Ultrasound-based radiomics technology in fetal lung texture analysis prediction of neonatal respiratory morbidity

JianQiao Zhou (✉ zhou30@126.com)  
Ruijin Hospital, Shanghai Jiaotong University School of Medicine

Yanran Du  
Ruijin Hospital, Shanghai Jiaotong University School of Medicine

Jing Jiao  
Department of Electronic Engineering, Fudan University

Chao Ji  
Putuo Hospital Affiliated to Shanghai University of Traditional Chinese Medicine

Man Li  
Obstetrics and Gynecology Hospital of Fudan University

Yi Guo  
Department of Electronic Engineering, Fudan University

Yuanyuan Wang  
Department of Electronic Engineering, Fudan University

Yunyun Ren  
Obstetrics and Gynecology Hospital of Fudan University

Research Article

Keywords: Radiomics, Fetal lung, Ultrasound, Pregnancy complications, Neonatal respiratory morbidity

Posted Date: March 10th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1410043/v1

License: © This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License
Abstract

Objectives To develop a novel method for predicting neonatal respiratory morbidity (NRM) by ultrasound-based radiomics technology.

Methods In this retrospective study, 430 high-throughput features per fetal-lung image were extracted from 295 fetal lung ultrasound images (four-chamber view) in 295 single pregnancies. Images had been obtained between 28\(^{+3}\) and 37\(^{+6}\) weeks of gestation within 72 hours before delivery. A machine-learning model was created using 20 radiomics features extracted from the images and 2 clinical features (gestational age and pregnancy complications) to predict the possibility of NRM.

Results Of the 295 standard fetal lung ultrasound images included, 210 in the training set and 85 in the testing set. The overall performance of the neonatal respiratory morbidity prediction model achieved AUC of 0.88 in the training set and 0.81 in the testing set, sensitivity of 84.32% in the training set and 77.78% in the testing set, specificity of 81.13% in the training set and 82.09% in the testing set, and accuracy of 81.90 in the training set and 81.18% in the testing set.

Conclusions Ultrasound-based radiomics technology can be used to predict NRM. The results of this study may provide a novel method for non-invasive approaches for the prenatal prediction of NRM.

1. Introduction

Neonatal respiratory morbidity (NRM), associated with prematurity, is the leading cause of mortality and morbidity\(^{[1]}\). Fetal lung maturity (FLM) was influenced by many factors, including gestational diabetes mellitus (GDM) and pre-eclampsia (PE), the two most common complications of pregnancy\(^{[2−3]}\). With the increasing use of assisted reproductive technology (ART), the incidence of gestational hypertension and GDM in these women is 11.0% and 15.1% respectively\(^{[4]}\). Accurate estimates of fetal lung development in pregnancies during complications will help obstetricians make clinical decisions that can avoid unnecessary premature birth and ensure optimal maternal and fetal outcomes. Although the methods and techniques have been improved since the L / S ratio was applied 25 years ago, FLM detection still cannot predict whether the fetal lung is mature or not\(^{[5]}\).

In recent years, the combination of ultrasound images with artificial intelligence technology has provided new ideas for the detection of FLM\(^{[6−7]}\). Radiomics is a technology that combines big data and medical imaging-assisted diagnosis. By extracting and mining high-throughput features from multi-modality images, it can quantitatively analyze the human molecular and genetic changes hidden behind medical images. This technology has been widely used in the analysis of ultrasound images\(^{[8−10]}\). But to the best of our knowledge, there is no published research on ultrasound-based radiomics technology being employed to study the development of fetal lungs during pregnancy complications.

In the present study, by collecting fetal lung ultrasound standard images, the fetal lung texture characteristics were analyzed and compared using ultrasound-based radiomics technology. A neonatal
respiratory morbidity prediction model was established by using the ultrasound image features of fetal lungs combined with clinical characteristics (gestational age and pregnancy complications), which may provide a new method for non-invasive prediction of NRM.

2. Results

2.1. Populations

The characteristics of the study cohort are summarized in Table 1. Included in the study were 295 standard fetal lung ultrasound images obtained within 72 hours before delivery, including 210 in the training set and 85 in the testing set. In the end, there were 69 (69/295, 23.4%) newborns with neonatal respiratory morbidity, among which 49 (49/69, 71.0%) newborns with transient tachypnea of the newborn and 20 (20/69, 29.0%) with respiratory distress syndrome.
Table 1
Characteristics of study cohort

| Characteristic                                 | Training set          | Testing set         |
|------------------------------------------------|-----------------------|---------------------|
|                                                | $(n = 210)$           | $(n = 85)$          |
| Maternal age (years)                           | $31 \pm 3.88$         | $31 \pm 4.23$       |
| GA at ultrasound (weeks)                       | $28–37$               | $29–37$             |
|                                                | $(35 \pm 2.42)$       | $(35 \pm 2.11)$     |
| Pregnancy complications (GDM or PE)            |                       |                     |
| With                                           | $73 (34.8\%)$         | $25 (29.4\%)$       |
| without                                        | $137 (65.2\%)$        | $60 (70.6\%)$       |
| Mode of delivery                               |                       |                     |
| Spontaneous vaginal                            | $75 (35.7\%)$         | $52 (61.2\%)$       |
| Cesarean                                       | $135 (64.3\%)$        | $33 (38.8\%)$       |
| Birth weight (g)                               | $3006 \pm 562$        | $3212 \pm 616$      |
| Sex of newborn                                 |                       |                     |
| Female                                         | $116 (55.2\%)$        | $51 (60.0\%)$       |
| Male                                           | $49 (44.8\%)$         | $34 (40.0\%)$       |
| 5-min Apgar score                              |                       |                     |
| $\leq 7$                                       | $4 (1.9\%)$           | $3 (3.5\%)$         |
| $> 7$                                          | $206 (98.1\%)$        | $82 (96.5\%)$       |
| Neonatal prognosis                             |                       |                     |
| No neonatal respiratory morbidity              | $159 (75.7\%)$        | $67 (78.8\%)$       |
| Neonatal respiratory morbidity                 | $51 (24.3\%)$         | $18 (21.2\%)$       |
| TTN                                            | $35 (16.7\%)$         | $14 (16.5\%)$       |
| RDS                                            | $16 (7.6\%)$          | $4 (4.7\%)$         |
| NICU admission                                  | $51 (24.3\%)$         | $18 (21.2\%)$       |

Data are presented as mean ± SD or $n$ (%). GA, gestational age; GDM, gestational diabetes mellitus; PE, pre-eclampsia; TTN, transient tachypnea of the newborn; RDS, respiratory distress syndrome; NICU, neonatal intensive care unit.

2.2. Neonatal respiratory morbidity prediction model
By permuting out-of-bag data feature of random regression forest, 20 radiomics features and 2 clinical features (GA and Pregnancy complications) were selected and input into RUSBoost classifier to predict the possibility of NRM. The confusion matrix and prediction performance of human neonatal respiratory morbidity prediction model are shown in Table 2. and Fig. 1. The diagnostic efficacy of the training group and the testing group collected by two radiologists using different machines was similar, with AUC of 0.88 in the training set and 0.81 in the testing set, sensitivity of 84.32% in the training set and 77.78% in the testing set, specificity of 81.13% in the training set and 82.09% in the testing set and accuracy of 81.90 in the training set and 81.18% in the testing set. The risk probability of NRM predicted by the model was 0.008–0.999 (0.796 ± 0.334) in NRM cases, while it was 0.001–0.999 (0.285 ± 0.268) in normal cases.

### Table 2
Algorithm performance for predicting neonatal respiratory morbidity on fetal lung ultrasound examination

| Neonatal respiratory morbidity prediction model | Training set | Testing set |
|-----------------------------------------------|--------------|-------------|
| ROI (n)                                       | 210          | 85          |
| TP (n)                                        | 43           | 14          |
| TN (n)                                        | 129          | 55          |
| FP (n)                                        | 30           | 12          |
| FN (n)                                        | 8            | 4           |
| Sensitivity                                   | 43/51 (84.31%) | 14/18 (77.78%) |
| Specificity                                   | 129/159 (81.13%) | 55/67 (82.09%) |
| Accuracy                                      | 172/210 (81.90%) | 69/85 (81.18%) |
| PPV                                           | 43/73 (58.90%) | 14/26 (53.85%) |
| NPV                                           | 129/137 (94.16%) | 55/59 (93.22%) |
| PLR                                           | 4.47         | 4.34        |
| NLR                                           | 0.19         | 1.24        |
| AUC                                           | 0.88         | 0.81        |

ROI = Region of interest; TP = True Positive; TN = True Negative; FP = False Positive;
FN = False Negative; PPV = Positive Predictive Value; NPV = Negative Predictive Value;
PLR = Positive Likelihood Ratio; NLR = Negative likelihood ratio; AUC, area under the receiver-operating-characteristics curve.

### 3. Discussion
The results of the present study revealed that fetal lung texture analysis by ultrasound-based radiomics technology can be used to predict the probability of neonatal respiratory morbidity by analyzing fetal lung ultrasound images and in combination with clinical characteristics (GA and pregnancy complications). It may provide a new method for noninvasive prediction of NRM.

The clinical utility of FLM assays has been largely debated \[11\]. At present, instead of studying several components of the amniotic fluid through amniocentesis, the application of prenatal corticoids and postnatal surfactant has become the main clinical measure to reduce neonatal respiratory diseases \[12\]. However, the recommended type of corticosteroid and the gestational window of treatment administration have not been clearly defined \[13\]. Studies have shown that there are potentially important risks of corticosteroids in neurodevelopment and fetal metabolic planning \[14–16\]. In a study of 278,508 live-born singletons of 24 weeks gestation or above in Finland, antenatal steroid was shown to be associated with the delivery of small fetus at birth \[17\]. The results of this study may provide a new method for non-invasive approaches for the prenatal assessment of FLM, which can not only avoid the fear and discomfort of amniocentesis, help to decide whether to use prenatal corticosteroids, but also refine the timing of delivery in high-risk pregnancies.

With the widespread use of ultrasound in obstetrics, several attempts have been made to evaluate fetal lung maturity noninvasively. Kim Sm et al \[18\] showed that a measured elevated acceleration-to-ejection time ratio of the fetal pulmonary artery doppler was independently associated with the development of RDS in preterm infants and thus a possible marker of lung maturity. Attempts to quantify fetal lung volume in normal pregnancies by using 3-dimensional ultrasonography though useful in cases like diaphragmatic hemia have not been shown to objectively evaluate FLM \[19–20\]. In addition, gray scale measurement \[21\], fetal lung tissue movement assessment \[22\], and evaluation of fetal lung images relative to fetal liver and fetal placenta images \[23\] have been tried to proposed as a possible tool for the assessment of fetal lung maturity. Unfortunately, the accuracy of this diagnosis is very poor, so no clinical significance is found. Recently, Palacio M et al. \[24\] reported that the quantitative ultrasound lung texture analysis could be used to evaluate fetal lung maturity and showed an accuracy similar to that of biochemical tests in amniotic fluid previously reported. In this study, the overall performance of neonatal respiratory morbidity prediction model based on fetal lung texture analysis by ultrasound-based radiomics technology achieved AUC of 0.81–0.88, sensitivity of 77.78–84.31%, specificity of 81.31–82.09% and accuracy of 81.18–81.90%. These ultrasound images, which appear indistinguishable to the naked eye, could quickly and accurately predict the risk of NRM in the fetus. And the images collected by different trained doctors using different machines do not affect the estimation results of the model.

Our previous research \[25\] reported that there were great differences in fetal lung texture between pregnancies with GDM, PE and normal pregnancy and between different gestational ages. In our study population, there were 33.2% (98/295) of pregnant women with GDM and PE. Among these, the proportion of newborns with NRM was nearly twice that in the normal pregnancy group (6.1% vs 3.2%). Therefore, in this study, the model was established by high-throughput radiomics features and two...
clinical features (pregnancy complications and gestational age). Studies\textsuperscript{[26]} have shown that the accuracy and PPV of tests on amniotic fluid in predicting NRM was 73.3\% (57.5–81.6\%) and 27.1\% (18.0–34.1\%) respectively. In this study, results showed improvements by about 8.2\% in accuracy (81.5\%) and 29.3\% in PPV (56.4\%).

Our study had several limitations: First, large amounts of data are necessary in radiomics for mining concealed prognostic information and to avoid overfitting. Expanding the sample size, especially the positive sample size, would improve the stability and accuracy of the model. Second, in this study, the ROIs of fetal lungs were performed manually. A computer system will be used to identify fetal lung tissue automatically, so that the model could be used more conveniently. Third, it is a single-center study, and image acquisition and delineation were performed by highly-trained personnel. But as the number of operators and settings increases, there will be many unqualified images. Multi-center research will be carried out in the future.

In conclusion, ultrasound-based radiomics technology can be used to predict neonatal respiratory morbidity. The results of this study may provide a new method for non-invasive approaches for the prenatal prediction of NRM.

4. Methods

4.1. Patients

Between July 2018 and October 2020, 2047 routine fetal-lung ultrasound images (either right or left lung) from 2047 women with singleton pregnancy were obtained, at gestational ages (GA) ranging from 27+3 to 42+0 weeks. All participating women included in the study gave written informed consent for the use of ultrasound images and clinical data. All the methods hereby explained were performed in accordance with the relevant guidelines and regulations and approved, together with the study protocol, by the ethics committee of the Obstetrics and Gynecology Hospital Affiliated to Fudan University (2018-73). Of these, 731 babies with GA 28+3–37+6 weeks were delivered within 72 hours after ultrasound examination in the hospital. According to the same enrolment criteria of previous studies, the final cohort comprised 295 women with singleton pregnancy, with a total of 295 fetal-lung ultrasound images. The flowchart for the study population is shown in Fig. 2. Gestational age was determined by last menstrual period and verified by first-trimester dating ultrasound (crown–rump length).

Pregnancy complications included GDM and PE. GDM was diagnosed using a 75-g oral glucose tolerance test at 24–28 weeks of gestation\textsuperscript{[27]}. Pre-eclampsia and gestational hypertension are characterized by the new onset of hypertension (> 140 mmHg systolic or > 90 mmHg diastolic) after 20 weeks gestation\textsuperscript{[28]}.

Analysis of neonatal clinical data was supervised by a neonatal doctor. NRM included respiratory distress syndrome (RDS) or transient tachypnea of the newborn (TTN). The diagnosis of RDS and TTN is based on symptoms, signs and radiological examination\textsuperscript{[7,29]}. Diagnostic criteria of RDS: tachypnea, snoring,
chest wall retraction, nasal dilatation, the need for supplemental oxygen and the appearance of chest X-
rays led to admission to the neonatal intensive care unit for respiratory support. Diagnostic criteria of
TTN: mild or moderate respiratory distress (isolated tachypnea, rare snoring, slight retraction) and a chest
X-ray (if done) showing alveolar and/or pulmonary interstitial effusion and prominent pulmonary
vascular patterns.

4.2. Ultrasound Imaging and Segmentation

All ultrasound images were obtained during routine prenatal ultrasound examinations within 72 hours
before delivery. Among which, the images of the training set were obtained by radiologist 1 with more
than 10 years’ experience in obstetric and gynecological ultrasound imaging, using a WS80A ultrasound
system (Samsung, Korea). The frequency of the CA1-7A probe was 1–7MHz, with a center frequency was
4.0MHz. The images of the testing set were obtained by radiologist 2 with 3 years’ experience in obstetric
and gynecological ultrasound imaging, using a VOLUSON E8 ultrasound system(GE, United States). The
frequency of the C1-5-D probe was 2–5MHz, with a center frequency was 3.5 MHz.

A detailed description of the standard image acquisition protocol and the method used of manual (free-
hand) delineation is fully described in a previous study[25]: Briefly, the standard fetal lung images
requiring: on an axial section of the fetal thorax at the level of the four-chamber cardiac view, the settings
were adjusted (depth, gain, frequency and harmonics) to ensure that at least one of the lungs had no
obvious acoustic shadowing from the fetal ribs. All the images were inspected for image quality control
and stored in DICOM format (.dcm) for offline analysis. Manual (freehand) delineation was performed in
each fetal lung by radiologist 3, selecting one side of the fetal lung, taking great care to ensure that only
the lung tissue was delineated, and avoiding blood vessels, rib shadows, and the lung capsule, as shown
in Fig. 3.

4.3. Radiomics Evaluation and Machine Learning

The research process is shown in Fig. 4.

Univariate analysis was used to describe the differences in features among the different categories. The
t-test was performed on each 430 continuous radiomics features. The $\chi^2$ test was performed for two
categorical clinical features, gestational age and pregnancy complications. $P$ value < 0.05 indicated a
significant difference.

The feature extraction method to analyze each ROI has been previously reported [25]. First, high-
throughput radiomics features importance per fetal lung image were ranked to selected features by
permuting out-of-bag data feature of random regression forest. If a feature is influential, permuting its
values would influence the model error testing with out-of-bag data. The more important a feature is, the
greater its influence will be [30]. As a result, 20 radiomics features and 2 clinical features (GA and
Pregnancy complications) were selected to classification, which are shown in Table 3. Then, with the high
imbalance of samples and the small sample size, RUSBoost (Random under-sampling with AdaBoost)
[31] was used to build the model. Finally, the risk probability of NRM in each fetal lung image was
obtained, which was the predicted score normalized to the range of 0–1 by softmax function of the RUSBoost. The cut-off point of the model was 0.5. The fetal lungs with risk probability higher than 0.5 were divided into the high-risk group, and lower than 0.5 were divided into the low-risk group. All classifier parameters were tuned with bootstrap 10-fold cross-validation, and the decision tree was employed as the base learner for RUSBoost.

### Table 3

**List of high-throughput sonographic features**

| Model                              | Feature name (P value)                                                                 |
|------------------------------------|---------------------------------------------------------------------------------------|
| Neonatal respiratory morbidity prediction model | GA (0.000), GDM or PE (0.002), Mean of contrast of approximation (0.005), Mean of covariance of diagonal (0.110), Short-run high grey-level emphasis (0.061), Busyness of diagonal (0.010), Mean of contrast of diagonal (0.031), Inverse difference moment normalized of approximation (0.360), Information measure of correlation 1 of approximation (0.270), Grey-level variance of diagonal (0.021), Energy of vertical (0.008), Run-length variance (0.014), Complexity of vertical (0.010), Skewness of diagonal (0.001), Sum entropy of diagonal (0.188), Mean of covariance of horizontal (0.653), Grey-level variance of vertical (0.021), Standard deviation of approximation (0.372), Short-run high grey-level emphasis of diagonal (0.036), Mean of covariance of vertical (0.916), Variance of vertical (0.041), Variance of approximation (0.055) |

GA, gestational age; GDM, gestational diabetes mellitus; PE, pre-eclampsia;

The prediction performance of the model was assessed for sensitivity (SENS), specificity (SPEC), accuracy, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (PLR), negative likelihood ratio (NLR) and area under the receiver operating characteristic curve (AUC).

All the feature extraction and image classifications were carried out using MATLAB R202018a and Toolbox Classification (MathWorks, Inc, Natick, Massachusetts, US).

### Declarations

### Acknowledgements

- The scientific guarantor of this publication is Jianqiao Zhou.
- This work was supported by the National Natural Science Foundation of China (Grant 61871135 and 82071928), the Science and Technology Commission of Shanghai Municipality (Grants 20DZ1100104), Science and Technology Innovation Project of Health System in Putuo District, Shanghai (ptkwws202114).
- The approval for this work were approved by the ethics committee of the Obstetrics and Gynecology Hospital Affiliated to Fudan University (2018-73).

### Author contributions
D.Y.R. proposed and designed the study and all the methods, and wrote the manuscript. J.J. proposed statistical analysis and established machine learning model. J.C. arranged and analyzed the data and proposed image segmentation. L.M. collected the ultrasound images and analyzed the data. Z.J.Q., R.Y.Y., G.Y. and W.Y.Y. provided supports for the research, and designed the method. All authors supplied comments and revised the paper.

**Data availability statement**

The data that support the findings of this study are available at the web repository of https://pan.baidu.com/s/1p9kat4pr3jFrE1jPE805wA and its extraction code can be obtained from the corresponding author upon a separate request.

**Additional Information**

All authors declare that they have no conflicts of interest.

**References**

1. Teune MJ, et al. A systematic review of severe morbidity in infants born late preterm. *Am J Obstet Gynecol.* 205, 374.e1-9 (2011)
2. Azad MB, et al. Diabetes in pregnancy and lung health in offspring: developmental origins of respiratory disease. *Paediatr Respir Rev.* 21,19-26 (2017)
3. Winn HN, Klosterman A, Amon E, Shumway JB, Artal R. Does preeclampsia influence fetal lung maturity? *J Perinat Med.* 28, 210-3 (2000)
4. Yang X, Li Y, Li C, Zhang W. Current overview of pregnancy complications and live-birth outcome of assisted reproductive technology in mainland China. *Fertil Steril.* 101, 385-91 (2014)
5. Grenache DG, Gronowski AM. Fetal lung maturity. *Clin Biochem.* 39, 1-10 (2006)
6. Bonet-Carne E, et al. Quantitative ultrasound texture analysis of fetal lungs to predict neonatal respiratory morbidity. *Ultrasound Obstet Gynecol.* 45, 427-33 (2015)
7. Burgos-Artizzu XP, Perez-Moreno Á, Coronado-Gutierrez D, Gratacos E, Palacio M. Evaluation of an improved tool for non-invasive prediction of neonatal respiratory morbidity based on fully automated fetal lung ultrasound analysis. *Sci Rep.* 9, 1950 (2019)
8. Li F, et al. Using ultrasound features and radiomics analysis to predict lymph node metastasis in patients with thyroid cancer. *BMC Surg.* 20, 315 (2020)
9. Hu HT, et al. Ultrasound-based radiomics score: a potential biomarker for the prediction of microvascular invasion in hepatocellular carcinoma. *Eur Radiol.* 29, 2890-2901 (2019)
10. Yao Z, et al. Preoperative diagnosis and prediction of hepatocellular carcinoma: Radiomics analysis based on multi-modal ultrasound images. *BMC Cancer.* 18, 1089 (2018)
11. Johnson LM, Johnson C, Karger AB. End of the line for fetal lung maturity testing. Clin Biochem. 71, 74-76 (2019)

12. Sengupta S, et al. Adverse neonatal outcomes associated with early-term birth. JAMA Pediatr. 167, 1053-9 (2013)

13. Hrabalkova L, Takahashi T, Kemp MW, Stock SJ. Antenatal Corticosteroids for Fetal Lung Maturity - Too Much of a Good Thing? Curr Pharm Des. 25, 593-600 (2019)

14. Eriksson L, Haglund B, Ewald U, Odlin V, Kieler H. Health consequences of prophylactic exposure to antenatal corticosteroids among children born late preterm or term. Acta Obstet Gynecol Scand. 91, 1415-21 (2012)

15. Alexander N, et al. Impact of antenatal synthetic glucocorticoid exposure on endocrine stress reactivity in term-born children. J Clin Endocrinol Metab. 97, 3538-44 (2012)

16. Jobe AH, Goldenberg RL. Antenatal corticosteroids: an assessment of anticipated benefits and potential risks. Am J Obstet Gynecol. 219, 62-74 (2018)

17. Rodriguez A, et al. Antenatal corticosteroid therapy (ACT) and size at birth: A population-based analysis using the Finnish Medical Birth Register. PLoS Med. 16, e1002746 (2019)

18. Kim SM, et al. Acceleration time-to-ejection time ratio in fetal pulmonary artery predicts the development of neonatal respiratory distress syndrome: a prospective cohort study. Am J Perinatol. 30, 805-12 (2013)

19. Bahmaie A, et al. Serial fetal lung volume measurement using three-dimensional ultrasound. Ultrasound Obstet Gynecol. 16, 154-8 (2000)

20. Osada H, et al. Application of lung volume measurement by three-dimensional ultrasonography for clinical assessment of fetal lung development. J Ultrasound Med. 21, 841-7 (2002)

21. Serizawa M, Maeda K. Noninvasive fetal lung maturity prediction based on ultrasonic gray level histogram width. Ultrasound Med Biol. 36, 1998-2003 (2010)

22. Cosmi EV, Anceschi MM, Cosmi E, Piazze JJ, La Torre R. Ultrasonographic patterns of fetal breathing movements in normal pregnancy. Int J Gynaecol Obstet. 80, 285-90 (2003)

23. Prakash KN, Ramakrishnan AG, Suresh S, Chow TW. Fetal lung maturity analysis using ultrasound image features. IEEE Trans Inf Technol Biomed. 6, 38-45 (2002)

24. Palacio M, et al. Fetal Lung Texture Team. Prediction of neonatal respiratory morbidity by quantitative ultrasound lung texture analysis: a multicenter study. Am J Obstet Gynecol. 217, 196.e1-196.e14 (2017)

25. Du Y, et al. Application of ultrasound-based radiomics technology in fetal-lung-texture analysis in pregnancies complicated by gestational diabetes and/or pre-eclampsia. Ultrasound Obstet Gynecol. 57, 804-812 (2021)

26. Ahmed B, Konje JC. Fetal lung maturity assessment: A historic perspective and Non-invasive assessment using an automatic quantitative ultrasound analysis (a potentially useful clinical tool). Eur J Obstet Gynecol Reprod Biol. 258, 343-347 (2021)
27. International Association of Diabetes and Pregnancy Study Groups Consensus Panel, et al. International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. *Diabetes Care.* 33, 676-82 (2010)

28. Tranquilli AL, et al. The classification, diagnosis and management of the hypertensive disorders of pregnancy: A revised statement from the ISSHP. *Pregnancy Hypertens.* 4, 97-104 (2014)

29. Consortium on Safe Labor et al. Respiratory Morbidity in Late Preterm Births. *JAMA.* 304, 419–25 (2010).

30. Loh WY, He X, Man M. A regression tree approach to identifying subgroups with differential treatment effects. *Stat Med.* 34, 1818-33 (2015).

31. Kang Q, Chen X, Li S, Zhou M. A Noise-Filtered Under-Sampling Scheme for Imbalanced Classification. *IEEE Trans Cybern.* 47, 4263-4274 (2017)

**Figures**

**Figure 1**

*Classification performance assessed by 10-fold cross-validation performed on fetal lungs.*

A and a: Results of training set; B and b: Results of testing set; A and B: Confusion matrix; a and b: ROC curves

**Figure 2**

*Flowchart of the selection of the study population*

NRM= Neonatal respiratory morbidity

**Figure 3**

*Fetal human lung ultrasound images with defined regions of interest*

a and a1 are images of training set, b and b1 are images of test set. (a, a1) Image of left lung at 36+1 weeks in woman with pre-eclampsia (PE). Cesarean delivery occurred 2 days after ultrasound examination, and baby was diagnosed with transient tachypnea of the newborn. The risk probability derived from the model is 0.829 (>0.5). (b, b1) Image of left lung at 34+0 weeks in woman with gestational diabetes mellitus (GDM). Cesarean delivery occurred immediately after ultrasound
examination, and baby was diagnosed with respiratory distress syndrome. The risk probability derived from the model is 0.843 (>0.5).

**Figure 4**

**Workflow of the fetal lung texture analysis system based on ultrasound-based radiomics technology**

Stage I: Fetal-lung US image (four-chamber view) was segmented manually. Stage II: 430 high-throughput radiomics features were extracted from each segmented image. Then features were selected by permuting out-of-bag data feature of random regression forest. And the prediction model was built using RUSBoost (Random under-sampling with AdaBoost). Finally, the risk probability of NRM in each fetal lung image was obtained and divided into the high-risk group or low-risk group. Stage III: According to results of confusion matrix, performance of prediction model was assessed by sensitivity (SENS), specificity (SPEC), accuracy (ACC) and area under receiver-operating-characteristics (ROC) curve. ROI= Region of interest; US= Ultrasound; NRM= Neonatal respiratory morbidity; Sens= Sensitivity; Spec= Specificity; Acc= Accuracy; ROC= Receiver operating characteristics.