

Short-Term Prediction of Adverse Outcomes Using the sFlt-1 (Soluble fms-Like Tyrosine Kinase 1)/PlGF (Placental Growth Factor) Ratio in Asian Women With Suspected Preeclampsia

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Abstract—Current diagnostic criteria have limited clinical value for prediction of preeclampsia and fetal adverse outcomes. The prediction of short-term outcome in pregnant women with suspected preeclampsia study in Asia (PROGNOSIS Asia) was a prospective, multicenter study designed to investigate the value of the sFlt-1 (soluble fms-like tyrosine kinase 1)/PlGF (placental growth factor) ratio for predicting adverse outcomes in pregnant Asian women with suspected preeclampsia. Seven hundred sixty-four pregnant women at gestational week 20+0 days (18+0 days in Japan) to 36+6 days were enrolled at 25 sites in Asia. The primary objectives were to demonstrate the value of the sFlt-1/PlGF ratio for ruling out preeclampsia within 1 week and ruling in preeclampsia within 4 weeks. The value of the ratio for predicting fetal adverse outcomes was also assessed. Seven hundred patients were evaluable for primary end point analysis. The prevalence of preeclampsia was 14.4%. An sFlt-1/PlGF ratio of ≤ 38 had a negative predictive value of 98.6% (95% CI, 97.2%–99.4%) for ruling out preeclampsia within 1 week, with 76.5% sensitivity and 82.1% specificity. The positive predictive value of a ratio of >38 for ruling in preeclampsia within 4 weeks was 30.3% (95% CI, 23.0%–38.5%), with 62.0% sensitivity and 83.9% specificity. An sFlt-1/PlGF ratio of ≤ 38 had a negative predictive value of 98.9% (95% CI, 97.6%–99.6%) for ruling out fetal adverse outcomes within 1 week and a ratio of >38 had a positive predictive value of 53.5% (95% CI, 45.0%–61.8%) for ruling in fetal adverse outcomes within 4 weeks. The sFlt-1/PlGF ratio cutoff of 38 demonstrated clinical value for the short-term prediction of preeclampsia in Asian women with suspected preeclampsia, potentially helping to prevent unnecessary hospitalization and intervention. (*Hypertension*. 2019;74:164-172. DOI: 10.1161/HYPERTENSIONAHA.119.12760.) • [Online Data Supplement](#)

Key Words: Asia ■ placenta growth factor ■ preeclampsia ■ prognosis ■ angiogenic factor ■ fms-like tyrosine kinase ■ pregnancy outcome

Preeclampsia is a heterogeneous, multiorgan disorder of pregnant women, which is associated with significant maternal and fetal morbidity and mortality. Preeclampsia represents a global public health burden, affecting an estimated 2% to 8% of pregnancies^{1–3} and posing substantial risks to the fetus, including placental abruption, iatrogenic preterm delivery, fetal growth restriction (FGR), and perinatal mortality.⁴ The risk of stillbirth is >7 -fold higher in pregnancies

complicated with preeclampsia compared with those without,⁵ and a recent study in China found a stillbirth rate of 21.9/1000 births in women with a hypertensive disorder of pregnancy.⁶

The current diagnostic criteria for preeclampsia include new onset of hypertension after 20 weeks' gestation coupled with new onset of 1 or more of the following conditions: proteinuria, renal insufficiency, impaired liver function, neurologic complications, thrombocytopenia, or uteroplacental

Received January 30, 2019; first decision February 17, 2019; revision accepted May 3, 2019.

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The online-only Data Supplement is available with this article at <https://www.ahajournals.org/doi/suppl/10.1161/HYPERTENSIONAHA.119.12760>.

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DOI: 10.1161/HYPERTENSIONAHA.119.12760

dysfunction.⁷ Clinical experience suggests that early detection of preeclampsia, timely referral to a specialist center, and active monitoring are beneficial to both the patient and the treating physician.⁸ The clinical presentation of preeclampsia is extremely variable, impacting the specificity and reliability of clinical assessments for the prediction of preeclampsia.^{7,9} Consequently, women with clinical signs and symptoms associated with preeclampsia may be unnecessarily hospitalized for intensive monitoring until preeclampsia is ruled out. Conversely, women who require hospitalization may be overlooked because of failure to predict preeclampsia based on the current diagnostic criteria. A reliable short-term predictor of disease and associated fetal adverse outcomes in women with suspected preeclampsia is needed to help alert healthcare workers to increase surveillance and provide improved antenatal care to ameliorate adverse outcomes in these pregnancies.^{6,10}

The angiogenic markers sFlt-1 (soluble fms-like tyrosine kinase 1) and PlGF (placental growth factor) are associated with placental dysfunction, and the sFlt-1/PlGF ratio is elevated in women with a confirmed diagnosis of preeclampsia.^{11,12} A high ratio is associated with an increased risk of preeclampsia and an increased risk of adverse pregnancy outcomes in women with preeclampsia.^{11–15} The previously published prediction of short-term outcome in pregnant women with suspected preeclampsia study (PROGNOSIS) was designed to investigate the value of the sFlt-1/PlGF ratio for the short-term prediction of preeclampsia. This study demonstrated that an sFlt-1/PlGF ratio of ≤ 38 can be used to rule out the occurrence of preeclampsia within 1 week with a negative predictive value (NPV) of 99.3% in women with suspected preeclampsia. The majority (>80%) of women enrolled in the PROGNOSIS study were white, with only $\approx 5\%$ of women being of Asian origin.¹⁶ Because both sFlt-1 and PlGF concentrations may be influenced by ethnicity,¹⁷ the PROGNOSIS Asia study was designed to validate the sFlt-1/PlGF ratio cutoff of 38 for the short-term prediction of preeclampsia/eclampsia/HELLP (hemolysis, elevated liver enzymes, low platelets) syndrome, as well as of fetal adverse outcomes, in a cohort of pregnant Asian women with suspected preeclampsia.

Methods

The authors declare that all supporting data are available within the article (and its [online-only Data Supplement](#)).

Study Overview

PROGNOSIS Asia was a prospective, multicenter, double-blind, observational study conducted at 25 sites in Asia (China, Hong Kong, Japan, Singapore, South Korea, and Thailand) between December 2014 and December 2016. A full list of participating sites and principal investigators is provided in Table S1 in the [online-only Data Supplement](#). The study was performed in compliance with the guidelines for Good Clinical Practice. The 2 laboratories responsible for sample analysis (Covance Central Laboratory Service in Singapore and Shanghai, China) were College of American Pathologists accredited. The country-specific regulations of the participating countries were respected for both clinical and laboratory evaluations.

Study Objectives

The primary objectives were to demonstrate that sFlt-1/PlGF ratio values of ≤ 38 can rule out the occurrence of preeclampsia/eclampsia/HELLP syndrome within 1 week after baseline visit, and sFlt-1/PlGF ratio values of >38 can rule in the occurrence of preeclampsia/

eclampsia/HELLP syndrome within 4 weeks after baseline visit. Secondary objectives included investigating the value of the sFlt-1/PlGF ratio for predicting fetal adverse outcomes within 1 week or 4 weeks, as well as the relationship between an sFlt-1/PlGF ratio of >38 and time to delivery and preterm delivery.

Study Participants

Eligible participants included pregnant women ≥ 18 years of age, at gestational week 20+0 to 36+6 days, with suspected preeclampsia according to protocol-defined criteria (Table S2). These included 1 or more of the following: new onset of hypertension (systolic blood pressure [BP] ≥ 140 mm Hg or diastolic BP ≥ 90 mm Hg, single measurement), aggravation of preexisting hypertension (systolic BP ≥ 160 mm Hg or diastolic BP ≥ 110 mm Hg, single measurement), new onset of proteinuria, aggravation of preexisting proteinuria, severe persistent right upper quadrant or epigastric pain unresponsive to medication and not accounted for by alternative diagnoses, new onset of visual disturbances (eg, blurred vision, diplopia), suspected FGR or abnormal uterine perfusion detected by Doppler sonography with mean pulsatility index >95 th percentile or bilateral notch, and partial HELLP syndrome (1 or 2 of the 3 features of HELLP syndrome present). Inclusion criteria differed slightly for the Japanese study population to match local practice guidelines (gestational week 18+0 days to 36+6 days and new onset of elevated systolic BP ≥ 130 mm Hg or diastolic BP ≥ 80 mm Hg and aggravation of preexisting hypertension [systolic BP >140 mm Hg or diastolic BP >90 mm Hg]). To avoid an overrepresentation of late-onset preeclampsia, the proportion of patients at gestational week $>32+0$ during enrollment was not to exceed 50% of all participants per study site. The proportion of women with suspected preeclampsia because of abnormal uterine perfusion was also not to exceed 25% at each site. Women who had manifest preeclampsia or a confirmed diagnosis of HELLP syndrome, those with multiple pregnancies, and those who had received treatment with an investigational medicine within 90 days before enrollment were excluded. Participants were enrolled in a consecutive series, and all participants provided written informed consent.

Study Design

The study was a prospective, noninterventional, multicenter study. Participation in the study had no impact on the subject's health. This study consisted of the following 2 parts: (1) collection of serum samples and clinical data collection and (2) measurement of sFlt-1 and PlGF in the collected serum samples. To prevent the results from influencing clinical decisions, sample measurements were not performed until after study completion. Clinical information, including medical history, clinical assessments, collection of serum samples, and maternal and neonatal outcomes were documented at defined study visits. Assessments according to standardized procedures were made at baseline visit, visit 2 (+7 to 14 days), visit 3 (+24 to 32 days), and at delivery, as well as at the postpartum visit. In addition, unscheduled visits also occurred in the event of pregnancy complications.

Diagnostic Criteria

Diagnostic criteria for classification of preeclampsia and preeclampsia-related disorders used in the study were based on the international guidelines of the International Society for the Study of Hypertension in Pregnancy, ensuring comparability of study results with the PROGNOSIS study (Table S3).⁷ Diagnostic criteria for preeclampsia were new onset of both hypertension (systolic BP ≥ 140 mm Hg or diastolic BP ≥ 90 mm Hg) and proteinuria ($\geq 2+$ protein on dipstick urinalysis, ≥ 300 mg of protein per 24-hour urine collection, ≥ 30 mg of protein per deciliter in a spot urine sample, or a ratio of protein to creatinine of ≥ 30 mg/mmol) after gestational week 20. The same diagnostic criteria were applied for the complete study population and the population meeting Japanese-specific inclusion criteria only. Diagnosis of preeclampsia and preeclampsia-related disorders according to local criteria not meeting the diagnostic criteria defined in the study protocol was not accepted. Preeclampsia status was classified as no preeclampsia, suspected preeclampsia, preeclampsia, superimposed preeclampsia, severe preeclampsia, eclampsia, and

HELLP syndrome or a combination of these outcomes. Protocol-defined fetal adverse outcomes were perinatal or fetal death, delivery at a gestational age <34 weeks, FGR, small for gestational age, placental abruption, respiratory distress, necrotizing enterocolitis, and intraventricular hemorrhage. Additional adverse outcomes defined for the analysis included hospitalization separate from the mother, stay at neonatal intensive care unit, hypoxia, neurological injury, low birth weight, and asphyxia. Protocol-defined maternal adverse outcomes (other than preeclampsia, eclampsia, or HELLP syndrome) were death, pulmonary edema, acute renal failure, cerebral hemorrhage, cerebral thrombosis, and disseminated intravascular coagulation. Additional adverse outcomes defined for the analysis included liver rupture, renal failure, stroke, cardiac arrest, adult respiratory distress syndrome, liver failure, preeclampsia-associated retinopathy, and stay in intensive care unit.

Assessment of sFlt-1 and PlGF

Maternal serum samples (2 mL) were collected according to a standard operating procedure and were frozen until analysis. Samples were analyzed retrospectively at 2 independent central laboratories in the region (Covance Central Laboratory Service in Singapore and Shanghai, China). Maternal serum levels of sFlt-1 and PlGF (measured in picogram per milliliter) were determined by the fully automated Elecsys sFlt-1 and PlGF immunoassays on cobas e analyzers (Roche Diagnostics, Mannheim, Germany) according to the method sheets. Measurement results were captured electronically both by the system of the central laboratory and simultaneously by the validated Roche evaluation software tool Windows-based computer-aided evaluation. The complete set of measurement results for sFlt-1 and PlGF were transferred at the end of the study to the Roche biostatistics department (Penzberg, Germany), where the sFlt-1/PlGF ratio was calculated.

Statistical Analysis

Sample size calculations were performed according to Pepe¹⁸ and suggestions provided by medical experts on the minimal requirements for NPV and positive predictive value (PPV). The prevalence of preeclampsia/eclampsia/HELLP syndrome in the observed target population of pregnant Asian women with suspicion of preeclampsia was estimated to be 10%–15%. The minimum acceptable NPV and PPV were defined as NPV=90% (lower limit of the 95% CI) and PPV=20% (lower limit of the 95% CI). Based on these values, a sample size of a minimum of 600 evaluable subjects was set to achieve study power of 90%.

Statistical analysis was performed using SAS 9.4 and R 3.2.2. Descriptive statistics for continuous data are reported by calculating median and interquartile range. Descriptive statistics for count data are reported by absolute (counts) and relative (percent) frequencies. Predictive performance of the ratio was assessed by estimating NPV and PPV, sensitivity and specificity, and the area

under curve (AUC) with receiver operating characteristic curves, with corresponding 95% CIs.

Results

Study Population

A total of 764 women with suspected preeclampsia were enrolled. Seven hundred participants were eligible for analysis of the primary objective (Figure 1). Not all patients included in the analysis of the primary objective met the criteria for inclusion in the analysis of secondary objectives. Despite a slight difference in the inclusion criteria between patients enrolled in Japan and those from the 5 other regions, there was no observed difference in the baseline characteristics of the entire patient population and those enrolled based on the Japanese-specific criteria only. Therefore, these populations were considered to be comparable, allowing the combined analysis of the entire population. Age and gestational age at baseline visit were comparable between participants who developed preeclampsia and those who did not develop preeclampsia. Systolic BP at baseline visit, diastolic BP at baseline visit, maximum systolic and maximum diastolic BP (at any time), and prepregnancy body mass index were significantly higher in the preeclampsia group than in the nonpreeclampsia group (Table 1). Gestational age at delivery was smaller in the preeclampsia group compared with the nonpreeclampsia group. Height and weight of the neonate were also lower in the preeclampsia group compared with the nonpreeclampsia group. Preeclampsia was diagnosed in 4.9% of patients within 1 week and in 10.1% within 4 weeks after baseline visit. The overall prevalence of preeclampsia in the study population was 14.4%. The distributions of the sFlt-1/PlGF ratio at baseline visit were similar across each of the different countries of origin.

Prediction of Preeclampsia

The median sFlt-1/PlGF ratio at baseline visit was higher in patients who developed preeclampsia within 1 week (193.8) compared with patients who did not develop preeclampsia within 1 week (7.5). The same pattern was also observed for patients who developed preeclampsia within 4 weeks (71.4) compared with those who did not develop preeclampsia within 4 weeks (6.9) and in patients who developed preeclampsia at any time (45.5) compared with those who did not (6.6;

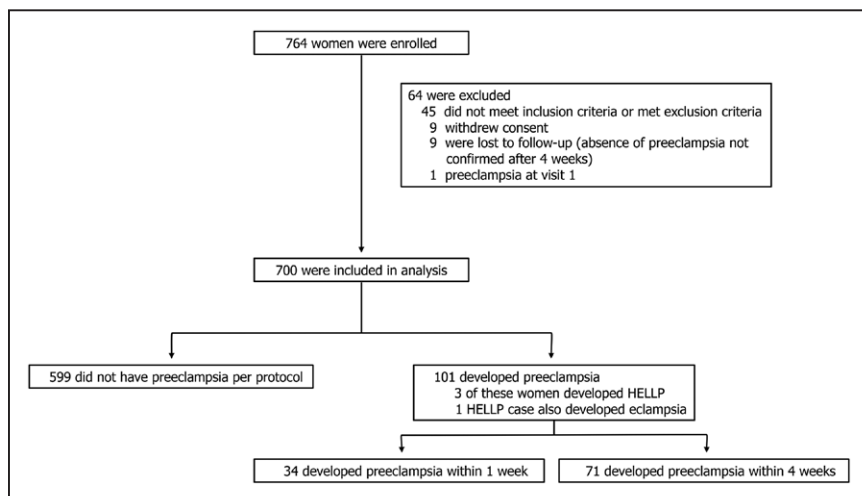


Figure 1. Standards for Reporting of Diagnostic Accuracy Studies flowchart for the primary study objectives and preeclampsia outcomes. The number of preeclampsia cases observed within 1 wk from study start is contained in the number of preeclampsia cases occurring within 4 wks. Equally, preeclampsia cases occurring at any point during the pregnancy contains the number of preeclampsia cases occurring within 4 wks. HELLP indicates hemolysis, elevated liver enzymes, low platelets.

Table 1. Baseline Characteristics of the Study Participants and Reasons for Suspicion of Preeclampsia*

Characteristic	All Patients (N=700)	No Preeclampsia/Eclampsia/HELLP (N=599)	Preeclampsia/Eclampsia/HELLP (N=101)
Median age, y (IQR)	33 (29–36)	33 (29–36)	33 (28–36)
Median week of gestation at baseline visit (IQR)	31.6 (27.2–34.6)	31.6 (26.9–34.6)	31.6 (28.0–33.7)
Median week of gestation at delivery (IQR)	38.1 (37.0–39.3)	38.3 (37.1–39.4)	36.4 (34.1–38.0)†
Median blood pressure at baseline visit, mm Hg (IQR)			
Systolic	134 (119–145)	132 (116–144)	144 (135–156)†
Diastolic	84 (71–93)	81 (70–92)	90 (84–99)†
Max systolic blood pressure at any time, mm Hg (IQR)	141 (129–155)	139 (125–149)	161 (151–170)†
Max diastolic blood pressure at any time, mm Hg (IQR)	90 (80–100)	88 (79–97)	102 (95–109)†
Median prepregnancy BMI, kg/m ² (IQR)	22.9 (20.5–26.2)	22.7 (20.4–25.9)	24.2 (21.2–28.7)‡
Smoking, N (%)			
Past	60 (8.6)	47 (7.8)	13 (12.9)
Current	11 (1.6)	8 (1.3)	3 (3.0)
Race, N (%)			
Asian	699 (99.9)	598 (99.8)	101 (100.0)
White	1 (0.1)	1 (0.2)	0 (0.0)
Height of neonate, cm (IQR)	48.0 (46.0–50.0)	49.0 (46.0–50.0)	46.0 (44.0–49.0)†
Weight of neonate, g (IQR)	2850 (2334–3250)	2896 (2450–3285)	2310 (1790–2965)†
Reasons for suspected preeclampsia N (%)§			
New onset of hypertension	363 (51.9)	300 (50.1)	63 (62.4)¶
Aggravation of preexisting hypertension	65 (9.3)	47 (7.8)	18 (17.8)‡
New onset of proteinuria	193 (27.6)	159 (26.5)	34 (33.7)
Aggravation of preexisting proteinuria	4 (0.6)	2 (0.3)	2 (2.0)
Suspected FGR/abnormal uterine perfusion	188 (26.9)	166 (27.7)	22 (21.8)
Visual disturbances	3 (0.4)	2 (0.3)	1 (1.0)
Partial HELLP syndrome	16 (2.3)	14 (2.3)	2 (2.0)

P Values were calculated with the use of the Mann-Whitney U test for continuous variables and Fisher exact test for categorical variables. BMI indicates body mass index; FGR, fetal growth restriction; HELLP, hemolysis, elevated liver enzymes, low platelets; and IQR, interquartile range.

*Preeclampsia, eclampsia, and the HELLP syndrome were diagnosed according to protocol-specified criteria.

†P<0.001.

‡P<0.01.

§There may have been more than 1 reason for suspected preeclampsia.

¶P<0.05 for the comparison with participants in whom preeclampsia, eclampsia, and HELLP syndrome did not develop.

Figure 2A). The NPV for ruling out preeclampsia within 1 week using an sFlt-1/PIGF ratio of ≤ 38 was 98.6% (95% CI, 97.2%–99.4%). The negative likelihood ratio was 0.29 (95% CI, 0.16–0.53; Table 2). In the receiver operating characteristic analysis, the AUC of the sFlt-1/PIGF ratio for ruling out preeclampsia within 1 week was 84.3% (95% CI, 75.6%–91.4%; Figure 2B). The PPV for ruling in preeclampsia within 4 weeks using an sFlt-1/PIGF ratio of >38 was 30.3% (95% CI, 23.0%–38.5%). The positive likelihood ratio was 3.86 (95% CI, 2.99–4.98; Table 2). The AUC for ruling in preeclampsia within 4 weeks was 81.2% (95% CI, 74.8%–86.6%; Figure 2B).

Prediction of Fetal Adverse Outcomes

Six hundred ninety patients were eligible for analysis of prediction of fetal adverse outcomes. Information on the occurrence of fetal adverse outcomes was not available for

10 patients. Fetal adverse outcomes occurred in 30 subjects within 1 week and in 125 subjects within 4 weeks (Figure S1). The median sFlt-1/PIGF ratio at baseline visit was higher in patients who experienced fetal adverse outcomes within 1 week (148.9) compared with those who did not (7.4). This pattern was also observed for patients who experienced fetal adverse outcome within 4 weeks (86.9) compared with those who did not (6.3; Figure 3A). The sFlt-1/PIGF ratio had an AUC of 91.0% (95% CI, 87.1%–94.5%) for any fetal adverse outcome within 1 week (Figure 3B) and an AUC of 83.1% (95% CI, 79.1%–86.9%) for any fetal adverse outcome within 4 weeks (Figure 3C). The AUC for the prediction of fetal adverse outcomes in subgroups of patients who either did or did not develop preeclampsia within 1 week (Figure 3B) or within 4 weeks (Figure 3C) is also shown. The NPV for ruling out fetal adverse outcomes within 1 week using an sFlt-1/PIGF

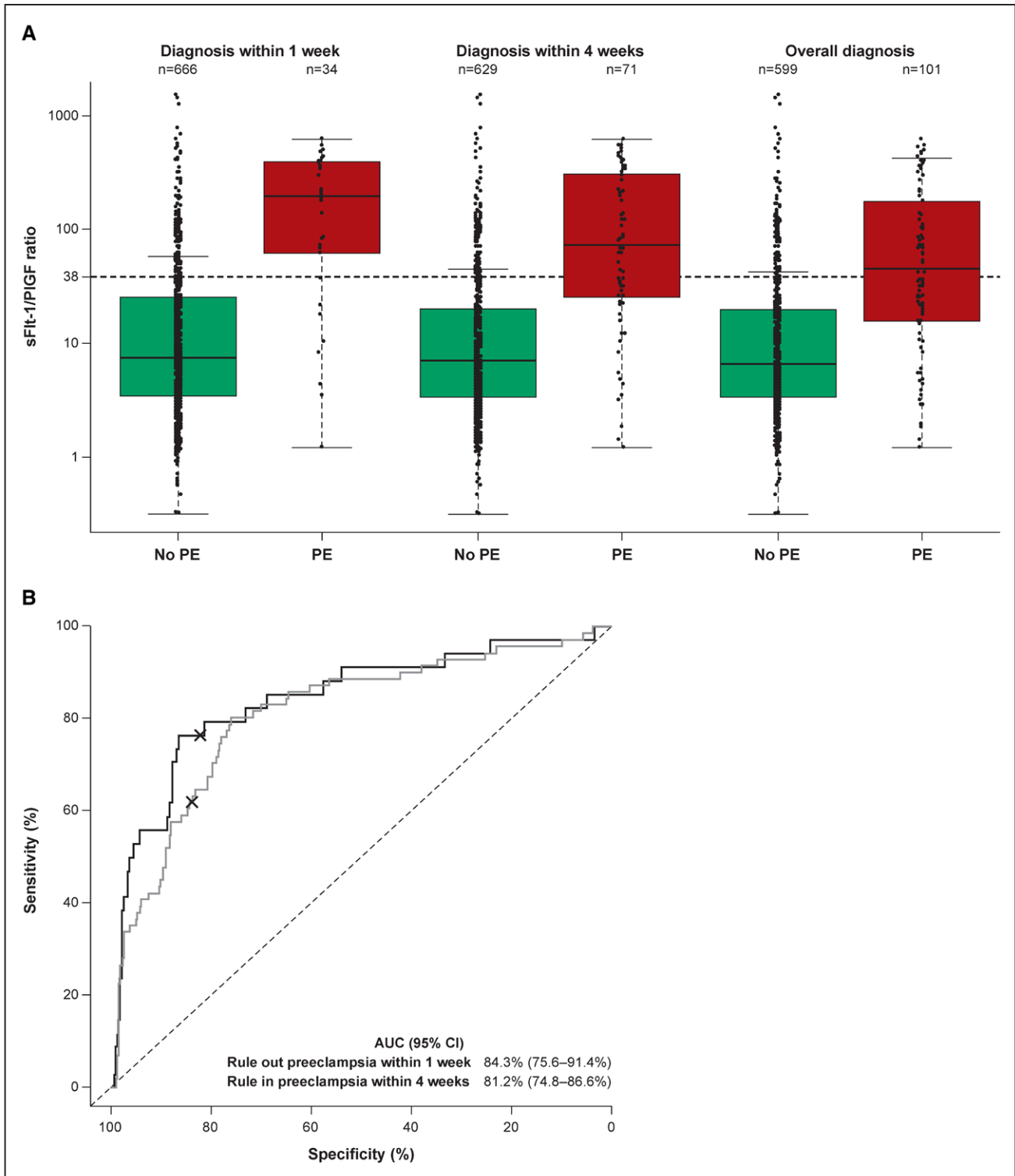


Figure 2. Predictive performance of the sFlt-1 (soluble fms-like tyrosine kinase 1)/PlGF (placental growth factor) ratio for developing preeclampsia within 1 wk and within 4 wks. **A**, The sFlt-1/PlGF ratio for participants with and without preeclampsia (preeclampsia/eclampsia/HELLP syndrome) within 1 wk, within 4 wks, and overall is shown. The boxes represent the first and third quartiles and the median value. The whiskers represent values that are 1.5× the interquartile range (IQR) or shorter in cases where the minimal/maximal value lies within 1.5× the IQR. The horizontal dotted line represents the cutoff point of 38 for the sFlt-1/PlGF ratio, with both levels measured in picogram per milliliter. **B**, The predictive performance of the sFlt-1/PlGF ratio is shown for ruling out preeclampsia within 1 wk (black) and ruling in preeclampsia within 4 wks (gray). The X shows sFlt-1/PlGF ratio =38. AUC indicates area under curve; and PE, preeclampsia.

ratio of ≤ 38 was 98.9% (95% CI, 97.6%–99.6%). The negative likelihood ratio was 0.24 (95% CI, 0.12–0.50; Table 3). The PPV for ruling in fetal adverse outcomes within 4 weeks

using an sFlt-1/PlGF ratio of >38 was 53.5% (95% CI, 45.0%–61.8%). The positive likelihood ratio was 5.19 (95% CI, 3.99–6.76; Table 3). In addition, 10 patients were observed

Table 2. Predictive Performance of the sFlt-1/PlGF Ratio for Developing Preeclampsia

sFlt-1/PlGF Ratio ≤38/>38	TN/FN	TP/FP	NPV, % (95% CI)	PPV, % (95% CI)	Sensitivity, % (95% CI)	Specificity, % (95% CI)	Negative LR (95% CI)	Positive LR (95% CI)
Within 1 wk	547/8	26/119	98.6 (97.2–99.4)	17.9 (12.1–25.2)	76.5 (58.8–89.3)	82.1 (79.0–85.0)	0.29 (0.16–0.53)	4.28 (3.34–5.48)
Within 4 wks	528/27	44/101	95.1 (93.0–96.8)	30.3 (23.0–38.5)	62.0 (49.7–73.2)	83.9 (80.8–86.7)	0.45 (0.34–0.61)	3.86 (2.99–4.98)

Seven hundred evaluable patients. FN indicates false negative; FP, false positive; LR, likelihood ratio; NPV, negative predictive value; PlGF, placental growth factor; PPV, positive predictive value; sFlt-1, soluble fms-like tyrosine kinase 1; TN, true negative; and TP, true positive.

to have a ratio of >400 at baseline visit without developing preeclampsia during the study period. However, 5 of these patients developed fetal adverse outcomes within 1 week, and all of the 10 patients developed fetal adverse outcomes within 4 weeks. Seven of these patients developed FGR and 9 experienced delivery before gestational week 34. There was no placental abruption in any of these cases.

Time to Delivery and Preterm Delivery

A ratio >38 at baseline visit was associated with a shorter pregnancy duration (for both patients who developed preeclampsia and those who did not develop preeclampsia; Figures S2 and S3). Higher sFlt-1/PlGF ratios were also observed in subjects with preterm delivery (<37 weeks) compared with term delivery in patients with both early- (<34 weeks) or late-onset (≥34 weeks) preeclampsia (Figure S4). Women with an sFlt-1/PlGF ratio >38 also had a shorter remaining time to delivery compared with women with an sFlt-1/PlGF ratio of ≤38, independent of whether they developed preeclampsia or not. In women with an sFlt-1/PlGF ratio of >38, the percentage of women with a preterm delivery was 62.1% compared with 15.2% in women with an sFlt-1/PlGF ratio ≤38. Cox regression analysis showed a hazard ratio of 3.5 for imminent delivery in women with an sFlt-1/PlGF ratio of >38 compared with women with an sFlt-1/PlGF ratio of ≤38 (Cox model adjusted for gestational age and final preeclampsia status).

Prediction of a Combined End Point of Preeclampsia or Adverse Outcomes

An analysis investigating the sFlt-1/PlGF ratio cutoff of 38 for prediction of the combined end point of preeclampsia/eclampsia/HELLP syndrome or adverse maternal or fetal outcomes resulted in an NPV of 97.8% (95% CI, 96.2%–98.9%) for ruling out the end point within 1 week and a PPV of 65.0% (95% CI, 56.6%–72.8%) for ruling in the end point within 4 weeks.

Prediction of a Combined End Point of Preeclampsia and Delivery

A further exploratory analysis investigating the sFlt-1/PlGF ratio cutoff of 38 for prediction of a combined end point of both the occurrence of preeclampsia and occurrence of delivery resulted in an NPV of 100.0% (95% CI, 99.3%–100.0%) for ruling out the combined end point within 1 week and a PPV of 25.7% (95% CI, 18.8%–33.6%) for ruling in the combined end point within 4 weeks (Table S4).

Prediction of Maternal Adverse Outcomes

Only one case of maternal adverse outcome (as defined per study protocol) occurred. This participant developed central serous chorioretinopathy, pulmonary edema, acute renal

failure, and disseminated intravascular coagulation >4 weeks after recruitment (sFlt-1/PlGF ratio, 349.8). Therefore, an elaborated analysis for prediction of maternal adverse outcomes was not possible comparing groups with and without these adverse outcomes.

Discussion

The PROGNOSIS Asia study demonstrated the value of sFlt-1/PlGF ratio cutoff of 38, determined with the Elecsys sFlt-1 and PlGF immunoassays, for the short-term prediction of preeclampsia and fetal adverse outcomes for the first time in Asian women with signs and symptoms of preeclampsia in singleton pregnancies. The NPV for ruling out preeclampsia observed in this study is comparable to the predictive performance demonstrated by other studies investigating the value of the sFlt-1/PlGF ratio in white women with suspected preeclampsia.^{16,19,20} Triage of pregnant women with signs and symptoms of preeclampsia is important to identify those women with risk of imminent preeclampsia, eclampsia, or fetal adverse outcomes who require more intensive monitoring or even hospitalization.^{6,8,10} Ruling out women at low risk for developing preeclampsia or fetal adverse outcomes within 1 week allows them to potentially be managed in an outpatient setting. A high NPV is vital to prevent the potentially devastating consequences to both the mother and the fetus of failure to detect imminent disease because of false-negative test results. The sFlt-1/PlGF cutoff of 38 has been demonstrated to be predictive in both Asian and white women with suspected preeclampsia and, therefore, represents a unifying clinical cutoff in these patients.

The observed PPV of the sFlt-1/PlGF ratio in the PROGNOSIS Asia study was 30.3%. This is higher than values previously reported for proteinuria and measurement of BP, which have been shown to have a PPV of only 20% for detecting preeclampsia-related adverse outcomes.²¹ The PPV reported in the PROGNOSIS Asia study is also similar to the PPV of 36.7% observed in the validation cohort of the PROGNOSIS study.¹⁶ The prevalence of preeclampsia/eclampsia/HELLP syndrome was 14.4% in the PROGNOSIS Asia study compared with a prevalence of 17.8% observed in the validation cohort of the PROGNOSIS study.¹⁶ Therefore, the slightly lower prevalence of preeclampsia reported for the PROGNOSIS Asia study likely contributes to the slightly lower PPV detected for the sFlt-1/PlGF ratio. The overall prevalence of preeclampsia observed in this study population is substantially higher than the 2% to 8% of pregnancies estimated to be affected globally.^{1–3} This is expected as the study enrolled women with signs and symptoms of preeclampsia and hence at higher risk of developing the disorder.

It should be mentioned that although eligible participants in the PROGNOSIS Asia study were pregnant women at

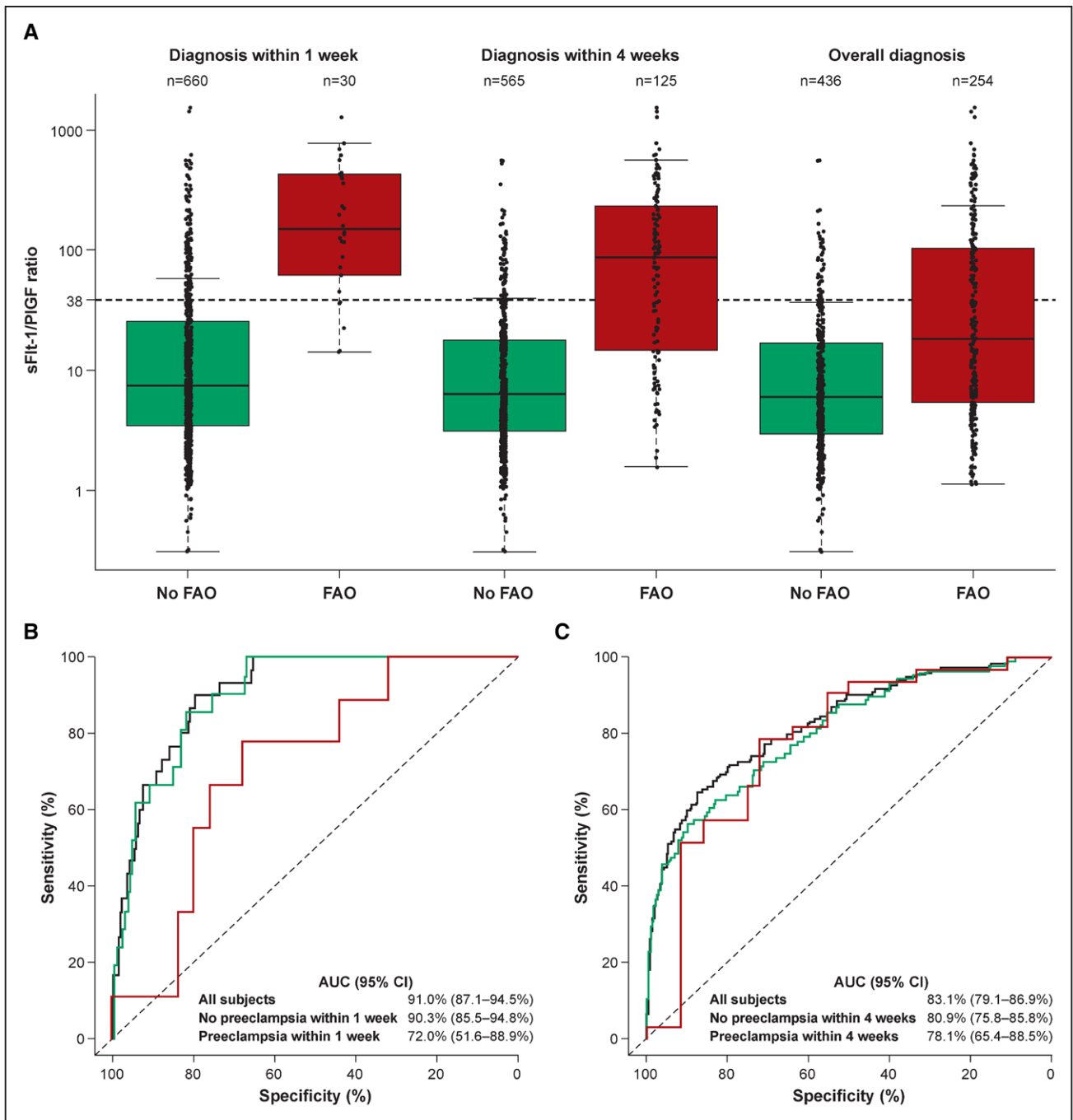


Figure 3. Predictive performance of sFlt-1 (soluble fms-like tyrosine kinase 1)/PlGF (placental growth factor) ratio for fetal adverse outcomes. **A**, The sFlt-1/PlGF ratio in women who did or did not experience fetal adverse outcomes within 1 wk, within 4 wks, and overall. The boxes represent the first and third quartiles and the median value. The whiskers represent values that are 1.5× the interquartile range (IQR) or shorter in cases where the minimal/maximal value lies within 1.5× the IQR. The horizontal dotted line represents the cutoff point of 38 for the sFlt-1/PlGF ratio, with both levels measured in picogram per milliliter. The predictive performance of the sFlt-1/PlGF ratio is shown for the prediction of fetal adverse outcomes within 1 wk (**B**) and within 4 wks (**C**) in all subjects (black), those without preeclampsia (green), and those with preeclampsia (red). AUC indicates area under curve; FAO, fetal adverse outcome; and PE, preeclampsia.

gestational week 20+0 to 36+6 days (18+0 to 36+6 days in Japan) compared with gestational week 24+0 to 36+6 days in the original PROGNOSIS study, excluding the enrolled women from gestational weeks 20+0 to 23+6 days (18+0 to 23+6 days in Japan) does not significantly affect the predictive performance of the sFlt-1/PlGF ratio for the primary study objectives. Therefore, the different inclusion criteria do not affect the comparability of the results between the 2 cohorts.

This study also found that an sFlt-1/PlGF ratio of ≤ 38 had value in predicting the absence or presence of fetal adverse outcomes within 1 and 4 weeks, respectively. Previous studies have demonstrated the added value of an elevated maternal sFlt-1/PlGF ratio in the prediction of adverse pregnancy outcomes associated with FGR. An sFlt-1/PlGF ratio >85 th percentile, in combination with ultrasound, has been shown to achieve a positive LR of 41.1 for preterm delivery

Table 3. Predictive Performance of the sFlt-1/PlGF Ratio for Developing Fetal Adverse Outcomes

sFlt-1/PlGF Ratio ≤38/>38	TN/FN	TP/FP	NPV, % (95% CI)	PPV, % (95% CI)	Sensitivity, % (95% CI)	Specificity, % (95% CI)	Negative LR (95% CI)	Positive LR (95% CI)
Within 1 wk	540/6	24/120	98.9 (97.6–99.6)	16.7 (11.0–23.8)	80.0 (61.4–92.3)	81.8 (78.7–84.7)	0.24 (0.12–0.50)	4.40 (3.46–5.60)
Within 4 wks	498/48	77/67	91.2 (88.5–93.4)	53.5 (45.0–61.8)	61.6 (52.5–70.2)	88.1 (85.2–90.7)	0.44 (0.35–0.55)	5.19 (3.99–6.76)

Six hundred ninety evaluable patients. FN indicates false negative; FP, false positive; LR, likelihood ratio; NPV, negative predictive value; PlGF, placental growth factor; PPV, positive predictive value; sFlt-1, soluble fms-like tyrosine kinase 1; TN, true negative; and TP, true positive.

of a small-for-gestational-age infant in nulliparous women at 28 weeks’ gestation.²² The current study provides further evidence, supporting the findings of previous investigations, for the use of sFlt-1 and PlGF for the prediction of clinically important fetal adverse outcomes.^{16,23,24}

It is worth noting that, although a recent study has reported a high rate of stillbirth in China,⁶ few instances of stillbirth were observed in this study. This difference in stillbirth rate is likely because of the different target populations investigated. The PROGNOSIS Asia study enrolled women at 25 sites across Asia, in contrast to the study by Xiong et al,⁶ which only investigated women from a Chinese population.

The current study also demonstrated that women with an sFlt-1/PlGF ratio of >38 had a 3.5-fold greater likelihood of an imminent delivery than subjects with a ratio of ≤38. This is comparable to the results of the PROGNOSIS study, which showed a 2.9-fold greater likelihood of imminent delivery.²⁵ Given the substantial risks to both the mother and the fetus associated with preeclampsia,² the ability to help predict complications may assist the healthcare team to balance the risk-benefit ratio for patient management.

This study has some limitations. The data were validated with the use of the Elecsys sFlt-1 and PlGF immunoassays. The optimal cutoff for the ratio to predict preeclampsia may be different when other assays are used. In addition, both PROGNOSIS and PROGNOSIS Asia were observational studies. Data from future trials in Asia are needed to establish whether use of the sFlt-1/PlGF ratio cutoff of 38 in clinical practice, as compared with the current standard of care, could reduce unnecessary hospitalizations and costs, as well as reducing fetal and maternal adverse outcomes. Only 1 maternal adverse outcome occurred in the present study. Therefore, it was not possible to evaluate the predictive performance of the sFlt-1/PlGF ratio separately for maternal adverse outcomes.

Perspectives

The PROGNOSIS Asia study demonstrated the clinical value of the sFlt-1/PlGF ratio cutoff of 38 for the short-term prediction of preeclampsia and fetal adverse outcomes, in women with signs and symptoms of preeclampsia but not fulfilling the diagnostic criteria, in an Asian population. The high NPV of the sFlt-1/PlGF ratio enables physicians in Asia to confidently rule out preeclampsia within 1 week in pregnant women with suspected preeclampsia. This may help to prevent unnecessary hospitalization and intervention, and the associated healthcare costs, for those women who will not develop preeclampsia.

Acknowledgments

The study was supported in the initial phase by Deirdre Allegranza from Roche Diagnostics International Ltd, Rotkreuz, Switzerland.

Medical writing assistance and editing services were provided by Laura Harrison and Fiona Jenkins, respectively, of Elements Communications Ltd, Westerham, United Kingdom, funded by Roche Diagnostics. Support for study conduct, monitoring, and measurement of sFlt-1 and PlGF was provided by the Contract Research Organization, Covance, Inc. We thank all of the participating sites and patients involved in the study for their valuable contribution. COBAS and ELECSYS are trademarks of Roche.

Sources of Funding

Funding for the study was provided by Roche Diagnostics International Ltd, Rotkreuz, Switzerland. Roche Diagnostics designed the study with scientific and practical input from a medical adviser and investigators from the Asian region. Data were analyzed by the sponsor’s biostatistics department.

Disclosures

A. Dietl, S. Grill, W.D.J. Verhagen-Kamerbeek, and M. Hund are employees of Roche Diagnostics Ltd. S. Grill and M. Hund hold stock in F. Hoffmann-La Roche. M. Hund reports being an inventor of patents related to sFlt-1/PlGF or endoglin/PlGF ratio to rule out onset of preeclampsia in pregnant women within a certain time period (PCT/EP2013/063115) and the dynamic of sFlt-1 or endoglin/PlGF ratio as indicator for imminent preeclampsia and HELLP syndrome (PCT/EP2012/072157). K.H. Tan reports receiving honoraria and travel support from Roche Diagnostics, during the conduct of the study. In addition, K.H. Tan reports having a patent granted for preeclampsia biomarkers on extracellular vesicles. T.K.-T. Li, H. Masuyama, A. Ohkuchi, and S. Saito report receiving other fees from Roche Diagnostics during the conduct of the study. X. Bian, K.J. Lee, T. Yamamoto, A. Biswas, X. Huang, J.S. Park, and J.-Y. Shim have nothing to disclose.

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Novelty and Significance

What Is New?

- This is the first study to demonstrate the clinical value of the sFlt-1 (soluble fms-like tyrosine kinase 1)/PIGF (placental growth factor) ratio cutoff of 38 for the short-term prediction of preeclampsia and fetal adverse events in a large Asian population.

What Is Relevant?

- An sFlt-1/PIGF ratio of ≤ 38 can rule out the occurrence of preeclampsia and fetal adverse outcomes within 1 week with a negative predictive value of 98.6% and 98.9%, respectively.
- An sFlt-1/PIGF ratio of >38 can rule in the occurrence of preeclampsia and fetal adverse outcomes within 4 weeks with a positive predictive value of 30.3% and 53.5%, respectively.

Summary

This study demonstrated the clinical value of the ratio of sFlt-1/PIGF for the short-term prediction of preeclampsia and fetal adverse outcomes in Asian women with suspected preeclampsia. This tool has the potential to aid clinicians in Asia to more confidently rule out the occurrence of preeclampsia and associated adverse outcomes within 1 week, preventing unnecessary hospitalization and intervention, reducing the associated costs, and alleviating patient anxiety.