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Glycosylated fibronectin - Point-of-care test for diagnosis of preeclampsia

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Abstract

The present study aims to evaluate and compare the diagnostic performance of soluble fms-like tyrosine kinase-1/placental growth factor (sFlt-1/PlGF) ratio and glycosylated fibronectin (GlyFn) in women with suspected PE, with a particular focus on their potential for improving risk stratification and guiding timely clinical management In this prospective cohort study, 124 pregnant women with clinical suspicion of PE were recruited at the University Clinic of Gynecology and Obstetrics in Skopje between May 2024 and May 2025. GlyFn was measured by a point-of-care test (Lumella™ PE), and sFlt-1/PlGF was determined by automated electrochemiluminescence immunoassay. Diagnostic performance was evaluated using sensitivity, specificity, predictive values, and receiver-operating characteristic (ROC) analysis.Of 124 women, 70 were diagnosed with PE and 54 with gestational hypertension (GH). Median biomarker levels were significantly higher in PE versus GH: sFlt-1/PlGF ratio 180 (IQR 111–477) vs. 17 (IQR 9–48), and GlyFn 454 µg/mL (IQR 385–601) vs. 252 µg/mL (IQR 220–298) (both p<0.001). At thresholds of ≥85 for sFlt-1/PlGF and ≥350 µg/mL for GlyFn, sensitivity was 84.3% and 80%, and specificity was 85.2% and 88.9%, respectively. Negative predictive values at 5% prevalence exceeded 98% for both markers. ROC analysis demonstrated excellent discrimination: AUC 0.946 (95% CI 0.905–0.978) for sFlt-1/PlGF and 0.906 (95% CI 0.844–0.958) for GlyFn. Both sFlt-1/PlGF and GlyFn reliably differentiate preeclampsia from gestational hypertension, with high diagnostic accuracy and excellent negative predictive value. While sFlt-1/PlGF remains the benchmark biomarker, GlyFn offers comparable performance and the advantage of rapid point-of-care testing, supporting its complementary role in diverse clinical settings

Keywords: PSreeclampsia, Glycosylated fibronectin, SSFlt-1/PLGF, Diagnosis

1. Introduction

Preeclampsia (PE) is part of the spectrum of hypertensive disorders in pregnancy, occurring in approximately 5% of all pregnancies, and represents a leading cause of maternal and perinatal mortality and morbidity [1–4].

The condition is clinically heterogeneous and traditionally diagnosed by new-onset hypertension and proteinuria after 20 weeks' gestation; however, these clinical criteria are often insufficient to predict adverse outcomes, as complications may occur in the absence of classic diagnostic features [5–7]. The International Society for the Study of Hypertension in Pregnancy (ISSHP) and other expert bodies now emphasize the importance of integrating utero-placental dysfunction and/or intrauterine growth restriction (IUGR) into the diagnostic criteria [6–8]. Compared to the traditional definition of the American College of Obstetricians and Gynecologists (ACOG) [6], the more inclusive ISSHP definition of maternal organ dysfunction has been shown to be more sensitive. The addition of uteroplacental dysfunction and biomarker imbalance in the broader definition optimizes the identification of women and newborns at risk, especially when angiogenic factors are included [9].

Among circulating biomarkers, the imbalance between angiogenic and antiangiogenic factors plays a central role in the pathogenesis of PE. Excess placental secretion of soluble fms-like tyrosine kinase-1 (sFlt-1) leads to reduced bioavailability of placental growth factor (PlGF), resulting in widespread maternal endothelial dysfunction [10–14]. Several landmark studies have established the diagnostic and prognostic value of the sFlt-1/PlGF ratio in women with suspected PE. An sFlt-1/PlGF ratio >85 before 34 weeks of gestation and >110 after

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34 weeks can be regarded as a diagnostic criterion for preeclampsia [15]. A markedly elevated ratio, defined as >655 before 34 weeks and >201 after 34 weeks of gestation, has been associated with the need for delivery within the following 48 hours [16–18]. On the other hand, an sFlt-1/PlGF ratio below 38 in women presenting with signs and symptoms suggestive of preeclampsia demonstrates a high negative predictive value (NPV 99.3%) for ruling out preeclampsia within one week, while a ratio ≥38 has moderate positive predictive value (PPV 36.7%) for ruling in preeclampsia within four weeks [19]. Incorporation of the sFlt-1/PlGF ratio into diagnostic algorithms is now recommended in many guidelines [15,17, 20].

While angiogenic markers have significantly improved prediction and management, they may not capture the full spectrum of pathophysiological processes in PE. Glycosylated fibronectin (GlyFn), a modified extracellular matrix glycoprotein, has recently emerged as a promising biomarker reflecting abnormal placentation and systemic endothelial dysfunction [21–23].

Glycosylated fibronectin can be used for the prediction of early PE as early as the first trimester, between the 11th and 13th gestational week [24], in women with newly diagnosed hypertension during pregnancy in the second and third trimesters for the prediction of PE in the following two weeks [25], or between the 35th and 37th gestational week for the prediction of delivery within the next three weeks due to PE or gestational hypertension (GH) [26]. Moreover, point-of-care testing of GlyFn has shown feasibility and clinical utility in low-resource settings, supporting its potential as an accessible diagnostic tool [27,31].

Taken together, angiogenic imbalance and extracellular matrix remodeling represent complementary biological pathways in the pathogenesis of PE. The sFlt-1/PlGF ratio has become a well-established clinical tool, while GlyFn is gaining recognition as an innovative biomarker with additive diagnostic value. The present study aims to evaluate and compare the diagnostic performance of these biomarkers in women with suspected PE, with a particular focus on their potential for improving risk stratification and guiding timely clinical management.

2. Methods

2.1 Study population

Between May 2024 and May 2025, a total of 124 pregnant women with singleton pregnancies presenting with clinical symptoms and signs of suspected preeclampsia were evaluated at the University Clinic of Gynecology and Obstetrics in Skopje. Patients were either referred by their primary obstetrician due to suspicion of preeclampsia or presented on their own because of symptoms of preeclampsia. Indications for evaluation and hospitalization included elevated blood pressure, proteinuria or one of the symptoms associated with preeclampsia, such as headache, visual disturbances, right upper quadrant abdominal pain, oedema or hypertension unresponsive to therapy.

Samples for analysis were obtained as part of the initial clinical evaluation: capillary blood from a finger prick was collected for the measurement of glycosylated fibronectin and venous blood was drawn for determination of the sFlt-1/PLGF ratio.

The study was approved by the Ethics Committee of the Faculty of Medicine in Skopje, and written informed consent was obtained from all participants.

2.2 Analysis of SFLT-1, PLGF, and GLYFN

Glycosylated fibronectin was measured using a point-of-care test (Lumella™ PE test; DiabetOmics, Inc., Hillsboro, OR, USA) from 5 µL of whole blood. Test strips were configured with monoclonal antibodies against GlyFn labelled with gold particles for quantification using a hand-held Lumella ™ reader system. Briefly, 5 µl of serum was diluted 1:350 in running buffer and 120 µl of diluted serum added to the test strip and inserted into the reader.

The GlyFn concentration is displayed on the reader after 10 minutes [27]. The concentrations of sFlt-1, PLGF, and the sFlt-1/PLGF ratio were determined on a fully automated ECLIA (electrochemiluminescence immunoassay) analyzer, Cobas e 411, using an immunoassay method with highly specific monoclonal antibodies against PLGF and sFlt-1 [20, 28].

2.3 Diagnosis and outcomes

The determination of clinical diagnosis was based on laboratory and clinical findings collected from the time of hospitalization until delivery. The diagnoses of preeclampsia and gestational hypertension were made according to the diagnostic criteria of the American College of Obstetricians and Gynaecologists (ACOG) from 2019 [29].

Preeclampsia was defined as blood pressure ≥ 140/90 mmHg on two occasions at least 2 hours apart but within 2 weeks after 20 weeks of gestation, accompanied by proteinuria ≥ 300 mg/24 h, or in the absence of proteinuria, but with thrombocytopenia <100,000 × 10^9/L, serum creatinine >97 μmol/L in the absence of underlying renal disease, hepatic dysfunction with blood transaminase concentrations more than twice the upper limit of normal, new-onset headache unresponsive to analgesics or visual symptoms. Gestational hypertension was defined as blood pressure meeting the above thresholds in the absence of proteinuria (proteinuria below the diagnostic threshold for preeclampsia). Proteinuria was defined as ≥ 2+ protein on urine dipstick or ≥ 300 mg in a 24-hour urine collection.

2.4 Statistical analysis

Continuous variables were tested for normality using the Shapiro-Wilk test. Normally distributed variables are presented as mean ± standard deviation (SD), while skewed data are presented as median with interquartile range (IQR).

Overall group differences were compared using a Kruskal–Walli's test for continuous variables. Pairwise comparisons between groups were made using a Wilcoxon rank sum test. Median biomarker values for women with and without clinical PE were calculated and compared. Final delivery outcomes were also described between groups, including gestational age at delivery and birthweight.

We estimated and compared the diagnostic accuracy (sensitivity, specificity) using thresholds of ≥350 microg/ml for GlyFn, provided by the manufacturer of the test [30,33] and threshold of ≥85 for sFlt-1/PLGF ratio based on previous studies [15, 17]. A level of significance of $P < 0.05$ was used.

Receiver-operating characteristic (ROC) curves, the area under the curve (AUC) and corresponding 95% confidence intervals (95% CI) for PE were generated using predicted probabilities from simple logistic regression models.

3. Results

3.1 Study population

The characteristics of the study groups are shown in Table 1. A total of 124 patients with symptoms and signs suggestive of preeclampsia were included in the study. Based on laboratory findings and clinical evaluation, 70 patients were diagnosed with preeclampsia and 54 with gestational hypertension. Table 1 shows the median age of the study group was 30.0 (26.0- 35.0), median gestational age at delivery was 37.0 weeks (33.6–39.0), and the median birthweight was 2,355 grams (1,260–3,100 g).

Patients with preeclampsia differed from those with gestational hypertension in terms of maternal age (p=0.04). Also, the two groups differed in terms of sFlt-1/PLGF ratio, GLYFN, proteinuria, birthweight and gestational age at birth (p< 0.001 for all).

Table 1. Clinical characteristics of the study groups

Parameter	All Patients	GH (Gestational Hypertension)	PE (Preeclampsia)	p-value (GH vs PE)
Maternal Age (years)	30.0 (26.0–35.0)	29.0 (25.0–33.0)	32.0 (26.2–35.8)	0.0466
sFlt-1/PLGF (ratio)	96.2 (23.8–252.6)	16.6 (9.1–47.7)	179.9 (111.4–477.4)	< 0.001
GlyFn (μg/mL)	353.0 (256.8–502.5)	251.5 (220.2–298.0)	454.0 (385.0–601.0)	< 0.001
Proteinuria (g/24h)	0.4 (0.1–1.5)	0.0 (0.0–0.2)	1.2 (0.5–3.1)	< 0.001
Birthweight, grams	2355.0(1260.0-3100.0)	3050.0 (2570.0–3410.0)	1775.0 (820.0–2400.0)	< 0.001
Gestational Age at birth (weeks)	37.0 (33.6–39.0)	38.1 (36.4–39.1)	35.2 (32.0–38.4)	< 0.001

* Values are median (interquartile range). PE: preeclampsia; GH: Gestational Hypertension; sFlt-1: soluble Fms-like tyrosine kinase; PLGF: placental growth factor; GLYFN: glycosylated fibronectin

3.2 Biomarker performance

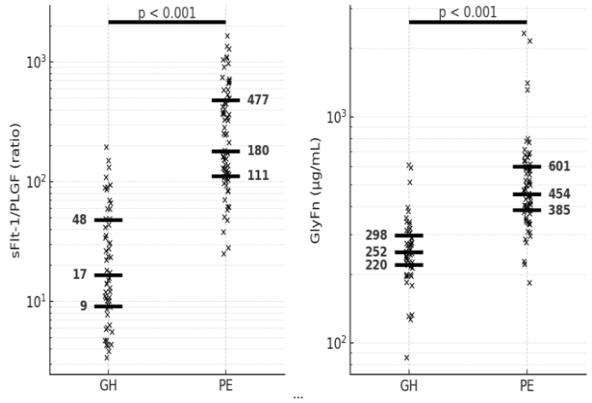

Fig. 1 Median levels and interquartile range of: a) soluble FMS-like tyrosine kinae-1/placental growth factor ratio (SFLT-1/PLGF) and b) glycosylated fibronectin (GLYFN), in patients with gestational hypertension vs preeclampsia. error bars represent interquartile range

Figure 1 shows the median (IQR**)** of sFlt-1/PLGF ratio and GlyFn in women with PE and GH. sFlt-1/PLGF ratio was markedly higher in women with PE compared with those with GH, PE: 180 (111–477), GH: 17 (9–48), ($p < 0.001$), which confirms the strong discriminatory capacity of the angiogenic ratio. The median (IQR) serum GlyFn levels were also significantly elevated in PE compared with GH, PE: 454 (385–601) µg/mL, GH: 252 (220–298) µg/mL, ($p < 0.001$). The narrower IQR compared to angiogenic ratio suggests more uniform elevation across affected patients, but the marker still showed a consistent and statistically significant distinction between groups.

Both biomarkers tested exhibited high performance for detection of PE. At a threshold of ≥350 µg/mL, GLYFN demonstrated 80% sensitivity and 88.9% specificity**,** with an NPV of 98.8% at a prevalence of 5%. Similarly, the sFlt-1/PlGF ratio at a cut-off of ≥85 yielded 84.3% sensitivity and 85.2% specificity**,** with an NPV of 99% (Table 2).

Table 2. Biomarker performance characteristics for diagnosis of PE.

Biomarker	Threshold	Sensitivity (%)	Specificity (%)	PPV (5%)	NPV (5%)
GlyFn (µg/mL**)**	≥350	80	88.9	27.5	98.8
sFlt-1/PLGF (ratio)	≥85	84.3	85.2	23	99

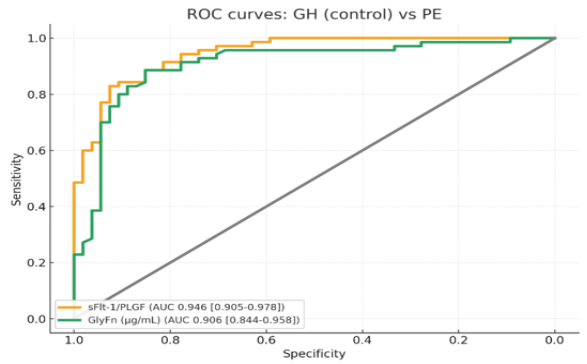

Fig. 2 Receiver-Operating Characteristic (ROC) curves and associated Area Under the Curve (AUC) for sFlt-1/PLGF and GLYFN for diagnosis of PE.

The sFlt-1/PlGF ratio demonstrated excellent diagnostic performance for distinguishing preeclampsia (PE) from gestational hypertension (GH), with an area under the ROC curve (AUC) of 0.946 (95% CI, 0.905–0.978)**.** Glycosylated fibronectin (GlyFn) also showed strong discriminative ability, with an AUC of 0.906 (95% CI, 0.844–0.958)**.** Although both biomarkers achieved high accuracy, the sFlt-1/PlGF ratio performed slightly better overall (Figure 2).

These findings indicate that while GlyFn has substantial diagnostic value as a novel biomarker, the sFlt-1/PlGF ratio remains the more robust single predictor. Importantly, the comparable performance of GLYFN suggests potential complementary use, particularly in settings where angiogenic assays may be less available or more costly.

4. Discussion

4.1 Clinical implications

In this prospective cohort of women with suspected preeclampsia, we observed that both the sFlt-1/PlGF ratio and the novel biomarker- GlyFn well discriminated preeclampsia (PE) from gestational hypertension (GH). Median values for both biomarkers were markedly higher in the PE group

compared with GH, with significant differences ($p < 0.001$).

These between-group differences translated into robust diagnostic performance: the sFlt-1/PlGF ratio achieved an area under the ROC curve (AUC) of approximately 0.95 (95% confidence interval [CI] 0.91–0.98), and GlyFn achieved an AUC of 0.91 (95% CI 0.84–0.96) for distinguishing preeclampsia from gestational hypertension in our cohort. This high discrimination is consistent with prior studies, which have also reported strong test accuracy for these biomarkers. For example, Nagalla et al. [27,32] found that GlyFn levels were significantly increased in preeclampsia and demonstrated an AUC of 0.99 (95% CI 0.98–0.99) for diagnosing PE, while PlGF and sFlt-1 had AUCs around 0.96 and 0.86, respectively. Our findings align with this literature, indicating that both angiogenic factors imbalance and altered fibronectin glycosylation are prominent in preeclampsia and can be of clinical significance for diagnosis.

Both biomarkers in our study showed a favorable balance of sensitivity and specificity. Importantly, at a low disease prevalence of ~5%, both the sFlt-1/PlGF ratio and GlyFn would yield an excellent negative predictive value (NPV) on the order of 98–99%, whereas the positive predictive value (PPV) would be more modest (approximately 30–50%). This pattern of a very high NPV but only moderate PPV mirrors the findings of the multicenter PROGNOSIS study by Zeisler et al. [19]. In that study, sFlt-1/PlGF ratio cut-off of 38 or below had a 99.3% NPV for ruling out preeclampsia in the week following testing. Conversely, a ratio above 38 had a PPV of only ~37% for the development of preeclampsia within four weeks. Thus, while a low ratio is highly reassuring, an elevated ratio must be interpreted with caution given the limited PPV, especially in low-prevalence settings. Our results reinforce this point – no diagnostic test is infallible, and a positive biomarker test does not equal certain disease.

Sokratous et al. [25] recently underscored that the predictive performance of these biomarkers in practice is only moderate, noting that all three tests (PlGF, sFlt-1/PlGF, and GlyFn) had relatively high false-positive rates and "relatively poor" positive predictive performance when used to predict imminent preeclampsia. This emphasizes that biomarker results should complement clinical judgment rather than replace it. Another study by Sokratous et al. [24] explored GlyFn in an entirely different context- first trimester screening for preeclampsia. Interestingly, they found that incorporating GlyFn into early screening models (alongside maternal factors, blood pressure, uterine artery Dopplers, etc.) yielded performance comparable to using PlGF, with detection rates around 79–81% for preterm preeclampsia at a 10% false-positive rate. This suggests that GlyFn might have broad applicability, from early risk stratification to point-of-care diagnostics in later pregnancy.

Our findings are in line with the established literature on angiogenic markers in preeclampsia. Numerous landmark studies have demonstrated the utility of the sFlt-1/PlGF ratio in diagnosing and predicting preeclampsia. For instance, Rana et al. [16] showed that women who went on to experience adverse outcomes had substantially higher sFlt-1/PlGF ratios at presentation (median ~47.0, IQR 15.5–112.2) compared to those who did not (median ~10.8, IQR 4.1–28.6), and adding the sFlt-1/PlGF ratio to clinical factors significantly improved the ability to predict adverse maternal-fetal outcomes, raising the AUC from 0.84 (clinical factors alone) to 0.93 with the biomarker included. Verlohren et al. [17] similarly reported that the sFlt-1/PlGF ratio is markedly elevated in preeclampsia compared to other hypertensive disorders of pregnancy and is a reliable tool for distinguishing preeclampsia from gestational hypertension at both early and late gestational ages. In that study, patients with preeclampsia had significantly higher ratios than those with chronic or gestational hypertension ($p < 0.001$), and those with the most extreme ratio elevations tended to require delivery imminently. These findings are in line with our data, which showed a roughly ten-fold higher median ratio in patients with preeclampsia than in patients with gestational hypertension. They also support the concept that higher ratio values are associated with more severe disease courses. In fact, clinical protocols have emerged from this body of evidence and many centres utilize a ratio threshold (often around 85–110, depending on gestational age) as a "rule-in" criterion for diagnosis of preeclampsia [15].

Beyond angiogenic factors, our study provides new evidence for the role of glycosylated fibronectin in

preeclampsia, and how it might complement existing biomarkers. GlyFn is a fibronectin with altered glycosylation that becomes elevated in the maternal circulation during preeclampsia, potentially due to oxidative stress and endothelial dysfunction unique to the disease [27]. Unlike sFlt-1 and PlGF, which directly reflect placental angiogenic imbalance, GlyFn may capture a different aspect of the pathophysiology related to maternal endothelial and extracellular matrix changes. The appeal of GlyFn lies not only in its accuracy but also in its practicality. In contrast to the sFlt-1/PlGF assays which require laboratory analyzers, the GlyFn assay can be performed on a point-of-care device within minutes [27].

4.2 Strengths and limitations

Our study has several strengths that lend confidence to the clinical relevance of the findings. First, the study was prospectively designed and conducted in a real-world tertiary referral setting. We enrolled patients as they presented with hypertensive symptoms or suspicion of preeclampsia and applied uniform inclusion criteria, which reduces selection bias. Second, we assessed the two biomarker tests in parallel. This same sample timing provides a direct comparison of sFlt-1/PlGF versus GlyFn performance. Third, we used rigorous diagnostic criteria for preeclampsia, which is important for evaluating any diagnostic test. Finally, by including a comparison group of gestational hypertension patients (those with hypertension but no proteinuria or end-organ signs), we addressed a clinically relevant question – distinguishing preeclampsia from look-alike conditions. Many prior studies have compared marker levels between preeclampsia and healthy normotensive pregnancies, which establishes biomarker differences, but our design specifically informs how these tests perform in the more challenging real-world scenario of differentiating preeclampsia from other hypertensive disorders.

Despite these strengths, our study also has important limitations. The limited sample may restrict the statistical power for subgroup analyses and could overestimate the diagnostic performance. Single-centre data may also reflect local referral patterns and population demographics that differ from other regions. Therefore, external validation is needed: a multicentre study or larger cohort would help confirm the optimal cut-offs and performance characteristics.

5. Conclusion

Taken together, these findings suggest that both biomarkers provide high diagnostic accuracy, with sFlt-1/PlGF showing slightly superior performance, but GlyFn offering complementary predictive information.

From a clinical standpoint, the combination of angiogenic markers and GlyFn may provide a more comprehensive assessment of placental dysfunction, capturing both vascular and extracellular matrix pathways. This dual-biomarker strategy may be especially valuable in stratifying risk among women with atypical presentations, borderline angiogenic ratios, or in low-resource settings where point-of-care GlyFn testing may be more feasible than automated immunoassays.

Interest disclosure statement

The authors have no relevant financial or non-financial interests to disclose.

The authors have no competing interests to declare that they are relevant to the content of this article.

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