The Journal of Maternal-Fetal & Neonatal Medicine

ISSN: 1476-7058 (Print) 1476-4954 (Online) Journal homepage: http://www.tandfonline.com/loi/ijmf20

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To cite this article: Erkan Kalafat, Jose Morales-Rosello, Basky Thilaganathan, Jasreen Dhother & Asma Khalil (2018): Risk of neonatal care unit admission in small for gestational age fetuses at term: a prediction model and internal validation, The Journal of Maternal-Fetal & Neonatal Medicine, DOI: 10.1080/14767058.2018.1437412

To link to this article: https://doi.org/10.1080/14767058.2018.1437412

Risk of neonatal care unit admission in small for gestational age fetuses at term: a prediction model and internal validation

Erkan Kalafat*†‡, Jose Morales-Rosello*, Basky Thilaganathan*, Jasreen Dhother*, Asma Khalil*

Short title: Predictive model of NNU admission in SGA

* Fetal Medicine Unit, St George's Hospital, St George's University of London, Cranmer Terrace, London SW17 0RE, UK
† Ankara University Faculty of Medicine, Department of Obstetrics and Gynecology, Ankara, Turkey
‡ Middle East Technical University, Department of Statistics, Ankara, Turkey

Correspondence to: Dr Erkan Kalafat, Ankara University Faculty of Medicine, Department of Obstetrics and Gynecology, 06100 Mamak, Ankara, Turkey; (e-mail: ekalafat@ankara.edu.tr) Phone: +905334736998

Funding details: None

Disclosure statement: Nothing to disclose.

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Keywords: Adverse outcome, neonatal unit, admission, cerebroplacental ratio, delivery, Doppler, prolonged, respiratory distress

ABSTRACT

Objective: Small for gestational age (SGA) fetuses are at increased risk of admission to the neonatal unit, even at term**.** We aimed to develop and validate a predictive model for the risk of prolonged neonatal unit admission in suspected SGA fetuses at term.

Methods: A single-centre cohort study of singleton pregnancies with SGA fetus, defined as estimated fetal weight (EFW) less than the 10th centile, at term. The variables included known risk factors for neonatal unit admissions: maternal characteristics, EFW, abdominal circumference (AC), fetal Dopplers, gestational age (GA) at delivery, and intrapartum risk factors (meconium, pyrexia). Logistic regression analysis was used for model building and the prediction models were validated internally using bootstrapping.

Results: 701 SGA pregnancies at term were included; 5.9% had prolonged neonatal unit admission (>48hours). The multivariable model (AUC 0.71; 95% CI: 0.63-0.79) included GA at delivery <39 weeks (OR 2.76; 95% CI 1.23-6.04, p=0.011), CPR MoM (OR 0.21; 95% CI 0.05-0.79, P=0.023), and EFW below the 3rd centile (OR 2.43; 95% CI 1.26-4.68, P<0.007). The combined model showed a sensitivity 30.9% (95% CI: 16.6-45.2%) for a fixed 10% false positive rate.

Conclusion: The prediction model shows good accuracy and good calibration for assessing the risk of neonatal unit admission in suspected SGA fetuses. It has the potential to be used for patient counseling, determining the timing of delivery and the individual risk.

Brief rationale

Objective: To determine the factors associated with prolonged neonatal unit admissions in small for gestational age fetuses at term.

What is already known: Fetal weight and Doppler parameters are associated with adverse outcome in small for gestational age fetuses. However, most studies use composite outcome criteria by combining neonatal unit admission with adverse delivery outcomes. A comprehensive model combining antenatal and intrapartum variables is also lacking.

What this study adds: Our model describes the association of antenatal and intrapartum variables with prolonged neonatal unit admission without using a composite adverse outcome measure. Estimated fetal weight, gestational age at delivery and the cerebroplacental ratio can be used to estimate the risk of prolonged neonatal unit admission. The risk estimation can be useful for patient counseling and to determine the time of delivery.

INTRODUCTION

Monitoring of the fetal growth is an integral part of the antenatal care. Studies have reported that the antenatal detection of small for gestational age (SGA) fetuses is associated with a lower risk of adverse neonatal outcome and neonatal unit (NNU) admissions, when compared with prenatally undiagnosed cases. [1-5] Nevertheless, most SGA fetuses do not suffer adverse neonatal outcome. [6] Therefore, identification of the cases that are truly at increased risk of adverse outcome would facilitate antenatal surveillance and intervention, in particular determining the timing of delivery and the need for neonatal care.

There are two principal reasons why using fetal size parameters alone is unlikely to be effective in detecting SGA fetuses at risk. Firstly, the predictive accuracy of antenatal ultrasound scans for the detection of SGA neonate is far from optimum, and therefore, antenatal ultrasound is not able to detect a significant proportion of SGA cases (false negative) and would falsely diagnose a significant proportion of SGA cases (false positive). [1] Secondly, most of SGA fetuses are in fact constitutionally small, and therefore, do not experience a significant adverse outcome. [6] Since SGA fetuses constitute roughly 10% of total births by definition, additional markers are needed for individual risk assessment, in order to better triage the cases that require additional care in this population.

Several studies and a meta-analysis of the published studies have reported associations between fetal Doppler assessment, in particular the cerebroplacental ratio (CPR), and adverse pregnancy outcomes in late-onset SGA fetuses. However, the results of these studies were often limited to reporting Doppler parameters without adjusting for potential confounders, such as gestational age (GA) at delivery or taking into account the intrapartum events. [7-13] A prediction model including both antenatal and intrapartum variables would be useful in this regard. Therefore, the aim of this study was to develop a prediction model using antepartum and intrapartum variables for robust estimation of the individual risk of NNU admissions in suspected SGA fetuses.

MATERIALS AND METHODS

This was a retrospective cohort study in a single tertiary referral center over an 18-year period from 1999 through 2017. The ViewPoint database (ViewPoint 5.6.8.428; ViewPoint Bildverarbeitung GmbH, Weßling, Germany) was used to identify cases evaluated at the Fetal Medicine Unit, St. George's Hospital, London, United Kingdom. The inclusion criteria were singleton pregnancies diagnosed with an SGA fetus, defined as EFW below the 10th centile for GA at 37 weeks or beyond. Pregnancies complicated by major structural fetal abnormalities, aneuploidy, elective cesarean deliveries or genetic syndromes were excluded from the analysis. GA was calculated from the crown-rump length measurement at 11-13 weeks, and only one (the last) examination per pregnancy was included. For the pregnancies where the first ultrasound performed was in the second trimester (>14 weeks' gestation), the pregnancy was dated according to the head circumference. Routine fetal biometry was carried out according to a standard protocol, and the estimated fetal weight (EFW) was calculated using the formula of Hadlock et al. [14-16] The umbilical artery (UA) and middle cerebral artery (MCA) Doppler waveforms were recorded using color Doppler, and the pulsatility index (PI) was calculated according to a standard protocol. In brief, the MCA PI values were obtained in the space where the artery passes by the sphenoid wing close to the Circle of Willis, and the UA PI values were obtained in the free loops of the umbilical cord. The measurements were obtained in the absence of fetal movement, and keeping the insonation angle with the examined vessels less than 30°.The CPR was calculated as the simple ratio between the MCA PI and the UA PI. All the Doppler indices were converted into multiples of median (MoM) correcting for GA using reference ranges, and birthweight values were converted into centiles). [17-19]

Intrapartum data included whether the labor was induced or spontaneous, presence or absence of meconium stained liquor (grade 2 or 3), use of oxytocin for the slow progress of labor, intrapartum pyrexia, intrapartum hemorrhage and the use of epidural analgesia. Data on maternal baseline characteristics and pregnancy outcomes were collected from the hospital obstetric and neonatal records. The main outcome in this study was the NNU admissions. The study was exempt from review by Wandsworth Research Ethics Committee.

Statistical analysis

The continuous variables were presented as median with interquartile ranges, while the categorical variables were presented as a fraction of the total with percentages. The distribution assumptions were tested with Shapiro-Wilk test and QQ-plots. The group comparison of the variables was performed using t-test, Mann-Whitney-U test or Chi-square test where appropriate. Logistic regression analysis was used to identify and adjust for potential confounders. There were no missing variables and imputation methods were not used. The parameters in the models were determined by a variable selection approach using Akaike information criterion. The Hosmer-Lemeshow test was used to test the calibration of the models.

The validation of the model was performed internally with bootstrapped datasets. Separate datasets (n:10.000) of same sizes were constructed using a bootstrapping technique. The variables were chosen at random with equal sampling probability and with replacement. The predictive accuracy of the final model was assessed with the receiver operator characteristics (ROC) curves. Bootstrapped datasets were used to establish optimism adjusted ROC curves. After determining the accuracy and the calibration of the final model, the probabilities of some

clinical examples were calculated to provide a better interpretation of the potential practical use of the model. The statistical analysis was performed using the RStudio (Version 1.0.136, RStudio, Inc.) statistical software.

RESULTS

We have identified 775 women eligible for inclusion in the study. In total, 701 women were included in the analysis after excluding structural anomalies, aneuploidy, genetic syndromes, missing outcomes and elective cesarean deliveries (n=74). The cohort included 187 (26.7%) fetuses with an estimated fetal weight below the 3rd centile, 249 (35.5%) fetuses with an abdominal circumference below the 3rd centile and 165 (23.5%) fetuses with an estimated fetal weight below the 10th centile and an abnormal CPR value (<0.676 MoM). The positive predictive value of SGA diagnosed antenatally for being SGA at birth was 83.8% (95% confidence interval [CI] 77.2-87.8). SGA using birthweight less than 10th centile (true SGA) was more prevalent in the NNU admission group compared to those that did not require neonatal admission (97.6% vs 83.0%, P=0.008) (Table 1).

Table 1 shows a comparison between the two study groups according to whether the neonates were admitted to the NNU or not. The pregnancies in the NNU admission group had a significantly higher prevalence of drug abuse (14.2% vs. 2.2%, P<0.001), intrapartum pyrexia (9.5% vs. 0.7%, P=0.001), lower EFW centile (P<0.001), abdominal circumference (AC) centile (P=0.003), higher UA PI MoM (P<0.001), and lower CPR MoM (P<0.001) (Table 1). There were no significant differences between the two study groups regarding maternal age (P=0.999), parity (P=0.412), smoking status (P=0.353), alcohol use (P=0.708), ethnicity (P=0.876) or ultrasound to delivery interval (P=0.139), labor induction (P=0.339), meconium stained liquor (P=0.480), labor augmentation using oxytocin (P=0.845), intrapartum hemorrhage (P=0.999), and the use of epidural analgesia (P=0.227) (Table 1). There were more SGA neonates in the NNU admission group (97.6% vs 83.0%, P=0.008), but since this variable cannot be obtained prior to delivery the parameter was not included in the logistic regression model.

The univariable logistic regression model demonstrates that the maternal body mass index (BMI) (P=0.003), drug abuse (P<0.001), AC centile (P=0.017), EFW centile (P<0.001), UA PI MoM (P=0.001), CPR MoM (P<0.001), GA at delivery beyond 39 weeks (P=0.002), and intrapartum pyrexia (P<0.001) were significantly associated with the risk of NNU admission (Table 2). A multivariable model was constructed using a variable selection approach. The parameters in the final multivariable logistic regression model were the GA at delivery, the CPR MoM (OR 0.21; 95% CI 0.05-0.79, P=0.023), and EFW below the 3rd centile (OR 2.43; 95% CI 1.26-4.68, P<0.007) (Table 3). Compared with model using only GA at delivery and EFW (AUC: 0.68, 95% CI: 0.60-0.76), the combined model showed higher accuracy (AUC: 0.71, 95% CI: 0.63-0.79) (Figure 1). However, the difference was not statistically significant (p=0.119, DeLong's test). However, the addition of the CPR improved the calibration of the model (supplementary Figure 1). The Hosmer-Lemeshow test showed that the final model had a good fit (p=0.975). The validation cohort constituted 10.000 bootstrapped datasets from the original dataset. These were used to establish optimism adjusted ROC curves. The optimism adjusted ROC curve had an AUC of 0.70 (supplementary Figure 2). The combined model showed a sensitivity 30.9% (95% CI: 16.6-45.2%) for a fixed 10% false positive rate, positive predictive value of 16.1% (95% CI: 9.2-26.3), negative predictive value of 95.0% (95% CI: 93.2-96.1), positive likelihood ratio (LR) of 3.09 and negative LR of 0.72.

Some hypothetical clinical scenarios and their predicted probabilities of prolonged neonatal unit admission are provided in Table 4. A combination of low EFW centile (<3%) and low CPR MoM conferred to greatest risk of NNU admission across different GA at delivery categories (21.2%, 14.8% and 9.7% for 37, 38 and 39 weeks' gestation respectively) (Table 4). The

risk of NNU admission was approximately halved for each additional week in utero after 37 weeks' gestation across all risk categories. The number needed to treat (NNT) to prevent one prolonged NNU admission via prolonging the pregnancy to 39 weeks' gestation was 8.7 and 50 for the high risk group (low CPR and EFW below 3rd centile) and low risk group (normal CPR and EFW above 3rd centile), respectively. The NNT to prevent one prolonged NNU admission via prolonging pregnancy to 38 weeks' gestation was 15.6 and 76.9 for the high and the low risk groups, respectively. A nomogram for risk calculation is provided (supplementary Figure 3).

DISCUSSION

Summary of the main findings

The current study illustrates that the risk of NNU admission in the antenatally detected SGA fetuses can be predicted with a modest accuracy (AUC 0.71; 95% CI: 0.63-0.79) using a combination of 3 parameters (GA at delivery, CPR MoM and EFW centile). The combined model can help physicians in deciding the optimal time of delivery, counseling patients about the neonatal risks of labor induction and weighing the risk of antenatal complications against the reduced risk of neonatal admission with prolonged gestation.

Interpretation of the findings and comparison with existing literature

The estimated fetal weight, conditional and customized centiles have been suggested to be important factors in predicting the pregnancy outcomes of SGA babies. [20-27] The CPR is emerging as an important marker for differentiating pathologic cases from constitutionally small fetuses. In agreement with our previous study, the multivariable logistic regression model in the current study has demonstrated that the CPR is an independent marker of the risk of NNU admission. [28-30] Our results are also consistent with the recent meta-analysis highlighting the role of abnormal CPR in small fetuses in determining the risk of NNU admission (OR 13.0; 95% CI 6.0-27.9). [31]

According to our model, fetuses at high risk of NNU admission benefited more from prolongation of the pregnancy compared to fetuses with normal CPR values and EFW above the 3rd centile (NNT: 8.7 vs. 50, respectively). It is also important to take into account that low EFW and CPR values are independent predictors of the antenatal adverse events and that parents should be counseled about the pros and cons associated with prolongation of the pregnancy at term. [29]

In addition to the fetal parameters, the maternal and intrapartum risk factors such as history of drug abuse or intrapartum pyrexia had a negative impact on the risk of NNU admission. An interesting observation in our study is the association between the maternal BMI and the risk of NNU admission, which is similar to that reported in the literature. [32,33]

Clinical and research implications

Fetal growth restriction (FGR) is associated with stillbirth, neonatal death, hypoxic ischemic encephalopathy and cerebral palsy. However, the majority of small babies are not growth restricted and do not experience an adverse pregnancy outcome. [6,20-22,34]The main problems with research in this area stem from the interchanging use of the terms FGR and SGA as if they were equivalent, and the difficulty in identifying fetuses which are truly growth restricted. Several studies used fetal size as a proxy of FGR; this could potentially have detrimental consequences in both clinical practice and research studies, as it leads to unnecessary medical interventions, failure to provide individualized care and tailored antenatal counseling. Furthermore, it would be wrong to generalize the results of research studies which

included only truly growth restricted fetuses to the management of all SGA fetuses. It is time for our community, both clinicians and researchers, to resolve this confusion. The main challenge in the management of FGR at term is its accurate identification. Fetal size alone has not been, and is unlikely to be, the tool to do so, certainly not when used as a sole marker. Therefore, the search for other markers must continue. CPR has been proposed as a promising marker in these pregnancies. [28-30]In an attempt to reach a consensus definition for placental FGR, late (beyond 32 weeks) FGR was defined using four parameters; EFW <10th centile, AC <10th centile, crossing centiles on growth charts of more than two quartiles, and CPR <5th centile. [35]
Approximately 10% of term babies may require NNU admission. [36] Early term deliveries are associated with increased rate of NNU admission. [10] Despite the fact that a high proportion of NNU admissions are short-term, with full recovery and discharge home, they represent a burden on healthcare resources and are associated with heightened parental anxiety.

Study strengths and limitations

The strengths of our study included large number of antenatally diagnosed SGA fetuses, the short interval between ultrasound and delivery, ascertainment of the outcome data and adjusting for possible confounding variables, and employing a comprehensive model including both antenatal and intrapartum risk factors. The prediction model had modest precision and very good calibration. An external cohort was not available, and therefore, the validation was performed internally using resampling methods. The limitations of our study include its retrospective design and the risk of intervention bias as the clinicians were aware that the fetus was SGA. However, the CPR values were not calculated before the analysis for this study, so the healthcare professionals providing the intrapartum care were effectively blinded to this value. The detection rate of true SGA fetuses in our study was similar to previously reported diagnostic performance of antenatal ultrasound. [1] These facts are likely to indicate that our study population reflects the real life clinical setting. The relative low incidence of NNU admission in our center compared to published literature is not a limitation per se, but external validation studies must adjust for the baseline variabilities in the NNU admission rates between our population and a tested validation cohort. We have also employed a robust methodology to ensure goodness fit and accuracy of the results while avoiding overestimation and overfitting. Finally, the study cohort will have been scanned by a large number of different operators, raising the risk of inter-observer variability in the measurements. The threshold for NNU admission is also likely to have been influenced by changing personnel and attitudes toward neonatal care over the 18-year period.

Conclusion

In summary, the risk of NNU admission in SGA fetuses identified antenatally can be estimated with a modest accuracy using the proposed model. Risk stratification according to this model could be beneficial for determining the timing of delivery and the need for neonatal care. Further validation studies should be performed to confirm the external applicability of this model.

REFERENCES

1. Sovio U, White IR, Dacey A, Pasupathy D, Smith GC. Screening for fetal growth restriction with universal third trimester ultrasonography in nulliparous women in the Pregnancy Outcome Prediction (POP) study: a prospective cohort study. Lancet. 2015 ;386:2089-97.
2. Aviram A, Yogev Y, Bardin R, Meizner I, Wiznitzer A, Hadar E. Small for gestational age newborns--does pre-recognition make a difference in pregnancy outcome? J Matern Fetal Neonatal Med. 2015 ;28:1520-4.
3. Verlijsdonk JW1, Winkens B, Boers K, Scherjon S, Roumen F. Suspected versus non-suspected small-for-gestational age fetuses at term: perinatal outcomes. J Matern Fetal Neonatal Med. 2012 ;25:938-43.
4. Lindqvist PG, Molin J. Does antenatal identification of small-for-gestational age fetuses significantly improve their outcome? Ultrasound Obstet Gynecol. 2005 ;25:258-64.
5. Visentin S, Londero AP, Grumolato F, Trevisanuto D, Zanardo V, Ambrosini G, Cosmi E. Timing of delivery and neonatal outcomes for small-for-gestational-age fetuses. J Ultrasound Med. 2014; 33: 1721-8.
6. Ananth CV, Vintzileos AM. Distinguishing pathological from constitutional small for gestational age births in population-based studies. Early Hum Dev 2009;85:653–8.
7. Prior T, Mullins E, Bennett P, Kumar S. Prediction of intrapartum fetal compromise using the cerebroumbilical ratio: a prospective observational study. Am J Obstet Gynecol 2013;208:124.e1–6.
8. Cruz-Martínez R, Figueras F, Hernandez-Andrade E, Oros D, Gratacos E. Fetal brain Doppler to predict cesarean delivery for nonreassuring fetal status in term small-for-gestational-age fetuses. Obstet Gynecol 2011;117:618–26.
9. Garcia-Simon R, Figueras F, Savchev S, Fabre E, Gratacos E, Oros D. Cervical condition and fetal cerebral Doppler as determinants of adverse perinatal outcome after labor induction for late-onset small-for-gestational-age fetuses. Ultrasound Obstet Gynecol. 2015 ;46:713-7.
10. Figueras F, Eixarch E, Gratacos E, Gardosi J. Predictiveness of antenatal umbilical artery Doppler for adverse pregnancy outcome in small-for-gestational-age babies according to customised birthweight centiles: population-based study. BJOG. 2008 ;115:590-4.
11. Sengupta S, Carrion V, Shelton J, Wynn RJ, Ryan RM, Singhal K, Lakshminrusimha S. Adverse neonatal outcomes associated with early-term birth. JAMA Pediatr. 2013 ;167:1053-9.
12. Karlsen HO, Ebbing C, Rasmussen S, Kiserud T, Johnsen SL. Use of conditional centiles of middle cerebral artery pulsatility index and cerebroplacental ratio in the prediction of adverse perinatal outcomes. Acta Obstet Gynecol Scand. 2016; 95: 690-6.
13. Dunn L, Sherrell H, Kumar S. Review: Systematic review of the utility of the fetal cerebroplacental ratio measured at term for the prediction of adverse perinatal outcome. Placenta. 2017; 54: 68-75.

14. Hadlock FP, Harrist RB, Sharman RS, Deter RL, Park SK. Estimation of fetal weight with the use of head, body, and femur measurements--a prospective study. Am J Obstet Gynecol. 1985 ;151:333-7.

15. Bhide A, Acharya G, Bilardo CM, Brezinka C, Cafici D, Hernandez-Andrade E, et al. ISUOG practice guidelines: use of Doppler ultrasonography in obstetrics. Ultrasound Obstet Gynecol 2013;41:233–9.

16. Robinson HP, Fleming JE. A critical evaluation of sonar "crown-rump length" measurements. Br J Obstet Gynaecol. 1975 ;82:702-10.

17. Poon LC, Tan MY, Yerlikaya G, Syngelaki A, Nicolaides KH. Birth weight in live births and stillbirths. Ultrasound Obstet Gynecol 2016;48:602–6.

18. Morales-Roselló J, Khalil A, Morlando M, Papageorghiou A, Bhide A, Thilaganathan B. Changes in fetal Doppler indices as a marker of failure to reach growth potential at term. Ultrasound Obstet Gynecol 2014;43:303–10.

19. Baschat AA, Gembruch U. The cerebroplacental Doppler ratio revisited. Ultrasound Obstet Gynecol 2003;21:124–7.

20. Pilliod RA, Cheng YW, Snowden JM, Doss AE, Caughey AB. The risk of intrauterine fetal death in the small-for-gestational-age fetus. Am J Obstet Gynecol 2012;207:318.e1-6.

21. McIntyre S, Blair E, Badawi N, Keogh J, Nelson KB. Antecedents of cerebral palsy and perinatal death in term and late preterm singletons. Obstet Gynecol 2013;122:869−77.

22. Bukowski R, Burgett AD, Gei A, Saade GR, Hankins GD. Impairment of fetal growth potential and neonatal encephalopathy. Am J Obstet Gynecol 2003;188:1011−5.

23. Savchev S, Figueras F, Cruz-Martinez R, Illa M, Botet F, Gratacos E. Estimated weight centile as a predictor of perinatal outcome in small-for-gestational-age pregnancies with normal fetal and maternal Doppler indices. Ultrasound Obstet Gynecol. 2012 ;39:299-303.

24. Leftwich HK, Stetson B, Sabol B, Leung K, Hibbard J, Wilkins I. Growth restriction: identifying fetuses at risk. J Matern Fetal Neonatal Med. 2017. [epub ahead of print]

25. Policiano C, Fonseca A, Mendes JM, Clode N, Graca LM. Small-for-gestational-age babies of low-risk term pregnancies: does antenatal detection matter? J Matern Fetal Neonatal Med. 2017. [epub ahead of print]

26. Karlsen HO, Johnsen SL, Rasmussen S, Kiserud T. Prediction of adverse perinatal outcome of small-for-gestational-age pregnancy using size centiles and conditional growth centiles. Ultrasound Obstet Gynecol. 2016;48 :217-23.

27. Chiossi G, Pedroza C, Costantine MM, Truong VTT, Gargano G, Saade GR. Customized vs population-based growth charts to identify neonates at risk of adverse outcome: systematic review and Bayesian meta-analysis of observational studies. Ultrasound Obstet Gynecol. 2017;50 :156-66.

28. Khalil AA, Morales-Rosello J, Elsaddig M, Khan N, Papageorghiou A, Bhide A, Thilaganathan B. The association between fetal Doppler and admission to neonatal unit at term. Am J Obstet Gynecol. 2015 ;213:57.e1-7.

29. Khalil A, Morales-Rosello J, Khan N, Nath M, Agarwal P, Bhide A, Papageorghiou A, Thilaganathan B.Is cerebroplacental ratio a marker of impaired fetal growth velocity and adverse pregnancy outcome? Am J Obstet Gynecol. 2017. doi: 10.1016/ j.ajog.2017.02.005.
30. Khalil AA, Morales-Rosello J, Morlando M, Hannan H, Bhide A, Papageorghiou A, Thilaganathan B.Is fetal cerebroplacental ratio an independent predictor of intrapartum fetal compromise and neonatal unit admission?Am J Obstet Gynecol. 2015 ;213:54.e1-10.
31. Nassr AA, Abdelmagied AM, Shazly SA. Fetal cerebro-placental ratio and adverse perinatal outcome: systematic review and meta-analysis of the association and diagnostic performance. J Perinat Med 2016;44:249-56.
32. Foo XY, Greer RM, Kumar S. Impact of Maternal Body Mass Index on Intrapartum and Neonatal Outcomes in Brisbane, Australia, 2007 to 2013. Birth. 2016 ;43:358-365.
33. Suk D, Kwak T, Khawar N, Vanhorn S, Salafia CM, Gudavalli MB et al. Increasing maternal body mass index during pregnancy increases neonatal intensive care unit admission in near and full-term infants. J Matern Fetal Neonatal Med. 2016 ;29:3249-53.

34. Pasupathy D, Wood AM, Pell JP, Fleming M, Smith GC. Rates of and factors associated with delivery-related perinatal death among term infants in Scotland. JAMA 2009;302:660–8.

35. Gordijn SJ, Beune IM, Thilaganathan B, et al. Consensus definition for placental fetal growth restriction: a Delphi procedure. Ultrasound Obstet Gynecol 2016 . doi: 10.1002/ uog.15884. [Epub ahead of print]

36. Alkiaat A, Hutchinson M, Jacques A, Sharp MJ, Dickinson JE. Evaluation of the frequency and obstetric risk factors associated with term neonatal admissions to special care units. Aust N Z J Obstet Gynaecol. 2013;53:277-82.

Table 1. Characteristics of the study cohort according to the need for neonatal unit admission

Pregnancy variables	**Neonatal unit admission (n=42)**	**No neonatal unit admission (n=659)**	**p value**
Antenatal variables			
Maternal age in years, median (IQR)	29.00 (24.00-32.00)	29.00 (25.00-33.00)	0.999
Body mass index in kg/m^2, median (IQR)	23.85 (21.45-26.10)	22.50 (20.50-25.20)	0.164
Nulliparous, n (%)	29 (69.0)	406 (61.6)	0.412
Ethnicity			0.867
Caucasian, n (%)	15 (35.7)	227 (34.4)	
African, n (%)	6 (14.2)	147 (22.3)	
Asian, n (%)	21 (50.0)	245 (37.1)	
Mixed, n (%)	0 (1.1)	8 (1.2)	
Other, n (%)	0 (0)	2 (0.3)	
Smoker, n (%)	8 (19.0)	89 (13.5)	0.353
Alcohol use, n (%)	2 (4.7)	29 (4.4)	0.708
Drug abuse, n (%)	6 (14.2)	15 (2.2)	<0.001
Ultrasound and Doppler variables			
Gestational age at ultrasound in weeks, median (IQR)	37.21 (36.29-38.46)	37.86 (36.71-39.00)	0.029
Interval between ultrasound and delivery in days, median (IQR)	8.00 (1.5-13.00)	9.00 (3.00-16.00)	0.139
Abdominal circumference in mm, median (IQR)	293.6 (276.1-301.6)	296.9 (287.5-306.3)	0.007
Abdominal circumference centile, median (IQR)	2.60 (0.60-5.47)	4.74 (2.13-7.65)	0.003
Estimated fetal weight in grams, median (IQR)	2214 (1972-2459)	2412 (2220-2634)	<0.001
Estimated fetal weight centile, median (IQR)	3.07 (0.80-6.27)	5.55 (2.97 -8.11)	<0.001

Umbilical artery pulsatility index, median (IQR)	1.0 (0.89-1.18)	0.94 (0.82-1.08)	0.004
Umbilical artery pulsatility index MoM, median (IQR)	1.15 (1.04-1.36)	1.07 (0.95-1.23)	<0.001
Middle cerebral artery pulsatility index, median (IQR)	1.40 (1.20-1.61)	1.43 (1.23-1.65)	0.568
Middle cerebral artery pulsatility index MoM, median (IQR)	1.17 (1.03-1.36)	1.19 (1.04-1.37)	0.086
Cerebroplacental ratio, median (IQR)	1.36 (1.18-1.71)	1.54 (1.27-1.87)	0.035
Cerebroplacental ratio MoM, median (IQR)	0.71 (0.61-0.87)	0.85 (0.69-1.02)	<0.001
Intrapartum variables			
Induction of labor, n (%)	19 (45.2)	353 (53.5)	0.339
Meconium stained liquor (grade 2 or 3), n (%)	3 (7.1)	31 (4.7)	0.480
Oxytocin use for slow progress in labor, n (%)	9 (21.4)	135 (20.4)	0.845
Intrapartum hemorrhage, n (%)	0 (0.0)	4 (0.6)	0.999
Intrapartum pyrexia, n (%)	4 (9.5)	5 (0.7)	0.001
Epidural analgesia, n (%)	9 (21.4)	204 (30.9)	0.227
Variables at birth			
Gestational age at delivery, median (IQR)	38.42 (37.71-39.86)	39.57 (38.43-40.43)	0.001
Birthweight in grams, median (IQR)	2305 (2030-2550)	2600 (2375-2880)	<0.001
Birthweight centile, median (IQR)	0.97 (0.34-2.55)	3.12 (1.06-7.95)	<0.001
Small for gestational age, n (%)	41 (97.6)	547 (83.0)	0.008

Table 2. Results of the univariable logistic regression analysis of the known risk factors associated with the neonatal unit admission

Risk factor	Odds ratio	95% Confidence interval	P-value
Maternal age in years	0.98	0.93-1.03	0.554
Body mass index in kg/m^2	1.98	1.03 -3.72	0.003
Multiparous	0.94	0.45-1.89	0.882
Ethnicity	0.87	0.60-1.25	0.470
Smoking	1.89	0.78-4.13	0.126
Drug abuse	7.15	2.43-18.78	<0.001
Alcohol use	1.31	0.20-4.63	0.715
Abdominal circumference centile	0.89	0.81-0.97	0.017
Estimated fetal weight centiles	0.82	0.73-0.92	<0.001
Umbilical artery pulsatility index MoM	4.87	1.88-13.70	0.001
Middle cerebral artery pulsatility index MoM	0.30	0.07-1.15	0.087
Cerebroplacental ratio MoM	0.11	0.03-0.40	<0.001
Gestational age at delivery beyond 39 weeks' gestation	0.37	0.19 -0.69	0.002
True small for gestational age (birthweight <10th centile)	8.39	1.79-149.65	0.036
Intrapartum Factors			
Induction of labor	0.96	0.49-1.91	0.926
Epidural analgesia	0.77	0.33-1.61	0.513
Intrapartum pyrexia	13.76	3.29-54.10	<0.001
Oxytocin used for slow progress	1.34	0.58-2.83	0.459
Meconium grade 2/3	1.89	0.43-5.69	0.310

MoM = multiples of median.

Table 3. Results of the multivariable logistic regression analysis of the risk factors associated with the neonatal unit admission

Risk factor	**Odds ratio**	**95% Confidence interval**	**P-value**
Cerebroplacental ratio MoM	0.21	0.05-0.79	0.023
Estimated fetal weight below the 3rd centile	2.43	1.26-4.68	0.007
Gestational age at delivery			
- Between 37 and 38 weeks' gestation	Reference		
- Between 38 and 39 weeks' gestation	0.68	0.28-1.60	0.376
- Above 39 weeks' gestation	0.36	0.16-0.80	0.011

MoM = multiples of median.

Table 4. Clinical scenarios and their predicted probabilities according to the final multivariable prediction.

	Gestational age at delivery	Estimated fetal weight centile	CPR MoM	Predicted probability of prolonged NNU admission (95% CI)
Patient 1	37 weeks	9%	1.6	2.7% (0.7-8.0)
Patient 2	37 weeks	9%	1.2	5.0% (2.3-10.0)
Patient 3	37 weeks	2%	0.6	21.2% (14.2-30.6)
Patient 4	38 weeks	9%	1.6	1.4 (0.4-4.3)
Patient 5	38 weeks	9%	1.2	2.9% (1.5-5.3)
Patient 6	38 weeks	2%	0.6	14.8% (10.4-20.4)
Patient 7	39 weeks	9%	1.6	0.7% (0.2-2.3)
Patient 8	39 weeks	9%	1.2	1.6% (0.7-3.0)
Patient 9	39 weeks	2%	0.6	9.7% (6.0-14.8)

CI=confidence interval. CPR=cerebroplacental ratio. MoM = multiples of median. NNU=neonatal care unit

FIGURE LEGENDS

Figure 1. The receiver operating characteristic (ROC) curve of the gestational age alone and estimated fetal weight model (dotted line), and the combined model with the cerebroplacental ratio (straight line).

Supplementary Figure 1. The calibration plot of two models; the model with gestational age and estimated fetal weight is presented with dotted line, while the combined model with the cerebroplacental ratio is presented with straight line.

Supplementary Figure 2. The bootstrapped validation receiver operating characteristics curves. The straight line represents the present curve (AUC: 0.71) and the dashed lines the optimism adjusted curves (AUC: 0.70).

Supplementary Figure 3. The nomogram of the combined model. The cerebroplacental ratio (CPR) multiples of median (MoM) is presented as continuous variable whereas gestational age at delivery (2=below 38 weeks', 1= between 38 and 39 weeks' and 0=beyond 39 weeks) and estimated fetal weight (1=below 3rd centile, 0=above 3rd centile) are presented as categorical variables. For each variable, an individual score can be estimated by drawing a straight line from the variable to the "Points" line above. After taking the sum of all points, the risk score (%) can be read by drawing a straight line from "Total Points" line down to "Risk of Neonatal Unit Admission"