

## Peer Review File

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### Reviewer A

It is a really interesting paper, congratulations for this review. I have some comments:

1. Q: Thank you to indicate in the title that is a narrative review.
2. Q: The title of your review can be confusing. It is not really a "clinical practice" review but "how to reduce the risk of POP". And to know "how", it is important for me to develop "why" are there POP? which are the risk factors?

Answer (Q1 and Q2): we agree with the reviewer; indeed, the title has been changed accordingly (see also point 2). The whole study and the abstract have been modified to the more appropriate format of a narrative review. General definition, causative mechanisms and risk factors for POP have been briefly summarized in the introductory part and throughout the text.

3. Q: lines 267-283: Why to conclude at the end of this paragraph?

A: Thank you for your suggestion. As the review address different points separately (that is, surgical approach first, then antibiotic prophylaxis and, finally, the impact of rehabilitation), our idea was to offer a "separate" conclusive sentences for each one, in order to improve readability and strengthen the take home messages. However, we moved this part to a more appropriate one.

4. Q: Concerning your conclusions: "Therefore, it is of a paramount [...] a VATS program or when upgrading to uniportal VATS procedures". Why uniportal is an upgrade procedure compared to three-port? it is subjective.

A: The reviewer is perfectly right. It was a completely inappropriate term (we just meant an "kind of surgery requiring higher videothoroscopic skills, and we agree this has nothing to do with a best performance patientwise). The sentence defining uniportal surgery as an "upgrade" of standard VATS has been deleted.

Q: "Robot-assisted thoracic surgery has shown the potential for reduction of POPs, probably by virtue of reduced surgical traumatism and better pain control". I don't agree with this point. There is some contradictory results in the literature and no RCT.

A: We agree with the reviewer; indeed, there are just limited observations on this. The sentence has been toned down accordingly.

Q: Finally, and the most important point, is that there is no definition of POP after lung surgery. How to determine POP? which diagnostic criteria were used in the different studies? Without a clear definition of this complication, it is difficult to

use it as a benchmark and to compare it between procedures.

POP after lung surgery is a very important topic because we use it as a benchmark or to compare some surgical technique. However, the definition of POP after lung surgery has not been studied and the international guidelines are not suitable for our lung cancer patients. So all studies on this topic are subject to very significant biases. I think that authors should have a more critical view.

A: We agree with the reviewer. In fact, we added in the introduction the recommended definition of POPs according to the Center for Disease Control and Prevention (with relative reference). The lack of a harmonized definition of POPs is certainly a factor that adds noise in the research regarding management of chest infections after minimally-invasive thoracic surgery in general. This might be, in a sense, considered one of the main findings of our review, and this consideration has been added accordingly in the discussion section! Furthermore, definition of POP per each study has been added in a new Table (as also suggested from another reviewer).

### **Reviewer B**

Q: It is a very readable review.

The focus on post-operative pneumonia is also considered clinically relevant.

Are there any notes on the bias caused by different definitions of postoperative pneumonia in different studies?

A: Thank you for your positive comments. We addressed the point of inhomogeneous definition of POPs in several points throughout the study, as also suggested by Reviewer 1. And we added POPs definition amongst studies in a new Table.

Q: The issues regarding prophylactic administration of antibiotics are understood. So what are the challenges of administering therapeutic antibiotics in the event of post-operative pneumonia? If so, we would like to know.

A: We agree that is an extremely important issue. Regarding this point, a reflection regarding therapeutic challenges in case of POP has been added in the dedicated section, even though this topic is beyond the goal of the present review.

### **Reviewer C**

Q: Thank you for allowing me to review the manuscript: Postoperative pneumonia in the era of minimally-invasive thoracic surgery: a clinical practice review.

- Line 91: It was not clear how publications were identified. Can the authors list the exact search terms in the manuscript or in a supplement?

A: Thank you for your comment. Search terms and other details have been added in a Table, as also per Journal's editorial guidelines.

Q: Line 97: Can the authors clarify 'a Q3 quality mark'? It is better to add the

citations if possible.

A: Thank you for your comment. The SCImago portal is a database of medical journals, where journals are classified according to the scientific quality of published papers (as well as other indicators). In this database, Q1 is regarded as the highest quality score. We decided arbitrarily not to consider studies published in journals with lowest quality mark (Q4), in order to avoid redundant and/or biased information. Again, this was just our own decision that was mainly made for practical reasons, without any prejudice against any journal, publisher or author. Link to the website has been added.

Q: Line 101-171: Can the authors create a table summarizing studies (year, country, type of study, number of patients, type of surgery, proportion of POPs, mortality, etc.) in this section?

- Can the authors add a brief closing paragraph at the end of each section

A: Thank you for your suggestion. We added a Table accordingly. As suggested, a brief closing remark has been also added – where appropriate – at the end of each section (embedded in the text).

Q: Line 191: Can the authors describe how many patients were included in the subgroup analysis?

A: Number of patients has been added here.

Q: Line 217: I wonder why the authors focus only on locoregional anesthesia. Multimodal analgesia is commonly used perioperatively, which may lead to decreasing the incidence of postoperative pulmonary complications such as POPs.

A: The reviewer is right, and multimodal analgesia is of a paramount importance in reducing POPs and other complications. We decided to focus just on LA because it is one of the mainstays of Enhancer Recovery After Surgery protocol in thoracic surgery (alongside with the idealistic concept of “opioid-free thoracic surgery”). Therefore, we considered this topic more “in line” with the basic conception of our review.

Q: Line 230: Is a main purpose of antibiotic prophylaxis to help decrease the risk of surgical site infections? I wonder if there is a good rationale regarding how antibiotic prophylaxis reduces POPs.

A: The reviewer is perfectly right. In fact, the problem here is that some of the reference studies current practice is founded on, not even had POPs as the primary outcome! The whole section regarding antibiotic prophylaxis has been rearranged in order to highlight this concept.

Q: Line 285-364: Can the authors create a table summarizing studies (year, country, type of study, number of patients, type of surgery, proportion of POPs, mortality, etc.) in this section?

A: Thank you for your suggestion. A Table has been added accordingly.

## **Reviewer D**

Q: What is the rationale in the methodology of using a cut-off 70 patient and to include studies from Q3 journals if less than 70?

A: Thank you for your comment. This was just an arbitrary cutoff, that was established in order to avoid excessive literature citations possibly leading to drawbacks (boring reading, foggy take-home messages, inclusion of low-quality studies, etc.). The size of 70 patient per group is the minimum needed to demonstrate a 4-fold reduction of POPs incidence in a two-tailed comparison (let us say, this is still a quite “permissive” limit!).

Q: Papers belonging to the category of letter, commentary and editorials were not included in the analysis. Was any analysis done? What is the number of studies met the criteria and included in the review?

A: For the “core” review topic (e.g., incidence of POPs after VATS vs Open surgery), the first search retrieved 372 studies. Of these, 22 were deemed eligible for this part of the review. This information was added to the text. For the other parts of the review, no specific criteria were adopted.

No formal data analysis was done, so that this sentence has been deleted accordingly.

Q: What is the percentage of ventilator associated pneumonia and hospital acquired pneumonia in the post-operative cases in both VATS and open?

A: Thank you for this pertinent comment. It would be quite interesting to investigate on this; unfortunately, to our knowledge, no study reported separate data for ventilator-associated pneumonia and HAP (some not even clearly defined POP!).

Q: Was the level of pain a factor in the development of POPs as it is presumed not taking deep breathing because of pain may increase pulmonary complications? Any data regarding this matter?

A: Unfortunately, no study provided us with a cutoff in this regard. There is a wide “informal” agreement amongst thoracic surgeons that a VAS score  $>7/10$  indicates a severe pain which is related with an increased risk of complications. In one of the cited studies only, VAS  $>3$  was regarded as “moderate-to-severe” degree of pain; however, this cutoff was not tested as a predictive factor for POP. Thereby, although the reviewer’s comment is very pertinent (and should be certainly addressed in future clinical studies) we were not able to apply any change to the text.

Q: What is the impact of pre-operative pulmonary function and the expected post-operative FEV1 on the development of pulmonary complications specifically POPs?

A: This is a very important question. Low FEV1 status certainly affects the risk of POPs after thoracic surgery, so that it has been even used by some authors to develop a reliable predictive model.

One sentence and the relative citation has been added in the text.

Q: This is an important topic that occurs commonly and has potentially significant clinical impact on patient morbidity and mortality following thoracic surgery. some minor grammar issues.

A: Thank you for your comment. Extensive language revision done.