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Should angiogenic markers be included in the diagnostic criteria of superimposed pre-eclampsia in women with chronic hypertension?

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What are the novel findings of this work?

The addition of angiogenic markers to the conventional diagnostic criteria proposed by the ISSHP improves detection rates of superimposed preeclampsia, as well as shows a high positive and negative predictive value in predicting adverse maternal outcomes in pregnant women with chronic hypertension and suspected superimposed preeclampsia.

What are the clinical implications of this work?

This study proves the clinical usefulness of angiogenic marker assessment in women with suspected superimposed preeclampsia and proposes the inclusion of their evaluation as a diagnostic criterion for superimposed preeclampsia. The routine use of angiogenic marker should be considered in guidelines on chronic hypertension in pregnancy.

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ABSTRACT

Background: Even though the most recent guidance by the International Society for the Study of Hypertension in Pregnancy (ISSHP) has highlighted the role of angiogenic markers in the diagnosis of preeclampsia in women with chronic hypertension, it has withheld recommending its implementation due to the limited available evidence in this group of women. Therefore, we aimed to evaluate sFlt-1 (soluble fms like kinase 1) and PlGF (placental growth factor) in women with suspected superimposed preeclampsia.

Methods: The study included 142 pregnant women with chronic hypertension. Women with chronic hypertension and singleton pregnancies with suspected superimposed preeclampsia were included. Preeclampsia was suspected in women presenting with symptoms of superimposed preeclampsia including worsening hypertension, epigastric pain, new-onset edema, dyspnea or neurological symptoms. The exclusion criteria were those who delivered within one week of assessment due to reasons other than preeclampsia, chronic kidney disease, history of cardiac disease, pregnancies with aneuploidy, genetic syndromes or major structural fetal anomalies or those with missing pregnancy outcomes. Maternal serum angiogenic markers were measured. The primary outcome was the utility of angiogenic markers for the diagnosis of superimposed preeclampsia. The diagnostic accuracy was assessed for different time points including within one week of assessment and any time before birth. The secondary outcome was comparison of maternal and perinatal adverse outcomes in superimposed preeclampsia diagnosed according to ISSHP traditional criteria and an extended criteria including angiogenic markers. The accuracy of each marker was assessed using receiver operating characteristics curves. Area under the curve (AUC) values were compared using De Long's test. A sensitivity analysis was planned for gestational age at assessment. Diagnostic accuracy of various variables for predicting composite adverse maternal and perinatal outcomes was assessed using binominal regression.

Results: 25 (17.6%) developed preeclampsia within one week of assessment, 52 (36.6%) developed preeclampsia at any time point before birth and 90 women (63.4%) delivered without preeclampsia. The predictive accuracy of maternal serum sFlt-1/PlGF ratio was superior to PlGF levels (AUC 0.91 vs 0.86, *P*=0.032) for superimposed preeclampsia within one week of assessment. The addition of angiogenic imbalance to traditional ISSHP diagnostic criteria was associated with increase in detection rate (35.1%, 95% credible interval: 16.6 – 53.6%), positive (9.6%, 95% credible interval: 0.0 – 20.6%) and negative predictive value (3.1%, 95% credible interval: 1.3 – 4.9%) for adverse maternal outcomes with high posterior probability (>99.9%, 95.6% and >99.9%, respectively) without a meaningful decrease in specificity. Maternal serum angiogenic imbalance was significantly associated with diagnosing superimposed preeclampsia within one week of assessment according to the ISSHP criteria ($p<0.001$).

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Conclusions: The addition of maternal serum angiogenic markers to the traditional diagnostic criteria significantly improved the sensitivity for predicting adverse outcomes. Implementation of angiogenic markers in chronic hypertension should therefore be considered.

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INTRODUCTION

Preeclampsia is a multisystem disorder that complicates approximately 3% of all pregnancies[1]. The diagnosis is based on raised blood pressure, as well as, symptoms and laboratory parameters related to the affected organ systems, such as proteinuria, low platelet count, visual symptoms, headaches, or seizures. The symptoms of preeclampsia are often non-specific and range from typical pregnancy related symptoms such as edema to upper abdominal pain, masking the onset of this life threating disease[2]. Hence, making a precise diagnosis can be challenging, especially when the diagnostic criteria of preeclampsia vary among the various national and international guidelines[3,4]. Recently, Lai *et al.* proposed a broader definition of preeclampsia, including angiogenic markers such as soluble fms-like tyrosine kinase-1 (sFlt-1) or placental growth factor (PlGF), which are more sensitive for the detection of maternal and neonatal adverse outcomes[5]. However, the superiority of one criterion over another or the optimal cut-offs of each angiogenic marker are yet to be determined, especially in high-risk groups such as in women with chronic hypertension[6-8].

The incidence of preeclampsia in women with chronic hypertension is up to 6-fold higher compared to normotensive women[9-11]. Proteinuria is the most common sign of organ dysfunction found in women affected by superimposed preeclampsia. Nevertheless, the diagnostic proteinuria cut-off is the same for all pregnant women whether affected by chronic hypertension or not[12]. The relevance of the arbitrary thresholds for proteinuria or change in baseline protein levels for diagnosing preeclampsia in pregnant women with chronic hypertension is debatable and more sensitive markers are desired[8,12]. Several studies evaluated the predictive accuracy of angiogenic markers for ruling-in preeclampsia[13-18]. However, the number of women with chronic hypertension or chronic kidney disease included in these studies was limited and various definitions of preeclampsia were used. Small sample sizes and methodological heterogeneity limit the applicability of these findings to women with chronic hypertension. A recent expert review highlighted the need for further studies in this field and the role of angiogenic markers for diagnosing preeclampsia in women with chronic hypertension[8]. The most recent International Society for the Study of Hypertension in Pregnancy (ISSHP) guideline also underlined that angiogenic markers could be beneficial for the diagnosis of superimposed preeclampsia but withheld a recommendation due to lack of sufficient evidence[3]. Even though the National Institute for Health and Care Excellence (NICE) guideline recommends PLGF testing for ruling out preeclampsia between 20 weeks and 34 weeks plus 6 days for women with chronic hypertension and suspected preeclampsia, it does not support diagnosing preeclampsia on the basis of PLGF testing[19].

This study aimed to assess the diagnostic performance of angiogenic markers in women with chronic hypertension. Furthermore, we aimed to compare adverse maternal and perinatal outcomes in women with superimposed preeclampsia according to existing guidelines or angiogenic marker-based diagnosis.

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METHODS

This was a retrospective analysis of prospectively collected data recorded in an electronic database (Viewpoint 5.6.8.428, Wessling, Germany) between January 2013 and October 2019. The study was approved by the local research ethics committee (approval number 1882/2018) of the Medical University of Vienna. No written informed consent for study participation was required.

The inclusion criteria were defined as women with chronic hypertension and singleton pregnancies with suspected superimposed preeclampsia during the antenatal period. Preeclampsia was suspected in women presenting with symptoms of superimposed preeclampsia including worsening hypertension, epigastric pain, new-onset edema, dyspnea or neurological symptoms (headache, visual symptoms etc.). Those who delivered within one week of assessment due to reasons other than preeclampsia (spontaneous preterm delivery, post-term induction or elective delivery for reason unrelated to preeclampsia, etc.), chronic kidney disease, history of cardiac disease, pregnancies with aneuploidy, genetic syndromes or major structural fetal anomalies were excluded. Women who did not deliver at the Department of Obstetrics and Fetomaternal Medicine at the Medical University of Vienna were also excluded due to missing detailed outcome parameters. As part of the routine assessment in women with suspected superimposed preeclampsia a blood sample was taken of all study participants by venipuncture and stored in a collection tube without anticoagulants to analyze maternal serum levels for sFlt-1, PlGF and their ratio. The angiogenic marker concentrations were assessed in parallel by commercially available fully automated assays on Elecsys® (Roche Diagnostics, Penzberg, Germany) platform. The analysis was undertaken by biomedical technicians, who were blinded to all clinical details, but the results were available to the healthcare professionals.

Chronic hypertension was diagnosed in women with high blood pressure (systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg) predating pregnancy or recognized prior to 20 weeks of gestation, use of antihypertensive medications before pregnancy or persistence of hypertension for >12 weeks after delivery[20]. Superimposed preeclampsia was defined according to the revised criteria of the International Society for the Study of Hypertension in Pregnancy (ISSHP) in 2018[3]. The diagnosis of superimposed preeclampsia was made when one or more of the following features of preeclampsia were present: new-onset significant proteinuria, acute kidney injury (creatinine ≥1mg/dL), elevated liver enzymes (transaminase levels >40 IU/L), low platelet count (<150.000/μL), or neurological symptoms of preeclampsia (i.e. persistent visual scotomata, altered mental status, blindness, stroke, hyperreflexia accompanied by clonus, severe headaches accompanied by hyperreflexia or eclampsia). Significant proteinuria was diagnosed with either protein/creatinine ratio (PCR) of ≥30mg/mmol or ≥300mg protein excretion in 24 hours. HELLP syndrome was defined as increased transaminases (aspartate aminotransferase and alanine aminotransferase concentrations > 2 × upper reference interval), reduced platelet count (<100,000/μL) plus at least one hemolysis criterion (increased lactate dehydrogenase concentration > 2 × upper reference intervals or serum indirect bilirubin concentration > 1.2

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mg/dL or reduced serum haptoglobin concentration < 0.3 g/L). Superimposed preeclampsia was not diagnosed solely based on worsening of hypertension or presence of fetal growth restriction (FGR).

The primary outcome of the study was the utility of angiogenic markers for the diagnosis of superimposed preeclampsia in patients with underlying chronic hypertension. The diagnostic accuracy was assessed for different time points including within one week of assessment and any time before birth. The secondary outcome was comparison of maternal and perinatal adverse outcomes in pregnant women with superimposed preeclampsia diagnosed according to ISSHP traditional criteria and an extended criteria including angiogenic markers. Maternal adverse outcomes included intensive care unit (ICU) admission, pulmonary edema, liver dysfunction, renal insufficiency, postpartum hemorrhage, seizures, and death. Adverse perinatal outcomes included stillbirth, neonatal death, preterm birth prior to 37 weeks' gestation due to superimposed preeclampsia, placental abruption, neonatal intensive care unit (NICU) admission, intraventricular hemorrhage, necrotizing enterocolitis, respiratory distress syndrome and ventilatory support. Suspected FGR was defined according to the ISUOG practice guideline for the diagnosis and management of small- for gestational age fetus and fetal growth restriction[21]. Neonatal birthweight centile was calculated using reference ranges reported by Poon *et al*.[22] Delivery due to superimposed preeclampsia was defined as women delivering due to maternal complications of preeclampsia including severe hypertension (≥170/110mmHg) despite two types of antihypertensive drugs, progressive thrombocytopenia, severe dyspnea, abnormal transaminase levels (aspartate aminotransferase and alanine aminotransferase concentrations > 2 × upper reference interval), HELLP syndrome, placental abruption and fetal compromise (abnormal fetal Doppler or abnormal cardiotocography).

Even though obstetricians were not blinded to the results of the sFlt-1/PlGF ratio, there was no local protocol recommending delivery based on increased sFlt-1/PlGF ratios nor diagnosing preeclampsia with angiogenic imbalance only at the time of the study period.

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Statistical analysis

Continuous variables were represented as median and interquartile range or mean and standard deviation depending on distribution assumptions. Categorical variables were represented as number and percentage of total. The Shapiro-Wilk test and visual inspection of quantile-quantile plots were used for verifying normality of continuous variables. Mann-Whitney-U, t-test, chi-squared or Fisher-Freeman-Halton tests were used for group comparison where appropriate. Gestational age corrected Z-scores were obtained for angiogenic markers using polynomial regression equations published by Perry et al[23]. The accuracy of angiogenic markers for predicting diagnosis of preeclampsia was assessed with binominal logistic regression. Angiogenic markers' effect was adjusted for confounding variables in multivariable regression models. Confounder variables were associated with both angiogenic markers and outcome of interest without being on the causal pathway between the exposure and outcome. The accuracy of each marker was assessed using receiver operating characteristics curves and area under the curve (AUC) values. AUC values were compared using De Long's test. A sensitivity analysis was planned for gestational age at assessment. Diagnostic accuracy of various factors for predicting composite adverse maternal and perinatal outcomes was also assessed with binominal regression. Both Youden-index cut-off and Z-score cut off were tested. Accuracy parameters were compared using a Bayesian approach. The posterior probability of increase or decrease in diagnostic accuracy parameters were obtained using a Random-walk Metropolis Markov chain Monte Carlo algorithm. An uninformative Beta prior (parameters: 0.5, 0.5) and binomial likelihood function was used. The posterior effect magnitudes with 95% credible intervals were calculated. Posterior probabilities above 95% were considered high. Convergence was checked with trace plots. P values below 0.05 were considered statistically significant. All analyses were performed using R for Statistical Computing Software (Version 4.0.2).

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RESULTS

A total of 142 pregnant women with chronic hypertension were included in the study. Of those women, 25 (17.6%) developed preeclampsia within one week of assessment, whereas 52 (36.6%) women developed preeclampsia at any time before birth and 90 women (63.4%) delivered without preeclampsia (Table 1). There were no significant differences between the pregnancies with superimposed preeclampsia within one week, or those with superimposed preeclampsia at any time of assessment when, compared to those without regarding maternal age (*P*=0.901 and 0.647, respectively), parity (*P*=0.064 and 0.142, respectively), smoking (*P*=0.431 and 0.154, respectively), use of assisted reproduction (*P*=0.652 and 0.194, respectively) and gestational age at assessment (*P*=0.989 and 0.052, respectively).

The comparison of the pregnancies with superimposed preeclampsia and those without is shown in Table 1. Women who developed superimposed preeclampsia within one week or any time before birth had significantly higher mean arterial pressure (127.3 and 120.1 vs 110.3 mmHg, *P*<0.001, both), lower body-mass index (median 28.4, IQR 23.5-31.6 and 28.6, IQR 23.8-31.7 vs 31.2, IQR 26.6-40.4 kg/m^2, *P*=0.004 and p=0.001, respectively), higher rate of new-onset edema (24.0% and 25.0% vs 4.4%, *P*=0.002 and <0.001, respectively) and FGR (52.0% and 42.3% vs 0.0%, *P*<0.001 for both). Women who developed superimposed preeclampsia had significantly higher maternal serum sFlt-1 levels, lower PlGF levels and higher sFlt-1/PlGF ratios (P<0.001 for all). The majority of pregnant women in the study cohort were receiving antihypertensive treatment, with no significant difference between those who developed preeclampsia and those who did not (p>0.05). However, women who developed superimposed preeclampsia were more likely to have severe hypertension (both systolic and diastolic; p<0.01 for both) (Table 1).

The values of angiogenic markers on raw scale, log scale and Z-scores, as well as their comparison, are shown in Table 1. Plots of the maternal serum angiogenic marker values in relation to the gestational age at assessment in women who developed superimposed preeclampsia and those who did not are shown in Figure S1. The plots include polynomial regression lines for expected mean, prediction intervals and equations for normal and abnormal ranges.

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Predictive accuracy of angiogenic markers for superimposed preeclampsia

Binomial regression models demonstrated that maternal serum sFlt-1/PlGF ratio, PlGF and sFlt-1 levels were all associated with the risk of superimposed preeclampsia within one week of assessment and preeclampsia at any time before birth (Table 2, P <0.001 for all). These associations remained statistically significant ($p<0.05$) even after adjusting for confounder variables such as body-mass index, smoking, mean arterial pressure and presence of FGR (Table 2). The AUC value of maternal serum sFlt-1/PlGF ratio was superior to PlGF levels (AUC: 0.91 vs 0.86, *P*=0.032) and similar to sFlt-1 levels (AUC: 0.92 vs 0.91, *P* =0.673) for predicting preeclampsia within one week of assessment. The AUC value of maternal serum sFlt-1/PlGF ratio Z-score was similar to PlGF levels (AUC: 0.87 vs 0.84, *P*=0.097) and sFlt-1 levels (AUC: 0.87 vs 0.86, *P*=0.514) for the same outcome (Figure 1a and 1b). The AUC value of maternal serum sFlt-1/PlGF ratio was similar to PlGF levels (AUC: 0.86 vs 0.83, *P*=0.257) and superior to sFlt-1 levels (AUC: 0.86 vs 0.78, *P*=0.006) for predicting superimposed preeclampsia at any time prior to birth (Figure 2a). However, the AUC value of maternal serum sFlt-1/PlGF ratio Z-score was superior to PlGF levels (AUC: 0.88 vs 0.84, *P*=0.017) and similar to sFlt-1 levels (AUC: 0.88 vs 0.85, *P*=0.133, Figure 2b). Gestational age corrected Z-scores had significantly higher AUC values for predicting superimposed preeclampsia at any time, while uncorrected raw values had higher AUC values for predicting preeclampsia within one week of assessment (Figure 1a and 2b). Overall, the maternal serum sFlt-1/PlGF ratio offered higher predictive accuracy compared to PlGF alone. The optimal cut-off of sFlt-1/PlGF ratio was 70 according to Youden index. We performed a sensitivity analysis for patients who were assessed prior to or after 32 weeks' gestation using various sFlt-1/PlGF cut-offs. The cut-off was chosen due to increase in normal sFlt-1/PlGF ratios starting from 32 weeks' gestation (Figure S1a). The change of other angiogenic markers over gestational weeks is available in Figure S1b and S1c. There was no significant change in accuracy using higher sFlt-1/PlGF ratio cut-offs (85 or 110) prior to or after 32 weeks' gestation (Table S1 and S2). However, maternal serum sFlt-1/PlGF ratio performed better at predicting preeclampsia within one week of assessment prior to 32 weeks compared to above 32 weeks (Table S1).

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Role of angiogenic markers for predicting adverse outcomes

Women with angiogenic imbalance at time of assessment, i.e. sFlt-1/PlGF ratio above the 97.5th centile, new-onset proteinuria and FGR were compared to pregnancies without proteinuria, angiogenic imbalance and pathological fetal growth, i.e. controls (Table 3). Women with angiogenic imbalance had significantly higher rates of maternal ICU admission (12.5% vs 0.0, *P*=0.003) and composite adverse maternal outcomes (21.9% vs 3.2%, P<0.001) compared to controls. Women with new-onset proteinuria had significantly higher rates of renal insufficiency compared to controls (14.3% vs 0.0%, P=0.008). The rate of adverse maternal outcomes did not differ between pregnancies with FGR and controls (P>0.05 for all, Table 3). Most perinatal outcomes including preterm birth due to preeclampsia, birthweight in grams, birthweight centile, NICU admission, respiratory distress, ventilatory support, stillbirth or neonatal death were significantly worse in women with angiogenic imbalance, new-onset proteinuria or FGR compared to controls (p<0.05 for all) (Table 3). Composite adverse perinatal outcomes were significantly worse in women with angiogenic imbalance, new-onset proteinuria or FGR compared to controls (75.0%, 64.3%, 68.8% vs 10.6%, respectively, P<0.001 for all). The standalone accuracy of angiogenic imbalance compared to new-onset proteinuria or FGR for predicting adverse perinatal or maternal outcomes was similar or better (Figure S2). sFlt-1/PlGF ratio > 97.5th centile had a higher accuracy compared to new-onset proteinuria (effect magnitude: 8.4% higher, 95% CrI: -0.01 to 14.8%, posterior probability: 95.9%) and similar accuracy compared to FGR for predicting adverse perinatal outcomes (posterior probability <90%).

Additive value of angiogenic markers to traditional diagnostic criteria

We compared composite adverse perinatal and maternal outcomes in women who developed superimposed preeclampsia within one week of assessment according to traditional diagnostic criteria and angiogenic imbalance as added criterion (Table S2). The addition of angiogenic imbalance as diagnostic criterion improved the detection rate for adverse perinatal outcome by 20.6% (95% credible intervals: 0.0 – 42.2%) with a high posterior probability (96.9%). There was a corresponding drop in specificity of 5.7% (95% credible interval: -13.6 – 2.3%) with a posterior probability of 91.8%. The addition of angiogenic imbalance improved the detection rate (mean change: 35.1% increase, 95% credible interval: 16.6 – 53.6%), positive (mean change: 9.6% increase, 95% credible interval: 0.0 – 20.6%) and negative predictive value (mean change: 3.1% increase, 95% credible interval: 1.3 – 4.9%) for adverse maternal outcomes with high posterior probability (>99.9%, 95.6% and >99.9%, respectively) without a meaningful decrease in specificity (mean change: -2.4% decrease, 95% credible interval: -12.7 – 8.0%, posterior probability: 67.2%).

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DISCUSSION

Summary of the key findings

Maternal serum angiogenic imbalance was significantly associated with the risk of superimposed preeclampsia within one week of assessment according to the ISSHP criteria. Maternal serum sFlt-1/PlGF ratio appeared to be superior compared to PlGF levels alone. The predictive accuracy of maternal serum angiogenic markers was best for earlier gestational ages (prior to 32 weeks' gestation), and the accuracy dropped slightly with advancing gestation. The addition of maternal serum angiogenic markers to the traditional diagnostic criteria significantly improved the sensitivity for predicting adverse perinatal outcomes. Furthermore, when compared to the traditional diagnostic criteria, the addition of angiogenic imbalance significantly improved the sensitivity, positive and negative predictive values for adverse maternal outcomes. Finally, we did not find any conclusive evidence for proposing gestational age-specific thresholds.

Strengths and weaknesses of this study

This study includes a relatively large number of pregnant women with chronic hypertension compared to the available literature. Moreover, we used Bayesian analysis to allow interpretation of results with effect magnitudes and probabilities without the constraints of hypothesis testing and p values as the latter may be affected by inadequate sample size. However, higher numbers of participating women and a prospective study design would be preferable for future studies as our sample size may not have been enough to draw firm conclusions. All participating women were assessed by angiogenic markers as part of routine antenatal clinical care in women presenting with suspected superimposed preeclampsia. Clinicians were not blinded to the sFlt-1/PlGF values, potentially leading to interventions like earlier delivery due to high sFlt-1/PlGF ratios in some cases. However, the diagnosis of preeclampsia was not based on angiogenic markers and there was no institutional protocol or guideline recommending delivery based on the maternal serum angiogenic markers only. Nevertheless, we cannot exclude the possibility of intervention bias due to the retrospective nature of the study. The angiogenic markers were adjusted for possible confounders and the significant effect on the prediction of superimposed preeclampsia using the maternal serum angiogenic marker imbalance was demonstrated to be persistent. Finally, we were able to report an additive value of maternal serum angiogenic marker imbalance for predicting adverse maternal and perinatal outcomes compared to the traditional diagnostic criteria.

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However, our study has some limitations. First, the possibility of intervention bias, which was already mentioned earlier in the manuscript, cannot be ruled out in a retrospective study. However, an intervention (i.e., early delivery) based on elevated maternal serum levels of angiogenic markers would have reduced the predictive accuracy of angiogenic markers for diagnosing superimposed preeclampsia, which we could not confirm with our data. Nevertheless, an earlier delivery due to a high sFlt-1/PlGF ratio cannot be ruled out completely. Second, we did not assess the value of repeat measurement of angiogenic markers as longitudinal assessment was not included in this study. Finally, the utility of angiogenic markers in pregnant women with chronic hypertension near term is yet to be determined, as most of these pregnancies delivered at 37 weeks' gestation.

Interpretation of the study findings and comparison with existing literature

The most recent ISSHP guideline[3] highlighted the importance of angiogenic markers but withheld a recommendation for its routine clinical use in diagnosing women with preeclampsia in the light of insufficient evidence. Recently, the utility of the sFlt-1/PlGF ratio for the differential diagnosis of superimposed preeclampsia was evaluated in a small cohort study of 42 women with chronic hypertension. According to this study by Hernandez-Pacheco *et al*.[17], the ratio was useful for triaging women with chronic hypertension and differentiating between superimposed preeclampsia and uncontrolled hypertension. However, the predictive accuracy was not reported and pre-specified cut-off points were not described. Similar findings were reported by Minhas *et al.*[18], who showed a more pronounced degree of angiogenic imbalance in women with uncontrolled hypertension and increased levels in those who developed superimposed preeclampsia in a cohort of 78 pregnant women with chronic hypertension. However, pre-specified cut-offs were again not characterized. Two studies reported on the angiogenic marker kinetics during pregnancy and the postpartum period [13,20]. Saleh et al.[14] and Bramham et al.[24] have demonstrated that women with steeper increase in angiogenic markers were more likely to develop complications and superimposed preeclampsia. Our data agree with these findings and demonstrate that angiogenic imbalance is a good predictor for the development of superimposed preeclampsia. Furthermore, we described the added utility of angiogenic imbalance to the traditional diagnostic criteria of superimposed preeclampsia. Therefore, our findings provide evidence to support the usage of angiogenic marker imbalance as a diagnostic criterion for superimposed preeclampsia. German speaking countries already adopted the sFlt-1/PlGF ratio as a potential marker of organ dysfunction for the diagnosis and management of hypertensive disorders of pregnancy[25]. This approach is likely to be embraced by international societies as evidence accumulates.

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Clinical and Research implications

Angiogenic marker imbalance is considered as a significant advancement in preeclampsia research in the last decade. After the landmark papers by Rana *et al*.[26] and Karumanchi *et al*.[27]., subsequent research has underlined the essential role of angiogenic marker imbalance in the development of preeclampsia [24,25]. Observational data on clinical utility of the sFlt-1/PlGF ratio in high risk pregnancies such as in women with chronic hypertension are scarce due to the low incidence of the disease in women of childbearing age.

Although our study provides evidence in support of using angiogenic markers for the prediction and detection of superimposed preeclampsia, more studies focusing on high-risk groups such as women with chronic hypertension or renal insufficiency are needed. It is well known that angiogenic markers such as sFlt-1 and PlGF show diminished performance near term [26]. Pregnant women with chronic hypertension are unlikely to be the exception in this regard, however the available literature is inadequate to answer this question. Further studies to determine suitable cut offs for diagnosing superimposed preeclampsia close to term are warranted. Moreover, data on the longitudinal changes of angiogenic markers and their prognostic value especially in this high-risk group are lacking. Pregnancies in women with chronic hypertension suffer from high rates of placental insufficiency, FGR, maternal renal insufficiency and endothelial dysfunction, all known to potentially affect angiogenic marker levels and kinetics. Therefore, additional studies are needed to demonstrate the utility of the longitudinal assessment of angiogenic markers as prognostic markers for adverse maternal and perinatal outcomes.

Conclusions

Angiogenic imbalance is a useful marker for predicting a diagnosis of superimposed preeclampsia in women with chronic hypertension. Maternal serum sFlt-1/PlGF ratio seems to be better than PlGF alone. The addition of maternal serum sFlt-1/PlGF ratio appears to outperform the traditional diagnostic criteria. Furthermore, the ratio also seems to be an important marker in predicting maternal and perinatal outcomes in these high-risk pregnancies.

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FIGURE LEGENDS

Figure 1. The receiver operating characteristic curves of maternal serum soluble fms-like tyrosine kinase-1 (sFlt-1, long-dashed line), placental growth factor (PlGF, short-dashed line), sFlt-1/PlGF (straight line) ratio (a) and the Z-score of each variables (b) for diagnosing superimposed preeclampsia within one week of assessment.

The area under the curve (AUC) value of maternal serum sFlt-1/PlGF ratio was superior to PlGF levels (AUC: 0.91 vs 0.86, *P*=0.032) and similar to sFlt-1 levels (AUC: 0.92 vs 0.91, *P*=0.673). The area under the curve (AUC) value of sFlt-1/PlGF ratio Z-score was similar to PlGF levels (AUC: 0.87 vs 0.84, *P*=0.097) and sFlt-1 levels (AUC: 0.87 vs 0.86, *P*=0.514).

Figure 2. The receiver operating characteristic curves of maternal serum soluble fms-like tyrosine kinase-1 (sFlt-1, long-dashed line), placental growth factor (PlGF, short-dashed line), sFlt-1/PlGF (straight line) ratio (a) and the Z-score of each variables (b) for diagnosing superimposed preeclampsia at any time.

The area under the curve (AUC) value of maternal serum sFlt-1/PlGF ratio was similar to PlGF levels (AUC: 0.86 vs 0.83, *P*=0.257) and superior to sFlt-1 levels (AUC: 0.86 vs 0.78, *P*=0.006). The AUC value of sFlt-1/PlGF ratio Z-score was superior to PlGF levels (AUC: 0.88 vs 0.84, *P*=0.017) and similar to sFlt-1 levels (AUC: 0.88 vs 0.85, *P*=0.133).

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Table 1. Comparison of maternal, pregnancy characteristics, symptoms and maternal serum angiogenic markers at the time of assessment between women who developed superimposed preeclampsia within one week of assessment, any time before birth and those delivered without superimposed preeclampsia.

Variables	**Superimposed preeclampsia within one week of assessment (n=25)**	**Superimposed preeclampsia at any time (n=52)**	**Delivery without superimposed preeclampsia (n=90)**	***P*** [a,c]	***P*** [b,c]
Maternal age in years, mean ± SD	32.8 ± 5.3	32.6 ± 5.6	33.3 ± 6.2	.901	.647
Nulliparous, n (%)	14 (56.0)	25 (48.1)	32 (35.5)	.064	.142
Smoker, n (%)	4 (16.0)	7 (13.5)	21 (23.3)	.431	.154
Maternal body-mass index in kg/m^2, median (IQR)	28.4 (23.5-31.6)	28.4 (23.8-31.7)	31.7 (26.6-40.4)	.004	.001
Assisted reproduction, n (%)	4 (16.0)	6 (11.5)	18 (20.0)	.652	.194
Gestational age in weeks, median (IQR)	31.1 (25.1-35.4)	28.6 (24.6-33.0)	31.2 (25.7-35.5)	.989	.052
MAP in mm/Hg, median ± SD	127.3 ± 16.3	120.1 ± 15.5	110.3 ± 12.0	<.001	<.001
FGR, n (%)	13 (52.0)	22 (42.3)	0 (0.0)	<.001	<.001
New onset edema, n (%)	6 (24.0)	13 (25.0)	4 (4.4)	.002	<.001
New onset proteinuria, n (%)	6 (24.0)	12 (23.1)	2 (2.2)	<.001	<.001
Elevated liver enzymes, n (%)	0 (0.0)	1 (1.9)	0 (0.0)	NA	.780
Low platelets, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	NA	NA
Systolic blood pressure in mmHg				.001	<.001
• <140	4 (16)	9 (17.3)	41 (45.6)		
• 140-160	12 (48.0)	29 (55.8)	40 (44.4)		
• >160	9 (36.0)	14 (26.9)	9 (10.0)		
Diastolic blood pressure in mmHg				<.001	.007
• <90	2 (8.0)	10 (19.2)	37 (41.1)		
• 90-110	17 (68.0)	36 (69.2)	50 (55.6)		
• >110	6 (24.0)	6 (11.6)	3 (3.3)		
On antihypertensive medication at assessment	22 (88.0)	40 (76.9)	72 (80.0)	.359	.665
Dyspnea, n (%)	1 (4.0)	2 (3.8)	0 (0.0)	.491	.256
Neurological symptoms, n (%)	4 (16.0)	7 (13.5)	2 (2.2)	.006	.008
sFlt-1/PlGF ratio, median (IQR)	114.5 (58.1 – 273.4)	41.1 (11.2 – 119.3)	4.7 (2.13 – 10.6)	<.001	<.001
PlGF in pg/mL, median (IQR)	73.5 (39.2 – 98.4)	92.2 (52.8 – 186.1)	366.6 (216.8 – 532.9)	<.001	<.001

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Log sFlt-1 in pg/mL, median ± SD	8.68 ± 0.55	8.25 ± 0.74	7.46 ± 0.65	<.001	<.001
Log PlGF in pg/mL, median ± SD	4.22 ± 0.99	4.57 ± 1.08	5.81 ± 0.69	<.001	<.001
Log sFlt-1/ PlGF ratio, median ± SD	4.49 ± 1.33	3.69 ± 1.57	1.55 (0.76 – 2.36)	<.001	<.001
Log sFlt-1/PlGF ratio Z-score, median ± SD [d]	2.40 ± 1.49	1.84 ± 1.46	-0.05 ± 1.00	<.001	<.001
PlGF Z-score, median ± SD [d]	-2.39 ± 1.63	-1.91 ± 1.59	-0.02 ± 1.00	<.001	<.001
sFlt-1 Z-score, median ± SD [d]	3.07 ± 1.87	2.40 ± 1.77	-0.01 ± 1.03	<.001	<.001

[a] Developed superimposed preeclampsia within one-week vs delivery without superimposed preeclampsia
[b] Developed superimposed preeclampsia any time before birth vs delivery without superimposed preeclampsia
[c] Wilcoxon rank sum test, t-test, chi-squared test where appropriate
[d] Z-scores were calculated from a population of chronic hypertensive women who delivered without superimposed preeclampsia after 5% trimming of the dataset and natural log transformation of response variable to achieve normality. A quadratic polynomial line provided the best fit for each variable.

Values are represented as mean ± SD and median (Q1-Q3) for continuous variables with normal and non-normal distribution, respectively. Categorical variables are represented as n (%)

sFlt-1: soluble fms-like tyrosine kinase-1, PlGF: placental growth factor, FGR: fetal growth restriction, MAP: mean arterial pressure

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Table 2. Factors associated with diagnosis of superimposed preeclampsia within one week of assessment and at any time before delivery. Angiogenic markers were adjusted for confounder variables in multivariable regression models.

Variables	**Developed preeclampsia within one week**				**Developed preeclampsia at any time**			
	OR (95% CI)	***P*** [a]	**aOR (95% CI)**[b]	***P*** [a]	**OR (95% CI)**	***P*** [a]	**aOR (95% CI)**[b]	***P*** [a]
Maternal characteristics								
Maternal age in years	0.94 (0.60 – 1.45)	.780	-	-	0.88 (0.62 – 1.24)	.480	-	-
Nulliparous	2.41 (0.99 – 6.04)	.054	-	-	1.74 (0.87 – 3.52)	.118	-	-
Smoker	0.74 (0.20 – 2.16)	.608	-	-	0.51 (0.19 – 1.25)	.159	-	-
Maternal body-mass index in kg/m^2	0.49 (0.27 – 0.82)	.012	-	-	0.49 (0.32 – 0.73)	<.001	-	-
Conception method								
Natural conception	Reference		-	-	Reference		-	-
Assisted conception	1.62 (0.23 – 7.35)	.564	-	-	0.94 (0.19 – 3.76)	.936	-	-
Pregnancy characteristics **at the time of assessment**								
Gestational age in weeks	1.18 (0.77 – 1.85)	.451	-	-	0.71 (0.50 – 1.00)	.056	-	-
Use of antihypertensive drug	2.20 (0.69 – 9.79)	.227	-	-	0.83 (0.37 – 1.94)	.665	-	-
MAP in mm/Hg	3.59 (2.06 – 7.09)	<.001	-	-	2.19 (1.42 – 3.61)	<.001	-	-
FGR	13.0 (4.70 – 38.2)	<.001	-	-	65.3 (12.8 – 1193.8)	<.001	-	-

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New onset edema	3.04 (0.95 – 9.05)	.049	-	-	7.17 (2.37 – 26.7)	.001	-	-
***Angiogenic markers* at the time of assessment**								
sFlt-1/PlGF ratio, logs	7.65 (3.91 – 17.9)	<.001	7.16 (3.22 – 20.3)	<.001	6.08 (3.50 – 11.8)	<.001	5.74 (2.94 – 12.8)	<.001
PlGF in pg/mL, logs	0.21 (0.10 – 0.38)	<.001	0.24 (0.10 – 0.47)	<.001	0.18 (0.09 – 0.31)	<.001	0.17 (0.08 – 0.34)	<.001
sFlt-1 in pg/mL, logs	9.03 (4.24 – 23.7)	<.001	7.06 (3.19 – 20.1)	<.001	3.52 (2.26 – 5.80)	<.001	3.11 (1.79 – 5.81)	<.001
sFlt-1/PlGF ratio, Z-score [c]	2.55 (1.86 – 2.76)	<.001	2.61 (1.76 – 4.24)	<.001	3.52 (2.41 – 5.62)	<.001	4.32 (2.59 – 8.30)	<.001
PlGF in pg/mL, Z-score	0.39 (0.25 – 0.55)	<.001	0.40 (0.24 – 0.61)	<.001	0.31 (0.20 – 0.45)	<.001	0.28 (0.16 – 0.45)	<.001
sFlt-1 in pg/mL, Z-score	3.10 (2.11 – 4.94)	<.001	3.13 (1.98 – 5.51)	<.001	3.57 (2.41 – 5.78)	<.001	4.89 (2.71 – 10.4)	<.001

[a] Binomial logistic regression

[b] Adjusted for body-mass index, smoking, mean arterial pressure and presence of fetal growth restriction.

[c] Z-scores were calculated from a population of chronic hypertensive women who delivered without superimposed preeclampsia after 5% trimming of the dataset and natural log transformation of response variable to achieve normality. A quadratic polynomial line provided the best fit for each variable.

MAP: mean arterial pressure, FGR: fetal growth restriction, sFlt-1: soluble fms-like tyrosine kinase-1, PlGF: placental growth factor, OR: odds ratio, aOR: adjusted odds ratio, CI: confidence interval

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Table 3. Maternal and perinatal outcomes in pregnancies with angiogenic imbalance, new onset proteinuria, fetal growth restriction and those without at the time of assessment.

Variables	**Angiogenic imbalance at the time of assessment (n=32)** [a]	**New-onset proteinuria at the time of assessment (n=14)**	**FGR at the time of assessment (n=22)**	**AGA without proteinuria or angiogenic imbalance (n=94)**
Maternal outcomes				
Maternal death, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Maternal ICU admission, n (%)	**4 (12.5)** [a]	1 (7.1)	0 (0.0)	0 (0.0)
Pulmonary edema, n (%)	1 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)
Liver dysfunction, n (%)	2 (6.2)	1 (7.1)	1 (4.5)	2 (2.1)
Renal insufficiency, n (%)	1 (3.1)	**2 (14.3)** [b]	0 (0.0)	0 (0.0)
Postpartum hemorrhage, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Seizures, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Composite adverse maternal outcome, n (%)	**7 (21.9)**	2 (14.3)	1 (4.5)	3 (3.2)
Perinatal outcomes				
Preterm birth due to preeclampsia complications (<37 weeks), n (%)	**25 (78.1)** [c]	**10 (71.4)** [c]	**14 (63.6)** [c]	13 (13.8)
Birthweight in grams, median (IQR)	**1730 (842 - 2015)** [c]	**1590 (1060-2628)** [c]	**1660 (665-2175)** [c]	3200 (2896-3582)
Birthweight centile, median (IQR)	**6.5 (1.8 - 24.5)** [c]	**19.7 (2.7-55.9)** [c]	**2.4 (0.9-3.0)** [c]	53.9 (31.0-75.8)
Placental abruption, n (%)	2 (6.2)	0 (0.0)	0 (0.0)	1 (1.1)
Apgar score <7 at 5th minute, n (%)	2 (6.2)	0 (0.0)	1 (4.5)	0 (0.0)

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NICU admission, n (%)	**18 (56.2) [c]**	**7 (50.0) [c]**	**11 (50.0) [c]**	7 (7.4)
Intraventricular hemorrhage, n (%)	1 (3.1)	0 (0.0)	1 (4.5)	0 (0.0)
Necrotizing enterocolitis, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Respiratory distress syndrome, n (%)	**17 (53.1) [c]**	**6 (42.8) [c]**	**10 (45.4) [c]**	5 (5.3)
Respiratory support, n (%)	**18 (56.2) [c]**	**7 (50.0) [c]**	**11 (50.0) [c]**	6 (6.4)
Stillbirth or neonatal death, n (%)	**3 (9.4) [b]**	**2 (14.3) [b]**	**3 (13.6) [b]**	1 (1.1)
Composite adverse neonatal outcome, n (%)	**24 (75.0) [c]**	**9 (64.3) [c]**	**15 (68.8) [c]**	10 (10.6)

[a] sFlt-1/PlGF ratio above the 97.5th centile according to gestational age

[b] Significantly different at a level of <.05 compared to AGA without proteinuria angiogenic imbalance group

[c] Significantly different at a level of <.001 AGA without proteinuria angiogenic imbalance group

NICU: neonatal intensive care unit, ICU: intensive care unit, FGR: fetal growth restriction, AGA: appropriate for gestational age

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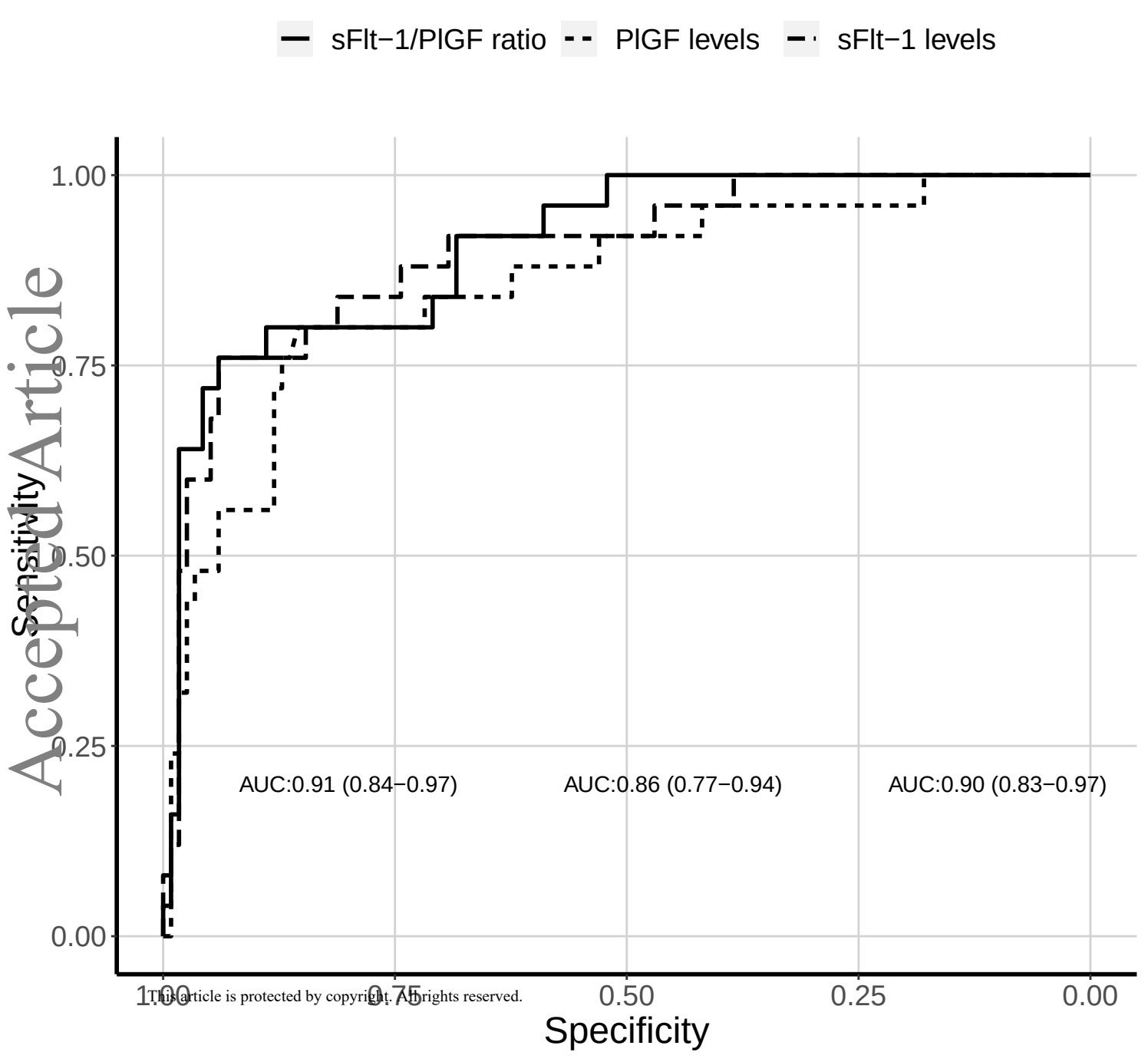

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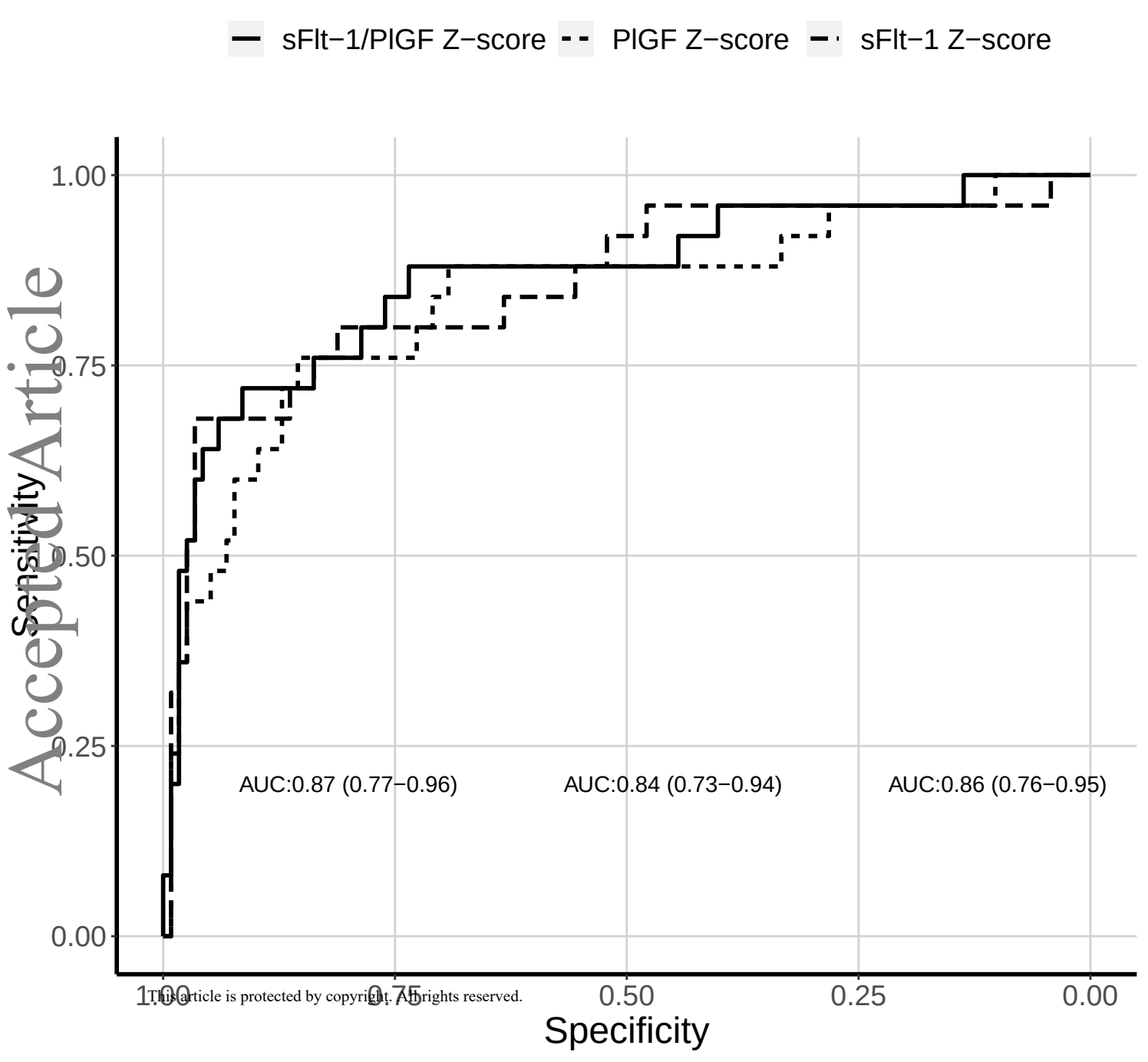

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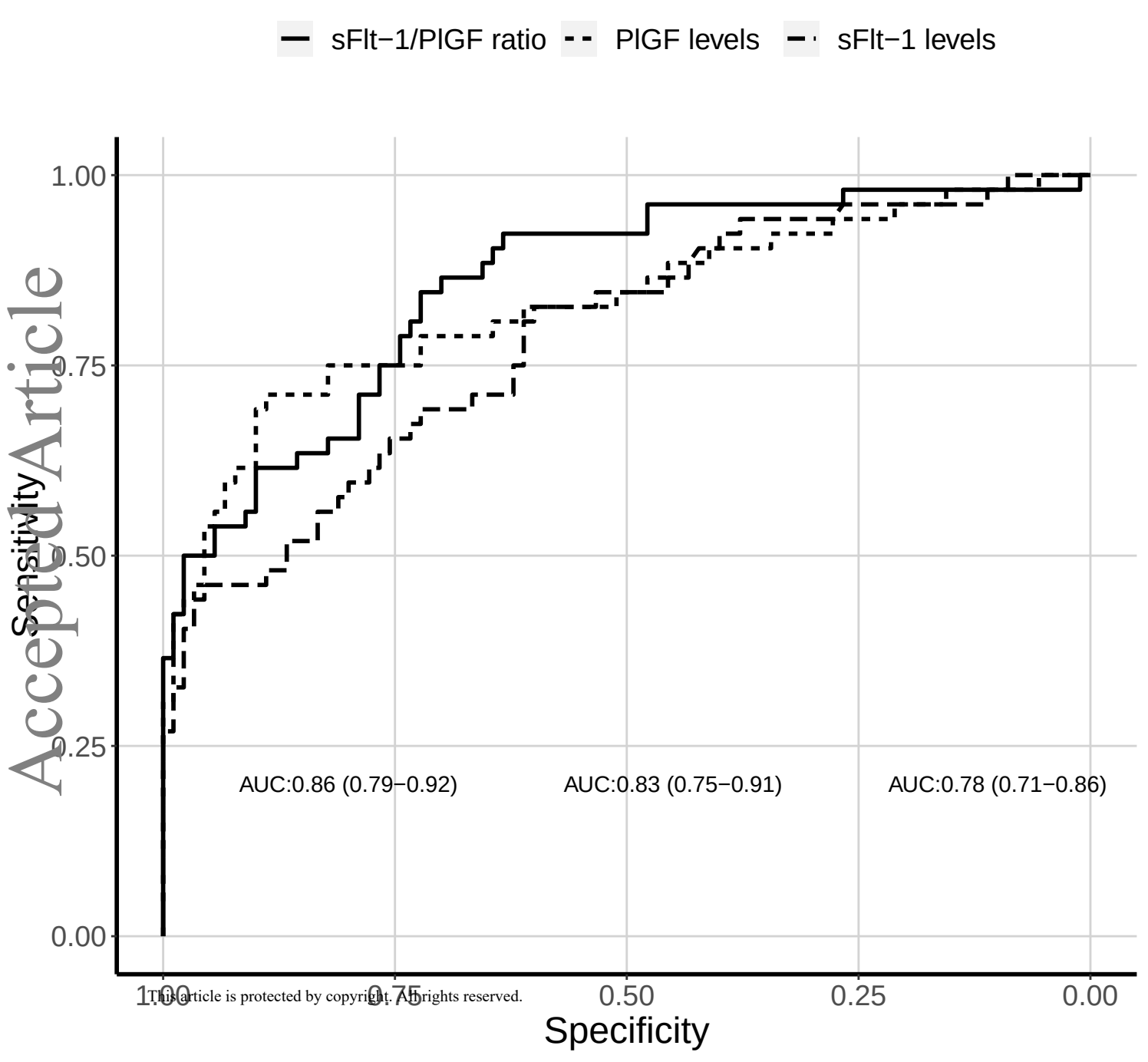

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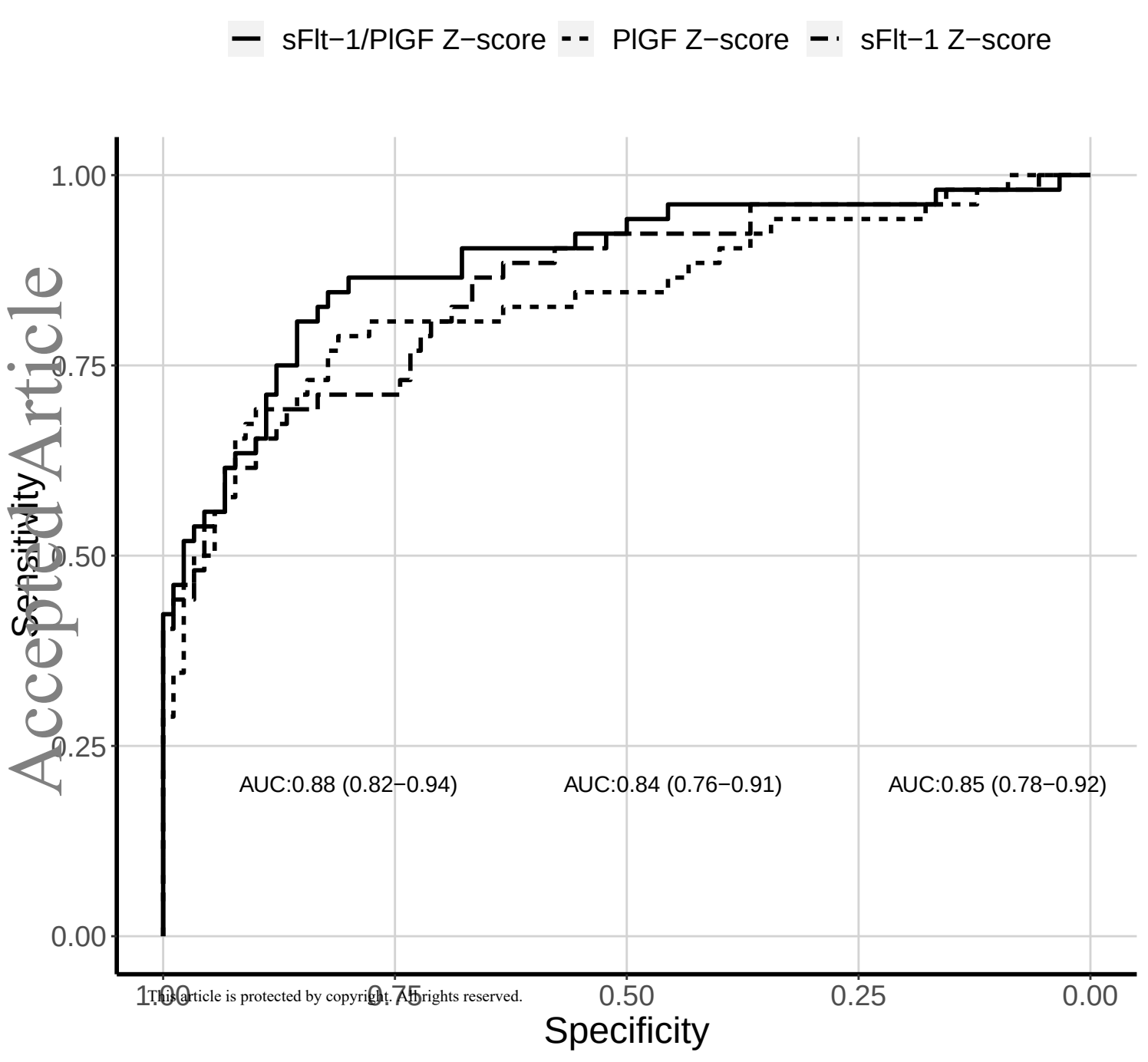

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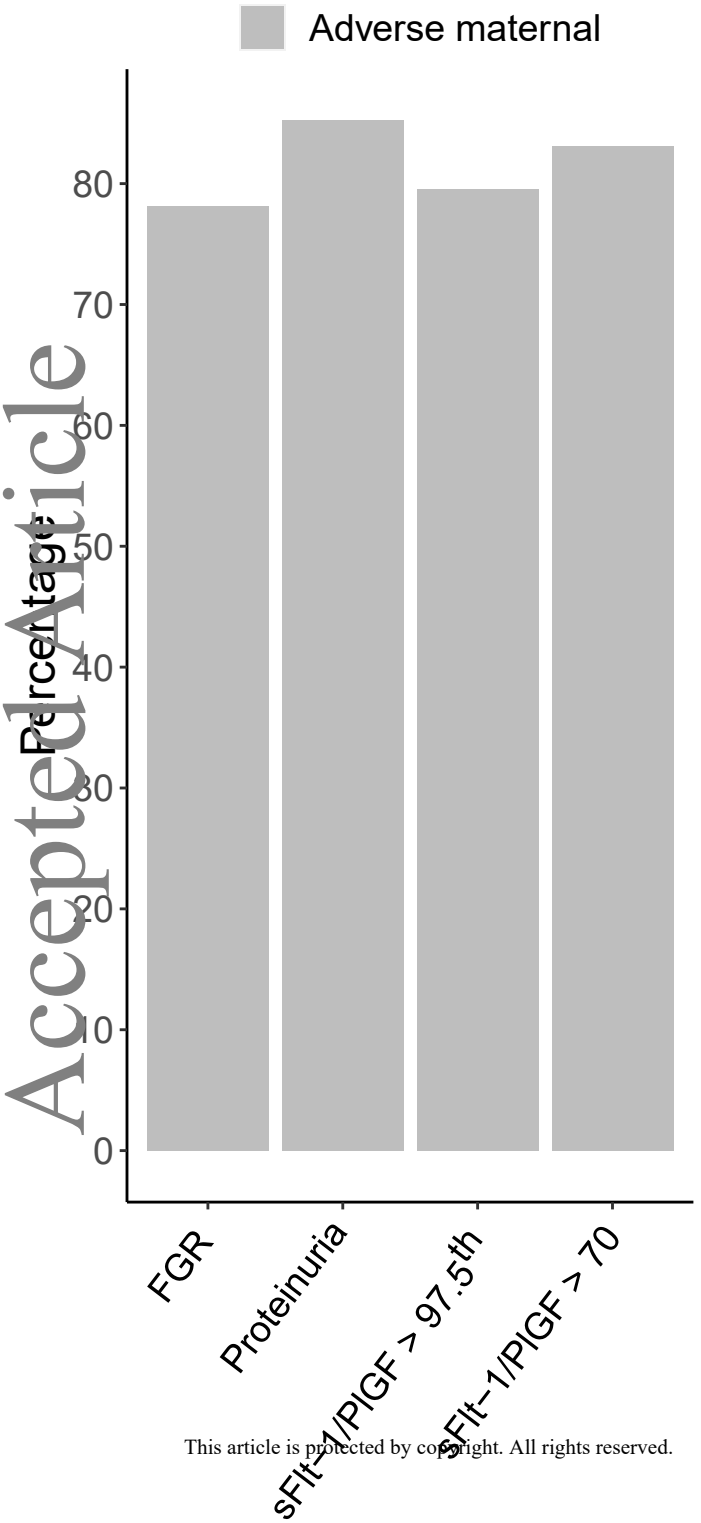

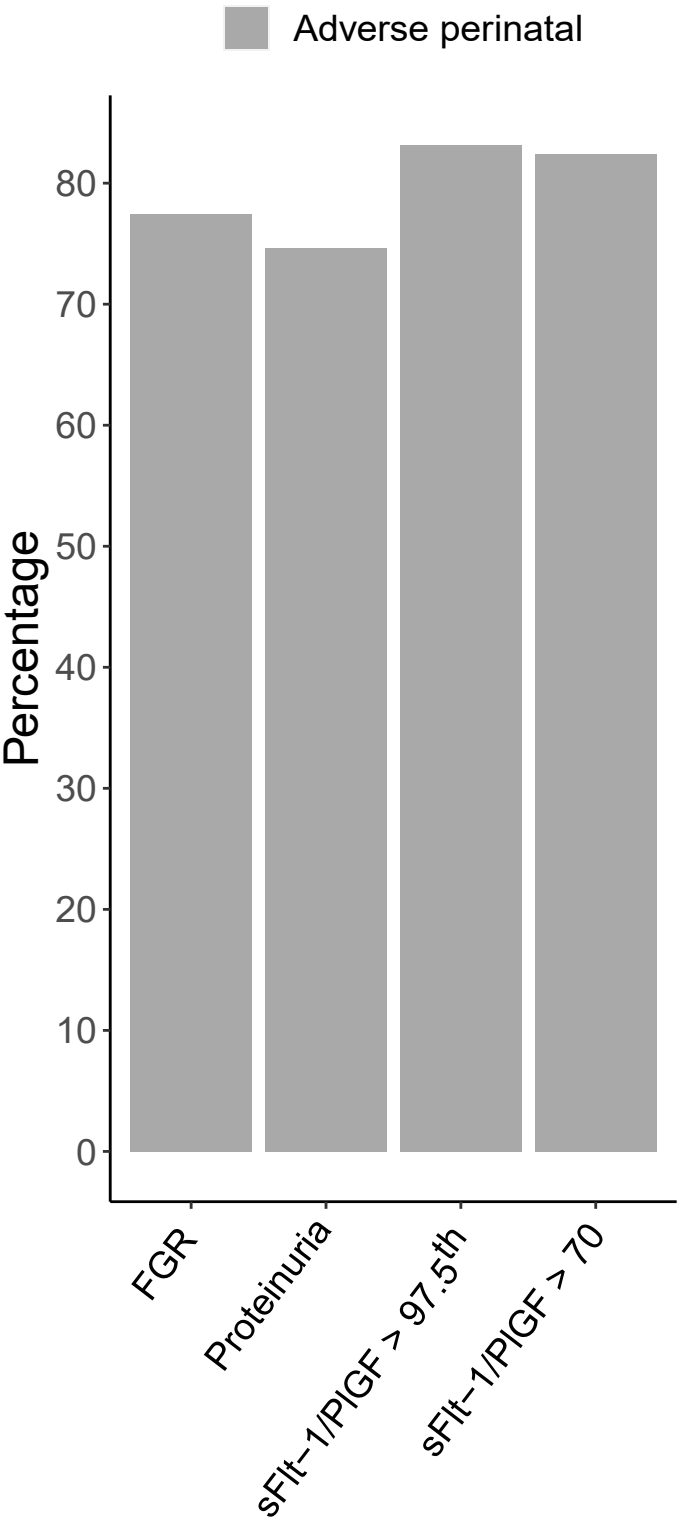

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