

Glycosylated fibronectin and SFLT-1/PLGF ratio for prediction of composite adverse pregnancy outcome in women with suspected preeclampsia: A prospective Tertiary-Center cohort study

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Abstract

To evaluate whether glycosylated fibronectin (GLYFN), placental growth factor (PIGF), soluble fMS-like tyrosine kinase-1/PIGF (sFlt-1/PIGF), and the exploratory GLYFN/PIGF index predict composite adverse maternal and/or fetal outcome in women undergoing tertiary-center assessment for suspected preeclampsia. We analyzed a prospective cohort of 135 singleton pregnancies evaluated for suspected preeclampsia beyond 20 weeks from May 2024 to May 2025. The primary outcome was a composite adverse maternal and/or fetal/neonatal outcome. Biomarkers were assessed as continuous predictors, by receiver-operating characteristic analysis, and for incremental value when added to clinical or clinical-laboratory models. Gestational age was included in adjusted models because biomarker concentrations and outcome risk are gestational age-dependent. A composite adverse outcome occurred in 76/135 women (56.3%). Women with adverse outcome presented earlier and had higher GlyFn, sFlt-1/PIGF and GlyFn/PIGF values, lower PIGF concentrations, greater proteinuria and more adverse biochemical findings. As standalone predictors, sFlt-1/PIGF showed the highest area under the curve (AUC 0.931), followed by GlyFn/PIGF (AUC 0.926), PIGF (AUC 0.906), and GlyFn (AUC 0.819). All four biomarkers remained associated with adverse outcome after gestational-age adjustment and after adjustment for maternal age, body mass index and null parity. Adding GlyFn/PIGF to the fully adjusted clinical model increased AUC from 0.888 to 0.962, similar to sFlt-1/PIGF (AUC 0.961). In suspected preeclampsia, GlyFn/PIGF provided prognostic information comparable to sFlt-1/PIGF and improved discrimination beyond clinical assessment. The findings support biomarker-assisted risk stratification rather than isolated biomarker-based delivery decisions.

Keywords: Preeclampsia, Glycosylated fibronectin, Placental growth factor, SFLT-1/PIGF, Adverse pregnancy outcome

Introduction

After 20 weeks of gestation, new-onset hypertension accompanied by proteinuria and/or maternal organ dysfunction defines preeclampsia; current concepts also place uteroplacental dysfunction and angiogenic imbalance within its broader disease spectrum [1,2]. Because the clinical phenotype may evolve rapidly, risk assessment after presentation with suspected disease must go beyond the binary question of whether diagnostic criteria are already fulfilled [3,4].

Modern prevention and screening studies support integrated multivariable risk assessment combining maternal characteristics, biophysical parameters and biochemical biomarkers [5,6]. The same principle is relevant in symptomatic women, in whom the clinician must decide whether surveillance can

continue safely, whether admission or transfer is needed, and whether deterioration is likely within a clinically meaningful interval.

Angiogenic biomarkers are the best validated molecular tools in this setting. Excess sFlt-1 and reduced PIGF link placental dysfunction to maternal endothelial injury [7-10], and PIGF or the sFlt-1/PIGF ratio have been evaluated for short-term rule-out, diagnosis, prediction of adverse outcome and triage in women with suspected preeclampsia [11-17]. Interventional, implementation and economic studies further suggest that access to angiogenic biomarker results can influence diagnostic confidence, admission decisions and resource use [18-25].

GlyFn provides a different biological signal. As a

modified extracellular-matrix and endothelial marker, it may capture matrix remodeling and trophoblast-endothelial interaction rather than angiogenic imbalance alone [26,27]. GlyFn has been investigated as a rapid point-of-care biomarker in symptomatic or high-risk pregnancies [28-35], but its incremental value over established clinical and angiogenic assessment remains incompletely defined.

The present study was designed as a prognostic analysis of a tertiary-care cohort of women assessed for suspected preeclampsia. Its aim was to compare GlyFn, PlGF, sFlt-1/PlGF and the exploratory GlyFn/PlGF index for prediction of composite adverse maternal and/or fetal outcome, to evaluate whether their associations persist after adjustment for gestational age and maternal covariates, and to determine whether biomarker information improves discrimination beyond clinical and clinical-laboratory models.

Methods

Study design and population

The cohort was prospectively assembled at the University Clinic of Gynecology and Obstetrics in Skopje, North Macedonia, a tertiary referral center for high-risk pregnancy. Recruitment took place from May 2024 through May 2025 and included women with singleton pregnancies evaluated beyond 20 weeks because of clinical concern for preeclampsia. Although these participants come from the same research program as a previously published diagnostic study of GlyFn and angiogenic testing, the endpoint examined here is different: composite adverse-outcome prediction rather than discrimination between preeclampsia and gestational hypertension [36].

Referral for suspected preeclampsia could be prompted by new or worsening hypertension, proteinuria, other suspected symptoms for preeclampsia, laboratory abnormalities, or fetal findings warranting additional evaluation. Eligibility for this prognostic analysis additionally required available biomarker measurements, a final clinical classification, and pregnancy outcome data. These criteria yielded a final analytical cohort of 135

women.

Clinical classification and outcome definition

Diagnostic classification followed contemporary clinical criteria [1,2]. Preeclampsia required hypertension developing after 20 weeks of gestation together with proteinuria or maternal end-organ dysfunction; gestational hypertension required new-onset hypertension after 20 weeks in the absence of proteinuria or other diagnostic criteria for preeclampsia.

The primary prognostic endpoint was a composite adverse maternal and/or fetal/neonatal outcome. Maternal components included placental abruption, eclampsia, HELLP syndrome, visual disturbances, serum creatinine $>97 \mu\text{mol/L}$, oliguria, postpartum hemorrhage and pulmonary edema. Fetal or neonatal components included fetal growth restriction or birthweight below the 10th percentile, mechanical ventilation, neonatal sepsis, respiratory distress syndrome, intraventricular hemorrhage, fetal or neonatal death and delivery before 34 weeks of gestation. Because the components differ biologically and clinically, the composite was interpreted as a marker of clinically relevant disease severity rather than evidence that each biomarker directly predicts every individual complication. Individual components were summarized descriptively.

Biomarker assessment

At inclusion, demographic variables, clinical characteristics and routine laboratory parameters were recorded. GlyFn was measured using the Lumella PE point-of-care test (DiabetOmics, Inc., Hillsboro, OR, USA), using the manufacturer-recommended procedure [37]. Serum sFlt-1 and PlGF concentrations were measured separately by Electrochemiluminescence Immunoassay (ECLIA) using the Elecsys sFlt-1 and Elecsys PlGF assays on a Cobas e 411 automated analyzer (Roche Diagnostics), and the sFlt-1/PlGF ratio was subsequently calculated from the corresponding measured concentrations [38].

The GlyFn/PlGF index was calculated by dividing the numerical GlyFn concentration reported in $\mu\text{g/mL}$ by the numerical PlGF concentration reported in Pg/mL .

Concentrations were retained in their original assay-reporting units and were not converted to a common mass unit. Therefore, GlyFn/PlGF should be interpreted as a scaled exploratory biomarker index, not as a dimensionless mass ratio. Conversion of GlyFn from $\mu\text{g/mL}$ to pg/mL would multiply all index values by 10^6 but would not change patient ranking, ROC curves, AUC estimates or statistical significance.

Only the first biomarker measurement obtained during the index clinical assessment was used for prognostic analysis. If repeat clinical measurements were performed later during hospitalization, these were not used for the primary analysis. Clinicians performing and interpreting the biomarker measurements were not blinded to the biomarker results during the index clinical assessment. Data on mode of delivery and other maternal and perinatal outcomes of interest were collected from obstetric records documented in the patients' medical charts.

Statistical analysis

Statistical analyses were performed using R version 4.5.3 (R Foundation for Statistical Computing, Vienna, Austria) in RStudio (Posit Software, PBC, Boston, MA, USA). Continuous variables are presented as median (interquartile range) unless otherwise stated; categorical variables are presented as number and percentage. Groups with and without composite adverse outcome were compared using the Mann-Whitney U test for continuous variables and Pearson chi-square or Fisher exact test for categorical variables, as appropriate. Two-sided p-values <0.05 were considered statistically significant.

Biomarkers were evaluated as continuous predictors in univariable logistic regression, in models adjusted only for gestational age at inclusion/sample collection, and in fully adjusted models including gestational age, maternal age, BMI and nulliparity. Gestational age was prioritized because PlGF, sFlt-1/PlGF, GlyFn and outcome risk are gestation-dependent, and because women with adverse outcomes presented substantially earlier than women without complications. Models including BMI used complete cases.

Standalone discrimination was assessed using ROC curves and AUC estimates with 95% confidence intervals. For PlGF, the analysis was oriented so that

lower values indicated higher risk. Pairwise comparisons of biomarker AUCs were performed using paired DeLong tests. The Youden index was used to identify data-derived exploratory thresholds; because these thresholds were generated internally, they require external validation and are not intended to serve as delivery triggers.

For additional assessment of biomarker performance at a common operating point, sensitivity was estimated at a fixed specificity target of approximately 90% (10% false-positive rate). Full regression coefficients for the gestational-age-adjusted and fully adjusted models, including coefficients for all covariates, are provided in the Supplementary Material.

Incremental value was assessed by comparing AUC values from predicted probabilities generated by logistic regression models. Two nested clinical model sets were evaluated: a gestational-age-only reference model and a fully adjusted clinical reference model including gestational age at admission, maternal age, BMI and nulliparity. Each biomarker was added separately to the corresponding reference model. The clinical-laboratory model included gestational age at admission, proteinuria, creatinine and uric acid. Paired changes in AUC and their 95% confidence intervals were evaluated by nonparametric patient-level bootstrap resampling. Model AUCs and changes in AUC were interpreted as internal classification performance, not as external validation.

Ethical approval

The Ethics Committee of the Faculty of Medicine, Ss. Cyril and Methodius University in Skopje, North Macedonia, approved the protocol (approval no. 03-6101/6). The study adhered to the Declaration of Helsinki and applicable institutional ethical requirements. Written informed consent was obtained from every participant, and analyses were performed on anonymized data.

Reporting of this observational cohort was guided by the STROBE recommendations [39].

Results

Composite adverse maternal and/or fetal outcome occurred in 76 of 135 women (56.3%); 59 women

(43.7%) had no recorded component of the composite adverse outcome. Maternal age, smoking status and BMI were comparable between groups. Nulliparity was more frequent among women with complications but did not reach statistical significance. Women with complications were sampled at a substantially earlier gestational age than women without complications, supporting the need for gestational age-adjusted analyses.

The adverse-outcome group had a distinctly abnormal biomarker profile. GlyFn, sFlt-1/PlGF and GlyFn/PlGF were higher, whereas PlGF was lower, in women with complications. Proteinuria, liver enzymes, lactate dehydrogenase, creatinine and uric acid were also higher, while platelet count was lower. Pregnancy outcomes were worse, with earlier delivery, lower birthweight and more frequent birthweight below the 10th percentile (Table 1).

Table 1. Clinical, laboratory and biomarker characteristics according to composite adverse outcome status

Parameter	All Patients (N=135)	Without Adverse Outcome (N=59)	With Adverse Outcome (N=76)	P-Value
Age, Years	30.0 (26.0-35.0)	30.0 (25.0-35.0)	30.0 (26.0-35.2)	0.597
Smoking, N (%)	29 (21.5)	13 (22.0)	16 (21.1)	0.89
BMI, Kg/M ²	33.5 (29.4-40.0)	34.0 (29.7-40.9)	33.3 (27.8-38.7)	0.246
Nulliparity, N (%)	85 (63.0)	32 (54.2)	53 (69.7)	0.064
Gestational Age At Inclusion/Sample Collection, Weeks	35.1 (32.0-37.8)	37.3 (36.0-38.4)	32.4 (30.3-35.1)	<0.001
Glyfn, Mg/Ml	368.0 (268.0-505.0)	266.0 (223.5-356.5)	450.5 (352.5-590.2)	<0.001
Plgf, Pg/Ml	78.9 (45.0-162.7)	170.0 (103.2-334.9)	48.7 (31.8-77.8)	<0.001
sflt-1/Plgf Ratio	103.3 (27.9-305.3)	23.4 (10.2-59.5)	230.6 (113.8-519.6)	<0.001
Glyfn/Plgf Index	5.1 (1.8-10.4)	1.6 (0.7-3.8)	8.7 (6.3-15.9)	<0.001
Proteinuria, G/24 H	0.2 (0.0-1.4)	0.1 (0.0-0.2)	1.1 (0.2-3.1)	<0.001
AST, U/L	22.0 (18.5-29.5)	21.0 (17.5-24.5)	24.5 (19.0-35.5)	0.001
ALT, U/L	15.0 (11.0-21.0)	13.0 (10.0-15.0)	17.5 (11.0-29.5)	<0.001
LDH, U/L	211.0 (182.0-254.5)	192.0 (174.0-245.5)	221.0 (194.2-260.2)	0.01
Creatinine, Mmol/L	51.6 (46.1-58.9)	47.8 (45.0-52.7)	56.2 (49.5-63.8)	<0.001
Uric Acid, Mmol/L	305.0 (250.0-374.5)	277.0 (228.0-311.0)	347.5 (283.5-401.8)	<0.001
Platelet Count, 10 ⁹ /L	225.0 (174.0-266.0)	235.0 (202.5-268.5)	210.0 (155.5-261.5)	0.042
Gestational Age At Delivery, Weeks	36.0 (32.4-38.2)	38.0 (37.0-39.0)	33.0 (30.6-35.3)	<0.001
Birthweight, G	2390.0 (1565.0-3110.0)	3130.0 (2830.0-3505.0)	1790.0 (1167.5-2195.0)	<0.001
Birthweight <10th Percentile, N (%)	56 (41.5)	3 (5.1)	53 (69.7)	<0.001

Note. Values are median (interquartile range) or n (%). BMI was available for 109/135 women and proteinuria for 131/135 women; other variables shown in this table were complete. p-values are from Mann-Whitney U tests for continuous variables and Pearson chi-square or Fisher exact tests for categorical variables

The composite was driven mainly by fetal and neonatal components. Fetal growth restriction or birthweight below the 10th percentile, respiratory distress syndrome and delivery before 34 weeks

were the most frequent components. Maternal complications were less frequent, with visual disturbances, HELLP syndrome, oliguria and placental abruption being the most common maternal events (Table 2).

Table 2. Components of the composite adverse maternal and/or fetal/neonatal outcome

Composite component	n (%)
Maternal complications	
Visual disturbances	15 (11.1)
HELLP syndrome	10 (7.4)
Oliguria	10 (7.4)
Placental abruption	9 (6.7)
Postpartum hemorrhage	3 (2.2)
Pulmonary edema	2 (1.5)
Creatinine >97 µmol/L	2 (1.5)
Eclampsia	1 (0.7)
Fetal/neonatal complications	
Fetal growth restriction or birthweight <10th percentile	52/56 (38.5/41.5)
Respiratory distress syndrome	50 (37.9)
Delivery before 34 weeks	45 (33.3)
Intraventricular hemorrhage	19 (14.3)
Mechanical ventilation	18 (13.5)
Neonatal sepsis	16 (12.0)
Fetal or neonatal death	5 (3.8)

Note. Percentages are calculated from the available data for each component. Individual components were not modeled separately because the number of events was small for several outcomes

In univariable analyses, higher GlyFn, higher sFlt-1/PlGF, higher GlyFn/PlGF and lower PlGF were each associated with greater odds of adverse outcome. All four associations persisted after adjustment for gestational age alone and after further adjustment for maternal age, BMI and nulliparity (Table 3).

Table 3. Univariable, gestational-age-adjusted and fully adjusted biomarker associations with composite adverse outcome

Biomarker	Scale	Unadjusted OR (95% CI); p-value	GA-adjusted OR (95% CI); p-value	Fully adjusted OR (95% CI); p-value
GlyFn	per 100 µg/mL increase	2.22 (1.60-3.06); p<0.001	2.07 (1.48-2.91); p<0.001	1.82 (1.27-2.61); p=0.001
PlGF	per 10 pg/mL increase	0.79 (0.72-0.87); p<0.001	0.80 (0.72-0.88); p<0.001	0.82 (0.75-0.91); p<0.001
sFlt-1/PlGF	per 10-unit increase	1.32 (1.19-1.47); p<0.001	1.29 (1.15-1.44); p<0.001	1.26 (1.12-1.42); p<0.001
GlyFn/PlGF	per 1-unit increase	1.75 (1.44-2.13); p<0.001	1.74 (1.38-2.19); p<0.001	1.70 (1.32-2.20); p<0.001

Note. Gestational-age-adjusted models included gestational age at inclusion/sample collection. Fully adjusted models additionally included maternal age, BMI and nulliparity and used complete cases for BMI. OR, odds ratio; CI, confidence interval

Table 4. Standalone ROC performance of biomarkers for prediction of composite adverse outcome

Biomarker	AUC (95% CI)	Exploratory cut-off	Sensitivity (%)	Specificity (%)	Selected DeLong comparison
GlyFn	0.819 (0.744-0.893)	≥307.0 µg/mL	90.8	69.5	Lower than PlGF (p=0.047), sFlt-1/PlGF (p=0.003) and GlyFn/PlGF (p<0.001)

PIGF	0.906 (0.852-0.952)	≤98.0 pg/mL	93.4	74.6	Not significantly different from sFlt-1/PIGF (p=0.157) or GlyFn/PIGF (p=0.226)
sFlt-1/PIGF	0.931 (0.885-0.969)	≥86.40	89.5	86.4	Not significantly different from GlyFn/PIGF (p=0.784)
GlyFn/PIGF	0.926 (0.878-0.967)	≥5.963	77.6	94.9	Not significantly different from PIGF or sFlt-1/PIGF

Note. For PIGF, the ROC analysis was oriented so that lower concentrations indicate higher risk. Cut-offs were derived internally using the Youden index and require external validation

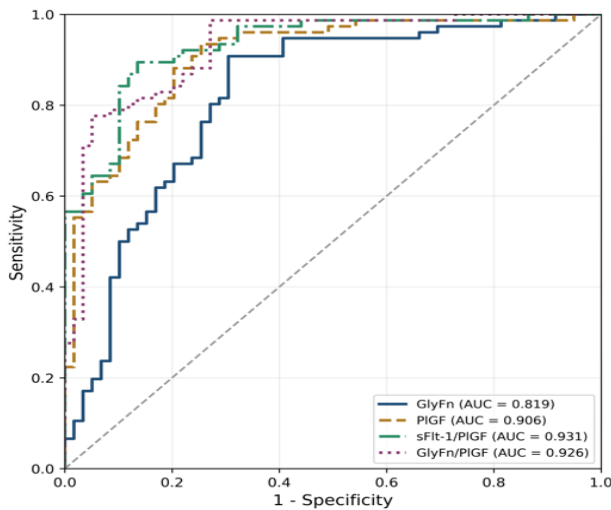


Figure 1. Receiver Operating Characteristic (ROC) curves of individual biomarkers for prediction of composite adverse maternal and/or fetal outcome

Standalone ROC analysis showed good to excellent discrimination. sFlt-1/PIGF had the highest AUC, GlyFn/PIGF was nearly identical, and PIGF also performed well. GlyFn alone had lower but clinically

relevant discrimination. Paired DeLong comparison showed that GlyFn had lower AUC than PIGF, sFlt-1/PIGF and GlyFn/PIGF, while the three strongest markers were not significantly different from each other (Table 4; Figure 1).

At the closest conservative empirical operating point to the fixed 90% specificity target (91.5%), sensitivity was 78.9% for GlyFn/PIGF, 67.1% for sFlt-1/PIGF, 64.5% for PIGF and 42.1% for GlyFn (Supplementary Table S2). Full coefficients for the gestational-age-adjusted and fully adjusted logistic regression models are reported in Supplementary Table S1.

Supplementary Table S1. Full coefficients of gestational-age-adjusted and fully adjusted logistic regression models for composite adverse outcome

Panel A. Gestational-age-adjusted models (n=135; 76 events)

Biomarker model	Predictor	β	SE	OR (95% CI)	p value
GlyFn	GlyFn, per 100 μ g/mL increase	0.734	0.174	2.084 (1.481–2.933)	<0.001
	Gestational age, per 1-week increase	−0.514	0.1	0.598 (0.491–0.728)	<0.001
PIGF	PIGF, per 10 pg/mL increase	−0.226	0.05	0.798 (0.723–0.881)	<0.001
	Gestational age, per 1-week increase	−0.535	0.119	0.586 (0.464–0.740)	<0.001
sFlt-1/PIGF	sFlt-1/PIGF, per 10-unit increase	0.253	0.058	1.287 (1.150–1.441)	<0.001
	Gestational age, per 1-week increase	−0.372	0.103	0.689 (0.563–0.843)	<0.001
GlyFn/PIGF	GlyFn/PIGF, per 1-unit increase	0.553	0.119	1.739 (1.377–2.196)	<0.001
	Gestational age, per 1-week increase	−0.487	0.116	0.614 (0.489–0.771)	<0.001

Panel B. Fully adjusted models (n=109; 55 events)

Biomarker model	Predictor	β	SE	OR (95% CI)	p value
GlyFn	GlyFn, per 100 $\mu\text{g/mL}$ increase	0.604	0.183	1.829 (1.278–2.618)	<0.001
	Gestational age, per 1-week increase	−0.686	0.148	0.503 (0.377–0.672)	<0.001
	Maternal age, per 1-year increase	−0.007	0.042	0.993 (0.915–1.078)	0.869
	BMI, per 1 kg/m^2 increase	0.064	0.045	1.066 (0.975–1.166)	0.158
	Nulliparity, yes vs no	1.46	0.656	4.306 (1.190–15.583)	0.026
PlGF	PlGF, per 10 pg/mL increase	−0.197	0.05	0.821 (0.745–0.906)	<0.001
	Gestational age, per 1-week increase	−0.723	0.181	0.485 (0.341–0.691)	<0.001
	Maternal age, per 1-year increase	0.022	0.05	1.023 (0.928–1.127)	0.652
	BMI, per 1 kg/m^2 increase	0.054	0.053	1.055 (0.951–1.171)	0.309
	Nulliparity, yes vs no	1.707	0.75	5.513 (1.267–23.984)	0.023
sFlt-1/PlGF	sFlt-1/PlGF, per 10-unit increase	0.232	0.061	1.261 (1.118–1.421)	<0.001
	Gestational age, per 1-week increase	−0.561	0.157	0.571 (0.419–0.777)	<0.001
	Maternal age, per 1-year increase	0.003	0.047	1.003 (0.915–1.100)	0.944
	BMI, per 1 kg/m^2 increase	0.1	0.056	1.105 (0.990–1.234)	0.074
	Nulliparity, yes vs no	1.366	0.761	3.919 (0.881–17.433)	0.073
GlyFn/PlGF	GlyFn/PlGF, per 1-unit increase	0.532	0.13	1.702 (1.318–2.198)	<0.001
	Gestational age, per 1-week increase	−0.637	0.168	0.529 (0.380–0.736)	<0.001
	Maternal age, per 1-year increase	−0.025	0.048	0.975 (0.887–1.071)	0.596
	BMI, per 1 kg/m^2 increase	0.011	0.057	1.011 (0.905–1.130)	0.841
	Nulliparity, yes vs no	1.878	0.859	6.540 (1.214–35.235)	0.029

Note. Each biomarker was entered in a separate logistic regression model. Gestational-age-adjusted models included the biomarker and gestational age at sampling. Fully adjusted models additionally included maternal age, BMI and nulliparity. Fully adjusted analyses were restricted to complete cases for BMI. β , logistic regression coefficient; SE, standard error; OR, odds ratio; CI, confidence interval. Intercepts are omitted because they are not clinically interpretable

Tertile analyses supported a graded relationship between biomarker distribution and outcome risk. Risk increased across tertiles of GlyFn, sFlt-1/PlGF and GlyFn/PlGF and decreased across increasing tertiles of PlGF. The most pronounced gradient was

observed for GlyFn/PlGF: adverse outcome occurred in 2/45 women in tertile 1, 31/45 in tertile 2 and 43/45 in tertile 3 (p for trend <0.001). These analyses were exploratory and were not used to define clinical thresholds.

Supplementary Table S2. Sensitivity of individual biomarkers at a fixed specificity target of approximately 90% for prediction of composite adverse outcome

Biomarker	Risk direction	Empirical operating threshold*	Specificity (%)	Sensitivity (%)	Detected adverse outcomes
GlyFn	Higher values indicate higher risk	>483 $\mu\text{g/mL}$	91.5	42.1	32/76
PlGF	Lower values indicate higher risk	<61.41 pg/mL	91.5	64.5	49/76
sFlt-1/PlGF	Higher values indicate higher risk	>127.38	91.5	67.1	51/76
GlyFn/PlGF	Higher values indicate higher risk	>5.170	91.5	78.9	60/76

Note. A fixed specificity target of approximately 90% (10% false-positive rate) was used. Because the no-adverse-outcome group contained 59 women, exactly 90% specificity was not attainable empirically; the closest conservative operating point with specificity $\geq 90\%$ was 91.5% (54/59 true negatives). Thresholds were derived from the same cohort and should therefore be regarded as exploratory rather than externally validated clinical cut-offs

Adding biomarkers to gestational-age-only and fully adjusted clinical models improved discrimination. In

the gestational-age-only models, all four biomarkers significantly increased AUC, with the largest

increment observed for GlyFn/PIGF and closely similar increments for sFlt-1/PIGF and PIGF. In the

fully adjusted clinical models, PIGF, sFlt-1/PIGF and GlyFn/PIGF significantly improved AUC, whereas

GlyFn alone produced a smaller, non-significant increment. In the clinical-laboratory model, both ratios again provided significant incremental improvement, whereas GlyFn alone provided a smaller, non-significant increase (Table 5).

Table 5. Incremental predictive performance of clinical, laboratory and biomarker-based models

Model	Predictors	N	Events	AUC (95% CI)	Reference	ΔAUC (95% CI)	p for ΔAUC
1	GA	135	76	0.850 (0.781-0.913)	-	-	-
2	Model 1 + GlyFn	135	76	0.916 (0.867-0.957)	Model 1	0.066 (0.019-0.116)	0.005
3	Model 1 + PIGF	135	76	0.951 (0.913-0.981)	Model 1	0.101 (0.042-0.161)	0.002
4	Model 1 + sFlt-1/PIGF	135	76	0.955 (0.920-0.981)	Model 1	0.105 (0.049-0.164)	<0.001
5	Model 1 + GlyFn/PIGF	135	76	0.957 (0.920-0.984)	Model 1	0.107 (0.046-0.169)	<0.001
6	GA + age + BMI + nulliparity	109	55	0.888 (0.822-0.943)	-	-	-
7	Model 6 + GlyFn	109	55	0.922 (0.869-0.963)	Model 6	0.033 (-0.001 to 0.071)	0.063
8	Model 6 + PIGF	109	55	0.955 (0.913-0.985)	Model 6	0.067 (0.013-0.123)	0.014
9	Model 6 + sFlt-1/PIGF	109	55	0.961 (0.927-0.986)	Model 6	0.073 (0.026-0.125)	0.002
10	Model 6 + GlyFn/PIGF	109	55	0.962 (0.928-0.987)	Model 6	0.074 (0.024-0.129)	0.003
11	GA + proteinuria + creatinine + uric acid	131	75	0.915 (0.864-0.958)	-	-	-
12	Model 11 + sFlt-1/PIGF	131	75	0.955 (0.921-0.981)	Model 11	0.041 (0.008-0.075)	0.014
13	Model 11 + GlyFn/PIGF	131	75	0.960 (0.927-0.986)	Model 11	0.045 (0.012-0.085)	0.004
14	Model 11 + GlyFn	131	75	0.935 (0.891-0.972)	Model 11	0.021 (-0.001 to 0.044)	0.068

Note. AUC values were calculated from predicted probabilities derived from logistic regression models. Paired changes in AUC were evaluated by nonparametric patient-level bootstrap resampling; the p-value refers to the AUC difference from the corresponding reference model and is not the p-value for an odds ratio. Models 1-5 used all 135 participants; Models 6-10 were calculated in complete cases for BMI (n=109); Models 11-14 were calculated in complete cases for proteinuria (n=131)

Discussion

The present analysis focuses on the prognostic value of the evaluated biomarkers for adverse pregnancy outcomes, rather than on their diagnostic performance for preeclampsia. In a tertiary-care cohort of women with suspected preeclampsia, adverse outcome was associated with earlier gestational age at clinical presentation, biochemical evidence of organ dysfunction and a highly abnormal

placental biomarker pattern. All four biomarkers were associated with the composite endpoint after adjustment for gestational age and maternal characteristics, but their strengths differed: sFlt-1/PIGF and GlyFn/PIGF were the strongest discriminative markers, PIGF performed similarly, and GlyFn alone was weaker but still informative.

The most important novel aspect is not the observation that GlyFn is elevated in preeclampsia,

which has already been described, but the comparison of a matrix-endothelial signal with angiogenic biomarkers for adverse-outcome prediction in the same symptomatic cohort. GlyFn/PlGF achieved an AUC almost identical to sFlt-1/PlGF and produced the largest AUC increment when added to the fully adjusted clinical model. This supports the hypothesis that combining a marker related to matrix/endothelial injury with a marker of angiogenic insufficiency may capture a broader placental-endothelial phenotype than either marker alone.

The result should not be interpreted as proof that GlyFn/PlGF is superior to sFlt-1/PlGF. Paired DeLong testing showed no statistically significant difference between these two ratios. The findings support a clinically comparable prognostic information of the two ratios, although formal equivalence was not assessed. GlyFn/PlGF may be attractive because GlyFn can be measured rapidly at the point of care. External validation is required before adopting the internally derived GlyFn/PlGF threshold.

The fixed-specificity analysis provided a complementary perspective: at approximately 90% specificity, GlyFn/PlGF identified 78.9% of adverse outcomes, compared with 67.1% for sFlt-1/PlGF, 64.5% for PlGF and 42.1% for GlyFn. This descriptive comparison should not be interpreted as evidence of statistical superiority, but it suggests that the relative performance of biomarkers may differ according to the operating point selected for clinical use.

These findings are consistent with risk-prediction literature showing that clinical and laboratory variables should be combined in hypertensive disorders of pregnancy. The fullPIERS and miniPIERS frameworks demonstrated the value of multivariable risk prediction for maternal complications [40-42], while more recent models and expectant-management studies support integrated assessment rather than reliance on isolated markers [43-45]. Our results extend this principle by showing that placental biomarkers add discrimination beyond gestational age, maternal characteristics and routine laboratory variables.

Comparison with recent GlyFn studies is important. Sokratous and colleagues reported that GlyFn had

similar short-term performance to PlGF and sFlt-1/PlGF for imminent preeclampsia in women with new-onset hypertension, but noted high screen-positive rates and modest performance in late gestation [32]. Wah and colleagues found that GlyFn and sFlt-1/PlGF had similar moderate rule-out performance when standardized thresholds were used, but poor rule-in positive predictive value [46]. Kluivers and colleagues, together with recent systematic and cohort data, support GlyFn as a promising biomarker, while also emphasizing the need for validation and clinically meaningful outcomes [31,33,34]. The present study differs by focusing on a composite adverse maternal and/or fetal outcome rather than imminent diagnosis alone.

GlyFn has also been proposed as a biomarker in first-trimester and late-gestation screening models [35,47]. Those studies address population screening before symptoms or at a scheduled gestational window, whereas the present study addresses triage after clinical suspicion. This distinction matters because screening biomarkers are commonly transformed to multiples of the median and adjusted for maternal characteristics. The lack of locally validated MoM conversion for PlGF, sFlt-1 and GlyFn is therefore an important limitation of the present analysis.

Gestational age and maternal size are particularly relevant sources of confounding. PlGF and sFlt-1/PlGF are gestation-dependent, and published data demonstrate changes in sFlt-1, PlGF and their ratio across pregnancy and between earlier and later preeclampsia [48,49]. In this cohort, women with adverse outcomes presented nearly five weeks earlier than those without complications. Adjusted models therefore included gestational age, BMI and other maternal covariates. This approach reduces but does not eliminate residual confounding; future analyses should use validated gestation- and weight-adjusted MoM values when available.

The composite outcome requires careful interpretation. The biomarkers are biologically linked most directly to placental dysfunction, endothelial activation and angiogenic imbalance. They should not be expected to predict all components equally, particularly events such as postpartum hemorrhage, neonatal sepsis or

intraventricular hemorrhage, which may be influenced by delivery timing, prematurity, management and postnatal factors. For that reason, the individual outcome components were summarized descriptively and not modeled as independent endpoints. The composite should be understood as a pragmatic indicator of clinically relevant deterioration in a high-risk referral cohort.

The study has several clinical implications. In a symptomatic tertiary-care population, high sFlt-1/PlGF or GlyFn/PlGF values should prompt closer maternal and fetal surveillance, repeat clinical and laboratory assessment and planning for potential deterioration. They should not be used as stand-alone indications for delivery. Conversely, low-risk biomarker profiles may support continued observation when integrated with blood pressure, symptoms, laboratory results and fetal status, consistent with biomarker-guided approaches used in suspected preterm preeclampsia [50]. Formal cost-effectiveness analysis was not performed. GlyFn point-of-care testing may offer logistical advantages by reducing turnaround time and laboratory dependence, but its economic value will depend on local assay cost, platform availability and whether testing changes management decisions.

Limitations include the single-center design, modest sample size, selected tertiary-care population, internally derived thresholds and absence of external validation. Several composite components were infrequent, limiting reliable component-specific modeling. PlGF and GlyFn were analyzed in original assay units rather than MoMs, and maternal weight adjustment was limited to inclusion of BMI in multivariable models.

Conclusion

In women undergoing tertiary-center assessment for suspected preeclampsia, GlyFn, PlGF, sFlt-1/PlGF and GlyFn/PlGF were associated with composite adverse maternal and/or fetal outcome. GlyFn/PlGF showed prognostic performance comparable to sFlt-1/PlGF and improved discrimination beyond clinical and clinical-laboratory models. The findings support biomarker-assisted risk stratification, but the internally derived thresholds and the exploratory GlyFn/PlGF index require external validation and

prospective clinical-utility assessment.

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Declaration of interest

Declarations of interest: none.

Data availability

Subject to the required institutional and ethics approvals, de-identified data supporting the findings may be requested from the corresponding author for scientifically justified purposes.

Author contributions

I.P. was responsible for study conception and design, participant recruitment, data collection and analysis, interpretation of the findings, and preparation of the initial manuscript draft. All other authors contributed to supervision, methodology, clinical interpretation, statistical review and critical revision of the manuscript. All authors should review and approve the final version before submission.

References

1. American College of Obstetricians and Gynecologists. Gestational hypertension and preeclampsia: ACOG Practice Bulletin, Number 222. *Obstet Gynecol.* 2020;135(6): e237-60. doi:10.1097/AOG.0000000000003891.
2. Magee LA, Brown MA, Hall DR, Gupte S, Hennessy A, Karumanchi SA, et al. The 2021 International Society for the Study of Hypertension in Pregnancy classification, diagnosis and management recommendations for international practice. *Pregnancy Hypertens.* 2022; 27:148-69. doi: 10.1016/j.preghy.2021.09.008.
3. Rana S, Lemoine E, Granger JP, Karumanchi SA. Preeclampsia: pathophysiology, challenges,

- and perspectives. *Circ Res*. 2019;124(7):1094-1112. doi:10.1161/CIRCRESAHA.118.313276.
4. Steegers EAP, von Dadelszen P, Duvekot JJ, Pijnenborg R. Pre-eclampsia. *Lancet*. 2010;376(9741):631-44. doi:10.1016/S0140-6736(10)60279-6.
5. Akolekar R, Syngelaki A, Poon L, Wright D, Nicolaides KH. Competing risks model in early screening for preeclampsia by biophysical and biochemical markers. *Fetal Diagn Ther*. 2013;33(1):8-15. doi:10.1159/000341264.
6. Rolnik DL, Wright D, Poon LC, O'Gorman N, Syngelaki A, de Paco Matallana C, et al. Aspirin versus placebo in pregnancies at high risk for preterm preeclampsia. *N Engl J Med*. 2017;377(7):613-22. doi:10.1056/NEJMoa1704559.
7. Maynard SE, Min JY, Merchan J, Lim KH, Li J, Mondal S, et al. Excess placental soluble fms-like tyrosine kinase 1 may contribute to endothelial dysfunction, hypertension, and proteinuria in preeclampsia. *J Clin Invest*. 2003;111(5):649-58. doi:10.1172/JCI17189.
8. Levine RJ, Maynard SE, Qian C, Lim KH, England LJ, Yu KF, et al. Circulating angiogenic factors and the risk of preeclampsia. *N Engl J Med*. 2004;350(7):672-83. doi:10.1056/NEJMoa031884.
9. Levine RJ, Lam C, Qian C, Yu KF, Maynard SE, Sachs BP, et al. Soluble endoglin and other circulating antiangiogenic factors in preeclampsia. *N Engl J Med*. 2006;355(10):992-1005. doi:10.1056/NEJMoa055352.
10. Verlohren S, Herraiz I, Lapaire O, Schlembach D, Moertl M, Zeisler H, et al. The sFlt-1/PlGF ratio in different types of hypertensive pregnancy disorders and its prognostic potential in preeclamptic patients. *Am J Obstet Gynecol*. 2012;206(1):58. e1-8. doi:10.1016/j.ajog.2011.07.037.
11. Zeisler H, Llurba E, Chantraine F, Vatish M, Staff AC, Sennstrom M, et al. Predictive value of the sFlt-1: PlGF ratio in women with suspected preeclampsia. *N Engl J Med*. 2016;374(1):13-22. doi:10.1056/NEJMoa1414838.
12. Zeisler H, Llurba E, Chantraine FJ, Vatish M, Staff AC, Sennstrom M, et al. Soluble fms-like tyrosine kinase-1 to placental growth factor ratio: ruling out pre-eclampsia for up to 4 weeks and value of retesting. *Ultrasound Obstet Gynecol*. 2019;53(3):367-75. doi:10.1002/uog.19178.
13. Bian X, Biswas A, Huang X, Lee KJ, Li TK, Masuyama H, et al. Short-term prediction of adverse outcomes using the sFlt-1/PlGF ratio in Asian women with suspected preeclampsia. *Hypertension*. 2019;74(1):164-72. doi:10.1161/HYPERTENSIONAHA.119.12760.
14. Verlohren S, Herraiz I, Lapaire O, Schlembach D, Zeisler H, Calda P, et al. New gestational phase-specific cutoff values for the use of the soluble fms-like tyrosine kinase-1/placental growth factor ratio as a diagnostic test for preeclampsia. *Hypertension*. 2014;63(2):346-52. doi:10.1161/HYPERTENSIONAHA.113.01787.
15. Rana S, Powe CE, Salahuddin S, Verlohren S, Perschel FH, Levine RJ, et al. Angiogenic factors and the risk of adverse outcomes in women with suspected preeclampsia. *Circulation*. 2012;125(7):911-9. doi:10.1161/CIRCULATIONAHA.111.054361.
16. Saleh L, Vergouwe Y, van den Meiracker AH, Verdonk K, Russcher H, Bremer HA, et al. Angiogenic markers predict pregnancy complications and prolongation in preeclampsia: continuous versus cutoff values. *Hypertension*. 2017;70(5):1025-33. doi:10.1161/HYPERTENSIONAHA.117.09913.
17. Chappell LC, Duckworth S, Seed PT, Griffin M, Myers J, Mackillop L, et al. Diagnostic accuracy of placental growth factor in women with suspected preeclampsia: a prospective multicenter study. *Circulation*. 2013;128(19):2121-31. doi:10.1161/CIRCULATIONAHA.113.003215.
18. Duhig KE, Myers J, Seed PT, Sparkes J, Lowe J, Hunter RM, et al. Placental growth factor testing to assess women with suspected preeclampsia: a multicentre, pragmatic, stepped-wedge cluster-randomised controlled trial. *Lancet*. 2019;393(10183):1807-18. doi:10.1016/S0140-6736(18)33212-4.

19. Hurrell A, Webster L, Sparkes J, Battersby C, Brockbank A, Clark K, et al. Repeat placental growth factor-based testing in women with suspected preterm pre-eclampsia (PARROT-2): a multicentre, parallel-group, superiority, randomised controlled trial. *Lancet*. 2024;403(10427):619-31. doi:10.1016/S0140-6736(23)02357-7.
20. Cerdeira AS, O'Sullivan J, Ohuma EO, Harrington D, Szafranski P, Black R, et al. Randomized interventional study on prediction of preeclampsia/eclampsia in women with suspected preeclampsia: INSPIRE. *Hypertension*. 2019;74(4):983-90. doi:10.1161/HYPERTENSIONAHA.119.12739.
21. Klein E, Schlembach D, Ramoni A, Langer E, Bahlmann F, Grill S, et al. Influence of the sFlt-1/PlGF ratio on clinical decision-making in women with suspected preeclampsia. *PLoS One*. 2016;11(5):e0156013. doi:10.1371/journal.pone.0156013.
22. Stepan H, Herraiz I, Schlembach D, Verlohren S, Brennecke S, Chantraine F, et al. Implementation of the sFlt-1/PlGF ratio for prediction and diagnosis of pre-eclampsia in singleton pregnancy: implications for clinical practice. *Ultrasound Obstet Gynecol*. 2015;45(3):241-6. doi:10.1002/uog.14799.
23. Herraiz I, Simon E, Gomez-Arriaga PI, Quezada MS, Garcia-Burguillo A, Lopez-Jimenez EA, et al. Clinical implementation of the sFlt-1/PlGF ratio to identify preeclampsia and fetal growth restriction: a prospective cohort study. *Pregnancy Hypertens*. 2018; 13:279-85. doi:10.1016/j.preghy.2018.06.017.
24. Dröge LA, Perschel FH, Stütz N, Gafron A, Frank L, Busjahn A, et al. Prediction of preeclampsia-related adverse outcomes with the sFlt-1/PlGF ratio in the clinical routine: a real-world study. *Hypertension*. 2021;77(2):461-71. doi:10.1161/HYPERTENSIONAHA.120.15146.
25. Schlembach D, Hund M, Schroer A, Wolf C. Economic assessment of the use of the sFlt-1/PlGF ratio test to predict preeclampsia in Germany. *BMC Health Serv Res*. 2018;18(1):603. doi:10.1186/s12913-018-3406-1.
26. Stubbs TM, Lazarchick J, Horger EO 3rd. Plasma fibronectin levels in preeclampsia: a possible biochemical marker for vascular endothelial damage. *Am J Obstet Gynecol*. 1984;150(7):885-7. doi:10.1016/0002-9378(84)90468-X.
27. Rasanen J, Quinn MJ, Laurie A, Bean E, Roberts CT Jr, Nagalla SR, et al. Maternal serum glycosylated fibronectin as a point-of-care biomarker for assessment of preeclampsia. *Am J Obstet Gynecol*. 2015;212(1):82. e1-82.e9. doi:10.1016/j.ajog.2014.07.052.
28. Huhn EA, Hoffmann I, Martinez de Tejada B, Lange S, Sage KM, Roberts CT, et al. Maternal serum glycosylated fibronectin as a short-term predictor of preeclampsia: a prospective cohort study. *BMC Pregnancy Childbirth*. 2020; 20:128. doi:10.1186/s12884-020-2809-2.
29. Nagalla SR, Janaki V, Vijayalakshmi AR, Chayadevi K, Pratibha D, Rao PV, et al. Glycosylated fibronectin point-of-care test for diagnosis of pre-eclampsia in a low-resource setting: a prospective Southeast Asian population study. *BJOG*. 2020;127(13):1687-94. doi:10.1111/1471-0528.16323.
30. Kesireddy S, Reddy P, Gayathri V, Reddy P, Reddy B. Glycosylated fibronectin point-of-care test for triage and surveillance of hypertension in pregnancy cases: a retrospective observational case control study. *J Obstet Gynaecol India*. 2022;72(Suppl 1):121-125. doi:10.1007/s13224-021-01566-y.
31. Kluivers ACM, Neuman RI, Kalra B, Kumar A, Visser W, Danser AHJ, et al. Glycosylated fibronectin as a biomarker for preeclampsia and preeclampsia-related complications. *Pregnancy Hypertens*. 2025; 39:101177. doi:10.1016/j.preghy.2024.101177.
32. Sokratous N, Bednorz M, Wright A, Nicolaides KH, Kametas NA. Prediction using serum glycosylated fibronectin of imminent pre-eclampsia in women with new-onset hypertension. *Ultrasound Obstet Gynecol*. 2023;62(5):653-659. doi:10.1002/uog.27458.
33. Liao L, Liu M, Yin Y, Xu Q, Yuan L, Xie S, et al. Glycosylated fibronectin in preeclampsia: a systematic review and meta-analysis. *BMC Pregnancy Childbirth*. 2025;25(1):228.

- doi:10.1186/s12884-025-07243-6.
34. Wirawan W, Krisnadi SR, Anwar AD, Nugrahani AD. Predictive value of glycosylated fibronectin (GlyFn)/placenta growth factor (PLGF) ratio for high-risk pregnancies: a cohort study. *BMC Pregnancy Childbirth*. 2025; 25:770. doi:10.1186/s12884-025-07853-0.
35. Sokratous N, Wright A, Syngelaki A, Kakouri E, Laich A, Nicolaides KH. Screening for pre-eclampsia by maternal serum glycosylated fibronectin and angiogenic markers at 36 weeks' gestation. *Ultrasound Obstet Gynecol*. 2024;63(1):88-97. doi:10.1002/uog.27481.
36. Paneva I, Samardziski I, Kochoski G, Simeonova Krstevska S, Petrovski O, Panev S, et al. Glycosylated fibronectin - point-of-care test for diagnosis of preeclampsia. *Perinatal Journal*. 2025;33(1):909-16. doi:10.57239/prn.25.03310098.
37. DiabetOmics, Inc. Lumella Preeclampsia Test System: instructions for use. LN-6002 Rev J. Hillsboro (OR): DiabetOmics, Inc.; 2022.
38. Roche Diagnostics. Elecsys sFlt-1 and Elecsys PlGF: sFlt-1/PlGF ratio for preeclampsia [Internet]. Basel: Roche Diagnostics; 2025 [cited 2026 Sep 8].
39. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet*. 2007;370(9596):1453-57. doi:10.1016/S0140-6736(07)61602-X.
40. Menzies J, Magee LA, Macnab YC, Ansermino JM, Li J, Douglas MJ, et al. Current CHS and NHBPEP criteria for severe preeclampsia do not uniformly predict adverse maternal or perinatal outcomes. *Hypertens Pregnancy*. 2007;26(4):447-62. doi:10.1080/10641950701521742.
41. von Dadelszen P, Payne B, Li J, Ansermino JM, Broughton Pipkin F, Cote AM, et al. Prediction of adverse maternal outcomes in pre-eclampsia: development and validation of the fullPIERS model. *Lancet*. 2011;377(9761):219-27. doi:10.1016/S0140-6736(10)61351-7.
42. Payne BA, Hutcheon JA, Ansermino JM, Hall DR, Bhutta ZA, Bhutta SZ, et al. A risk prediction model for the assessment and triage of women with hypertensive disorders of pregnancy in low-resourced settings: the miniPIERS multi-country prospective cohort study. *PLoS Med*. 2014;11(1):e1001589. doi:10.1371/journal.pmed.1001589.
43. Saleh L, Alblas MM, Nieboer D, Neuman RI, Vergouwe Y, Brusse IA, et al. Prediction of pre-eclampsia-related complications in women with suspected or confirmed pre-eclampsia: development and internal validation of a clinical prediction model. *Ultrasound Obstet Gynecol*. 2021;58(5):698-704. doi:10.1002/uog.23142.
44. Ganzevoort W, Rep A, de Vries JIP, Bonsel GJ, Wolf H. Prediction of maternal complications and adverse infant outcome at admission for temporizing management of early-onset severe hypertensive disorders of pregnancy. *Am J Obstet Gynecol*. 2006;195(2):495-503. doi: 10.1016/j.ajog.2006.02.012.
45. Perales A, Delgado JL, de la Calle M, Garcia-Hernandez JA, Escudero AI, Campillos JM, et al. sFlt-1/PlGF for prediction of early-onset pre-eclampsia: STEPS study. *Ultrasound Obstet Gynecol*. 2017;50(3):373-82. doi:10.1002/uog.17373.
46. Wah IYM, Sahota DS, Wong NKL, Lee NMW, Liu CJ, Lau CSL, et al. Intermanufacturer assessment of diagnostic performance of angiogenic ratio vs glycosylated fibronectin in women with suspected pre-eclampsia. *Ultrasound Obstet Gynecol*. 2024;64(5):620-625. doi:10.1002/uog.29107.
47. Sokratous N, Wright A, Syngelaki A, O'Gorman N, Nicolaides KH. Screening for pre-eclampsia by maternal serum glycosylated fibronectin at 11-13 weeks' gestation. *Ultrasound Obstet Gynecol*. 2023;61(2):179-85. doi:10.1002/uog.26303.
48. Suzuki H, Hirashima C, Nagayama S, Takahashi K, Shirasuna K, Matsubara S, et al. Increased serum levels of sFlt-1/PlGF ratio in preeclamptic women with onset at <32 weeks compared with ≥32 weeks. *Pregnancy Hypertens*. 2018; 12:96-103. doi: 10.1016/j.preghy.2018.03.008.
49. Cheng YKY, Law LW, Leung TY, Chan OK, Sahota DS. Soluble fms-like tyrosine kinase-1,

placental growth factor and their ratio as a predictor for pre-eclampsia in East Asians. *Pregnancy Hypertens.* 2018; 11:61-65. doi: 10.1016/j.preghy.2017.12.002.

50. National Institute for Health and Care Excellence.

PLGF-based testing to help diagnose suspected preterm pre-eclampsia. HealthTech guidance HTG630 [Internet]. London: NICE; 2022.