SIEMENS Healthineers

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Short-term Prediction of Preeclampsia with Severe Features Among Women Hospitalized with Hypertensive Disorders of Pregnancy

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Background

Preeclampsia (PE) is estimated to occur in 2–8% of all pregnancies worldwide and is one of the leading causes of maternal morbidity.[1,2] PE and the other hypertensive disorders of pregnancy (HPD) also remain a leading cause of maternal, neonatal, and fetal mortality worldwide. PE with severe features is characterized by severe hypertension and significant end-organ dysfunction of one or multiple major organs, such as the heart, brain, liver, or kidneys. PE with severe features is responsible for 11%–14% of maternal mortality globally and is the second most frequent direct obstetrical cause of death.

As defined by the American College of Obstetricians and Gynecologists (ACOG), PE is characterized by high blood pressure, defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg, and end-organ dysfunction with or without proteinuria after 20 weeks gestation.[3] Some of the known risk factors of PE include nulliparity, PE with previous pregnancy, and chronic hypertension, yet in many cases of PE patients do not have identifiable risks.[3] Though the underlying pathophysiology has not been fully elucidated for PE, the literature currently supports a spectrum of disease with differences with timing of PE onset.[3,4] This multi-factor process involves placental dysfunction and angiogenic imbalance. Biomarkers characterizing this imbalance are used in combination as measurements of soluble Fms-like tyrosine kinase-1 (sFlt-1) and placental growth factor (PlGF).

In a prior US multi-center study, results indicated that the BRAHMS KRYPTOR sFlt-1/PlGF ratio (PE ratio), at a cut-off of 40, aids in the risk assessment of pregnant women hospitalized for HPD for progression to preeclampsia with severe features (as defined by the ACOG guidelines) within 2 weeks of presentation.[5,6] The purpose of this study was to evaluate the clinical performance of the PE ratio generated using the Atellica IM sFlt-1 and PlGF assays as an aid in the prediction of PE with severe features among women hospitalized with HDP.

Samples and Method

Samples. Subjects enrolled in the PRAECIS validation cohort (N= 715 samples), without signs of PE with severe features at enrollment were eligible for this study (N= 556 samples).[7] Of the eligible samples collected as part of the PRAECIS validation cohort, 35 had insufficient volume to evaluate on the Atellica IM sFlt-1 and PlGF assays to generate the PE ratio, leaving a total of 521 samples included in the evaluation on Atellica IM sFlt-1 and PlGF. The PRAECIS validation study enrolled pregnant women aged ≥18 years old admitted to hospital between 23+0 and 34+6/7 gestational weeks with a singleton pregnancy and a HDP across 18 tertiary and community U.S. hospitals. Serum samples and patients' demographic and clinical characteristics were collected at enrollment; outcomes including the development of PE with severe features were prospectively collected within the two weeks after enrollment. The primary outcome was the prediction of clinically adjudicated diagnosis of PE with severe features within two weeks after enrollment (Figure 1).

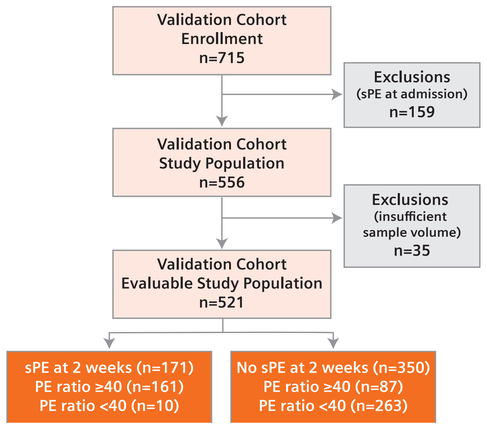

Figure 1. PRAECIS Validation Cohort Enrollment Consort Diagram

Testing. Serum samples were tested in singlicate at a single US site using the Siemens Healthineers Atellica IM sFlt-1 and Atellica IM PlGF assays run on an Atellica IM Analyzer system. The clinical performance (sensitivity [SE], specificity [SP], positive predictive value [PPV], and negative predictive value [NPV]) of the PE ratio was evaluated using the cutoff of 40 in relation to PE with severe features diagnostic status within two weeks after admission. Note: sPE: preeclampsia with severe features.

Results

Participants. Women were enrolled from 18 U.S. tertiary care and community hospitals in both urban and suburban environments to ensure heterogeneity of pregnant women in the United States. A total of 521 samples collected in the PRAECIS validation cohort were used for this study. The distribution of demographic and clinical characteristics of all subjects included in the clinical study are summarized in Table 1. The mean age of subjects was 32 years, and the mean gestational age at enrollment was 30 weeks. Roughly half (53%) of the subjects were White/Caucasian, 31% Black, 6% Asian and the remaining 10% were either American Indian/Alaskan Native, Hawaiian/ Pacific Islander, other or unknown.

Table 1. PRAECIS Validation Cohort Subject Demographics and Clinical Characteristics at Enrollment in Study.

Characteristics		Total, N=556		Included, N=521	
		N	%	N	%
Race	White/Caucasian	296	53.2%	275	52.8%
	Asian	33	5.9%	31	6.0%
	Black/African American	169	30.4%	162	31.1%
	Am. Indian/Alaskan Native	3	0.5%	3	0.6%
	Hawaiian/ Pacific Islander	3	0.5%	3	0.6%
	Other	24	4.3%	23	4.4%
	Unknown	28	5.0%	24	4.6%
Ethnicity	Hispanic	90	16.2%	84	16.1%
Smoker (Current)	Yes	47	8.5%	44	8.5%
History of Chronic HTN	Yes	313	56.3%	300	57.6%
History of Diabetes	Yes	79	14.2%	75	14.4%
History of Kidney Disease	Yes	25	4.5%	25	4.8%
History of PE	Yes	150	27.0%	141	27.1%
Chronic HTN	Yes	232	41.7%	224	43.0%
Gestational Hypertension	Yes	113	20.3%	111	21.3%
PE	Yes	71	12.8%	70	13.4%
Superimposed PE	Yes	68	12.2%	64	12.3%
Maternal Age (Years)		556	31.7 (5.8)	521	31.8 (5.8)
Gestational Age (Weeks)		556	30.4 (3.1)	521	30.4 (3.1)
Gestational Age (Weeks + Days)		30 w + 3 days (± 3 days)			
BMI at Enrollment (kg/m2)		510	37.3 (9.8)	477	37.3 (9.8)
Gravidity		556	2.9 (2.0)	521	2.9 (2.1)
Highest Diastolic BP (mmHg)	Mean (SD)	550	95 (13.6)	515	94.5 (13.8)
Highest Systolic BP (mmHg)		551	158 (21.0)	516	158.3 (21.1)
Platelets (x103/µL)		543	250 (72)	508	250 (71)
ALT (U/L)		511	20 (38.6)	477	20.5 (39.6)
AST (U/L)		510	21 (16.3)	476	20.9 (16.3)
Highest Urine Protein: Creatinine		387	109 (82.5)	365	109 (82.2)

Note: PE=Preeclampsia; BP= blood pressure; HTN=hypertension; Am=American; AST=aspartate transaminase; ALT=alanine transaminase

The median Atellica IM PE ratio was 312 (Q1: 109, Q3: 645) among women who developed PE with severe features compared with 8 (Q1: 3, Q3: 39) in those who did not develop PE with severe features. The PE ratio using a cutoff of 40 showed high clinical performance in relation to the development of PE with severe features within two weeks (SE=94.2% (95% CI: 89.6-96.8%); SP=75.1% (95% CI:70.4-79.4%); PPV= 64.9% (95% CI: 58.8–70.6%); NPV= 96.3% (95% CI: 93.4–98.0%)), which was similar to the clinical performance of the BRAHMS KRYPTOR PE ratio at the cutoff of 40 in the PRAECIS cohort (SE=94%, SP=75%, PPV=65%, NPV=96%)[7]. Similarly, high PPVs and NPVs were observed for HDP subjects across maternal age groups (<35 vs ≥35 years) and gestational age groups (<30 weeks vs ≥30 weeks). The positive likelihood ratio (LR+) was 3.79 (95% CI: 3.15–4.56) and the negative likelihood ratio (LR–) was 0.08 (95% CI: 0.04–0.14).

Table 2. Prognosis to PE with Severe Features Within 2 Weeks After Enrollment Among Total Population (N=521)

		PE with severe features				95% CI
PE ratio	Total	present	absent	SE	**94.20%**	89.6%–96.8%
ratio ≥ 40	248	161	87	SP	**75.10%**	70.4%–79.4 %
ratio < 40	273	10	263	PPV	**64.90%**	58.8%–70.6%
Total	521	171	350	NPV	**96.30%**	93.4%–98.0%
		LR+	95% CI		LR–	95% CI
PE ratio ≥ 40 (positive)		3.79	3.15–4.56		0.08	0.04–0.14

Note: PE=preeclampsia; SE=sensitivity; SP=specificity; PPV= positive predictive value; NPV=negative predictive value; CI=confidence interval; LR=likelihood ratio

Table 3. Prognostic Performance by Hypertensive Disorder

Hypertensive Disorder	n	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95%)	NPV (95% CI)
PE	121	98.6% (92.2%, 99.7%)	59.6% (46.1%, 71.8%)	76.4% (66.6%, 84.0%)	96.9% (84.3%, 99.5%)
Superimposed PE	64	93.3% (78.7%, 98.2%)	55.9% (39.5%, 71.1%)	65.1% (50.2%, 77.6%)	90.5% (71.1%, 97.4%)
Gestational Hypertension	111	87.5% (69.0%, 95.7%)	78.2% (68.4%, 85.5%)	52.5% (37.5%, 67.1%)	95.8% (88.3%, 98.6%)
Chronic Hypertension	224	91.7% (80.4%, 96.7%)	81.8% (75.5%, 86.8%)	57.9% (46.7%, 68.4%)	97.3% (93.3%, 99.0%)

Note: PE=preeclampsia; PPV=positive predictive value; NPV=negative predictive value; CI=confidence interval

Table 4: Prognostic Performance by Maternal Age at Enrollment

Maternal age	n	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
<35 years	343	95.0% (89.4%, 97.7%)	79.5% (73.7%, 84.2%)	71.1% (63.6%, 77.6%)	96.7% (93.1%, 98.5%)
≥35 years	178	92.3% (81.8%, 97.0%)	67.5% (58.9%, 75.0%)	53.9% (43.6%, 63.9%)	95.5% (89.0%, 98.2%)

Table 5: Prognostic Performance by Gestational Age at Enrollment

Gestational age	n	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
<30 weeks	173	98.5% (92.0%, 99.7%)	84.0% (75.8%, 89.7%)	79.5% (69.6%, 86.8%)	98.9% (94.0%, 99.8%)
≥30 weeks	348	91.4% (84.4%, 95.4%)	71.3% (65.3%, 76.6%)	57.6% (50.0%, 64.9%)	95.1% (90.9%, 97.4%)

Note: PPV=positive predictive value; NPV=negative predictive value; CI=confidence interval

There were slight differences in prognostic performance by subgroup. Additionally, visual inspection of the subgroup results suggest that results are similar as displayed by overlapping confidence intervals, apart from specificity for superimposed PE and chronic hypertension in Table 3 as well as PPV for gestational age in Table 5.

Individual Analyte Performance. The median Atellica IM sFlt-1was 20,265 pg/mL (Q1: 11,744 pg/mL, Q3: 34,050 pg/mL) among women who developed PE with severe features compared with 2,362 pg/mL (Q1: 1,242 pg/mL, Q3: 5,248 pg/mL) in those who did not. The median Atellica IM PlGF concentration was 75 pg/mL (Q1: 47 pg/mL, Q3: 106 pg/mL) among women who developed PE with severe features compared with 254 pg/mL (Q1: 125 pg/mL, Q3: 492 pg/mL) in those who did not.

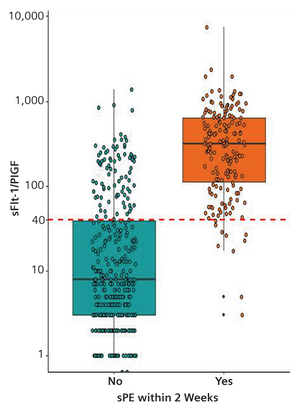

Figure 2. Serum sFlt-1/PlGF Ratio in Women Who Develop or Do Not Develop PE with severe features over 2 Weeks. Vertical Axis Log Scaled. The median Atellica IM PE ratio was 312 (Q1: 109, Q3: 645) among women who developed PE with severe features compared with 8 (Q1: 3, Q3: 39) in those who did not.

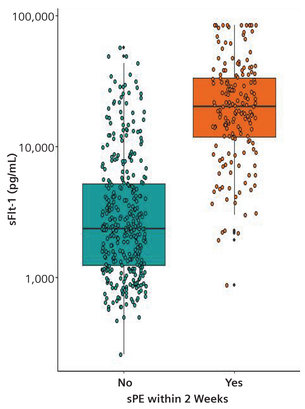

Figure 3. Distribution of sFlt-1 in Women Who Develop or Do Not Develop PE with severe features over 2 Weeks. Vertical Axis Log Scaled. The median Atellica IM sFlt-1 concentration was 20,265 pg/mL (Q1: 11,744 pg/mL, Q3: 34,050 pg/mL) among women who developed PE with severe features compared with 2,362 pg/mL (Q1: 1,242 pg/mL, Q3: 5,248 pg/mL) in those who did not.

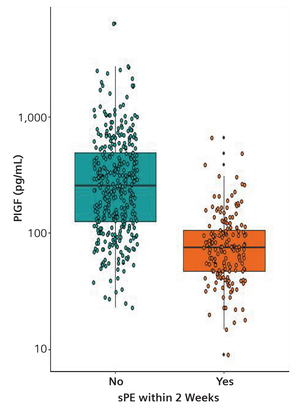

Figure 4. Distribution of PlGF in Women Who Develop or Do Not Develop PE with severe features over 2 Weeks. Vertical Axis Log Scaled. The median Atellica IM PlGF concentration was 75 pg/mL (Q1: 47 pg/mL, Q3: 106 pg/mL) among women who developed PE with severe features compared with 254 pg/mL (Q1: 125 pg/mL, Q3: 492 pg/mL) in those who did not.

Conclusion

The Atellica sFlt-1/PlGF ratio using a cutoff of 40 demonstrated:

- sensitivity of **94.2%** (95% CI: 89.6%–96.8%),
- specificity of **75.1%** (95% CI: 70.4%–79.4%),
- PPV of **64.9%** (95% CI: 58.8%–70.6%), and
- NPV of **96.3%** (95% CI: 93.4%–98.0%).

Additionally, the positive likelihood ratio and negative likelihood ratio were:

- (LR+) = **3.79** (95% CI: 3.15–4.56),
- (LR–) = **0.08** (95% CI: 0.04–0.14).

Performance characteristics were similar across subgroups, including maternal age, gestational age, and hypertensive disorder at presentation.

These findings support the potential utility of the Siemens Healthineers Atellica IM sFlt-1/PlGF ratio for further investigation in hospitalized patients with hypertensive disorders of pregnancy, in relation to subsequent development of PE with severe features.

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