Author's response to reviews

Title: Preoperative levels of Hemoglobin and B-Type Natriuretic Peptide are associated with postoperative morbidity in heart surgery

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Author's response to reviews: see over
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The Biomed Central Editorial Team

Object: MS: 1344704907686564 - Hemoglobin and B-type natriuretic peptide preoperative values but not inflammatory markers, are associated with postoperative morbidity in cardiac surgery: A prospective cohort analytic study

Thank you for consideration of our manuscript for publication in your journal. We have reviewed the above manuscript according to your reviewer’s comments.

Reviewer # 1 Dr. Ari - Timerman
Reviewer's Comments: None

Reviewer # 2 Dr Daniel Bolliger
Reviewer's Comments:

Definitions are not clear and should be inserted. Most importantly, the authors’ definition for diabetes mellitus (IDDM or NIDDM or only treated DM with insulin and/or oral hypoglycemics), postoperative acute myocardial infarction (how was AMI diagnosed in the postoperative period?), death (only death due to cardiac causes or all-cause death?), re-hospitalization (every hospitalization or only hospitalization due to cardiac causes?), obesity etc. In the Statistics section, the authors state that all outcomes were prespecified and a uniform definition was applied. Please indicate these definitions.

The definitions have been inserted on page 34, after TITLES OF TABLES AND FIGURES section.

Statistics: This reviewer thinks that too many variables were inserted into the regression model. For regression models, not more than 1 variable per 10 to 15 events should be used. As the exact number of events is unclear in this manuscript, this reviewer has some restrictions regarding the regression model.

The number of variables was discussed in detail with the chief project statistician during study design. The conclusion of the research group in this regard was described in the draft of the original manuscript and was written in an explanatory paragraph which was then deleted in order to adjust the number of words to the usual publication requirements:

The association between the dependent primary variable (DEATH/AMI/REHOSPITALIZATION) and the independent variables was
evaluated, adjusting for the covariables, to define a model of association by means of logistic regression analysis. Later, the association between each of the dependent secondary variables and the independent variable was evaluated, adjusting for the covariables; it was modeled by means of logistic regression of association (evaluating interaction) for dichotomous outcomes. In the multivariate model all the covariables were included together with the exposure variables in accordance with the concept proposed by Kleinbaum (19) of which the best model (if not the most parsimonious) is the one that controls for all the confusion variables. OR and confidence intervals of 95 % were calculated for each of the outcomes.

In accordance with Dr. Daniel Bolliger’s recommendations, this paragraph has been included in the manuscript again in Statistical Methods on page 8.

Results section: Please indicate the reasons for patient exclusion.

The reasons for excluding these subgroups are summarized as follows: Emergency surgery is always a high-risk procedure and would introduce difficult-to-control variables into the study. In maze surgery, there are frequent postoperative rhythm disorders, and hospital stays are usually longer; thus, many of these outcome variables would be altered for reasons intrinsic to the surgical procedure. In atrial septal closures, the possibility of complications is very low, and this subgroup of patients would not provide information to the study; pulmonary disease and chronic kidney disease alter hemoglobin, and both can raise BNP, which are the exposure variables being evaluated. Similarly, patients with diseases that could alter inflammatory markers were excluded. This paragraph has been included in the manuscript in METHODS section on page 9.

Results section: Please do not use 60 +/- 11.21 years, just use 60 +/- 11 years. SD should not use more numbers after the comma than the original numbers (e.g. in this example patient age in years).

Done

Please describe the patient characteristics only in the text or in tables to avoid duplicity.

Done

The Results section should be completely rewritten. Please focus on the important results that help you to prove your hypothesis.

The results section has been completely re-written according to the reviewer’s recommendations. The word count has been reduced from 2,641 to 1,462.

- Not normally distributed data as ICU or hospital stay should be presented as median and range. The use of mean and SD is questionable. Do not use 1.99 days but 2 days. For more explanations, see my comments above.
Outcomes should be presented in Tables. For example, the number of deaths during hospitalization and follow-up is unclear.

The outcomes are described in Table 6.

Is atrial fibrillation an outcome in your study? Then you need to define it in the methods section.

Atrial fibrillation is in fact defined in the Methods section under the subtitle: “Study design and variables”

Discussion: Please refer with your first sentence to your study hypothesis.

AF was not used in your study hypothesis. You should therefore not discuss AF in the second sentence.

In the Methods section, under the subtitle: “Study design and variables”, it states that the study hypothesis is that there is an association between preoperative levels of BNP or Hb and postoperative mortality or morbidity. In turn, morbidity refers to the measured outcomes, which include AF:

“The primary objective was to determine whether there is an association between the preoperative value of any of these biomarkers and morbidity and mortality in the first 12 months postoperatively. The most important event for the study (primary outcome) was a combination of death/myocardial infarction/cumulative rehospitalization at 12 months postoperatively. Taking anesthetic induction as the starting time, all clinically relevant outcomes were recorded: postoperative bleeding requiring reoperation, death from any cause during hospitalization, prolongation of stay in the ICU or the hospital, number of red blood cells transfused postoperatively, lowest postoperative Hb level, surgical wound infection, PLCO, acute renal failure, cerebrovascular events, atrial fibrillation (AF), ventricular tachycardia or ventricular fibrillation, perioperative myocardial infarction, and use of inotropes (over 24 hours) postoperatively. All events that took place from the time of hospital discharge until the last day of the 12-month follow-up (death from any cause, rehospitalization, acute coronary syndrome (ACS),
cerebrovascular events, or further revascularization procedures or valve repair) were also recorded.

In the discussion, you should focus more on your study hypothesis. Try to compare it with other studies investigating similar questions. For example, what is the value of BNP in patients undergoing cardiac surgery in other studies? There is no reference to this topic in your manuscript. The same is true for preoperative hemoglobin value.

The study hypothesis is that there is an association between preoperative levels of BNP/Hb and postoperative mortality and morbidity; the results confirm that there is indeed an association with several morbidity outcomes which were defined a priori during the study design, including postoperative AF. This association having been described in the results, we focused the discussion on explaining the characteristics of each of the associations found.

This reviewer recognizes the work of the authors and the value of their data. However, given all these limitations mentioned above, I cannot support the publication of this manuscript at the moment.

Additionally, I advise the authors to look for the help of a statistical advisor.

**Done**

**Level of interest:** An article of importance in its field  
**Quality of written English:** Not suitable for publication unless extensively edited

The new version has been translated and edited by Elsevier Webshop Language services

**Statistical review:** Yes, and I have assessed the statistics in my report.  
**Done**

**Declaration of competing interests:**  
I declare that I have no competing interests.
I have reviewed with interest your manuscript on the evaluation of preoperative risk markers and outcomes (death, ACS, rehospitalization through 1 year). In this prospective cohort of 554 patients, the variables that conveyed a higher and independent risk for postoperative adverse outcomes were: elevated BNP and low Hb levels. The manuscript is clear and well written, it has acceptable graphics and the results support the conclusions.

However, there are some issues and comments to consider prior to publication:

The study was performed at an Institution located in a city very high above sea level. The expected normal values and definitions for relative anemia need to be clarified in the manuscript as these results would only apply to comparable sites. These would explain why the identified value of Hb < 13 mg/dL does not compare to previous reports or generally accepted low Hb levels (known to correlate with adverse effects).

The reference values at the clinic where this research took place, (located in Bogotá, a city 2,600 meters above sea level), are: 14 gr/dl to 18 gr/dL for men and 12 gr/dL to 16 gr/dL for women. Although studies of anemia as a risk factor in multiple clinical scenarios report specific cut-off points to define high risk populations, most authors suggest a linear relationship or “dose-dependent” effect between lowered hemoglobin values and an increase in morbidity and mortality. This was the case in our series, where the unadjusted data showed a linear relationship between progressively lower Hgb levels and an increase in all the evaluated outcomes. This is the reason that expected normal values and definitions of relative anemia are not stated, since for any Hgb level below 16.1 gr/dL there is an increased risk.

Note that this clarification applies to Hb, it is unknown if patients with some degree of pulmonary hypertension at high altitude would have higher levels of BNP at baseline (when compared to sea level individuals).

In effect, circulating levels of BNP correlate with mean pulmonary arterial pressure and pulmonary vascular resistance in patients with pulmonary arterial hypertension. Our cohort is made up of patients with significant cardiopathy and it is to be expected that some proportion of them might have pulmonary hypertension; regarding serum BNP levels, this factor is probably more important than the altitude of residence, since the variation in pulmonary pressure between healthy subjects who live at Bogotá’s altitude and those that live in Lima (100 meters above sea level), is only 3 mmHg (Heart Disease in Latin America The Heart and Pulmonary Circulation at High Altitudes Healthy Highlanders and Chronic Mountain sickness Dante Penaloza, MD; Javier Arias-Stella, MD. Circulation. 2007; 115: 1132-1146)

Level of interest: An article of importance in its field
Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests:
None.

Reviewer # 4: Juan Carlos Villar
Reviewer's comments:

This study tackles an important question for the field, identifying newer or better forms to stratify the risk of adverse events among patients undergoing cardiac surgery. This manuscript has several strengths, including a sizable cohort and number of events, and the completeness of the data collection and follow up. I want to congratulate the authors for maintaining such a cohort, an unusual task for a study originating in a busy hospital in Colombia. The medical community of this field will benefit from having access to the results of this effort to pursue such an important question.

Weaknesses of the study, however, include the choice of statistical plan, and some aspects of the organization of the manuscript. In the first aspect, my recommendation would be to re-analyze the data using survival analysis and cox regression analysis in order to make a better and complete use of the whole data collection (currently the results are based on logistic regression with measures of association based on comparisons of the 5th and 1st quintile, that is 40% of the data).

Because the defined primary endpoint was the estimation of the significance and magnitude of the association between each of the exposure variables and the outcome variable, we decided that these significance values could be ascertained by multiple regression or logistic analysis more than by analysis of survival or time to event.

On the later aspect, I would recommend to organize the methods and results sections using subtitles to facilitate the reading of this important study. The reader will certainly benefit from a flowchart of the cohort inception, a separate description of the outcome measures and their hierarchies, and a separation of the results that follows the organization of the tables.

The methods and results sections have been completely re-written. Figure 1 corresponds to the cohort flowchart

In short, I found sufficient merit and interest in the field for this study to deserve publication. Nonetheless, the work itself should improve if re-constructed in terms of the statistical analysis and itemization of the contents to convey its message and explode the richness of the data in a better way. I would be more than happy to review a new version of the manuscript, if re-submitted to the journal.

Major compulsory revisions:
- Conduct a survival analysis to this cohort

See comment above
Use a flowchart to describe the inception and representativeness of the cohor
t. Done

Use subtitles for the section of methods and results, following the tables and
figures. Done

Minor and discretionary revisions:
Differed until seeing a new version of the manuscript
Level of interest: An article of importance in its field
Quality of written English: Needs some language corrections before being
published

The new version has been translated and edited by Elsevier Webshop
Language services

Statistical review: Yes, and I have assessed the statistics in my report. Done

Declaration of competing interests:
I know and I have worked with some of the authors (in issues other than those
related with this manuscript)