## PEER REVIEW HISTORY



## ARTICLE DETAILS

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| **TITLE (PROVISIONAL)** | Development of a nomogram for the prediction of in-hospital mortality in patients with acute ST-elevation myocardial infarction after primary percutaneous coronary intervention: a multicentre, retrospective, observational study in Hebei Province, China |
| **AUTHORS** | Wang, Yudan; Wang, Wenjing; Jia, Shengqi; Gao, Man; Zheng, Shihang; Wang, Jiaqi; Dang, Yi; Li, Yingxiao; Qi, Xiaoyong |

## VERSION 1 – REVIEW

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| **REVIEWER** | Riccardo Rinaldi<br>Catholic University of the Sacred Heart |
| **REVIEW RETURNED** | 30-Sep-2021 |

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| **GENERAL COMMENTS** | In this interesting research article, Wang et al developed a nomogram for the individual prediction of in-hospital mortality in STEMI patients after PCI. The problem of STEMI mortality is not negligible, and therefore the identification of validated prediction models is a major unmet clinical challenge.<br>The study population is very large (more than 800 patients), and many variables have been assessed. However, the retrospective nature of the study is an important limitation. The investigators reported that age, BMI, blood pressure, haemoglobin, random blood glucose, EF after PCI, use of aspirin before admission, N/L ratio, long lesions and TIMI flow grade 0-1 before PCI were the variables independently associated with in-hospital mortality. The results are well explained and justified in the discussion, addressing the underlying pathophysiologic mechanisms and with a good review of existing literature.<br><br>However, this study has some issues that should be addressed:<br>1) The criteria of distinction in “training” and “testing” set is not well explained in the manuscript. Please explain why the authors decided to divide the patients in the two groups.<br>2) The statistical results according to “training” and “testing” set are very different. Indeed, even the variables reported as independently associated with in-hospital mortality are not significant in both groups. Please explain the observed differences in the manuscript.<br>3) The statistical analysis should be checked. Indeed, some variables resulted significantly different between the 2 groups with similar incidence in the 2 groups (i.e: previous CABG, number of stents).<br>4) A table reporting the characteristics of all patients (both "training" and "testing" set) should be reported.<br>5) Some variables prognostically relevant wasn't assessed in the study: - use of inotropic drugs; -therapy established post-PCI; -type of P2Y12 inhibitor chosen; use of GP IIb/IIIa at the time of PCI; - more information regarding the PCI procedure. If not available, these should be reported as limitation and discussed by the authors. |

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| | 6) Methods should be better defined. Indeed, the following definitions are lacking: -long stenosis; -residual stenosis; -bleeding.<br>7) The authors should state and explain on which population they performed the logistic regression analysis (“training set”, “testing set” or both). However, they should reported the analysis performed on the overall population.<br>8) The authors reported a relative high rate of coronary perforation in the “training set” analysis (3.8%). How do the authors justify this observation?<br>9) Variables with a significant impact on patients’ outcomes were reported as significantly associated with in-hospital mortality (cardiogenic shock, use of ventilator, total ischemic time). The authors should justify these results and explain how they decided to exclude these variables from the nomogram. Indeed, they were included in the nomogram from Gao et al (ref 60) reported by the authors.<br>10) The authors reported only the number of LAD as culprit vessel. However, the frequency of all culprit vessels should be reported.<br>11) In a recent work from Del Buono et al (doi: 10.2459/JCM.0000000000001168), a higher Killip Class was associated with worse in-hospital clinical outcome. In addition, the authors didn’t include Killip Class in the nomogram. Please cite, comment and justify the choice.<br>12) The authors reported only the multivariate logistic regression analysis. Please report also the univariate analysis.<br>13) The authors reported N/L ratio as a marker of inflammation following STEMI. However, no inflammatory index are reported (e.g.: PCFR). If these data are not available, the authors should add this as a limitation of the study.<br>14) The authors should reported the frequency of multivessel CAD in the study population. In addition, they should report if complete revascularization has been achieved during index hospitalization.<br>15) Are data available regarding the incidence of infection during the ICU hospitalization? The incidence of septic shock could be a confounder when assessing in-hospital mortality. |

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| **REVIEWER** | Junxian Cao<br>First Affiliated Hospital of Harbin Medical University |
| **REVIEW RETURNED** | 01-Dec-2021 |

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| **GENERAL COMMENTS** | The article《A nomogram for the prediction of in-hospital mortality in patients with acute ST-elevation myocardial infarction after primary percutaneous coronary intervention》 established a clinical prognostic nomogram for predicting in-hospital mortality after PCI among patients with STEMI. The study included 855 patients from 39 hospitals in the Hebei province, which has representative significance in central China. A nomogram was established in this study for predicting in-hospital mortality of STEMI after PCI, which was verified to be validated in this article.<br>There are some comments about this study.<br>1.In the second paragraph of Introduction, the author said, “these studies often exclude patients with advanced age, liver or kidney dysfunction, and other comorbidities and complications. Therefore, the generalizability of those studies is limited, and it is difficult to summarize and reflect the real-world treatment situation comprehensively.”However， in this study, biochemical indicators such as creatinine and liver enzymes were not included in the analysis model. Also lipid, blood oxygenation level, and so on. Liver or kidney dysfunction could influence the prognosis and these |

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| | indicators should be included in this article and be analyzed like glucose.<br>2.In discussion, the author mentioned the reference 60, which also provided a nomogram for predicting in-hospital mortality of patients with STEMI after PCI. The patients also from Hebei province in China. Although patients in the two articles admitted to hospital in different years , they were both STEMI patients treated with primary PCI. However, the predictors were completely different. As we all know, some variables (the left main coronary artery disease, grading of thrombus,TIMI classification, slow flow,symptom-to-door time, symptom-to-balloon time...) are closely related with prognosis. But these variables were not observed in this study. How to explain this?<br>3.In table 1, Age between two groups in training set has obvious difference while no difference in testing set. As a rule of thumb, this set of data should be statistically significant (59.8±12.4 Vs 74.4±9.6).<br>4.The discussion was too long and it was suggested to simplify. For example,the beginning of the third paragraph in discussion on page 12 may be deleted. |

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| **REVIEWER** | Yan Li<br>Xuanwu Hospital |
| **REVIEW RETURNED** | 02-Dec-2021 |

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| **GENERAL COMMENTS** | The paper entitled " A nomogram for the prediction of in-hospital mortality in patients with acute ST-elevation myocardial infarction after primary percutaneous coronary intervention" uses a new risk model to predict in-hospital mortality for patients after STEMI. There is a carefully done study and the findings are of considerable interest. A few major revisions are list below.<br>1. The authors should show us the sample size calculation. If they want to create a new risk model, they should have enough sample size, and how the sample size was calculated should be show to us.<br>2. The risk model has satisfactory performance to predict in-hospital mortality for patients after PCI, but the authors don't have enough discussion about the risk model. Please discuss the more about the clinical implications of the study, rather than discuss the risk factors used in the risk model.<br>3. In the results section, the authors should mention the mean duration of hospital stay for both cohorts. |

**VERSION 1 – AUTHOR RESPONSE**

Reviewer: 1

*1) The criteria of distinction in "training" and "testing" set is not well explained in the manuscript. Please explain why the authors decided to divide the patients in the two groups.*

Thanks for your constructive advice. We didn't describe it clearly. The inclusion and exclusion criteria of the two groups of patients in the training set and the test set are the same. Here we divided them into two groups in chronological order because the nomogram needs to verify the prediction results of the risk model before making it. Common validation processes include internal validation and external validation. Internal validation (training set) refers to the use of modeled data to verify the predictive effect of the model. External validation (test set) is to use another set of patients' data (namely external data) to verify the prediction accuracy of the model. Patients in the test set can be people in different regions at the same time period, or people in different time periods. Here, we enrolled patients in different time periods for external validation. The results showed that the C index in the internal validation is 0.947 and 0.891 in the external validation, indicating that there is a good level of

consistency between the predicted probability and the actual situation of the outcome event. We have explained in the article. (P.7 Line 5-8)

*2) The statistical results according to "training" and "testing" set are very different. Indeed, even the variables reported as independently associated with in-hospital mortality are not significant in both groups. Please explain the observed differences in the manuscript.*

We thank the reviewer. One possible reason for the difference between the two groups is that there was a total of 396 patients in the training set (132 in-hospital deaths, with a mortality rate of 33.3%), and a total of 459 patients in the validation set (91 in-hospital deaths, with a mortality rate of 19.8%). Another possibility reason is that there may be bias. Here we still use this group of patients as the validation set because considering that in practical applications, the patients may also be different from the patients in our model. In the follow-up, we will continue to select multi-center patients to expand the sample size of the validation set in order to reduce the cost as much as possible to obtain a more accurate risk model.

*3) The statistical analysis should be checked. Indeed, some variables resulted significantly different between the 2 groups with similar incidence in the 2 groups (i.e: previous CABG, number of stents).*

Thank you for pointing this out. We are sorry about that because we didn't explain clearly in table 1 which caused you trouble. In Table 1, the representation method of the count data is n (%). If the measurement data conforms to the normal distribution, it shall be represented by the mean ± standard deviation; the non-normal distribution shall be represented by the median (interquartile range). Here, like previous CABG, it uses n (%). The total number of deaths in the training set is 132. One person has a history of CABG, so the incidence rate is 0.8%, P=0.157; there are 91 deaths in the verification concentration, and one person has a history of CABG, so the incidence is 1.1 %, P=0.05. The number of stents is represented by the median (interquartile range). I have bolded the data representation method in Table 1 (P.27-31), so as to make it easier for readers to understand.

*4) A table reporting the characteristics of all patients (both "training" and "testing" set) should be reported.*

We thank the reviewer. The table reported the characteristics of all patients of both cohorts had already added in the table 1(P.27-31).

*5) Some variables prognostically relevant wasn't assessed in the study: - use of inotropic drugs; -therapy established post-PCI; -type of P2Y12 inhibitor chosen; use of GP IIb/IIIa at the time of PCI; -more information regarding the PCI procedure. If not available, these should be reported as limitation and discussed by the authors.*

We thank the reviewer. The treatment strategy after PCI of surviving patients is determined by the doctor in charge in accordance with relevant guidelines. We revised the method of the manuscript. Since 23 (17.2%) died during the PCI in the training set, postoperative treatment is not available, so we did not show it in the study. We have added the use of GP IIb/IIIa (38 (28.8) vs. 54 (20.5), *P*=0.064) and the chosen of P2Y12 inhibitor in table 1 (P.29-30). About some other variables, this is indeed a limitation of our study. We have not obtained the other more information during the PCI and inflammation indicators, we have rewritten the limitation (P.17 Line 18-20). We will try to improve this information in future researches.

*6) Methods should be better defined. Indeed, the following definitions are lacking: -long stenosis; -residual stenosis; -bleeding.*

We thank the reviewer. Long lesions was defined as the stenosis that has as ≥ 50% reduction and more than 20mm in luminal diameter[1]. Residual stenosis was defined as＞30% residual stenosis of the target lesion after PCI. Bleeding was defined as a composite of major bleeding according to Bleeding Academic Research Consortium Definition for Bleeding (BARC) type 3 or 5, but was not related to coronary-artery bypass grafting (CABG)[2]. We have revised the manuscript. We have added this section to the manuscript (P.8 Line 6-12)

*7) The authors should state and explain on which population they performed the logistic regression analysis ("training set", "testing set" or both). However, they should reported the analysis performed on the overall population.*

We thank the reviewer. Indeed, we did not describe it clearly. We did the logistic regression on the training set, and used the results of multivariate logistic regression analysis to build the nomogram. In this study, based on the data from the training set, we created a risk model and it performed well. In order to verify whether this model can be widely used in clinical practice, we used another set of data for external validation, namely the test set. In external validation, this model continues to perform well and is able to assess the prognosis of the patients. These are enough to prove the usefulness of this model, and other related studies have used a similar statistical process[3]. So, we don't think we need to validate the overall population here.

*8) The authors reported a relative high rate of coronary perforation in the "training set" analysis (3.8%). How do the authors justify this observation?*

Thanks for your comment, coronary perforation is a rare and serious complication of PCI, with an incidence of 0.1%-3%[4], and the incidence of CTO lesions can be as high as 5%. In our study, the incidence of coronary perforation in the total population was 0.8% (n=7). Among the 5 patients with coronary perforation in the training set death group, the age was 73.6±4.04 years, 3 were women, 4 were long lesions, 4 were calcified lesions, and 4 were type C lesions. Except for 2 patients with type I [5] and no special treatment, the other 3 patients suffered cardiac tamponade and died during the operation after pericardiocentesis. In the training set, the incidence of coronary perforation was 3.8%. The reasons may be :1. The blood vessel condition of this part of the patients is relatively poor; 2. Due to the multi-center study, the level of the surgeon in each center will affect the experimental results interference. We will work with more centers to expand the sample size and analyze the impact of coronary perforation on in-hospital mortality more objectively.

*9) Variables with a significant impact on patients' outcomes were reported as significantly associated with in-hospital mortality (cardiogenic shock, use of ventilator, total ischemic time). The authors should justify these results and explain how they decided to exclude these variables from the nomogram. Indeed, they were included in the nomogram from Gao et al (ref 60) reported by the authors.*

Thank you for pointing this out. We think that there are three possible reasons for the different risk factors of the two studies: 1. The research methods are different. Gao's study is a retrospective cohort study, and we are a case-control study. This led to a large difference in the proportion of deaths in the two parts of the patient population (8.1% vs. 33.3% in the training set). Both research methods have their own advantages and disadvantages. Generally, case-control studies are used to screen suspicious causes and establish hypotheses as the first stage of etiological research, and retrospective cohort studies are used to test hypotheses as the second stage. 2. The hospitals and time nodes that included patients are different. The two studies included patients in 2016-2018 and

2018-2019. Gao's patients were from three hospitals in Shijiazhuang, Baoding and Cangzhou, and our patients were from 39 hospitals in Hebei Province. 3. Different statistical methods. Gao's research used Lasso regression, and we used logistics regression. Usually because of the stability of Lasso regression, it is considered superior to logistics regression, but it also has the disadvantages of limited number of features (usually only one feature can be selected for each set of features) and low interpretability of the model for low-dimensional situations. In fact, we plan to combine the two parts of patients to get a more accurate risk model of in-hospital mortality. We have discussed this in the manuscript. (P.17 Line 13-16)

*10) The authors reported only the number of LAD as culprit vessel. However, the frequency of all culprit vessels should be reported.*

Thanks a lot for your professional comment. We have added the frequencies of LCX (20 (15.2) vs. 39 (14.8), *P*=0.921) and RCA (40 (30.3) vs. 101 (38.3), *P*=0.119) in Table 1 (P.29).

*11) In a recent work from Del Buono et al (doi: 10.2459/JCM.0000000000001168), a higher Killip Class was associated with worse in-hospital clinical outcome. In addition, the authors didn't include Killip Class in the nomogram. Please cite, comment and justify the choice.*

In our multivariate analysis, the higher Killip Class is not a predictor of in-hospital mortality in STEMI patients. However, in a recent work from Del Buono et al[6], it was proved that a higher Killip Class is an independent risk factor for MACE events and in-hospital mortality in patients with anterior myocardial infarction. This the first study including only patients with STEMI in the anterior location and excluding patients with history of cardiovascular diseases in order to reduce the heterogeneity of the population enrolled. This may be one of the reasons for the inconsistency of the two studies. Nevertheless, Killip classification is a simple and convenient clinical tool that can quickly stratify the risk of ACS patients and is likely to become an independent predictor of long-term follow-up results again. (P. 16 Line 6-15)

*12) The authors reported only the multivariate logistic regression analysis. Please report also the univariate analysis.*

Considering the Reviewer's suggestion, we have added the univariate analysis to table2 (P.32).

*13) The authors reported N/L ratio as a marker of inflammation following STEMI. However, no inflammatory index are reported (e.g.: PCFR). If these data are not available, the authors should add this as a limitation of the study.*

Thank you for pointing this out. Because it is a multi-center retrospective study, there are differences in the specific content of some biochemical examinations of patients by the doctor in charge. The inflammatory markers are not available. We have already explained this in the limitation. (P.19 Line 18-20)

*14) The authors should reported the frequency of multivessel CAD in the study population. In addition, they should report if complete revascularization has been achieved during index hospitalization.*

Thanks for your professional comment. We added the frequency of multivessel CAD in Table 1 (P.

29) and Study design and patients of the PATIENTS AND METHODS (P. 7 Line 16-18). In fact, almost all patients have only undergone revascularization of the criminal vessels. Surviving patients with multivessel CAD will undergo non-criminal disease PCI within 15-45 days after the first PCI on a voluntary basis. We did not include patients who were re-admitted to the hospital in this study. In the future, we may develop related randomized trials to discuss the impact of complete and incomplete revascularization on the in-hospital mortality of STEMI patients after PCI.

*15) Are data available regarding the incidence of infection during the ICU hospitalization? The incidence of septic shock could be a confounder when assessing in-hospital mortality.*

Unfortunately, because it is a multi-center retrospective study, many patients and doctors are involved, and some indexes cannot be obtained uniformly. We have not obtained more data during ICU hospitalization, and we have not validated this risk model in ICU patients. As far as we know, of the 223 patients who died in the hospital (132 in the training set and 91 in the test set), 1 died of septic shock. We plan to launch a prospective study, focusing on collecting more data on the infection index and applying our model to more critically ill patients in order to obtain a more accurate model and truly reduce the mortality of STEMI patients. (P. 18 Line 2-5)

Reviewer: 2

*1) In the second paragraph of Introduction, the author said, "these studies often exclude patients with advanced age, liver or kidney dysfunction, and other comorbidities and complications. Therefore, the generalizability of those studies is limited, and it is difficult to summarize and reflect the real-world treatment situation comprehensively." However， in this study, biochemical indicators such as creatinine and liver enzymes were not included in the analysis model. Also, lipid, blood oxygenation level, and so on. Liver or kidney dysfunction could influence the prognosis and these indicators should be included in this article and be analyzed like glucose.*

Thanks a lot for your professional comment. The patient's creatinine level has been added to Table 1 (P. 30), and the lipid is processed according to the count data. Because this is a multi-center retrospective study, we are sorry that we have not collected relevant information about the liver and blood oxygenation level, we have already mentioned this in the limitation. In the follow-up, we are planning to carry out prospective studies to collect patient data as comprehensively as possible in order to obtain more accurate prediction models. (P. 17 Line 18-20)

*2) In discussion, the author mentioned the reference 60, which also provided a nomogram for predicting in-hospital mortality of patients with STEMI after PCI. The patients also from Hebei province in China. Although patients in the two articles admitted to hospital in different years, they were both STEMI patients treated with primary PCI. However, the predictors were completely different. As we all know, some variables (the left main coronary artery disease,*

*grading of thrombus, TIMI classification, slow flow, symptom-to-door time, symptom-to-balloon time...) are closely related with prognosis. But these variables were not observed in this study. How to explain this?*

Thank you for pointing this out. We think that there are three possible reasons for the different risk factors of the two studies: 1. The research methods are different. Gao's study is a retrospective cohort study, and we are a case-control study. This led to a large difference in the proportion of deaths in the two parts of the patient population (8.1% vs. 33.3% in the training set). Both research methods have their own advantages and disadvantages. Generally, case-control studies are used to screen suspicious causes and establish hypotheses as the first stage of etiological research, and retrospective cohort studies are used to test hypotheses as the second stage. 2. The hospitals and time nodes that included patients are different. The two studies included patients in 2016-2018 and 2018-2019. Gao's patients were from three hospitals in Shijiazhuang, Baoding and Cangzhou, and our patients were from 39 hospitals in Hebei Province. 3. Different statistical methods. Gao's research used Lasso regression, and we used logistics regression. Usually because of the stability of Lasso regression, it is considered superior to logistics regression, but it also has the disadvantages of limited number of features (usually only one feature can be selected for each set of features) and low interpretability of the model for low-dimensional situations. In fact, we plan to combine the two parts of patients to get a more accurate risk model of in-hospital mortality. We have discussed this in the manuscript. (P.17 Line 13-16)

*3) In table 1, Age between two groups in training set has obvious difference while no difference in testing set. As a rule of thumb, this set of data should be statistically significant (59.8±12.4 Vs 74.4±9.6).*

It is indeed our mistake. The age in the test set was 59.8±12.4 vs. 70.2±11.3, *P*<0.001. We have checked and revised. (P. 27)

*4) The discussion was too long and it was suggested to simplify. For example, the beginning of the third paragraph in discussion on page 12 may be deleted.*

We have simplified the discussion part. Thanks for your constructive advice.

Reviewer: 3

*1) The authors should show us the sample size calculation. If they want to create a new risk model, they should have enough sample size, and how the sample size was calculated should be show to us.*

Thank you for pointing this out. Like the reviewer said, sample size estimation is very important. According to Harrell criterion[3], when the outcome event is a binary variable, the sample size should be greater than 10 times the number of predictors. In our research, there are 396 people in the training set, which can accommodate up to 39 predictors. After t-test and chi-square test, we finally have 39 predictor variables into the multivariate regression analysis, and 10 into the nomogram.

*2) The risk model has satisfactory performance to predict in-hospital mortality for patients after PCI, but the authors don't have enough discussion about the risk model. Please discuss the more about the clinical implications of the study, rather than discuss the risk factors used in the risk model.*

Thanks a lot for your professional comment. The nomogram is a simple and intuitive representation of the mathematical model. It can simplify the statistical prediction model to the numerical probability of disease recurrence or death. The identification and stratification of patients becomes a simple tool with many advantages. The most prominent advantage is that it can predict individualized risks based on patient and disease characteristics. Secondly, it is easy to use and can help doctors develop individualized treatment plans. However, although the current clinical use of nomograms has increased, there are limited data on patient satisfaction or quality of life after it assists in medical decision-making. In addition, although nomograms are widely used clinically, they are rarely evaluated prospectively to determine whether their use actually improves the prognosis of patients. Therefore, it remains to be explored how this research model can be better applied to the clinic. This was added to the Discussion. (P. 16 Line 16-21; P. 17 Line 1-7)

*3) In the results section, the authors should mention the mean duration of hospital stay for both cohorts.*

Thank you for pointing this out. The hospital stay was 8.51±5.11 days in the training set and 8.32±4.70 days in the test set. (P.11 Line 11)

**VERSION 2 – REVIEW**

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| **REVIEWER** | Riccardo Rinaldi<br>Catholic University of the Sacred Heart |
| **REVIEW RETURNED** | 14-Jan-2022 |

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| **GENERAL COMMENTS** | I really thank the author for the excellent and exhaustive response to my comments. The paper gained a lot of value thanks to the useful and valuable comments of all reviewers, and therefore it is rather acceptable for publication.<br>However, I still have some little suggestions that may further improve it:<br>1) The overall introduction could be simplified for a better understanding of the readers. For example:<br>P1 L16 This sentence could be simplified "Nevertheless, even if such patients receive timely PCI and/or appropriate antiplatelet drugs, the prognosis is still poor, and a substantial number of STEMI patients still die in-hospital after PCI (about 6%). Therefore, there is still room for improving the short-term outcomes of these patients on top of a timely PCI.<br>P1L7: "Myocardial infarction is the main cause of global morbidity, mortality, and major cardiovascular events (MACEs), representing 15% of the annual deaths worldwide 5." This sentence is generic for all patients with myocardial infarction. It could be deleted and reported just for STEMI in the first sentence "ST-segment elevation myocardial infarction (STEMI), a type of coronary artery disease (CAD), is a common clinical emergency and critical illness".<br>2) The correct term for the vessel not responsible for STEMI is "non-culprit vessel" and not "non-criminal". Please correct and change it throughout the manuscript. |

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| | 3) P16L13: "We think there may be three main reasons: different research methods, the hospitals and time nodes that included patients are different and different statistical methods. Nevertheless, we are planning to combine the two parts of patients to get a more accurate risk model of in-hospital mortality."<br>This sentence is not clear. Maybe I suggest to change it this way "Three main reasons fame justify the different predictors we found in our study: different research methods, the hospitals and time nodes that included patients are different and different statistical methods. Nevertheless, we are planning to combine the two parts of patients to get a more accurate risk model of in-hospital mortality."<br>4) P14L6: "The total ischemic time in patients with AMI is inversely proportional to the drop in HGB concentration 46. "<br>Please justify this sentence and link it with the concept you are explaining in the text.<br>5) Please double check the manuscript for typo errors.<br>e.g.: P13L5 "Therefore, the N/L ratio (, as) IS an index for systemic inflammatory status and usually increases after STEMI 30-32." |

**VERSION 2 – AUTHOR RESPONSE**

Reviewer: 1

*1) The overall introduction could be simplified for a better understanding of the readers. For example: P1 L16 This sentence could be simplified "Nevertheless, even if such patients receive timely PCI and/or appropriate antiplatelet drugs, the prognosis is still poor, and a substantial number of STEMI patients still die in-hospital after PCI (about 6%). Therefore, there is still room for improving the short-term outcomes of these patients on top of a timely PCI. P1L7: "Myocardial infarction is the main cause of global morbidity, mortality, and major cardiovascular events (MACEs), representing 15% of the annual deaths worldwide 5." This sentence is generic for all patients with myocardial infarction. It could be deleted and reported just for STEMI in the first sentence "ST-segment elevation myocardial infarction (STEMI), a type of coronary artery disease (CAD), is a common clinical emergency and critical illness".*

Thank you for pointing this out. We have revised in the manuscript. (P5L14-18)

*2) The correct term for the vessel not responsible for STEMI is "non-culprit vessel" and not "non-criminal". Please correct and change it throughout the manuscript.*

We thank the reviewer. We have corrected in the manuscript.

(P7L17)

*3) P16L13: "We think there may be three main reasons: different research methods, the hospitals and time nodes that included patients are different and different statistical methods. Nevertheless, we are planning to combine the two parts of patients to get a more accurate risk model of in-hospital mortality." This sentence is not clear. Maybe I suggest to change it this way "Three main reasons fame justify the different predictors we found in our study: different research methods, the hospitals and time nodes that included patients are different and different statistical methods. Nevertheless, we are planning to combine the two parts of patients to get a more accurate risk model of in-hospital mortality."*

Considering the Reviewer's suggestion. We have revised in the manuscript. (P17L16-20)

*4) P14L6: "The total ischemic time in patients with AMI is inversely proportional to the drop in HGB concentration 46. "Please justify this sentence and link it with the concept you are explaining in the text.*

Thank you for pointing this out. In the study from Shacham Y et al, they revealed the longer the total ischemic time, namely an ongoing inflammatory process, the lower admission HGB levels. So, HGB levels and inflammation are closely related. HGB levels and inflammation are closely related. In patients with STEMI, inflammation block occurs, that is, an abundance of hepcidin leads to poor uptake of iron from the gastrointestinal tract, iron sequestration in macrophages, little iron recycling to the erythron for red-cell production, and microcytic anemia, which can cause a lower HGB level. We have revised in the manuscript. (P15L7-9)

*5) Please double check the manuscript for typo errors.e.g.: P13L5 "Therefore, the N/L ratio (, as) IS an index for systemic inflammatory status and usually increases after STEMI 30-32."*

Thanks for your comment. We have revised in the manuscript. (P14L6-7)

**VERSION 3 – REVIEW**

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| **REVIEWER** | Riccardo Rinaldi<br>Catholic University of the Sacred Heart |
| **REVIEW RETURNED** | 18-Jan-2022 |

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| **GENERAL COMMENTS** | I would like to thank again the authors for responding to my comments. I think that the paper is now acceptable for publication. |