Peer Review File

Article information: https://dx.doi.org/10.21037/jtd-23-1667

Reviewer A

During the past few years, the topic of single versus two lung ventilation during esophagectomy has acquired relevance with few case-series reported. The authors presented here their experience on the same topic with the difference that the technique used for one lung ventilation was bronchial blockade and no double lumen tube as most of the previous studies have used and reported previously.

The authors should describe the decision-making process to determine patients undergoing one-lung versus two-lung ventilation: was it surgeon-preference? Was it determined by the anesthesia team? Were there any attributes that made some patients more likely to be selected for a particular group?
Reply 1: Thank you for your suggestion. During the study period, both SLET and bronchial blocker were frequently used in our institution for MIE; double lumen tubes were used seldomly because the surgeons believe they increase the difficulty of lymph node dissection along the left RLN. Usually, a bronchial blocker is selected based on the anesthesiologists' preference. The decision regarding intraoperative ventilation strategy was mostly made by the attending anesthesiologists, with the surgeons' agreement. Other than this, there were no attributes that influenced group selection. We have added this information to the "Methods" section of the revised manuscript (please see Page 8, line 120).
Changes in the text: In our institution, use of a bronchial blocker is at the attending anesthesiologists' discretion. (Page 8, line 120)

The authors did not disclose technical details or postoperative complications that can have a direct effect on outcomes, postoperative pulmonary complications, and length of stay; such us: number of harvested lymph nodes along RLN, pyloric drainage procedure, use of nasogastric drainage, incidence of RLN injury/hoarseness, anastomotic leak, conduit ischemia, chylothorax, among others.
Reply 2: Thank you for the comment. We agree with the reviewer that technical details of the surgery and postoperative complications are important information that could have a direct effect on outcomes, especially on length of hospital stay. We have collected data on major non-pulmonary postoperative complications (i.e., the incidence of RLN injury, anastomotic leak, wound infection and chylothorax) and the results showed that these major postoperative complications did not significantly differ between the two groups. However, because of the retrospective design, data including the number of harvested lymph nodes along the RLN and number of drains used were not available for analysis. There was limited evidence on the influence of drainage procedures on the occurrence of PPCs, which was our main outcome. However, the number of harvested lymph nodes along the RLN could be related to PPCs because of

its impact on RLN injury. Although this specific data could not be collected, we added information on the incidence of RLN injury, which was more directly related to the occurrence of PPCs. On the other hand, the pathology and location of the esophageal tumor did not significantly differ between the two groups. Therefore, we argue that a certain level of uniformity and consistency of the surgical techniques were promised because all patients underwent standard procedures by the same group of surgeons from the same general ward. Nevertheless, we agree with the reviewer that the technical details of the procedure could have an effect on length of hospitalization; the present evidence might be insufficient to make conclusions about the relationship between different ventilation strategies and the secondary outcome of length of hospital stay. We have addressed this study limitation in the revised manuscript. We have also modified the "Conclusion" section to be more precise. Results of major non-pulmonary postoperative complications are shown in Table 4 (please see Page 9, line 148, Page 11, line 193, Page13, line 231, Page 15, line 281 and Page 27, line 467).

Changes in the text: The number of re-intubations and tracheotomies in the first 3 days, occurrence of major non-pulmonary postoperative complications including RLN injury, anastomotic leak, wound infection, and chylothorax, and length of hospital and ICU stays were also recorded. (Page 9, line 148) Incidence of other major PPCs and major non-pulmonary postoperative complications did not differ significantly between the groups (Table 3 and 4). (Page 11, line 193) However, the length of hospital stay was significantly longer in the TLV group (13.0 vs. 11.0 days), even though the two groups did not differ significantly in other major non-pulmonary complications. (Page 13, line 231) Third, certain technical details of the procedure (e.g. the number of the harvest lymph nodes along the RLN and details of the drainage procedure) were not collected. However, the incidence of RLN injury, which is more directly related to the occurrence of PPCs, was analyzed. (Page 15, line 281)

Table 4. Incidence of major non-pulmonary postoperative complications during hospitalization

	TLV Group (n=197)	OLV Group (n=73)	χ^2	P Value
Recurrent laryngeal nerve injury	5(4.4%)	1(1.6%)	-	>0.99
Anastomotic leak	25(12.7%)	7(8.7%)	0.490	0.49
Chylothorax	1(0.5%)	1(1.4%)	-	0.47
Wound infection	3(1.5%)	2(2.7%)	-	0.62

Data shown are numbers (%)

TLV, two-lung ventilation; OLV, one-lung ventilation

The outcomes presented differ from the previously reported studies and the authors discussed it could have been due to the lung isolation technique used: single lumen ventilation with bronchial blocker in contrast to the double-tube single lumen ventilation technique used mostly in the other studies. The lack of intraoperative ventilator parameters significantly limits the assessment and analysis of the results.

Reply 3: Thank you for stating your concern. We appreciate the reviewer's

consideration and agree that it is an important limitation. Regrettably, because of the retrospective design, some potentially crucial data, such as intraoperative ventilator parameters, could not be collected. The underlying mechanism for our unexpected results could not be addressed because of lack of data. The speculation of a possible link between ventilation strategy and PPCs was discussed based on several previous studies. To fully comprehend this issue, further investigations (particularly prospective randomized controlled trials) are warranted. We have addressed this limitation in the "Discussion" section and modified the "Conclusion" section (please see Page 15, line 277 and Page 16, line 289).

Changes in the text: Second, potentially crucial intraoperative data such as ventilator parameters (tidal volume, positive end-expiratory pressure, and peak airway pressure) were not included for analysis because of the retrospective design. These data may have an impact on PPCs. (Page 15, line 277) Compared with OLV with bronchial blockade, TLV with CO_2 pneumothorax did not reduce the incidence of early PPCs after MIE. Further investigation is needed to understand the underlying mechanism, particularly prospective randomized controlled trials. (Page 16, line 289)

Concluding that total lung ventilation prolonged the length of hospital stay without addressing all the other factors that could have played a role, may not be supported by the evidence presented.

Reply 4: Thank you for the comment. We agree with the reviewer that factors other than the intubation technique could have played a significant role in prolonging the length of hospital stay. For example, there is a significant correlation between the occurrence of other major postoperative complications and the length of hospital stay. We are very grateful to the reviewers for their previous suggestions to add content related to major non-pulmonary complications including RLN injury, anastomotic leak, wound infection, and chylothorax. We have added the relevant data to enrich the evidence, and further discussed this issue. In spite of this, we agree that it might be insufficient to conclude a relationship between the ventilation strategy and prolongation of hospital stay based on the present evidence. Therefore, we have removed this conclusion from our manuscript to be more precise. We have also added data to the "Results" section and modified text in the "Methods" and "Discussion" section of the revised manuscript (please see Page 9, line 148, Page 11, line 193, Page 13, line 231 and Page 16, line 289).

Changes in the text: The number of re-intubations and tracheotomies in the first 3 days, occurrence of major non-pulmonary postoperative complications including RLN injury, anastomotic leak, wound infection, and chylothorax, and length of hospital and ICU stays were also recorded. (Page 9, line 148) Incidence of other major PPCs and major non-pulmonary postoperative complications did not differ significantly between the groups (Tables 3 and 4). (Page 11, line 193) However, the length of hospital stay was significantly longer in the TLV group (13.0 vs. 11.0 days), even though the two groups did not differ significantly in other major non-pulmonary complications. (Page 13, line 231) Compared with OLV with bronchial blockade, TLV with CO_2 pneumothorax did not reduce the incidence of early PPCs after MIE. Further investigation is needed to

understand the underlying mechanism, particularly prospective randomized controlled trials. (Page 16, line 289)

Reviewer B

Dear Authors, I read with great interest your study. PPCs after esophagectomy represent a big challenge for all physicians involved in the Perioperative care for these patients. You found that TLV when compared to OLV did not significantly affect early PPCs incidence. I think this is important and try to shed light into a grey zone.
I hav some comments that I would like you to address before reconsider the paper for publication:

1) TITLE: I would suggest to include "early" before pulmonary complications as you investigated only the first 3 days after surgery and not all the patient's hospital stay;
Reply 1: Thank you for your suggestion. We have revised the Title of the manuscript as the reviewer suggested (please see Page 1, line 2).
Changes in the text: Comparison of early postoperative pulmonary complications between two-lung ventilation with artificial pneumothorax and one-lung ventilation with bronchial blockade in patients undergoing minimally invasive esophagectomy: A retrospective propensity score-matched cohort study (Page 1, line 2)

2) INTRODUCTION: ref 2--> this is a major point, please consider this article Tumori. 2021 Dec;107(6):525-535. doi: 10.1177/0300891620979358.
Reply 2: Thank you for this suggestion. We found this article very enlightening. We have added this new reference to better comprehend this issue (please see Page 11, line 312).
Changes in the text: Reference 2. Deana C, Vetrugno L, Stefani F, et al. Postoperative complications after minimally invasive esophagectomy in the prone position: any anesthesia-related factor? Tumori. 2021;107(6):525-535. (Page 11, line 312)

Lines-74-76: I think this is not the appropriate location for this sentence. Please, put it in the M&M section.
Reply 3: Thank you for your suggestion. We have moved this sentence to the “Methods” section as the reviewer advised (please see Page 10, line 159).
Changes in the text: Propensity score matching (PSM) was performed to reduce confounding bias by balancing group differences in patient characteristics and PPC risk factors. (Page 10, line 159)

3) METHODS: Anesthesia procedures --> Was neuromuscular block monitored? Moreover, at the end of surgery did you revert NMB with sugammadex or prostigmine for example? This is important since PORC may affect PPCs outcome.
Reply 4: Thank you for your suggestion. We agree with the reviewer that PORC is indeed an important factor that may affect PPCs. During the study period, neuromuscular blockade was not routinely monitored during surgery, however, it was

monitored in the post-anesthesia care unit during the recovery process, before extubation. At the end of surgery, neuromuscular blockade was routinely reversed using neostigmine. We have added this information in the "Methods" section of the revised manuscript (Please see Page 9, line 134).
Changes in the text: Neostigmine was routinely used for the reversal of neuromuscular blockade, and the recovery of neuromuscular blockade was monitored before extubation. (Page 9, line 134)

PEEP setting: I think this is an important missing value. As you know, intraoperative PEEP could induce lung derecruitment, atelectasis, atelectrauma and PPC. Please, add values if they are at your disposal.
Reply 5: Thank you for your advice. Regrettably, because of the retrospective design, intraoperative ventilator parameters such as PEEP could not be collected. We appreciate the reviewer's consideration and agree that this is an important limitation. This has now been addressed in the "Discussion" section of the revised manuscript (please see Page 15, line 277).
Changes in the text: Second, potentially crucial intraoperative data such as ventilator parameters (tidal volume, positive end-expiratory pressure, and peak airway pressure) were not included for analysis because of the retrospective design. (Page 15, line 277)

Tidal volume: was it calculated on predicted body weight or actual body weight?
Reply 6: Thank you for your question. The tidal volume was routinely calculated using predicted body weight. We have added this information in the "Methods" section of the revised manuscript (please see Page 8, line 122).
Changes in the text: Tidal volume during the thoracic phase of surgery was set at 4 to 6 mL/kg (calculated based on predicted body weight) in both groups; it was set at 6 mL/kg throughout the remainder of the procedure. (Page 8, line 122)

Statistical analysis is adequate.

RESULTS: I would reduce the content of lines 156-166. Please, remove the parameters for PSM analysis as you did already put in the Methods section.
Reply 7: Thank you for your suggestion. We have modified the "Results" section in accordance with the reviewer's advice in the revised manuscript (please see Page 11, line 175).
Changes in the text: This sentence is removed from the manuscript "Propensity scores were calculated to account for differences in age, BMI, pulmonary comorbidities, smoking status, intraoperative fluid intake, operative blood loss volume, and duration of surgery." (Page 11, line 175)

I cannot see in the tables the differences in terms of fluid intake, bloodless and surgery duration before after PSM. Please, add.
Reply 8: Thank you for your suggestion. We have modified Table 2 to include intraoperative data before PSM (please see Page 25, line 456).

Change in the text: In terms of intraoperative data, the groups significantly differed in terms of intraoperative fluid intake, operative blood loss volume, surgery duration, and anesthesia duration before PSM. After matching, intraoperative data were comparable between the groups except for anesthesia duration (P <0.01), which was defined as the time between entering and leaving the operating room (Table 2). (Page 25, line 456)

Table 2. Intraoperative data before and after propensity score matching

Variables	Before Matching (n=593)			After Matching (n=270)		
	TLV Group (n=513)	OLV Group (n=80)	P Value	TLV Group (n=197)	OLV Group (n=73)	P Value
Fluid intake, mL	2250.0(2000.0-2500.0)	2350.0(2000.0-2600.0)	0.04*	2300.0(2000.0-2625.0)	2300.0(2000.0-2600.0)	0.30
Blood loss, mL	100.0(50.0-100.0)	100.0(62.5-100.0)	0.04*	100.0(50.0-100.0)	100.0(100.0-100.0)	0.24
Urinary output, mL	300.0(200.0-500.0)	400.0(200.0-600.0)	0.10	350.0(200.0-500.0)	400.0(275.0-600.0)	0.15
Duration, min						
Surgery	201.0(185.0-227.0)	229.5(195.0-259.5)	<0.01*	225.4 ± 44.8	233.0 ± 45.9	0.22
Anesthesia	250.0(232.0-280.0)	300.0(250.0-327.0)	<0.01*	278.1± 50.1	297.0 ± 50.2	<0.01*

Data shown are medians (interquartile range) or means ± standard deviation

*significant

TLV, two-lung ventilation; OLV, one-lung ventilation

Do you have some data about inflammatory markers such as C-reactive protein, WBC or procalcitonin for the first 3 days?

Reply 9: Thank you for the comment. During the study period, inflammatory markers such as C-reactive and procalcitonin were not routinely monitored, whereas white blood cell count was monitored after surgery. However, WBC values were not recorded considering that pneumonia (the main outcome) was defined as "new or progressive radiological infiltrate and at least two of the following: body temperature > 38°C, leukocytosis or leukopenia, and purulent secretions". We only recorded whether the patient had leukocytosis or leukopenia. We appreciate the reviewer's consideration, however, we can not further discuss this issue because of a lack of data.

DISCUSSION: I would start with "The main findings of this study are..." and not with an important general statement as you did in line 178-179.

Reply 10: Thank you for your suggestion. We have removed this paragraph and modified the "Discussion" section as the reviewer advised (please see Page 12, line 212).

Changes in the text: The main finding of this study was that TLV with CO_2

pneumothorax did not reduce the incidence of early PPCs after MIE compared with OLV with bronchial blockade. (Page 12, line 212)

I suggest to reorganise your discussion as following: first, put the main findings of your study (so, TLV and OLV did not differ in terms of PPCs after esophagectomy). Then, compare your result with available literature.
Reply 11: Thank you for your suggestion. We have reorganized the "Discussion" section as suggested (please see Page 12, line 212).
Changes in the text: The main finding of this study was that TLV with CO_2 pneumothorax did not reduce the incidence of early PPCs after MIE compared with OLV with bronchial blockade. Among the 270 matched patients… (Page 12, line 212)

Please, remove from discussion the term "we believe...". Beliefs do not reconcile with a scientific paper. Probably it is better to say "we argue...".
Reply 12: Thank you for your suggestion. We have revised our manuscript accordingly (please see Page 15, line 263).
Changes in the text: Therefore, we argue that airway injury is less of an issue in patients intubated using a bronchial blocker, especially in the hands of skilled anesthesiologists. (Page 15, line 263)

I cannot find how frequently Bronchial blocker displaced during surgery. Do you have this info? If yes, please add...In this light, see this article which could be helpful for the discussion-->J Thorac Dis. 2019 Aug;11(8):3257-3269. doi: 10.21037/jtd.2019.08.57.
Reply 13: Thank you for your suggestion. Regrettably, we were not able to collect data on whether there was displacement of bronchial blocker during surgery because of the study's retrospective design. This has now been addressed in the "Discussion" section of the revised manuscript. We appreciate the reviewer's suggestion, and we have found this article enlightening. This reference is included to enrich evidence in the "Discussion" section of the revised manuscript (please see Page 15, line 271).
Changes in the text: In addition, prolonged anesthesia duration may also be related to a higher malposition rate of bronchial blocker (44). Because of the study's retrospective design, we could not collect data on this issue. (Page 15, line 271)

To support some your statements in the discussion, I suggest to include, if you agree, this recent review which covers all the aspects you evaluated: J Thorac Dis. 2021 Oct;13(10):6037-6051. doi: 10.21037/jtd-21-940.
Reply 14: Thank you for your advice on this review article. We have found it very intriguing and have included it in our manuscript to support some of the current evidence (please see Page 6, line 75, Page 6, line 78 and Page 13, line 234).
Changes in the text: Better lung protection is also expected with MIE performed in the prone position since OLV, a known risk factor for lung damage, can be avoided (12). (Page 6, line 75) OLV during MIE can be performed using either a double double-lumen endotracheal tube (DLET) or a bronchial blocker (12, 14, 15). (Page 6, line 78) Our results contrast with the theory that OLV acts as a risk factor for lung damage, and may

cause more lung damage because of higher lung volume and ventilation pressure in the ventilated lung and atelectasis and ischemia–reperfusion injury in the collapsed lung (12,38). (Page 13, line 234)

Finally, I suggest an English revision because some sentences need more fluency.
Reply 15: Thank you for your suggestion. The manuscript has been re-edited by a professional English editing company.