Author’s response to reviews

Title: Pharmacotherapy and the risk for community-acquired pneumonia: A case-control study of hospitalized older adults

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Author’s response to reviews: see over
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Melissa Norton, MD.
Editor-in-Chief,
BioMed Central-Geriatrics

Dear Dr. Norton:

On behalf of our study team, I would like to thank you for reviewing our paper entitled “Pharmacotherapy and the risk for community-acquired pneumonia: A case-control study of hospitalized older adults.” We greatly appreciate the valuable comments and suggestions provided by the reviewers and the editor. We believe that these helpful suggestions have strengthened the paper considerably.

The revised paper being submitted to BioMed Central-Geriatrics integrates the suggestions and comments from the reviewers. The authors also attest that the work presented in this revised manuscript has not been published elsewhere nor will we submit manuscripts in the future that duplicate this paper.

In summary, we have made the following major changes:

1. As we are requested to look at the acute gastrointestinal (GI) disease discharge diagnosis among case and control groups, we took this opportunity to review all cases and controls whose records have been reviewed and available on files. We have found that additional cases that can be included in the final data analysis; therefore, we have added 17 new cases—all are with atypical presentation—to the community-acquired pneumonia group, and 12 new cases to the control group. We have eliminated 12 pneumonia cases with metastatic diseases from cancers or active lung cancers, which were not previously recognized on the first submission. With the above change, pneumonia group has a net gain of 5 cases.

2. We have created a new Appendix Table that revealed the discharge diagnosis of acute GI illness among study patients. We found no significant difference between PPI users versus non-users in the proportions of acute GI discharge diagnosis. We feel this table is not essential (therefore can be presented as an appendix Table) but may be helpful for some readers to understand our study better.

3. We have revised the multiple logistic regression model, which includes serum albumin level, ex-smoker and current smoker status, both β2 agonist and anticholinergic bronchodilators. We have eliminated COPD past medical history and prior pneumonia history in the new model as medication use (such as β2 agonist and anticholinergic bronchodilators as well as inhaled corticosteroids) is a better indicator of disease diagnosis rather relying on the medical history. Results were summarized in the revised Table 2.

We authors believe that this new model provides new information in two folds; 1) we demonstrated that lower serum albumin levels are a major risk factor for CAP after adjusting for other risk factors. The new model reveals that the risk of CAP can be reduced
by 65% by increasing serum albumin level by 1 gm/deciliter. The information is new (in terms of risk reduction by the concentration) to the best of our knowledge. 2). With the inclusion of serum albumin levels in the new model, we demonstrated that other known risk factors such as smoking history, the use of atypical antipsychotic drugs and inhaled corticosteroids, but not the use of PPI, are still associated with an increased risk of CAP. Our study is the only one that have included serum albumin levels in the multiple logistic regression model to analyze the relationship between the use of PPI and the risk of CAP among those studies that were published in the literature.

4. We have added two new references regarding the nutritional status as a risk for CAP in older adults. We also eliminated some redundant expressions or words found in our previously submitted manuscript.

**Our responses to the reviewers’ comments are as follows. Please note that all changes made to the text and tables appear in yellow highlighting.**

**Reviewer # 1: Reviewer: Graziano Onder**

**- Major Compulsory Revisions**

1. Assessment of medication use before admission was based on self report. This may be a potential problem, given the fact that patients admitted to hospital may have cognitive problems and this may lead to an underreport of medication use. Another issue is the risk of recall bias: those with pneumonia may be more likely to recall pneumological drugs rather than controls;

**Authors’ reply:** We would like to clarify on the ‘self-report of medication use” in our study. The medication use information was obtained from medical records (either from physician’s notes or from the medication reconciliation forms). Please note that nursing home patients almost have medication administration forms sent with patients from the nursing facilities. The medication administration forms are documented with what medications are given during the nursing home stay. For those patients with cognitive impairment admitted from their homes, most patients have caregivers available on hospitalization because they are often not able to call ambulance for emergency care without caregivers’ assistance.

   We agree with the reviewer that many older adults admitted to hospitals have cognitive impairment problem, and they are often not well documented (or not well assessed) during the acute hospital stay. When we reviewed all of the recorded data from all the study patients when preparing this revised manuscript, we found that only three patients could not recall the medications they used. These 3 cases were excluded from the final data analysis. We have added the above clarification information into the method and discussion section of this revised manuscript.

   Regarding the risk of recall bias, data collection on the medication use was systemically collected based on medication reconciliation report and documented records. Though we acknowledge that patients and caregivers have high levels of medical knowledge, we do not believe that patients with pneumonia will recall using “pneumological medications” more often than the controls.
2. Cases seem sicker than controls (they have more diseases and use more drugs). This raises the question on how the selection of controls was performed. Were controls cases from the same hospital and from the same wards than cases?

Authors' reply: The authors agree with reviewer that cases are sicker than the controls. The selection of the controls is described in details in the method section. The controls are those without the diagnosis of pneumonia or acute exacerbation of COPD, and they are all from the same hospital and from the same wards. Appendix Table (see below) will also give readers about the discharge diagnoses among the study patients.

3. Which were the most common causes for hospitalization among controls? There may be a bias related to causes of hospitalization (i.e. if controls are hospitalized for GI bleeding or GI problems, it is not possible to assess the effect of PPI);

Authors' reply: We have created a new table (Appendix Table) to illustrate the discharge diagnosis among study patients. We choose to categorize the discharge diagnosis based on PPI use because this is the concern raised by the reviewers whether controls have more GI problems than pneumonia patients. Though it is common for older adult patients to have multiple discharge diagnosis, most of them are either admitted for cardio-respiratory or gastrointestinal problems. Appendix Table revealed that PPI users and non-users have a similar proportion in the discharge diagnosis of acute GI illness or acute fractures (except the pneumonia). We hope the newly created Appendix Table will give readers a picture of acute illness that study patients were admitted for.

4. Data on cognitive status are not presented. This may be an important confounder in the analysis and, again, patients with cognitive problems may have difficulty in recalling drug data;

Authors' reply: We agree with that cognitive problem will affect patients’ ability of recalling drug use. Because our study design is retrospective, our data could not possibly include patients’ cognitive status assessment on admission. However, we feel that such a factor probably does not affect the reliability of obtaining drug information from our patient population. This is because “self-reported medication use” was actually obtained either from medication reconciliation form or from physicians’ documentation on medical records. (Please also refer to authors’ reply to the Concern #1 from the first reviewer). Furthermore, nursing home patients (which constituted about 18% of our study patients) have medication administration records sent with patients to the emergency department regardless of patient’s cognitive status. For community-residing residents, those patients with dementia often have caregivers with them at the emergency department.

The fact that the rate of current smokers in our study (101/1140 or 8.9%) is very close to the national rate at 10% in those aged ≥ 65 years old (American Lung Association,
According to the data of American Lung Association, 20% of adults were “current smoker” in 2007, which is consistent with our data that about 18.5% of study patients were ex-smokers (i.e., they were “current smoker” before the age of 65 years old). The above statistical findings suggest the overall reliability of our data collection.

5. Why the variable for anticholinergic bronchodilator was not entered in the final model? It seems that the use of any inhaled drug is associated with increased risk of pneumonia (alpha 2 agonist, corticosteroid and anticholinergic drugs). This may raise the issue of confounding by indication. Therefore, it may be reassuring to show that the effect on pneumonia is limited to anticholinergic drugs and not extended to all inhaled drugs;

Authors’ reply: We agree with reviewers, and have included β2 agonist and anticholinergic bronchodilators as well as inhaled corticosteroids in the new model (as shown in Table 2). We remove the past medical history of COPD in the new model because patients with COPD often use at least one of the above medications, which can be confounded. The other reason is that medication use is a better indicator of disease status than the past medical history itself. We have included the above statement in the statistical analysis section.

6. Same for antipsychotics. It may be reassuring to see a 3 level variable including also typical antipsychotics (no antipsychotics, atypical, typical) to show that the effect on pneumonia is limited to atypical antipsychotics.

Authors’ reply: Among our study patients, very few used “typical” antipsychotic drugs prior to admission. This is confirmed when we reviewed all the cases during the preparation for this revision. We have included the statement in the method section.

Reviewer #2 (Claudio Pedone)

Major compulsory revisions:
1) The paper is somewhat disorganized and the underpinning logical hard to follow in places. For example, in the Introduction the authors report data on PPI, then data on IC, then again data on PPI.

Authors’ reply: We have revised the introduction section by a better-organized presentation. We also emphasized the importance of nutritional status in the risk of CAP in older adults as our study has revealed important information from the new multiple logistic regression analysis after we have included serum albumin levels in the model.

In table 1, the authors report the frequency of only two discharge diagnoses (heart failure and C. difficile infection) without providing any rationale for this choice.

Authors’ reply: We have deleted the discharge diagnosis in Table 1 as we agree that it is not relevant here. However, we created the Appendix Table that will show readers the major discharge diagnoses among our study patients.
Also the way of analyzing smoke exposure is unclear: the authors state in the Results (last sentence) that the ORs were unchanged when current smoking status was used instead of previous smoking status in the model, but that is confusing: how were current smokers considered in the first model? Were they excluded?

Authors' reply: We have included both ex-smoker and current smoker in the logistic regression model (Table 2). Interestingly, we found that current smokers have a higher risk than ex-smokers, and there is no colinearity between these two. In the method section, we also added the statement on how we defined smoking status.

2) If I understand the Methods right (page 8, second para), the authors excluded people with an admission diagnosis of pneumonia, but without the typical symptoms. If this is the case, it would be important to know how many people were excluded on this basis, as atypical presentation is rather typical in the elderly.

Authors' reply: We greatly appreciate the reviewer's valuable suggestion and we have integrated that suggestion into this revised manuscript. Because radiographic evidence provides a more definite diagnosis, we have included those patients with "atypical presentation" (such as mental status changes, increasing lethargy, or accidental falls without the classic symptoms such as cough, dyspnea, or fever). After reviewing all data on file, we added 17 new cases (all are with atypical presentations) and excluded 12 cases (with either active lung cancers or systemic metastatic diseases from malignancy that were not previously recognized). We have added the statement in the method section.

3) It would be important to know what were the most common discharge diagnoses in the control group. A high prevalence of gastro-intestinal diagnoses in this group could explain the lack of association between PPI and CAP (people admitted for GI symptoms are more likely to be on PPIs, and this would dilute the association between CAP and PPI).

Authors' reply: We agree with the suggestions. As mentioned previously by the first reviewer, we created an appendix Table for the discharge diagnoses among our study patients. We categorized the results based on the use of PPI. As shown in the appendix table, PPI users and non-users have no significant difference in the discharge diagnosis of acute GI problems or diagnosis (except in the case of pneumonia).

4) The authors state that they adjusted their model for pneumonia... I am not sure I understand this: do they mean hospital-acquired pneumonia? That should not be included, as it cannot be a confounder in this setting.

Authors' reply: The original model reported in previous manuscript included “prior pneumonia history". With better indicators of risk factors included—i.e., the use of several medications (such as antibiotic use prior to admission) and the smoking status—we feel that excluding the variable “prior pneumonia history" is a better model for our data base.
Therefore, we have excluded the “prior pneumonia” variable from the final multiple regression model.

5) The rationale behind the association between the drugs of interest and CAP should be clearly explained. For example, in the discussion the authors hint that the mechanism linking PPIs and CAP could be aspiration pneumonia. If this is the case, then people with aspiration pneumonia should not be excluded from the study.

Authors’ reply: We excluded such a statement (implying the mechanism that PPI therapy increases the risk of CAP by aspiration) in the discussion. We excluded clinically-evident aspiration pneumonia (due to dysphagia and gastric tube for feeding) because patients with aspiration pneumonia differ from those with CAP in the pathophysiology and risk factors. [Please refer to reference #19 in the revised manuscript].

6) The authors state that there were missing data, and that information on the number of missing observations is reported in tables’ footnotes. That is not the case in my copy of the manuscript.

Authors’ reply: What we mean is that “Smoking status was unknown in 3 patients of cases and in 3 patients of controls” in Table 1. In order to avoid misleading the readers, we deleted the statement in the method section because we feel it is clearly stated and not necessary to mention this.

7) The general logic behind the analytic plan should be better explained: why were some variables included (e.g. anti-hypertensive medications, diagnosis of atrial fibrillation...).

Authors’ reply: We excluded the use of diuretics and antihypertensive in Table 1 as we feel that they do not give further information. We mentioned the inclusion of atrial fibrillation in the past medical history (as it is a common co-morbidity in the elderly) in the Method section.

Minor Essential Revisions
1) The authors found an association between CAP and iron supplementation. Can they comment on this? What was the rationale for including this variable in the analysis?

Authors’ reply: After including serum albumin levels in the new multiple logistic regression model, the association between iron supplement and the risk of ACP disappears, suggesting that the association is due to confounding by serum albumin levels (or due to nutritional status). Because the relationship is no longer significant after the adjustment, we feel it is not essential to mention the role of iron supplement in the discussion section.

2) In table 1, there is no need to use footnotes to indicate statistically significant results, as the P-value is reported.
Authors' reply: We have deleted the footnote as suggested by reviewer in Table 1.

3) In table 2, there is no need to use footnotes to indicate statistically significant results as the confidence intervals already convey this information.

Authors' reply: We have deleted the footnote as suggested by reviewer in Table 2.

Reviewer #3: Cinzia Maraldi

The paper by Gau and Colleagues investigate the association between pharmacotherapy with PPI, inhaled corticosteroids, and atypical antipsychotics and likelihood of CAP in hospitalised older adults. The main finding of the study is the confirm that the use of inhaled corticosteroids and atypical antipsychotics was associated with CAP. From this point of view results from this study are limited and add no innovative information to the current evidence, and the study is flawed by some methodological issues.

Authors' reply: We disagree with the opinion of this reviewer. We believe that our study is intended to examine the relationship between several forms of pharmacotherapy and the risk of CAP from another perspective of a rural community. Our study, though not perfect, is intended to provide the best data that a retrospective study can collect, including clinical presentation symptoms, discharge and admission diagnosis, and laboratory test results (serum albumin levels and WBC counts). We believe that our study has more reliability in classifying cases and controls than other studies. Our study also demonstrated that the cases have significantly lower serum albumin levels and higher WBC counts, which are important aspects of pneumonia cases, than the controls. We strongly believe that our study does provide different perspectives to the existing literature.

Finally, we sincerely appreciate the comments and suggestions provided by the reviewers and the editor and we are confident that the revised paper represents a considerable improvement from the initial version submitted to this Journal. We sincerely hope that our paper will be accepted for publication in your prominent journal. If you have any questions or need additional information, please contact me at your convenience.

Respectfully,

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