**Author's response to reviews**

**Title:** Performance of the Pediatric Index of Mortality 2 (PIM-2) in cardiac and mixed Intensive Care Units in a tertiary children's referral hospital in Italy

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**Author's response to reviews:** see over
To the Editor
BMC Pediatrics

Dear Editor,

We thank both Referees for their careful revision of our manuscript, and for their valuable comments. We have modified the text as suggested in their reports; answers to the issues raised are reported below.

Reviewer: Angela Czaja

Major Compulsory Revisions

Abstract:
1. I’m unclear why the conclusion is solely focused on the cardiac aspect of the results. There seemed to be several conditions under which the PIM-2 performed similarly (e.g. PICU 1 +/- PICU2, non-surgical, middle age range, etc). I might broaden the conclusions, although I recognize the authors were interested in the performance of a separate CICU. Furthermore, I think the last sentence needs to be better worded (please see my comment in the conclusion section of this review).

We recognize the importance to broaden the Abstract’s conclusion and to reword the last sentence. The conclusion has thus been rephrased as follows:

“We recognize the importance to broaden the Abstract’s conclusion and to reword the last sentence. The conclusion has thus been rephrased as follows:

“Proportion of cardiac-surgical patients and patients age-distribution should be considered in interpreting SMRs estimated by different Units by applying the PIM-2 prediction model. More appropriate cardiac-focused risk-adjustment models should be developed, while the role of age on risk of death needs to be further explored.”

Methods

1. Please explain more completely the decision to consider a readmission as a separate admission only if occurred past 48 hrs from discharge. Along the same lines, please clarify how the authors approached multiple readmissions (and the frequency of multiple admissions per patient) since most of the analysis was performed on the subject level. For example, the reasons for admission, LOS, etc...

We considered children who returned to the PICU/CICU within 48 hours to represent one single admission accordingly to the multicentre PIM2 validation study conducted in Italy in
We have also clarified that analysis was conducted at patient admissions level, rather than at subject level: i.e., all consecutive patient admissions to one of the four hospital PICUs/CICU from 1 January 2009 to 31 December 2011 were included in the study. As regards multiple admissions occurring >48 hours, we have added a description of their characteristics in Results. Overall, in the study period 174 patients were readmitted to the same PICU/CICU >48 hours from being transferred to another hospital ward. These patients accounted for a total of 387 admissions, representing 13% of all patient admissions included in the study (2,912). Patients who were readmitted in PICU/CICU experienced a median number of 2 admissions (range: 2-5 admissions). Main reason for admission was cardiac surgical for the majority of cases (169/387, 43.7%), followed by medical (130; 33.6%) and other surgical (88; 22.7%). Median length of stay in PICU/CICUs was 4 days per admission (range: 0-244 days).

2. I am unclear why the regression analysis was performed for this study – am not sure it added to the value of the study, particularly when the PIM-2 was used as an adjustment tool and yet is being evaluated in its performance.

In the context of a tertiary care children’s Hospital with three PICUs and one CICU, it was felt relevant to verify if the differences in mortality rates observed between PICU/CICU and by patient admission characteristics (i.e., age-group, main reason for PICU/CICU admission) would be confirmed after adjusting for PIM2 mortality risk. Multivariable regression analysis was thus aimed at assessing the possible effect of other factors, among those already explored at univariable level, that could significantly predict risk of death independently from PIM2 score. As expected, PIM2 was the strongest predictor of death (the Odds Ratio increases of 53.2 times for each PIM2 incremental point). However, main reason for PICU/CICU admission, categorized in cardiac surgical, other surgical and medical, and age class resulted to be independently associated with mortality risk, while Unit and year were not. In particular, the logistic multivariable analysis showed that cardiac surgical admissions have a significantly lower risk of death compared to medical admissions, while other surgical admissions do not. We thus feel that this finding supports the conclusion that proportion of cardiac surgical patients and patient age distribution should be taken into account when comparing SMRs of different Units. To clarify this issue we have added a sentence in the Methods section, and in the Discussion as well (see also answers to Results, point 6, and Discussion, point 3).

Results

2. First paragraph + table 1 – it was a bit confusing in the text when the authors describe “cause of admission” whether they are referring to reason for PICU admission vs hospital admission. This could be an important distinction. For instance, a patient admitted for chemotherapy related to their cancer treatment might be admitted to the ICU for sepsis or respiratory distress. The hospital discharge diagnoses might be helpful for identifying reason for PICU admission in some patients but more helpful for identifying chronic conditions in others. I would be more interested in more detail about the reason for PICU admission to better understand the differences in case-mix between the different ICUs.
In the text, we have now clarified the distinction between main discharge diagnosis and main reason for PICU/CICU admission. As reported in the Methods, the variable “main reason for CICU/PICU admission” was created using information on surgical procedures performed before transfer to intensive care, and patient diagnosis at discharge. It was then categorized in the following three groups: recovery from cardiac surgical procedure (cardiac surgical patients); recovery from other surgery (other surgical patients); other reasons than recovery from surgery (medical patients). We agree with the Reviewer that more detail about the reason for admission to intensive care would have been of interest, however unfortunately it is not available; we have mentioned this limitation in the Discussion.

3. Please describe what types of cardiovascular disease might have been admitted to the CICU beyond surgical.

Other admissions to CICU were also mostly in patients with cardiovascular congenital malformations or cardiovascular diseases, but did not report recovery from cardiac surgery as main reason for admissions. We have added this information to the text.

4. Although the authors describe that the observed mortality rates were higher in neonates and adolescents, they did not further interpret the performance of the PIM-2 based on age category. Again, not clear why they choose to analyze this particular characteristic but because they did, I would like to see more discussion of the findings.

As reported in the discussion, in our study the observed mortality was highest in the first month of life and in adolescents. In these age groups, the PIM-2 standardized mortality was very close to the observed mortality (indicating good PIM2 calibration), while it was significantly lower in children >1 month to 12 years of age. Therefore, the higher risk of dying in newborns, neonates and adolescents observed in multivariate analysis points to outcome differences independent from patients severity at PICU/CICU admission as measured by PIM2. In fact, both patients < 1 month of age and adolescents have specific characteristics, and suffer from higher mortality risk compared to pre- and school-age children. Regarding the analysis by age, please see also answer to Minor Essential Revisions, Methods, point 5.

5. Although the authors describe the calibration within risk groups, they did not report the overall calibration (with a statistically significant chi-squared p-value) which demonstrates poor goodness-of-fit. Certainly, this appears to be primarily driven by the highest risk group. Along these lines, the H-L is described and labeled as deciles of risk—however, as presented, these are not actually deciles (e.g. 0-10, 10-20, etc) but appears they were grouped by sample size. Not inappropriate, but needs to be correctly described and labeled.

The overall calibration has been included in the text and is reported in Table 3, along with its correspondent p-value (SMR: 0.7; P-value < 0.001). The table has been relabeled from “Hosmer-Lemeshow goodness of fit test for deciles of mortality risk”, to “Hosmer-
Lemeshow goodness of fit test for groups of mortality risk”. Also in the text, we now refer to goodness of fit analysis by risk groups.

6. Again, I am not sure why the multivariate regression was performed. This was not meant to be a comprehensive analysis of factors associated with death in this population (as exemplified by the limited variables included) so I do not believe this adds much value to the paper.

As pointed out in the answer to point 2 of Methods, the aim of this analysis was not to study all factors possibly related to mortality, but to verify if relevant Unit and patient characteristics, such as type of Unit, year of admission, age-group and reason for PICU/CICU admission, could predict the risk of death independently from PIM2 adjustment. In fact, logistic regression analysis can add further insight for assessing if differences in PIM-2 adjusted SMR observed among Units can be related to differences in patients characteristics or are most likely due to differences in the care provided by different Units. See also answer to point 1 of Discussion.

Discussion

1. I would like to see an expanded discussion about why the performance of the PIM-2 might have varied between units. For example, what is it about PICU2 that might have led to better performance (by these indicators) than the other units? It would be helpful for the authors to tease out differences in performance based on risk group vs unit vs underlying problems/admitting diagnoses.

This is a very interesting point, which we believe may find an answer in the results of multivariable regression analysis. In fact, better CICU results are most likely due to the lower risk of death in cardiac surgical patients, who represent the vast majority of CICU admissions, while PICU1 results can be related to the high proportion of patients from 1 month to 12 years of age, who also have a lower risk of death. We have thus expanded the discussion to consider these issues.

2. I am not sure why the authors chose to focus most of the discussion on cardiac patients alone when their data also finds the PIM-2 performed similarly in nonsurgical patients. is the better explanation that the score performed best in “other surgical” population? Although it may not be inaccurate to say that cardiac-focused prediction models may be needed, I think further discussion about the why the model did not perform well in other populations within their study.

Our results show that calibration of PIM-2 model was good, while discrimination was poor particularly in the highest mortality risk group of cardiac surgical patients. This was actually the main reason for the relevance given to this result in the discussion. The other differences in SMRs observed among Units were further investigated with a regression analysis approach, which showed that cardiac surgical patients and patients from 1 month to 12 years of age had a lowest risk of dying independently from PIM-2. The role of these variables on mortality risk can explain why expected deaths did significantly differ from
observed mortality in some Units or patient admission groups. We have expanded discussion to this regard.

3. the paragraph beginning with “as an additional assessment of…” – I do not believe this is what the authors are doing. There are many other variables that impact a particular subject’s risk of mortality, not necessarily captured by those included within the PIM-2 model (as exemplified by the much more expanded number of variables for calculating other pediatric ROM scores such as PRISM).

If the authors choose to keep this part of the analysis in the study, I think a more thorough explanation of decision to perform this analysis as well as the findings is warranted.

We agree that the paragraph needed to be better explained, and we’ve modified it as follows:

“At the light of the statistically significant difference in observed mortality found between Units, main reasons of admission to intensive care and patient age class, we performed a multivariable analysis to simultaneously explore the effect of these variables on risk of death, adjusting for PIM2 score.

We found that, independently from PIM-2, main reason for admission and age remain significant predictors of the observed mortality, with lower risk in cardiac surgical patients and in children from 1 month to 12 years of age, and higher risk in medical patients and in babies < 1 month of age or adolescents. It is interesting to note that the two Units with SMRs significantly lower than 1 admitted mostly patients in the cardiac surgical group (CICU) or from 1 month to 12 years of age (PICU1), confirming the importance of differences of patient case-mix.”

Conclusion

1. the last sentence needs to be carefully worded—in what way do these groups need to be separately analyzed? One might argue that for those included in a general ICU, the performance of the PIM-2 on the whole population (as it was intended to be used) might actually improve if they have a similar case-mix of patient-types (not necessarily severity of illness upon presentation as in the original development cohort). Furthermore, as raised in the above comments, what about the other patient populations in which the PIM-2 did not perform well?

Again, we have rephrased this sentence, clarifying that the proportion of cardiac surgical patients and patient age distribution should be considered in interpreting SMRs estimated by different Units by applying the PIM-2 prediction model, as variable case-mix could distort the overall results and bias comparisons.

Minor Essential Revisions

Abstract

1. a statement about the overall calibration as well as overall AUC should be included

The abstract has been modified as suggested
3. Please include in that discrimination and calibration were also assessed on the unit-level as presented in the results. 

*We have clarified that discrimination was assessed on the total sample, by Unit, main reason of PICU/CICU admission (i.e., cardiac surgical, other surgical and medical), year and age class, and calibration was assessed on the total sample and by main reason of PICU/CICU admission.*

4. The authors’ description of discrimination (“the ability of the PIM-2 score to correctly predict patients’ survival”) might be better worded as the ability to distinguish between survivors and non-survivors. It may seem subtle but if all non-survivors had a higher PIM-2 score than all survivors, the discrimination would be perfect—yet does not say anything about how well it actually accurately predicted the probability. For example, for PICU3, the AUC is 0.91 yet the SMR is 0.6.

*We have modified the sentence accordingly*

5. I am wondering about the decision to evaluate by age category – please provide more explanation why this particular characteristic was focused upon

*Most published studies evaluating PIM-2 performance do analyze data by age group (see references 7, 10, 16). We have chosen as reference categories the ones adopted in 2005 by the International Sepsis Forum and we have included the reference in the text.*

**Results**

1. Please clarify why PIM-2 was not completed for all patients – missing data, excluded patients, etc

*PIM-2 was not completed for 282 patients because the data for calculating the score were missing. We have added this information to the text.*

4. I might also describe that PICU3, while not meeting statistical significance, had an SMR 0.6 as well.

*As suggested, we have described this finding in the Results.*

**Discretionary Revisions**

**Methods**

1. The authors state that the study was part of the hospital QI program – please specify in what way

*We have specified that the collection and analysis of PIM-2 data for estimating Standardised Mortality ratios (SMRs) in each Intensive Care Unit was one of the objectives of the 2009-2011 annual Hospital Quality Improvement Programs, that were reviewed and approved annually by the Hospital Quality Committee.*
Reviewer: Andrea Wolfler

Minor revisions

Background page 4, line 19: I suggest “multidisciplinary medical/surgical (M/S)”

As suggested, the terms “multidisciplinary pediatric” have been modified in multidisciplinary medical/surgical pediatric”.

Methods, setting page 5, line 9 instead of “the three PICUs” I suggest “the three M/S PICUs”

As indicated, the terms “the three PICUs” have been changed in “the three M/S PICUs”.

Methods data collection page 5, line 16: I suggest to add “all consecutive” , line 22 instead of “sex” I suggest “gender”

I suggest to change in all the paper the two words cardiosurgery and cardiosurgical with cardiac surgery and cardiac surgical

I suggest to change in all the paper “non surgical” in “medical”

All the suggested changes have been made.

Discretionary revisions

Results: it could be useful to add how the 7 missing death children are distributed for age and main reason of admission.

We have included in the text a description of the 7 missing deaths. In detail, four of these children (aged 5, 10, 12 and 13 years, respectively) were admitted in PICU/CICU for medical causes and the remaining three (aged 11, 14 and 15 years respectively) for other surgical procedures.

Discussion page 10 line 1: it is not clear when the authors comment the higher risk of death for neonate and newborn resulted from the multivariate analysis.

They reported that independently from PIM2 score, these two age categories have a higher risk of death, and seems to justify this result with a poor calibration of the PIM score. I think this is not an appropriate explanation.

The discussion about risk of death by age has been expanded and it has been underlined that the role of age on mortality risk needs to be further explored. In our study, the observed mortality was highest in the first month of life and in adolescents. In these age groups, the PIM-2 standardized mortality was very close to the observed mortality, while it was significantly lower in children from 1 month to 12 years of age. The highest risk of dying in newborns, neonates and adolescents observed in multivariate analysis could be due to differences in outcome independent from patients severity at PICU/CICU admission. In fact, both patients < 1 month of age and adolescents have specific
characteristics, and a well known higher mortality risk compared to pre-and school-age children.

Thanking you in advance for your consideration.

Sincerely,

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