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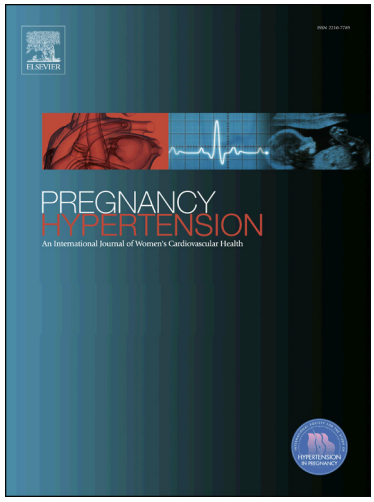

Development and internal validation of a multivariable model to predict perinatal death in pregnancy hypertension

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Development and internal validation of a multivariable model to predict perinatal death in pregnancy hypertension.

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ABSTRACT

Objective: To develop and internally validate a prognostic model for perinatal death that could guide community-based antenatal care of women with a hypertensive disorder of pregnancy (HDP) in low-resourced settings as part of a mobile health application.

Study Design: Using data from 1688 women (110 (6.5%) perinatal deaths) admitted to hospital after 32 weeks gestation with a HDP from five low-resourced countries in the miniPIERS prospective cohort, a logistic regression model to predict perinatal death was developed and internally validated. Model discrimination, calibration, and classification accuracy were assessed and compared with use of gestational age alone to determine prognosis.

Main outcome measures: Stillbirth or neonatal death before hospital discharge.

Results: The final model included maternal age; a count of symptoms (0, 1 or ≥ 2); and dipstick proteinuria. The area under the receiver operating characteristic curve was 0.75 [95% CI 0.71 - 0.80]. The model correctly identified 42/110 (38.2%) additional cases as high-risk (probability >15%) of perinatal death compared with use of only gestational age <34 weeks at assessment with increased sensitivity (48.6% vs. 23.8%) and similar specificity (86.6% vs. 90.0%).

Conclusion: Using simple, routinely collected measures during antenatal care, we can identify women with a HDP who are at increased risk of perinatal death and who would benefit from transfer to facility-based care. This model requires external validation and assessment in an implementation study to confirm performance.

Key Words: pre-eclampsia; prognosis; perinatal death; stillbirth; low-resourced setting

INTRODUCTION

Perinatal death, including stillbirth and neonatal death up to 28 days of life, remains a significant health burden, globally. By most recent estimates, there were an estimated 2.64 million stillbirths in 2009, 76.2% of which were in Sub-Saharan Africa or South Asia (1, 2). Global neonatal and child death rates show a similar trend, with an estimated 2.00 million early neonatal deaths in 2013 and 80% of all child deaths reported in just 26 low- and middle- income countries (3). The hypertensive disorders of pregnancy are responsible for an estimated 9-20% of all perinatal deaths (2, 11, 12, 13, 14).

Like maternal death, perinatal death is increased in low- and middle- income countries compared with high-income countries due to a lack of access to effective antenatal and emergency obstetric care, as well as demographic and social risk factors which include advanced and very young maternal age, being unmarried, low socioeconomic status, illiteracy, and undernutrition. (5-7). As such, the majority of these deaths are preventable (4-6), by improving both the access to, and quality of, maternal antenatal care (8-10). For women with the hypertensive disorders of pregnancy, this improvement in care would include improved diagnosis in the community and timely referral to a higher-level facility, should a woman be identified to be at risk of a serious complication.

We have previously developed and validated the miniPIERS (Pre-eclampsia Integrated Estimate of RiSk) model that can identify which women with a hypertensive disorder of pregnancy are at greatest risk of poor maternal outcome (15). This model has been converted into a mobile health (mHealth) application, called PIERS on the Move (16), for use by frontline health workers as a decision aid for diagnosis and timely triage of women with hypertension identified in the

community. In order to broaden the impact of the PIERS on the Move tool and facilitate improvements in perinatal outcomes, a complimentary model for community-level identification of hypertensive pregnant women who are at greatest risk of perinatal death is required.

Using data from the miniPIERS cohort, the objective of this study was to determine if the maternal demographics and clinical symptoms and signs measured during antenatal surveillance could be used to identify the fetuses at greatest risk of perinatal death.

MATERIALS AND METHODS

Study design and population

The miniPIERS cohort is a prospective, multicentre cohort of women with a hypertensive disorder of pregnancy collected from July 2008 – March 2012. A detailed description of the cohort has been previously published (15). The study was approved by the University of British Columbia clinical research ethics board and each participating institutions clinical research ethics board. All participating women provided written informed consent for inclusion into the miniPIERS cohort.

Women were included in miniPIERS if they were admitted to a participating institution with any of the hypertensive disorders of pregnancy: chronic hypertension, gestational hypertension, pre-eclampsia, or isolated HELLP (Hemolysis Elevated Liver enzyme Low Platelet) syndrome. Women were excluded if: (i) they had suffered a primary maternal outcome for the main study prior to admission to hospital, or (ii) they had been admitted to hospital with either a CD4 count <250 or an AIDS-defining illness, as these were felt to be significant confounders of the disease-maternal outcome relationship. These inclusion and exclusion criteria have been previously described (15).

For this study, the cohort was further restricted to include only singleton pregnancies and cases with admission after 32 weeks gestation, to optimize the clinical relevance of the model. First, perinatal risk in the very early preterm period before 32 weeks gestation would be driven almost entirely by gestational age. Second, in under-resourced settings, neonatal survival is unlikely when delivery occurs prior to 32 weeks, but thereafter, survival is likely in any setting with basic newborn care (17). Having a model that identifies those women likely to benefit from facility-based care for their high-risk neonates after 32 weeks gestation is therefore needed.

Candidate predictor variables

For this study, candidate predictor variables were defined prior to analysis as: (i) those demonstrated to increase risk of stillbirth or neonatal death in previous studies (19, 20) as well as (ii) those related to the severity of the maternal condition in the miniPIERS model (15). Specifically, we assessed gestational age on admission (weeks), parity (primaparous or multiparous), maternal age (years), smoking status (non-smoker/smoker), blood pressure (mmHg), dipstick proteinuria, and the maternal symptoms of headache, visual disturbances, chest pain, dyspnoea, right upper quadrant pain or epigastric pain, nausea/vomiting, and vaginal bleeding with abdominal pain.

The value of the candidate predictor used in the model development process was the worst measured within the first 24hrs of admission. There was no missing data for candidate predictors within this timeframe in the miniPIERS cohort. As this was a secondary analysis of the existing cohort, during ascertainment of the predictor variables data collectors were unaware of the outcome status of the baby.

Perinatal outcome

A composite of stillbirth or neonatal death was used to define the primary outcome. The study cohort was restricted to those women admitted after 32 weeks gestation, so only cases of stillbirth occurring after admission at this time point are considered. Neonatal death was limited to that occurring during hospital admission, as follow-up post-discharge for women or their babies was not possible.

Sample size

The sample size required for model development was determined based on the minimum standard of 10 events per effective variable considered, according to the

formula N=(nx10)/I where N is the sample size, n is the number of candidate predictor variables and I is the estimated event rate in the population (21). As this was a secondary analysis of an existing cohort of known size, this formula was used to determine the number of candidate predictor variables that could reasonably be tested in a multivariable model. Based on a perinatal death rate of 6.5% in the miniPIERS cohort and the cohort size of 1688 women, we determined that a maximum of 10 candidate predictor variables should be considered.

Statistical analysis

Descriptive analysis of the cohort

Women with and without perinatal death were compared using the Mann-Whitney U test for continuous variables and the chi-squared or Fischer's exact test for categorical variables.

Selection of candidate predictor variables

Associations with perinatal death were estimated using logistic regression to determine univariate and gestational age-adjusted odds ratios for all candidate predictor variables. Also, associations between candidate predictor variables were estimated by using either the Pearson product moment correlation coefficient or two-by-two tables and the chi-squared statistic, where appropriate; this was done in order to reduce possible correlation between predictor variables included in the model. Final predictor variables to be included in the multivariable model were selected based on the strength of the gestational age-adjusted association with perinatal death, as well as the lack of evidence of correlation with other predictors. A final selection rule based on a minimum change in area under the receiver operating characteristic curve (AUC ROC) of 0.2 after inclusion of the candidate predictor

variable being considered was implemented to ensure that the final model was as parsimonious as possible, given the environment in which it is meant to be used.

Final model development and evaluation

Multivariable logistic regression was used to estimate the strength of association between the final predictors included in the model with perinatal death, the primary outcome. This final model was evaluated based on discrimination ability using the area under the receiver-operating-characteristic curve (AUC ROC). An AUC ROC ≥0.70 is considered as evidence of good discrimination (22).

Calibration of the final multivariable model was assessed based on the Hosmer-Lemeshow goodness-of-fit test and, visually, by plotting predicted probability of perinatal death against the observed rate of the outcome in each decile. Stratification capacity of the model was tabulated in five groups of predicted probability as the number of events in each group out of the total cases in that group. Groups were defined so that the lowest and highest groups included only those women with significantly lower or higher predicted probabilities than the population prevalence of perinatal death (6.5%). Predictive performance, defining high-risk cases based on the threshold of predictive probability used to define each of the five risk groups, was estimated using the sensitivity, specificity, positive predictive value and negative predictive value. Finally, a likelihood ratio was estimated for each risk group individually (23).

Model validation

Internal validity of the final multivariable model was assessed using Efron's enhanced bootstrap method (24). Also, evaluation of the final model for classification accuracy was based on a comparison with both the published miniPIERS model and

gestational age alone. To accomplish this, a classification table was used in which women were classified as high-risk based on a miniPIERS maternal model predicted probability ≥25% or a gestational age at admission <34 weeks; these results were compared with the perinatal model using a risk-threshold of >15% predicted probability of perinatal death. Gestational age alone was chosen as a comparator to reflect the standard of practice in the study settings; it is the most commonly used indicator for risk of stillbirth and neonatal death in this population.

Sensitivity analyses were performed to assess the performance of the model based on its discrimination ability when the outcome was restricted to either stillbirth or neonatal death before discharge. Further sensitivity analyses assessed the performance of the model when the cohort was restricted to those women admitted after 34 weeks gestation or after 36 weeks gestation.

All statistical analyses were performed using STATA version 13.1 (STATA Corp, Texas, US).

RESULTS

Of the 2081 women in the miniPIERS cohort, 1688 (81.1%) were included in this study after exclusion of 78 cases with multiple gestation and 323 cases admitted prior to 32 weeks gestation. Among these 1688 women, there were 110 (6.5%) perinatal deaths, of which 79 were stillbirths and 31 were neonatal deaths prior to hospital discharge. Only 6.9% of those neonates who survived remained in hospital for follow-up to 7 days postpartum.

Women who had a perinatal death, compared with those who did not, showed more severe maternal disease indicators, such as earlier gestational age at admission, higher median blood pressure and dipstick proteinuria values, greater occurrence of symptoms and higher incidence of adverse maternal outcomes (Table 1). However, there was no difference between the groups in the rate of delivery due to maternal indication. Women who had a perinatal loss were less likely to be delivered by cesarean, an association that was more pronounced when the outcome was restricted to stillbirth alone (OR 0.32 [95% CI 0.22-0.48] vs. OR 0.21 [95% CI 0.13-0.36], respectively).

The univariate risk factors for perinatal death in this cohort were gestational age at admission, blood pressure (both systolic and diastolic), dipstick proteinuria and all maternal symptoms. In order to make interpretation of the impact of systolic blood pressure more clinically meaningful, the univariate and multivariate odds ratio reported for this variable reflect a 10 mmHg change in blood pressure value (Table 2).

Selection of candidate predictors for model development

Systolic and diastolic blood pressures were highly correlated. Based on the strong association found in previous studies between systolic blood pressure and stroke risk (25), and the fact that it can be measured without a manometer, it was decided to retain systolic blood pressure for consideration in the final model.

All symptom variables were associated with each other ($p<0.001$ for the chi-squared test). To avoid potential errors in estimation due to multicollinearity, a count of symptoms present categorized as zero, one, or greater than or equal to two was retained for the final model.

Maternal age was retained for the final model despite its lack of significance in the univariable analysis, as maternal age is a well-established risk factor for perinatal death within this population (14).

When the requirement that AUC ROC increase by ≥0.02 in order for a variable to be included in the final model, symptoms, dipstick and maternal age were selected as the most significant contributors to model performance. Addition of blood pressure to the model did not have any effect on AUC ROC compared to a model without blood pressure (AUC ROC 0.753 vs. 0.753) and addition of gestational age at admission had only minimal effect on the AUC ROC (AUC ROC 0.753 vs. 0.761).

Final multivariate model

The equation for the final perinatal death model was: logit (logarithm of the odds)(pi)= -4.75 + 0.024(maternal age) + 0.389(indicator for presence of one symptom) + 1.338(indicator for presence of two or more symptoms) + 1.119(indicator for dipstick proteinuria of 2+ or 3+) + 1.457(indicator for dipstick proteinuria of 4+).

Performance of the model

Discrimination ability of the model was good with an AUC ROC of 0.75 [95% CI 0.71 - 0.80] (Figure 1). Among these women who were admitted at 32 weeks or beyond, gestational age alone as a predictor of perinatal death was associated with an AUC ROC of 0.60 [95% CI 0.54 - 0.66]. When the miniPIERS *maternal* model was used to predict perinatal death in this study, the AUC ROC was 0.70 [95% CI 0.65 - 0.75].

This model was well-calibrated with a Hosmer-Lemeshow goodness of fit test statistic of 2.14 (p=0.98). The calibration of the model is further demonstrated by the model calibration curve, where the 95% confidence interval around the observed rate of outcome in each decile group of predicted probability crosses the perfect fit line (Figure 2).

Stratification of the cohort based on the model is moderate, with the majority of women (54.9%) estimated to have a probability of perinatal death less than 5% and 25% of whom have a predicted probability <2%, which is significantly less than the overall prevalence within the cohort. Sixteen percent of the women were assigned a predicted probability in the highest risk group (Table 3).

Table 3 shows the sensitivity, specificity, positive and negative predictive values differed based on the threshold used to define a positive test (i.e. women at high-risk of a perinatal loss). As the threshold used to define high-risk increases, the sensitivity decreases but the likelihood ratio increases. In no risk group does the likelihood ratio result in values that would indicate that the test could be used to clearly rule-in or rule-out the risk of perinatal death. Using gestational age at delivery less than 34 weeks to define a high-risk subgroup in this cohort was associated with a sensitivity of 23.6%, specificity 90.0%, positive predictive value 14.1% and negative predictive value 94.4%.

Model validation

After 500 iterations of bootstrapping, model optimism was estimated as 0.01 indicating minimal overfitting of the model to the data.

The final perinatal death model correctly identifies significantly more high-risk women compared with either gestational age only (42/110, 38.2% additional women, Table 4a) or the miniPIERS maternal model (35/110, 31.8% additional women, Table 4b). This improvement in classification of true positive cases occurred with a small increase in the false-positive rate compared with using gestational age alone (213/1578, 13.5% vs. 159/1578, 10.1%, respectively) or the miniPIERS maternal model (213/1578, 13.5% vs. 101/1578, 6.4%, respectively).

The sensitivity analysis to assess performance of the model using stillbirth or neonatal death before discharge as the primary outcome, or when restricting the cohort to greater than 34 weeks or 36 weeks gestation on admission, demonstrated that the model's discrimination ability was well maintained (Table 5).

DISCUSSION

In this study we have developed and internally validated a novel perinatal risk model using simple measures available at antenatal assessment. Previous work to predict risk of stillbirth or perinatal death has been restricted to high-resource neonatal intensive care settings and very preterm infants (26). Similarly, the existing neonatal risk scores, such as the CRIB II score, are designed for use in an advanced neonatal intensive care settings and rely on data available at birth. This is not comparable in scope or proposed environment to our model, which is designed for use in a low-resourced community setting prior to delivery to identify those fetuses at risk of perinatal death and for whom facility-based care should be a priority.

The model developed in this study improves our ability to correctly identify women whose fetuses are at risk of perinatal death beyond that of gestational age alone or the miniPIERS maternal model. Addition of this perinatal model to the miniPIERS maternal risk model as part of the PIERS on the Move mHealth application (16) would result in an improvement in community-level triage by identifying approximately 38% more women at increased risk of perinatal loss as a result of a hypertensive disorder of pregnancy. This would bring us closer to the ultimate goal of supporting scale-up of community level antenatal care, including effective diagnosis and triage of the hypertensive disorders of pregnancy, and ultimately, to reduce maternal and perinatal deaths.

The data for this study were taken from the miniPIERS cohort, designed for maternal outcome prediction, and this may have limited the final predictive performance of a perinatal risk model. The miniPIERS cohort may be missing important potential risk factors for stillbirth and neonatal death but no such omissions were identified based on published literature. This was a secondary analysis of an existing cohort, so we

were unable to gather additional data in order to test a greater number of candidate predictors. A second limitation of the study was use of a composite perinatal mortality outcome. It could be argued that stillbirth and neonatal death will have distinct risk factors and should be modeled separately, given that they often have distinct causes. For example, late neonatal deaths are often related to postnatal infection and undernutrition. It is also important to mention that the study cohort did not include complete follow-up to 28 days postpartum for most neonates and had only limited follow-up to 7 days postpartum (7% completeness). This lack of follow-up means late neonatal deaths were not recorded and the model is skewed towards prediction of events proximate to birth. Combining stillbirth and immediate neonatal death does reflect known limitations in our ability to differentiate these two events during data collection, as well as the routine practice of combining these events in pre-established epidemiologic surveillance (27). A final limitation of this study is the use of gestational <34 weeks as the "gold-standard" comparator for predictive performance of the model. This variable was chosen as it reflects common practice in the study settings of basing assessment of risk of perinatal loss on gestational age alone. There is no other established gold-standard prognostic test for this purpose.

Among the strengths of our study is that it is based on a large cohort of well-characterized women from five LMICs, making results applicable across multiple under-resourced settings. Second, by focusing on women admitted at or after 32 weeks gestation, we have assessed risk factors for perinatal death beyond gestational age alone and removed some of the effect of prematurity on the occurrence of our primary outcome. In addition, by focusing on only those predictor variables that add significantly to the performance of the final model we have been

able to develop a simple and useful model given the data available on assessment in a community setting, making its implementation by community health workers easier.

Any intervention applied in an under-resourced setting should demonstrate added value above what already exists, while considering resource and health system implications. In this case we would increase rates of urgent referral from the community by approximately 9.0%, above what would have been indicated by the maternal model alone, in order to identify an additional 30% of high-risk women. Put differently, for every 1000 hypertensive pregnant women identified, an additional 90 would be urgently referred to facility to avoid not referring 21 women who would suffer certain perinatal death in the community. We believe this to be a reasonable trade-off, even though all of those perinatal deaths would not necessarily be avoidable, due to factors such as very preterm gestational age.

In conclusion, this model shows great promise as a tool to identify those hypertensive pregnant women at greatest risk of perinatal death. The model requires further validation in a new cohort, but once this has been accomplished, the model could be incorporated into the PIERS on the Move tool and evaluated in an implementation study that would have the potential to reduce maternal and perinatal mortality simultaneously.

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Table 1: Demographics of women in the total cohort comparing women with and without perinatal death (N=1688). Results for continuous variables presented as mean (± sd) when data normally distributed or median [interquartile range] for skewed data.

Characteristic	Women with adverse neonatal outcomes (n= 110 women)	Women without adverse neonatal outcomes (n= 1578 women)	P*
Demographics (within 48h of eligibility)			
Maternal age at EDD (yr)	28 [25, 32]	28 [24, 32]	0.336
Age >40 years	7 (6.3%)	73 (4.6%)	0.407
Gestational age at admission (wk)	36.6 [34.1, 38.6]	37.6 [35.9, 39.1]	**<0.001**
Parity ≥ 1	61 (55.5%)	824 (52.2%)	0.554
Smoking in this pregnancy	1 (0.9%)	47 (3.0%)	0.366
Hypertensive disorder description			
Pre-eclampsia	91 (82.7%)	911 (57.7%)	**<0.001**
miniPIERS maternal predicted probability (%)	12.2 [7.6, 22.3]	7.2 [5.2, 11.7]	**<0.001**
Clinical measures (within 24h of eligibility)			
Systolic BP	160 [150, 180]	150 [140, 170]	**<0.001**
Diastolic BP	110 [100, 120]	100 [90, 110]	**<0.001**
Worst dipstick proteinuria	2+ [2+, 3+]	1+ [negative, 3+]	**<0.001**
Maternal symptoms			
Headache	77 (70.0%)	640 (40.6%)	**<0.001**
Visual disturbances	52 (47.3%)	335 (21.2%)	**<0.001**
Chest pain	7 (6.4%)	35 (2.2%)	**0.017**
Dyspnoea	11 (10.0%)	60 (3.8%)	**0.005**
Epigastric / right upper quadrant pain	47 (42.7%)	222 (14.1%)	**<0.001**
Abdominal pain with vaginal bleeding	20 (18.2%)	113 (7.2%)	**<0.001**

Nausea / vomiting	43 (39.1%)	215 (13.6%)	**<0.001**
Interventions at any time			
Corticosteroid administration	41 (37.3%)	348 (22.1%)	**0.001**
Antihypertensive medications administered	105 (95.5%)	1457 (92.3%)	0.345
MgSO4 administered	66 (60.0%)	638 (40.4%)	**<0.001**
Maternal indication for delivery	91 (82.7%)	1224 (77.6%)	0.204
cesarean delivery	42 (38.2%)	1034 (65.5%)	**<0.001**
Pregnancy outcomes			
Admission-to-delivery interval (all cases) (d)	1 [1, 3]	1 [1, 4]	0.102
Delivery-to-discharge or death interval (d) ǂ	2 [2, 4]	3 [2, 4]	0.098
Gestational age on delivery (wk)	36.8 [34.3, 39.3]	38.0 [36.6, 39.3]	**<0.001**
Birth weight (g)	1801.3 (± 771.7)	2758.7 (± 653.7)	**<0.001**
Birth weight <3rd percentile (N babies)	51 (46.4%)	254 (16.1%)	**<0.001**
Maternal adverse outcome	37 (33.6%)	234 (14.8%)	**<0.001**

BP = blood pressure; EDD = estimated date of delivery; HDP = hypertensive disorder of pregnancy; $MgSO_4$ = magnesium sulphate
*P values calculated using chi-squared test for categorical variables or Mann-Whitney U for continuous variables, as appropriate.
ǂ excluding stillbirth cases.

Table 2: Univariate and adjusted analysis of predictors for perinatal death.

Candidate predictor	Univariate OR [95% CI]	Adjusted for gestational age at admission OR [95% CI]
Age at EDD (years)	1.01 [0.98 - 1.05]	1.01 [0.98 - 1.04]
Gestational age at admission (weeks)	0.85 [0.79 - 0.92]	n/a
Parity ≥1	1.14 [0.77 - 1.68]	1.09 [0.74 - 1.62]
Smoking (y/n)	0.30 [0.04 - 2.19]	0.27 [0.04 - 1.95]
Systolic BP (10 mmHg)	1.16 [1.08 - 1.24]	1.13 [1.05 - 1.22]
Diastolic BP (10 mmHg)	1.34 [1.21 - 1.49]	1.33 [1.19 - 1.48]
Proteinuria		
Negative/trace/ 1+	Reference	Reference
2+/ 3+	4.48 [2.71 - 7.40]	4.13 [2.49 - 6.85]
4+	6.71 [3.62 - 12.5]	6.24 [3.35 - 11.61]
Pre-eclampsia (y/n)	3.51 [2.12 - 5.81]	3.12 [1.87 - 5.20]
Symptoms (y/n)		
Headache	3.42 [2.25 - 5.20]	3.36 [2.20 - 5.12]
Visual disturbances	3.33 [2.24 - 4.93]	3.29 [2.21 - 4.89]
Chest pain	3.00 [1.30 - 6.91]	2.76 [1.18 - 6.44]
Dyspnoea	2.81 [1.43 - 5.52]	2.95 [1.49 - 5.84]
RUQ pain	4.56 [3.04 - 6.82]	4.23 [2.82 - 6.36]
Nausea/vomiting	4.07 [2.70 - 6.13]	4.06 [2.69 - 6.13]
Abdominal pain	2.88 [1.71 - 4.85]	3.03 [1.79 - 5.13]
Number of symptoms		
0	reference	reference
1	1.99 [1.12 - 3.55]	1.97 [1.10 - 3.52]
≥2	6.44 [3.98 - 10.42]	6.28 [3.87 - 10.19]

BP= blood pressure; EDD= estimated date of delivery; OR= odds ratio; RUQ= right upper quadrant

Table 3: Risk stratification table to assess the performance of the model for predicting perinatal outcome at varying cut-off values to define a positive test.

Predicted probability	**# event/ # in range (%)**	**Sens**	**Spec**	**PPV**	**NPV**	**LR [95% CI]**
0.0% - 1.9%	7/415 (1.7%)	n/a	n/a	n/a	n/a	0.24[0.11-0.53]
2.0% - 5.0%	15/511 (2.9%)	93.6%	29.2%	8.4%	98.5%	0.43[0.26-0.69]
5.1% - 8.0%	24/372 (6.5%)	79.8%	57.3%	11.5%	97.6%	0.99[0.68-1.43]
8.1% - 15%	10/123 (8.1%)	57.8%	79.4%	16.2%	96.5%	1.26[0.68-2.35]
>15.0%	54/267 (20.2%)	48.6%	86.6%	20.0%	96.1%	3.64[2.90-4.57]

LR= positive likelihood ratio (calculated using the method of Deeks et al.); NPV=negative predictive value; PPV=positive predictive value; Sens=sensitivity; Spec=specificity

Table 4: Classification table to compare classification accuracy of the final model (using a predicted probability of >15.0% to define high-risk) vs. (a) gestational age alone (using a gestational age of 32-34 weeks at delivery to define high-risk) or (b) the published miniPIERS model (using predicted probability ≥25% to define high-risk)

(a) GA alone	**Final multivariate model**		**Total**
Women with events	**Low-risk**	**High-risk**	
Low-risk	42	42	84
High-risk	14	12	26
Total	56	54	110
Women without events			
Low-risk	1230	189	1419
High-risk	135	24	159
Total	1365	213	1578

(b) miniPIERS maternal model	**Final multivariate model**		**total**
Women with events	**Low-risk**	**High-risk**	
Low-risk	54	**35**	89
High-risk	**2**	19	21
Total	73	47	110
Women without events			
Low-risk	1359	**118**	1477
High-risk	**45**	56	101
Total	1404	174	1578

GA= gestational age

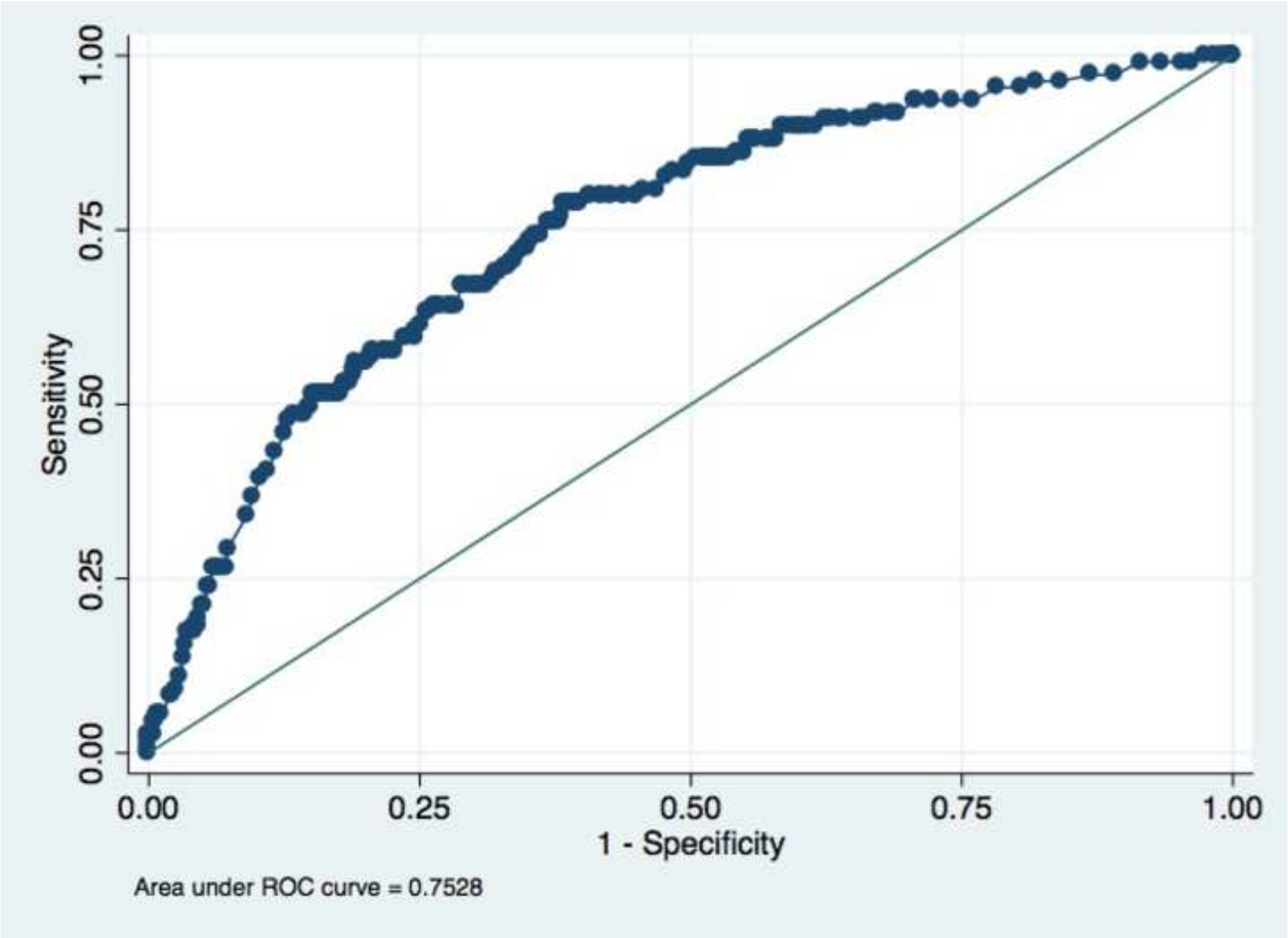
Table 5: Results of sensitivity analyses performed using various outcome definitions

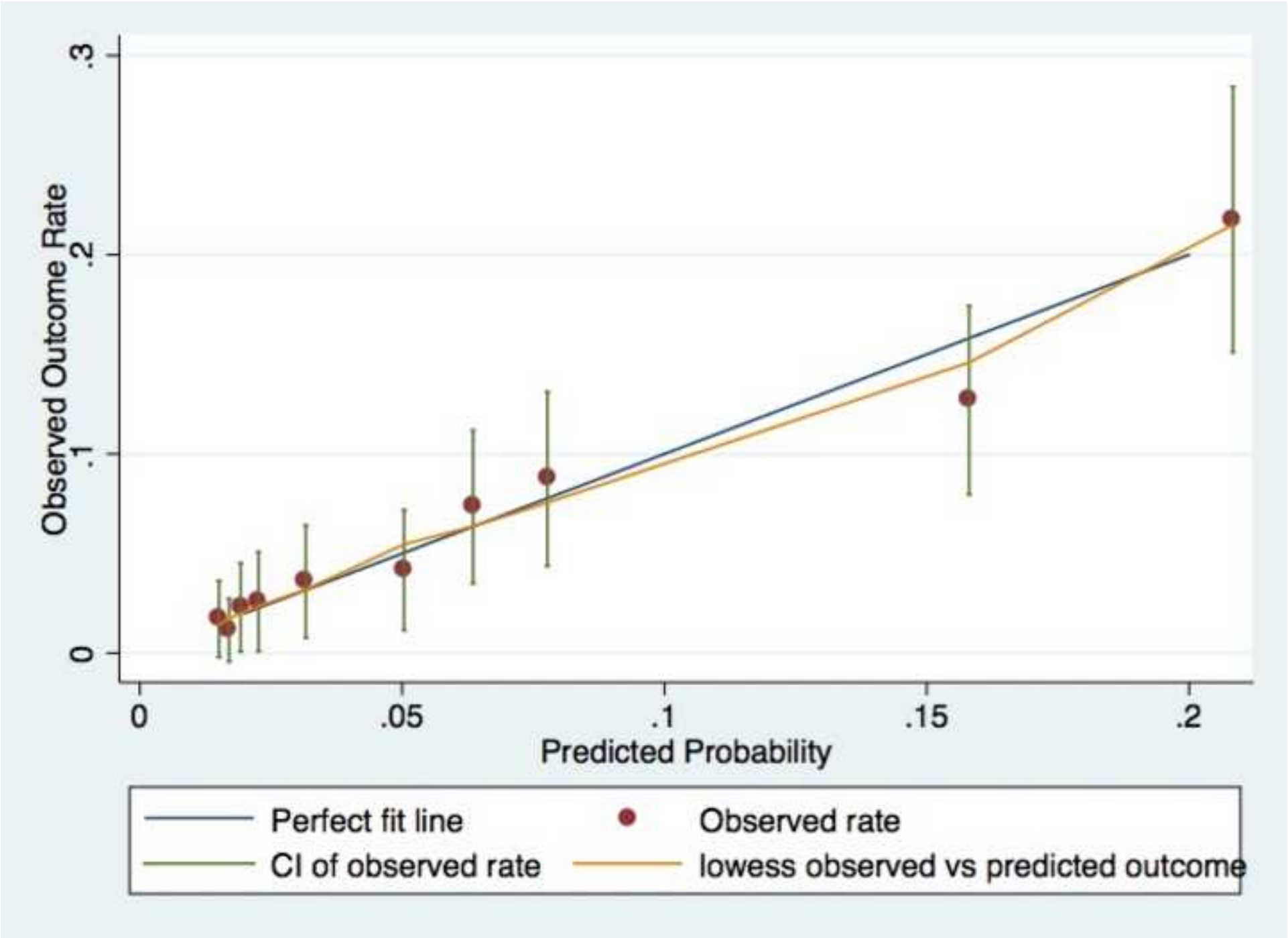
Cohort description	n/N	AUC ROC [95% CI]
Including only stillbirth as adverse neonatal outcome	79/1686	0.78 [0.73, 0.82]
Including only neonatal death before discharge as adverse neonatal outcome	32/1686	0.68 [0.57, 0.78]
Including only cases with gestational age >34 weeks at onset of disease	84/1502	0.74 [0.68, 0.80]
Including only cases with gestational age >36 weeks at onset of disease	62/1226	0.73 [0.66, 0.80]

*AUC ROC = area under the receiver operating characteristic curve

Figure 1: Receiver operating characteristic curve for the final miniPIERS perinatal death model including maternal age (years), dipstick proteinuria (negative/ trace/ 1+ vs. 2+/ 3+ or 4+) and a count of symptoms present (0 vs. 1 or ≥2).

Figure 2: Calibration plot of the miniPIERS neonatal outcome model red line represents line of perfect fit between observed and predicted outcomes.





HIGHLIGHTS:

- Symptoms, dipstick proteinuria and maternal age identify fetuses at risk of perinatal death.
- The area under the receiver operating characteristic curve of the model was 0.75 [95% CI 0.71 - 0.80]
- This perinatal risk model improves detection of perinatal risk beyond gestational age alone.