Assessing the Incremental Value of Blood Oxygen Saturation (SpO_2) in the miniPIERS (Pre-eclampsia Integrated Estimate of RiSk) Risk Prediction Model

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Abstract

Objective: To assess the incremental value of blood oxygen saturation (SpO_2) as a predictor in the miniPIERS model, a risk prediction model for adverse outcomes among women with a diagnosis of hypertensive disorder of pregnancy (HDP) in low-resourced settings.

Methods: Using data from a prospective cohort including 852 women admitted to hospital for a HDP, the association between SpO_2 and adverse maternal outcome was assessed using logistic regression. The miniPIERS model was recalibrated and extended to include SpO_2. The incremental value of adding SpO_2 to the model was measured using a net reclassification index (NRI), sensitivity, specificity, positive and negative predictive values, and likelihood ratios.

Results: SpO_2 of < 93% was associated with a 30-fold increase in risk (95% CI 14 to 68) of adverse maternal outcome compared to women with SpO_2 > 97%. After recalibration and extension, the miniPIERS model including SpO_2 (vs. not including SpO_2) had improved sensitivity (32.8% vs. 49.6%) at the cost of minimally decreased specificity (91.5% vs. 96.2%) with a NRI of 0.122.

Conclusion: SpO_2 is a significant independent predictor of risk in women with a HDP. Adding SpO_2 to the miniPIERS model improved the model's ability to correctly identify high-risk patients who would benefit most from interventions.

Key Words: Preeclampsia, prognosis, recalibration, pulse oximetry

Competing Interests: See Acknowledgements.

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Résumé

Objectif : Évaluer la valeur cumulative de la saturation en oxygène (SaO_2) à titre de facteur prédictif dans le cadre du modèle miniPIERS, soit un modèle de prévision des risques en ce qui concerne les issues indésirables chez les femmes ayant obtenu un diagnostic de trouble hypertensif de la grossesse (THG) dans des milieux qui ne disposent que de faibles ressources.

Méthodes : Grâce à des données issues d'une cohorte prospective ayant porté sur 852 femmes hospitalisées en raison d'un THG, l'association entre la SaO_2 et les issues indésirables maternelles a été évaluée au moyen d'une régression logistique. Le modèle miniPIERS a été recalibré et élargi de façon à inclure la SaO_2. La valeur cumulative de l'ajout de la SaO_2 à ce modèle a été mesurée en ayant recours à l'indice NRI (*net reclassification index*), à la sensibilité, à la spécificité, aux coefficients de prévision d'un test positif et d'un test négatif et aux rapports de vraisemblance.

Résultats : La SaO_2 < 93 % a été associée à un risque 30 fois plus élevé (IC à 95 %, 14 - 68) de constater une issue maternelle indésirable, par comparaison avec une SaO_2 > 97 %. Après avoir été recalibré et élargi, le modèle miniPIERS comprenant la SaO_2

(par comparaison avec le modèle ne comprenant pas la SaO_2) présentait une sensibilité améliorée (32,8 % vs 49,6 %); cela a toutefois mené à une baisse minime de la spécificité (91,5 % vs 96,2 %) en présence d'un indice NRI de 0,122.

Conclusion : La SaO_2 constitue un facteur prédictif indépendant significatif pour ce qui est du risque auquel sont exposées les femmes qui présentent un THG. L'ajout de la SaO_2 au modèle miniPIERS a mené à l'amélioration de la capacité de ce dernier à identifier correctement les patientes exposées à des risques élevés qui tireraient le plus avantage de la tenue d'interventions.

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INTRODUCTION

Preeclampsia is the second leading cause of maternal death and morbidity in low-resource countries, accounting for an estimated 18.5% of all maternal deaths each year.[1] These deaths are thought to be due to delays in case identification and a shortage of health workers trained to manage the disorder.[2] In the past 20 years, some progress has been made in reducing preeclampsia-related maternal deaths (an estimated 69 800 in 1990 vs. 47 100 in 2010).[1] To maintain this progress, innovative tools to improve management of the condition are required. Task-shifting aspects of pregnancy care to community-based health workers has been proposed as a means to save maternal lives.[3]

In low-resource settings, current approaches to assessing the severity of HDP-related illness and guiding clinical decisions are based on assessment of blood pressure and symptoms alone.[4] The goal of the "mini" Pre-eclampsia Integrated Estimate of RiSk (miniPIERS) project was to reduce adverse pregnancy outcomes by providing community-based health workers in low-resource settings with an evidence-based and low-cost tool to improve diagnosis and initial management of preeclampsia. miniPIERS is a clinical risk prediction model that uses symptoms and signs (parity, gestational age at assessment, chest pain/dyspnea, headache/visual disturbances, vaginal bleeding with abdominal pain, systolic blood pressure, and dipstick proteinuria) to determine the risk of adverse pregnancy outcomes occurring within 48 hours of assessment of the hypertensive woman.[5] A risk threshold of 25% predicted probability assigned by the miniPIERS model was found to be 85.5% accurate in identifying women at increased risk of adverse maternal outcomes. This model was designed for use as an aid for decision-making in the triage of women with a HDP in low-resourced, community settings. Identifying high-risk women using this tool would allow community-based health workers to target interventions, such as use of antihypertensives, administration of magnesium sulphate, and transfer to a facility, to those women most in need. Although this model shows great promise, improvements in the model's accuracy may be possible with the addition of more sensitive risk markers. We have previously shown that blood oxygen saturation measured by pulse oximetry is a significant independent predictor of the risk of complications in women with preeclampsia in an institutional setting.[6] Perturbations in SpO_2 level in the hypertensive woman likely reflect the consequences of endothelial dysfunction that is characteristic of maternal hypertensive disorders leading to increased permeability of the pulmonary vasculature and impaired pulmonary diffusion capacity.[7] Given the recent development of a low-cost mobile phone–based pulse oximeter, the Phone Oximeter,[8] the objective of this study was to assess the incremental value of adding SpO_2 to the miniPIERS model.

ABBREVIATIONS

AUC	area under the curve
HDP	hypertensive disorder of pregnancy
$MgSO_4$	magnesium sulphate
NRI	net reclassification index
POM	PIERS on the Move
ROC	receiver operating characteristic
SpO_2	blood oxygen saturation

METHODS

Data for this study were collected prospectively. Women were included in the study cohort if they were admitted to a participating institution with new (onset after 20 weeks' gestation) or chronic hypertension (systolic BP ≥ 140 mmHg or diastolic BP ≥ 90 mmHg on at least two occasions between 4 and 24 hours apart, after 20 weeks) during pregnancy, with or without proteinuria or other adverse conditions. The participating institutions were:

1. Tygerberg Hospital, Cape Town, South Africa;
2. Aga Khan University Hospital and its secondary level hospitals at Garden, Karimabad and Kharadar, and Jinnah Post-graduate Medical College, Karachi, Pakistan; and
3. Aga Khan Maternity & Child Care Centre, and Liaqat University of Medical Sciences, Hyderabad, Pakistan.

Data collected for this study included demographics (parity, gestational age, maternal age, medical history), symptoms (headache, visual disturbances, chest pain, dyspnea, abdominal pain with vaginal bleeding, epigastric pain, nausea and vomiting) and clinical signs (blood pressure, dipstick proteinuria, and SpO_2). At Tygerberg Hospital, Cape Town,

Figure 1. miniPIERS equation

miniPIERS linear predictor (lp) = $-5.77 + (-2.98 \times 10^{-1} \times$ indicator for multiparity) + $([-1.07] \times$ log gestational age at admission) + $(1.34 \times$ log systolic blood pressure) + $([-2.18 \times 10^{-1}] \times$ indicator for 2+ dipstick proteinuria) + $([4.24 \times 10^{-1}] \times$ indicator for 3+ dipstick proteinuria) + $([5.12 \times 10^{-1}] \times$ indicator for 4+ dipstick proteinuria) + $(1.18 \times$ indicator for occurrence of vaginal bleeding with abdominal pain) + $([4.22 \times 10^{-1}] \times$ indicator for headache and/or visual changes) + $(8.47 \times 10^{-1} \times$ indicator for chest pain and/or dyspnea)

South Africa, data were collected using the PIERS on the Move mHealth application and the Phone Oximeter.[8] The POM application was designed in collaboration with nurses and midwives in South Africa, Pakistan, India, and Nigeria[9] as a decision aid for community health workers incorporating both the miniPIERS model, a novel mobile phone-based pulse oximeter[8] and the WHO recommendations for management of women with preeclampsia and eclampsia.[4] In this study, POM was used only as a data collection instrument; treatment and management of women was not influenced by the POM application. The study staff assessed consenting women and collected relevant clinical data every four days during their inpatient stay. At the Aga Khan University Hospitals in Karachi and Hyderabad, Pakistan, data were abstracted from medical records of women admitted for care due to a HDP.

In both settings, the frequency of evaluations and timing in relation to hospital admission were kept consistent and followed the hospital's mandated standard of care. For the purpose of this study, data from the first clinical assessment after admission to hospital were used. If a relevant measure was missed during the first assessment, data from subsequent assessments occurring within 24 hours of admission were imputed to resolve any missing values.

The primary outcome for this study was a composite adverse maternal outcome, defined as maternal mortality or one or more of serious central nervous system, cardiorespiratory, renal, hepatic, hematological, or other morbidity. A list of components of the adverse maternal outcome is provided at the PRE-EMPT (Pre-eclampsia and Eclampsia, Monitoring, Prevention and Treatment) website.[10] The components of the composite outcome were determined by Delphi consensus[11] for the purpose of the original PIERS model development and validation project.[12] Data were collected on the occurrence of all outcome components at any time during admission, but for the purpose of this study only those that occurred within 48 hours of admission were considered. All study sites were instructed to collect information on any "other" adverse events the woman experienced during pregnancy or immediately postpartum as part of the regular data collection process. This was done to ensure balanced reporting of events across all sites. Any reported "other" events were adjudicated by the study Working Group during regular meetings, at which time the decision was made whether or not to include the reported outcome as a study outcome.

The published miniPIERS equation was used to calculate a linear predictor variable for all women in the study cohort. This equation[5] is shown in Figure 1.

The predicted probability of adverse maternal outcome was determined using the following equation:

$$p = e^{lp}/1 + e^{lp}$$

A threshold of 25% predicted probability was used to define the high-risk population based on the optimal threshold identified during development and validation of the miniPIERS model.[5]

Simulation studies have demonstrated that the sample size requirement to identify any issues with model calibration is 100 cases with an adverse outcome and 100 cases with no adverse outcome.[13,14] Therefore, data collection was planned to continue until a minimum of 100 adverse outcomes had occurred within the study cohort.

Demographics for women from each study setting were described using means and standard deviations or medians with interquartile ranges, when not normally distributed, for continuous variables and based on counts with frequencies for categorical variables.

The association between SpO_2 and the composite adverse maternal outcome was assessed using logistic regression. Multivariable logistic regression was used to further adjust for the other predictor variables in the miniPIERS model, as these are known to be significantly associated with risk of adverse maternal outcome. The ability of SpO_2 to discriminate between women who did and did not meet the outcome criteria was assessed based on the area under the curve of the receiver operating characteristic curve. In order to confirm that the observed relationship was generalizable

to non-respiratory outcomes, the relationship between SpO_2 and the adverse maternal outcome was assessed against both the complete composite adverse maternal outcome and a restricted adverse outcome in which cardiorespiratory events were removed from the composite outcome. A final sensitivity analysis was performed to assess the effect of SpO_2 on outcome in each study site to rule out any possibility of confounding by centre.

Recalibration and extension of the miniPIERS model to include SpO_2 was performed by fitting a new model using the study cohort that included two variables:

1. the linear predictor from the original miniPIERS model; and
2. a continuous measure of SpO_2.[15]

This simple method of updating the model was chosen to make the best use of the previously validated miniPIERS model. Should the pulse oximeter ever fail to work in the field, the model could still be used by simply reverting back to the original miniPIERS equation because the parameters remain fixed within this recalibrated and extended model.

Performance of the extended model and the original miniPIERS model applied to this cohort were assessed for discrimination ability based on the AUC ROC and calibration using the Hosmer-Lemeshow goodness of fit test. The two models were then compared based on stratification capacity and classification accuracy using a reclassification table.[16] Net change in model performance based on inclusion of SpO_2 was also assessed using an NRI and by evaluating the change in true- and false-positive rates[17,18] at the previously published 25% predicted probability threshold for a positive test. The NRI is calculated as the improvement in classification for each of the sub-groups of the study population with and without events using the formula:

$$\text{NRI} = (P[\text{up} \mid \text{event}] - P[\text{down} \mid \text{event}]) + (P[\text{down} \mid \text{nonevent}] - P[\text{up} \mid \text{nonevent}])$$

where "up" refers to reclassification by the extended model to the higher-risk group and "down" refers to reclassification by the extended model to the lower-risk group. The sensitivity, specificity, positive and negative predictive values, and positive and negative likelihood ratios of various cut-points of predictive probability were also calculated for both models to compare performance across multiple risk categories.

For assessment of model performance, an AUC ROC of > 0.70 was considered "good" according to established standards in interpretation.[19] The following categories for interpretation of the likelihood ratios were used: informative (LR < 0.1 or > 10); moderately informative (LR 0.1 to 0.2 or 5 to 10); and uninformative (LR 0.2 to 5).[20]

All statistical analyses were performed using STATA v.11.0 (StataCorp LP, College Station, TX).

This study received ethics approval from the UBC Clinical Research Ethics Board, the Aga Khan University Research Ethics Board, and the Stellenbosch University Clinical Research Ethics Board.

RESULTS

Between January 1, 2011, and March 31, 2012, 617 women were recruited to the study in Pakistan, while 235 women were recruited in South Africa between November 1, 2012, and December 31, 2013. These two groups combined to create a study cohort of 852 women, of whom 119 (14.0%) experienced one or more component of the composite adverse maternal outcomes within 48 hours of admission. A total of 147 women (17.3%) experienced one or more component of the composite adverse maternal outcome at any time during hospital admission. The women recruited from South Africa tended to be earlier in gestation and more often admitted with a diagnosis of preeclampsia rather than gestational hypertension alone. This more severe case-mix is reflected in the increased use of corticosteroids and $MgSO_4$ in the South African cohort. The overall rates of both maternal and perinatal adverse outcomes were comparable between sites, as presented in Table 1.

The most common adverse outcomes in the cohort were need for blood transfusion, pulmonary edema, and postpartum hemorrhage. There were no maternal deaths in the study population but there were 14 cases of eclampsia. A complete description of outcomes occurring in the cohort at any time and within 48 hours of admission is provided in Table 2.

Increased SpO_2 was significantly associated with a decreased risk of adverse maternal outcome (OR 0.648; 95% CI 0.587 to 0.716). This association remained after adjustment for all other miniPIERS predictor variables of parity, gestational age at admission, chest pain/dyspnea, headache/visual disturbances, abdominal pain with vaginal bleeding, systolic blood pressure, and dipstick proteinuria (univariate adjusted OR 0.702; 95% 0.622 to 0.793). As shown in Table 3, women with $SpO_2 \leq 93\%$ were 30.7-fold (95% CI 13.9 to 67.7) more likely to have an adverse outcome than women with $SpO_2 > 97\%$. The results were also similar when assessing the effect of SpO_2 on outcome in the data from Pakistan and South Africa individually, with ORs of 0.681 (95% CI 0.609 to 0.761) and 0.533 (95% CI 0.417 to 0.682), respectively.

Table 1. Demographics and clinical status at admission for women admitted to the study from either Pakistan or South Africa

Characteristic	Pakistan cohort (n = 617 women)	South African cohort (n = 235 women)
Demographics		
Maternal age at EDD, years	29 [26, 33]	27 [23, 33]
Gestational age at eligibility, weeks	37.2 [35.4, 38.2]	34.6 [30.0, 37.9]
Multiple pregnancy	13 (2.1)	1 (0.4)
Parity ≥ 1	320 (51.9)	126 (53.6)
Preeclampsia description		
Preeclampsia*	343 (55.6)	173 (73.6)
Other HDP	274 (44.4)	62 (26.4)
Clinical measures within 24 hours of admission		
Systolic BP	150 [140, 160]	146 [140, 160]
Diastolic BP	100 [90, 110]	96 [90, 101]
Dipstick proteinuria	2+ [trace, 2+]	2+ [1+, 3+]
SpO_2	97 [95, 98]	97 [96, 98]
Interventions		
Corticosteroid administration	146 (23.7)	143 (60.9)
Antihypertensive medications administered	596 (96.6)	234 (99.6)
$MgSO_4$ administered	231 (37.4)	186 (79.1)
Pregnancy outcomes		
Intrauterine fetal death (≥ 20+0 wk and/or ≥ 500 g)	59 (9.6)	21 (8.9)
Neonatal death (before discharge)	22 (3.4)	7 (3.0)
Maternal adverse outcome (within 48 hours of admission)	91 (14.7)	28 (11.9)

*Preeclampsia defined as hypertension (blood pressure greater than 140/90 mmHg with proteinuria greater than 2+ on a dipstick test

EDD: estimated date of delivery

Maternal, gestational age, BP, proteinuria and SpO_2 values are median [IQR].

SpO_2 alone and adjusted for the other miniPIERS predictor variables resulted in AUC ROC values of 0.728 (95% CI 0.681 to 0.776) and 0.810 (95% CI 0.764 to 0.856), respectively. When a sensitivity analysis was performed using only non-cardiorespiratory outcomes, SpO_2 maintained its discriminatory ability with an AUC ROC of 0.690 (95% CI 0.636 to 0.744) when unadjusted and 0.753 (95% CI 0.694 to 0.813) when adjusted for the other miniPIERS risk factors.

When the original miniPIERS model was applied to our study cohort the AUC ROC was 0.781 (95% CI 0.729 to 0.832) and the Hosmer-Lemeshow goodness of fit *P* value was 0.162. After model recalibration and extension, the AUC ROC was 0.798 (95% CI 0.752 to 0.846) with a goodness of fit *P* value of 0.701. The ROC curves for both models are presented in Figure 2.

Comparison of the models based on their ability to classify women correctly as high-risk using a threshold of predicted probability of 25% is presented in Table 4. When extending the model to include SpO_2, the number of women who are correctly reclassified into the high-risk group and who did in fact have an adverse maternal outcome is 22 (18.5% of all 119 cases with an adverse outcome); in addition, two women who were incorrectly reclassified by the extended model as low-risk did in fact suffer an adverse outcome. This resulted in an overall change in true-positive rate of 0.168. In the low-risk group presented in Table 4, there were four women correctly reclassified as low-risk with the extended model and 38 women incorrectly reclassified as high-risk who did not suffer an adverse maternal outcome, resulting in an overall change in true-negative rate of −0.046. The overall rates of change in true-positive and true-negative rates were combined to calculate an NRI of 0.122.

Sensitivity, specificity, positive and negative predictive values and likelihood ratios for cut-points of 15%, 25%, and 35% predicted probabilities are presented for comparison in Table 5. The extended model had improved sensitivity and negative predictive value at all risk thresholds evaluated but decreased specificity, positive

Table 2. Maternal adverse outcomes occurring in the study cohort. Full definitions of all outcomes are available as supplementary Table 1

One or more of maternal morbidity or mortality:	Within 48 hours	Any time
Total		
Maternal death	0	0
Central nervous system		
Eclampsia (≥ 1)	10	14
Glasgow coma score < 13	7	8
Stroke or reversible ischemic neurological deficit	1	1
Cortical blindness or retinal detachment	3	3
Posterior reversible encephalopathy	0	1
Cardiorespiratory		
Positive inotropic support	1	1
Infusion of a third parenteral antihypertensive	0	0
Myocardial ischemia/infarction	1	3
≥ 50% $Fi0_2$ for > 1 hour	1	2
Intubation (other than for Caesarean section)	3	3
Pulmonary edema	23	32
Hematological		
Transfusion of any blood product	46	53
Platelets < 50 x 10^9/L with no transfusion	2	2
Hepatic		
Dysfunction	1	1
Hematoma/rupture	0	0
Renal		
Acute renal insufficiency (creatinine > 150 µmol/L; no pre-existing renal disease) (creatinine > 200 µmol/L; pre-existing renal disease)	4	4
Dialysis	0	1
Placental outcomes		
Placental abruption	2	7
Postpartum hemorrhage	24	26
Other adverse events		
Severe ascites	15	20
Other*	3	5

*Includes two cases of pulmonary embolism, two cardiac arrests, and one case of ruptured uterus

Table 3. Adverse outcome rate by strata of SpO_2 (n = 852) and odds ratio for occurrence of adverse maternal outcome in each stratum compared to odds of outcome in women with SpO_2 greater than 97%

SpO_2 level, %	Women in the cohort n (%)	Women with adverse outcomes n (%*)	Univariate OR (95% CI)
≤ 93	38 (4.5)	25 (65.8)	30.7 (13.9 to 67.7)
94 to 95	153 (18.0)	34 (22.2)	4.6 (2.6 to 8.0)
96 to 97	271 (31.8)	37 (13.7)	2.5 (1.5 to 4.4)
≥ 98	390 (45.8)	23 (5.9)	Reference

*Denominator used is number of women in cohort with SpO_2 in the given range.

Figure 2. ROC curve for the original (blue) and extended (red) miniPIERS model. Area under the curve for the original model was 0.781 (95% CI 0.729 to 0.832) and for the extended model was 0.798 (95% CI 0.752 to 0.846).

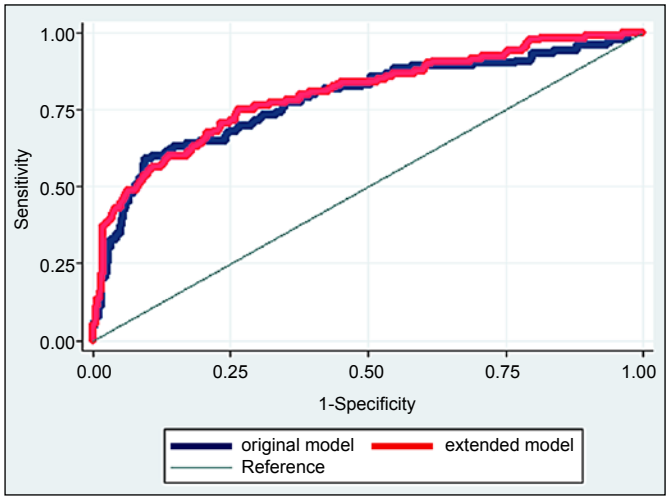

Table 4. Classification table comparing miniPIERS model with and without addition of SpO_2

	Model with SpO_2		
Model without SpO_2	0% to 24.9%	≥ 25.0%	Total
Women with events, %			
0 to 24.9	58	22	80
≥ 25.0	2	37	39
Total	60	59	119
Women without events, %			
0 to 24.9	667	38	705
≥ 25.0	4	24	28
Total	671	62	733

predictive value, and likelihood ratios. For example, at the 25% predicted probability threshold, comparing the original model to the extended model resulted in sensitivity of 32.8% versus 49.6%; specificity of 96.2% versus 91.5%; positive predictive value of 58.2% versus 48.8%; negative predictive value of 89.9% versus 91.8%; positive likelihood ratio of 8.6 versus 5.9; and negative likelihood ratio of 0.7 versus 0.6, respectively. For all measures, confidence intervals overlapped.

DISCUSSION

In this study we demonstrated that SpO_2 is a significant predictor of risk of adverse maternal outcomes in women with a HDP, with a threshold of ≤ 93% SpO_2 associated with a 30-fold increase in risk compared with women with normal oxygen saturation (at or above 98%). This association was consistent across study settings and after adjustment for other risk factors included in the miniPIERS model. A sensitivity analysis performed to assess the effect of SpO_2 as a predictor of non-respiratory outcomes alone also demonstrated a consistent predictive effect. This suggests that reduced pulmonary function measured as decreased SpO_2 is a marker of severe disease in general and is not specific to risk for pulmonary edema alone.

The performance of the miniPIERS model with or without SpO_2 found in this study is consistent with that found during development and external validation of the original model, in which the AUC ROC was 0.768 (95% CI 0.735 to 0.801) in the development dataset and 0.713 (95% CI 0.658 to 0.768) on external validation.[5] The independent effect of SpO_2 on maternal outcome is also consistent with previously published results, in which SpO_2 ≤ 93% was associated with an approximately 18-fold increase in the risk of the same combined adverse maternal outcome (95% CI 8.1 to 40.1) in a population of women with preeclampsia admitted to tertiary perinatal units in high-resourced settings.[6] This supports the conclusion that the effects seen in this study are accurate and generalizable to other settings.

Strengths of this study include the large sample size and high quality data collected. In a cohort of over 800 women, we were able to collect complete data for all cases enrolled. Using this large and well-characterized prospective cohort, we were able to meet the stated objectives of the study.

Another major strength of this study is in the methodology used. Rather than simply presenting an updated model that includes SpO_2, we have carefully considered the incremental value of the new predictor. This is particularly important given the target low-resourced setting in which we want to implement the miniPIERS tool. In this case, we demonstrate that the improvement would be an approximately 20% increase in the health worker's ability to detect high-risk patients (true positives), but at the expense of a small (5%) increase in the number of low-risk women incorrectly classified as high risk (false positives). Addition of SpO_2 would be warranted in these settings if the added resource requirements, in the form of an accompanying increase in false-positive cases, could be properly balanced with clinically relevant improvements in outcomes for the additional high-risk patients identified. It will depend on the local setting's resource availability as to whether this is manageable.

The main limitation of this study is a result of inclusion of data from two sites, collected in two distinct ways. Combining the populations from our two study sites was

Table 5. Performance measures for the original miniPIERS model and the extended model at various cut-points of predicted probability used to define a positive test

	15%		25%		35%	
	Original model	Extended model	Original model	Extended model	Original model	Extended model
Sensitivity (95% CI)	50.4 (41.2–59.7)	68.1 (58.8–76.1)	32.8 (24.6–42.1)	49.6 (40.3–58.8)	20.2 (13.6–28.7)	39.5 (30.8–48.9)
Specificity (95% CI)	91.7 (89.4–93.6)	77.9 (74.7–80.8)	96.2 (64.5–97.4)	91.5 (89.2–93.4)	98.0 (96.6–98.8)	96.3 (94.6–97.5)
PPV (95% CI)	49.6 (40.4–58.8)	33.3 (27.5–39.7)	58.2 (45.5–69.9)	48.8 (39.6–58.0)	61.5 (44.7–76.2)	63.5 (51.5–74.2)
NPV (95% CI)	91.9 (89.7–93.8)	93.8 (91.5–95.5)	89.9 (87.4–91.8)	91.8 (89.5–93.6)	88.3 (85.9–90.4)	90.7 (88.4–92.6)
LR+ (95% CI)	6.1 (4.5–8.2)	3.1 (2.6–3.7)	8.6 (5.5–13.4)	5.9 (4.3–7.9)	9.9 (5.3–18.2)	10.7 (7.0–16.5)
LR− (95% CI)	0.5 (0.5–0.6)	0.4 (0.4–0.6)	0.7 (0.6–0.8)	0.6 (0.5–0.7)	0.8 (0.7–0.9)	0.6 (0.5–0.7)

PPV: positive predictive value; NPV: negative predictive value; LR+: positive likelihood ratio; LR−:negative likelihood ratio

necessary in order to meet sample size requirements for model recalibration, but it may have introduced additional biases due to differential misclassification of predictors or measurement errors that may have occurred when using the clinically available pulse oximeter and data from the medical record in Pakistan. We attempted to reduce these biases by ensuring data collection in South Africa was done in a similar manner and at the same time-points as in Pakistan. We also ensured that clinical practice guidelines for treatment and management of women with hypertensive disorders of pregnancy were consistent across both settings. The consistent effect of the predictors within each cohort supports combining data from the two sites. In addition, using data from two sites may also be considered a strength of the study because it increases the generalizability of our results to multiple locations.

The main clinical consideration in the interpretation of this study's results is the trade-off required between true and false-positives when applying a tool such as miniPIERS as a screening test for individual risk within a population. If the risk threshold used to define the high-risk group is set too high, the consequence would be that many women who truly need referral and further treatment would be missed; if the risk threshold is set too low, there will be an increase in false positives, and this may result in overburdening the higher-level health facilities with women who do not require more care.

During development of the original miniPIERS model we undertook a survey of clinical consultants at all study sites and within the study working group to determine the priority (sensitivity vs. specificity) when setting the risk threshold used to define the high-risk population. We focused on the use of the 25% predicted probability as the optimal risk threshold because it was felt to demonstrate adequate performance as a rule-in test without increasing the false-positive rate above approximately 10%. A similar pattern in results was found in this study.

The miniPIERS model, with SpO_2 included, when applied as a screening tool in a hypertensive pregnant population, allows health workers to accurately stratify women into useful risk groups. By doing so, health workers can assess individual women for their risk of complications related to hypertension in pregnancy occurring within 48 hours of assessment. This time frame would allow decisions to be made regarding treatment and referral to a higher level of care that could make the difference in a woman's life. This is currently the only tool of its kind available for this purpose. Confirmation of this impact in clinical care is required through an implementation study. This implementation study is now underway as part of the PRE-EMPT (Pre-eclampsia and Eclampsia, Monitoring, Prevention and Treatment) initiative, called the Community Level Interventions for Pre-eclampsia (CLIP) study.[21]

CONCLUSION

Addition of SpO_2 to the miniPIERS model does confer a net improvement in model accuracy based on an increase in the model's sensitivity. Inclusion of SpO_2 in the model translated into an additional 22 high-risk women (18.5%) being correctly identified. Clinically, this is a significant improvement in screening ability and suggests that including pulse oximetry into routine antenatal assessments

of women with HDP could save lives. For now, clinicians should consider including measurement of SpO_2 by pulse oximetry into routine assessments of women with hypertension in pregnancy.

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