

Peer Review File

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Reviewer A

Comments: This is very nice work on risk prediction model for postoperative delirium in patients with off-pump coronary artery bypass grafting.

Reply: Thank you very much for your comments.

Changes in the text: None.

Reviewer B

Thank you for allowing me the opportunity to review this paper about a risk prediction model for postoperative delirium after OPCABG. The authors should be congratulated for their excellent work. I read the manuscript with interest. My comments are as follow:

Comment 1: I would like you to evaluate the lowest systolic blood pressure, fluid balance, and RsO₂ during surgery. In addition, more information is needed whether the proximal anastomosis was performed using side clamp or a device?

reply 1: I totally agree with you that the lowest systolic blood pressure, fluid balance, and RsO₂ during surgery are very important variables associated with postoperative delirium in patients with OPCABG. These variables will be evaluated in our future studies.

Changes in the text: None.

Comment 2: Postoperative course is an important factor in the development of delirium. What about stroke, infectious complications, ventilation time, postoperative heart failure and so on? If the postoperative course plays a role in the occurrence of delirium, it may be necessary to exclude these patients for predicting model.

Reply 2: We fully agree with you that the risk factors in the postoperative stage could potentially influence the occurrence of postoperative delirium, however our present model attached more importance on preoperative variables.

Changes in the text: None.

Comment 3: OPACBG (Page 8, line 15) is the first time the abbreviation appears. Please state the official name.

Reply 3: The abbreviation of OPCABG has been stated in the Introduction section as it first appeared in the main text (see Page 5, line 4).

Changes in the text: None.

Comment 4: Did this predictive model correlate with duration of delirium and recovery?

Reply 4: The associations between predictors of our present model and duration of delirium or recovery were not analyzed as the primary endpoint of this study is the occurrence of post-surgery delirium.

Changes in the text: None.

Reviewer C

Thank you for this interesting paper on an important topic in coronary artery bypass surgery.

In this manuscript, the authors examine the risk factors for postoperative delirium and come up with a risk prediction modal for postoperative delirium in patients undergoing off pump CABG. The manuscript is well written, but I would like to draw the author's attention to a few points.

Here are my comments:

Introduction:

Comments 1: Page 4 – “Compared with cardiopulmonary bypass, OPCABG, a coronary artery bypass grafting procedure performed on a beating heart, reduces trauma to the human body” – please back this statement with a reference or two since from my experience and knowledge this is not the case.

Reply 1: The sentences you mentioned had been revised according to your suggestions and 2 reference (3, 4) backed our statement had been added. The references in the revised manuscript had been renumbered accordingly. Compared with on-pump coronary artery bypass grafting, OPCABG, a technique in which the anastomoses are performed on the beating heart, can reduce myocardial injury by preserving native coronary blood flow.

Changes in the text: Page 5, line 4-6.

Materials and methods:

Comments 2: What percentage of your CABG surgery is done off pump? The majority? Minority? Please add this data which will help with context for the reader

Reply 2: In our center, the majority of coronary artery bypass grafting surgery were performed using the off-pump method. Only if intraoperative hemodynamic instability or serious arrhythmia occurred, the operation would switch to on-pump.

Changes in the text: Page 7, line 17-19

Comments 3: The clinical data of patients who underwent OPCABG and POD evaluation at the” – do all patients undergo POD evaluation? Or only high-risk patients? According to the “postoperative indicators” part all patients undergo this evaluation. If so, there is no need to mention this at the beginning of the methods section

Reply 3: I agree with you about the comments. The POD evaluation at the beginning of the methods section had been removed according to your suggestions.

Changes in the text: Page 6, line 9.

Comments 4: “systemic vascular resistance one day before surgery” – is this measured routinely at your center? Based on echocardiography?

Reply 4: Systemic vascular resistance is measured routinely at our center based on echocardiography.

Changes in the text: None.

Discussion:

Comments 1: “and coronary artery bypass grafting accounts for about 21.1% of all cardiac surgeries (18).” – I believe this to be a major underestimation, CABG accounts for more than 21.1% of cardiac surgeries. On what did you base this? And what is the relevance of citation 18 to this?

Reply 1: The percentage of 21.1% was based on the data released by the Chinese Society of Extracorporeal Circulation (ChSECC) in 2023. It is important to emphasize that the data are exclusively domestic statistics of China. The reference 18 had been replaced by the “White book of Chinese cardiovascular surgery and extracorporeal circulation in 2022” in the revised manuscript.

Changes in the text: Page 10, line 14.

Comments 2: “OPCABG has a lower risk of post-operative delirium compared to other types of bypass grafting surgery” – what is the relevance of citation 19 to this statement?

Reply 2: The reference 19 had been replaced by reference 6.

Changes in the text: None.

Comments 3: “POD significantly increases the short- and long-term mortality rate of patients after surgery, and affects the physiological and social functions of patients” – could POD be just a surrogate marker for older and sicker patients and not a risk factor

on its own? Looking at the risk factors in your model such as age, carotid artery disease and MMSE for example, implies that patients with POD are older and sicker. Is there proof that reducing POD reduces mortality?

Reply 3: Previous studies had demonstrated that POD was associated with increased short- and long-term morbidity and mortality. Two new references (24, 25) had been added to support this statement.

Changes in the text: Page 10, line 19.

Comments 4: “As depressurization may be performed during OPCABG surgery” – what do you mean by “depressurization”?

Reply 4: “depressurization” is not an accurate expression and had been replaced by “anti-hypertension”.

Changes in the text: Page 12, line 2.

Comments 5: Please add a paragraph to the discussion regarding early interventions and preventive measures available for POD. I believe there are only a few evidence based interventions and a predictive tool for an outcome that we have a limited ability to prevent and treat is itself limited.

Reply 5: Several previously published studies had reported that preoperative and intraoperative interventions could attenuate the risk of postoperative delirium. Preoperative measures mainly include education and psychological comfort, rehabilitation training, shortening preoperative fasting water duration, hearing or visual assistance, improving sleep quality, correcting anemia and hypoproteinemia, strengthening nutritional support, controlling infection, and standardized management of blood glucose and blood pressure. Using bispectral index (BIS) to maintain the appropriate depth of anesthesia and appropriate use of dexmedetomidine intraoperatively could reduce the incidence of postoperative delirium as well. References 40-46 were newly added for these statements.

Changes in the text: Page 11/line 3, and Page 12/line 15-22.

Comments 6: There are eight predictors in your model. While some make much sense (such as age and MMSE score), some seem like a chance statistical correlation without a plausible mechanistic explanation (aortic sinus diameter, ventricular septal thickness). You should check the model without these parameters and see if it is still valid and if so consider removing them from the model altogether. You discuss plausibility of the ventricular septal thickness and relate it to hypertension. Was a history of hypertension not associated with POD? If not, how do you explain this discrepancy? On that note, the explanation for aortic sinus diameter as a risk for POD seems a bit far-fetched. More likely this is a chance statistical finding.

Reply 6: Interventricular septal thickening is common in patients with long-term hypertension and poor blood pressure control. The interventricular septal thickness did not increase in patients with a history of hypertension but well controlled blood pressure. However, in the final results of this study, the history of hypertension was not included, indicating that having a history of hypertension but well controlled blood pressure had no significant effect on the occurrence of postoperative delirium.

The aortic sinus is the initial part of the aorta, which helps balance blood flow and cardiac function. When the aortic sinus is significantly widened and accompanied by hemodynamic changes, it will cause cerebral blood supply insufficiency. In OPCABG, moving the heart and taking near cardiac controlled hypotension will lead to hemodynamic changes, which may be the reason why aortic widening becomes a risk factor for postoperative delirium.

Changes in the text: None.

Comments 7: I couldn't find an answer to the question if high MAP or low MAP was associated with POD.

Reply 7: Evidences suggests that intraoperative hypotension, including low mean arterial pressure, is significantly associated with postoperative delirium. This statement was based on the following studies.

1 Duan W, Zhou C-M, Yang J-J, Zhang Y, Li Z-P, Ma D-Q, et al. A long duration of intraoperative hypotension is associated with postoperative delirium occurrence following thoracic and orthopedic surgery in elderly. *J Clin Anesth* 2023;88: 111125.

2 Wachtendorf LJ, Azimaraghi O, Santer P, Linhardt FC, Blank M, Suleiman A, et al. Association between intraoperative arterial hypotension and postoperative delirium after noncardiac surgery: a retrospective multicenter cohort study. *Anesth Analg* 2022;134:822–33.

Changes in the text: None.

Reviewer D

Comments: Very well paper

Reply: Thank you very much for your comments.

Changes in the text: None.