Author’s response to reviews

Title: Chronic Periodontitis and Community-acquired Pneumonia: A Population-based Cohort Study
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Author’s response to reviews:

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BMC Pulmonary Medicine
Dear Editor:

We would like to thank the editors and reviewers for their constructive comments, which have substantially improved our manuscript, “Chronic Periodontal Diseases and Community-acquired Pneumonia: A Population-based Cohort Study” (PULM-D-18-00613).

The detailed changes made to address the comments from the editors and reviewers are described below in our point-by-point response. We would like to thank the editors and reviewers for their suggestions and look forward to having our manuscript published in BMC Pulmonary Medicine.

Sincerely,

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Response to Reviewer 1’s (Te Chun Shen) comments:

(1) Definition:
1. Hospital-acquired pneumonia (HAP) refers to pneumonia occurring 48 hours after admission. It's right, but if a pneumonia develops within 3 days from the last discharge; it is also considered to be a HAP. How do you exclude the condition? Furthermore, in the study design, I do not see the method to exclude HAP from the overall pneumonia (J12-J18). (The coding in the database is usually a discharge diagnosis, which could not distinguish CAP or HAP.)

We would like to thank the reviewer for this comment, which has helped us address an important limitation that we initially overlooked. After reviewing several studies on HAP, pneumonia that developed within 10 days after last discharge was also confirmed as the definition of HAP. We accepted this comment and reflected it in the study group, leading to the exclusion of 1,314 HAP subjects. However, the direction of results was not altered. We added this information into the materials and methods section as shown below, and revised Table 1 to add the exclusion criteria.

Page 4, lines 66-69:
“HAP refers to pneumonia occurring 48 hours after admission or within 10 days after discharge from a hospital without incubating, and CAP refers to an acute infection of the lungs in people who have not been hospitalized recently and are not regularly exposed to the healthcare system [8, 9].”

Page 5, lines 100-101:
“Finally, to exclude subjects who had HAP during the follow-up period, 1,314 participants diagnosed with pneumonia within 10 days from last discharge were excluded (Figure 1).”

2. CAP refers to an acute infection of the lungs in people who have not been recently hospitalized and are not regularly exposed to the health care system. So how do you manage those people who are regularly exposed to the health care system, such as people undergoing regular hemodialysis or those living in the nursing home? (NOT a CAP)

We would like to thank the reviewers for pointing out these important aspects of the research design. We agree that patients with hemodialysis who are regularly exposed to the healthcare system, as well as those living in nursing homes, should also be excluded.

We excluded people who were potentially undergoing hemodialysis or who were exposed to the healthcare system from the study population as exclusion criteria in Table 1. The direction of the results was not altered.
1) Glomerular diseases (ICD-10 codes N00-N08)
2) Renal failure (ICD-10 codes N17-N19)
3) Other kidney diseases (ICD-10 codes N25-N28)
4) Dependence on renal dialysis (ICD-10 codes Z99.2)
5) Problems related to care-provider dependency (ICD-10 codes Z74)

Page 5, lines 98-100:
“We also excluded those who were suffering from renal failure that were likely to be exposed to the healthcare system, such as those undergoing regular hemodialysis, and those who living in nursing homes.”

3. In the study design, the main outcome was "admission by CAP”. As we know, many CAPs can be treated in the out-patient department (without admission). Therefore, the study could not catch all CAP events. The authors should clarify this. Maybe the authors need to consult a chest man to revise the study design.

We would like to thank the reviewer for this comment, which has helped us improve our manuscript substantially. In order to accurately diagnose CAP, the following criteria must be met. First, CAP should undergo a chest radiograph to establish the diagnosis and the presence of complications (pleural effusion, multilobar disease). Second, patients with CAP should undergo assessment of gas exchange (oximetry or arterial blood gas), routine blood chemistry and blood counts, and two sets of blood cultures.

However, NHIS data do not contain valuable clinical indices for CAP. We believe the NHIS data are well-organized NHIS, but we have set the main outcome to be strict so as to collect a more certain CAP target.

Also, in epidemiological analysis, CAP outpatients were excluded on the basis of not overestimating the main outcome. It is more reliable to tease out key results regarding the main outcome of more obvious and severe subjects.

The corresponding author, a professor in the Department of Family Medicine, had several peers review the research design.

(2) Abstract
You have a statement that "Compared to individuals without CP, individuals under the age of 65 who had CP had an increased risk of CAP (HR, 1.11; 95% confidence interval, 1.04-1.18)” in the abstract. I did not see the related analysis in the text and table, why? And if the statement is correct, the association between CP and pneumonia is really existed.

Thank you for your comment.
This phrase was left in the manuscript erroneously and should have been removed after adjustment for covariates. No statistically significant results were found after adjusting for all covariates, and we deleted this phrase from the text.

(3) Analysis
The authors should clearly define the end point of the study.

We would like to thank the reviewer for their insightful comment addressing this omission. In this study, there are three possible end points to analysis using the Cox proportional hazards regression model.

1. Event occurrence (admission by CAP)
2. No events occur until the follow-up period
3. Death during follow-up

Events occurring during the follow-up observation period were set as the main outcome and those that did not occur until the end of the follow-up period or died were set as censored data.

Page 6, lines 117-119:
“From the index date, participants were followed until the date of admission for pneumonia or until the day when the main outcome did not occur and survived or died on the way.”

How do you calculate multiple pneumonia events in one person?
As noted by the reviewer, coding in the database means that CAP and HAP are typically indistinguishable, so different types of pneumonia events were not calculated, but multiple cases in a single person can be expressed by calculation. However, our hypothesis was that chronic periodontitis would affect CAP. Because of this, the main purpose was to be hospitalized by diagnosed with CAP from index date; therefore, multiple pneumonia events were not calculated.

The authors should present the incidence density rate (events/person-years), not only the event numbers in their Results and Tables. This will help to know the true difference between CP and non-CP groups.
We agree that showing the incidence rate makes it easier to understand the data.
As requested, we calculated the incidence rate and added this information to the manuscript.

Page 3, line 47-48:
“The incidence rates of participants with CP and non-CP were 5.91 and 5.16, respectively (103 per person-year).”

Page 10, Table 4

(4) Discussion
Since you have mentioned that CP may have the possible association to aspiration pneumonia (J69.0), could you provide the data of incident aspiration pneumonia in your CP and non-CP groups?

Thank you for your comment.
We also considered this. A total of 1,477 subjects experienced aspiration pneumonia (J69) during the follow-up period, and the ratios in the CP and non-CP groups are as shown in the table below. However, the number of aspiration pneumonia cases was comparatively small and we decided not to include these data because we were concerned that it did not align with the focus of this paper.

<table>
<thead>
<tr>
<th>Aspiration pneumonia (J69; no. of cases)</th>
<th>Severity of CP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Healthy</td>
</tr>
<tr>
<td>Present</td>
<td>1,032</td>
</tr>
<tr>
<td>Absent</td>
<td>254,151</td>
</tr>
</tbody>
</table>

(5) Limitation
The absence of the detailed type, severity, and pathogens of CAP should be noticed. We would like to thank the reviewer for this comment, which has helped us improve our manuscript considerably. As requested, we have described in greater detail the limitations of NHIS data, which do not include detailed information about CAP-related clinical variables, in the Discussion section.

Page 13-14, line 217-220:
“Similarly, the lack of clinical information such as chest radiographs, blood samples, and pulmonary gas exchange data is a major limitation when defining CAP. To evaluate the causality between CP and CAP, pneumonia diagnosis needs to be supported by specific pathogen information to assess type and severity, so further studies involving specific laboratory data will be particularly informative on this topic.”

(6) Conclusion
I think the results do not fully support and reach the conclusion now.

We agree that readers could potentially find the basis of our conclusions insufficient. Thus, we modified the Discussion section to more clearly state our findings.

Minor points:
1. The title shows "chronic periodontal diseases", but the text usually shows "chronic periodontitis". I think it is better to use the same term, chronic periodontitis, in the whole article.

2. The abbreviation, CP (chronic periodontitis), should be defined again in the Background section, not only in the Abstract.

3. Table 1: "periodontitis" should be revised to "chronic periodontitis".

4. Table 2 and Table 3: "healthy" subjects should not be included into chronic periodontitis.

5. Table 3: "chronic periodontal diseases" should be revised to "chronic periodontitis".
6. Table 4: "chronic periodontal diseases and non-chronic periodontal diseases" should be revised to "severe chronic periodontitis and non-severe chronic periodontitis".

7. Table 5: "chronic periodontal diseases" should be revised to "severe chronic periodontitis" and "pneumonia" should be revised to "community-acquired pneumonia".

All of the changes listed above have been made.
We really appreciate the reviewer’s feedback.

Response to Reviewer 2’s(Rafael Stelmach) comments:

Interesting paper showing negative results according previous publications, which is quite rare nowadays in scientific scenario
Data came from a Korean health care databank, following a common way to explore controversial clinical hypothesis, to accept or denied itself
Eligibility criteria and study designed are clever, but the criteria to define the severity of research trial morbidity (chronic periodontitis - CP) is based in treatment procedure and not the one accepted in clinical manners
The authors justified this option because the databank did not contain this precise information
We would like to thank the reviewer for this comment, which has helped us improve our study design. We agree that we have based our criteria on treatment procedures instead of clinical data that are officially used, such as probing depth or periapical photographs.

Although treatment procedures are not formally a criterion for determining the severity of CP, we used them based on some dental specialists’ advice on a new operational definition for the CP. We attempted to take this into account using a combination of diagnosis and CP-related procedure codes, an operational definition that has been used in previous reports.

We recognize that the logic of justifying the limitations of the data is a critical limitation of our study design; therefore, we strictly defined exposure (CP) and the main outcome (CAP) to compensate for this drawback.

Page 14, line 225-228:
“Based on this paper, subjects with extractions were also classified into the severe CP group in the present study. Although treatment procedure codes are not a formal basis for determining the severity of CP, we sought to create a new operational definition based on input from dental specialists.”

The chosen tools to diagnose CP severity are also clever but could underestimate worse cases, which impacts in the characteristics of participants according to periodontitis severity: 69.9% healthy participants, with only 17% with severe disease

We would like to thank the reviewer for their valuable comment and efforts to improve the manuscript.
According to the most recent report on the staging and grading of periodontitis published by the American Academy of Periodontology and European Federation of Periodontology in 2018, tooth loss attributable to periodontitis needs to be incorporated in the definition of severity.

In this paper, subjects with extractions were also included in the severe CP group, with a high rate of 17%. In our study, 15% of the severe CP group had extractions due to periodontal disease. In order to investigate the relationship between CAP and CP, we also collected and analyzed the worse cases except for subjects who were diagnosed with chronic periodontal disease and underwent tooth extraction. However, these numbers were very small and there were no significant findings.

In our classification of CP, it is possible to underestimate the worst cases that may arise from the characteristics of the subject, as noted by the reviewer. However, in order to resolve this problem, we adjusted for Charlson comorbidity index, which can predict the prognosis of comorbid diseases, as a covariate.

Page 14, line 225-227:
“Third, it is possible that the new operational definition of CP is inaccurate. As the severity of CP increases, it would be logical for the percentage of subjects to decrease, but the severe CP group included the largest number of subjects. However, in a recent study that classified the stages of periodontal disease, subjects who had teeth removed were at high risk of periodontal disease [46].”

I wonder this discrepancy could avoid the results usually showed in clinical trials with a very small number of participants, linking CP with pneumonia, especially because clinical studies explained that CP is attributed to severe or atipical hospital and community acquired pneumonia. Considering that authors choosed to look only for community acquired pneumonia, the study could have to different bias leading to no significant results.

Thank you for your comment. We agree that we observed a different outcome from some reports with a small number of patients and may have different biases by focusing on community-acquired pneumonia.

We have already described this as a possible reason that CP may not lead to CAP in the Discussion section.

Page 12, line 172-177:
“de Melo Neto JP et al. demonstrated that moderate and severe CP were associated with CAP [29]; however, the study had a small sample size (140 patients) and was conducted for only 17 months. In addition, the control group was formed from hospitalized patients and did not involve
the general population. In contrast, this cohort study was the result of an 8-year follow-up of patients hospitalized with CAP according to presence of CP, with the general population at baseline at relatively low risk of disease compared to the subjects of de Melo Neto JP’s study. This could explain why our results differ from those of previous studies.”

List of references for this response:

