Author’s response to reviews

Title: Effects of sevoflurane and propofol on the development of pneumonia after esophagectomy: a retrospective cohort study

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Author’s response to reviews:

Dear Editor and Reviewers:

First of all, we would like to express our sincere thanks to you for your constructive and positive comments on our manuscript, which are valuable for improving the quality and the scientific strength of it.

We have read your comments and revised our manuscript accordingly. The amendments have been marked in red in the revised manuscript. Point-by-point responses to the comments and suggestions of the Editor and Reviewers are listed below this letter. We would like to re-submit our revised manuscript for your consideration. If you have any question, please contact us without hesitate.

Looking forward to hearing from you soon.

With kindest regards,

Yours Sincerely

Guo-Hua Zhang
Replies to the Editor:

1) English form should be reviewed

Answer: Thank you very much. As suggested, our revised manuscript has been reviewed by someone who is fluent in English. Thank you again.

2) Please further clarify criteria for the diagnosis of postoperative pneumonia (e.g. microbiological criteria, radiographic criteria) Answer: Thank you very much for your comment. As suggested, we have further clarified criteria for the diagnosis of postoperative pneumonia. All changes and added contents have been marked in red. Thank you again.

3) Postoperative analgesia is one of the major determinants of postoperative respiratory function. Please clarify if you took into account the quality of analgesia and the type of analgesia (e.g. different opioids or analgesic schemes). If not, please discuss this issue among limitations of your study.

Answer: Dear Editor, we would like to express our sincere thanks to you for pointing out this problem for us. Indeed, we did not take into account the quality of analgesia and the type of analgesia (e.g. different opioids or analgesic schemes) in our study. In our revised manuscript, limitations of this issue of our study have been discussed in detail. All changes and added contents have been marked in red. Thank you again.

Replies to Reviewer #1:

1) A lack of clear definition of PP: what kinds of blood tests? the white counts as well as the diagnosis on image? What are the following treatments and the outcomes? Because the PP after esophagectomy is the main result, unclear definition is not acceptable. Pulmonary complications remain to be the major concerned after esophagectomy, however, other complications such as empyema, pleural effusion also exist. The definition of PP should be clearly demonstrated.

Answer: Thank you very much for pointing out these problems for us. As suggested, we have clearly demonstrated the definition of PP in our revised manuscript. The added contents “The primary outcome was the occurrence of postoperative pneumonia which was suspiciously diagnosed based on clinical features (body temperature ≥38°C, leukocyte count >11.0×10⁹/L or <4.0×10⁹/L and purulent secretions) and confirmed by radiographic findings (infiltrative abnormalities) or tracheal aspirates culture [1, 19]. Once diagnosed as pneumonia, patients were generally treated with antibiotics, physical therapy (taking deep breath, coughing, chest percussion, atomization inhalation, aspiration of sputum), and if necessary, mechanical
ventilation according to hospital protocol.” have been marked in red in our revised manuscript. Thank you you again.


2) As the authors hypothesized that the anesthetics may alter the postoperative inflammation, there are no data available for readers to suggest more inflammatory responses.

Answer: Dear reviewer, thank you very much for your comment. In our hospital, patients’ blood samples are not regularly obtained to measure levels of inflammatory markers such as IL-6, IL-8 and IL-10. Although we hypothesized that the anesthetics may alter the postoperative inflammation, there are no data available to suggest postoperative inflammation alteration given the retrospective and observational design of our study. The incidence of PP following esophagectomy ranges from 8.7% to 38% according to many previous studies. We only compared the effect of anesthetics on the incidence of postoperative pneumonia following esophagectomy. It is a limitation of our study and we have pointed it out in discussion section. All changes and added contents have been marked in red. Thank you again.

3) It would be better if Line 156-160 was shown in introduction.

Answer: Thank you very much for your comment and recommendation. As suggested, Line 156-160 has been shown in Introduction in our revised manuscript. Thank you again.

4) Please show the extubation time after operation to rule out the postoperative ventilatory injuries.

Answer: Dear reviewer, thank you very much for your comment. Ventilator-associated pneumonia (VAP) is defined as pneumonia in patients receiving mechanical ventilation for at least 24 h. In our hospital, most of patients were routinely extubated at the end of surgery in the operating theatre and then transferred to the PACU. They usually stayed in the PACU for at least 30 minutes and then assessed according to STEWARD SCORE system and surgical requirements (e.g. chest tube drainage is patent, and the amount, color and consistency of thoracic drainage keeps normal ) to decide if the patients should be discharged from PACU. Only
those who did not meet the extubation standards were transferred to the ICU while maintaining intubation and ventilation. Besides, some patients who underwent reoperation or those who developed severe respiratory dysfunction (PaO2 < 60mmHg and/or PaCO2 > 55mmHg) due to various causes in surgical ward after surgery were re-admitted to ICU for ventilator support. Some patients transferred to ICU only received close observation and further treatment without being ventilated. In our cohort of 1659 patients, 92 (5.5%) were admitted or readmitted to the ICU. Only 38 (2.3%) patients did not meet the extubation standards and 33 (2.1%) were reintubated for mechanical ventilation. As the proportion of postoperative intubation and ventilation is very small, we did not show the extubation time after operation in our study. We have clarified this issue in Methods section in our revised manuscript. Changes and added contents have been marked in red. Thank you again.

5) As BMI of most patients remain within normal range, the results should be carefully interpreted.

Answer: Thank you very much for pointing out this problem for us. As suggested, this result has been interpreted much more carefully in our revised manuscript. Corresponding changes have been marked in red. Thank you again.

Replies to Reviewer #2:

1) I do not understand why to perform the analysis without propensity score matching.

Answer: Thank you very much for your comment. In order to compare outcomes between different groups, it is important to first assure that the groups are comparable. If multiple baseline covariates are significantly different between the 2 groups, the accuracy of the unadjusted treatment effect will become questionable. Propensity score analysis is an increasingly applied statistical method in retrospective observational studies to reduce the uneven distribution of baseline characteristics between two groups. The results from the two comparable groups are more objective. Cases produced by propensity score matching were selected from the entire cohort. We perform the analysis without propensity score matching to present the characteristics and results of all 1659 patients in both groups. Despite the advantage of propensity score analysis, this method is not unified to use in retrospective observational studies. Besides, most published studies using this method showed the analysis and results with and without propensity score matching. Thus, we performed the analysis without propensity score matching in our study. Thank you again.
2) COPD and preoperative pulmonary infections has not been considered in the comorbidities.

Answer: Thank you very much for your comment. COPD and preoperative pulmonary infections were not considered as comorbidities in this study as these diseases were rare in our hospital. Our hospital is a specialized cancer center. Most patients in our hospital were in better conditions and of less comorbidity than that in general hospitals. In fact, hypertension, diabetes mellitus and coronary artery disease were main comorbidities suffered by our patients (25.1%, 7.1%, 4.5%, respectively) and the percentages of other comorbidities such as COPD and preoperative pulmonary infections were very low. Thus, COPD and preoperative pulmonary infections has not been considered in the comorbidities in our study. It is a limitation of our study and we have pointed it out in discussion section. All changes and added contents have been marked in red. Thank you again.

3) It were not considered the type of neuromuscolar blockers and reversal.

Answer: Thank you very much for pointing out this problem for us. Indeed, we did not consider the type of neuromuscular blockers and reversal in our study. In our hospital, there are only two types of neuromuscular blockers: cisatracurium and rocuronium. Neostigmine 2 mg and atropine 1 mg were routinely injected to reverse the action of neuromuscular blockers at the end of surgery. In our hospital, most of patients were routinely extubated at the end of surgery in the operating theatre and then transferred to the PACU. They usually stayed in the PACU for at least 30 minutes and then assessed according to STEWARD SCORE system and surgical requirements (e.g. chest tube drainage is patent, and the amount, color and consistency of thoracic drainage keeps normal ) to decide if the patients should be discharged from PACU. Only those who did not meet the extubation standards were transferred to the ICU while maintaining intubation and ventilation. Besides, some patients who underwent reoperation or those who developed severe respiratory dysfunction (PaO2 < 60mmHg and/or PaCO2 > 55mmHg) due to various causes in surgical ward after surgery were re-admitted to ICU for ventilator support. Some patients transferred to ICU only received close observation and further treatment without being ventilated. In our cohort of 1659 patients, 92 (5.5%) were admitted or readmitted to the ICU. Only 38 (2.3%) patients did not meet the extubation standards and 33 (2.1%) were reintubated for mechanical ventilation. Thus, we did not consider the type of neuromuscular blockers and reversal in our study. Thank you again.

4) The type of ventilation used during the intraoperative period has not been clear (low vs high tidal volume, OLV etc)

Answer: Dear reviewer, thank you very much for pointing out this problem for us. In our practice, patients were ventilated by volume-controlled model. During two-lung ventilation and
OLV, tidal volume was set to 6–8 mL/kg with PEEP (5-10 cm H2O) if necessary and peak inspiratory pressure kept under 35 cm H2O. The fraction of inspired oxygen was adjusted to achieve oxygen saturation by pulse oximetry >95% and the respiratory rate set to maintain end-tidal CO2 concentrations between 35 to 45 mmHg. More sentences have been added to describe exactly what we did. All added contents have been marked in red. Thanks again.

5) It was not evaluate the use of NIV in the postoperative period.

Answer: Dear reviewer, thank you very much for pointing out this problem for us. Just as the above mentioned, patients in our hospital were routinely extubated at the end of surgery in the operating theatre and then taken to the surgical ward. Only those who did not meet the extubation standards were transferred to the ICU while maintaining intubation and ventilation. Those who suffered from postoperative complications in surgical ward or underwent reoperation were readmitted to ICU for close observation and careful treatment. Patients in ICU might receive noninvasive ventilation or invasive ventilation (the latter being most frequently used). In our cohort of 1659 patients, 92 (5.5%) were admitted or readmitted to the ICU. Among them, only 2 (0.1%) patients received NIV. As the proportion of NIV is very small, we did not evaluate the use of NIV in the postoperative period in our study. We have clarified this issue in Methods section in our revised manuscript. Changes and added contents have been marked in red. Thank you again.

Reply to Reviewer #3:

1) I only suggest to revise the paper following the STROBE checklist for observational retrospective studies to make it as much effective as possible.

Answer: Dear reviewer, thank you very much for giving us such a good advice. As suggested, we have revised our manuscript following the STROBE checklist to make it as much effective as possible. In order to conform to the journal style, the order of some items in the STROBE checklist may be changed or combined in our revised manuscript. Thank you again.