

Peer Review File

Article information: <https://dx.doi.org/10.21037/jtd-23-822>

Reviewer A

To summarize the aim of the study: in thoracic surgery patients requiring ICU respiratory support for PALI, the authors investigated the causes and consequences of "non-surgical lung injury."

This was a retrospective, observational study.

The paper is well written and well structured. The length is optimal. Tables and the figure are informative. The paper is interesting and the subject is relevant.

Interestingly and surprisingly, patient with ipsilateral lung injury have a better outcome.

I have some concerns about the study in its present form.

Reply: Thank you very much for your positive comments and constructive suggestions. All changes to the manuscript have been highlighted or indicated by using tracked changes. And we have taken all these comments and suggestions into account as follows:

Title: OK

Abstract: OK

Introduction:

Comment 1: interest of EIT in this study line 115 page 6 is not adequately stated.

Reply 1: Thanks for your comment, which is highly appreciated. We have added the sentence that "Electrical impedance tomography (EIT) is an emerging noninvasive radiation-free technique that enables dynamic bedside monitoring of functional ventilation in lung volume changes. It provides images based on the tissue electrical conductivity of the chest and is able to accurately assess regional ventilation distribution."

Changes in the text: P5 Line 127-131.

Comment 2: Reading the introduction, we don't know why authors stated in their hypothesis that "In the present study, we aimed to test the hypothesis that lung injury on the non-surgical side following lung cancer surgery is associated with a high mortality rate

Reply 2: Thanks for your kind suggestion, and we have changed the sentence as "In the present study, we aimed to assess the prognosis of PALI following lung cancer surgery on different injury sides."

Changes in the text: P6 Line133-136.

Methods

-Study design OK

Comment 3: Participants: Line 128: « Patients requiring respiratory support with for severe hypoxemia after thoracic surgery for lung resection... », may be better?

Reply 3: We appreciate it very much for this good suggestion, and we have done it according to your idea.

Changes in the text: P6 Line 148-149.

Comment 4: Misspelling line 148 RRALE and not RREAL.

Reply 4: We are very sorry for our mistake and it is rectified.

Changes in the text: P7 Line 174.

Comment 5: EIT monitoring:

This part is the most difficult to read.

Please specify when the measurements were taken.

How the IM is given by the pulmovista

It's hard to understand what normalization of IM means (line 187)?

This whole section is difficult to understand. Perhaps it would be best to provide a more detailed description in the ESM.

Reply 5: Thanks for your kind suggestions, which are valuable in improving the accuracy of the manuscript. We are very sorry for our negligence of the explanation. We have added the sentence that “Data were collected on the day the patient received respiratory support, ...” to the study protocol (Line 210). And in Line 215-217, we changed the sentences as that “Differences in tidal ventilation (TV) between the left and right lungs (or the surgical-side and nonsurgical-side lungs) were calculated. ;

$$TV_R = TV_{ROI1} + TV_{ROI3} \quad TV_L = TV_{ROI2} + TV_{ROI4}.$$

Thanks to your suggestions, we have improved these concepts in the supplement section.

Changes in the text: P8-9 Line 210-224; Supplementary Figure 2.

-Data collection: OK

-Outcomes: OK

Comment 6: Statistical analysis: In my opinion, according to the number of patients included, only non-parametric tests can be used.

Reply 6: We appreciate it very much for this good suggestion, and we have done it according to your ideas.

Changes in the text: P10 Line 245-248.

Results

Globally, the number of included of patients is small.

Comment 7: Data were given in tables, so text can be reduced.

table 1: characteristics of included patients. Surgical characteristics are lacking.

Classification of types of surgery: lobectomy, segmentectomy, bilobectomy

Classification of surgical approaches: Thoracotomy, VATS, Robotic surgery?

Reply 7: Thanks very much for your comment, which is highly appreciated. We added more baseline data in Table 1.

Changes in the text: Table 1

-Table 2: outcomes OK

- Fig 1: OK

-Fig 2: KM curve Ok

-Fig 3: OK good

Discussion

Comment 8: The link with the PSILI index is not as obvious. The authors are too quick to attribute PALI to PSILI.

Reply 8: Thanks for your kind suggestions. The discussions section has been significantly amended. We have changed the sentence as “The combined chest X-ray or CT films with EIT images showed that some patients with lung injury on the nonsurgical side had strong ventilation on the injured side, and radiological signs showed unilateral diffuse infiltrates on the nonsurgical lung (Figure 3). Based on the good ventilation at the deep injured lung, we speculated that patient self-inflicted lung injury (P-SILI) might be one of the reasons for this type of PALI after lung cancer surgery. Several studies have demonstrated that vigorous spontaneous breathing exacerbates preexisting lung injury. However, the lack of monitoring of ventilator variables in non-intubated patients has resulted in limited evidence for P-SILI. Overall, diagnosis and management of P-SILI remains controversial. Excessive transpulmonary energy delivery and uneven ventilation distribution are among the multiple mechanisms contributing to P-SILI.”

Changes in the text: P14 Line 356-367.

Comment 9: Limitations: the small number of patients is the real limitation of the study.

Reply 9: We agree with the reviewer's point of view, and we have changed the sentence as “First, as the incidence of PALI after lung cancer surgery has been greatly reduced in recent years, the number of patients enrolled in this study was too small for further statistical analysis, which had a certain impact on the results. We were unable to perform further risk factor analysis.”

Changes in the text: P15 Line 381-384.

ESM1: very clear, good

Comment 10: ESM 2: can be improved to allow reader to understand EIT. It seems to be the part c of fig 3

Reply 10: We are extremely grateful for the positive comments and constructive suggestions. We have added the sentences that “EIT measurements were conducted using the Dräger PulmoVista 500 device (Lübeck, Germany) in accordance with the international consensus statement. Tidal impedance variation was averaged from each minute and analyzed in four regions of interest (ROI), defined as quadrants, which has been shown to be correlated with tidal volume (TV). The differences in TV between the left and right lungs, or the surgical-side and nonsurgical-side lungs, were calculated. The sum of the TV signals from all pixels representing the left and right hemithorax was separately determined. The TV signals within each hemithorax were quantified as a percentage of the total TV signals from both lungs. Two coefficients were then calculated by taking the root mean square value of the cyclic components mentioned above for each VT signal. These coefficients were labeled as TV_L and TV_R , representing tidal ventilation in the left and right lung respectively. The coefficients TV_S and TV_{NS} represented tidal ventilation within the surgical side and nonsurgical side of the lungs respectively.”

Changes in the text: Supplementary Figure 2.

Reviewer B

This manuscript describes a single center retrospective study of post-operative lung injury and mortality after unilateral lung resection for cancer. The authors identified a group of 16 patients who had been treated for hypoxemia in a surgical intensive care unit following thoracic surgery. They grouped the patients based on the ratio of radiologic assessments of lung edema scores between each lung; 9 had higher edema scores in their non-surgical lung and 7 had higher edema scores in their surgical lung. Their primary outcome was mortality at 90 days with secondary outcomes of 28-day in-hospital mortality, ICU and hospital length of stay. They examined electrical

impedance tomography parameters of ventilation in a subset of 9 patients. They found that 67% patients with high edema scores in their non-surgical lung (6 / 9) died within 90 days of surgery and no patients with higher edema scores in the surgical lung died (0 / 7). They found differences among secondary outcomes. They attribute the mortality to a patient self-inflicted lung injury, an interesting and controversial topic. Thanks to reviewer: We would like to emphasize how grateful we are for your constructive and useful comments. We have studied comments carefully and have made corrections that we hope you will agree with. All changes to the manuscript have been highlighted or indicated by using tracked changes.

There are numerous major problems with this manuscript and the study:

Comment 1: First, it is not adequately powered to make essentially any claims. No clear statistical plan is described (lots of tests are listed, but not linked to the discrete variable of interest – i.e. what was the test used for the primary outcome?).

Reply 1: Thanks for your constructive suggestion. Due to the limited number of cases, we employed exclusively non-parametric tests, utilizing the Mann-Whitney test for continuous variables and the Fisher exact test for rates. The primary outcome was assessed using Fisher's precision test.

Changes in the text: P10 Line 245-248..

Comment 2: No sample size calculation is presented.

Reply 2: Thanks for your kind suggestion. Given that our study was conducted at a single center with a relatively low incidence of severe PALI, fewer eligible patients were enrolled. Owing to the absence of a comprehensive database, we could only review data from the previous two years in our HIS system and respiratory record list prior to 2019. Consequently, sample size calculation based on these data could not be included in this study report. We are currently conducting further investigations that will include patients after 2021 when clinical data may be more extensive and sample sizes larger.

Comment 3: Also, a six-month outcome is mentioned several times, but never listed as a secondary outcome.

Reply 3: We sincerely apologize for our oversight, and have incorporated secondary outcomes into the analysis of 6-month survival rates.

Changes in the text: P9 Line 237-239.

Comment 4: Also, half of this study was conducted during the COVID pandemic. Do the authors have any data on coronavirus infection in their subjects?

Reply 4: No COVID-19 patients were included in this study.

Comment 5: Second, the study is described as a retrospective study, but numerous references to ‘enrollment’ and it is stated that ‘written informed consent was obtained from all participants before enrollment’. Can the authors please clarify the nature of the study? Was it a registry study where all ICU patients were included and they have selected a subgroup from the registry? Or do all patients receive all the tests described in the methods?

Reply 5: Thanks for your kind suggestions. The study was indeed a retrospective study. All patients or their legal representatives had signed an informed consent for the collection of clinical information upon hospital admission. Additionally, all participants or their legal representatives were contacted through telephone calls and signed informed consent forms for this study. It wasn't a registry study where all ICU patients were included. The tests mentioned in the Methods section are part of our regular work routine, and we follow these routines for the perioperative management of all patients.

Changes in the text: P6 Line 141-145.

Comment 6: Third, the timing of the x-rays used to make the determinations for the groupings are not clear. If this is defined as a delayed phenomenon, can the authors provide RALE scores showing the delayed development of edema?

Reply 6: The timing of the x-ray used to make the determinations for the groupings was the day the patient underwent respiratory support (P8 Line 196-197). Prior to ICU admission, some patients did not undergo any chest radiograph or only received one postoperative chest radiograph. Although the availability of chest radiographs in the ICU is relatively comprehensive, time constraints are currently limit our work. If necessary, please allow us extra time to provide additional imaging.

Comment 7: Why was a ratio used to group the patients as opposed to simply using the raw RALE scores?

Reply 7: There was no difference in total RALE score between the two groups if they were grouped according to raw scores. However, we observed clinically that the prognosis of nonsurgical side lung injury was poorer, which is why we grouped them according to RALE score ratios.

Comment 8: The authors claim that the ratio they are using indicates “severe lung injury” on a given side, but that is not necessarily true. It is important to remember that edema may be evidence of more than “lung injury”.

Reply 8: Thank you very much for this helpful comment. The availability of CT scans is limited, whereas chest radiography is accessible to all individuals. A review of the literature has shown that the RALE score is a superior method of assessing pulmonary edema. No alternative approach to objectively differentiate the extent of bilateral injury has been identified. The disadvantages of RALE score had been detailed in Limitations (P15 Line390-397).

Comment 9: Further, the ratio can only tell you about the direction and magnitude of the difference between the two sides. Both lungs could have normal RALE scores (i. e. with scant evidence of edema) but have a ratio above or below 1.

Reply 9: The possibility of having both normal postoperative RALE scores and severe hypoxia is quite low, particularly in our specific case. There may be varying degrees

of exudation or atelectasis on the surgical side, making it highly unlikely for the score of 0. It should be noted that pulmonary embolism does not account for the occurrence of hypoxia without pulmonary edema in our patients.

Comment 10: The actual RALE score for each lung is more informative. Also, using the RALE scoring system, some subjects could have a score of 0. How would one interpret the ratio if the non-surgical side was scored as 0?

Reply 10: The RALE scores of the surgical and nonsurgical sides were presented in Table 1. None of our patients exhibited a score of zero on either side. We just distinguished which side of the lung is more severely injured with the help of the RALE score, either by a ratio or by the difference between the two sides being greater than, equal to, or less than zero.

Comment 11: Finally, the manuscript tries to achieve too many goals. With 16 subjects it is difficult to determine multiple outcomes or differences. As such, introducing two new variables derived from electrical impedance tomography to describe 9 of these subjects is not reasonable. These approaches need validation against other methods. Plus, in this reviewer's opinion, the substitution of these EIT parameters into a claimed approximation of mechanical power is greatly flawed. In this respect, the discussion contains too many speculative statements without data to support them.

Reply 11: As you mentioned, we also acknowledge that the sample size of 16 patients is insufficient to determine multiple outcomes or differences. Moreover, the number of EITs was even smaller, rendering it impossible to verify a new parameter with these data. Therefore, there was no empirical support for replacing mechanical power with EIT parameters - a concept that was fundamentally flawed. Consequently, we have removed this section from our study. Nevertheless, as the use of EIT continues to increase in clinical practice, we remain hopeful that future research will identify an objective parameter through non-invasive means that can detect early-stage damage caused by excessive spontaneous breathing in patients.

Changes in the text: P8-9 Line 213-224.

Comment 12: The manuscript needs to address the discrete outcomes clearly, refrain from using unvalidated analyses, and remain objective throughout the discussion in order to teach us something about postoperative lung injury.

Reply 12: Due to the limited sample size, the majority of continuous variables did not adhere to a normal distribution. Consequently, we conducted a revised statistical analysis employing non-parametric tests exclusively in order to enhance test efficiency. We followed your suggestion, and significantly amended the discussion.

Changes in the text: P10 Line 245-248; P13-14 Line 333-379.