Peer Review File
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Reviewer A

This was a retrospective database study investigating the association of aspirin use with mortality in patients with chronic COPD admitted with sepsis to the ICU for more than 24 hrs.

I have several overarching questions and concerns, followed by specifics after these, below.

There are several potential questions that are important to your study interpretation that are unclear from the manuscript:
Comment 1 It is unclear if patients were on aspirin prior to admission or not? Or if this is a study looking only at de novo initiation of aspirin in the hospital. Your exclusion criteria state you excluded patients with aspirin use prior to ICU admission. Are these patients that were on the floor receiving aspirin, and then transferred to ICU? I assume you are looking at patients on chronic aspirin therapy that was continued in the hospital? But this is not clear from the manuscript, and is the basis for your study. If so, we need to know what they were on aspirin for, if it was continued in the hospital, and for how long, etc. This changes your overarching concluding statements completely, potentially.
Reply 1: Thanks. In this study, we focused on aspirin use during the current hospitalization. Since sepsis is a major cause of ICU admissions and mortality among critically ill patients, and all patients included in the study were admitted to the ICU, our primary focus was on the use or not use of aspirin after ICU admission. For aspirin users, if the time from the start of aspirin use minus ICU admission time was greater than 0, this indicated that aspirin was used after ICU admission (2.1 section). On the other hand, only 57 patients used aspirin before ICU admission during hospitalization, which has a minimal impact on the generalizability of our findings. However, this may introduce a selection bias, which should be noted as a study limitation (4.1 section). Additionally, based on the reviewers' comments, we investigated the relationship between the duration of aspirin use and both in-hospital and 28-day mortality. Overall, the findings show a negative correlation (2.4 section; 3.4 section; Supplementary Figure 1). The database only recorded the use of aspirin without specifying the reasons for its use. However, we discussed the potential effects of the drug based on previously published literature (Discussion section, paragraph 5).

Comment 2 How did you choose your covariates and from what potential list? How did you build your model? This is important, and the lack of this information is suspect. For example, you did not adjust for vasopressor use, though collected it, which would clinically be plausible to have significant effect on, and thus association with, mortality. You did not control for time, but one expects mortality to improve over time.

Furthermore, have you considered doing a propensity score matched analysis, like other MIMIC IV database studies attempting to provide data on similar questions? This may provide us, the readers, with a more “true” representation of the potential effect aspirin use may have on patients with COPD admitted to the ICU with sepsis.

Reply 2: Thanks. These variables were collected based on a literature review of indicators related to COPD or sepsis and then retrieved from the MIMIC-IV database. We constructed logistic regression models and Cox proportional hazards regression models to analyze the use of aspirin and different outcomes, adjusting for various variables to eliminate the impact of confounding factors (Section 2.4, second paragraph). This approach aims to achieve a result consistent with the effect of propensity score matching analysis, thus obtaining conclusions relatively close to real data. When classifying covariates based on their different attributes, we established various models, ultimately constructing a fully adjusted model. Initially, vasopressor use was not included in the subsequent analysis because there was no significant difference between the aspirin use group and the non-use group. However, we acknowledge the reviewer's suggestion and have now included vasopressor use in both the logistic regression and Cox regression analyses. The results still indicate that the use of aspirin is associated with a reduced risk of in-hospital and 28-day mortality (3.2 section; supplemental tables 1-4).

To control for the timing of death, the study set different death outcomes, including in-hospital death, death within 28 days after discharge, death within 90 days after discharge, and death one year after discharge."

My other overarching concerns are:

Comment 3 The statements and conclusions are much too strong and absolute, from what can be concluded from this study design with its limitations. Nothing can be “proven” or causally-linked from this study. The findings from this study require external validation and prospective, blinded, randomized, controlled-study to validate.

Reply 3: Thanks. We have revised the strong and absolute statements and conclusions. The term "causal relationship" in the text has been changed to "significantly associated." A prospective study will be designed to further investigate this relationship in the future. (Conclusion section)

Comment 4 You only included patients admitted to the ICU>24 hours. This limits generalizability and findings as there are likely patients with COPD and sepsis admitted to the floor that are not captured in your dataset.

Reply 4: Thanks. We excluded these patients based on methods reported in previous ICU studies [PMID: 36747139; PMID: 36446854]. However, as you correctly pointed out, this might lead to omissions. Therefore, we have included this issue in the limitations section. In addition, the exclusion of patients with ICU stays of less than 24 days involved only 156 individuals, representing approximately 5% of the total population. This small proportion suggests that the overall results remain broadly applicable. However, this exclusion introduces the potential for sample selection bias, which is a limitation of this study. (4.1 section)

Comment 5 There is not mention of a very likely conclusion: that aspirin use is a marker for a less comorbid patient potentially explaining your findings. Despite controlling for some potential covariates, there still exists many potential covariates to explain your associations found. Patients on aspirin therapy chronically are more likely to seek medical care regularly, and earlier, than those that aren't. Patients that had aspirin therapy continued during their ICU stay for sepsis are likely less acutely ill in ways you can't measure (e.g., if someone is dying of septic shock, DIC, MOSF, I am not concerned about continuing their aspirin therapy). Again, this is unclear based on your manuscript whether this would be a potential concern, based on your inclusion/exclusion criteria.

Reply 5: Thanks. Based on your comment, we have revised the study's inclusion/exclusion criteria and conclusions to make the manuscript clear. (2.1 section; Conclusion section).

Comment 6 A comorbidity index would likely be helpful, outside of your individual covariates you attempted to control for.

Reply 6: Thanks. All the subjects have COPD and sepsis, and the comorbidity index includes COPD as well. Therefore, incorporating the comorbidity index would cause multicollinearity and may affect the results.

Comment 7 There are several small observational studies cited (and some inappropriately cited) as support for your similar findings. However, I believe there needs to be more mention of ANTISEPSIS trial, given this is prospective RCT data on a related topic, which disagrees with your findings. This likely deserves specific mentioning and discussion in your Discussion section. How do you explain your findings (with your study design and limitations) in relation to ANTISEPSIS?

Reply 7: Thanks. The ANTISEPSIS trial was a prospective study, but its conclusion that low-dose aspirin does not improve the prognosis of elderly sepsis patients is not entirely consistent with our findings. We discussed the reason in the discussion section. The discrepancy may be due to differences in the study populations, such as age differences or differences in the study subjects, as the ANTISEPSIS trial focused on sepsis patients without comorbid COPD (seen in the fourth paragraph of the discussion).

Comment 8 The lack of a dose-dependent effect is not further proof in my eyes for aspirin therapeutically reducing mortality in COPD patients admitted to the ICU with sepsis, but rather the contrary. For biological plausibility in observational studies, one requires and expects often a biologically plausibly mechanism of action to explain a finding, and in a dose-dependent manner. Your study, if anything, has a point estimate of increased odds of mortality with higher dose aspirin use compared to lower dose. How do you explain such?

Reply 8: Thanks. As you mentioned, confirming the observed relationships through biological experiments would indeed be ideal; however, due to practical constraints, we were unable to conduct such experiments. In our study, we found that while the aspirin dosage was not significantly associated with mortality (with an estimate of 1.024 [0.728,

1.426]), there seems to be a trend indicating a positive correlation between higher doses and increased mortality, which might not align with expected outcomes. This discrepancy could be due to the uneven distribution of patients in the high and low-dose groups: out of 1,642 patients using aspirin, 1,292 were in the low-dose group, while only 350 were in the high-dose group. Therefore, the dose-response effect of aspirin needs to be validated in future prospective studies with larger, multicenter populations (seen in the fourth paragraph of the discussion).

Specific points/questions below:

Comment 9 Abstract conclusion: you are not able to conclude, given observational nature, and scientific method, that aspirin use causally reduced in-hospital and 28-day mortality. There are likely many potential unmeasured and non-controlled covariates. I would change the wording of your conclusion. You can only conclude that aspirin use was associated with reduced mortality
Reply 9: Thanks. The conclusion has been revised to "Aspirin use is associated with a reduction in mortality." (Abstract conclusion)

Comment 10 Page 2, What is the implication box: a major implication is that aspirin use should be prospectively studied, because your study design does not allow comment on the ability of aspirin to improve short- and long-term outcomes
Reply 10: Thanks. The implication box has been reviewed based on your comments. (Highlight box)

Comment 11 Page 3, line 38: this reads to imply that you must treat COPD specifically, in addition to treating the sepsis. Do you mean to imply that "… treating patients with COPD and sepsis…"
Reply 11: Thanks. The phrase has been modified to mean the treatment of patients with COPD and sepsis.

Comment 12 Page 3, line 43: your ref 14 for aspirin to treat sepsis and pulmonary complications is an article on competency-based medical education
Reply 12: Thanks. Original ref 14 has been deleted and added an another ref [PMID: 26494395].

Comment 13 Page 3, line 44: your ref 15 does not provide evidence for treating sepsis in COPD patients with aspirin, specifically, but the association of the use of chronic aspirin in patients admitted with acute exacerbation of COPD and mortality.
Reply 13: Thanks for your kind reminder. We have made corrections and modified the related content.

Comment 14 Page 3, line 44: again, your ref 16 for this statement is a retrospective study. Its findings cannot be worded this strongly in your paper, as they did not show that aspirin improved patient outcomes. This was not an RCT of aspirin as a therapeutic

in sepsis.
Reply 14: Thanks. Based on your comments, we have modified the relevant statements.

Comment 15 Page 3, line 48: "inhibit" implies that aspirin would be aiming to prevent the development of or phenotype expression of COPD and/or sepsis.
Reply 15: Thanks. "inhibit" was changed to "treat". (Page 5, line 63)

Comment 16 Page 4, line 69: for your exclusion criteria, do you just mean aspirin use in the hospital prior to ICU admission was excluded? If not, I find it hard to understand and believe that of 5119 COPD patients admitted, only 57 were on aspirin prior to admission, and 2964 were started on aspirin in the ICU, as a new medication de nova, and were included. Can you elaborate on this? Did you exclude any patient that took aspirin prior to admission for this acute episode?
Reply 16: Thanks. In this study, we focused on aspirin use during the current hospitalization. Since sepsis is a major cause of ICU admissions and mortality among critically ill patients, and all patients included in the study were admitted to the ICU, our primary focus was on the use or not use of aspirin after ICU admission. For aspirin users, if the time from the start of aspirin use minus ICU admission time was greater than 0, this indicated that aspirin was used after ICU admission (2.1 section). On the other hand, only 57 patients used aspirin before ICU admission during hospitalization, which has a minimal impact on the generalizability of our findings. However, this may introduce a selection bias, which should be noted as a study limitation (4.1 section). For 5,119 COPD patients with sepsis, we first excluded 1,942 people who did not have complete information on vital signs or laboratory findings, leaving 3,177. From these 3,177 patients, we further excluded 156 patients with an ICU stay of less than 24 hours, leaving 3,021. Among these 3,021 samples, 57 had used aspirin before ICU admission.

Comment 17 Page 4, line 65: you should be more clear that you are only including patients that were admitted to the ICU. I would suggest more clearly laying out all of your specific inclusion/exclusion criteria. Furthermore, this limits generalizability, because many patients with COPD and sepsis were likely admitted to the floor, and not ICU, and are therefore not captured in this study.
Reply 17: Thanks. Relevant data were retrieved and downloaded from the MIMIC-IV database, and all patients were admitted to the ICU. We have specified the inclusion and exclusion criteria. Only 156 patients, accounting for about 5% of the total population, were excluded for having an ICU stay of less than 24 hours. This small percentage is unlikely to significantly affect the overall results, so the findings of this study are still considered generalizable. However, this limitation may introduce sample selection bias, which is a limitation of this article. (2.1 section; 4.1 section)

Comment 18 Page 4, line 82: need more specifics regarding how you calculated your primary outcomes, since you have two, that are similar. Was 28-day mortality only in-hospital as well? Meaning if you were discharged alive on day 2, but died at home on day 27, were they counted as having the primary outcome of 28-day mortality? Did you

follow all patients up until day 28 (and day 90 and 1 year, for that matter)? If so, how did you follow them up to ensure you had complete mortality data for all of your outcomes? This would be a limitation.
Reply 18: Thanks. The mortality within 28 days, 90 days, and 1 year refers to the follow-up period after discharge (from the first day of discharge to the 28th, 90th, and 365th days). We have described this in detail in the reviewed manuscript. (2.3 section)

Comment 19 Page 5, line 99: how did you arrive at these covariates? Which did you consider? How did you build your model, stepwise regression? This is extremely important as well. For example, you did not adjust for vasopressor use (though MIMIC IV collected this data), which would plausibly have a strong influence and thus association with mortality.
Reply 19: Thanks. These variables were determined based on a literature review, integrating findings from multiple studies. Key variables were identified using stepwise regression analysis. When classifying covariates based on their different attributes, we established various models, ultimately constructing a fully adjusted model. Initially, vasopressor use was not included in the subsequent analysis because there was no significant difference between the aspirin-use group and the non-use group. However, we acknowledge the reviewer's suggestion and have now included vasopressor use in both the logistic regression and Cox regression analyses. The results still indicate that the use of aspirin is associated with a reduced risk of in-hospital and 28-day mortality (2.4 section; 3.2 section; supplemental tables 1-4).

Comment 20 Page 5, line 102: multivariable logistic regression cannot determine the predictive role, but the odds of a specific factor. Would suggest softening this language.
Reply 20: Thanks. This sentence has been softened. (page 8, line 150)

Comment 21 Page 5, line 110: in Methods you state you are reporting medians and IQR for continuous data, but report average (read: mean) age here. Later on the next line you are reporting median ages.
Reply 21: Thanks. This has been modified to the median. (3.1 section)

Comment 22 Tables 1 and 2: would suggest removing the "yes" and "no" reporting for each variable, as it confuses the table. Just report rates of "Yes" and we can deduce how many didn't have vasopressor use, for example.
Reply 22: Thanks. Table 1 and Table 2 have been reviewed according to your comments. (Table 1-revised; Table 2-revised)

Comment 23• Page 6, line 124: multivariable logistic regression does not assess "risk" but odds of mortality. I would change language for this throughout manuscript. Your other analyses assess risk of mortality.
Reply 23: Thanks. This point has been reviewed based on your comments in all manuscript

Comment 24• Page 6, line 128: would be good and informative to include the full model with all covariates in supplementary, especially since your covariates were all essentially significantly different between aspirin users and non-users.
Reply 24: Thanks. Based on your suggestions, we have added a the full model with all covariates in supplementary. (Supplementary tables 1-4)

Comment 25• Page 6, line 145: you are putting conclusions/discussion with interpretation in the Results section. Furthermore, one could conclude that aspirin use "causing" reduced mortality is not plausible or likely since, if it was, it would be expected to be a dose-dependent effect. I would remove this statement completely from the Results section, and would elaborate more on its [cautious] interpretation in the Discussion section. Furthermore, there should be a reason a patient is on high dose aspirin (read: other specific comorbidities or indications acutely) and would be a marker of likely a more comorbid patient (retrospectively), and thus may not have an association with mortality given such. You see this with your point estimate trending towards increased odds of mortality with high-dose aspirin use, which does not make sense with your conclusions as well.
Reply 25: Thanks. Our study results found that although the aspirin dosage was not significantly associated with mortality, the estimated value was 1.024 (0.728, 1.426), indicating a tendency for higher doses to be positively correlated with mortality. Therefore, the corresponding conclusion has been appropriately revised. Additionally, a discussion on the relationship between dosage and mortality has been added in the discussion section. (See fourth paragraph of discussion)

Comment 26• Page 7, line 162: your ref 13 is a study of aspirin use in diabetic cystopathy, not sepsis. Therefore cannot conclude that this contributes to "extensive study in sepsis."
Reply 26: Thanks. The original ref 13 has been deleted.

Comment 27• Page 7, line 162: your ref 24 is a review. I would only use primary data and research to make your claim of "aspirin use extensively studied in sepsis."
Reply 27: Thanks. The original ref 24 has been deleted.

Comment 28• Page 7, line 162: you don't cite/mention the ANTISEPSIS trial here, a prospective RCT on this topic, which did not show benefit in a more controlled study design than yours. This requires mentioning, rather than review articles and observational studies you cite.
Reply 28: Thanks. Based on your comments, we have deleted this sentence and original references 13, 17, 24, 25.

Comment 29• Page 7, line 164: again, it is not clear from your methods even if patients were on aspirin chronically in this study, or not, and whether you were isolating new initiation of aspirin use in the ICU only.
Reply 29: Thanks. We have specified the inclusion/exclusion criteria as previously

mentioned. (2.1 section)

Comment 30• Page 7, line 170: wouldn't you expect, biologically, that in patients with acute respiratory failure (represented as requiring invasive mechanical ventilation in your study) would have the most benefit of aspirin use? Your data shows this is one of the 16 subgroup analyses done that did not have an association with reduced mortality. Furthermore, your explanation with for "uncontrolled platelet activation may promote COPD progression…" would suggest that aspirin use may lead to less comorbid patients who then have an acute illness (e.g., sepsis) and therefore would be expected to have reduced mortality compared to more comorbid patients. This explanation you provide here is the crux of the issue with this study design. You cannot conclude that aspirin is "therapeutically treating" sepsis in patients with COPD leading to reduced mortality.
Reply 30: Thanks. We have made corrections based on your opinions and explained the reason for the significant correlation between aspirin and reduced mortality from the perspective of aspirin reducing comorbidities in patients. (See fifth paragraph of discussion)

Comment 31• Page 8, line 178: much too strong of a statement. You have not provided evidence, in this current study design, or in studies you cite, to be able to conclude "…aspirin effectively reduces mortality in COPD patients with sepsis."
Reply 31: Thanks. Based on your comment, the paragraph has been revised (see the third paragraph of the discussion).

Comment 32• Page 8, line 179: this paragraph is not the only interpretation (or even most logical, as I read it). See above regarding the same issue.
Reply 32: Thanks. Based on your comment, the fourth paragraph of the discussion has been rewritten. (see the fourth paragraph of the discussion).

Comment 33• Page 8, line 196: Included only patients admitted to the ICU >24 hrs. Limits generalizability and findings as there are likely patients with COPD and sepsis admitted to the floor that are not captured in your dataset.
Reply 33: Thanks. This limitation has been added to the "limitation" section. (4.1 section)

Comment 34• Another limitation: limited to one institution
Reply 34: Thanks. This limitation has been added to the "limitation" section. (4.1 section)

Reviewer B

Aspirin use reduces the mortality risk in chronic obstructive pulmonary disease with sepsis: a retrospective study using the MIMIC-IV database

Summary: This retrospective study aimed to analyze the association of aspirin use in the ICU with the morality risk in chronic COPD patients with sepsis. The authors concluded that aspirin use significantly reduced in-hospital and 28-day mortality risk in COPD patients with sepsis.

Critique: The data and results are interesting, however, some items need to be clarified before consideration for publication.

Comment 1 Introduction section states “However, some studies indicate that aspirin does not significantly inhibit COPD and sepsis (18, 19). “ These two references separately investigate aspirin use, they are not synergistic.
Reply 1: Thanks. We have revised the sentence to clarify the relationship between aspirin and COPD and sepsis, and to cite original references 18 and 19 separately. (Introduction section, paragraph 3)

Comment 2 Method section: Which SOFA calculation did the authors use? The SOFA calculation which includes creatinine, MAP, vasopressor use, GCS, bilirubin, platelet (range 0-24) or the version which only includes respiratory rate, mental status and systolic blood pressure (range 0-3)? The reason I ask is on page 17, table 1, it appears the range 2-4. The Sequential Organ Failure Score is more comprehensive rather than the qSOFA.。

Reply 2: Thanks. We used the SOFA score you mentioned. This SOFA score consists of six organ system scores, each ranging from 0 to 4 points. The patient's score is the sum of these six parts. We have added the corresponding references to the article. (2.1 section)

Comment 3 Why not list those patients in pure septic shock, SBP <90? The authors” method is mixing sepsis, severe sepsis and septic shock. SOFA is used for prognostic and stratification, is its use proper in a retrospective study?
Reply 3: Thanks. Because all types of sepsis were included in this study, the diagnostic criteria mentioned in the text are the sepsis diagnostic criteria (ref PMID: 26903335). In retrospective studies, SOFA cannot be used for prognosis and stratification, as it is one of the diagnostic criteria for sepsis and does not comply with data analysis principles. (2.1 section)

Comment 4 The exclusion criteria included incomplete information on vital signs, which vital signs? Admission vitals? Emergency Department vitals? In the same area, incomplete laboratory findings? Which laboratory findings and at which time point? Why excluded patients with ICU stays < 24 hours?
Reply 4: Thanks. Vital signs included heart rate, SBP, DBP, and SpO2 in the Emergency Department. Those signs were important for COPD patients with sepsis. The patient data involved in this study were all sourced from the MIMIC-IV public database. During data collection in this database, data omission issues can occur, leading to

missing data. Therefore, some laboratory data results such as glucose, hematocrit, platelets, WBC, prothrombin time, and urine output are incomplete. In this study, we collected the test data from the first admission of such patients (2.1 section). We excluded these patients with ICU stays < 24 hours based on methods reported in previous ICU studies [PMID: 36747139; PMID: 36446854]. However, this might lead to omissions. Therefore, we have included this issue in the limitations section. In addition, the exclusion of patients with ICU stays of less than 24 days involved only 156 individuals, representing approximately 5% of the total population. This small proportion suggests that the overall results remain broadly applicable. However, this exclusion introduces the potential for sample selection bias, which is a limitation of this study. (4.1 section)

Comment 5 57 patients were excluded for aspirin use before ICU admission. Does this study refer to chronic aspirin use or aspirin use beginning with admission to the hospital? This is not clear. In the results section, the authors refer to those that receive aspirin and those that did not; however, in the Methods section, the authors refer to aspirin users and non-users suggesting that patients were on aspirin before they presented to the hospital; Very confusing. Also, close to half the patients in the initial screen were excluded due to missing data, so are these results compromise due to high exclusion rate?

Reply 5: Thanks. In this study, we focused on aspirin use during the current hospitalization. Since sepsis is a major cause of ICU admissions and mortality among critically ill patients, and all patients included in the study were admitted to the ICU, our primary focus was on the use or not use of aspirin after ICU admission. For aspirin users, if the time from the start of aspirin use minus ICU admission time was greater than 0, this indicated that aspirin was used after ICU admission (2.1 section). On the other hand, only 57 patients used aspirin before ICU admission during hospitalization, which has a minimal impact on the generalizability of our findings. However, this may introduce a selection bias, which should be noted as a study limitation (4.1 section). Although we excluded most of the missing data, our total sample size is 2964, with approximately a 1:1 ratio between the two groups (aspirin users and aspirin non-users). In the analysis, we adjusted for potential covariates and eliminated the influence of potential confounding factors, making this study relatively close to the results of a real-world data investigation.

Comment 6 Data collection lists a wide variety of laboratory values, but why not lactate? Lactate is the most common laboratory finding measured.

Reply 6: Thanks. There were many missing lactate data in the MIMIC-IV data, so this indicator was deleted.

Comment 7 Statistical Section: How were the items in the Models chosen? Why not correct all at once in the analysis?

Reply 7: Thanks. The items in the model were selected based on the classification of all patient information. For example, Model 1 adjusts for the patient's demographic characteristics and comorbidities, while Model 2 adjusts for the measured indicators.

Model 3 adjusts for all indicators. Different models were constructed to explore the respective confounding impacts of the different categories on the outcomes. (2.4 section)

Comment 8 The Database ranged from 2008 to 2019, a lot of changes occurred during that period regarding sepsis care and since many patients were excluded, did one year have a higher number of exclusion relative to other years? Did the authors investigate compliance to the sepsis bundle?
Reply 8: Thanks. Since the MIMIC-IV data only includes patient IDs without specific admission years, we cannot determine which year had the most exclusions. This study did not investigate the adherence to sepsis bundle therapy, and we have mentioned this point in the limitations section. (4.1 section)

Comment 9 Interesting concept but manuscript is confusing and should be made more concise and clear to the reader
Reply 9: Thanks. Based on the reviewers' comments, we have revised the manuscript to enhance its readability.