**Title: Parameterization of the mid-trimester drop in blood pressure trajectory during pregnancy and its utility for predicting preeclampsia**

**Short tittle: Blood pressure trajectory and preeclampsia**

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**Abstract:**

**Objectives:** The purpose of this study was to parameterize mid-trimester drop in blood pressure (BP) trajectory during pregnancy and to evaluate its utility for predicting preeclampsia. **Methods:** To develop parametric models for BP trajectory during pregnancy, we used data from 7,923 Chinese pregnant women with 24,810 routines antenatal care visits to develop parametric models for BP trajectory during pregnancy. Then, we evaluated the utility of BP trajectory parameters for predicting clinician-diagnosed preeclampsia in the separate sample of 3,524 pregnant women from a randomized controlled trial of prenatal vitamin supplementation conducted in the same area. We focused on parameters related to the mid-trimester BP drop, including the gestational age and BP value at the nadir (lowest point), change in BP, velocity, and area under curve during two periods (from 12 weeks of gestation to the nadir and from the nadir to 33 weeks of gestation). **Results:** All participants in our analysis had a mid-pregnancy drop in their systolic (SBP), diastolic (DBP), and mean arterial pressure (MAP) trajectories. There were high correlations (|r|>0.90) among trajectory parameters of the same BP measure. The final prediction model included selective parameters of SBP, DBP, and MAP trajectories, pre-pregnancy body mass index and gestational age at the first antenatal care visit. The area under the receiver operating curve for predicting preeclampsia was 0.886 (95% confidence interval 0.846~0.926) in the training dataset and 0.802 (0.708~0.895) in the validation dataset. **Conclusions:** Our novel BP trajectory parameters are informative and can predict preeclampsia at a clinically acceptable level.

**Condensed Abstracts:**

The mid-trimester-drop-related parameters of blood pressure trajectory during pregnancy might have important biological meanings and clinical implications. There is no in-depth research on the utility of those factors for predicting preeclampsia. We successfully derived a series of mid-trimester-drop-related BP parameters based on individual-specific BP trajectories. These novel BP parameters could predict preeclampsia at a clinically acceptable level.

**Key words:** Blood pressure, Gestational Hypertension, Preeclampsia, Predict model, Trajectory

**Abbreviations and symbols:**

BP, blood pressure

SBP, systolic blood pressure

DBP, diastolic blood pressure

MAP, mean arterial pressure

AUC, area under curve

CMCHWs, community maternal and child health workers

AUC-ROC, area under the receiver operating curve

NPV, negative predictive value

PPV, positive predictive value

BMI, body mass index

CI, confidence interval

**Introduction**

Blood pressure (BP) during pregnancy represents maternal adaptive responses to meet the circulatory needs of the mother and the developing fetal-placental unit[1]. Changes in BP during pregnancy reflect hemodynamic changes, as a result of complex relationship between blood volume (increasing) and total peripheral vascular resistance (decreasing) during pregnancy[2]. Abnormal BP is associated with risks of some maternal and neonatal morbidities (i.e., gestational hypertension, preeclampsia, and small-for-gestational-age birth)[3-7].

Most of previous studies have used changes in BP between fixed gestational ages or trimesters to describe the BP trajectories (other names: patterns and trends) during pregnancy[8-10]. This approach assumes that the biological meaning of BP at a given fixed gestational age may be the same among individuals, which seems unrealistic among pregnant women with large biological variation. Instead, a more appealing way of examining changes in BP during pregnancy is to model individual BP trajectories based on repeated measures during pregnancy. Modeling and parameterizing individual BP trajectories can substantially advance our understanding of hemodynamic changes during pregnancy, as well as facilitate in-depth research on the associations between changes in BP and pregnancy complications. For example, for most pregnant women, there are a decrease in both systolic and diastolic BP between 12-14 weeks and 18~24 weeks, and then a rise until delivery[11-13]. The whole process is called “mid-trimester drop” and may result from competition between decreasing peripheral vascular resistance and increasing blood volume[9,14-16]. Specifically, the decrease in peripheral vascular resistance is more influential than the increase in the blood volume from 12-14 weeks and 18~24 weeks (mid-trimester), which makes BP fall gradually. However, as pregnancy proceeds, the magnitudes of influence on BP of decreasing peripheral vascular resistance and of increasing blood volume become closer to each other and eventually are equal, at which the BP nadir occurs. After the nadir, BP starts to increase, as a result of large influence of increasing blood volume and decreasing in peripheral vascular resistance.

Some studies have examined the role of the mid-trimester drop in BP[3,9,15,17-19]. Absence of this drop might be an early indication of pregnancy-induced hypertension or the development of early-onset of preeclampsia[3,9,18]. In addition, among women with a mid-trimester drop, there is still substantial variation in characteristics of this important turning point, such as the nadir of drop, initial timing of drop, pre-nadir velocity, timing of the nadir, BP at the nadir, change in BP between initial drop and the nadir, area under curve (AUC) between the initial drop and the nadir and post-nadir change, velocity and AUC. Those mid-trimester-drop-related parameters might have important biological meanings and clinical implications. For example, the pre-nadir velocity reflects maternal hemodynamic change as the results of the competitive relationship between decreasing peripheral vascular resistance and increasing blood volume. However, to our best knowledge, there is no in-depth research on these novel and potentially valuable characteristics of the mid-trimester drop.

Therefore, we had three aims in the current study: 1) to build parametric models to fit BP trajectories starting from 12 weeks of gestation (the common onset of decrease in BP[11-13]); 2) to estimate the mid-trimester-drop-related BP parameters and exam correlations among those parameters; and 3) to evaluate the clinical utility of using the mid-trimester-drop-related BP parameters to predict preeclampsia.

**Methods**

**Study sample**

*Reference sample used to build parametric model for BP trajectory (Aim 1) and estimate the mid-trimester-drop-related parameters (Aim 2).* We used secondary electronic data of 24,810 routines antenatal care visits by 7,923 pregnant women between July 1, 2015 and October 31, 2017 in 3 rural counties (Xunyi, Bin, and Changwu) in Shaanxi Province, Northwestern China. This system was designed by the Chinese Department of Maternal and Child Health and maintained by local Departments of Health. We extracted BP, gestational age, and basic demographics from general antenatal care records. To assure sufficient data points to accurately estimate BP trajectories starting from 12 weeks of gestation, eligible pregnant women must have at least one visits in each of the first (≤13 weeks), second (14 to 27 weeks), and third (28 weeks or later) trimesters. Based on this criterion, 4,297 (54.2%) pregnant women and their 17,859 (72.0%) visits were included into the final model to build parametric model for BP trajectory and estimate the mid-trimester-drop-related parameters.

*Prediction sample used to evaluate utility of the mid-trimester-drop-related BP parameters for predicting preeclampsia (Aim 3).* The electronic data used to build parametric model for BP trajectory and estimate the mid-trimester-drop-related parameters was inappropriate for building models to predict preeclampsia, because that 1) routinely recorded diagnoses of pregnancy complications including preeclampsia were incomplete or invalid and 2) it lacked of information on some important potential predictors of preeclampsia such as family history of hypertension and other vascular disease, household income, and age at menarche. Alternatively, we used research data from a community-based randomized controlled trial (RCT, 2015-2019) conducted in the same three counties above to develop and validate a prediction model for preeclampsia using the mid-trimester-drop-related BP parameters. Briefly, this RCT aimed to investigate the effect of multiple-micronutrient supplementation on preventing congenital heart diseases. Details on this RCT can be found in the ClinicalTrials.gov (No. NCT02537392)[20] . The eligibility criteria included: 1) being aged 15-49 years, 2) in early pregnancy (≤ 20 weeks) at enrollment, 3) not smoking cigarettes or drinking alcohol since 3 months before the current pregnancy, and 4) relatively healthy without diagnosed chronic diseases (e.g., hypertension, heart disease, renal disease, diabetes or epilepsy). A total of 4,024 eligible pregnant women were enrolled at preconception or antenatal care visits at township health care centers (**Figure 1**). All participants received usual care including (1) blood pressure measurement; (2) urine testing for bacteriuria and proteinuria; (3) blood testing to detect syphilis and severe anemia; (4) folic acid supplementation; and (5) weight/height measurement[21]. They were then randomly assigned to one of three treatments: vitamin B complex supplementation group (N=1,279), iron supplementation group (N=1,026), and usual care only group (N=1,219). However, 530 participants were excluded due to loss to follow-up (n=453) and had no information on validated diagnosis of preeclampsia (n=77). Among the remaining 3,524 participants, we further excluded 1,279 (36.3%) ones in the vitamin B complex supplementation group from the current analysis, because we observed substantial reduction in the prevalence of preeclampsia by the vitamin B complex supplementation group (1.4% vs. 3.0%, P value=0.005). All the remaining 2,245 participants met the aforementioned criteria of estimating the mid-trimester-drop-related BP parameters. Therefore, these 2,245 participants and their 10,050 antenatal care visits were included to the final analysis on evaluating utility of the mid-trimester-drop-related BP parameters for predicting preeclampsia. The study protocol (No. 20120008) was approved by the Institute Review Board of Xi’an Jiaotong University Health Science Center.

**BP measures**

Community maternal and child health workers (CMCHWs) used an automatic oscillometric BP monitor (YUYUE 660d, YUYUE Medical Equipment & Supply Co., Jiangsu, China) to measure systolic and diastolic BP at antenatal care visits. This BP monitor had been used in previous research[22,23], and validated by our research team against a mercury sphygmomanometer among 15 pregnant women (r=0.97 and mean difference=3.83 mmHg for systolic BP; r=0.64 and mean difference=-1.92 mmHg for diastolic BP). Specifically, BP was measured from the right arm of seated participants using a standard adult size cuff (arm circumference range: 22 to 32 cm). To reduce the “white coat” effect and increase stabilization of BP values[24], each participant was asked to rest for five minutes prior to the actual measures[25]. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) values were measured three times at intervals of one minute. The average of three BP values was recorded in antenatal care records. We used this as our measure of BP in analyses. We also calculated mean arterial pressure (MAP) using the equation, MAP = SBP + DBP × 2/3. Gestational age was calculated as the difference between the last menstruation date and the date when BP was measured.

**Preeclampsia measures**

In our trial, obstetricians diagnosed preeclampsia based on BP values and urine protein tests from antenatal and delivery records. Before delivery, obstetric nurses at maternity hospitals measured BP using the same protocol as previously described. Urine protein was measured via dipstick urinalysis with a reagent strip and analyzed with an automated urine sediment analyzer. Urine protein results were reported on a semi-quantitative scale: negative, +/-, 1+, 2+, 3+, and 4+.

According to the Guidelines on Diagnoses and Treatments of Hypertensive Disorders in Pregnancy by Chinese Society of Obstetrics and Gynecology[26], preeclampsia was diagnosed if the pregnant woman had both gestational hypertension and proteinuria. Gestational hypertension was defined as occurrence of SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg starting at or after 20 weeks of gestation. Proteinuria was defined as the urine protein at 1+ or higher level in a single random urine specimen in the dipstick test.

**Covariate and other measures**

The potential confounders considered in this study included socio-demographics, pregnancy characteristics, and group assignment (iron supplementation vs. usual care) in the RCT[27,28]. During face-to-face interviews at enrollment, pregnant women reported their age, parity, educational attainment, occupation, family history of hypertension and other vascular diseases. Educational attainment was grouped into three categories: 8 years or less, 9 to 11 years, and 12 years or above. Occupation was grouped into two categories: farmer and others. Seasons at the first antenatal care visit were grouped into four categories: spring, summer, autumn, and winter. Height was measured with a stadiometer (LD-SG01, Ningbo Land Corp., Ningbo, China) to the nearest 0.1 cm at enrollment. After removing all heavy clothing and shoes, participants were weighed using an electronic scale (Tanita HD-305, Tanita [Shanghai] Trading Co., Ltd., Shanghai, China) to the nearest 0.1 kg at enrollment and then each subsequent antenatal care visit. Similar to previous research[29], we estimated pre-pregnancy weight from individual-level gestational weight trajectory (median number of weight measures: 4.9 [range: 3 to 12] from 5 week to 32 week) fitted with a mixed model containing fractional polynomial terms of gestational age (Weight=-1381.39+463.64×week (-2) -1974.62×week (-1) +3000.13×week (-0.5)+367.40×ln (week) -52.633×week0.5). Accordingly, we calculated pre-pregnancy body mass index (BMI) as estimated pre-pregnancy weight in kg divided by the square of measured height in meters at enrollment.

**Statistical analysis**

Maternal socio-demographic and pregnancy characteristics were summarized using mean ± standard deviation (SD) for continuous variables, and count (proportion) for categorical variables. Analysis of variance (ANOVA) and Chi-square tests were used to compare maternal characteristics between reference and excluded samples.

Similar to a previous study by Thompson et al.[30] , we used a fractional polynomial approach to model BP trajectories as a function of gestational age. Further information on the fitting of trajectory model was included in **Supplemental Text 1**. Based on the gestational BP trajectory, we were interested in eight characteristics or parameters around the nadir of mid-trimester BP drop, an important BP trajectory milestone. As shown in **Figure 2**, these parameters included BP value and gestational age at the nadir; change in BP, velocity and AUC between the 12 weeks of gestation and the nadir, as well as between the nadir and 33 weeks of gestation.We chose 12 weeks as the milestone in early pregnancy because previous studies indicated that the decrease in BP usually started from 12 weeks of gestation[11-13]. The 33 weeks was chosen as the end of mid-trimester because 1) previous research suggested most preeclampsia cases (98.7%) were diagnosed after 33 weeks of gestation[31], and 2) we aimed to use mid-trimester-drop-related BP parameters to predict preeclampsia. Details about these procedures was showed in **Supplemental Text 2**.

Furthermore, we evaluate the utility of using those mid-trimester-drop-related BP parameters to predict preeclampsia.In this step, the prediction sample was randomly divided into *training* (80%) and *validation* datasets (20%). In the *training* dataset, we used mid-trimester-drop-related BP parameters as both continuous and binary variables to predict preeclampsia. We identified the optimal cut-off point of the binary BP parameters to predict preeclampsia based on the Youden Index (sensitivity+specificity-1). Then, we calculated the area under the receiver operating curve (AUC-ROC) from logistic regression models to evaluate average discrimination accuracy of each of the eight BP parameter as a continuous or binary variable in predicting preeclampsia. After that, we selected the best combination of BP trajectory parameters within each of SBP, DBP and MAP trajectories for predicting preeclampsia by using backward stepwise selection method, the significance level of the score chi-square for entering a parameter into the model is 0.05 in logistic regression models. Finally, we added significant or marginally significant socio-demographic and pregnancy characteristics (p-value less than 0.2 in univariate analyses) into the model with the best combination of BP trajectory parameters in the *training* dataset. In the *validation* dataset, we calculated the predicted probability of preeclampsia for each woman by using the observed values of predictors and their corresponding coefficients in the final prediction model selected in the *training* dataset.

We evaluated performance of the final prediction model in the *validation* dataset by calculating sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV) at different cut-off points of preeclampsia probability (1% ~ 9.5%). A prediction model was considered clinically useful if its AUC-ROC is at or above 0.70. The model calibration, i.e., the extent of matching between predicted and observed probability of preeclampsia, was assessed with the Hosmer-Lemeshow (H-L) test.

Statistical analyses were performed using SAS version 9.4 (SAS Institute, Inc., Cary, NC). All statistical tests were two-sided, and P-values less than 0.05 were considered statistically significant.

**Results**

**Sample characteristics**

As shown in **Table 1**, there were no substantial differences in maternal age, educational attainment, or occupation between the reference sample for constructing BP trajectory models (Aim 1 and Aim 2) and the excluded sample. However, women in the reference sample had more antenatal care visits (4.2 ± 0.8 vs 1.9 ± 1.2) on average and were less likely to be nulliparous (71.3% vs 77.7%) than the excluded sample.

**Table 2** shows socio-demographic, pregnancy characteristics, neonatal outcomes, and the intervention group assignment of pregnant women in the prediction sample for evaluating utility of the mid-trimester-drop-related BP parameters for predicting preeclampsia (Aim 3), by diagnosis of preeclampsia. Women with preeclampsia were significant poorer (Chinese Yuan: 7,096± 4,667 vs 8,421 ± 6,882), older at menarche (Year: 15.1 ± 1.9 vs 14.6 ± 1.6), more C-section deliveries (50% vs 30.9%) and delivery earlier (week: 38.0 ± 6.6 vs 39.3 ± 1.9). There were no substantial differences in other socio-demographic and pregnancy characteristics, neonatal outcomes, or intervention group assignment.

**Model selection for gestational BP trajectories**

The autoregressive variance-covariance structure had the lowest Bayesian information criterion (BIC) in the BP model with all eight gestational age polynomials, and was thus chosen for all subsequent models. As shown in the **Supplemental Table 1**, the best model (lowest BIC) for SBP trajectories was “SBP=2,953.4-617.8×week (-2) +3,070.0×week (-1)-5,572.0×week (-0.5)-958.8×ln (week) +283.6×week0.5-7.4×week”. The best model for DBP trajectories was “DBP=2,131.8-421.5×week (-2) +2,151.9×week (-1)-3,999.5×week (-0.5)-706.3×ln (week) +212.4×week0.5-5.3×week”. The best model for MAP trajectories was “MAP=303.2-55.5×week (-2) +256.5×week (-1)-435.2×week (-0.5)-67.0×ln (week) +14.1×week0.5”.

**Mid-trimester-drop-related BP trajectory parameters and their correlations**

Based on the best fitted mixed model, all participants in our reference sample had a mid-pregnancy drop with a nadir in their SBP, DBP, and MAP trajectories. **Table 3** shows characteristics of mid-trimester-drop-related BP trajectory parameters. The mean gestational age at the nadir was 22.8 ± 8.5 weeks for SBP, 20.6 ± 5.4 weeks for DBP, and 16.6 ± 5.0 weeks for MAP; the mean BP value at the nadir was 106.8 ± 3.4 mmHg for SBP, 67.7 ± 2.3 mmHg for DBP and 80.7 ± 2.7 mmHg for MAP. There were very high correlations (|r|>0.90) among mid-trimester-drop-related BP trajectory parameters of the same BP measure (SBP, DBP, or MAP), whereas the correlations between SBP and DBP parameters were medium (|r|<0.70) (**Supplemental Table 2**).

**Utility of different mid-trimester-drop-related BP trajectory parameters in predicting preeclampsia**

**Table 4** shows predictive values for preeclampsia by single mid-trimester-drop-related BP trajectory parameters in the *training* dataset (N=1,796) of our prediction sample. All AUC-ROC values were in a moderate range (0.668 ~0.735) when each of these parameters was used as a continuous or binary variable. **Figure 3** shows predictive values for preeclampsia by the best combination of mid-trimester-drop-related BP trajectory parameters and two (marginally) significant pregnancy characteristics (pre-pregnancy BMI and gestational age at the first antenatal visit). Note, group assignment in the RCT (iron supplementation vs usual care) was not a significant predictor (P value=0.253) of preeclampsia and thus not included from the final model. Overall, combination models had better predictive performance than single parameter models. The predictive value for preeclampsia based on the combination of mid-trimester-drop-related trajectory parameters of DBP (AUC-ROC:0.810, 95% CI: 0.735~0.885) was higher than that based on those trajectory parameters of SBP (0.706, 95% CI: 0.634~0.777) or MAP (0.683, 95% CI: 0.603~0.763). Combining SBP, DBP, and MAP parameters could increase AUC-ROC to 0.838. Adding pre-pregnancy BMI, seasons and gestational age at the first antenatal care visit further enhanced AUC-ROC to 0.845 (95% CI: 0.781~0.910). The final prediction model for preeclampsia was, “Logit (Risk of preeclampsia) =139.7 + 1.04×Velocity of SBP from the nadir to 33 weeks (0 if ≤0.06 mmHg/week, 1 if >0.06 mmHg/week) + 1.36×Gestational age at the nadir in DBP trajectory (week) - 2.38×DBP at the nadir (mmHg) + 14.69×Change in DBP from 12 weeks to the nadir (mmHg) – 146.1×Velocity of DBP from the nadir to 33 weeks (mmHg/week) + 10.93×Change in DBP from 12 weeks to the nadir ( 0 if ≤ 0.06 mmHg , 1 if >0.06 mmHg) + 8.17×AUC of DBP from 12 weeks to the nadir (0 if ≤ 682.5 mmHg×week,1 if >682.5 mmHg×week) + 0.96×AUC of MAP from the nadir to 33 weeks (0 if ≤ 1,461 mmHg×week,1 if >1,461 mmHg×week) + 0.03×Pre-pregnancy BMI (Kg/m2) + 0.33×Gestational age at the first antenatal care visit (1 if 13~15 weeks, 0 otherwise) - 0.54×Gestational age at first antenatal care visit (1 if >15 weeks, 0 otherwise) + 0.40×seasons at the first antenatal care visit (1 if summer, 0 otherwise) + 0.12×seasons at the first antenatal care visit (1 if autumn, 0 otherwise) -0.04×seasons at the first antenatal care visit (1 if winter, 0 otherwise)”.

This final prediction model yielded an AUC-ROC of 0.835 (95% CI: 0.710~0.960) in the *validation* dataset (N=449) of our prediction sample (**Figure 4**). **Table 5** shows predictive values of the final prediction model under different cut-off points (range, 1.0%~9.5%) of preeclampsia probability in the *validation* dataset. The cut-off point of preeclampsia probability that maximized the Youden Index was 5.0% (Sensitivity=87.5%, Specificity=76.9%, PPV=13.9%, NPV=99.3%, Youden Index=64.4%), which was similar with the observed risk (prevalence) of preeclampsia (4.1%) in this dataset.

**Discussion**

In this study, we used repeated BP measures to successfully build three fractional polynomial mixed models for SBP, DBP, and MAP trajectories during pregnancy, respectively. Accordingly, we were able to estimate mid-trimester-drop-related BP parameters including BP value and gestational age at the nadir; change in BP, velocity and AUC between the 12 weeks of gestation and the nadir; as well as between the nadir and 33 weeks of gestation. These parameters were moderately or highly corrected with each other. Importantly, we constructed and validated a clinically useful prediction model for risk of preeclampsia by including several key mid-trimester-drop-related BP parameters in SBP, DBP and MAP trajectories, pre-pregnancy BMI, and gestational age at first antenatal care visit.

**Mid-trimester-drop-related BP parameters**

Previous studies that explored the associations between the mid-trimester BP drop and preeclampsia used various methodologies and reported results from different perspectives[3,10,17]. The Generation R study from the Netherlands estimated the existence (Yes/No) of the mid-trimester BP drop using linear mixed model, and found the absence of the mid-trimester BP drop was not significantly related to preeclampsia (Odds Ratio: 1.39, 95% CI: 0.71~2.79)[17]. Another study from the Avon Longitudinal Study used linear spline models to describe changes in SBP and DBP during pregnancy, and reported DBP rose more rapidly after the mid-trimester drop (around 18 weeks) in preeclampsia pregnancies compared with normotensive pregnancies (mean difference in DBP velocity from 18 to 30 weeks: 0.24 mmHg/week, 95% CI: 0.13~0.35)[3]. In this study, we advanced the science by estimating some key mid-trimester-drop-related BP parameters including BP value and gestational age at the nadir, change in BP, velocity and AUC between the 12 weeks of gestation and the nadir, as well as between the nadir and 33 weeks of gestation. These novel BP parameters may have important physiological meanings, although more research is needed to explore. For example, the gestational age at the nadir could reflect the timing of balance between blood volume expansion and peripheral vascular resistance reduction[32], and we found late gestational age at the nadir of SBP, DBP, or MAP trajectory was a risk factor for preeclampsia. In addition, change in BP, velocity, and AUC may represent the magnitude of the BP drop, speed of BP change, and cumulative BP load during 3 phases (drop, nadir, and rebound of BP) around the mid-trimester-drop, respectively. We found high AUC of SBP, DBP, or MAP from 12 weeks to the nadir was a risk factor for preeclampsia.

**Predictive values of mid-trimester-drop-related BP parameters for preeclampsia**

A few studies investigated the predictive value of single BP measures for preeclampsia[33,34]. A meta-analysis of 34 studies in this field by Conssen et al. concluded that the MAP value in the first or second trimester of pregnancy was a better predictor for preeclampsia than SBP, DBP, or the change in BP from the first to second trimester (AUC-ROC:0.76, 95% CI: 0.70~0.82)[33] . In our study, we evaluated the performance of SBP, DBP, MAP values at the nadir for predicting preeclampsia, and found MAP yielded higher AUC-ROC (0.700) than SBP (0.670) or DBP (0.690). Additionally, our combination of mid-trimester-drop-related parameters of SBP, DBP, and MAP could further improve performance for predicting preeclampsia (AUC-ROC: 0.838). Furthermore, based on our theoretical model, the predictive period could be moved up as early as 12 gestation weeks, which could be valuable for early screening of preeclampsia.

Previous studies suggested that prediction of preeclampsia could be improved by adding other non-BP factors, such as socio-demographics, family history of cardiovascular disease, pregnancy characteristics, as well as biomarkers related to endothelial function and placental development (e.g., PLGF, IL-1Ra, CRP/HbF)[28,34-37] . In this study, we considered and tested a comprehensive list of socio-demographic and pregnancy characteristics. But only pre-pregnancy BMI and gestational age at the first antenatal care visit met our criteria of at least marginal significance and were thus added into the final prediction model to improve performance (AUC-ROC=0.845).

It is worthy to note that, compare to the high clinical sensitivity laboratory test method (e.g.: Triage PLGF)[37] , our prediction model is relatively cost-effective to consider as a first-stage screening tool for detecting preeclampsia, as it only requires repeated BP measures and three pregnancy characteristics. After screening the high-risk pregnant women, we can then apply more accurate but more expensive test for diagnosis preeclampsia. Our next step is to develop an online software to assist health professionals to derive mid-trimester-drop-related BP parameters and calculate the predicted probability of preeclampsia of each pregnant woman, after they enter her values of repeated BP measures (for a long enough period to cover nadir), pre-pregnancy BMI, seasons and gestational age at the first antennal care visit.

**Study limitations and strengths**

Our study had several important limitations. First, we were unable to distinguish early- and late-onset preeclampsia cases, due to unavailable information on timing of preeclampsia diagnosis. These two types of preeclampsia have different etiology, severity, and consequences[18], and thus may need separate prediction models in which mid-trimester-drop-related BP parameters may play different roles. Second, our individual-specific BP trajectory model and estimated mid-trimester-drop-related BP parameters might be inaccurate, because pregnant women in our study had only a mean of 4.3 (SD, 2.7) repeated BP measures, similar to some other studies in this field[9,19,38]. Theoretically, the accuracy of BP trajectories could be improved with more frequent BP measures throughout pregnancy, e.g., 10 visits per women in a study by Macdonald-Wallis et. al.[3] Third, our study population was from two rural counties in Northwestern China. Most of our participants had Han ethnicity and were nulliparous. We hoped but did not have an opportunity to validate the best-fitting models in an external population from more diverse ethnicity, parity and geographic areas. Previous studies reported the substantial ethnic differences in blood pressure levels during pregnancy and risk of preeclampsia; and Chinese might have a lower prevalence of preeclampsia than Caucasians[39,40]. Also, multiparous is a risk factor for preeclampsia[41]. Thus, our best-fitting models for BP trajectories and estimated mid-trimester-drop-related BP parameters might not be generalizable to other populations. However, our methods for modeling BP trajectories and estimating mid-trimester-drop-related BP parameters can be broadly used in other studies. Therefore, we recommend other researchers first select the best-fitting models for BP trajectories and estimate the corresponding mid-trimester-drop-related BP parameters based on our methods, rather than use our best-fitting model directly. Fourth, our prediction model was limited by the small PPV indicating high chance of false positives. Similar in some other studies in this field[28], the small PPV could be largely due to the low prevalence of preeclampsia (2.9%) in our relatively healthy pregnant population. We expect that PPV may be much higher if our prediction model is used in high-risk pregnant women (e.g., nulliparity, family history and pre-existing history of preeclampsia, maternal age≥40 and so on [27]) in future. Finally, the clinical definition for diagnosing preeclampsia used in our study only based on the presence of both hypertension and proteinuria[26], which is not the new criteria used by most clinical researchers, might underestimate the incidence of preeclampsia [38,42]. Even though we could not diagnose preeclampsia based on the new criteria with the limitation of medical laboratory resource and training obstetricians of rural primary health-care system in China, previous study indicated that the performance of screening for preeclampsia by maternal predictive factors (e.g.: MAP, UtA-PI and PLGF) was similar when the condition was defined within different criteria, which means that the criteria used in our study is acceptable[43].

Our study had some unique strengths worthy to mention. First, to our knowledge, it was the first study to build parametric models to derive mid-trimester-drop-related BP parameters throughout pregnancy. Our findings supported the utility of these parameters for predicting risk of preeclampsia at a clinically acceptable level. Second, we evaluated prediction models in an independent validation dataset using well-established approaches[28,44,45]. This internal validation could help to assess the performance of our prediction models in the real world. Finally, our predictive model is a relatively simple and economic tool to screen preeclampsia, and could be widely used in routine antenatal care including low source settings. It is based on easily accessible BP measures along with pre-pregnancy BMI and gestational age at the first antenatal visit, and it does not require expensive and time-consuming lab tests of biomarkers.

**Conclusions**

In a relatively large sample of Chinese pregnant women, our successfully derived a series of mid-trimester-drop-related BP parameters based on individual-specific BP trajectories. These novel BP parameters could predict preeclampsia at a clinically acceptable level. Adherence to routine antenatal care visits and careful BP monitoring may help on early identification of women at risk of developing preeclampsia. Further research should externally validate our final prediction model in other populations and geographic areas, and consider adding other convenient measures (e.g., weekly self-monitoring BP and urine protein test at home) to improve its predictive values.

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**Legends for illustrations**

**Figure 1. Flow of participants**

**Figure 2．Selected characteristics for each BP trajectory of a hypothetic pregnant women.** SBP, Systolic blood pressure; DBP, Diastolic blood pressure (DBP); AMP(mean arterial pressure). BP at the three milestone (12 weeks of gestation, the nadir, 33 weeks of gestation), change in BP, velocity, and AUC cross those three milestone were estimated.

**Figure 3． Predictive values of combinations of SBP, DBP, and MAP trajectories for preeclampsia in the training dataset.**

The model 1 was, “Logit (Risk of preeclampsia)=-4.16 + 6.87×Velocity of SBP from the nadir to 33 weeks (0 if ≤0.06 mmHg/week, 1 if >0.06 mmHg/week)”.

The model 2 was, “Logit (Risk of preeclampsia)=160.30 + 1.67×Gestational age at the nadir in DBP trajectory (week) - 2.77×DBP at the nadir (mmHg) +16.23×Change in DBP from 12 weeks to the nadir (mmHg) – 125.00×Velocity of DBP from the nadir to 33 weeks ( mmHg/week) + 11.54×Change in DBP from 12 weeks to the nadir ( 0 if ≤ 0.06 mmHg , 1 if >0.06 mmHg) + 7.72×AUC of DBP from 12 weeks to the nadir (0 if ≤ 682.5 mmHg×week,1 if >682.5 mmHg×week)”.

The model 3 was, “Logit (Risk of preeclampsia)=-4.74 +0.01×AUC of MAP from the nadir to 33 weeks (0 if ≤ 1,461 mmHg×week,1 if >1,461 mmHg×week)”.

The model 4 was. “Logit (Risk of preeclampsia)=142.0 + 1.07×Velocity of SBP from the nadir to 33 weeks (0 if ≤0.06 mmHg/week, 1 if >0.06 mmHg/week) + 1.39×Gestational age at the nadir in DBP trajectory (week) - 2.42×DBP at the nadir (mmHg) + 14.85×Change in DBP from 12 weeks to the nadir (mmHg) - 145.40×Velocity of DBP from the nadir to 33 weeks ( mmHg/week) + 11.20×Change in DBP from 12 weeks to the nadir ( 0 if ≤ 0.06 mmHg , 1 if >0.06 mmHg) + 8.34×AUC of DBP from 12 weeks to the nadir (0 if ≤ 682.5 mmHg×week,1 if >682.5 mmHg×week) + 0.99×AUC of MAP from the nadir to 33 weeks (0 if ≤ 1,461 mmHg×week,1 if >1,461 mmHg×week)”.

The model 5 was, “Logit (Risk of preeclampsia) =139.7 + 1.04×Velocity of SBP from the nadir to 33 weeks (0 if ≤0.06 mmHg/week, 1 if >0.06 mmHg/week) + 1.36×Gestational age at the nadir in DBP trajectory (week) - 2.38×DBP at the nadir (mmHg) + 14.69×Change in DBP from 12 weeks to the nadir (mmHg) – 146.1×Velocity of DBP from the nadir to 33 weeks (mmHg/week) + 10.93×Change in DBP from 12 weeks to the nadir ( 0 if ≤ 0.06 mmHg , 1 if >0.06 mmHg) + 8.17×AUC of DBP from 12 weeks to the nadir (0 if ≤ 682.5 mmHg×week,1 if >682.5 mmHg×week) + 0.96×AUC of MAP from the nadir to 33 weeks (0 if ≤ 1,461 mmHg×week,1 if >1,461 mmHg×week) + 0.03×Pre-pregnancy BMI (Kg/m2) + 0.33×Gestational age at the first antenatal care visit (1 if 13~15 weeks, 0 otherwise) - 0.54×Gestational age at first antenatal care visit (1 if >15 weeks, 0 otherwise) + 0.40×seasons at the first antenatal care visit (1 if summer, 0 otherwise) + 0.12×seasons at the first antenatal care visit (1 if autumn, 0 otherwise) -0.04×seasons at the first antenatal care visit (1 if winter, 0 otherwise)”.

**Figure 4． Receiver operating characteristic curve of the final prediction model for preeclampsi**

**Table 1. Characteristics of the reference sample for constructing BP trajectory models and the excluded samples from antenatal care records in study area, Shaanxi, China, 2015-2018**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **Reference sample (N=4,297)** | |  | **Excluded sample (N=3,626)** | | **P-value** |
|  | **Mean ± SD** | **N (%)** |  | **Mean ± SD** | **N (%)** |  |
| **Total number of antenatal care visits** |  | 17,859 |  |  | 6,951 |  |
| **Average number of antenatal care visits** | 4.2 ± 0.8 |  |  | 1.9 ± 1.2 |  | ＜0.001 |
| **Age, year** | 26.7 ± 4.3 |  |  | 26.6 ± 4.5 |  | 0.365 |
| <24 |  | 1,835 (42.7) |  |  | 1,644 (45.4) | 0.046 |
| 25~29 |  | 1,757 (40.9) |  |  | 1,383 (38.1) |
| ≥30 |  | 705 (16.4) |  |  | 599 (16.5) |
| **Education attainment, year** |  |  |  |  |  |  |
| ≤8 |  | 3,425 (79.7) |  |  | 2,930 (80.8) | 0.440 |
| 9~11 |  | 576 (13.4) |  |  | 471 (13.0) |
| ≥12 |  | 296 (6.9) |  |  | 225 (6.2) |
| **Farmer** |  | 2,652 (97.0) |  |  | 1,852 (97.0) | 0.997 |
| **Nulliparous** |  | 3,059 (71.3) |  |  | 2,815 (77.7) | <0.001 |

**Table 2. Characteristics of normotensive pregnant women and those with preeclampsia in the prediction sample for evaluating utility of the mid-trimester-drop-related BP parameters for predicting preeclampsia (N=2,245)**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **Pregnant women without preeclampsia**  **(N=2,181)** | |  | **Pregnant women with preeclampsia**  **(N=64)** | | **P-value** |
|  | **Mean ± SD** | **N (%)** |  | **Mean ± SD** | **N (%)** |
| **Socio-demographic characteristics** |  |  |  |  |  |  |
| Age, years | 25.5 ± 4.8 |  |  | 25.7 ± 4.4 |  | 0.675 |
| 20~24 |  | 1,001 (45.9) |  |  | 32 (50.0) | 0.571 |
| 25~29 |  | 856 (39.3) |  |  | 21 (32.8) |
| ≥30 |  | 323 (14.8) |  |  | 11 (17.2) |
| Annual income per household member, Chinese Yuan | 8,421 ± 6,882 |  |  | 7,096 ± 4,667 |  | 0.031 |
| Education attainment, year |  |  |  |  |  |  |
| ≤8 |  | 275 (12.6) |  |  | 5 (7.8) | 0.515 |
| 9~11 |  | 1,110 (50.9) |  |  | 35 (54.7) |
| ≥12 |  | 796 (36.5) |  |  | 24 (37.5) |
| Farmer |  | 1,936 (88.8) |  |  | 57 (89.1) | 0.941 |
| Family history of hypertension and other vascular disease |  | 98 (4.5) |  |  | 5 (7.8) | 0.211 |
| Age at menarche, years | 14.6 ± 1.6 |  |  | 15.1 ± 1.9 |  | 0.017 |
| **Pregnancy characteristics** |  |  |  |  |  |  |
| Nulliparous |  | 1,091 (50.0) |  |  | 33 (51.6) | 0.808 |
| SBP at baseline, mmHg | 105.1 ± 16.6 |  |  | 108.7 ± 16.5 |  | 0.093 |
| DBP at baseline, mmHg | 67.0 ± 11.3 |  |  | 69.9 ± 11.4 |  | 0.051 |
| MAP at baseline, mmHg | 79.6 ± 12.6 |  |  | 82.7 ± 12.8 |  | 0.063 |
| Height, cm | 159.8 ± 5.3 |  |  | 159.7 ± 4.7 |  | 0.943 |
| Pre-pregnancy BMI, kg/m2 | 21.7 ± 4.2 |  |  | 22.9 ± 2.7 |  | 0.141 |
| Lean (<18.5) |  | 256 (11.7) |  |  | 7 (10.9) | 0.816 |
| Normal (18.5~23.9) |  | 1514 (69.4) |  |  | 45 (70.3) |
| Overweight (24~27.9) |  | 332 (15.2) |  |  | 11 (17.2) |
| Obesity (≥28) |  | 79 (3.6) |  |  | 1 (1.6) |
| Weeks at first antenatal care visits, week | 12.2 ± 6.5 |  |  | 12.4 ± 5.6 |  | 0.879 |
| ≤12 |  | 809 (37.1) |  |  | 29 (45.7) | 0.131 |
| 13~15 |  | 414 (19.0) |  |  | 15 (23.9) |
| ≥15 |  | 958 (43.9) |  |  | 20 (30.4) |
| Seasons at the first antenatal care visit |  |  |  |  |  |  |
| Spring |  | 504 (23.1) |  |  | 8 (12.5) | 0.161 |
| Summer |  | 617 (28.3) |  |  | 17 (26.6) |
| Autumn |  | 684 (31.4) |  |  | 26 (40.6) |
| Winter |  | 375 (17.2) |  |  | 13 (20.3) |
| Number of antenatal care visits per pregnancy | 4.5 ± 2.7 |  |  | 4.0 ± 2.8 |  | 0.312 |
| **Neonatal characteristics** |  |  |  |  |  |  |
| Method of delivery |  |  |  |  |  |  |
| Vaginal |  | 1057 (69.1) |  |  | 32 (50.0) | 0.015 |
| C-section |  | 674 (30.9) |  |  | 32 (50.0) |
| Gestational age at delivery, week | 39.3 ± 1.9 |  |  | 38.0 ± 6.6 |  | <0.01 |
| Preterm birth (≤37 week) |  | 155 (7.1) |  |  | 5 (8.5) | 0.748 |
| >37 week |  | 2026 (92.9) |  |  | 59 (91.4) |
| Birth weight, g | 3236.0 ± 433.2 |  |  | 3206.4 ± 460.6 |  | 0.688 |
| Birth length, cm | 50.2 ± 2.3 |  |  | 50.7 ± 2.0 |  | 0.397 |
| Large-for-gestational age,% |  | 131 (6.0) |  |  | 4 (6.3) | 0.935 |
| Small-for-gestational age,% |  | 318 (14.6) |  |  | 5 (8.0) | 0.100 |
| Apgar score (5 minutes) | 10.0 ± 0.3 |  |  | 9.9 ± 0.3 |  | 0.605 |
| **Intervention group assignment** |  |  |  |  |  |  |
| Iron supplementation |  | 998 (45.8) |  |  | 28 (43.8) | 0.751 |
| Usual care |  | 1,183 (54.2) |  |  | 36 (56.3) |

**Table 3. Mid-trimester-drop-related BP trajectory parameters in the reference sample for constructing BP trajectory models (N=4,297)**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **SBP** | **DBP** | **MAP** |
| Gestational age at the nadir, week | 22.8 ± 8.5 | 20.6 ± 5.4 | 16.6 ± 5.0 |
| BP at the nadir, mmHg | 106.8 ± 3.4 | 67.7 ± 2.3 | 80.7 ± 2.7 |
| Change in BP from 12 weeks to the nadir, mmHg | 0.3 ± 1.9 | -0.5 ± 1.3 | -0.3 ± 0.8 |
| Velocity of BP from 12 weeks to the nadir, mmHg/week | 0.0 ± 0.1 | 0.0 ± 0.1 | 0.0 ± 0.0 |
| AUC of BP from 12 weeks to the nadir (mmHg×week) | 1625.3 ± 808.2 | 873.8 ± 299.9 | 729.2 ± 314.6 |
| Change in BP from the nadir to 33 weeks, mmHg | 0.8 ± 0.9 | 1.2 ± 0.7 | 1.0 ± 0.4 |
| Velocity of BP from the nadir to 33 weeks, mmHg/week | 0.1 ± 0.1 | 0.1 ± 0.0 | 0.1 ± 0.0 |
| AUC of BP from the nadir to 33 weeks (mmHg×week) | 1396.6 ± 806.3 | 890.0 ± 371.7 | 1350.9 ± 442.8 |

**Table 4. Predictive values of single parameter of SBP, DBP, and MAP trajectories for preeclampsia in the training dataset of prediction sample for evaluating utility of the mid-trimester-drop-related BP parameters for predicting preeclampsia (N=1,796)\***

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Continuous variables** |  | **Binary variables** | | |  | **H-L**  **test P-value†** |
|  | **AUC-ROC**  **(95% CI)** |  | **Cut-off Value\*** | **OR (95% CI)**  **(above vs. below cut-off point)** | **AUC-ROC**  **(95% CI)** |  |
| **Parameters derived from SBP trajectory** |  |  |  |  |  |  |  |
| Gestational age at the nadir, week | 0.722 (0.650~0.794) |  | 19 | 5.891 (3.150~11.687) | 0.708 (0.641~0.775) |  | 0.014 |
| SBP at the nadir, mmHg | 0.700 (0.629~0.771) |  | 107.7 | 0.191 (0.096~0.358) | 0.695 (0.629~0.762) |  | <0.01 |
| Change in BP from 12 weeks to the nadir, mmHg | 0.706 (0.635~0.776) |  | 0.91 | 0.190 (0.097~0.351) | 0.697 (0.629~0.765) |  | <0.01 |
| Velocity of BP from 12 weeks to the nadir, mmHg/week | 0.696 (0.623~0.768) |  | 0.06 | 0.162 (0.076~0.316) | 0.707 (0.646~0.769) |  | <0.01 |
| AUC of BP from 12 weeks to the nadir (mmHg×week) | 0.735 (0.660~0.810) |  | 1212 | 5.812 (3.107~11.529) | 0.707 (0.640~0.773) |  | 0.29 |
| Change in BP from the nadir to 33 weeks, mmHg | 0.694 (0.621~0.767) |  | 0.959 | 0.163 (0.076~0.317) | 0.707 (0.645~0.768) |  | <0.01 |
| Velocity of BP from the nadir to 33 weeks, mmHg/week | 0.706 (0.634~0.777) |  | 0.084 | 0.165 (0.083~0.309) | 0.711 (0.644~0.778) |  | <0.01 |
| AUC of BP from the nadir to 33 weeks (mmHg×week) | 0.672 (0.593~0.750) |  | 1,488 | 0.191 (0.098~0.353) | 0.696 (0.628~0.764) |  | <0.01 |
| **Parameters derived from DBP trajectory** |  |  |  |  |  |  |  |
| Gestational age at the nadir, week | 0.691 (0.610~0.773) |  | 19.33 | 4.953 (2.649~9.821) | 0.689 (0.623~0.756) |  | <0.01 |
| DBP at the nadir, mmHg | 0.670 (0.588~0.753) |  | 68.58 | 0.209 (0.114~0.378) | 0.679 (0.606~0.752) |  | <0.01 |
| Change in DBP from 12 weeks to the nadir, mmHg | 0.696 (0.615~0.778) |  | 0.059 | 0.155 (0.084~0.281) | 0.703 (0.631~0.776) |  | <0.01 |
| Velocity of BP from 12 weeks to the nadir, mmHg/week | 0.672 (0.590~0.755) |  | -0.01 | 0.202 (0.109~0.365) | 0.685 (0.613~0.757) |  | <0.01 |
| AUC of BP from 12 weeks to the nadir (mmHg×week) | 0.700 (0.615~0.785) |  | 682.5 | 6.185 (3.416~11.414) | 0.700 (0.628~0.773) |  | <0.01 |
| Change in BP from the nadir to 33 weeks, mmHg | 0.668 (0.586~0.749) |  | 1.408 | 0.169 (0.085~0.317) | 0.708 (0.642~0.775) |  | <0.01 |
| Velocity of BP from the nadir to 33 weeks, mmHg/week | 0.675 (0.594~0.756) |  | 0.108 | 0.213 (0.116~0.385) | 0.677 (0.605~0.750) |  | <0.01 |
| AUC of BP from the nadir to 33 weeks (mmHg×week) | 0.693 (0.612~0.773) |  | 1,043 | 0.164 (0.089~0.297) | 0.699 (0.626~0.771) |  | <0.01 |
| **Parameters derived from MAP trajectory** |  |  |  |  |  |  |  |
| Gestational age at the nadir, week | 0.687 (0.607~0.768) |  | 15.06 | 5.451 (2.915~10.812) | 0.700 (0.633~0.767) |  | <0.01 |
| MAP at the nadir, mmHg | 0.690 (0.611~0.769) |  | 81.38 | 0.186 (0.095~0.344) | 0.699 (0.631~0.767) |  | <0.01 |
| Change in MAP from 12 weeks to the nadir, mmHg | 0.694 (0.615~0.773) |  | -0.07 | 0.193 (0.102~0.353) | 0.693 (0.623~0.764) |  | <0.01 |
| Velocity of BP from 12 weeks to the nadir, mmHg/week | 0.690 (0.611~0.770) |  | -0.02 | 0.211 (0.114~0.380) | 0.678 (0.606~0.751) |  | <0.01 |
| AUC of BP from 12 weeks to the nadir (mmHg×week) | 0.712 (0.628~0.796) |  | 579 | 5.749 (3.074~11.405) | 0.706 (0.639~0.772) |  | 0.07 |
| Change in BP from the nadir to 33 weeks, mmHg | 0.675 (0.596~0.755) |  | 1.131 | 0.201 (0.106~0.367) | 0.689 (0.619~0.760) |  | <0.01 |
| Velocity of BP from the nadir to 33 weeks, mmHg/week | 0.677 (0.598~0.756) |  | 0.066 | 0.196 (0.103~0.358) | 0.692 (0.621~0.762) |  | <0.01 |
| AUC of BP from the nadir to 33 weeks (mmHg×week) | 0.683 (0.603~0.763) |  | 1,461 | 0.173 (0.087~0.324) | 0.706 (0.639~0.773) |  | <0.01 |

\* the optimal cut-off point of the binary BP trajectory parameters to predict preeclampsia

† The Hosmer-Lemeshow test was only suitable for single continues variable or multiple variables in logistic regression.

**Table 5. Performance of the final prediction model at different cut-off points of preeclampsia probability in the validation dataset (N=449, preeclampsia prevalence 4.1%) of prediction sample for evaluating utility of the mid-trimester-drop-related BP parameters for predicting preeclampsia \***

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Cut-off point of**  **preeclampsia**  **probability (%)** | **SE (%)**† | **SP (%)** | **PPV (%)** | **NPV (%)** | **Youden**  **Index (%)** |
| 1.0 | 93.8 | 23.4 | 5.0 | 98.9 | 17.2 |
| 1.5 | 93.8 | 39.6 | 6.2 | 99.3 | 33.4 |
| 2.0 | 87.5 | 50.5 | 7.0 | 99.0 | 38.0 |
| 2.5 | 87.5 | 58.8 | 8.3 | 99.1 | 46.3 |
| 3.0 | 87.5 | 64.9 | 9.6 | 99.2 | 52.4 |
| 3.5 | 87.5 | 68.1 | 10.4 | 99.2 | 55.6 |
| 4.0 | 87.5 | 71.3 | 11.5 | 99.3 | 58.8 |
| 4.5 | 87.5 | 73.7 | 12.4 | 99.3 | 61.2 |
| **5.0** | **87.5** | **76.9** | **13.9** | **99.3** | **64.4** |
| 5.5 | 81.3 | 80.1 | 14.8 | 99.0 | 61.4 |
| 6.0 | 75 | 81.6 | 14.8 | 98.7 | 56.6 |
| 6.5 | 68.8 | 84 | 15.5 | 98.4 | 52.8 |
| 7.0 | 68.8 | 84.8 | 16.2 | 98.5 | 53.6 |
| 7.5 | 68.8 | 85.4 | 16.7 | 98.5 | 54.2 |
| 8.0 | 62.5 | 86.7 | 16.7 | 98.2 | 49.2 |
| 8.5 | 56.3 | 88.3 | 17.0 | 97.9 | 44.6 |
| 9.0 | 50 | 89.1 | 16.3 | 97.7 | 39.1 |
| 9.5 | 50 | 90.2 | 17.8 | 97.7 | 40.2 |

\*Highlighted optimal cut-off points associated with the highest value of Youden Index. Using fixed coefficients of the logistic regression model derived from the *training* dataset: Logit (Risk of preeclampsia) =139.7 + 1.04×Velocity of SBP from the nadir to 33 weeks (0 if ≤0.06 mmHg/week, 1 if >0.06 mmHg/week) + 1.36×Gestational age at the nadir in DBP trajectory (week) - 2.38×DBP at the nadir (mmHg) + 14.69×Change in DBP from 12 weeks to the nadir (mmHg) – 146.1×Velocity of DBP from the nadir to 33 weeks (mmHg/week) + 10.93×Change in DBP from 12 weeks to the nadir ( 0 if ≤ 0.06 mmHg , 1 if >0.06 mmHg) + 8.17×AUC of DBP from 12 weeks to the nadir (0 if ≤ 682.5 mmHg×week,1 if >682.5 mmHg×week) + 0.96×AUC of MAP from the nadir to 33 weeks (0 if ≤ 1,461 mmHg×week,1 if >1,461 mmHg×week) + 0.03×Pre-pregnancy BMI (Kg/m2) + 0.33×Gestational age at the first antenatal care visit (1 if 13~15 weeks, 0 otherwise) - 0.54×Gestational age at first antenatal care visit (1 if >15 weeks, 0 otherwise) + 0.40×seasons at the first antenatal care visit (1 if summer, 0 otherwise) + 0.12×seasons at the first antenatal care visit (1 if autumn, 0 otherwise) -0.04×seasons at the first antenatal care visit (1 if winter, 0 otherwise)

†SE, Sensitivity; SP, Specificity; NPV, negative predictive value; PPV, positive predictive value.