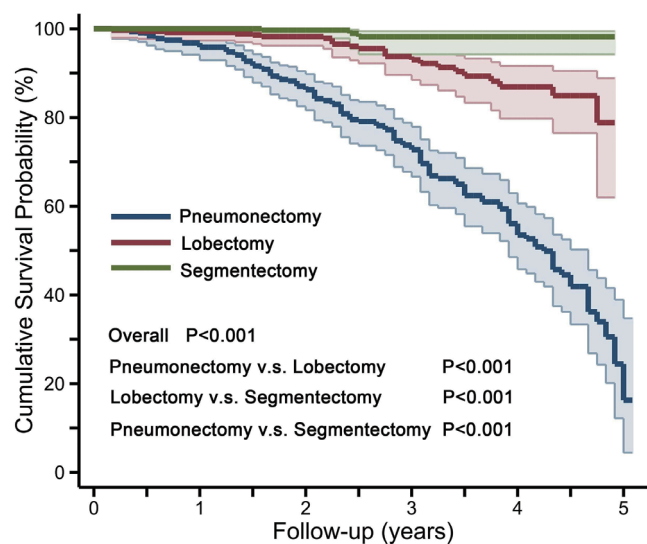


Figure 4 Kaplan-Meier survival curve showing post-discharge survival of patients who underwent pneumonectomy, lobectomy or segmentectomy, with 95% CI (shaded area). CI, confidence interval.

Also, the inconsistent findings of studies observing right atrial enlargement (15,16) after pneumonectomy made it hard to ascribe POAF to right atrial stretch.

Possible mechanism for higher POAF risk after pneumonectomy

Numerous studies have identified the importance of PV in the initiation and maintenance of AF (13,17), owing to its special anatomical and electrophysiological characteristics including (I) myocardial sleeve facilitating trigger activity; (II) the presence of pacemaker, Purkinje and transitional cells; and (III) unique distribution of ion channels (18). One distinguishing characteristic of pneumonectomy is that after removing one side of lung, all pulmonary circulation is forced to flow through the residual pulmonary vessels, increasing intra-PV pressure and PV wall tension, which probably facilitate POAF onset. Previous studies (19,20) have documented that mechanical stretch on PV could induce AF by enhancing PV myocardium automaticity, slowing local conduction, and complicating myocardial activation, hence facilitating AF onset and maintenance. During pneumonectomy procedure, AF onset was observed after clamping the pulmonary artery, even before other stressors took effect, suggesting substantial AF-facilitating effect of hemodynamic change.

On the other hand, inflammation and ischemia adjacent to resection margin could remodel gap junction (21), increase local conduction heterogeneity and trigger AF (22). Therefore, from segmentectomy to pneumonectomy, POAF morbidity elevated remarkably as surgical scope expanded. A recent study also reported a lower POAF incidence in segmentectomy than in lobectomy (23).

Our EPS files showed that in AF patients with pneumonectomy history, PV stumps tend to be electrically active, possibly due to variable fibrosis in PV remnants and up-regulated autonomous nerve tone (24,25). Moreover, remaining PVs could also serve as AF trigger, responsible for AF initiation and maintenance, further substantiating the importance of PV in AF after pneumonectomy. Because it would be inappropriate and risky to perform postoperative EPS, we could only indirectly assess AF mechanism for patients with lung resection history through EPS files.

RFs for POAF

Previous studies have suggested that RFs for POAF following lung resection included advanced age, male sex, ischemic heart disease, valvular heart disease, heart failure, higher resected lung volume, intraoperative blood transfusion, and mediastinal lymph dissection (4,5,26). Albeit speculation was made that pneumonectomy patients had higher POAF risk (5), further investigation was absent. To the best of our knowledge, this is the first large study that focused on POAF in pneumonectomy patients and observed significantly higher POAF risk within this subgroup. From an epidemiological perspective, human aging is associated with an increased possibility of developing AF (27), and advanced age is a widely validated RF for POAF in numerous studies (28). And LA enlargement tends to suggest underlying structural remodeling, which is deemed as the main contributor for initiation and persistence of AF (29). Therefore, it is reasonable that age >60 years and LAd ≥ 35 mm predicted POAF within this subgroup.

Impact of POAF on clinical outcomes

Although POAF predicts adverse clinical outcomes after cardiac surgery (30), it remains unclear if such correlation exists among pneumonectomy patients. In our study, POAF, along with infection and hemorrhage, was a predictor of death in pneumonectomy, raising mortality risk by 16-fold relative to patients without POAF. And pneumonectomy patients with longer total AF duration and higher AF

burden seemed to possess a potentially higher risk of perioperative death. The exact mechanism underlying this possible predictive effect is still unknown. POAF onset indicates that normal cardiac electrical activity is severely affected, which seemed irrelevant to other complications. Yet postoperative complications including POAF could be deemed a consequence of accumulated substrate exceeding patients' tolerance, including pre-existing substrate and surgery-related substrate such as inflammation, autonomous nervous system activation, stress and mechanical stimulus. And compared with lobectomy and segmentectomy, pneumonectomy group undertook greater surgical impact, with lower POAF threshold due to drastic pulmonary circulation change as a special surgery-induced substrate. Therefore, the presence of POAF may serve as an indicator for severe surgical-related impact which could induce fatal complications. Close observation and even precautionary measures should be applied to prevent adverse outcomes. Since pneumonectomy for pleural mesothelioma and benign diseases, such as tuberculosis destroyed lung, aspergilloma and bronchiectasis, share the same hemodynamic change as pneumonectomy for primary lung cancer, the implication of POAF could be the same.

However, POAF didn't predict adverse long-term outcomes after pneumonectomy. This is reasonable since POAF occurs with aggravation of surgery-induced stress, which gradually alleviates as patients' convalescence proceeds, therefore unable to affect long-term outcomes. In our study, senior age and advanced tumor stage predicted adverse long-term outcomes, which is consistent with a previous study (31).

Limitations

The present study has several limitations. Firstly, it is a retrospective, descriptive and non-randomized study. Secondly, patients undergoing lobectomy and segmentectomy were selected via stratified sampling, which might have introduced selection bias. Thirdly, the sample size of the present study is still limited in spite of considerable number of pneumonectomy patients. Fourthly, EPS files were not from the same cohort studied, in whom it was inappropriate to perform EPS right after lung resection; therefore, results from this assessment are only suggestive of a possible mechanism for POAF.

Conclusions

POAF in pneumonectomy occurred mostly as a solitary

complication in-hospital, with higher incidence and risk than those for lobectomy and segmentectomy. Pneumonectomy patients aged >60 years or with LAd ≥ 35 mm were at higher risk for POAF. Active PV potential originating from stump and non-stump PVs might potentially underlie POAF. POAF, along with infection and hemorrhage, was predictive of perioperative mortality in pneumonectomy.

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Footnote

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