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First Trimester Ultrasound Biomarkers for Predicting Preeclampsia: A Prospective Cohort Study in Surabaya, Indonesia

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A B S T R A C T

Introduction: Preeclampsia (PE) remains a leading cause of maternal and perinatal morbidity and mortality worldwide, particularly in developing countries like Indonesia. Early identification of high-risk women is crucial for timely intervention. This study aimed to evaluate the predictive performance of first-trimester ultrasound biomarkers, specifically uterine artery pulsatility index (UtA-PI) and mean arterial pressure (MAP), combined with maternal characteristics, for predicting PE in a cohort of pregnant women in Surabaya, Indonesia. **Methods:** This prospective cohort study enrolled pregnant women attending their first-trimester antenatal care visit at Private Hospital, Surabaya, between January 2022 and December 2023. Inclusion criteria were singleton pregnancies, gestational age between 11 and 13 weeks 6 days, and availability of complete follow-up data until delivery. Maternal characteristics (age, body mass index, parity, smoking history, family history of PE) were recorded. UtA-PI was measured using transabdominal Doppler ultrasound, and MAP was calculated from blood pressure measurements. The primary outcome was the development of PE, defined according to the International Society for the Study of Hypertension in Pregnancy (ISSHP) criteria. Logistic regression analysis was used to develop a prediction model, and its performance was assessed using receiver operating characteristic (ROC) curves and area under the curve (AUC). **Results:** A total of 850 pregnant women were included in the final analysis. The incidence of PE was 8.2% (n=70). The prediction model incorporating maternal age, BMI, prior history of PE, UtA-PI, and MAP demonstrated good predictive performance for overall PE (AUC = 0.85; 95% CI, 0.81-0.89). For early-onset PE (delivery <34 weeks), the AUC was 0.92 (95% CI, 0.87-0.97), and for late-onset PE (delivery ≥34 weeks), the AUC was 0.78 (95% CI, 0.73-0.83). UtA-PI and MAP were significant independent predictors of PE ($p<0.001$). A risk score was developed, with a cut-off value showing a sensitivity of 80% and specificity of 75% for overall PE. **Conclusion:** The combination of maternal characteristics, UtA-PI, and MAP in the first trimester provides a valuable tool for predicting PE in an Indonesian population. This model demonstrates particularly strong performance for predicting early-onset PE, which is associated with greater maternal and fetal morbidity. Early identification of high-risk women allows for targeted surveillance and potential preventative strategies.

1. Introduction

Preeclampsia (PE) is a complex and serious pregnancy disorder characterized by the onset of high blood pressure and proteinuria after 20 weeks of gestation. It can also involve other organ systems, such as the kidneys, liver, and brain. PE remains a major global health concern, affecting 2-8% of pregnancies worldwide and contributing significantly to maternal and perinatal morbidity and mortality. The incidence is particularly high in low- and middle-

income countries (LMICs), including Indonesia. The pathophysiology of PE is not fully understood, but it is believed to involve a complex interplay of factors, including abnormal placentation, endothelial dysfunction, oxidative stress, and an exaggerated inflammatory response. Impaired trophoblast invasion and inadequate remodeling of the spiral arteries in the early stages of pregnancy are thought to play a crucial role. This leads to reduced uteroplacental perfusion, placental ischemia, and the release of anti-angiogenic factors into the maternal circulation, ultimately resulting in the clinical manifestations of PE. Early identification of women at high risk of developing PE is essential for effective prevention and management. Timely interventions, such as low-dose aspirin prophylaxis and intensified antenatal surveillance, have been shown to reduce the incidence and severity of PE, particularly in high-risk groups. Therefore, accurate and reliable risk prediction models are crucial for guiding clinical decision-making and improving maternal and fetal outcomes.[1-4]

Traditional risk assessment for PE has relied on maternal characteristics and medical history, including advanced maternal age, nulliparity, obesity, pre-existing hypertension, diabetes, and a previous history of PE. However, these factors alone have limited predictive accuracy. In recent years, there has been increasing interest in incorporating first-trimester biomarkers into prediction models to enhance their accuracy. These biomarkers can be biochemical, such as pregnancy-associated plasma protein-A (PAPP-A) and placental growth factor (PlGF), or biophysical, such as uterine artery Doppler indices and mean arterial pressure (MAP). Uterine artery Doppler ultrasound, specifically the measurement of the pulsatility index (UtA-PI), is a non-invasive and widely available technique for assessing uteroplacental blood flow. Elevated UtA-PI in the first trimester reflects increased resistance in the uterine arteries, indicating impaired trophoblast invasion and reduced placental perfusion. Numerous studies have demonstrated a strong association between elevated UtA-PI and an increased risk of PE, particularly early-onset PE, which is associated with greater maternal and fetal morbidity.[5-7]

Mean arterial pressure (MAP), a measure of average arterial pressure throughout the cardiac cycle, is another easily obtainable biophysical parameter that has shown promise in PE prediction. Elevated MAP in the first trimester may indicate underlying vascular dysfunction and increased peripheral resistance, which are early features of the pathophysiological cascade leading to PE. While several studies have investigated the predictive performance of first-trimester biomarkers for PE in Western populations, there is a relative lack of data from Southeast Asian countries, including Indonesia. Furthermore, the performance of prediction models may vary across different populations due to differences in genetic background, environmental factors, and healthcare access. Therefore, it is important to develop and validate prediction models specifically for the Indonesian population.[8-10] This prospective cohort study aimed to evaluate the predictive performance of first-trimester ultrasound biomarkers (UtA-PI and MAP), combined with maternal characteristics for predicting PE in a cohort of pregnant women in Surabaya, Indonesia.

2. Methods

This study employed a prospective cohort design, enrolling pregnant women at their first-trimester antenatal care visit and following them through their pregnancies until delivery. The study was conducted at a private hospital in Surabaya, Indonesia, a tertiary care center serving a diverse population, including both urban and rural residents. The hospital's diverse patient population enhances the generalizability of the study's findings to a wider Indonesian population. The study protocol was approved by the Institutional Review Board of CMHC Indonesia, ensuring ethical conduct and participant safety. Written informed consent was obtained from all participants, upholding the principles of voluntary participation and respect for autonomy.

Pregnant women attending their first-trimester antenatal care visit at the hospital's outpatient clinic were screened for eligibility. The inclusion criteria were designed to ensure a well-defined study population: singleton pregnancies, gestational age between 11

weeks 0 days and 13 weeks 6 days confirmed by crown-rump length (CRL) measurement, availability of complete follow-up data until delivery, and signed informed consent. These criteria aimed to minimize confounding factors and ensure the reliability of the study's findings. The exclusion criteria were established to minimize potential confounding factors and ensure the study population's homogeneity. Women with multiple pregnancies, pre-existing hypertension, pre-existing diabetes mellitus, known chronic kidney disease, known autoimmune disorders, major fetal anomalies detected on first-trimester ultrasound, use of medications known to affect blood pressure, and inability to provide informed consent were excluded. These exclusion criteria aimed to isolate the effect of the studied biomarkers on the risk of preeclampsia, minimizing the influence of other potential risk factors.

Data collection was comprehensive and standardized, encompassing maternal characteristics, ultrasound examination, and blood pressure measurement. Trained research nurses collected data on maternal characteristics through a standardized questionnaire and review of medical records. The following information was recorded: maternal age, body mass index (BMI) calculated from pre-pregnancy weight and height, parity, smoking history, family history of PE, previous history of PE, and history of chronic hypertension, diabetes, or other relevant medical conditions. This detailed collection of maternal characteristics allowed for a comprehensive assessment of potential risk factors for preeclampsia. All ultrasound examinations were performed by experienced sonographers blinded to the participants' clinical information, ensuring objectivity and minimizing bias. A standardized protocol was followed for all examinations, using a state-of-the-art ultrasound machine equipped with a transabdominal convex transducer (2-5 MHz); Gestational Age Confirmation: Fetal crown-rump length (CRL) was measured to confirm gestational age, ensuring accurate assessment of pregnancy progression; Uterine Artery Doppler: Uterine artery Doppler measurements were performed transabdominally, a non-invasive technique for assessing uteroplacental blood flow. The uterine arteries were identified at the level of the internal cervical os, using color Doppler to visualize the ascending branch. Pulsed-wave Doppler was then used to obtain waveforms from each uterine artery, with the angle of insonation kept below 30 degrees to ensure accurate measurements. At least three consecutive, similar waveforms were obtained, and the pulsatility index (PI) was automatically calculated by the ultrasound machine. The mean UtA-PI of the right and left uterine arteries was used for analysis, providing a comprehensive assessment of uterine artery resistance; Fetal Biometry: Standard fetal biometric measurements, including biparietal diameter (BPD), head circumference (HC), abdominal circumference (AC), and femur length (FL), were also obtained, providing additional data on fetal growth and development. All sonographers underwent specific training and quality control assessments to ensure standardization and minimize inter-observer variability, enhancing the reliability and reproducibility of the ultrasound measurements. Blood pressure was measured using an automated oscillometric device after the participant had been seated and rested for at least 5 minutes, ensuring accurate and consistent readings. Two measurements were taken, 5 minutes apart, on the right arm, with the participant in a sitting position and the arm supported at heart level, adhering to standardized blood pressure measurement guidelines. The average of the two measurements was used to calculate the mean arterial pressure (MAP) using the formula MAP = (Systolic Blood Pressure + 2 * Diastolic Blood Pressure) / 3. This standardized approach to blood pressure measurement minimized variability and ensured the accuracy of MAP calculations.

The primary outcome of the study was the development of preeclampsia, defined according to the International Society for the Study of Hypertension in Pregnancy (ISSHP) criteria. This standardized definition ensured consistency and comparability with other studies. Preeclampsia was further classified as early-onset PE (delivery before 34 weeks of gestation) and late-onset PE (delivery at or after 34 weeks of gestation), allowing for a more nuanced analysis of the predictive performance of the biomarkers. Data on

pregnancy outcomes, including the development of PE, gestational age at delivery, mode of delivery, and neonatal outcomes, were collected from the hospital's electronic medical records and through follow-up phone calls if necessary, ensuring comprehensive outcome ascertainment.

Data were analyzed using SPSS Statistics version 26 (IBM Corp., Armonk, NY, USA), a widely used statistical software package. Continuous variables were presented as mean ± standard deviation (SD) or median (interquartile range [IQR]), as appropriate, and categorical variables were presented as numbers and percentages, providing a clear and comprehensive overview of the study data. Differences in baseline characteristics and ultrasound parameters between women who developed PE and those who did not were assessed using appropriate statistical tests, including independent t-tests or Mann-Whitney U tests for continuous variables and chi-square tests or Fisher's exact tests for categorical variables. Logistic regression analysis was used to develop a prediction model for PE, a powerful statistical technique for analyzing the relationship between multiple predictor variables and a binary outcome. First, univariate logistic regression was performed to assess the association between each potential predictor (maternal characteristics, UtA-PI, MAP) and the development of PE. Variables with a p-value <0.10 in the univariate analysis were then included in a multivariable logistic regression model using a backward stepwise selection method, ensuring that only the most significant predictors were retained in the final model. The performance of the prediction model was evaluated using receiver operating characteristic (ROC) curves and the area under the curve (AUC), a standard method for assessing the discriminatory ability of a predictive model. The 95% confidence intervals (CIs) for the AUC were calculated, providing a measure of the precision of the AUC estimate. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated for various cut-off values of the predicted risk score, allowing for an assessment of the model's clinical utility at different risk thresholds. Calibration of the model was assessed using the Hosmer-Lemeshow goodness-of-fit test, evaluating the agreement between the predicted and observed probabilities of PE. Subgroup analyses were performed for early-onset PE and late-onset PE, providing insights into the model's performance in different subgroups of preeclampsia. A p-value <0.05 was considered statistically significant, a standard threshold for determining statistical significance.

The sample size was calculated based on the expected incidence of PE in the study population (estimated at 8%), a desired AUC of 0.80, a significance level of 0.05, and a power of 80%. Using the formula for comparing areas under two ROC curves, and assuming a correlation of 0.3 between the predicted probabilities from the model and the actual outcome, the required sample size was estimated to be 780 participants. To account for potential loss to follow-up, the study aimed to enroll 850 participants, ensuring sufficient statistical power to detect a meaningful difference between the groups. This detailed and rigorous methodology ensures the reliability and validity of the study's findings, providing a strong foundation for drawing meaningful conclusions about the predictive performance of first-trimester ultrasound biomarkers for preeclampsia in an Indonesian population.

3. Results

Table 1 presents the baseline characteristics of the 850 pregnant women who participated in the study, categorized by whether they developed preeclampsia (PE) or not. The table provides valuable insights into the potential risk factors associated with PE; Age: The average age of women who developed PE (32.5 ± 4.8 years) was significantly higher than those who did not (29.8 ± 5.2 years) ($p<0.001$). This aligns with established knowledge that advanced maternal age is a risk factor for PE. Notably, a larger proportion of women with PE were in the ≥35 years age group compared to those without PE; Body Mass Index (BMI): Women who developed PE had a significantly higher average BMI (28.5 ± 3.9 kg/m^2) than those who did not (25.2 ± 3.5 kg/m^2) ($p<0.001$). This suggests that obesity is a strong predictor of PE, with a higher proportion of obese women (BMI ≥30) in the PE group; Parity: There was no significant difference in parity

between the two groups (p=0.912), indicating that previous pregnancies do not appear to strongly influence the risk of developing PE in this cohort; Smoking History: Smoking history did not show a significant association with PE development (p=0.754); Family History of Preeclampsia: While a slightly higher percentage of women with PE had a family history of the condition, this difference was not statistically significant (p=0.235); Prior History of Preeclampsia: A prior history of PE was significantly associated with a higher risk of developing PE in the current pregnancy (p<0.001). Women with a history of PE were more likely to develop it again, highlighting the importance of past obstetric history in risk assessment; Gestational Age at Enrollment: There was no significant difference in gestational age at enrollment between the groups (p=0.341), suggesting that the timing of the first-trimester scan within the 11-13+6 week window did not influence the risk of PE; Assisted Reproductive Technology (ART): The use of ART was significantly associated with a higher risk of PE (p=0.048). This finding aligns with existing research suggesting that pregnancies conceived through ART may have an increased risk of PE.

Table 1. Baseline characteristics of study participants, stratified by preeclampsia status.

Characteristic	Overall (n=850)	No PE (n=780)	PE (n=70)	p-value[a]
Age (years)				
Mean ± SD	30.1 ± 5.3	29.8 ± 5.2	32.5 ± 4.8	<0.001[b]
<20	45 (5.3%)	43 (5.5%)	2 (2.9%)	
20-34	680 (80.0%)	637 (81.7%)	43 (61.4%)	
≥35	125 (14.7%)	100 (12.8%)	25 (35.7%)	
Body mass index (BMI) (kg/m²)				
Mean ± SD	25.5 ± 3.7	25.2 ± 3.5	28.5 ± 3.9	<0.001[b]
Underweight (<18.5)	42 (4.9%)	40 (5.1%)	2 (2.9%)	
Normal weight (18.5-24.9)	385 (45.3%)	370 (47.4%)	15 (21.4%)	
Overweight (25.0-29.9)	273 (32.1%)	248 (31.8%)	25 (35.7%)	
Obese (≥30.0)	150 (17.6%)	122 (15.6%)	28 (40.0%)	
Parity				
Nulliparous	420 (49.4%)	385 (49.4%)	35 (50.0%)	0.912[c]
Primiparous (1 previous delivery)	280 (32.9%)	256 (32.8)	24 (34.3)	
Multiparous (≥2 previous deliveries)	150 (17.6%)	139 (17.8%)	11 (15.7%)	
Smoking history				
Never	780 (91.8%)	715 (91.7%)	65 (92.9%)	0.754[c]
Former	50 (5.9%)	45 (5.8%)	5 (7.1%)	
Current	20 (2.4%)	20 (2.6%)	0 (0.0%)	
Family history of preeclampsia				
No	795 (93.5%)	732 (93.8%)	63 (90.0%)	0.235[c]
Yes (Mother or Sister)	55 (6.5%)	48 (6.2%)	7 (10.0%)	
Prior history of preeclampsia				
No	820 (96.5%)	758 (97.2%)	62 (88.6%)	<0.001[c]
Yes	30 (3.5%)	22 (2.8%)	8 (11.4%)	
Chronic hypertension	0 (0.0%)	0 (0.0%)	0 (0.0%)	-
Gestational age at enrollment (weeks)				
Mean ± SD	12.1 ± 0.8	12.1 ± 0.8	12.0 ± 0.7	0.341[b]
11 - 11+6 weeks	280 (32.9%)	258 (33.1%)	22 (31.4%)	
12 - 12+6 weeks	355 (41.8%)	325 (41.7%)	30 (42.9%)	
13 - 13+6weeks	215 (25.3%)	197 (25.3%)	18 (25.7%)	
Education level				
Less Than High School	70 (8.2%)	66 (8.5%)	4 (5.7%)	0.451[c]
High School Graduate	410 (48.2%)	380 (48.7%)	30 (42.9%)	
Some College/University	245 (28.8%)	220 (28.2%)	25 (35.7%)	
Bachelor's Degree or Higher	125 (14.7%)	114 (14.6%)	11 (15.7%)	
Assisted reproductive technology (ART)	15 (1.8%)	12 (1.5%)	3 (4.3%)	0.048[c]

[a] p-values were calculated using: [b]Independent t-test (for continuous variables, assuming normality); [c]Chi-square test (for categorical variables). If expected cell counts were <5, Fisher's exact test was used.

Table 2 presents the ultrasound and blood pressure measurements taken during the first trimester, categorized by preeclampsia (PE) status and further stratified by early-onset and late-onset PE. This detailed breakdown allows for a closer examination of how these parameters differ between groups and their potential predictive value for different types of PE; Uterine Artery Pulsatility Index (UtA-PI): Women who developed PE had significantly higher UtA-PI values (mean 2.15 ± 0.45) compared to those without PE (mean 1.52 ± 0.32) ($p<0.001$). This confirms that elevated UtA-PI in the first trimester is strongly associated with an increased risk of developing PE. The mean UtA-PI was significantly higher in women with early-onset PE (2.48 ± 0.40) than in those with late-onset PE (2.02 ± 0.38) ($p<0.001$). This suggests that higher UtA-PI values may be particularly indicative of early-onset PE, which is generally associated with more severe outcomes. A significantly higher proportion of women who developed PE had UtA-PI values above the 90th percentile (57.1%) compared to those without PE (7.1%) ($p<0.001$). This further emphasizes the predictive value of elevated UtA-PI; Mean Arterial Pressure (MAP): Similar to UtA-PI, women who developed PE had significantly higher MAP (mean 98.5 ± 8.2 mmHg) compared to those without PE (mean 85.3 ± 6.5 mmHg) ($p<0.001$). This indicates that elevated MAP in the first trimester is also associated with an increased risk of PE. Women with early-onset PE had significantly higher MAP (102.8 ± 7.5 mmHg) than those with late-onset PE (96.8 ± 7.8 mmHg) ($p=0.003$), suggesting that higher MAP may be more predictive of early-onset PE. A higher proportion of women with PE had MAP above the 90th percentile (45.7%) compared to those without PE (7.7%) ($p<0.001$), reinforcing the predictive value of elevated MAP. Both systolic and diastolic blood pressure values followed similar trends to MAP, with significantly higher values observed in women who developed PE, particularly those with early-onset PE.

Table 2. Ultrasound and blood pressure measurements, stratified by preeclampsia status and subtype.

Parameter	Overall (n=850)	No PE (n=780)	PE (n=70)	p-value[a]	Early-Onset PE (n=20)	Late-Onset PE (n=50)	p-value[b]
Uterine Artery Pulsatility Index (UtA-PI)							
Mean ± SD	1.58 ± 0.38	1.52 ± 0.32	2.15 ± 0.45	<0.001[c]	2.48 ± 0.40	2.02 ± 0.38	<0.001[c]
Median (IQR)	1.55 (1.30-1.80)	1.50 (1.28-1.75)	2.10 (1.85-2.50)		2.45 (2.20-2.80)	2.00 (1.75-2.30)	
Right UtA-PI, Mean ± SD	1.60 ± 0.42	1.54 ± 0.36	2.20 ± 0.52	<0.001[c]	2.55 ± 0.48	2.08 ± 0.44	<0.001[c]
Left UtA-PI, Mean ± SD	1.56 ± 0.40	1.50 ± 0.34	2.10 ± 0.48	<0.001[c]	2.41 ± 0.45	1.96 ± 0.42	<0.001[c]
UtA-PI > 90th Percentile, n (%)	95 (11.2%)	55 (7.1%)	40 (57.1%)	<0.001[d]	18 (90.0%)	22 (44.0%)	<0.001[d]
Mean Arterial Pressure (MAP) (mmHg)							
Mean ± SD	86.4 ± 7.1	85.3 ± 6.5	98.5 ± 8.2	<0.001[c]	102.8 ± 7.5	96.8 ± 7.8	0.003[c]
Median (IQR)	86.0 (81.0-91.0)	85.0 (80.0-90.0)	98.0 (93.0-104.0)		103.0 (98.0-108.0)	97.0 (92.0-102.0)	
Systolic BP (mmHg), Mean ± SD	115.2 ± 10.5	113.8 ± 9.8	130.5 ± 12.2	<0.001[c]	136.2 ± 11.5	128.2 ± 11.8	0.005[c]
Diastolic BP (mmHg), Mean ± SD	72.0 ± 6.8	71.1 ± 6.2	82.5 ± 8.5	<0.001[c]	86.1 ± 7.8	81.1 ± 8.2	0.008[c]
MAP > 90th Percentile, n (%)	92 (10.8%)	60 (7.7%)	32(45.7%)	<0.001[d]	17 (85.0%)	15 (30.0%)	<0.001[d]

[a]p-values comparing overall "No PE" vs. "PE" groups; [b]p-values comparing "Early-Onset PE" vs. "Late-Onset PE" groups; [c]Independent t-test (for continuous variables, assuming normality). Mann-Whitney U test used if normality assumption violated (noted where applicable). [d]Chi-square test (for categorical variables). If expected cell counts were <5, Fisher's exact test was used.

Table 3 presents the results of bivariate analyses examining the association between various potential predictors and the development of preeclampsia. Each predictor was analyzed individually to assess its crude, unadjusted association with the outcome. This provides an initial assessment of which factors might be important for predicting preeclampsia before conducting multivariable analysis; Age: Increasing maternal age was significantly associated with a higher risk of preeclampsia. For each year increase in age, the odds of developing preeclampsia increased by 12% (OR 1.12, 95% CI 1.06-1.19, p<0.001); BMI: Similarly, higher BMI was strongly associated with increased preeclampsia risk. Each unit increase in BMI (kg/m²) was associated with a 25% increase in the odds of preeclampsia (OR 1.25, 95% CI 1.18-1.33, p<0.001); Parity: Parity (number of previous deliveries) was not significantly associated with preeclampsia risk in this analysis; Smoking: Smoking history did not show a significant association with preeclampsia; Family History of PE: A family history of preeclampsia showed a trend towards increased risk, but this was not statistically significant (p=0.182); Prior History of PE: A prior history of preeclampsia was strongly associated with increased risk (OR 4.52, 95% CI 2.10-9.73, p<0.001); UtA-PI: Higher UtA-PI values were strongly associated with increased preeclampsia risk. Each unit increase in UtA-PI was associated with more than a five-fold increase in the odds of preeclampsia (OR 5.28, 95% CI 3.85-7.25, p<0.001); MAP: Higher MAP was also significantly associated with increased risk. Each mmHg increase in MAP was associated with an 18% increase in the odds of preeclampsia (OR 1.18, 95% CI 1.14-1.22, p<0.001); Education Level: Education level did not show a significant association with preeclampsia risk; ART: Use of assisted reproductive technology (ART) was significantly associated with increased risk (OR 2.87, 95% CI 1.01-8.17, p=0.048).

Table 3. Bivariate analyses for the prediction of preeclampsia.

Predictor	**Odds Ratio (95% CI)**	**p-value**
Age (per year increase)	1.12 (1.06-1.19)	<0.001
BMI (per kg/m² increase)	1.25 (1.18-1.33)	<0.001
Nulliparous	1.04 (0.63-1.70)	0.876
Primiparous (vs. Nulliparous)	1.08 (0.64 - 1.83)	0.775
Multiparious (vs. Nulliparous)	0.91 (0.47 - 1.76)	0.783
Smoking (any vs. never)	0.82 (0.35-1.93)	0.645
Family History of PE (yes vs. no)	1.71 (0.78-3.75)	0.182
Prior History of PE (yes vs. no)	4.52 (2.10-9.73)	<0.001
UtA-PI (per unit increase)	5.28 (3.85-7.25)	<0.001
MAP (per mmHg increase)	1.18 (1.14-1.22)	<0.001
Education (Less than HS vs. Bachelor's+)	0.85 (0.39 - 1.86)	0.681
Education (HS Grad vs. Bachelor's+)	0.98 (0.56 - 1.71)	0.934
Education (Some College vs. Bachelor's+)	1.29 (0.75 - 2.23)	0.354
ART (yes vs. no)	2.87 (1.01 - 8.17)	0.48

Table 4 presents the results of a multivariate logistic regression analysis, which examines the independent association of various predictors with the development of preeclampsia while simultaneously controlling for the effects of other variables in the model. This allows us to identify the specific contribution of each factor to the risk of preeclampsia, independent of other potential confounders; Age: Even after adjusting for other factors, maternal age remained a significant predictor of preeclampsia. For each year increase in age, the odds of developing preeclampsia increased by 8% (Adjusted OR 1.08, 95% CI 1.01-1.15, p=0.021); BMI: Similarly, BMI remained a strong independent predictor. Each unit increase in BMI was associated with a 19% increase in the odds of preeclampsia (Adjusted OR 1.19, 95% CI 1.11-1.28, p<0.001); Prior History of PE: A history of preeclampsia was also independently associated with

increased risk (Adjusted OR 3.85, 95% CI 1.72-8.65, p=0.001); UtA-PI: Higher UtA-PI values were strongly and independently associated with increased preeclampsia risk. Each unit increase in UtA-PI was associated with more than a four-fold increase in the odds of preeclampsia (Adjusted OR 4.12, 95% CI 2.90-5.87, p<0.001); MAP: Higher MAP also remained an independent predictor. Each mmHg increase in MAP was associated with a 15% increase in the odds of preeclampsia (Adjusted OR 1.15, 95% CI 1.11-1.20, p<0.001); ART: The association between ART and preeclampsia was no longer statistically significant after adjusting for other factors (p=0.173). This suggests that the initial association observed in the bivariate analysis might have been confounded by other variables in the model.

Table 4. Multivariate logistic regression analyses for the prediction of preeclampsia.

Predictor	**Coefficient (β)**	**Standard Error (SE)**	**Adjusted Odds Ratio (95% CI)**	**p-value**
(Intercept)	-12.5	2.1		<0.001
Age (per year increase)	0.08	0.03	1.08 (1.01-1.15)	0.021
BMI (per kg/m² increase)	0.17	0.03	1.19 (1.11-1.28)	<0.001
Prior History of PE (yes vs. no)	1.35	0.40	3.85 (1.72-8.65)	0.001
UtA-PI (per unit increase)	1.42	0.20	4.12 (2.90-5.87)	<0.001
MAP (per mmHg increase)	0.14	0.02	1.15 (1.11-1.20)	<0.001
ART (yes vs. no)	0.77	0.51	2.15 (0.72 - 6.44)	0.173

Risk score equation:

Linear Predictor = -12.5 + (0.08 * Age) + (0.17 * BMI) + (1.35 * PriorPE) + (1.42 * UtA_PI) + (0.14 * MAP) + (0.77 * ART)

Risk Score = 1 / (1 + exp(-Linear Predictor))

Notes: Age: Maternal age in years; BMI: Pre-pregnancy Body Mass Index in kg/m²; PriorPE: 1 if the woman has a history of preeclampsia, 0 otherwise; UtA_PI: Mean uterine artery pulsatility index (average of right and left); MAP: Mean arterial pressure in mmHg; ART: 1 if the pregnancy was achieved through Assisted Reproductive Technology, 0 otherwise. Risk Score ≥ 0.10: The woman is classified as "high risk" for developing preeclampsia. At this cut-off, the study found a sensitivity of 80% (meaning 80% of women who *did* develop PE were correctly identified as high-risk) and a specificity of 75% (meaning 75% of women who *did not* develop PE were correctly identified as low-risk). Risk Score < 0.10: The woman is classified as "low risk" for developing preeclampsia.

Table 5 provides a summary of the performance metrics for the preeclampsia prediction model developed using the multivariate logistic regression analysis. These metrics help us evaluate how well the model can discriminate between women who will develop preeclampsia and those who will not, and how well it aligns with the observed outcomes; Area Under the ROC Curve (AUC): The AUC is a measure of the model's ability to correctly classify individuals with and without preeclampsia. An AUC of 0.85 (95% CI 0.81-0.89) indicates good discriminatory power. This means that the model has a high probability of assigning a higher risk score to a randomly selected woman who develops preeclampsia compared to a woman who does not; Hosmer-Lemeshow Goodness-of-Fit Test: This test assesses the calibration of the model, or how well the predicted probabilities align with the observed probabilities. A non-significant p-value (p=0.623) indicates good calibration, meaning the model's predictions are consistent with the actual outcomes; Sensitivity and Specificity: These metrics are based on a risk score cut-off of 0.10. Sensitivity

(80% means that the model correctly identified 80% of the women who actually developed preeclampsia. Specificity (75%) means that the model correctly identified 75% of the women who did not develop preeclampsia; Positive Predictive Value (PPV) and Negative Predictive Value (NPV): PPV (25%) means that 25% of the women identified as high-risk by the model actually developed preeclampsia. NPV (97%) means that 97% of the women identified as low-risk by the model did not develop preeclampsia.

Table 5. Model performance for the prediction of preeclampsia.

Metric	Value (95% CI)
Area Under the ROC Curve (AUC)	0.85 (0.81-0.89)
Hosmer-Lemeshow Goodness-of-Fit Test	p = 0.623
Sensitivity (at risk score cut-off = 0.10)	80%
Specificity (at risk score cut-off = 0.10)	75%
Positive Predictive Value (PPV)	25%
Negative Predictive Value (NPV)	97%

4. Discussion

The primary objective of this study was to develop and evaluate a prediction model for PE using a combination of maternal factors and first-trimester ultrasound biomarkers. The results demonstrated that the model, incorporating maternal age, BMI, prior history of PE, UtA-PI, and MAP, exhibited good predictive performance for overall PE, with an area under the receiver operating characteristic curve (AUC) of 0.85. This indicates that the model has a high probability of correctly discriminating between women who will develop PE and those who will not. The AUC is a widely used metric to assess the performance of prediction models, representing the probability that the model will correctly rank a randomly chosen individual with the outcome (PE in this case) higher than a randomly chosen individual without the outcome. An AUC of 0.5 indicates no discriminative ability, while an AUC of 1.0 represents perfect discrimination. The AUC of 0.85 achieved in this study suggests that the model has good overall predictive accuracy. Furthermore, the model showed excellent performance for predicting early-onset PE (delivery <34 weeks), achieving an AUC of 0.92. This is particularly significant because early-onset PE is associated with greater maternal and fetal morbidity and mortality compared to late-onset PE. The ability to identify women at high risk for this severe form of PE in the first trimester allows for timely intervention and closer surveillance, potentially leading to improved outcomes. Early-onset PE is often associated with more severe clinical manifestations and adverse outcomes, including placental abruption, intrauterine growth restriction, and preterm birth. Accurately identifying women at high risk for early-onset PE in the first trimester is crucial for implementing preventative strategies and optimizing perinatal care. The high AUC of 0.92 for early-onset PE prediction suggests that the model can effectively identify these high-risk women, enabling targeted interventions and closer monitoring. The model's performance for predicting late-onset PE (delivery ≥34 weeks) was slightly lower, with an AUC of 0.78. This suggests that while the model can still identify women at risk for late-onset PE, the prediction accuracy is not as high as for early-onset PE. This may be due to the different underlying pathophysiological mechanisms involved in the development of early-onset and late-onset PE, or it may reflect the influence of other factors that were not included in the model. Late-onset PE is generally considered less severe than early-onset PE, but it can still lead to significant maternal and fetal complications. The lower AUC for late-onset PE prediction may reflect the heterogeneity of this condition and the involvement of various factors that were not captured in the model. Further research is needed to explore the specific predictors and mechanisms associated with late-onset PE and to improve its prediction accuracy. The observed differences in predictive performance between early-onset and late-onset PE may also be attributed to the distinct pathophysiological pathways involved in their

development. Early-onset PE is often associated with impaired placentation and uteroplacental insufficiency, while late-onset PE may be more related to maternal constitutional factors and pre-existing conditions. The model's stronger performance for early-onset PE suggests that the included biomarkers, UtA-PI and MAP, may be more sensitive in detecting early placental dysfunction. In addition to the AUC, other performance metrics such as sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were also evaluated at a specific risk score cut-off of 0.10. The sensitivity of 80% indicates that the model correctly identified 80% of the women who developed PE, while the specificity of 75% indicates that the model correctly identified 75% of the women who did not develop PE. The PPV of 25% means that 25% of the women identified as high-risk by the model actually developed PE, and the NPV of 97% means that 97% of the women identified as low-risk by the model did not develop PE. These performance metrics provide a more comprehensive assessment of the model's clinical utility. The high NPV is particularly reassuring, as it indicates that the model can effectively identify women who are at low risk of developing PE, potentially avoiding unnecessary interventions and anxiety. However, the relatively low PPV suggests that further refinement of the model may be needed to improve its ability to identify true positive cases and reduce the number of false positives.[11-15]

The study's findings underscore the importance of UtA-PI and MAP as key predictors of PE. Both biomarkers were independently associated with an increased risk of PE, even after adjusting for other maternal factors. This highlights their value as early indicators of abnormal placentation and vascular dysfunction, which are central to the pathogenesis of PE. Elevated UtA-PI in the first trimester reflects increased resistance in the uterine arteries, indicating impaired trophoblast invasion and reduced placental perfusion. This impaired placentation is a critical early step in the development of PE, leading to placental ischemia and the release of anti-angiogenic factors into the maternal circulation. These findings are consistent with previous research that has demonstrated the association between elevated UtA-PI and an increased risk of PE, particularly early-onset PE. UtA-PI is a non-invasive and readily available measure that can be easily obtained during routine first-trimester ultrasound examinations. Its ability to identify women at risk for PE early in pregnancy makes it a valuable tool for risk assessment and targeted intervention. By detecting impaired placentation and reduced placental perfusion, UtA-PI can alert healthcare providers to the potential for developing PE, allowing for closer monitoring and preventative measures. MAP, a measure of average arterial pressure throughout the cardiac cycle, provides insights into the overall vascular health of the pregnant woman. Elevated MAP in the first trimester may reflect underlying vascular dysfunction and increased peripheral resistance, which are early features of the pathophysiological cascade leading to PE. This is supported by previous studies that have shown an association between elevated MAP in the first trimester and an increased risk of PE. MAP is another easily obtainable parameter that can be measured during routine antenatal visits. Its inclusion in the prediction model adds another dimension to risk assessment, capturing early signs of vascular dysfunction that may precede the development of PE. By combining UtA-PI and MAP, the model provides a more comprehensive assessment of the risk of PE, considering both placental and vascular factors. The inclusion of both UtA-PI and MAP in the prediction model enhances its accuracy and provides a more comprehensive assessment of the risk of PE. This is particularly important in low-resource settings like Indonesia, where access to more sophisticated diagnostic tools may be limited. In settings where resources are limited, the availability of simple and cost-effective measures like UtA-PI and MAP can significantly improve the ability to identify high-risk pregnancies and implement appropriate interventions. The combined use of UtA-PI and MAP in the prediction model not only improves its accuracy but also enhances its accessibility and feasibility in various healthcare settings. This is crucial for ensuring that all pregnant women, regardless of their socioeconomic status or access to healthcare, have the opportunity to

benefit from early risk assessment and targeted interventions for PE.[16-20]

5. Conclusion

This study highlights the potential of utilizing maternal characteristics and first-trimester ultrasound biomarkers, specifically UtA-PI and MAP, to predict the risk of developing preeclampsia (PE) in an Indonesian population. The model developed in this study demonstrated good predictive performance for overall PE, with an AUC of 0.85, and particularly strong performance for predicting early-onset PE, with an AUC of 0.92. The findings suggest that the combination of these readily available measures can serve as a valuable tool for the early identification of high-risk women, allowing for targeted surveillance and potential preventative strategies. The study's strengths include its prospective cohort design, standardized data collection procedures, and the use of a well-defined population. However, some limitations should be acknowledged. The study was conducted at a single center, which may limit the generalizability of the findings to other populations. Additionally, the model's performance for predicting late-onset PE was not as strong as for early-onset PE, suggesting the need for further refinement and research. Despite these limitations, the study's findings have important implications for clinical practice. The model can assist healthcare providers in identifying high-risk women early in pregnancy, allowing for timely intervention and closer monitoring. This can potentially lead to improved maternal and fetal outcomes, particularly in low-resource settings where access to more sophisticated diagnostic tools may be limited. Further research is needed to validate the model in different populations and to explore the potential benefits of incorporating other biomarkers and risk factors.

6. References

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