Author’s response to reviews

Title: Prognostic nomogram for inpatients with asthma exacerbation

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Author’s response to reviews:

Dr. Alessandro Marcon,
Epidemiology and Public Health Editor,
BMC Pulmonary Medicine.
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Dear Dr. Marcon,

Response to the Reviewers’ comments: Manuscript ID: PULM-D-16-00290 ‘Prognostic nomogram for inpatients with asthma exacerbation’.
We thank the Editor and reviewers for their careful and comprehensive review of our manuscript, and their pertinent comments and recommendations. We have used these to refine and revise our manuscript, and have addressed each question in point-by-point fashion below. You will find the changes in the main manuscript in red font.

We believe that the revised manuscript is now substantially improved. We would be most grateful if you would reconsider it for possible publication in BMC Pulmonary Medicine.

We look forward to hearing from you at your earliest convenience.

Sincerely yours,

Reviewer reports:

Editor's comments: I have a major comment on the statistical analysis. There are two reasons why I recommend not to apply logistic regression. The first reason is that your data are longitudinal and time at risk (from admission to hospital discharge or death) or time to event are of interest. My second reason for concern regards the fact that your outcome is rare and thus you have few events (deaths) even if your dataset is very large. Some of the cells formed by the outcome and categorical predictor variable have no or just few observations and this may cause model instability, especially in multivariable analysis. I think that applying models that are appropriate for longitudinal data, such as survival analysis or models for incidence rates (events/person-time at risk) would fix both issues.

>Thank you for your comments. In accordance with your recommendation, we have re-analyzed the factors associated with all-cause in-hospital mortality and re-built the nomogram using the Cox proportional hazards regression analysis, shown in Figure 1. We also revised the calibration plot in Figure 2. The new results of the analysis for all-cause in-hospital mortality are now shown in Table 4.

We have also revised the Methods section as follows:

“Cox proportional hazards regression analysis was undertaken to assess factors associated with all-cause in-hospital mortality, and the variables identified were used to build a nomogram to predict in-hospital all-cause death.”

Furthermore, we have revised the Results section as follows:

“Table 4 shows the results of the Cox proportional hazards regression analysis for all-cause in-hospital mortality. Higher mortality in the asthma exacerbation patients was associated with
older age, male sex, disturbance of consciousness, severe dyspnea, intubation within two days after admission, pneumonia and heart failure on admission.”

“Using the same variables identified in the Cox proportional hazards regression analysis, we built a nomogram, which is shown in Figure 1. The concordance index of the model was 0.869.”

Finally, we have revised the Discussion section as follows:

“Higher mortality in asthma exacerbation was associated with older age, male sex, disturbance of consciousness, severe dyspnea, endotracheal intubation within two days after admission, pneumonia and heart failure on admission.”

Minor comments:

- Please explain which ICD codes identify subjects admitted for an asthma exacerbation.

  > We identified patients with asthma exacerbation using ICD-10 code J45 (asthma) and J46 (status asthmaticus) as the main diagnosis or the disease that required hospitalization.

We have added the following to the Methods section:

“We included patients aged 18 years or older who were diagnosed with asthma exacerbation (ICD-10 code, J45 asthma or J46 status asthmaticus as the main diagnosis or the disease that required hospitalization) and who received systemic corticosteroid therapy within 2 days of admission.”

- Did your patients have either (1) an asthma exacerbation diagnosis on admission, or (2) they received systemic corticosteroids therapy within two days after admission, or both criteria together (1+2)? Also, report how many met each of these conditions.

  > We thank the Editor for this comment. Patients included in this study had a diagnosis of asthma exacerbation diagnosis on admission and received systemic corticosteroid therapy within 2 days of admission. We identified 24,279 patients with a diagnosis of asthma exacerbation on admission, and 25,120 who received systemic corticosteroid therapy within 2 days of admission.

We have added the following to the Results section:

“…March 2013, we identified 24,279 patients diagnosed with asthma exacerbation on admission, and 25,120 who received systemic corticosteroid therapy within 2 days of admission in the database. Then, we identified 19,684 patients…”
Can you give instructions on how to use the nomogram and provide an example? (e.g. add a note to Figure 1).

> Thank you for this comment; we have added an example to Figure 1 as follows:

“...(for example, an 80-year-old (100 points) woman with pneumonia on admission (20 points), but with grade I dyspnea and who is alert, with no evidence of heart failure and who did not require tracheal intubation would score 120 points. Her 30-day survival probability is 0.95 to 0.99).”

Please revise: “Median length of day from admission to intubation”; it could be “median time from admission to intubation”.

> Thank you for your advice. We have changed “Median length of day from admission to intubation” to “median time from admission to intubation” in the Results section.

Amend “somnolence” in figure 1.

> We amended “somnolent” in Figure 1 and corrected “dyspnea grade I, II, III, IV” to “I to IV”.

Please put extra care in responding to query 3 from reviewer 1 (why patients who died in the first 2 days were excluded? how are your results affected by this selection?) and queries from reviewer 2 on the advantages of using a nomogram and the use of both discrimination and calibration.

Thank you very much for your comments. We have replied to the relevant comments below.

Reviewer #1: In this study the authors have used a large nationwide inpatient database in Japan in order to investigate the possible associations of several clinical features and factors to in-hospital mortality in patients admitted with asthma exacerbations. Furthermore, the authors are generating a nomogram to predict in hospital prognosis for these patients.

This is a very interesting study showing factors that seem to influence the outcome of asthmatic patients admitted to the hospital due to asthma exacerbations.
The main strength of the study is the large number of data that it includes. However, its retrospective design leads to some limitations that cannot be ignored.

1. The authors do not specify if they have excluded smokers or what was the effect of smoking history in the outcome of asthma exacerbations. It is known that the outcome of asthmatic smokers is worse compared to non-smokers and this is an important variable that had to be tested.

> Thank you for your helpful comments. We did not exclude smokers from our analysis. Although the DPC inpatient database records smoking index, it does not identify current or ex-smokers. Furthermore, as a large of proportion of smoking data were missing, we could not discuss the influence of smoking history on the outcome of asthma exacerbation. We have added the following to the limitations of our study in the Discussion section:

“Finally, because of missing data, we could not investigate the influence of smoking history on the outcome of asthma exacerbation.”

2. Were patients with concomitant COPD (i.e. patients with ACOS) excluded? If not, this might be an important bias.

> Thank you for this important comment. We did not exclude patients with COPD. We identified 2,933 patients with COPD, including 25 in-hospital deaths. In-hospital mortality was not significantly influenced by a diagnosis of COPD (p = 0.054). We have added this information to the Methods section, Table 2 and the Discussion:

“The following comorbidities were also identified using ICD-10 codes and text data in Japanese: chronic obstructive pulmonary disease (COPD, J44), pneumonia…”

“Some patients with clinical features of both asthma and COPD have been referred to as having ‘asthma COPD overlap’ (ACO) syndrome. Our previous study demonstrated that compared with asthma alone, patients with ACO exhibited significantly higher in-hospital mortality. In this study, although the in-hospital mortality of patients with ACO was higher than patients with asthma alone, the difference was not significant, probably because of the low death rate among the study population.”

3. I do not totally understand why patients who died due to asthma exacerbation in the first two days after admission were excluded from the analysis. Especially to these patients the health status on admission might have played an important role. I believe that these patients should be also included to the total number of patients with bad outcome and the authors might also
divide patients who died, in those with early (i.e within the 2 first days) or late (after the 2 first days) mortality.

> Thank you for your advice. As endotracheal intubation within 2 days of admission was adopted as a predictor of in-hospital death, it was therefore necessary to remove deaths within 2 days of admission. If we had included deaths within 2 days of hospitalization in our outcome, patients in extremis who died very soon after admission before they could be intubated would have been included in the ‘non-intubation group’, which would have weakened the relationship between endotracheal intubation and in-hospital death. We have discussed this as a limitation of our study:

“We also excluded patients who died within 2 days of admission; as endotracheal intubation within 2 days of admission was adopted as a predictor of in-hospital death, we removed those who died within 2 days of admission from the analysis.”

4. The authors do not include therapy in their analysis. The use of ICS is of major importance and as stated to the introduction section lack of its use has been related to more adverse outcomes.

> Thank you for your advice. Unfortunately, we have no data on the use of ICS or rescue medication before or after admission, and have acknowledged this as a limitation:

“Second, because the DPC database does not include detailed clinical information such as drugs used before or after admission, the results of pulmonary function or blood tests, socioeconomic variables, or symptoms before admission, the baseline status of the patients was not evaluated in this study.”

5. The use of rescue medication should also be included.

> Unfortunately, we have no data on the use of rescue medication before or after admission, and have acknowledged this as a limitation.

6. Socioeconomic variables (which might also affect adherence to therapy should be also included to the analysis)

> Unfortunately, we have no data on socioeconomic variables, and have acknowledged this as a limitation.
7. Were all deaths asthma related? Were any deaths related to other factors? Such as sepsis, heart failure, ischemic heart disease etc?

> Thank you for your comment. We recorded all-cause deaths, as the DPC database does not include cause of death. We have added this information to the Methods section:

“Other extracted data were patient outcome, including length of hospital stay and all-cause in-hospital death.”

Reviewer #2: To authors:

Overall, the work of the manuscript BMC Pulmonary Medicine - PULM-D-16-00290 is an interesting contribution to the literature in this area.

The authors have built a novel prognostic model using nomogram for inpatients with asthma exacerbation and identified the risk factors including older age, male, lower level of consciousness, more severe dyspnea, endotracheal intubation within two days after admission, pneumonia and heart failure. A great number of 19,684 asthma patients from the Japanese Diagnosis Procedure Combination database was been used to find the prognostic factors which could predict in-hospital mortality in patients with asthma exacerbation.

However, the study was still not very convincing for its claims because of lack of the consideration of some important prognostic factors, the details in the statistical section in terms of some indispensable evaluation and it is also lack of discussion on advantage of the prognostic nomogram which is usually used in oncology.

Here, I list my specific concerns for the manuscript below:

Background: P3. Line36 - Line41; Discussion: P10. Line9 - Line12:

As the authors claimed nomograms were widely used as prognostic tools in oncology. It would be better to discuss more about the advantages of using nomogram on the basis of the multivariable logistic regression analysis and its impacts on helping the physicians to make clinical decision for asthma patients.

> Thank you for your helpful comments. One of the advantages of a nomogram is its ability to estimate individualized risk in an easy and straightforward way. The variables in our nomogram are easy to estimate without the need for complex examination or investigations, helping physicians, other healthcare professionals and even patients to make clinical decisions. Our study is the first to describe a nomogram to estimate in-hospital death in patients with asthma exacerbations. We have added the following to the Discussion section:
“Our nomogram enables a patient’s individual risk of in-hospital death to be predicted by evaluating simple parameters such as personal characteristics, medical history and physical status on admission, without the need for complex examination or investigations. One of the advantages of a nomogram is its ability to estimate individualized risk in a simple and straightforward way.”

“Previous studies have identified the risk factors for death in patients with asthma, but did not identify means of predicting the probability of death of individual patients. A nomogram can integrate variables and relevant determinants of disease into a prognosis. With the present nomogram, physicians can easily estimate a patient’s individual probability of death, which is helpful for clinical decision making.”

Methods: P5. Line31 - Line56:

The authors identified the patients' characteristics including age, sex, BMI, consciousness level and etc., yet they did not include some relevant factors e.g. family history of asthma, ever smoking, the presence of wheezing or whistling, current asthma medication use, tests of lung function and etc. which might also influence the asthma exacerbation. These genetic and environmental factors may also contribute to the mortality in patients with asthma exacerbation who required hospitalization. And it would be necessary to present the descriptive tables of these factors if they had the data, and include them in the selection model.

> Thank you for this helpful comment. As you point out, genetic and environmental factors are important risk factors for in-hospital death in patients with asthma exacerbation. Unfortunately, as this study was a retrospective analysis of an inpatient database and all data are anonymized, we could not review patients’ clinical records. We have no information about family history of asthma, the presence of wheezing or whistling on admission, current asthma drug use, current smoking status or pulmonary function test results. All the patients who received systemic steroids presumably were found to have wheeze, and moreover, to the best of our knowledge, there is no relationship between family history and death in patients with asthma exacerbation. Family history, clinical signs on admission and lung function test results would detract from the construction of a simple nomogram and would not have fitted with the aims of our study. We have discussed these issues as potential limitations of our study:

“Second, because the DPC database does not include detailed clinical information such as drugs used before or after admission, the results of pulmonary function or blood tests, socioeconomic variables, or symptoms before admission, the baseline status of the patients was not evaluated in this study.”
Methods: P6. Line2:

Chi-square tests are usually used in the data with normal distribution. However, the authors did not describe what were the distributions of the sample. It should first present appropriate normality test and then use the corresponding methods to compare the groups.

> Thank you for your comment. The chi-squared test is used to compare proportions of categorical data. All the variables presented in the Tables are categorical variables.

Methods: P6. Line7 - Line9:

The authors only applied the bootstrapping method for internal validation. They did not claim whether the data was from only one center or several different centers. If the data was from multiple centers, external validation could be performed to test the robustness of the model in a separate validation cohort of patients who were prospectively recruited from different centers.

> Thank you for your comment. The data used in this study was derived from many different centers across Japan, and we undertook bootstrap resampling from the entire cohort. External validation is usually needed for data that were not used to develop the model. As you mention, external validation should be performed using a different dataset in a future study.

Also, it is common to use both the discrimination and the calibration of the model to evaluate the predictive performance of the model. It would be better to provide the discrimination ability of the prognosis model as well.

> Thank you for your comment. We calculated the concordance index to quantify the predictive performance of the model and the index (concordance index, 0.869), and have included it in the Results section. In addition, a new calibration plot has been included in Figure 2.

Discussion: P10. Line1 - Line3:

The authors have first found the associations of lower level of consciousness and more severe dyspnea and asthma mortality in adults. It would better to discuss more about the possible mechanism of these newfound factors.

> Thank you for your advice. In accordance with the Editor’s comments, we re-analyzed factors associated with all-cause in-hospital mortality using Cox proportional hazards regression. The results showed no significant relationship between dyspnea level and in-hospital mortality. Thus, we have only added the following to the Discussion:
“Hypercapnia is associated with severe airway obstruction in patients with asthma, and may impair level of consciousness and the ability to talk or move. One previous study reported no significant relationship between hypercapnia and death in outpatients with asthma, while another showed higher partial pressure of arterial CO2 was associated with increased mortality in patients admitted to ICU with asthma exacerbation. Thus, hypercapnea may be a potential risk factor of mortality for patients in extremis. Our study included such patients, which may explain the association between impaired consciousness and asthma mortality in adults.”

Additionally, it has been reported there was association between persistent asthma and cardiovascular diseases. Markers of inflammation like C-reactive protein, IL6, fibrinogen were significantly elevated among persistent asthma patients. It would be interesting if they also include these variable in the analysis if the data is available, as this study also found the association of heart failure and asthma mortality.

> Thank you for your advice. Unfortunately, the DPC database does not record the results of investigations such as serum C-reactive protein, IL6 or fibrinogen concentration. We have discussed this as a limitation of our study:

“Second, because the DPC database does not include detailed clinical information such as drugs used before or after admission, the results of pulmonary function or blood tests, socioeconomic variables, or symptoms before admission, the baseline status of the patients was not evaluated in this study.”