



Alternatives of Risk Prediction Models for Preeclampsia in a Low Middle-Income Setting

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Abstract

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AIM: To develop prediction models for the first-trimester prediction of PE (PE) using the established biomarkers including maternal characteristics and history, mean arterial pressure (MAP), uterine artery Doppler pulsatility index (UtA-PI), and Placental Growth Factor (PIGF)) in combination with Ophthalmic artery Doppler peak ratio (PR).

METHODS: This was a prospective observational study in women attending a first-trimester screening at 11-14 weeks' gestation. Maternal characteristics and history, measurement of MAP, ultrasound examination for UtA-PI measurement, maternal ophthalmic PR Doppler measurement, and serum PIGF collection were performed during the visit. Logistic regression analysis was used to determine if the maternal factor had a significant contribution in predicting PE. The Receiving Operator Curve (ROC) analysis was used to determine the area under the curve (AUC), positive predictive value (PPV), negative predictive value (NPV) and positive screening cut-off in predicting the occurrence of PE at any gestational age.

RESULTS: Of the 946 eligible participants, 71 (7.50%) subjects were affected by PE. Based on the ROC curves, optimal high-risk cutoff value for prediction of preeclampsia at any gestational age for model 2 (primary care model) in this Indonesia study population were 63% with the sensitivity and specificity of 71.8% and 71.2%, respectively. Both sensitivity and specificity for model 3 (complete model) were 70.4% and 74.9%, respectively for the cutoff value 58%. The area under the curve of model 2, model 3 was 0.7651 (95% CI: 0.7023-0.8279) and 0.7911 (95% CI: 0.7312-0.8511), respectively, for predicting PE. In addition, PPV and NPV for model 2 were 16.8% and 96.9%, respectively. PPV and NPV for model 3 were 18.55 and 96.9%, respectively.

CONCLUSION: The prediction models of preeclampsia vary depending upon healthcare resource. Complete model is clinically superior to primary care model but it is not statistically significant. Prognostic models should be easy to use, informative and low cost with great potential to improve maternal and neonatal health in Low Middle Income Country settings.

Introduction

Preeclampsia (PE) approximately affects about 2%–8% of pregnancies and is a leading cause of maternal and perinatal mortality and morbidity [1], [2]. PE has remained a significant public health threat in developing countries. At present, there is not a single reliable and cost-effective screening test for PE which can be recommended for use in most developing countries. However, accurate first-trimester prediction of PE would allow for an early prevention of the disease [1]. Therefore, many studies have attempted to develop the most accurate model to predict PE. A combination of maternal characteristics and history, biophysical, ultrasound, and maternal serum biochemical markers were initially evaluated to screen for risks of PE [3], [4], [5], [6], [7], [8]. Ultimately, the International Federation of Gynecology and Obstetrics (FIGO) initiative on PE recommended

a combined measurements of maternal risk factors, mean arterial pressure (MAP), uterine artery pulsatility index (UtA-PI), and placental growth factor (PIGF) as a superior technique to calculate a patient-specific risk for preterm PE [1]. However, there are a few such predictive models which are applicable to the healthcare in low middle-income countries (LMICs) and there are no locally developed or evaluated statistical risk models.

Maternal ophthalmic artery Doppler assessment is proposed as one of the promising predictors for PE occurrence at both early and late trimester [9], [10], [11]. This procedure is considered safe and reproducible for assessing the maternal hemodynamic change of cerebral vasculature that occurs during the development of PE [12]. The ophthalmic peak ratio (PR) or the ratio of the second to first systolic velocity was established as the most useful index in the ophthalmic artery Doppler assessment [13], [14]. Little was reported on the performance of ophthalmic artery Doppler as a

first-trimester prediction model [15]. This study aimed to develop prediction models which incorporated maternal risk factors, mean UtA-PI, ophthalmic artery Doppler PR, and PIGF for the first trimester prediction of PE that can be applied corresponding to health-care resource.

Methods

Population

Data were collected from women who attended their first-trimester screening at Harapan Kita National Women and Children's Hospital in Indonesia between August 2019 and October 2020. Gestational age was determined by the measurement of fetal crown-rump length (CRL). 11⁰-13⁶ weeks gestation ultrasound scans, maternal characteristics, and medical history were obtained. Maternal blood pressure (BP) was measured by automated devices (3BTO-A2; Microlife, Taipei, Taiwan) based on the protocol recommended by Poon *et al* [16], [17]. An adult BP cuff was used, selecting the proper size for each participant. Pressure reading at phase V of Korotkoff sounds represents of diastolic BP. Mean arterial BP was obtained by the equation $(2\text{Diastolic BP} + \text{Systolic BP})/3$. Pulsatility index (PI) of both the left and right uterine artery was examined by transabdominal color Doppler ultrasound using the E8 Voluson™ machine [18]. All ultrasound studies were performed by sonographers who had received the Certificate of Competence from The Fetal Medicine Foundation (www.fetalmedicine.com) for the 11 to 13 weeks pregnancy scan and PE screening. Serum PLGF was measured using the Electrochemiluminescence assay method (Cobas E411 analyzer, Roche Diagnostics, USA) [19]. The right ophthalmic PR was assessed at the visit according to the protocol established by the previous researchers [15], [20]. Click or tap here to enter text. In a supine position with the head inclined approximately at 15° to 30°, a small amount of gel was placed on the closed eyelid of the participant. The transducer was gently positioned in a horizontal direction and the ophthalmic Doppler flow at the lateral aspect of the eye lens was identified by tilting the probe up and down. An under 20° insonation angle was ensured between the sound beam and the ophthalmic artery with the sample size set to 2 mm and the filter frequency that was maintained between 50 and 100 Hz. Three consecutive waveforms of similar size and shape were obtained with the pulsed Doppler mode, and the PR was measured in a single waveform. The PR was defined as the ratio of the second to first peak velocity. The subjects included in this study underwent a singleton pregnancy with a screening for aneuploidy at the first trimester (week 11–13 of gestation) or a fetal CRL of 45–84 mm. Pregnancies with major fetal defects or non-viable pregnancies (delivery/abortion before <24 weeks gestation) were excluded from the study.

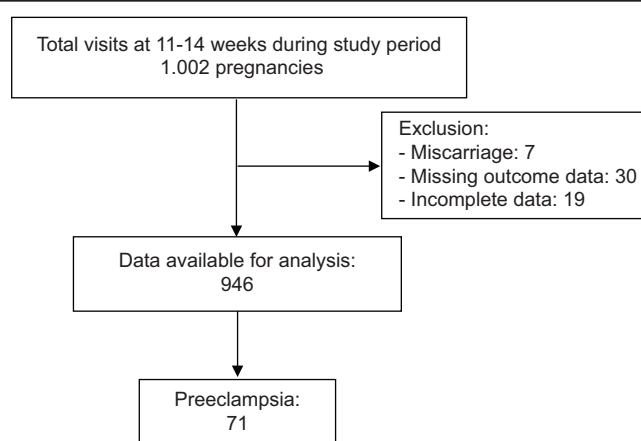


Figure 1: Flow chart showing the number of participants in the study

Patient characteristics

The recorded variables are as follows: Maternal age, parity (parous or nulliparous), pregnancy interval (<1 year or more than 10 years), method of conception (spontaneous or *in vitro* fertilization), history of chronic hypertension (yes or no), history of PE in a previous pregnancy (yes or no), history of gestational diabetes in a previous pregnancy (yes or no), history of maternal cardiac diseases (yes or no), history of maternal renal diseases (yes or no), smoking during pregnancy (yes or no), family history of PE in mother or sister (yes or no), pre-existing type 2 or type 1 diabetes mellitus (yes or no), history of systemic lupus erythematosus or anti-phospholipid syndrome (yes or no), use of aspirin (yes or no), use of anti-hypertension drug (yes or no), use of insulin (yes or no), birthweight (gram) and gestational age (weeks) of the last viable pregnancy, and body mass index (in kg/m²).

Outcome

Data on obstetrics and neonatal outcomes were collected from the midwife and the hospital medical records. The primary outcome was the gestational age of delivery with PE (weeks). PE is defined by the International Society of Hypertension in Pregnancy as a gestational hypertension at or after week 20 of gestation that is accompanied by ≥1 of the following new-onset conditions: Proteinuria, acute kidney injury, liver involvement, neurological complications, hematological complications, and/or uteroplacental dysfunction [21].

Statistical analysis

Maternal characteristics, pregnancy details and factors of the risk calculation algorithm were expressed in absolute numbers for dichotomous variables. Logistic regression analysis was used to determine if the maternal factor had a significant contribution in predicting PE. The performance of screening was determined by receiver operating characteristic (ROC) curves. The performance

of different methods of screening was compared by the areas under the ROC curves (AUROC). STATA version 14 software was used for the model evaluation.

Results

Characteristics of the study population

There were 1002 singleton pregnancies included in our first-trimester screening. We excluded 37 (3.76%) subjects who suffered a miscarriage (n = 7) and those with missing outcome data (n = 30). Of the 946 remaining cases, 71 (7.49%) subjects were affected by PE (Figure 1). Maternal and pregnancy characteristics are shown in Table 1. The PE group had a higher

median BMI than the unaffected group. The proportion of previous gestational hypertension, previous PE, previous gestational diabetes, chronic hypertension, type 2 diabetes mellitus, and family history of PE was also higher in the PE group. The unaffected group had more subjects who had an IVF pregnancy and those with a > 10 years delivery interval.

The prediction models were constructed according to health-care resource. They are shown in Table 2.

Table 1: Maternal and pregnancy characteristics in the study population

Characteristics	No PE (n = 875), n (%)	PE (n = 71), n (%)	Total (n = 946), n (%)	p
Age of women	29 (5)	30 (6)	29 (5)	0.19
Age of women				
< 35	761 (87.0)	55 (77.5)	816 (86.3)	0.025
≥ 35	114 (13.0)	16 (22.5)	130 (13.7)	
Gravida				
1	392 (44.8)	33 (46.5)	425 (44.9)	0.41
2	282 (32.2)	18 (25.4)	300 (31.7)	
3+	201 (23.0)	20 (28.2)	221 (23.4)	
BMI classification				
< 28	717 (81.9)	40 (56.3)	757 (80.0)	<0.001
≥ 28	158 (18.1)	31 (43.7)	189 (20.0)	
Smoking habit				
No	866 (99.0)	70 (98.6)	936 (98.9)	0.76
Yes	9 (1.0)	1 (1.4)	10 (1.1)	
Diabetes type 2				
No	869 (99.3)	68 (95.8)	937 (99.0)	0.003
Yes	6 (0.7)	3 (4.2)	9 (1.0)	
Previous gestational DM				
No	874 (99.9)	70 (98.6)	944 (99.8)	0.022
Yes	1 (0.1)	1 (1.4)	2 (0.2)	
Chronic hypertension				
No	868 (99.2)	62 (87.3)	930 (98.3)	<0.001
Yes	7 (0.8)	9 (12.7)	16 (1.7)	
History of the previous eclampsia				
No	855 (97.7)	57 (80.3)	912 (96.4)	<0.001
Yes	20 (2.3)	14 (19.7)	34 (3.6)	
Method of conception				
Normal	827 (94.5)	68 (95.8)	895 (94.6)	0.65
IVF	48 (5.5)	3 (4.2)	51 (5.4)	
Gestational week (weeks)				
11	125 (14.3)	13 (18.3)	138 (14.6)	0.45
12	430 (49.1)	31 (43.7)	461 (48.7)	
13	254 (29.0)	24 (33.8)	278 (29.4)	
14	66 (7.5)	3 (4.2)	69 (7.3)	
SBP (mmHg)				
< 140	856 (97.8)	59 (83.1)	915 (96.7)	<0.001
≥ 140	19 (2.2)	12 (16.9)	31 (3.3)	
DBP (mmHg)				
< 80	734 (83.9)	29 (40.8)	763 (80.7)	<0.001
≥ 80	141 (16.1)	42 (59.2)	183 (19.3)	
PLGF in MoM				
≥ 0.7	601 (68.9)	37 (52.1)	638 (67.7)	0.004
< 0.7	271 (31.1)	34 (47.9)	305 (32.3)	
PLGF concentration (pg/ml)				
≥ 39.5	627 (71.7)	35 (49.3)	662 (70.0)	<0.001
< 39.5	248 (28.3)	36 (50.7)	284 (30.0)	
Final MAP (mmhg)				
< 90	696 (79.5)	20 (28.2)	716 (75.7)	<0.001
≥ 90	179 (20.5)	51 (71.8)	230 (24.3)	
Mean Uta PI				
< 1.9	532 (60.8)	30 (42.3)	562 (59.4)	0.002
≥ 1.9	343 (39.2)	41 (57.7)	384 (40.6)	
Ophthalmic peak ratio				
< 0.65	617 (70.5)	31 (43.7)	648 (68.5)	<0.001
≥ 0.65	258 (29.5)	40 (56.3)	298 (31.5)	

Data are presented as mean (SD) for continuous measures, and n (%) for categorical measures. SD: Standard deviation, PE: Preeclampsia, BMI: Body mass index, DM: Diabetes mellitus, MAP: Mean arterial pressure, Uta PI: Uterine artery pulsatility index, PLGF: Placental growth factor, SBP: Systolic blood pressure, DBP: Diastolic blood pressure.

Table 2: Prediction models

Parameters	Model 1 (using all variables)	Model 2 (limited resource)	Model 3 (complete health-care resource)
All PE			
Age > 35 years	1.07 (0.52–2.18)		
BMI > 28	1.78 (1.00–3.18)	2.05*(1.17–3.61)	1.95* (1.11–3.44)
Chronic hypertension	4.26* (1.26–14.4)	5.31** (1.70–16.6)	4.31* (1.33–14.0)
History PE	3.01* (1.24–7.33)	3.61** (1.55–8.39)	3.44** (1.47–8.06)
DBP over 80 mmHg	4.00*** (2.22–7.21)	4.40*** (2.49–7.77)	4.14*** (2.31–7.40)
DM type 2	1.06 (0.17–6.52)		
Mean Uta PI ≥ 1.9	1.12 (0.53–2.37)		1.31 (0.63–2.71)
Peak ophthal ≥ 0.65	1.85* (1.06–3.24)		1.86* (1.08–3.20)
PLGF con<39.5	1.87* (1.07–3.26)		
Pseudo R ²	0.193	0.173	0.183
aic	427.0	427.1	425.8
df_m	9	4	6
Observations	946	946	946

Exponentiated coefficients; 95% CIs in brackets. LR of Akaike. Source of data: Jakarta. *p < 0.05, ** p < 0.01, ***p < 0.001. CI: Confidence intervals, LR: Likelihood ratio, df_m: Degrees of freedom of the model, PE: Preeclampsia, BMI: Body mass index, DM: Diabetes mellitus, Uta PI: Uterine artery pulsatility index, PLGF: Placental growth factor, DBP: Diastolic blood pressure.

The patient-specific risk for each hypertensive disorder was calculated from the formula: odds/(1 + odds), where odds = e^x and X were derived from multivariate logistic regression analysis of the disease-specific maternal facto-derived. Where x = (x₁, ..., x_p) is a vector of explanatory variables consisting of:

Model 1 (complete variables)

Age (x₁); x₁ = 1 if > 35 0 if < 35, body mass index (x₂); x₂ = 1 if > 28,0 if < 28, chronic hypertension (x₃); x₃ = 1 if < yes, 0 if ≥ no, previous Preeclampsia (PE) (x₄); x₄ = 1, if yes, 0 if no, type 2 diabetes mellitus (x₅); x₅ = 1, if yes, 0 if no; diastolic blood pressure (x₆); x = 1 if x₆ > 80, x = 0 if x₆ < 80, ophthalmic artery (x₇); x₇ = 1, if > 0.65, 0 if < 0.65, mean uterine artery PI (x₈); x₈ = 1, if > 1.9, 0 if < 1.9. PLGF (x₉); x₉ = 1, if > 40.0 if < 40.

Model 2 (limited resource for primary healthcare)

Body mass index (x₁); x₁ = 1 if > 28, 0 if < 28, chronic hypertension (x₂); x₂ = 1 if < yes, 0 if ≥ no, previous PE (x₃); x₃ = 1, if yes, 0 if no, diastolic blood pressure (x₄); x = 1 if x₄ > 80, x = 0 if x₄ < 80.

Model 3 (complete healthcare resource)

Body mass index (x₁); x₁ = 1 if > 28, 0 if < 28, chronic hypertension (x₂); x₂ = 1 if < yes, 0 if ≥ no, previous PE (x₃); x₃ = 1, if yes, 0 if no, diastolic blood pressure (x₄); x = 1 if x₄ > 80, x = 0 if x₄ < 80, ophthalmic artery (x₅); x₅ = 1, if > 0.65, 0 if < 0.65, mean uterine artery PI (x₆); x₆ = 1, if > 1.9, 0 if < 1.9.

Performance of the screening algorithm for preeclampsia

Parsimonious multivariable prediction models of PE at any gestational age were developed. Model 1 consists of complete variables derived from multivariate analysis, model 2 represents for healthcare with limited resource setting (primary healthcare), and model 3 represents for complete healthcare resource but more simple and fewer variables than model 1.

Based on the ROC curves, optimal high-risk cutoff value for prediction of PE at any gestational age for model 2 in this Indonesia study population were 63% with the sensitivity and specificity of 71.8% and 71.2%, respectively. Both sensitivity and specificity for model 3 were 70.4% and 74.9%, respectively, for the cutoff value 58%. The area under the curve of model 2, model 3 was 0.7651 (95% confidence interval [CI]: 0.7023–0.8279) and 0.7911 (95% CI: 0.7312–0.8511), respectively, shown in Figure 2, for predicting PE. In addition, PPV and NPV for model 2 were 16.8% and 96.9%, respectively. PPV and NPV for model 3 were 18.55 and 96.9%, respectively.

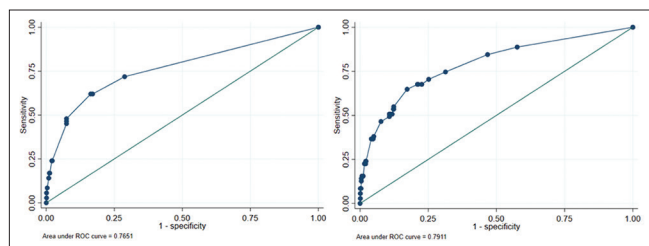


Figure 2: ROC curve of model 3. Comparison test using Chi-square with 1° of freedom ($p = 0.069$)

Discussion

Main findings

This prospective study has produced parsimonious multivariable prediction models of PE at any gestational age. Our prediction models are anticipated that every healthcare in every resource setting could use prediction model. Healthcare in remote rural areas would be able to use the model prediction and it will allow them to refer patient early and women at high risk for PE attending in central healthcare would be identified and prevented from first trimester.

The sophisticated prediction models for PE are predicated on access to ultrasound and laboratory testing and have been advocated by the International FIGO [1]. Given contextual differences between high and low-and-middle income countries, many of the prediction models which have been developed in high income countries at present may not be applicable in most low-and-middle income countries. This is because these prediction models included biomarkers as predictors in addition to maternal clinical characteristics. At present, PLGF

is not widely available in many low-and-middle income countries. Therefore, prediction models using biomarker may not be routinely applied in these settings. However, this may be impracticable in most LMICs.

For global application of a prognostic model, predictors that are generalizable rather than context dependent are preferable especially if they can be collected fast, easy, at point of care and low costs. Applicability of a model in LMIC could be considered during model derivation by selecting predictors that are appropriate for the setting in which the model will be implemented. In addition, within this process, incremental value assessment of specific predictors can be considered to improve performance in certain settings, or the derivation of “add on” models with a basic set of predictors that can be expanded on with more advanced predictors depending on resources available [22], [23]. In view of health-care resource setting, we selected certain variables based on applicability, availability, and simplicity that are integrated into prediction models of PE. Model 2 represents healthcare with limited resource and model 3 represents healthcare.

Even though risks can be calculated online including only baseline data (history, BP, and body mass index), women are often unaware of their own obstetric history. Well-performing PE prediction models need to be assessed in resource-challenged LMICs where populations have low health literacy [1]. Furthermore, models need to be integrated beyond single pregnancy risks and available as apps as online access is often sporadic in LMIC primary health centers where most maternity care is provided globally.

Taking the maternal history and recording BP are the cheapest and ubiquitously accessible screening tools. We chose 11–13 weeks as the gestation for screening because this is emerging as the first hospital visit of pregnant women at which combined sonographic and biochemical testing for chromosomal and other major defects is carried out.

Diastolic BP mainly reflect peripheral resistance which essentially depends on the tone of small arteries but it also decreases with increasing stiffness in the aorta [24]. Pregnant women tend to be young and traditionally greater emphasis has been given to diastolic rather than systolic BP as the predictor of the adverse consequences of pregnancy hypertension. The World Health Organization recommended that in the classification of PE only the diastolic BP should be considered and that use of MAP will not only increase the possibility of errors in recording of both systolic and diastolic BP but would also be unacceptable to physician because they would have to calculate the MAP [25].

Comparison with the previous study

miniPIERS

Once a pregnant woman has developed hypertension it is important to understand that woman's

individual level of risk. Two validated tools have been developed to guide the care of women from 20 weeks' gestation to post-term pregnancy and the early puerperium. These tools are the PIERS outcome prediction models, miniPIERS, and fullPIERS [9], [22], [26], [27], [28], [29], [30], [31], [32]. Following the ASpirin for evidence-based PE prevention (ASPRE) trial, aspirin (150–162 mg/day, ideally taken in the evening), commenced before 16 weeks' gestation, reduces the risk of early-onset PE in women identified to be at high risk (odds ratio [OR]: 0.38, 95% CI: 0.20, 0.74; $p = 0.004$) [33]. The study underlined the importance of screening prevention approach that should be ideally done in the first trimester. However, this important result relied on risk identification through an outcome prediction model that included both Doppler ultrasound and PIGF; these are surveillance tools not widely available in LMICs to date.

The PIERS models have been tested against their ability to predict a combined adverse maternal outcome that includes maternal death and severe central nervous system (CNS), cardiorespiratory, renal, and hepatic outcomes.

The miniPIERS multivariable model was developed using data from 2081 hypertensive pregnant women admitted to hospitals in Brazil, Fiji, Pakistan, South Africa, and Uganda. Designed to be used in the absence of access to laboratory testing, miniPIERS includes parity, gestational age, chest pain and/or dyspnea, headache and/or visual changes, vaginal bleeding with abdominal pain, and systolic blood pressure. The miniPIERS model was well-calibrated and had an AUC ROC of 0.77 (95% CI: 0.74, 0.80). Including only women admitted with diagnosis of PE, the AUC ROC was 0.77 (95% CI: 0.73, 0.81) [22]. The discriminatory performance of miniPIERS is improved by the addition of pulse oximetry [32].

fullPIERS

The fullPIERS model was developed using data from 2023 women with PE admitted to hospital in Australia, Canada, New Zealand, and the UK, and compared with miniPIERS, is dependent on additional access to laboratory tests [30]. The independently predictive components of fullPIERS are: Gestational age, chest pain and/or dyspnea, oxygen saturation, platelet count, and creatinine and aspartate transaminase concentrations. The fullPIERS model predicted adverse maternal outcomes within 48 h of admission (AUC ROC 0.88, 95% CI: 0.84, 0.92) and has been externally validated using data from the miniPIERS cohort for LMICs [27]. The model has been fully externally and temporally validated in high income countries (HIC) [31].

Strength and limitation

The strengths of this study are: The prospective examination of a population of pregnant women attending for routine care in a well-defined gestational age; the use of a validated automated device and

appropriately trained doctors to measure BP, Doppler studies on ultrasound.

Clinical implications

Our results indicate that PE screening in the first trimester is feasible and could be implemented into clinical practice in LMICs. In addition, screening by calculating individual risks by maternal, biophysical, and biochemical markers seems superior to the current guidelines' approach by solitary maternal characteristics. The definition of optimal risk cutoffs is important to identify women that should be offered low-dose aspirin prophylaxis.

Conclusion

The prediction models of PE vary depending upon healthcare resource. Complete model is clinically superior to primary care model but it is not statistically significant. Prognostic models should be easy to use, informative and low cost with great potential to improve maternal and neonatal health in LMIC settings.

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