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Quantitative ultrasound texture analysis of fetal lungs to predict neonatal respiratory morbidity

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KEYWORDS: fetal lung maturity; image quantitative analysis; neonatal respiratory morbidity; texture analysis

ABSTRACT

Objective *To develop and evaluate the performance of a novel method for predicting neonatal respiratory morbidity based on quantitative analysis of the fetal lung by ultrasound.*

Methods *More than 13 000 non-clinical images and 900 fetal lung images were used to develop a computerized method based on texture analysis and machine learning algorithms, trained to predict neonatal respiratory morbidity risk on fetal lung ultrasound images. The method, termed 'quantitative ultrasound fetal lung maturity analysis' (quantusFLM™), was then validated blindly in 144 neonates, delivered at 28 + 0 to 39 + 0 weeks' gestation. Lung ultrasound images in DICOM format were obtained within 48 h of delivery and the ability of the software to predict neonatal respiratory morbidity, defined as either respiratory distress syndrome or transient tachypnea of the newborn, was determined.*

Results *Mean (SD) gestational age at delivery was 36 + 1 (3 + 3) weeks. Among the 144 neonates, there were 29 (20.1%) cases of neonatal respiratory morbidity. Quantitative texture analysis predicted neonatal respiratory morbidity with a sensitivity, specificity, positive predictive value and negative predictive value of 86.2%, 87.0%, 62.5% and 96.2%, respectively.*

Conclusions *Quantitative ultrasound fetal lung maturity analysis predicted neonatal respiratory morbidity with an accuracy comparable to that of current tests using amniotic fluid. Copyright © 2014 ISUOG. Published by John Wiley & Sons Ltd.*

INTRODUCTION

Neonatal respiratory morbidity, defined as respiratory distress syndrome or transient tachypnea of the newborn, is the leading cause of mortality and morbidity associated with prematurity[1,2]. Neonatal respiratory morbidity is not restricted to very preterm births and remains high among late-preterm and early-term infants born before 39 weeks' gestation[3–5]. Fetal lung maturity (FLM) is determined mainly by pulmonary surfactant and it can only be assessed with laboratory tests on amniotic fluid[6–10]. The need for amniocentesis has resulted in a decline in the use of this information clinically. The non-invasive prediction of FLM by fetal lung ultrasound images has been attempted for a quarter of a century by means of gray-level measurements, lung tissue motion and relative features of lung-to-placenta or -liver images, among others[11–16]. These studies revealed a good correlation with respiratory morbidity, but the diagnostic accuracy was inadequate for clinical use.

Over the years, powerful quantitative techniques for ultrasound image analysis have been developed thanks to improvements in computer capacity and image resolution[17]. Specifically, texture analysis approaches are computerized methods that can analyze medical images and identify subtle changes in the aspect, or texture, that are invisible to the human eye[18]. These textural patterns can then be used to train algorithms to predict clinical information. Recent studies have demonstrated that texture analysis of fetal lung ultrasound images is able to identify patterns of features that correlate strongly with gestational age[19], or with the results of FLM tests on amniotic fluid[20]. These studies provided a proof of concept of the potential of texture-based methods, but

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common problems of other quantitative imaging methods remained, such as the lack of robustness of blind testing due to variable acquisition conditions. To date, the ability of texture analysis of fetal lung ultrasound images to predict blindly the risk of neonatal respiratory morbidity has not been demonstrated.

To address these limitations, we have developed a new method termed 'quantitative ultrasound fetal lung maturity analysis' (quantusFLM™), which combines various image texture extractors and machine learning algorithms. In this study, we describe the basic principles of this novel method and the results of a validation study to predict blindly the risk of neonatal respiratory morbidity.

METHODS

A novel quantitative ultrasound fetal lung maturity analysis was planned to offer automatic assessment of the risk of neonatal respiratory morbidity using an ultrasound image of the axial section of the fetal thorax at the level of the four-chamber view of the fetal heart. quantusFLM was designed specifically to be composed of two modules, a texture feature extractor and a classifier. The latter uses information from the extracted features to assess the risk of respiratory morbidity (Figure 1). The performance of the algorithm was then validated using blind samples in order to evaluate its potential for use in clinical practice.

The first aim was to develop a textural feature extractor module that showed the highest robustness when tested using images acquired under different conditions. This module is used to compact all the information contained in an image (or a region of an image) to a few features that contain relevant information. For a given application, a feature extractor module obtains the relevant information of an image. In this way, it can represent the information conveyed by the pixels of an image by a much more compact, application-dependent set of values. Features should be invariant to clinical acquisition conditions such as changes in lighting, shadows, rotation or resolution due to lack of accessibility and control over the fetal position during the image acquisition procedure. The region of interest (ROI) for the analysis is the region corresponding to fetal lung tissue, which is delimited manually by the operator. Hence, the feature extractor module must be invariant to the shape and size of the ROI.

Different existing methods for image texture extraction based on wavelets, co-occurrence matrix, histogram gradients, binary patterns, scale and rotation-invariant features methods and standard first- and second-order statistical measures were evaluated[21–26]. Our previously reported method for feature extraction, AQUA[27], was also tested in these series of experiments, but was discarded after the first round of experiments owing to poor robustness with respect to image variability. For each different extractor method, the process may be considered to be robust when the same or similar features are obtained for the same image acquired under different conditions. Robustness is demonstrated within a certain range, since certain acquisition parameters can be controlled to some degree (for instance, minimum ROI size or shadows). Moreover, to ensure the feasibility of quantusFLM, the method should not require an area bigger than 400 pixels to extract robust features.

OUTEX[28] and PHOTEX[29] databases, composed of texture images acquired using different controlled parameters such as illumination, spatial resolution and rotation angles, were used for this purpose. A total of 13 171 images were used for illumination and rotation experiments and 11 178 were used for resolution ones. Each of these images was divided automatically into 25 non-overlapping equal-sized images and into 30 overlapping different-sized regions to test the robustness with respect to the ROI. Affinity and measures such as correlation, city block, Chebyshev or Euclidean distance, were used to evaluate the performance of the methods tested.

A newly developed feature extractor was then further refined and tuned up using real fetal lung ultrasound scans. The images used were a set of 957 samples obtained in a

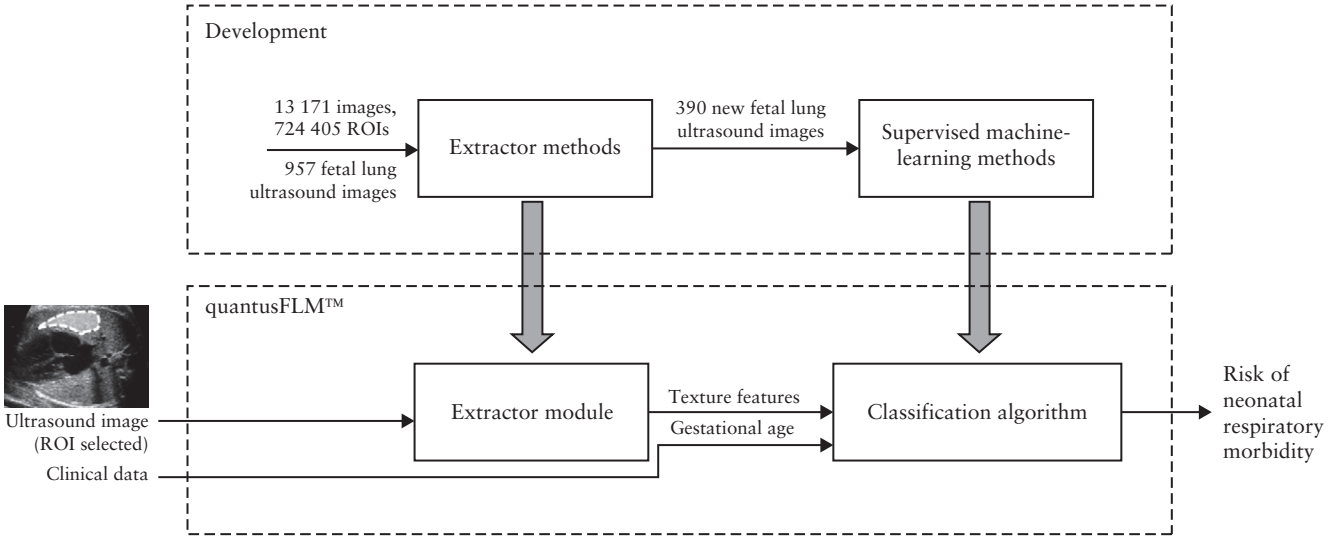

Figure 1 Diagram summarizing quantusFLM™ development and final algorithm. ROI, region of interest.

previous study[19]. Using real lung images was critical for determining the final combination of textural features in a manner that maximizes the robustness of the extracted features under those variations that occur in fetal lung ultrasound acquisition in clinical practice. Over 7 billion computerized experiments were performed to construct the quantusFLM feature extractor module, which combines the features that have been shown to be invariant to geometric and photometric transformations (under the range of conditions commonly used for acquisition).

The classification algorithm must combine the features obtained with the first module to predict the occurrence of neonatal respiratory morbidity. Different supervised machine learning methods, including regression models, classification trees and neural networks, were trained to combine the appropriate subset of features in order to identify those images that contain the relevant information needed to classify fetuses as having a high or low risk of respiratory morbidity[30–34]. The final quantusFLM classification algorithm is a sequence of various machine learning steps that combines the textural features selected (previously obtained with the extractor module) with clinical data (gestational age) to generate the estimate. The parameters of this model were estimated and tuned up using 390 fetal lung ultrasound images that were obtained prospectively from a cohort of women with singleton pregnancies at between 24 + 6 weeks' and 41 + 6 weeks' gestation. The cases that were used for training the algorithm had not been used in any previous study. Lung ultrasound scans were obtained within 48 h of delivery, and the occurrence of neonatal respiratory morbidity was recorded. Ethical board review approval was obtained (ID 2013/8892) and informed consent was given in all cases, both for constructing the algorithm and for validating it. The final algorithm combined hundreds of textural features associated with the occurrence of neonatal morbidity. The theoretical diagnostic performance achieved was: accuracy, 87% (95% CI, 82–90%); sensitivity, 91% (95% CI, 77–98%); specificity, 86% (95% CI, 82–90%); positive predictive value, 47% (95% CI, 35–59%); and negative predictive value, 98% (95% CI, 96–99%).

Validation of the algorithm was carried out at the Maternal–Fetal Medicine Department at Hospital Clinic Barcelona. The validation group consisted of new cases, recruited prospectively for the purposes of this study until the sample size fixed for the validation ($n = 150$), according to the study design, had been reached. In this validation study, the population included singleton pregnancies with gestational ages between 28 + 0 and 39 + 0 weeks. Validation samples were not used for the generation of the algorithm or in other previous studies.

Pregnant women who were scheduled for delivery, or at risk of delivery, within 48 h were considered eligible. This included patients scheduled for elective delivery or Cesarean section, or patients with pregnancy complications including threatened preterm labor, rupture of membranes or various pregnancy complications, mainly pre-eclampsia and intrauterine growth restriction. Multiple pregnancies, and those with fetal structural or chromosomal anomalies, were considered non-eligible. In all pregnancies, gestational age was calculated based on the crown–rump length at first-trimester ultrasound examination. At enrollment, an ultrasound scan of the fetal lungs was obtained but only patients actually delivering within 48 h were finally included in the study. Maternal baseline features and neonatal outcomes were recorded prospectively. As already mentioned, neonatal respiratory morbidity was defined as respiratory distress syndrome or transient tachypnea of the newborn. Respiratory distress syndrome was defined as respiratory symptoms (e.g. grunting, flaring, tachypnea, retractions) or a need for supplemental oxygen, together with compatible chest radiography findings and admission to the neonatal intensive care unit for respiratory support. Transient tachypnea of the newborn was determined by chest radiography and clinical diagnosis established by the clinician in charge[3].

Ultrasound images were obtained by clinicians using a pre-established acquisition protocol at the day assessment unit of the department. An axial section of the fetal thorax at the level of the four-chamber view of the fetal heart was acquired (Figure 2). Images were obtained with either Siemens Sonoline Antares (Siemens Medical Systems, Malvern, PA, USA) or Voluson 730/830 Pro (GE Healthcare Ultrasound, Milwaukee, WI, USA) ultrasound equipment, with 3–7.5-MHz curved linear transducers. For purposes of validation, the preset used to perform the ultrasound scan did not contain any type of post-processing options, such as image smoothing options, nor any Doppler measurements, calipers or pointers. The use of tissue harmonic imaging, and adjustment of image settings such as gain, frequency and time-gain compensation, were at the discretion of the physician performing the ultrasound scan. Images were collected digitally in the original Digital Imaging and Communication in Medicine (DICOM) format and stored for offline analysis.

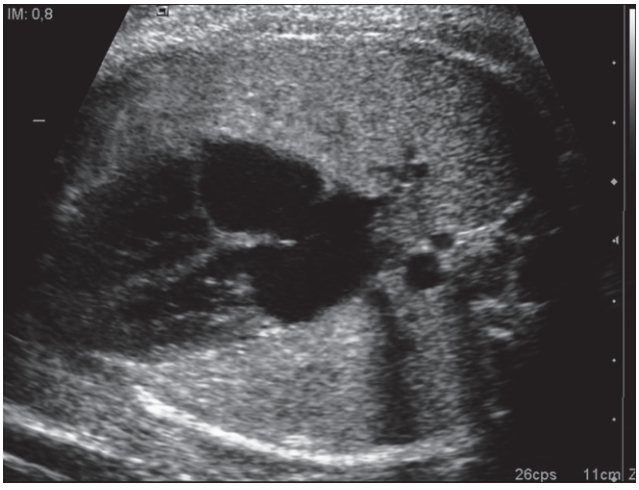

Figure 2 Standard axial section ultrasound image of the fetal thorax in the four-chamber view, as used for image analysis to identify neonatal respiratory morbidity.

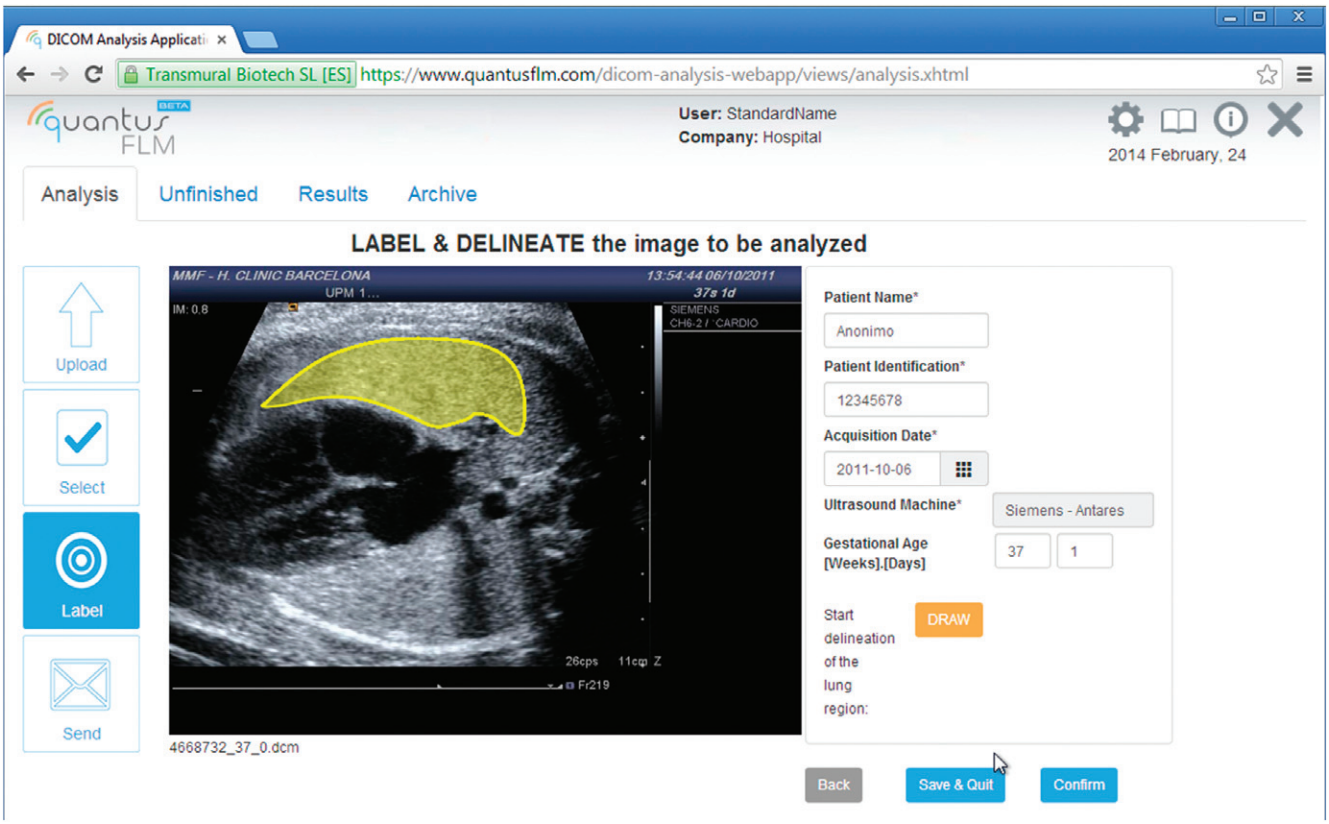

Figure 3 Platform delineation screen showing manual delineation of the region of interest (yellow shading) in the ultrasound image of the lung, proximal to the transducer.

All DICOM images were inspected for quality control by two members of the research team (A.P-M. and E.B-C.). Images were discarded if the lung area contained calipers or obvious acoustic shadows created by bony structures. Images that passed the quality criteria were processed by clinicians (T.C. and M.P.) using specific software that enabled the delineation of the ROIs for analysis. Delineation aimed to include the largest possible area of the fetal lung proximal to the transducer (Figure 3). Care was taken to delineate only lung tissue, avoiding the heart, great vessels and surrounding areas. In order to ensure the robustness of the analysis, the software did not accept an ROI containing fewer than 400 pixels. The same software was used to perform the automatic analysis. Neonatal outcomes were collected (J.P.P.) and data analysis was performed by one member of the research team (J.C.R.) who had not participated in the other steps of the study.

The sample size for the study was arbitrarily established at 150 subjects, since it was estimated that this would allow the inclusion of 25–35 cases of neonatal respiratory morbidity. Descriptive statistics were performed with R language (R Foundation for Statistical Computing, Vienna, Austria)[35].

RESULTS

A total of 150 ultrasound images, obtained from different pregnancies, were analyzed in this study. After analysis of the images for quality criteria, six (4.0%) images were excluded, leaving a total of 144 images for further analysis. Baseline characteristics of the study population are given in Table 1 and perinatal outcomes of the pregnancies included are displayed in Table 2. Mean (SD) gestational age at delivery was 36 + 1 (3 + 3) weeks. There were 29 (20.1%) cases of neonatal respiratory morbidity, of which 15/29 (51.7%) corresponded to respiratory distress syndrome and 14/29 (48.3%) to transient tachypnea of the newborn.

Table 1 Baseline characteristics of 144 women with singleton pregnancy who underwent fetal lung ultrasound examination at 28–39 weeks' gestation to validate the algorithm created to identify neonatal respiratory morbidity

Characteristic	*Value*
Maternal age (years)	32.8 ± 5.7
Nulliparous	86 (59.7)
Antenatal corticosteroids administered	52 (36.1)
Gestational age at scan (weeks)	(36 + 0) ± (3 + 3)
Gestational age at scan:	
28 + 0 to 33 + 6 weeks	38 (26.4)
≥ 34 + 0 weeks	106 (73.6)

Data are given as mean ± SD or *n* (%).

Quantitative ultrasound fetal lung maturity analysis predicted neonatal respiratory morbidity with a sensitivity, specificity, positive predictive value and negative predictive value of 86.2%, 87.0%, 62.5% and 96.2%, respectively. Performance stratified by gestational age showed similar values for cases delivering at 28 + 0 to 33 + 6 weeks' gestation to the values of those delivering at 34 + 0 to 39 + 0 weeks' gestation (Table 3).

Table 2 Perinatal outcome of 144 women with singleton pregnancy who underwent fetal lung ultrasound examination at 28–39 weeks' gestation to validate the algorithm created to identify neonatal respiratory morbidity

Perinatal outcome	*Value*
Gestational age at delivery (weeks)	(36 + 1) ± (3 + 3)
Gestational age at delivery:	
28 + 0 to 33 + 6 weeks	36 (25.0)
34 + 0 to 39 + 0 weeks	108 (75.0)
Reason for delivery between 28 + 0 and 33 + 6 weeks ($n = 36$)	
Spontaneous preterm labor	12 (8.3)
Maternal/fetal conditions	24 (16.7)
Reason for delivery between 34 + 0 and 39 + 0 weeks ($n = 108$)	
Spontaneous preterm labor*	3 (2.1)
Maternal/fetal conditions*	19 (13.2)
Early-term elective delivery†	86 (59.7)
Cesarean delivery	97 (67.4)
Birth weight (g)	2644 ± 888
Umbilical artery pH < 7.10‡	6 (4.2)
5-min Apgar score < 7	0
Admission to NICU	53 (36.8)
Respiratory morbidity	29 (20.1)
Duration in NICU (days)§	25.6 ± 33.1
Neonatal death	0

Data are given as mean ± SD or *n* (%). *Between 34 + 0 and 36 + 6 weeks. †Between 37 + 0 and 39 + 0 weeks. ‡pH available for only 132 newborns. §Of those admitted. NICU, neonatal intensive care unit.

DISCUSSION

This study provides evidence that quantitative texture analysis of lung ultrasound images predicts neonatal respiratory morbidity with similar accuracy to that of current tests using amniotic fluid.

Previous studies exploring quantitative assessment of fetal lung ultrasound to predict FLM used a variety of techniques. Prakash *et al.*[12] compared ratios of fetal lung to liver image feature values, with reported accuracies ranging from 73% to 96%. La Torre *et al.*[15] correlated accurately several patterns of fetal breathing movements with fetal lung maturity tests. Tekesin *et al.*[13] evaluated the mean gray value of fetal lungs, showing a changing pattern with fetal lung development. However, no significant differences were observed beyond 32 weeks' gestation. Later, Serizawa and Maeda[14] tried to predict fetal lung immaturity by comparison of the ultrasonic gray level histogram width (GLHW) of the fetal lung and liver in 22 fetuses with respiratory distress syndrome and in 25 controls. In that study, GLHW combined with gestational age identified differences associated with the occurrence of respiratory distress syndrome, with a theoretical sensitivity of 96% and specificity of 72%. In general, previous studies have demonstrated a correlation between quantitative image analysis and FLM, but either the diagnostic accuracy was low or results were not validated blindly, preventing the implementation of quantitative image analysis to predict FLM in clinical practice.

To our knowledge, this is the first study reporting blind validation of quantitative imaging analysis software designed specifically to predict neonatal respiratory morbidity. One difference between this study and previous ones is that the software was constructed using a large number of theoretical and real images in order to address the main difficulties of quantitative analysis in practice. The first difficulty is the variability in image acquisition, which may create false associations in small sample-size studies. The texture extractor used here works with textural features selected after millions of computer tests, which are highly correlated with the ultrasound texture of the fetal lung, and are highly robust to changes in the angle of insonation and to the adjustments of image settings occurring in the real practice of fetal ultrasound. In these respects, this approach represents a huge step forward and a completely new approach in relation to our previously reported methodology, AQUA[27]. While AQUA was a useful method for demonstrating proof of principle, as a texture extractor it had important limitations in terms of robustness, which were addressed by the newly developed feature extractors of quantus-FLM. The second challenge of quantitative analysis is automation. Thus, once robust textures have been selected, automated classifiers are required, which entails very large databases of real cases to avoid spurious

Table 3 Algorithm performance for identifying neonatal respiratory morbidity on fetal lung ultrasound examination (US) in 144 singleton pregnancies, stratified by gestational-age subgroup

	Gestational age at US (weeks)		
Variable	*28 + 0 to 39 + 0* (n = *144*)	*28 + 0 to 33 + 6* (n = *38*)	*34 + 0 to 39 + 0* (n = *106*)
Neonatal respiratory morbidity (*n* (%))	29 (20.1)	21 (55.3)	8 (7.5)
True positive (*n*)	25	19	6
True negative (*n*)	100	16	84
False positive (*n*)	15	1	14
False negative (*n*)	4	2	2
Accuracy (%)	86.8	92.1	84.9
Sensitivity (%)	86.2	90.5	75.0
Specificity (%)	87.0	94.1	85.7
Positive predictive value (%)	62.5	95.0	30.0
Negative predictive value (%)	96.2	88.9	97.7

associations in the selected textural features. Again, quantusFLM represents a completely new approach, since it incorporates highly robust machine learning classification algorithms that have been trained extensively and that allowed a fully automated performance and immediate clinical use.

The performance of the proposed algorithm is comparable with that reported for tests that are currently used on amniotic fluid[36–40]. Thus, the average reported sensitivity and specificity of the lecithin/sphingomyelin ratio were 74% (range, 48–96%) and 98% (range, 81–100%), respectively. Lamellar body count has a reported sensitivity and specificity of 86% (range, 71–100%) and 86% (range, 60–100%); the phosphatidylglycerol test has a sensitivity and specificity of 91% (range, 86–94%) and 72% (range, 67–79%); and the surfactant/albumin ratio has a sensitivity and specificity of 90% (range, 83–96%) and 76% (range, 64–88%), respectively. The average sample size used in these studies was 167 (range, 28–301), which is similar to that in this study.

The results of this study open the possibility of using non-invasive approaches for the prenatal prediction of FLM. Despite improvements in clinical practice such as administration of prenatal corticoids and postnatal surfactant, respiratory morbidity remains a leading cause of neonatal morbidity and mortality in those delivered late preterm (34 + 0 to 36 + 6 weeks' gestation) and even in early term (37 + 0 to 38 + 6 weeks) gestations[3,41]. It is clear that, for some indications, delivery should occur regardless of FLM results. However, there is an open debate about the value of FLM testing in the decision-making process for relative indications or borderline clinical situations in which late-preterm or early-term delivery may seem a reasonable option but delivery could be postponed if fetal lung immaturity was assessed[2,42–44]. In fact, recent data show that approximately 1 in 15 neonates were delivered late-preterm after induction or Cesarean delivery with no recorded indication[45,46]. Determining FLM without the need for an invasive technique might have a tremendous impact on the clinical management of such cases. Aside from economic implications, avoiding the need for amniocentesis would be associated with less discomfort and fewer related complications for the patient, and controversies about indications for FLM assessment could be approached from a different perspective.

This study has some limitations that should be acknowledged. It used a single-center cohort, and image acquisition and delineation were performed by highly-trained personnel in a clinical research setting. In this study, only 4.0% images were excluded, but we acknowledge that this number could be higher with a larger number of operators and settings. However, we believe that the rate of failed acquisitions would be low with minimal training, since the axial sections used are the standard of practice for any healthcare provider trained in fetal ultrasonography. The sample size in this study was similar to those of clinical studies that validated amniotic fluid tests, but it prevented the evaluation of performance within narrow gestational-age ranges. We acknowledge that a larger sample size should be used to obtain this information. A multicenter international study to validate the results reported here is now underway.

In summary, this study provides evidence that software specifically developed for the purpose, based on quantitative texture analysis of fetal lung ultrasound images, predicts neonatal respiratory morbidity. The performance obtained was similar to that reported for commercial FLM tests using amniotic fluid. These results should be confirmed in larger multicenter studies.

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