DOI:
10.1161/HYPERTENSIONAHA.116.08706

Document Version
Peer reviewed version

Title: EXTERNAL VALIDATION OF THE FULLPIERS MODEL FOR PREDICTING ADVERSE MATERNAL OUTCOMES IN PREGNANCY HYPERTENSION IN LOW-AND-MIDDLE-INCOME COUNTRIES

Manuscript number: HYPE201608706R2

Author(s): U Vivian Ukah, University of British Columbia
Beth Payne, University of British Columbia, Vancouver
Tang Lee, University of British Columbia, Vancouver
Laura Magee, St. George's at University of London
Peter von Dadelszen, St. George's, University of London

EXTERNAL VALIDATION OF THE FULLPIERS MODEL FOR PREDICTING ADVERSE MATERNAL OUTCOMES IN PREGNANCY HYPERTENSION IN LOW-AND-MIDDLE-INCOME COUNTRIES. MS ID: HYPE201608706

U. Vivian Ukah, MPH[1,2*], Beth Payne, PhD [3], Tang Lee, Msc[1,2], Laura A. Magee, Professor[4,5], Peter von Dadelszen, Professor[4,5], for the fullPIERS and miniPIERS Working Groups.

Affiliations:

1. Department of Obstetrics and Gynaecology, University of British Columbia, Vancouver, BC, Canada

2. Department of Anaesthesiology, Pharmacology and Therapeutics, University of British Columbia, Vancouver, BC, Canada

3. Healthy Starts Theme, BC Children's Hospital Research, Vancouver, BC, Canada

4. Molecular & Clinical Sciences Research Institute, St George's, University of London, London, UK

5. Department of Obstetrics and Gynaecology, St George's University Hospitals NHS Foundation Trust, London, UK

Address for correspondence: U. Vivian Ukah, 950 W 28th Avenue, Department of Obstetrics and Gynaecology, University of British Columbia, Vancouver BC, V5Z 4H4, Canada; Telephone: +1604-875-2424x6112; Email: Vivian.Ukah@cw.bc.ca

Short title: fullPIERS validation in low-and-middle-income countries

Word Count (including references and tables): 5377 (Abstract – 217); Total figures - 2

ABSTRACT

The hypertensive disorders of pregnancy are leading causes of maternal mortality and morbidity, especially in low-and-middle-income countries. Early identification of women with pre-eclampsia and other HDP at high risk of complications will aid in reducing this health burden. The fullPIERS model was developed for predicting adverse maternal outcomes from pre-eclampsia using data from tertiary centres in high-income countries and uses maternal demographics, signs, symptoms, and laboratory tests as predictors. We aimed to assess the validity of the fullPIERS model in women with the hypertensive disorders of pregnancy in low-resourced hospital settings. Using miniPIERS data collected on women admitted with hypertensive disorders of pregnancy between July 2008 and March 2012 in seven hospitals in five low-and-middle-income countries, the predicted probability of developing an adverse maternal outcome was calculated for each woman using the fullPIERS equation. Missing predictor values were imputed using multivariate imputation by chained equations. The performance of the model was evaluated for discrimination, calibration, and stratification capacity.

Among 757 women with complete predictor data (complete case analyses), the fullPIERS model had a good area under the receiver operating characteristic curve of 0·77 (95% CI 0·72-0·82) with poor calibration (*p*-value <0·001 for the Hosmer-Lemeshow goodness-of-fit test). Performance as a rule-in tool was moderate (likelihood ratio 5·9, 95% CI 4·23-8·35) for women with ≥ 30% predicted probability of an adverse outcome. The fullPIERS model may be used in low-resourced setting hospitals to identify women with hypertensive disorders of pregnancy at high-risk of adverse maternal outcomes in need of immediate interventions.

Key words: pregnancy hypertension, pre-eclampsia, prediction, maternal outcomes, prognosis

INTRODUCTION

Hypertension during pregnancy is one of the top three causes of maternal morbidity and mortality worldwide.[1,2] The hypertensive disorders of pregnancy (HDPs), which include pre-eclampsia, super-imposed pre-eclampsia, gestational hypertension, and chronic hypertension, complicate approximately 5-10% of pregnancies.[1,3] Maternal complications that result from HDPs include stroke, eclampsia, and renal dysfunction; and adverse fetal outcomes include stillbirth, pre-term delivery, and cerebral palsy.[4] These severe consequences of the HDPs make them a global health burden, especially in the low-and-middle-income countries (LMICs) where greater than 90% of HDP-related deaths occur.[2,5] To reduce this burden, there is a need to correctly identify women at high risk of developing adverse outcomes in time to avoid their occurrence. Accurate risk assessment can aid decision-making around the management of HDPs, including timing of delivery, administration of antenatal corticosteroids for acceleration of fetal pulmonary maturity or Magnesium sulfate for seizure prophylaxis, and maternal transfer to a higher level of care.[1,3]

To facilitate risk stratification and improve the management of HDPs, the fullPIERS (Pre-eclampsia Integrated Estimate of RiSk) model was developed to predict adverse maternal outcomes occurring in the 48 hours following hospital admission with pre-eclampsia in high-income countries. The adverse outcomes predicted by the model included major organ dysfunction and death.[6] The fullPIERS model is based on maternal demographics, signs,

symptoms, and laboratory tests, with the final model consisting of six predictor variables: gestational age, chest pain or dyspnoea, oxygen saturation (SpO_2), platelet count, serum creatinine, and serum aspartate aminotransferase (AST). Upon internal validation, the fullPIERS model predicted an adverse maternal outcome within 48h of hospital admission with an area under the receiver operating characteristic curve (AUC ROC) of 0·88 (95% CI 0·84-0·92).[6,7] A preliminary external validation using the Pre-eclampsia Eclampsia TRial Amsterdam (PETRA) study cohort of high risk women was also reassuring (AUC ROC 0·97, 95% CI 0·94–0·99).[8]

To ensure the generalizability of the fullPIERS model before it is implemented into clinical practice to improve maternal care,[9,10] we sought to assess the model's potential for use in a LMIC setting where the majority of HDP-related morbidity and mortality occur. The objective of this study was to use data from the miniPIERS cohort[11], collected prospectively in LMICs, to assess the broader validity of the fullPIERS model.

METHODS

Ethical approval for this validation study was obtained from the Research Ethics Board of the University of British Columbia (CREB#: H07-02207). The PIERS projects were undertaken as a consented research or/and as a continuous quality improvement project depending on local ethics committee requirements.[6]

The fullPIERS cohort (Development cohort)

The methods and results of the fullPIERS model have been published.[6] In brief, the cohort consists of 2,023 women diagnosed with pre-eclampsia who were admitted into tertiary hospital units, from September 2003 to January 2010 in four well-resourced countries: Canada, New Zealand, Australia, and the United Kingdom.[6] Pre-eclampsia was defined as hypertension and one of proteinuria, hyperuricaemia, or HELLP (Haemolysis Elevated Liver enzyme Low Platelet) syndrome.[6] An adverse maternal outcome referred to a composite of maternal death or morbidity, as determined by Delphi consensus for the fullPIERS study[6] and outlined in appendix table S1. Women were excluded if they had already experienced an adverse maternal outcome before hospital admission or data collection or if they were admitted in spontaneous labour.

The miniPIERS cohort (Validation cohort)

The methods and results of the miniPIERS study have been published[11]. In brief, the cohort consists of 2,081 women who were admitted to a participating hospital unit with a HDP (i.e., pre-eclampsia, gestational hypertension, or chronic hypertension) and who had not yet experienced an adverse maternal outcome, from July 2008 to March 2012 in five LMICs: Fiji, Uganda, South Africa, Brazil, and Pakistan. Pre-eclampsia was defined as in the fullPIERS cohort; gestational hypertension was defined as blood pressure (BP) ≥140/90 mmHg (at least one component, twice,

≥4 hours apart, ≥20^{+0} weeks) without significant proteinuria, and chronic hypertension as BP ≥140/90 mmHg (at least one component, twice, ≥4 hours apart, <20^{+0} weeks' gestation). Adverse maternal outcomes were defined as in fullPIERS (appendix table S1). Women were excluded from the cohort if they experienced an adverse outcome before hospital admission or data collection or if they were admitted in spontaneous labour.

Further details of the development and validation cohorts have been described elsewhere.[6;11]

Statistical Analyses

The distribution of patient characteristics in the development (fullPIERS) and validation (miniPIERS) cohorts were compared using *Chi*-squared test for nominal data and Mann-Whitney U test for continuous data. Univariate comparison of patient characteristics between the women in the validation cohort who experienced an adverse outcome and those who did not, was also performed. A p-value of <0·05 was considered to be statistically significant.

Using the worst values (pre-defined in the model development study as the highest or lowest where appropriate)[7] for the model predictors recorded within 24 h of admission to HDP, the

The fullPIERS Logistic Regression Equation for the prediction of adverse maternal outcomes from pre-eclampsia: logit(pi)=2·68+(–5·41×10^{-2}; gestational age at eligibility)+1·23(chest pain or dyspnoea)+(–2·71×10^{-2}; creatinine)+(2·07×10–¹; platelets)+(4·00×10^{-5}; platelets^{2})+(1·01×10^{-2}; aspartate trans aminase)+(–3·05×10^{-6}; AST^{2})+(2·50×10^{-4}; creatinine×platelet)+(–6·99×10^{-5}; platelet×aspartate transaminase)+

(–2·56×10^{-3}; platelet×SpO2)

fullPIERS equation was applied to the miniPIERS data and the predicted probability of adverse outcomes for each individual with complete predictor data (complete-case) was calculated.

Before assessing the performance of the model, the model intercept was updated (baseline adjustment)[10] due to the difference in the adverse maternal outcome rates between the fullPIERS (6·5%) and the miniPIERS population (12·5%).[6,11]

Missing data and sensitivity analyses

To be consistent with the fullPIERS study, missing SpO_2 values were imputed with 97%, the population median for women without adverse outcomes.[6]

After imputation of missing SpO2 data, complete case analysis was used to assess model performance in the validation cohort, meaning only women with complete predictor data were included. However, to determine if any bias in the model performance was present due to missing data, sensitivity analyses were carried out using multiple imputations by chained equations (MICE) to generate plausible values for the missing variables.[12-20] More details on the imputation technique are given in the appendix.

We also conducted a sensitivity analysis using data of women admitted with only pre-eclampsia to assess the discriminatory performance of the model in this subgroup.

Performance evaluation in the final validation cohort

The performance of the model was evaluated based on discrimination and calibration ability, and stratification accuracy.[13,14] Discriminative ability was assessed using the AUC ROC and was interpreted using the following criteria: non-informative (AUC ≤ 0·5), poor discrimination (0.5 < AUC ≤ 0·7), good discrimination (AUC > 0·7).[15] Calibration was assessed by estimating the slope on a calibration plot of predicted versus observed outcome rates in each decile of predicted probability.[13] Similar to the AUC ROC, a calibration slope of 1 was interpreted as ideal, >0·5 to

<0·7 as poor, and ≤ 0·5 as non-informative. Calibration was also assessed based on the fit of the model in the validation cohort using the Hosmer-Lemeshow goodness of fit test, in which a *p*-value > 0·05 signifies a good fit between the model and data.[14] The stratification capacity of the model to classify the women into low- and high- risk categories was assessed using a classification table with generated risk groups (defined based on categories established in the model development study).[16,17] The true and false positive rates, negative predictive values (NPVs), and positive predictive values (PPVs) were computed for each group. The Likelihood Ratios (LRs) were calculated for each group using the Deeks and Altman method for a multi-category diagnostic test.[18]

All statistical analyses were performed using R version 3·1·3 (The R Project for Statistical Computing).

Sample size

Simulation studies recommend at least 100 events and 100 non-events for adequate power in validation studies. [19] This number of events was calculated to give 80% power at the 5% significance level. We used this guideline to determine whether we had adequate statistical power in our study.

RESULTS

Description

Of the 2,081 women in the miniPIERS cohort, 261 (12·5%) developed an adverse maternal outcome(s) within 48 hours of hospital admission with a HDP. 757 (36·4%) women had information for all variables in the fullPIERS model and these women were used for this validation study (complete case analysis).

Of the 757 complete cases, 109 (14·4%) women had an adverse maternal outcome(s) within 48 hours of hospital admission. The most common adverse outcomes encountered were blood transfusion (52 women), eclampsia (14 women), and pulmonary oedema (18 women). Other notable outcomes are listed in appendix table S2. There was no case of maternal death recorded in the validation dataset.

Women in the miniPIERS validation cohort vs. the fullPIERS development cohort were different with regards to demographics and pregnancy characteristics (i.e., slightly younger, more often parous, and less likely to be a smoker or have a multiple pregnancy), clinical measures (i.e., lower dipstick proteinuria, lower platelet count, and lower creatinine), interventions (i.e., more likely to receive antenatal corticosteroids, antihypertensive therapy, and $MgSO_4$), and outcomes (i.e., shorter admission to delivery interval, higher infant birth weight but a higher infant mortality before hospital discharge) (Table 1).

Within the miniPIERS validation dataset, women who had adverse outcome (vs. those who did not) were slightly younger, more often nulliparous, and had hypertensive disorders of greater severity, including higher BP, more frequent antihypertensive therapy and $MgSO_4$, early

gestational age at delivery, and lower infant birth weight compared to women without an adverse outcome (Table 2).

Data completeness and imputation analysis

Seven hundred and fifty-seven (36·4%) women (568 pre-eclampsia and 189 with other HDPs) in the miniPIERS dataset had complete fullPIERS variables. All women in the miniPIERS cohort had data for the gestational age at eligibility and chest pain/dyspnoea; missing SpO2 values (1423, 68·3%) were substituted with 97% similar to the fullPIERS model development and multiple imputations were carried out for missing platelet count (1297, 62·3%), serum creatinine (1282, 61·6%), and AST (923, 44·4%). Imputation of missing values did not appear to alter the model performance significantly (Appendix).

External validation

Within 48 hr of eligibility, the fullPIERS model predicted an adverse maternal outcome in the miniPIERS validation cohort with good discriminative performance as indicated by an AUC ROC of 0·77 (95% CI 0·72-0·82) (Figure 1). There was no significant change in the model performance using only cases with pre-eclampsia.

Figure 2 shows the calibration plot of the fullPIERS model when applied to the miniPIERS validation cohort. The calibration performance of the model was poor with a slope of 0·67 and intercept of -0·53 showing underestimation of risk at the lower risk ranges and overestimation of risks at the high risk ranges. The Hosmer-Lemshow test indicated a poor fit of the model's expected outcomes with those observed in the validation cohort ($p<0·05$).[13] Table 3 presents

tabular information about calibration and classification accuracy. In the fullPIERS development cohort, more women (35%) fell into the predicted risk category of <1·0% than any other category, whereas in the miniPIERS complete-case validation cohort, the 5·0-9·9% range was the most common (with 23·5% of women). The majority of women who experienced an adverse outcome in both cohorts were in the predicted risk category of ≥ 0·30 (i.e., 59% for fullPIERS and 50% for miniPIERS). Thus, the model classified a greater proportion of women without outcomes into the middle group, indicating lower stratification accuracy for the low-risk groups although stratification accuracy remained good for the high-risk group in the validation cohort.

Table 4 presents the negative and positive predictive values, and the true and false positive rates for the different risk groups. Using the highest predicted probability cut-off of 0·30, the category into which most women with adverse outcomes fell, the likelihood ratio was moderate at 5·9 (95% CI 4·2-8·4) with a PPV of 50% (95% CI 0·40-0·60). Overall, the negative predictive values remained high (> 90%) across all the risk.

DISCUSSION

Main findings

We externally validated the fullPIERS model using the miniPIERS cohort of women in low-resourced settings for the prediction of adverse maternal outcomes related to the HDP within 48 hr of hospital admission. The model had good discriminative ability with AUC ROC of 0·77 (95% CI 0·72-0·82) within 48 hr of admission, but this was significantly lower than its original performance in the development cohort (AUC ROC 0·88, 95% CI 0·84-0·92). Despite updating the model intercept to account for the baseline differences in adverse outcomes between the development and validation cohorts, the fullPIERS model had a poor fit in the miniPIERS dataset reflected by the poor calibration performance. However, the fullPIERS model performed moderately as a 'rule-in' test in the highest probability risk group with likelihood ratio of 5·9 (95% CI 4·23 – 8·35).[18]

The decrease in the discriminative performance of the model in this study is in contrast with the fullPIERS validation study by Akkermans *et al* which reported a high discriminative performance of the model with AUC ROC of 0·97 (95% CI 0.94-0·99).[8] The study used the PETRA cohort collected in the Netherlands which is similar to the fullPIERS development cohort in that both cohorts were derived from tertiary centres in high-income settings, with similar management for women with HDPs. Compared with our validation cohort and the development cohort, the prevalence of adverse maternal outcomes in their study was also very high (34%).

A possible reason for the decrease in the performance of the fullPIERS model in our study was the heterogeneity between the development cohort and our validation cohort. Differences

between the development cohort and our validation cohort existed in the inclusion criteria, outcome prevalence, data collection settings (high-resourced vs low-resourced countries), and predictor distribution such as AST and platelet count (Table 1). Such low- and middle- income settings as our validation cohort settings are more likely to have more co-morbidity, lower socioeconomic status, less availability of resources and differences in disease management compared to high-income settings (reflected by more co-interventions and the shorter admission-to delivery interval in the validation cohort shown in Table 1). Such factors may result in case-mix differences, and may also alter the effect of the predictors on the outcome.[2,7] Therefore, the extreme predictions observed in the calibration slope may have been as a result of differences in the predictor effects in the validation and development cohort.[10] These factors may have resulted in the reduced performance of the model.[10,13]

Another study by Agrawal and Maitra which assessed the validity of the fullPIERS model in a low income setting reported a high LR (17.53) for ruling out adverse outcomes. [22] However, the rate of adverse outcomes (18.3%) and management of HDPs in their study cohort differed from the fullPIERS development cohort and our cohort. In addition, the study was underpowered and did not report AUC ROC.

Strengths

A strength of our study is that this the first study to externally validate the fullPIERS model in a broader population (in a low-resourced setting with any HDP) using a fully powered sample size. While internal and external validation using a similar patient cohort are important, validating a model in a different geographical setting is needed to evaluate the generalizability of the prediction model in other settings with a more diverse group of patients.[10] This external

validation study conducted using data from LMICs is particularly useful as most of the global burden of mortality and morbidity from the HDPs is borne by low-resourced settings.

The observed LR (5·9) at the highest classification group suggests that the fullPIERS model can be used as a moderate 'rule-in' tool for adverse outcomes from pre-eclampsia and other HDPs in low-resourced settings. For clinical practice in these settings, the recommended predicted probability of 0·3 can also be used as the optimal cut-off point to guide decisions around the need for immediate interventions. Half of the women with an adverse outcome fell in this risk category while the model still maintained a good likelihood ratio at a low false positive rate (7·6%). This has the added advantage of focusing limited resources on those who most need assistance in LMICs.

Limitations

The major limitation of this study is the high proportion of missing values since the miniPIERS data were not originally collected explicitly for the purpose of this study. Using only complete-case analysis can lead to biased estimates of the predictions if the validation subset is not truly representative of the population at risk.[20,21] Imputation of all missing values did not show any significant change in the model performance. Therefore, it unlikely that selection bias contributed significantly to the drop in performance of the fullPIERS model in the complete case analysis compared with the development performance. Even when missing values were excluded, the complete-case analysis had sufficient power (109 outcomes) to externally validate the model as recommended by simulation studies.[19]

Of note, most of the variables were missing since laboratory measurements for pre-eclampsia and the other HDPs are usually ordered based on the severity of other clinical measurements.

This clinical management practice reflects the scarcity of resources in LMIC public hospitals and should draw attention to the need for lower cost point-of-care laboratory measurement techniques for these important laboratory measures. In the validation cohort we demonstrated that there were worse clinical measures and pregnancy outcomes observed in the women with complete laboratory data compared to those with missing laboratory results (appendix table S4). This suggests that clinicians in these settings are able to identify higher risk women based on clinical assessment alone but that there remains a delay in timely intervention, so women continue to experience poor outcomes. Reducing the delay between assessments of laboratory measures and intervening when indicated should improve these women's outcomes.

Perspectives

The fullPIERS model showed moderate utility for the prediction of adverse maternal outcomes in women with HDPs in our validation cohort collected in low-resourced setting hospitals, with some limitations in the lower risk groups. The stratification accuracy and discriminative ability of the fullPIERS model within the highest risk group makes it a valuable tool to aid clinicians in the identification of women at highest risk of adverse outcomes and allow for timely delivery of appropriate interventions such as transfer to a higher level of care for delivery, and administration of antenatal corticosteroids.[3] To determine applicability of the model in other well-resourced settings, future validation studies using more similar cohorts to that in which the model was developed are still needed.[19,22]

Acknowledgements: We are grateful to the members of the miniPIERS working group.[11]

Funding: This study was supported by the Canadian Institutes of Health Research (CIHR operating grants). The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Conflicts of interests: None.

Details of Ethics Approval: This study was approved by the Clinical Research Ethics Board at the University of British Columbia on March 1, 2014 (UBC CREB number: H07-02207).

What was already known about the topic concerned:

The fullPIERS model for predicting adverse maternal outcomes in women with pre-eclampsia performs well in high-income countries.

REFERENCES

1. von Dadelszen P, Magee LA. Pre-eclampsia: An update. *Curr Hypertens Rep*. 2014;16:1-14.

2. Khan KS, Wojdyla D, Say L, Gülmezoglu AM, Van Look PF. WHO analysis of causes of maternal death: A systematic review. *The Lancet*. 2006;367:1066-1074.

3. Magee LA, Pels A, Helewa M, Rey E, von Dadelszen P. Diagnosis, evaluation, and management of the hypertensive disorders of pregnancy. *Pregnancy Hypertension: An International Journal of Women's Cardiovascular Health*. 2014;4:105-145.

4. Hutcheon JA, Lisonkova S, Joseph KS. Epidemiology of pre-eclampsia and the other hypertensive disorders of pregnancy. *Best Practice & Research Clinical Obstetrics & Gynaecology*. 2011;25:391-403.

5. Wulf S, Johns N, Lozano R. Non-fatal burden of maternal conditions: Country-level results from the GBD 2010 study. *Lancet*. 2013;381:149-149.

6. von Dadelszen P, Payne B, Li J, et al. Prediction of adverse maternal outcomes in pre-eclampsia: Development and validation of the fullPIERS model. *The Lancet*. 2011;377:219-227.

7. Payne B. Performance of the fullPIERS model in predicting adverse maternal outcomes in pre-eclampsia using patient data from the PIERS (pre-eclampsia integrated estimate of RiSk) cohort, collected on admission. *BJOG: An International Journal of Obstetrics & Gynaecology*. 2013;120: 113-118.

8. Akkermans J, Payne B, Dadelszen Pv, et al. Predicting complications in pre-eclampsia: External validation of the fullPIERS model using the PETRA trial dataset. *European Journal of Obstetrics & Gynecology and Reproductive Biology*. 2014;179:58-62.

9. Moons KGM, Kengne AP, Grobbee DE, et al. Risk prediction models: II. external validation, model updating, and impact assessment. *Heart*. 2012;98:691-698.

10. Neeman T. Clinical prediction models: A practical approach to development, validation, and updating by ewout W. steyerberg. *International Statistical Review*. 2009;77:320-321.

11. Payne BA, Hutcheon JA, Ansermino JM, et al. A risk prediction model for the assessment and triage of women with hypertensive disorders of pregnancy in low-resourced settings: The miniPIERS (pre-eclampsia integrated estimate of RiSk) multi-country prospective cohort study. *PLoS Medicine*. 2014;11:1-13.

12. Buuren v, Stef, Groothuis-Oudshoorn K. Mice: Multivariate imputation by chained equations in R. *Journal of Statistical Software*. 2011;45:1-67.

13. Steyerberg EW, Vickers AJ, Cook NR, et al. Assessing the performance of prediction models: A framework for traditional and novel measures. *Epidemiology*. 2010;21:128-138.

14. Van Hoorde K, Vergouwe Y, Timmerman D, Van Huffel S, Steyerberg EW, Van Calster B. Assessing calibration of multinomial risk prediction models. *Stat Med*. 2014;33:2585-2596.

15. Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. *Radiology*. 1982;143:29-36.

16. Pepe MS, Feng Z, Janes H, Bossuyt PM, Potter JD. Pivotal evaluation of the accuracy of a biomarker used for classification or prediction: Standards for study design. *J Natl Cancer Inst*. 2008;100:1432-1438.

17. Janes H, Pepe MS, Gu W. Assessing the value of risk predictions by using risk stratification tables. *Ann Intern Med*. 2008;149:751.

18. Deeks JJ, Altman DG. Diagnostic tests 4: Likelihood ratios. *BMJ*. 2004;329:168-169.

19. Vergouwe Y, Steyerberg EW, Eijkemans MJC, Habbema JDF. Substantial effective sample sizes were required for external validation studies of predictive logistic regression models. *J Clin Epidemiol*. 2005;58:475-483.

20. Cummings P. Missing data and multiple imputation. *JAMA Pediatrics*. 2013;167:656-661.

21. Clark T, Altman D. Developing a prognostic model in the presence of missing data: An ovarian cancer case study. *J Clin Epidemiol*. 2003;56:28-37.

22. Royston P, Altman D. External validation of a cox prognostic model: Principles and methods. *BMC MEDICAL RESEARCH METHODOLOGY*. 2013;13:33-33.

NOVELTY AND SIGNIFICANCE

What is new:

- In this article, we have externally validated the fulPIERS model for predicting maternal adverse outcomes from pre-eclampsia using data from multi-settings in LMICs.
- Our study is adequately powered and shows a moderate prediction performance of the model at the pre-recommended predicted probability cut-off of ≥30%.
- We have also assessed the performance of the model after imputation which has not been done by the previous studies. Even upon imputation of missing values, the model still identified high risk women moderately.

What is relevant:

- Hypertension in pregnancy is a major contributor to maternal morbidity and mortality, especially in LMICs. Identifying the women at highest risk of adverse maternal outcome from HDPs is crucial in the settings to avert severe complications.

Summary:

- This study supports the existing literature and provides evidence that the fullPIERS model might be a useful tool in low-resourced settings. This finding is important to aid in reducing maternal morbidity and mortality resulting from HDP in such areas where these events occur the most.

Figures legend:

- Figure 1: Receiver operating characteristic curve for performance of the fullPIERS model in predicting adverse maternal outcome in the miniPIERS (complete-case) cohort within 48hr after admission.
- Figure 2: Calibration plot of the fullPIERS model performance in the miniPIERS (complete-case) cohort.

Table 1. Maternal characteristics within 48 hours of eligibility for the development (fullPIERS) and validation (complete-case miniPIERS) cohorts† (N (%) or median [interquartile range])

Characteristics	miniPIERS cohort (complete cases, validation) (757 women)	fullPIERS cohort (development) (2,023 women)	*p*-Value *
DEMOGRAPHICS & PREGNANCY CHARATERISTICS			
Maternal age at EDD (yr)	28 [24, 33]	31 [27, 36]	<0·0001
Parity ≥1	406 (53·6%)	581 (28·7%)	<0·0001
Gestational age at eligibility (wk)†	36·6 [33·1, 38·1]	36 [33, 38·3]	0·43
Multiple pregnancy	18 (2·4%)	192 (9·5%)	<0·0001
Smoking in this pregnancy	48 (6·3%)	249 (12·3%)	<0·0001
CLINICAL MEASURES			
Systolic BP (mm Hg)	160 [150, 170]	160 [150, 176]	0·58
Diastolic BP (mm Hg)	100 [100, 110]	102 [97·8, 110]	0·53
Worst dipstick proteinuria	+2 [+1, +3]	+2 [+1, +4]	<0·0001
Chest pain/dyspnoea†	30 (4·0%)	90 (4·4%)	0·65
Lowest platelet count ($\times 10^9$ per L)†	187 [150, 231]	192 [150, 241·5]	0·04
Highest AST (U/L)†	30 [20, 35]	28 [21, 41]	0·51
INTERVENTIONS DURING ADMISSION			
Corticosteroids	253 (33·4%)	550 (27·2%)	<0·0001
Antihypertensive therapy	704 (92·9%)	1381 (68·3%)	<0·0001
$MgSO_4$	376 (49·7%)	690 (34·1%)	<0·0001
PREGNANCY OUTCOMES			
Admission-to-delivery interval, GA <34 weeks (d)	1 [1, 3]	2 [1, 5]	0.0029
Gestational age at delivery (wk)	37·1 [34·4, 38·6]	36.9 [34·1, 38·6]	0·15
Birth weight (g)	2500 [1896, 2433]	2141 [1441, 2807]	<0·0001
Infant death (before discharge)	26 (3·4%)	26 (1·3%)	<0·0001

AST (aspartate aminotransferase), BP (blood pressure), EDD (estimated date of delivery), $MgSO_4$ (magnesium sulphate)

** p-Values calculated using chi-squared test for categorical variables and Mann-Whitney U for continuous variables.*

† Variables included in the model

Table 2. Demographics of the 757 women in the miniPIERS complete-case validation cohort according to the occurrence of the adverse maternal outcomes (N (%) women or median [interquartile range])

Characteristics	Women with an adverse outcome (109 women)	Women without an adverse outcomes (648 women)	*p*-Value *
DEMOGRAPHICS			
Maternal age at EDD (yr)	27 (±5·82)	29 (±6·46)	0·03
Parity ≥1	46 (42·2%)	360 (55·6%)	0·01
Gestational age at eligibility (wk)	36·5 [31·3, 37·9]	36.6 [33·4, 38·2]	0·16
Multiple pregnancy	1 (0·9%)	17 (2·6%)	0·49
Smoking in this pregnancy	4 (3·7%)	44 (6·8%)	0·29
CLINICAL MEASURES (WITHIN 24 HR OF ELIGIBILITY)			
Systolic BP (mm Hg)	170 [156, 190]	151 [145, 170]	<0·0001
Diastolic BP (mm Hg)	110 [107, 120]	100 [100, 110]	<0·0001
Worst dipstick proteinuria	+3 [+2, +3]	+2 [+0.5, +3]	0·84
INTERVENTIONS AT ANY TIME DURING ADMISSION			
Corticosteroids	35 (32·1%)	218 (33·6%)	0·09
Antihypertensive therapy	106 (97·2%)	598 (92·3%)	<0·0001
$MgSO_4$	83 (76·1%)	293 (45·2%)	<0·0001
PREGNANCY OUTCOMES			
Admission-to-delivery interval (d)	1 [1, 1]	2 [1, 5]	<0·0001
GA on delivery (wk)	36·6 [31·3, 38·1]	37·1 [34·7, 38·1]	<0·0001
Birth weight (g)	2390 [1380, 2820]	2500 [1950, 3000]	<0·0001
Infant death before discharge	4 (3·7%)	22 (3·4)	0·78

AST (aspartate aminotransferase), BP (blood pressure), EDD (estimated date of delivery), $MgSO_4$ (magnesium sulphate)

** p-Values calculated using chi-squared test for categorical variables and Mann-Whitney U for continuous variables.*

Table 3. Distribution of women with and without an adverse maternal outcome within 48h across categories of the predicted scores in the development and validation cohorts (N (%) women)

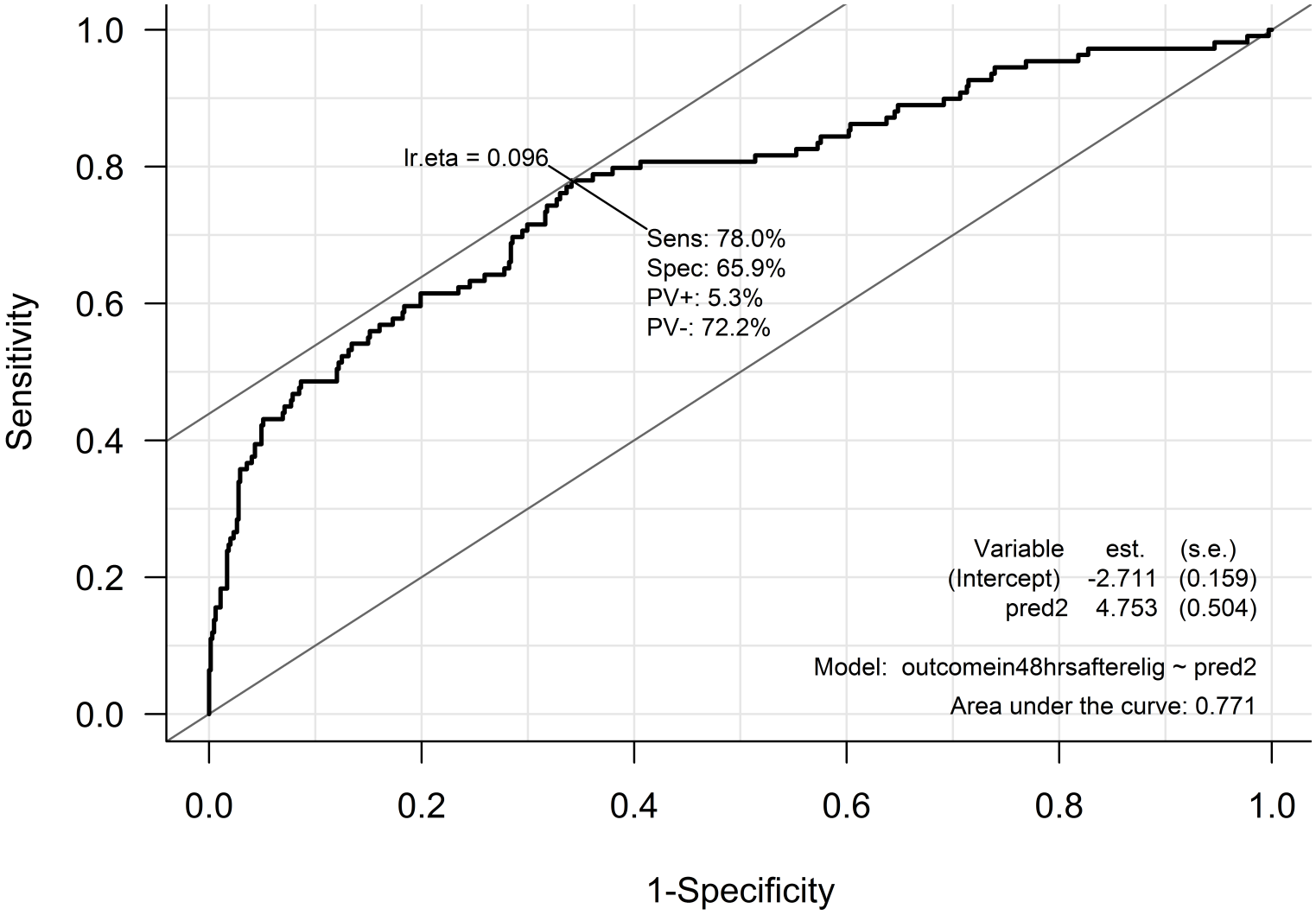
	N women in range		N women with outcome	
Prediction score range	**fullPIERS development cohort (1,935 women)**	**miniPIERS complete case validation cohort (757 women)**	**fullPIERS development cohort (98 women)**	**miniPIERS complete case validation cohort (109 women)**
0-0·99%	671 (34·7%)	30 (4·0%)	3 (0·4%)	2 (6·7%)
1·0-2·4%	586 (30·3%)	107 (14·1%)	11 (1·9%)	3 (2·8%)
2·5-4·9%	314 (16·2%)	140 (18·5%)	9 (2·9%)	12 (8·6%)
5·0-9·9%	160 (8·3%)	178 (23·5%)	8 (5·0%)	8 (4·5%)
10·0-19·0%	98 (5·1%)	157 (20·9%)	14 (14·3%)	26 (16·6%)
20·0-29·9%	32 (1·7%)	47 (6·1%)	9 (28·3%)	9 (19·2%)
≥30·0%	74 (3·8%)	98 (12·9%)	44 (59·5%)	49 (50%)

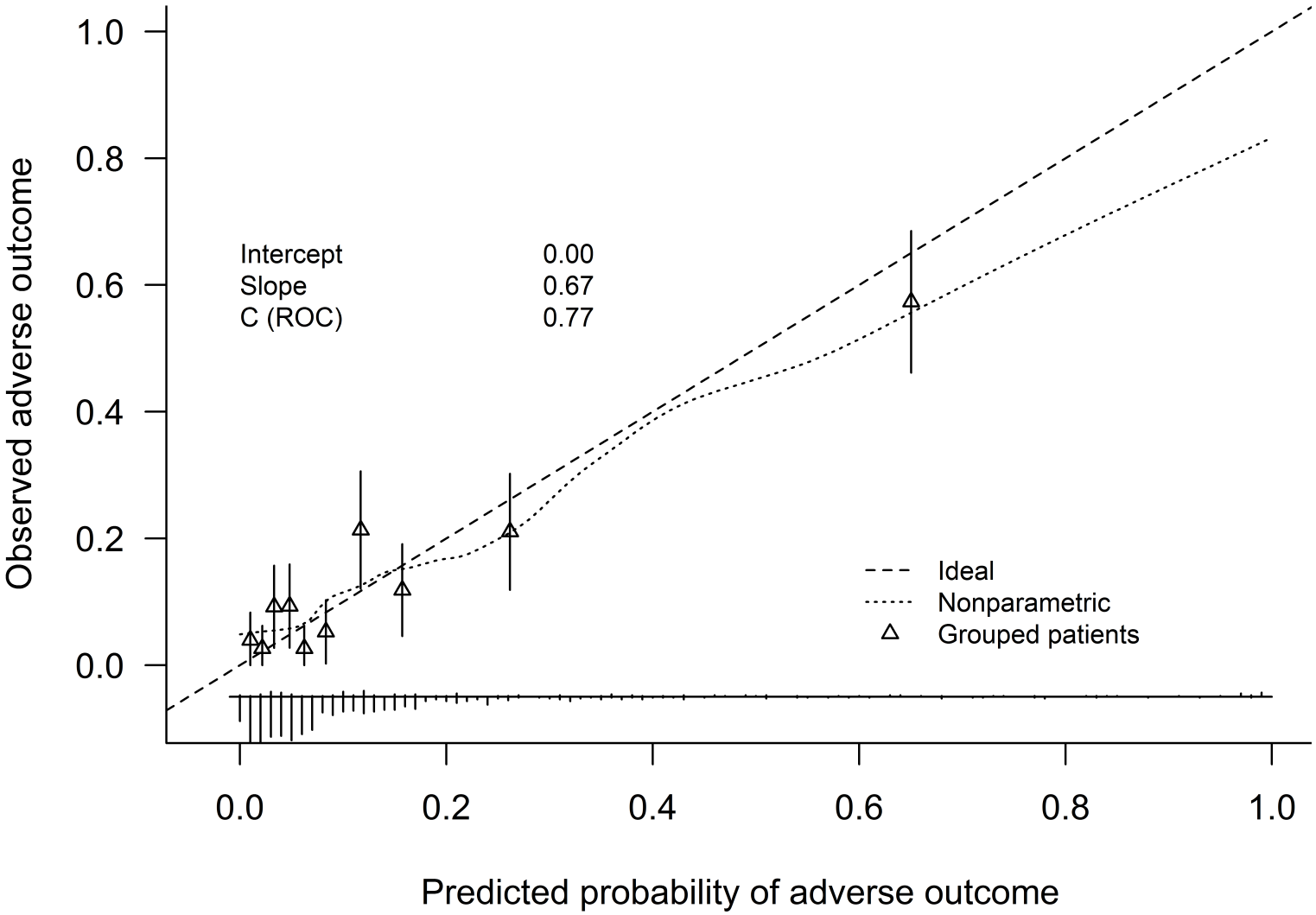
Table 4. Risk stratification table to assess the performance of the fullPIERS model for predicting maternal outcome at varying predicted probability cut-off values within 48h.

Prediction score range	n observed Events/n in Range (%) [95% CI]	LR [95% CI]	NPV (%) [95% CI]	PPV (%) [95% CI]	*True positive rate (%) [95% CI]	False positive rate (%) [95% CI]
1·0-2·4%	2.8 [0.96-7.92]	0·17 [0·06-0·53]	93 [0·76-0·99]	15 [0·12-0·18]	98 [0·93- 0·99]	95·6 [0·94-0·97]
2·5-4·9%	8.6 [4.97-14.38]	0·56 [0·32-0·97]	96 [0·91-0·99]	17 [0·14-0·20]	95·4 [0·89-0·98]	79·6 [0·76- 0·83]
5·0-9·9%	4.5 [2.29-8.61]	0·28 [0·14-0·55]	94 [0·90-0·96]	19 [0·16-0·23]	84·4 [0·76-0·90]	59·9 [0·56-0·64]
10·0-29·9%	16.6 [11.56-23.16]	1·23 [0·91-1·67]	95 [0·92-0·96]	28 [0·23-0·33]	77·1 [0·68-0·84]	33·6 [0·30-0·37]
≥30·0%	50.0 [40.29-59.71]	5·9 [4·23-8·35]	91 [0·88-0·93]	50 [0·40-0·60]	45 [0·36-0·55]	7·6 [0·06-0·10]

LR, Likelihood ratios; PPV, positive predictive value; NPV, negative predictive value.

**True positive rate (or Sensitivity), false positive rate (1-Specificity)*


1.0
0.8
0.6
0.4
0.2
0.0
Sensitivity
lr.eta = 0.096
Sens: 78.0%
Spec: 65.9%
PV+: 5.3%
PV-: 72.2%
Variable est. (s.e.)
(Intercept) -2.711 (0.159)
pred2 4.753 (0.504)
Model: outcomein48hrsafterelig ~ pred2
Area under the curve: 0.771
0.0
0.2
0.4
0.6
0.8
1.0
1-Specificity


Observed adverse outcome
1.0
0.8
0.6
0.4
0.2
0.0
Intercept 0.00
Slope 0.67
C (ROC) 0.77
Ideal
Nonparametric
Grouped patients
0.0
0.2
0.4
0.6
0.8
1.0
Predicted probability of adverse outcome