Author's response to reviews

Title: Atrial fibrillation after pulmonary lobectomy for lung cancer affects long-term survival in a prospective single-center study

Authors:
Andrea Imperatori (andrea.imperatori@uninsubria.it)
Giovanni Mariscalco (giovannimariscalco@yahoo.it)
Giuditta Riganti (giu.riga@teletu.it)
Nicola Rotolo (nicola.rotolo@uninsubria.it)
Valentina Conti (v.conti@hotmail.it)
Lorenzo Dominioni (lorenzo.dominioni@uninsubria.it)

Version: 2 Date: 18 December 2011

Author's response to reviews: see over
Dear Editor,

we thank you and the Reviewers for the suggestions and observations to our manuscript, entitled: “Atrial fibrillation after pulmonary lobectomy for lung cancer affects long-term survival in a prospective single-center study”.

The response point-by-point to the reviewers’ detailed and valuable comments are listed into the following pages.

We hope that we have answered all questions, and that the manuscript has now improved in such a way that it can be found acceptable for publication in the Journal of Cardiothoracic Surgery.

NOTE: Pages and lines referred to in the following authors’ replies are of the REVISED MANUSCRIPT
Reviewer #1: Ken Kodama

The authors investigate the impact of postoperative AF on early and late outcomes after pulmonary lobectomy for lung cancer. Their results indicate that hospital mortality is higher in patients with postoperative AF than those without AF. Among the 5-year survivors, postoperative AF independently predicts poorer long-term survival. As independent AF predictors, they picked-up preoperative paroxysmal AF, blood infusion, and FBS. This report is convincing, and seems to be including new evidence.

I think that the mechanisms involving postoperative AF will be separated into two categories; one of them is the volume or pressure overloading on the atrium due to the decrease of lung volume, blood infusion, etc. Another one is conduction defect affected by CAD, DM, advanced age, etc. High catecholamine states secondary to pain may also become a trigger of AF.

1.1. When the authors focused on the postoperative AF for the patients with lobectomy for lung cancer, the influence of systematic mediastinal lymph node dissection on the postoperative arrhythmia should be added in the analysis or discussion.

REPLY: 
As stated in *Materials and Methods* section, *Patient management* paragraph (page 5, line 6), “Mediastinal sampling lymphadenectomy was routinely performed.” Consequently, we have not the possibility to compare sampling vs. systematic mediastinal lymphadenectomy in our series. We added in the Discussion section (page 11, line 25): “Similarly, we cannot evaluate the possible role of systematic mediastinal lymph node dissection, because we routinely performed mediastinal sampling lymphadenectomy performed mediastinal sampling lympho-adenectomy.”

1.2. They should also discuss about the reason that postoperative AF more frequently involved in the patients with left lobectomy than right lobectomy.

REPLY: The observation of the Reviewer is interesting. Our univariable analysis revealed that patients undergoing left lobectomy were affected by postoperative AF more frequently than those subjected to right lobectomy (62% vs. 38%, p = 0.011). A reason could be related to the major manipulation and the increased trauma of the left cardiac structures (left atrial auricular and left pulmonary vein) as suggested by literature (Mathew et al. *JAMA* 1996;276:300-6). However, this statistical relationship was not confirmed after multivariable analysis, probably suggesting the preeminent role of other observed predictors. Nevertheless, following the suggestions, we have now mentioned this issue in the discussion, as follows: (page 9, lines 21-25) “An intriguing observation of the present study was an increased AF occurrence in patients undergoing left lobectomy compared with those subjected to right one (62% vs. 38%). A plausible reason could be related to the increased manipulation and increased trauma of the left cardiac structures (left atrial auricular and left pulmonary vein) [17]. However, this statistical relationship was not confirmed at multivariable level.”
Reviewer #2: Felice Mucilli

2.1. Major compulsory revision: Percentage of patients with postoperative AF (table 1, 7 pts 36.6%) is uncorrect and may affect the p value.

REPLY: We apologize for the error and we have promptly corrected it in Table 1 (page 17, line 9).

2.2 It would also be useful to consider in the discussion and literature review the article by Shawn S. Groth and Colleagues: "Conditional Cancer-Specific versus cardiovascular-Specific Survival after lobectomy for Stage I non-small cell Lung Cancer" Ann Thorac Surg, 2010,90,375-82.

REPLY: We thank the Reviewer for his relevant suggestion. Although our study and analysis was not conceived to deeply investigated the role of cardiovascular disease as cause of mortality in these setting of patients, certainly the observation concerning the risk cancer-specific mortality reduction over time can be observed. Accordingly to Groth and co-workers (new ref. 20), we documented that the risk of dying for lung cancer exceeds the risk of dying of cardiovascular disease in the early period of follow-up, as expected in lung cancer patients. However, that observation diminished with time, and postoperative AF is certainly a mirror of cardiac status. Therefore, an important implications in 5-year survivors after pulmonary lobectomy for cancer is the need for a long-term surveillance and prophylaxis of arrhythmias along with the planned oncologic follow-up. We have now added in the “Discussion section” this relevant clinical implications, as follows: (page 11, lines 11-15) “Our findings are consistent with the data presented by Groth and co-workers [20]. The risk of dying for lung cancer exceeds the risk of dying of cardiovascular disease immediately after lung surgery, but this relation diminished with time. Being postoperative AF a mirror of cardiac status, an important implications for NSCLC survivors is the need for a long-term surveillance and prophylaxis of arrhythmias along with the planned lung follow-up.”
Reviewer #3: Jiro Okami

The survival analysis of this study revealed that postoperative AF did not affect the 5-year survival but associated with late survival.

3.1.
It is worthwhile to report that AF did not affect the 5-year survival because the association between the survival and AF is still controversial among the previous reports. Please show the survival curve as a figure.

REPLY:
We have now added the requested figure as Figure 1; the legend has been added on page 21, line 3.

3.2.
However, it is very difficult to understand the clinical significance of the association between perioperative AF and the late survival. Even though there is a statistical difference, does this result provide any useful information for surgeons?

The authors should state the possible mechanism why perioperative AF associates the late survival but not the 5-y survival. In addition, the authors are required to describe the potential utility of this result for surgeons.

REPLY:
Certainly, the observation of the Reviewer is important, but according with Groth and colleagues we believe that our observations could have relevant implications for surgeons and clinicians. Postoperative AF has been largely demonstrated in literature to be a mirror cardiac patient status. Literature also shows that the risk of dying for lung cancer exceeds the risk of dying of cardiovascular disease immediately after lung surgery, but this relation diminished with time. The need for a long-term surveillance and prophylaxis of arrhythmias along with the planned lung follow-up in NSCLC patients could be suggested. We have now briefly discussed this issue in the “Discussion section” (page 11, lines 11-15).

3.3. and 3.4.
Moreover, the authors are asked to show the data in detail regarding the association between AF and the late survival. The background of 5-year survivors according to the status of AF and the survival curves are at least required. Otherwise, the result of the association between AF and the late survival should be deleted.

REPLY:
We have now added a new figure (Figure 1) showing the survivals in patients after lobectomy for primary lung cancer, stratified according to postoperative AF. Although the small number of patients with postoperative AF could restrain this ambition (among 151 5-year survivors only 12 had postoperative AF, as shown in Figure 1), in 5-year survivors cardiovascular disease represented by postoperative AF seems to constitute an important risk factor, as shown also by Groth et al (ref 20). Accordingly to the kind request of the Reviewer, we consequently added in the Results section (page 8, lines 23-24) such data, as follows: “Among 151 5-year survivors, a similar difference of cardiovascular disease mortality was also observed (40% vs. 21%, p=0.336).”

3.5.
Postoperative AF is not a big concern for surgeons if AF is transient. But it sometimes prolongs for a few days. Prolonged AF usually requires medication or other treatments and may causes circulatory dysfunction and any other serious complication as a result. Is it possible to categorize the AF patients according to the severity?

REPLY:
As stated in Materials and Methods section, AF monitoring and definition paragraph, “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. Subsequent 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 was defined by physician assessment, on the basis of a telemetry strip or a 12-lead ECG recording.”, we do not use any severity score for AF. However, 40/42 (95.2%) AF patients were treated by anti-arrhythmic medications (amiodarone, digoxin, calcium-channel blocker, beta-blocker) (see response to point 3.7); the remained 2 patients were successfully treated with correction of the electrolyte imbalance (potassium). and in two patients.

3.6.
Please describe the timing of AF and the duration of AF in detail. Are there any relationships between these two variables?
REPLY:
We described timing and duration in the “results” section (page 7, lines 12-14). The peak on postoperative day 2 has been well documented by several authors (Cardinale et al, Ann Thorac Surg 1999;68:1827 –31; Amar et al, Ann Thorac Surg 2006;82:1057– 62). In our series there is no correlation between timing and duration of postoperative AF, also because of small numbers of late events.

3.7.
Please describe the indication of medication for postoperative AF at the authors' institution. How many patients required the medication? The treatment was effective for all AF patients?
REPLY:
We thank the Reviewer for the question and we apologize for this lack of information. Among the 45 patients with postoperative AF, 27 (60%) were treated by amiodarone, 7 (16%) by digoxin, 4 (9%) by calcium-channel blocker, and 2 (4%) by beta-blocker on Cardiologist prescription and recommendation. The remained 5 patients were treated with a simple correction of the electrolyte imbalance (potassium). The treatment was effective in all AF patients except two who were discharge with persisting AF, as already reported in “Results” section (page 7, lines 18). We added in the “Results” section the detailed treatment as follows (page 7, lines 15): “Among the 45 patients with postoperative AF, 27 (60%) were treated by amiodarone, 7 (16%) by digoxin, 4 (9%) by calcium-channel blocker, and 2 (4%) by beta-blocker. The remained 5 patients were treated with a simple correction of the electrolyte imbalance (potassium). In all cases the choice of medication was based on Cardiologist prescription.”

3.8.
Are there any factors associated with severe AF?
REPLY:
Please see reply to point 3.5..

3.9.
The analysis for predictive factors is interesting.
Predictive factors should be preoperative (or intraoperative) factors.
REPLY:
We thank the reviewer for his observation. As a matter of fact, our independent predictor of postoperative AF (paroxysmal AF, blood transfusion and FBS) were all preoperative and intraoperative factors suggesting a possible theoretical preventive AF strategies.
3.10. For what purpose did the authors performed fibro-bronchoscopy? If it was diagnostic preoperatively, the authors should indicate the indication for fibro-bronchoscopy. If fibro-bronchoscopy was performed to drainage of airway secretion postoperatively, please analyze the predictive factors again excluding this factor.

REPLY:
All patients received preoperatively fibro-bronchoscopy, as indicated in the International diagnostic guidelines. In the analysis of predictors of postoperative AF we considered only postoperative fibro-bronchoscopy that was defined, as reported in “Material and methods” section, as follows: “Postoperative fibro-bronchoscopy (FBS) was performed in case of lung atelectasis, and in order to obtain bronchial secretion samples for microbiological examinations.”

3.11. Left lung tumor was not the independent factor associated with AF. Are there any confounding variables with left lung tumor?

REPLY:
Our univariable analysis revealed that patients undergoing left lobectomy were affected by postoperative AF more frequently than those subjected to right lobectomy (62% vs. 38%, p = 0.011). A reason could be related to the major manipulation and the increased trauma of the left cardiac structures (left atrial auricular and left pulmonary vein) as suggested by literature (Mathew et al. JAMA 1996;276:300-6). However, this statistical relationship was not confirmed after multivariable analysis, probably suggesting the preeminent role of other observed predictors. Nevertheless, following the suggestions, we have now mentioned this issue in the discussion, as follows: “An intriguing observation of the present study was an increased AF occurrence in patients undergoing left lobectomy compared with those subjected to right one (62% vs. 38%). A plausible reason could be related to the increased manipulation and increased trauma of the left cardiac structures (left atrial auricular and left pulmonary vein) [17]. However, this statistical relationship was not confirmed at multivariable level.”

3.12. The authors pointed out the higher mortality in the AF patients. The episode of AF does not cause patient deaths. Please describe whether AF was secondary after any other postoperative complications. The reviewer would like to know the detail of the clinical courses in the mortalities.

REPLY:
As shown, in Table 2 patients affected by AF had an increased need of blood transfusion, respiratory failure and fibro-bronchoscopy to postoperatively drain airway secretion requirement. Certainly, their exact temporal and causative link to AF in producing hospital mortality remain speculative.

In details, one patient (male, 64 years old; with preoperative chronic renal failure treated by hemodialysis) died on postoperative day 26 due to pneumonia; one patient (male, 77 years old; with Parkinson disease and COPD; abscessed squamous cell carcinoma pT2, pN0, G3) died on postoperative day 54 for cardiac dysrhythmias in Cardiology Unit; one patient (male, 69 years old; with monolateral carotid stenosis; necrotic abscessed squamous cell carcinoma pT3, pN2, G2) died on postoperative day 52 due to respiratory failure and sepsis.

3.13. Tables are very complicating, so that it is difficult to find the important data.
The left column in table 2 and table 3 is not informative.

**REPLY:**
Following the suggestion, we deleted the column 2 (All patients (n=454)) in Table 2 (page 18) and column 2 (Wald $X^2$) in Table 3 (page 19).

Best regards,

Andrea Imperatori
on behalf of all authors.