

ORIGINAL ARTICLE



Point-of-Care Placental Growth Factor for Predicting Adverse Outcomes in Sierra Leone

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BACKGROUND: PIGF (placental growth factor) concentrations are lower in preeclampsia, a major cause of maternal death; testing improves diagnosis and outcomes. We evaluated 2 novel, whole blood, point-of-care PIGF tests (RONIA and Lepzi Quanti) in a low-resource setting for predicting adverse outcomes.

METHODS: A prospective observational cohort study was conducted in women with hypertension in Sierra Leone, each of which were 24 to 36⁺ weeks of gestation. Eligible women underwent concealed RONIA and Lepzi Quanti PLGF testing. Optimal rule-out and rule-in thresholds were determined for predicting maternal (death and eclampsia) and perinatal (stillbirth, termination pre-viability, and neonatal death) composite outcomes. Sensitivity, specificity, negative predictive values, and positive predictive values were assessed.

RESULTS: Analysis included women with RONIA (n=488) and Lepzi Quanti (n=140) PIGF tests. Optimal thresholds were >60 or >90 pg/mL (rule-out) and <20 or <12 pg/mL (rule-in) for RONIA and Lepzi Quanti, respectively. For tests <34 weeks, RONIA <60 pg/mL had high sensitivity and negative predictive value for ruling out maternal (94.9% and 94.6%) and perinatal (100%) composite outcomes. RONIA <20 pg/mL indicated higher risk (positive predictive values, 16.3% and 40.9% respectively). Lepzi Quanti <90 pg/mL had 100% sensitivity and negative predictive value for ruling out maternal and perinatal composites. Conversely, with Lepzi Quanti <12 pg/mL, nearly a quarter and a half of pregnancies experienced the maternal and perinatal composites (positive predictive values, 22.0% and 48.0%). Performance declined slightly at later gestations.

CONCLUSIONS: Point-of-care PIGF testing shows accurate rule-out performance for serious outcomes, with potential for risk stratification in low-resource settings. For both tests, a minority of cases fell into an intermediate category, which would warrant increased surveillance to determine progress. (*Hypertension*. 2025;82:1719–1728. DOI: 10.1161/HYPERTENSIONAHA.125.24526.) • **Supplement Material.**

Key Words: eclampsia ■ maternal mortality ■ point-of-care systems ■ pre-eclampsia ■ pregnancy

Preeclampsia and other hypertensive disorders of pregnancy affect 10% of pregnancies¹ and are a leading cause of maternal death. It is estimated that around 40 000 maternal deaths and 500 000¹ neonatal deaths annually are associated with preeclampsia, the majority occurring in low- and middle-income countries (LMICs). Most deaths can be avoided with early identification, enabling timely management (antihypertensives, anticonvulsants, and appropriately planned birth).

Preeclampsia is often asymptomatic, even in the presence of severe disease,² making diagnosis challenging, particularly in LMICs, due to limited access to blood pressure (BP) monitoring equipment, urine dipsticks, blood tests, and ultrasound scans to assess fetal well-being. Even when diagnostics are available, BP and urine have demonstrated poor sensitivity for predicting adverse pregnancy outcomes (18%–36%) in a large US-based cohort study,³ limiting their clinical utility to stratify risk

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NOVELTY AND RELEVANCE

What Is New?

For the first time, we have prospectively demonstrated that 2 novel whole blood point-of-care PIGF (placental growth factor) tests can accurately rule out maternal death, eclampsia, and stillbirth in women with suspected preeclampsia in a low-resource setting.

What Is Relevant?

Preeclampsia accounts for 25% of maternal deaths in low- and middle-income countries and is linked to a 2- to 6-fold increased risk of hypertension and cardiovascular disease. Most deaths are preventable with early detection and risk stratification to enable timely management.

Clinical/Pathophysiological Implications?

Point-of-care PIGF can accurately rule out serious preeclampsia-related adverse pregnancy outcomes and could support clinicians to plan the timing of delivery, especially valuable in settings with limited neonatal resources.

Nonstandard Abbreviations and Acronyms

BP	blood pressure
LMICs	low- and middle-income countries
NPV	negative predictive value
PIGF	placental growth factor
POC	point-of-care
PPV	positive predictive value

and determine management. While typically underresearched in LMICs, this is likely generalizable.

The advent of angiogenic biomarker testing, such as PIGF (placental growth factor) alone and sFlt-1 (soluble fms-like tyrosine kinase)/PIGF ratio, has transformed the ability to identify high-risk women,^{4,5} and PLGF-based testing is now incorporated into the National Institute for Health and Care Excellence national UK guidelines⁶ for management of women with suspected preeclampsia and into International Society for the Study of Hypertension in Pregnancy guidelines in the definition of preeclampsia.⁷

The few PIGF studies that have been undertaken in LMICs include a blinded prospective cohort study⁸ and an operational pilot study of plasma PIGF measurement⁹ in women presenting with suspected preeclampsia in Mozambique, where low PIGF concentration was significantly associated with shorter time to delivery and adverse pregnancy outcomes, and a small pilot study in India where 50 women with hypertension underwent third-trimester sFlt-1/PIGF and high risk ratios were associated with more severe preeclampsia and pregnancy complications.¹⁰

However, to date, PIGF-based measurements for routine clinical use and study settings, including in LMICs,

are not suitable for point of care (POC) and require centrifugation. This is prohibitive to sustainable implementation in Sierra Leone and other LMICs. RONIA is a small, POC-PIGF platform, using innovative upconverting nanoparticle technology, which enables high-sensitivity, quantitative immunoassays from a single drop of whole blood (20 μ L), with a result in 30 minutes. Lepzi Quanti PIGF is a small, portable, fluorescence immunoassay for quantitative determination of PIGF in ethylenediamine-tetraacetic acid anticoagulated whole blood or plasma samples, requiring 200 μ L of venous whole blood, with a result in 15 minutes. Our objective was to evaluate the prognostic test performance of novel whole blood RONIA and Lepzi Quanti PIGF devices for serious adverse pregnancy outcomes in a low-resource setting.

METHODS

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Design

This prospective observational cohort study was undertaken between June 2022 and April 2024 in a tertiary government maternity hospital in Freetown, Sierra Leone. Consecutive women aged ≥ 16 years presenting or referred with symptoms or signs of suspected or actual preeclampsia between 24⁺⁰ to 36⁺⁶ weeks of gestation, with a singleton or twin pregnancy, were eligible. Participants were included when the attending health care provider deemed that the women required evaluation for preeclampsia, with symptoms or signs such as headache, visual disturbances, epigastric or right upper quadrant pain, hypertension, dipstick protein, or suspected fetal growth restriction. Written study information was provided and explained verbally, and participants signed or marked the consent form by thumbprint for those unable to write. BP measurement was

taken as part of routine care, with women sitting, and with the right arm supported at the level of the heart, using a pregnancy-validated device. BP measurement was repeated if hypertension was detected on the first reading, and the second reading was recorded. Normotensive readings were not repeated.

All women underwent RONIA testing. During the study period, we had an additional opportunity to collect samples for Lepzi Quanti PIGF, and therefore, a subset of women had both PIGF tests. For the RONIA test, 20 µL of whole blood was collected by finger prick, and for the Lepzi Quanti PIGF test, 200 µL of whole blood was collected by venous draw according to the manufacturers' instructions. Both samples were immediately analyzed using RONIA and Lepzi Quanti readers, respectively, to determine PIGF concentration. Results were concealed from the clinical team. Pregnancy outcome details for the woman and infant were obtained from case note review, and data quality checks were performed by an external researcher, including adjudication by an obstetrician or neonatologist. The study was approved by King's College London Research Ethics Committee (RECSM22/23-22669) and Sierra Leone Ethics and Scientific Review Committee (10/03/2022).

The prespecified primary maternal outcome was a composite of maternal death or eclampsia. Additional maternal outcomes are given as follows: individual components of the composite; parameters defined in the miniPIERS consensus, where available and reported in this setting (excluding blood transfusion as this was commonly performed for reasons other than preeclampsia-related)¹¹: early delivery (<37 weeks of gestation, within 7 and 14 days of test; severe hypertension (BP $\geq 160/110$ mmHg); high dependency unit admission; use of magnesium sulfate; and use of intravenous antihypertensives. Perinatal outcomes included a composite of 1 or more of stillbirth, neonatal death before discharge, or termination previability (to protect maternal life). Additional perinatal outcomes are given as follows: components of the composite; mode of delivery; gestational age at delivery (by best clinical estimate);

birthweight; birthweight centile; neonatal unit admission; sepsis with clinical evidence of infection; antibiotics for possible serious bacterial infection; Apgar score at 5 and 10 minutes; clinical diagnosis of hypoxic ischemic encephalopathy (low Apgar score at birth, no crying, and need for resuscitation); neonatal seizures; respiratory distress syndrome; supplementary oxygen required: use of continuous positive airway pressure ventilation; clinical diagnosis of necrotizing enterocolitis (abdominal distension with a history of formula feeding); hypoglycemia (<2.6 mmol) requiring intervention; hypothermia (single documented temperature <36.5°C); neonatal jaundice requiring phototherapy; and nasogastric feeding.

Statistical Analysis

Women were classified according to their gestation at the time of the PIGF test, <34 weeks of gestation, and 34 to 36⁺⁶ weeks of gestation based on the best clinical estimate. Descriptive statistics were used to summarize the demographic data, and POC-PIGF results were presented using mean (SD) or median (interquartile range) depending on distribution. Optimal rule-in and rule-out cut-points were selected from a range of thresholds taking into account the balance between sensitivity and specificity and prediction of maternal and perinatal composite outcomes. To determine the prognostic performance for these and other predefined end points, sensitivity, specificity, positive predictive values (PPVs), and negative predictive values (NPVs) were calculated based on the selected rule-in and rule-out thresholds, and the area under the receiver operating characteristic curve was generated. Median and interquartile ranges from time from POC-PIGF testing to delivery were calculated. We did a sensitivity analysis on the primary maternal and perinatal outcomes excluding twin pregnancies. Analysis was performed with statistical support from King's College London Life Course Sciences (STATA/SE, version 18). The study is reported in accordance with the Standards for the Reporting of Diagnostic Accuracy Studies guidelines (Figure S1).

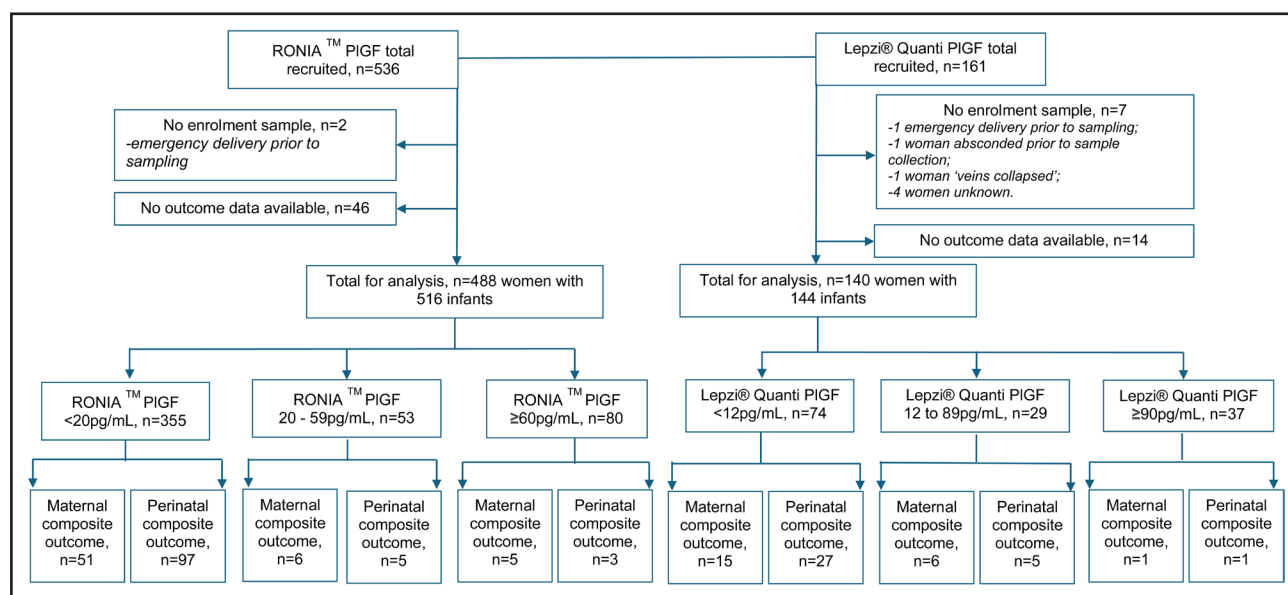


Figure 1. Flow diagram of participants through the study. PIGF, placental growth factor.

Table 1. Maternal Demographics, Admission Characteristics, Delivery Details, and Maternal and Perinatal Outcomes

Demographic, admission, delivery, and outcome variables	RONIA PIGF			Lepzi Quanti PIGF		
Gestation at PIGF testing, wk	<34	34–36	All	<34	34–36	All
Demographic details, n	267	221	488	82	58	140
Age, y	27.0 (6.3)	27.3 (6.2)	27.1 (6.3)	27.6 (5.9)	27.2 (6.7)	27.4 (6.2)
Primiparous	92 (35.0)	73 (33.0)	165 (34.1)	25 (30.5)	25 (43.1)	50 (35.7)
Admission characteristics						
Gestation at enrollment, wk	32.0 (29.0–34.0)	36.0 (35.0–36.0)	33.0 (30.0–36.0)	30.0 (28.0–32.0)	36.0 (35.0–36.0)	32.0 (29.0–36.0)
Maximum SBP, mm Hg	174 (19)	172 (22)	173 (21)	176 (17)	173 (26)	175 (21)
Maximum DBP, mm Hg	119 (17)	117 (18)	118 (17)	121 (18)	117 (17)	120 (18)
Admission urine dipstick, n	203	172	375	53	33	86
>1	40 (19.7)	27 (15.7)	67 (17.9)	12 (22.6)	3 (9.1)	15 (17.4)
>2	34 (16.7)	31 (18.0)	65 (17.3)	14 (26.4)	6 (18.2)	20 (23.3)
>3	102 (50.2)	65 (37.8)	167 (44.5)	21 (39.6)	14 (42.4)	35 (40.7)
Admission creatinine, n	69	74	143	2	10	12
Highest creatinine	90.0 (71.6–111.0)	76.0 (67.0–96.5)	81.7 (68.3–105.0)	70.0 (68.0–72.0)	61.0 (54.0–67.0)	64.5 (55.0–70.0)
Delivery details and maternal outcomes						
Twin pregnancy	14 (5.2)	18 (8.1)	32 (6.6)	3 (3.7)	5 (8.6)	8 (5.7)
Gestation at delivery, wk	32.0 (29.0–34.0)	36.0 (35.0–37.0)	34.0 (32.0–36.0)	31.5 (28.0–33.0)	36.0 (35.0–36.0)	34.0 (31.0–36.0)
Preterm birth <34 wk	183 (72.3)	0 (0.0)	183 (38.7)	61 (78.2)	0 (0.0)	61 (45.2)
Preterm birth <37 wk	234 (92.5)	159 (72.9)	393 (83.4)	69 (88.5)	48 (84.2)	117 (86.7)
Maternal outcomes, n						
Composite maternal outcome	39 (14.6)	23 (10.4)	62 (12.7)	14 (17.1)	8 (13.8)	22 (15.7)
Maternal death	12 (4.5)	5 (2.3)	17 (3.5)	6 (7.3)	1 (1.7)	7 (5.0)
Eclampsia	30 (11.2)	20 (9.0)	50 (10.2)	10 (12.2)	8 (13.8)	18 (12.9)
Severe hypertension (SBP ≥160/110 mm Hg)	225 (84.3)	162 (73.3)	387 (79.3)	73 (89.0)	46 (79.3)	119 (85.0)
Mode of birth, n	264	221	485	80	58	140
Cesarean section	124 (47.0)	126 (57.0)	250 (51.5)	35 (43.8)	32 (55.2)	67 (47.9)
Vaginal birth	140 (53.0)	95 (43.0)	235 (48.5)	45 (56.3)	26 (44.8)	71 (50.7)
Resource-dependent outcomes						
HDU admission*	16 (6.1)	7 (3.2)	23 (4.8)	6 (7.3)	1 (1.8)	7 (5.1)
Use of magnesium sulfate	237 (91.0)	179 (81.4)	416 (86.5)	74 (90.2)	48 (82.8)	122 (87.1)
Use of IV antihypertensives	128 (50.6)	75 (35.2)	203 (43.6)	57 (71.2)	25 (44.6)	82 (60.3)
Perinatal outcomes (where recorded), n	277	239	516	82	63	145
Composite perinatal outcome	89 (32.1)	18 (7.5)	107 (20.7)	28 (34.1)	5 (7.9)	33 (22.8)
Stillbirth	74 (26.7)	14 (5.9)	88 (17.1)	21 (25.6)	4 (6.3)	25 (17.2)
Termination previability for maternal health	3 (1.1)	0 (0)	3 (0.6)	0 (0)	0 (0)	0 (0)
Live births	200 (72.2)	225 (94.1)	425 (82.4)	61 (74.4)	59 (93.7)	120 (82.8)
Neonatal unit admission	88/185 (47.6)	42/218 (19.3)	130/403 (32.3)	26/59 (44.1)	12/58 (20.7)	38/117 (32.5)
Neonatal death before discharge	12/145 (8.3)	4/202 (2.0)	16/347 (4.6)	7/54 (13.0)	1/56 (1.8)	8/110 (7.3)
Live births, n	200	225	425	61	59	120
Birthweight	2000 (1500–2400)	2800 (2300–3100)	2400 (1900–2900)	2000 (1400–2400)	2500 (2200–2900)	2300 (1900–2700)
SGA (<tenth customized birth-weight centile)	31/174 (17.8)	27/204 (13.2)	58/378 (15.3)	9/51 (17.6)	9/55 (16.4)	18/106 (17.0)

(Continued)

Table 1. Continued

Demographic, admission, delivery, and outcome variables	RONIA PIGF			Lepzi Quanti PIGF		
SGA (<third customized birth-weight centile)	13/174 (7.5)	17/204 (8.3)	30/378 (7.9)	4/51 (7.8)	6/55 (10.9)	10/106 (9.4)
SGA (<first customized birth-weight centile)	8/174 (4.6)	7/204 (3.4)	15/378 (4.0)	4/51 (7.8)	2/55 (3.6)	6/106 (5.7)

Results are presented as mean (SD), n (percentage), and median (interquartile range). DBP indicates diastolic blood pressure; HDU, high dependency unit; PIGF, placental growth factor; SBP, systolic blood pressure; and SGA, small for gestational age.
*Only 4 HDU, high dependency beds available at any one time.

RESULTS

Five hundred thirty-six women were recruited and underwent RONIA testing; 161 women also underwent Lepzi Quanti PIGF testing. We recruited all those who were approached, eligible, and consented (Figure 1). No adverse events were reported related to performing PIGF testing. Outcome measures were collected in full on 488 of 536 and 140 of 161 occasions for RONIA and Lepzi Quanti tests, respectively. Women without a valid PIGF result (RONIA, n=2; LEPZI Quanti, n=7) and those lost to follow-up (RONIA, n=46; LEPZI Quanti, n=14) were excluded. The characteristics of the remaining women are shown in Table 1, along with maternal and perinatal outcomes, with additional adverse maternal and perinatal outcomes in Tables S1 and S2, respectively. Proportions of women by hypertension category and maternal and perinatal adverse events stratified by PIGF are shown in Figure 2. The diagnostic accuracy of PIGF for predicting maternal and perinatal composite outcomes is shown in Tables 2 and 3 based on our selected thresholds: <20 and <60 pg/mL for RONIA PIGF and <12 and <90 pg/mL for Lepzi Quanti PIGF.

For the maternal composite (n=62), abnormal RONIA PIGF <60 pg/mL had a high sensitivity of 91.9% (95% CI, 82.2%–97.3%) and an NPV of 93.8% (95% CI, 86.2%–98.0%) for women tested at all gestations. Sensitivity and NPV for the maternal composite improved still further for women tested at <34 weeks of gestation to 94.9% (95% CI, 82.7%–99.4%) and 94.6% (95% CI, 81.8%–99.3%), respectively, and for maternal death (n=17), where sensitivity and NPV were 100%. Abnormal Lepzi Quanti PIGF <90 pg/mL had 100% sensitivity and NPV for the maternal composite (n=22; Table 2) and for individual components of the composite, declining slightly at later gestations, except for maternal death (n=7) where 100% sensitivity and NPV were maintained across all gestations (Tables S3 and S4).

For the perinatal composite outcome (n=105), abnormal RONIA PIGF <60 pg/mL had a high sensitivity of 97.1% (95% CI, 91.8%–99.4%) and an NPV of 96.3% (95% CI, 89.6%–99.2%) at all gestations tested, and these were improved in women tested <34 weeks of gestation with sensitivity and NPV of 100% (95% CI, 95.8%–100.0% and 90.5%–100%, respectively; Table 3). Lepzi Quanti PIGF had 100% sensitivity and

NPV for the perinatal composite outcome (Table 3), and for the individual components of the composite for women tested at <34 weeks of gestation, declining slightly at later gestations tested, except for neonatal death before discharge, where 100% sensitivity and NPV were maintained across all gestations tested (Tables S5 and S6).

Among women who underwent RONIA testing at all gestations, there were 8 false negative cases (1 maternal death, 4 eclampsia, 1 stillbirth, and 2 neonatal deaths before discharge). The maternal death was attributed to a known seizure disorder, with a PIGF of 254.92 pg/mL, while sepsis was reported in 1 of the babies who had a neonatal death (with normal birthweight; PIGF, 692.34 pg/mL). None of the false negative eclampsia cases had borderline PIGF results: 115, 677, 102, and 697 pg/mL. For Lepzi Quanti PIGF, there were 2 false negative cases (1 eclampsia case; PIGF, 276.44 pg/mL; 1 severe adverse neonatal event; PIGF, 92.68 pg/mL). Both of these cases were verified against the source notes, but, due to limited documentation, it was not possible to determine whether additional diagnoses may have contributed to or caused their outcomes.

Test performance for additional clinical outcomes is presented in Tables S7 through S11. For both abnormal RONIA <60 pg/mL and Lepzi Quanti <90 pg/mL, sensitivity and NPV were 100% for women tested <34 weeks for SGA <third centile, albeit in small numbers of women (Table S8).

For RONIA PIGF <20 pg/mL, PPV for delivery within 14 days was 88.0% (95% CI, 84.0%–91.2%), and for preterm delivery <37 weeks of gestation, it was 87.1% (95% CI, 83.0%–90.4%), which improved to 97.4% (95% CI, 94.0%–99.1%) for women tested <34 weeks of gestation. For RONIA PIGF <60, although sensitivity was high (>90%) for both delivery within 14 days and preterm delivery <37 weeks of gestation, for women tested <34 weeks of gestation, NPV was modest due to high prevalence of the outcome (Tables S10 and S11). For Lepzi Quanti PIGF <12 pg/mL, PPV for prediction of delivery within 14 days was 87.2% (95% CI, 74.3%–95.2%) for women tested <34 weeks of gestation, improving at later gestations. For preterm delivery <37 weeks of gestation, PPV was 97.8% (95% CI, 88.5%–99.9%) for women tested <34 weeks of gestation, declining at later gestations. However, despite modest overall performance in determining time to delivery,

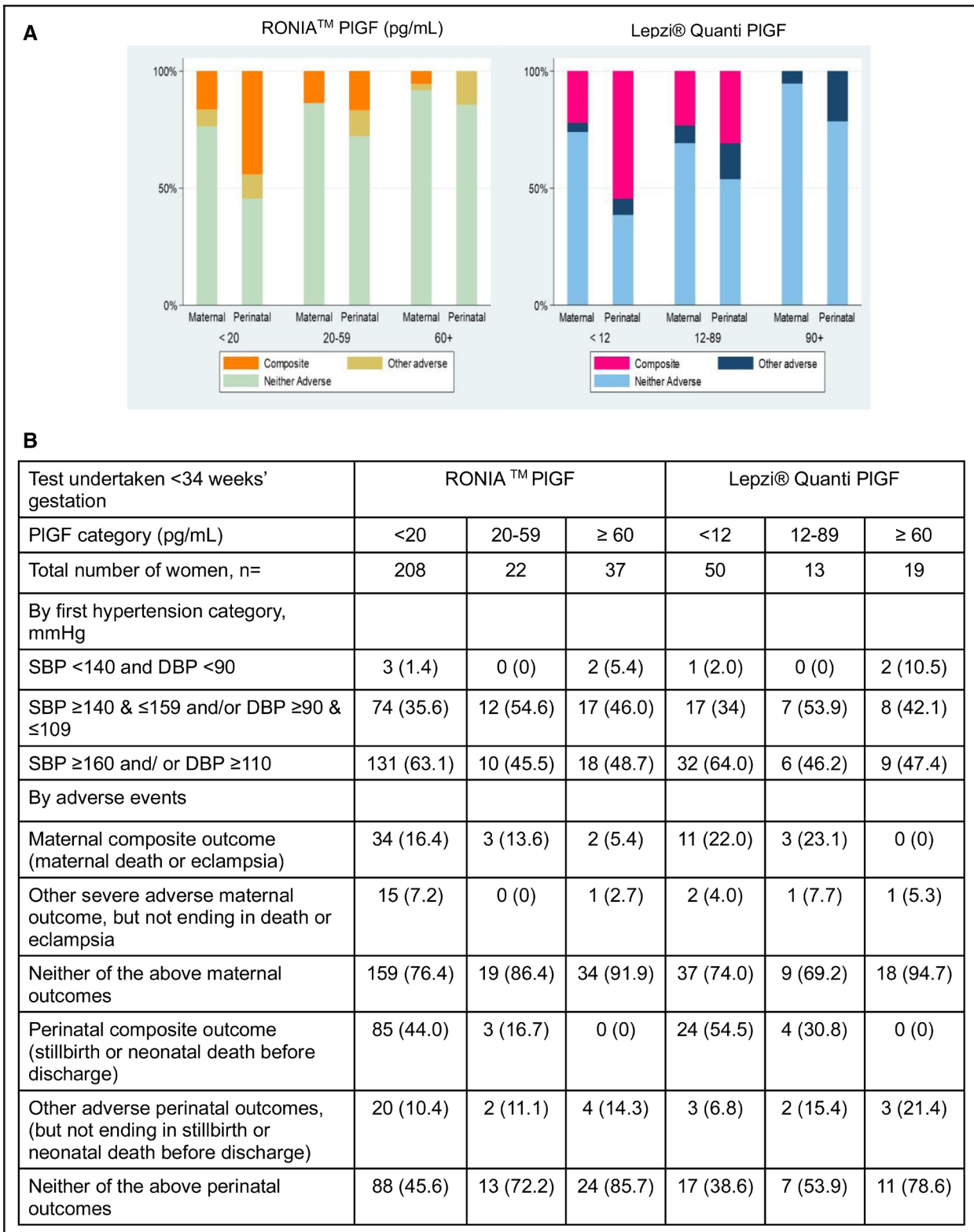


Figure 2. Adverse maternal and perinatal outcome stratified by PIGF (placental growth factor) category in women with tests done at <34 weeks' gestation for RONIA™ and Lepzi® Quanti PIGF.

A, Final maternal and perinatal outcomes, stratified by PIGF category. **B**, Hypertension category and adverse maternal and perinatal outcomes stratified by PIGF category. DBP indicates diastolic blood pressure; and SBP, systolic blood pressure.

Table 2. RONIA and Lepzi Quanti PIGF Prediction of Composite Maternal Outcome Based on PIGF Thresholds of <20 and <60 pg/mL, and <12 and <90 pg/mL, Respectively

Composite maternal outcome (death or eclampsia)						
PIGF device	RONIA PIGF			Lepzi Quanti PIGF		
Gestation at testing, wk	<34	34–36 ⁺⁶	All	<34	34–36 ⁺⁶	All
Prevalence, n (%)	39 (14.6)	23 (10.4)	62 (12.7)	14 (17.1)	8 (13.8)	22 (15.7)
PIGF threshold	<20 pg/mL, % (95% CI)			<12 pg/mL, % (95% CI)		
Sensitivity	87.2 (72.6–95.7)	73.9 (51.6–89.8)	82.3 (70.5–90.8)	78.6 (49.2–95.3)	50.0 (15.7–84.3)	68.2 (45.1–86.1)
n/N	34/39	17/23	51/62	11/14	4/8	15/22
Specificity	23.7 (18.3–29.7)	34.3 (27.8–41.4)	28.6 (24.4–33.2)	42.6 (30.7–55.2)	60.0 (45.2–73.6)	50.0 (40.7–59.3)
n/N	54/228	68/198	122/426	29/68	30/50	59/118
Positive predictive value	16.3 (11.6–22.1)	11.6 (6.9–17.9)	14.4 (10.9–18.5)	22.0 (11.5–36.0)	16.7 (4.7–37.4)	20.3 (11.8–31.2)
n/N	34/208	17/147	51/355	11/50	4/24	15/74
Negative predictive value	91.5 (81.3–97.2)	91.9 (83.2–97.0)	91.7 (85.7–95.8)	90.6 (75.0–98.0)	88.2 (72.5–96.7)	89.4 (79.4–95.6)
n/N	54/59	68/74	122/133	29/32	30/34	59/66
PIGF threshold	<60 pg/mL			<90 pg/mL		
Sensitivity	94.9 (82.7–99.4)	87.0 (66.4–97.2)	91.9 (82.2–97.3)	100.0 (76.8–100.0)	87.5 (47.3–99.7)	95.5 (77.2–99.9)
n/N	37/39	20/23	57/62	14/14	7/8	21/22
Specificity	15.4 (10.9–20.7)	20.7 (15.3–27.0)	17.8 (14.3–21.8)	27.9 (17.7–40.1)	34.0 (21.2–48.8)	30.5 (22.4–39.7)
n/N	35/228	41/198	76/426	19/68	17/50	36/118
Positive predictive value	16.1 (11.6–21.5)	11.3 (7.0–16.9)	14.0 (10.8–17.8)	22.2 (12.7–34.5)	17.5 (7.3–32.8)	20.4 (13.1–29.5)
n/N	37/230	20/177	57/407	14/63	7/40	21/103
Negative predictive value	94.6 (81.8–99.3)	93.2 (81.3–98.6)	93.8 (86.2–98.0)	100.0 (82.4–100.0)	94.4 (72.7–99.9)	97.3 (85.8–99.9)
n/N	35/37	41/44	76/81	19/19	17/18	36/37
AUROC	0.53 (0.45–0.62)	0.51 (0.40–0.63)	0.54 (0.47–0.61)	0.63 (0.52–0.74)	0.60 (0.41–0.79)	0.63 (0.53–0.72)

Results are presented as n (percentage) and percentage (95% CI). AUROC indicates area under the receiver operating characteristic curve; and PIGF, placental growth factor.

the median time between test and delivery was markedly longer in women with a normal PIGF result for both tests (Figure 3): RONIA (34 versus 4 days) and Lepzi Quanti (21.5 versus 3 days). A prespecified sensitivity analysis excluding women with twin pregnancies showed very similar results (Tables S12 and S13).

DISCUSSION

Whole blood RONIA and Lepzi Quanti PIGF accurately identified women admitted with hypertension, clinical features of preeclampsia, or both who did not go on to have a serious adverse event, especially in those tested <34 weeks of gestation, in a challenging LMIC environment. For maternal and perinatal composite outcomes, this was represented by sensitivities of 94.9% and 100.0%, respectively (RONIA) and 100.0% for both (Lepzi Quanti). The median time to delivery was markedly shorter for women tested <34 weeks with abnormal RONIA and Lepzi Quanti PIGF values (compared with those with normal results).

There were 17 (3.5%) maternal deaths, 50 eclampsia cases, and 106 perinatal deaths compared with previous studies informing UK national guidelines,^{4,5,12} where no

maternal mortality and few stillbirths have occurred. In the context of managing these women, we specifically wanted to rule out very severe outcomes to avoid delivery as previously stated. This is a unique analysis and different from previous studies, regarding the prediction of severe features, which would be meaningless in this setting given the relatively high prevalence of serious outcomes.

In this high-risk population, the majority of women had an abnormal PIGF. Most women with a very abnormal PIGF did not die or have eclampsia, explaining the low PPV and specificities for both tests. However, given the severity of outcomes, we accept a high false positive rate, and action, for example, early delivery, could reasonably be considered to avoid a 10% risk of maternal death and a 30% risk of stillbirth. This is in keeping with interventions across maternity care, but this test improves stratification enabling the action to be better targeted. The PPVs for the composite maternal and perinatal outcomes are similar to those presented by Duhig et al,⁵ for a less serious outcome in a high-income setting (preeclampsia requiring delivery within 14 days), which has changed clinical practice, and are likely to be informative. Furthermore, including additional severe features (eg, from

Table 3. RONIA and Lepzi Quanti PIGF Prediction of Composite Perinatal Outcome Based on PIGF Thresholds of <20 and <60 pg/mL, and <12 and <90 pg/mL, Respectively

Composite perinatal outcome (stillbirth and neonatal death before discharge)						
PIGF device	RONIA PIGF			Lepzi Quanti PIGF		
Gestation at testing, wk	<34	34–36 ⁺⁶	All	<34	34–36 ⁺⁶	All
Prevalence	88 (33.0)	17 (7.7)	105 (21.5)	28 (34.1)	5 (8.6)	33 (23.6)
PIGF threshold	<20 pg/mL, % (95% CI)			<12 pg/mL, % (95% CI)		
Sensitivity	96.6 (90.4–99.3)	70.6 (44.0–89.7)	92.4 (85.5–96.7)	85.7 (67.3–96.0)	60.0 (14.0–94.7)	81.8 (64.5–93.0)
n/N	85/88	12/17	97/105	24/28	3/5	27/33
Specificity	31.3 (24.6–38.6)	33.8 (27.4–40.8)	32.6 (28.0–37.6)	51.9 (37.8–65.7)	60.4 (46.0–73.5)	56.1 (46.1–65.7)
n/N	56/179	69/204	125/133	28/54	32/53	60/107
Positive predictive value	40.9 (34.1–47.9)	8.2 (4.3–13.8)	27.3 (22.8–32.3)	48.0 (33.7–62.6)	12.5 (2.7–32.4)	36.5 (25.6–48.5)
n/N	85/208	12/147	97/355	24/50	3/24	27/74
Negative predictive value	94.9 (85.9–98.9)	93.2 (84.9–97.8)	94.0 (88.5–97.4)	87.5 (71.0–96.5)	94.1 (80.3–99.3)	90.9 (81.3–96.6)
n/N	56/59	69/74	125/133	28/32	32/34	60/66
PIGF threshold	<60 pg/mL			<90 pg/mL		
Sensitivity	100.0 (95.9–100.0)	82.4 (56.6–96.2)	97.1 (91.9–99.4)	100.0 (87.7–100.0)	80.0 (28.4–99.5)	97.0 (84.2–99.9)
n/N	88/88	14/17	102/105	28/28	4/5	32/33
Specificity	20.7 (15.0–27.3)	20.1 (14.8–26.3)	20.4 (16.4–24.8)	35.2 (22.7–49.4)	32.1 (19.9–46.3)	33.6 (24.8–43.4)
n/N	37/179	41/204	78/383	19/54	17/53	36/107
Positive predictive value	38.3 (32.0–44.9)	7.9 (4.4–12.9)	25.1 (20.9–29.6)	44.4 (31.9–57.5)	10.0 (2.8–23.7)	31.1 (22.3–40.9)
n/N	88/230	16/177	102/407	28/63	4/40	32/103
Negative predictive value	100.0 (90.5–100.0)	93.2 (81.3–98.6)	96.3 (89.6–99.2)	100.0 (82.4–100.0)	94.4 (72.7–99.9)	97.3 (85.8–99.9)
n/N	37/37	41/44	78/81	19/19	17/18	36/37
AUROC	0.67 (0.62–0.72)	0.52 (0.38–0.66)	0.67 (0.62–0.72)	0.72 (0.63–0.80)	0.65 (0.43–0.87)	0.72 (0.66–0.79)

Results are presented as n (percentage) and percentage (95% CI). AUROC indicates area under the receiver operating characteristic curve; and PIGF, placental growth factor.

mini-piers consensus) may have improved these values. However, the absence of laboratory diagnostics in the study hospital made this neither pragmatic nor possible.

We present the time from test to delivery based on the PIGF category (Figure 3) but did not include this in our primary outcome because timing of delivery is often resource or practitioner-dependent and not a reliable proxy for disease severity in the study setting.

This first study to evaluate whole blood POC-PIGF showed that it is feasible and accurate in a hospital in Sierra Leone, a country with high reported maternal (443/100 000¹³) and neonatal (3/1000¹⁴) mortality rates, challenging infrastructure (38% of health facilities lack reliable electricity¹⁵), and was acceptable (only 4 women refused). As diagnostic criteria for preeclampsia require resources often unavailable (eg, proteinuria dipsticks and ultrasound scans), we could not stratify analysis by suspected and confirmed preeclampsia although the mean BP was extremely high (173/118 mmHg). PIGF was blinded to clinical teams, so care decisions, including delivery, were not influenced.

PIGF test performance has been demonstrated prospectively in LMIC settings; a Mozambique study found that abnormal PIGF in suspected preeclampsia

was associated with higher risk of preeclampsia diagnosis, shorter time to delivery, and perinatal death.⁸ In a follow-up study, one-third of women with very abnormal PIGF had a stillbirth; the area under the receiver operating characteristic curve is 0.78 (95% CI, 0.70–0.86), with a sensitivity of 76.9% (95% CI, 60.7%–88.9%) and a specificity of 74.1% (95% CI, 68.0%–79.5%).⁹ In our study, with twice the number of stillbirths, both RONIA and Lepzi Quanti PIGF had higher sensitivity (98.8% and 95.8%) but more modest specificity (19.8% and 31.5%). A small prospective Indian study (n=50) found that abnormal SFIt-1/PIGF was significantly associated with severe preeclampsia (90.91% versus 8.00%; $P<0.0001$) and maternal complications (18.18% versus 0%; $P=0.04$) compared with 40.0% versus 8.0% in women tested <34 weeks of gestation in our study.¹⁰

All studies, to date, have used benchtop PIGF analyzers, requiring centrifugation, challenging in Sierra Leone and similar settings. PIGF alone and SFIt-1/PIGF ratio are both National Institute for Health and Care Excellence–recommended, with no differences in predictive ability^{16,17} However, POC testing with 2 assays is more complex and currently unavailable.

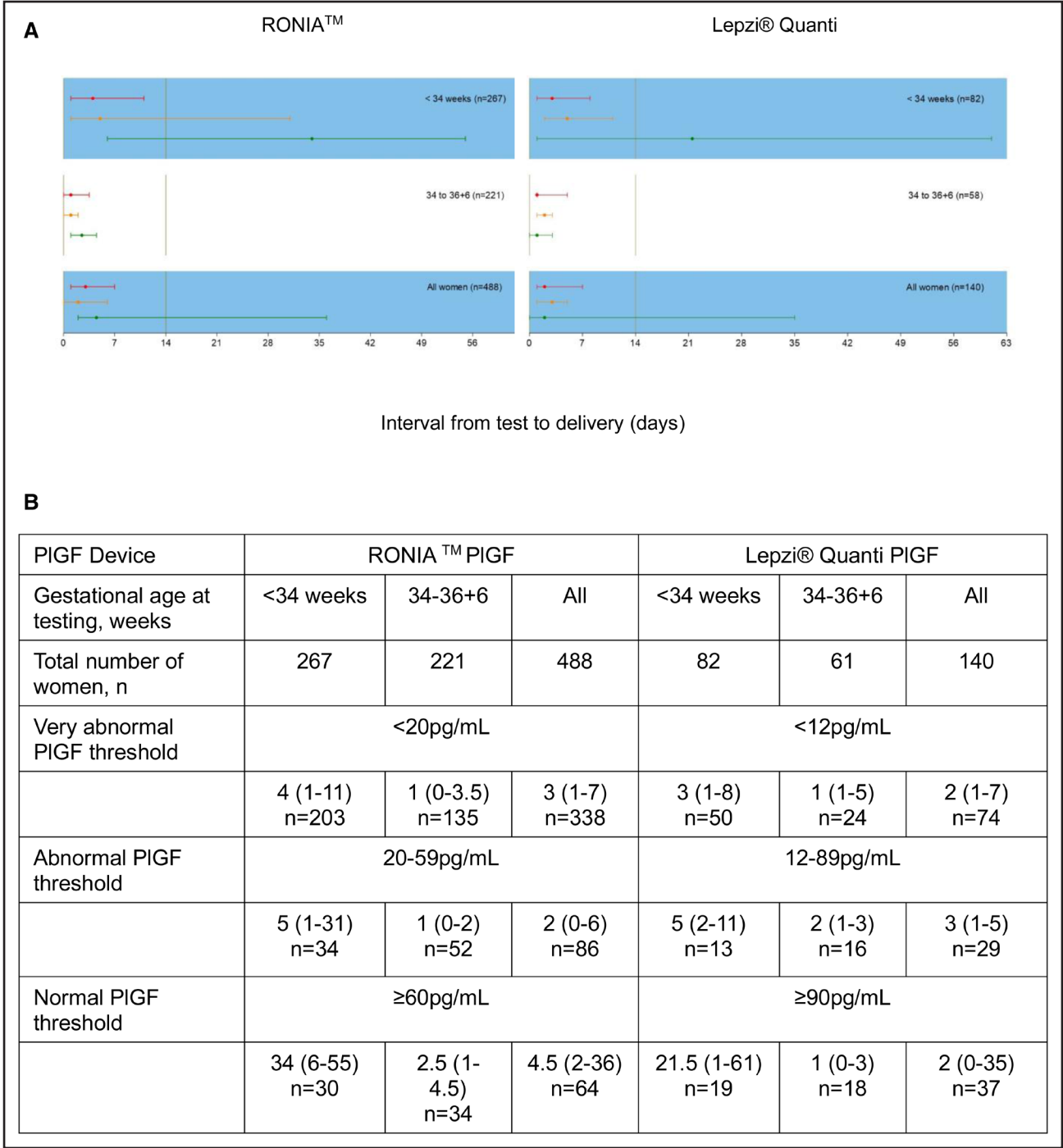


Figure 3. Time to delivery (median, interquartile range) stratified by RONIA and Lepzi Quanti PIGF (placental growth factor) concentration for all participants. **A**, Time to delivery (median, IQR) stratified by RONIA™ and Lepzi® Quanti PIGF concentration for all participants. **B**, Time to delivery (median, IQR) stratified by RONIA™ and Lepzi® Quanti PIGF concentration for all gestational age categories at testing.

CONCLUSIONS

This study indicates that both whole blood RONIA and Lepzi Quanti POC-PIGF testing could enable targeted management, avoiding unnecessary intervention with a normal result, and is feasible in challenging settings.

PERSPECTIVES

This is the first prospective observational study of novel whole blood POC-PIGF testing. Women with a very abnormal PIGF had up to a 20% chance of death or eclampsia (PPVs of 14.4 and 20.3%) and would be routinely delivered

based on these risks in well-resourced settings. However, if it is unlikely to happen, there is considerable benefit in avoiding preterm delivery in resource-limited settings, and therefore, high sensitivity and NPV, representing a reliable rule-out test, have important clinical utility. For women falling into the intermediate abnormal PIGF category, increased surveillance is justified to monitor progress. We think that the current results add considerable value to management as a significant minority (up to 26% of women with normal PIGF) would change management. This should be evaluated in prospective trials and is the subject of the current PAPAGAO (Preterm preeclampsia: Placental Growth factor for reduction of Adverse Outcomes) trial in Brazil, India, and Sierra Leone using these POC tests. POC testing is likely considerably cheaper than current PIGF-based tests. Given the cost of existing devices and tests (>\$2200/device; >\$30 USD/test),⁸ it is likely that POC alternatives could be adopted globally.

ARTICLE INFORMATION

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Author Contributions

All authors contributed to the conception and planning of the work. K. Kuhrt, R. Cole, and M. M'Bayoh contributed to carrying out the work. K. Kuhrt led the writing. All authors contributed to analysis and interpretation of the work, writing the article, final approval of this version, and agree to be accountable for all aspects of the work.

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Disclosures

None.

Supplemental Material

Tables S1–S13
Figures S1 and S2

APPENDIX

Pineapple Study Group

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REFERENCES

- Duley L. The global impact of pre-eclampsia and eclampsia. *Semin Perinatol*. 2009;33:130–137. doi: 10.1053/j.semperi.2009.02.010
- Milne F, Redman C, Walker J, Baker P, Black R, Blincowe J, Cooper C, Fletcher G, Jokinen M, Moran PA, et al; PRECOG II Group. Assessing the onset of pre-eclampsia in the hospital day unit: summary of the pre-eclampsia guideline (PRECOG II). *BMJ*. 2009;339:b3129. doi: 10.1136/bmj.b3129
- Zhang J, Klebanoff MA, Roberts JM. Prediction of adverse outcomes by common definitions of hypertension in pregnancy. *Obstet Gynecol*. 2001;97:261–267. doi: 10.1016/s0029-7844(00)01125-x
- Chappell LC, Duckworth S, Seed PT, Griffin M, Myers J, Mackillop L, Simpson N, Waugh J, Anumba D, Kenny LC, et al. Diagnostic accuracy of placental growth factor in women with suspected preeclampsia: a prospective multicenter study. *Circulation*. 2013;128:2121–2131. doi: 10.1161/CIRCULATIONAHA.113.003215
- Duhig KE, Myers J, Seed PT, Sparkes J, Lowe J, Hunter RM, Shennan AH, Chappell LC; PARROT Trial Group. Placental growth factor testing to assess women with suspected pre-eclampsia: a multicentre, pragmatic, stepped-wedge cluster-randomised controlled trial. *Lancet*. 2019;393:1807–1818. doi: 10.1016/S0140-6736(18)33212-4
- National Institute of Health and Care Excellence. Hypertension in pregnancy: diagnosis and management: NG 133 2019. Accessed March 21, 2025. <https://www.nice.org.uk/guidance/ng133>
- Magee LA, Brown MA, Hall DR, Gupta S, Hennessy A, Karumanchi SA, Kenny LC, McCarthy F, Myers J, Poon LC, et al. The 2021 International Society for the Study of Hypertension in Pregnancy classification, diagnosis & management recommendations for international practice. *Pregnancy Hypertens*. 2022;27:148–169. doi: 10.1016/j.preghy.2021.09.008
- Ukah UV, Mbofana F, Rocha BM, Loquiha O, Mudenyanaga C, Usta M, Urso M, Drebit S, Magee LA, von Dadelszen P. Diagnostic performance of placental growth factor in women with suspected preeclampsia attending antenatal facilities in Maputo, Mozambique. *Hypertension*. 2017;69:469–474. doi: 10.1161/HYPERTENSIONAHA.116.08547
- Manriquez Rocha B, Mbofana F, Loquiha O, Mudenyanaga C, Ukah UV, Magee LA, von Dadelszen P. Early diagnosis of preeclampsia using placental growth factor: an operational pilot study in Maputo, Mozambique. *Pregnancy Hypertens*. 2018;11:26–31. doi: 10.1016/j.preghy.2017.12.005
- Soundararajan R, Suresh SC, Mueller A, Heimberger S, Avula S, Sathyanarayana C, Mahesh S, Madhuprakash S, Rana S. Real life outpatient biomarker use in management of hypertensive pregnancies in third trimester in a low resource setting: ROBUST study. *Pregnancy Hypertens*. 2021;23:97–103. doi: 10.1016/j.preghy.2020.11.010
- Payne BA, Hutcheon JA, Ansermino JM, Hall DR, Bhutta ZA, Bhutta SZ, Biryabarema C, Grobman WA, Groen H, Haniff F, et al; miniPIERS Study Working Group. A risk prediction model for the assessment and triage of women with hypertensive disorders of pregnancy in low-resourced settings: the miniPIERS (Pre-eclampsia Integrated Estimate of RiSk) multicountry prospective cohort study. *PLoS Med*. 2014;11:e1001589. doi: 10.1371/journal.pmed.1001589
- Hurrell A, Webster L, Sparkes J, Battersby C, Brockbank A, Clark K, Duhig KE, Gill C, Green M, Hunter RM, et al; PARROT-2 trial group. Repeat placental growth factor-based testing in women with suspected preterm pre-eclampsia (PARROT-2): a multicentre, parallel-group, superiority, randomised controlled trial. *Lancet*. 2024;403:619–631. doi: 10.1016/S0140-6736(23)02357-7
- World Bank. World bank gender data portal 2024. Accessed March 21, 2025. <https://genderdata.worldbank.org/en/economies/sierra-leone#:~:text=443%20women%20die%20per%20100%2C000,2000%20to%20443%20in%202020>
- World Bank. Mortality rate, neonatal (per 1,000 live births) - Sierra Leone 2024. Accessed March 21, 2025. <https://data.worldbank.org/indicator/SH.DYN.NMRT?locations=SL>
- SEforALL. Powering Social Infrastructure in Sierra Leone: Market Assessment and Roadmap for Health Facilities 2024. Accessed March 21, 2025. <https://www.seforall.org/publications/powering-social-infrastructure-in-sierra-leone-market-assessment-and-roadmap>
- McCarthy FP, Gill C, Seed PT, Bramham K, Chappell LC, Shennan AH. Comparison of three commercially available placental growth factor-based tests in women with suspected preterm pre-eclampsia: the COMPARE study. *Ultrasound Obstet Gynecol*. 2019;53:62–67. doi: 10.1002/uog.19051
- Hurrell A, Webster L, Sparkes J, Battersby C, Brockbank A, Clark K, Duhig KE, Gill C, Green M, Hunter RM, et al; PARROT-2 Trial Group. Repeat placental growth factor-based testing in women with suspected preterm preeclampsia: a stratified analysis of the PARROT-2 trial. *Hypertension*. 2024;81:1561–1573. doi: 10.1161/HYPERTENSIONAHA.123.22411