Comparing childhood asthma prediction models in terms of risk classification: suggestions for future research

Dear Editor,

We would like to thank Owora et al. for their interest in our systematic review of childhood asthma prediction models and welcome their subsequent analyses and recommendations for future research regarding childhood asthma predictions.

In their letter, Owora et al. rightly highlight that prediction models can be classified as either diagnostic or prognostic models, with diagnostic models predicting the presence of a disease of interest at the time of prediction whilst prognostic models predict the presence of the disease of interest at a future time-point. We agree with the authors that studies often do not make it clear as to which class of prediction model they have developed or are reviewing. Having acknowledged that the authors also found the scope of our systematic review to be unclear, we would like to clarify that our systematic review was limited to prognostic prediction models for childhood asthma. As detailed in our inclusion criteria, we only considered studies which offered predictions for children aged ≤5 years on their risk of developing the future outcome of childhood asthma or wheeze persistence at school-age (6-13 years old)[1].

Following their meta-analysis of externally validated regression-based models, Owora et al. concluded that based on their pooled estimates of sensitivity, specificity and AUC, existing models offer poor predictive performance, particularly among clinically relevant ranges of sensitivity and specificity. We are pleased that Owora et al. were able to offer quantitative support for our initial inference that existing models offer moderate performance with modest generalisability. Furthermore, their bivariate-random effects meta-regression analysis identified external validation and the use of machine learning approaches as significant moderators of prognostic model sensitivity. These findings corroborate our recommendations for the exploration of novel methodologies and/or biomarkers in the development of future prediction models in order to improve their predictive power, to provide

clinical utility. Although Owora et al. identified that externally validated models had a significantly higher sensitivity than non-validated models, we note that external validation is ultimately performed at the discretion of the researchers with regard to i) the chosen study design; ii) the model's potential based on its initial performance in the developmental population; and iii) the availability of independent data. Therefore, we interpret this finding as external validation acting as an important milestone in the developmental process, to not only assess the true generalisability of a model, but also offer confidence in its performance and potential clinical viability. Indeed, as mentioned in our systematic review, the lack of external validation limits studies as exploratory, with little clinical utility, thus, we again emphasise the need for external validation in all future studies.

Owora et al. propose the use of reclassification tables to stratify the results of asthma prediction models into distinct risk groups corresponding to different clinical decisions. Reclassification tables, and net reclassification indices, were initially proposed to assess whether the addition of a marker provides any clinically relevant improvement to an existing prediction model[2,3]. However, we agree that the use of reclassification tables could offer additional insight for physicians when choosing between models, particularly given the trade-off between model sensitivity and specificity. To provide an illustrative example of the potential insight offered by reclassification tables, we compared two existing asthma prediction models for which data was available in the Isle of Wight Birth Cohort (described elsewhwere[4]) - the updated PIAMA[5] and PARS[6] models. Of the 1456 individuals enrolled in the IOWBC, 837 individuals who had complete data for all predictors used in the two models, and whom had a defined asthma outcome at age 10, were included in the analysis. First, we evaluated overall model performance based on the commonly used measure of area under the receiver operating curve (AUC). We then used a reclassification table to compare the risk classification predicted by each model (as referred to by Owora et al. in reference 3), and reported the results separately for asthmatics and non-asthmatic children at age 10. Risk classification, into low (<15% risk), moderate (15-39% risk) and high (≥40% risk) categories, were matched between the two scores as detailed in their original publications (Table 1).

In our analysis, both prognostic prediction models indicated approximately equivalent model discrimination (Figure 1), with AUC of 0.76 (95% CI: 0.70-0.81) and 0.77 (95% CI: 0.71-0.82) for the updated PIAMA and PARS models, respectively. However, using the reclassification table (Table 1), we uncovered a substantial inconsistency in the risk categorisation of asthmatic and non-asthmatic individuals between the two models. With respect to the risk classifications made by the updated PIAMA model, 45% of asthmatic children at age 10 were reassigned into a more appropriate (higher) risk category by the PARS model. However, this was accompanied by 13% of non-asthmatic children also being reclassified into a less appropriate (higher) risk category by the PARS model compared to that made by the updated PIAMA model. Therefore, by providing insight into predictions made by prognostics models on an individual-level, and evaluating them separately for asthmatic cases and non-asthmatic controls, reclassification tables can be useful tools for comparing between models rather than using AUC alone. For example, although not evident from the ROC plot, the reclassification table suggests that predictions made by the updated PIAMA model are skewed towards underestimating asthma risk in the IOWBC when compared against the PARS model. This could potentially be informative for policy decision-making depending on whether the clinical intention is to detect true future asthmatics at high risk (PARS preferred), or discount true future non-asthmatics at low risk (updated PIAMA preferred), for primary or secondary interventions.

Whilst we agree with Owora et al. and promote the use of reclassification tables, their use requires prediction models to be compared within a single population. In our systematic review, we highlighted the need for a single cohort, of sufficient size, with data available for all predictors used by the existing models. However, this remains an unrealistic ask, which, at present, hinders an objective comparison between existing asthma prediction models. Owora et al.'s second recommendation to estimate and meta-analyse the predicted outcome probabilities across different time-points could offer beneficial insight into the consistency and reliability of a model's predictive power over time. However, the execution of this may also be hindered by the need for a longitudinal cohort with data available for all predictors and the asthma outcome across multiple time-points, with high retention rates.

The final recommendation for future studies offered by Owora et al. highlighted the importance of developing prognostic models that predict beneficial or adverse responses to primary and secondary interventions. Whilst this was beyond the scope of our systematic review, which focused on models that predicted the development of childhood asthma, we agree that this is a logical progression of research in the field, which could offer beneficial clinical insight. Where data availability permits, we welcome these recommendations for future exploration in childhood asthma predictions.

Tables and Figures

Table 1. Reclassification of predicted asthma risk using the PARS risk score instead of the updated PIAMA risk score

	Predicted risk (PARS)				Reclassified by PARS (%)			
Predicted risk (updated PIAMA)	**Low**	**Moderate**	**High**	**Total**	**Increased risk**	**Decreased risk**	**Correctly reclassified**	**NRI**
No asthma at age 10 (n=716)								
Low	605	**82**	**2**	689				
Moderate	**1**	18	**7**	26	91(13%)	1(<1%)	1(<1%)	-0.13
High	**0**	**0**	1	1				
Total	606	100	10	716				
Asthma at age 10 (n=121)								
Low	48	**42**	**0**	90				
Moderate	**0**	12	**13**	25	55(45%)	0(0%)	55(45%)	0.45
High	**0**	**0**	6	6				
Total	48	54	19	121				
				Total	146	1	56	

Using the updated PIAMA as the reference prognostic model, the table shows the changes in individual risk classification if the PARS model (which offers marginally higher model discrimination) was used instead. For both the updated PIAMA and the PARS models, risk strata were categorised as low=<15% risk (updated PIAMA score: 0-12, PARS score: 0-4); moderate=15-39% risk (updated PIAMA score: 13-19, PARS score: 5-8); high=≥40% risk (updated PIAMA score: 20-23, PARS score: 9-14) as defined in their original publications. Results are presented separately for individuals who were asthmatic and non-asthmatic at age 10. Values in bold identify the number of individuals who were reclassified into a more appropriate (green) or less appropriate (red) risk group by the PARS model with respect to the risk classifications made by the updated PIAMA model. NRI=net reclassification index.

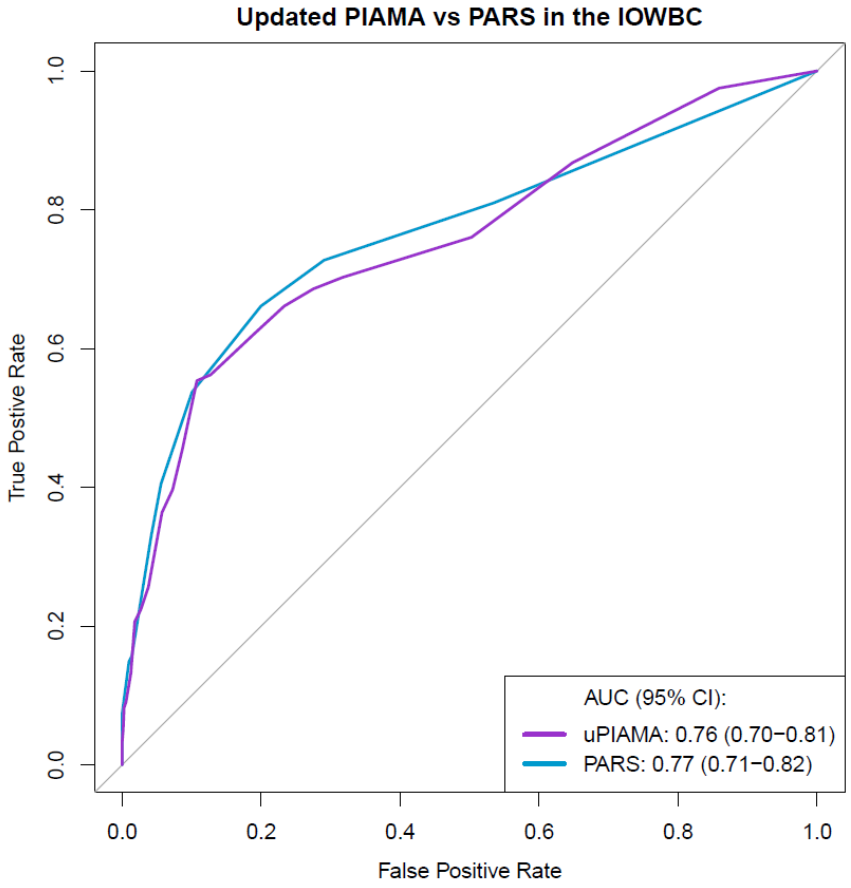

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Figure 1. ROC plot comparing the performance of the updated PIAMA (uPIAMA) and PARS models in the IOWBC.

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