Author’s response to reviews

Title: Adjunctive Corticosteroid Therapy for Inpatients with Mycoplasma pneumoniae Pneumonia

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Author’s response to reviews:

To: Dr. Atsushi Nambu, Editor, BMC Pulmonary Medicine

From: Masato Tashiro

Ref. No.: PULM-D-17-00196

Thank you very much for reviewing our manuscript ‘Adjunctive Corticosteroid Therapy for Inpatients with Mycoplasma pneumoniae Pneumonia’ (Ref.No.:PULM-D-17-00196). We have modified our manuscript following the comments and suggestions from reviewers. Please review our revised manuscript.
All the authors have agreed to submit this article with the understanding that if the manuscript is accepted for publication, the copyright of the article shall be assigned exclusively to the journal. The material presented in this article has not been published or submitted elsewhere.

If you find any errors in our manuscript, please contact me.

Sincerely yours,
Masato Tashiro, M.D., Ph.D.

Reviewer #1 (Keith Wong)
---Reviewer #1 comments---

The research question concerned severe pneumonia - could the authors describe how the was population selected? The population studied was very unwell, with a long length of stay, but the participant inclusion criteria (Patient selection section, lines 135 onwards) make no mention of pneumonia severity.

---Author’s reply---

We appreciate your comments. We included not only severe pneumonia cases but also mild to moderate pneumonia cases in this analysis; therefore we removed the term “severe” from the research question.

During revising processes, we succeeded to acquire new data of patient characteristics regarding pneumonia severity such as A-DROP system evaluation, which is modified version of CURB65 established in UK. Therefore we adopted these pneumonia severity parameters and removed some previous characteristics associated with patient severity such as consciousness level (Japan Coma Scale), immunoglobulin use, sivelestat sodium use, blood transfusion, and hemodialysis. Unfortunately A-DROP data was missing in some patients; therefore patients who had any missing data were excluded from the analysis, which is the third exclusion criteria of the revised manuscript.

3) Study patients for analysis of the revised manuscript were changed from previous analysis because exclusion criteria were changed as Reviewer 2 suggested. New exclusion criteria is as follows: 1) discharge within 2 days of admission, 2) start corticosteroid therapy after day 2
and 3) existence of any missing data. We have conducted statistical reanalysis and made a necessary correction throughout the revised manuscript, the figure, and tables.

---Reviewer #1 comments---

Practically, in applying this knowledge, how will we know if the patient has mycoplasma pneumonia at the time we would like to commence steroids? Perhaps in future the authors could look at whether the findings are similar using less strict definitions for mycoplasma pneumonia, and also looking at pneumonia in general.

---Author’s reply---

Thank you for your comments. Before we started this study, we had hypothesized that corticosteroid therapy might be beneficial for treatment of M. pneumoniae pneumonia despite it might not be beneficial for treatment of other bacterial pneumonia. However, from the results of this study, ruling out of M. pneumoniae pneumonia might not be so important for improvement of treatment strategy about aspect of corticosteroid use.

---Reviewer #1 comments---

Regarding 30-day mortality could some of these events have been missed if patients died after their discharge from hospital? On line 127 it is stated that follow up ended at the time of discharge, transfer or death.

---Author’s reply---

Thank you for your comments. Theoretically the answer is Yes. If patients discharged before 30 days after admission and died after their discharge, those events were missed from this analysis. However most patients should not discharge from hospital before improvement of their status. Therefore, it would not be due to pneumonia if patients died after discharge.

Reviewer #2 (Todd A Lee)

MAJOR CONCERNS

---Reviewer #2 comments---

1. The exclusion criteria and how they impact the patients included in the analysis raise some concerns. First, the initial exclusion of individuals discharged within two days of admission is supposedly in an effort to avoid immortal time bias. However, it is not clear how this
exclusion would avoid immortal time bias. It may be reasonable to exclude these individuals if they are not 'at risk' for receiving corticosteroids but the 2 day discharge doesn't seem to have an impact on immortal time so long as the person time is appropriately categorized. Second, it is not clear why individuals were excluded if they used steroids for less than three days. How was an 'unexposed group' defined if those not using corticosteroids were excluded? Moreover, exclusion of this group ensures that those exposed to steroids will have at least 3 days in the hospital which would bias the findings to longer lengths of stay in the steroid exposed groups. With this as an exclusion criterion it is not at all surprising that those in the exposed groups have longer lengths of stay. Finally, the third exclusion criterion certainly raises concern about immortal time bias which is a major concern for this study. Individuals that were included had to start treatment within 7 days of admission to be included. So, if a patient started corticosteroids on day 7 they were eligible for inclusion and classified as steroid exposed. This is a classic case of introducing immortal time bias because these individuals are 'immortal' for the first six days in the hospital. This immortal time is attributed to the exposed groups, when in actuality the person wasn't exposed to corticosteroids until the 7th day of their stay. So these patients could not have been discharged during that time, could not have died during that timeframe and certainly would incur drug costs. This criterion would bias the results in the direction that was observed for both costs and length of stay. It would also bias the results toward corticosteroids looking protective for mortality and so perhaps the conclusion that there is no difference in mortality is biased and in fact there may be an increased risk associated with corticosteroid exposure.

---Author’s reply---

Thank you for your comments. We deleted a sentence “(to avoid immortal time bias)” from sentences of the initial exclusion criteria. We believe that any patients who discharged within 2 days of admission should not be suitable for evaluation of effectiveness of any treatment dispensed after admission because of its too short observational period.

In addition, after consideration of your valuable suggestions, we changed a definition of corticosteroid-treated patients from “who were administered corticosteroid within 7 days” to “who were administrated within 2 days after admission”. Therefore, we defined the second exclusion criteria as patients who started corticosteroid therapy after day 2 from admission. Previous exclusion criteria, patients who used steroid for less than 3 days, was removed as you indicated.

During revising processes, we succeeded to acquire new data of patient characteristics regarding pneumonia severity such as A-DROP system evaluation, which is modified versoin of CURB65 established in UK. Therefore we adopted these pneumonia severity parameters and removed some previous characteristics associated with patient severity such as consciousness level (Japan Coma Scale), immunoglobulin use, sivelestat sodium use, blood transfusion, and hemodialysis. Unfortunately A-DROP data was missing in some patients; therefore patients who had any
missing data were excluded from the analysis, which is the third exclusion criteria of the revised manuscript.

Study patients for analysis of the revised manuscript were changed from previous analysis because exclusion criteria were changed. We have conducted statistical reanalysis and made a necessary correction throughout the revised manuscript, the figure, and tables.

---Reviewer #2 comments---

2. The exclusion criteria are also confusing in understanding how a no corticosteroid group was defined. If those with no corticosteroid use in the first 7 days of the admission and those that used for less than three days are excluded, who makes up the 'unexposed' group? I am unable to determine the patients that were included as unexposed in the analysis given these exclusion criteria. It would be helpful to more fully describe exactly how each of the exposure groups was determined. This is true of the corticosteroid groups also. It appears that a threshold was used for differentiating the high and low dose groups (pg 7, lines 145-146), but was this on any day during the hospitalization or is it the average corticosteroid dose? In understanding how to interpret the results it is important to understand the details of how the groups were defined.

---Author’s reply---

We appreciate your comments. New exclusion criteria is as follows: 1) discharge within 2 days of admission, 2) start corticosteroid therapy after day 2 and 3) existence of any missing data. Therefore patients of no corticosteroid group were defined as patients who were treated without any corticosteroid during hospitalization, and patients of corticosteroid treated group were defined as patients who were administered any corticosteroid within 2 days after admission. The starting dosages of methylprednisolone was used for a threshold for differentiating the low and high groups. We added “the starting dosages” in the sentence (pg 7, lines 9).

---Reviewer #2 comments---

3. Propensity scores were used to try and account for differences between groups; however it is not clear why a propensity score was developed for low dose versus high dose and yet comparisons were high dose vs. no corticosteroid and low dose vs. no corticosteroid. In this case the propensity score predicts the likelihood of being high dose compared to low dose and may not at all balance on variables that are confounders between any exposure and no exposure and the outcomes in the study. Was the predicted probability from the regression for low dose vs. high dose applied to the no corticosteroid group? What were the propensity score distributions like in each of the two exposure groups compared to those in the no
corticosteroid group? While matching helps to alleviate some of the concerns with non-overlapping propensity score distributions, the approach may not balance on factors associated with use versus no use.

---Author’s reply---

Thank you for your comments. We did not develop a propensity score for low dose versus high dose. We actually calculate a propensity score and performed one-to-one matching for no corticosteroid and low-dose group. And separately, we also calculate a propensity score and performed one-to-one matching for no corticosteroid and high-dose group. We modified Figure 1, of which previous version might confuse readers.

---Reviewer #2 comments---

4. It is not clear when the covariates used in the propensity score were measured. Were these measured over the entire duration of the hospitalization? If yes, that is in appropriate as some of those factors may have been a consequence of the exposure and not a prediction of the exposure. In developing the propensity scores, the covariates should only include those that were available or occurred before the exposure. This may be quite challenging for those without an exposure, but again it is not clear how this group was defined.

---Author’s reply---

We appreciate your comments. We assessed medications administered and interventions performed within 2 days of admission except the endpoints.

---Reviewer #2 comments---

5. There needs to be an adjusted or accounting of within hospital correlation. As there may be different practice patterns across hospitals, different case mixes, and different outcomes that may not be a consequence of corticosteroid use it is necessary to account for these across hospital differences. Simply including hospital as a covariate in the propensity score model does not sufficiently account for within hospital correlation. There are a number of approaches that could be used, a couple of examples include matching individuals within hospitals (however this may not be feasible if there is a predominant practice within hospitals) or conducting a hierarchical analysis that accounts for the within hospital correlation.

---Author’s reply---
Thank you for your comments. We tried to use information of academic hospital and average number of patients (which mean all inpatients) in hospital per day as hospital characteristics. We adopted these factors as covariates in the propensity score analysis.

---Reviewer #2 comments---
6. Why is 30-day mortality exclusive of in-hospital mortality? Shouldn't these deaths be counted as deaths in the 30-day analysis? These patients died before the end of 30 days.

---Author’s reply---
Thank you for your comments. We removed in-hospital mortality from outcomes because it confuse readers as you indicated.

---Reviewer #2 comments---
7. The study is certainly underpowered for the mortality outcomes. In the matched analysis, there are twice as many deaths in the high dose group as the no corticosteroid group.

---Author’s reply---
Thank you for your comments. Number of patients in matched groups for re-analysis increased more than that of previous analysis because we changed exclusion criteria as mentioned above. Previous number of death in matched groups was too small for analysis; on the other hand, enough number of death is recognized in matched groups in re-analysis.

---Reviewer #2 comments---
MINOR CONCERNS
8. Presentation of the unmatched findings is not particularly helpful as these are likely confounded by disease severity.

---Author’s reply---
Thank you for your comments. We understand your idea. However we believe that Table 1 is needed because the unmatched data is fundamental data.