

## Peer Review File

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### Reviewer A

This manuscript is a very systematic and informative.

My major concern is the discrepancy between the objective and the content of this review.

Authors aimed to review the main advantage and disadvantage of intubated and non-intubated VATS. However, the comparison between intubated and non-intubated was introduced in only small paragraph. Most of the content is about the inflammatory response by thoracotomy, thoracoscopy, and mechanical ventilation itself.

So, it would be better to revise the title and aim of the manuscript according to the main contents.

**Authors:** Thank you for your kind review and valuable comments. Based on your suggestions, we changed the title and abstract, as well. See it on title page and page 2 (abstract).

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### Reviewer B

In this manuscript the authors present a review of studies that cover the inflammatory and immune responses in thoracic surgeries. They compare video-assisted thoroscopic surgery (VATS) to open thoracotomy technique, ventilation strategies used during surgery such as single lung ventilation and low tidal volume, various general anesthetic approaches, and intubated versus non-intubated approaches. The body of their review covers an increase in inflammatory markers to open thoracotomy, single lung ventilation, general anesthesia, and overall positive pressure ventilation. They are attempting to make the argument that non-intubated VATS procedures have a favorable, or diminished, inflammatory response.

Major points:

1. Abstract: this manuscript reviews the inflammatory responses to VATS compared to open thoracotomy, ventilation strategies such as single lung ventilation and low tidal volume, general anesthesia approaches, and intubated versus non-intubated VATS procedures. This is not presented in the abstract in a meaningful way.

a. Though the objective is stated as “To reveal and review the main advantages and disadvantages of intubated and non-intubated video-assisted thoracic surgery (VATS) associated with immune responses and clinical outcomes,” this is a very small portion of the manuscript.

b. The background as stated in the abstract summarizes many of the concepts discussed in the manuscript. I recommend a much more brief background giving the reader the “why” this review focuses on the inflammatory process after these surgical techniques. As it is a review and does not require the organization of “objective, background, methods and conclusion,” I offer the authors to structure the abstract in a similar way to Kozik and Tweddell: Characterizing the Inflammatory Response to Cardiopulmonary Bypass in Children, published in *Annals of Thoracic Surgery* in 2006. This would give readers a general understanding of what the manuscript will review.

**Authors:** We are grateful for your thorough views and comments. The abstract has been changed to cover the majority of the manuscript. However, we are not allowed to write an abstract as you wished (Kozik and Tweddell: Characterizing the Inflammatory Response to Cardiopulmonary Bypass in Children, published in Annals of Thoracic Surgery in 2006), because there is a narrative checklist for authors that requires the previously showed objective, introduction, methods and conclusion in even review articles. You can find the refreshed abstract on page 2.

2. I believe this manuscript needs more focus and organization. In its current form, it is very difficult to elucidate the author's intent.

a. In the last sentence of the introduction (line 37), the intent of the review it is not clear. What exactly are the authors reviewing? Why? How does this add to the literature? It is my opinion that these questions should make up the bulk of the introductory paragraph, and the rest should be addressed in the review itself.

b. In the body of the manuscript, I recommend the authors use the subtitles to direct the reader to what will be reviewed. For instance in line 52: "The innate and acquired immunological benefits of minimal access surgery" is unclear. The ensuing paragraphs discuss the inflammatory response to VATS as compared to open thoracotomy. A suggested subtitle is "Cellular, immune and inflammatory response to VATS as compared to open thoracotomy" for the first section.

**Authors:** We totally agreed with your points, therefore we modified the introduction section ( line 27-43) and the subtitle as you suggested (line 58).

3. I recommend to heavily proof read for structure and grammatical errors. Unfortunately, the sentence structures and grammatical errors prevented me from understanding the authors meaning on multiple occasions.

a. For example the sentence starting on line 61 "By contrast..."

b. Another example: the sentence starting on line 75 "In addition..."

c. The sentence starting line 133 is unclear, as is the one starting on line 136.

**Authors:** Thank you for indicating, we proofread the manuscript and corrected the grammatical errors.

4. Throughout the manuscript the authors suggest that changes in inflammatory responses they are describing will decrease the risk of cancer metastasis (lines 70-74, 87-89, 219-222). This concept is unsupported by the data the authors present. West et al, (Interact Cardiovasc Thoracic Surg. 2007) reviewed 409 papers that discussed the oncologic equivalence between open thoracotomy and VATS approaches. These data were not referenced here. Also, in contrast to the suggestion by the authors, Nakano et al, (Annals of Cardiovasc Surg 2015), did a single center retrospective review of patients who underwent open thoracotomy approach versus VATS in patients who had tumors > 5 cm and though it was not statistically significant, there was a trend toward more recurrence in the VATS group as compared to the thoracotomy group and worsened survival at 5 years. I strongly caution the authors away from making any clinical inferences that are not represented by data presented here (including line 255-257). If the included articles that focus on inflammatory responses discuss particular clinical outcomes as part of their results, then it is reasonable to include them.

**Authors:** We agreed that our former statements sounded inconsistent and unsupported. Thus, we completed the manuscript with new references that emphasized the discrepancies and that patients' long-term survival and benefits remain to be elucidated (line 69-88, 112-122). We also included a figure to outline the main effects attributed to tumor growth.

5. Similar to the objective in the abstract, the conclusion focuses only on non-intubated versus intubated VATS, and focuses on a small subset of patient populations discussed (those with NSCLC). This is a very small portion of the overall manuscript. I recommend a conclusion that represents more of the bulk of the review manuscript.

**Authors:** We modified the conclusion to focus on the whole manuscript. See line 298-309.

Minor points:

1. Line 25 – specify what kind of surgical trauma – for instance, surgical trauma in open thoracotomies? **See line 28-30.**
2. Line 29 - 33 – these concepts need references **References were added (line 37)**
3. Methods state it is a systematic review, however the submission does not include the PRISMA checklist as stated in the author submission guidelines **Checklist is included.**
4. Make sure to define all acronyms prior to using them (i.e. line 8 NSCLC and line 63 Th2)  
**We corrected all the acronyms.**
5. Sentence ending on line 84 needs a reference **Added in line 109**
6. Line 118 – were these changes when patients were ventilated with low tidal volumes? **Exactly, with low tidal volumes. We corrected the sentence. Line 152**
7. Sentence ending on line 208 needs a reference **Line 240**
8. Line 230 – what was the control group? **Line 263. The control group was intubated VATS patients.**
9. The table could be better organized with similar subgroups/subtitles to how it is presented in the body of the manuscript **See Table 1.**