Author's response to reviews

Title: A simple clinical model for planning transfusion quantities in heart surgery

Authors:

Felicetta Simeone (drfelix@libero.it)
Federico Franchi (franchif@unisi.it)
Gabriele Cevenini (cevenini@unisi.it)
Antonino Marullo (marullo@unisi.it)
Vittorio Fossmombron (v.fossmombron@ao_siena.toscana.it)
Sabino Scolletta (scolletta@unisi.it)
Bonizella Biagioli (biagiolib@unisi.it)
Pierpaolo Giomarelli (giomarelli@unisi.it)
Paolo Barbini (barbini@biolab.med.unisi.it)

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Author's response to reviews: see over
REPLIES TO REVIEWERS

Executive Editor

Commentary: One of the referees has indicated that they are not clear on the wider applicability of your study. We would invite you to consider this question and suggest that you make this aspect clearer in your discussion.

We would be grateful if you could address the comments in a revised manuscript and provide a cover letter giving a point-by-point response to the concerns. It is likely that we will seek further advice from the referees regarding your revised manuscript.

Please also highlight (with 'tracked changes/coloured/underlines/highlighted text) all changes made when revising the manuscript to make it easier for the Editors to give you a prompt decision on your manuscript.

Reply: We have addressed each reviewer’s comments in the revised manuscript and in the present cover letter we provide point-by-point replies. We have also analyzed some points in the discussion to clarify the applicability of the study (see third paragraph – page 14). Finally, we have highlighted all changes in yellow.
Reviewer: Hosam Fawzy

Criticism 1. In the abstract it is mentioned that "model output highlighted some important aspects of perioperative risk of blood-transfusion related complications" but nothing was mentioned about the blood transfusion complications in the text.

Reply: We thank the reviewer, because in the original version of the manuscript there was a typing error (perioperative instead of postoperative). We have changed the text (see Abstract – last sentence).

Criticism 2. The methods used are appropriate. However, for model design, it is preferable to use prospective randomized-controlled studies rather than using retrospective observational ones. Multi-centers studies also play a major role in setting up protocols and guidelines for clinical practice.

Reply: We agree with the reviewer about the superiority of a prospective study and we now debate this point in the discussion (see third paragraph – page 14).

Criticism 3. The name of the institution was repeated twice in the patient set section (lines 6 and 10 page 5).

Reply: We have removed the name of the institution from line 10 – page 5.

Criticism 4. There is a controversy in the patient's consent as it was stated that "Due to the retrospective nature of the study, the need for informed consent was waived." line 14 page 5 while it was mentioned that "Written informed consent was obtained from all patients." lines 19 & 20 page 5.

Reply: We agree. Actually the sentence "written informed consent was obtained from all patients" referred to the fact that all patients gave their informed consent to transfusion before heart surgery and not to the present retrospective study. Lines 19 & 20 of page 5 have therefore been deleted.

Criticism 5. Results are presented twice both in the text (paragraph 5, lines 25-30, page 9) and in table 3.

Reply: The reviewer’s observation is right. We have modified the text (paragraph 4, page 9).

Criticism 6. Definitions of group I, II and III are confusing (paragraph number 1 page number 10):
- Group I (303 patients, 9.1%): appreciably fewer transfusions (more than 2 packs) than estimated by the model (“less transfused” patients);
- Group II (2574 patients, 77.7%): absolute difference between number of packs transfused and number estimated by model not more than 2 packs (“well transfused” patients);
- Group III (438 patients, 13.2%): appreciably more transfusions (more than 2 packs) than estimated by model (“over transfused” patients).

Reply: We accept the reviewer’s observation and have modified the text (see highlighted changes – bottom of page 9 and top of page 10).

Criticism 7. In lines 19, 20 &21 page 10:" Percentage morbidity was about 28% in patients for whom the model fitted the actual data exactly, while the highest differences were associated with very high morbidities." It is not clear if blood transfusion causing morbidities or it is given when there are postoperative morbidities.
Reply: We have now more fully considered this point in the discussion (see third paragraph – page 14).

Criticism 8. The sentence: "When patients managed by transfusion therapy contrary to our blood conservation strategy and those with unpredictable adverse events were removed from the sample, the percentage of cases with a difference of more than two packs between the model estimate and the actual number transfused decreased to only 7%." In the second paragraph page number 11, needs to be better presented to avoid confusion.

Reply: We have removed this sentence from the results and considered this point in the discussion (second paragraph – page 14).

Criticism 9. Table 4, page 25, lines 2 &3: " actual numbers of packs or red blood cells (PRBC): >2 PRBC = less transfused patients; <2 PRBC = over transfused patients;" It is different from what has been mentioned in the first paragraph, page 10.

Reply: In the original version of the manuscript the table caption was confusing form. We have now changed the caption (see Table 5 in the new version of the manuscript).

Criticism 10. In page 15, the first three paragraphs are summarizing the study and are not conclusions. The last three lines are the conclusions.

Reply: The Conclusions have been modified.

Criticism 11. Key messages: - In the first message it was mentioned that: "Unnecessary blood transfusions in heart surgery increase healthcare costs and risks." No estimated numbers of blood transfusion costs were presented in the study.

Reply: The key messages have been removed.
Reviewer: Juan C Duchesne

Criticism. Although a very well designed statistical analysis the data is extremely hard to read due to the abundance of unnecessary descriptions and variables of no use. I can't read nor follow this manuscript. Please condense.

Reply: We have eliminated the subsection “Variable set” from the methods and removed all preoperative and intraoperative variables not included in the model from the Results (see also Table 5 in the new version of the manuscript). In the results we kept some postoperative variables and analyzed the association between a number of essential postoperative variables and the three groups of patients identified by the model (see page 10 – last paragraph). Finally we have modified some parts of the manuscript to make them clearer.
Reviewer: Peng Wei

Major Compulsory Revisions

Criticism 1. Since the predictive model was fitted using the training data, the training and testing data should be treated differently when looking at the discrepancy between the estimated and actual PRBC. However, the authors pooled all patients (in the training and testing sets) together and divided them into Groups I, II & III (top of page 10). Could the authors justify it?

Reply: After the general definition of Groups I, II & III we have added a new paragraph to explain why we pooled all patients (training and testing sets) for further analyses (see highlighted changes – bottom of page 9 and top of page 10).

Criticism 2. Because the dataset used to build the predictive model is observational in nature, it’s not convincing to conclude causal effect based on association, i.e., unnecessary transfusions lead to increased morbidity rate. It could be that adverse events during hear surgery increased PRBC and subsequent postoperative morbidity. It seems that the authors tended to conclude that over transfusion led to increased morbidity. The authors need to elaborate more on this.

Reply: This point is now more fully considered in the Discussion (see third paragraph – page 14).

Criticism 3. Third paragraph in “Model design and validation” (page 7): the authors stated that “A regression model without an intercept was used…” This seems problematic to me. Unless the data have been centered, there should be an intercept term.

Reply: We thank the reviewer, because we did not explain the choice of a regression model without an intercept in the original version of the manuscript. In fact in a linear regression model with only dummy variables, the intercept term represents the mean level of the study variable at the baseline categories of all categorical variables. In the new version of the manuscript we fully explain our choice in the situation under study (see third paragraph in “Model design and validation” – pages 6-7).

Minor Essential Revisions

Criticism 4. Last paragraph on page 8: “A statistical significance of 95% (p<0.05) was used for all statistical tests” should be changed to something like “p<0.05 was ascertained as statistical significant for all statistical tests”.

Reply: We have changed the sentence according to the reviewer’s suggestion.

Criticism 5. Table 4: statistical tests of association between variables and three groups should be provided.

Reply: In the new version of the manuscript we have added a paragraph to clarify the association between variables and the three groups (see page 10 – last paragraph).

Discretionary Revisions

Criticism 6. Table 4: it would be better if variables included in the final predictive model are highlighted.

Reply: We have modified the table (Table 5 in the new version of the manuscript).