Author's response to reviews

Title: Relationship between peripheral airway function and patient reported outcomes in COPD: a cross-sectional study

Authors:

Akane Haruna (akaneh@kuhp.kyoto-u.ac.jp)
Toru Oga (ogat@df7.so-net.ne.jp)
Shigeo Muro (smuro@kuhp.kyoto-u.ac.jp)
Tadashi Ohara (tohara@kuhp.kyoto-u.ac.jp)
Susumu Sato (ssato@kuhp.kyoto-u.ac.jp)
Satoshi Marumo (marumo@kuhp.kyoto-u.ac.jp)
Daisuke Kinose (dkinose@kuhp.kyoto-u.ac.jp)
Kunihiko Terada (terada@kuhp.kyoto-u.ac.jp)
Michiyoshi Nishioka (mnishiok@kuhp.kyoto-u.ac.jp)
Emiko Ogawa (eogawa@kuhp.kyoto-u.ac.jp)
Yuma Hoshino (yuma@kuhp.kyoto-u.ac.jp)
Toyohiro Hirai (t_hirai@kuhp.kyoto-u.ac.jp)
Kazuo Chin (chink@kuhp.kyoto-u.ac.jp)
Michiaki Mishima (mishima@kuhp.kyoto-u.ac.jp)

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Author's response to reviews: see over
Reply to Dr. Diong’s comments

This paper describes a study to determine the correlation between 3 objective pulmonary function tests/measurements (spirometry, IOS and CT) to 3 patient reported outcomes (SGRQ, MRC, HADS) in COPD. The question posed by the authors is well defined, the methods appropriate and well described, and the data appear to be sound. Moreover, the manuscript adheres to the relevant standards for reporting and data deposition, the writing is better than acceptable and the discussion and conclusions well balanced and adequately supported by the data. The authors also clearly acknowledge the works upon which they are building, and the paper’s title and abstract accurately convey what has been found.

Thank you for your kind words about our manuscript. We have revised our manuscript based on your comments.

However, the limitations of the work are not properly stated: this study’s population consists only of men. The same study may (or may not) find gender differences if women are also part of the study. This significant limitation should be added to the last paragraph of the Discussion section.

[ This is a Major Compulsory Revision ]

We appreciate your comment. We have included only male patients in the present study, because there are far fewer female patients. The past smoking trends in Japan may have
resulted in COPD being limited almost exclusively to men. Therefore, we have explained this in the part of the Discussion listing the limitation of the study.

In the revised manuscript:

“Second, this study included only male patients, as there are relatively few female patients. This may be due to the gender difference in the past smoking trends in Japan, and possibly reflects the present features of Japanese COPD patients. Thus, the generalization of the results to females is unwarranted.” (Page 18 in the revised manuscript)

The following are Minor Essential Revisions (with suggested changes underlined; these markings appear in the Word format version of this report e-mailed to the editorial staff):

1. In Table 1, the height characteristics of the study population should be included; this is because several studies (see Oostveen et al, Eur Respir J 2003;22:1026-1041) have documented the strong correlation between height and IOS values (in normal subjects)

Based on your comment, we have added the height of the study subjects to Table 1.

(Table 1 in the revised table file)

2. Last line of MS page 2: "... investigated the .."

3. 2nd para of MS page 4 "... IOS measures lung resistance and reactance, ...

4. 2nd para of MS page 5 "... assessments consisting of conventional …"
The following are Discretionary Revisions (with suggested changes underlined; these markings appear in the Word format version of this report e-mailed to the editorial staff):

Thank you for your comments. We have changed the wording as you suggested.

1. 2nd para of MS page 9, consider deleting the sentence "Additionally, for the ordinal variable ... " since it serves little purpose.

According to your comment, we have deleted the sentence you mentioned.

2. 2nd para of MS page 12 "... and the total SGRQ and ..."

3. 1st para of MS page 14 "... the HADS, and neither did the pulmonary function test parameters or CT."

4. 2nd para of MS page 14 "... features of COPD"

5. 2nd para of MS page 14 "... by IOS consistently correlated with ..."

6. 2nd para of MS page 17 "... in male patients with COPD."

7. 2nd para of MS page 17 "... assess the male COPD patient’s ..."

8. Reference 4 “... Eng P ...”

We appreciate your comments. We have revised the wording as you recommended except for the above comment 3 regarding the 1st paragraph on page 15 of the original
In the original manuscript:

“We demonstrated that peripheral airway measurements by IOS (R5-R20 and X5) were significantly correlated with the SGRQ and MRC scores, but not with the HADS. Multiple regression analyses also revealed that they accounted for the SGRQ and MRC scores more significantly than FEV\textsubscript{1} and CT measurements.” (Page 14 in the original manuscript)

In the revised manuscript:

“Here, we demonstrated that peripheral airway measurements by IOS (R5-R20 and X5) were significantly correlated with the SGRQ and MRC scores. No measurements of pulmonary function, IOS and CT were significantly correlated with the HADS. Multiple regression analyses revealed that R5-R20 or X5 accounted for the SGRQ and MRC scores more significantly than FEV\textsubscript{1} and CT measurements ($r^2 = 0.09$ to 0.26).” (Page 15 in the revised manuscript)
Reply to Dr. Borghi-Silva’s comments

The manuscript: “Relationship between peripheral airway function and patient reported outcomes in COPD: a cross-sectional study” showed that IOS measurements, especially indices of peripheral airway function, are significantly correlated with health status and dyspnea in patients with COPD and that IOS is a useful clinical tool not only for detecting pulmonary functional impairment, but also to assess the patient’s quality of daily life and well-being.

This manuscript is relevant and adds important information; however, I have some suggestions:

We appreciate your reviewing our manuscript. We have revised the manuscript according to your suggestions below.

ABSTRACT

Background

The background text is not clear; the sentences are loose in paragraph and must be reformulated.

We appreciate your comments. We have therefore reformulated the Background section of the Abstract as follows:

In the original manuscript:

“Health status, dyspnea and psychological status are important clinical outcomes in
chronic obstructive pulmonary disease (COPD). Forced expiratory volume in one second (FEV₁), the standard measurement of airflow limitation, has only a weak relationship with these outcomes. Impulse oscillometry (IOS) measuring airway resistance and lung reactance is increasingly used to assess pulmonary functional impairment.” (Page 2 in the original Background section of the Abstract)

In the revised manuscript:

“Health status, dyspnea and psychological status are important clinical outcomes in chronic obstructive pulmonary disease (COPD). However, forced expiratory volume in one second (FEV₁) measured by spirometry, the standard measurement of airflow limitation, has only a weak relationship with these outcomes in COPD. Recently, in addition to spirometry, impulse oscillometry (IOS) measuring lung resistance (R) and reactance (X) is increasingly being used to assess pulmonary functional impairment.” (Page 3 in the revised Background section of the Abstract)

Results

As described it is difficult to understand the reader who is not familiar with the measures of IOS (R5-R20, X5 and R20). Please rewrite this idea more clearly

As you suggested, we have explained the IOS measurements in the methods in the Background and Methods sections of the Abstract as follows:

In the revised manuscript:

“Recently, in addition to spirometry, Impulse oscillometry (IOS) measuring lung resistance (R) and reactance (X) is increasingly being used to assess pulmonary
functional impairment.” (Page 2 in the revised Background section of the Abstract)

“For the IOS measurements, we used lung resistance at 5 and 20 Hz (R5 and R20, respectively) and reactance at 5 Hz (X5). Because R5 and R20 are regarded as reflecting total and proximal airway resistance, respectively, the fall in resistance from R5 to R20 (R5-R20) was used as a surrogate for the resistance of peripheral airways. X5 was also considered to represent peripheral airway abnormalities.” (Pages 3 to 4 in the revised Methods section of the Abstract)

BACKGROUND

The idea of introduction is appropriate, however I have some comments:
The paragraphs are too long. The authors should fragment it without changing the original idea. In addition the authors should try to connect more ideas between paragraphs.

We appreciate your comment. We have now shortened the Background section and have divided it into paragraphs without changing the original idea. Furthermore, we have made efforts to connect more ideas between paragraphs in the revised manuscript.

Is necessary to standardize the writing of the word “patient-reported” (throughout the text there is the word with or without hyphen).

According to your comment, we have standardized this expression as “patient-reported” (with hyphen) in the revised manuscript throughout the text.
Methods

Subjects

It is unclear whether the authors assessed more patients than those recruited (65) and the reasons why they were excluded. Important to add this information.

What the authors consider regular outpatient clinic attendance?

We appreciate your comment. Firstly, we assessed just 65 patients who satisfied the inclusion criteria. Secondly, regular outpatients clinic attendance means that we manage and treat patients at our respiratory clinic regularly. Therefore, we have revised this description follows:

In the original manuscript

“3) regular outpatient clinic attendance over 6 months;” (Page 5 in the original Methods)

In the revised manuscript

“3) regular management and treatment at our outpatient clinic over 6 months;” (Page 7 in the revised Methods)

Describe uncontrolled comorbidities ....

Following your comment, we have described the comorbidities in the revised manuscript.
In the original manuscript

“6) no uncontrolled comorbidities.” (Page 6 in the original Methods)

In the revised manuscript

“6) no uncontrolled comorbidities such as severe cardiovascular diseases and malignant disorders;” (Page 7 in the revised Methods)

How was the intellectual capacity the patients to answer the questions? Add criteria of exclusion.

Only subjects with sufficient cognitive function to complete the questionnaire were included in this study. We have added this as an inclusion criteria.

In the revised manuscript

“7) having sufficient cognitive function to complete the questionnaire.” (Page 7 in the revised Methods)

The patients signed an informed consent to participate in the study?

Yes, the patients gave written informed consent. We have now added a sentence on this.

In the revised manuscript

“The research protocol was approved by the Ethics Committee of Kyoto University and the subjects gave written informed consent.” (Page 7 in the revised Methods)

Outcome measures
“Subjects underwent IOS and spirometry 15 minutes after inhaling the bronchodilators salbutamol (400 g) and ipratropium bromide (80 g)”. Written in this way (15 minutes after) appears that the measurements were made simultaneously, rewrite this expression

First, subjects underwent IOS, then did spirometry. We have modified the sentence as follows:

In the original manuscript

“Subjects underwent IOS and then spirometry 15 minutes after inhaling the bronchodilators salbutamol (400µg) and ipratropium bromide (80µg).” (Page 6 in the original Methods)

In the revised manuscript

“Subjects underwent IOS and then spirometry 15 minutes after inhaling the bronchodilators salbutamol (400µg) and ipratropium bromide (80µg).” (Page 8 in the revised Methods)

Statistical analysis

“Results are expressed as means±SD”. Delete “s” of means. Was applied a test to verify normal distribution? The sample size was appropriate?

We appreciate your comments about statistical analysis. First, we have deleted “s” of means as you recommended. Second, we verified that data were essentially normally distributed. Third, we consider that the sample size was relatively small. Therefore, we
have added the following sentences describing this as a limitation of the present study.

In the revised manuscript

“Third, the number of the patients included in this study was relatively small. However, our results have generated an interesting hypothesis that small airways disease results in certain symptomatology and this must be tested on new cohorts of patients in order to validate the hypothesis.” (Page 18 in the revised Discussion)

Results

Baseline characteristics

Reduce the amount of acronyms in Table 1, when not possible to create a legend

According to your comment, we have defined the abbreviations used in the footnote to Table 1-3. (Table 1-3 in the revised table file)

The authors should include body mass index data.

We have added body mass index data to Table 1. (Table 1 in the revised table file)

Pay attention to the table titles. Some are written in different letters compared to the text.

We apologize for the inconsistency in the use of font between the table titles and the text. We have now changed this to uniform use of “Times” throughout.
“Relationships between IOS measurements and objective parameters” and
“Relationships between objective parameters and patients reported outcomes”
The authors must explain what means “objective parameters” in this subtitle
Table 2: Correlation coefficient between IOS, pulmonary function and CT
measurements. I see no need to show the table 2, the authors are showing the same
data described in the text, also the table 2 does not show clearly the results, some
data without significance need not be cited

We appreciate the comments. First, we have revised the expression “objective
parameters” more specifically as follows:

In the original manuscript;

“Relationships between IOS measurements and objective parameters” (Page 11 in
the original Results)

In the revised manuscript;

“Relationships between IOS measurements, and pulmonary function and CT” (Page
12 in the revised Results)

In the original manuscript;

“Relationships between objective parameters and patients reported outcomes” (Page
12 in the original Results)

In the revised manuscript;
“Relationships between pulmonary function, IOS, CT and patient-reported outcomes” (Page 13 the revised Result)

Second, as you suggested, we have deleted Table2. Accordingly, we have revised the following sentence.

In the original manuscript:

“R20 showed a weak or non-significant correlation with R5-R20 and X5, indicating that R20, R5-R20 and X5 would reflect different physiological aspects.” (Page 11 in the original Results)

In the revised manuscript:

“R20 showed a weak or non-significant correlation with R5-R20 and X5 ($r = 0.29, p = 0.02$, and $r = -0.19, p = 0.13$, respectively), indicating that R20 reflects different physiological parameters from R5-R20 and X5.” (Page 12 in the revised Results)

The author wrote in the text…….Table 3 shows the correlation coefficients between objective parameters and patient reported outcomes and in the table title…….”Table 3: Correlation coefficients between pulmonary function, IOS, CT, and patient reported outcomes” is necessary to standardize to avoid confusion and facilitate the reading. Moreover, also my suggestion is that the data are shown in the text or display in the table, but only significant data, is unclear. Because DLCO/VA, R20 and WA% showed no significant relationships with health status and dyspnea in linear regression analyses, we did not use them as independent variables in multiple regression analyses. …… this information is obvious
therefore should be removed from the text. I also suggest the inclusion of graphics with the most important results.

We appreciate your comments. First, we have revised the sentence you mentioned and the title of the original Table 3 (revised Table 2) as follows:

In the original manuscript:

“Table 3 shows the correlation coefficients between objective parameters.” (Page 12 in the original Results)

In the revised manuscript:

“Table 2 shows the correlation coefficients between pulmonary function, IOS, CT and patient-reported outcomes.” (Page 13 in the revised Results)

In the original manuscript:

“Correlation coefficients between pulmonary function, IOS, CT, and patient reported outcomes” (Page 2 in the title of the original Table 3)

In the revised manuscript:

“Analysis of the relationships between pulmonary function, IOS, CT, and patient reported outcomes.” (Page 3 in the title of the revised Table 2)

Second, we have deleted the following explanation from the text, and, have also omitted the sentence you mentioned. Accordingly, we have deleted the $\text{DL}_{\text{CO}}$/VA, R20 and WA% values from the original Table 4 (revised Table 3).

In the original manuscript:
“Neither anxiety nor depression on the HADS was correlated with these objective measurements \((p > 0.05)\).” (Page 12 in the original Results)

In the original manuscript:

“Because \(DL_{CO}/VA\), R20 and WA% showed no significant relationships with health status and dyspnea in linear regression analyses, we did not use them as independent variables in multiple regression analyses.” (Page 12 in the original Results)

Third, we have added Figure 1 which shows the relationship between the IOS measurement (R5-R20) and SGRQ total score.

In the revised manuscript:

“The relationship between R5-R20 and the total SGRQ is shown in Figure 1.” (Page 13 in the revised Results)

Table 4: Results of stepwise multiple regression analyses to predict health status and dyspnea... This title is not appropriate for what it proposes. The same comments from the tab 2 and 3 also are valid for this table.

Based on the above comment, we have changed the original title of “Results of stepwise multiple regression analyses to predict health status and dyspnea” to “Analysis of the relationships of health status and dyspnea to pulmonary function, IOS and CT by stepwise multiple regression analyses”.

At no time did the authors discuss the strength of the correlation coefficients and if
were positive or negative. Few were the correlation coefficient greater than 0.6 which I interpret as really significant. So the authors should discuss the actual data showing the data with greater force. Likewise do my comments to the results of regression, \( r^2 = 0.27 \) was one of the values obtained when the idea was to identify variables that could best predict another. This low predictive ability suggests that other factors are involved in the prediction of these data ....... authors should suggest possible factors for this........

Thus all the discussion should be rewritten based on the values of correlation and regression found not only based on statistical significance. In addition, the conclusion that presents is also not appropriate is a very strong statement on the weakness of the data presented.

We appreciate your comments. As you pointed out, \( r^2 \) is relatively small in the present analyses. Therefore, we have revised the manuscript, citing the \( r^2 \) values in some parts.

First, as other factors possibly involved in the generation of these data, we consider that systemic effects such as reduced exercise capacity or systemic inflammatory status might be relevant to these results. Therefore, we have discussed this point in the revised manuscript.

In the revised manuscript:

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“The values for the coefficient determinations were relatively small in Table 3 (cumulative \( r^2 = 0.09 \) to 0.38), indicating that other factors might be contributing to outcome. In the present study, we did not assess systemic consequences of COPD, such as exercise capacity and inflammatory biomarkers. These are known to be significantly
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correlated with health status or dyspnea independently of FEV$_1$ [5-7, 45]. As COPD is regarded as a systemic disease [1], in future, a more comprehensive approach including these parameters might be informative for better understanding the systemic effects of COPD compared to airway diseases in the future.” (Page 17 to 18 in the revised Discussion)

Second, we might have over-interpreted the results in some parts of the papers based on statistical significance although the coefficient determinations were relatively small. Therefore, we have revised the following parts of the text, including the conclusion, not to be so strong.

In the original manuscript:

“IOS is a useful clinical tool not only for detecting pulmonary functional impairment but also to assess the patient’s quality of daily life and well-being.” (Page 3 in the original Abstract)

In the revised manuscript:

“IOS may be a useful clinical tool not only for detecting pulmonary functional impairment easily but also to some extent at least for estimating the patient’s quality of daily life and well-being.” (Page 4 in the revised Abstract)

In the original manuscript:

“Multiple regression analyses also revealed that they accounted for the SGRQ and MRC scores more significantly than FEV$_1$ and CT measurements. Thus, the novel finding in this study is that peripheral airway measurements by IOS are useful in
assessing not only pulmonary impairments but also health status and dyspnea in patients with COPD.” (Page 14 in the original Discussion)

In the revised manuscript:

“Multiple regression analyses revealed that R5-R20 or X5 accounted for the SGRQ and MRC scores more significantly than FEV\textsubscript{1} and CT measurements ($r^2 = 0.09$ to 0.26). Thus, the novel finding in this study is that peripheral airway measurements by IOS were useful not only for assessing pulmonary impairments but also because they have certain relationships with health status and dyspnea in patients with COPD.” (Page 15 in the revised Discussion)

In the original manuscript:

“Thus, the present study indicates that the peripheral airway is important in determining pulmonary impairments as well as health status and dyspnea in patients with COPD, which can easily be assessed using IOS.” (Page 15 in the original Discussion)

In the revised manuscript:

“Thus, the present study indicates that the peripheral airway may be important in determining pulmonary impairments as well as health status and dyspnea to some extent in patients with COPD, which can easily be assessed using IOS.” (Page 16 in the revised Discussion)

In the original manuscript:

“IOS is a useful clinical tool not only for detecting pulmonary functional
impairment, but also to assess the patient’s quality of daily life and well-being.” (Page 3 in the original Abstract)

In the revised manuscript:

“Therefore, in addition to its simplicity and non-invasiveness, IOS may be a useful clinical tool not only for detecting pulmonary functional impairment, but also to some extent at least for estimating the patient’s quality of daily life and well-being.” (Page 4 in the revised Abstract)

I suggest to the authors to add information about study limitations…..

In addition to the limitation in our original discussion, we have added two more limitations to the revised discussion. As one limitation, I have already described the small number of the patients involved in the reply for statistical comments. The other limitation is that this study's population consists only of men, as another reviewer pointed out. This was described as follows:

In the revised manuscript:

“Second, this study included only male patients, as there are relatively few female patients. This may be due to the gender difference in past smoking trends in Japan, and possibly reflects the present features of Japanese COPD patients. Thus, the generalization of the results to females is unwarranted.” (Page 18 in the revised Discussion)

Finally, I think we should encourage this paper to be published only after extensive
review of the results and discussion of the data found.

We thank you for constructive comments, which have helped us improve our manuscript significantly. We look forward to your reply.