Predictive values of multiple serum biomarkers in women with suspected preeclampsia: a prospective study

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Research article

Keywords: preeclampsia, prediction, serum biomarker, prospective, cohort

Posted Date: June 9th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-33584/v1

Abstract

Background

Early preeclampsia (PE) prediction has been shown to improve the maternal and fetal outcomes in pregnancy. We aimed to evaluate the PE prediction values of a series of serum biomarkers.

Methods

The singleton pregnant women with PE-related clinical and/or laboratory presentations were recruited and had the blood drawn at their first visits. The prospective cohort was further divided into the PE-positive and PE-negative groups based on the follow-up results. The following markers were tested with the collected serum samples: sFlt-1, PlGF, M, tPAI-C, compliment factors C1q, B, H, BUN, GlyFn, PAPP-A2, BUN, Cre, UA and Cysc.

Results

Totally 196 women suspected for PE were recruited with follow-up medical records. Twenty-five percent of the recruited subjects developed PE before delivery and 75% remained PE-negative. The serum levels of sFlt-1, BUN, Cre, UA, Cysc and PAPP-A2 were significantly elevated and the PlGF was significantly decreased in the PE-positive patients. The AUCs were listed in the order of decreasing values: UA (AUC = 0.73), sFlt-1/PlGF (AUC = 0.67), Cysc (AUC = 0.66), GlyFn/PlGF (AUC = 0.65), PlGF (AUC = 0.64), PAPP-A2/PlGF (AUC = 0.64), sFlt-1 (AUC = 0.63), BUN (AUC = 0.63), Cre (AUC = 0.63), and PAPP-A2 (AUC = 0.60) in the ROC analyses. The Logistic regression analysis showed that UA and PAPP-A2 were independent risk factors for PE development with the odds ratios of 3.3 and 2.2 respectively. Moreover, the PPVs of UA and PAPP-A2 were 48.9%, and 40.4%; the NPVs of UA and PAPP-A2 were 82.1% and 81.9%.

Conclusions

Further studies are warranted to confirm the clinical utilities of the serum markers in PE prediction.

Introduction

As one of the most common complications during pregnancy, preeclampsia (PE) that is estimated to have an incidence rate of 2–8% worldwide (1) may lead to serious maternal or fetal morbidity and mortality if not managed properly (2). According to the 2019 American College of Obstetricians and Gynecologists (ACOG) practice guideline, preeclampsia is defined as the new onset of hypertension and proteinuria or significant end-organ damage with or without proteinuria after 20 weeks of gestation (3). Although tremendous advances have been made in the field of preeclampsia study, its underlying pathogenesis remains largely unknown. Based on the anatomical evidence at the placental site and other laboratory findings, the following mechanisms are considered as the major contributors to preeclampsia: spiral artery remodeling, placental ischemia and oxidation, systemic inflammatory response and imbalance of angiogenic and antiangiogenic factors (2, 4).

Extensive studies have been focused on the preventative strategies for women who are at high risk for developing PE (3, 4) and low-dose aspirin is the only drug with proven evidence of benefit in reducing the risk of PE (5). Besides, early pregnancy prediction or diagnosis of PE has been shown to improve the maternal and fetal outcomes by employing appropriate management, such as fetal lung maturity treatment with corticosteroids, severe hypertension treatment and early delivery (6). More interestingly, it was reported that with the help of the angiogenic makers, the number of patients that were falsely identified positive for PE was decreased with a significant financial cost reduction per patient (7). Historically, maternal characteristics such as parity, ethnicity, social risk factors, family and previous medical history and so on, were used to predict the development of PE, with a prediction rate of no higher than 30% (8). Later on, many clinical studies sought to apply imaging tests such as uterine artery Doppler analysis to predict women at increased risk of PE (9, 10). Due to the high false positive rate which resulted in unnecessary patient anxiety and extra health care cost, the imaging tests alone or in combination with maternal characters were not recommended for screening for PE in early pregnancy (10).

At the same time, great amount of efforts have been invested in discovering and developing reliable serum biomarkers in PE early prediction. The angiogenic factors including vascular endothelia growth factor (VEGF) and placental growth factor (PlGF), and the antiangiogenic factors including soluble endoglin (sEng) and soluble fms-like tyrosine kinase 1 (sFlt-1), were found to be significantly altered in ischemic trophoblasts of PE patients (2). More specifically, according to a systemic review study in 2012 (11), the sEng and sFlt-1 were found to be significantly increased in the women that developed PE; whereas the serum VEGF and PlGF concentrations were lower in these women, suggesting the balance was tipped in favor of the antiangiogenic pathway in PE patients. Moreover, the sFlt-1/PlGF ratio of 38 was shown to be able to effectively exclude the presence of PE with a negative prediction value (NPV) of 99.3% (12). In addition, a series of serum biomarkers have been proven to be associated with the presence or severity of preeclampsia. For instance, the maternal pregnancy-associated plasma protein-A2 (PAPP-A2) serum concentration was found to be upregulated in PE patients, resulting in local activation of insulin-like growth factor (IGF) signaling pathways (13). The maternal serum glycosylated fibronectin (GlyFn) was reported to be elevated in all three trimesters of PE patients and further recommended as a point-of-care biomarker for assessment of preeclampsia (14). In uteroplacental thrombosis which is one of the major mechanisms of preeclampsia, several thrombotic and fibrinolytic factors, such as circulating soluble thrombomodulin (TM) and tissue plasminogen activator (tPA) were found to be elevated in PE and correlated with the severity of proteinuria (15, 16). The dysregulation of complement pathways also contributes to the development of PE. Differential expression of complement factors C1q, B and H were found in specific trimesters of severe PE patients (17).

However, regardless the parameters or models used, low positive predictive values (PPV) (8–33%) were observed in most of the previous studies seeking to screen for PE in general population (3). As a result, most of the screen-positive or false-positive patients who will not develop PE may be exposed to unnecessary tests and prophylactic interventions that will not benefit them. In this work, we aimed to evaluate the predictive value of the following serum biomarkers in a prospective study with the women suspected to develop preeclampsia: sFlt-1, PlGF, PAPP-A2, GlyFn, TM, tissue plasminogen activator inhibitor complex (tPAI-C), compliment factors C1q, B, H, and renal function tests including uric acid (UA), blood urea nitrogen (BUN), creatinine (Cre), cystatin C (Cysc).

Materials And Methods

Subjects

The enrollment criteria for the women suspected for PE were described as follows. The recruited singleton pregnant women should be at least 18 years old, between 20–36 gestational weeks and present with new onset of hypertension or proteinuria, aggravation of preexisting hypertension or proteinuria, or one of the following symptoms: upper abdominal pain, edema, headache, visual impairment, abnormal weight gain (> 1 kg/week), decreased platelets, elevated liver transaminase, fetal growth restriction, abnormal uterine ultrasound perfusion during mid-pregnancy, or uterine artery flow notching. The women were excluded if one or more of the criteria were met: confirmed diagnosis of preeclampsia or Hemolysis Elevated Liver enzymes and Low Platelets (HELLP) syndrome, anti-hypertensive treatment during this pregnancy. The pregnant subjects meeting the inclusion and exclusion criteria were enrolled and had their blood draw at their first visits to Beijing Obstetrics and Gynecology Hospital, with follow-up for the presence ("PE-positive" group) or absence ("PE-negative" group) of PE until delivery.

The PE diagnosis was determined with the diagnostic criteria proposed by the 2019 ACOG Practice Bulletin (3), in which PE was defined as gestational hypertension (systolic/diastolic blood pressure ≥ 140/90 mmHg) in previously normotensive women accompanied by proteinuria (urine protein ≥ 300 mg/24 hours) or end-organ damage after 20 weeks of gestation. Twenty PE diagnosed patients ("PE-diagnosed" group) and 20 maternal age and gestational age matched healthy pregnant women were enrolled during the same study period ("healthy control" group).

Serum Samples, Reagents And Methods

The maternal blood from each participant (3 ml) was drawn when they were enrolled and left to clot for 30 min, and centrifuged for 10 min at 2300 g. The serum aliquots (1 ml) were separated and stored at -80℃ until being tested.

The maternal levels of sFlt-1 (Cat No. YZB/GER5424-2014, Germany, Roche Diagnostics) and PlGF (Cat No. YZB/GER5425-2014, Germany, Roche Diagnostics) were measured on the fully automated electrochemiluminescence immunoassay platform COBAS e411 (Germany, Roche Diagnostics). Both of the maternal serum PAPP-A2 (Cat No. AL109, USA, AnshLabs) and GlyFn (Cat No. AL160, USA, AnshLabs) were measured by the enzyme-linked immunosorbent assay (ELISA) according to the manufacturer's instructions. The ELISA standard operation protocol was as previous described (18)(19). The serum TM (HISCL® TM Assay Kit, Japan, Sysmex) and tPAI-C (HISCL® tPAI-C Assay Kit, Japan, Sysmex) levels were determined by the fully automated HISCL-5000 Chemiluminescence Analyzer (Japan, Sysmex). The measurements of complement factors C1q (Cat No. 20170922, China, Shanghai Beijia Biochemical Reagent), B (Cat No. 20020803, China, Shanghai Beijia Biochemical Reagent) and H (Cat No. 20183020, China, Shanghai Beijia Biochemical Reagent) and were performed on the fully automated ARCHITECT ci16200 Integrated System Chemistry/Immunology Analyzer (USA, Abbott). The renal function tests including UA (Cat No. 3P39-21, USA, Abbott), BUN (Cat No. 7D75-21, USA, Abbott), Cre (Cat No. 8L24-31, USA, Abbott) and Cysc (Cystatin C Assay Kit, China, Beijing Jiuqiang Biotech) were also performed on the ARCHITECT ci16200 Analyzer (USA, Abbott).

Statistical analysis

Data analysis was performed using statistical software SPSS 22.0. Comparisons between the two groups were performed using the t-test or Mann Whitney-U test. $P < 0.05$ was considered statistically significant. The receiver operating characteristics (ROC) curve was used to analyze the predictive values of the markers for preeclampsia. The continuous variables were converted to binary variables according to the cut-off values determined in the ROC analyses. The multivariate forward method of Binary Logistic regression analysis was used to identify the risk factors for PE development.

Results

The flowchart for the patient recruitment and the study designed was presented in Fig. 1. From January 2018 to March 2019, with the enrollment and excluding criteria described above, a total of 200 subjects with PE related clinical and/or laboratory presentations were recruited, including the 4 patients that were lost to follow-up. Of the remaining 196 patients, 25% (49/196) (PE-positive group) developed PE before delivery and 75% (147/196) (PE-negative group) maintained PE negative for the rest of the pregnancy. At the end, the collected serum samples of the PE-positive (n = 49) and PE-negative (n = 147) patients, together with those collected from the PE-diagnosed (n = 20) and healthy control (n = 20) groups, were subjected to the following serum marker measurements: sFlt-1, PlGF, PAPP-A2, GlyFn, TM, tPAI-C, compliment factors C1q, B, H, UA, BUN, Cre, and Cysc.

As summarized in Table 1, there was no significant difference in maternal age or blood sampling gestational weeks (GW) between the PE-positive and PE-negative groups (the prospective cohort). Similar findings were observed between the PE-diagnosed and healthy control groups ($p > 0.05$ for both age and sampling GW). On average, the time interval from serum collection to PE occurrence was 7.0 weeks in the PE-positive patients (Table 1).

Table 1
Demographic data for the recruited subjects in current PE prediction study

	Age (years)	Sampling GW[a]	Interval (weeks)[b]
PE-diagnosed	33.1 ± 4.8	31.8 ± 3.9	NA[c]
Healthy control	32.8 ± 2.5	32.5 ± 1.8	NA
p value (t-test)	0.612	0.225	
PE-positive	34.0 ± 4.4	29.0 ± 5.1	7.0 ± 4.2
PE-negative	32.9 ± 4.7	28.6 ± 7.2	NA
p value (t-test)	0.431	0.785	
a: gestational weeks. b: the interval between sampling and PE occurrence. c: not available.			
The data in Table 1 were presented as mean ± standard deviation.			

To evaluate the PE predicting values of the interested markers in present study, we first compared their mean serum concentrations that were determined with our laboratory devices and platforms. As shown in Table 2, a panel of analytes representing various biological functions were found significantly elevated in the patients that developed PE in later pregnancy (PE-positive) compared to the PE-negative group, including sFlt-1 ($p = 0.007$), BUN ($p = 0.009$), Cre ($p = 0.006$), UA ($p < 0.001$), Cysc ($p = 0.001$) and PAPP-A2 ($p = 0.032$). The PlGF ($p = 0.004$) was the only exception that was found to be significantly decreased in the PE-positive patients, resulting in more profoundly increased ratios in the PE-positive group, including sFlt-1/PlGF ($p < 0.001$), GlyFn/PlGF ($p = 0.002$), and PAPP-A2/PlGF ($p = 0.003$). These significantly changed serum markers either from direct laboratory measurements or from the ratio calculations were subjected to the ROC analyses, According to Fig. 2, the areas under curve (AUCs) were listed in the order of decreasing values: UA (AUC = 0.73), sFlt-1/PlGF (AUC = 0.67), Cysc (AUC = 0.66), GlyFn/PlGF (AUC = 0.65), PlGF (AUC = 0.64), PAPP-A2/PlGF (AUC = 0.64), sFlt-1 (AUC = 0.63), BUN (AUC = 0.63), Cre (AUC = 0.63), and PAPP-A2 (AUC = 0.60). Then these continuous variables were converted to binary variables and used as covariates in the following Binary Logistic regression analysis. The Logistic regression analysis showed that UA ($P = 0.020$) and PAPP-A2 ($P = 0.036$) were independent risk factors ($p < 0.05$) for PE development with the prospective cohort. And they increased the risk for preeclampsia at the odds ratios of 3.3 (1.5-7.0) and 2.2 (1.0-4.6) respectively (Table 3). As shown in Table 3, with the cut-off values obtained with the highest Youden Index (sum of sensitivity and specificity minus one) in the ROC analyses, the PPVs of UA and PAPP-A2 were 48.9%, and 40.4%; the NPVs of UA and PAPP-A2 were 82.1% and 81.9% (Table 3).

Table 2
Comparison of serum PE predictors in the PE-positive and PE-negative groups

		PE-positive n = 49	PE-negative n = 147	p value
sFlt-1(pg/ml)	Mean	2814.0	2036.0	0.007**
	Range (25th -75th)	1785.0 -4799.5	1548.0-3113.0	
PlGF(pg/ml)	Mean	209.1	301.4	0.004**
	Range (25th -75th)	69.5-293.3	135.7-511.9	
sFlt-1/PlGF	Mean	13.3	6.8	< 0.001**
	Range (25th -75th)	6.8–65.0	3.6–21.7	
TM (TU/ml)	Mean	10.7	9.9	0.405
	Range (25th -75th)	8.8–12.3	8.7–10.2	
tPAI-C (ng/ml)	Mean	5.4	5.9	0.154
	Range (25th -75th)	3.7–6.8	4.5–7.3	
BUN (mmol/L)	Mean	3.3	2.8	0.009**
	Range (25th -75th)	2.5–4.3	2.4–3.4	
Cre (μmol/L)	Mean	46.6	41.8	0.006**
	Range (25th -75th)	38.1–51.1	36.8–44.8	
UA (μmol/L)	Mean	295.7	232.3	< 0.001**
	Range (25th -75th)	233.2–336.0	201.5-280.1	
Cysc (mg/ml)	Mean	1.2	1.0	0.001**
	Range (25th -75th)	0.9–1.4	0.8–1.1	
C1q (mg/L)	Mean	198.4	204.5	0.845
	Range (25th -75th)	170.0-226.0	177.0-228.0	
B facstor (mg/L)	Mean	345.8	336.9	0.122
	Range (25th -75th)	328.5-369.3	308.0-365.0	
H factor (mg/L)	Mean	398.0	401.7	0.264
	Range (25th -75th)	358.0-436.8	372.0-429.0	
GlyFn (mg/ml)	Mean	285.4	259.1	0.061
	Range (25th -75th)	227.1-421.9	220.1-323.3	

		PE-positive n = 49	PE-negative n = 147	p value
PAPP-A2 (mg/ml)	Mean	91.8	52.9	0.032*
	Range (25th -75th)	38.3-192.7	31.4-103.7	
GlyFn/PlGF	Mean	1.5	0.9	0.002**
	Range (25th -75th)	0.8-6.0	0.5–2.3	
PAPP-A2/PlGF	Mean	0.5	0.2	0.003**
	Range (25th -75th)	0.1–2.3	0.1–0.7	
* P < 0.05 for the comparison between two groups.				
** P < 0.01 for the comparison between two groups.				

Table 3
The performances of UA, PAPP-A2 and PAPP-A2/PlGF for predicting preeclampsia

Performance	UA	PAPP-A2
Cut-off	300 μmol/L	106 mg/ml
PPV[a]	48.9%	40.4%
NPV[b]	82.1%	81.9%
OR[c]	3.3 (1.5-7.0)	2.2 (1.0-4.6)
a: positive predictive value. b: negative predictive value. c: odds ratio.		

Discussion

Albeit with more and more research focus on the PE prediction in pregnancy, very few serum prediction markers have been successfully implemented in clinical practice. One of the non-negligible hurdles associated with PE was its relatively low prevalence (2–8%), requiring the biomarker tests to be highly sensitive and specific for accurate PE prediction. According to the two recent systemic reviews by De Kat et al. (19) and Mosimann et al. (20), the majority of the previous PE prediction studies, whether focusing solely on serum markers or in combination of other measurements such as maternal characters and ultrasound metrics, were performed as screening studies on the general pregnant population. For instance, even with the NICE guideline study in which 16747 women were screened, only 2.8% of the enrolled patients developed PE (21). In the prediction studies with smaller cohorts and fewer PE positive subjects, the potential pitfall of “data overfitting” was not uncommon in a quality review for first trimester risk-prediction models analysis (22). In the publication for evaluating the PE predictor of sFlt-1/PlGF by Zeisler et al., the authors narrowed down the targeting patients who presented with PE-related clinical and/or laboratory presentations (12). As a result, about 20% of those recruited subjects "with suspected preeclampsia" developed PE within 4 weeks, which significantly increased the incidence rate of PE in the prediction study and generated potentially higher power in the subsequent statistical analysis (12). Similar patient recruiting strategy was adopted in our study and a PE positive rate of 25% (49/196) was observed, with straight focus on the subgroup of pregnancy who were more likely to develop PE.

According to a meta-analysis on the sFlt-1/PlGF ratio which was considered one of the most promising serum markers in PE prediction in the past few years, the authors found this particular ratio marker had an overall sensitivity of 80%, a specificity of 92%, a positive likelihood ratio of 10.5 and a negative likelihood ratio of 0.22 after pooling 15 studies involving 534 cases and 19587 controls (23). With the valuable research accumulation, the 4-week observation window along with the 38 cut-off was applied in the Zeisler's paper, which showed that the sFlt-1/PlGF ratio could accurately exclude the PE occurrence in the suspicious patients, with the AUC of 0.90 in the ROC analysis, compared to the AUC of 0.67 in our study with follow-up until delivery (12). However, the rest of the markers included in present study, the observation window was not yet defined previously and the delivery remained the mainstream endpoint for most of the PE prediction evaluation studies (19, 20). Interestingly, the average interval between blood sampling and PE occurrence was 7.0 weeks with our prospective cohort, which provided important clinical evidence for future refined validation studies.

The hemostatic factors such as TM and tPAI-C have been found to be related with the incidence and severity of PE decades ago (15, 16, 24). Whether or not they could be useful in PE prediction was not investigated before. In the comparison between PE-diagnosed and healthy controls, we also found the both TM ($p = 0.025$) and tPAI-C ($p < 0.001$) to be significantly elevated in the PE group (Supplementary Table 1). However, such difference was not observed in the prospective cohort (Table 2), indicating their limited values in PE predicting.

It has been reported that excessive activation and poor regulation of the complement system at the maternal-fetal interface contributed to the development of PE (25). More importantly, a recently study by Jia et al. showed that the complement factors C1q, B and H were able to differentiate early-onset severe PE with AUCs of 0.81, 0.74 and 0.68 respectively. To further evaluate their potential utility in PE prediction, the circulating levels of complement factors C1q, B and H were determined in present study. Unfortunately, no significant difference was found either in the PE-positive and PE-negative groups comparison (Table 2) or in the PE-diagnosed and healthy control groups comparison (Supplementary Table 1). Future studies about the proper clinical settings in which the complement factors can be applied should be investigated for PE related research.

The two glycoproteins, GlyFn and PAPP-A2 that were included in our testing panel, have been widely studied in preeclampsia. As an abundant protein with a wide spectrum of functions, the serum GlyFn was found to be highly elevated in both early and late pregnancies of the PE patients(14, 26). More interestingly, in a 2020 study by Huhn et al., the GlyFn was reported with a good PE predicting performance in a short term and with an AUC of 0.94 in the ROC analysis, in which a prospective cohort identified with PE-specific high-risk factors was used. In Table 2 and Supplementary Table 1, the GlyFn was significantly increased in the PE-diagnosed patients, but not in the PE-positive group who was not diagnosed with PE at the time of blood sampling but experienced PE development afterwards. This apparent discrepancy may be introduced by the difference of GlyFn measurement reagents as well the patient recruiting criteria. The other glycoprotein PAPP-A2 involved in cleaving insulin-like growth factor binding protein in placenta, was found to be helpful in diagnosing (13) and predicting PE (27). In our study, the PAPP-A2 was one of the only two independent risk factors in the Logistic regression test, indicating its potential importance in PE prediction although further validation should be conducted to refine its optimum cut-off value. Interestingly, the PAPP-A protein with similar biological functions as PAPP-A2, which was a more extensively studied marker for aneuploidies and PE prediction, was found to be decreased in most of the previous PE research works.

As one of the essential criteria for the diagnosis of preeclampsia (3), proteinuria itself was not a sufficient predictor for the occurrence or the adverse outcomes of PE (28). However, the common renal function tests such as BUN, Cre, UA and Cysc were shown to be potential valuable markers for PE diagnosis and/or prediction. For example, the BUN (29) and BUN/Cre ratio (30) were both found increased in the PE patient compared with normal controls. Cysc, the alternative test of Cre used in glomerular filtration rate estimation, was found elevated in PE patients (31) and was able to predict PE in combination of neutrophil gelatinase-associated lipocalin (AUC = 0.88) (32). Moreover, Cysc was reported as a predictor of preterm labor in severe PE, although the physiological increase of Cysc during pregnancy may pose an additional confounding factor in its clinical evaluation (33). In a prospective study with relatively large cohort (n = 9522) by Rezk et al., the serum UA was found to be a useful PE predictor for women at moderate or low risk (34). More interestingly, the elevated UA was later reported to be a risk factor for women with gestational hypertension to develop PE and deliver small-for-gestational-age infants (35). We observed similar findings that all the renal markers included (BUN, Cre, UA and Cysc) were significantly increased in the patients that developed PE before delivery. Of them, the UA, the other independent risk factor in current study, was the most promising predictor with the greatest AUC (0.73) of the ROC analyses (Fig. 2), as well as NPV of 82.1% and PPV of 48.9% (Table 3).

In conclusion, with the prospective cohort that were suspected for PE development and followed up until delivery, a series of serum markers were tested and evaluated. The angiogenic modulators of sFlt-1, PlGF, the renal function tests of BUN, Cre, UA, Cysc, and the glycoprotein PAPP-A2 were statistically changed. The UA was further found to be an independent risk factor or PE development and the most prominent predictor with the greatest AUC in the ROC analyses.

Abbreviations

sFlt-1, soluble fms-like tyrosine kinase 1; PlGF, placental growth factor; PAPP-A2, pregnancy-associated plasma protein-A2; GlyFn, glycosylated fibronectin; TM, thrombomodulin; tPAI-C, tissue plasminogen activator inhibitor complex; UA, uric acid; BUN, blood urea nitrogen; Cre, creatinine; Cysc, cystatin C

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Beijing Obstetrics and Gynecology Hospital, Capital Medical University (approval number: 2017-KY-078-01). The verbal consents from the participants were required as no clinical intervention was involved, which was approved by the ethical committee of our institute.

Consent for publication

Not applicable.

Availability of data and materials

The original GlyA and FPG datasets generated during the current study are available and provided as supplementary files (Supplementary Table 1). However, according to the patients' verbal consents, the raw testing results, their biometrics and pregnancy outcomes are only available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no conflict of interest.

Funding

This work was supported by the Beijing Municipal Administration of Hospitals Incubating Program (No. PX2020060) and the National Natural Science Foundation of China (No. 81702057). The funding body did not take part in the design of the study, the collection, analysis and interpretation of the data, or writing the manuscript.

Authors' contributions

All authors have certified the author list and the contribution description. All authors have read and approved the submitted manuscript and any substantially modified version of the manuscript. Contribution to work: J.W., H.H., X.L., S.Z., Y.Z., J.Z., Z.Z., Y.Z., J.Z. and Z.C. were involved in conception and design of the study and patient recruitment; L.C., C.Z., X.X. were involved in performing experiments, acquisition of data, analysis and interpretation of data; H.H. and Z.C. were involved in drafting of the article and critical approval of the final article; Y.D., J.L., and Y.L. were involved in the statistical analysis and figure preparation.

Acknowledgements

The sFlt-1 and PlGF reagents were kindly provided by Beijing United JoinScience Medical Technology Co, Ltd., China. The TM and tPAI-C reagents were kindly provided by Beijing Lihaiweida Trading Co., Ltd,

China. The complement component C1q, complement factors B and H reagents were kindly provided by Shanghai Beijia Biochemical Reagent Co. Ltd, China. The PAPP-A2 and GlyFn reagents were kindly provided by Guangzhou Kangrun Biotech Co. Ltd., Guangdong, China.

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Figures

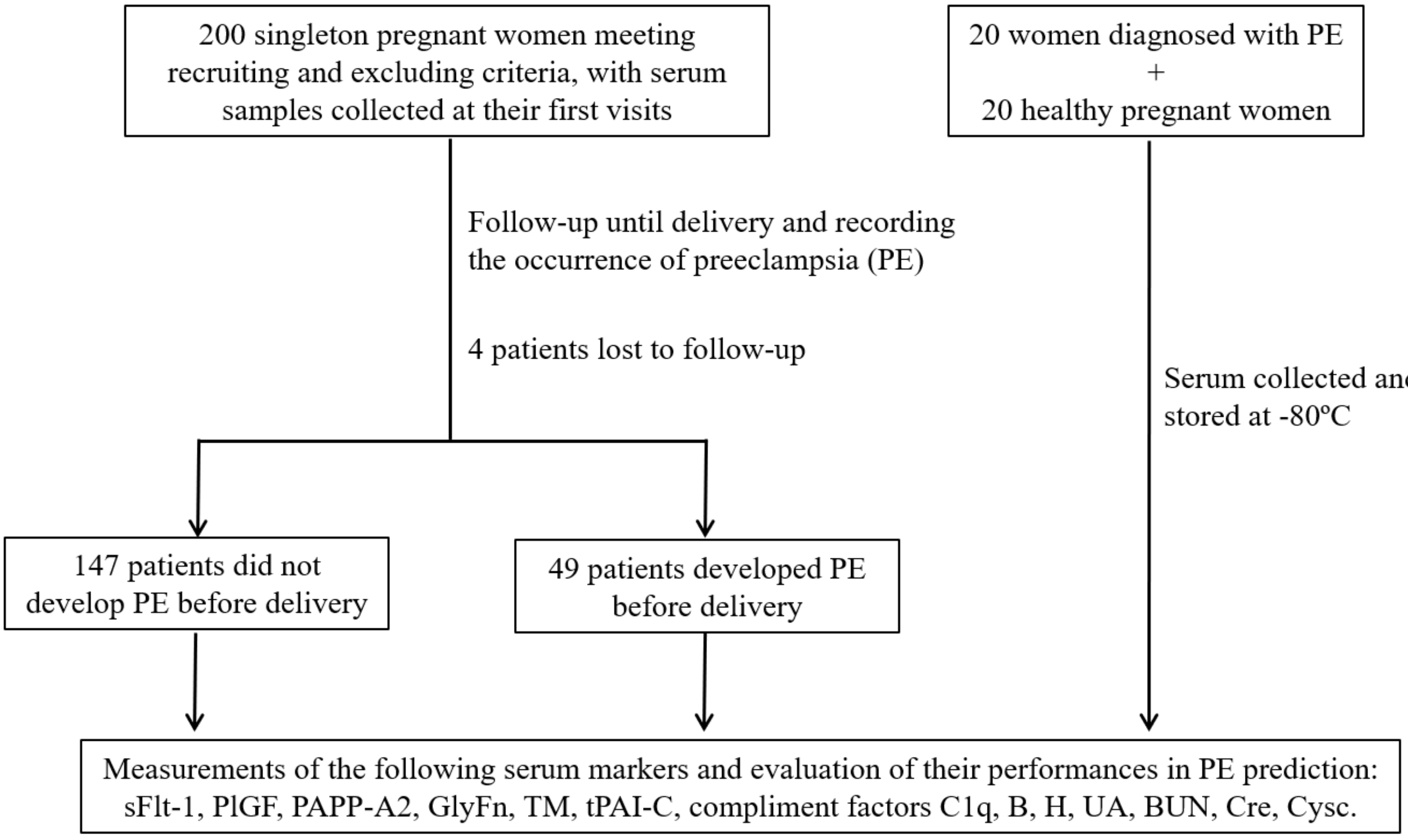

Figure 1

Schematic diagram for patient recruitment and study design. Abbreviations: sFlt-1, soluble fms-like tyrosine kinase 1; PlGF, placental growth factor; PAPP-A2, pregnancy-associated plasma protein-A2; GlyFn, glycosylated fibronectin; TM, thrombomodulin; tPAI-C, tissue plasminogen activator inhibitor complex; UA, uric acid; BUN, blood urea nitrogen; Cre, creatinine; Cysc, cystatin C.

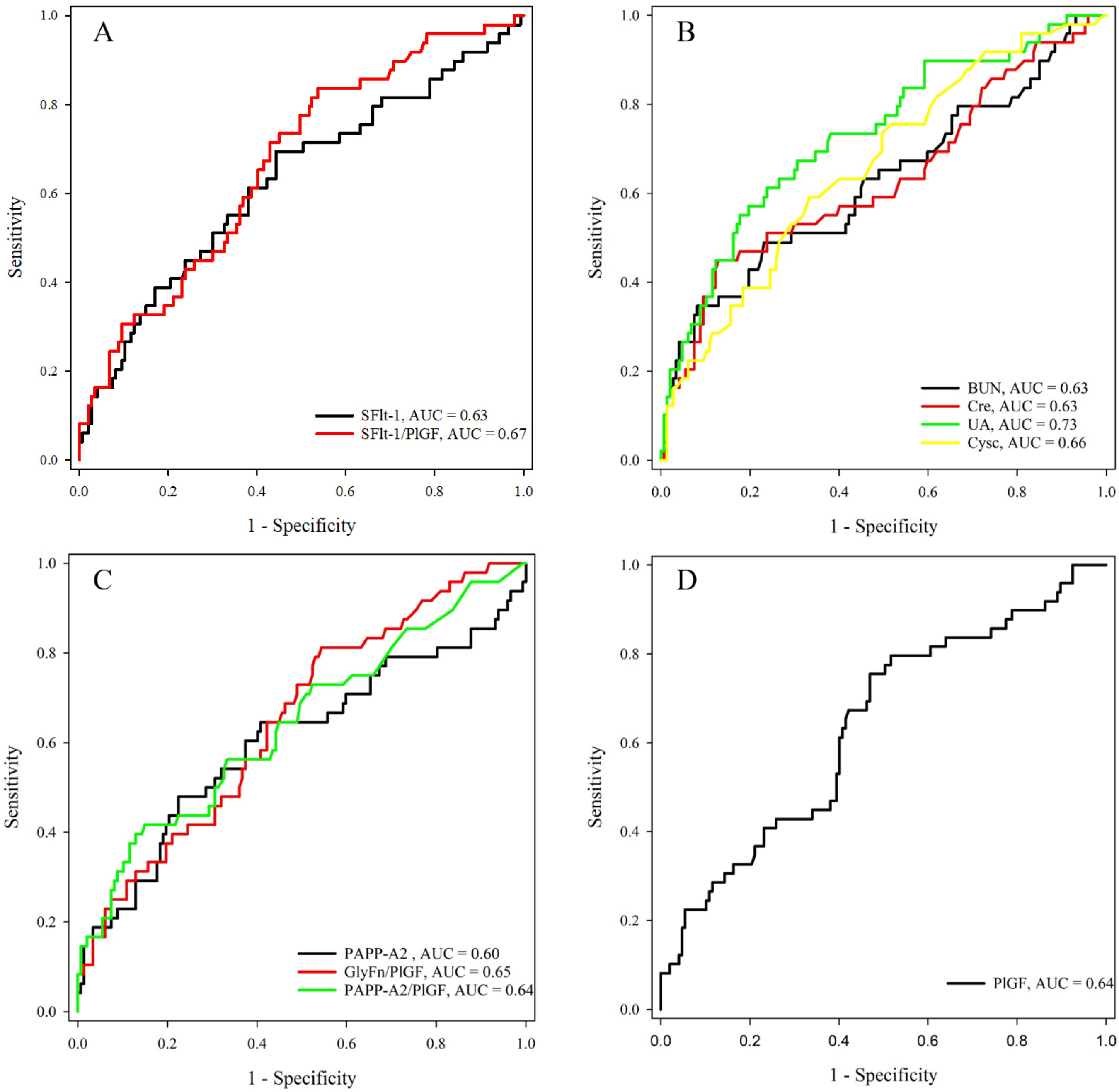

Figure 2

ROC analyses of the serum markers in PE prediction with the prospective cohort with PE related clinical or laboratory presentations. A: ROC analyses for sFlt-1 (AUC=0.63) and sFlt-1/PlGF (AUC=0.67), B: BUN (AUC=0.63), Cre (AUC=0.63), UA (AUC=0.73) and Cysc (AUC=0.66), C: PAPP-A2 (AUC=0.60), GlyFn/PlGF (AUC=0.65) and PAPP-A2/PlGF (AUC=0.64), D: PlGF (AUC=0.64).

Supplementary Files

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