Peer review file

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Reviewer A

Comment 1: The most important point is that I struggle to understand the clinical target of the study. How authors think this study might help our everyday clinical life? I think introduction should be modified in this perspective.

Reply 1: We appreciate and agree with the reviewer's comment. We thought that the measurement of respiratory impedance by MostGraph was possible even in the early postoperative period. However, it is unclear how the measurement of respiratory impedance changes before and after lung surgery and whether the measurement of respiratory impedance itself is meaningful. This study aimed to clarify this change in respiratory impedance and to determine the clinical relevance of the respiratory impedance measurement. We intended to earlier identify the factors predicting postoperative complications according to changes in respiratory impedance during the perioperative period.

Changes in the text: We have modified the 1st, 3rd, and 4th paragraphs in the "Introduction" section as follows:

"Pulmonary function declines after lung surgery. However, this is difficult to assess with spirometry because it requires the patient's maximum exhalation effort, which is hindered early after surgery due to pain, cough, and sputum." (see Page 5, lines 76-78)

"MostGraph 02 (Chest M.I., INC, Tokyo, Japan) can measure Rrs and Xrs in a moment during tidal breathing and may be performed even early after surgery. However, it is unclear how the measurement of respiratory impedance changes before and after lung surgery and whether the measurement of respiratory impedance itself is meaningful for postoperative care. This study aimed to clarify respiratory impedance changes in lobectomy and determine the clinical relevance of this measurement. We hoped that if adverse events such as respiratory failure and pneumonia could be predicted and detected early after surgery by assessing respiratory impedance, it would be possible to prevent exacerbations and provide early intervention." (see Page 6, lines 99-107)

“Therefore, in this study, we revealed changes in respiratory impedance during the perioperative period of lobectomy and investigated the correlation of respiratory impedance in the pre- and postoperative periods with various clinical factors, such as physical characteristics, comorbidities, length of surgery, intraoperative blood loss, postoperative complications, and subjective symptoms.” (See Page 6, lines 108-112)

Comment 2: Concurrently, conclusion should stress a take home message, rather than limitations of the study.

Reply 2: Indeed, per the reviewer’s comment, what we wanted to convey was a take-home message, not a limitation.

Changes in the text: We have modified the last paragraph in the "Conclusions" section as follows:

“In conclusion, this study clarified changes in respiratory impedance during the perioperative period of radical lobectomy for lung cancer and the correlation between this measurement and other clinical factors. Respiratory impedance parameters were different postoperatively, but their measurement did not predict or diagnose early postoperative complications. However, some respiratory impedance parameters were correlated with clinical factors associated with the clinical course. In particular, Fres on POD1 was correlated with hypoxia, which may be an important predictor of early detection of hypoxemia and acute exacerbation in patients with IP. There are many confounding factors, and the exact clinical factor associated with a specific respiratory impedance parameter remains unclear. Eliminating confounders is difficult; however, the postoperative course can be further enhanced by analyzing more cases and comparing changes in respiratory impedance over a longer period using conventional spirometry, combined with anatomical evaluations by CT. Further, because MostGraph could measure respiratory impedance even in the early postoperative period, we expect that MostGraph can be used in the future for evaluating respiratory function in the early postoperative period instead of spirometry”. (See Pages 16 and 17, lines 359-373)

Comment 3: The number of patients enrolled in the study is quite small. Why did authors exclude non-oncological patients? Why did authors include a patient who had no POD 7 evaluation, but they exclude patients who had late postoperative reoperation?

Reply 3: As the reviewer pointed out, the number of registered patients in this study

was small. More patients refused to participate in the study than we expected. Also, at our hospital, we perform lobectomy only in patients with primary lung cancer. In this study, we aimed at targeting only lobectomy patients.

Since the total number of patients was small, we included a patient without POD7 evaluation, but she was out of the protocol, so we excluded her and performed the analysis again. The patient with reoperation was excluded from the study because she declined to participate in the study after surgery.

Changes in the text: We have modified the second sentence of the first paragraph in the "Results" section as follows:

"From a total of 11 patients without lung cancer who were diagnosed with benign illnesses by intraoperative rapid pathological examination, one declined to participate in the study after surgery, and one was discharged on POD6. These patients were consequently excluded from the study." (See Page 9, lines 193-196)

We have also corrected the changes in the numbers accordingly.

Comment 4: Results: if no patients received neoadjuvant therapy, it can be omitted from the body of the results.

Reply 4: We thank the reviewer for pointing out the mistake. This has been corrected.

Changes in the text: We have deleted the irrelevant part from the "Results" section.

Comment 5: Complication rate is quite high, but I guess authors include all kind of complications. It would be useful to add the number of patients in each CTCAE group.

Reply 5: Indeed, as pointed out by the reviewer, we included all complications, even minor ones. We have added information on CTCAE grade 2 and 3 postoperative complications.

Changes in the text: We have added the following to the 4th paragraph in the "Results" section:

"Postoperative complications of CTCAE grade 2 and 3 were observed in 11 patients (27.3%) and 1 (2.3%) patient, respectively. Among these, CTCAE grade 2 or higher respiratory complications was observed in 8 patients (18.2%), as follows: pneumonia in 3 patients (6.8%), hypoxemia in 4 (9.1%), atelectasis requiring bronchoscopy in 1 (2.3%), and prolonged pulmonary fistula in 1 (2.3%) patient". (See Page 10, lines 214-218)

Comment 6: Why did authors not compare respiratory impedence of POD 1 and POD 7?

Reply 6: Initially, we wanted to examine the changes in respiratory impedance from the preoperative time and identify the factors that affect the clinical course; therefore, we omitted the comparison of changes in POD1 and POD7. However, as the reviewers pointed out, changes in POD1 and POD7 must be investigated, and we have added a description on it.

Changes in the text: We have added the following to the "Perioperative changes in respiratory impedance" subsection of the "Results" section and "Figure 1":

"From POD1 to POD7, only the mean value of X5 improved significantly ($p = 0.018$)". (See Page 11, line 225)

Comment 7: As authors mentioned in the discussion, a multivariable analysis might have helped to discriminate confounding factors: why did authors did not perform it?

Reply 7: As the reviewer pointed out, we thought that a multivariate analysis could be useful for confounding factor exclusion and should be performed. We performed multiple logistic regression analysis on respiratory impedance and each clinical factor, but we could not determine a significant factor because the number of patients was small. Therefore, we have considered the results of univariate analysis and have not performed multivariate analysis at this time.

Changes in the text: We apologize, but we have not made any changes.

Comment 8: English is fine, but minor grammar mistakes and typos should be checked

Reply 8: Thank you for your suggestion.

We have checked the grammar, spelling, and typos again, requested proofreading from Editage, and resubmitted it.

Reviewer B

DETAILED EVALUATION

Methods:

Comment 1: This section displays the main limitations of this study.

Reply 1: We appreciate your valued feedback.

Changes in the text: Our responses are given below.

Patients:

Comment 2: The Authors reported in the exclusion criteria ".. at least a thoracotomy or bilobectomy…". In Methods they reported "thoracotomy or thoracoscopic surgery was performed..". The Authors should better explain.

Reply 2: We thank the reviewer for pointing out our error. We erroneously stated that the exclusion criteria should be "... a total pneumonectomy or bilobectomy ..." as "... at least a thoracotomy or bilobectomy ...".

Changes in the text: We have revised the exclusion criteria to

"Patients who were not indicated for lobectomy, those who had difficulty in preoperative MostGraph measurements, those who had a history of lung surgery, or those who required bilobectomy or total pneumonectomy were excluded from the study. ". (See Page 7, lines 123-125)

Inclusion criteria:

Comment 3: It is not correct to compare different types of procedures: VATS and thoracotomic lobectomies. It is mandatory to divide the patients in 2 different groups.

Reply 3: We apologize for the confusion about the exclusion criteria.

As we answered in "Comment 2", the description of our exclusion criteria was incorrect. "Thoracotomy" is not included in the exclusion criteria. As the reviewers pointed out, we agree that it would be better to divide into two groups. However, there was no significant difference in any of the variables among subgroups, so we added the analysis results to the "Results" section.

Changes in the text: We have added a subheading for "subgroup analysis" to the "Methods" section and added the text as follows: "We similarly divided the surgical procedure into subgroups comprising VATS and thoracotomy and compared the measured respiratory impedance values at each measurement time point. The independent t-test was used for normally distributed variables, and Welch's t-test was used for non-normally distributed variables to obtain a significant difference." (See Page 9, lines 187-190)

Text was added to the "Results" section as follows: "In the subgroup analysis of the

surgical procedure, there was no significant difference at any time point for any measurement." (See Page 11, lines 230-231)

Reviewer C

Comment 1: Thank you for asking me to review the manuscript entitled Perioperative changes in respiratory impedance in lobectomy and their clinical impact. The authors described the changes in respiratory impedance after pulmonary lobectomy.

The study is interesting and has the advantage of a prospective planning. The negative aspects, as stated by the authors, is the low the number of patients and there are many confunding factors.

However, we consider it an alternative evaluation that could integrate the spirometric data in future studies.

Reply 1: Thank you for evaluating the future of this research.

As you pointed out, the number of patients is limited, that multivariate analysis does not give significant results, and there are many confounding factors. However, we believe that this study will greatly contribute to evaluating respiratory function in the future.

Reviewer D

Comments 1: The authors the term "imaginary parts" in their introduction. Presumably this has a more concrete meaning in the arena of mathematics and engineering, but to a clinician it is not clear what these terms mean. The authors should consider using a different description.

Reply 1: As the reviewers point out, we agree that "imaginary parts" are unfamiliar to clinicians.

Changes in the text: Following the reviewer's suggestion, in the "Introduction" section, the description of the real and imaginary parts of the respiratory impedance has been modified as follows: "Zrs is expressed using respiratory resistance (Rrs) and respiratory reactance (Xrs) as follows; (Zrs)2 = (Rrs)2 + (Xrs)2." (See Page 5, lines 83-84)

Comment 2: Overall, parts of their introduction and methods rely too heavily on technical descriptions such as from lines 68-81.. These are good, but I would suggest

that they critically re-evaluate the use of their technical terms and translate them into terms that are more clinically relevant and understandable to convey a more understandable message. Otherwise, the current technical terminology they are using loses the interest of the readers. An example is the use of impedance in describing FOT. Perhaps putting this in a language that is more simplified and uses alternative language such as an inverse of impedance like resistance, if possible, would make their terms more intuitive and appreciable. These are just thoughts that if the authors feel are unnecessary then that is understandable too.

Reply 2: As the reviewer pointed out, the "Introduction" and "Methods" sections have many technical terms, and we do not want our readers to lose interest. In the "Introduction" we describe the variables measured by MostGraph. This is because we suspect that most readers, especially thoracic surgeons, are not familiar with MostGraph, and that its variables are not well known. We believe this explanation is necessary. Also, the term "respiratory impedance" may not be intuitive. However, MostGraph is an instrument measuring respiratory impedance, which is expressed by respiratory resistance and respiratory reactance. In response to Comment 1, we added the statement "Zrs is expressed using respiratory resistance (Rrs) and respiratory reactance (Xrs) as follows; (Zrs)2 = (Rrs)2 + (Xrs)2" in the text, and we think this might ease comprehension. However, following your suggestion, we have simplified some of the descriptions of R5-R20.

Changes in the text: The description of R5-R20 in the "Introduction" has been changed as follows: "R5-R20 is only a frequency dependence of Rrs." (See Page 5, line 90)

Comment 3: In the methods section, the authors do not need to be as verbose. They can condense their description by indicating they maintained patient anonymity or eliminate it altogether as institutional review board approval implies as much. Also, their following paragraph on exclusion criteria seem to be a rather random collection of unique elements. They may want to be more general or even more specific as presently it seems that they could include other random disease process such as uncontrolled diabetes or history of metastatic disease, as illustrative examples of how their criteria such as cognitive decline seems to fall into a nonspecific category.

Reply 3: As the reviewer pointed out, we have modified the lengthy part. This study included only patients who underwent lobectomy for the first time in their lives for non-

small cell lung cancer, therefore patients who had previously undergone lung surgery and who required bilobectomy or total pneumonectomy were excluded. We also excluded patients with metastatic lesions, a history of uncontrolled diabetes or severe heart disease, and patients without indication for lobectomy. We mentioned cognitive function and sitting position to convey that we excluded patients who had difficulty measuring MostGraph. We have modified the exclusion criteria to a more general expression.

Changes in the text: We have shortened "assigned an identification code to the subject and used the identification code for case report reports, data aggregation, etc. to ensure that the respondents' anonymity was maintained" to "maintaining the respondents' anonymity".

We have modified the exclusion criteria to

“Patients who were not indicated for lobectomy, those who had difficulty in preoperative MostGraph measurements, those who had a history of lung surgery, or those who required bilobectomy or total pneumonectomy were excluded from the study.” (See Page 7, lines 123-125)

Comment 4: The authors have a second “Methods” subheading within their methods section. They should probably rename the subheading as it is confusing.

Reply 4: We agree that it is confusing, so we have modified it as follows.

Changes in the text: We have renamed the second “Methods” section to “Surgical procedures and perioperative management.” (See Page 7, line 127)

Comment 5: Lines 86-91 in their introduction would appear to fit better under the measurement of respiratory impedance section of their methods due to its very technical description (please consider comments above).

Reply 5: As the reviewer pointed out, we agree that lines 86-91 of our introduction are certainly technical statements. However, this describes an important advantage of MostGraph and is a premise leading to the start of this study, so we would like to retain it in the "Introduction" section.

Changes in the text: We apologize, but we have not made any changes.

Comment 6: It is unusual that a patient who was enrolled in the study was discharged

and went unaccounted for on POD6. This observation almost seems like a break in protocol. Can they elaborate on this irregularity with a brief comment?

Reply 6: As the reviewers pointed out, a patient discharged on POD 6 is a protocol interruption. Thank you for pointing this out. We excluded her from our data and performed the analysis again.

Changes in the text: We have modified the second sentence of the first paragraph of "Results" as follows:

"From a total of 11 patients without lung cancer who were diagnosed with benign illnesses by intraoperative rapid pathological examination, one declined to participate in the study after surgery, and one was discharged on POD6. These patients were consequently excluded from the study." (See Page 9, lines 193-196)

We have also corrected the changes in the numbers accordingly.

Comment 7: One component of the authors' study that is escaping the reader is that not an insignificant number of patients appear to have advanced lung diseases separate from their lung cancers. These other diseases need to be characterized a bit further because I feel as though the authors are missing an opportunity to explain some meaningful value of measuring respiratory impedance in this specific subgroup of patients.

Reply 7: Indeed, many patients had a history of lung disease other than lung cancer; in particular, 11 patients had COPD. We divided them into subgroups of patients without lung disease, COPD patients, IP patients, and CPFE patients, and we tested the statistical differences in FOT measurements at each time point. Although many did not show a significant difference due to the reduced number of patients, there was a significant difference in the Xrs variable in POD1. We were able to support the later "Conclusion" section. Thank you for your suggestion.

Changes in the text: We have added the "Subgroup analysis" subheading to the methods section and "Figure 2" to the results section to clarify the statistical differences in FOT measurements between subgroups of lung disease and added the following text to the subheading "Perioperative changes in respiratory impedance" in the "Methods" and "Results" section: "We enrolled patients without respiratory disease into the control group, and patients with a history of COPD, IP, and CPFE into subgroups, and compared respiratory impedance measurements at each time point. Normally distributed variables were tested for homoscedasticity with the Levene test. One-way

ANOVA was used for homoscedastic distributed variables to obtain statistically significant differences in subgroups at each time point. For non-homoscedastic distributed variables, Welch's t-test was performed; for non-normally distributed variables, the Kruskal-Wallis test was used." (See Page 9, lines 179-186)

"In the subgroup analysis of respiratory disease, at most time points, there was no significant difference in FOT measurements between the subgroups, but there was a significant difference in X5, Fres, and ALX on POD1 ($p = 0.035$, 0.045, and 0.035, respectively; Figure 2)". (See Page 11, lines 226-229)

Comment 8: As the reader moves through the manuscript, it becomes readily apparent that one oversight in their introduction and even in their discussion is that the authors have not fully explained better and convincingly WHY measuring respiratory impedance is truly meaningful and important? In measuring respiratory impedance, they certainly explain the what, to some extent, and the how, to a greater extent, but greater clinical relevance is lacking. Weaving this theme into their text would be very helpful especially in the beginning. When presenting their impedance data, it is not clear why it matters based on their results. Furthermore, their measurements carry no clinical information that is imminently useful. To a clinician the Rs, Fres, and ALX increasing while the X5 is decreasing is meaningless.

Reply 8: As the reviewer pointed out, it is very important to clarify the clinical meaning of respiratory impedance measurement, and we agree that this is what clinicians want to know.

FOT's measurement of respiratory impedance is useful primarily for determining the effects of therapy on bronchial asthma and is widely used.

It is clear that lung function declines after lung surgery, but spirometry, traditionally used as a respiratory function test, is difficult to accurately assess early after surgery. This is because spirometry requires the patient's maximum exhalation effort, but this maximum exhalation effort is difficult early after surgery due to pain and cough.

Besides, since FOT's measurement of respiratory impedance, such as MostGraph, can be performed with breathing at rest, we figured it could be measured even in the early postoperative period. However, it is unclear how the measurement of respiratory impedance changes before and after lung surgery and whether the measurement of

respiratory impedance itself is meaningful. This study aimed to clarify this change in respiratory impedance and to determine the clinical relevance of the measurement. We have corrected this in the "Introduction" section to make it easier to understand.

As mentioned in the limitation part of the "Conclusions" section, there are no established reference values or prediction formulas for MostGraph measurements, so the meaning of simple measurements remains unclear. However, we were able to clarify how the respiratory impedance changes before and after surgery, which was previously unclear. In addition, although it is a univariate analysis, we investigated the correlation with clinical factors such as postoperative complications and were able to identify the measurements of respiratory impedance with a relatively high correlation. We believe that seeing these highly correlated combinations will be the first step leading to early prediction and prevention of postoperative complications in the future. We have corrected this in the "Conclusions" section to aid to comprehension.

Changes in the text: We have modified the 1st, 3rd, and 4th paragraphs in the “Introduction” section as follows:

“Pulmonary function declines after lung surgery. However, this is difficult to assess with spirometry because it requires the patient's maximum exhalation effort, which is hindered early after surgery due to pain, cough and sputum.” (See Page 5, lines 76-78)

“MostGraph 02 (Chest M.I., INC, Tokyo, Japan) can measure Rrs and Xrs in a moment during tidal breathing and may be performed even early after surgery. However, it is unclear how the measurement of respiratory impedance changes before and after lung surgery and whether the measurement of respiratory impedance itself is meaningful for postoperative care. This study aimed to clarify respiratory impedance changes in lobectomy and determine the clinical relevance of this measurement. We hoped that if adverse events such as respiratory failure and pneumonia could be predicted and detected early after surgery by assessing respiratory impedance, it would be possible to prevent exacerbations and provide early intervention”. (See Page 6, lines 99-107)

“Therefore, in this study, we revealed changes in respiratory impedance during the perioperative period of lobectomy and investigated the correlation of respiratory impedance in the pre- and postoperative periods with various clinical factors, such as

physical characteristics, comorbidities, length of surgery, intraoperative blood loss, postoperative complications, and subjective symptoms". (See Page 6, lines 108-112)

In addition, we have modified the 3rd, 5th, and last paragraphs in the "Conclusions" section as below, respectively:

"Subjective symptoms are one of the most clinically important factors in assessing the usefulness of respiratory impedance measurements before and after lung resection. Subjective symptom scores based on the mMRC and mCAT scores increased after surgery. However, while the mMRC score improved rapidly from POD1 to POD7, the mCAT score did not improve by POD7. After surgery, mMRC score, which shows only dyspnea on exertion, may have improved in a short period by removing the chest drainage tube. However, sputum and cough, which persisted, were also considered in the mCAT score; therefore, improvement may have been insufficient. In POD7, respiratory impedance measurements, other than R5-R20, showed a relatively weak correlation with the mMRC score. Unfortunately, it was difficult to correlate subjective symptoms with respiratory impedance because the mMRC score can be affected by postoperative complications." (See Page 14, lines 309-319)

"We initially thought it would be beneficial for patients if we could predict or diagnose postoperative complications early by measuring respiratory impedance. However, in reality, few postoperative complications required treatment, and many were insignificant, so the expected results were not obtained. However, on POD1, Fres was moderately correlated with hypoxemia and cough requiring antitussives. In particular, 3 out of 4 patients with postoperative hypoxemia had a history of IP. Considering that Fres is a marker of pulmonary fibrosis in IP (8, 9), the increase in Fres in the early postoperative period may predict hypoxemia in patients with IP and useful for early intervention after surgery. Although the number of patients in each subgroup of respiratory disease was small, the subgroup analysis results of respiratory impedance provided limited support to this hypothesis". (See Pages 15-16, lines 333-342)

"In conclusion, this study clarified changes in respiratory impedance during the perioperative period of radical lobectomy for lung cancer and the correlation between

respiratory impedance and other clinical factors. Respiratory impedance parameters were different postoperatively, but its measurement did not predict or diagnose early postoperative complications. However, some respiratory impedance parameters were correlated with clinical factors associated with the clinical course. In particular, Fres on POD1 was correlated with hypoxia, which may be an important predictor of early detection of hypoxemia and acute exacerbation in patients with IP. There are many confounding factors, and the exact clinical factor associated with a specific respiratory impedance parameter remains unclear. Eliminating confounders is difficult; however, the postoperative course can be further enhanced by analyzing more cases and comparing changes in respiratory impedance over a longer period using conventional spirometry, combined with anatomical evaluations by CT. Further, because MostGraph could measure respiratory impedance even in the early postoperative period, we expect that MostGraph can be used in the future for evaluating respiratory function in the early postoperative period instead of spirometry." (See Page 16, lines 359-373)

Comment 9: The presentation of their results is so fragmented that following their central message is very confusing. They may want to consider relegating some of their information to a supplemental section or combining certain subsections such as the "Correlation" sections. The use of so many acronyms without meaningful clinical correlates also renders their results section too arduous to read at times and also makes it read very bland.

Reply 9: We are sorry for the confusion. As the reviewer suggested, we have added the summarized "Correlation between respiratory impedance and clinical factors" subsection.

Changes in the text: We have modified it in Pages 12 and 13, lines 246-282.

Comment 10: It is not clear how anyone would expect to see meaningful changes in the symptom scores associated with more chronic or longer-term conditions with interventions that may only be associated with transient worsening changes. Furthermore, it is not clear how the impedance really is relevant in this context. As a result, this assessment seems to be of unrelated significance, in general, and of unclear value at best. They need to establish a better argument for its value in this study.

Reply 10: We apologize for this confusion. We consider that one of the most clinically

important factors in assessing the usefulness of respiratory impedance measurements before and after lung resection is subjective symptoms. Indeed, mMRC and mCAT are chronic respiratory distress scales, but since we could not find any other internationally accepted scale of subjective symptoms, we adopted them as scales for this factor. There were several correlated combinations on POD7 subjective symptoms and respiratory impedance. Unfortunately, it was difficult to associate subjective symptoms with respiratory impedance because the mMRC score may be affected by postoperative complications.

Changes in the text: We modified the part of the discussion about subjective symptoms in the "Conclusions" section as follows: "Subjective symptoms are one of the most clinically important factors in assessing the usefulness of respiratory impedance measurements before and after lung resection. Subjective symptom scores based on the mMRC and mCAT scores increased after surgery. However, while the mMRC score improved rapidly from POD1 to POD7, the mCAT score did not improve by POD7. After surgery, mMRC score, which shows only dyspnea on exertion, may have improved in a short period by removing the chest drainage tube. However, sputum and cough, which persisted, were also considered in the mCAT score; therefore, improvement may have been insufficient. In POD7, respiratory impedance measurements, other than R5-R20, showed a relatively weak correlation with the mMRC score. Unfortunately, it was difficult to correlate subjective symptoms with respiratory impedance because the mMRC score can be affected by postoperative complications." (See Page 14, lines 309-319)

Comment 11: Also, the presentation of the complications in their results along with the discussion on this topic in their discussion seems misplaced and a bit superfluous. It may be worth considering emphasizing this point to a much lesser degree in both locations.

Reply 11: Certainly, as the reviewer pointed out, we agree that there were some misplaced and unnecessary parts. However, we initially thought it beneficial for patients if we could predict or diagnose postoperative complications early by measuring respiratory impedance. In reality, few postoperative complications required treatment, and many were insignificant; therefore, the expected results were not obtained. However, hypoxemia appears to be associated with Fres on POD1, which may detect

hypoxia and acute exacerbations, especially in IP patients, at an early stage.

Changes in the text: We modified the part of complications in “Conclusions” section as follows: “We initially thought it would be beneficial for patients if we could predict or diagnose postoperative complications early by measuring respiratory impedance. However, in reality, few postoperative complications required treatment, and many were insignificant, so the expected results were not obtained. However, on POD1, Fres was moderately correlated with hypoxemia and cough requiring antitussives. In particular, 3 out of 4 patients with postoperative hypoxemia had a history of IP. Considering that Fres is a marker of pulmonary fibrosis in IP (8, 9), the increase in Fres in the early postoperative period may predict hypoxemia in patients with IP and useful for early intervention after surgery. Although the number of patients in each subgroup of respiratory disease was small, the subgroup analysis results of respiratory impedance provided limited support to this hypothesis. Fortunately, no postoperative acute exacerbation of IP was observed in this study, but the fatality rate is high when it develops, and early diagnosis and treatment are important. In this regard, measuring respiratory impedance can be advantageous”. (See Pages 15-16, lines 333-345)

Comments 12: The discussion is much too long. In the perioperative period and without a more solid basis, they are making too much of the lung expansion, shifting, and twisting in the acute postoperative setting to the extent that it seems somewhat contrived.

Reply 12: Exactly as the reviewers pointed out, bronchial twists and lung deviations were not important during the acute postoperative phase and were irrelevant to discuss. We deleted the related part.

Changes in the text: We deleted the related part in the "Conclusions" section.

Comment 13: Similar to issues with the introduction there are parts of their discussion which have limited clinical relevance. For example, the discussion regarding the use of MostGraph is not very clinically pertinent.

Reply 13: The reviewer’s comment is reasonable. However, as we replied in Comment 5, we think it is very important in this study to emphasize that MostGraph is a minimally invasive test that can be performed early after surgery.

However, it is correct that the reference values and prediction formulas do not need to

be lengthy, so we shortened them into the limitation section.

Changes in the text: We deleted the paragraph about the prediction equation and modified the part on the reference values of MostGraph. We have added “there were no specific reference values for MostGraph (1, 24, 25)” in the limitations section. (See Page 16, lines 349-350)

Comment 14: Presently the manner in which the authors have presented their study seems more suitable for a bioengineering or IEEE societal journal. A massive shortcoming of the authors current manuscript is that they are not making the message relatable to a clinician. Reconfiguring their message would require a substantial overhaul. Also, the authors’ study and manuscript appear to be trying to address too many points and consequently, lacks focus. It also seems to be relying on overstated assertions and assumptions.

Reply 14: Thank you very much for taking the time for such a detailed response.

Following the reviewer's previous suggestions, we have made significant revisions to the text. We removed unnecessary statements and rewrote the exaggerated claims and assumptions. This study demonstrated that postoperative respiratory impedance measurements are minimally invasive for patients and can be an alternative to spirometry. In the future, we are confident that this study will be the first step in clinical practice to prove that respiratory impedance measurement is useful for perioperative management of lung surgery to detect postoperative complications early in the postoperative period.

Changes in the text: We have sincerely replied to the issues pointed out by the reviewer and revised the text significantly.