

Author’s response to reviews

Title: Early prediction of preeclampsia and small-for-gestational-age via multi-marker model in Chinese pregnancies: a prospective screening study

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Version: 1 Date: 15 Jul 2019

Author’s response to reviews:

Dear Editor Andrea Dall’Asta,

Thank you for giving us this opportunity for revision, and we are extremely grateful to the two reviewers for their detailed and insightful comments on our manuscript entitled “Early prediction of Preeclampsia and Small-for-Gestational-Age via multi-markers model in Chinese pregnancies: a prospective screening study” (PRCH-D-19-00138).

After careful review of all the questions posed, we have made revisions accordingly, highlighted in yellow in the draft paper, and have also provided response to each query listed below:
Response to Reviewer 1 (Prof. Daniela Di Martino)

Q1: Since there are really few cases of early PE, a sample size analysis to evaluate the power of the ROC curve should be added.

Response: Regarding your suggestion, we then conducted the power assessment of the ROC curve by using R package for sample size analysis. The final results showed that for both early and late PE, our study has enough power: with the current sample size, the early PE group has the power of 99.65%, and 99.99% for the late PE group. Even if with the power of 80% (commonly used), four cases and 1,351 controls for early PE, and six cases and 516 controls for late PE are still adequate.

We have included the result of sample analysis into the supplementary materials, and we also mentioned it in paragraph 6 under the Discussion section (discussing the limitation of our study).

Q2: The priority risk (page 6, line from 12 to 17) not consider smoke, previous pregnancy with PE and/or SGA, modality of conception.

Response: Apology for not making the part of “Calculation of risks” under Method section clearly. Therefore, we have rewritten it to provide a more logical and detailed description and calculation workflow (please see the Method section in revised manuscript).

In the study, we used a well-developed software from Perkin Elmer Company, called “Pre-eclampsia Predictor” to calculate PE risk, through which we could obtain prior risk and posterior risk for each pregnancy. But the default setting for ‘prior risk’ only considers five main risk factors, namely, BMI, ethnicity, parity, history of PE and chronic hypertension. In addition, we would like to clarify that “history of PE” includes the information that the pregnancy had PE history of herself and her mother.

The software includes smoking state to adjust the MoM values of PLGF and PAPP-A used in posterior risk calculation, while it does not put smoking and method of conception as risk factors into calculation for prior risk. But these factors are fixed in the software into which no additional factors such as previous pregnancy with SGA, method of conception are allowed to be incorporated.

Q3: The author used the MoM of the variables (page 6, line 18), why in the analysis adjusted a second time for gestational age?

Response: We think there must be a minor error in that part. Gestational age was used in MoM calculation, and we have already corrected it in the “Measurement of MAP, maternal serum
PLGF and PPAP-A” part of Method section. You can see it has been marked in yellow in the revised manuscript.

The statement of “The posterior risk was assessed by combining the prior risk with the results of MAP, PAPP-A and PLGF converted into multiples of the median (MoM) and adjusted for gestational age, BMI, ethnicity and smoking status” now has been corrected to “Multiples of the median (MoM) were calculated for markers (MAP, PAPP-A, PLGF) and were adjusted for BMI, ethnicity and smoking status, additionally gestation days were used in MoM calculation;” and more detailed steps you could find in the manuscript.

Q4: Page 8 line 17 in early PE group, at risk cut off 1 in 100, the DRs of prior and posterior risks were 25.00% versus 87.50% with 0.5% of FPR for priory risk (see table 3). I wonder if the DR would increase if a FPR of 5% was chosen. An a priori risk with a DR of 25% is not acceptable.

Response: Previously, we simply wanted to show that at the same cutoff, how did these four risks perform. But as you mentioned, the data was not acceptable and we should compare the DRs at the same and fixed FPR, which can be seen in Table 4.

And we reconsidered and re-analysed the whole data. We replaced the old Table 3 with a new one and also improved Figure 2 because the former way of data presentation was not very clear and meaningful.

We added two ROC curves of prior risk for early and late PE separately into the Figure 2 (a) and (b), so the ROC curves of both prior risks and posterior risks in early and late PE group are presented in the updated Figure 2. According to Figure 2, we concluded that posterior risk (combing maternal characteristics with results of MAP, PLGF, PAPP-A) performed much better than prior risk (maternal characteristics only).

To provide a clearer explanation of the 25% DR of prior risk for early PE, we hope to explain it more here. At cutoff 1:54, DR of prior risk for early PE was 25% and it was the same when the FPR increased to 5.36% at cutoff 1:219. When adjusting the cutoff to 220, the DR was up to 37.5%, and the FPR jumped to 52.49% (also not acceptable). Therefore, we concluded that the prior risk is not suitable and useful for predicting early PE, and we believe that this finding also could be one of our conclusions (discussed in our manuscript).

Q5: Page 8 line 20 and under late PE, the respective DRs were 45.27% versus 71.43. It is illogical that the DR is higher for late PE and not for early. It is well acknowledged that the DR is always higher for the early PE. The authors should fix the FPR at the same level to allowing a comparison between early and late.
Response: I think there might be a small misunderstanding. The DRs of 45.27% and 71.43% were, respectively, for prior risk of late PE and posterior risk of late PE (at same cutoff level 1:100), not DRs of early PE and late PE. In fact, our result is consistent with the data in previous studies that the DR for early PE is higher than DR for late PE (which you can see in Table 4).

As we have discussed in Q4, the old Table 3 was not appropriate, so we adopted a new way to present our data in the new Table 3 and Figure 2. Also, we compared the DRs at the same and fixed FPR in Table 4.

Q6: Table 3. I'm not sure that for early PE a cut-off of 1:20 is useful. Of course, the DR is very low since the incidence of the disease is something like 1:150.

Response: In fact, your opinion is also one of our conclusions. Firstly, we found that the default setting cutoff 1:20 (according to the Predictor software) is neither suitable nor effective to define high-risk PE pregnancy due to low DRs (25.00% in early PE, 34.29% in late PE). Yet, through our analysis, the best posterior risk cut-offs were 1 in 45 for early PE group (DR 87.50%, FPR 3.94%), and 1 in 151 for late PE (DR 80.00%, FPR 25.81%).

Moreover, as we have explained in Q4&5, based on our re-analysis, we concluded that prior risk for early PE is not as useful and efficient as the posterior risk. We think the updated Figure 2 and new Table 3 can better illustrate these results and conclusions. And you will find these changes in both sections of Results and Discussion in our revised manuscript.

Q7: Table 3. The cut off value that author choose, should consider the incidence of preeclampsia in their population (0.24% for early PE).

Response: Actually, we did consider the incidence of PE in our population. We used MedCalc statistic software to calculate cutoffs and obtained the ROC curves during the process of calculating. This method actually took the incidence of PE as a factor.

Q8: Added the PI of uterine arteries in the posterior risk would have been useful in terms of test sensibility and economy, instead of use two placental protein (PAPP-A and PIgf).

Response: I have to admit that UTPI is a valuable and useful marker in predicting PE and SGA, but in our hospital, even many other hospitals in China, UTPI is not a part of routine ultrasound scan. Our sonographers are generally not aware that UTPI could bring many benefits to patients and provide further assessment of pregnancy complication. So I wonder if more research could be done to prove the clinical utility of UTPI, so that more sonographers in China will adopt it.
Moreover, the high-quality and accurate UTPI measurement requires professional training of sonographers. But in our research, it was difficult to achieve uniformity of results by different operators because our sonographers have not received standard professional training before.

Considering the above reasons, plus our study has already been completed, it is now almost not possible for us to add the UTPI in the calculation of posterior risk. Nevertheless, we discussed and summarized such limitation in paragraph 6 under Discussion section.

Our future plan is, firstly, to launch a program providing standardized professional training to sonographers in our hospital. Their competence in measuring UTPI would be assessed by professional and experienced experts or recognized institutions. Secondly, when satisfactory UTPI results could be produced, we will add UTPI into the posterior risk calculation and enlarge our sample size in our next research.

Q9: Page 4 line 59 the authors should describe how many times they measured blood pressure, describe the modality of measurement and specify if the sphygmomanometer was validated for pregnant women.

Response: We have added a standard protocol with more details about how to achieve a reliable results of MAP to the Method section, which you could see in the revised manuscript.

Q10: Table 4. The authors should comment why the DR for early PE are the same at different FPR 5%,10%,15%).

Response: The reason of the same DRs for early PE at different FPRs is that among eight early PE cases, there were seven with their posterior risks of early PE ranging from 1:5 to 1:45. They were all beyond risk cut-off 1:64 (at FPR5%). But the posterior risk of the single remaining one was 1:2989, which means even if the risk cutoff is adjusted to 1:293 (at FPR15%), the DR remains the same.

Q11: The authors found a good sensibility for SGA+PE. They should repeat the analysis consider a classification that use and consider a pathophysiological mechanism of placental damage: PE+AGA versus PE+IUGR.

Response: Given your suggestion, we re-classified PE into four subgroups: early PE with SGA, early PE with AGA, late PE with SGA and late PE with AGA. We improved Table 4 and added DRs of the PE with AGA groups. When comparing PE+SGA group with PE+AGA group, the DRs differed substantially (at 10% FPR, 100% versus 66.67 % in early groups; 60.00% versus
44.00 % in late groups). Although we tried to discuss the possible pathophysiological mechanism behind PE and SGA, it remains an area pending further research and development.

Response to Reviewer 2 (Prof. Thomas Everett)

Q1: Abstract: the same FPR rate should be used in both cases in the results section (ie use FPR10%) so that comparison is easier

Response: In the Abstract, we have replaced the part--“Detection rates of early preeclampsia and early SGA, at 10% false-positive rates, were 87.50% and 41.67%, respectively; detection rates of late preeclampsia and late SGA, at 15% false-positive rates, were 60.00% and 40.00%, respectively” with a revised version--“At 10% false positive rates, detection rates of early preeclampsia, early SGA, late preeclampsia and late SGA were 87.5%, 41.67%, 48.57% and 28%, respectively. ”

Q2: Discussion : P 9 L 25-26: It cannot be concluded that placentation is different as there is no histology in this study. This comment should be removed.

Response: Thank you very much for pointing this out. We have removed it accordingly.

Q3: Are the values in Table 4 early PE and early PE with SGA really the same across all FPR percentages or is this an error?

Response: The reason of the same DRs for early PE at different FPRs is that among eight early PE cases, there are seven with their posterior risks of early PE ranging from 1:5 to 1:45. They were all beyond risk cut-off 1:64 (at FPR5%). But the posterior risk of the single remaining one is 1:2989, which means even if the risk cutoff is adjusted to 1:293 (at FPR15%), the DR remains the same.

The same thing also occurred in cases of early PE with SGA. The five cases came from the eight early PE, whose posterior risks range from 1:5 to 1:42. At 5% FPR, the risk cut off is 1:64. Therefore, all of these cases are high risk subjects in our prediction model, and the DR is 100%. With the increase of FPR, the risk cut off also rises. For example, risk cut off is 1:172 at 10% FPR; it rises to 1:293 when the FPR increases to 15%. 
So far, we believe that the above issues raised by the reviewers have been carefully and thoroughly addressed. We hope that our revised manuscript could fulfill the requirements for publication in BMC Pregnancy and Childbirth.

Thank you again for all your precious suggestions and comments. We look forward to your kind reply. Should you have any questions, please do not hesitate to contact us.

Best regards,

Jing Zhang and Luhao Han, on behalf of all the authors