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RESEARCH

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Which is more accurate measuring pulmonary artery resistance index or 4D lung volume for prediction of neonatal respiratory distress in preterm pregnancies?

Basma Samir Eldeeb[1], Kholoud H. El-Shourbagy[1*], Shahinaz H. El-Shorbagy[2] and Lamees M. Ghith[1]

Abstract

Background Neonatal respiratory distress syndrome (RDS) is a leading cause of neonatal respiratory failure and neonatal mortality. It is frequent in preterm infants, because deficient surfactant needed to keep the airways (alveoli) open to assist infants breathe after birth. Nonetheless, it was also seen in full-term pregnancies. Noninvasive approaches for predicting the development of neonatal respiratory distress (RD) in preterm newborns include comparing the prenatal clinical outcome with the pulmonary artery resistance index (PA-RI) and fetal lung capacity as assessed by the virtual organ computer-aided analysis (VOCAL). Our study aimed to estimate optimal cutoff values and compare measurements of fetal pulmonary artery resistance index (PA-RI) and fetal lung volume (LV) assessed by VOCAL as noninvasive measures to predict neonatal RD development in preterm pregnancies to show which is more accurate.

Results Out of the examined 147 women who delivered 147 living newborns, 59 of newborn (40.1%) developed neonatal RD. PA-RI has a higher value in 45 (76.27%), while fetal lung volume (FLV) was significantly lower in 43 (72.88%) of neonates who developed RD. Combining both measurements of PA-RI and FLV could predict all cases of RDS 59 (100%). Thirty of RDS neonates had mechanical ventilation and died (50.85%). Cutoff values of PA-RI $\geq$ 0.75 with 76.27% sensitivity, 82.95% specificity and 81.5% accuracy, whereas a cutoff of FLV $\leq$ 28 cm^3 with sensitivity of 72.88%, specificity of 65.91% and accuracy of 74.8%, for prediction of RDS. Combining both cutoffs generated a more accurate detection 100%, specificity of 65.91% and 66.3% positive predictive value (PPV) and 100% negative predictive value (NPV) and 83% accuracy.

Conclusions Both PA-RI and FLV are promising noninvasive tools which help in predicting RD fetuses with high sensitivity and specificity. PA-RI is more accurate than FLV cm^3 in prediction of neonatal RDS. Combining these parameters increases the predictive value.

Keywords Fetal lung, Doppler, Fetal pulmonary artery flow, Neonatal RD, Fetal lung volume

Background

The lungs are the last organ to develop throughout embryogenesis. The fetus starts to manufacture surfactant about 26 weeks during pregnancy. Therefore, children born before to 37 weeks of gestation may not have created sufficient surfactant to keep alveoli open, hence avoiding the development of respiratory distress

*Correspondence:
Kholoud H. El-Shourbagy
khokha_hamdy@yahoo.comc
[1] Diagnostic Radiology Department, Faculty of Medicine, Tanta University, Tanta, Egypt
[2] Departments of Obstetrics and Gynecology, Faculty of Medicine, Tanta University, Tanta, Egypt

syndrome. Furthermore, RD was detected in full-term fetuses [1].

Previously, all biochemical testing for lung maturity required an invasive technique: amniocentesis, which has considerable risks, such as preterm premature membrane rupture, placental abruption, preterm labor, fetomaternal hemorrhage and sometimes maternal or fetal death [1]. This prompted us to investigate noninvasive techniques for predicting the onset of respiratory distress syndrome in preterm newborns.

Few studies have performed to predict infant respiratory distress, using Doppler pulmonary artery blood flow in preterm-delivery patients [2]. Using the fetal pulmonary artery flow (FPAF) waveform, several neonatal RD diagnostic characteristics were discovered [3].

The pulmonary artery resistance index (PA-RI) and fetal lung volume (FLV) may be used to predict infant respiratory distress syndrome (RDS). As gestational age grows, the structural and fetal lung functional progress development correlates with a shift in the echogenicity pattern of this organ [4, 5]. Moreover, it has been shown that the waveforms of fetal pulmonary artery flow velocity change with increase in gestational age [6, 7]. Following surfactant administration, the Doppler-measured pulmonary artery pressure decreased in infants with RDS [8].

This study estimated optimal cutoff values and compared measurements of fetal PA-RI and fetal lung volume assessed by VOCAL as noninvasive measures to predict neonatal RD development in preterm pregnancies to decrease rate of neonatal morbidity and mortality.

Methods

Methodology

This prospective study was conducted from December 2019 to March 2022 after being approved from the institutional review board (code: 35811/9/22) on 147 pregnant women fulfilling the inclusion and exclusion criteria were examined. The inclusion criteria included mothers aged between 20 and 40 years; accurate gestational dating 32–36 (defined as dating by a certain last menstrual period and confirmed by first trimesteric ultrasound); singleton pregnancy; only fetuses delivered within 24 h of admission were included. Exclusion criteria were prelabor rupture of membranes; cases taking IM corticosteroids for lung maturity in the previous week; abnormal fetal growth or fetal malformation; admission-to-delivery time exceeding 24 h (to exclude increased fetal age); and associated medical disorder (HTN, autoimmune disease, diabetes mellitus "DM," etc.). Doppler findings (PA-RI) and FLV cm^3 were compared with the fetal clinical outcome.

Data collection

Women included in this study were subjected to

Full history taking includes [personal history, past history (diabetes or hypertension history)], obstetric history (stillbirth, abortion, congenital mal-formations, preterm birth, macrosomic neonate and previous gestational diabetes) and menstrual history (last menstrual period, regularity of the cycle).

Obstetric U/S: On admission, real-time 2D U/S was performed using Voluson E6 (General Electric Healthcare®, Waukesha, WI, USA). To exclude macrosomia and intrauterine growth restriction (IUGR), all available methods used to ascertain the fetal gestational age (GA) and estimated fetal weight. In addition, umbilical artery Doppler was performed to evaluate amniotic fluid index and placental location.

To measure PA-RI, structural examination of the fetal heart with a three-vessel view of fetal heart, four-chamber view: superior vena cava, pulmonary artery, and aorta was observed. Doppler flow waveforms received resistance index was measured. The measurements were taken at the level of the main pulmonary artery midway between the pulmonary valve and bifurcation of the right and left branches. The angle of insonation was within 15 degrees.

To measure fetal lung volume

FLV was calculated using three-dimensional ultrasonography. After obtaining the fetal chest longitudinal section, the three-D window, full electronic sweep, VOCAL program and manual option with 30° rotation steps were engaged. In the 3D multiplanar view, a chosen box was shown. From the peak of the lung to its base, a sketch was created. After six rotations along the longitudinal axis for each lung, the FLV is automatically computed for each lung. Same operator (experience not less than 3 years) took three FLV measurements, and the average of these values was recorded. All measures were taken with the fetus at rest and making no noticeable movements. Following-up was done in all cases after delivery.

Neonatal RDS diagnosis

*Upon delivery, we recorded the delivery route. Senior neonatologist blinded to the fetal PA-RI and fetal lung volume done neonatal resuscitation and assessment. We recorded sex of neonates, Apgar score (at 1 and 5 min) and neonatal birth weight (NBW).

*The development of RDS diagnosed by the presence of at least two of the following three criteria according to European Consensus Guidelines by:

a—Respiratory compromise evidence shortly after delivery and a persistent oxygen requirement for longer than 24 hours.

b—Response to administration of exogenous pulmonary surfactant.

c—Radiographic evidence of hyaline membrane diseases as ground glass appearance.

*The number of newborns with RD admitted to neonatal ICU was recorded.

Statistical analysis

The data were analyzed using SPSS version 15.0 (SPSS Inc, Chicago, IL, USA). Using the Student test, imaging data expressed as 95% CI and mean. The Mann–Whitney test was used to present demographic data as medians and IQR. The optimal cutoff values for PA-RI and FLV were found using ROC analysis. We analyzed the odds ratios with 95% CI, as well as the probability ratio for a positive test result, for each cutoff value. *P* was deemed statistically significant if it was equal to or less than 0.05. Multivariate logistic regression was performed.

Results

PA-RI and three-D fetal lung volume were evaluated for 185 women with preterm labor. Thirty eight women were excluded (21 were not delivered within 24 h, 6 had meconium aspiration syndrome, failure of taking accepted Doppler in 7 women, and 4 had postnatal proven neonatal sepsis) (Fig. 1). Overall, 59 out of 147 fetuses (40.14%) of neonates exhibited neonatal RDS and were admitted to ICU and 30 of them died. Table 1 illustrates basic characteristics and main outcomes.

There was a significantly difference between the predicted number of fetuses who had RDS and those who did not, as measured by either PA-RI, lung volume or a combination of the two (Table 2). In addition, a significantly difference between both RDS (+ve) and RDS (−ve) was detected regarding mode of delivery and maternal age.

GA had significantly decreased in those who developed RDS. Male babies were found to have a higher occurrence of RDS. PA-RI was considerably higher in those who developed RDS, whereas fetal lung volume had considerably decreased in those developed RDS compared to those who did not. RDS neonates had considerably lower Apgar scores at 5 min, lower birth weight and were all admitted to neonatal ICU, than did the healthy neonates ($P < 0.001$) (Table 3).

ROC curve analysis revealed a cutoff value of ≥ 0.75 for prediction of neonatal RDS, with PA-RI 82.95% specificity and 76.27% sensitivity, whereas a cutoff ≤ 28 cm^3 for fetal lung volume predicted neonatal RDS development with 65.91% specificity and 72.88% sensitivity (Figs. 2, 3). Combining both indices together yielded a more sensitive and specific predictor with 100% sensitivity, 65.91% specificity and 66.3% PPV and 100% NPV and 83% accuracy (Table 4 and Fig. 4 (ROC diagrams1-4).

After correcting for GA at delivery, a multivariable logistic regression study demonstrated that the link between fetal FLV and PA-RI and the eventual RDS development remained significant.

Discussion

Neonatal RDS is defined as respiratory failure that occurs after birth due to the absence of lung surfactant, which is required to prevent alveolar collapse. The introduction of prenatal steroids and exogenous surfactant improved the outcomes of RDS, which remains a leading cause of infant morbidity and death [9].

According to global studies, the neonatal RDS incidence born before 30 weeks of gestation is 50%, and this incidence decreases with increasing gestational age, from around 60 to 80% in babies born between 26 and 28 weeks to approximately 15 and 30% in those born between 32 and 36 weeks [10].

This comes in agreement with our study as premature newborns included in our study who developed RD had significant lower gestational age (GA). Our study showed also that both gestational age and fetal weight were significantly lower and were inversely proportion to those who developed neonatal RDS. This is similar to the findings of the previous reports [11]**.** Our study also showed that RDS was more common in male fetuses. This is in accordance to the previous researcher's, who found a higher occurrence of male babies in RDS [12].

There were statistically significant variations in the predicted number of fetuses with and without RDS, depending on whether PA-RI, lung capacity or both were assessed. PA-RI was statistically substantially greater (mean 0.81), although fetal lung capacity had considerably decreased among those with RDS. This corresponded with previous research by Laban et al. [13]. The RDS fetuses in this study had considerably lower Apgar scores at 1 and 5 min, lower birth weight and were admitted to NICU, than did the healthy neonates ($P < 0.001$). This came in line with the findings of Moety et al. [11].

The main pulmonary artery RI evaluation revealed greater values in newborns with RDS, with a cut point of PA-RI ≥ 0.75 with sensitivity, specificity and accuracy of 76.27, 82.95 and 81.5 percent, respectively. This is consistent with the results of Laban et al. [13], who established a cutoff value of > 0.77 for predicting newborn RDS in preterm infants using the pulmonary artery resistance index. Moety et al. [11] developed a

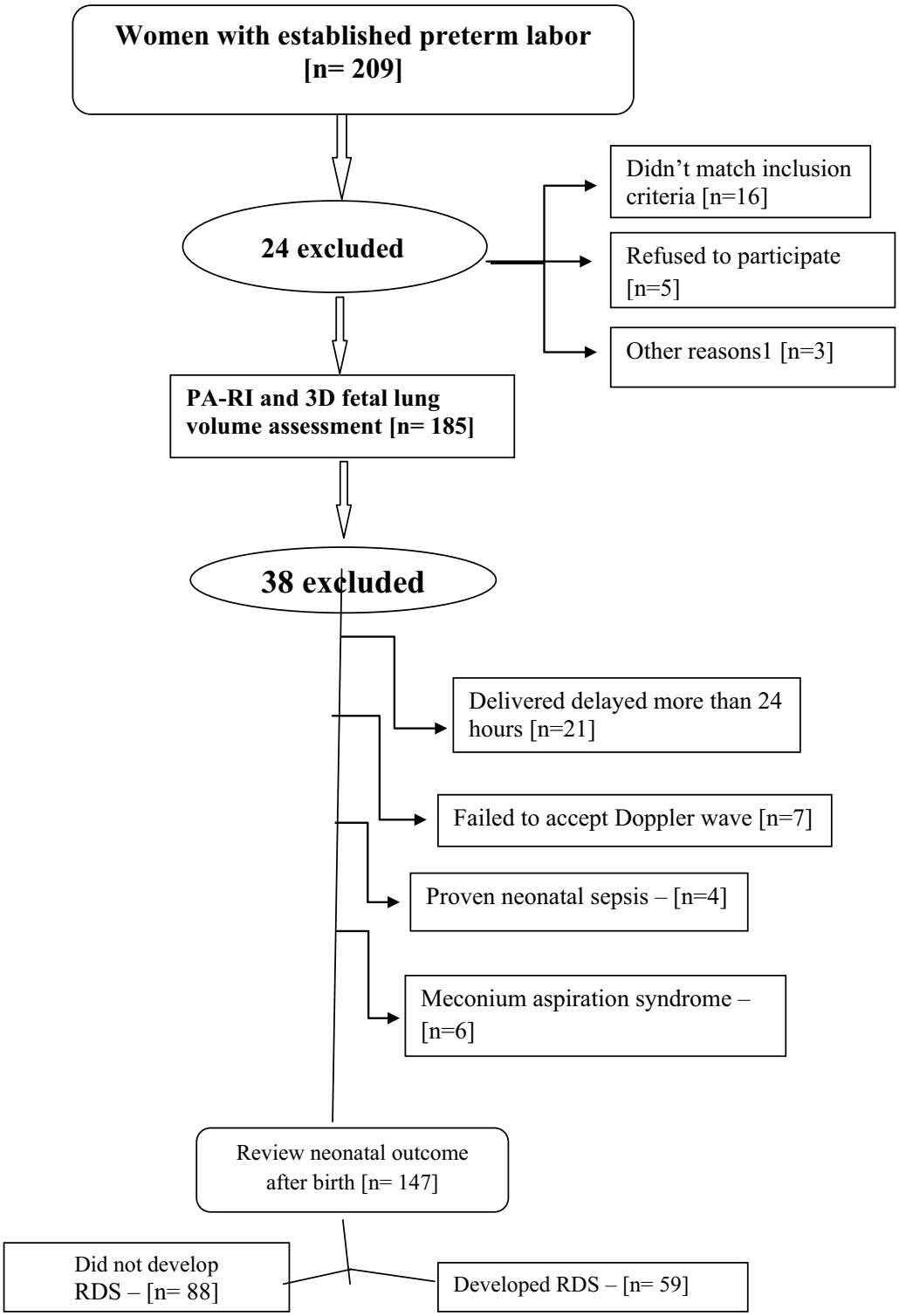

Fig. 1 The process of handling of the study population

Table 1 Demographic data of the included women regarding (maternal age, gestational age, and mode of delivery, PA-RI, lung volume and fetal outcome)

Baseline characteristics				
Maternal age	Range	20	–	38
	Mean ± SD	29.871	±	5.906
GA	Range	32	–	36
	Mean ± SD	33.789	±	1.536
Mode of delivery	Normal	74		50.34
	Cesarean	73		49.66
PA-RI	Range	0.67	–	0.88
	Mean ± SD	0.760	±	0.060
Lung volume	Range	18.3	–	40.5
	Mean ± SD	31.633	±	7.482
BW	Range	1700	–	3100
	Mean ± SD	2213.333	±	479.078
Apgar score at 1 min	Range	3	–	9
	Mean ± SD	6.490	±	2.698
Apgar score at 5 min	Range	4	–	10
	Mean ± SD	7.007	±	2.459
RD	Developed RDS	59		40.14
	Did not develop RDS	88		59.86
Developed RDS	Grade I	21		35.59
	Grade II	14		23.73
	Grade III	16		27.12
	Grade IV	8		13.56
ICU	Yes	59		40.14
	No	88		59.86
ICU duration (days)	Range	2	–	6
	Mean ± SD	4.000	±	1.306
Neonatal mortality	No	117		79.59
	Yes	30		20.41
Need for respiratory support	No	88		59.86
	Noninvasive	29		19.73
	Mechanical ventilation	30		20.41

GA gestational age, *PA-RI* pulmonary artery resistance index, *RD* respiratory distress, *RDS* respiratory distress syndrome, *BW* body weight, *ICU* intensive care unit

cutoff value of PA-RI > 0.77, a sensitivity of 67.3% and a specificity of 43.5% for predicting newborn RDS in fetuses delivered between 34 and 36 weeks + 6 days and between 37 and 38 weeks + 6 days of gestation.

A cutoff ≤ 28 cm^3 or less successfully indicated the presence of newborn RDS with a sensitivity of 72.88 percent and a specificity of 65.50 percent. The combination of the two indices resulted in a more sensitive and specific predictor with 100% sensitivity, 65.91% specificity, 66.30% positive predictive value (PV), 100% negative predictive value (NPV) and 83% accuracy. This is comparable to the identification of RDS in full-term pregnancies by Laban et al. [14].

Limitations of study

Small number of women were collected who fulfill the inclusion and exclusion criteria. Out of 209 women, only 147 review neonatal outcome after birth. Small number of fetuses develop RDS only 59 out of 147 living fetuses.

Conclusions

Both PA-RI and FLV are promising noninvasive tools which help in predicting RDS fetuses with high sensitivity and specificity. PA-RI is more accurate than FLV cm^3 in prediction of neonatal RDS. Combining these parameters increases the predictive value.

We suggest that a fetus with a PA-RI more than or equal to 0.75 or a FLV less than or equal to 28 cm^3 be

Table 2 Comparison of predictive number for detection of RDS using either PA-RI or Lung volume or by combining both measurements

Items	RD						Chi-Square	
	Developed RDS		Did not develop RDS		Total			
	N	%	*N*	%	*N*	%	X^2	*P* value
PA-RI								
Negative	14	23.73	73	82.95	87	59.18	51.286	< 0.001*
Positive	45	76.27	15	17.05	60	40.82		
Lung volume								
Negative	16	27.12	58	65.91	74	50.34	21.259	< 0.001*
Positive	43	72.88	30	34.09	73	49.66		
Combining these parameters								
Negative	0	0.00	58	65.91	58	39.46	64.228	< 0.001*
Positive	59	100.00	30	34.09	89	60.54		

Table 3 Comparison between fetuses with and without neonatal respiratory distress (RDS)

Items		RD						*t* test	
		Developed RDS			Did not develop RDS				
								t	*P* value
Age	Range	20	–	35	22	–	38	− 2.535	0.012*
	Mean ± SD	28.390	±	6.314	30.864	±	5.429		
GA	Range	32	–	33	33	–	36	− 17.316	< 0.001*
	Mean ± SD	32.254	±	0.439	34.818	±	1.078		
Sex	Female	24 (40.6%)			42 (47.7%)			–	–
	Male	35 (59.4%)			46 (52.3%)			–	–
Chi-square		*N*		%	*N*		%	X^2	*P* value
Mode of delivery	Normal	44		74.58	30		34.09	23.158	< 0.001*
	Cesarean	15		25.42	58		65.91		
PA-RI	Range	0.73	–	0.88	0.67	–	0.79	9.781	< 0.001*
	Mean ± SD	0.806	±	0.056	0.729	±	0.039		
Lung volume	Range	18.3	–	38.5	25	–	40.5	− 5.623	< 0.001*
	Mean ± SD	27.780	±	7.373	34.216	±	6.393		
BW	Range	1700	–	1990	1900	–	3100	− 11.524	< 0.001*
	Mean ± SD	1810.169	±	111.641	2483.636	±	439.001		
Apgar score at 1 min	Range	3	–	4	8	–	9	− 69.516	< 0.001*
	Mean ± SD	3.254	±	0.439	8.659	±	0.477		
Apgar score at 5 min	Range	4	–	5	9	–	10	− 254.541	< 0.001*
	Mean ± SD	4.017	±	0.130	9.011	±	0.107		
ICU	No	0		0.00	88		100.00	64.228	< 0.001*
	Yes	59		100.00	0		0.00		
ICU duration (Days)	Range	4	–	6	2	–	3	13.560	< 0.001*
	Mean ± SD	4.763	±	0.837	2.500	±	0.509		
Neonatal mortality	No	29		49.15	88		100.00	56.219	< 0.001*
	Yes	30		50.85	0		0.00		
Need for respiratory support	No	0		0.00	88		100.00	147.000	< 0.001*
	Noninvasive	29		49.15	0		0.00		
	Mechanical ventilation	30		50.85	0		0.00		

GA gestational age, *PA-RI* pulmonary artery resistance index, *RD* respiratory distress, *RDS* respiratory distress syndrome, *BW* body weight, *ICU* intensive care unit

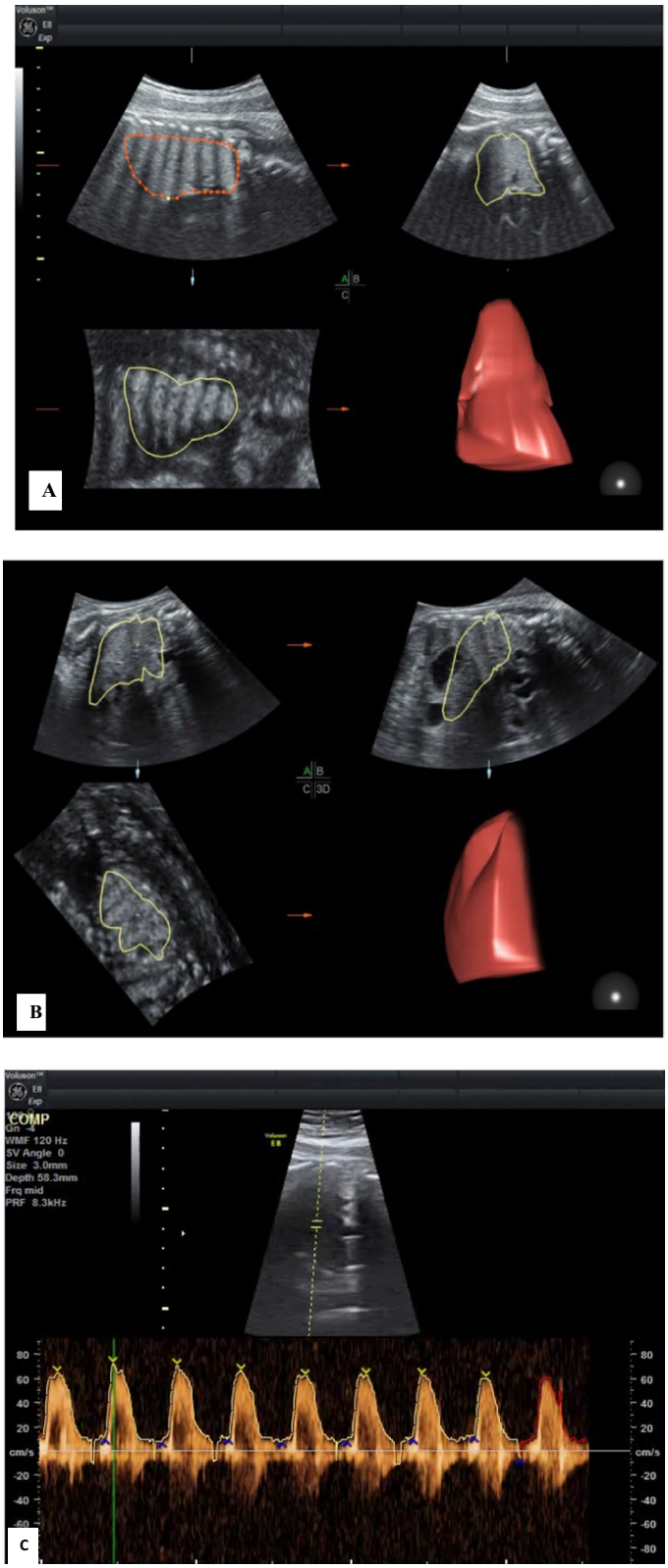

Fig. 2 **A**–**C** Lung volume of pregnant patient 23 years old, GA = (34 wks + 0 ds) calculated by 3D US using VOCAL technique showing: the volume of right lung (**A**) and left lung (**B**) 31 cm^3 and 29 cm^3, respectively. **C** The pulmonary artery resistance index (RI) of the same patient measured by pulsed Doppler RI = 0.74. (Neonate with mild RD admitted to ICU for 2 days)

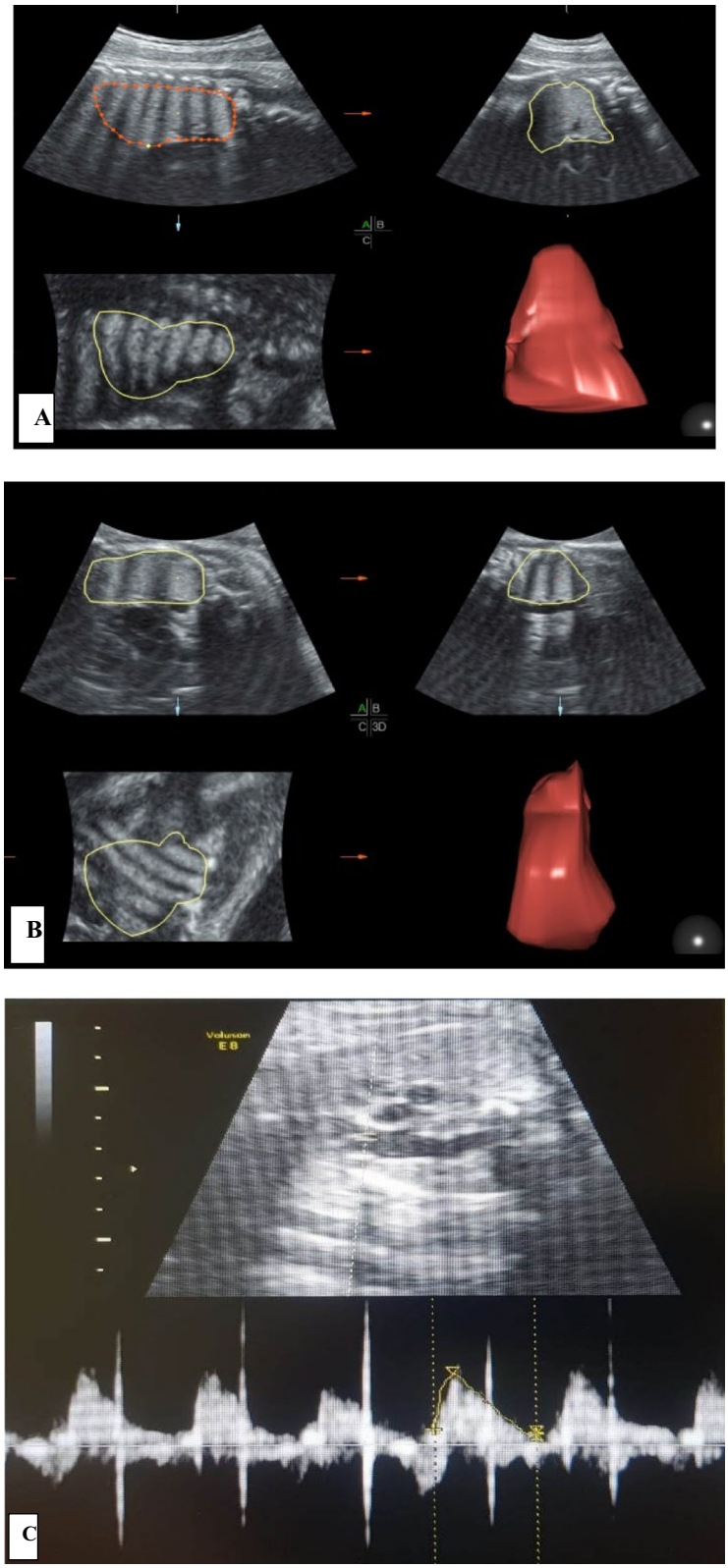

Fig. 3 **A**–**C** Lung volume of pregnant patient 29 years old, GA = (32 wks + 3 ds) calculated by 3D US using VOCAL technique showing: the volume of right lung (**A**) and left lung (**B**) 30 cm^3 and 28 cm^3, respectively. **C** The pulmonary artery resistance index (RI) of the same patient measured by pulsed Doppler RI = 0.84. (RD neonate admitted to ICU)

Table 4 Receiver operating characteristic curves (ROC) between developed RDS and did not develop RDS

ROC curve between developed RDS and did not develop RDS						
	Cutoff	**Sens**	**Spec**	**PPV**	**NPV**	**Accuracy (%)**
PA-RI	> 0.75	76.27	82.95	75.0	83.9	81.5
Lung volume	≤ 28	72.88	65.91	58.9	78.4	74.8
Combined lung volume and PA-RI	> 0.75 and ≤ 28	100.00	65.91	66.3	100.0	83

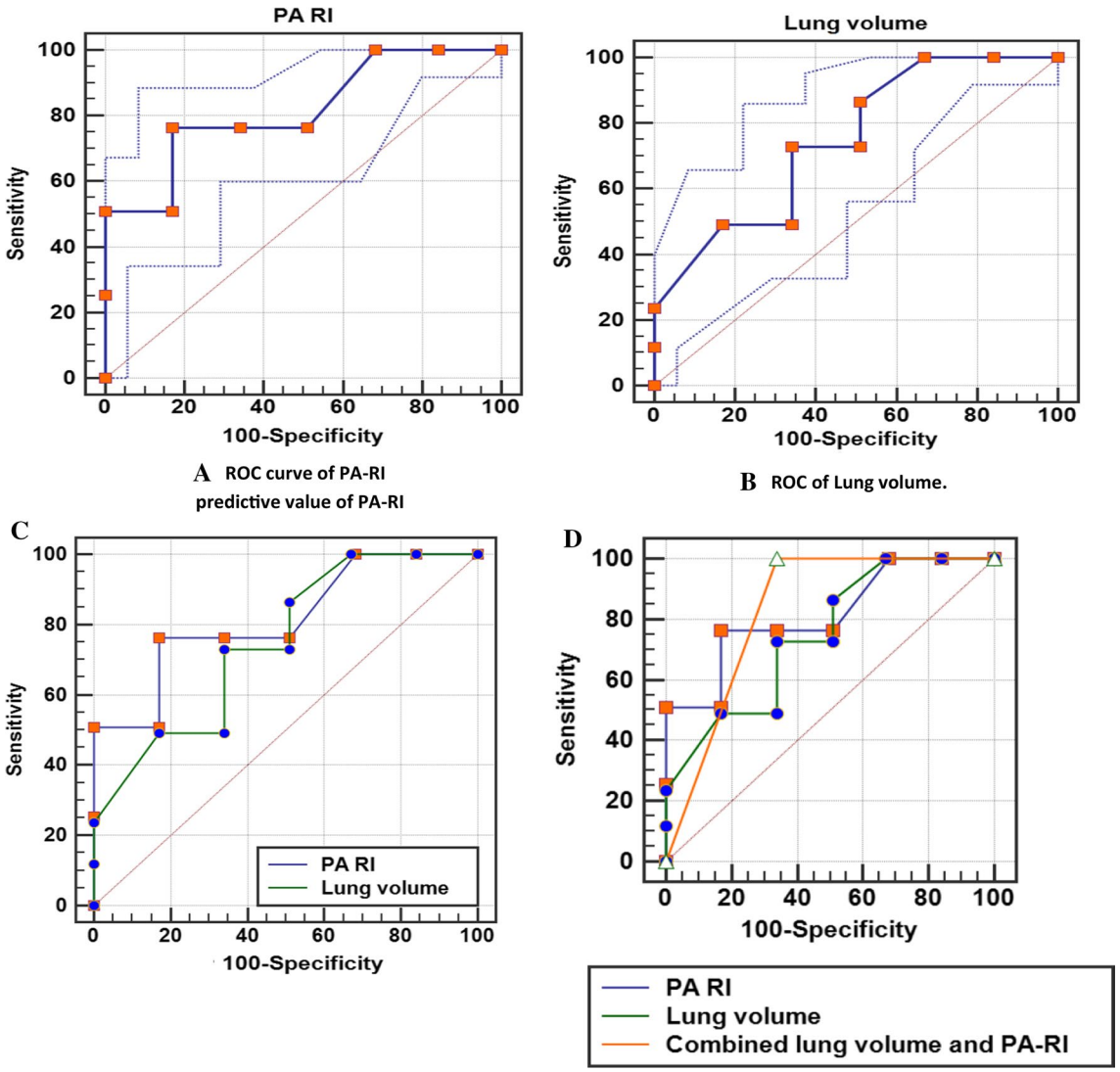

Fig. 4 Receiver operating curve (ROC) of the **A** PA-RI, **B** LV, **C** PA-RI and LV and **D** Combined PA-RI and LV for showing cutoff value predicting neonatal respiratory distress syndrome (RDS)

delivered in a hospital with respiratory support facilities and medical treatments with corticosteroids and surfactant due to the risk of newborn RDS.

Abbreviations

RDS	Respiratory distress syndrome
RD	Respiratory distress
VOCAL	Virtual organ computer-aided analysis
PA-RI	Pulmonary artery resistance index

FLV	Fetal lung volume
LV	Lung volume
PPV	Positive predictive value
NPV	Negative predictive value
FPAF	Fetal pulmonary artery flow
U/S	Ultra/sound
ICU	Intensive care unit
NBW	Neonatal birth weight
SD	Standard deviation
ORs	Odds ratios
ROC	Receiver operating characteristic curves
LR+	Likelihood ratio for a positive test result
CI	Confidence interval
IUGR	Intrauterine growth restriction

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Author contributions
BD and KH made substantial contribution to the main research idea; design of the work; acquisition, analysis and interpretation of the data; writing of the manuscript, and revision of the work. LG collected the patients, wrote the clinical picture and followed up treatments and shared in writing the manuscript and analysis of the data. Professor SH shared in substantial contribution to the main research idea; design of the work; acquisition; and interpretation of the data. All authors read and approved the final manuscript.

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Availability of data and materials
All data and materials are available.

Declarations

Ethics approval and consent to participate
This prospective interventional study was carried out following the approval of the Research Ethical Committee of Faculty of Medicine, Tanta University, from November 1, 2021 to March 31, 2022 (Approval code: 35811/9/22), on two hundred nine (209) patients with established preterm labor, collected from hospitals; ICU and out patients clinic. Twenty-four women excluded, followed by another 38 women during the course of the study. The remaining 147 pregnant women fulfilling the inclusion and exclusion criteria were examined and followed up to delivery. Overall, 59 out of 147 fetuses (40.14%) of neonates exhibited neonatal RDS, and admitted to ICU and 30 of them died.

Consent for publication
All patients included in this research gave written informed consent to publish the data contained within this study approved by Research Ethical Committee of Faculty of Medicine, Tanta University (Approval code:35811/9/22).

Competing interests
The authors declare that they have no competing interests.

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