Peer Review File

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First round peer review

Reviewer A

Comment 1: English editing is highly suggested for this manuscript to meet the level of academic writing.

Reply 1: Thank you very much for your useful comment. We regret that our article writing has not reached the level it should have. As non-native English language researchers, English proficiency does limit our ability to write and express ourselves. Due to the need for originality, our organization and the academic foundation that supported this research did not allow us to hire additional English editors to modify the paper. Nevertheless, we will do our best to polish the language of our paper, reduce grammatical errors, and try our best to clearly convey the message of this research.

Changes in the text: We have modified our text and references as advised (see Page 2, line 26-28,31-33; Page 2, line 44-56; Page 4, line 64-77; Page 9, line 168-187; Page 12, line 246-250; Page 13, line 251-271; Page 14, line 272-277, 284-284; Page 16, line 326-331; Page 17, line 339-341).

Comment 2: Reporting the propensity score matched (PSM) results is more appropriate than the unmatched results. It is not necessary to report the both results in the abstract section.

Reply 2: Thank you very much for your helpful comment. We have revised the Abstract section as advised.

Changes in the text: We have modified our text and references as advised (see Page 2; line 26-28,31-33).

Comment 3: There are many important previous studies on the studied issue, including more recent studies in these two years were not cited.

Reply 3: Thank you for your comment. It was our fault not to update the citation in time. We reconstructed a search retrieval and conducted a systematic search on PubMed. The following keywords and/or corresponding medical subject heading terms were used: nosocomial infection or hospital infection or healthcare associated infection or cross infections; and pneumonia or hospital acquired pneumonia or healthcare associated pneumonia or respiratory tract infection; and risk factors or associated factors. The time range of the search was From January 1, 2019 to the present, and after screening, we obtained relevant studies as shown below(1-5):

Author	Year	Title	Journal
Lukasewicz et al.	2022	Factors predicting non-ventilated hospital-acquired pneumonia: systematic review and meta-analysis	J Hosp Infect

Strassle et al.	2022	Incidence and risk factors of non-device-associated pneumonia in an acute-care hospital	Infect Control Hosp Epidemiol
Goncalves-et al.	2021	Incidence and impact of hospital-acquired pneumonia: a Portuguese nationwide four-year study	J Hosp Infect
Yin et al.	2021	Clinical and microbiological characteristics of adults with hospital-acquired pneumonia: a 10-year prospective observational study in China	Eur J Clin Microbiol Infect Dis
Feng et al.	2019	Differences in microbial etiology between hospital-acquired pneumonia and ventilator-associated pneumonia: a single-center retrospective study in Guang Zhou	Infect Drug Resist

We have cited and compared these recent studies and other previous studies as appropriate in the Introduction or Discussion section.

Changes in the text: We have modified our text as advised (see Page 3; line 44-55).

Comment 4: The uniqueness and importance of adding this new study should be emphasized. From the data of this study, it appeared that the overuse of corticosteroids is a very common practice in China, as the study could easy identify a big cohort of patient who were prescribed with corticosteroids in short time. If it is the uniqueness, the authors should clearly state it in the introduction section.

Reply 4: Thank you for your good suggestion. We have revised our Introduction section and state the uniqueness of our study.

Changes in the text: We have modified our text as advised (see Page 4; line 66-74).

Comment 5: The study aims should be clearly stated at the end of the introduction section.

Reply 5: Thank you for your helpful comment. We have added the study aims in the Introduction section as advised.

Changes in the text: We have modified our text as advised (see Page 4; line 74-77).

Comment 6: The authors stated that the main application of the medical database is to monitor antibiotic utilization in the regional medical system. Is the medical database contained all patients or only the part of patients who are prescribed with antibiotics? It is very important to clarify the content of this database, as it related to the patient recruitment.

Reply 6: Thank you for the comment. The medical database comes from the hospital information system (HIS) of several hospitals. It contains all out-patient and in-patient data from those hospital (except the patient's personal information) not only the part of patients who are prescribed with antibiotics. In fact, antibiotic utilization monitoring needs the data of those patients who are not prescribed with antibiotics. For example, Antibiotics Utilization Ratio and Antibiotics Use Density are the most important indicators to monitor the antibiotic utilization in China. The above two indicators are calculated as follows:

1) Antibiotics Utilization Ratio = NO. of discharged patients receiving antibiotics / NO. of hospital discharges during the same period × 100%

2) Antibiotics Use Density = Accumulative DDDs of antibiotics × 100 / (NO. of hospital discharges during the same period × Average length of stay in the hospital during the same period)

Obviously, if we want to calculate these two formulas, we can't just have data on patients receiving antibiotics. However, the description of the database does lead to misunderstandings among readers, so we will add explanations in the manuscript.

Changes in the text: We have modified our text as advised (see Page 6; line 84-85).

Comment 7: The authors stated their study was retrospective, anonymous and non-interventional, the ethical review and informed consent were waived. All studies did not show patient's names (anonymous). Ethical review can be waived only if the" database" is anonymous and delinked. The authors should carefully rewrite their statement.

Reply 7: Thank you for your comment. We recognize that ethical review is particularly important for clinical research. Before the study begins, we will submit all research proposals to the Ethics Committee and determine whether a review is needed. This database has been anonymized before the integration of the data from each hospital. All personal information, including name, address, ID number, contact information and so on, has not been integrated into the database. In the original database and in our study, all patients were located only by two encrypted codes, one representing the hospital and the other representing the patient.

As you suggested, our description of ethical review is not accurate enough and we revise the new statement to: *"The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Because the study was retrospective, anonymous, non-interventional and subjects cannot be identified, directly or through identifiers linked to the subjects, the ethical review and individual consent for this retrospective analysis was waived by the Ethics Committee of Shanghai Fourth People's Hospital Affiliated to Tongji University School of Medicine."*

Changes in the text: We have modified our text as advised (see Page 5-6; line 101-105).

Comment 8: The operation definition of HAP is unclear. The author should clearly define the outcome of HAP and explain how to exclude ventilator associated pneumonia and aspiration pneumonia by only check the discharge diagnosis of bacterial pneumonia (ICD-10: J13.x-J18.x) if not exist in their admission diagnosis lists.

Reply 8: Thank you for your comment. It is very important to define the outcome of a study. Vague definition of outcome will lead to a lot of misclassification and even get conclusions that are completely contrary to the facts.

One of the exclusion criteria for the study population was continuous mechanical ventilation, which means each patient in the study was on the ventilator for less than 2 hours. Patients are usually billed on an hourly basis for ventilator use, so the total time spent on the ventilator can be accurately calculated from billing records. After such

selection, we conclude that ventilator-associated pneumonia is unlikely to occur in the outcome. In addition, in order to reduce the interference of transient ventilator use (have a ventilator use record, but the total time <2 hours) on the outcome of the study, we included it as one of the covariables in the statistical model.

Aspiration pneumonia is commonly represented by a diagnosis of *"Pneumonitis due to solids and liquids (ICD-10: J69)"*, *"Pneumonitis due to food and vomit (ICD-10: J69.0)"* or *"aspiration pneumonia (ICD-10: J69.001)"* in the database.

The current definition of the outcome in the manuscript is too brief, we will give a fuller and more accurate definition of the ending for readers to understand.

Changes in the text: We revised the definition of outcome as advised (see Page 6; line 115-120).

Comment 9: Statistical analysis: conditional regression must be applied when propensity score matched cohort is employed.

Reply 9: Thank you for your useful comment. In our study, we use the absolute standardized difference (ASD) to detect the difference of the covariate between the exposed and unexposed. If the ASD of the covariate is more than 0.1, it will be considered an unbalanced covariate. which will be incorporated into the regression model for adjustment. After PSM, we find that the ASD of all covariates is less than 0.1, which means all covariates have been balanced after PSM (**Figure 1**). Therefore, the odds ratio can be calculated by the univariate analysis (a univariable logistic

regression or χ^2 test). We will add a description of these methods in the part of statistical analysis.

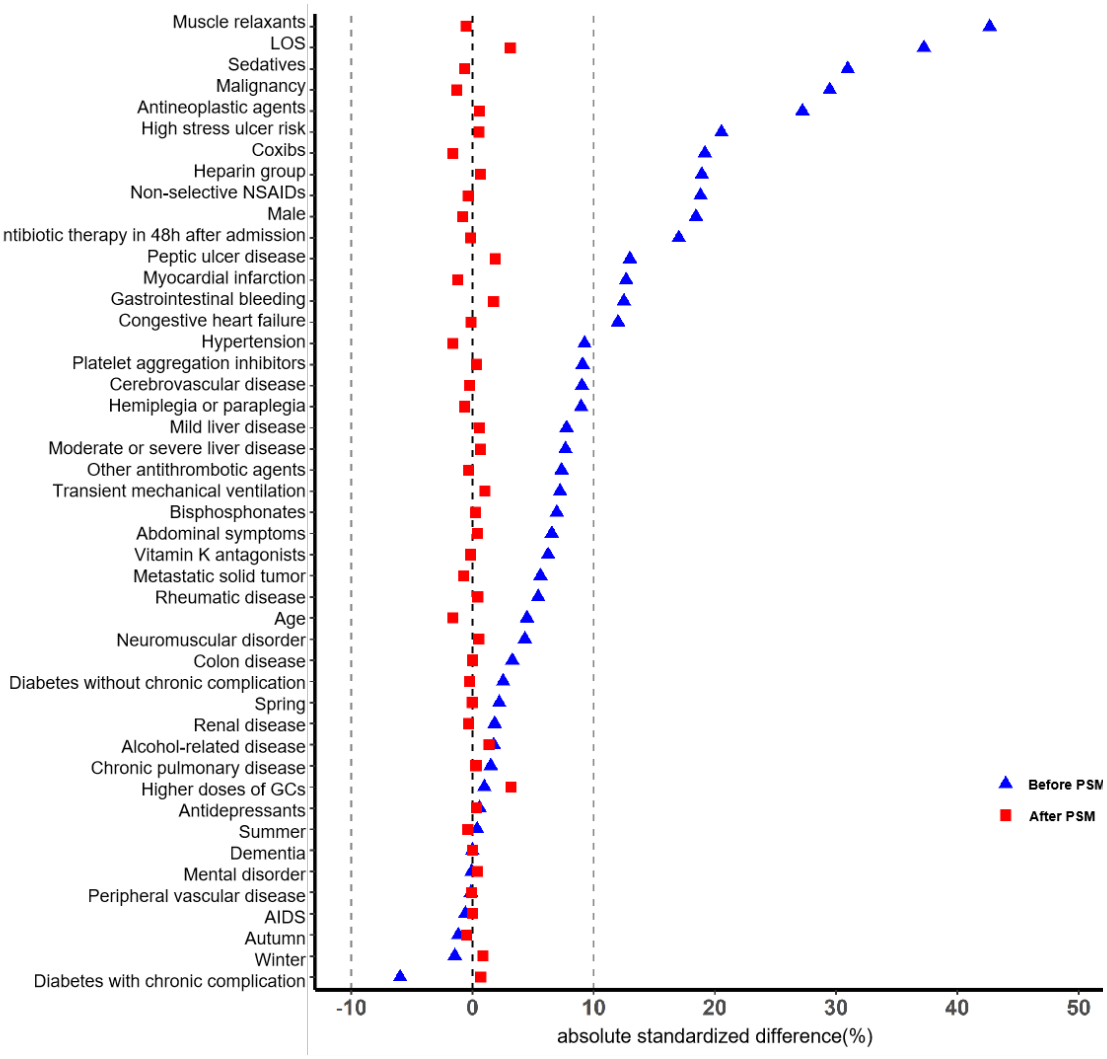

Figure 1. Absolute standardized difference of all covariates before and after PSM.

Changes in the text: We revised statistical analysis in Methods section as advised (see Page 8; line 154-155).

Comment 10: The second sensitivity analysis is vague. As the authors stated that "PPIs treatment might occur after HAP and would produce several misclassifications

based on the original exposure definition." It appeared that the original cohort is mixed with the patients with HAP unrelated and related to PPIs, since the definition of PPI related HAP is very unclear. As stated in item 3, the definition of HAP, or the authors can consider to use the PPI-related HAP, should be refined before the statistical analysis performed. The definition of outcome should include the index date and time consideration of event order.

Reply 10: Thank for you're the comment. We though the definition of the exposure and outcome are the most important part in our study and we will describe the process in detail.

The lack of information on the temporal association between PPIs use and date of diagnosis of HAP is a study limitation. We could not find a reasonable index in the database to determine the exact time of HAP occurrence. And there is no way to extract all the medical records for a medical chart review because all the original medical records have not been uploaded to the database due to anonymity. This was addressed through a sensitivity analysis in which all patients who received their first dose of PPIs more than 48 hours into their hospitalization were reclassified as not having received PPIs. According to the original definition of HAP, all HAP must occur 48 hours after admission. By this redefinition, we can guarantee that all exposures occur before the outcome in the second sensitive analysis. Although the OR for the main effect decreased from 1.4 to 1.3, some attenuation was expected because this approach biased the result toward the null. Moreover, we ascertain the percentage of orders for PPIs that occurred within the first 48 hours of admission. As is shown in

Figure 2 and **Figure 3**, before PSM, for 65.2% of patients prescribed PPIs, they were prescribed within 48 hours of admission. And 88.4% were within 72 hours of admission. And the proportions are similar after PSM.

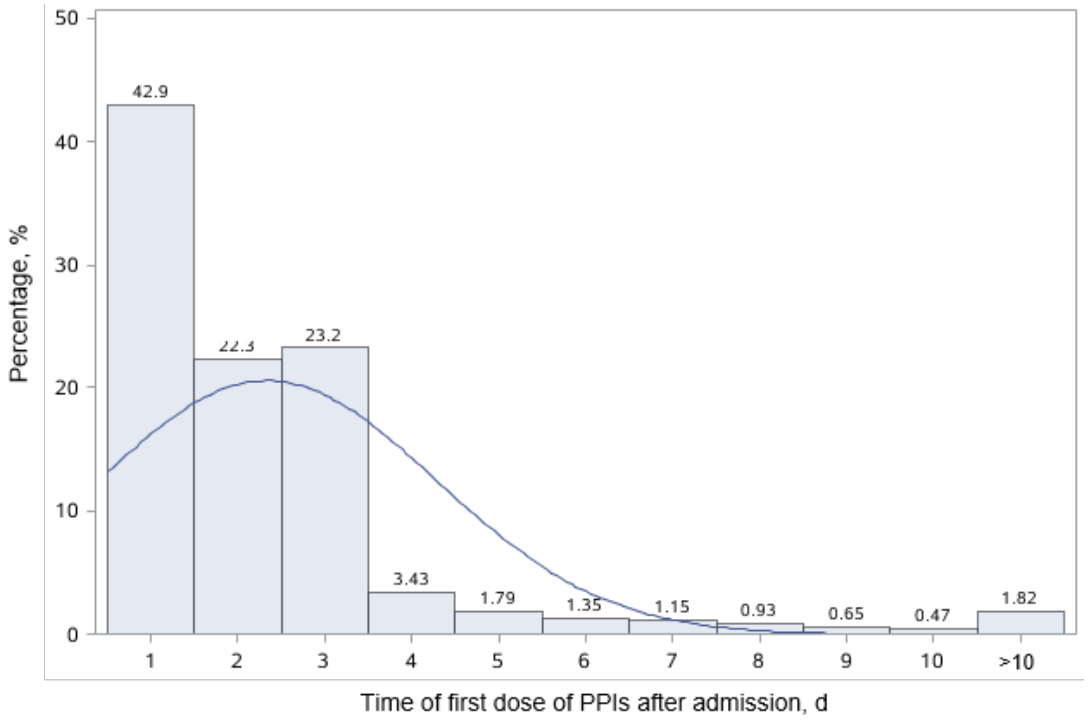

Figure 2. Frequency histogram of the time of first dose of PPIs after admission before PSM.

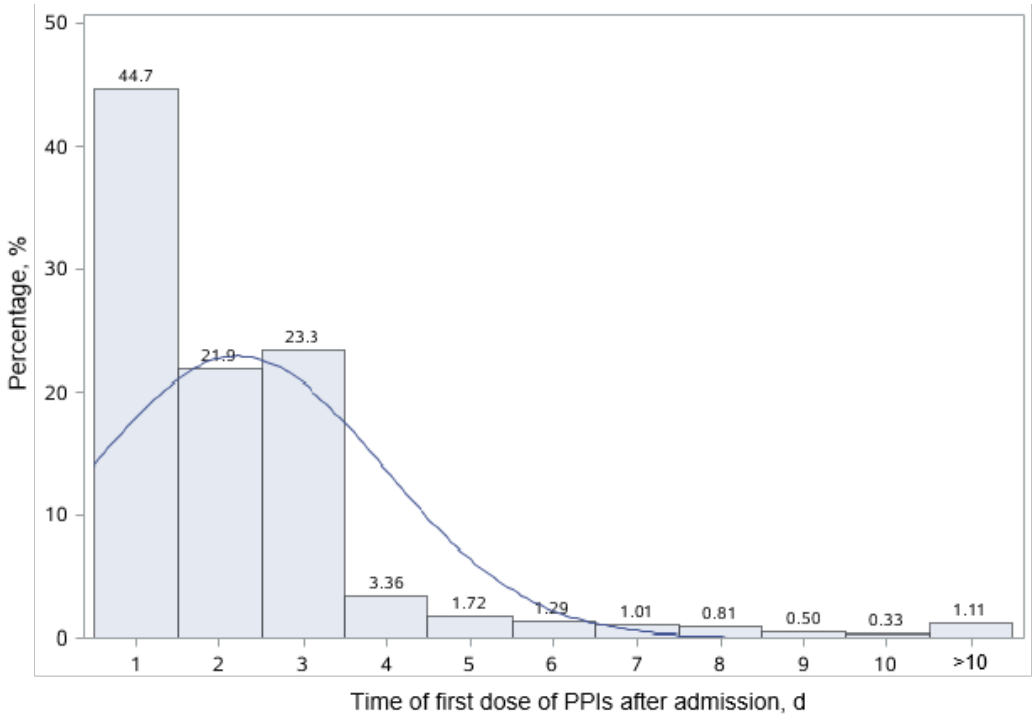

Figure 3. Frequency histogram of the time of first dose of PPIs after admission after PSM.

Nevertheless, misclassification still exists, such as patients admitted to hospital with community-acquired pneumonia who are not accurately identified on admission, leaving them without a pneumonia-related diagnosis on admission but with a diagnosis of bacterial pneumonia on discharge. We will elaborate on the explanation of misclassification about the research limitations in Discussions section.

Changes in the text: We revised the text as advised (see Page 9; line 168-187).

Comment 11: It can also be considered whether to report the unmatched results in the main manuscript, as the unbalanced cohorts introduced significant bias. The process of selecting PSM cohort should be stated in the Figure 1 and report only the results of PSM cohorts. If the authors really like to report the unmatched data, it is suggested to list the results in a separate appendix.

Reply 11: Thank for the comment. We have modified the Figure 1 and put unnecessary content into the appendix, including Table 1 and Table 2 and simplify the Table 6 and Table 7.

After internal discussion among all authors, we consider that we still need to report the unmatched data. Our reasons are as follows:

1) In the dose-effect relationship analysis, we stratify on the PPIs dose into several subgroups. However, subgrouping after matching will distort comparability, which means the biases that propensity score matching (PSM) originally resolved will be observed again by stratifying on the research variable. These subgroups likely are not comparable to each other and are also each no longer comparable to the control group, which approximates the exposed group overall. These biases compound with the exclusion of patients who did not make it into the original matched cohort. Thus, looking at this subgroup provides even less internal validity and generalizability than looking at unadjusted data(6). This is the most important reason we want to keep the data related to the original cohort.

2) The cohort after propensity score matching PSM has a much better baseline and has less statistical bias. The results based on this cohort will be more accurate. But one of its limitations is that the characteristics of the cohort after PSM deviate from the real-world population. In our study, the exposed group was much elder in the original cohort than that after PSM. Many old age admissions had been excluded from the final cohort because the subject was unmatched. And for the outcome of our study, the elderly is likely to be of interest to us. Older adults, for example, have a higher

risk of HAP, or a dose-effect relationship is easier to observe. It means that the PSM involve loss of information and may impact the generalizability. This is called *"Matching Always Involves Trade-Offs Between Internal Validity and Generalizability"*(6). Therefore, we consider that keeping the unmatched population will be more appropriate.

3) The other reason is that we want to evaluate the effect of PSM by comparing the absolute standardized differences of all the covariates before and after PSM(7). We found that it might be better to keep both the original cohort and final cohort for validation when we needed to choose an appropriate method in all PSM algorithms **(Figure 1)**. The matching affect was not very well in the first few methods such as the Caliper Algorithm until we found this one (Greedy Matching Algorithm).

Changes in the text: We have modified the Figure 1 and put unnecessary content into the appendix, including Table 1 and Table 2 (Now Appendix Table 1 and Appendix Table 2) and simplify the Table 6 and Table 7 (Now Table 4 and Table 5). (See Figure 1, Table Section, Appendix Section).

Comment 12: Carefully re-perform the main analysis and sensitivity analysis after refine the definition of outcome is required.

Reply 12: Thank you for your comment. As the replies for **Comment 8** and **Comment 10,** by determining the time of first use of PPIs, we found that 65.2% of PPIs were administered within 48 hours of admission, and 88.4 % within 72 hours of admission. After the PSM, the two figures changed to 66.6% and 90.0%. HAP, on the

other hand, must occur as soon as 48 hours after admission. We think that most of the exposure may have occurred before the outcome. We also fully explained this limitation with the second sensitivity analysis, which redefined exposure as receiving PPIs within 48 hours of admission. This definition of exposure, combined with the time required for HAP generation, ensures that all exposures occur before the outcome. Although this analysis slightly reduced the main effect OR of the study, the result was still statistically significant. For this part, we will explain it in the Discussion section.

Changes in the text: We have modified the discussion as advised (See Page 16; line 323-331).

Comment 13: It seems like the patients used related high dose of PPI, as a large group of patients used high DDD of PPI. Please confirm if the author correctly performs the calculation of DDD.

Reply 13: Thank you for your reminding. We calculate PPIs usage per patient from billing records (more accurate than orders). For example, the cumulative cost of omeprazole is calculated as follows:

Cumulative DDDs of omeprazole = (Total charging for omeprazole use / Charging per unit dose of omeprazole) / The defined daily dose of omeprazole

The cumulative DDDs for all PPIs categories were then added, including omeprazole, lansoprazole, pantoprazole, rabeprazole and esomeprazole. Frequency histogram of the cumulative dose of PPIs during hospitalization is shown in **Figure 4**.

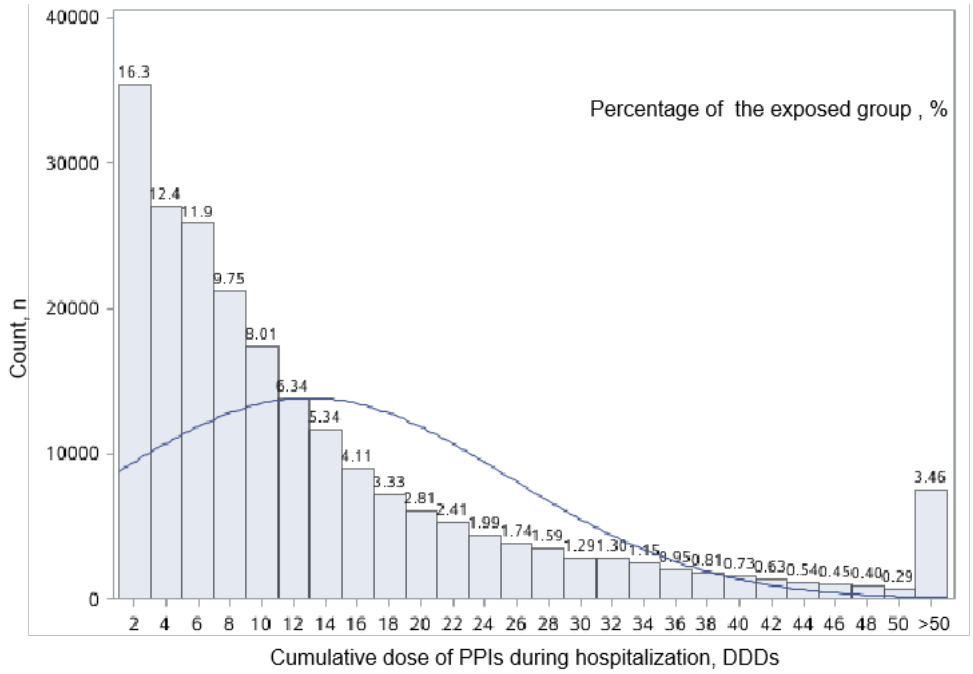

Figure 4. Frequency histogram of the cumulative dose of PPIs during hospitalization in the exposed group.

One of the reasons we initiated this study was because we found that the overuse of PPIs was clinically common. A very important reason for overuse is that PPIs use does not have clear indications for discontinuation in the guidelines. This results in almost all patients receiving PPIs for the first time continuing to use them until discharge.

Changes in the text: None.

Comment 14: The study has good stand to be published, as the comparisons were made in the population all have been prescribed corticosteroids. This new angel is interesting and should raise attention on it. If the definition of outcome and statistical analysis are adjusted correctly, it is believed the results will provide the same

direction of conclusion. Carefully rewrite the discussion section according to the new results will help the manuscript merit to be published with strong evidence.

Reply 14: Thank you for the comment. We are very grateful for your professional guidance, which has given us a new perspective on this research. In the process of revising the article, we carefully read each amendment, modified it to the best of our ability, and explained in detail where we chose to keep it.

As the replies for **Comment 8**, **Comment 10** and **Comment 12**, we will add explanations in the Discussion section.

Changes in the text: We have modified the discussion as advised (See Page 6; line 115-120; Page 9; line 168-187; Page 16; line 326-331).

Comment 15: The indications for steroids in the study population are lacking. It may be useful to understand and discuss the differences between treatment and control groups; and look into how the differences, if any, influence the outcomes of HAP.

Reply 15: Thank you for the comment. It is important to analyze the characteristics of the study population. However, we encountered an unsolvable difficulty when analyzing the indications of glucocorticoids. That is, as a common medication, glucocorticoids have too many indications, and it is difficult to classify them by ICD code. Corticosteroid therapy is attempted in almost all wards for specific diseases. But we think that by comparing the disease diagnostic profiles between the study group and the control group, we can partially detect the problem (**Table 1, Table 2**).

Table 1. The top ten diagnoses in the cohort before PSM.

Rank	PPIs exposed			Unexposed		
	ICD-10 Code	Diagnosis	Percentage (%)	ICD-10 Code	Diagnosis	Percentage (%)
1	I10	Essential (primary) hypertension	19.5	I10	Essential (primary) hypertension	16.0
2	S06	Intracranial injury	8.2	J38	Diseases of vocal cords and larynx, not elsewhere classified	7.7
3	I25	Chronic ischaemic heart disease	7.3	I25	Chronic ischaemic heart disease	5.4
4	J98	Other respiratory disorders	7.3	M51	Other intervertebral disc disorders	4.9
5	K80	Cholelithiasis	6.4	E11	Type 2 diabetes mellitus	4.8
6	K76	Other diseases of liver	5.5	E04	Other nontoxic goitre	4.6
7	E11	Type 2 diabetes mellitus	4.9	X59	Exposure to unspecified factor	4.5
8	M51	Other intervertebral disc disorders	4.4	J98	Other respiratory disorders	4.1
9	I50	Heart failure	4.4	K76	Other diseases of liver	3.9
10	S02	Fracture of skull and facial bones	4.2	J32	Chronic sinusitis	3.9

Table 2. The top ten diagnoses in the cohort after PSM.

Rank	PPIs exposed			Unexposed		
	ICD-10 Code	Diagnosis	Percentage (%)	ICD-10 Code	Diagnosis	Percentage (%)
1	I10	Essential (primary) hypertension	16.2	I10	Essential (primary) hypertension	16.2
2	I25	Chronic ischaemic heart disease	6.4	J38	Diseases of vocal cords and larynx, not elsewhere classified	6.4
3	K80	Cholelithiasis	6.4	I25	Chronic ischaemic heart disease	6.4
4	J98	Other respiratory disorders	5.8	E11	Type 2 diabetes mellitus	5.8
5	J38	Diseases of vocal cords and larynx, not elsewhere classified	5.5	M51	Other intervertebral disc disorders	5.5

6	S06	Intracranial injury	5.5	X59	Exposure to unspecified factor	5.5
7	N04	Nephrotic syndrome	4.8	E04	Other nontoxic goitre	4.8
8	E11	Type 2 diabetes mellitus	4.8	J98	Other respiratory disorders	4.8
9	K76	Other diseases of liver	4.5	K76	Other diseases of liver	4.5
10	M51	Other intervertebral disc disorders	4.1	J32	Chronic sinusitis	4.1

It was found that the diagnostic spectrum of the exposed and unexposed groups was generally similar, with an increase in the proportion of PPIS-related diseases in the exposed group relative to the non-exposed group. On the one hand, this can indicate that the baseline status of the study population is less different between the two groups, reducing the potential research bias. On the other hand, it may be suggested that the use of many PPIs in hospitalized patients is unnecessary because the diagnosis in the exposed group is not strongly related to the indication for PPIs.

Changes in the text: None.

Comment 16: There are a plenty of studies, meta-analysis and review have been published in recent years. It is suggested that the discussion section and references to be fortified with careful review and comparing the previous publications.

Reply 16: Thank you for the helpful comment. As explained in the response to Comment 3, we reconstructed a search strategy to include the last three years of studies on risk factors for nosocomial pneumonia infection. In an earlier study, we also selected several representative studies to compare our results.

Changes in the text: We have modified our text as advised (see Page 12-13, line 246-257; Page 13-14; line 261-277).

References

1. Lukasewicz Ferreira SA, Hubner Dalmora C, Anziliero F, et al. Factors predicting non-ventilated hospital-acquired pneumonia: systematic review and meta-analysis. J Hosp Infect 2022;119:64-76.
2. Strassle PD, Sickbert-Bennett EE, Klompas M, et al. Incidence and risk factors of non-device-associated pneumonia in an acute-care hospital. Infect Control Hosp Epidemiol 2020;41:73-9.
3. Goncalves-Pereira J, Mergulhao P, Nunes B, et al. Incidence and impact of hospital-acquired pneumonia: a Portuguese nationwide four-year study. J Hosp Infect 2021;112:1-5.
4. Yin Y, Zhao C, Li H, et al. Clinical and microbiological characteristics of adults with hospital-acquired pneumonia: a 10-year prospective observational study in China. Eur J Clin Microbiol Infect Dis 2021;40:683-90.
5. Feng DY, Zhou YQ, Zou XL, et al. Differences in microbial etiology between hospital-acquired pneumonia and ventilator-associated pneumonia: a single-center retrospective study in Guang Zhou. Infect Drug Resist 2019;12:993-1000.
6. Leisman DE. Ten Pearls and Pitfalls of Propensity Scores in Critical Care Research: A Guide for Clinicians and Researchers. Crit Care Med 2019;47:176-85.
7. Austin PC. An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies. Multivariate Behav Res 2011;46:399-424.

Reviewer 2

Comment 1: The authors presented statistical analysis in multiple ways, including sensitive analysis. Although this is important to decrease the risk of bias, authors should refrain from presenting all the data. As conclusions were similar, reference to these results (as confirmatory of the main results) will be enough and help to focus the common reader. If authors intend to provide further data (including the sensitive analysis), they can do that as Supplementary material. Table 1 can also be provided as Supplementary file. Table 2 (before propensity matching) do not provide any relevant information and can be removed. For the same reason, tables 6 and 7 should be simplified.

Reply 1: We are very appreciating for your helpful comment. We decide to simplify our results as you advised. Firstly, we create an appendix and take the *Table 1* and *Table 2* as the supplements. We simplify the *Table 6* and *Table 7* (Now *Table 4* and *Table 5*) then. But we want to report the result about the original cohort, the reasons are as follows:

1) In the dose-effect relationship analysis, we stratify on the PPIs dose into several subgroups. However, subgrouping after matching will distort comparability, which means the biases that propensity score matching (PSM) originally resolved will be observed again by stratifying on the research variable. These subgroups likely are not comparable to each other and are also each no longer comparable to the control group, which approximates the exposed group overall. These biases compound with the exclusion of patients who did not make it into the original matched cohort. Thus,

looking at this subgroup provides even less internal validity and generalizability than looking at unadjusted data(1). This is the most important reason we want to keep the data related to the the original cohort.

2) The cohort after propensity score matching PSM has a much better baseline and has less statistical bias. The results based on this cohort will be more accurate. But one of its limitations is that the characteristics of the cohort after PSM deviate from the real-world population. In our study, the exposed group was much elder in the original cohort than that after PSM. Many old age admissions had been excluded from the final cohort because the subject was unmatched. And for the outcome of our study, the elderly is likely to be of interest to us. Older adults, for example, have a higher risk of HAP, or a dose-effect relationship is easier to observe. It means that the PSM involve loss of information and may impact the generalizability. This is called *"Matching Always Involves Trade-Offs Between Internal Validity and Generalizability"*(1). Therefore, we consider that keeping the unmatched population will be more appropriate.

3) The other reason is that we want to evaluate the effect of PSM by comparing the absolute standardized differences of all the covariates before and after PSM(2). We found that it might be better to keep both the original cohort and final cohort for validation when we needed to choose an appropriate method in all PSM algorithms **(Figure 1)**. The matching affect was not very well in the first few methods such as the Caliper Algorithm until we found this one (Greedy Matching Algorithm).

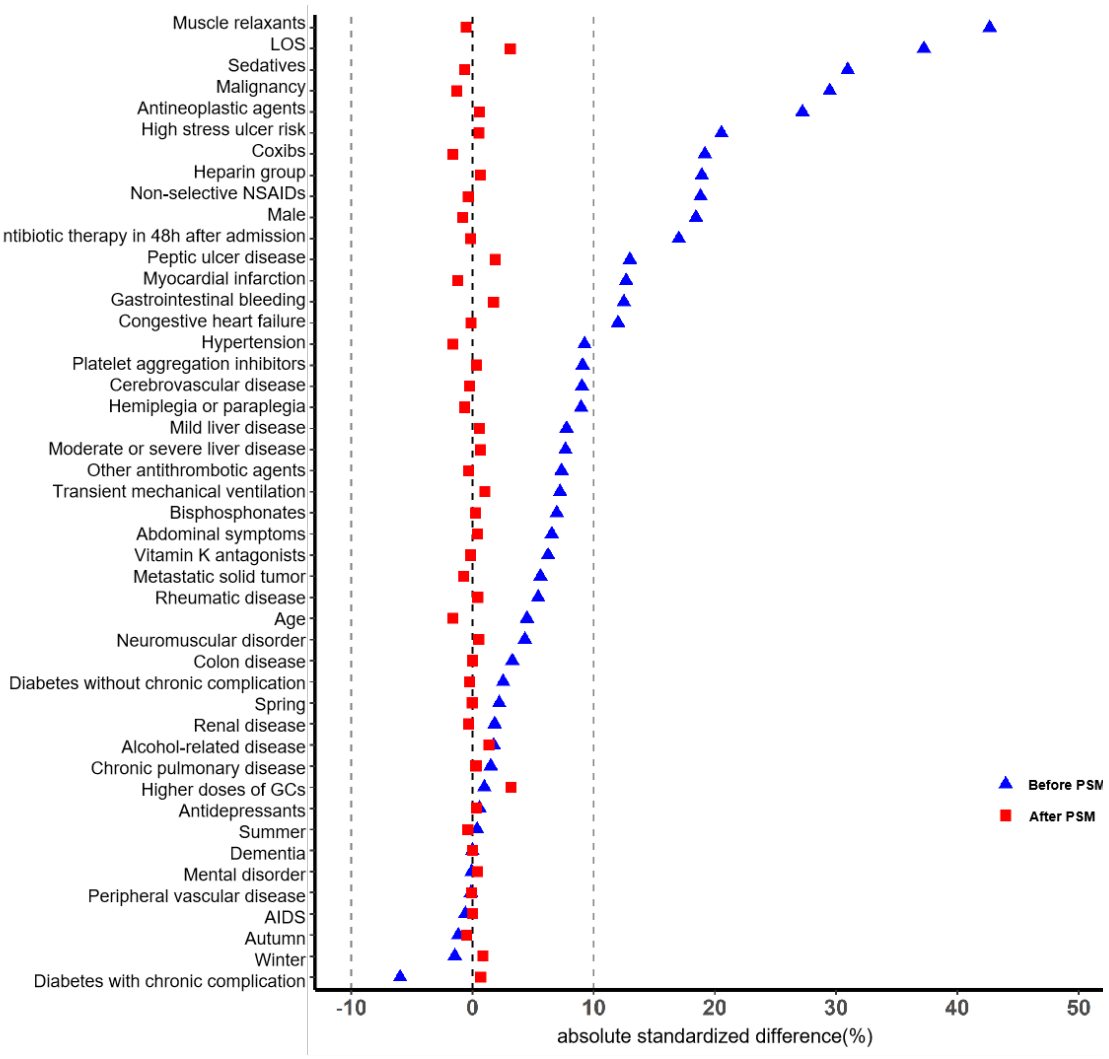

Figure 1. Absolute standardized difference of all covariates before and after PSM.

Changes in the text: We have modified our tables as advised (see Table Section and Appendix Section).

Comment 2: Why did the authors restricted their population to those that received corticosteroids? Although they provide some justification, including GC as a covariate instead of an inclusion criterion would have been more informative. This should be further explained.

Reply 2: We had conducted a previous study about the off-label use of PPIs base on this database and the result had been published in a Chinese journal (only had Chinese version). We found that of all PPIs used by inpatients, 32% were off-label use and more than half off-label use of PPIs might be associated with systemic corticosteroid(3). In another word, corticosteroids are very important factors in the unnecessary use of PPIs. We thought it might make more sense to focus our study population on unnecessary use or overuse.

The second reason is more practical. Glucocorticoids (GCs) is very important covariate not only for our outcome (HAP) but for the exposure (PPIs). It is difficult to adjust the intrinsic bias by simply categorizing variables because there are so many primary diagnoses for patients treated with GCs. The spectrum of disease varies widely between people who use GCs and those who do not.

Moreover, GCs are commonly understood to increase the incidence of infectious diseases, but some researches shew that the GCs might be associated with HAP , which has both benefits and safety(4). It also seems to make it difficult to interpret the results. For the above reasons, we chose the current study populations.

Changes in the text: We add some text in the paper (See Page 13-14, line 270-277).

Comment 3: In Introduction authors state the adverse events associated with PPIs. I think it is important to include CAP (see for instance, Expert Review of Clinical Pharmacology. 2013; 6.4: p443) or Expert Opinion on Drug Safety, DOI: 10.1080/14740338.2018.1519545).

Reply 3: Thank you for your helpful comment. Community-acquired pneumonia (CAP) is one of the adverse effect of PPIs. We discussed this disease in the Discussions section but had mistakenly omitted it in the Introduction section. After carefully reading these two expert reviews(5, 6) and the related introductions in UpToDate, we have improved our understanding of adverse effects to PPI and revised the Introduction section.

Changes in the text: We have modified our text and references as advised (see Page 3, line 52-54).

Comment 4: In results authors only provide median age; mean age is also relevant and usually more informative.

Reply 4: Thank you for the comments. We have added the mean and standard deviation of age in *Table 2* and *Table 3* (Now *Appendix Table 2* and *Table 1*).

Changes in the text: We have modified the data (see Table Section).

Comment 5: In Discussion authors refer to several articles that discussed risk of VAP (eg, references 19,20, 23). As VAP and these patients are excluded from the study population, their discussion should be referred to studies addressing HAP in the ward population (eg, Am J Infect Control 2018;46:2e7. https://doi.org/10.1016/j.ajic.2017.08.036; Infect Control Hosp Epidemiol 2020;41:73e9. https://doi.org/10.1017/ ice.2019.300; J Hosp Infect 2021;112:1–5. https://doi.org/10.1016/j.jhin.2021.03.012).

Reply 5: Thank you for your helpful suggestion. We have added the studies addressing HAP as advised. Even though reference 23 titled "*Comparison between esomeprazole 20 mg Vs 40 mg as stress ulcer prophylaxis (SUP) in critically ill patients: A retrospective cohort study*" discussed the outcome which include both HAP and VAP (VAP may be more because in critically ill patients), we want to keep this study as our reference. The reason is that this research had discussed about the dose-effect relationship between PPIs and pneumonia in the hospital, which is very rare in the HAP study and very relevant to our research.

Changes in the text: we have modified our text and references as advised (see Page 12-13, line 246-257)

Comment 6: Furthermore, J Hospital Infection DOI:https://doi.org/10.1016/j.jhin.2021.09.024 is a recently published metanalysis providing information on risk factors for HAP. It will be interesting to discuss this in comparison with authors results.

Reply 6: Thank you for your comment. It's very useful. We have read the study carefully and added this study to our Discussions.

Changes in the text: We have modified our text and references as advised (see Page 13, line 253-255).

Comment 7: In line 79 (inclusion criteria) it is not clear if authors only considered the first hospital admission during the study period.

Reply 7: Thank you for your comment. We want to describe our database used in our study to reply this comment. The database consists of electronic medical records of several hospitals and is stored in the form of structured data (eg, Subdatabases, data tables, columns). There is a table in the database that identifies the inpatients' visit information including admission date, discharge date and so on. Because the patient's personal identification information is absolutely anonymous, it locates each visit with 3 pieces of information: a code representing the hospital called Hospital Code, a patient ID number called Patient ID, and a number representing the number of visits called Visit ID. These three pieces of information are combined to form data items that will not be repeated, known in database terminology as Primary Keys.

The next step is to simply set the Visit ID to 1 before extracting the data we want. This means that all medical records are from the first hospital admission by controlling Visit ID to 1. These are preparatory work for the study and are therefore not detailed in the manuscript. We will revise the description of this part.

Changes in the text: We have modified our text as advised (see Page 5, line 94).

Comment 8: In line 306 authors are referring to the time relationship

Reply 8: Thank you for the comment. There are problems with this expression. We will revise the description of this part.

Changes in the text: We have modified our text as advised (see Page 16, line 323).

References

1. Leisman DE. Ten Pearls and Pitfalls of Propensity Scores in Critical Care Research: A Guide for Clinicians and Researchers. Crit Care Med 2019;47:176-85.
2. Austin PC. An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies. Multivariate Behav Res 2011;46:399-424.
3. Xufeng Mao, Yang Z. Medical big data analysis of the clinical off-label use of proton pump inhibitors. Journal of Pharmaceutical Practice 2020;38:184-8.
4. Klompas M. Risk factors and prevention of hospital-acquired and ventilator-associated pneumonia in adults. In: File TM, editor. UpToDate. UpToDate, Waltham, MA. (Accessed on Sep 10, 2021).
5. Liapikou A, Cilloniz C, Torres A. Drugs that increase the risk of community-acquired pneumonia: a narrative review. Expert Opin Drug Saf 2018;17:991-1003.
6. Wilhelm SM, Rjater RG, Kale-Pradhan PB. Perils and pitfalls of long-term effects of proton pump inhibitors. Expert Rev Clin Pharmacol 2013;6:443-51.

Second round peer review

Comment 1: This revision has been revised partially. As the authors stated that their institution does not allow English editing, it is highly suggested for the authors to carefully rewrite the manuscript for this manuscript to meet the level of academic writing. The authors can reduce the extensive use of first-person statements to keep the writing objectively. Scientific academic writing requires evidence to supports the

viewpoint. Never write statement arbitrary without evidences and supports. Line 261-262 is an example. Please check and rewrite according to these principles throughout the manuscript.

Reply 1: Thank you very much for your useful comment. We regret that our article writing has not reached the level it should have. We resubmitted the application for language editing and article polishing services to the scientific research Management department of our institution, and supplemented the manuscript, the reviewer's comments during the two revisions, and the commitment to originality of the article. After review, we are allowed to obtain English editorial services finally.

Comment 2: The uniqueness and importance of adding this new study is the overuse of corticosteroids and PPIs is a very common practice in China, as the study could easy identify a big cohort of patient who were prescribed with corticosteroids in short time. In this revision, the authors added one sentence (Line 64-65), however, references are required to support your evidence.

Reply 2: Thank you very much for your helpful comment. Research on this topic is mostly published in Chinese journals. After revision, we cited two references(1, 2). One of them was our previous study on the off-label use of proton pump inhibitors based on the same database as this study. The study shows that of all PPIs used by inpatients, 32% were off-label use and more than half off-label use of PPIs might be associated with systemic corticosteroid.

(http://yxsj.smmu.edu.cn/en/article/doi/10.3969/j.issn.1006-0111.201909086)

In another study, 99.55% of acute exacerbation of chronic obstructive pulmonary disease patients treated with glucocorticoids in a Chinese hospital were combined with proton pump inhibitors, of which only 60.78% had clear indications. (http://www.china-pharmacy.com//attached/wenjian/14/201701/20134206_4545.pdf)

Changes in the text: We have modified the references as advised (see Page 27; line 427-430).

Comment 3: The study aims should be clearly stated at the end of the introduction section. The description of study aims (Line 72-77) is subjective and not delicate. Please sophisticatedly explain the study aims.

Reply 3: Thank you for your comment. We have revised the study aim as follows: "*The HAP risk associated with the widespread use of PPIs in patients treated with GC therapy has not been effectively assessed in the Chinese hospital-care setting. Therefore, we conducted this study with the aim of exploring whether the use of PPIs in patients treated with GC therapy causes additional HAP risk, if such risk exists, and to understand the optimal dose to not increase HAP risk if PPI therapy is required.*"

Changes in the text: We have modified our text as advised (see Page 4; line 74-79).

Comment 4: In this version, the authors have not clearly described the database resource. It seems like the system is an electronic health records (EHR) for general use. Is there a separate function to allow the researchers easily identified the patients

prescribed with antibiotics and to monitor antibiotic utilization? It is very important to clarify the content of this database, as it related to the patient recruitment.

Reply 4: Thank you for your comment. The database is based on data from the hospitals it contains. For example, after a patient is discharged from one of the hospitals, his hospital electronic medical record will be uploaded to the database used by our research institute and stored in a structured form. With the exception of patient personally identifiable information, almost all patient-related data will be recorded, including patient demographic characteristics, clinical diagnosis, medications used, imaging and laboratory tests, and billing records. The database was originally used to monitor the use of antibiotics, but in fact, the database included all hospitalized patients who had not used antibiotics, and all drugs used during the hospitalization of all patients could be found. We usually have two ways to identify patients who are on antibiotics. One is a clinical pharmacy and drug utilization review software called *"Rbase"* developed based on this database, through which patients can be selected to complete antibacterial drug monitoring. The other is for database technicians to write SQL programs to extract the required data from the database, which is generally used for scientific research. Since the database includes all patients using or not using antibiotics, all the data needed for the study can be completely obtained with the help of the database technicians. We have revised the description of the data source, as you suggested.

Changes in the text: We have modified our text as advised (see Page 5; line 86-89).

Comment 5: The authors have not able to clarify the issue of waiving ethical review in this revision. Ethical review can be waived only if the "database" is anonymous and delinked. The authors stated "Because the study was retrospective, anonymous, non-interventional and subjects cannot be identified, directly or through identifiers linked to the subjects" This statement is even more confused.

If the data source, Medication Data Management Center of the Hospital, is delinked database, the researchers are unable to identify the patients and the study can be waived from ethical review. If the researchers can still see the patients' names from the data source retrieved, the study does not meet the international standard of ethical review waiving.

Reply 5: Thank you for your helpful comment. This database has been anonymized before the integration of the data from each hospital. All personal information, including name, address, ID number, contact information and so on, has not been integrated into the database. In the original database and in our study, all patients were located only by two encrypted codes, one representing the hospital and the other representing the patient. During the study, all the study participants and data extractors could not see the patient names and other information, nor could they track the patients in the database through the compiled patient ID numbers, because all the information was not uploaded to the research database through these associated hospitals.

We have revised the statement of ethical review based on your suggestion. The revised ethics review statement reads as follows: *The database used in this study is*

anonymous and delinked and the researchers were unable to identify the patients, therefore the ethical review and individual consent for this retrospective analysis was waived by the Ethics Committee of Shanghai Fourth People's Hospital Affiliated to Tongji University School of Medicine.

Changes in the text: We have modified our text as advised (see Page 6; line 108-112).

Comment 6: 1. Line 261-262 stated" Despite the controversy in various aspects of the study, we believe our results are robust." The statement is inappropriate and unscientific.

Reply 6: Thank you for the comment. We regret that our presentation was not appropriate. What we meant to say was that a large sample size is needed to avoid type II errors due to the low incidence of HAP and the small advantage after drug exposure. Therefore, we speculate that our study may have some advantages in the case that there is some controversy between the results of previous studies with smaller sample sizes and the results of this study. However, due to the problem of our language expression ability, the current statement seems to be very arbitrary and subjective, lacking scientific and objective. In the revised manuscript we deleted this sentence. As we have applied for the English editing service, the latest revision may meet the requirements of scientific paper writing.

Changes in the text: We have modified our text as advised (see Page 14; line273).

Reference

1. Xufeng Mao, Yang Z. Medical big data analysis of the clinical off-label use of proton pump inhibitors. Journal of Pharmaceutical Practice 2020;38:184-8.
2. HU J, SU Y, DU L, et al. Investigation and analysis of prophylactic application of PPIs in AECOPD patients after glucocorticoid use in a hospital. China Pharmacy 2017;28:161-4.