Author's response to reviews

Title: Comorbidities as a driver of the excess costs of community-acquired pneumonia in U.S. commercially-insured working age adults

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Author's response to reviews: see over
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BioMed Central Journal
Dr. Jack Chen
Editor

Dear Dr. Chen:

Enclosed is a revision of our manuscript entitled “Comorbidities as a driver of the excess costs of community-acquired pneumonia in U.S. commercially-insured working age adults” (MS: 8858049636754158).

We thank reviewers for their insightful and important comments that have helped us to improve the quality of the manuscript. We have addressed those comments and made changes in the manuscript when appropriate.

We look forward to your review. Please contact me if further clarifications are needed,

Sincerely,

Dan Polsky, PhD
Corresponding author

Authors’ Responses to Reviewers, Ref. MS: 8858049636754158
Review 1: Manabu Akazawa

Comment: The authors present the economic burden of pneumonia depending on various comorbid conditions using large databases. Also, because the target population of this study was working-age adults, they had unique opportunity to exam both medical and productivity costs together. The manuscript is well written, however, I would like to make sure various points to understand the findings well as follows and require compulsory revisions.

Response: We agree.

Comment: Introduction. With various references, the authors describe that pneumonia risks are elevated for certain groups including several common comorbidities. In order to understand the importance of this study, please summarize the current clinical evidence that describes the selected conditions (asthma, diabetes COPD and CHF) increase pneumonia risks for working-age adults.

Response: As suggested, we have revised our introduction to help the reader better understand the importance of the study. In this clarified version, we do not focus on the elevated risks as much as the fact that the comorbidities of interest are common and that these comorbidities have been been singled out as potential risk factors for complications and or mortality during or following a pneumonia episode. Nevertheless, we do clarify the evidence on increased pneumonia risks among these comorbidities which generally supports the higher risks for asthma and COPD, but not CHF or diabetes.

Comment: Methods. The database that can be used to estimate productivity losses is uncommon. Please explain the HPM database more in detail, especially what kind of information is available and how these data are collected.

Response: We have added an abridged version of the following explanation into the manuscript: In general, the development of the MarketScan Databases is conducted
separately from analysis using that data. A significant portion of Truven Health Analytics’ business is to assist large self-insured employers in administering and adjudicating their health insurance claims. For a subset of these employers, Truven Health also helps them administer their payroll systems, including missed work, which is captured in the HPM database. The HPM database includes data on absenteeism, short term disability, and worker’s compensation (not included in the current analysis). HPM data has been widely used and published, including a related paper on this current topic. Below is a list of selected HPM publications since 2011, some of which have been cited in the paper.


**Comment: Methods.** For costs of short-term disability, the authors used an assumption that a patient receives 70% of wages while on disability. Please explain rational of this assumption. Is it common in the previous literatures? Usually employees should pay 100% of wages regardless employees’ conditions.

**Response:**

We have amended the text at the end of the cost variables section to reflect the following: We discounted short term disability wages by 30% because that reflects the typical wage replacement used by the employers whose payroll is managed by Truven Health Analytics. This approach is consistent with previously published work using this data:


While some employers do cover short term disability at 100%, we chose to use a conservative approach to estimating the indirect cost associated with community-acquired pneumonia.

**Comment: Methods.** Please explain how to estimate the annualized costs. Assuming that pneumonia often happens in winter season, follow-up time and seasonality should affect the total costs. Please check with a limited population who had 12 months follow-up from index date.

**Response:**
We checked and this issue did not seem to present a problem with our study as we annualized costs and there is little difference between treatment and controls. While it is true that patients may be more likely to enter in the winter, dropout rates were similar across months with the exception of December, where patients are more than twice as likely to disenroll than any other month. The increased rate of dropouts in December is similar between pneumonia cases (19%) and their controls (21%). Below are drop-outs rates by month for pneumonia cases and controls:

January: 9% (both cases and controls)
February: 9% (both cases and controls)
March: 7% (cases) versus 8% (controls)
April: 6% (both cases and controls)
May: 6% (both cases and controls)
June: 6% (both cases and controls)
July: 7% (both cases and controls)
August: 7% (both cases and controls)
September: 8% (both cases and controls)
October: 8% (both cases and controls)
November: 10% (both cases and controls)
December: 19% (cases) versus 21% (controls)

Comment: Results. Please use 95% confidence intervals to show the variance around the estimate instead of using SE.

Response:

As suggested by the reviewer, we have now added (in addition to SEs) 95% CI for all the cost components estimates which are in the single summary table: Table 4. We decided not to add 95% CI in Tables 2 and 3, because we have reported standard deviations (SDs) and standard errors (SEs) for different estimates to reflect either variation around sample means (SDs) or variation around the population means (SEs). Adding 95% CI to these tables would have been very confusing as cost distribution of the sample means are known to be very right skewed and therefore would have included negative values of cost, which are not possible.

Comment: Results. In order to compare the excess costs among patients with certain comorbidities, comparability between groups is very important. Please describe the baseline characteristics are equally distributed in each comorbidity group. If not, please consider matching process conducted separately for each sub-group.

Response:

The standardized differences within each of the comorbidity subgroups was higher than the standardized difference for the entire pneumonia group where the propensity score match was conducted in order to create a relevant control group.
However, it was rare that these standardized differences were more than 2 fold higher suggesting that the covariate adjustment approach that we took in this paper within each subgroup was sufficient. Given that a propensity score match within each subgroup would not affect the results compared to the regression-based method, we did not engage in a separate matching process for each sub-group.

Comment: Discussion. For respiratory diseases, pneumonia would worsen the condition (exacerbation). Thus, the estimated excess cost related pneumonia is understandable. However, how about diabetes and CHF? Please describe the clinical evidence or mechanism why the pneumonia cause the excess costs for these patients. The pneumonia would worsen the baseline condition or the comorbid condition would increase severity of pneumonia?

Response:

This is an excellent point. We have added to our discussion some evidence as to the mechanism, although the evidence is not conclusive. The sentence in the discussion is: “The higher costs, particularly for CHF and even for COPD may be explained by the clinical evidence which suggests that the pre-existing condition has a detrimental effect on pneumonia prognosis [22, 23], but there is also evidence that pneumonia contributes to an exacerbation of the original condition [22, 24]”

Comment: Discussion. The economic burden of pneumonia for CHF patients was the highest if considering medical costs (especially, inpatient costs); however, the lowest by considering absenteeism. Suppose if patients need to absent from work to be hospitalized, the findings are inconsistent. Please explain why it happens.

Response:

Productivity data is only available on employees, not dependents. Also, the productivity data does not include long term or permanent disability because that is typically provided through a separate insurance rider for employers (and not available in the payroll system data which feeds the productivity data used in this current analysis. We have added this to the study limitations.

Comment: Table. Please explain how to calculate the standardized difference (%).

Response:

The standardized difference was calculated using the following formula for continuous variables:
\[ d = \frac{100(\bar{x}_T - \bar{x}_C)}{\sqrt{\frac{s_T^2 + s_C^2}{2}}} \]

And the following formula for dummy variables:

\[ d = \frac{100(\hat{p}_T - \hat{p}_C)}{\sqrt{\frac{\hat{p}_T(1-\hat{p}_T) + \hat{p}_C(1-\hat{p}_C)}{2}}} \]

In Excel, these formulas look like:

=100*(meanX-meanY)/SQRT((SDX^2+SDY^2)/2)

And:

=100*(X-Y)/SQRT((X*(1-X)+Y*(1-Y))/2)
Reviewer 2: Jack Chen

Comment: I think the authors have made an important analysis to estimate possible excess cost of the CAP and added a much needed research on the topic which has potential important policy implications. However, I have a few questions and comments as follows.

Response:

We thank the reviewer for his/her assessment of the importance of this study as well as for the clarification request.

Comment: I would suggest the authors to re-organize the main text in the format of “background, method, results, discussion” which is consistent with the abstract format. The current format is not common in a biomedical journal.

Response:

We have made this change.

Comment: The validity of the results is highly dependent on the success of ‘propensity score match’. There are different ways in conducting the propensity score matching and it would be more convincing if the authors elaborate on if some sensitivity analyses have been done to ensure the best ‘matching methods’ chosen and results achieved. If no such extensive analyses were being done, a note of limitation in the discussion may be warranted.

Response:

We did not do a comparison of matching methods in this paper and we have added a limitation. However, my understanding of the matching literature is that there is not large variation in results between different matching techniques particularly when the match performs as well as the match that we have used here.

Comment: I would like to see some clarification about the sub-group definition. Does the subgroup ‘asthma’ include the CAP patients with asthma as the only comorbidity (i.e., not having diabetes, COPD, CHF) or it is possible that the CAP patients with asthma sub-group could also have diabetes, COPD, CHF? If it is latter, the information about how many CAP patients have the multiple comorbidities may be also presented.

Response:

The patient subgroups were not mutually exclusive (i.e., patients were allowed to be included in more than one subgroup. This is now noted in the text of the paper. Below is a table showing the correlation of each of the four conditions:
Not unexpectedly, some of the conditions do appear together. Below is a cross-tab showing the prevalence of each condition within each of the condition subgroups. For example, of pneumonia patients with CHF, 22% also have COPD at baseline, 36% also have diabetes at baseline and 12% also have asthma at baseline.

<table>
<thead>
<tr>
<th>Condition Subgroup</th>
<th>CHF</th>
<th>COPD</th>
<th>Diabetes</th>
<th>Asthma</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHF</td>
<td>1.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>COPD</td>
<td>0.08</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.10</td>
<td>0.03</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Asthma</td>
<td>0.01</td>
<td>0.08</td>
<td>-0.02</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Comment: In paragraph 1 of Page 10, the authors stated “For inpatient costs, absenteeism, and short-term disability, two-part models were used”. Were the same control variables used for two-part model for each outcome?

Response:

Yes, the same control variables were used across the sets of two-part models.

Comment: In Paragraph 2, page 12, “A recent European of patients” should be “A recent European study of patients …”

Response:

Thanks. Change has been made.

The authors thank the reviewers for their thoughtful comments. By addressing them, we have improved the clarity of the manuscript.