Prediction of Short-Term Outcome in Pregnant Women with Suspected Preeclampsia: The PROGNOSIS Study

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Introduction

- Preeclampsia is a heterogeneous, multisystem disorder in pregnancy, defined by new onset of hypertension and proteinuria after 20 weeks of gestation.
- Preeclampsia is associated with high risks of maternal/fetal morbidity and mortality.[1,2]
- In preeclampsia, placental expression of angiogenic factors is altered[3–5]
  - Anti-angiogenic soluble fms-like tyrosine kinase-1 (sFlt-1) is increased
  - Pro-angiogenic placental growth factor (PlGF) is decreased.
- A high sFlt-1/PlGF ratio in maternal serum has been linked with preeclampsia indicating a potential predictive role.[4,6]
- Blood pressure measurement and determination of proteinuria are poorly predictive for the onset of preeclampsia; there remains a high unmet need for reliable short-term prediction of preeclampsia in women with suspected preeclampsia.
- The sFlt-1/PlGF ratio is currently CE/IVD approved for use as an aid in the diagnosis of preeclampsia and, recently, approved as an aid in short-term prediction of preeclampsia (rule out/rule in) in pregnant women with suspicion of preeclampsia (in conjunction with other clinical findings).[7,8]
- **PROGNOSIS** (**Pr**ediction of short-term **o**utcome in pre**gn**ant w**o**men with **s**uspected preeclamps**i**a **s**tudy)
  - Investigated the utility of the sFlt-1/PlGF ratio in the short-term prediction of preeclampsia/eclampsia/hemolysis, elevated liver enzymes and low platelet count (HELLP) syndrome
  - Explored the correlation of the sFlt-1/PlGF ratio with maternal and fetal adverse outcomes.

Methods

Study design and subjects

- PROGNOSIS was a prospective, double-blind and non-interventional study,[9] which enrolled pregnant women (weeks 24 to 36+6 days at first visit) with suspicion of preeclampsia (**Table 1**).

Table 1. Protocol-defined criteria for suspicion of preeclampsia

Suspicion of preeclampsia (≥1 required for enrollment)	• New onset of hypertension/ aggravation of existing hypertension • New onset of proteinuria/ aggravation of existing proteinuria	• 'Other' reasons: epigastric pain, excessive edema, headache, visual disturbances, sudden weight gain, low platelets, elevated liver transaminases, intrauterine growth restriction, abnormal uterine perfusion

- The study derived and validated a **cut-off-based prediction model** in a two-step approach (feasibility and validation)
  - Data from 500 subjects were used to assess the feasibility of an sFlt-1/PlGF ratio cut-off-based prediction model, which was validated with 550 further subjects.
- **Subject assessment points:** visit 1 (baseline), visit 2 (7+2 days from visit 1), visit 3, 4, and 5 (7±2 days after previous visit), delivery and postpartum.
- **Primary objectives**
  - To demonstrate whether low ratios of sFlt-1/PlGF predict absence of preeclampsia/ eclampsia/HELLP syndrome for one week after visit 1 ('rule out')
  - To demonstrate whether high sFlt-1/PlGF ratios predict diagnosis of preeclampsia/ eclampsia/HELLP syndrome within four weeks after visit 1 ('rule in').
- **Secondary objectives** included correlation of sFlt-1/PlGF ratios with maternal and fetal preeclampsia-related adverse outcomes.
- Correlation of sFlt-1/PlGF ratio with combined outcomes (preeclampsia/eclampsia/ HELLP syndrome and/or maternal adverse outcomes and/or fetal adverse outcomes) was exploratory.

sFlt-1/PlGF assessment

- Serum samples (≥2 mL) were measured retrospectively at an independent laboratory by fully automated Elecsys® sFlt-1 and PlGF assays on the cobas® e immunoassay platform (Roche Diagnostics GmbH, Germany) using a common standard operating procedure.

Statistical analyses[9]

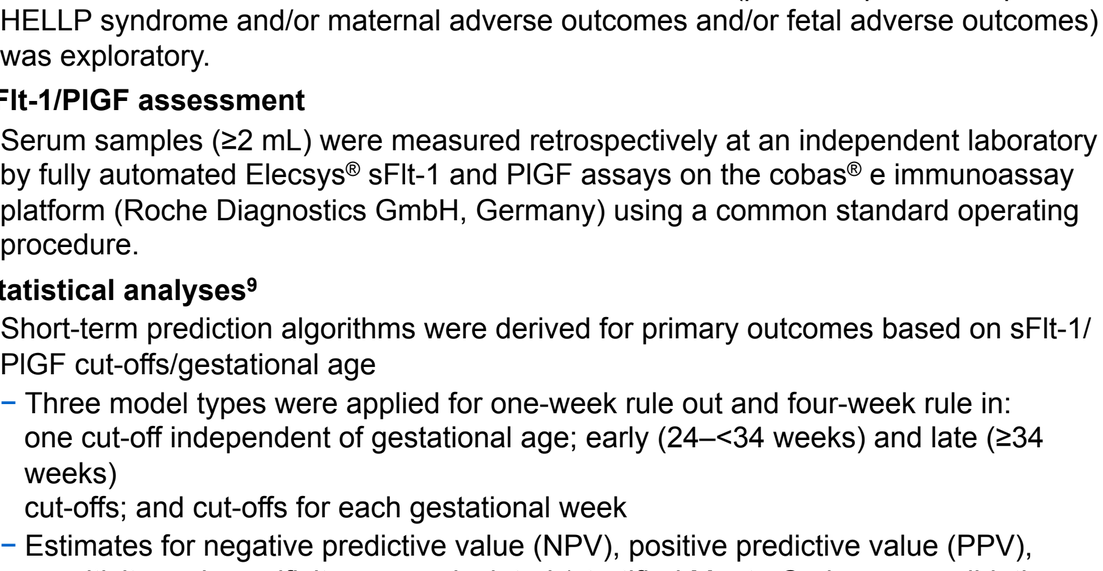
- Short-term prediction algorithms were derived for primary outcomes based on sFlt-1/ PlGF cut-offs/gestational age
  - Three model types were applied for one-week rule out and four-week rule in: one cut-off independent of gestational age; early (24–<34 weeks) and late (≥34 weeks) cut-offs; and cut-offs for each gestational week
  - Estimates for negative predictive value (NPV), positive predictive value (PPV), sensitivity and specificity were calculated (stratified Monte Carlo cross-validation, 1999 replicates, training:test ratio 2:1).[10]
- For validation, NPV, PPV, sensitivity and specificity, and area under the curve (AUC) with receiver operating characteristics (ROC) curves, with corresponding 95% confidence intervals (CIs), were calculated.

Results

Subjects

- Between December 2010 and January 2014, 1,273 subjects were enrolled at 30 sites in 14 countries (**Figure 1**).

Figure 1. Subject disposition through the PROGNOSIS study



- The most common reasons for suspicion of preeclampsia were new onset of elevated blood pressure and new onset of protein in urine (**Table 2**).
- Age, gestational age, pre-pregnancy body-mass index, and smoking status were not significantly different between subjects who developed preeclampsia, and those who did not (data not shown).
- The prevalence of protocol-defined preeclampsia and/or HELLP syndrome was 20.2% in the feasibility cohort, 17.8% in the validation cohort, and 19.0% in the overall study population.

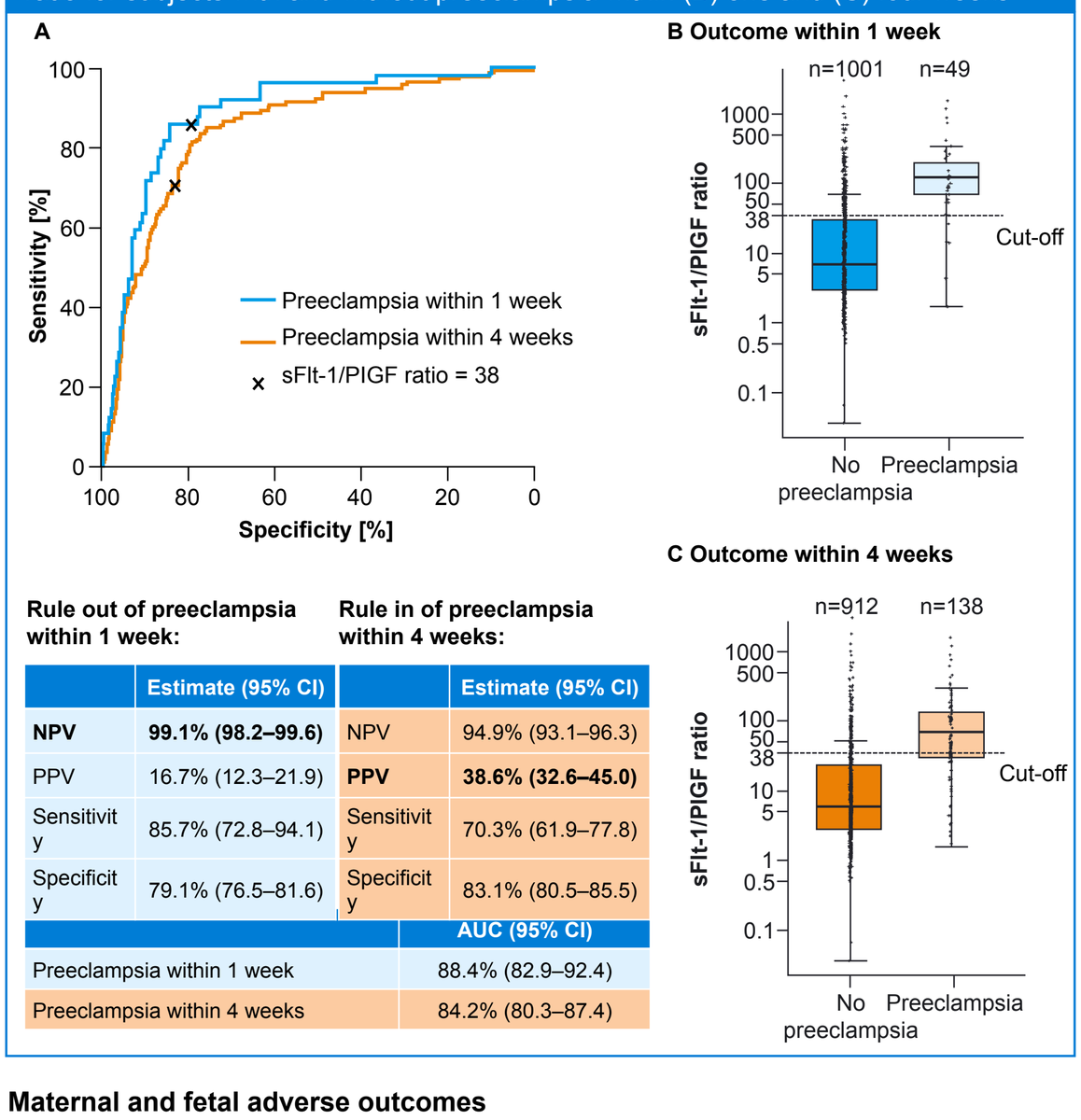
Table 2. Reasons for suspicion of preeclampsia (more than one may apply) (n=1050)

Reason	n (%)
New onset of elevated blood pressure	310 (29.5)
Aggravation of pre-existing hypertension	145 (13.8)
New onset of protein in urine	386 (36.8)
Aggravation of pre-existing proteinuria	12 (1.1)
Other reason(s)	829 (79.0)

Full dataset (feasibility and validation cohorts, n=1050)

- The application of a **single cut-off value of 38 for all gestational ages** was appropriate as a simple prediction model to be validated for both primary objectives.
- The **sFlt-1/PlGF ratio cut-off of 38** showed high predictive performance for absence of preeclampsia within one week with an **NPV of 99.1%** (95% CI 98.2–99.6) **(rule out)** or prediction of preeclampsia within four weeks with a **PPV of 38.6%** (95% CI 32.6–45.0) **(rule in)** (**Figure 2A**).
- High sFlt-1/PlGF ratios were associated with diagnosis of preeclampsia within one or four weeks (**Figures 2B and 2C**).

Figure 2. (A) Prediction of preeclampsia/eclampsia/HELLP syndrome using the sFlt-1/PlGF ratio cut-off of 38 (rule out and rule in) (n=1050); and the sFlt-1/PlGF ratio for subjects with and without preeclampsia within (B) one and (C) four weeks



Rule out of preeclampsia within 1 week:

	Estimate (95% CI)
NPV	**99.1% (98.2–99.6)**
PPV	16.7% (12.3–21.9)
Sensitivity	85.7% (72.8–94.1)
Specificity	79.1% (76.5–81.6)

Rule in of preeclampsia within 4 weeks:

	Estimate (95% CI)
NPV	94.9% (93.1–96.3)
PPV	**38.6% (32.6–45.0)**
Sensitivity	70.3% (61.9–77.8)
Specificity	83.1% (80.5–85.5)

	AUC (95% CI)
Preeclampsia within 1 week	88.4% (82.9–92.4)
Preeclampsia within 4 weeks	84.2% (80.3–87.4)

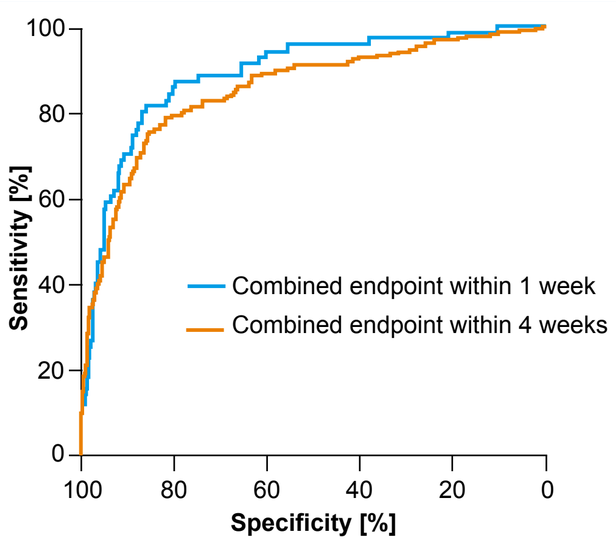
Maternal and fetal adverse outcomes

- There were only two maternal adverse outcomes. One subject (sFlt-1/PlGF ratio 143.7) developed severe preeclampsia and cerebral hemorrhage within one week. One subject (sFlt-1/PlGF ratio 64.4) developed cerebral thrombosis within four weeks.
- There was a correlation between an elevated sFlt-1/PlGF ratio and fetal adverse outcomes within one week (n=109) and within four weeks (a further 39 events, total n=148).

Combined endpoint

- The sFlt-1/PlGF ratio cut-off of 38 was able to predict the combined endpoint of preeclampsia/eclampsia/HELLP syndrome and/or maternal and fetal adverse outcomes within one week with an AUC of 88.8% (95% CI 83.9–92.4) (**Figure 3**).

Figure 3. Prediction of the combined endpoint (preeclampsia/eclampsia/HELLP syndrome, maternal/fetal adverse outcomes) using the sFlt-1/PlGF ratio cut-off of 38 (rule out and rule in) (n=1050)



Combined endpoint within 1 week:

	Estimate (95% CI)
NPV	98.5% (97.4–99.2)
PPV	24.9% (19.5–30.9)
Sensitivity	83.1% (72.3–91.0)
Specificity	81.4% (78.7–83.8)

Combined endpoint within 4 weeks:

	Estimate (95% CI)
NPV	90.5% (88.2–92.4)
PPV	61.6% (55.1–67.8)
Sensitivity	66.1% (59.4–72.3)
Specificity	88.7% (86.3–90.8)

	AUC (95% CI)
Within 1 week	88.8% (83.9–92.4)
Within 4 weeks	85.1% (81.7–88.0)

Conclusions

- PROGNOSIS validated the utility of the Elecsys® sFlt-1/PlGF ratio cut-off of 38 for the short-term prediction of preeclampsia, as well as the prediction of adverse outcomes for mother and fetus.
- The addition of the sFlt-1/PlGF ratio to current protocols has the potential to avoid unnecessary hospitalizations by ruling out preeclampsia, and to reduce fetal and maternal morbidity and mortality by ruling in the syndrome allowing optimized prenatal care.
- Current standard of practice should be re-evaluated in women with suspected preeclampsia with respect to these new data.

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