Competing risks model for prediction of small-for-gestational-age neonates from maternal characteristics and medical history

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Contribution

What are the novel findings of this work?

A new model for SGA prediction in which gestational age at delivery (GA) and birth weight z - scores (Z) are treated as a continuous variables. In pregnancies at low-risk for SGA the joint distribution of GA and Z is shifted to higher GA and Z values and in high-risk pregnancies the model shifts the joint distribution towards lower values.

What are the clinical implications of this work?

Prediction of SGA generally involves dichotomization of both GA and Z. A continuous model has been developed, where any specific cut - off of Z and GA can be applied to define a risk. Therefore a single model can be used for any choice of cut - offs for Z and GA. This model will form the basis for a Bayesian update by adding biomarkers.

ABSTRACT

Background: The established method of identifying a group of women at high-risk of delivering SGA neonates, requiring increased surveillance, is use of risk scoring systems based on maternal demographic characteristics and medical history. Although this approach is relatively simple to perform, it does not provide patient-specific risks and has an uncertain performance of predicting SGA. Another approach to predict delivery of SGA neonates is to use logistic regression models that combine maternal factors with first-trimester biomarkers. These models provide patient-specific risks for different pre-specified cut-offs of birth weight percentile and gestational age at delivery.

Objectives: First, to develop a competing risks model for prediction of SGA based on maternal demographic characteristics and medical history in which gestational age at the time of delivery (GA) and birth weight z - scores (Z) are treated as a continuous variables. Second to compare the predictive performance of the new model for SGA neonates to that of previous methods.

Methods: This was a prospective observational study in 124,443 women with singleton pregnancies undergoing routine ultrasound examination at 11^{+0} - 13^{+6} weeks' gestation. The dataset was randomly divided into a training and a test dataset. The training dataset was used to develop a model for the joint distribution of GA and Z from variables of maternal characteristics and medical history. This patient specific joint Gaussian distribution of GA and Z allows risk calculation for SGA defined in terms of different birth weight percentiles and gestational age. The new model was then validated in the test dataset to assess performance of screening and we compared its' predictive performance to that of logistic regression models for different SGA definitions.

Results: In the new model the joint Gaussian distribution of GA and Z is shifted to lower GA and Z values, resulting in an increased risk for SGA, by lower maternal weight and height, Black, East Asian, South Asian and Mixed racial origin, medical

history of chronic hypertension, diabetes mellitus and systemic lupus erythematosus or antiphospholipid syndrome, conception by *in vitro* fertilization or ovulation induction and smoking. For parous women variables from the last pregnancy that increased the risk for SGA were history of preeclampsia or stillbirth, decreasing birth weight z-score and decreasing gestational age at delivery of the last pregnancy and inter-pregnancy interval <0.5 years. In the test dataset, at a screen positive rate of 10%, the new model predicted 30.1%, 32.1%, 32.2% and 37.8% of cases of SGA neonates with birth weight <10th percentile delivered at <42, <37, <34 and <30 weeks' gestation, respectively, which were similar or higher to the respective values achieved by a series of logistic regression models. The calibration study demonstrated good agreement between the predicted risks and the observed incidence of SGA in both the training and test datasets.

Conclusions: A new competing risks model, based on maternal characteristics and medical history, provides estimation of patient-specific risks for SGA in which GA and Z are treated as a continuous variables. Such estimation of the *a priori* risk for SGA is an essential first step in the use of Bayes theorem to combine maternal factors with biomarkers for the continuing development of more effective methods of screening for SGA.

INTRODUCTION

Small for gestational age (SGA) neonates are at increased risk of adverse perinatal outcome and development of metabolic and cardiovascular diseases in adult life.[1-5] The expectation that these risks can be potentially reduced by medical interventions, national societies from many developed countries have issued guidelines on monitoring and criteria for delivery of such pregnancies.[6] However, there remains considerable uncertainty as how best to identify SGA fetuses.[7] The established method of identifying a group of women at high-risk of delivering SGA neonates, requiring increased surveillance, is use of risk scoring systems; although this approach is relatively simple to perform, it does not provide patient-specific risks and has uncertain performance of predicting SGA neonates.[8] Another approach to early prediction of delivery of SGA neonates is to use logistic regression models that combine maternal factors with first-trimester biomarkers.[9-12] These models provide patient-specific risks for different pre-specified cut-offs of birth weight percentile and gestational age at delivery, which has led to an arbitrary dichotomization of the disease; different models for different SGA definitions are required and adding new biomarkers requires re-fitting the whole model.

An alternative approach for prediction of SGA neonates is to consider SGA as a spectrum disorder whose severity is continuously reflected in both the gestational age at delivery and z-score in birth weight for gestational age. The concept of this approach is similar to that of the competing risks model in the assessment of risks for Preeclampsia (PE).[13-15] In this approach, which is based on a survival-time model, every woman has a personalized distribution of gestational age at delivery with PE and it is assumed that if the pregnancy were to continue indefinitely all women would develop PE; whether PE occurs or not depends on competition between delivery before or after development of PE. The risk of delivery with PE before a specified gestational age, assuming no other cause delivery, is given by the area under the probability density curve. The new model for SGA prediction uses a continuous personalized joint bivariate Gaussian distribution of gestational age at delivery and z-

score of birth weight. The risk for any desired SGA definition is the volume under the surface of the joint probability distribution.

The objectives of this study are first, to develop a new model for prediction of SGA neonates, based on maternal characteristics and history, in which gestational age at the time of delivery and birth weight z-score are treated as continuous variables, and second, to compare the predictive performance of the new model for SGA neonates to that of previous methods.

METHODS

Study population

The data for this study were derived from prospective screening for adverse obstetric outcomes in women attending for their routine first hospital visit in pregnancy at King's College Hospital, London and Medway Maritime Hospital, Gillingham, UK, between March 2006 and December 2016. In this visit, at 11^{+0}- 13^{+6} weeks' gestation, we recorded maternal characteristics and medical history and performed combined screening for aneuploidies.[16]Gestational age was determined by the measurement of fetal crown-rump length.[17] The participants gave written informed consent for the study which was approved by the UK National Health Service Research Ethics Committee.

The inclusion criteria for the study were singleton pregnancy delivering a non-malformed live birth or stillbirth at ≥24 weeks' gestation. We excluded pregnancies with aneuploidies and major fetal abnormalities and those ending in termination, miscarriage, or fetal death at <24 weeks' gestation.

Patient characteristics

Patient characteristics included maternal age, racial origin (White, Black, South Asian, East Asian, and Mixed), method of conception (natural or assisted by IVF or use of ovulation drugs), cigarette smoking during pregnancy, medical history of chronic hypertension, diabetes mellitus, systemic lupus erythematosus or antiphospholipid syndrome, family history of preeclampsia in the mother of the patient, and obstetric history that included parity (parous or nulliparous if no previous pregnancies at ≥24 weeks' gestation), previous pregnancy with preeclampsia, previous stillbirth, gestational age at delivery and birth weight of the neonate in the last pregnancy, interval in years between birth of the last child and estimated date of conception of the current pregnancy. Maternal weight and height were measured, and the BMI was calculated.

Outcome measures

Data on pregnancy outcome were collected from hospital maternity records or the

general medical practitioners of the women. The outcome measures of the study were birth of a neonate at or below different thresholds of birth weight percentile for different cut-offs of gestational age at delivery. The Fetal Medicine Foundation fetal and neonatal population weight charts were used to convert birth weight to percentiles and Z scores.[18]

Statistical analyses

Model development

The new approach uses a single continuous model that provides a personalized joint Gaussian distribution of birth weight expressed in z scores (Z) and gestational age at delivery (GA) (Figure 1). Therefore any specific cut - off for Z and GA can be applied to define a risk. Our model for personalized bivariate Gaussian distribution of Z and GA was specified by the following elements; a regression model for the mean for Z determined from maternal characteristics; a regression model for the mean for GA determined from the mean for Z and maternal characteristics; standard deviations for GA and Z which were assumed to be the same for all women and independent from maternal factors; the correlation coefficient between GA and Z which was assumed constant for all women and independent from maternal factors. We assumed Gaussian distributions, constant standard deviations and constant correlation coefficient for the simplicity of the interpretation. The model was fitted using Markov chain Monte Carlo techniques which enabled all parameters to be estimated within a single analysis. To focus the model fit on preterm SGA, gestational ages greater than 37 weeks were treated as censored observations at 37 weeks and z scores >-1.2816 were censored at -1.2816 (Figure 2). The risk for SGA, is given by the volume under the distribution surface for the region defined by the chosen birth weight z scores and gestational age cut-offs (Figure 1). Established risk factors, including maternal age in years, weight in kg, height in cm, racial origin, method of conception, chronic hypertension, diabetes mellitus and systemic lupus erythematosus or antiphospholipid syndrome were included as covariates. For the parous women inter-pregnancy interval in years, gestational age at delivery of previous pregnancy in weeks, previous birth weight z-score, history of preeclampsia and history of stillbirth

were included as factors in our analysis. For maternal height, previous pregnancy birth weight z-score and gestational age at delivery in the previous pregnancy a linear association was assumed, for maternal weight quadratic terms were used, and for inter-pregnancy interval fractional polynomials were adopted.

Training and test datasets

Data were partitioned into a training and test datasets by random assignment of the sample of 124,443 into a training data set of 62,221 and a test data set of 62,222. The training data were used for model development and fitting. The model was then assessed on the test data set for the internal validation's purposes.

Predictive performance

The predictive performance of model was assessed by first, the ability of the model to discriminate between the SGA and non-SGA groups using the area under the receiver operating characteristic (AUROC) curve and the detection rate (DR) of SGA neonates of different severities (<10^{th} and <3^{rd} percentiles) at different gestational age cut-offs (<42, <37, <34 and <30 weeks), at fixed false positive rates (FPR) of 5%, 10% and 20%, and second, calibration by measurements of calibration intercept and slope using logistic regression analysis of outcome incidence against the logit of the respective risks.

Comparisons with previous definitions of SGA and logistic regression models

There is an apparent contradiction in the relation between ultrasonographic EFW and birth weight charts. Although the EFW recorded within a few days of birth correlates strongly with birth weight and for a given gestational age they have essentially the same median,[19] in reported reference ranges the median birth weight with gestational age for babies born preterm is substantially lower than that of the EFW.[9,20,21] This difference is likely to be the consequence of pathological fetal growth in a high proportion of preterm births. Reference ranges of EFW are representative of the whole population, whereas in the construction of reference ranges of birth weight, particularly for gestational ages at <37 weeks, there is overrepresentation of pathological pregnancies. One third of preterm births are iatrogenic mainly for

hypertensive disorders and / or suspected fetal growth restriction, but there is also evidence that in a substantial proportion of spontaneous preterm births there is impaired placentation.[22-24]This problem of underestimation of growth restriction in preterm births has been overcome through the construction of a birth weight chart for the population of all babies at a given gestational age, including those still in *utero.*[18]

We constructed a series of logistic regression models to predict SGA (<10th and <3rd percentiles for gestational ages at birth <42, <37, <34 and <30 weeks' gestation), defined by the Fetal Medicine Foundation birth weight charts.[18] All these models were also validated in the test dataset.

The model was fitted within a Bayesian framework using Markov chain Monte Carlo (MCMC) implemented in WinBUGS.[25] The statistical software package R was also used for data analyses.[26]

RESULTS

Characteristics of the study population

The study population included 124,443 singleton pregnancies and the maternal and pregnancy characteristics are given in Table 1.

Model for prediction of SGA neonates

The new model provides a personalized joint distribution of birth weight z score and gestational age at delivery. The model for the mean of this joint distribution is specified; first by a regression model for the mean of Z; and second by a regression model for the mean GA given the mean of Z. Therefore the mean GA is determined from the mean of Z so that when the mean of Z is low, babies tend to be born earlier. This is reflected in the coefficient of mean Z in the gestational age model (Table 2). Given the effect of smallness on GA the new model quantifies the simultaneous effect of other variables on GA (Table 2).

This joint distribution depicted in a 2 dimensional plane is a contour plot (Figure 1). The centre of this contour plot is defined by the predicted mean Z and the predicted mean GA (Table 2, Figure 1). Therefore the coordinates of the contour plot's centre are governed by maternal characteristics and medical history. The risk for SGA, is given by the volume under the distribution surface for the region defined by the chosen birth weight z scores and gestational age cut-offs (Figure 1, Appendix). The lower the predicted mean z score and the predicted mean gestational age the more the contour plot falls within the chosen region, the higher the risk for SGA (Figure 1).

The factors that decreased birth weight z score were Black, South Asian, East Asian and Mixed racial origin, conception by IVF, smoking, preeclampsia in the previous pregnancy, history of stillbirth in the previous pregnancy, chronic hypertension, systemic lupus erythematosus and/or antiphospholipid syndrome whereas parity increased birth weight z score (Table 2). The effect on birth weight z score for categorical variables is shown in Figure 3. The effect of maternal height was linear whereas the effect of maternal weight on birth weight z score was positive and

quadratic (Figure 4). Application of fractional polynomials revealed that inter-pregnancy interval had a non linear effect on birth weight z score with a positive peak at 2 years (Figure 4). The smaller the birth weight for gestational age in the last pregnancy and the earlier the gestational age at delivery the lower birth weight z score in the index pregnancy (Table 2).

The factors that decreased gestational age at delivery were conception by IVF, chronic hypertension, systemic lupus erythematosus and/or antiphospholipid syndrome, history of stillbirth and diabetes melitus whereas parity increased predicted gestational age at delivery (Table 2). The effect on gestational age at delivery for categorical variables is shown in Figure 5. The earlier the gestational age at delivery in the last pregnancy, the earlier the predicted gestational age at delivery.

Model evaluation

The prediction for several SGA definitions and fixed false positive rates (FPR) is presented in Table 3. The prediction was progressively better for earlier gestations and increasing severity of SGA and parous women. The detection rates (DR) were lower in the test dataset as expected.

We assessed the agreement between the predicted risks by the competing risks model for SGA and the observed incidence for different SGA definitions. The new model had satisfactory calibration for all the outcomes (Figure 6, Table 4).

Comparison of performance of the new model with logistic regression models

The predictive performance of the new model for SGA <10th and <3rd percentiles for gestational ages at birth <42, <37, <34 and <30 weeks' gestation, for fixed false positive rates, was comparable to several logistic models (Table 6). The internal validation revealed that the new model is more stable with superior performance for the preterm SGA (Table 5).

DISCUSSION

Principal findings

We developed a new model based on maternal characteristics and history which provides estimation of patient-specific risks for birth of SGA neonates in which gestational age at the time of delivery and birth weight z scores are treated as continuous variables. All women have a personalized joint Gaussian distribution of z score birth weight and gestational age at delivery and maternal risk factors modify the mean of this distribution. The mean of such joint distribution is comprised by two coordinates. The first coordinate is the predicted mean z score birth weight and the second coordinate is the predicted mean of gestational age at delivery conditional to the predicted mean z score birth weight. In pregnancies at low-risk for SGA the distribution is shifted upwards and right towards higher z scores and gestational weeks. In the high-risk pregnancies the model shifts the distribution downwards and to the left towards lower z scores and gestational age values (Figure 1). A single continuous model can be used for any choice of birth weight z-score and gestational age at delivery cut - offs.

Internal validation, which is actually the clinical application of the model, revealed that a single unified equation has better performance compared to a series of different logistic regression models that were separately fitted for the different SGA definitions (Table 6). The new model is more stable with similar performance in the training and validation dataset. On the contrary the logistic regression approach loses discrimination in the validation dataset, especially for the preterm cases. These observations provide support for the argument that SGA should be treated as a spectrum disorder rather than being arbitrarily fragmented by different cut-offs according to birth weight percentile and gestational age at delivery. The study has also demonstrated that the calibration of the model is good and this may improve stratification of pregnancy care based on risk assessment, especially for the high risk cases for preterm SGA.

Comparison with previous studies

Previous first trimester studies that aimed to predict delivery of SGA neonates reported similar sensitivities compared to the one achieved by the new model.[9-12] However, the predictive performance of the new approach is actually higher than that of previous models because our definition of SGA was based on the new Fetal Medicine Foundation birth weight charts; these charts modeled efficiently the overrepresentation of preterm SGA pregnancies and this has led to an increasing percentage of SGA for lower gestational age cut-offs.[18] Thus we are predicting an outcome that is less extreme, compared to the previous definitions, and consequently more difficult to predict.[9,18]

Implications for clinical practice

The building block of the new model for SGA prediction is an individualized joint Gaussian distribution that is defined by maternal characteristics and medical history. An important functionality of the new approach, is the ability of a clinician to select any desired cut-off in birth weight z-score and gestational age at delivery. The selected cut-off for birth weight z-score may depend on local resources. The gestational age cut-off can be changed several times during the pregnancy and this flexibility will probably enhance efficient risk stratification. Such a prior model augmented by the Bayesian incorporation of biophysical and biochemical markers will improve prediction of SGA fetuses and will inevitably lead to improved future research for preventative therapeutic interventions and stratification of intensity of pregnancy monitoring. Ultimately this may lead to an improved perinatal outcome for the fetuses that suffer from growth restriction.

Strengths and limitations

The strengths of this study are first, the large number of prospectively examined pregnancies in which maternal characteristics were recorded and specific questions were asked to obtain the medical history, as a part of an implemented screening program; second, application of a multivariate analysis that best describes the effect of each predictor; third, use of a joint distribution model that allows estimation of patient-specific risks for any desired SGA definition; and fourth, potential for use of

the model to derive the prior distribution in a Bayesian update process at different stages of pregnancy.

We have used internal validation to examine the internal validity of our model. We estimated the discrimination and the calibration of the model, if it is to be trained by a dataset and then applied to a new dataset. Therefore, we know what to expect by the model in our population. A limitation of the study is the lack of external validation; we cannot demonstrate the applicability of our results in other populations and independent data from different sources are required.

Conclusions

Birth weight deviation and gestational age are intimately related; SGA is defined by its severity and prematurity. These two important elements can be combined and reflected in a continuous joint distribution. Such unified approach facilitates the understanding and interpretation of these two important determinants of perinatal outcome. The same coefficients provide effective screening for any SGA definition. The new method of screening support the hypothesis that SGA is one disease with a continuous severity spectrum and arbitrary dichotomization of the condition should be avoided.

A new efficient clinical tool, with clinical applicability, has been developed. The new approach provides a framework where different desired cut-offs in gestational age at delivery and birth weight z-score may be used in the context of the same model. This model will form the basis for a Bayesian update by various biomarkers at different stages in pregnancy.

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FIGURE LEGENDS

Figure 1. Contour plot of the joint Gaussian distribution of birthweight Z scores and gestational age at delivery in a high risk case and a low risk case. Birth weight expressed in percentiles is also seen in the vertical right axis. 50%, 75% and 95% contours are presented. The shaded area corresponds to the risk of delivery before 34 weeks' gestation with SGA below the 10th percentile.

Figure 2. Cases with birth weight above the 10th percentile or gestational age at delivery after 37 weeks were censored (gray dots).

Figure 3. Factors' effect on mean birth weight Z score.

Figure 4. Nonlinear effect of maternal weight and inter-pregnancy interval on mean birth weight Z score.

Figure 5. Factors' effect on mean gestational age at delivery.

Figure 6. Calibration plot for the prediction of SGA <3rd percentile born before <37 weeks' gestation. The horizontal interrupted line represents the mean observed incidence whereas the vertical interrupted line represents the mean predicted risk by the new model.

Appendix: Risk calculation

Table 1. Maternal and pregnancy characteristics in the study population.

Variables	**Dataset (n=124443)**
Maternal age (years)	31.1 (26.9-35.3)
Maternal weight (kg)	67 (57.9-76.1)
Maternal height (cm)	164 (160 - 169)
Body mass index (kg/m^2)	24.5 (21.4 - 27.8)
Gestational age (weeks)	12.7 (12.3 - 13.1)
Racial origin	
White	93954 (75.5%)
Black	19699 (15.8%)
South Asian	5297 (4.3%)
East Asian	2454 (1.9%)
Mixed	3039 (2.4%)
Conception	
Natural	120302 (96.7%)
Ovulation induction	1492 (1.2%)
In-vitro fertilization	2649 (2.1%)
Medical history	
Chronic hypertension	1569 (1.3%)
Diabetes mellitus	1075 (0.8%)
SLE/APS	244 (0.2)
Cigarette smokers	12572 (10.1%)
Family history of preeclampsia	5303 (4.3%)
Parity	
Nulliparous	58492 (47.0%)
Parous with previous PE or SGA <10th percentile	12557 (10.1%)
Parous with previous SGA <10th percentile	8580 (6.9%)
Parous with previous PE and SGA <10th percentile	924 (0.7%)
Pregnancy interval (years)	3 (1.5 - 4.5)
Gestation of last birth (weeks)	40 (39.5 - 40.5)

Values are given as median (interquartile range) or number (%)

SLE = systemic lupus erythematosus; APS = antiphospholipid syndrome; PE = preeclampsia; SGA = small for gestational age

Table 2. Model for the joint distribution of Birth weight Z score (Z) and gestational age at delivery (GA). Posterior means, standard deviation (SD), lower (LCL) and upper (UCL) credibility limits

Birthweight Z	**Est**	**SD**	**LCL**	**UCL**
Intercept	0.4358	0.0222	0.3923	0.4793
Black	-0.5436	0.0241	-0.5909	-0.4963
East Asian	-0.0468	0.0603	-0.1650	0.0714
South Asian	-0.4902	0.0390	-0.5667	-0.4137
Mixed	-0.2533	0.0545	-0.3601	-0.1465
Height(cm) -165	0.02789	0.00146	0.0250	0.0308
Weight (kg) - 69	0.01138	0.00079	0.009832	0.012928
(Weight (kg) - 69)^2	-0.0002005	0.0000216	-0.0002428	-0.0001582
IVF	-0.1838	0.0593	-0.2999	-0.0677
Smoker	-0.6602	0.0271	-0.7133	-0.6071
Chronic hypertension	-0.6267	0.0675	-0.7590	-0.4944
SLE/APS	-0.3309	0.1845	-0.6925	0.0307
Multiparous	0.05933	0.07173	-0.0813	0.1999
Last GA (weeks)- 40	0.06155	0.00563	0.0505	0.0726
Previous BW (Z)	0.3665	0.0113	0.3444	0.3886
Interval (years) $^{-1}$	-0.6062	0.1179	-0.8373	-0.3751
Interval (years) $^{-0.5}$	1.2990	0.1911	0.9244	1.6736
Previous PE	-0.1499	0.0513	-0.2505	-0.0493
Previous IUD	-0.1589	0.1010	-0.3569	0.0391
SD for Z	1.3850			
Gestational Age	**Est**	**SD**	**LCL**	**UCL**
Intercept	46.790	0.1863	46.4249	47.1551
Mean birth weight (Z)	1.680	0.0519	1.5784	1.7816
IVF	-1.469	0.3111	-2.0788	-0.8592
Chronic hypertension	-1.827	0.3361	-2.4858	-1.1682
SLE/APS	-1.929	0.8833	-3.6603	-0.1977
Diabetes Mellitus	-4.744	0.3832	-5.4951	-3.9929
Previous IUD	-1.604	0.4373	-2.4611	-0.7469
Multiparous	0.339	0.1086	0.1261	0.5519
Last GA (weeks)-40	0.538	0.0271	0.4850	0.5912
SD for GA	6.1865			
Correlation	0.3761			

SLE, systemic lupus erythematosus; APS, antiphospholipid syndrome; PE, preeclampsia; SGA, small for gestational age; IUD, intrauterine demise

Table 3. Performance of the new model in the prediction of small for gestational age neonates in the training (Tr) and test (Te) datasets

Outcome measure	AUROC Tr	AUROC Te	False positive rate					
			5% Tr	5% Te	10% Tr	10% Te	20% Tr	20% Te
<42 weeks SGA <10th								
All pregnancies	0.7185	**0.7175**	18.4	**17.9**	30.0	**30.1**	47.5	**48.6**
Nulliparous	0.6535	**0.6585**	13.7	**13.8**	23.9	**24.2**	39.4	**41.4**
Parous	0.7648	**0.7559**	24.5	**23.5**	37.5	**37.6**	57.1	**55.6**
<42 weeks SGA <3rd								
All pregnancies	0.7442	**0.7357**	21.4	**20.5**	34.0	**33.1**	52.3	**51.5**
Nulliparous	0.6783	**0.6751**	15.1	**15.6**	25.8	**25.5**	43.7	**44.3**
Parous	0.7936	**0.7792**	29.8	**27.0**	43.1	**41.7**	62.3	**58.9**
<37 weeks SGA <10th								
All pregnancies	0.7324	**0.7155**	24.0	**21.5**	33.8	**32.1**	51.0	**48.6**
Nulliparous	0.6422	**0.6291**	13.1	**12.8**	22.3	**21.2**	37.9	**37.0**
Parous	0.7972	**0.7717**	34.6	**30.1**	47.1	**45.5**	64.3	**61.0**
<37 weeks SGA <3rd								
All pregnancies	0.7462	**0.7271**	25.2	**21.9**	35.7	**32.2**	53.0	**50.3**
Nulliparous	0.6597	**0.6370**	13.5	**12.8**	23.1	**21.7**	40.4	**38.3**
Parous	0.8091	**0.7905**	37.1	**33.6**	50.1	**48.2**	67.3	**62.1**
<34 weeks SGA <10th								
All pregnancies	0.7398	**0.7151**	26.1	**24.2**	36.0	**32.2**	52.2	**49.5**
Nulliparous	0.6459	**0.6249**	12.3	**14.0**	20.8	**20.6**	38.8	**38.5**
Parous	0.8052	**0.7742**	39.8	**35.9**	53.6	**48.1**	65.9	**61.2**
<34 weeks SGA <3rd								
All pregnancies	0.7480	**0.7189**	25.7	**22.8**	36.2	**30.8**	52.8	**48.4**
Nulliparous	0.6566	**0.6212**	11.1	**14.0**	21.2	**21.0**	40.2	**39.0**
Parous	0.8155	**0.7870**	42.2	**35.4**	54.6	**48.3**	64.9	**61.2**
<30 weeks SGA <10th								
All pregnancies	0.7325	**0.7355**	26.2	**28.7**	35.5	**37.8**	50.0	**53.0**
Nulliparous	0.6141	**0.6604**	9.3	**21.0**	18.6	**26.3**	32.6	**42.1**
Parous	0.8062	**0.7827**	40.7	**40.0**	54.7	**50.0**	67.4	**63.3**
<30 weeks SGA <3rd								
All pregnancies	0.7467	**0.7326**	28.8	**27.9**	39.6	**38.6**	51.1	**50.7**

Nulliparous	0.6280	**0.6504**	10.2	**19.2**	20.3	**27.4**	33.3	**39.7**
Parous	0.8240	**0.7835**	44.3	**37.3**	58.6	**50.8**	68.6	**61.2**

SGA, small for gestational age; AUROC, area under the receiver operating characteristic curve

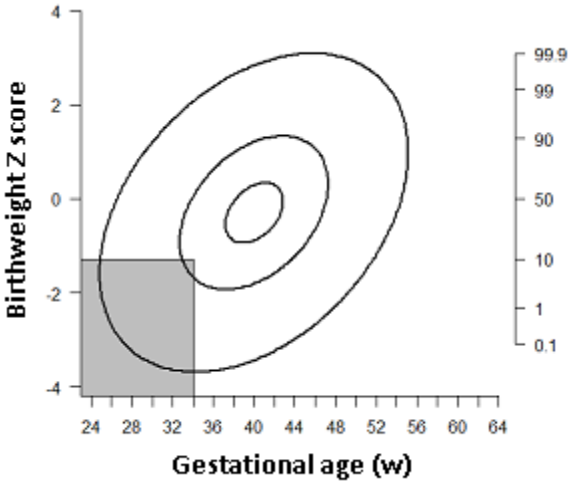
Table 4. Calibration study for the new model for prediction of SGA neonates with birth weight <10thand 3rd percentile, for different gestational cut -offs in the training and test datasets.

Outcome measure birth at:	Birth weight <10th percentile		Birth weight <3rd percentile	
	Calibration		Calibration	
	Slope	Intercept	Slope	Intercept
<42 weeks - Training	0.99573	0.99574	0.97292	0.65287
<42 weeks - Test	0.97931	0.98209	0.92914	0.62484
<37 weeks- Training	0.96260	0.03388	0.91743	0.10603
<37 weeks- Test	0.87160	0.00327	0.83798	0.06913
<34 weeks- Training	0.90030	-0.10263	0.8621	0.05647
<34 weeks- Test	0.83078	-0.09771	0.78224	0.05558
<30 weeks- Training	0.79227	0.39565	0.79904	0.55026
<30 weeks- Test	0.7761	0.45864	0.74863	0.54341

Table 5. Comparisons of performance of screening between the new model and logistic regression models in the training (Tr) and test (Te) datasets.

Outcome measure	AUC Tr	AUROC Te	False positive rate					
			5% Tr	5% Te	10% Tr	10% Te	20% Tr	20% Te
<42 weeks SGA <10th								
New model	0.7185	**0.7175**	18.4	**17.9**	30.0	**30.1**	47.5	**48.6**
Logistic regression	0.7101	**0.7193**	18.9	**18.1**	30.4	**30.6**	47.9	**48.5**
<42 weeks SGA <3rd								
New model	0.7442	**0.7357**	21.4	**20.5**	34.0	**33.1**	52.3	**51.5**
Logistic regression	0.7423	**0.7325**	21.1	**20.2**	33.6	**32.5**	52.3	**50.5**
<37 weeks SGA <10th								
New model	0.7324	**0.7155**	24.0	**21.5**	33.8	**32.1**	51.0	**48.6**
Logistic regression	0.7299	**0.7158**	23.2	**21.8**	33.3	**31.4**	50.5	**48.5**
<37 weeks SGA <3rd								
New model	0.7462	**0.7271**	25.2	**21.9**	35.7	**32.2**	53.0	**50.3**
Logistic regression	0.7497	**0.7318**	24.6	**22.5**	36.3	**32.7**	55.0	**51.4**
<34 weeks SGA <10th								
New model	0.7398	**0.7151**	26.1	**24.2**	36.0	**32.2**	52.2	**49.5**
Logistic regression	0.7521	**0.7256**	27.4	**22.1**	38.3	**33.6**	55.9	**50.6**
<34 weeks SGA <3rd								
New model	0.7480	**0.7189**	25.7	**22.8**	36.2	**30.8**	52.8	**48.4**
Logistic regression	0.7512	**0.7230**	27.2	**22.7**	41.7	**32.3**	56.5	**49.6**
<30 weeks SGA <10th								
New model	0.7325	**0.7355**	26.2	**28.7**	35.5	**37.8**	51.2	**53.0**
Logistic regression	0.7534	**0.7205**	29.0	**23.0**	41.9	**31.4**	55.8	**47.0**
<30 weeks SGA <3rd								
New model	0.7467	**0.7326**	28.8	**27.9**	39.6	**38.6**	51.1	**50.7**
Logistic regression	0.7677	**0.7278**	32.3	**25.0**	45.3	**30.2**	56.8	**45.0**

High Risk



Low risk