Peer Review File

Article information:

Congratulations for your work on risk stratification/risk factors for pulmonary complications after lung resections in elderly patients. This is a single-center retrospective observational study and the messages are well-communicated.

I have some comments though:

1) Figure 1 (Flowchart): Which information was missing in the 95 incomplete information patients? As you mention in the limitations section, it is almost 20% of the cohort that was excluded due to missing data. I believe it is important to clarify what was missing.

Reply 1: It is include 43 missing pulmonary function test, 17 missing Blood Report, 35 missing Histological type.

Changes in the text: add the information of 95 incomplete information patients in Figure 1 annotation (see page 15 Figure 1).

2) Page 5, Line 145: what do you mean by writing that `pulmonary bulla` was considered a surgical complication?

Reply 2: It is means that rupture of pulmonary bulla after surgical resection.

Changes in the text: pulmonary bulla change to rupture of pulmonary bulla (see Page 5, Line 145).

3) You describe that FEV1 and DLCO were not found to be significant risk factors after PSM, although they were before PSM. However in the PSM parameter you included smoking status, COPD, FEV1 and DLCO among others (as you describe in lines 163 to 169). Would it be possible to show statistical significance after PSM when you include these factors in the parameters.

Reply 3: There are no differences were observed in parameters between the PPC group and non-PPC groups.

Changes in the text: we have modified our text as advised (see page 6, line 188).

4) In Table 1 you report a very low percentage of COPD (only 3 patients out of 314) in the primary cohort of the non-PPC group. However, after PSM you present 10 patients in the subgroup of 135 Non-PPC patients. I think you have to check the numbers here.

Reply 4: Sorry the data is wrong, I will correct it.

Changes in the text: I have corrected the numbers of percentage of COPD and the p-value in table 1. (see page 17, table 1)

I reviewed the manuscript entitled "Risk stratification of postoperative pulmonary complications in elderly patients undergoing lung cancer resection: a propensity score-matched study." This report was interesting because it was important to assess the postoperative complications in the elderly patients who underwent surgery for lung cancer, however, it has some limitations.

Comments-

1. Although the authors assessed the risk stratification of postoperative complications in elderly patients undergoing lung cancer resection and reported significant results that the higher ASA classification and open thoracotomy were associated with the postoperative complications, I didn't think that there were new aspects which can help management of elderly patients with lung cancer. The ASA classification is sometimes referred to for the management of surgery preoperatively. Therefore, it is thought that the use of ASA classification is usual for thoracic surgeons. Moreover, I couldn't understand why the authors defined patients over 65 years-old as elderly patients because I thought less than 75 years-old patients were not recognized as elderly patients in recent years and the authors referred a paper which reported the analysis of octogenarian patients with lung cancer. As per the Cabinet Office of the Japanese Government, people think those aged over 70-75 should be considered elderly (Ouchi Y, et al. Geriatr Gerontol Int. 2017, https://onlinelibrary.wiley.com/doi/10.1111/ggi.13118). What do the authors think of those new guidelines?

Reply 1: Our study aimed to evaluate potential clinical predictors (patient-, clinical-, and procedure-related factors) of PPCs in elderly lung cancer patients, and the result is from real-world study, we think it is not only for thoracic surgeons, but also help for anesthesiologist.

We defined patients over 65 years-old as elderly patients based on international regulations, people over 65 years old are designated as elderly; and in article 2 of China's Law on the Protection of the Rights and Interests of the Elderly stipulates that the starting age standard for the elderly is 60 years old. But, we think 60-65 years old is slightly young, so we defined patients over 65 years-old as elderly patients.

Changes in the text: None.

2. I wondered if the authors didn't evaluate a prolonged air leakage as a factor of postoperative complications. I think that the prolonged air leakage is a more important factor among postoperative complications. Therefore, I recommend the authors re-evaluate other factors containing the prolonged air leakage, and so on.

Reply 2: In our study PPCs included respiratory failure, pneumonia, pulmonary embolism, pleural effusion. But surgical site infection, empyema, chylothorax, subcutaneous emphysema, rupture of pulmonary bulla, and prolonged air leaks were considered surgical complications and thus were not included as PPCs in this study.

Changes in the text: None.

3. I thought that the complication ratio was too high, and so I wondered if the assessments were appropriate to evaluate the complications of elderly patients undergoing lung cancer resections.

Reply 3: The diagnosis of PPCs was based on clinical symptoms [such as a productive cough,

fever, oxygen saturation (SpO2) below 90%, and dyspnea] and findings on postoperative chest X-rays or computed tomography (CT) scans (such as pleural effusion, atelectasis, pulmonary consolidation, and infiltrates).

Changes in the text: None.

4. This analysis was conducted for patients who underwent surgery in one institution. Nevertheless, some researchers were contained as co-authors from other institutions, I couldn't understand why these researchers, especially Japanese doctors, were contained in this study and how they contributed to this study.

Reply 4: Our study is single-center, it is our study's limitation, we look forward to d the multi-center study in the future. The authors from Japan, USA, Italy, give us lots of help, especially in writing.

Changes in the text: None.

Reviewer C

In this manuscript, 14 authors join to study retrospectively 609 patients with lung cancer undergoing resection to determine specific postoperative respiratory complications in "elderly" patients. The complications are selected to exclude surgical, technical and other complications. They conduct a propensity analysis, comparing patients with to those without respiratory complications, and find that American Society of Anesthesiologists class and open vs. minimally invasive surgical approach were associated with these complications. They conclude that elderly patients should be comprehensively evaluated and managed with enhanced recovery methods.

Comments

1. The definition of "elderly" is not understandable. The usual mean age in Asian and Western surgical series for this disease is in the mid-seventh decade, around 65. The mean age of all patients undergoing lung resection for cancer in their institution is not provided. The concept of "elderly" implies that patients of that age have specific risks that are distinct from the general patient population – in other words, physiology of age rather than comorbidity has a decisive impact on operative outcome. Mean age of the study group according to Table 1 is 69; the study group is therefore not enriched with patients in their eighth or ninth decade of life, of whom it might be argued that their age-related physiology impairs their candidacy for operation. The problem with their study of age is twofold: the young patients who could provide the intra-institutional comparison are a priori excluded, while results of the truly aged patients, those 80 years and above, are not separated and disappear in the larger cohort. This in my opinion is a fatal flaw in such a study, before considering that a cohort of less than 500 patients is quite small to study age.

Reply 1: We defined patients over 65 years-old as elderly patients based on international regulations, people over 65 years old are designated as elderly; and in article 2 of China's Law on the Protection of the Rights and Interests of the Elderly stipulates that the starting age standard for the elderly is 60 years old. But, we think 60-65 years old is slightly young, so we

defined patients over 65 years-old as elderly patients. In this study, we performed a retrospective analysis of 456 lung cancer patients with an average age of 69.11±3.68 years.389 patients at the age of 65 to 75, only 23 patients' age more than 80 years old.
Changes in the text: None

2. The authors exclude surgical complications on the unsupported premise that their incidence is not influenced by age. The reader is therefore deprived of a full account of complications in this institution, even before further realizing that operative mortality remains unmentioned. If the authors had wished to study that respiratory, but not surgical or technical, complications are increased in the "elderly", this might have been an interesting study question. However, the omission of certain results from this study represents a sanitizing of outcome that impairs all other analyses. For example, the control group in the propensity analysis is assumed to be complication-free – but what about those patients who have surgical, but not respiratory, complications? We do not know about them.
Reply 2: In this study we mainly focus on PPCs included respiratory failure, pneumonia, pulmonary embolism, pleural effusion, in the non-PPC group some patients have surgical complications like subcutaneous emphysema, prolonged air leaks.
Changes in the text: None.

3. The authors note in their Discussion that FEV1 is not predictive of postoperative pulmonary complications. And they quote as support a study of Berry and co-authors. The Berry study, like the current manuscript, was underpowered with 340 patients and only studied thoracoscopic procedures where pulmonary complications are infrequent. Here, they study FEV1 as a categorical, rather than continuous, variable. Furthermore, they use two different categorizations: in Table 2, they separate into more or less than 80%, while in the multivariate analysis (Figure 4) the categorization occurs along a separation at 60%. In contrast, most larger outcome studies analyze FEV1 at 10% or similar increments to provide a near- or semi-continuous variable. Since FEV1 reflects obstruction in a patient population prone to emphysema, the variable is of central importance to their study. If the authors attempted using FEV1 as a continuous variable without success, they should comment accordingly.
Reply 3: At earlier in our study, we compared four group of FEV1 stage included ＜60%，60-70%，70%-80%，＞80%，only in ＜60%，60-70% showed significant, so we included ＜60%，60-70% in binary logistic regression. In Table 2, we merged the variables into two categories. Because there are too many classifications of some variables, which leads to a small number of people in some classifications. In this case, the Chi-squared test results are not very reliable.
Changes in the text: None.

4. The results are essentially known from many other studies. There is no new information. The institution, according to the Methods section, worked during the entire study interval with an "ERAS protocol". If they conclude that "enhanced recovery methods should be implemented", what are these in addition to those that were in force at the time of the operation? The Discussion omits that point.

Reply 4: Nowadays, lots of studies have confirmed that implement EARS protocol can help patient's recovery, and all the patients who under the lung surgical resection in our hospital are under the EARS protocol. According to result, FEV1 was not predictive of PPCs after PSM so we think it may be related to the implementation of preoperative preventive measures based on an ERAS protocol.
Changes in the text: None.

You performed a retrospective study aiming to identify perioperative predictors of PPCs among elderly patients undergoing pulmonary resection for lung cancer using a propensity score match analysis.

I have several comments:

Comment 1: why did you choose the age of 65 instead of 70 as cut off to define elderly patients?
Reply 1: We defined patients over 65 years-old as elderly patients based on international regulations, people over 65 years old are designated as elderly; and in article 2 of China's Law on the Protection of the Rights and Interests of the Elderly stipulates that the starting age standard for the elderly is 60 years old. But, we think 60-65 years old is slightly young, so we defined patients over 65 years-old as elderly patients.
Changes in the text: None.

Comment 2: line 102: please define better inclusion and exclusion criteria...did you include only patients undergoing lung surgery? type of resection?
Reply 2: We include all patients underwent pulmonary resection for lung cancer, type of resection include lobectomy, sub-lobectomy(pulmonary segment resection, pulmonary wedge resection, double lobectomy, sleeve resection, pneumonectomy)
Changes in the text: we have modified our text as advised (see Page 4, line 109)

Comment 3: line 132: the title is surgical treatment but you stated some consideration about pre and Postoperative treatment, not on surgery operative.
Reply 3: Yes, we add the surgery operative treatment description.
Changes in the text: we have modified our text as advised (see Page 5, line 136).

Comment 4: the extention of resection was not significant in your analysis? you grouped lobar, more than lobar and sublobar. Was "more than lobar" a pneumonectomy or an extended lobectomy (with thoracic wall resection for example?) or a sleeve resection?
Reply 4: The type of resection include lobectomy, sub-lobectomy (pulmonary segment resection, pulmonary wedge resection, double lobectomy, sleeve resection, pneumonectomy).
Changes in the text: None

The paper by Huang et al is an observational retrospective analysis of a large series of elderly patients undergoing surgery for lung cancer.
This study aimed at identifying predictors of pulmonary postoperative complications (PPCs). The Authors retrospectively reviewed a series of 456 patients (age >65 years). Propensity score matching (PSM) was performed to compare preoperative data and clinical characteristics between the PPC and non-PPC groups, followed by binary logistic regression to evaluate

predictors of PPCs. Both PSM and binary logistic regression analysis identified American Society of Anesthesiologists (ASA) class <2 and video-assisted thoracoscopic surgery (VATS) as protective factors for PPCs.

These results are well-known and can be found in many papers.

Despite the lack of originality and my reserve on the eventual tangible groundbreaking scientific value, the paper is methodologically well designed and well written even though it is a bit wordy in the intro and discussion section as well as results are expressed in a very large number of table and figures that are all self.explaining and correct. In this regard I have several questions, whose answers could contribute to making the discussion and the paper perspective more interesting or at least more suitable for a dedicated audience:

Comment 1: People 65 year-old are improperly defined as elderly population nowadays. How many are >75 years old in the reported series?

Reply 1: 389 patients at the age of 65 to 75, only 67 patients' age more than 75 years old.

Changes in the text: None

Comment 2: How could the Authors identify the ASA class? Which parameters have been used?

Reply 2: ASA class I: patient has no major physical problems, the body can tolerate most surgeries and anesthesia, risk is low; ASA class II: patient has a certain level of locality, but the body is within the compensatory range; ASA class III: patients have many underlying diseases, and there are certain risks associated with surgery and anesthesia; ASA class IV: patients have many underlying diseases, and even their organ functions are in a state of decompensation, posing a high risk of anesthesia; ASA class V: patients will be at great risk of being intoxicated, even life-threatening, and should not undergo surgery. In this study, we divided ASA class into two groups that ASA class≤II or ASA > II.

Changes in the text: None.

Comment 3: Which kind of thoracotomy has been used? How many minimal muscle-sparing or postero-lateral?

Reply 3: We choose both front or rear lateral incision path for thoracotomy, and 1 case was underwent VATs transfer to thoracotomy, they all have damage to the integrity of muscles.

Changes in the text: None.

Comment 4: What were the indications to VATS approach? Tumor dimension? N status?
All this information needs to be specified in the paper, with perhaps a further subdivision into subgroups. According to the possible found differences, to revise the conclusions might be appropriate.

Reply 4: In this study the patients choose VATS approach based on the relationship between tumors and pulmonary hilus or the pulmonary hilar vessels was encapsulated by tumor or not.

Changes in the text: I have corrected the numbers of percentage of COPD and the p-value in table 1. (see page 5, line 137)