Author's response to reviews

Title: Evaluation of the PaO2/FiO2 ratio after cardiac surgery as a predictor of outcome during hospital stay.

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Author's response to reviews: see over
To the Editorial Team of *BMC Anesthesiology*,

On behalf of my co-authors, I submit the enclosed manuscript for consideration by the Journal. It has not been published in this or a substantially similar form (in print or electronically, including on a web site), nor accepted for publication elsewhere, nor is it under consideration by another publication. There are not possible conflicts of interest (including financial and other relationships) for each author.

Appropriate Ethics Committee approval has been obtained for the research reported (if you need committee writing documents we would be glad to show yours).

All authors send this letter as confirmation that they have read and approved the paper, have met the criteria for authorship as established by the International Committee of Medical Journals Editors, believe that the paper represents honest work, and are able to verify the validity of the results reported.

I hope it will be of your interest. Thank you for this opportunity of submitting our report. If you need further information, please contact us,

Sincerely, on behalf of all authors,

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Addendum to the Editorial Team after reviewer’s response,

The present manuscript has been deeply reviewed by a native English speaker specialized in medical manuscripts.

The concerns to reviewer’s questions are also specifically addressed giving a point-by-point response (see below). Major changes in response to the reviewers are underlined in yellow within the text.

We think our manuscript conforms to the journal style and our files are correctly formatted. If we have done any mistake, please contact us in order to correct it.

Thank you very much for your cooperation,

Juan Carlos Lopez-Delgado.
Reviewer's report.
Title: Evaluation of the PaO2/FiO2 ratio after cardiac surgery as predictor of outcome during hospital stay. Version:3  Date:17 June 2014.

Reviewer 1: Gennaro Depascale.
The authors present a study where they investigated the role of postoperative PaO2/FiO2 ratio as predictor of mortality and ICU length of stay in patients undergoing cardiac surgery. Although it is well know that post-operative respiratory failure significantly impacts upon patients outcome, the paper describes a large prospective population following a clear and correct methodological method. The manuscript is well written. However I would like to address some minor essential revisions

Minor Essential Revisions.

1. Methods: May the authors provide more details upon mostly common used intraoperative ventilatory strategies?
   Intraoperative ventilatory strategies were based on an individual approach, depending on the patient’s prior respiratory status. Volume-controlled ventilation with a tidal volume of around 8 mL·kg$^{-1}$ and a minimum PEEP were used to provide adequate ventilation and oxygenation, to prevent atelectasis and to keep inspiratory plateau pressure $<30$ cmH$_2$O. Minimum FiO2 was used to guarantee adequate oxygenation, even in the presence of CPB. All ventilatory parameters were modified in response to intraoperative analyses. This paragraph has been added to the manuscript.

2. Page 6, line 13: please add “corresponding to” before an inconclusive outcome.
   Done.

3. Table 5: please indicate in the table (or in the 'results' section) which variables were not included in the multivariate analysis since having p<0.1.
   Multivariate analysis was a proportional hazards Cox regression model to evaluate the effect of staging in one of the 3 Pa/Fi 3h groups and the differences between subgroups. We included all variables with a p<0.1 and age based on those variables from ANOVA and Bonferroni post-hoc tests from the comparisons between each of the groups. For reasons of space, we show only the significant results and do not include variables with a p>0.1 between groups.

4. Discussion paragraph: I would consider the absence of information regarding the reasons leading to low P/F ratio values a limit of the study.
   We address the issue of respiratory complications, but we do not specifically address the reasons for the low P/F ratio values. We have underlined this limitation at the end of the discussion: "It was not the purpose of our study to differentiate between causative conditions of the low PaO2/FIO2 ratio. Thus, our results do not specifically address the cause of a low PaO2/FIO2 ratio in patients after cardiac surgery (which may represent a limitation of the study), but rather they serve to evaluate outcome in this scenario".

5. Discussion paragraph, page 10, line 1-4: Please reformulate the sentence.
   Done. “Our results may be clinically relevant since a simple determination of PaO2/FIO2 ratio may provide very important information for determining outcome, both in terms of mortality and length of stay, in the postoperative care of cardiac surgery patients”.

6. Conclusions: I would shorten the second and last sentence
   Done. We have deleted the redundant information and have shortened both sentences.

Level of interest: An article whose findings are important to those with closely related research interests.
Quality of written English:Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests: ‘I declare that I have no competing interests’ below
Reviewer 2: Matthias Eikermann.
The authors determined the optimal cut-off values of PaO2/FIO2 ratio to predict mortality in patients after cardiac surgery. The authors found that P/F ratio time-point 3 h after the case provided the best predictive value for mortality - expectedly, the uni-dimensional model was still inferior to dedicated mortality prediction instruments such as APACHE or SAPS.
Major points:
1. The authors should make a better point as to whether or not mortality prediction based on a variable that describes the function of a single organ is important. Naturally, mortality prediction based on multiple variables will always be better. Why focusing on P/F ratio and not APACHE score or vasopressors requirement and/or urinary output? Why should a clinician use P/F ratio for mortality prediction?
First of all, the P/F ratio is already used daily in current clinical practice in ICUs because it can reflect the oxygenation status and pulmonary function. Oxygenation status is crucial for assessing the current physiological cell function. However, the role and the weight of P/F for predicting mortality have not been assessed previously in the cardiac surgery population. As we stress in our study, the aim was to evaluate the usefulness of the P/F ratio to predict mortality in this population. Of course, we agree that mortality prediction based on multiple variables will always be better but it is difficult to assess outcome in the first hours of the postoperative period, in spite of the crucial importance of the early postoperative period. APACHE score needs 24h for calculation. Vasopressor requirement may vary during 24h depending on the patient’s hemodynamic and volume status, as well as urinary output (UO), which can ultimately be modified by diuretics. We also agree that vasopressor requirement and UO may be potentially studied as predictors of outcome in this population, but these variables are not immediately available. However, as we said above, P/F represents the single function of the lungs, which is responsible of the normal function of other organs.
In addition, during surgery atelectasis may lead to intraoperative gas exchange abnormalities, which may be increased by the inflammation triggered by the surgery itself, leading to postoperative lung dysfunction even in patients without preexisting lung injury. Despite protective mechanical ventilation during and after surgery, including recruitment maneuvers, a lower P/F may be a reflection of a persistent lung dysfunction which can influence outcome. We have added a reference in order to emphasize why the function of a single organ is so important.
Thus, despite the limitations of the P/F ratio for predicting mortality, clinicians should use it because it is easy to obtain and can potentially assess outcome earlier than other variables.
2. The statistical methods need to be described in more detail, and the language used for making this description needs to be improved. I request that the paper will be assessed by a statistician.
The manuscript has been re-assessed by Michael Maudsley, editor at the language services at the Universitat de Barcelona.
The statistical methods were described by Konstantina Skaltsa (MD.PhD.Prof.) who is a statistician from the Department of Public Health at the University of Barcelona.
3. The esteemed authors should invite a native English speaking medical scientist to revise their paper. Example: First sentence of discussion "This study shows the importance and meaning of PaO2/FIO2 ratio for prognosis at the postoperative period of cardiac surgery, being evaluated from cost-minimization criterion not used before." I am also not sure what a "cost minimization criterion" means.
"Cost minimization criterion” is a synonym of “optimum threshold estimation”. We have now rewritten this sentence. The statistical method has been described in the manuscript by Prof.
4. The P/F ratio groups differ in their characteristics, and it is unclear to me if P/F ratio or for example rather the PEEP or cross clamping time (which both differed between groups) were the more important mortality predictor. When we analyzed differences between survivors and non-survivors, in the multivariate analysis we included the presence of a PaO2/FiO2 ratio <202 at 3h after admission as a categorized variable. Multivariate analysis was a logistic stepwise regression model (dependent variable in-hospital mortality) which includes PEEP (cross clamping time did not show differences between survivors and non-survivors) and retrieved P/F ratio <202 at 3h as an independent predictor for in-hospital mortality. We do not present the complete data due to the lack of space and because assessment of the P/F as a predictor of outcome was not the most important/novel result of our study. As we noted in introduction, a low P/F ratio has been associated with increased mortality and hospital stay in patients admitted to ICU. In addition, the PEEP differences between groups are the result of the differences in the P/F ratio between groups.

5. Table 5: What does "multivariate analysis" mean?
Multivariate analysis was a proportional hazards Cox regression model to evaluate the effect of staging in one of the three Pa/Fi 3 h groups and the differences between subgroups. We included all variables with a p<0.1 and age based on those variables from ANOVA and Bonferroni post-hoc tests from the comparisons between each of the groups. For reasons of space, we show only the significant results (the same question and answer as to Reviewer 1 Gennaro Depascale)

6. I would like to understand if P/F ratio explains variance of mortality independent of known predictors of mortality. I would be happy if the authors would present their a-priori-defined model used for confounder control.
We think we have already answered this point in our response to question 4. See also below our answer to question 5 of reviewer 3, which is similar.

Level of interest: An article whose findings are important to those with closely related research interests
Quality of written English: Not suitable for publication unless extensively edited.
Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.
Declaration of competing interests: none.
Reviewer 3: Angela Lipshutz.  
In this prospective observational study, Esteve et al. evaluate the utility of PaO2/FiO2 ratio to predict mortality in a large cohort of post-operative cardiac surgery patients. They perform a robust and sophisticated analysis, and find that a P/F ratio of < 202 at 3 hours after ICU admission is associated with increased ICU mortality. Although it is not surprising that patients with a lower P/F ratio fare more poorly, this has not previously been studied, and thus represents an interesting and novel addition to the literature on this topic. I believe it would beof interest to the readers of BMC Anesthesiology, and will likely be ready for publication pending the following revisions:

Major Compulsory Revisions
1. The manuscript would greatly benefit from editing by a native English speaker.  
The manuscript has been re-assessed by Michael Maudsley, editor at the language services at the Universitat de Barcelona.  
2. Please revise first sentence of introduction to reflect new Berlin criteria for ARDS (no longer “ALI”). Done.  
3. You state (results page 6, first paragraph) that the P/F ratio is “better than the cardiac surgery scores” and “when compared with ICU scores, there are slight differences, except in the case of APACHE II score which is clearly superior.” If you compared each of the scoring systems to the P/F ratio, please provide the p-value for each comparison and include a description of this analysis in your methods section.  
This statement is about empirical ROC curves. We have rewritten this sentence because it was somewhat confusing. The p-values for each comparison are shown in Table 2 and the analysis is described in statistical analyses in the methods section.  
4. It would be interesting to look at fluid administration, blood product administration, and fluid balance among the three different P/F ratio groups (could add this data to Table 3).  
We do not have data on fluid administration or fluid balance. Our local protocols seek to avoid positive fluid balance and excessive fluid administration: our recommendation is cautious fluid administration in order to prevent pulmonary edema, especially in severely ill. We have added the need for blood product in table 3; it did not show statistical differences.  
5. Recommend including table showing results of multivariate analysis evaluating P/F ratio with outcome of ICU mortality. Is P/F ratio an independent predictor of ICU mortality, when controlling for severity of illness (using APACHE, for instance) and comorbidities (COPD, etc)? It is important to make this clear, since we know that Group 3 patients are sicker (higher severity of illness, more co-morbidities). Based on the text in your discussion section, P/F ratio is an independent predictor, but this is not obvious from your tables (Table 5 is somewhat confusing).  
We evaluated the PaO2/FiO2 ratio as a mortality risk factor after cardiac surgery analysing differences between survivors and non-survivors. For this purpose we categorized PaO2/FiO2 ratio values. In addition, a multivariate analysis was performed after adjusting for preoperative and postoperative scores and comorbidities. For reasons of space we present only partial information on the P/F as an independent predictor (see results, last paragraph: “When we categorized the presence of a PaO2/FiO2 ratio <202 at 3h after admission, we confirmed its value as a predictor for in-ICU mortality (OR: 1.364; 95% CI: 1.212-1.625, p<0.001)”.
6. How is measuring/knowing the P/F ratio at 3h post-op going to decrease ICU readmission rates? (page 8, line 20) Will you keep patients in the ICU longer if they are clinically ready for discharge if you know their P/F ratio at 3h was low?  
Patients with the lowest P/F ratio at 3h post-op are at risk of respiratory complications such as tracheal reintubation, a common cause of ICU readmission. These complications negatively affect prognosis. In our opinion, identifying patients at risk by means of the P/F ratio may
potentially serve to develop strategies for respiratory weaning and to minimize these complications, thus at least improving prognosis. We now stress this point by modifying the last sentence of the paragraph.

Minor Essential Revisions

1. **Introduction line 9-10:** I am not sure what is meant by “showing an increase in age and higher rates of comorbidities.” Is this compared to other surgical patients? Other ICU patients? Historical cohorts of cardiac surgery patients? Please clarify.
   
   We mean that the cardiac surgery population is expected to be older and to have more comorbidities compared with past series, because of the trend towards higher age in the general population ([http://esa.un.org/wpp/other-information/faq.htm](http://esa.un.org/wpp/other-information/faq.htm)). We have modified this sentence for clarity.

2. **Methods:** All cases were done with moderate hypothermia and antegrade cardioplegia? No DHCA? Never retrograde cardioplegia? MAP 60 was maintained for every case?

   All cases were treated with moderate hypothermia and antegrade cardioplegia. Deep hypothermic circulatory arrest was not used since there was no surgery that required it. Mean MAP was superior to 60mmHg but was adapted to the characteristics of each patient. For example, some patients with uncontrolled hypertension needed a higher MAP (about >65mmHg) to maintain adequate urine output.

3. **Results p6 line 2-4:** No-survivors should be “non-survivors”; in-ICU mortality can simply be called “ICU mortality”. Done.

4. **Page 6 line 29-30:** Please clarify statement regarding BMI. Do you mean BMI of group 3 is greater than that of patients in groups 1 and 2?

   We mean that BMI tended to be higher in those patients in group 3, but did not reach statistical significance. We mention this point because in some series higher BMI is related with worse P/F ratios.

5. **What cost-minimization criterion are you referring to on page 7, line 33?**

   “Cost minimization criterion” is a synonym of “optimum threshold estimation”. We have now rewritten this sentence. The statistical method has been described in the manuscript by Prof. Skaltsa (see Skaltsa K, Jover L, Carrasco JL: Estimation of the diagnostic threshold accounting for decision costs and sampling uncertainty. *Biom J* 2010; 52:676-97).

Level of interest: An article whose findings are important to those with closely related research interests.

Quality of written English: Needs some language corrections before being published.

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

Declaration of competing interests: I declare that I have no competing interests.