

ABBREVIATIONS

| | |
|-------|------------------------------|
| AF | = atrial fibrillation |
| FBS | = fibrobronchoscopy |
| CI | = confidence interval |
| CXR | = chest roentgenogram |
| CT | = computed tomography |
| HR | = hazard ratio |
| ICU | = intensive care unit |
| NSCLC | = non small cell lung cancer |
| OR | = odds ratio |

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INTRODUCTION

Atrial fibrillation (AF) remains the most common medical complication after thoracic surgery, with an incidence ranging from 10% to 20% after pulmonary lobectomy, and as much as 40% after pneumonectomy [1-7]. Postoperative AF typically occurs between postoperative days 1 to 5, with a maximal incidence of the first episode (60-70%) in the 2nd postoperative day (Figure 1). Only a minority of patients present several relapses [1-7].

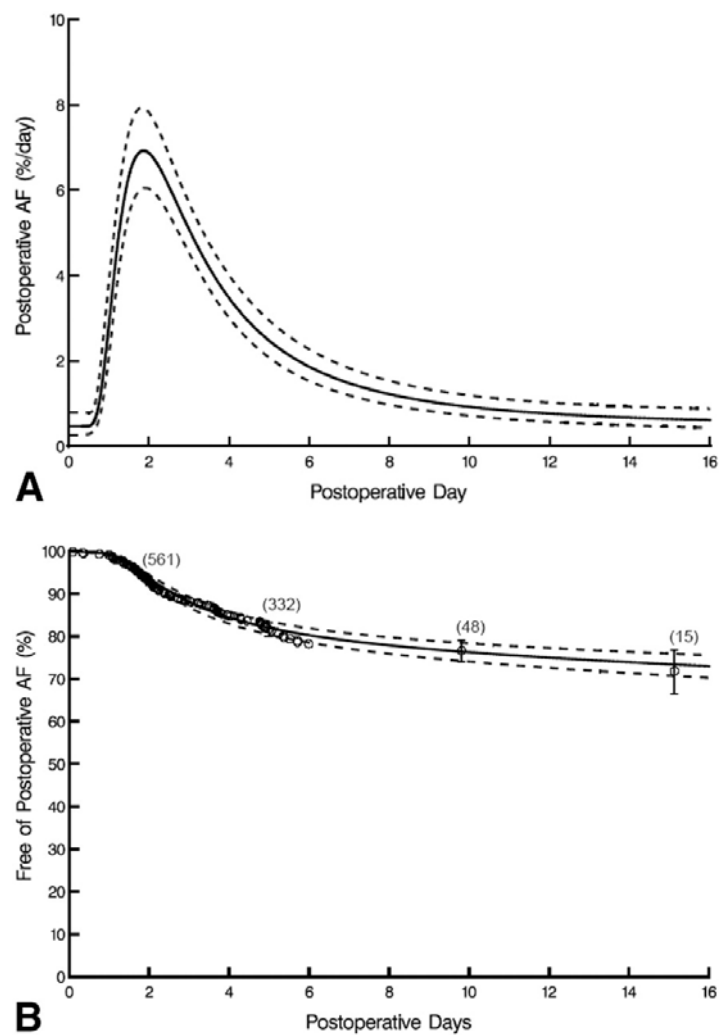


Figure 1. AF complicating lung cancer resection. A, Hazard (instantaneous risk). *Solid line* is parametric estimate enclosed within *dashed* 68% confidence limits. B, Freedom from AF. Each *circle* represents onset of AF; *vertical bars* are asymmetric 68% CLs, and numbers in parentheses are patients remaining at risk. *Solid line* is parametric estimate enclosed within *dashed* 68% CLs. Based on Roselli et al. [3].

Postoperative AF has been shown to be a harbinger of worse prognosis, being correlated with increasing hospital morbidity and mortality, considerable increases of hospital stay and costs [1-6]. However, the prognostic implications of this arrhythmia after thoracic surgery remain controversial [4-6]. Although there are many studies examining the consequences of perioperative AF, none has managed to present compelling data that support an independent association between this arrhythmia and late mortality [4-6].

Etiopathogenesis

Several risk factors for AF have been observed and include patient related (preexisting cardiovascular disease, postural change, limited pulmonary reserve), surgery related (extensive procedure, intrapericardial pneumonectomy, extrapleural pneumonectomy, anesthetic agents, major bleeding), or treatment related (previous thoracic irradiation) [1-8]. However, opinions differ about the importance of these risk factors, and the patient age has consistently been demonstrated to be the most important predictor for postoperative AF [9, 10]. A possible explanation is the dilatation and fibrosis of the atria, with a loss of side-to-side electrical coupling between groups of atrial muscle fibers [1-10].

Although these occurrences are recognized, the pathophysiology in noncardiac surgery remains poorly defined [8,9,14]. In some studies, echocardiograms suggest that increased right heart pressure and increased pulmonary vascular resistance may predispose to clinically significant supraventricular tachycardias after pulmonary surgery [9,10]; although these concepts are controversial [11]. In addition, prolonged oxygen supply (causing dilatation of the pulmonary vessels) has failed to demonstrate any benefit to the prevention of postoperative AF [7,12].

Hospital implications

Many studies have identified a strong impact of AF on hospital resource utilization and sanitary costs [1-6]. Roselli and colleagues [3] studied a series of 604 patients who underwent anatomic lung cancer resection reported a higher postoperative complications rate (30% vs. 9%, $p < 0.004$), a prolonged hospital stay (median 8 vs. 5 days, $p < 0.001$) with higher costs (cost ratio 1.8, 68%

confidence limits 1.6 to 2.1), and a higher hospital mortality (8% vs. 0%, $p = 0.01$). In consideration of the high number of patient undergoing thoracic surgery per year, economic implications related to this arrhythmia are considerable.

Postoperative survival

The prognostic significance of this arrhythmia is difficult to interpret as it can be associated or induced by other complications, such as heart failure associated with pulmonary edema [7]. No difference was observed between the AF group and the non-AF group regarding short-term or long-term mortality or regarding long-term atrial fibrillation recurrences [4,7,14]. However, other authors have reported an increase of arrhythmia related mortality [5,9,13,14]. Amar and associates [5] in a population of 78 patients with non small cell lung cancer (NSCLC), reported that early supraventricular tachydysrhythmia (SVT) was associated with poor long-term survival (Figure 2). Conversely, Cardinale and colleagues [4] recorded no differences in late mortality between patients with AF and patients without it; these authors prospectively enrolled 233 consecutive patients undergoing lung cancer operations, observing similar survival rate between the AF and the no-AF group (82% vs. 84%) at the end of follow-up.

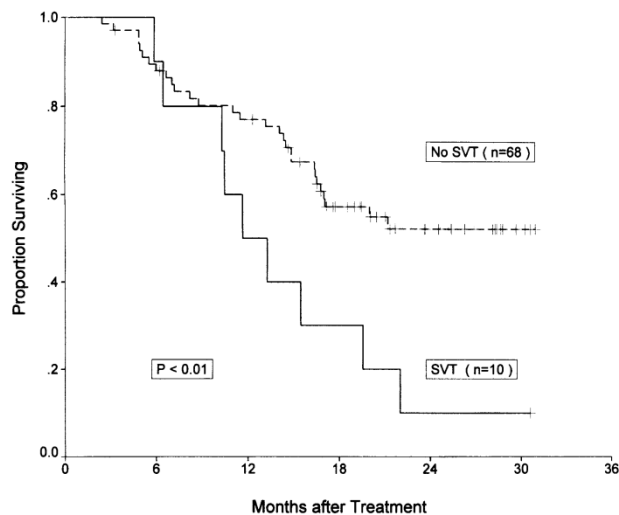


Figure 2. Kaplan-Meier survival curve of patients in AF and no-AF patients. Based on Amar et al. [5].

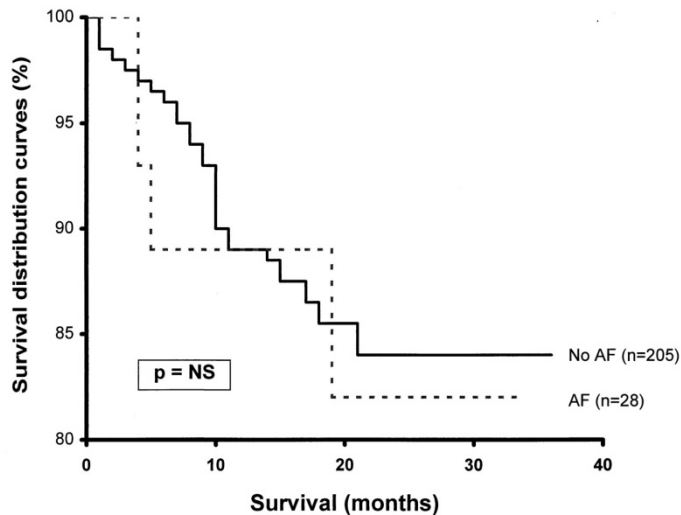


Figure 3. Kaplan-Meier survival curves of patients with and without AF in the early postoperative period (*NS* = not significant.). Based on Cardinale et al. [4].

Treatment and prophylaxis

Digoxin. Administration of digoxin after thoracic surgery as prophylactic treatment was investigated in three randomized controlled trials [16-18]. One study described 140 thoracotomy patients [16]. Another study reported 80 patients undergoing thoracic esophageal resection, of which 54 were for malignancy [17]. The third study enrolled 111 elective pulmonary surgery patients [18]. In none of these studies a decreased AF incidence after the use of digoxin was found in comparison with the placebo group. The overall incidence of arrhythmia ranged from 37% to 46%, with AF accounting for almost 50% of all patients. No statistical differences were registered between digoxin patients and control group [16-18]. Overall mortality ranged from 0.9% to 6.25%, with a arrhythmia correlation founded in one patient only [16-18].

Flecainide. Flecainide was examined in two randomized trials by Borgeat and colleagues [19,20]. A constant rate infusion was compared with a placebo in 30 noncardiac thoracic surgery patients [19], whereas in the other report flecainide was compared with digoxin in 30 pulmonary surgery patients [20]. Flecainide was proven to prevent arrhythmias in the first trial ($p = 0.01$)

and to significantly reduce its incidence in the second one ($p < 0.05$). No toxic drug levels were measured and mortality was absent [19,20].

Beta-Blockers. A successful AF prevention with by beta-blocker agents has been investigated with controversial results [22,23]. Patients treated with metoprolol showed less changes in heart rate and cardiac index, with a reduction in oxygen consumption. Only two randomized controlled trials studied the prophylactic antiarrhythmic effects of beta-blocking agents [22,23]. Metoprolol, initiated preoperatively and continued once daily postoperatively, reduced the AF incidence from 40% to 67% ($p < 0.05$) after elective lung operations [22]. No difference was observed between the metoprolol and the placebo group in the incidence of other arrhythmias or complications [22].

Amiodarone. Amiodarone is certainly the drug of choice for preventing postoperative AF development. A prospective randomized trial comparing the administration of amiodarone, verapamil, and a placebo as prophylactic treatment for supraventricular dysrhythmias after pulmonary surgery [24] was interrupted after 64 patients, because severe life-threatening side effects (adult respiratory distress syndrome; ARDS) occurred in 3 postpneumonectomy patients in the amiodarone group. Conversely, a retrospective analysis of all cases of pulmonary resection ($n = 552$) was performed [25]. Despite the apparently high incidence of ARDS after the use of intravenous amiodarone after pneumonectomy, the favorable results on the use of prophylactic oral amiodarone after pulmonary resection supports the need for prospective randomized trials [25].

Calcium antagonists. In another subsequent trial, the administration of the placebo was compared with verapamil, administered as a 10 mg bolus followed by a 30-minute infusion of 0.375 mg/min and then 0.125 mg/min for 3 days [26]. AF occurred in 15% of the patients receiving a placebo and in 8% of the patients receiving verapamil (p not significant). This study registered an interruption of the infusion in 9% of the patients caused by bradycardia and in 14% of patients caused by related hypotension. A smaller trial analysed the effects of verapamil on

right ventricular pressure and supraventricular dysrhythmias (SVD) [10]. No cardiac arrhythmias occurred in the verapamil group, whereas 6 patients (50%) in the placebo group suffered from supraventricular arrhythmias ($p < 0.05$) [10]. Furthermore, the increase in both end-diastolic right ventricular pressure and central venous pressure in 30% of the control patients was associated with atrial tachyarrhythmia, whereas this was not observed in the verapamil group [10]. Only one randomized controlled trial investigated diltiazem in thoracic surgery subjects [27]. A loading dose of 0.25 mg/kg was given on admission to the postanesthesia care unit, followed by a 0.1 mg/kg/h intravenous infusion for 18 to 24 hours [27]. The controls received intravenous placebo-loading doses, followed by a placebo infusion at 0.1 mL/kg/h. Starting in the morning on postoperative day 1, patients received either diltiazem slow release (SR) 120 mg or a placebo orally for 14 days. Postoperative SVD occurred in 15% of patients treated with diltiazem and 25% of the placebo group ($p = 0.03$). No differences were observed in major postoperative complications, overall duration, or costs of hospitalization [27].

Magnesium sulfate. There is only one randomized controlled trial investigating the prophylactic antiarrhythmic role of magnesium sulfate in noncardiac surgery [28]. Two hundred patients were enrolled and randomized to receive either an MgSO₄ infusion, no treatment, or digoxin [28]. The incidence of atrial tachyarrhythmias, mainly AF (90% in the magnesium and 85% in the control group), was reduced from 26.7% in the control group to 10.7% in the magnesium group ($p = 0.008$).

AIMS

The aim of this thesis were (I) to identify specific risk factors of AF after pulmonary lobectomy for primary lung cancer, and (II) to assess the impact of postoperative AF on hospital resource utilization, early and late survival in patients undergoing after pulmonary lobectomy for primary lung cancer.

MATERIAL AND METHODS

Population and study design

Between January 1996 and June 2009, 473 consecutive patients undergoing lobectomy for primary lung cancer at Varese University Hospital were considered for this study. Of these, 19 subjects were excluded from analysis because they had chronic AF (n=8), pace-maker devices (n=4), or incomplete data (n=7). Emergency procedures were also excluded from the analysis. Patients with a history of paroxysmal AF but in sinus rhythm at operation were included [3]. The final study cohort comprised 454 patients (81.3% male), with mean age of 65.4 ± 8.8 years (range: 28 to 84). Patient characteristics are listed in Table 1.

Throughout the study period a computerized database was used to prospectively record the data of all patients, including information about demographics, comorbidities, medical and surgical history, preoperative respiratory and cardiac testing, operative details and postoperative events during hospital stay. After discharge, follow-up was conducted according to the ACCP guidelines [29], with physical examination, and imaging study (either chest roentgenogram (CXR) or computed tomography (CT)) every 6 months for 2 years and then annually. For patients who died during follow-up the date of death was recorded. For patients lost to follow-up the vital status was ascertained at the end of study, by linkage with the Lombardy region health system registry. The vital status of residents outside this region was ascertained by contacting family members or clarified by the general practitioner. Survival follow-up was closed on May 31, 2007.

Although all data were prospectively recorded into the hospital computerized database registry that remained consistent over the study period, this was an observational retrospective study. The protocol of this study was in compliance with the institutional clinical research ethics and received full approval

Patient management

All patients underwent preoperative clinical cardiologic and anesthesiologic evaluations, CXR and CT, with pulmonary function tests. Preoperative medications, including β -blockers, diuretics,

antihypertensives, statins, and calcium-channel blockers were routinely omitted on the day of the operation and restarted on postoperative day one, unless clinically contraindicated.

Operability was determined according to established guidelines for lobectomy [30,31]. All pulmonary resections were performed by open thoracotomy, by the same thoracic surgical team. Standardized surgical approach and anesthesiologic management were routinely used and remained constant over the study. Briefly, short-term antibiotic prophylaxis was routinely used by intravenous administration of ampicillin/sulbactam 3 gr before anaesthesia. An epidural catheter for postoperative pain relief was offered to all patients and premedication with midazolam was done before induction of general anaesthesia. After administration of rocuronium bromide (0.15 mg/kg) and orotracheal intubation with double-lumen tube, anesthesia was maintained by 50% O₂ and sevoflurane (2%). Mediastinal sampling lymphadenectomy was routinely performed. Two chest tubes were routinely placed on water seal at the end of the operation and removed when no air leaks were present and pleural drainage output was < 150 mL/24 h. Postoperative pain control was achieved mainly by epidural analgesia and/or by systemic opioids combined with non-steroidal anti-inflammatory drugs.

After surgery patients were transferred to a general intensive care unit (ICU) for the first 12/24 hours. Heart rate, ECG, central venous and arterial pressures, and acid-base/blood gases were continuously monitored during the ICU stay. Inotropic support was provided if the ventricular contractility was markedly impaired, to achieve stable hemodynamic conditions. Perioperative need for blood products was determined on an individual, patient-by-patient basis; in general, blood transfusions were administered when hemoglobin was < 8 g/dL. Postoperative fibrobronchoscopy (FBS) was performed in case of lung atelectasis, and in order to obtain bronchial secretion samples for microbiologic examination. All patients had an active program of postoperative physiotherapy including deep-breathing exercises.

AF monitoring and definition

Cardiac rhythm assessment followed the daily practice of an integrated clinic encompassing ICU and ward level, sharing the same routines and data collection system. Patients were monitored by

continuous ECG during a minimum of 48 hours postoperatively. Subsequently, the monitoring was by repeated daily observations by nurses and physicians, at least every 2 hours. In case of rhythm disturbance reported by nurse or patient, a 12-lead ECG recording was obtained, and continuous ECG monitoring was restarted if necessary. Additional recordings were collected at clinical suspicion of AF. The arrhythmia, as defined by physician assessment, was on the basis of a telemetry strip or a 12-lead ECG recording. Amiodarone, either oral or intravenously administered, constituted the standard pharmacological treatment of AF. Digoxin was administered if necessary to reduce high ventricular rate. In case of AF recurrence, the same protocol was applied. In this study the definition of postoperative AF includes the successfully treated AF as well as AF persistent at discharge.

Statistical analysis

Extracted database variables were tabulated using Microsoft Excel[®] (Microsoft Corp, Redmond, WA) and statistical analysis was computed using SPSS, release 16.0 for Windows[®] (SPSS Inc, Chicago, IL). Continuous variables were tested for normal distribution by the Kolmogorov-Smirnov test and compared between groups with unpaired Student's *t* test for normally distributed values; otherwise, the Mann-Whitney *U* test was employed. In case of dichotomous variables, group differences were examined by chi-square or Fisher exact tests as appropriate.

A stepwise logistic regression model was developed to identify predictors for postoperative AF. The model was built with univariable predictors with a *p* value < 0.25. The stepwise approach was however confirmed by backward and forward methods. The strength of the association of variables with the dependent ones was estimated by calculating the odds ratio (OR) and 95% confidence intervals (CI). The model was calibrated by the Hosmer-Lemeshow goodness-of-fit test, while model discrimination was evaluated by using the area under the receiver operating characteristic (ROC) curve.

Kaplan-Meier estimates and log-rank test were performed for the postoperative mortality rate comparison of patients with/without AF. Hazard ratios (HRs) were generated by a Cox regression analysis. To measure survival differences, the final Cox proportional hazards model was adopted

to construct adjusted survival curves. Patients who died within 30 days of operation were excluded from the final analysis of long-term survival.

A *p* value less than 0.05 was considered statistically significant. Results are expressed as mean \pm SD for continuous variables and frequencies for the categorical ones.

RESULTS

AF features and early outcome

Hospital mortality accounted for 7 (1.5%) subjects, while AF occurred in 9.9% of the patients (45 of 454) and its frequency peaked on the second postoperative day (69% of patients). Mean AF duration was 9.2 ± 7.1 hours (range: 1-24) (Figure 4). Of the 45 patients with postoperative AF, 29 (64%) subjects had a single arrhythmia episode, while 16 (35%) experienced multiple episodes. At discharge, persistent AF was present in 2 of 45 (4.4%) patients.

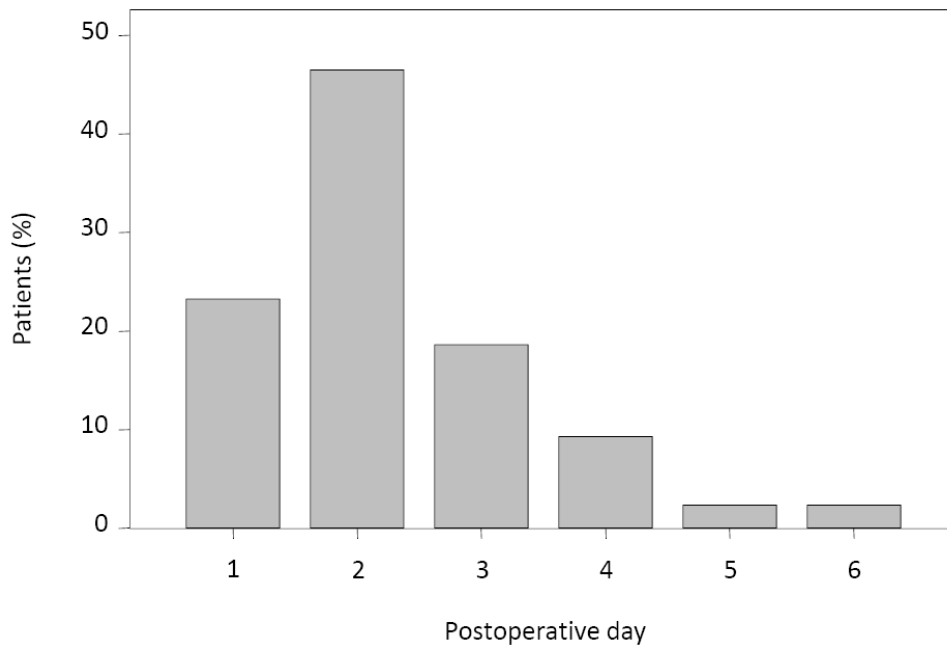


Figure 4. AF development with reference to the postoperative day of occurrence.

Patients with AF were older and more frequently they had a history of paroxysmal AF and coronary artery disease ($p = 0.008$, $p < 0.001$ and $p = 0.009$, respectively) (Table 1).

Other comorbidities, preoperative medications and pulmonary function tests did not reveal significant differences between patients with AF and without it. Moreover, no correlation was observed between postoperative AF and lung cancer stage, histological type of cancer and administration of neoadjuvant cancer therapy ($p = 0.568$, $p = 0.281$ and $p = 0.756$, respectively).

Table 1. Patient Characteristics

| Variable* | All patients (n=454) | No AF (n=409) | AF (n=45) | P value† |
|--------------------------------|-------------------------|------------------|--------------|----------|
| <i>Demographic</i> | | | | |
| Age (y) | 65.4 ± 8.8 | 65.0 ± 8.9 | 68.6 ± 6.8 | 0.008 |
| Male (n,%) | 369 (81.3) | 332 (81.2) | 37 (82.2) | 0.864 |
| BMI (kg/m ²) | 25.6 ± 4.1 | 25.7 ± 4.2 | 24.7 ± 3.3 | 0.116 |
| <i>Comorbidities</i> | | | | |
| Paroxysmal AF (n,%) | 45 (9.9) | 38 (8.8) | 7(36.8) | <0.001 |
| CAD (n,%) | 56 (12.3) | 45 (11.0) | 11 (24.4) | 0.009 |
| Prior AMI (n,%) | 15 (3.3) | 12 (2.9) | 3 (6.7) | 0.178 |
| Hypertension (n,%) | 183 (40.3) | 161 (39.4) | 22 (48.9) | 0.216 |
| Diabetes (n,%) | 58 (12.8) | 53 (13.0) | 5 (11.1) | 0.999 |
| Dyslipidemia (n,%) | 71 (15.6) | 60 (14.7) | 11 (24.4) | 0.087 |
| Current smokers (n,%) | 182 (40.1) | 164 (40.1) | 18 (40.0) | 0.990 |
| PVD (n,%) | 115 (25.3) | 106 (25.9) | 9 (20.0) | 0.386 |
| CVA (n,%) | 19 (4.2) | 16 (3.9) | 3 (6.7) | 0.421 |
| <i>Basal biochemical data</i> | | | | |
| Creatinine (basal, mg/dL) | 1.0 ± 0.5 | 1.0 ± 0.4 | 1.2 ± 1.1 | 0.287 |
| Hb (g/L) | 13.8 ± 1.6 | 13.8 ± 1.5 | 13.6 ± 1.8 | 0.352 |
| <i>Basal pulmonary data</i> | | | | |
| FEV ₁ (% predicted) | 88.1 ± 21.9 | 88.2 ± 21.7 | 86.9 ± 24.1 | 0.716 |
| PaO ₂ (mmHg) | 94.5 ± 21.9 | 94.3 ± 20.9 | 96.3 ± 29.2 | 0.558 |
| <i>Preoperative therapy</i> | | | | |
| B-blockers | 36 (7.9) | 29 (7.1) | 7 (15.6) | 0.046 |
| Calcium antagonists | 58 (12.8) | 51 (12.5) | 7 (15.6) | 0.556 |
| ACE-Inhibitors (n,%) | 67 (14.8) | 59 (14.4) | 8 (17.8) | 0.547 |
| ARBs (n,%) | 33 (7.3) | 29 (7.1) | 4 (8.9) | 0.659 |
| Statins (n,%) | 45 (9.9) | 39 (9.5) | 6 (13.3) | 0.429 |
| Neoadjuvant therapy (n,%) | 30 (6.6) | 28 (6.8) | 2 (4.4) | 0.756 |

*For continuous variables, mean ± SD; for categorical variables, absolute number and percent.

†For continuous variables, Student *t* test or the Mann-Whitney *U* test; for categorical variables, Fisher exact test or χ^2 .

Abbreviations: ACE, angiotensin converting enzyme; AF, atrial fibrillation; AMI, acute myocardial infarction; ARB, angiotensin receptor blocker; BMI, body mass index; CAD, coronary artery disease; CVA, cerebrovascular accident; FEV₁, forced expiratory ventilation in 1 second; Hb, hemoglobin; PaO₂, partial arterial oxygen pressure; PVD, peripheral vascular disease.

Cancer location in the right lung was associated with higher prevalence of AF ($p = 0.011$).

Postoperatively, patients with AF had a higher prevalence of respiratory failure (11.1% vs. 0.7%, $p < 0.001$), of postoperative FBS (24.4% vs. 7.1%, $p < 0.001$) and required a larger amount of

blood transfusions (28.9% vs. 8.8%, $p < 0.001$) (Table 2). Moreover, patients with AF had longer hospital stay (15.3 ± 10.1 vs. 12.2 ± 5.2 days, $p = 0.001$), higher ICU admission rate (13.3% vs. 3.9%, $p = 0.015$), and higher hospital mortality (6.7% vs. 1.2%, $p = 0.036$).

Table 2. Peri- and Post-operative Patient Data

| Variable | All patients (n=454) | No AF (n=409) | AF (n=45) | P value |
|------------------------------------|-------------------------|------------------|-----------------|---------|
| <i>Lung cancer characteristics</i> | | | | |
| Cancer location (n,%) | | | | 0.011 |
| Right lung | 255 (55.7) | 229 (57.7) | 26 (37.8) | |
| Left lung | 198 (44.3) | 183 (42.3) | 15 (62.2) | |
| UICC Stage (n,%)* | | | | 0.568 |
| Stage I | 235 (54.0) | 211 (54.0) | 24 (54.5) | |
| Stage II | 93 (21.4) | 86 (22.0) | 7 (15.9) | |
| Stage III/IV | 107 (24.4) | 94 (24.0) | 13 (29.5) | |
| Histology (n,%) | | | | 0.281 |
| Squamous cell | 161 (35.5) | 140 (34.2) | 21 (46.7) | |
| Adenocarcinoma | 230 (50.7) | 209 (51.1) | 21 (46.7) | |
| Large cell | 25 (5.5) | 24 (5.9) | 1 (2.2) | |
| Other | 38 (8.3) | 36 (8.8) | 2 (4.4) | |
| <i>Perioperative data</i> | | | | |
| Lymph node dissection (n,%) | 452 (99.6) | 407 (99.5) | 45 (100) | 0.999 |
| Ventilation time (h) | 3.2 ± 0.7 | 3.2 ± 0.7 | 3.2 ± 0.7 | 0.540 |
| Blood transfusions (n,%) | 49 (10.8) | 36 (8.8) | 13 (28.9) | <0.001 |
| <i>Postoperative data</i> | | | | |
| Reoperation for bleeding (n,%) | 3 (0.7) | 3 (0.7) | 0 (0) | 0.999 |
| FBS (n,%) | 44 (8.8) | 31 (7.1) | 13 (24.4) | <0.001 |
| AMI (n,%) | 4 (0.9) | 2 (0.5) | 2 (4.4) | 0.051 |
| CVA (n,%) | 9 (2.0) | 7 (1.7) | 2 (4.4) | 0.221 |
| AKI (n,%) | 17 (3.7) | 14 (3.4) | 3 (6.7) | 0.232 |
| Respiratory failure (n,%) | 8 (1.8) | 3 (0.7) | 5 (11.1) | <0.001 |
| Pneumonia (n,%) | 7 (1.5) | 5 (1.2) | 2 (4.4) | 0.146 |
| Length of stay (days) | 12.5 ± 5.9 | 12.2 ± 5.2 | 15.3 ± 10.1 | 0.001 |
| ICU admission (n,%) | 22 (4.8) | 16 (3.9) | 6 (13.3) | 0.015 |
| Hospital Mortality (n,%) | 7 (1.5) | 4 (1.0) | 3 (6.7) | 0.024 |

*UICC not applicable for 19 (4.2%) patients.

Abbreviations: AKI, acute kidney injury (according RIFLE criteria); AMI, acute myocardial infarction; CVA, cerebrovascular accident (stroke + transient ischemic attack); FBS, fibrobronchoscopy; ICU, intensive care unit; PaO₂, partial arterial oxygen pressure; UICC, Union International Contre le Cancer.

At multivariable analysis, independent predictors of postoperative AF were preoperative paroxysmal AF (OR 5.91, 95%CI 2.07 to 16.88), need of perioperative blood transfusions (OR 3.61, 95%CI 1.67 to 7.24), and postoperative FBS (OR 3.39; 95%CI 1.48 to 7.79) (Table 2). The Hosmer-Lemeshow goodness-of-fit test (χ^2 [1 d.f.] = 0.61, $p = 0.433$) and ROC analysis (AUC of 0.70) revealed good calibration and discrimination for the multivariable analysis.

AF and late outcome

Follow-up was completed for all 447 discharged patients, with median follow-up of 36 months (maximum: 179 months). Kaplan-Meier analysis of subjects without AF revealed 1-, 5- and 10-year overall survival of 99%, 71% and 24%, respectively, similar to 98%, 68%, and 16% survival of patients with AF ($p = 0.169$). At multivariable Cox analysis, the only variables independently associated with long-term mortality were neoadjuvant therapy (HR 2.27; 95%CI 1.33 to 3.88) and hypertension (HR 1.47; 95%CI 1.09 to 1.98). Moreover, when the 5-year survivors were separately considered, AF was another independent predictor of poor survival (HR 2.24; 95%CI 1.03 to 4.91), along with neoadjuvant therapy (HR 2.79; 95%CI 1.12 to 6.97) and lung cancer stage (HR 1.65; 95%CI 1.101 to 2.70) (Figure 5). The difference in the mortality patterns of all patients discharged was not age related.

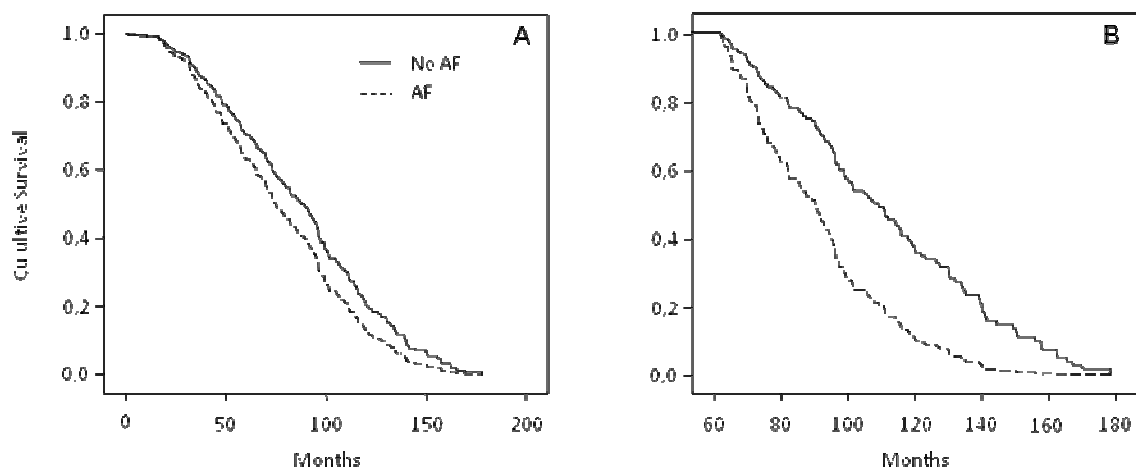


Figure 5. Risk adjusted survivals in patients after lobectomy for primary lung cancer, stratifying according to postoperative AF, (panel A) for all discharged patients and (panel B) for 5-years survivors.

DISCUSSION

Despite improvements in surgical and anesthesiological techniques, incidence of AF after thoracic surgery remained substantially unchanged, with little change over the past two decades [1-7]. Although several studies have analysed the risk factors for this arrhythmia and its possible preventive strategies, its exact pathophysiology has not yet been elucidated.. Furthermore, few data are available regarding the impact of AF on postoperative survival [4-7]. Our study confirms the negative impact of AF on hospital mortality. Moreover, it provides evidence that among patients surviving 5 years after lobectomy for primary lung cancers, those affected by postoperative AF have a reduced survival rate.

Our data also identified preoperative paroxysmal AF, postoperative FBS and blood transfusions as independent predictors of postoperative AF. While paroxysmal AF and transfusion requirement are well-known AF risk factors, because of the electrical and histological abnormalities of patient atrial tissue and because of the amplified inflammatory response by direct infusion of different inflammatory mediators [2,32-34], the correlation between postoperative FBS and AF has not been previously observed. A possible explanation of such correlation is the operative trauma subsequent to the FBS procedure, resulting in a hyperadrenergic state with increased levels of catecholamines. The latters enhance triggered activity and automaticity, which are key factors in the development of the atrial arrhythmia [35,36].

Our data confirm that AF following lobectomy for lung cancer increases early postoperative mortality and causes significant adverse effects, prolonging the length of ICU and hospital stay [2-4]. Postoperative AF was here associated with a three- to fourfold increased risk of both hospital mortality and ICU admission, and a 2- to 3-day increase in total hospital length.

An intriguing finding of our study was the impact of postoperative AF on long-term survival. Previous studies on the subject have focused on the perioperative period and have failed to include survival data after five years [4-6]. The association between postoperative AF and a poor long-term survival is controversial [4-6]. Amar and co-workers [5] first demonstrated that early supraventricular tachydysrhythmias (SVT) were associated with reduced postoperative survival, in a population of 78 patients with non-small cell lung carcinoma. At the conclusion of that study (median follow-up: 17 months), only 1 of 10 patients with SVT was alive, whereas 39 of 68 (57%) who did not develop SVT were alive ($p = 0.01$) [5]. Murthy and colleagues [6] reported the association of postoperative AF with increased risk of late adverse outcomes in 198 patients after esophagectomy. In this case series, drawn from 921 patients, median survival was shorter for those affected by AF compared with controls (11.5 vs. 14.5 months); however, when hospital mortality was excluded from the analysis, survival was not different (14.5 vs. 16.9 months) [6]. Cardinale and colleagues [4] recorded no differences in late mortality between patients with AF and patients without it; these authors prospectively enrolled 233 consecutive patients undergoing lung cancer operations, observing similar survival rate between the AF and the no-AF group (82% vs. 84%) at the end of follow-up (mean 18 ± 8 months).

All the above mentioned studies analysing a possible direct association between postoperative AF and mortality after thoracic surgery, however, have limitations due to heterogeneous cancer populations, small sample size, incomplete matching and exclusion of many patients from the analysis [4-6]. In addition, a relative short follow-up period in the same studies did not allow to examine adequately the detrimental effects of AF on late survival [4-6]. On one hand, the results of our study suggest that in the early postoperative years the most powerful determinant of survival is the stage of lung cancer. On the other hand, among 5-year survivors the occurrence of postoperative AF was an independent predictor of long-term mortality (Figure 5).

The possible mechanisms by which postoperative AF is associated with mortality in later years are difficult to analyse. Despite attempts to account for confounding mechanisms, it is possible

that AF is associated with mortality because it usually occurs in patients with a more severe comorbidity profile [1-3]. Plausible mechanisms supporting a direct effect of postoperative AF include heart failure and the potential AF recurrence with attendant thromboembolic sequelae [37,38].

Limitations

There are several limitations to the present study. Firstly, this is a single center study and its design is retrospective, although data were prospectively collected. Secondly, the statistical analysis is limited by the large difference between the number of patients with AF and without it. Thirdly, our study does not provide a direct mechanistic explanation for late mortality, a difficulty shared by other researches on the same topic [4-6]. The association we observed between AF and late mortality does not necessarily indicate causation, although studies on the general population affected by chronic AF and studies reporting the outcome of cardiac surgery patients with postoperative AF, revealed a direct AF effect in causing late mortality [37,39]. In addition, our study considered all-cause mortality only; autopsy details were not available and we did not collect information about post-discharge AF recurrence. Because of these limitations, the mechanisms by which mortality is explained by postoperative AF remain speculative.

CONCLUSIONS

The present study confirms that AF after pulmonary lobectomy for cancer increases utilization of health resources and is associated with several serious adverse events. It also provides the first evidence that postoperative AF predicts poorer long-term survival in 5-year survivors. In this setting of patients, long-term postoperative surveillance and prophylaxis of arrhythmia seem justified after the occurrence of AF.

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CONFLICTS OF INTEREST

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