Peer Review File

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Reviewer A

Thank you very much for your efforts in improving our study "Admission Oxygen Saturation and All-Cause In-Hospital Mortality in Acute Myocardial Infarction Patients: Data From the MIMIC-III Database". Here, we are writing to address all these questions and suggestions. Please refer to our point to point responses below.

Comment 1: This study requires that you can rely on the data source MIMIC-III, have any insight into how valid data is? Must expect that many different clinicians have been envolved in registering.

Reply 1: We thank the reviewer for this valuable comment. Medical Information Mart for Intensive Care III (MIMIC-III) database is a large, freely-available database comprising deidentified health-related data associated with over forty thousand patients who stayed in critical care units of the Beth Israel Deaconess Medical Center between 2001 and 2012 (1). Over one hundred articles related to the MIMIC database could be searched in the Pubmed database, and some of these studies have been published in several high-quality journals such as *Intensive Care Med* (IF: 18.9) (2), *Chest* (IF: 9.6) (3), and *Critical Care* (IF: 6.9) (4). Therefore, we thought that the data in the MIMIC-III database are valid.

Changes in the text: None.

Comment 2: I have a little heard to understand table s2, is it to validate MIMIC-III and see what values are correlated with mortality? To have a DPB should be protective and a SOFA score registered

negative?

Reply 2: We appreciate the reviewer's efforts in reviewing this manuscript. Actually, Table S2 in our article was used to show the missing number for risk variables. As extensive missing data might lead to bias, variables with over 30% missing values were not included in this study. Correspondingly, multivariate imputation (MI) was used for variables with less than 30% missing values (5, 6). To make Table S2 more understandable, we referred to the recently published article by Zhao et al (7) and have revised Table S2. In addition, I am sorry that variables of 'DPB' and 'SOFA' were not found in the Table S2.

Changes in the text: We have revised our Table S2. (see 'Tables' file, Page 7-8, line 70).

Comment 3: table with missing data should be erased, and missings should be showed in together with the other tables.

Reply 3: We greatly appreciate the reviewer's efforts in reviewing this manuscript. Table S2 in our article was used to show the missing number for risk variables. As extensive missing data might lead to bias, variables with over 30% missing values were not included in this study. Correspondingly, multivariate imputation (MI) was used for variables with less than 30% missing values (5, 6). We think that missing numbers (%) for characteristics were important data, which could be showed in a separate table. To make our manuscript more understandable, we have referred to the recently published articled by Zhao et al (7) and have revised the Table S2.

Changes in the text: We have revised our Table S2. (see 'Tables' file, Page 7-8, line 70).

Comment 4: It's a critical care database, how many patients were mechanical ventilated?

Reply 4: Thank you very much for your question. In this study, the variable of 'oxygen therapy' was extracted from the MIMIC-III database and studied as an important covariate. Oxygen therapy in this study could refer to several methods of oxygen supply such as nasal cannula, face mask, non-invasive mechanical ventilation, or invasive mechanical ventilation. In our study, 51.41% (949/1846) patients underwent oxygen therapy. Among them, 21.45% (396/1846) patients underwent non-invasive or invasive mechanical ventilation.

Changes in the text: None.

Reviewer B

Thank you very much for your efforts in improving our study "Admission Oxygen Saturation and All-Cause In-Hospital Mortality in Acute Myocardial Infarction Patients: Data From the MIMIC-III Database". Here, we are writing to address all these questions and suggestions. Please refer to our point to point responses below.

Comment 1: Abstract：The results section contains statements, without supporting data. Please include key data within the section.

Reply 1: Thank you very much for your comment. We have added supporting data in the 'results' section of our abstract.

Changes in the text: We have revised our text in the "Abstract" part of our article. (see Page 5, line 111-114).

Comment 2: In Supplementary table 2 with missing variables, it mentions that 514 patients did not have troponin T. Are these 514 out of the 1,846 patients included in the study i.e27.8%? If this is the

case then it is a major limitation as 28% of the study population had no troponin levels. This is vital information as an elevated troponin level is among the major components in the definition of myocardial infarction.

Reply 2: Thank you very much for your valuable comment. We completely agree with this point that each patient's troponin T level is one of vital information in the definition of myocardial infarction. However, in this study, we included patients diagnosed with AMI by using International Classification of Diseases (ICD)-9 diagnosis codes between 410.00 and 410.92 in the MIMIC-III database. We think using ICD-9 diagnosis codes could ensure the accuracy of the diagnosis though some patients' troponin T data were missing. In addition, multivariate imputation (MI) was used for variables with less than 30% missing values to avoid bias caused by missing data (5, 6, 8). In the sensitivity analyses, we excluded patients with missing data, and 1,049 patients remained in the final cohort. Similarly, we found the consistent results. Thanks for your careful work again.

Changes in the text: None.

Comment 3: A major concern with the utilization of pulse oximetry is that the patients in a low perfusion state such as those with low cardiac output can have inaccurate pulse oximetry readings (Crit Care. 2015 Jul 16;19:272. doi: 10.1186/s13054-015-0984-8). It will be important to define variables such as EF, hemodynamics of these critically ill patients of Acute myocardial infarction as that can affect the pulse oximetry oxygen saturation. This can also be an important factor in patients presenting with cardiogenic shock or cardiac arrest. Also, can the authors provide blood gas arterial oxygen saturation in these patients to confirm correlation with pulse oximetry.

Reply 3: Thank you very much for your advice. There were too many missing data on the hemodynamic variables such as 'EF' and 'cardiac output' in the MIMIC-III database. Therefore, we excluded these variables. However, to avoid inaccuracy of SpO_2 caused by low perfusion state and assess the patients' perfusion state, we added new variables of 'Comorbidities: cardiogenic shock and cardiac arrest'. A series of corresponding subgroup analyses were used to validate the robustness of our findings. Additionally, too many data on blood gas arterial oxygen saturation were missing. However, we thought that SpO_2 provides pragmatic advantages over SaO_2, including the ability to measure blood oxygenation inexpensively, noninvasively and repeatedly (9). Therefore, it is common practice to use SpO2 as a surrogate for SaO2. Furthermore, one recent study has found that the agreement between SpO2 and SaO2 is sufficient to use them interchangeably (mean difference 1 ± 2%), and the specificity of the latest generation devices to detect hypoxemia is >95% (10). In addition, the values of SpO2 were measured multiple times within the first 24 hours after ICU admission, and the average values were used in our analysis as a measure of the central tendency of patients' condition, which might avoid erroneous readings caused by one measurement.

Changes in the text: We have revised manuscript. (see Page 10, line 208; see Page 13, line 274-275; see Page 15, line 310; see Page 15, line 320-321, see "Tables" file: Table 1 and Table S3).

Comment 4: Many of the patients with acute myocardial infarction can present with acidosis which can also affect the pulse oximetry findings. Can the authors provide details regarding it and if they were adjusted in the models during comparison?

Reply 4: Thank you very much for your advice. We have added the variable of PH to avoid the

bias caused by the disorder of acid-base balance, and adjusted for it as a covariate in the multivariable Cox model.

Changes in the text: We have revised manuscript. (see Page 10, line 214; see Page 13, line 283; see "Tables" file: Table 1 and Table S3).

Comment 5: Overall mortality reported in this database was 31.8% of the AMI patients. In previously reported data on AMI mortality have ranged between 4-12%. Can authors comment on the extremely high mortality observed in their study.

Reply 5: Thank you very much for your advice. First, patients who were enrolled in this study were in a relatively serious condition. Compared with similar studies, patients in this study were older, had higher incidence rate of cardiogenic shock and cardiac arrest. Lower proportion of patients in this study received PCI treatment. Second, the primary end-point of this study was all-cause mortality, and death caused by any disease during hospitalization was regarded as an outcome event. Third, this study is a single-center study, and this limitation has been discussed in the manuscript. Similar to a recent study by Wang et al. (8), they included AMI patients from the MIMIC database, and they reported a one-year mortality rate of nearly 24%, which was also higher than the 10% reported in the latest European AMI guidelines.

Changes in the text: None.

Comment 6: Can the authors provide us the information regarding the type of reperfusion in these patients? Patients with CABG are usually intubated and may have a lower oxygen saturation than other AMI patients which could be a confounding variable. Did they adjust for the type of reperfusion

strategies in their models?

Reply 6: Thank you very much for your advice. We have added the variable of reperfusion treatment including percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG), and adjusted for them as covariates in the multivariable Cox model.

Changes in the text: We have revised manuscript (see Page 15, line 311; see Page 15, line 323; see "Tables" file: Table 1 and Table S3).

Comment 7: As mentioned on page 21 in the discussion section administration of supplemental oxygen during AMI and concluded that oxygen therapy did not benefit patients with baseline normal peripheral oxygen saturations levels –90%" However, in this study authors have showed that patients with oxygen saturation less than 94% showed higher mortality in comparison to 94-96%. Can they elaborate and explain this finding in the discussion section?

Reply 7: Thank you very much for your advice. At least six randomized controlled trials (RCTs) investigated the effect of administration of supplemental oxygen during AMI and concluded that oxygen therapy did not benefit patients with baseline normal peripheral oxygen saturations levels ≥90% (11-16). In these studies, they mainly focused on the comparison of clinical effect between routine oxygen therapy and ambient air, and didn't explore the relationship between admission oxygen saturation and in-hospital mortality. In fact, in our study, 51.41% (949/1846) patients underwent oxygen therapy and 48.59% (897/1846) people did not receive oxygen therapy. Our univariable Cox analysis showed that oxygen therapy was not associated with mortality compared to the ambient-air group, and our findings were consistent with the findings of these six RCTs. Furthermore, these previous studies didn't identify the optimal range of SpO_2, and the

target values for SpO_2 in the oxygen therapy group were arbitrary. Our subgroups analyses showed targeting SpO_2 between 94% and 96% might optimize survival for patients with or without receiving oxygen therapy. We have added these points in the 'discussion' section of our manuscript.

Changes in the text: We have revised manuscript (see Page 20, line 428-432).

Reviewer C

Thank you very much for your efforts in improving our study "Admission Oxygen Saturation and All-Cause In-Hospital Mortality in Acute Myocardial Infarction Patients: Data From the MIMIC-III Database". Here, we are writing to address all these questions and suggestions. Please refer to our point to point responses below.

Comment 1: Too many important data are missing in the manuscript. For example, in Line 1-16, Page 15, I could not understand the meaning from the results. The authors should clear the results and other data.

Reply 1: Thanks for your careful work. We have revised our manuscript and added all the missing data to make our article more understandable.

Changes in the text: We have revised manuscript (Page 12-16).

Comment 2: Some of the statistical methods are incorrect. For instance, the author evaluate the association between SpO2 level and mortality using cox proportional hazards model. They construct three stages of one model, not three cox regression models. The authors should ask professional statisticians to reanalyze the data.

Reply 2: Thank you very much for your advice. According to your suggestion, we have asked some professional statisticians to improve our statistical methods. Additionally, we have revised our 'Statistical analysis' section in our manuscript.

Changes in the text: We have revised manuscript. (see Page 12, line 244).

Comment 3: The authors describe the professional vocabularies incorrectly. For example, the authors use "low blood oxygenation" and "high blood oxygenation" in Line 21-22, Page 15. What's the meaning "low/high blood oxygenation"? They should revise the manuscript using professional expressions.

Reply 3: **According to your suggestions, we have checked our manuscript thoroughly and revised our manuscript with more professional expressions or terms.**

Changes in the text: We have revised manuscript. (see Page 14, line 290-292).

Comment 4: What's the difference between the two figures in Fig.1? The authors should depict the figures in detail in figure legends.

Reply 4: Thank you very much for your advice. The first picture in Fig 1 showed the relationship between SpO_2 and mortality based on the whole study cohort. The second picture magnified the U-shaped part of the first picture to show the flattest part of Fig 1 and the cutoff values of SpO_2, which were used to identify the optimal oxygen saturation range. We have revised our figure legends to make it more understandable.

Changes in the text: We have revised figure legends. (see "figure legends" file).

Comment 5: Too many tables and figures have been uploaded repeatedly.

Reply 5: Thank you very much for your advice. We will no longer make this kind of mistake.

Changes in the text: None.

Comment 6: The manuscript has several English grammar errors. It is hard to read in several sections. The manuscript should be edited by someone whose native language is English.

Reply 6: Thank you very much for your advice. We have asked an English language editing company and corresponding experts for help. The editing certificate has also been uploaded. In addition, we have checked our manuscript thoroughly. We hope the revised version of the study can meet your requirement. Thanks again for your excellent work.

Changes in the text: We have revised our manuscript. (see Page 5, line 92; see Page 5, line 109; see Page 6, line 130; see Page 7, line 134-135; see Page 12, line 243-247; see Page 12, line 264-266; see Page 18, line 360-362).

Reference

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