ANSWERING REVIEWERS

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Outcomes and long-term survival of coronary artery surgery: The controversial role of opium as risk marker

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Reviewer 1, 01482015
Dear Editor: Dr. Najafi and colleagues investigated the associaiton of chronic opinum use with mortality during a 6.8 years period in Iranian patients with isolated CABG. In general, the paper was well written and some issues should be addressed.
1. According to the results, they found BMI was inversely associated with the mortality in a long-term follow-up. Current evidence showed that the obesity paradox might be weak after 5 years follow-up in patients with CAD (Lin GM. et al. Int J Cardiol 2013 Sep 20;168(1):616-20.and Li YH, et al. Int J cardiol 2013 Oct 9;168(4):4315-8). AS we noted, there were 41% of the study cohort with icomplete follow up which may lead to a bias. The authors should report this limitation and cite the references to enrich the discussion.

Reply: We revised the discussion on BMI by adding three references and two comments on how BMI is inversely associated with the mortality in our long term follow up. This part of discussion has been completely changed.

2. One possible way we may use to differentiate the effect of opinium use and smoking: whether the use of opinum and smoking continued after the CABG. As we know, patients may discontinue smoking after CABG but the habit of opinium use was unknown. If there were data regarding the habit of opinium use and smoking status after CABG. A mediation effect could be analyzed to see the effect coming from smoking or opinium use.

Reply: Thanks for comments on differentiating the effects of opium and cigarette smoking. We will consider the proposal of respected reviewer in our ten years follow up which is being completed up to the end of 2016.

3. Some English grammar should be revised.

Reviewer 2, 02638028
This manuscript revealed the effect of preoperative chronic opium consumption on long-term outcome in patients with coronary artery bypass surgery. The issue is intriguiing, however some points should be addressed.
1. What is the mechanism of the effect of opium on cardiovascular system? Discussion about it should be added.

Reply: We added a paragraph to discussion to talk briefly about different effects of opium on cardiovascular system. We have added two citations one of them is a comprehensive review of cardiovascular effects of opium in nature cardiology review. The other is a large cohort study investigating the relationship between opium addiction and risk of all-cause mortality in a sample of general population.

2. Was there any data about the cardiovascular medications?

Reply: An important part of our cohort's questionnaire was dedicated to details of patients' medications. Then we categorized their medication into four groups of nitrates, statins, beta blockers, and ARBs. However, most of our patients were under treatment with all these four groups. Outcome prediction was the focus of this paper. So, we didn't add them to our primary analysis assuming that they have not changed the outcome.

3. How about the details of cardiac death?

Reply: As we have reported, out of total deaths 40.9% was cardiac and 59.1% was of non-cardiac cause. Cardiac causes were the sum of myocardial infarction 34.1%, sudden cardiac death 4.5%, and other cardiac causes 4.5%.

Reviewer 3, 00227375

This is an interesting manuscript about the effects of opium consumption on all-cause mortality in patients undergoing CABG surgery. The data demonstrated that the opium users have a trend to worse long-term survival as compared to non-opium consumers. After additional adjustment for smoking history, however, opium is not a predictor for long-term mortality anymore. This manuscript is interesting and has novelty. However, there are several problems about this manuscript. I'll show the questionable points those the authors may need to revise. Just consider the following comments. (Comments)

1. Page 2, Abstract, Results, lines 1-2 Page 11, Opium-stratified survival, lines 1-5 Page 13, Discussion, 2nd paragraph, line 2 I'm afraid I have doubts about these data. I think 6.5-year overall survival for all patient, opium users, and non-opium users are 90.6% (513/566), 84.1% (69/82), and 91.7% (444/484), respectively. Sorry if I have got it wrong.

Reply: We have checked these numbers with our statistician several times. These are not simple percentages but the results of survival analysis. So we should not calculate them by dividing crude numbers. These numbers are survival probabilities which are estimated using Kaplan-Meier method as has been described in method section.

2. Page 10, Results, 4th paragraph, lines 3-4 Forty one percent had diabetes mellitus and 3.3% had history of cerebral vascular disease. Judging from Table 2, I think the authors probably make a mistake, not 3.9% but 3.3%.

Reply: We changed the percentage and corrected the number in text.

3. Page 13, Discussion, 3rd paragraph, lines 1-4 For opium consumption (p =0.052) and functional class (p = 0.653), these factors are not statistically significant. Therefore, both factors don't independently and significantly predict all-cause mortality. Please consider.

Reply: We changed the text in results and discussion and omitted these two variables from the list of significant predictors. We wonder whether or not iterations and rewriting of the text has caused such important correction to be missed.

4. Page 30, Table 3 The listed hazard ratios aren't for survive but for death. Therefore, I think the authors should change the title to "Multivariable model for all-cause mortality using Cox regression".
In addition, I think hazard ratio (95% CI) for age (per 10 years increase) is not 2.46 (1.64-370) but 2.46 (1.64-3.70).
Correct to "CVA = cerebral vascular disease". 5. References [1] Correct to "Hebeler RF Jr". [2] Correct to "de la Cruz KI". [8] Correct to "Soliman Hamad MA". [16] Correct to "293-8".

Reply: All corrections were performed. We didn't find respected reviewer's comment about reference number 2.