sFlt1/PlGF among patients with suspected preeclampsia when considering hypertensive status

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BACKGROUND: In high-resource settings, biomarkers of angiogenic balance, such as the soluble fms-like tyrosine kinase-1 (sFlt1)/placental growth factor (PlGF) ratio, have been studied extensively to aid in evaluation of patients with suspected preeclampsia (PE), and have been incorporated into the 2021 International Society for the Study of Hypertension in Pregnancy definition of PE. The utility in under-resourced settings has not been as well characterized.

OBJECTIVE: This analysis sought to identify the role of the sFlt1/PlGF ratio in the evaluation of patients with or without hypertension who are suspected of having PE without other diagnostic information.

STUDY DESIGN: This is a secondary analysis of a prior prospective study of patients who were presented with suspected PE at ≥20+0 weeks' gestation at a single academic tertiary care center. Patients were recruited in the parent study from July 2009 to June 2012. In the original study, clinicians were masked to biomarker results, and patients were followed by chart review. In this analysis, the performance of the sFlt1/PlGF ratio (≤38, >38, or >85) was assessed alone in identifying both hypertensive and non-hypertensive patients at risk of evolving into PE with severe features (PE-SF; American College of Obstetricians and Gynecologists' definition) within two weeks of the triage visit ($PE\text{-}SF_2$). Hypertension was defined as a blood pressure (BP)≥140/90 mmHg.

RESULTS: There were 1043 patients included in the analysis; of whom, 579 (55.5%) and 464 (44.5%) presented with or without hypertension, respectively. In triage, 332 (75.4%) of hypertensive patients presented due to BP concerns, and the remainder were evaluated due to other features (new-onset headache, proteinuria, or edema). On triage evaluation, 66.8% of all patients had a normal sFlt1/PlGF ratio ≤38, and 17.0% had an elevated ratio >85. Among hypertensive patients, a sFlt1/PlGF ratio ≤38 was a good rule-out test for $PE\text{-}SF_2$ (negative likelihood ratio [LR-] of 0.15), and a ratio >85 was a good rule-in test (positive likelihood ratio [LR+] of 5.75). Among normotensive patients, sFlt1/PlGF was useful as a rule-in test for ratio >38 (LR+ 5.13) and >85 (LR+ 12.80). Stratified by gestational age, sFlt1/PlGF continued to be a good rule in and good rule out test at <35 weeks among those with hypertension but did not have good test performance ≥35 weeks. sFlt1/PlGF had a good test performance as a rule in test for >85 regardless of gestational age. In triage, 4.3% (30/693) of patients with sFlt1/PlGF ratio <38 had concurrent laboratory evidence of PE, compared with 15.9% (28/176) patients with ratio >85.

CONCLUSION: These findings support the potential for the use of sFlt1/PlGF and BP measurement alone in resource-limited settings where other laboratory tests or clinical expertise are unavailable for risk stratification. Performance of the biomarker varied by the presence of hypertension and gestational age.

Key words: angiogenic biomarkers, low resource settings, preeclampsia

Introduction

Hypertensive disorders of pregnancy (HDPs) affect at least 10% of pregnancies worldwide, with reports of 46,000 maternal and 500,000 fetal/neonatal deaths from preeclampsia annually.[1,2] The World Health Organization (WHO) estimates that 16% of maternal deaths in low- and middle-income countries (LMICs) are a result of HDPs, with eclampsia being the most common direct cause of death.[3,4] In high-income countries (HICs), progression from preeclampsia to eclampsia complicates fewer than 1% of cases; however, in LMICs, progression is at least double that, at approximately 2.3%.[4]

Prediction of adverse maternal outcomes in preeclampsia can be achieved with integration of maternal laboratory testing and clinical assessment.[5,6] In

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Why was this study conducted?

- This study was conducted to simulate the predictive value of sFlt1/PlGF with and without hypertension in a low resource setting.

What are the key findings?

- sFlt1/PlGF is a good rule in test for patients regardless of hypertension, and a good rule out test for those with hypertension.

What does this add to what is known?

- This study identifies potential utility of angiogenic markers in a low resource setting.

under-resourced settings where hematologic and biochemical laboratory tests are not routinely available, maternal signs and symptoms can be used, but with reduced predictive performance.[7]

Among patients with suspected or confirmed preeclampsia, angiogenic biomarkers can improve the identification of patients at highest risk of adverse outcomes.[8,9] The two biomarkers most widely studied for their predictive performance are soluble fms-like tyrosine kinase-1 (sFlt1) and placental growth factor (PlGF).[10,11] Increased sFlt1 levels, decreased PlGF levels, and an increased sFlt1/PlGF ratio are seen in preeclampsia and are thought to contribute to its characteristic endothelial dysfunction.[10–12] Based on demonstration that, among patients with suspected preeclampsia, an increased sFlt1/PlGF ratio improves identification of patients most likely to progress to preeclampsia within one week, as well prediction of related adverse outcomes, the 2021 International Society for the Study of Hypertension in Pregnancy (ISSHP) guidelines incorporated angiogenic imbalance into their definition of preeclampsia.[12–14] A recent large multisite study in the United States found high positive and negative predictive values for the sFlt1/PlGF ratio to predict progression to preeclampsia with severe features (PE-SF; American College of Obstetrics and Gynecology definition) within 2 weeks among patients admitted with HDPs.[15,16]

Prior studies of angiogenic biomarkers have been performed primarily in HICs. However, angiogenic biomarkers have potential in LMICs where there is limited availability of trained health professionals and limited ability to perform and interpret a full laboratory evaluation. The early identification of LMIC-resident patients at greatest risk for adverse outcomes from HDPs may reduce maternal and perinatal mortality, by facilitating earlier referral to better-resourced hospitals and optimizing the allocation of limited resources.[17] Potentially, assessing angiogenic imbalance could identify those patients who would benefit cost-effectively from full laboratory workup to identify complications of preeclampsia (e.g., hemolysis, elevated liver enzymes and low platelet (HELLP) syndrome, disseminated intravascular coagulation).

This study tested whether the use of the sFlt1/PlGF ratio and blood pressure (BP) measurement alone could provide sufficient information to best direct patient care in patients with suspected preeclampsia, according to whether they were normotensive or hypertensive in triage.

Materials and Methods

This is a secondary analysis of a previously published prospective cohort study of patients with a singleton gestation who presented to obstetric triage for evaluation of suspected preeclampsia at ≥20+0 weeks' gestation, at a single academic tertiary care center. In brief, patients were recruited in the parent study from July 2009 to June 2012 at a medical center in Boston, Massachusetts (research ethics approval 2009P-000084),[18,19] underwent standard preeclampsia evaluation and a blood draw for sFlt1 and PlGF levels, and were managed according to institutional standards of care. Clinicians were masked to sFlt1/PlGF results, and the electronic health record was reviewed for maternal and neonatal care and maternal and perinatal outcomes.

The primary outcome was the sFlt1/PlGF ratio test performance (utilizing cutoffs of ≤38, >38, or >85) in identifying patients at low or high risk of developing PE-SF within two weeks of the triage visit ($PE\text{-}SF_2$), stratified by hypertension status on enrollment. Hypertension was defined as a single BP recording of a systolic BP (sBP)≥140 mmHg or diastolic BP (dBP)≥90 mmHg in obstetric triage, regardless of the HDP type or HDP diagnosis. The normotensive group included patients without elevated BP, including those with either chronic or gestational hypertension whose BP was controlled by antihypertensive medication.

The secondary outcomes, stratified by hypertension status in triage, were the sFlt1/PlGF ratio (≤38, >38, or >85) test performance in identifying patients at low or high risk of adverse maternal or perinatal outcomes. Adverse maternal outcomes included at least one of the following: severe hypertension (defined as sBP≥160 mmHg or dBP≥110 mmHg), HELLP syndrome, disseminated intravascular coagulation (DIC), placental abruption, intracranial hemorrhage, pulmonary edema, eclampsia, acute renal failure, or death. Adverse perinatal outcomes included at least one of the following: fetal death, neonatal death, or birthweight less than the 10th percentile for gestational age and sex.[20]

Statistical Analysis

Baseline characteristics, the nature of presentation to obstetric triage, the assessment results, and pregnancy outcomes were evaluated descriptively, according to hypertension status in obstetric triage. Results were presented as frequency counts and proportions for categorical variables, and median (interquartile range [IQR]) for continuous variables. Skewed distributions of continuous data were observed visually and confirmed using the Shapiro-Wilk test. Differences between those with and without hypertension were evaluated

with a Mann Whitney U test, chi-square, or Fisher's Exact test, as appropriate.

To evaluate the diagnostic test properties of the sFlt1/PlGF ratio, sensitivity, specificity, likelihood ratios (negative [LR-] and positive [LR+]), and area under the receiver operating curve were calculated for PE-SF_2. Cutoffs for sFlt1, PlGF, and clinical markers were based on previously established cutoffs.[11,16,18,19] A LR- <0.20 was considered to demonstrate good diagnostic test performance in ruling out PE-SF_2, whereas a LR+ >5.0 was considered to demonstrate good performance in ruling in the possibility of PE-SF_2; these cut-offs correspond to a 30% difference in the probability of the outcome.[21,22] Areas under the receiver-operator curve (AUC), and associated 95% confidence intervals (CI), were calculated using logistic regression.

Sensitivity analyses were undertaken for the primary and secondary outcomes, stratified by hypertension in triage for test performance of PlGF alone (using the published cut-off of >100pg/mL as normal),[23–25] and dichotomizing the cohorts into patients who presented from 20+0 to 34+6 weeks gestation and those who presented ≥35+0 weeks.

Results

Overall, 1043 patients were included in the analysis, of whom 464 patients presented with normotension and 579 with hypertension. On triage evaluation, 697 (66.8%) patients had a normal sFlt1/PlGF ratio ≤38, and 177 (17.0%) had an elevated ratio >85. Table 1 shows that there were many differences in baseline patient characteristics, nature of presentation and evaluation in triage, and pregnancy outcomes according to the presence or absence of hypertension in triage.

In this cohort, patients presented at a median age of 32 years (IQR 28, 35) and had a median body mass index (BMI)>30 kg/m^2; 4.4% were smokers and 15.9% were Black/African American. 24.5% of patients had a history of chronic hypertension and 8.4% had a history of pre-gestational diabetes. Patients with hypertension were slightly older, more often nulliparous, and more often had a history of chronic hypertension, compared with normotensive patients.

At presentation to obstetric triage with suspected preeclampsia, the median gestational age was 35.6 weeks (IQR 32.6, 37.1), median sBP 138 mmHg (IQR 128, 149), median dBP 87 mmHg (IQR 79, 95). Generally, patients were assessed in triage due to concerns about BP, headache, and visual symptoms. As expected, hypertensive patients had higher BP levels than normotensive patients, with more frequent severe hypertension, and more frequent presentations with concerns about BP. However, just over half of the normotensive patients presented because of BP concerns, and there were no differences with regards to other presenting symptoms. Patients with hypertension had higher sFlt1-, lower PlGF-levels, and a higher sFlt1/PlGF ratio, although 54.5% of values were normal (≤38) in this cohort.

Following assessment in obstetric triage, hypertensive patients were more frequently admitted to hospital, and their pregnancy outcomes were more likely to be unfavorable. This included more HDPs (preeclampsia and PE-SF_2, specifically), earlier gestational ages at giving birth (with a higher frequency of preterm birth and birth within two weeks), and more adverse maternal outcomes, particularly severe hypertension and HELLP syndrome.

Among hypertensive patients, an sFlt1/PlGF ratio ≤38 was a good rule-out test for the development of PE-SF_2, (as highlighted in green, reflecting a LR-<0.20), and a ratio >85 was a good rule-in test for PE-SF_2 (as highlighted in red, reflecting a LR+ >5.00). This was confirmed in the good discriminative ability of the models in hypertensive patients, both for an sFlt-1/PlGF ratio >38 (AUC 0.78, 95% CI: 0.75, 0.82) and an sFlt1/PlGF ratio >85 (AUC 0.78, 95% CI: 0.74, 0.83) (Table 2). In normotensive patients, an sFlt1/PlGF ratio >38 and >85 were good rule-in tests for PE-SF_2. Similar results were seen for patients at 20+0 - 34+6 weeks, irrespective of whether or not hypertension was present. At or after 35+0 weeks, only for normotensive patients at a cut-off of >85, was the ratio a good rule-in test for PE-SF_2.

In terms of prediction of maternal adverse outcomes, for those with hypertension, an sFlt-1/PlGF ratio of >85 did not perform well as a rule-in test at any gestational age. In contrast, for normotensive patients, an sFlt-1/PlGF ratio >85 was a good rule-in test for prediction of maternal adverse outcomes in patients at both 20+0 - 34+6 weeks (LR + 5.38) and ≥ 35+0 weeks (LR+ 5.00; Supplementary Table 1).

Table 3 shows that PlGF alone was not a good rule-in (at <100pg/mL) or rule-out (at ≥100pg/mL) test for PE-SF_2, in hypertensive or normotensive patients, at any gestational age, with all LR- results ≥0.20 and all LR+ results ≤5.0. Similar findings were seen for the use of PlGF alone for the prediction of maternal adverse outcomes (Supplementary Table 1). In contrast, PlGF≤100pg/mL was a good rule-in test for prediction of adverse perinatal outcomes in normotensive patients (+LR 6.70; Supplementary Table 2).

Hypertensive patients with an sFlt1/PlGF ratio >85 were more likely to have elevated liver function tests (LFTs) in triage than those with a ratio ≤38 (12.23% vs 0.64%, P<.0001) and more likely to have thrombocytopenia (2.88% vs 0.64%, respectively, P=.06). Similarly, amongst normotensive patients, those with an sFlt1/PlGF ratio >85 were more likely to have elevated LFTs than those with an sFlt1/PlGF ratio ≤38 (8.11% vs 2.11%, P=.10) and more likely to have thrombocytopenia (5.41% vs 0.53%, respectively, P=.045), Supplementary Table 3.

The test performance of biomarkers to predict abnormal laboratory results in preeclampsia was then investigated. Overall, 21 (2.01%) patients had abnormal creatinine, 11 (1.05%) had abnormal platelet counts, and 33 (3.16%) had abnormal LFTs in triage. In terms of prediction of abnormal laboratory results within two weeks, for those with hypertension, a ratio of >85 performed well as a modest rule-in test at any gestational age for transaminitis (LR+

TABLE 1
Characteristics of Study Subjects Stratified by Hypertension in Triage

	Entire Cohort N = 1043	No Hypertension N = 464	Hypertension N = 579	*P*-Value
Demographics				
Maternal age, *years*	32 (28, 35)	32 (28, 35)	32 (29, 36)	.01
Body mass index, *kg/m²*	32.4 (28.7, 37.1)	32.4 (28.5, 37.4)	32.3 (28.9, 36.9)	.81
Nulliparous	601 (57.6%)	242 (52.2%)	359 (62.0%)	.001
Current smoker	46 (4.4%)	23 (5.0%)	23 (4.0%)	.74
Race				.33
White/Caucasian	692 (66.4%)	317 (68.3%)	375 (64.9%)	
Black/African American	166 (15.9%)	73 (15.7%)	93 (16.1%)	
Asian	73 (7.0%)	24 (5.2%)	49 (8.5%)	
Other	43 (4.1%)	20 (4.3%)	23 (4.0%)	
Unspecified	68 (6.5%)	30 (6.5%)	38 (6.6%)	
Hispanic ethnicity	104 (10.0%)	49 (10.6%)	55 (9.5%)	.80
Past medical history				
Chronic hypertension	256 (24.5%)	82 (17.7%)	174 (30.1%)	<.0001
Diabetes	88 (8.4%)	41 (8.8%)	47 (8.1%)	.68
Nature of suspected PE *(Presenting characteristics)*				
GA at presentation, *weeks*	35.6 (32.6, 37.1)	35.6 (32.0, 37.4)	35.6 (32.7, 37.1)	.79
BP in triage				
Systolic BP, *mmHg*	138 (128, 149)	127 (120, 134)	148 (141, 156)	<.0001
Diastolic BP, *mmHg*	87 (79, 95)	79 (72, 84)	94 (90, 99)	<.0001
Severe hypertension (≥ 160/110)	110 (10.6%)	0 (0%)	110 (19.0%)	<.0001
Presenting symptoms				
BP concerns	670 (65.2%)	240 (52.4%)	430 (75.4%)	<.0001
Proteinuria	145 (14.3%)	72 (15.9%)	73 (13.0%)	.20
Headaches	301 (29.4%)	142 (31.1%)	159 (28.0%)	.27
Visual changes	103 (10.1%)	51 (11.2%)	52 (9.2%)	.29
Persistent epigastric/RUQ Pain	74 (7.3%)	34 (7.5%)	40 (7.1%)	.79
Edema	141 (13.9%)	63 (13.9%)	78 (13.8%)	.96
Routine laboratory values in triage				
Platelet count, *K/μL*	237 (196, 281)	241 (199, 285)	233 (192, 276)	.09
Low platelet count, *<100 K/μL*	11 (1.1%)	4 (0.9%)	7 (1.2%)	.76
Creatinine, *mg/dL*	0.6 (0.5, 0.7)	0.6 (0.5, 0.6)	0.6 (0.5, 0.7)	<.0001
Elevated creatinine, *>1.1 mg/dL*	21 (2.0%)	7 (1.5%)	14 (2.4%)	.30
AST, *U/L*	22 (17, 31)	21 (17, 26)	24 (18, 34)	.02
ALT, *U/L*	16 (12, 23)	15 (12, 21)	17 (12, 24)	.04
Elevated AST or ALT, *>80 U/L*	33 (3.2%)	12 (2.6%)	21 (3.6%)	.34
Hematocrit, *%*	34.5 (32.4, 36.5)	34.2 (32.1, 36.2)	34.9 (32.6, 36.8)	.003
Uric acid, *mg/dL*	4.6 (3.9, 5.5)	4.3 (3.7, 5.1)	4.9 (4.1, 5.9)	<.0001

(continued)

TABLE 1
Characteristics of Study Subjects Stratified by Hypertension in TriagePlease provide significance of "f" in phrase "Fetal adverse outcomef" in table 1. *(continued)*

	Entire Cohort N = 1043	No Hypertension N = 464	Hypertension N = 579	*P*-Value
Other triage characteristics				
ACOG severe PE definition[a]	105 (10.1%)	22 (4.7%)	83 (14.3%)	<.0001
Angiogenic biomarkers in triage				
sFlt1	3458 (2054, 6451)	2613 (1669, 4606)	4514 (2591, 8090)	<.0001
PlGF	203 (105, 433)	301 (152, 607)	160 (85, 313)	<.0001
sFlt1/PlGF	16.6 (4.3, 57.5)	9.4 (3.1, 25.7)	31.1 (8.6, 81.7)	<.0001
≤ 38	693 (66.8%)	379 (82.0%)	314 (54.5%)	<.0001
39–85	169 (16.3%)	46 (10.0%)	123 (21.4%)	
> 85	176 (17.0%)	37 (8.0%)	139 (24.1%)	
Antenatal management following triage				
Admitted following triage	457 (43.8%)	133 (28.7%)	324 (6.0%)	<.0001
Delivery and pregnancy outcomes				
Final hypertensive diagnosis				<.0001
Chronic hypertension	171 (16.4%)	66 (14.2%)	105 (18.1%)	
Gestational hypertension	258 (24.7%)	97 (20.9%)	161 (27.8%)	
PE or superimposed PE	364 (34.9%)	87 (18.8%)	277 (47.8%)	
Severe features	182 (50.0%)	35 (40.2%)	147 (53.1%)	.04
Normal	233 (22.3%)	201 (43.3%)	32 (5.5%)	
Other *(Gestational Proteinuria)*	17 (1.6%)	13 (2.8%)	4 (0.7%)	
PE-SF within two weeks of triage	145 (13.9%)	23 (5.0%)	122 (21.1%)	<.0001
Outcomes				
GA at delivery, *weeks*	37.9 (36.3, 39.1)	38.6 (37.1, 39.4)	37.3 (35.7, 38.6)	<.0001
Preterm delivery <37 weeks	142 (13.6%)	30 (6.5%)	112 (19.3%)	<.0001
Preterm delivery <34 weeks	99 (9.5%)	21 (4.5%)	78 (13.5%)	<.0001
Delivered within two weeks	610 (59.2%)	214 (46.7%)	396 (69.1%)	<.0001
Indicated delivery	425 (72.4%)	102 (50.8%)	323 (83.7%)	<.0001
Caesarean delivery	562 (54.4%)	238 (51.9%)	324 (56.4%)	.15
Birthweight, *grams*	3010 (2355, 3505)	3280 (2730, 3625)	2815 (2185, 3360)	<.0001
Macrosomia	39 (6.6%)	18 (8.8%)	21 (5.4%)	.12
Maternal adverse outcome[b]	181 (17.4%)	23 (5.0%)	158 (27.3%)	<.0001
Severe hypertension	146 (14.0%)	13 (2.8%)	133 (23.0%)	<.0001
HELLP	42 (4.0%)	7 (1.5%)	35 (6.0%)	.0002
DIC	2 (0.2%)	1 (0.2%)	1 (0.2%)	.88
Placental abruption	14 (1.3%)	3 (0.7%)	11 (1.9%)	.08
Pulmonary edema	5 (0.5%)	0 (0%)	5 (0.9%)	.07
Cerebral hemorrhage	1 (0.1%)	0 (0%)	1 (0.2%)	.37
Death	1 (0.1%)	1 (0.2%)	0 (0%)	.44
Eclampsia	1 (0.1%)	0 (0%)	1 (0.2%)	.37
Acute renal failure	5 (0.5%)	2 (0.4%)	3 (0.5%)	.84

(continued)

TABLE 1
Characteristics of Study Subjects Stratified by Hypertension in TriagePlease provide significance of "f" in phrase "Fetal adverse outcomef" in table 1. *(continued)*

	Entire Cohort N = 1043	No Hypertension N = 464	Hypertension N = 579	*P*-Value
Fetal adverse outcome[b]	38 (3.6%)	12 (2.6%)	26 (4.5%)	.10
Fetal death	4 (0.4%)	0 (0%)	4 (0.7%)	.13
Neonatal death	5 (0.5%)	2 (0.4%)	3 (0.5%)	.84
Birthweight<10th percentile	31 (5.3%)	10 (4.9%)	21 (5.5%)	.78

[a] Defined as platelet count<100, AST or ALT>80, or creatinine>1.1 either (a) in the presence of chronic hypertension, or (b) severe hypertension (BP>160/110) without chronic hypertension.; [b] Categories are non-exclusive, where subjects can experience multiple adverse outcomes.

Abbreviations: ACOG (American College of Obstetricians and Gynecologists), ALT (alanine aminotransferase), AST (aspartate aminotransferase), BMI (body mass index), BP (blood pressure), DIC (disseminated intravascular coagulation), GA (gestational age), HELLP (Hemolysis, Elevated Liver Enzymes Low Platelet) syndrome, PCR (protein:creatinine ratio), PE (preeclampsia), PE-SF (preeclampsia with severe features) PlGF (placental growth factor), RUQ (right upper quadrant) abdominal, sFlt1 (soluble fms-like tyrosine kinase-1).

3.19) and thrombocytopenia (LR+ 3.74). A cut-off of 38 had a good rule out for thrombocytopenia among all patients (LR- <0.2). In contrast, for normotensive patients, an sFlt1/PlGF ratio >85 was a good rule-in test for prediction of both transaminitis and thrombocytopenia (LR+ 5.71 and 8.14, respectively; Table 4). In addition, among those who had normal laboratory values in triage and with an sFlt1/PlGF ratio <38 only 0.90% developed any abnormal laboratory results within 2 weeks compared with 9.93% among those with an sFlt1/PlGF ratio >85 (*P*<.0001).

Discussion

Principal Findings

Among both normotensive and hypertensive patients with suspected preeclampsia, our findings suggest that the sFlt1/PlGF ratio is a useful test for risk-stratification. Among hypertensive patients, an sFlt1/PlGF ratio <38 performed well as a rule-out test for subsequent development of PE-SF$_2$, especially for those presenting at <35+0 weeks' gestation, and an sFlt1/PlGF ratio >85 was a good rule-in test. Among normotensive patients, an sFlt1/PlGF ratio >38 was a good rule-in test (and >85 was excellent) for

TABLE 2
Test Performance of sFlt1/PlGF for PE-SF Within Two Weeks of Triage, Stratified by Blood Pressure in Triage

	SENS	SPEC	LR -	LR +	AUC (95% CI)
All Patients *(N = 145 / 1043, 13.90%)*					
Hypertension	0.84	0.49	0.33	1.65	0.67 (0.63, 0.70)
sFlt1/PlGF > 38	0.90	0.66	0.15	2.65	0.78 (0.75, 0.82)
sFlt1/PlGF > 85	0.69	0.88	0.35	5.75	0.78 (0.74, 0.83)
No Hypertension	0.16	0.51	1.65	0.33	0.67 (0.63, 0.70)
sFlt1/PlGF > 38	0.77	0.85	0.27	5.13	0.81 (0.72, 0.90)
sFlt1/PlGF > 85	0.64	0.95	0.38	12.80	0.79 (0.69, 0.90)
20-34 Weeks *(N = 85 / 459, 18.52%)*					
Hypertension	0.82	0.52	0.35	1.71	0.67 (0.62, 0.72)
sFlt1/PlGF > 38	0.93	0.70	0.10	3.10	0.81 (0.77, 0.86)
sFlt1/PlGF > 85	0.84	0.86	0.19	6.00	0.85 (0.80, 0.90)
No Hypertension	0.18	0.48	1.71	0.35	0.67 (0.62, 0.72)
sFlt1/PlGF > 38	0.79	0.91	0.23	8.78	0.85 (0.73, 0.96)
sFlt1/PlGF > 85	0.71	0.94	0.31	11.83	0.83 (0.70, 0.95)
≥ 35 Weeks *(N = 60 / 584, 10.27%)*					
Hypertension	0.87	0.47	0.28	1.64	0.67 (0.62, 0.72)
sFlt1/PlGF > 38	0.87	0.64	0.20	2.42	0.75 (0.70, 0.81)
sFlt1/PlGF > 85	0.48	0.89	0.58	4.36	0.68 (0.61, 0.76)
No Hypertension	0.13	0.53	1.64	0.28	0.67 (0.62, 0.72)
sFlt1/PlGF > 38	0.75	0.81	0.31	3.95	0.78 (0.62, 0.94)
sFlt1/PlGF > 85	0.50	0.96	0.52	12.50	0.73 (0.54, 0.91)

Green shading reflects use to reassure (i.e., as a good "rule-out" test), whereas red shading reflects use to confirm concern (i.e., as a "rule-in" test). Values in yellow may be considered to confirm concern based off a positive likelihood ratio cutoff of 3.0. Indented values are reported among those individuals meeting the definition of the larger category heading. Hypertension included patients with BP≥140/90 mmHg in triage, whereas patients with no hypertension had BP < 140/90.

Abbreviations: PE (preeclampsia), SENS (sensitivity), SPEC (specificity), LR- (negative likelihood ratio), LR+ (positive likelihood ratio), AUC (area under the receiver operating characteristic curve), BP (blood pressure), PlGF (placental growth factor), sFlt1 (soluble fms-like tyrosine kinase-1), PE-SF (preeclampsia with severe features).

TABLE 3
Test Performance of PlGF for PE-SF Within Two Weeks of Triage, stratified by Blood Pressure in Triage

	SENS	SPEC	LR -	LR +	AUC (95% CI)
All patients *(N=145/1043, 13.90%)*					
Hypertension	0.84	0.49	0.33	1.65	0.67 (0.63, 0.70)
PlGF≤100	0.68	0.77	2.96	0.42	0.72 (0.68, 0.77)
No hypertension	0.16	0.51	1.65	0.33	0.67 (0.63, 0.70)
PlGF≤100	0.50	0.90	5.00	0.56	0.70 (0.59, 0.81)
20−34 weeks *(N=85/459, 18.52%)*					
Hypertension	0.82	0.52	0.35	1.71	0.67 (0.62, 0.72)
PlGF≤100	0.77	0.73	2.85	0.32	0.75 (0.69, 0.81)
No hypertension	0.18	0.48	1.71	0.35	0.67 (0.62, 0.72)
PlGF≤100	0.57	0.90	5.70	0.48	0.74 (0.60, 0.87)
≥35 Weeks *(N=60/584, 10.27%)*					
Hypertension	0.87	0.47	0.28	1.64	0.67 (0.62, 0.72)
PlGF≤100	0.56	0.79	2.67	0.56	0.68 (0.60, 0.75)
No hypertension	0.13	0.53	1.64	0.28	0.67 (0.62, 0.72)
PlGF≤100	0.38	0.90	3.80	0.69	0.64 (0.46, 0.82)

Green shading reflects use to reassure (i.e., as a good "rule-out" test), whereas red shading reflects use to confirm concern (i.e., as a "rule-in" test). Indented values are reported among those individuals meeting the definition of the larger category heading.

Abbreviations: PE (preeclampsia), SENS (sensitivity), SPEC (specificity), LR- (negative likelihood ratio), LR+ (positive likelihood ratio), AUC (area under the receiver operating characteristic curve), BP (blood pressure), PlGF (placental growth factor), sFlt1 (soluble fms-like tyrosine kinase-1), PE-SF (preeclampsia with severe features).

subsequent development of PE-SF_2, especially for those presenting at <35+0 weeks' gestation; test performance was poor as a rule-out test. A PlGF threshold of 100pg/mL did not perform well as either a rule-in or rule-out test. Finally, although very few (<2%) of patients with suspected preeclampsia had concurrent abnormal laboratory results, or went on to develop them, at <35+0 weeks' gestation, an sFlt1/PlGF ratio <38 was reassuring regardless of BP, and a ratio >85 was concerning.

Results in the Context of What is Known

Many studies have shown that angiogenic biomarkers, specifically sFlt-1, PlGF, and their ratio, can be used to predict development of preeclampsia and adverse maternal and perinatal outcomes. Previous studies have shown that a low ratio has a high negative predictive value for development of preeclampsia within one week of presentation and prediction of adverse outcomes within two weeks.[26−28] In addition, the ratio has additive value in patients with confirmed preeclampsia for the prediction of adverse outcomes.[9] Most published studies have been conducted in HICs where a multitude of tests and monitoring would be available; however, ready access to testing and monitoring may not be the case in LMICs.[7,18,19,29]

Our findings demonstrate utility of these angiogenic makers for prediction of preeclampsia with severe features regardless of hypertension status in triage. In addition, our findings show that these biomarkers can be used for risk assessment amongst those with suspected preeclampsia. Although not directly, our study supports findings published in a prior study that showed utility of biomarkers for risk stratification and determine who needs further surveillance or transfer to higher level of care.[30]

Clinical and Research Implications

With increasing knowledge and availability of interventions, preeclampsia-related maternal and perinatal mortality have decreased significantly in HICs; however, the same cannot be said for LMICs.[31] According to the WHO, the disease burden in LMICs is seven times higher than in HICs.[32] Protocols are needed for early detection and prognostication to improve evidence-based resource allocation in LMICs.

The current results demonstrate that using a BP cuff and the sFlt1/PlGF ratio, without recourse to further testing, can identify those patients who will develop PE-SF_2; this will enable the identification of those patients who need to be transferred to higher levels of maternal and neonatal care. In addition, the results demonstrate that abnormal laboratory results (thrombocytopenia, transaminitis) are uncommon among patients with a low sFlt1/PlGF ratio. Consideration can be made for using the sFlt1/PlGF ratio alongside BP measurement as opposed to a full laboratory panel to optimize the use of limited resources. For example, sFlt1/PlGF testing might be performed as the first test and a full battery of preeclampsia laboratory tests limited to patients with a sFlt1/PlGF ratio >85. In addition, a sFlt1/PlGF ratio <38 on initial evaluation would cost-effectively eliminate repeated clinical laboratory testing among patients with normal initial evaluation laboratory results.

Studies in Europe, South America, and the United States have looked at the cost-effectiveness of adding the sFlt1/PlGF ratio with a cut-off of 38 to standard diagnostic criteria. The results were notable for a significant reduction in hospitalizations, resulting in substantial cost-saving.[28,33−35] Implementing the sFlt1/PlGF ratio with a rule-in at >85 may be lifesaving in LMIC settings, regardless of the presence of hypertension. Although not directly evaluated by this study, the test could be used in

TABLE 4
Test Performance of sFlt1/PlGF for Predicting Abnormal Labs Within Two Weeks, Stratified by Blood Pressure in Triage

	SENS	SPEC	LR -	LR +	AUC (95% CI)
Prediction of Transaminitis (Among Patients with Normal Liver Function Tests in Triage) *(N = 20 / 1010, 1.98%)*					
sFlt1/PlGF > 38	0.80	0.69	0.29	2.58	0.71 (0.65, 0.77)
sFlt1/PlGF > 85	0.60	0.85	0.47	4.00	0.72 (0.66, 0.79)
Hypertension	0.75	0.45	0.56	1.36	0.57 (0.51, 0.64)
sFlt1/PlGF > 38	0.87	0.57	0.23	2.02	0.73 (0.68, 0.79)
sFlt1/PlGF > 85	0.67	0.79	0.42	3.19	0.77 (0.70, 0.85)
No Hypertension	0.25	0.55	1.36	0.56	0.57 (0.51, 0.64)
sFlt1/PlGF > 38	0.60	0.83	0.48	3.53	0.60 (0.48, 0.72)
sFlt1/PlGF > 85	0.40	0.93	0.65	5.71	0.59 (0.48, 0.70)
Prediction of Thrombocytopenia (Among Patients with Normal Platelets in Triage) *(N = 14 / 1032, 1.36%)*					
sFlt1/PlGF > 38	0.93	0.68	0.10	2.91	0.77 (0.70, 0.85)
sFlt1/PlGF > 85	0.71	0.84	0.35	4.44	0.78 (0.69, 0.88)
Hypertension	0.50	0.45	1.11	0.91	0.51 (0.40, 0.61)
sFlt1/PlGF > 38	1.00	0.55	0.00	2.22	0.74 (0.65, 0.82)
sFlt1/PlGF > 85	0.86	0.77	0.18	3.74	0.80 (0.69, 0.91)
No Hypertension	0.50	0.56	0.89	1.14	0.51 (0.40, 0.61)
sFlt1/PlGF > 38	0.86	0.83	0.17	5.06	0.82 (0.69, 0.95)
sFlt1/PlGF > 85	0.57	0.93	0.46	8.14	0.77 (0.61, 0.93)
Prediction of Abnormal Creatinine (Among Patients with Normal Creatinine in Triage) *(N = 8 / 1022, 0.78%)*					
sFlt1/PlGF > 38	0.57	0.67	0.64	1.73	0.50 (0.41, 0.59)
sFlt1/PlGF > 85	0.29	0.83	0.86	1.71	0.51 (0.44, 0.58)
Hypertension	0.75	0.45	0.56	1.36	0.58 (0.50, 0.67)
sFlt1/PlGF > 38	0.80	0.54	0.37	1.74	0.54 (0.43, 0.66)
sFlt1/PlGF > 85	0.40	0.76	0.79	1.67	0.54 (0.46, 0.63)
No Hypertension	0.25	0.55	1.36	0.56	0.58 (0.50, 0.67)
sFlt1/PlGF > 38	0.00	0.82	1.22	0.00	0.54 (0.37, 0.70)
sFlt1/PlGF > 85	0.00	0.92	1.09	0.00	0.52 (0.40, 0.65)

Green shading reflects use to reassure (i.e., as a good "rule-out" test), whereas red shading reflects use to confirm concern (i.e., as a "rule-in" test). Indented values are reported among those individuals meeting the definition of the larger category heading.

Abnormal laboratory values are defined as platelet count<100, AST or ALT>80, or creatinine>1.1.

Abbreviations: PE (preeclampsia), SENS (sensitivity), SPEC (specificity), LR- (negative likelihood ratio), LR+ (positive likelihood ratio), AUC (area under the receiver operating characteristic curve), PlGF (placental growth factor), sFlt1 (soluble fms-like tyrosine kinase-1).

high-risk pregnancies as well, such as multiple gestation. As a rule-out test among those with hypertension, this ratio may best allocate resources to those who truly are at higher risk of adverse outcomes. Additionally, the diagnosis of hypertensive disorders currently requires clinical expertise, but discrete cutoff points for the sFlt1/PlGF ratio and hypertension would allow those with limited training to assess and triage patients. There have been prior studies on the cost-effectiveness of the use of biomarkers; however, none have been done in the LMIC setting.[35,36] Further studies are needed to evaluate the cost effectiveness of implementation in the LMIC setting, given the need for running the tests and setting up the test platform.

Strengths and Limitations

A major strength of this study is the large sample size. Additionally, the data from the parent study were collected in a prospective manner by trained research staff using standardized forms; thus, there were minimal missing data. Limitations of this study include that the absolute number of adverse events was small. The parent data were collected in the United States in a tertiary care center. Real world data from an LMIC is needed for validation of these results. The tests performed in this study were on a laboratory grade system - a point of care system may be more applicable to the LMIC setting and test performance needs to be evaluated in that setting. Another limitation of the study is that time to blood draw from the time of corticosteroid administration was not collected in the original study; however, we do not anticipate that many, if any, patients would have received corticosteroids in triage when the blood was drawn. Furthermore, the specific diagnosis in triage is limited by the data collected during the original study, as the diagnosis assigned by the clinicians was not collected as part of the study.

Conclusions

Our findings support the use of the sFlt1/PlGF ratio for both normotensive and hypertensive patients with suspected preeclampsia, in resource-limited settings where other laboratory tests or clinical expertise may not be readily available. Test performance as a

rule out and rule in test varied according to gestational age and cutoff used. The ratio can be used for risk stratification and resource allocation to the most at-risk patients. ■

Declaration of competing interest

S. Rana reports serving as a consultant for Roche Diagnostics, Thermo Fisher, Beckman Coulter, Siemens and has received research funding from Roche Diagnostics and Siemens for work related to angiogenic biomarkers unrelated to the submitted work. A. Mueller reports serving as a statistical consultant to Roche Diagnostics for a study related to the use of angiogenic factors in preeclampsia. S.V. received speaker fees and participated in advisory boards from Roche Diagnostics, ThermoFisher, Siemens and Beckman Coulter outside the submitted work. All other authors report no conflict of interest. No commercial organization was involved in the conception or delivery of this work.

CRediT authorship contribution statement

Easha Patel: Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology. **Sunitha Suresh:** Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Conceptualization. **Ariel Mueller:** Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Formal analysis, Conceptualization. **Courtney Bisson:** Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Conceptualization. **Katherine Zhu:** Writing – review & editing, Writing – original draft. **Stefan Verlohren:** Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Conceptualization. **Peter Von Dadelszen:** Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Conceptualization. **Laura Magee:** Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Conceptualization. **Sarosh Rana:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Patient Consent

This is a secondary analysis of prior prospective study during which written informed consent was taken for collection of data.

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Presentation

Preliminary data was presented as poster at the 23rd World Congress of the International Society for Study of Hypertension in Pregnancy from Aug 28-31, 2022, in Montpellier, Occitanie, France.

Condensation

sFlt1/PlGF and blood pressure measurement alone can be used in resource-limited settings to identify high risk patients.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.xagr.2024.100359.

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