

## Peer Review File

Article information: <https://dx.doi.org/10.21037/jtd-23-1539>

### Reviewer A

Dr. Yamanaka and his colleague submitted the manuscript regarding the risk assessment for postoperative home oxygen therapy. The efforts to improve the post operative outcomes should be admired.

#### Comment 1:

What is the criteria in your department to consider anatomical resection or sublobar resection. There must be the patients who was considered non-surgical candidates during the study periods. Thus, this study was performed on the pre-selected patients and the authors should elaborate the criteria to be a surgical candidate.

#### Reply 1:

**Thank you for your comment. Although we chose anatomical resection for the lung cancer patient, we selected sublobar resection for elderly patients, those with many comorbidities, or poor pulmonary function. We added the following description to the manuscript.**

Changes in the text:

(Page 7, lines 14-16) Lobectomy with curative intention was performed, except for patients with low pulmonary function or severe comorbidity, who underwent sublobar resection.

#### Comment 2:

The cutoff values of 80% for %FEV1 and ppo%FEV1 may not be appropriate. As you know, ppo%FEV1 higher than 40% is appropriate to be surgical candidate. GOLD criteria for COPD defines moderate (Gold 2) as %FEV1 50-80% and severe (Gold 3) as %FEV1 30-50%. It might be reasonable to have 50% as cutoff for %FEV1?

#### Reply 2:

**Thank you for bringing this point to our attention.**

**It was difficult to determine the cutoff value for ppoFEV1. Initially, we considered setting the cutoff value at 50%, but there were many cases with ppoFEV1 >50% that was HOT, and only 5 cases with ppoFEV1 <50% that were HOT. In this study, the cutoff value was determined based on the point at which postoperative COPD was calculated to be moderate.**

Change in text: none

#### Comment 3:

What is the benefit of creating a regression model calculating the risk of HOT with variables including postoperative outcomes (postoperative complications). We can see the significance of impact of postoperative complications from multivariable analysis. I feel this regression analysis makes the manuscript unnecessarily complicated.

#### Reply 3:

**Thank you for your comment. We believe that we could gain a deep understanding of the risk of HOT by using regression analysis and the formula.**

Change in text: none

#### **Reviewer B**

This paper addresses an interesting topic. I think that the authors nicely laid out their objectives and methodology, and the presentation of their results, in general, is quite clear.

One criticism of this paper is that in many ways, the results are a « foregone conclusion », i.e. one would expect patients with more severe pulmonary disease and postoperative respiratory complications to be more at risk for postoperative home oxygen therapy. So the real question becomes, how does this study impact clinical care. Certainly, as the authors point out, it does allow a more informed risk vs benefit discussion with the patient. But then there are other important questions as well.

Comment 4:

What is the exact outcome that the authors were looking at : was it home oxygen therapy AT DISCHARGE (that may be only temporary, until full respiratory recovery)? Or rather the requirement for prolonged, or « permanent » home oxygen therapy (and how was this defined)? Oxygen supplementation would typically be weaned before discharge, and so what were the authors' criteria for deciding that weaning was not successful and that home oxygen therapy would be necessary?

I think that the discussion can be a bit more elaborate.

**Reply 4:**

**Thank you for bringing this point to our attention. We apologize that the definition of the outcome of this study was not written accurately.**

**In this study, most patients were on respiratory rehabilitation for at least 1 week postoperatively. We defined cases in which HOT was necessary due to inadequate oxygenation as cases in which HOT was necessary after the rehabilitation.**

Change in text:

(Page 8, line 7-10) Patients received respiratory rehabilitation for at least one week postoperatively. Despite the rehabilitation, patients with percutaneous oxygen saturation (SpO<sub>2</sub>) <90% at rest or on exertion were considered for HOT at discharge.

Comment 5:

I wonder how acceptable of an outcome is home oxygen therapy? Do the authors consider it an acceptable consequence of surgical resection if the alternative is sub-optimal cancer treatment, or is a significant possibility of postoperative oxygen therapy something that should invalidate surgical treatment? Although most would probably answer the latter, this does remain an open question.

**Reply 5: Thank you for your comment.**

**In previous report, patients who start HOT decrease their quality of life, which is a problem. Whether surgery should be avoided and other treatment options chosen if the risk of HOT is high is debatable. However, at the least, patients should be informed of multiple treatment options and their complications, and their willingness should be confirmed.**

**We added the following sentences and reference.**

Change in text: (Page 15, lines 3-7) In a previous report, patients who started HOT decreased their quality of life, which was a problem (21). It is still under argument that whether or not surgery should be avoided and other treatment options chosen if the HOT high-risk patient. However, at the least, we should esteem patient willingness and inform multiple treatment options and their complications to the patient.

Jacobs SS, Krishnan JA, Lederer DJ, et al. Home oxygen therapy for adults with chronic lung disease. An official American thoracic society clinical practice guideline. *Am J Respir Crit Care Med* 2020;202:e121-e141.

Comment 6:

The authors briefly mention the possibility that (presumably preoperative?) pulmonary rehabilitation may be useful to reduce the need for postoperative oxygen therapy. I think that the authors could discuss prehabilitation modalities a bit more and provide some references that the reader can use.

**Reply 6: Thank you for your comments.**

**We added references on preoperative rehabilitation. In the references, preoperative rehabilitation included respiratory muscle training, aerobic exercise, and lower extremity endurance training, decreased postoperative respiratory complications, and decreased hospital stay.**

Change in text: (Page 13, lines 16-18) Previous studies indicated preoperative rehabilitation decreased postoperative pulmonary complications and hospital stay. The rehabilitation included muscle training, aerobic exercise and lower extremity endurance training, which continued for roughly two to four weeks, at least a week.

In addition, we added following three references.

Morano MT, Araujo AS, Nascimento FB, et al. Preoperative pulmonary rehabilitation versus chest physical therapy in patients undergoing lung cancer resection: a pilot randomized controlled trial. *Arch Phys Med Rehabil* 2013;94:53-8.

Lai Y, Wang X, Zhou K, et al. Impact of one-week preoperative physical training on clinical outcomes of surgical lung cancer patients with limited lung function: a randomized trial. *Ann Transl Med* 2019;7:544.

Gravier FE, Smondack P, Prieur G, et al. Effects of exercised training in people with non-small cell lung cancer before lung resection: a systematic review and meta-analysis. *Thorax* 2022;77:486-96.

Comment 7:

It is also reasonable to surmise that an effective ERAS or similar postoperative recovery pathway could be equally beneficial; what do the authors think? Did they change their practice at all as a result of their study?

**Reply 7: Thank you for your comments. In past studies, ERAS and similar postoperative recovery pathways were to be effective in preventing postoperative pulmonary complications. These are likely to be patients without HOT after surgery. In our institution, we are working on ERAS to get the results of this study.**

Change in text: (Page 14, lines 5-11) In addition, a recent study showed that patients with lung cancer in the enhanced recovery after surgery (ERAS) program patients had fewer postoperative pulmonary complications. Perioperative management, including such as ERAS program, rather than preoperative rehabilitation only, might be important to reduce respiratory complications. Adequate perioperative management would be to play a key role in preventing postoperative HOT.

Comment 8:

I agree with the authors that preventing air leakage is not straightforward. However, there are various techniques that aim to minimize air leakage, whether advanced stapling systems, buttresses, sealants, digital drainage systems, and so forth; in addition, a handful of groups are investigating lung biomechanics with a view to addressing exactly this problem. So there is indeed something to say about air leaks.

**Reply 8: Thank you for bringing this point to our attention.**

**As you say, there are various ways to reduce postoperative air leakage, such as fibrin glue, a stapler with a PGA sheet, or postoperative drain management using water seals and digital drainage systems. The use of these devices may reduce postoperative air leakage and HOT. We added the following script.**

Change in text: (Page14, line14-18) Various techniques that aim to minimize postoperative air leakage were reported, such as fibrin glue spread during operation, using a stapler with the polyglycolic acid sheet, or postoperative drain management using water seals and digital drainage systems. The combination usage of these devices/techniques potentially reduces postoperative air leakage and, as a result of HOT.

Comment 9:

Obviously, as the authors stated, postoperative pulmonary complications and prolonged air leaks can be both a result of poor lung function (that in itself contributes to the risk of postoperative oxygen therapy), as well as direct contributing factors themselves. This should stand out in the text.

**Reply 9: Thank you for your comments. What you pointed out was a very important aspect of this study, and so we highlighted it in the manuscript.**

Change in text: (Page 13, line 11-15) While pulmonary comorbidities and postoperative pulmonary complications were both risk factors for HOT, pulmonary comorbidities were directly a risk factor for pulmonary complications. Therefore, postoperative management of lung cancer patients with pulmonary comorbidities should be very cautious.

Comment 10:

In the authors' practice, how do these various considerations affect the extent of parenchymal resection? In lines 102-108 I am not quite sure that I completely understood the relationship between the extent of resection, pre and postoperative predicted FEV1, and the risk for postoperative oxygen requirement. Could the authors clarify this section, or rephrase? (see also section below « miscellaneous comments »).

**Reply 10: Thank you for your comment. We changed the text for clarity.**

Change in text: (Page 10, line 1-4) More patients with low pulmonary function were included in the HOT group. Nevertheless, there were no difference in the choice of procedure between the two groups, and postoperative lung function was predicted to be lower in the HOT group than in the non-HOT group.

In conclusion, I think this is a good study overall. Addressing the above comments may help improve the paper.

Miscellaneous comments:

Comment 11

Line 57 : The cited studies supporting that HOT does not improve survival in patients « with other chronic lung diseases » are outdated (1980 and 1981 respectively). Please add a more recent reference.

Line 87 : Could the authors add a reference for the anatomy of pulmonary subsegments.

Lines 88-89 : What is meant by « partial resection »?

**Reply 11: Thank you for your bringing this point to our attention.**

**We added the following references. We used the term of “Partial resection” as “wedge resection”. Partial resection in manuscript and table corrected to wedge resection.**

Jacobs SS, Krishnan JA, Lederer DJ, et al. Home oxygen therapy for adults with chronic lung disease. An official American thoracic society clinical practice guideline. Am J Respir Crit Care Med 2020;202:e121-e141.

Nakahara K, Ohno K, Hashimoto J, et al. Prediction of postoperative respiratory failure in patients undergoing lung resection for lung cancer. Ann Thorac Surg 1988;46:549-52

Comment 12:

I cannot comment on the derivation of an equation from the data; in my opinion a statistician is required for validation.

I don't understand the correlation analyses between preoperative FEV1 and predicted FEV1; the predicted value is calculated from the preop value; and so the relationship between the two is therefore a mathematical function, by definition.

**Reply 12: No complex statistical analysis was performed, and we considered that the statistician's intervention was not necessary for these analyses.**

**As you pointed out, the relationship between the preoperative FEV1 and ppoFEV1 was a mathematical function. We removed the correlation analysis and supplemental figure 1 as it was misleading.**

Change in text: (Page 10, line 8-13) Ppo%FEV1 was a more substantial reflection of postoperative lung function than preoperative %FEV1 since ppoFEV1 also calculated the lung loss due to the surgery.

The supplemental figure was deleted.

Comment 13:

The cutoff value for FEV1 used in the statistical analyses is 80%; in fact this is a definition of COPD; most patients we operate on have a FEV1 of below 80%. So I am having trouble understanding how this is helpful in making any meaningful predictions about the requirement for postoperative oxygen therapy.

**Reply 13: Thank you for your comments.**

**As you commented, FEV1 80% is the borderline between moderate and mild COPD in the GOLD classification. Although %FEV1 was included in the comparison items, we thought that only %FEV1 was not sufficient as a measure of postoperative lung function, so we added a surgical component to the ppo%FEV1 item.**

Change in text. none

### Reviewer C

I reviewed the manuscript entitled “What are the risk factors for postoperative home oxygen therapy in patients with lung cancer?” This report contained interesting contents because home oxygen therapy is required for some patients after surgery for lung cancer, and it is very important to assess the risk factors preoperatively, however, it has some limitations.

Major comments-

Comment 14:

Although I agreed with the results that the combined pulmonary diseases and the development of postoperative pulmonary complication were risk factors after the surgery for lung cancer, I thought that the results would be expected from previous reports. Furthermore, I felt that the postoperative complications were postoperative factors and could not be assessed preoperatively. Therefore, I wondered if it was meaningful to assess the postoperative complications for elucidating the risk factors for home oxygen therapy after the surgery.

**Reply 14: Thank you for your comment.**

**As you say, this study also included postoperative factors for HOT. Although postoperative complications were not a preoperative assessment item, we thought that adding postoperative factors would help focus attention on postoperative management. It provided a deeper understanding of patients at risk for HOT.**

Change in text. none

Comment 15:

As for analyzing the risk factors for home oxygen therapy after the surgery, all patients who underwent lung resection were indicated in this study. It is better to more strictly analyze the patients with low respiratory functions because while we aren't worried about introducing

home oxygen therapy for the patients with normal pulmonary function, we have to consider home oxygen therapy to the patients with low pulmonary function. Actually, in the stage of preoperative informed consent, we sometimes experience some cases that reject the surgical approach as lung cancer treatment owing to the possibility of the introduction of home oxygen therapy after surgery.

**Reply 15: Thank you for your comment. As you commented, most patients with HOT had low pulmonary function. On the other hand, 16% of patients who underwent postoperative HOT had normal preoperative respiratory function. So, we analyzed all patients in this study.**

Change in text: none

Comment 16: The proposed formula was very interesting, and it would be beneficial if the formula was effectively used for lung cancer strategy. I hope that the authors will report the usefulness of the formula if they have already assessed them preoperatively.

**Reply 16: Thank you for your comment. We began to use this formula and had a few patients who were expected to need HOT. However, we have not yet gathered enough data to demonstrate its usefulness.**

Change in text: none

Minor comments

Comment 17:

I think that DLCO is an important factor while assessing the risk factor of home oxygen therapy after surgery. Even if the authors didn't test the DLCO in all patients, I expected that DLCO were tested preoperatively in some patients. These data should be shown.

**Reply 17: Thank you for your comment. We would like to show you the data for DLCO, but unfortunately, the data approved by the Ethics Committee did not contain DLCO, and we were unable to provide you with the data.**

Change in text: none

Comment 18:

Formatting for multiple authors was insufficient in some sections. Please check your manuscript before submission. I think that it is obvious that cut-and-paste was used for many authors.

**Reply 18: Thank you for your comment, and sorry for the inappropriate description.**

Change in text: Provision of study materials or patients: T Yamanaka, Y Sakairi, Y Sata, T Toyoda, T Ito, T Inage, K Tanaka, H Suzuki, and Y Matsui

Comment 19:

I thought that the rate of postoperative pneumonia was high. I think that one of the reasons would depend on the smoking status. How long does the preoperative duration of cessation of smoking set into the author's institution? Furthermore, do the authors introduce the pre- and post-respiratory rehabilitation or ERAS to avoid postoperative pneumonia? It is recommended

that the authors add some comments regarding the efforts to avoid pulmonary complications in the discussion section.

**Reply 19:**

**Thank you for your comment. We required patients to smoke cessation for 4 weeks before surgery, with a minimum of 2 weeks. During the period of this study, respiratory rehabilitation was only provided post-operatively, but interventions are now provided preoperatively. Comments 6 and 7 also pointed out the perioperative respiratory rehabilitation and ERAS, and we added sentences to the manuscript.**

Change in text: Please see “change in text” in comments 6 and 7.