

Peer Review File

Article information: <https://dx.doi.org/10.21037/jtd-22-383>

Reviewer A

Congratulations to your data. This is an interesting study of comparing different tests for evaluating pre-op lung function and predicting post-op complication. However, several points should be clarified. The following are my comments.

Comment 1: I would recommend to use abbreviations for the keyword such as “dynamic perfusion digital radiography” and “pulmonary perfusion scintigraphy” in the abstract and try to be consistent throughout the manuscript while using them. A bit tedious in the introduction section while reading them, may consider to make it short and concise, some of them could be moved to discussion section. Try to clearly demonstrate your aim of study.

Reply 1: Thank you very much for your invaluable comments. “Dynamic perfusion digital radiography” and “pulmonary perfusion scintigraphy” in abstract cannot be abbreviated per journal guideline. Therefore, we did not use the abbreviations, DPDR and PPS, as you suggested. However, the redundant first and second paragraphs in the Introduction have been shortened (Page 5, Lines 67-78). In addition, the Methods in the Abstract (Page 3, Lines 38-39) and the last paragraphs of the Introduction (Page 7, Lines 101-103) have been modified to clarify the purpose of this study.

Comment 2: With regard to the complication, the type of the complications should be provided. Such as commonly encountered ones (e.g., prolonged air leaks, arrhythmia, pneumonia...etc)

Reply 2: Thank you for your comment. We targeted postoperative complications, as described in the Clavien-Dindo classification, and respiratory failure. The complications that occurred in this study were in close agreement with the commonly encountered complications, and are described, including the number of occurrences, on Page 11, Lines 176-181.

Comment 3: What is the cost-effectiveness of the compared two methods in predicting post-op complication for patients? You are encouraged to define and explain this point.

Reply 3: Thank you very much for your invaluable comments. We apologize for not being able to present the numerical values because we have not calculated the costs required for the one actual inspection. PPS imposes a large capital investment and the preparation of nuclides each time for the institution. Furthermore, PPS imposes an exposure of 0.85 mGy (185 MBq) or more and a long examination time for the patient.

However, the initial capital investment required for DPDR is only for digital chest radiography systems and dynamic image analysis workstations, which are cheaper than gamma camera equipment. After purchase, its cost is similar to that of standard chest radiography. If DPDR can provide the same information as PPS, it can be expected to be highly cost-effective. We changed the sentence in Page 6, Lines 86-88 to “Dynamic perfusion digital radiography (DPDR) is a simple and cost-effective examination method (e.g., requiring low facility investment, no nuclide preparation, a short examination time, and low radiation exposure) to provide qualitative and quantitative information about dynamic pulmonary circulation (22,23).”

Comment 4: Figure 3 was formed incompletely. Table 1 should be reorganized in a straightforward understandable manner.

Reply 4: Thank you for your suggestion. We have made modifications to Table 1. For Figure 3, if you suggest any correction points, we are ready to correct accordingly.

Comment 5: At last, minor language polishment in the current manuscript is suggested to improve the readability.

Reply 5: Thank you very much for your important suggestion. We have substantially improved the readability of the current manuscript.

Reviewer B

Comment: This is a very interesting and statistically sound work. However, in my opinion, the work does not provide any new insights. It is very similar to reference 24 and probably uses most of the same data. The conclusion is also the same.

Reply: Thank you very much for your important comments. The previous report was only an interim report with some data from this study that reached the number of subjects to be enrolled. In contrast to the previous report, which showed the correlation in the blood flow ratios between DPDR and PPS, this report further evaluated the agreement between the two methods in the accuracy of predicting postoperative complications and postoperative pulmonary functions. All figures and tables in this manuscript are new and not reused from previous papers.

Reviewer C

Comment: The authors explored the utility of DDR in assessing lung function and complications after lung cancer surgery. I agree with the authors' conclusions, but request answers to the following questions.

Is this a prospective observational study? The study design needs to be clarified. Why

are half of the subjects evaluated only with the DPDR, and is there a limitation to receiving both the DPDR and the PPS? This could create bias. The authors need to explain this reason along with the study design.

Also, please specify the primary endpoint - is it the correlation between DPDR and PPS? The distinction between the endpoints is ambiguous and can cause confusion.

Reply: Thank you very much for your important comments. This study was originally designed as a prospective study to evaluate the usefulness of BFR, calculated from DPDR, in predicting postoperative lung function and complication. Pulmonary perfusion scintigraphy was not a requirement for patient enrollment. However, to clarify the usefulness of DPDR, we thought that it was necessary to confirm similar or enhanced prediction by PPS. Therefore, we decided to assess the agreement between the two methods. Moreover, the study design was changed to a retrospective nature, with comparative analysis of cases with preoperative PPS. To avoid unnecessary radiation exposure, preoperative PPS was excluded from cases without comorbidity or pulmonary function abnormality. As a result, the number of cases was approximately half of the total. While this eligibility criterion may be the cause of selection bias, it may also allow us to address a particular patient group in need of postoperative complication prediction. We added the above reason to the Patient in the Method (Page 7, Lines 112-114), and also stated the possibility of selection bias in the limitation, including the need for further verification (Page 15-16, Lines 269-272).

We also apologize for the lack of clarity on the primary endpoint. The purpose of this study is to evaluate whether DPDR is a reliable alternative to PPS. As such, we not only evaluated the correlation of BFR measured by DPDR and PPS, but also determined the accuracy of postoperative complication prediction using postoperative predictive lung function calculated from each BFR. In addition, the Methods in the Abstract (Page 3, Lines 38-39) and the last paragraphs in the Introduction (Page 7, Lines 101-103) have been modified to clarify the purpose of this study.

Reviewer D

General comments

In this paper, the authors investigated the significance and accuracy of dynamic perfusion digital radiography (DPDR) for assessing pulmonary perfusion as compared pulmonary perfusion scintigraphy (PPS) and predicting postoperative lung function and compliance. They demonstrated that DPDR and PPS showed a high correlation with the blood flow or postoperative blood flow ratio and concluded that DPDR can be a good alternative to PPS for predicting postoperative pulmonary function of postoperative respiratory complications including the need for postoperative oxygen therapy. The text was well described and data analysis was fairly adequate although main text feels too long. The following points should be addressed.

Specific comments:

Comment 1: Introduction page 5-6 line 62-94; The 1st paragraph, which explained the importance of perioperative risk assessment for pulmonary surgery and the 2nd, described methods and problems of each tool for predicting postoperative pulmonary functions and perfusion, is felt too long. These two paragraphs would be summarized and more shortened with cited adequate references.

Reply 1: Thank you very much for your helpful recommendations. We have summarized the two paragraphs that were pointed out (Page 5, Lines 67-78).

Comment 2: Methods and Figure 1; There was large difference between number of subjects who underwent postoperative examination including spirometry (n=90) and those who was analyzed DPDR and PPS (n=44). In the manuscript, the reason of this difference, those who PPS did not undergo, was not mentioned clearly. Authors should analyzed and described reasons for this difference.

Reply 2: Thank you very much for your important comments. This study was originally designed as a prospective study to evaluate the usefulness of BFR, calculated from DPDR, in predicting postoperative lung function and complication. Pulmonary perfusion scintigraphy was not a requirement for patient enrollment. However, in order to clarify the usefulness of DPDR, we thought that it was necessary to confirm similar or enhanced prediction by PPS. Therefore, we decided to assess the agreement between the two methods. Therefore, the study design was changed to a retrospective nature, with comparative analysis of cases with preoperative PPS. To avoid unnecessary radiation exposure, preoperative PPS was excluded from cases without comorbidity or pulmonary function abnormality. As a result, the number of cases was approximately half of the total. We added the above reason to the Patient subsection of the Method section (Page 7, Lines 112-114).

Comment 3: Methods: page 9, pulmonary function test: The procedure for measuring DLco could be described as whether single-breath method or others.

Reply 3: We apologize for our insufficient explanation. Although not specifically mentioned in the text, it is measured by the single-breath method.

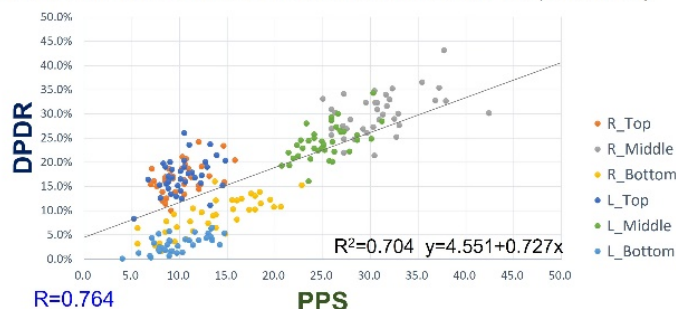
Comment 4: Method and Discussion: As authors discussed, I think that DPDR may have a weakness for assessing lung perfusion in the left lower lung area, especially non-peripheral area, because of coincided with the heart. Was there any difference in sensitivity or specificity in assessing pulmonary perfusion with DPDR between patients who underwent left-sided lung resection and those who right-sided lung operation?

Reply 4: Thank you for your very valuable suggestions. However, we have not examined in detail the comparison between the left and right sides of DPDR. Therefore, we do not have enough information to present. Regarding the prediction of

complications within 1 month after surgery using ppo% DLco, the sensitivity and specificity of the left and right sides were 100%, 95% and 100%, 100% respectively. While the prediction accuracy was comparable between the left and right sides, the limitation associated with the small number of cases cannot be denied. The figure below (unpublished) shows a comparison of DPDR and PPS for each blood flow distribution when the frontal chest radiograph is divided into six regions. Compared with PPS, DPDR showed a significant result in the upper lung field, likely because of the difference in radiographic conditions. Therefore, although PPS may be superior in blood flow evaluation in the left middle and lower lung fields, the lung volumes at areas that overlap with cardiac shadows may not have a significant impact.

Blood flow distribution

Correlation between BFRs obtained from DPDR and PPS (6 divisions)



Comment 5: Results; page 12, line 198-199: The sentence, “it was suggested that blood flow evaluation by DPDR is comparable to that by PPS”, could be transferred to the Discussion part.

Reply 5: Thank you for your helpful recommendation. This sentence has been removed because the first paragraph in the Discussion contains the same content.

Comment 6: Method and Result; Induction of postoperative oxygen therapy→ Induction of postoperative long term oxygen therapy (LTOT). If some post-operative subjects was not induced to LTOT (“home oxygen therapy”) but just oxygen therapy in the post-operative phase, that should be clearly divided and mentioned in the text.

Reply 6: We apologize for our insufficient explanation. All cases were long term oxygen use cases with HOT induced. We changed “the induction of postoperative oxygen therapy.” to “postoperative long term oxygen therapy” in the Results section (Page 12, Line 211 and Page 13, Line 214). In Table 1, it is described as home oxygen therapy.

Comment 7: Method and Result; Data of arterial blood gas, including PaO₂ (SpO₂ also permitted), after the surgery would be needed for proving the validity of induction of LTOT. Pulmonary hypertension after the surgery also permitted as the reason of LTOT.

Reply 7: Thank you very much for your important comments. As you have mentioned, indication criteria using data of arterial blood gas, including PaO₂ or SpO₂, are important for the introduction of LTOT. We usually observe with SpO₂ and focus not only on resting hypoxemia, but also hypoxemia and/or dyspnea on effort. In fact, LTOT is introduced in cases where SpO₂ falls below 90% during the 6-minute walk test. Approximately 3 to 6 months after surgery, we confirm SpO₂ recording for 24 hours with a pulse oximeter. To assess the relationship between content of exertion and SpO₂ values, we determine the need to continue LTOT. In this study, all cases required continuation for 3 months or longer. Postoperative pulmonary hypertension has not been evaluated in this target case. We have added the criteria for LTOT to the method in the revised manuscript.

Comment 8: Results; page 11, line 185-186: "Surgery-based respiratory and/or circulatory-related events occurring up to 6 months after surgery", which had been extracted from analysis, would be defined and its content shown in a little detail.

Reply 8: Thank you for your recommendation. We targeted postoperative complications described in the Clavien-Dindo classification and respiratory failure. We removed "Surgery-based" because it confuses the meaning. The complications that occurred in this case are described on Page 11, Lines 176-181.

Comment 9: Result: page 13, line 223: A sentence, "Nevertheless, the target cases below each cut-off value were the same." is unclear description. Could you explain again or in detail?

Reply 9: Thank you for your helpful recommendation. We apologize for the lack of clarity in the explanation. Cases of postoperative complications with ppo%DLco_PPS and ppo%DLco_DPDR below their respective cut-off values were 6 of 11 (54.5%) and 5 of 6 (83.3%), respectively. The sentence you pointed out means that while the detection rates are different, we detected the same five cases. For that reason, this sentence was changed to "Therefore, the number of cases below each cut-off value was different. However, the same cases with respiratory complications were detected." (Page 12, Lines 206-208).

Comment 10: Discussion and Conclusion: The merit of DPDR, especially from the point of lower radiation exposure and medical cost, would be mentioned in the discussion and the conclusion for clinicians and readers.

Reply 10: Thank you very much for your invaluable comments. We apologize for not being able to present the numerical values because we have not calculated the costs required for the actual one inspection. PPS imposes a large capital investment and the preparation of nuclides each time for the institution. Furthermore, PPS imposes an exposure of 0.85 mGy (185 MBq) or more and a long examination time for the patient. However, the initial capital investment required for DPDR is only for digital chest

radiography systems and dynamic image analysis workstations, which are cheaper than gamma camera equipment. After purchase, it only costs about the same as standard chest radiography. If DPDR can provide the same information as PPS, it can be expected to be highly cost-effective. We changed the sentence in Page 6, Line 86-88 to “Dynamic perfusion digital radiography (DPDR) is a simple and cost effective examination method (e.g., requiring low facility investment, no nuclide preparation, a short examination time, and low radiation exposure) that can provide qualitative and quantitative information about dynamic pulmonary circulation (22,23).”.

Reviewer E

This is a well-written paper that summarises an interesting clinical question well, and addresses it using a unique imaging modality. I would suggest some minor areas for improvement or change.

Comment 1: Abstract, Results – I think this is too vague; I would include some key results in this section, for example the R number and P-value mentioned on line 204. Abstract, Methods – are you not assessing agreement between two methods, rather than just correlation? This is an important distinction to make when making the comparison between two measurement methods.

Reply 1: I’m sorry that the explanations are vague in the Results and Methods part of the Abstract. In the Results part, we added the R number and P-value in the description (Page 3, Lines 43-45).

Also, in the Methods part, I changed “We confirmed the correlation between” to “We confirmed the agreement between two methods” (Page 3, Lines 38-39).

Comment 2: Patient demographics – 38/44 patients are male, and 15/44 have COPD. This is certainly not representative of Japanese (or international) lung cancer demographics (DOI: 10.1016/j.je.2016.12.010). Whilst I acknowledge that you discuss this in your ‘limitations’ section, I would make it more clear to the reader that further work needs to be done to address the applicability of these findings in a more representative cohort.

Reply 2: Thank you very much for your invaluable comments. The target cases were biased compared to the background of general lung cancer cases. Since cases without pulmonary dysfunction or comorbidity were excluded, it is presumed that this is due to the bias of preoperative PPS cases. We added to the limitation, including the need for further verification (Page 16, Lines 274-275).

Comment 3: Patient demographics – I would question the inclusion of the 1 individual with pulmonary fibrosis. IPF is known to affect ventilation/perfusion (DOI: 10.1183/16000617.0062-2017). Why not exclude this individual from your cohort?

Did you consider analysing separately those with and without COPD? COPD too may affect ventilation/perfusion.

Reply 3: Thank you very much for your helpful recommendations. We understand that comorbidities, such as IP and COPD, affect the patient's ventilation/perfusion. For lung physiological analysis or the establishment of general predictive formulas using DPDR, special cases should be omitted considering the effects of differences in background factors. In this study, we assessed agreement of the measurement methods between DPDR and PPS using risk prediction of postoperative complications. Therefore, its detection is important, even in patients with various backgrounds. In IP case, the BFR on the affected side was 0.436 by DPDR and 0.432 by PPS, which were relatively consistent. While we also considered comparisons with and without COPD, the sample size was small in this study. However, we plan to evaluate this topic in the future, including cases that did not undergo PPS. If required editorially, we are ready to respond to a review in cases where IP is omitted.

Comment 4: Line 95 / line 125 – DCR is a quick and straightforward imaging modality. It is performed in a similar setup to a standard chest radiograph, and the equipment footprint is similar to that of a standard radiography suite. This is not made clear to the reader in your description. I would emphasise the ease of performing DCR, as this is surely one of its unique selling points, especially in a lung cancer population who are likely to be older and more infirm, thus unable to perform more complex tests such as spirometric gas transfer or scintigraphy.

Reply 4: Thank you very much for your helpful comments. We added to the Introduction about the useful points of the DCR that you presented (Page 6, Lines 90-93).

Comment 5: Line 205 – I think you mean 9.1%, rather than 0.091%.

Reply 5: We apologize for our error. We have corrected it (Page 11, Lines 189).

Comment 6: Line 261-262 – can you justify this statement?

Reply 6: Thank you for your comment. Two previous papers (doi.org/10.1378/chest.12-2395 and [doi:10.1016/j.jacc.2014.07.944](https://doi.org/10.1016/j.jacc.2014.07.944)) recommend that the evaluation of respiratory function, including pulmonary diffusing capacity, and the risk assessment of the cardiovascular system should be considered. We have also added these papers to the reference (references 9 and 10 in the revised manuscript). The algorithm of risk prediction for postoperative complications, routinely used in clinical practice, adds not only predictive postoperative lung function values but also measurement of maximal oxygen consumption for high-risk patients. This observation shows that a single prediction method is insufficient. In addition, we performed multivariate analysis between preoperative clinical factors and complications in the target cases of this study.

The results revealed that hypoalbuminemia (<3.9 mg/dL), postoperative induction of home oxygen therapy, and histological type of non-adenocarcinoma were independent factors. By devising a risk prediction formula for the occurrence of postoperative complications using this result, prediction accuracy may be higher. While predictions that include more clinical factors are more accurate, this study emphasized convenience of prediction. I added a reference to the indicated sentence (Page 14, Line 245).

Comment 7: Line 270 – if I understand correctly from your first paper (Hanaoka et al 2021), your DCR protocol involved a single 10s breath hold manoeuvre. You mention that DCR can offer functional information on moving thoracic structures. I would mention the distinction between your DCR protocol (breath hold) and the protocol needed to acquire functional thoracic information (breath in / out). Inclusion of both protocols in the same sitting would of course increase/double the ionising radiation exposure to the patient, so it is worth explaining the distinction to the reader, who may not appreciate this, or may question why this information was not included in your paper.

Reply 7: Thank you very much for your invaluable comments. Because pulmonary blood flow analysis can only be evaluated during breath-holding, DPDR was also an analysis during breath-holding after resting inspiration. Therefore, in the previous paper, I mentioned only “All participants were scanned in a sitting position for approximately 10 second while holding their breath.” Since the original purpose of this study was to analyze respiratory physiology with images taken by DCR, the following DCR protocol was used: the subject was scanned during 12 seconds of resting breathing, 16 seconds of deep breathing, 10 seconds of breath-holding after inspiration, and 10 seconds of breath-holding after expiration according to automated voice, for a total imaging time of 48 seconds and an exposure dose of less than 1.5 mGy (similar to the exposure dose during frontal and lateral chest X-ray). Images during breath-holding after inspiration and expiration were obtained, and the difference in the effect on blood flow distribution in these states was considered for future analysis. Therefore, we do not currently have enough results to present.

Comment 8: Line 288 – unnecessary exposure to what? I assume you mean to radiation?

Discussion, first paragraph – I would reiterate the numerical values of your key results in this paragraph.

Reply 8: We apologize for our unclear description of exposure. We have changed to “radiation exposure” (Page 16, Line 272).

Thank you for your helpful recommendation. We have added key results to the first paragraph in the Discussion (Page 13, Lines 223-224).

Comment 9: Line 292-293 – CT volumetry can certainly calculate lung volumes with good accuracy. But DCR can do so too (DOI: 10.1016/j.ejrad.2021.109866).

Reply 9: Thank you very much for your invaluable comments. The reference paper you gave is an important report on the development of a multilinear models for predicting FVC and other PFT parameters from the lung field areas measured by DCR. Since our postoperative prediction is lung function after lobectomy, we need both unilateral lung volume and the volume in each lobe. It would be best if lung volume was measured with DCR alone. However, it is difficult to measure lung volume from anteroposterior view alone as in this study. Therefore, CT volume is presented in this manuscript.

Reviewer F

Comment: Thank you very much for inviting me to review the manuscript which was submitted for publication in Journal of Thoracic Disease. I have reviewed the manuscript entitled “Reliability of dynamic perfusion digital radiography as an alternative to pulmonary perfusion scintigraphy in predicting postoperative lung function and complications”. The authors prospectively compared dynamic perfusion digital radiography with conventional pulmonary perfusion scintigraphy in terms of measuring bilateral pulmonary blood flow, postoperative blood flow ratio of the operative side, and the accuracy for predicting postoperative pulmonary function values and the risk of postoperative complications. I am afraid that some of the data from most subjects analyzed in this study had been already used in the authors’ previous manuscript published in the other journal (Hanaoka J, Yoden M, Hayashi K, et al. Dynamic perfusion digital radiography for predicting pulmonary function after lung cancer resection. World J Surg Oncol 2021;19:43.). Please check whether or not the data and figures from this study and their previous manuscript were repeated.

Reply: Thank you very much for your important comments. The previous report was only an interim report using some data from this study that reached the number of subjects to be enrolled. In contrast to the previous report, which showed the correlation in the blood flow ratios between DPDR and PPS, this report further evaluated the agreement between the two methods in the accuracy of predicting postoperative complications and postoperative pulmonary functions. All figures and tables in this manuscript are new and not reused from previous papers.