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

Joost Akkermans [a,*], Beth Payne [d,f], Peter von Dadelszen [d,f], Henk Groen [b], Johanna de Vries [c], Laura A Magee [d,e,f], Ben Willem Mol [g], Wessel Ganzevoort [a]

[a] Departments of Obstetrics and Gynecology, University of Amsterdam, Academic Medical Center, Amsterdam, The Netherlands
[b] Department of Epidemiology, University of Groningen, University Medical Center, Groningen, The Netherlands
[c] Departments of Obstetrics and Gynaecology, VU University Medical Center, Amsterdam, The Netherlands
[d] Departments of Obstetrics and Gynecology, University of British Columbia, Vancouver, Canada
[e] Department of Medicine, University of British Columbia, Vancouver, Canada
[f] The Child and Family Research Institute, University of British Columbia, Vancouver, Canada
[g] The Robinson Institute, School of Paediatrics and Reproductive Health, University of Adelaide, Adelaide, Australia

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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.

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

* Corresponding author at: University of Amsterdam, Obstetrics and Gynaecology, Academic Medical Center, Amsterdam, The Netherlands. Tel.: +31 627011117.
E-mail address: j.akkermans@me.com (J. Akkermans).

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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