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Predicting complications in pre-eclampsia: external validation of the fullPIERS model using the PETRA trial dataset

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ABSTRACT

Objective: The internally validated fullPIERS model predicts adverse maternal outcomes in women with pre-eclampsia within 48 h after eligibility. Our objective was to assess generalizability of this prediction model.

Study design: External validation study using prospectively collected data from two tertiary care obstetric centers.

Methods: The existing PETRA dataset, a cohort of women ($n = 216$) with severe early-onset pre-eclampsia, eclampsia, HELLP syndrome or hypertension-associated fetal growth restriction was used. The fullPIERS model equation was applied to all women in the dataset using values collected within 48 h after inclusion. The performance (ROC area and R-squared) of the model, risk stratification and calibration were assessed from 48 h up to a week after inclusion.

Results: Of 216 women in the PETRA trial, 73 (34%) experienced an adverse maternal outcome(s) at any time after inclusion. Adverse maternal outcome was observed in 32 (15%) cases within 48 h and 62 (29%) within 7 days after inclusion. The fullPIERS model predicted adverse maternal outcomes within 48 h (AUC ROC 0.97, 95% CI: 0.87–0.99) and up to 7 days after inclusion (AUC ROC 0.80, 95% CI: 0.70–0.87).

Conclusions: The fullPIERS model performed well when applied to the PETRA dataset. These results confirm the usability of the fullPIERS prediction model as a 'rule-in' test for women admitted with severe pre-eclampsia, eclampsia, HELLP syndrome or hypertension-associated fetal growth restriction. Future research should focus on intervention studies that assess the clinical impact of strategies using the fullPIERS model.

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Introduction

Hypertensive disorders, such as pre-eclampsia, gestational hypertension and chronic hypertension are frequent complications of pregnancy [1,2] and occur in 5–8% of all pregnancies [3]. In general, the course of these disorders is self-limiting and mild [4]. However, a subgroup of women, approximately 2.5%, experience an adverse maternal outcomes (such as death, stroke, or liver rupture) and/or perinatal outcomes (such as permanent infant handicap or learning disabilities).

Despite the many known risk factors for adverse maternal or perinatal outcomes, risk assessment is poorly quantified and knowledge on mutual dependence of risk factors is limited [5]. Because of the potentially severe consequences of adverse outcomes, many non-evidence based treatment strategies, such as iatrogenic preterm delivery, are applied to large numbers of women.

There is a need for a method to predict adverse outcomes in pre-eclampsia to allow for discrimination of women who need

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immediate transfer to a high-care facility and delivery, from those who may receive temporising management. To meet this need, several prediction models have been developed. Amongst them is the fullPIERS model [6], a promising model that stratifies risk for adverse maternal outcomes within 48 h of eligibility in women with pre-eclampsia. The model was generated from a prospectively followed cohort of 2023 women. After state-of-the-art evaluation, six predictor variables were selected: gestational age, presence of chest pain or dyspnoea, oxygen saturation (SpO_2), platelet count, serum creatinine and serum AST to generate a probability of adverse maternal outcomes. Some weaknesses of this model have been described [7] and the clinical applicability is not yet fully established. Internal validation of the prediction model was promising [6]. The next required step in model evaluation is external validation in a different population to assess the generalizability of the model [8].

Materials and methods

Subjects

For the external validation of the fullPIERS model, we used an existing dataset from The Netherlands ($n = 216$). The cohort used for this analysis was derived from the Pre-eclampsia Eclampsia TRial Amsterdam (PETRA) [9], a randomized trial of temporizing management, with or without plasma volume expansion, in women with HELLP syndrome, severe pre-eclampsia, eclampsia, or hypertension-related fetal growth restriction and gestational ages between 24 and 34 weeks of pregnancy ($n = 216$). Women were enrolled in the Department of Obstetrics at the Academic Medical Center ($n = 118$) and the VU University Medical Center ($n = 98$), Amsterdam, The Netherlands, between April 2000 and May 2003. Both are university hospitals that provide tertiary care for a community of approximately 2.5 million inhabitants with diverse cultural and geographical backgrounds. Women were eligible for inclusion in PETRA if they met at least one of the following inclusion criteria: HELLP syndrome (defined as haemolysis, elevated liver enzymes, low platelets, with or without hypertension, and proteinuria); severe pre-eclampsia (diastolic blood pressure (DBP) $\geq$110 mm Hg and proteinuria $\geq$0.3 g per 24 h); eclampsia (generalised convulsions in pregnancy not caused by epilepsy); or fetal growth restriction (estimated fetal weight $<$10th centile) with pregnancy induced hypertension (PIH, DBP $\geq$90 mm Hg with the absence of proteinuria). Relevant exclusion criteria were absence of consent, signs of fetal distress or maternal disease demanding immediate delivery, or a pre-existing diagnosis of a lethal fetal congenital abnormality.

Data collection

Data for the PETRA trial were collected prospectively. For the purpose of this study, further retrospective data collection was performed by one author (JA) to reduce the amount of missing fullPIERS model parameters in the dataset and to recode adverse maternal outcomes according to the fullPIERS definition. This process was finished before data analysis and the author was unaware of the model parameters of the subject while screening their charts for adverse outcome parameters and vice versa. All data handling and analysis procedures were similar to the original fullPIERS-paper. Values recorded in the first 48 h after inclusion in the PETRA trial were included for analysis. If data were missing, the method of last observation carried forward was used. Preceding observations recorded within two weeks for laboratory values, and within 12 h prior to inclusion for clinical assessments, were regarded as current data.

The model

A predicted probability for combined adverse maternal outcome was calculated for each woman in the dataset by means of published fullPIERS model equation [6].

Adverse outcome

Adverse maternal outcome was defined in accordance with the definition for combined adverse maternal outcome in the fullPIERS model development study [6]. Complications of HELLP were included as outcomes, not the diagnosis or recurrence of HELLP. Recurrent eclampsia was used as an outcome among women who were included with eclampsia.

Statistical analysis

Performance of the fullPIERS model was assessed by limiting predictor variables to the worst values of the available data within 48 h of admission (e.g. lowest platelet count, highest AST level etc.). These values were used for predicting combined adverse maternal outcome within 48 h and up to 7 days after inclusion, by applying the fullPIERS prediction equation.

We aimed to analyse whether fullPIERS probability differed according to the treatment randomization allocation in the PETRA trial by chi-square testing; if no significant difference could be detected, both allocation groups would be combined for further analysis.

Stratification capacity, calibration ability and classification accuracy were evaluated using a risk stratification table [10] in order to assess the models capability to distinguish between high- and low-risk women and its performance in predicting maternal complications.

The area under the curve (AUC) of the receiver operating characteristics curve (ROC) with 95% confidence intervals was calculated for combined adverse maternal outcome within 48 h and up to 7 days after inclusion, with 24 h intervals. AUC ROC was interpreted using five categories: non-informative ($AUC = 0.5$); poor accuracy ($0.5 < AUC \geq 0.7$); moderate accuracy ($0.7 < AUC \geq 0.9$); high accuracy ($0.9 < AUC < 1$); and perfect accuracy ($AUC = 1$) [11].

Likelihood ratios were calculated according to the method of Deeks and Altman [12] for a multicategory diagnostic test. This method allows the calculation of likelihood ratios for each risk group individually, and is not directly related to the sensitivity and specificity of the dichotomised test result. The following categories for the interpretation of the likelihood ratios were used: informative (LR $<$0.1 or $>$10); moderately informative (LR 0.1–0.2 or 5–10); and non-informative (LR 0.2–5.0).

Calibration was assessed by estimating the slope of the linear predictor resulting from application of the fullPIERS model to the study data; this is termed the calibration slope. A model with perfect calibration should result in a slope equal to 1.0 [13]. Further assessment of model calibration was performed by adjusting the intercept of the fullPIERS model to reflect the difference in prevalence of outcome in the current dataset compared to the original dataset used for model validation and re-estimating the calibration slope as previously described.

ROC curve analyses were performed with SPSS (IBM SPSS Statistics 20 for Windows, released 2011, Armonk, NY, USA: IBM) we used MS Excel (Microsoft Excel 2007 for Windows, released 2007, Redmond, WA, USA: Microsoft) to generate risk stratification tables.

Results

Between April 1, 2000, and May 31, 2003, a total of 216 women were randomized as part of the PETRA trial, 111 to plasma volume

Table 1
PIERS prediction in both PETRA arms, plasma volume expansion (PVE) versus standard care.

	PVE ($n = 111$)	Control ($n = 105$)	*P*-value
Adverse outcome within 48 h	16 (14%)	16 (15%)	
Adverse outcome at any time	36 (32%)	37 (35%)	
fullPIERS probability median (IQR)	0.029 (0.015–0.090)	0.031 (0.014–0.141)	0.696
fullPIERS probability mean (SE)	0.119 (0.020)	0.158 (0.025)	

IQR: Interquartile range, SE: standard error. *P*-value by Mann–Whitney *U* test.

expansion and 105 to no plasma volume expansion (control group). There was no between-group difference in the fullPIERS probability of adverse maternal outcome (Table 1). As such, the data for the two groups were combined into one PETRA cohort for this external validation study of the fullPIERS model.

Of the 216 women in PETRA, 73 (34%) experienced an adverse maternal outcome(s) after inclusion. Table 2 shows that women with an adverse outcome were slightly younger statistically. Most were nulliparous and enrolled at a gestational age of ~30 weeks. Ninety-five women were diagnosed with severe pre-eclampsia, 54 women had HELLP-syndrome, 123 women met the criteria for fetal growth restriction and five suffered from eclampsia. Most women had moderate to severe hypertension. Women who developed an adverse maternal outcome(s) had a lower platelet count and higher AST within the first 48 h of admission, during which time they were less likely to be treated with antihypertensive therapy and more likely to be treated with magnesium sulphate, although only 58% of them received this. The median prolongation of the pregnancy after inclusion was 8 days and pregnancy outcome was otherwise similar.

For all participants in PETRA, successful collection of the missing fullPIERS model predictor variables and adverse outcomes was achieved by reviewing their charts. The only variable that was often irretrievable was oxygen saturation; in 194 (90%) cases, oxygen saturation was imputed with the value of 97% as was done in the fullPIERS model development by von Dadelszen et al [6].

An adverse maternal outcome was observed in 32 (15%) PETRA cases within 48 h, 62 (29%) within 7 days, and 73 cases (34%) at any time after inclusion in PETRA. The most common adverse maternal outcomes were thrombocytopenia (platelet count $<50 \times 109$, 21 (10%) within 48 h and 30 (14%) within 7 days), blood transfusion (5 (2%) within 48 h and 11 (5%) within 7 days), ≥50% fraction of inspired oxygen (FiO_2) (4 (13%) within 48 h and 11 (11%) within 7 days) and pulmonary oedema (2 (6%) within 48 h and 8 (13%) within 7 days). None of the following outcomes occurred: Glasgow Coma Score <13, stroke, transient ischaemic attack, cortical blindness, positive inotropic support, infusion of a third parenteral antihypertensive drug, myocardial ischaemia, intubation or dialysis.

Of all women in PETRA, 194 (90%) had pregnancy prolongation of at least 48 h after inclusion, and 119 (55%) women had pregnancy prolonged by at least 7 days. Thirty-four women had an adverse outcome leading to delivery within 1 day of occurrence. In 6 cases the adverse maternal outcome occurred after delivery ranging from 1 to 5 days post-partum.

Within 48 h of admission, the fullPIERS model predicted adverse maternal outcome with high accuracy (AUC ROC 0.97, 95% CI: 0.94–0.99), with a positive predictive value (PPV) of 70.7% (95% CI: 54.2–84.0) and a negative predictive value (NPV) of 98.3% (95% CI: 95.1–99.6). Up to 7 days after inclusion, the model predicted adverse outcome with moderate accuracy (AUC ROC 0.80, 95% CI: 0.72–0.87), with a PPV of 32.2% (95% CI: 25.3–39.7) and a NPV of 85.7% (95% CI: 71.5–94.6) (Fig. 1).

As shown in Table 3, fullPIERS successfully stratified the PETRA population into clinically relevant risk categories. For prediction of adverse maternal outcome within 48 h after admission, 157 (72%) women were classified into a low-risk group (predicted probability <10%); two had an adverse maternal outcome (NPV 98%). Twenty-nine (13%) were stratified into the highest risk group (predicted probability ≥30%), 26 of whom had an adverse outcome (PPV 90%). For prediction of an adverse maternal outcome within 7 days after admission, the fullPIERS model maintained a high PPV (93%) and a modest NPV of 87% using the same cut-off values for high- and low risk groups. We calculated the post-test probability for women in the high risk group with a predicted probability of ≥0.30 using the observed prevalence in our cohort. For prediction of an adverse outcome within 48 h post-test probability was 89% and for prediction within 7 days the post-test probability was 93%.

Table 2
Baseline characteristics of the women in the PETRA trial. Comparison of women who had an adverse outcome at any time after admission and women without an adverse outcome.

	Women with adverse outcomes ($n = 73$)	Women without adverse outcomes ($n = 143$)	*P*-value
Demographic characteristics			
Maternal age at EDD (years)	28 (26–32)	31 (27–35)	0.04
Gestational age at inclusion (weeks)	29.3 (27.1–31.3)	30.3 (27.6–31.4)	0.15
Gestational age <32 weeks	61 (84%)	112 (78%)	0.36
Parity ≥1	18 (25%)	47 (33%)	0.09
Clinical measures within 48 h after inclusion			
Mean arterial pressure (mm Hg)	120 (110–127)	123 (113–130)	0.50
Systolic blood pressure (mm Hg)	160 (140–160)	160 (145–170)	0.32
Diastolic blood pressure (mm Hg)	100 (95–110)	105 (95–110)	0.15
Lowest platelet count ($\times 10^9$/L)	88 (41–185)	187 (122–242)	<0.01
Highest aspartate transaminase (U/L)	98 (28–270)	26 (19–52)	<0.01
Interventions			
Corticosteroids administration	55 (75%)	98 (69%)	0.29
Antihypertensive drugs administered	52 (71%)	119 (83%)	0.04
$MgSO_4$ administered	42 (58%)	47 (33%)	<0.01
Pregnancy outcomes			
Admission-to-delivery interval, all cases (days)	8 (4–14)	8 (4–16)	0.84
Gestational age at delivery (weeks)	30.6 (29.3–32.3)	31.5 (28.9–33.3)	0.15
Birth weight (g)	1170 (860–1436)	1232 (832–1556)	0.77
Intrauterine fetal death	6 (8%)	14 (10%)	0.70
Neonatal death	5 (7%)	13 (9%)	0.57

Data are median (IQR) or number (%), EDD: expected date of delivery.

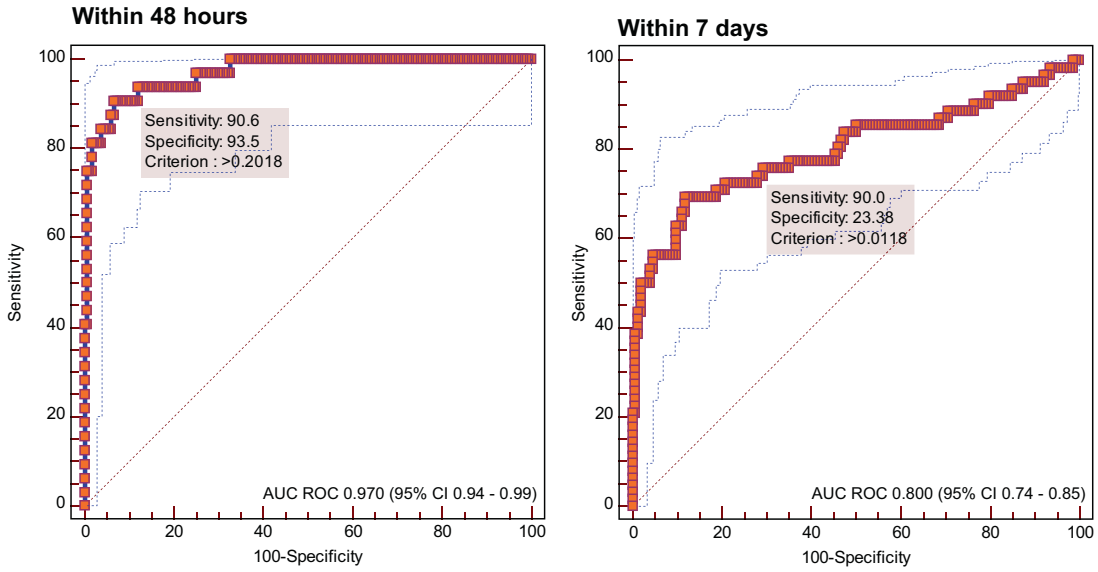

Fig. 1. Receiver operating characteristic (ROC) curves. Performance of the fullPIERS model in the PETRA dataset. Predicting adverse outcome within 48 h and within 7 days using predictor values from the first 48 h after admission.

The calibration slope of the original fullPIERS model applied to the PETRA data used in this study was estimated to be 1.69 (95% CI: 110–228), reflecting poor calibration of the model in this dataset. When the fullPIERS model was adjusted to account for differences in the underlying prevalence of maternal outcomes in this study population, as compared with the original population used for model development, the calibration slope was estimated to be 1.67 (95% CI: 109–226).

Comments

Before adopting a new prediction model, it is important to evaluate its validity in two ways [14]. First, one should evaluate the performance of the model among patients not included in the development model but drawn from a similar population through internal validation in order to correct for overestimation of the initial model [15]. Second, to evaluate generalizability, the accuracy and calibration of the model's predictions should be validated in a new patient population with the same disease but with different enrolment methods and patient characteristics, a process known as external validation [16].

Main Findings

We externally validated the fullPIERS model in an existing cohort of women with severe early-onset hypertensive disorders with placental insufficiency. In this cohort, the model performed better than in the development cohort. Specifically, the AUC ROC for the 48 h outcome time point was 0.97 (95% CI: 094–099), higher than the 0.88 (95% CI: 084–092) seen in the fullPIERS model development study; this shows better discrimination of the model in this cohort. The likelihood ratios for the model as a predictor of an adverse maternal outcome in 48 h were also improved in this cohort. Calibration of the model was less optimistic in this cohort even after adjusting for differences in outcome prevalence in the external validation dataset; this error in calibration suggests overfitting of the model to the original dataset but it is not felt to be significant as the other performance measures demonstrate

Table 3
Risk stratification, assessing fullPIERS performance by predicted probability of adverse maternal outcome within 48 h and 7 days.

Predicted probability	Number of women (%)	Number of women with outcome (%)	Number of women without outcome (%)	LR	95% CI	Post-test probability
Prediction of a complication within 48 h						
0.00–0.0099	37 (17%)	0 (0%)	37 (100%)	0	0.000–1.234	
0.010–0.024	59 (27%)	0 (0%)	59 (100%)	0	0.000–0.768	
0.025–0.049	34 (16%)	1 (3%)	33 (97%)	0.17	0.024–1.229	
0.050–0.099	27 (13%)	1 (4%)	26 (96%)	0.22	0.031–1.573	
0.10–0.19	17 (8%)	1 (6%)	16 (94%)	0.35	0.049–2.616	
0.20–0.29	13 (6%)	3 (23%)	10 (77%)	1.72	0.502–5.928	
≥0.30	29 (13%)	26 (90%)	3 (10%)	49.83	16.024–154.981	89.0%
Total	216	32	184			
Prediction of a complication within 7 days						
0.00–0.0099	37 (17%)	6 (16%)	31 (84%)	0.48	0.211–1.095	
0.010–0.024	59 (27%)	7 (12%)	52 (88%)	0.33	0.161–0.695	
0.025–0.049	34 (16%)	4 (12%)	30 (88%)	0.33	0.122–0.901	
0.050–0.099	27 (13%)	4 (15%)	23 (85%)	0.43	0.156–1.198	
0.10–0.19	17 (8%)	6 (35%)	11 (65%)	1.35	0.524–3.503	
0.20–0.29	13 (6%)	8 (62%)	5 (38%)	3.97	1.353–11.677	
≥0.30	29 (13%)	27 (93%)	2 (7%)	33.53	8.221–136.766	92.9%
Total	216	62	154			

LR: Likelihood ratio, CI: confidence interval.

maintenance of clinical utility in this cohort. The stratification table (Table 3) shows that for prediction of an adverse outcome within 48 h. The model performs well both as a 'rule-in' test (with high likelihood ratios in the higher probability stratification groups) and a 'rule-out' test (with low likelihood ratios and high NPVs in the lower probability stratification groups).

Strengths and limitations

An important strength of the PETRA trial population is the homogeneity resulting in similar adverse maternal outcomes after treatment in two tertiary care centers. Also, the rate of an adverse maternal outcome was higher than in PIERS, yet, the model still had a high NPV that will aid clinicians in establishing which women with 'severe' pre-eclampsia by diagnostic criteria: (i) are not likely to become acutely ill within the next 48 h and as such, their pregnancies can be prolonged to allow for maximal effect of antenatal corticosteroids remote from term, or (ii) can be managed in their home maternity unit.

A possible limitation of our study is the secondary and retrospective nature of the analysis. First, data from PETRA were not explicitly collected for the purpose of validating a prediction model. Consequently, there were discrepancies between the adverse maternal outcome definitions used in PETRA and those used in the fullPIERS model; the impact of this limitation was minimized by retrospectively reviewing all women's medical records to make sure outcomes were coded according to definitions used in the fullPIERS study. It needs to be stressed, however, that almost all data were acquired in a meticulously maintained database as a part of a prospective study. Importantly, the model was not in use during this study, and as such, did not influence the management or outcomes, thus minimising the 'intervention paradox' that sometimes complicate studies of the prediction of an adverse outcomes.

Another limitation is our small sample size. However, PETRA enrolled a high-risk hypertensive population among whom adverse maternal outcome rates were high (34%) compared to the fullPIERS population (13%), leading to sufficient power to give reasonable estimates of model performance. Although higher prevalence is associated with higher PPV, which we observed, higher prevalence is also associated with lower NPV; yet, our NPV was still good; this strengthens the application of the PIERS model as a 'rule-out' test.

Interpretation

The fullPIERS model has the potential to be a useful clinical tool for stratifying women with pre-eclampsia into low- and high-risk groups for the development of an adverse maternal outcome.

Future research should focus on the model's ability to predict adverse maternal outcome when the model is used in sequential risk assessment as is done in clinical practice during pregnancy prolongation (temporizing care), as well as in a less severe population of women with a hypertensive disorder of pregnancy. Also, can the model predict an adverse perinatal outcome, a critical ability required to balance maternal risk. Finally, the impact on outcomes of fullPIERS model implementation into clinical practice must be examined, ideally in a RCT.

Conclusion

The fullPIERS model performed well in a subgroup of women with severe hypertensive disorders of pregnancy. It achieved a high level of accuracy with an AUC ROC of 0.97 for the prediction of an adverse maternal outcome within 48 h of eligibility, and maintained moderate level of accuracy while predicting combined adverse maternal outcome up to one week after eligibility with an AUC ROC of 0.80. These results strengthen the usability of the fullPIERS prediction model as 'rule-in' test for women admitted with severe pre-eclampsia, eclampsia and HELLP syndrome.

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