

Prediction of adverse maternal outcomes in pre-eclampsia: development and validation of the fullPIERS model

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Summary

Background Pre-eclampsia is a leading cause of maternal deaths. These deaths mainly result from eclampsia, uncontrolled hypertension, or systemic inflammation. We developed and validated the fullPIERS model with the aim of identifying the risk of fatal or life-threatening complications in women with pre-eclampsia within 48 h of hospital admission for the disorder.

Methods We developed and internally validated the fullPIERS model in a prospective, multicentre study in women who were admitted to tertiary obstetric centres with pre-eclampsia or who developed pre-eclampsia after admission. The outcome of interest was maternal mortality or other serious complications of pre-eclampsia. Routinely reported and informative variables were included in a stepwise backward elimination regression model to predict the adverse maternal outcome. We assessed performance using the area under the curve (AUC) of the receiver operating characteristic (ROC). Standard bootstrapping techniques were used to assess potential overfitting.

Findings 261 of 2023 women with pre-eclampsia had adverse outcomes at any time after hospital admission (106 [5%] within 48 h of admission). Predictors of adverse maternal outcome included gestational age, chest pain or dyspnoea, oxygen saturation, platelet count, and creatinine and aspartate transaminase concentrations. The fullPIERS model predicted adverse maternal outcomes within 48 h of study eligibility (AUC ROC 0.88, 95% CI 0.84–0.92). There was no significant overfitting. fullPIERS performed well (AUC ROC >0.7) up to 7 days after eligibility.

Interpretation The fullPIERS model identifies women at increased risk of adverse outcomes up to 7 days before complications arise and can thereby modify direct patient care (eg, timing of delivery, place of care), improve the design of clinical trials, and inform biomedical investigations related to pre-eclampsia.

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Introduction

Pre-eclampsia, more than being proteinuric gestational hypertension alone, is a state of exaggerated systemic inflammation and remains a leading direct cause of maternal morbidity and mortality worldwide.¹ Reduction of the burden of illness associated with pre-eclampsia² will address in part the aims of Millennium Development Goal 5.^{3,4} In high-income countries, this excess maternal morbidity and mortality relates to both uncontrolled hypertension and the pulmonary and hepatic consequences of systemic inflammation.^{5,6} The only cure for pre-eclampsia is delivery. For pre-eclampsia arising remote from term, supportive and temporising measures (expectant management) are used to improve perinatal outcomes. However, the magnitude of the maternal risks associated with expectant management is unclear.¹ The perinatal benefits of expectant management near term are even less clear.¹ Concerns around maternal risk have caused experts to hesitate in recommending expectant management either remote from or close to term.¹ At term, maternal benefits derive from a policy of effecting delivery.⁷

The best method of risk assessment in pre-eclampsia pregnancies being managed expectantly or during induction of labour remains unclear.⁸ Currently, assessment is directed by expert opinion-based guidelines that perform poorly when tested for their ability to predict adverse maternal outcomes.⁹ A validated tool that allows real-time maternal risk stratification is needed to guide care (eg, expectant management both remote from term or during induction of labour). Previous modelling was unsuccessful for prediction of adverse outcomes occurring at any time after admission with preeclampsia.¹⁰ However, being able to predict adverse maternal outcomes within a timeframe that would inform and guide clinical care (eg, 48 h to 7 days) would optimise both the management of women admitted with pre-eclampsia and the use of resources.

Standardisation of antenatal and postnatal assessment and surveillance of pre-eclampsia with protocols that recognise the systemic inflammatory model of preeclampsia¹ have been associated with reduced maternal morbidity.¹¹ Using this standardised approach, we aimed to develop and internally validate a pre-eclampsia outcome prediction model—the fullPIERS (Preeclampsia Integrated Estimate of RiSk) model. fullPIERS was designed for use in well resourced settings.

Methods

Patients and model design

fullPIERS was developed and internally validated in a prospective, multicentre study of women who fulfilled a research definition of pre-eclampsia, and who were admitted to participating academic tertiary obstetric centres in Canada, New Zealand, Australia, and the UK (see Acknowledgments). All centres had a general policy of expectant management remote from term to maximize temporal exposure of the cohort to the natural history of the disorder. PIERS was undertaken as either a continuous quality improvement (four sites) or a consented research (four sites initially, eventually only one) project depending on local ethics committee requirements. Inpatient women with either suspected or confirmed pre-eclampsia received care that included predetermined guidelines for initial assessment and ongoing surveillance.^{11,12}

Women were included if they were admitted with pre-eclampsia or had developed pre-eclampsia after admission. Pre-eclampsia was defined as: i) blood pressure $\geq 140/90$ mm Hg (at least one component, twice, ≥ 4 h apart, after 20 weeks) and either proteinuria (of $\geq 2+$ by dipstick, ≥ 0.3 g per day by 24-h collection, or ≥ 30 mg/mmol by urinary protein:creatinine ratio) or hyperuricaemia (greater than local upper limit of local non-pregnancy normal range);¹¹ ii) HELLP (haemolysis,

elevated liver enzymes, low platelets) syndrome, even in the absence of hypertension or proteinuria;¹³ or iii) superimposed pre-eclampsia (rapidly increasing requirements for antihypertensive drugs, systolic blood pressure >170 mm Hg or diastolic blood pressure >120 mm Hg, new proteinuria, or new hyperuricaemia). This definition, although differing from many international definitions,¹⁴ reflects both the variable and multisystem nature of pre-eclampsia at presentation and the range of women seen in clinical practice.¹⁵ Women were excluded if they were either admitted in spontaneous labour or had achieved any component of the maternal outcome before either fulfilling eligibility criteria or collection of predictor data.

The candidate maternal and fetal predictor variables chosen were those that were predictive, available, measurable, frequent, and reliable (see panel).¹⁶ Symptoms, although difficult to quantify, were included for face validity because of their use in classification of severe disease,^{12,14} and potential predictive performance in pre-eclampsia.²⁰ Although some of the candidate predictors were associated with components of the outcome (eg, the predictor of creatinine and the outcome component of renal insufficiency or failure) they were retained for consideration in the model because we were interested in predicting the development of adverse events in the future on the basis of information available at the time of admission. Since our study criteria specifically

Panel: Variables considered in PIERS modelling	
Demographic characteristics	(Continued from previous column)
Maternal age at expected date of delivery (years)	Haematological tests
Number of fetuses	Total leucocyte count (×10 ⁹ /L)
Gestational age at eligibility (weeks)	Platelet count (×10 ⁹ /L)
Gestational age at delivery (weeks)	Mean platelet volume (fL)
Weight on admission (kg)	Mean platelet volume/platelet ratio
Body-mass index (kg/m ²)	International normalised ratio
Gravidity (n)	Activated partial thromboplastin time (s)
Parity (n)	Fibrinogen (µmol/L)
Smoking in this pregnancy (yes/no)	Renal signs and tests
Past obstetric history	Dipstick (categorical)†
Gestational hypertension (yes/no)	Dipstick (continuous)‡
Gestational proteinuria (yes/no)	24-h urine protein (g per day)
Gestational diabetes mellitus (previous pregnancy) (yes/no)	Urinary protein:creatinine ratio (mg/mmol)
Gestational diabetes mellitus (this pregnancy) (yes/no)	Creatinine (µmol/L)
Past medical history	Uric acid (mmol/L)
Hypertension (yes/no)	Hepatic tests
Renal disease (yes/no)	Aspartate transaminase (U/L)
Diabetes mellitus (yes/no)	Alanine transaminase (U/L)
Symptoms	Lactate dehydrogenase as a ratio of the local normal range midpoint (U/L)
Severe nausea and vomiting (yes/no)	Bilirubin (µmol/L)
Frontal headache (yes/no)	Albumin (g/L)
Visual disturbance (yes/no)	Random glucose (mmol/L)
Right upper quadrant/epigastric pain (yes/no)	Fetal assessment tests
Chest pain/dyspnoea (yes/no)	Fetal heart rate (normal/suspicious/pathological)§
One or more symptom (yes/no)	Estimated fetal weight ¹⁷ (percentile category)¶
Cardiorespiratory signs	Abdominal circumference (percentile category)¶
Diastolic blood pressure at eligibility (mm Hg)	Umbilical artery Doppler end diastolic flow
Systolic blood pressure at eligibility (mm Hg)	
Mean arterial pressure at eligibility (mm Hg)	
SpO ₂ (%) / SpO ₂ (filled)* (%)	
(Continues in next column)	

SpO₂—oxygen saturation (pulse oximetry). *Missing data filled assuming 97% (described in the Methods). †Classified as 0, trace, 1+, 2+, 3+, and 4+. ‡Classified as 0, 0.5, 1, 2, 3, and 4. §On the basis of Royal College of Obstetricians and Gynaecologists definitions.¶Classified as <1.0%, 1.0-2.4%, 2.5-4.9%, 5.0-9.9%, 10.0-49.9%, 50.0-89.9%, 90.0-94.9%, 95.0-97.4%, 97.5-98.9%, ≥99.0% on the basis of BC Women's Hospital published data.²⁰

excluded women who had achieved any component of the outcome, all women included in the modelling had the potential to remain free of adverse outcomes.

The components of the combined adverse maternal outcome were: maternal mortality or one or more serious CNS, cardiorespiratory, hepatic, renal, or haematological morbidity. This outcome was developed by iterative Delphi consensus.^{21,22} One case of Bell's palsy and two cases of severe ascites were included because the onset and resolution were temporally related to the clinical course of the pre-eclampsia.

Data quality and missing data

Customised case report forms and database were used by all participating sites. Data were obtained from patient medical records, and predictor variables were collected within 48 h of eligibility. If absent, the method of last observation carried forward was used by which any preceding observation recorded within 2 weeks of admission was regarded as current unless replaced by a more recent value. Although not universally supported,²³ this method is consistent with clinical practice since clinicians do not re-evaluate what they believe has not changed, and is conservative in underestimating the effect of any given variable in modelling. For example, 24-h urine proteinuria of 0.6 g per day measured 4 days previously could be carried forward to the day of delivery for the purpose of the analyses.

With respect to lead-time bias, we selected either the date or time of admission with pre-eclampsia or the post-admission development of pre-eclampsia (whichever was later) to standardise for the level of clinical concern justifying admission and the concurrent presence of pre-eclampsia. To account for missing values and misclassification we undertook abstractor training, checked the data collection methods, monitored data logic, and did random re-abstraction of charts (randomly in 102 [5%] cases and for all adverse maternal or perinatal outcomes were suspected or confirmed). Cases of uncertainty (n=13 [1%]) were resolved by iterative discussion between PvD, LAM, BP, and the relevant site investigator.

One highly informative variable, oxygen saturation by pulse oximetry (SpO₂), was prone to missing data before all participating centres achieved regular pulse oximetry. Missing pulse oximetry data points were assigned a value (97%) to lie within the normal range (95–100%), assuming that non-use of oximetry was associated with better clinical state, and biasing analyses to underestimate the effect of falling SpO₂ to identify increasing maternal risk.¹⁶ For lactate dehydrogenase, values were corrected to the midpoint of the relevant laboratory's normal range to standardise across sites. For women who developed de novo postpartum pre-eclampsia, gestational age was defined as the gestational age at delivery.

Statistical analysis

In response to a falling incidence of adverse outcomes noted for all centres, and previously reported in one site,¹¹ an early decision was made to assess the model iteratively once 200 women were entered into the database, and monthly thereafter, so that non-informative variables ($p > 0.2$) could be abandoned. The study size was 1731 women, on the basis of the following calculation: $N = (n \times 15)/I$, where N was the sample size, n was the number of informative, non-convergent variables to be considered in the model ($n = 15$), and I was the incidence of the combined adverse outcome (0.13 at any time after eligibility).²⁴⁻²⁶

Only candidate predictor variables available for 80% or more of women were included in modelling, since routine use is a prerequisite for day-to-day clinical usefulness. Consequently, we considered 54 independent variables recorded during the first 48 h to predict the combined adverse maternal outcome occurring within the first 48 h after eligibility (panel). The so-called worst value (eg, highest systolic blood pressure or lowest platelet count) measured before outcome occurrence or completion of the 48-h period, whichever was first, was used. A 48-h window was chosen because this timeframe would improve perinatal outcomes by allowing time for steroid administration remote from term and would inform decisions about the place of delivery or in utero transfer from level 1 and 2 units.

The relation between each predictor variable and the combined adverse maternal outcome was assessed by univariable logistic regression. Continuous variables were modelled with quadratic terms, and categorised on the basis of risk thresholds to evaluate the potential for non-linearity. Variables associated with the outcome ($p < 0.1$) were included in the initial multivariable regression model along with variables deemed important, a priori, on clinical grounds. To avoid collinearity, the correlation between variables was assessed and the more clinically relevant variable of a pair of highly correlated variables was included. Clinical expectations regarding possible interactions were specifically examined.

Stepwise backward elimination was used to build the parsimonious final model. We calculated the AUC of the receiver operating characteristic (ROC) using standard methods.²⁷ The final model was internally validated using Efron's enhanced bootstrap method (details available on PIERS study website).^{25,28,29} Such a bootstrap validation is recommended over alternative validation approaches (eg, splitting of data into training and test datasets) because it maximises statistical efficiency and directly validates the final model.²⁵

We assessed performance using calibration ability, stratification capacity, and classification accuracy.³⁰ Additionally, we prospectively assessed the predictive ability of fullPIERS in a broader range of women with pregnancy hypertension. First, women admitted with pre-eclampsia to five level 1 or 2 obstetric centres in British Columbia (n=4) and Western

	Women with adverse outcomes (n=261)	Women without adverse outcomes (n=1762)	p value
Demographic characteristics (within 48 h of eligibility)			
Maternal age at EDD (years)	31 (27–35)	31 (27–36)	0.68
Gestational age at eligibility (weeks)	33.9 (30.0–36.6)	36.3 (33.4–38.3)	8.2×10^{-28}
Gestational age at eligibility <34 weeks	133 (51%)	503 (29%)	3.3×10^{-22}
Multiple pregnancy	36 (14%)	156 (9%)	0.02
Parity ≥ 1	72 (28%)	509 (29%)	0.71
Smoking during this pregnancy	26 (10%)	223 (13%)	0.26
Pre-eclampsia description			
Hypertension and proteinuria	178 (68%)	1164 (66%)	0.53
Hypertension and hyperuricaemia	21 (8%)	303 (17%)	8.9×10^{-5}
HELLP without hypertension or proteinuria	23 (9%)	29 (2%)	8.0×10^{-8}
Superimposed pre-eclampsia	39 (15%)	266 (15%)	1.0
Clinical measures (within 48 h of eligibility)			
Peak blood pressure			
Mean arterial pressure (mm Hg)	123 (116–133)	120 (113–129)	5.2×10^{-5}
Systolic blood pressure (mm Hg)	170 (155–181)	160 (150–175)	1.7×10^{-9}
Diastolic blood pressure (mm Hg)	104 (98–112)	101 (97–110)	0.02
Worst dipstick proteinuria (+)	3 (1–4)	2 (trace–3)	6.7×10^{-11}
Lowest platelet count ($\times 10^9$ per L)	170 (121–230)	194 (153–243)	2.8×10^{-9}
Highest aspartate transaminase (U/L)	31 (22–51)	26 (20–36)	4.5×10^{-7}
Interventions			
Corticosteroid administration	114 (44%)	436 (25%)	5.8×10^{-10}
Antihypertensive drugs administered	214 (82%)	1167 (66%)	6.9×10^{-8}
MgSO ₄ administered	161 (62%)	529 (30%)	4.7×10^{-22}
Pregnancy outcomes			
Admission-to-delivery interval, all cases (days)	2 (1–6)	2 (1–5)	0.14
Admission-to-delivery interval, <34 th weeks (days)	4 (1–9)	5 (2–16)	0.01
Gestational age at delivery (weeks)	34.7 (30.7–37.0)	37.0 (34.6–38.7)	8.2×10^{-20}
Birthweight (g)	1938 (1189–2750)	2685 (1935–3300)	4.5×10^{-18}
Birthweight lower than third percentile*	22 (8%)	143 (8%)	0.90
Intrauterine fetal death, $\geq 20^{\text{th}}$ weeks or ≥ 500 g	4 (2%)	16 (1%)	0.31
Neonatal death, before 28 days	5 (2%)	15 (1%)	0.17
Infant death before hospital discharge or 6 weeks	7 (3%)	19 (1%)	0.07
Data are median (IQR) or number (%). EDD=expected date of delivery. HELLP=haemolysis, elevated liver enzymes, low platelets. *Data from Kramer and colleagues. ²⁵			

Table 1: Characteristics of women in the PIERS study

Australia (n=1). Second, women admitted to BC Women’s Hospital and Health Centre (Vancouver, BC, Canada) with either preexisting or gestational hypertension.¹² Third, women with pre-eclampsia admitted to three academic centres in countries with low and middle incomes (Fiji, South Africa, and Uganda). R (version 2.9.2) was used for all analyses related to model building. Descriptive analyses of the cohort were done with SPSS (v17.0).

Role of the funding source

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.

Results

Between Sept 1, 2003, and Jan 31, 2010, data for 2023 women (2221 fetuses) were entered into the fullPIERS database from eight international sites (table 1). There were 261 (13%) combined adverse maternal outcomes at any time after eligibility. By comparison with women who did not develop adverse outcomes, women who did were of lower gestational age at eligibility, and were less likely to be either parous, to smoke during the pregnancy, or to be eligible on the basis of hyperuricaemia. They were more likely to develop HELLP syndrome and to receive both antihypertensive drugs or antenatal corticosteroids, or both (for either fetal lung maturation or HELLP). Maternal blood pressure indices, dipstick proteinuria, and aspartate transaminase concentration were higher in women who developed adverse outcomes, whereas platelet counts were lower. The eligibility-to-delivery interval did not vary between groups, except in women eligible at less than 34 weeks’ gestation. Such women who developed outcomes had briefer eligibility to-delivery intervals. Women who developed adverse outcomes were more likely to receive MgSO₄ during their clinical course and to deliver babies earlier and of lower birthweight. Perinatal and infant mortality did not differ significantly between groups.

The median eligibility-to-outcome interval was 4 days (IQR 1–6). Table 2 lists adverse maternal outcomes for which one or more maternal mortality or morbidity event occurred. These adverse outcomes occurred antenatally in 120 (6%) women, intrapartum in 59 (3%), and postnatally in 82

	Within 48 h of eligibility	Within 7 days of eligibility	At any time
Total	106 (5%)	203 (10%)	261 (13%)
Maternal death	0	0	0
CNS			
Eclampsia (≥1)	6	10	11
Glasgow coma score <13	1	1	3
Stroke or reversible ischaemic neurological deficit	0	0	1
Transient ischaemic attack	0	1	1
Cortical blindness or retinal detachment	0	0	0
Posterior reversible encephalopathy	0	0	0
Cardiorespiratory			
Positive inotropic support	0	0	3
Infusion of a third parenteral antihypertensive drug	0	1	3
Myocardial ischaemia or infarction	1	1	1
SpO ₂ <90%	11	30	41
≥50% FiO ₂ for >1 h	12	21	32
Intubation (other than for caesarean section)	1	4	6
Pulmonary oedema	22	52	63
Haematological			
Transfusion of any blood product	28	63	85
Platelet count <50×10 ⁹ per L, with no transfusion	22	36	40
Hepatic			
Dysfunction	9	11	12
Haematoma or rupture	0	0	0
Renal			
Acute renal insufficiency (creatinine >150 µmol/L; no pre-existing renal disease) ²¹	3	4	6
Acute renal failure (creatinine >200 µmol/L; pre-existing renal disease) ²²	4	4	4
Dialysis	0	0	1
Placental abruption	15	24	34
Other adverse events			
Severe ascites	1	2	2
Bell’s palsy	0	1	1

SpO₂=oxygen saturation (pulse oximetry). FiO₂=fraction of inspired oxygen. *Definitions available on the PIERS study website.

Table 2: Occurrence of adverse maternal outcomes by mortality or morbidity event*

(4%). The most common outcomes reached were pulmonary oedema (63 [3%] patients) and blood product transfusion (85 [4%]).

Having excluded some historically important variables after univariable modelling, we modelled using variables with possible explanatory power (table 3; a full list of tested variables and univariable relations with the combined adverse outcome is available on the PIERS study website). Developed with data from 1935 women with complete data (of the 2023 in the cohort in total), fullPIERS predicted adverse maternal outcomes within 48 h of eligibility (AUC ROC 0.88, 95% CI 0.84–0.92; figure 1). The final fullPIERS equation was: $\text{logit}(\pi) = 2.8 + (-5.1 \times 10^{-2}; \text{gestational age at eligibility}) + 1.3 (\text{chest pain or dyspnoea}) + (-2.1 \times 10^{-2}; \text{creatinine}) + (2.7 \times 10^{-1}; \text{platelets}) + (4.0 \times 10^{-5} \text{platelets}^2) + (1.1 \times 10^{-2}; \text{aspartate transaminase}) + (-3.5 \times 10^{-6} \text{AST}^2) + (2.50 \times 10^{-4}; \text{creatinine} \times \text{platelet}) + (-6.99 \times 10^{-5}; \text{platelet} \times \text{aspartate transaminase}) + (-2.56 \times 10^{-3}; \text{platelet} \times \text{SpO}_2)$. A fullPIERS probability calculator is available on the study website. After 200 cycles of bootstrapping the average optimism was 0.02 (95% CI –0.03 to 0.06), suggesting minimal overfitting.

fullPIERS successfully stratified the population into clinically relevant risk categories (table 4), with a large percentage (65%) of women classified into a low-risk group (predicted probability of <0.025), and 4% of women into the highest risk group (predicted probability ≥ 0.30). The majority (59%) of women with a predicted probability of 0.30 or greater had an adverse outcome. Conversely, the adverse outcome only occurred in 1% of women with a predicted probability lower than 0.025, and

	n (%)	Odds ratio (95% CI)	p value	AUC ROC (95% CI)
Demographic characteristics				
Maternal age at EDD (years)	2020 (>99%)	0.99 (0.96–1.02)	0.57	0.51 (0.46–0.57)
Gestational age at eligibility (weeks)	2020 (>99%)	0.91 (0.88–0.95)	3.2×10^{-3}	0.61 (0.55–0.67)
Number of fetuses (n)	2020 (>99%)	0.86 (0.43–1.70)	0.66	0.51 (0.45–0.57)
Gravidity (n)	2020 (>99%)	0.894 (0.81–0.99)	0.03	0.56 (0.50–0.61)
Weight at eligibility (kg)	1784 (88%)	0.99 (0.97–0.998)	0.03	0.59 (0.53–0.65)
BMI (kg/m ²)	1647 (81%)	0.99 (0.95–1.02)	0.45	0.55 (0.49–0.61)
Height (cm)	1763 (87%)	0.99 (0.97–1.02)	0.62	0.52 (0.46–0.58)
Past medical history				
Hypertension	2015 (>99%)	0.57 (0.29–1.11)	0.10	0.53 (0.48–0.58)
Symptoms				
Severe nausea and vomiting	2020 (>99%)	2.14 (1.22–3.73)	0.008	0.54 (0.48–0.60)
Right upper quadrant/epigastric pain	2020 (>99%)	2.92 (1.94–4.39)	2.7×10^{-7}	0.61 (0.55–0.66)
Headache	2020 (>99%)	1.23 (0.83–1.83)	0.30	0.53 (0.47–0.58)
Visual disturbance	2020 (>99%)	0.99 (0.60–1.63)	0.96	0.50 (0.45–0.56)
Chest pain or dyspnoea	2020 (>99%)	6.13 (3.56–10.54)	5.6×10^{-11}	0.58 (0.52–0.66)
Number of symptoms (n)	2020 (>99%)	1.49 (1.26–1.76)	3.2×10^{-8}	0.62 (0.57–0.68)
Cardiovascular signs				
DBP at eligibility (mm Hg)	2020 (>99%)	1.04 (1.02–1.05)	8.6×10^{-3}	0.63 (0.57–0.68)
SBP at eligibility (mm Hg)	2020 (>99%)	1.03 (1.02–1.04)	1.1×10^{-8}	0.65 (0.59–0.70)
MAP at eligibility (mm Hg)	2019 (>99%)	1.04 (1.03–1.06)	4.6×10^{-8}	0.65 (0.60–0.71)
Respiratory				
SpO ₂ (filled; %)*	2020 (>99%)	0.63 (0.58–0.70)	4.8×10^{-22}	0.72 (0.67–0.78)
Renal				
Dipstick (continuous) †	1949 (96%)	1.43 (1.24–1.66)	1.6×10^{-9}	0.65 (0.59–0.71)
Creatinine (µmol/L)	2000 (99%)	1.02 (1.02–1.03)	4.2×10^{-3}	0.63 (0.57–0.69)
Uric acid (mmol/L)	2008 (99%)	1.004 (1.00–1.01)	1.1×10^{-4}	0.59 (0.53–0.65)
Haematological				
Platelet count (x10 ³ per L)	2015 (>99%)	0.99 (0.98–0.99)	4.9×10^{-17}	0.69 (0.63–0.75)
MPV (fL)	1953 (97%)	1.00 (0.88–1.13)	0.939	0.51 (0.46–0.57)
MPV x10 ³ /platelet count ratio	1952 (96%)	45.46 (1.63–1269)	2.9×10^{-25}	0.66 (0.59–0.72)
International normalised ratio	1758 (87%)	2710 (143–51381)	1.3×10^{-7}	0.64 (0.58–0.70)
Activated partial thromboplastin time (s)	1759 (87%)	1.04 (1.02–1.07)	1.7×10^{-4}	0.64 (0.58–0.70)
Hepatic				
Aspartate transaminase (U/L)	1947 (96%)	1.005 (1.00–1.01)	1.6×10^{-14}	0.73 (0.67–0.79)
Alanine transaminase (U/L)	2011 (99%)	1.005 (1.00–1.01)	7.9×10^{-18}	0.72 (0.66–0.78)
Lactate dehydrogenase (U/L)	1623 (80%)	1.63 (1.43–1.86)	2.0×10^{-13}	0.75 (0.68–0.81)
Bilirubin (µmol/L)	1911 (94%)	1.15 (1.11–1.18)	8.7×10^{-17}	0.67 (0.60–0.73)
Albumin (g/L)	1749 (86%)	0.92 (0.88–0.96)	7.8×10^{-3}	0.62 (0.56–0.68)
Fetal assessment tests				
Fetal heart rate	1829 (90%)	2.15 (1.47–3.14)	6.9×10^{-3}	0.58 (0.51–0.64)
Estimated fetal weight (percentile category)	1665 (82%)	0.99 (0.98–0.99)	5.9×10^{-3}	0.61 (0.55–0.68)
Abdominal circumference (percentile category)	1665 (82%)	0.99 (0.98–0.99)	5.8×10^{-3}	0.61 (0.55–0.68)

AUC ROC=area under the curve of the receiver operating characteristic. EDD=expected date of delivery. BMI=body-mass index. DBP=diastolic blood pressure. SBP=systolic blood pressure. MAP=mean arterial pressure. SpO₂=oxygen saturation (pulse oximetry). MPV=mean platelet volume. *Missing data filled assuming 97% (described in Methods). †Classified as 0, 0.5, 1, 2, 3, 4.

Table 3: Univariable analyses of candidate predictor variables with p<0.1 and obtained in more than 80% of cases

in less than 1% of women with a predicted probability lower than 0.01 (negative predictive value >99%).

The classification accuracy of fullPIERS was good. For example, using a predicted probability of 0.05 as a threshold, fullPIERS identified more than 75% of women who subsequently had events as being at high risk, whereas only 16% of the population was incorrectly identified as being at high risk. In practice, the predicted probability would best be used as a continuous value, probability of an adverse outcome, to customise management.

fullPIERS also performed well for prediction of adverse maternal outcomes from 2 to 7 days after eligibility (ie, AUC ROC >0.7; figure 2). The AUC and risk stratification findings were replicated for women admitted with pre-eclampsia before 34+0 weeks (AUC ROC 0.85, 95% CI 0.79–0.92) and for primigravid women admitted with pre-eclampsia defined solely as proteinuric gestational hypertension (AUC ROC 0.87, 95% CI 0.82–0.93; tables available on PIERS study website). Preliminary assessments of fullPIERS in a broader range of women with pregnancy hypertension confirmed its performance (ie, AUC ROC >0.7). The AUC ROC for fullPIERS was 0.77 (95% CI 0.45–1.00) for women admitted to level 1 or 2 centres with pre-eclampsia (six outcomes in 139 women), 0.85 (95% CI 0.65–1.00) for those admitted to one tertiary centre (level 3) with a non-pre-eclampsia hypertensive disorder of pregnancy (four outcomes in 224 women), and 0.80 (95% CI 0.66–0.94) in those with pre-eclampsia admitted to centres in countries with low and middle incomes (17 outcomes in 145 women).

Discussion

We undertook a prospective, international study to develop and validate a maternal outcome prediction model for women admitted to tertiary units with pre-eclampsia. In women admitted to hospital with pre-eclampsia, fullPIERS predicted adverse maternal outcomes occurring within the first 48 h after eligibility. The model included gestational age at

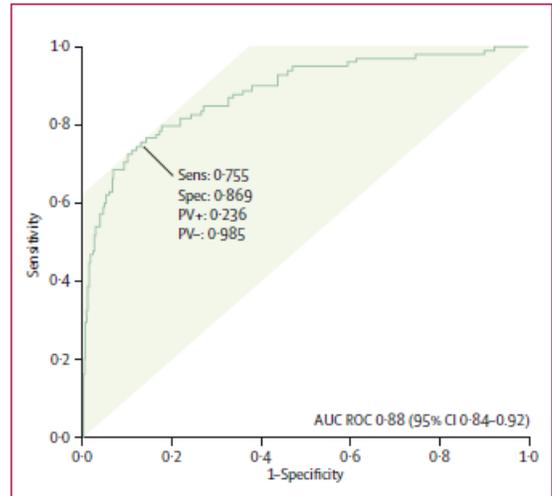


Figure 1: Performance of the fullPIERS model, developed with data from first 48 h after eligibility

Combined adverse maternal outcomes predicted within 48 h of eligibility on the basis of only data recorded before the outcome (an online tool to calculate fullPIERS probabilities is available on the study website). AUC ROC=area under the curve of the receiver operating characteristic. PV-=negative predictive value. PV+=positive predictive value. Sens=sensitivity. Spec=specificity.

	Number of women (%)	Number of women with outcome (%)	Number of women without outcome (%)	True positive rate*	False positive rate*
0.00-0.0099	671 (35%)	3 (<1%)	668 (>99%)	--	--
0.01-0.024	586 (30%)	11 (2%)	575 (98%)	0.969	0.636
0.025-0.049	314 (16%)	9 (3%)	305 (97%)	0.857	0.323
0.050-0.099	160 (8%)	8 (5%)	152 (95%)	0.765	0.157
0.10-0.19	98 (5%)	14 (14%)	84 (86%)	0.684	0.073
0.20-0.29	32 (2%)	9 (28%)	23 (72%)	0.541	0.029
≥0.30	74 (4%)	44 (59%)	30 (41%)	0.449	0.016
Total	1935	98	1837	--	--

Table 4: Risk stratification table assessing the value of the fullPIERS model in risk prediction, by predicted probability of adverse maternal outcome within 48 h

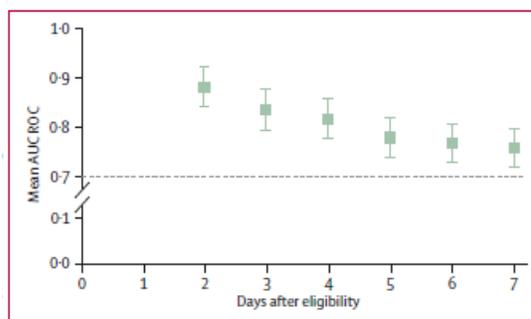


Figure 2: Mean fullPIERS area under the curve of the receiver operating characteristic, 2-7 days after PIERS study eligibility
Error bars show 95% CIs. AUC ROC=area under the curve of the receiver operating characteristic.

eligibility, chest pain or dyspnoea, SpO₂, platelet count, serum creatinine, and aspartate transaminase as predictors. PIERS modelling identified SpO₂, a clinical variable that has not been included traditionally in lists of adverse features. All components of the model fulfilled the requirement for clinical face validity, in view of the particular risks of pre-eclampsia,⁵ especially remote from term.¹ fullPIERS attained similar stratification capacity, calibration ability, and classification accuracy as established cardiovascular, adult critical care, and neonatal critical care scores.^{33–35} fullPIERS should assist decisions around delivery, especially at gestational ages when expectant management has important perinatal advantages.¹

There are several limitations to this study. First, to attain generalisability, our population included women who fulfilled a broad definition of pre-eclampsia, including women without significant proteinuria. Restriction of the analysis to the tightest possible research definition (primigravid women with proteinuric hypertension) did not significantly change the AUC ROC. Second, although components of our combined adverse maternal outcome are not of equal value, all components were assessed and validated by iterative Delphi consensus^{21,22} and are independently worthy of avoidance. Third, the study was undertaken solely in high-income country tertiary obstetric units and in women fulfilling our research definition of pre-eclampsia. We have begun to address these limitations through initial assessments of the predictive ability of fullPIERS across the range of hypertensive disorders of pregnancy and are developing and validating a specific, symptom-based and sign-based version of PIERS (miniPIERS) for use in rural and remote settings in countries with high, middle, and low incomes.

A fourth limitation was the fairly small sample size, especially in view of the low rate of adverse maternal outcomes. This factor might be particularly important for uncommon outcomes such as eclampsia, since headache and visual symptoms did not contribute independently to fullPIERS. Therefore, our bootstrap validation was only able to confirm the predictive ability of fullPIERS for the occurrence of the combined maternal outcome. Since internal validation methods such as the bootstrap have limitations,³⁶ we have begun a process of external validation of fullPIERS through new datasets. The fifth limitation is that fullPIERS is limited to maternal surveillance and does not address the acknowledged excess perinatal risks associated with pre-eclampsia.¹

fullPIERS accurately predicted adverse maternal outcomes for up to 48 h, a clinically useful period that allows steroid administration, transfer, or induction. Also, fullPIERS maintained good performance (AUC ROC >0.8) beyond 3 days post-eligibility and maintained reasonable performance (AUC ROC >0.7) up to 7 days post-eligibility. Remote from term, measurable perinatal gains accrue at weekly intervals.³⁷ However, similarly to Ganzevoort and colleagues,¹⁰ we were unable to predict adverse maternal outcomes at any time after admission to hospital with pre-eclampsia. This finding was anticipated, since deteriorating maternal and fetal status directs clinical decision making, especially remote from term.

In the PIERS cohort, gestational age at admission to hospital for pre-eclampsia was significantly lower, and independently predictive, in women destined to develop complications. Disease onset at less than 32 weeks' gestation is associated with a 20-times increased risk of maternal mortality.¹

Many traditional clinical variables of importance were not included in the final model, either because they were recorded in less than 80% of cases (eg, 24-h urine), they lacked univariable association with the combined adverse outcome,⁹ or they were displaced within the multivariable

modelling (eg, blood pressure, heavy proteinuria, uric acid, alanine transaminase, and lactate dehydrogenase) by variables with greater independent explanatory power. Our findings support the view that once significant proteinuria has been identified, serum creatinine can be used to monitor renal function and risk in women with pre-eclampsia.³⁸

For face validity, we did examine whether or not blood pressure could be forced into fullPIERS. Blood pressure did not independently predict adverse maternal outcomes in the multivariable model, perhaps because it is the sole element of the maternal syndrome that is amenable to intervention. Effective antihypertensive agents exist for severe and non-severe pregnancy hypertension.¹ During the first 48 h after eligibility, women who proceeded to develop adverse outcomes had blood pressure indices 3–10 mm Hg higher than did women with uncomplicated courses. We do not advocate that blood pressure measurement in women with suspected or confirmed pre-eclampsia be abandoned. Severe systolic (≥ 160 mm Hg) and diastolic hypertension (≥ 110 mm Hg) convey important maternal risks and should be brought into the non-severe or normotensive range.¹

Our results suggest that only one of aspartate transaminase or alanine transaminase need to be measured, and that the measurement of lactate dehydrogenase is redundant in these women. Other tests that could reasonably be abandoned in view of these data are urea and routine coagulation studies. Why were 24-h collections done in fewer than 50% of the women in our study? Pragmatically, we believe that clinicians faced with a hypertensive woman with proteinuria on dipstick analysis at term will decide to advise delivery rather than accept the delay inherent in a 24-h collection; a decision supported by both the HYPITAT trial,⁷ and the inaccuracy of 24-h urine collections for proteinuria estimation in pregnancy.³⁸ We suggest that dipstick proteinuria, despite its inherent flaws, be used to screen and identify women at risk.^{1,38}

The low rate of MgSO₄ administration to women who developed adverse outcomes (62%) in these academic tertiary centres was surprising; these women all developed significant personal complications of pre-eclampsia. Although the results of the randomized controlled trials of MgSO₄ as eclampsia prophylaxis are compelling,³⁹ for women with mild pre-eclampsia there remains apparent uncertainty about when, and with whom, to start MgSO₄.¹²

How do we suggest that these findings be used to direct care? First, we believe that these data will help clinicians to gain a fuller sense of disease evolution. This process could be what underlies the reduced incidence of adverse maternal outcomes associated with the single site introduction of the PIERS assessment and surveillance guidelines.¹¹ Second, we propose that gestational age, maternal symptoms, pulse oximetry, serum creatinine, platelet count, and aspartate transaminase be used to stratify maternal risk during the assessment and surveillance of women admitted with pre-eclampsia using the fullPIERS equation (available at study website). The derived fullPIERS probability has similar performance characteristics as those of established cardiovascular and critical care models.^{33–35} Third, abandoning of redundant tests seems reasonable. For example, the testing of aspartate transaminase, alanine transaminase, and lactate dehydrogenase might be replaced by aspartate transaminase alone without the loss of important information and with reduced laboratory costs.

An important effect of fullPIERS might be identification of women at lowest risk of adverse outcomes, who can be offered expectant management either remote from term for perinatal benefit

or at or near term during induction of labour.⁷ By grouping of women according to the risk of adverse maternal outcomes, fullPIERS should also contribute to our understanding of the pathophysiology of pre-eclampsia. Analogous to the use of POP-Q in pelvic floor prolapse,⁴⁰ fullPIERS might, over time, aid description of the heterogeneous populations in pre-eclampsia research and enhance the development of new treatments and interventions. Although the model-making process is not finished,⁴¹ we hope that the planned external validation (through prospective data collection and use of extant international databases) and implementation of fullPIERS will help to reduce the risk of the life-ending, life-altering (eg, stroke), and life-threatening (eg, eclampsia) complications that make pre-eclampsia so important.

Contributors

PvD, JMA, MJD, AG, PMK, JMM, MPM, J-MM, GNS, JJW, KRW, BNW, SKL, JAR, and LAM participated in study design. PvD, BP, FBP, AMC, AG, PMK, PL, JMM, ALM, MPM, J-MM, ABO, GNS, JJW, BNW, and LAM took part in data collection. PvD, BP, JL, JMA, JMM, FQ, and LAM contributed to database architecture. PvD, BP, JL, JAH, KSJ, TL, and LAM contributed to data analysis. All authors contributed to data interpretation and preparation of the report.

Conflicts of interest

We declare that we have no conflicts of interest.

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