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Comparison of the Soluble fms-Like Tyrosine Kinase 1/Placental Growth Factor Ratio Alone versus a Multi-Marker Regression Model for the Prediction of Preeclampsia-Related Adverse Outcomes after 34 Weeks of Gestation

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Mini-Summary

What does this study add to current knowledge?

- This retrospective study compares the predictive performance of a multi-marker regression model including the sFlt-1/PlGF ratio versus the sFlt-1/PlGF ratio alone for preeclampsia-related maternal and fetal adverse outcomes. In our study, we focused on late-onset preeclampsia, which is more common than early-onset preeclampsia and accounts for 90% of all cases. Our regression model integrated standard clinical information and the sFlt-1/PlGF ratio. This correctly reclassified as low risk 24.5% of patients without adverse outcome that were classified as high-risk based on the sFlt-1/PlGF ratio alone.

What are the clinical implications of this work?

- The real-world cohort better reflects the heterogeneity of patients in the clinical routine and is a necessary addition to prospective studies when evaluating new clinical predictive tools. Our regression model integrating available clinical data plus the sFlt-1/PlGF ratio enhances the predictive accuracy for preeclampsia-related maternal and fetal adverse outcomes. Precise prediction of adverse outcomes in late-onset disease is important to prevent maternal and fetal complications and stratify care.

Keywords
Preeclampsia · Prediction · Soluble fms-like tyrosine kinase 1/placental growth factor · Late-onset preeclampsia · Adverse outcome

Abstract
Introduction: The objective of this retrospective study was to compare the predictive performance of the soluble fms-like tyrosine kinase 1 (sFlt-1)/placental growth factor (PlGF) ratio

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alone or in a multi-marker regression model for preeclampsia-related maternal and/or fetal adverse outcomes in women >34 weeks of gestation. ***Methods:*** We analyzed the data collected from 655 women with suspected preeclampsia. Adverse outcomes were predicted by multivariable and univariable logistic regression models. The outcome of patients was evaluated within 14 days after presentation with signs and symptoms of preeclampsia or diagnosed preeclampsia. ***Results:*** The full model integrating available, standard clinical information and the sFlt-1/PlGF ratio had the best predictive performance for adverse outcomes with an AUC of 72.6%, which corresponds to a sensitivity of 73.3% and specificity of 66.0%**.** The positive predictive value of the full model was 51.4%, and the negative predictive value was 83.5%. 24.5% of patients, who did not experience adverse outcomes but were classified as high risk by sFlt-1/PlGF ratio (≥38), were correctly classified by the regression model. The sFlt-1/PlGF ratio alone had a significantly lower AUC of 65.6%. ***Conclusions:*** Integrating angiogenic biomarkers in a regression model improved the prediction of preeclampsia-related adverse outcomes in women at risk after 34 weeks of gestation.

Introduction

Preeclampsia (PE) is a multisystem hypertensive disorder in pregnancy and remains the leading cause of maternal and fetal mortality and morbidity [1]. PE affects 2–8% of pregnancies and causes 12% of perinatal maternal deaths worldwide [1, 2].The clinical presentation can vary, and potential maternal adverse outcomes (AOs) include severe hypertension, liver dysfunction, acute kidney failure, thrombocytopenia, pulmonary edema, and cerebral edema. PE also affects the fetus and can cause preterm delivery, respiratory distress syndrome, fetal death, placental abruption and may be associated with intrauterine growth restriction [3–5]. Early detection of PE and prediction of its AOs is crucial as delivery is the only causal treatment for PE [6]. Thus, a precise prediction of AOs may reduce maternal morbidity and mortality by adapting monitoring intervals, referral to perinatal care centers, and timely delivery. In our study, we focused on late-onset PE after 34 weeks of gestation, which is more common than early-onset PE and accounts for 90% of all cases [7, 8].

PE was defined for a long time as the new onset of hypertension and proteinuria after 20 weeks of gestation [4]. However, it has been proven that blood pressure measurements and estimation of proteinuria have a low positive predictive value (PPV) for predicting AOs of approximately 20% [9]. A substantial improvement in prediction of adverse events in patients with suspected PE has been achieved by the implementation of the angiogenic biomarkers soluble fms-like tyrosine kinase 1 (sFlt-1) and placental growth factor (PlGF) in the diagnostic workup in women at risk [10–17]. Recently, our study that included pregnant women with suspected PE of all gestational ages has shown that including the sFlt-1/PlGF ratio in a multi-marker prediction model may further improve predictive accuracy in the clinical routine [18]. The objective of this retrospective study was to compare the predictive performance for PE-related maternal and/or fetal AOs of the sFlt-1/PlGF ratio alone or in a multi-marker regression model in women with suspected PE after 34 weeks of gestation within 14 days.

Methods

Study Population

The data for this study were derived from a single-center database retrospectively recording outcomes in women with suspected PE between July 2010 and March 2019. A previous analysis of a subset of this database, collected at Charité – University Medicine Berlin, has been published recently [18]. The database has been expanded, and the current analysis was limited to women with suspected PE >34 weeks of gestation and an available outcome within 14 days after presentation.

Inclusion criteria were age ≥18 years, singleton pregnancy, new onset of or preexisting hypertension (>140/90 mm Hg) or proteinuria (>300 mg/24 h or a protein-to-creatinine ratio of 30 mg/mmol or urine dipstick +), preeclamptic symptoms such as visual disturbances, epigastric pain, headache, progressive edema, or weight gain ≥1 kg per week. Women with diagnosed PE according to the definition of International Society for the Study of Hypertension in Pregnancy (ISSHP) from 2012 definition were also included in the study [19]. Patients with suspicion of small for gestational age or fetal growth restriction (FGR) and with pathological Doppler measurements were also enrolled. Exclusion criteria were the presence of fetal malformations or chromosomal abnormalities, lack of sFlt-1/PlGF measurements at inclusion, or incomplete outcome data. The Ethics Committee of the Charité approved the study.

Study Design

The clinical endpoint of our study was the occurrence of a composite of either maternal and/or fetal AOs within 14 days after presentation. Maternal AOs included the diagnosis of HELLP syndrome, acute renal failure, disseminated intravascular coagulation, pulmonary edema, intracerebral hemorrhage, eclampsia, and maternal death. Fetal AOs included the occurrence of respiratory distress syndrome, necrotizing enterocolitis, intraventricular hemorrhage, placental abruption, fetal death, and neonatal death [3]. PE was defined as the new onset hypertension and proteinuria after 20 weeks of gestation according

to the definition of ISSHP from 2012 and American College of Obstetricians and Gynecologists (ACOG) from 2002 [4, 19]. FGR was determined as a fetal weight below the tenth percentile and/or non-percentile proper fetal growth and abnormal Doppler resistance parameters of the uterine artery, umbilical artery, or oligohydramnios [20, 21]. Small for gestational age was defined as a weight below the tenth percentile for the gestational age [20]. The diagnosis of PE was not defined as an AO. Patients were treated according to standard clinical guidelines. However, measurement data of the sFlt-1/PlGF ratio was not blinded and thus available to the treating physician.

Measurements of the sFlt-1/PlGF Ratio and Doppler Examinations

The assessment of serum biomarkers and Doppler resistance parameters was performed as part of the standard clinical management of the patients. The concentration of sFlt-1 and PlGF was determined on the Cobas electrochemiluminescence immunoassay platform (Elecsys®, Roche Diagnostics, Rotkreuz, Switzerland). In patients with multiple serum marker measurements, the timepoint closest to the median of gestational age for blood sampling visits was selected for analyses using single measurements. Women with an sFlt-1/PlGF ratio ≥38 were categorized as high risk and patients with an sFlt-1/PlGF ratio <38 as low risk. In a second evaluation, we applied the "traffic light scheme," where patients with an sFlt-1/PlGF ratio <38 are classified as low risk, patients with values between 38 and 110 as intermediate risk, and patients with an sFlt-1/PlGF ratio of ≥110 as high risk. The outcome of patients was evaluated within 14 days after presentation at our clinic with signs and symptoms of a PE or diagnosed PE. Pulsatility index of the uterine, umbilical, and middle cerebral arteries was measured at the time of assessment of the sFlt-1/PlGF ratio ± 2 days.

Statistical Analysis

The data for our study were collected from medical records and entered into an Excel datasheet. Adjustment to the gestational age at measurement was done prior to modeling. For women without AO, time trends were analyzed by generalized additive models with integrated smoothness estimation. Based on model prediction, residuals were computed for all women, and median was added to rescale data. This approach is comparable to the computation of multiple of medians but is not dependent on either external median data or sufficiently large samples for computation of medians with sufficient time resolution.

Descriptive statistics for categories and measurements were computed. AOs were predicted by multivariable and univariable logistic regression models. Due to the "real-world data" nature of this data set, missing data were encountered in different frequencies across variables. We decided not to impute missing data, while thereby reducing sample size for multivariable analyses. As all potential predictors have missing values independently, increasing the number of predictors is reducing the sample size. As a first step, the following predictors were selected: proteinuria, new onset of hypertension, upper abdominal pain, headache, visual disturbances, progressive edemas, low platelet count, elevated liver enzymes, BMI (kg/cm^2), the presence of antiphospholipid syndrome, PE in previous pregnancy, preexisting diabetes, preexisting kidney disease, nulliparous, age >40, chronic hypertension, gestational hypertension, sFlt-1, PlGF, sFlt-1/PlGF ratio, systolic and diastolic blood pressure, and umbilical artery pulsatility index.

Therefore, selection based solely on p values from univariate analyses does not take into account correlations/interactions between potential predictors; odds ratios (ORs) and confidence levels were computed in a multivariable generalized linear model. This is followed by univariable generalized linear models for all predictors, based on the maximum number of subjects for the respective predictor. The second model was reduced and did not include most of the risk factors except nulliparity and preexisting hypertension. The reduced model included the following predictors: proteinuria, new onset of hypertension, upper abdominal pain, headache, visual disturbances, progressive edemas, low platelet count, elevated liver enzymes, BMI (kg/cm^2), nulliparous, chronic hypertension, sFlt-1, PlGF, sFlt-1/PlGF ratio, systolic and diastolic blood pressure, and umbilical artery pulsatility index.

The third model contained only predictors with at least a statistical trend ($p \leq 0.1$: proteinuria, new onset of hypertension, visual disturbances, nulliparous, sFlt-1, PlGF, sFlt-1/PlGF ratio, systolic and diastolic blood pressure, and umbilical artery pulsatility index). This threshold was selected due to the fact that predictive value may increase after inclusion of covariates and thus reach significance in the multivariable analysis. Our models are aiming primarily at detection of potential predictors for more systematic evaluation in prospective analyses.

The predictive performance of sFlt-1/PlGF ratio alone was proved in the fourth model. In the fifth model, the predictive value of blood pressure and proteinuria was demonstrated. Optimal cutoff values and corresponding specificity and sensitivity were computed from a receiver operating characteristics (ROC) analysis. Area under the curve (AUC) for ROCs is compared by DeLongs method.

Data were tested for normal distribution by the Kolmogorov-Smirnov test. Comparisons between two groups (with and without AO) were done by the t test for measures following a normal distribution or the Wilcoxon test otherwise. Comparisons between multiple groups were done by linear models or by the Kruskal-Wallis rank sum test accordingly. Categorical data are analyzed by the Fisher's exact test.

Results

Baseline Characteristics

Between July 2010 and March 2019, a total of 655 patients >34 week of gestation with suspected or present PE from our clinic were included in the analysis. Within 2 weeks, a total of 219 patients (33.4%) developed AOs; in 197 (30.0%) cases, both mother and fetus were affected; and in 22 (3.3%) cases, only the mother developed AO. During the study period, one fetal death occurred. PE was diagnosed in 251 women (38.3%), FGR in 40 (6.1%), and both in 23 (3.5%). The frequency of each AO is shown in online supplementary Table S1 (for all online suppl. material, see https://doi.org/10.1159/000529781). The maternal characteristics of patients with and without AOs are compared in Table 1. In the

Table 1. Baseline characteristics of the study population with and without AO

Variable	*n* No AO	*n* AO	mean ± SD No AO	mean ± SD AO	*p*
Age	436	219	32.3±5.8	32.0±6.4	= 0.538 n.s.
Height, cm	436	217	166±7	166±6	= 0.490 n.s.
Prepregnancy weight, kg	432	218	75.4±19.2	73.7±18.6	= 0.274 n.s.
Prepregnancy BMI, kg/cm^2	432	217	27.4±6.7	26.9±6.5	= 0.350 n.s.
Birth weight	436	218	3,148±553	2,594±671	<0.001 ***
Proteinuria, mg/dL	168	91	987±2,694	1,231±2,679	= 0.486 n.s.
Systolic blood pressure	405	203	135±22	139±22	= 0.028 *
Diastolic blood pressure	405	203	83.5±14.5	85.7±15.4	= 0.090 +
UtA mean PI	234	129	0.98±0.40	1.18±0.44	<0.001 ***
MCA PI	98	80	1.55±0.40	1.52±0.39	= 0.530 n.s.
UA PI	417	204	0.867±0.181	0.988±0.248	<0.001 ***
sFlt-1	436	219	4,780 (3,042/7,867)	6,770 (3,655/10,931)	<0.001 ***
PlGF	436	219	122 (76/239)	92 (50/167)	<0.001 ***
sFlt-1/PlGF	436	219	45 (14/88)	85 (30/178)	<0.001 ***

n, number of cases; SD, standard deviation; BMI, body mass index; UtA PI, uterine artery pulsatility index; MCA PI, middle cerebral artery pulsatility index; UA PI, umbilical arterial pulsatility index; sFlt-1, soluble fms-like tyrosine kinase 1; PlGF, placental growth factor; *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$; n.s., not significant; adj., adjusted; +$p < 0.10$. Statistical significance with $p < 0.001$.

group of patients with AOs, a lower birth weight as well as increased uterine and umbilical artery pulsatility indices were noted ($p < 0.001$). However, other diagnostic markers such as elevated liver enzymes ($p = 0.723$) and low platelet count ($p = 0.503$) did not differ statistically in the groups. No correlation was found between the occurrence of PE-associated symptoms such as weight gain ($p = 0.783$), progressive edemas ($p = 0.371$), epigastric pain ($p = 0.655$), headache ($p = 0.187$), visual blurring ($p = 0.084$), and the subsequent development of AOs. Women who developed an AO gave birth earlier than women without AO (36+3 [35+2/37+3] vs. 38+2 [37+2/39+2], $p < 0.001$).

Predictive Performance of the Model

AO was predicted by multivariable and univariable logistic regression models. In the univariable model, the umbilical artery pulsatility index showed the highest predictive impact with an OR of 7.26 ($p < 0.001$). Univariable regression analysis also demonstrated a significant contribution from new onset of hypertension (OR, 1.47; $p = 0.021$), sFlt-1/PlGF ratio (OR, 1.03; $p < 0.001$), proteinuria (OR, 1.57; $p = 0.010$), systolic (OR, 1.12; $p = 0.004$) and diastolic blood pressure (OR, 1.14; $p = 0.026$), preexisting kidney disease (OR 1.67; $p = 0.405$), progressive edemas (OR, 1.3; $p = 0.380$), elevated liver enzymes (OR, 1.17; $p = 0.649$), low platelet count (OR, 1.24; $p = 0.512$), and age >40 (OR, 1.33; $p = 0.386$) in prediction of AOs.

Using multivariable logistic regression analysis, umbilical artery pulsatility index (OR, 5.93; $p < 0.001$), preexisting kidney disease (OR, 7.24; $p = 0.047$), progressive edemas (OR, 2.14; $p = 0.038$), new onset of hypertension (OR, 1.17; $p = 0.556$) as well as upper abdominal pain (OR, 1.57; $p = 0.207$) showed a relevant predictive impact. Summary of multivariable and univariable logistic regression models is shown in Figure 1.

As expected, the full model had the best predictive performance for AOs with AUC of 72.6%, which corresponds to a sensitivity of 73.3% and specificity of 66.0%. The PPV of the full model was 51.4%, and NPV was 83.5%. The anamnestic risk factors did not influence the predictive performance of a model ($p = 0.335$). ROC curve comparison showed significantly greater ($p < 0.001$) predictive performance of the full model over sFlt-1/PlGF ratio alone (AUC 65.6%) and the model containing blood pressure and proteinuria (AUC 58.3%). Comparison of the predictive values of the full model with reduced models is shown in Table 2.

Change of the Risk Category by Applying the Regression Model

We compared the predictive performance of the model with the performance of the sFlt-1/PlGF ratio alone at the cutoffs <38 (low risk) and ≥38 (high risk) (Fig. 2). When comparing the two models, the kappa was 0.5478338. We first looked at patients who did not experience AOs

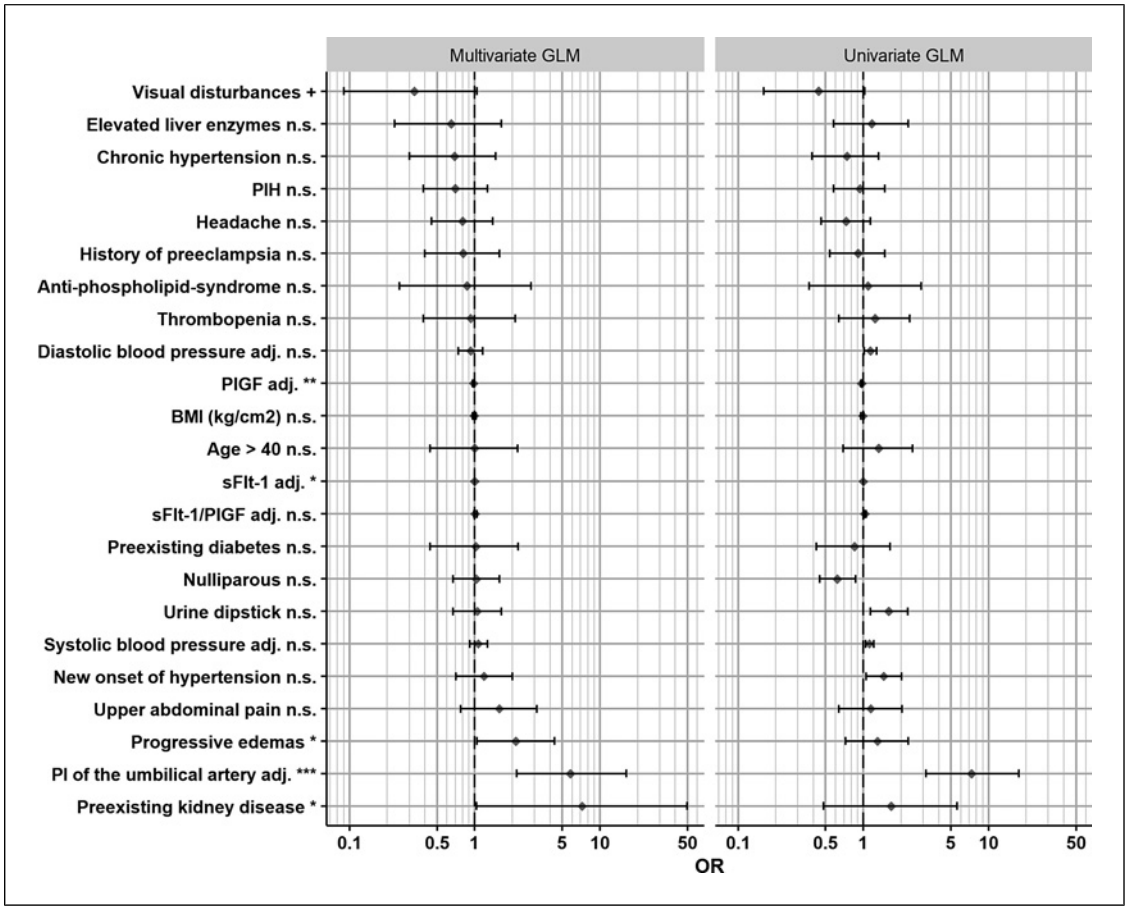

Fig. 1. Comparison of OR of selected risk factors in multivariable and univariable logistic regression models. *p < 0.05; **p < 0.01; ***p < 0.001; +p < 0.10. OR, odds ratio; Pl, pulsatility index; sFlt-1, soluble fms-like tyrosine kinase 1; PlGF, placental growth factor; n.s., not significant; adj., adjusted.

Table 2. Comparison of predictive performance of the full model and reduced models

Model	AUC (CI)	Specificity	Sensitivity	NPV	PPV	p versus full model
Full model	72.6% (68.0–77.2)	66.0%	73.3%	83.5%	51.4%	
Reduced model	72.3% (67.6–76.9)	65.8%	73.9%	83.7%	51.4%	0.335
Reduced model based on p = 0.1	70.8% (66.0–75.5)	67.9%	66.7%	80.6%	50.4%	0.063
sFlt-1/PlGF alone	65.6% (60.6–70.7)	71.7%	57.2%	77.4%	49.8%	0.001
BP + Proteinuria	58.3% (53.2–63.4)	73.6%	42.2%	72.3%	43.9%	0.001

NPV, negative predictive value; AUC, area under the curve; PPV, positive predictive value; sFlt-1, soluble fms-like tyrosine kinase 1; PlGF, placental growth factor; BP, blood pressure. Statistical significance with p < 0.001.

(Fig. 2a). 90 patients (24.5%) who did not experience AOs but were classified as high risk by sFlt-1/PlGF ratio (≥38) were correctly classified by the regression model. In the group without AO, in 153 (41.6%) patients, both the regression model and sFlt-1/PlGF ratio <38 correctly classified patients into the low-risk group. The classification in the high-risk group was incorrect in 112 (30.4%) cases, both by our model and by the sFlt-1/PlGF ratio

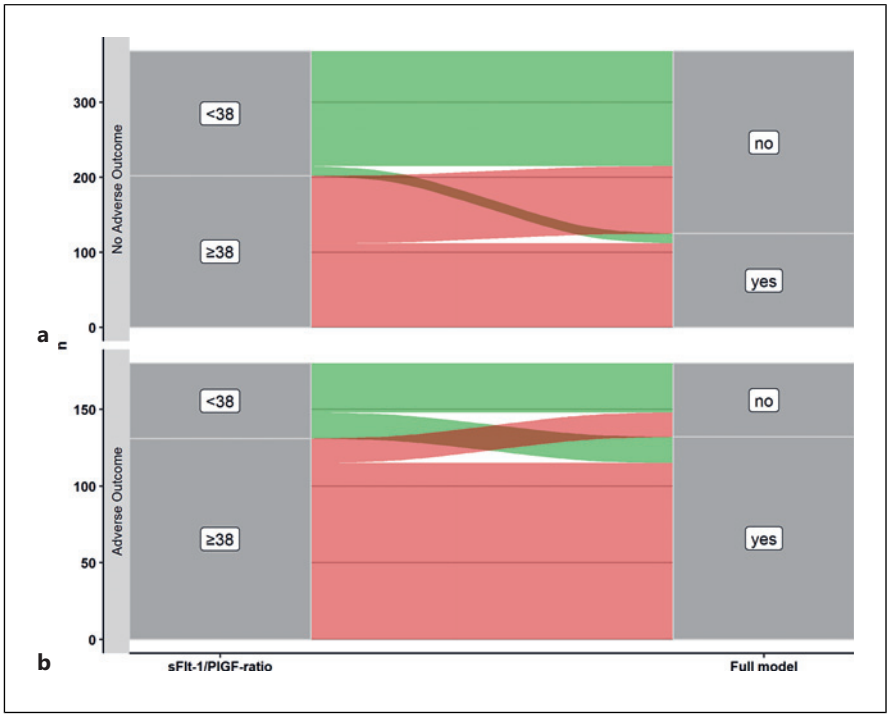

Fig. 2. Comparison of the full model and sFlt-1/PlGF ratio with a cutoff value of 38 in cohorts with and without AOs. Patients with a sFlt-1/PlGF ratio ≥38 were classified as high risk and with sFlt-1/PlGF ratio <38 as low risk. Each color symbolizes a cutoff value of sFlt-1/PlGF ratio: red ≥38 and green <38. *N* indicates the number of cases in each group. **a** The lines show differences between the prediction of AOs by the sFft-1/PlGF ratio and the full model in the group without AOs. **b** The lines show differences between the prediction of AOs by the sFft-1/PlGF ratio and the full model in the group with AOs.

≥38. In 13 (3.5%) cases, the sFlt-1/PlGF ratio <38 alone was a better predictor of AOs than the full model.

We next looked at patients with AO (Fig. 2b). Here, the regression model correctly classified 17 patients (9.4%) who had been classified as low risk when only considering their sFlt-1/PlGF ratio <38. In the AO group, in 115 (63.9%) patients, both the regression model and sFlt-1/PlGF ratio ≥38 correctly classified patients into the high-risk group. In 32 (17.8%) cases, both the full model and the sFlt-1/PlGF ratio <38 incorrectly qualified the patients as the low-risk group. The sFlt-1/PlGF ratio ≥38 in AO group was more accurate than our model in 16 (8.9%) cases.

In Figure 3, we compared the predictive performance of the model with the performance of the sFlt-1/PlGF ratio alone at the cutoffs <38 (low risk), 38–110 (intermediate risk), and ≥110 (high risk). In the group without AOs (Fig. 3a), the regression model correctly classified 80 patients (21.7%) as low risk who had been classified as intermediate risk and 10 patients (2.7%) labeled as high risk based on their sFlt-1/PlGF ratio. The classification in the high-risk group was incorrect in 54 (14.7%) cases, both by our model and by the sFlt-1/PlGF ratio >110. In 58 (15.8%) cases, the sFlt-1/PlGF ratio between 38 and 110 classified patients into the intermediate-risk group, while the regression model incorrectly placed them in the high-risk group. In the group with AOs (Fig. 3b), 38 patients (21.1%) who had been classified as intermediate risk based on their sFlt-1/PlGF ratio were correctly categorized as high risk by the regression model. The regression model and sFlt-1/PlGF ratio ≥110 in the AO group achieved the same results in 77 (42.8%) of cases. The sFlt-1/PlGF ratio categorized 13 (7.2%) women in the intermediate-risk group, while our model incorrectly placed them in the low-risk group. Furthermore, in 3 (1.7%) cases, the sFlt-1/PlGF ratio >110 was a better predictor of AOs than the full model.

Discussion

Main Findings

The objective of our study was to compare the predictive performance of the sFlt-1/PlGF ratio alone or as part of a regression model for PE-related maternal and fetal AOs within 2 weeks in women presenting women with signs and symptoms of a PE or a diagnosis of a PE >34 weeks of gestation. The main result of our study is that a multi-marker regression model including the sFlt-1/PlGF ratio which is superior to sFlt-1/PlGF ratio or standard clinical measurements such as hypertension and proteinuria alone. The full model achieved AUC of 72.6%, which corresponds to a sensitivity of 73.3% and specificity of 66.0%, while the sFlt-1/PlGF ratio alone had AUC of

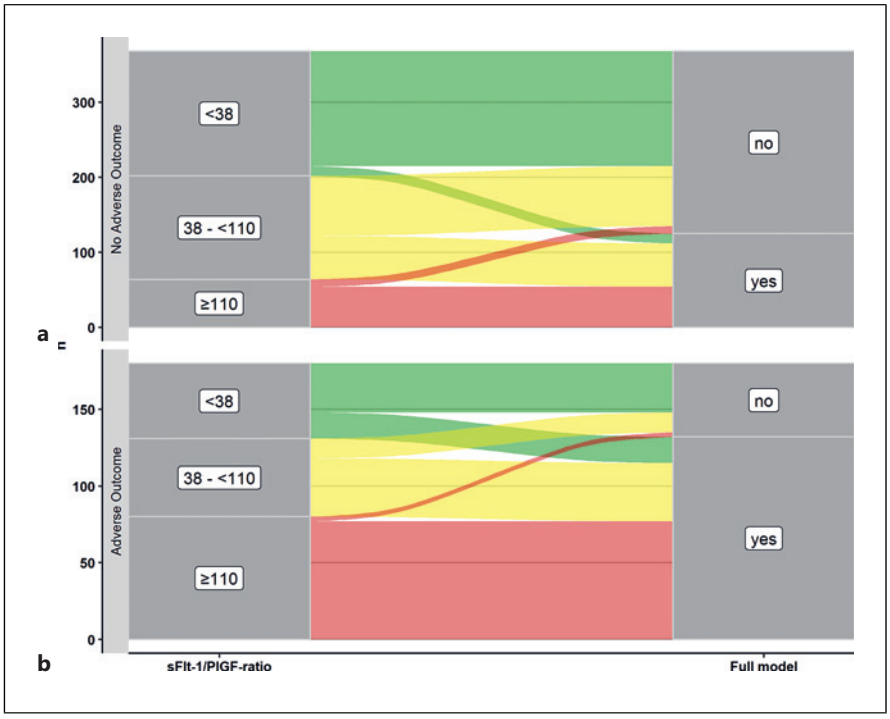

Fig. 3. Comparison of the full model and sFlt-1/PlGF ratio with cutoff values of <38, 38–110, and ≥110 in cohorts with and without AOs. Patients with a sFlt-1/PlGF ratio <38 were classified as low risk, sFlt-1/PlGF ratio between 38 and 110 was defined as intermediate risk, and a sFlt-1/PlGF ratio ≥110 as high risk. Each color symbolizes a cutoff value of sFlt-1/PlGF ratio: red ≥110, yellow 38–110, and green ≤38. *N* indicates the number of cases in each group. **a** The lines show differences between the prediction of AOs by the sFft-1/PlGF ratio and the full model in the group without AOs. **b** The lines show differences between the prediction of AOs by the sFft-1/PlGF ratio and the full model in the group with AOs.

65.6%, corresponding to a sensitivity and specificity of 57.2% and 71.7%, respectively. We were able to show that the regression model correctly classified additional 24.5% of the patients who did not experience an AO but were classified as being at risk based on the sFlt-1/PlGF ratio ≥38 alone. Moreover, the regression model correctly excluded a risk for an AO in 2.7% of patients, despite having a cutoff value of sFlt-1/PlGF ratio ≥110. In total, 17 patients (9.4%) with an sFlt-1/PlGF ratio <38 and AO were correctly classified with our regression model. The regression model significantly decreased the false-positive rate but did not significantly improve PPV.

Results in Context of the Literature

Multi-marker regression models, including the combination of risk factors, assessment of the sFlt-1/PlGF ratio, and other clinical tests to predict PE-related AOs, have been investigated in a multitude of studies [22–32]. In a prospective study of n = 616 women, Rana et al. reported that a cutoff value of the sFlt-1/PlGF ratio of 85 shows an AUC of 89% when predicting maternal and perinatal AOs within 2 weeks. Combining proteinuria, hypertension, and the sFlt-1/PlGF ratio as predictors for an AO increased the AUC to 92% in this study [33]. The use of sFlt-1/PlGF ratio as predictor in our investigation lead to an AUC of 65.6%, while our full model that included sFlt-1/PlGF ratio, risk factors, symptoms, and umbilical artery resistance parameters achieved an AUC of 72.6%. However, Rana et al. included patients <34 weeks of gestation, while we focused on patients presenting >34 weeks. The PROGNOSIS study validated a cutoff value of 38 of the sFlt-1/PlGF ratio to rule development of a PE and/or PE-related maternal and/or fetal complications in or out: In a prospective multicenter design, n = 1,050 patients with suspected of PE after 20 weeks of gestation were enrolled, angiogenic biomarkers reached an AUC of 86%, which corresponded to a sensitivity of 65.5% and specificity of 90%. The PPV was 65.5% and NPV was 90% [15]. The present study that investigated only women after 34 weeks of gestation showed inferior results of the sFlt-1/PlGF ratio alone when predicting AOs, but our full model obtained comparable results with an AUC of 72.6%, specificity of 66.0%, sensitivity of 73.3%, PPV of 51.4%, and NPV of 83.5%, respectively. However, the endpoint in PROGNOSIS was PE and not AOs and also included patients <34 weeks of gestation. Furthermore, the definition of AOs varied slightly between studies. In the PROGNOSIS study, maternal AOs additionally include PE and cerebral thrombosis, and fetal AOs include delivery at <34 weeks of gestation and intrauterine growth restriction.

Dröge et al. have recently demonstrated that a multimarker regression model including maternal and fetal factors, other clinical tests, and angiogenic biomarkers

improved the predictive accuracy in prediction of AOs compared to the use of sFlt-1/PlGF ratio alone. This retrospective that stems from the same database as the current study involved 1,117 pregnant women at high risk of PE throughout gestation. Their regression model predicted maternal and fetal adverse events with the best accuracy of 88.7% as compared to 85.7% by sFlt-1/PlGF ratio alone [18]. However, also there the focus was overall gestational range from 20 weeks – term. Moreover, one of the criteria for AOs was delivery before 34 weeks of gestation.

In a prospective multicenter study, van Dadelszen et al. have shown that the FullPIERS model (Preeclampsia Integrated Estimate of Risk) achieved an AUC of 88% for prediction of maternal AOs. This study involved 2023 pregnant women with clinical PE, while in our study, a major part of the patients were those who were at high risk of PE [34].

Strengths and Limitations

Our analysis relies on real-world data. On the one hand, the results of our study better represent the heterogeneity of patients in the clinical routine. On the other hand, all clinical data including the sFlt-1/PlGF ratio were available to the attending physicians and might have contributed to treatment bias and confounding. Though the sFlt-1/PlGF ratio alone is not used as an indication for delivery, it may have influenced clinical decision-making. We measured the sFlt-1/PlGF ratio on the Elecsys® platform. It is noteworthy that the cutoff values may differ using assays from other platforms [35].

Strength is the rigorous definition of our cohort. We limited the analysis to late-onset PE with an available outcome within 14 days from presentation. As a result, we describe a true late PE high-risk cohort. PE occurred in 38.3% of the studied patients, which is a higher rate than the most high-risk cohorts including the PROGNOSIS study, where 19% of patients developed PE. Adverse events also affected a greater percentage of our study population than in the PROGNOSIS study. AOs occurred in 219 of patients out of 655 women (33.4%) with suspected PE, while in PROGNOSIS, only 18% of women at high risk for PE had an AO. This may indicate a selection bias due to the real-word data nature of the database.

Conclusion

It is well established that the sFlt-1/PlGF ratio, which is an excellent predictor for early-onset PE and associated AOs, has a lower predictive performance in late-onset PE [13, 36, 37]. Late-onset disease is more frequent, and even though it shows milder clinical courses in most cases, AOs can still be devastating. The lower predictive accuracy of the standard clinical tools in late-onset PE, especially for predicting PE-related AOs, causes a diagnostic dilemma with unnecessary interventions on the one hand side and unexpectedly severe AOs on the other hand [38, 39]. In a large cohort of women with suspected disease after 34 weeks, we have shown that integrating available routine clinical information including the sFlt-1/PlGF ratio into a multimarker regression model had an improved predictive accuracy for late AOs as compared to the sFlt-1/PlGF ratio or other clinical markers such as hypertension and proteinuria alone. A full integration of all available clinical data into algorithms, ideally deployed in automated decision support tools, has the potential to improve decision-making and therefore reduce maternal and fetal morbidity and mortality.

Acknowledgments

We thank our doctoral students for their contribution in collecting data and all patients for their confidence.

Statement of Ethics

This study protocol was reviewed and approved by the Ethics Committee of the Charité, approval number EA1_252_19. The need for informed consent was waived by the Ethics Committee of the Charité.

Conflict of Interest Statement

Stefan Verlohren received speaker fees and participated in advisory boards from Roche Diagnostics, ThermoFisher, and Alexion. All other authors do not report any conflicts of interest.

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Author Contributions

Stefan Verlohren and Lisa-Antonia Lorenz-Meyer contributed to the concept and design of the study. Stefan Verlohren and Dorota Sroka collaborated in drafting the article and edited and reviewed the final version. Andreas Busjahn

conducted the statistical analysis and collaborated in drafting the article. Valerie Scherfeld and Julie Thoma collected data. Stefan Verlohren and Wolfgang Henrich provided overall guidance. All authors performed a critical revision of the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material files. Further inquiries can be directed to the corresponding author.

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