Author’s response to reviews

Title: Risk factors of postoperative pulmonary complications in patients with asthma and COPD

Authors:
Takanori Numata (t-numata@jikei.ac.jp)
Katsutoshi Nakayama (kat_n1@hotmail.com)
Satoko Fujii (satt_rosa@yahoo.co.jp)
Yoko Yumino (yyumino@ab.cyberhome.ne.jp)
Nayuta Saito (nayutasaito@jikei.ac.jp)
Masahiro Yoshida (yoshida-masa@jikei.ac.jp)
Yusuke Kurita (y-kurita@jikei.ac.jp)
Kenji Kobayashi (k.kpetshopboy@gmail.com)
Saburo Ito (sabu-s55@jikei.ac.jp)
Hirofumi Utsumi (hiro173@jikei.ac.jp)
Haruhiko Yanagisawa (haruhikov@mac.com)
Mitsuo Hashimoto (mitsuoha-georgetown@live.jp)
Hiroshi Wakui (hwakui0304@gmail.com)
Shunsuke Minagawa (shunske@jikei.ac.jp)
Takeo Ishikawa (takeoishfa2@gmail.com)
Hiromichi Hara (hirohara@jikei.ac.jp)
Jun Araya (araya@jikei.ac.jp)
Yumi Kaneko (yukanekomi@jikei.ac.jp)
Kazuyoshi Kuwano (kkuwano@jikei.ac.jp)

Version: 1 Date: 04 Nov 2017
Author’s response to reviews:

PULM-D-17-00336

Risk factors of postoperative pulmonary complications in patients with asthma and COPD

Dear Editor and Reviewers

Thank you very much for reviewing our manuscript, “Risk factors of postoperative pulmonary complications in patients with asthma and COPD (PULM-D-17-00336)”. We really appreciate the valuable comments made by reviewers. I attach here our revised manuscript, as well as point-by-point responses to the reviewers’ comments.

We believe that the manuscript has been significantly improved as a result of your suggestion and we hope that we have adequately addressed all of your comments.

Thank you in advance for your kind consideration of this paper.

Sincerely yours,

Corresponding author
Takanori Numata, MD, PhD
Division of Respiratory Diseases,
Department of Internal Medicine
The Jikei University School of Medicine, Tokyo, JAPAN
3-25-8, Nishi-Shimbashi, Minato ward, Tokyo 105-8461 JAPAN
+81-3-3433-1111(ex 3271)
t-numata@jikei.ac.jp

RESPONSE TO REVIEWER 1

We wish to express our appreciation to the Reviewer for the insightful comments, which have helped us significantly improve the paper.

Comment #1

The statistical analysis and methods require further details being added, specifically the regression analysis methods, eg how were confounders dealt with? which ones were included/excluded? criteria for elimination/inclusion?

Response #1
We appreciate the reviewer's comment on this point.

To exclude the influence of confounders, we referred to previous studies and selected age, gender and other variables with $p < 0.20$ in the univariate model as candidates for the multivariable model.

Based on the reviewer’s comments, we have added the following text:

“In patients with asthma, we selected age, gender (male), smoking index ($\geq 20$), peripheral blood eosinophil count ($\geq 200$/mm$^3$), GINA STEP ($\geq 3$), $\%$FEV$1$, upper abdominal surgery, perioperative systemic steroid therapy and operation time (minutes) for the multivariate analysis. However, in patients with COPD, we selected age, gender (male), COPD treatment, upper abdominal surgery and operation time ($\geq 5$ h) for the multivariate analysis.”

(p10 line 9~)

Comment #2

only those asthmatics/COPD patients who saw a respir specialist are analyzed. I understand that there is not much data on others available, however it would be useful to investigate how the patients seen by a respire specialist differ in age and sex from those asthmatics/COPD patients NOT seen by respire specialist before operation.

Response #2

We appreciate the reviewer's comment on this point.

We retrospectively analyzed patients seen by pulmonologists among all patients who underwent surgery, and patients not seen by the pulmonologists were excluded.

Please see Figure 1. A total of 8687 patients were excluded by screening in each department and were not seen by pulmonologists. Our clinicians were unable to detect patients with asthma/COPD who did not meet the three selected criteria and had no PPCs. Unfortunately, we could not diagnose patients with asthma/COPD if specific information was not available in their medical records.

RESPONSE TO REVIEWER 2

We wish to express our appreciation to the Reviewer for the insightful comments, which have helped us significantly improve the paper.

Comment #1
The preoperative procedure is still not clear to me. In your preoperative pulmonary rehabilitation program you asked all patients for known/established pulmonary diseases, and you also performed pulmonary functions tests in all patients. Did you also detect and newly diagnose previously unknown pulmonary diseases? Which pulmonary function tests did you perform? Please insert a consort diagram that clearly states the procedure. How many files did you screen? How many missing values did you have in your retrospective sample?

Response #1

We apologized for the reviewer’s confusion conferred by our insufficient explanation.

The criteria for a preoperative consultation with a pulmonologist were the following: (1) the patient had any pulmonary diseases in the present or past, (2) the patient had an abnormal result in a screening test performed using spirometry for general anesthesia, or (3) the patient had abnormal chest images. Sometimes, we detected new pulmonary diseases, such as interstitial pneumonia, pulmonary infection and malignant diseases, during these screening examinations. We have included a new figure and added text to the section Study subjects and results. (p7 line 14- and figure 1)

We collected all patient information from the medical records of the 346 selected patients. However, six of the patients (three with asthma and three with COPD) could not undergo a preoperative pulmonary function test because of an emergency. We performed complete case analysis for the multivariate analyses.

Comment #2

You state that patients with asthma received inhaled or systemic corticosteroids (p.6, lines 19-22). On page 8, lines 8ff you further outline your intervention strategy. You state that patients with uncontrolled symptoms received oral corticosteroid treatment and other 'mostly' got their inhaled CS escalated. Does this mean that all (!) asthmatics with an ACT <20 received OCS prior to surgery? On what basis was intervention in controlled asthmatics based? Please clarify how a structured approach across all patients of the study cohort was established.

Response #2

We appreciate the reviewer's comment on this point.

The GINA document mentions that “meticulous attention should be paid preoperatively to achieving good asthma control”. A primary target was to achieve a safe surgery, and we therefore referred to this document. After a first visit to our department, patients with severe/uncontrolled asthma were treated with escalated ICS and revisited for a final decision regarding the advisability of surgery. We introduced OCS to patients with GINA STEP ≥ 3, neurosurgery, emergency surgery, or a history of PPCs. We also introduced OCS to patients with low ACT scores (a score of approximately < 22) after an ICS dose escalation.
Hence, patients with ACT scores < 20 at the first visit were not always received OCS.

To clarify the intervention protocol used in this study, we have replaced the original text with the following sentences in the relevant paragraph of the Intervention section (p9 line 3~):

“Our standard baseline therapy for bronchial asthma is based on the GINA stepwise approach. We primarily targeted safe surgeries and referred to this document. To prevent perioperative bronchospasm, we increased the dose of inhaled corticosteroids (ICS) administered to most patients. After the first visit to our department, patients with severe/uncontrolled asthma revisited the department for a final decision regarding whether surgery was advisable. In patients with GINA STEP≥ 3, neurosurgery, emergency treatment, PPC history, or low ACT scores (approximately < 22) after ICS dose escalation, we introduced systemic corticosteroids, such as prednisolone (e.g., 20 mg/day, p.o.) for several days before surgery and a short-acting corticosteroid, such as hydrocortisone (e.g., 100 mg i.v. every 8 h) on the day of the surgery[10].”

Comment #3

You state that 346 adults with abnormal pulmonary function and a diagnosis of asthma or COPD were included (p.7, l. 9-10). Does this mean that patients with asthma with normal lung function were excluded from this study? What about patients with abnormal lung function to causes other than asthma or COPD, were they also excluded? Please clarify the in and exclusion criteria of your sample and the study procedure.

Response #3

We apologized for the reviewer’s confusion conferred by our insufficient explanation.

Patients with asthma and normal pulmonary functions were included in the present study. However, patients with abnormal pulmonary functions for reasons other than asthma or COPD were excluded from the analysis.

To clarify this point, we have added the criteria used for preoperative consultations to the Study subjects section as follows: “Patients with other pulmonary diseases were excluded from this study.”

(p7, line 21~)

(These reviewer’s comments are related to those presented in comment#1. We have included a new figure to address these concerns).

Comment #4
You assessed the ACT for patients with asthma. Did you also assess a symptom score for patients with COPD, e.g., CAT? In your definition of PPC you included 'bronchospasm' and 'respiratory failure with oxygen therapy' (p.8, l. 3-4). Please clarify how these outcomes were measured.

Response #4

We appreciate the reviewer's comment on this point.

Although we also evaluated COPD assessment test (CAT) scores, 61 of the 89 patients with COPD (69%) had no CAT scores. Hence, we did not include them in the study presented in this manuscript.

We defined bronchospasm as symptoms (wheezing, shortness of breath, and cough) that required medication, such as a bronchodilator or corticosteroids, and we defined respiratory failure as hypoxia requiring more oxygen therapy or prolonged oxygen therapy than was initially expected. We reviewed all medical records to measure these outcomes.

Based on the reviewer’s comment, we have included the following sentences in the Data collection section (p8, line 14~):

“We defined bronchospasm as symptoms (wheezing, shortness of breath, and cough) requiring additional medications, and we defined respiratory failure as hypoxia requiring more than oxygen therapy or prolonged oxygen therapy. We reviewed all medical records to measure these outcomes.”

Comment #5

You state that smokers were asked to quit smoking. Did you also offer any structured intervention programs? Did you follow-up on their smoking habits and were patients excluded from surgery if they did not quit smoking?

Response #5

We appreciate the reviewer's comment on this point.

We did not use an intervention program to help the patients to quit smoking. To decrease the risk of PPCs, pulmonologist, anesthesiologist, and other co-medical staff explained the importance of smoking cessation. However, we did not exclude current smokers from surgery.
In your hospital 14,194 surgeries were carried out between 04/14 and 03/15. Subtracting cataract surgery and lung resection leaves app. 10,200 surgeries. How many pediatric surgeries do you have? 90 patients with COPD seems surprisingly low. Please include a consort diagram.

Response #6

We appreciate the reviewer's comment on this point.

We performed 1081 pediatric surgeries (under 15 years old) in our hospital between April 2014 and March 2015. (p7 line 11~)

Moreover, we treated approximately 4200 patients aged 40 years old and older with general anesthesia. The prevalence of COPD was 8% in Japanese patients aged 40 years old and older (Fukuchi Y et al. Respirology 2004), and an estimated 330 patients had COPD in the present study. The proportion of surgeries in which general anesthesia was used was 20% in otolaryngology (including only 3% in malignancy), 15% in orthopedics, 13% in gynecology, 12% in gastrointestinal surgery, and 10% in neurosurgery.

The number of cases in which cardiovascular diseases, esophageal cancer or laryngopharyngeal cancer coexisted with COPD was small, and we excluded lung cancer surgeries.

Furthermore, 12 surgeries were cancelled because of severe COPD with very low pulmonary function, and these were excluded from the present study. We think that the inclusion of the remaining 89 COPD patients in the present study was appropriate, based on these facts.

These data are shown in Figure 1, and the characteristics of our hospital are described in the Limitations section. (p19 line 2~)

Comment #7

If you treat patients with severe/ uncontrolled asthma with oral CS as part of your intervention it is not very surprising that this is also a result of your study, is it?

Comment #8

Your main finding is that ,the perioperative systemic corticosteroid treatment for asthma significantly seemed to increase the risk of PPC in univariate analyses. Please explain this conclusion derived from a retrospective cohort study without control group.

Response #7& #8

We appreciate the reviewer's comment on this point.
Because it is difficult to precisely evaluate risk factors using a univariate analysis, we further evaluated them in a multivariate logistic regression analysis. As described in this manuscript, early reports demonstrated that OCS was effective as a precaution against PPC in patients with asthma. Hence, we think that may be unethical to perform a prospective study using a control group. In our protocol, systemic corticosteroid treatment tended to be introduced in patients with GINA STEP 3, 4 or 5. Our multivariate logistic regression analysis showed that severe/unstable asthma patients had significantly more PPC events. Because the severity of PPCs was mild in most of the cases, we propose that in clinical practice, OCS effectively minimizes the severity of PPCs in patients with asthma.

Based on the reviewer’s comment, we have added and changed the relevant sentences in the Discussion (p14 line 21~) and limitations section (p18 line 19~).

RESPONSE TO REVIEWER 3

We wish to express our appreciation to the Reviewer for the insightful comments, which have helped us significantly improve the paper.

Comment #1

There are typographical errors and misuse of English throughout. I suggest a review of the writing style and use of firm scientific language to support the main text, discussion and conclusions.

Response #1

We apologized for typographical errors and misuse in our manuscript.

We used English language editing service.

Comment #2

The COPD group only has 9 subjects, I suggest more data be added to this sample in order to make a stronger statically argument.

Response #2

We appreciate the reviewer's comment on this point.

We also found that the number of PPCs was relatively smaller in COPD patients than in those with asthma. The following are several potential causes for this finding. (1) First is the proportion of each type of surgery because otolaryngology patients comprised approximately 20% of all patients who were treated with general anesthesia, and these patients often had
asthma; whereas relatively few cardiovascular or laryngopharyngeal surgeries were related to smoking. (2) This was a retrospective study, and in some cases, we sought to clinically reduce PPCs by cancelling the surgery or avoiding the use of general anesthesia. However, it is desirable that multi-center studies with longer terms should be performed.

Based on the reviewer’s comment, we have added the relevant text to the Limitations section as follows: (P19 line 4~)

“Otolaryngology patients comprised approximately 20% of all patients treated with general anesthesia, and these patients often had asthma. However, the number of cases in which cardiovascular diseases, esophageal cancer or laryngopharyngeal cancer coexisted with COPD was small. Hence, multicenter cohort studies are desirable for collecting balanced data.”

In addition, the number of patients with COPD and that of PPC were less than expected. However, the reason for a small number of PPC events would be the fact that we conducted management to reduce PPC in clinical practice.

Comment #3

Please include more detail on lung function data (baseline and post bronchodilator response, proportion of patients that meet the GINA reversibility criteria. ACT score data should be included.

Response #3

We appreciate the reviewer's comment on this point.

Because a reversibility test was performed in only 20 of the 257 cases (8%) and 10 of the 20 cases (50%) that met the GINA criteria, we did not show these data.

We preoperatively evaluated the ACT scores of 198 of the 257 patients with asthma (77%).

Based on the reviewer’s comment, we have added the relevant text and a new Table that shows the data for ACT scores according to GINA STEP. (p11 line23~ and Table 3)

Comment #4

Page 11 line 2 and 3 - describes mild/moderate bronchospasm as PPCs, how was this assessed?

Response #4

We appreciate the reviewer's comment on this point.
We referred to GINA, and we retrospectively reviewed all medical records and assessed symptoms and additional medications.

Based on the reviewer’s comment, we have included the following sentences in the Data collection section:

“We defined bronchospasm as symptoms (wheezing, shortness of breath, and cough) requiring additional medications, and we defined respiratory failure as hypoxia requiring more than oxygen therapy or prolonged oxygen therapy. We reviewed all medical records to measure these outcomes.”

Comment #5

abbreviation PD is not listed.

Response #5

According to the reviewer’s comments, we have changed PD to “pulmonary disease”.

Comment #6

The section on limitations should be expanded in order to show the authors awareness of the study limitations.

Response #6

We appreciate the reviewer's comment on this point.

Based on the reviewer’s comment, we added the following text:

“The number of patients with asthma or COPD analyzed in the present study may depend on the proportion of surgical cases per department. Otolaryngology patients comprised approximately 20% of all patients treated with general anesthesia, and these patients often had asthma. However, the number of cases in which cardiovascular diseases, esophageal cancer or laryngopharyngeal cancer coexisted with COPD was small. Hence, multicenter cohort studies are desirable for collecting balanced data.

Second, although the total number of patients was 346, it would be preferable to register more patients. In addition, fewer patients than expected suffered from COPD and PPC. However, the reason for the small number of PPC events observed in this study could be that we managed our patients in a manner aimed at reducing PPCs.”

(p19, line 2~)