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ORIGINAL PAPER

Ophthalmic artery Doppler for pre-eclampsia prediction at the first trimester: a Bayesian survival-time model

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Abstract

Objective To develop a Bayesian survival-time model for the prediction of pre-eclampsia (PE) at the first trimester using a combination of established biomarkers including maternal characteristics and history, mean arterial pressure (MAP), uterine artery Doppler pulsatility index (UtA-PI), and Placental Growth Factor (PlGF)) with an ophthalmic artery Doppler peak ratio (PR) analysis.

Methods The receiving operator curve (ROC) analysis was used to determine the area under the curve (AUC), detection rate (DR), and positive screening cut-off value of the model in predicting the occurrence of early-onset PE (< 34 weeks' gestation) and preterm PE (< 37 weeks' gestation).

Results Of the 946 eligible participants, 71 (7.49%) subjects were affected by PE. The incidences of early-onset and preterm PE were 1% and 2.2%, respectively. At a 10% false-positive rate, using the high-risk cut-off 1:49, with AUC 0.981 and 95%CI 0.965–0.998, this model had an 100% of DR in predicting early-onset PE. The DR of this model in predicting preterm PE is 71% when using 1:13 as the cut-off, with AUC 0.919 and 95%CI 0.875–0.963.

Conclusion Combination ophthalmic artery Doppler PR with the previously established biomarkers could improve the accuracy of early and preterm PE prediction at the first trimester screening.

Keywords Bayesian · Ophthalmic artery · Pre-eclampsia · Survival model

Introduction

Pre-eclampsia (PE) approximately affects about 2–8% of pregnancies and is a leading cause of maternal and perinatal mortality and morbidity [1, 2]. Accurate first-trimester prediction of PE would allow for early prevention of the disease [2]. Therefore, many studies have attempted to construct the most accurate model to predict PE. A combination of maternal characteristics and history, biophysical, ultrasound, and maternal serum biochemical markers

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were initially evaluated to screen for risks of PE [3–8]. Ultimately, the International Federation of Gynecology and Obstetrics (FIGO) initiative on PE recommended combined measurements of maternal risk factors, mean arterial pressure (MAP), uterine artery pulsatility index (UtA-PI), and Placental Growth Factor (PlGF) as a superior technique to calculate a patient-specific risk for preterm PE through the Bayesian Approach [2]. The approach is developed based on a survival-time model utilizing a selection of variables that calculates the probability of a patient having the delivery with PE [8, 9].

Maternal ophthalmic artery Doppler assessment is proposed as one of the promising predictors for PE occurrence at both the early [10] and late trimester [11–13]. This procedure is considered safe and reproducible for assessing the maternal hemodynamic change of cerebral vasculature that occurs during the development of PE [14]. Several conflicting evidences have observed the change in ophthalmic artery Doppler which may precede the onset of PE or its complications [15–18].

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 [19, 20]. The promising predictive values of the second- trimester Ophthalmic artery Doppler as a single predictor and in combination with previously established biomarkers were recently published in several studies [13, 19, 21]. However, little was reported on the performance of ophthalmic artery Doppler as one of predictors in a first-trimester model [10]. This study aimed to develop a Bayesian survival-time model which incorporated maternal risk factors, mean UtA-PI, ophthalmic artery Doppler PR, and PlGF for the first trimester prediction of PE.

Methods

Population

Data were collected from women who attended their first-trimester screening at Harapan Kita National Women and Children's Hospital between August 2019 and October 2020. Gestational age was determined by the measurement of fetal crown-rump length (CRL). 11^0–13^6 weeks gestation ultrasound scans, maternal characteristics, and medical history were obtained. Maternal MAP was measured by automated devices (3BTO-A2; Microlife, Taipei, Taiwan) based on the protocol recommended [22, 23]. Pulsatility Index (PI) of both the left and right uterine artery were examined by transabdominal color Doppler ultrasound using the E8 Voluson™ machine [24]. All ultrasound studies were performed by sonographers who had received the Certificate of Competence from The Fetal Medicine Foundation (www.fetalmedicine.com) for the 11–13 weeks pregnancy scan and PE screening. Serum PLGF was measured using the Electrochemiluminescence assay method (Cobas E411 analyser, Roche Diagnostics, USA) [25]. The right ophthalmic PR was assessed at the visit according to the protocol established by the previous researchers: [26, 27]. In a supine position with the head inclined approximately at 15 to 30 degrees, 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-degree 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 and100 Hz. Three consecutive waveforms of similar size and shape were obtained with the pulsed Doppler mode, and the peak ratio (PR) was measured in a single waveform. Two peaks appeared on the beginning of each waveform are considered as the first and second systolic wave. The PR was defined as the ratio of the second to first peak velocity (Fig. 1). The inclusion criteria were 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. Low dose aspirin (80 mg/day) is considered to be offered for high risk patient which is traditionally determined by the local protocol.

Patient characteristics

The recorded variables are as follows: maternal age, parity (parous or nulliparous), pregnancy interval (less than 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/m^2).

Outcome

Data on obstetrics and neonatal outcomes were collected from the midwife and the hospital medical records. The

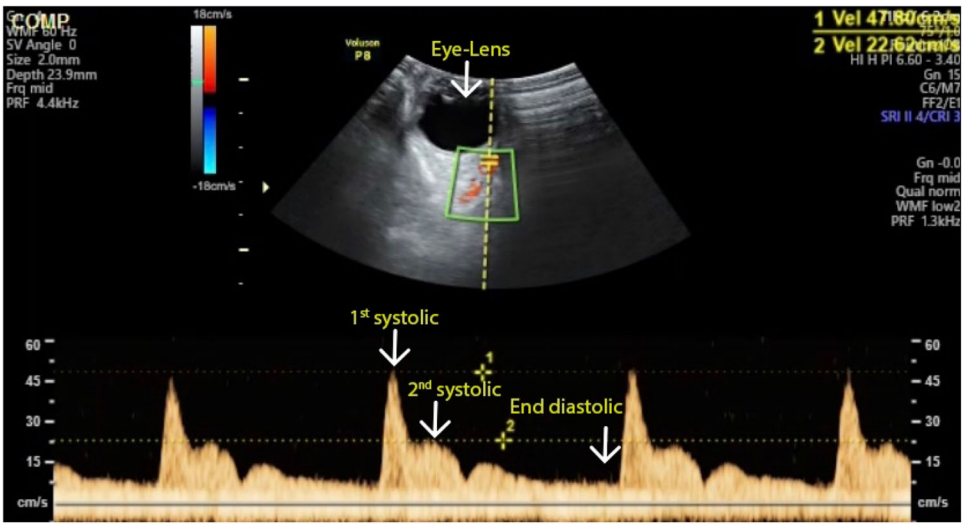

Fig. 1 Ophthalmic artery Doppler assessment. At the bottom is the waveform of the ophthalmic artery obtained by pulsed Doppler illustrating the first and second peak systolic velocity

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 [28]. Early-onset PE is characterised as delivery with PE at < 34 + 0 weeks' gestation while preterm PE at < 37 + 0 weeks was defined as PE with delivery weeks' gestation [2].

Statistical analysis

FIGO favoured the Bayesian approach as a statistical technique for the first-trimester screening study of PE due to its more superior performance as compared to the multivariate regression analysis [2, 8]. Thus, a Bayesian Accelerated Failure-Time model for the gestational age of delivery with PE was developed in this study. Information from the maternal risk factors and biomarkers log10 MoM values were used as foundation of the Bayesian approach. In developing the model, gestational age was assumed to follow a Weibull distribution. Due to its flexibility in accommodating constant, decreasing, or increasing function which often occurs in a real population. Correlation tests were also performed to detect any multicollinearity among the numerical determinants (uterine artery PI, MAP, Ophthalmic PR, and Plgf).

The continuous variables of maternal characteristics and history were converted into categorical variables. The values of uterine artery PI, MAP, Ophthalmic PR, and Plgf were $\log_{10}$ transformed to make the distribution normal. Each value was presented as a multiple of median (MoM) to measure the deviation of individual values from the study population median. Statistical model to predict the probability of having delivery with PE before a specified gestational age was developed using the eligible explanatory variables (maternal risk factors, biophysical markers, and biochemical marker). Model accuracy, detection rate, false-positive rate, and cut-off points to differentiate low risk and high-risk groups were assessed using the Receiver Operating Curve (ROC) analysis. R Software (GNU General Public License, Auckland, New Zealand) and SPSS 26.0 (SPSS Inc., Chicago, IL, USA) were used to perform all statistical analyses in this study.

Results

Characteristics of the study population

There were 1002 singleton pregnancies included in our first-trimester screening. UtA-PI and PlGF were successfully measured in 98.30% of the subjects whereas Ophthalmic PR was assessed in all subjects. 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. The incidence of early-onset and preterm PE were respectively 1% (9/946) and 2.2% (21/946). Women in the PE group underwent deliveries earlier than those who were unaffected by PE (Fig. 2). The mean gestational age of delivery with PE and non-PE group were respectively 38.89 and 37.00 weeks. Maternal and pregnancy characteristics of both groups are compared 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

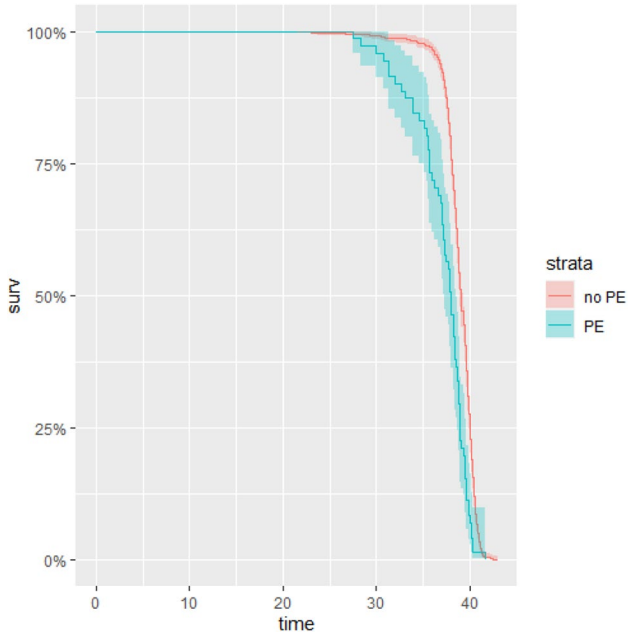

Fig. 2 Survival analysis curve of gestational age at delivery from PE and non-PE group

had more subjects who had an IVF pregnancy and those with a > 10 years delivery interval. While Log_{10} MoM MAP, Log_{10} MoM Mean UtA-PI, and Log_{10} MoM Ophthalmic PR were higher in the PE group, Log10 MoM Plgf was lower in the PE group (Table 2).

Model for gestational age at delivery with PE

The final model for mean gestational age of delivery with PE is provided in Table 3. The effect of categorical variables on the gestational age at delivery with PE is shown in Fig. 3. Previous history of PE and type 2 DM were significantly associated with an earlier delivery with PE. Those with previous history of PE were 3.5 times more likely to have an earlier delivery than those unaffected with PE. Additionally, subjects with type 2 DM were 6.27 times more likely to deliver earlier than those in the unaffected group.

The regression formula is:

$\log\gamma = \beta_1 z_1 + \ldots \beta_p z_p$ and

$$S(t, Z) = \exp(-\lambda t^p)^\gamma$$

where $Z = \left(z_1, \ldots, z_p\right)$ is a vector of explanatory variables consisting of:

First Pregnancy (z_1); $z_1 = 1 if Yes, 0 if No$, class_pregninterval (z_2); $z_2 = 1 \text{if} < 1 \text{year}, 0 if \geq 10 \text{years}$, conception (z_3); $z_3 = 1, \text{if IVF}, 0 \text{if Spontaneous}$, PreviousPE (z_4); $z_4 = 1 \text{if Yes}, 0 \text{if No}$, DM2 (z_5); $z_5 = 1, ifYes 0, ifNo$, ChronicHT (z_6); $z_6 = 1, ifYes 0, ifNo$, FamHistofPE (z_7); $z_7 = 1, ifYes 0, ifN$, Age (z_8), BMI (z_9), Log_{10} MoM MAP (z_{10}), Log_{10} MoM Mean UtA-PI (z_{11}), Log10 MoM Ophthalmic PR (z_{12}), Log10 MoM Plgf (z_{13}). λ is the parameter scale, and p is the parameter shape.

The model had good accuracy in predicting both the early-onset (Fig. 4) and preterm PE (Fig. 5). The area under the curve of this model were 0.991 (95%CI 0.965–0.998) and 0.919 (95%CI 0.875–0.963) for predicting early-onset and preterm PE, respectively.

At a 10% false-positive rate, using the cut-off 1:49, this model had an 100% of detection rate in predicting early-onset PE. The detection rate of this model in predicting

Table 1 Maternal and pregnancy characteristics in the screening population

Variable	PE ($n=71$)	Unaffected ($n=875$)
Maternal age (year)	29.19 (7.71)	28.50 (6.36)
Maternal weight, kg	64 (22)	58 (15)
Maternal height, cm	156 (8)	156 (7)
Body mass index, kg/m^2	26.17 (8.05)	23.78 (5.85)
Gestational age, wk	12 (1)	12 (1)
Racial origin, *n* (%)		
South Asian	0 (0)	4 (0.5%)
East Asian	71 (100%)	871 (99.5%)
Medical history		
Previous gestational hypertension	1 (1.4%)	1 (0.1%)
Previous PE	14 (19.7%)	20 (2.3%)
Previous gestational diabetes	1 (1.4%)	1 (0.1%)
Chronic hypertension	9 (12.7%)	7 (0.8%)
Type 2 diabetes mellitus	3 (4.2%)	6 (0.7%)
Systemic lupus erythematosus/antiphospholipid syndrome	0 (0%)	2 (0.2%)
Family history of PE	6 (8.5%)	32 (3.7%)
Parity		
Nulliparous	37 (52.1%)	456 (52.1%)
Parous	34 (47.9%)	419 (47.9%)
Pregnancy interval		
< 1 year or first pregnancy	69 (97.2%)	847 (96.8%)
> 10 years	2 (2.8%)	28 (3.2%)
Conception		
Spontaneous	68 (95.8%)	827 (94.5%)
In vitro fertilization	3 (4.2%)	48 (5.5%)
Medication during pregnancy		
Aspirin	4 (5.6%)	4 (0.5%)
Anti-hypertension	4 (5.6%)	1 (0.1%)
Insulin	0 (0%)	1 (0.1%)

Table 2 Biophysical and Biomarker measurement values and Log_{10} MoM in PE and unaffected group

Variables	PE $n=71$	Unaffected $n=875$
Measurement values		
MAP (mmHg)	93.50 (10.5)	82.60 (11)
Final Mean UtA-PI	1.94 (0.58)	1.76 (1.76)
Ophthalmic PR	0.69 (0.25)	0.56 (0.18)
PlGF (pg/ml)	43.07 (34.24)	49.82 (30.69)
Log_{10} MoM Values		
Log_{10} MoM MAP	0.050 (0.05)	− 0.0034 (0.06)
Log_{10} MoM Final Mean UtA-PI	0.037 (0.13)	− 0.0049 (0.17)
Log_{10} MoM Ophthalmic PR	0.083 0.17)	− 0.0077 (0.14)
Log_{10} MoM PlGF	− 0.098 (0.36)	0.0038 (0.26)

Data are given as median (interquartile range)

MAP mean arterial pressure; *UtA-PI*, Uterine Artery Pulsatility Index; *Ophthalmic PR* Ophthalmic Artery Peak Ratio; *PlGF* placental growth factor

Table 3 Bayesian accelerated failure-time model for the mean gestational age at delivery with PE

Term	Regression coefficients
Shape	16,5
Scale	2.65e-28
First Pregnancy	0.370
Pregnancy Interval	− 0.377
Conception	0.304
Previous PE	1190
Type 2 DM	1550
Chronic Hypertension	0.123
Family history of PE	0.345
Age	− 1.26e-05
BMI	− 0.014
Log_{10} MoM MAP	22,600
Log_{10} MoM Mean UtA-PI	2570
Log_{10}MoM Ophthalmic PR	0.989
Log_{10} MoM Plgf	− 1590

DM diabetes mellitus; *PE* pre-eclampsia; *BMI* body mass index; *MAP* mean arterial pressure; *UtA-PI*, Uterine Artery Pulsatility Index; *Ophthalmic PR* Ophthalmic Artery Peak Ratio; *PlGF* placental growth factor

preterm PE is 71% when using 1:13 as the positive cut-off (Table 4).

Discussion

Our finding supports the previous study that multimodal first-trimester screening with the addition of ophthalmic artery Doppler PR demonstrates an acceptable performance for the detection of PE. Sarno and Coworkers [13] conducted a prospective study in 2287 women who attended routine visits at 35–37 weeks' gestation to assess the role of maternal ophthalmic artery Doppler combined with the established biomarkers of PE. They reported that with the addition of the adjusted ophthalmic PR to maternal risk factor, MAP, and PlGF, the detection rate (DR) for delivery with PE at any time after a risk assessment was 70.8% at a 10% of false-positive rate (FPR). In another study with a similar method performed at 19–23 weeks' gestation, it was reported a 90.3% DR at 10% FPR after combining ophthalmic PR with maternal factors, MAP, UtA-PI plus PlGF for the prediction of PE [21]. In our population, at 10% FPR, using the cut-off 1:49, the model had an 100% of DR in predicting early-onset PE. The DR of this model in predicting preterm PE is 71% when using 1:13 as the high-risk cut-off. We found no parallel study regarding the model development of first-trimester screening for PE prediction that incorporating ophthalmic Doppler assessment as one of their test components.

In our analysis, we found that the median of first-trimester Ophthalmic PR artery Doppler was higher in women who suffered from PE at later gestations than women in the non-PE group (0.69 versus 0.56). Alves and Colleagues (2014) [26] reported a first-trimester ophthalmic artery Doppler reference data that was developed from 409 normal pregnancies. They found that the reference value for Ophthalmic PR was 0.5860 ± 11. The ophthalmic PR artery Doppler were not significantly different among the control (0.58 ± 0.11), early PE (0.63 ± 0.13), and late PE (0.59 ± 0.15) group.

On the contrary, in several other studies, a higher level of Ophthalmic PR was found in the PE group at the second trimester and puerperal period of the pregnancy. Takata et al. [29] conducted a study to assess the characteristics of endothelial dysfunction in various degrees of PE by performing Doppler ultrasonography on the uterine, ophthalmic, and brachial arterial blood flow of women with normal, intrauterine growth restriction (IUGR), mild PE, and severe PE. The Ophthalmic PR were significantly different between the normal, mild, and severe-PE group (0.47 ± 0.07, 0.70 ± 0.10, and 0.81 ± 0.12, respectively). However, there was no significant difference in the Ophthalmic PR between the normal and IUGR group. Borges et al. [30] performed an ophthalmic artery assessment of 44 postpartum preeclamptic women and 49 normal postpartum women at the immediate (10 days), late (45 days), and remote (90 days) period of puerperium. The Ophthalmic PR was persistently higher in the PE group than non-PE group at all three-time intervals. The ophthalmic artery Doppler profile of preeclamptic women at the puerperium period was then presumed to explain the persistent signs of hyper perfusion of the orbital vascularization. In another prospective cohort study

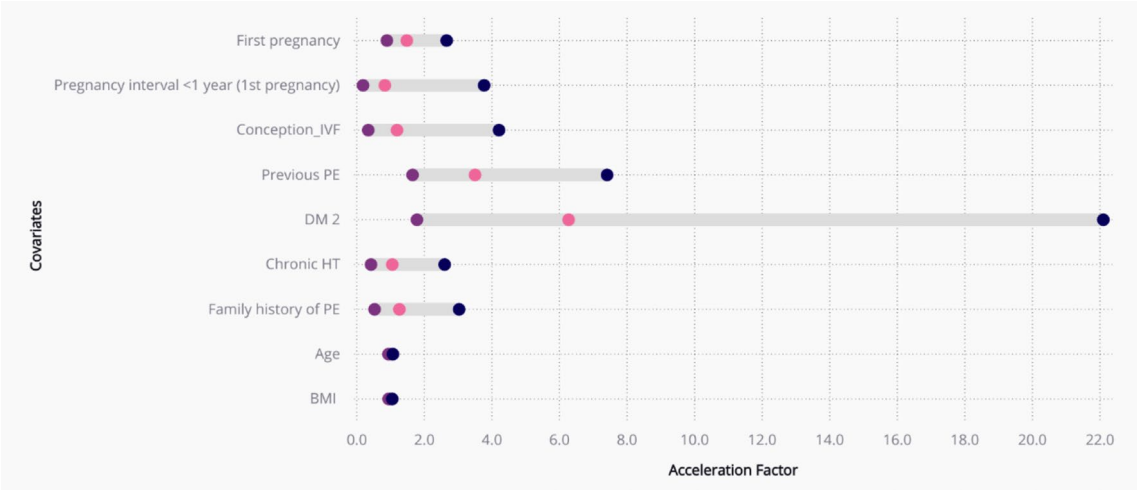

Fig. 3 Effect of categorical variables on gestational age at delivery with PE

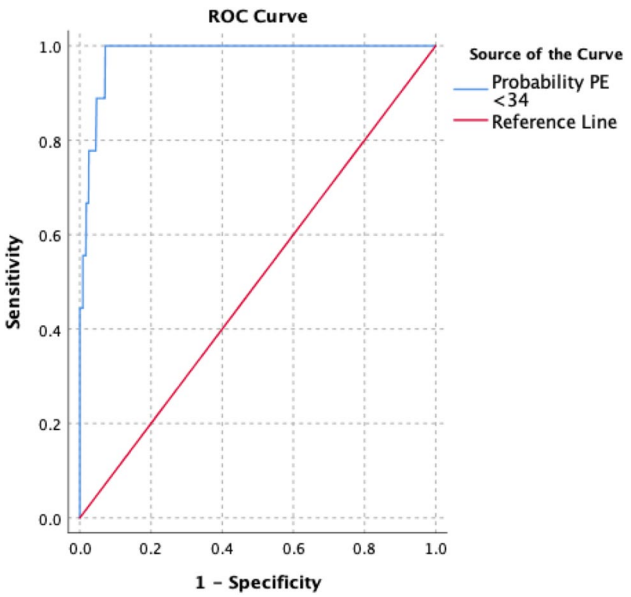

Fig. 4 ROC curve of our model to predict early-onset PE (AUC =0.981, 95%CI 0.965–0.998)

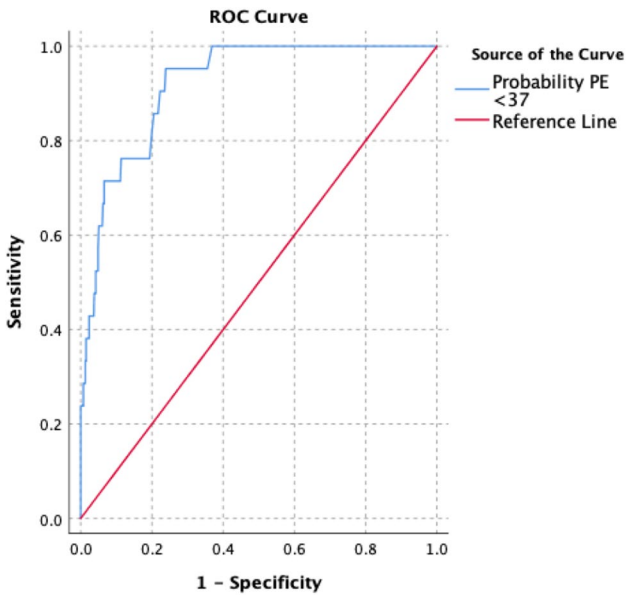

Fig. 5 ROC curve of our model to predict preterm PE (AUC =0.919, 95%CI 0.875–0.963)

by Matias and Colleagues [16] on 305 pregnant women at 20- to 28 weeks' gestation, ophthalmic PR was significantly higher in women who subsequently experienced PE compared to the control group (0.57 ± 0.10 versus 0.49 ± 0.11, P value < 0.001).

We found conflicting findings on the ophthalmic artery Doppler ability to predict PE. It has been suggested that the combination of uterine PI and Ophthalmic PR Doppler ultrasound at the first-trimester screening to predict PE delivery of small-for-gestational-age neonates, without considering maternal risk factors and MAP, resulted only in a 25.9% detection rate with a 10% false positivity rate and a 0.78 area under the curve (AUC) (95%CI 0.65–0.92) [31]. It was also indicated the inaccuracy of ophthalmic artery resistive index between 24 and 28 weeks of pregnancy as a predictor for PE with an AUC of 0.694 (CI 0.543–0.845) [18]. Sapantzoglou et al. [21] studied the capability of ophthalmic artery Doppler at 19–23 weeks' gestation alone in predicting the occurrence of PE at later gestation and in combination with the previously established PE biomarkers. They found that ophthalmic PR strengthened the prediction of preterm PE offered by maternal factors, MAP, UtA-PI and PlGF from 85.5% to 90.3%, at FPR of 10%. The ophthalmic PR also improved

Table 4 Screening Performance of PE prediction model with the addition of Ophthalmic PR

FPR (%)	Early-Onset PE (< 34 WGA), $N=9$			Preterm PE (<37 WGA), $N=21$		
	Risk Cutoff	Screen + Rate	Detection Rate	Risk cutoff	Screen + Rate	Detection rate
5	1:30	6.0%	89%	1:8	6.3%	62%
10	1:49	11.2%	100%	1:13	11.7%	71%
15	1:65	15.6%	100%	1:18	17.2%	76%

the prediction of term PE offered by maternal factors, MAP, UtA-PI plus PlGF from 45.2 to 53.4% at FPR of 10%. A prospective cohort study on 440 singleton pregnancies at week 11–14 of gestation to assess the PE prediction performance of maternal risk factors, UtA-PI, and ophthalmic artery first diastolic peak velocity[10].

The combination of maternal factors with either UtA-PI or first diastolic peak velocity led to a 67% detection rate of early PE [26]. A 2020 study discovered that a second systolic peak velocity of the ophthalmic Doppler ultrasound could improve the accuracy of a clinical-based prediction model from 0.77 (95% CI 0.72–0.82)] to 0.84 (95% CI 0.79–0.88) [16]. Nonetheless, a limited study has elucidated the PE prediction capability of ophthalmic artery Doppler at the first trimester.

The change in Doppler flow of the maternal vascular might be a promising marker in the prediction of PE. This theory was supported by several studies that showed the maternal vascular changes since the first trimester of pregnancy which could subsequently be affected by PE [32, 33]. In other words, the alterations of maternal cerebral circulation reflected in the changes of the ophthalmic arteries measurement index could precede to the development of PE [34].

The strengths of this study are: (1) It is the first to combine maternal ophthalmic artery Doppler with previously established biomarkers including maternal risk factor, MAP, UtA-PI, and PlGF for PE prediction at the first trimester screening, (2) to our knowledge, this study had the largest number of participants and hence the largest data of maternal ophthalmic Doppler for the PE prediction model, (3) the Bayesian approach that was applied to develop the survival-time model has been established by FIGO as a superior statistical method for the first trimester PE screening program [2], (4) the first trimester screening and Doppler assessment of ophthalmic artery were conducted by trained and certified sonographers using a standardized techniques, and (5) the number of participants affected by PE in this study represented a regional or larger population.

In this study, we analyzed only the ophthalmic PR in our prediction model rather than considering any other ophthalmic artery Doppler measurement indexes such as pulsatility index, resistive index, peak systolic velocity, or peak diastolic velocity. Despite this limitation, ophthalmic PR was chosen in this study based on the recommendation of previous studies with a large population [19, 20]. In a further study we need to assess the potential performance of ophthalmic artery PR and combining biomarkers in the first-trimester prediction of PE.

Conclusion

The combination of ophthalmic artery Doppler PR analysis and the previously established biomarkers resulted in a considerably accurate first trimester prediction model for early and preterm PE. The predictive values of each predictor with the ophthalmic PR, however, should be explored and validated in a larger study.

Author contributions The study was designed and conceived by RAK. RAK and AN performed data collection and interpretation. RAK and AN drafted the early version of the manuscript. DSN, DD, SA and IS critically reviewed and revised the content. All authors approved the final version of the manuscript.

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Data availability Data are available upon reasonable request.

Declarations

Conflict of interest The authors declared that they have no conflict of interest.

Ethical approval All participants had signed a written informed consent approved by Medical and Health Research Ethics Committee, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada/Dr Sardjito Hospital, Yogyakarta, Indonesia (KE/0295/03/2020).

Informed consent All patients have given their consent to participate in this study.

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