Author’s response to reviews

Title: Hypertension, mitral valve disease, atrial fibrillation and low education level predict delirium and worst outcome after cardiac surgery in older adults.

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Response to reviewers – Rebuttal letter

Technical Comments:

1. Editor Comments: - please explain in your rebuttal letter why data are so old (> 5 years)

Response:

The manuscript is a result of a study that includes the one-year follow-up of patients. We had to wait the one-year follow for all patients included in the study. This fact and the complexity of data involving several different aspects of clinical and surgical variables were the main reasons for the relative delay in publishing them. Moreover, the manuscript was previously sent for publication but was not accepted after a long period of discussion with editor/reviewers.

- move the ethical statements (including those concerning informed consent) to the methods section

Response:

OK. Thanks for the suggestion. Done.
- how do the authors explain the potential role of mitral valve surgery in predisposing to delirium? do the authors really believe that it plays any role? please discuss

Response:

To our knowledge this is the first study that reports a significant association between mitral valve disease and delirium after heart surgery. In our sample, there were 43 patients with mitral valve disease and 17 of them had also atrial fibrillation. We speculate that the simultaneous conditions like mitral valve disease, atrial fibrillation in patients with a large left atrium leading to microembolization phenomena could be responsible for the greater occurrence of delirium.

- explain better the aim of the study: at least include the incidence and risk factors for delirium as the study is about delirium

Response:

OK. Thanks for the suggestion. Done.

- perform major revision for English Editing and language

Response:

OK. Thanks for the suggestion. We performed English language revision and editing.

- add a limitation section, discussing all the bias, including the consideration that the study is not propensity matched.

Response:

Thanks for the suggestion. A study limitations session was included covering these aspects.

2. REVIEWER 1 (Alessandra Marcone)

First, I agree with the consideration that this cohort is peculiar for very low education level (from 3.59 to 2 years) (table 2). However, the rate of delirium is similar to that usually reported in the literature in post-cardiac surgery in elderly patients. A very interesting (and curious) result is that the AAs found an association between delirium and low education level and not between delirium and cognitive decline (comparing pre- and post-op test scores). The patients do not seem to get worse over time or develop overt dementia. Now, considering that the education level is a proxy of cognitive reserve and that a low level is a risk factor for cognitive decline, it can be deduced from the paper that the low education level alone can represent a risk factor for delirium, even in the absence of cognitive decline. If this conclusion is correct, how can the AAs explain it? Could the delirium be an expression of the reduced skills of low educated patients to cope with new, complex and stressful situations such as ICU? I advise that the AAs would better explain their interpretation by adding to page 9 in the discussion section.
Response:

We thank the reviewer for the interesting comments. We also expected that the association between cognitive decline (comparing pre- and 12-18 months post-op test scores) and the occurrence of delirium would be significant. We hypothesize that the relative short follow-up time of 12-18 months was not enough to detect a difference. It’s also true that education level is frequently considered a proxy of cognitive reserve but we think that, in this sample, baseline low education level alone represents a risk factor for delirium. On the other hand, we speculate that in a longer follow-up a significant decline could be detected. In other words, in this 12-18 months follow-up study, having low education level and not cognitive decline is a stronger enough to be detected as a risk factor for delirium. We included in the manuscript some of this thoughts and considerations.

I would also make some methodological observation. MMSE alone, associated with a semantic verbal fluency test (a test sensitive to education level) is not enough to exclude cognitive decline. Lacking an extensive neuropsychological assessment of patients, the AAs should report the absence of impairment in activities of daily living (ADL) in the cohort to exclude a dementia syndrome in the pre-operative phase. Since the AAs did not observe any cognitive decline in their patients at 12 and 18 months follow-up, dementia could be excluded. However, some of patients with lower test scores could fulfill the clinical criteria of Mild Cognitive Impairment (MCI) in the inclusion phase of study. MCI is a clinical condition including cognitive deficit (in the single amnestic domain or in multiple domains) without overt functional impairment in ADL (no dementia). MCI may convert to dementia and the rate of transition from MCI to dementia is 10% to 20% per year. A risk factor for MCI, as for dementia, is a low education level. In conclusion, in some patients, MCI would be a risk factor for delirium. The AAs should consider this hypothesis in the discussion.

Response:

Thanks for the comments. We included a study limitations session where this and other aspects we discussed.

3. REVIEWER 2 (Ary de Serpa Neto)

ABSTRACT

1. There is no objective described. I suggest correcting it

Response:

OK. Thanks for the suggestion. Done.
2. The authors describe that the primary outcome is a composite one of death, infection and perioperative MI. However, it appears that the study is about delirium, and I think that development of delirium is their primary outcome.

Response:

Our study evaluated delirium after cardiac surgery in older patients in different aspects: firstly, delirium was the outcome and we studied the predisposing and precipitating factors for its occurrence after intervention. Secondly, we evaluated delirium as a predictor of morbidity and mortality in 30 days, considering death, infection and perioperative infarction as a composite outcome. Finally, after one year, we assessed the association between delirium and cognitive decline. We performed modifications and improvements for better comprehension.

3. What the authors want to say with "atrial fibrillation after surgery represented the triggering factor"? I think that atrial fibrillation is a risk factor as the others described.

Response:

Several authors classify risk factors for delirium into predisposing and precipitating agents 5,16,38. Predisposing factors represent the patient's vulnerability to delirium and are generally non-modifiable. Precipitating factors or insults are those related to the acute illness, to its treatment or to the environment in which the patient is, and are usually modifiable. Therefore, all the factors related to the perioperative period were considered precipitating. After multivariate analysis, atrial fibrillation that occurred after cardiac surgery was considered an independent precipitating factor for the occurrence of delirium.

INTRODUCTION 1. Needs to be improved, with more information and contextualization. For example, there are a lot of publications addressing delirium after cardiac surgery that were not included and discussed.

Response:

The Introduction session was intensively reformulated.

METHODS

1. I suggest removing the number of patients from this section, these should be placed on Results and in a Flowchart of inclusion

Response:

Thanks for the suggestion. The manuscript was reformulated and a Flowchart was included.

2. Please describe better your inclusion and exclusion criteria.

Response:
Thanks for the suggestion. The manuscript was reformulated and inclusion/exclusion criteria were clarified.

3. Which type of professional applied the CAM? Psychiatrist? Neurologist? Other? This should be addressed

Response:

CAM and CAM-ICU were applied by the principal investigator (cardiologist and intensive care specialist).

4. Also, who confirmed the diagnosis of postoperative delirium by DSM-IV?

Response:

All CAM and CAM-ICU data, as well as the DSM-IV diagnosis of delirium were performed by the principal investigator and registered in the patient chart.

5. The p value < 0.1 used to include variables in the multivariable were tested how? Univariable logistic regression? Simple bivariate comparison? This should be explained

Response:

Initially, univariate logistic regression was performed and those variables with p-value < 0.1 were selected for an initial multivariate logistic model. The manuscript was reviewed and rewritten to make it clearer in these aspects.

6. Which variables were considered in the first model (17 as stated). This should be described

Response:

Seventeen variables are listed in Table 2.

RESULTS

1. The results of table 3 are the core of the paper and should be described in the text

Response:

OK. Thanks for the suggestion. Done.

2. How did the authors split the factors in "risk factor" and "triggering factors"? This is not usual

Response:
We have provided explanation for this classification in the manuscript. The timeline of the study (the different time window when these events occurred) was responsible for our choice to report it in this way. Some other studies use this same definition that is, indeed, strongly related to the development of the events.

3. Why a cut-off of OIT of 900 minutes? Why not use it as continuous instead of dichotomized? Please explain

Response:

The variable OIT is very skewed to the right, so we decided to create categories. Nine hundred minutes was the value that better discriminates the outcome.

4. Please include all other variables considered in the final multivariable models (Table 3 and 5). Avoid selective reporting. Prognostic factors were considered in the model for the composite outcome?

Response:

We performed a profound reviewing of the manuscript clearing potential misunderstanding phrases. All predictors (prognostic) factors of clinical significance were reported.

5. How changes in VFT and MMSE were assessed? This should be described in the Methods since this is important for the study and should consider special methods to avoid regression to the mean

Response:

OK. Thanks for the suggestion. We performed a new version of the methods and statistics session to make it clearer.

6. I suggest a Kaplan-Meier stratified by the presence or not of delirium and with mortality (or composite) as outcome

Response:

Thanks for the suggestion. We included time to death Kaplan-Meier curve as Figure 2.