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RESEARCH

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Postoperative atrial fibrillation after thoracic surgery (PoAF): risk factors and outcome

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Abstract

Background Postoperative AF (PoAF) is a common complication of the early postoperative period of noncardiac, thoracic surgery and is associated with prolonged hospital stay. In order to investigate the predictors of PoAF in the specific setting of lung surgery of oncologic patients, we retrospectively analyzed 338 consecutive patients admitted to our department to be operated for lung cancer with a thoracotomy approach (i.e., open surgery). We determined this population's prevalence, risk factors, and consequences of PoAF.

Results PoAF occurred in 35/338 (10.4%) patients and was significantly more frequent in older patients, with a best predictive value of 71 years at ROC curve analysis (*AUC* 0.70, $p < 0.001$) and in those with chronic renal failure ($p = 0.01$). The left atrial area was also significantly associated with the risk of PoAF (*AUC* 0.78, $p = 0.000$). PoAF was more frequent in patients with small cell and squamous cell carcinoma ($p = 0.03$). The occurrence of PoAF was associated with a longer hospital stay ($p = 0.001$) but not with higher long-term mortality (follow-up mean length: 3.3 ± 0.3 years). At multivariable analysis, the only independent predictors of PoAF were age (OR for 1-year increase 1.089, 95% *CI* 1.039–1.141, *p* 0.001) and open surgery (*OR* 2.07, 95% *CI* 1.0–4.29, *p* 0.047). At the 3-year follow-up, all patients were in sinus rhythm.

Conclusions The present study shows the association between age and open surgery with PoAF, furtherly highlighting that the incidence of arrhythmia leads to a longer hospital stay. Left atrium dilatation could identify at-risk patients. Those results suggest that older patients — especially those with larger left atrium areas — might benefit most from a VATS approach to further reduce the arrhythmia incidence. Such a finding supports the indication of a systematic echocardiographic evaluation before elective lung surgery, especially in patients with known clinical risk factors.

Highlights

Key findings

• In a setting of lung cancer surgical patients, postoperative atrial fibrillation (PoAF) is more frequent in older patients and in those with larger left atrial dimension.

What is known and what is new?

• Left atrial area is a known predictor of atrial fibrillation after cardiac surgery.

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- Only few data reported the association of left atrial area with atrial fibrillation after thoracic surgery for lung cancer

What is the implication and what should change now?

- Echocardiography should be part of preoperative evaluation of all patients undergoing thoracic surgery for lung cancer.
- In order to further reduce the risk of PoAF, video-assisted thoracic surgery might be the preferred surgical approach to be proposed for older patients with larger left atrial area.

Keywords Lung cancer, Thoracic surgery, Atrial fibrillation, Prognosis

Background

Among the secondary causes of atrial fibrillation (AF), the most frequent is postoperative AF (PoAF) [1]. PoAF is a common, early complication after various types of surgery, especially cardiac and noncardiac thoracic surgery. PoAF secondary to cardiac surgery, occurring in 25 to 40% of patients, is associated with increased morbidity (e.g., a 3-fold increase in perioperative stroke, infections, renal failure, heart failure, and myocardial infarction) and an estimated 9.7% increase in mortality [1]. The prevalence of PoAF after noncardiac, thoracic surgery is 10–15% after lobectomy and 20–30% after pneumonectomy [2, 3].

Many factors have been implicated in the pathophysiology of PoAF, including physical trauma to the atria and pericardium, local ischemia, hypoxia, and inflammation, and systemic effects such as neurohumoral activation (including sympathetic activation), volume redistribution, and electrolyte disturbances [4].

Although induced by the homeostatic alterations related to surgery, there is evidence that PoAF is not a mere stand-alone transitory event, bearing considerable prognostic consequences. Patients with PoAF have prolonged postoperative hospital stays and substantially higher healthcare costs both during and after hospitalization [5].

The specific setting of PoAF secondary to lung surgery in oncologic patients has been poorly investigated. Hence, this study was aimed at assessing the risk factors for and the consequences of PoAF in patients undergoing thoracic surgery for lung cancer in a single, third-level center.

Methods

We retrospectively analyzed all consecutive patients operated for lung cancer with curative intent from 1 January 2019 to 31 January 2020. This study period was selected because it is antecedent to the COVID-19 pandemic, also allowing at least 12 months of follow-up. Cancer staging was determined according to the TNM classification [6]. Patients enrolled were operated on by an anatomic lung resection (lobectomy and pneumonectomy), with either a thoracotomy approach or video-assisted thoracoscopy (VATS). The technique and type of resection selection were based on cancer anatomic localization, extension, staging, and équipe clinical judgment; in particular, open surgery was generally adopted in the presence of hilar tumors, great cancer masses, and/or diffuse mediastinal lymphatic involvement. Our equipe of thoracic surgeons performed all interventions, being 3 to 5 per procedure. Description of techniques has been provided in the following section.

Data for analysis, fully anonymized, were retrieved from electronic hospital charts. The local ethics committee (Regional Ethics Committee of Tuscany for Experimental Medicine, section: Area Vasta Centro, n 21093_oss) approved the study and, in accordance with Italian laws for observational studies, granted a waiver of informed consent from study participants.

Prior or current AF or other supraventricular arrhythmias on admission, and age < 18 years, were taken as exclusion criteria for the analysis.

The diagnosis of new-onset PoAF was based on electrocardiograms performed during the postoperative days, the first one immediately after surgery, and thereafter on clinical indication (irregular pulse or symptoms such as palpitations). Demographic, echocardiographic, pre- and postoperative laboratory data, pre- and postoperative vital parameters, type of surgery, histology, and the inhospital clinical course, including complications (i.e., the need for transfusion, acute renal failure defined as an increase of serum creatinine at least ≥ 0.3 mg/dL within 48 h and/or urine excretion < 0.5 mL/kg/h for at least 6 h, and fever with body temperature > 37.5 °C), were all recorded in a dedicated database. Preoperative echocardiography was performed on individual clinical judgment.

The primary and secondary study endpoints were the prognostic impact and the predictors of PoAF, respectively.

The duration of follow-up was calculated from the date of thoracic surgery. We performed a clinical, electrocardiographic, and echocardiographic evaluation of the patients who developed PoAF in July 2022. Data from regional registries updated the follow-up of all other patients.

Surgical techniques

All surgical procedures were conducted during one-lung ventilation (OLV). When performing open surgery, the mainly adopted approaches were muscle-sparing ones in order to minimize blood loss coming from muscle resection and the time required for opening and closing the incisions. Lateral and posterolateral thoracotomy with their variants (e.g., axillary thoracotomy, anterior thoracotomy, and Shaw-Paulson approach) were the main surgical approaches in open surgery. These incisions provided maximum exposure to most of the thoracic structures and were advantageous for repeat surgical resection (REDO) and more complex procedures.

On the other hand, when employing minimally invasive surgery, the preferred techniques were the "uniportal" and "triportal" VATS. In the uniportal technique [7], an approximately 2.5-cm incision was made in the anterior axillary line in the fifth or sixth intercostal space to facilitate good access to hilar structures and lymph node stations. Uniportal VATS allowed for reduced surgical trauma and consequent decreased postoperative pain. In the "triportal technique" — according to the Copenhagen approach [8] — a 5-cm anterior utility incision between the breast and the lower angle of the scapula in the fourth intercostal space just anterior to the latissimus dorsi muscle and two additional accesses of 1–1.5 cm below the fourth intercostal space were made. This approach granted safe transection of major vessels, with easy blood loss control in case of hemorrhage. Upon necessity, conversion to a muscle-sparing anterior thoracotomy was easily carried out by expanding the anterior utility incision.

Statistical analysis

The multivariable analysis included the type of surgery (open- or video-assisted thoracoscopy, VATS) and the variables associated with the primary and secondary endpoints at univariable analysis with a p-value < 0.10. Echocardiographic parameters were excluded from multivariable analysis, as they were available only for approximately half of the patients.

Descriptive statistics of clinical variables are presented as frequency and percentage for categorical variables and mean ± SD or median (with interquartile range) for continuous variables. We used the chi-square test and the t-Student or the Mann–Whitney tests to compare, respectively, proportions and continuous variables with normal or non-normal distribution. We performed univariable and multivariable analyses using logistic regression and general linear models. We used the Kaplan–Meier method to estimate the univariate survival analysis and the Cox regression to identify the multivariable associations with mortality and estimate their hazard ratio with a 95% confidence interval. A 2-sided p-value < 0.05 was considered to indicate statistical significance. All analyses were conducted using SPSS, version 27.

Results

Of 338 patients enrolled, 326 (96.4%) were operated with lobectomy, whilst 12 (3.6%) were operated with pneumonectomy. A thoracotomy was performed in 135 cases (40%), whilst VATS was adopted in the remaining 203 (60%). PoAF developed in 35 (10.4%) patients; of these, 16 (45.7%) had arrhythmia in the sub-intensive care unit and the remaining in the next part of hospitalization. Pre-operative echocardiography was performed in 186 (55.0%) patients. All patients were discharged on sinus rhythm.

Patients with PoAF were older and more frequently had pre-operative chronic renal failure (Table 1). None of the other pre- and postoperative laboratory variables or of pre- and postoperative vital parameters was associated with PoAF (Table 1). At the receiver operative characteristic (ROC) curve analysis, an age of 71 years had the highest sensitivity and specificity for PoAF (*AUC* 0.70, $p = 0.000$). Among echocardiographic parameters, the left atrial area was positively associated with PoAF (Table 2) with a best predictive value of 21 cm^2 at ROC analysis (*AUC* 0.78, $p = 0.000$). Tumor histology was also associated with PoAF, with a significantly higher incidence in patients with small-cell and squamous-cell carcinoma (Table 3). None of the postoperative complications studied were significantly associated with PoAF development (Table 4).

The occurrence of PoAF determined a significant increase in the length of hospitalization (Table 1).

At multivariable analysis, only age (*OR* 1.089 per year, 95% *CI* 1.039–1.141, $p < 0.001$) and open surgery (*OR* 2.07 vs. VATS, 95% *CI* 1.0–4.29, $p = 0.047$) were independently associated with the risk of PoAF (Table 5).

The mean duration of follow-up was 3.3 ± 0.3 years. PoAF was not associated with increased mortality, either at univariable or at multivariable analysis including histology and cancer stage.

The 35 patients who developed PoAF were contacted for the follow-up: 12 had died, and 23 were in stable sinus rhythm and did not report cardio, cerebrovascular events, or arrhythmia relapses. Only one patient was on oral anticoagulant therapy for a previous deep vein thrombosis. None of the other patients received long-term oral

Table 1 Baseline characteristics

Variable	PoAF		*p*-value
	No ($N = 303$)	Yes ($N = 35$)	
Men, *n* (%)	173 (57.1)	24 (68.6)	0.21
Age (years), median (IQR)	68 (67–70)	75 (74–79)	0.001
BMI, median (IQR)	25.1 (24.8–25.8)	26.8 (24.1–28.1)	0.36
TSH (μU/ml), median (IQR)	1.6 (1.4–1.8)	1.14 (0.95–1.88)	0.27
Creatinine (mg/dl), median (IQR)	0.85 (0.82–0.88)	0.93 (0.88–1.05)	0.06
Na^+ (mEq/l), median (IQR)	142 (142–143)	141 (140–144)	0.52
K^+ (mEq/l), median (IQR)	4.3 (4.3–4.4)	4.5 (4.2–4.5)	0.30
Ca^{2+} (mEq/l), median (IQR)	9.2 (9.2–9.3)	9.2 (9.1–9.4)	0.98
COPD, *n* (%)	104 (34.3)	15 (42.9)	0.18
Hypertension, *n* (%)	166 (54.8)	22 (62.9)	0.21
Diabetes, *n* (%)	43 (14.2)	6 (17.1)	0.60
Dyslipidemia, *n* (%)	118 (38.9)	11 (31.4)	0.71
Chronic renal failure, n (%)	194 (64)	30 (85.7)	0.01
Pacemaker, *n* (%)	3 (1)	0 (0)	0.57
Beta-blockers, *n* (%)	74 (24.4)	9 (25.7)	0.66
Calcium-channel blockers, *n* (%)	59 (19.5)	7 (20)	0.76
RAS inhibitors, *n* (%)	130 (42.9)	18 (51.4)	0.20
Diuretics, *n* (%)	57 (18.8)	8 (22.9)	0.41
Antiarrhythmic, *n* (%)	4 (1.3)	0 (0)	0.51
Length of inhospital stay (days), median (IQR)	7 (7–8)	11 (8–15)	0.001

Chronic renal failure is defined as *GFR* < 60 mL/min/1.73 m^2

BMI body mass index, *TSH* thyroid-stimulating hormone, *Na^+* sodium, *K^+* potassium, *Ca^{2+}* calcium, *COPD* chronic obstructive pulmonary disease, *RAS* renin-angiotensin system

Table 2 Preoperative cardiac ultrasound in a subset of patients undergoing thoracic surgery for cancer treatment ($n = 186$)

Variable	PoAF		*p*-value
	No	Yes	
EF (%), median (IQR)	60 (60–62)	60 (58–63)	0.92
TAPSE, mean (± SD)	24 (± 3)	25 (± 6)	0.62
Left atrium area (cm^2), median (IQR)	21 (19–23)	23 (22–26)	0.02
Mitral dysfunction, *n* (%)	1 (0.3)	1 (2.9)	0.18
Aortic dysfunction, *n* (%)	3 (1)	2 (5.7)	0.07

EF ejection fraction, *TAPSE* tricuspid annulus plane systolic excursion

anticoagulant therapy, despite a CHA_2DS_2-VASc score [1] of at least 1 (all patients were older than 65 years).

Discussion

One of the main findings of our study was the univariate association of left atrial dimensions with the occurrence of PoAF after lung cancer surgery, as it had been previously shown in cardiac surgery. This observation, in accordance with the study of Anile et al. [9], supports the indication of a systematic echocardiographic evaluation

Table 3 Host, procedure, and malignancy-related risk factors

Variable	PoAF		*p*-value
	No ($N = 303$)	Yes ($N = 35$)	
Histology, *n* (%)			
Adenocarcinoma	150 (49.5)	20 (57.1)	0.03
Small cell carcinoma	3 (1)	2 (5.7)	
Large cell carcinoma	13 (4.3)	0 (0)	
Squamous cell carcinoma	52 (17.2)	9 (25.7)	
Other	85 (28.1)	4 (11.4)	
Stage TNM, *n* (%)			
I	127 (57.7)	14 (42.4)	0.23
II	50 (22.7)	12 (36.4)	
III	40 (18.2)	7 (21.2)	
IV	3 (1.4)	0 (0)	
Type of surgery, *n* (%)			
VATS	187 (61.7)	16 (45.7)	0.07
Open (thoracotomy)	116 (38.3)	19 (54.3)	
Lobectomy, *n* (%)	291 (96)	35 (100)	0.39
Post-surgery Horovitz index, median (IQR)	343 (322–373)	331 (253–409)	0.43
Acute renal failure, *n* (%)	8 (2.6)	3 (8.6)	0.08

Table 4 Procedural complications

	PoAF		*p*-value
	No (*N* = 303)	**Yes (*N* = 35)**	
Fever > 37.5 °C, *N* (%)	146 (48%)	15 (43%)	0.55
Need for transfusion, *N* (%)	22 (7%)	4 (11%)	0.38
Acute renal failure, *n* (%)	8 (3%)	3 (8%)	0.08

Table 5 Multivariable analysis of predictors of PoAF in patients undergoing thoracic surgery for cancer treatment

	OR (95% *CI*)	*p*-value
Age[a]	1.089 (1.039–1.141)	< 0.001
Open surgery	2.07 (1.0–4.29)	0.047

[a] OR per year

before elective lung surgery, especially in patients with known clinical risk factors. In our multivariable analysis, only advanced age (i.e., beyond 71 years) and the open surgery approach independently predicted PoAF. In contrast, previous studies [8–14, 15, 16] reported several other risk factors, such as male gender, history of heart disease, more advanced cancer stages, postoperative serum potassium, and need for transfusions. This difference might be attributed to different exclusion criteria (we excluded patients with a history of previous episodes of paroxysmal AF), different diagnostic methods (we might have missed short, asymptomatic episodes of paroxysmal AF), and larger samples of some of those studies.

As most of the patients (i.e., 96% of the non-PoAF group and 100% of the PoAF group) were operated on with lobectomy, comments on whether a different extent of resection is associated with PoAF could not be drawn.

Instead, open surgery and age (i.e., > 71) were independently associated with PoAF development, as identified in other previous study [17]; therefore, adopting VATS as the main surgical approach in older patients with larger left atriums might be advantageous. This could result in a reduced risk for PoAF, with a contribution both in terms of long-term morbidity and mortality [1] and in furtherly reducing hospital stays and, hopefully, hospitalization-related complications.

When looking at the possible role of postoperative complications, we did not find any significant association at univariable analysis, although the proportion of acute renal failure was higher in patients with PoAF (Table 4, $p = 0.08$). Moreover, chronic renal failure patients were more likely to develop PoAF. Indeed, atrial fibrillation is known to increase the risk of prerenal acute kidney injury (AKI) [18], and AKI is in return linked to atrial fibrillation due to reduced pro-inflammatory cytokines clearance and increased atrium stretching for volume overload [19].

Patients' pharmacological history was provided, and no therapeutic regimens were quitted before or after the intervention. However, we failed to demonstrate a protective role of a specific therapeutic regimen, but our study was not powered for this purpose. Some studies suggested that beta-blockers or amiodarone may be effective for the primary prevention of PoAF [11], whilst other recent evidence [4] claimed that statins may be protective against PoAF, thanks to their antioxidant and anti-inflammatory properties. Other anti-inflammatory strategies include steroids or colchicine. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers have been shown to reduce the incident risk of AF, but this issue has not been adequately explored in the context of lung cancer surgery. Beta-blockers alone, however, are still the therapeutic cornerstone of therapy [11]. An improved pre-operative risk stratification, including left atrial measurement and consideration of other potential risk factors, might improve and potentially personalize a preventive strategy for PoAF after lung surgery.

Although there is growing evidence that PoAF significantly increases the risk of stroke and global long-term mortality [20], our data do not confirm this finding in the setting of lung cancer surgery, where several issues regarding its management and prevention of potential complications are still unclear. In particular, it still remains uncertain whether patients with PoAF should be anticoagulated as those with spontaneous AF. Our experience does not support, in the field of lung surgery, the need for aggressive management as recommended by the most recent guidelines [1] in patients with PoAF.

Future research aimed at improving preventive and management strategies should address the molecular and genetic basis of susceptibility to PoAF after noncardiac, thoracic surgery, an issue still relatively unexplored [21, 22, 23], whereas several studies [17–20] have evaluated such a susceptibility after coronary artery revascularization procedures.

This study has several limitations to be acknowledged: first, its retrospective, single-center, nature with limited sample size. Second, the study covers a period of time (2019–2020) that was antecedent to the last international AF guidelines [1], which recommended a more aggressive anticoagulation management of PoAF. Third, we could have underestimated the real incidence of atrial fibrillation in our population missing some asymptomatic events, as patients were not continuously rhythm monitored; instead, ECG was performed the first day immediately after surgery and in case of symptoms. Fourth, as we performed pre-operative echocardiographic evaluation in half of the patients enrolled only, our findings may not be strong enough, yet their clinical meaning is undoubted.

Conclusions

Despite limitations, our study demonstrated that advanced age and open surgery are independently associated with an increased risk of PoAF in lung cancer surgery and suggests that left atrial enlargement is a possible, further, risk factor. This novel finding indicates that an echocardiographic evaluation should be recommended in all older patients to identify those at the highest risk of PoAF, who should be offered a less invasive surgical approach to furtherly reduce the arrhythmia development. Prevention of the occurrence of PoAF is nowadays crucial among all thoracic surgical patients to contribute in shortening postoperative hospital stays; however, efforts are often unsuccessful. Our investigation could give also insights into how to identify higher-risk patients in whom preventive strategies might be prospectively tested in clinical trials.

Abbreviations

AF	Atrial fibrillation
PoAF	Postoperative atrial fibrillation
VATS	Video-assisted thoracoscopy
AKI	Acute kidney injury

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Authors' contributions
VS projected the study, analyzed and interpreted the data, and wrote the manuscript. SM, JG, AD, NC, GV, AS, MT, and SM collected the data for analysis and contributed to writing the manuscript. NM and RM revised the manuscript. LV and SB performed the surgical interventions and revised the final version of the manuscript. BA performed clinical follow-up and contributed to the clinical management of patients. All authors read and approved the final manuscript.

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Availability of data and materials
Data and material are available on a reasonable request from the author.

Declarations

Ethics approval and consent to participate
The study's protocol was approved by the local ethics committee (Comitato Etico di Area Vasta Centro, CEAVC — section of Comitato Etico Regionale della Regione Toscana, DGRT 418/2013).

Consent for publication
All authors give their consent for publication in the journal.

Competing interests
The authors declare that they have no competing interests.

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