Preterm preeclampsia screening using biomarkers: combining phenotypic classifiers into robust prediction models

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BACKGROUND: Preeclampsia screening is a critical component of antenatal care worldwide. Currently, the most developed screening test for preeclampsia at 11 to 13 weeks' gestation integrates maternal demographic characteristics and medical history with 3 biomarkers—serum placental growth factor, mean arterial pressure, and uterine artery pulsatility index—to identify approximately 75% of women who develop preterm preeclampsia with delivery before 37 weeks of gestation. It is generally accepted that further improvements to preeclampsia screening require the use of additional biomarkers. We recently reported that the levels of specific metabolites and metabolite ratios are associated with preterm preeclampsia. Notably, for several of these markers, preterm preeclampsia prediction varied according to maternal body mass index class. These findings motivated us to study whether patient classification allowed for combining metabolites with the current biomarkers more effectively to improve prediction of preterm preeclampsia.

OBJECTIVE: This study aimed to investigate whether metabolite biomarkers can improve biomarker-based preterm preeclampsia prediction in 3 screening resource scenarios according to the availability of: (1) placental growth factor, (2) placental growth factor+mean arterial pressure, and (3) placental growth factor+mean arterial pressure+uterine artery pulsatility index.

STUDY DESIGN: This was an observational case–control study, drawn from a large prospective screening study at 11 to 13 weeks' gestation on the prediction of pregnancy complications, conducted at King's College Hospital, London, United Kingdom. Maternal blood samples were also collected for subsequent research studies. We used liquid chromatography–mass spectrometry to quantify levels of 50 metabolites previously associated with pregnancy complications in plasma samples from singleton pregnancies. Biomarker data, normalized using multiples of medians, on 1635 control and 106 preterm preeclampsia pregnancies were available for model development. Modeling was performed using a methodology that generated a prediction model for preterm preeclampsia in 4 consecutive steps: (1) z-normalization of predictors, (2) combinatorial modeling of so-called (weak) classifiers in the unstratified patient set and in discrete patient strata based on body mass index and/or race, (3) selection of classifiers, and (4) aggregation of the selected classifiers (ie, bagging) into the final prediction model. The prediction performance of models was evaluated using the area under the receiver operating characteristic curve, and detection rate at 10% false-positive rate.

RESULTS: First, the predictor development methodology itself was evaluated. The patient set was split into a training set (2/3) and a test set (1/3) for predictor model development and internal validation. A prediction model was developed for each of the 3 different predictor panels, that is, placental growth factor+metabolites, placental growth factor+mean arterial pressure+metabolites, and placental growth factor+mean arterial pressure+uterine artery pulsatility index+metabolites. For all 3 models, the area under the receiver operating characteristic curve in the test set did not differ significantly from that of the training set. Next, a prediction model was developed using the complete data set for the 3 predictor panels. Among the 50 metabolites available for modeling, 26 were selected across the 3 prediction models; 21 contributed to at least 2 out of the 3 prediction models developed. Each time, area under the receiver operating characteristic curve and detection rate were significantly higher with the new prediction model than with the reference model. Markedly, the estimated detection rate with the placental growth factor+mean arterial pressure+metabolites prediction model in all patients was 0.58 (95% confidence interval, 0.49–0.70), a 15% increase ($P<.001$) over the detection rate of 0.43 (95% confidence interval, 0.33–0.55) estimated for the reference placental growth factor+mean arterial pressure. The same prediction model significantly improved detection in Black (14%) and White (19%) patients, and in the normal-weight group ($18.5 \leq$body mass index<25) and the obese group (body mass index≥ 30), with respectively 19% and 20% more cases detected, but not in the overweight group, when compared with the reference model. Similar improvement patterns in detection rates were found in the other 2 scenarios, but with smaller improvement amplitudes.

CONCLUSION: Metabolite biomarkers can be combined with the established biomarkers of placental growth factor, mean arterial pressure, and uterine artery pulsatility index to improve the biomarker component of early-pregnancy preterm preeclampsia prediction tests. Classification of the pregnant women according to the maternal characteristics of body mass index and/or race proved instrumental in achieving improved prediction. This suggests that maternal phenotyping can have a role in improving the prediction of obstetrical syndromes such as preeclampsia.

Key words: algorithms, biomarkers, first-trimester screening, phenotypes, prediction, preeclampsia, pregnancy, preterm

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AJOG MFM at a Glance

Why was this study conducted?

This study aimed to investigate whether metabolite biomarkers can improve biomarker-based preterm preeclampsia prediction in 3 screening resource scenarios according to the availability of: (1) placental growth factor (PlGF), (2) PlGF +mean arterial pressure (MAP), and (3) PlGF+MAP+uterine artery pulsatility index (UTA-PI).

Key findings

Prediction models were developed on the basis of patient phenotyping and combining metabolites with the established biomarkers PlGF, MAP, and UTA-PI. Improved preterm preeclampsia prediction was achieved when modeling with metabolites compared with the reference models without metabolites. Improved prediction was also observed in race classes (Black/White), and body mass index (BMI) classes of 18.5 to <25 and ≥30, but not for the BMI class of 25 to <30.

What does this add to what is known?

Metabolites can improve the biomarker-based component of preterm preeclampsia prediction when maternal characteristics are considered.

Introduction

Preeclampsia complicates approximately 5% of pregnancies globally[1,2] and remains a significant cause of maternal and fetal morbidity and mortality.[3,4] In the United States, there is an increasing incidence of hypertensive disorders of pregnancy.[5,6] Preeclampsia screening is a crucial component of antenatal care worldwide.[7] The confirmation that timely initiation of aspirin prophylaxis in pregnant women identified at risk of preeclampsia significantly reduces the incidence of preterm preeclampsia[8] reaffirmed the clinical utility of effective early pregnancy screening.[9,10] This spurred the exploration of novel prediction technologies,[11,12] and improvements to established prediction solutions[13] to better identify pregnant women who would benefit from pharmaceutical intervention,[14] tailored prenatal care,[15] and education.[16]

In many countries, clinical practice continues to rely exclusively on the tabulation of maternal risk factors for determining preeclampsia risk,[17−20] which has limitations in terms of predictive accuracy. In contrast, the screening test for preeclampsia risk developed by the Fetal Medicine Foundation (FMF) combines maternal risk factors into a competing risk model,[21] and then uses Bayes' theorem to combine the resulting previous-risk distribution with biomarker multiples of the median (MoM) to derive patient-specific risks of delivery with preeclampsia before 37 weeks of gestation.[22] In the most performant version of the FMF prediction model, patients' previous risks are updated with the following biomarkers: Doppler velocimetry of the uterine arteries (uterine artery pulsatility index [UTA-PI]), mean arterial pressure (MAP), and blood levels of the placental growth factor (PlGF) protein.[23] A machine learning−based classifier using the same input variables did not markedly improve detection rate (DR) over the original FMF prediction model,[13] reaffirming the need for additional variables to improve prediction efficiency further.

We recently verified the association between early-pregnancy plasma levels of specific metabolites and metabolite ratios, and preterm preeclampsia, whereby for several of these biomarkers the preterm preeclampsia prediction varied with maternal body mass index (BMI),[24] corroborating the contemporary concept that different maternal risk profiles exist.[25−27]

Herein we investigate whether metabolite biomarkers can improve the prediction performance of the progressively more performant biomarker panels currently used in risk prediction, namely, PlGF, PlGF+MAP, and PlGF+MAP+UTA-PI. These 3 reference models reflect 3 scenarios of availability of screening resources: access to laboratory testing only (PlGF), additional access to primary prenatal care (PlGF+MAP), and finally a setting with access to certified sonographers (PlGF+MAP+UTA-PI).

We used maternal traits associated with different a priori risks as putative proxies for ≥1 underlying discrete maternal risk profiles.[24] With both maternal BMI[28,29] and maternal race[5,6,21,30,31] being well-documented phenotypic traits associated with preeclampsia rates, we used BMI classification[32] and maternal race to create patient strata.

Because patient spectrum effects are hypothesized to explain the poor generalizability of biomarker findings in preeclampsia,[25,33,34] we adopted a machine-learning methodology whereby a selection of sparse classifiers, as developed within different patient strata, were aggregated into a final prediction model.[35] For any patient, the risk score is therefore the result of averaging all scores across each stratum the patient belongs to.

In this follow-up analysis of a previously reported early-pregnancy biomarker data set,[24] we first evaluated the machine-learning methodology used to develop predictive models. All available preterm preeclampsia cases (n=106) and control pregnancies (n=1635) were split into a training set (2/3) and test set (1/3) for model development and subsequent internal validation. Next, model development was repeated using the complete data set to enable the assessment of predictive performance within the different patient strata.[36] To gauge the added value of considering metabolite biomarkers in the biomarker-based component of preterm preeclampsia screening tests, the preterm preeclampsia prediction of the 3 resulting prediction models was compared with that of their respective reference biomarker models, that is, PlGF, PlGF+MAP, and PlGF+MAP+UTA-PI.

TABLE 1
Baseline characteristics of the study population

Characteristic	Preterm PE (n=106)	Controls (n=1635)
Gestational age at sampling (wk)	12.6 (12.22–12.98)	12.7 (12.3–13.0)
Maternal age (y)	30.5 (27.5–35.4)	32.1 (28.4–35.5)
Race/ethnicity[a]		
White	48 (45.3)	1025 (62.7)
Black	51 (48.1)	433 (26.5)
South Asian	4 (3.8)	66 (4.0)
East Asian	1 (0.9)	52 (3.2)
Mixed	2 (1.9)	59 (3.6)
Height (cm)	164 (160–167)	165 (160–169)
Weight (kg)[a]	75.2 (65.8–87.0)	65.4 (59.0–75.7)
Body mass index class (kg/m^2)[a]		
<18.5	1 (0.9)	33 (2.0)
18.5 to <25	32 (30.2)	911 (55.7)
25 to <30	33 (31.1)	419 (25.6)
≥30	40 (37.7)	272 (16.6)
Conception		
In vitro fertilization	7 (6.6)	45 (2.8)
Ovulation drugs	1 (0.9)	13 (0.8)
Smoking	4 (3.8)	91 (5.6)
Diabetes mellitus		
Type 1	0 (0.0)	11 (0.7)
Type 2	4 (3.8)	15 (0.9)
SLE/APS	1 (0.9)	6 (0.4)
Chronic hypertension[a]	15 (14.2)	24 (1.5)
Family history of PE[a]	11 (10.4)	58 (3.5)
Gestational age at delivery (wk)[a]	34.2 (31.6–35.7)	39.2 (38.7–39.5)
Birthweight (g)[a]	1771 (1354–2093)	3295 (3100–3515)
Birthweight percentile (%)[a]	0.48 (0.03–10.14)	47.13 (29.19–66.87)

Data are represented as median (interquartile range) or number (percentage).

APS, antiphospholipid syndrome; *PE*, preeclampsia; *SLE*, systemic lupus erythematosus.

[a]Chi-square or Mann–Whitney U test, as appropriate (P<.01).

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Materials and Methods

Study population

This observational case–control study was drawn from a large prospective screening study at 11^0 to 13^6 weeks' gestation on the prediction of pregnancy complications conducted at King's College Hospital, London, United Kingdom, between 2010 and 2015.[23] Pregnant women received a complete first-trimester assessment according to the FMF-described protocols,[21,23] including collecting blood samples for first-trimester biochemical screening and biobanking.

Pregnancy outcome data were collected for the study participants, and the American College of Obstetricians and Gynecologists (2019) criteria were applied for preeclampsia diagnosis.[37] All women in the screening study provided written informed consent; the UK National Research Ethics Committee approved the study (reference number 02-03-033).

The case–control study involved singleton pregnancies only. All major adverse pregnancy outcomes, that is, preeclampsia, fetal growth restriction, gestational diabetes mellitus, and spontaneous preterm birth (n=866) were represented, as well as uncomplicated pregnancies (n=1635); the latter served as controls in biomarker analyses.

Herein we report on the nested data for preterm preeclampsia (n=106) vs controls. Preterm preeclampsia was defined as delivery with preeclampsia before 37 weeks of gestation. Descriptive statistics were generated and presented as means (SD), median (interquartile range [IQR]), and frequency of observations (percentages), as appropriate. Comparisons of patient characteristics and pregnancy outcomes between women with preterm preeclampsia and controls were performed using chi-square or Mann–Whitney U tests (Table 1).

Biomarker data

PlGF, MAP, and UTA-PI measurements were made available by the FMF (London, United Kingdom). With the MAP data generated while adhering to strict quality assurance,[15,38,39] random Gaussian noise (coefficient of variance 10%) was added to MAP to render it more representative of routine practice.[40–42] Ordinarily, UTA-PI measurement quality is subject to a sonographer certification program (FMF); therefore, UTA-PI data were used unaltered.

Relative concentrations of 50 metabolite biomarkers previously associated with adverse pregnancy outcomes were available from the previously reported biomarker study[24]; the metabolites are listed in Supplemental Table 1. Concentration ratios for all metabolite pairs were also generated because metabolite ratios are more strongly associated with preeclampsia than single metabolites.[24] Before modeling, observed predictor values were normalized using MoM,[43]

as described earlier,[24] and summarized in the Supplemental Methods.

Development prediction models

The following predictors (biomarkers) were used for model development: PlGF, MAP, UTA-PI, 50 metabolites, and all metabolite ratios. The complete statistical modeling workflow is summarized in Supplemental Figure 1.

Modeling methodology

Modeling was performed using a methodology (SQU4RE, Lokeren, Belgium) that generates prediction models in 4 consecutive steps: (1) z-normalization of predictor values, (2) combinatorial modeling of classifiers in the unstratified patient set and in discrete patient strata based on BMI and/or race, (3) selection of classifiers, and (4) aggregation of classifiers (ie, bagging) into the final prediction model. The modeling methodology steps are fully detailed in the Supplemental Methods.

The predictive performance of the final models was estimated using DR at a 10% false-positive rate (FPR). The area under the receiver operating curve (AUC) and DR at 10% FPR were reported as point estimates and 95% confidence intervals (CIs), and plotted as point estimate and IQR, using DeLong's method and bootstrapping (2000 iterations), respectively.[44,45]

Evaluation of the modeling methodology

The patient set was split into a training set (2/3) and test set (1/3) for predictor development and internal validation (detailed in Supplemental Methods). Preterm preeclampsia prediction models were developed in the training set using the following prediction panels: PlGF+metabolites, PlGF+MAP+metabolites, and PlGF+MAP+UTA-PI +metabolites.

The modeling methodology was evaluated by comparing model prediction in the train and test set using the AUC statistic.[44] The internal validation criterion was the absence of statistically significant difference in AUC in all 3 scenarios (DeLong test, $P<.05$, no correction for multiple testing).

Preterm preeclampsia prediction models

Following its evaluation, the modeling methodology was applied to the complete data set as recommended.[36] This permitted estimating model performance across patient strata by maximizing sample size. A model was developed for each of the 3 biomarker panels (Supplemental Figure 2). Prediction performances of the models were compared in all patients and in the following patient strata based on BMI classes and main races: normal weight ($18.5 \leq BMI < 25$), overweight ($25 \leq BMI < 30$), obese ($BMI > 30$), Black, and White. The final 3 models were benchmarked on AUC and DR at 10% FPR against their respective reference marker panels: PlGF, PlGF+MAP, and PlGF+MAP+UTA-PI (Table 2). A bootstrap test was used to estimate the significance of the difference in DR between the model with metabolites and the reference model (10^5 iterations; $P<.05$; no correction for multiple testing).

All statistical analyses were performed in R software (R Core Team, Vienna, Austria).[46]

Results

Within the study population (Table 1), patients of self-reported Black race and with higher BMIs were more likely to develop preterm preeclampsia. Most of the patients identified as White or Black; 7 cases (6.6%) and 177 controls (10.8%) were from other maternal race groups. Across BMI classes, case numbers increased proportionally with BMI, with case−control ratios ranging from 1 to 33 in the underweight group ($BMI < 18.5$) to 1 to 6.8 in the obese group ($BMI > 30$). In the preterm preeclampsia group, the median gestational age at delivery was 34.2 weeks, and the median birthweight was 1771 g. Both outcome metrics were significantly lower than in the control group, with medians of 39.2 weeks and 3295 g, respectively.

Evaluation of the modeling methodology

The AUCs for the 3 models were not significantly different in the test set and the training set for the different predictor panels considered (Figure 1). In both training and test sets, the observed DRs at 10% FPR for the models were all >50%. Compared with the training set, the DRs were 3% to 8% lower in the test set (Supplemental Table 3). These results confirm that the modeling methodology effectively limits model overfitting.

Preterm preeclampsia prediction models

In accordance with the 3 scenarios under evaluation, 3 models for preterm preeclampsia prediction were developed using the complete data set.

The Venn diagram in Figure 2 summarizes the biomarkers used in the 3 models. Of the 26 metabolites used in any of the 3 models, 21 metabolites were selected in at least 2 models, respectively. Of note, the 21 recurrent metabolites cover different chemical classes (Figure 2). Typically, the metabolites feature primarily as metabolite ratios in the classifiers (Supplemental Figure 2).

Under the selection criteria applied, only classifiers comprising at most 4 predictors were forwarded for bagging (not shown). Respectively, 30, 40, and 54 classifiers were combined to construct the final models for the 3 panels: PlGF+metabolites, PlGF+MAP+metabolites, and PlGF+MAP+UTA-PI +metabolites.

The prediction statistics in Table 2 and the plotted DRs at 10% FPR (Figure 3) show that in each of the 3 biomarker-availability scenarios investigated, the prediction models with metabolites yielded significantly improved prediction performances.

In view of assessing clinical utility, DRs at 10% FPR are deemed more informative than AUC. With an increase of 15% in DR ($P<.001$), the prediction with the PlGF+MAP+metabolites model was markedly higher than that of the PlGF+MAP reference model. For this model, similar improvements in DR were observed across the maternal race and BMI strata. In Black and White patients, 14% ($P<.05$) and 19% ($P<.01$) more cases were detected compared with the reference model. In

TABLE 2
Prediction statistics for biomarker models developed for the 3 scenarios considered

		Panel 1 Model: PIGF+metabolites Reference: PIGF				Panel 2 Model: PIGF+MAP+metabolites Reference: PIGF+MAP				Panel 3 Model: PIGF+MAP+UTA-PI+metabolites Reference: PIGF+MAP+UTA-PI			
		AUC (95% CI)		DR at 10% FPR (95% CI)		AUC (95% CI)		DR at 10% FPR (95% CI)		AUC (95% CI)		DR at 10% FPR (95% CI)	
Patient stratum	Patient numbers	Model	Reference	Model	Reference	Model	Reference	Model	Reference	Model	Reference	Model	Reference
All	PT-PE=106 Ctrls=1635	0.81[a] (0.77–0.85)	0.76 (0.71–0.81)	0.52[b] (0.42–0.61)	0.44 (0.34–0.54)	0.85[c] (0.81–0.89)	0.81 (0.77–0.85)	0.58[c] (0.49–0.70)	0.43 (0.33–0.55)	0.86[a] (0.82–0.90)	0.83 (0.79–0.87)	0.62[b] (0.53–0.73)	0.55 (0.44–0.66)
Black	PT-PE=51 Ctrls=433	0.81[b] (0.75–0.87)	0.77 (0.69–0.84)	0.53 (0.39–0.65)	0.47 (0.33–0.61)	0.85[b] (0.79–0.91)	0.82 (0.76–0.88)	0.63[b] (0.47–0.78)	0.49 (0.33–0.67)	0.86 (0.81–0.92)	0.84 (0.78–0.89)	0.67 (0.49–0.80)	0.59 (0.41–0.75)
White	PT-PE=48 Ctrls=1025	0.81[a] (0.75–0.87)	0.75 (0.67–0.83)	0.54 (0.40–0.69)	0.46 (0.29–0.63)	0.85[a] (0.79–0.91)	0.80 (0.74–0.85)	0.58[a] (0.42–0.73)	0.40 (0.25–0.54)	0.84[a] (0.79–0.90)	0.80 (0.74–0.87)	0.60 (0.46–0.73)	0.54 (0.38–0.69)
18.5≤BMI<25	PT-PE=32 Ctrls=911	0.85[a] (0.80–0.91)	0.78 (0.69–0.87)	0.56 (0.38–0.75)	0.44 (0.25–0.66)	0.91[a] (0.87–0.95)	0.85 (0.80–0.90)	0.69[a] (0.50–0.84)	0.50 (0.31–0.66)	0.92[b] (0.88–0.96)	0.89 (0.83–0.94)	0.75 (0.56–0.91)	0.72 (0.56–0.88)
25≤BMI<30	PT-PE=33 Ctrls=419	0.76 (0.67–0.86)	0.74 (0.63–0.85)	0.48 (0.30–0.67)	0.52 (0.33–0.67)	0.78 (0.70–0.87)	0.76 (0.68–0.85)	0.45 (0.24–0.73)	0.39 (0.21–0.58)	0.81 (0.73–0.89)	0.80 (0.72–0.89)	0.55 (0.36–0.73)	0.55 (0.33–0.73)
BMI ≥30	PT-PE=40 Ctrls=272	0.82 (0.76–0.89)	0.78 (0.70–0.85)	0.53 (0.35–0.68)	0.40 (0.25–0.60)	0.87[b] (0.81–0.92)	0.82 (0.76–0.89)	0.68[a] (0.50–0.80)	0.48 (0.30–0.65)	0.86[b] (0.80–0.91)	0.81 (0.75–0.88)	0.60[b] (0.43–0.75)	0.45 (0.28–0.63)

Predictive performances of models and their references are represented (AUC and DR at 10% FPR).

AUC, area under the receiver operating characteristic curve; *BMI*, body mass index; *CI*, confidence interval; *Ctrls*, controls; *DR*, detection rate; *FPR*, false-positive rate; *MAP*, mean arterial pressure; *PT-PE*, preterm preeclampsia; *UTA-PI*, uterine artery pulsatility index.

Difference in predictive performance between model and reference: DeLong or bootstrap test as appropriate.

[a]$P<.01$. [b]$P<.05$. [c]$P<.001$.

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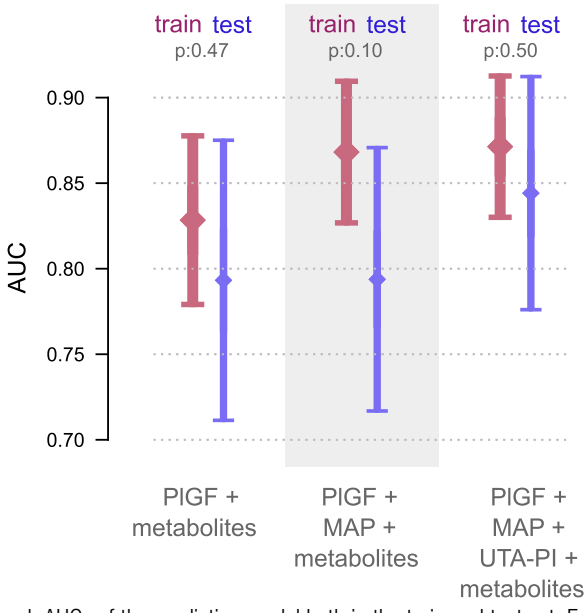
FIGURE 1
Modeling methodology evaluation



Per biomarker panel: AUCs of the prediction model both in the train and test set. Estimated AUC and 95% confidence interval. *P* values: test for differences in AUC, train vs test set, DeLong's method, no correction for multiple testing.

AUC, area under the receiver operating characteristic curve; *MAP*, mean arterial pressure; *UTA-PI*, uterine artery pulsatility index.

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obese patients, the increase in DR amounted to 20% ($P<.01$), and in normal-weight patients ($18.5\leq BMI<25$) to 19% ($P<.01$). Interestingly, the AUC surpassed the symbolic value of 0.90 in the normal-weight group (Table 2; Supplemental Figures 3 and 4). In the overweight group ($25\leq BMI<30$), the PlGF +MAP+metabolites model only showed a modest DR increase (6%; nonsignificant [ns]) compared with the reference model.

In comparison, both PlGF+metabolites and PlGF+MAP+UTA-PI+metabolites increased DR by 8% over their respective reference models in all patients. For PlGF+metabolites, all the observed differences in DRs relative to the PlGF reference model were positive across the different race and BMI strata (ranging from 6%−13%), albeit not meeting significance. No improvement was found in the overweight class (−3%; ns). Likewise, PlGF+MAP+UTA-PI +metabolites delivered improved DRs ranging from 3% (normal weight; ns) to 15% (obese; $P<.05$) over its reference across the different patient strata, with no improvement observed in the overweight class (0%).

Of note, the PlGF+MAP+metabolites model achieved prediction similar to that of the third reference model (ie, PlGF+MAP+UTA-PI), with AUCs of 0.85 (95% CI, 0.81−0.89) and 0.83 (95% CI, 0.79−0.87) and DRs at 10% FPR of 0.58 (95% CI, 0.49−0.70) and 0.55 (0.44 −0.66) for the developed model and the reference model, respectively (Table 2).

Post hoc examination of the selected classifiers for bagging in the PlGF +MAP+metabolites panel confirmed that for the overweight stratum, other than the reference model, only 2 classifiers met the inclusion criterion. Therefore, the performance observed in the overweight stratum was primarily driven by classifiers selected on patients with any BMI. A similar lack of prediction improvement in the overweight class was also found for the other 2 prediction models developed.

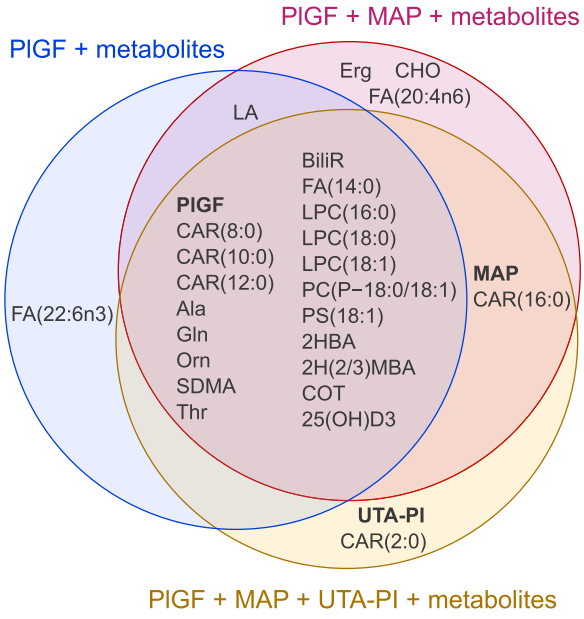
Comment

Principal findings

We demonstrated that specific panels of metabolite biomarkers can effectively be combined with the best available early-pregnancy biomarkers for preterm preeclampsia, namely PlGF, MAP, and UTA-PI, to further improve biomarker-based prediction.

A machine-learning methodology based on combining a selection of sparse classifiers into a final prediction model was devised and successfully evaluated. The modeling methodology was applied to develop 3 new prediction models by combining metabolites either with PlGF, PlGF and MAP, or PlGF, MAP, and UTA-PI. The subclassification of the study population into discrete maternal phenotypes, based on BMI and race, yielded sparse phenotypic biomarker-based classifiers with enhanced associations with preterm preeclampsia for combination into the final prediction models. Within the 50 metabolites available for modeling,[24] 26 metabolites featured in any of the 3 prediction models, with 21 being common between at least 2 of the models. Notably, metabolites were typically present as metabolite ratios. The 3 models' prediction performances were evaluated using DR at 10% FPR, a gauge of clinical usability, and compared with the performance of the reference models, PlGF, PlGF+MAP, and PlGF+MAP +UTA-PI. We found every time that including metabolites in the prediction models significantly improved DRs for preterm preeclampsia at a 10% FPR over the respective comparator models, whereby the amplitude DR improvements exceeded the observed 3% to 8% overfitting found during evaluation of the modeling methodology. The prediction models delivered consistent increases in DRs for both Black and White women. Using BMI-based grouping, the prediction models typically improved DRs in the normal-weight group and the obese group, but not in the overweight group. The magnitude of the increases in DRs was found to be the largest when metabolites were combined with PlGF and MAP.

FIGURE 2
Biomarkers in the 3 prediction models



The Venn diagram summarizes the biomarkers selected in the 3 final prediction models independently developed in the 3 biomarker panels investigated.

2H(2/3)MBA, 2-hydroxy-(2/3)-methylbutyric acid; *2HBA*, 2-hydroxybutyric acid; *25(OH)D3*, 25-hydroxyvitamin D3; *Ala*, alanine; *BiliR*, bilirubin; *CAR(2:0)*, acetylcarnitine; *CAR(8:0)*, octanoylcarnitine; *CAR(10:0)*, decanoylcarnitine; *CAR(12:0)*, dodecanoylcarnitine; *CAR(16:0)*, palmitoyl carnitine; *CHO*, choline; *COT*, cotinine; *Erg*, ergothioneine; *FA(14:0)*, myristic acid; *FA(20:4n6)*, arachidonic acid; *FA(22:6n3)*, docosahexaenoic acid; *Gln*, glutamine; *LA*, lactic acid; *LPC(16:0)*, 1-palmitoyl-2-hydroxy-sn-glycero-3-phosphocholine; *LPC(18:0)*, 1-stearoyl-2-hydroxy-sn-glycero-3-phosphocholine; *LPC(18:1)*, 1-oleoyl-2-hydroxy-sn-glycero-3-phosphocholine; *MAP*, mean arterial pressure; *Orn*, ornithine; *PC(P-18:0/18:1)*, 1-(1Z-octadecenyl)-2-oleoyl-sn-glycero-3-phosphocholine; *PS(18:1)*, 1-(9Z-octadecenoyl)-sn-glycero-3-phospho-L-serine; *SDMA*, symmetric dimethylarginine; *Thr*, threonine; *UTA-PI*, uterine artery pulsatility index.

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Results in the context of what is known

Romero et al[47] recently demonstrated that a subclassification of obstetrical syndromes by placental pathology led to stronger associations between biomarkers and obstetrical diseases. Our translational research applied the same conceptual framework to improve biomarker-based preterm preeclampsia prediction by assuming the existence of distinct maternal risk phenotypes,[26,34] for which prediction may require different combinations of biomarkers. Without readily available methods to effectively discern maternal risk phenotypes, we used maternal characteristics of "race" and "BMI" for disaggregating the study population into patient strata and eliciting phenotypic prediction performance. In a further recognition of the complexity of predicting a syndrome, the applied modeling methodology involved a machine-learning technique, that is, bagging. This technique is highly effective in applications wherein finding a good model in 1 step is impossible because of the complexity and scale of the problem,[48] and achieves more precise predictions by averaging the predictions from the different classifiers.[49]

Our data suggest that self-identified maternal race can align with differential risk profiles and can be used to expose differential preterm preeclampsia risk prediction. The prospect of using biomarkers to enhance prediction in Black women is noteworthy given that they experience higher incidences of preeclampsia and have poorer perinatal outcomes.[6,30,31]

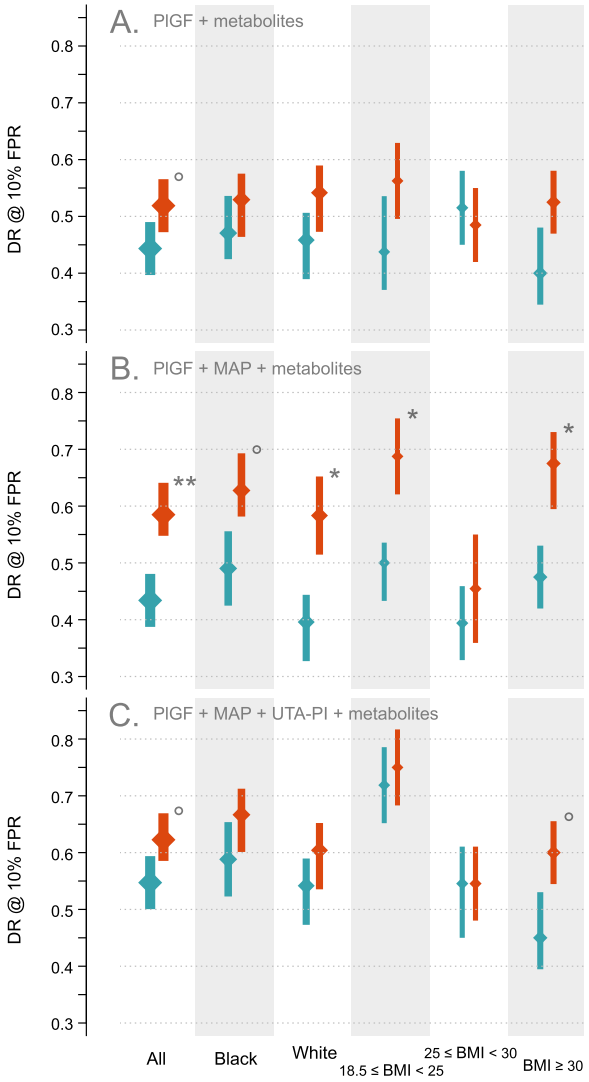
The modeling methodology did not yield effective prediction improvement in the overweight group. This is likely attributable to poor alignment of the patients within this group with a dominant risk profile, blunting the added value of subclassification to expose enhanced prediction. Phenotyping pregnant women on the basis of a metabolite fingerprint of BMI[50] instead of their calculated BMI may further improve preterm preeclampsia prediction using our methodology.

In this research, metabolite biomarkers were selected into models on the basis of their ability to improve the prediction performance of established biomarkers. Many of the metabolites selected in ≥2 of the prediction models overlapped with ones that we confirmed to be significantly associated ($P<.05$) with preterm preeclampsia in all women, or associated specifically with preterm preeclampsia in the BMI<25 class or the BMI≥30 class.[24] In addition, we identified an additional set of metabolites that were not significantly associated with preterm preeclampsia on their own,[24] but played a role in improving existing biomarkers. 1-Palmitoyl-2-hydroxy-sn-glycero-3-phosphocholine was reported previously to be associated with small for gestational age,[51] and 1-stearoyl-2-hydroxy-sn-glycero-3-phosphocholine was shown to differentiate between preeclampsia and gestational diabetes mellitus in a previous study.[52] Palmitoylcarnitine and lactic acid were reported to be associated with late-onset preeclampsia,[53,54] 1-(9Z-octadecenoyl)-sn-glycero-3-phospho-L-serine with preeclampsia,[55] and myristic acid with gestational diabetes mellitus.[56,57] With smoking status being negatively associated with preeclampsia risk,[58] the selection of cotinine, a nicotine metabolite,[59] was unsurprising.

Clinical implications

The performance of the FMF prediction model, which combines the competing risk model (for maternal risk factors) with the biomarkers PlGF, MAP, and UTA-PI for preterm preeclampsia prediction, has been validated in many independent settings,[15] and its clinical utility in conjunction with aspirin prophylaxis has been demonstrated.[8,9,60,61]

FIGURE 3
Predictive performance of the models developed for the 3 biomarker panels



DRs at 10% FPR for all patients and in the patient strata defined by maternal race (Black and White) and maternal BMI class (normal weight, overweight, obese). DR at 10% FPR: point estimates (interquartile range). Orange: biomarker model comprising metabolites; cyan: reference biomarker model without metabolites. **A,** Biomarker panel PIGF+metabolites. **B,** Biomarker panel PIGF+MAP+metabolites. **C,** Biomarker panel PIGF+MAP+UTA-PI+metabolites. Comparison of DRs between a model with metabolites and a model without metabolites (reference model): bootstrap test, no correction for multiple testing. *Cirlce* denotes $P<.05$; *Asterisk* denotes $P<.01$; *double asterisks* denote $P<.001$.

BMI, body mass index; *DR*, detection rate; *FPR*, false-positive rate; *MAP*, mean arterial pressure; *UTA-PI*, uterine artery pulsatility index.

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However, the need for adherence to strict protocols for blood pressure measurement and the limited availability of certified sonographers have thus far hampered its widespread implementation in settings such as the United States. In recognition of this clinical reality, this translational research considered 3 scenarios for prediction model development reflecting 3 levels of availability of screening resources. At a minimum, access to laboratory testing for blood-borne biomarker analyses was assumed (PlGF+metabolites), possibly augmented with access to primary care (PlGF+MAP+metabolites), and ideally with access to certified sonographers (PlGF+MAP+UTA-PI+metabolites). Similarly, we added noise to the available best-practice MAP data to render the study data more representative of routine practice.[41,42] Our research indicates that the inclusion of metabolites into laboratory testing can improve preterm preeclampsia prediction in each resource scenario. In this context, it is notable that the PlGF+MAP+metabolites model delivered similar preterm preeclampsia prediction to that of the combination of biomarkers PlGF+MAP +UTA-PI used in the FMF prediction model.

Our research also indicates that biomarkers can be combined to refine prediction in maternal phenotypes with low previous risks, such as women with normal BMI, or high previous risks, such as women identifying as Black. This opens an avenue to address the lack of prediction accuracy inherent to the common checklist-based risk assessments; for instance, the United States Preventive Services Task Force guidance will disregard women of normal BMI and, at the same time, consider any Black woman to be at moderate risk.[17]

Research implications

Taken together with other recent research,[47,62,63] this study adds further credence to the concept that subclassification in obstetrical syndromes will be critical to improving their understanding and prediction.[25] Currently, differential associations between maternal characteristics and preeclampsia risk are solely accounted for in previous risk assessments. However, our research indicates that after adjusting for confounding, new subsets of biomarkers can be elicited by comparing cases and controls in groups of women that differ in maternal characteristics. Evaluation of new biomarker candidates and reevaluation of existing biomarkers in function of risk-modifying maternal characteristics, or other pregnancy characteristics such as fetal sex,[64,65] may

unlock further improvements to preeclampsia prediction models.

In future research, we will: (1) investigate the most effective way to combine the developed prediction models with previous risk information, as contained in maternal risk factors, so that the added value of phenotypic prediction is preserved when determining a patient's posttest probability of preterm preeclampsia[66]; and (2) confirm conservation of prediction performance upon conversion of the metabolite analyses by research-grade assays into clinical laboratory−grade liquid chromatography−tandem mass spectrometry (LC−MS/MS) assays.[67,68]

With the primary aim of this research being translational, it is explicitly building on the current best available set of biomarkers for preterm preeclampsia. We argue that incremental improvements are an appropriate way to shorten the time to clinical application. By explicitly integrating the current state of the art, it allows for effective control of patient risk upon implementation. In view of the generalizability and transportability of the developed prediction models to other settings, the combined use of multiplex analysis of metabolite panels using LC−MS/MS technology and the aggregation of many models into a final prediction model lends itself well to targeted updating of the models to local settings[69] and to regular updating in response to population changes over time.[70,71]

Strengths and limitations

Key strengths of this study include the following: (1) the size of the study population, which allowed for creation of patient strata with sufficient preterm preeclampsia cases to generate phenotypic classifiers for aggregation into the final prediction models; (2) the use of a rigorous modeling methodology to limit overfitting and overestimation of prediction performance; and (3) the application of translational research with a singular focus on improving clinical usability throughout. Among the limitations of this study, we note the following: (1) the possibility of a selection bias in the metabolite biomarkers considered given that most of these were identified in biomarker discovery studies with participants primarily identifying as White and with BMI distributions centering around population averages; (2) absence of phenotypic classifiers for aggregation from patients of racial origins other than White or Black, or from BMI classes such as the underweight (BMI<18.5) or morbidly obese (BMI≥40); and (3) the use of ill-defined maternal characteristics for defining patient strata, which may have blunted phenotypic prediction performances.

Conclusions

This study confirmed a panel of metabolite biomarkers that can effectively be combined with the best currently available biomarkers for preterm preeclampsia early in pregnancy, namely PlGF, MAP, and UTA-PI, to further improve prediction. Three prediction models were developed for 3 scenarios reflecting different levels of screening resources available. Improvements over the established biomarkers were in part achieved by accounting for the existence of different maternal risk profiles. This allowed for the combination of specific metabolites and established biomarkers into classifiers with enhanced prediction performance in certain patient strata and the aggregation of such classifiers into prediction models. ■

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Supplementary materials

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R.T. and A.P. are employees of Metabolomic Diagnostics. G.T. is the owner of SQU4RE, an independent statistics and data-mining provider. G.T. and R.T. are named inventors on several patent applications regarding the use of metabolites to predict preeclampsia risk. The associated rights are assigned to Metabolomic Diagnostics. A.S., K.H., A.P.M., and K.H.N. report no conflict of interest.

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