Evaluation of Diaphragmatic Dysfunction Associated with Ventilator Weaning Failure in Neonates by Diaphragmatic Ultrasound

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ABSTRACT
Background: Mechanical ventilation is extensively used in neonatal intensive care units. However, many risk factors are associated with mortality rates in neonates on mechanical ventilation. Various techniques have been introduced to assess the weaning time from mechanical ventilation with least risks including diaphragmatic ultrasound. This study aimed at evaluating the role of diaphragmatic ultrasound in predicting failure of weaning from mechanical ventilation in both Full Term (FT) and Preterm (PT) neonates by measuring diaphragmatic excursion before extubation using and determines a cut off value for diaphragmatic excursion for expecting weaning failure.
Patients and Methods: A prospective cohort study was performed in the neonatal intensive care unit (NICU) of Mataria Teaching Hospital (MTH) from June 2018 to May 2019. All full and pre-term neonates who need mechanical ventilation from first day of admission were included major congenital anomalies, need surgical intervention, congenital diaphragmatic hernia, weaned before 72 hours, pleural effusion, hepato-splenomegaly were excluded.
Results: Neonates with low gestational age, presence of respiratory distress, longer period on mechanical ventilation and higher ventilator setting were more prone to weaning failure. Additionally, excellent sensitivity and specificity of diaphragmatic ultrasound in prediction of weaning failure in neonates especially in full term whether using excursion of right and left hemidiaphragm. **Conclusion:** Bedside ultrasound can predict weaning failure through measuring right or left diaphragmatic excursion in full term and preterm neonates.
Keywords: Weaning failure, Diaphragmatic ultrasound, Diaphragmatic excursion, Cohort study, Mataria Teaching Hospital, Neonatal intensive care unit.

INTRODUCTION
Neonatal Intensive care units have been significantly improved to decrease their morbidity and mortality rates. These results have been achieved via efficient respiratory and cardiovascular support. Mechanical ventilation can improve mortality rate in ICUs as it improves the work of breathing and attain proper gas exchange for critically ill patients [(1)]. Unfortunately, incidence of high mortality in neonatal Mechanical Ventilation (MV) has been recorded [(2)].

Despite the ventilation timing, mechanical ventilation has been associated with acute complications such as; reduced cardiac output, unintended respiratory alkalosis, amplified intracranial pressure, and gastric distension [(3)], acute lung injury (ALI) [(4)], upper airway trauma, Ventilator Associated Pneumonia (VAP), pneumothorax [(5)], and ventilator induced lung injury (VILI) [(6)] which in turn lead to weaning failure and reintubation with advanced morbidity and mortality rates[(1)]. In addition, it affects the major respiratory muscle i.e. the diaphragm by what is called Ventilator-Induced Diaphragmatic Dysfunction (VIDD) [(7)]. Failure of a spontaneous breathing trial (SBT) or the need to resume mechanical ventilation after extubation within 48 h to seven days is described as weaning failure. Successful weaning in patients requiring Prolonged Mechanical Ventilation (PMV) is low which was estimated by 38% - 78% [(8)]. Consequently, reintubation has been associated with bad consequences such as; extended duration of MV& hospital stay, and advanced mortality rate even in adults [(9)].

The ideal moment for neonatal extubation cannot be predicted by single test as most of tests are of low sensitivity and specificity [(10)], so there is a need for stronger confirmatory criteria [(11)] to detect proper timing for weaning which can decrease ventilation and hospitalization days with better outcome [(12)]. Many researches have directed toward examination of diaphragmatic muscle contraction as it accounts for 75% of lung volume during effortless respiration [(13)]. Dysfunction of diaphragm presents by non-comprehensive symptoms as lung collapse, repeated pneumonia, respiratory distress and/or unsuccessful weaning from invasive mechanical ventilation [(14)].

The pathological features associated with diaphragmatic dysfunction are disuse atrophy and microstructural changes[(15)]. From physiological point of view, diaphragmatic dysfunction describes the decrease in power of diaphragmatic muscle to create a negative intra-thoracic pressure [(12)]. The prevalence of diaphragmatic dysfunction has been reported to be double the limb muscle weakness [(16)] and as high as 80% in patients with ICU-acquired weakness entering the weaning process [(17)].

Diaphragmatic muscles in ventilated patients can be assessed by different tools; first, the maximum Static Inspiratory Pressure (PI max) but they have variable values as they are affected by lung diseases and they are not specific for diaphragmatic muscle only [(7)]. Second, stimulation of the phrenic nerve by electric or magnetic twitch [(18)]. Third, fluoroscopy, but it carries the risk of exposure to ionizing radiation, transportation of critically ill patient [(1,19)]. Unfortunately, all the previous tools need experienced personnel, highly specialized equipment and access to ICU [(20)]. Even though combination of these tests is essential for better diagnosis [(21)].

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Ultrasound can examine the shape and function of the diaphragm [(24)]. It is a bedside test which can be repeated at any time with low cost, free of ionizing radiation exposure, easy to do tool as diaphragmatic ultrasound [(22)]. Diaphragmatic excursion (DE) represents the diaphragmatic motion between expiration and inspiration status in relation to time and allows precise measurement of diaphragmatic displacement over a respiratory cycle [(14)].

The primary aim was to evaluate the role of diaphragmatic ultrasound in predicting weaning failure from mechanical ventilation in both FT and PT neonates by measuring diaphragmatic excursion before extubation. Secondary aim was to determine a cut off value for diaphragmatic excursion at which weaning failure was expected.

PATIENTS AND METHODS

This prospective cohort study was performed in the NICU of MTH from June 2018 to May 2019.

Inclusion criteria include all full and pre-term neonates who need ventilation from first day of admission. Exclusion criteria; neonates with major congenital anomalies, need surgical intervention, congenital diaphragmatic hernia, pleural effusion, hepato-splenomegaly, weaned before 72 hours.

Procedure of handling neonates:

The initial setting of ventilator was pressure control differ according to disease specific criteria using protective lung ventilation strategy. All ventilated neonates were weaned using under the following ventilator and clinical conditions; all were on Pressure Support Ventilator mode (PSV); fraction inspired oxygen of 30% positive end expiratory pressure 5mmhg, RR support was 20 with appropriate blood gas and hemodynamically stable without vasopressor and sedation. The following criteria were used to define the need for reintubation; a) respiratory acidosis (partial pressure of carbon dioxide in the arterial blood or $PaCO_2$ >50 mmHg and pH <7.25; b) significant number of apnea episodes (>6 during 6 hours); c) apnea episodes requiring resuscitation d) consistent increase (>2 hours) in the need for oxygen higher than 50% to keep SaO_2 within the desired range (92-95%) [(23)].

Sample size:

Estimated sample size for two-sample comparison of means was calculated to be 46 neonates assuming alpha error 0.05 (two-sided), power 0.80. Mean DER is 2.24 (SD 0.6) and 1.7 (SD 0.7) in successful and unsuccessful weaning groups respectively [(24)]. Sample size was calculated using STATA program version 10.

Ultrasound:

The right and left copula were examined during sleeping and at least one hour after feeding while the patient was in a semi-setting position (raising the head of the bed to a 30° angle). Diaphragmatic excursion was measured three times by a single experienced doctor to avoid variation, using a 5-8 Hz linear transducer of a Sonosite portable ultrasound machine; and a mean of the three measurements was calculated. Plenty amount of warmed gel was used on examination to delineate clear image to the three diaphragmatic layers (pleural, peritoneal membranes, and muscular layer). On M-mode study, the image of the diaphragm appears as a thick echogenic line and permits recording of diaphragmatic movement against a time curve. The transducer was placed in the right costal margin in the mid- clavicular line (liver window). The left diaphragm (splenic window) was assessed through putting the probe in the left anterior axillary line. Assessment of diaphragmatic excursion was done by assessing the respiratory diaphragmatic motion in the plane perpendicular to the diaphragm. Diaphragmatic excursion on M-mode was calculated by measuring the vertical distance between the greatest caudal descent (at the end of inspiration) & the greatest cranial elevation (at the end of expiration) of the posterior third of the diaphragm; as in figure (1).

Ethical approval:

This study was approved by the Committee of Ethics of General Organization of Teaching Hospital and Institutes (GOTHI) and informed consent was taken from the parents. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis

The collected data were coded, processed and analyzed using the SPSS (Statistical Package for Social Sciences) version 22 for Windows® (IBM SPSS Inc, Chicago, IL, USA). Descriptive statistics using mean, standard deviation (SD), median and interquartile range (IQ) were used for quantitative data and percentage for qualitative data. Two sample student's t test was used to compare means. Correlation coefficient (R^2) was calculated to study relation between two quantitative variables. Linear regression, multiple regression analysis and plot were used to determine independent factors affecting quantitative variables. Receiver operating characteristic (ROC) curve was drawn; sensitivity and specificity were calculated at different cut off values for quantitative data. The statistical significance was set at p-value $\leq$0.05.

RESULTS

A prospective cohort study included 48 mechanically ventilated neonates; 15 e full term and 33 preterm infants. Gestational age ranged from 27-41 weeks, average weight was 2.1 kg, 21 females (43.8%) and 27 were males (56.2%). Causes of ventilation were shown in figure (3). The neonates received Total Ventilation Days (TVD) of 8.4 (SD 3.6) days on pressure support ventilation (PSV) mode. The days on ventilators before first extubation were 6.94 (SD 2.75) days. Eight neonates had died (16%).

Table (1): Descriptive statistics of the included neonates.

Variable	GA (weeks)	Weight (Kg)	TVD (Days)	TFW	PIP	PEEP
Mean±SD	33.9±4.0	2.1±0.9	8.4±3.6	6.9±2.8	23.5±**3.0**	6.5±**1.5**

PIP: Peak Inspiratory Pressure; PEEP: Positive end-expiratory pressure; TVD Total ventilation days; FWD: timing of first weaning.

The median MV duration was 7 days (IQR, 4–15). The median neonatal stay was 9 days (IQR, 7–23). Patients' characteristics are summarized in Table 2. For all patients, the ventilator mode was initially set as pressure control.

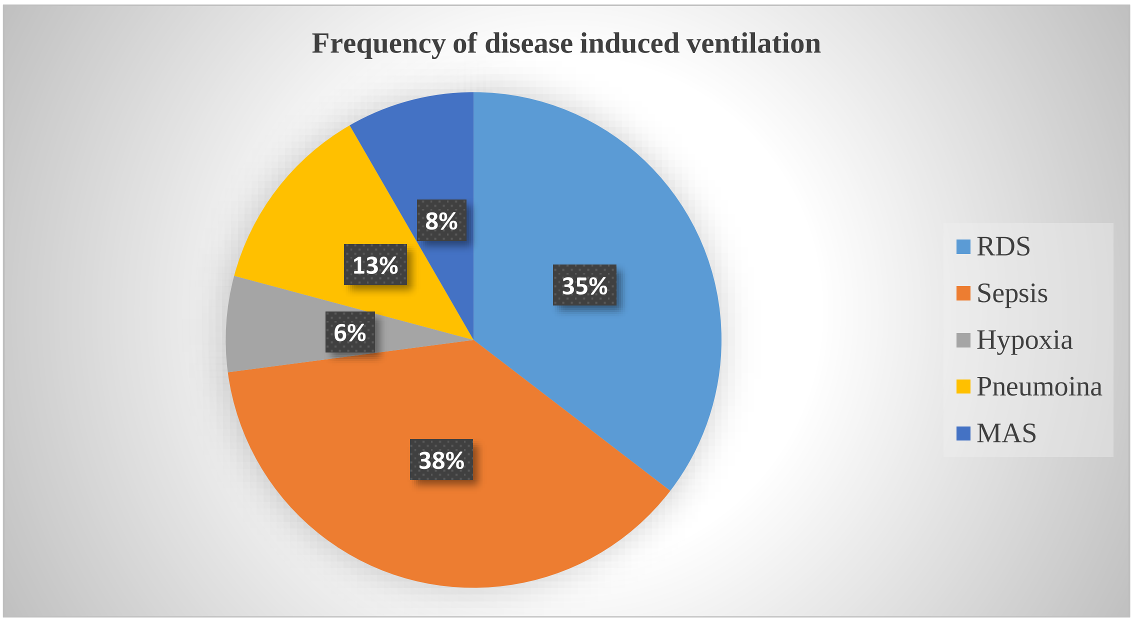


Figure (1): The distribution of the diseases among neonates who required ventilation.

Table (2): Patients clinical characteristics.

Variable	Full Term (N=15)	Pre-Term (N=33)	P value
	Mean ± SD	**Mean ± SD**	
GA(weeks)	38.9 ± 1.03	31.6 ± 2.4	<0.01
Gender:			
Male	9 (60.0%)	18 (54.5%)	>0.05
Female	6 (40.0%)	15 (45.5%)	
Weight(Kg)	3.34 ± 0.44	1.51 ± 0.46	<0.01
Diagnosis on admission (N, %)			
RDS	0	17 (51.5%)	<0.01
Pneumonia	2 (13.3%)	4 (12.1%)	>0.05
HIE	3 (19.6%)	0	<0.01
MAS	4 (26.7%)	0	<0.01
Sepsis	6 (40.0%)	12 (36.4%)	>0.05
Initial ventilator setting			
PIPP	23 ± 3.7	23.4 ± 2.6	>0.05
PEEP	6.2 ± 1.1	6.6 ± 1.7	>0.05
FiO2	66 ± 16.4	53.6 ± 17.1	<0.05
RR	50 ± 9.2	59.6 ± 7.3	<0.01
Outcome			
First weaning days	7.7 ± 1.7	6.6 ± 1.1	>0.05
TVD	9.2 ± 2.13	7.9 ± 1.6	
Mortality	3 (20%)	8 (24%)	>0.05
DER	2.8 ± 0.89	2.85 ± 0.61	>0.05
DEL	3 ± 0.7	3.1 ± 0.51	>0.05

RDS: respiratory distress syndrome; MAS: meconium aspiration syndrome; HIE: hypoxic ischemic encephalopathy; PIP: Peak Inspiratory Pressure; PEEP: Positive end-expiratory pressure; TVD: total ventilation days; DER: excursion of right. Hemi-diaphragm DEL: excursion of left hemi-diaphragmatic.

Studying factors affecting weaning failure were shown in table 3. Comparing weaning success or failure reveals a significant difference regarding gestational age respiratory distress PIP PEEP, respiratory rate days on mechanical were significantly related to weaning failure (p <0.05).

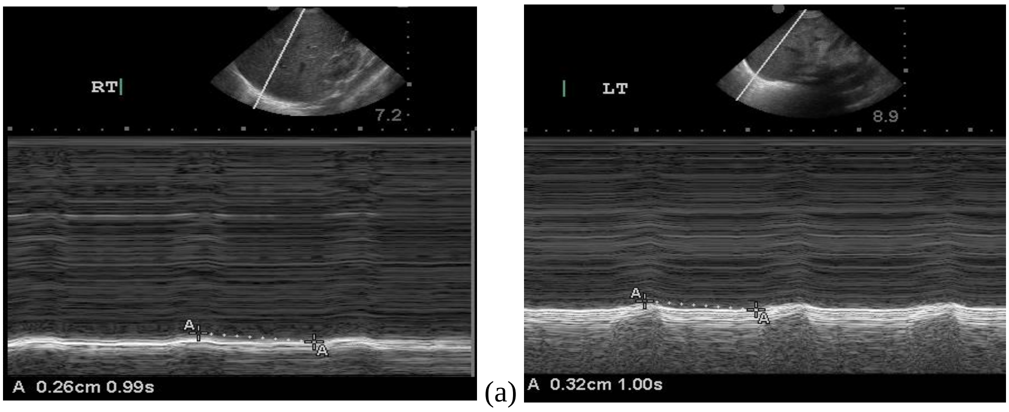
Table (3): Comparison of patients' characteristics regarding successful and failure of weaning.

Variable	Successful weaning N 23 (48%)	Failure of weaning N 25 (52%)	P value
	Mean ±SD	**Mean ±SD**	
GA	35.3 ± 3.7	32.7 ± 3.9	<0.001
Weight (Kg)	2.3 ± 0.9	1.9 ± 0.9	>0.05
Sex : Female	11 (52.4%)	10 (47.8%)	>0.05
Diagnosis on admission (N, %)			
RDS	4 (23.5%)	13 (67.5%)	<0.05
Pneumonia	5 (83.3%)	1 (16.7%)	>0.05
HIE	3 (100%)	0 (0.0%)	>0.05
MAS	2 (50%)	2 (50%)	>0.05
Sepsis	9 (50%)	9 (50%)	>0.05
Initial ventilator setting Mean ± SD			
PIPP	22.5 ± 3.2	24.5 ± 2.4	<0.05
PEEP	6 ± 1.3	6.9 ± 1.6	<0.05
FiO2	53 ± 12.4	61 ± 14.3	>0.05
RR	53.4 ± 9.2	59.6 ± 8.1	<0.05
Outcome Mean ± SD			
TVD	7.2 ± 2.9	9.4 ± 3.8	<0.05
First weaning age	6.9 ± 2.8	6.9 ± 1.6	>0.05
Mortality	3 (13%)	8 (32%)	<0.05
FT	1 (4.3%)	2 (8%)	
PT	2 (8.7%)	6 (24%)	
DER	3.6 ± 0.8	2.6 ± 0.55	< 0.00
DEL	3.4 ± 0.7	2.3 ± 0.43	< 0.003

Measuring the diaphragmatic excursion at the time of extubation was assessed and revealed no significant difference on measuring: excursion of right and left hemi-diaphragm in weaning failure group (Table 4).

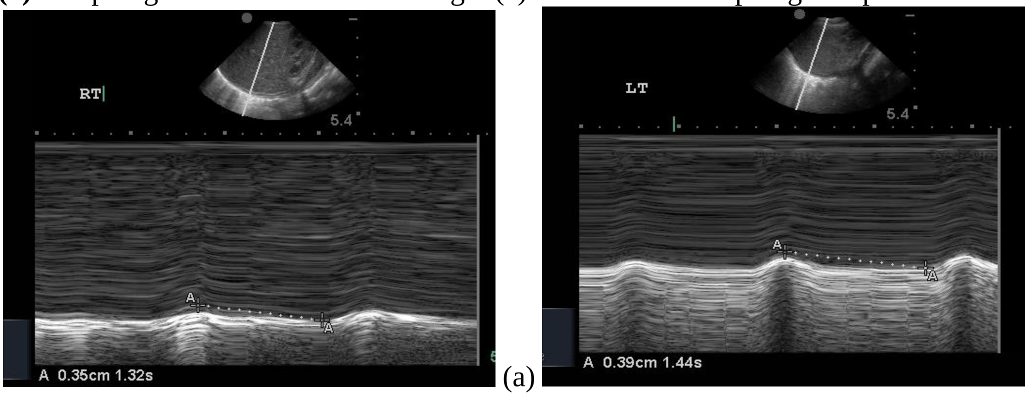
Table (4): Comparison between excursion of right and left hemi-diaphragm in weaning failure group

Variable	Mean ± SD		P value
	Before	**After**	
DEL	2.64 ± 0.45	2.6 ± 0.47	>0.05
DER	2.32 ± 0.35	2.28 ± 0.41	>0.05



(a) (b)

Figure (2): Diaphragmatic excursion on the right (a) and left hemi-diaphragm in preterm neonate.



(a) (b)

Figure (3): Diaphragmatic excursion on the right (a) and left hemi-diaphragm in FT neonate

Comparing excursion of right and left hemi-diaphragm in full and preterm neonates did not reveal significant difference with almost similar parameters (Table 5).

Table (5): Comparison between full term and preterm regarding diaphragmatic excursion before and after extubation in weaning failure group.

Variable	FT (mean ± SD)		P value	PT (mean± SD)		P value
	Before	After		Before	After	
DER	1.8 ± 0.49	1.8 ± 0.5	>0.05	2.4 ± 0.36	2.4 ± 0.37	>0.05
DEL	2.4 ± 0.7	2.36 ± 0.7	>0.05	2.7 ± 0.35	2.69 ± 0.41	>0.05

A strong positive correlation between PIP and (DER) (R^2 = 0.09) (P value of 0.04, CI: -0.22 to 0.01) as shown in (Figure 4a).

As regard correlation between DER and patients' characteristics, there was no relation between DER value and the weight of the infant, gender, cause of the ventilation, oxygen requirement, nor the PEEP. However; there was a strong significant linear correlation between the DER and the gestational age (R^2=0.75, P value of 0.012, CI: -0.06: - 0.46) as shown in (Figure 4b).

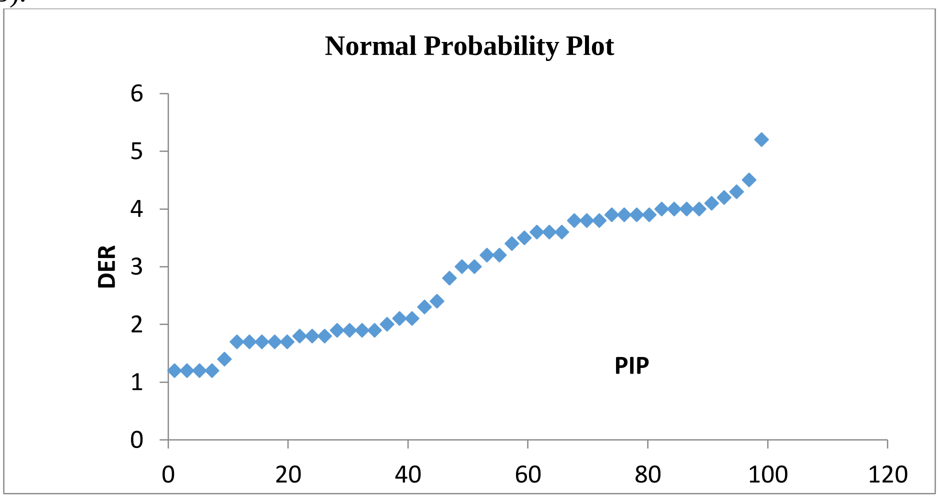


Figure (4a): The positive correlation between the PIP and DER.

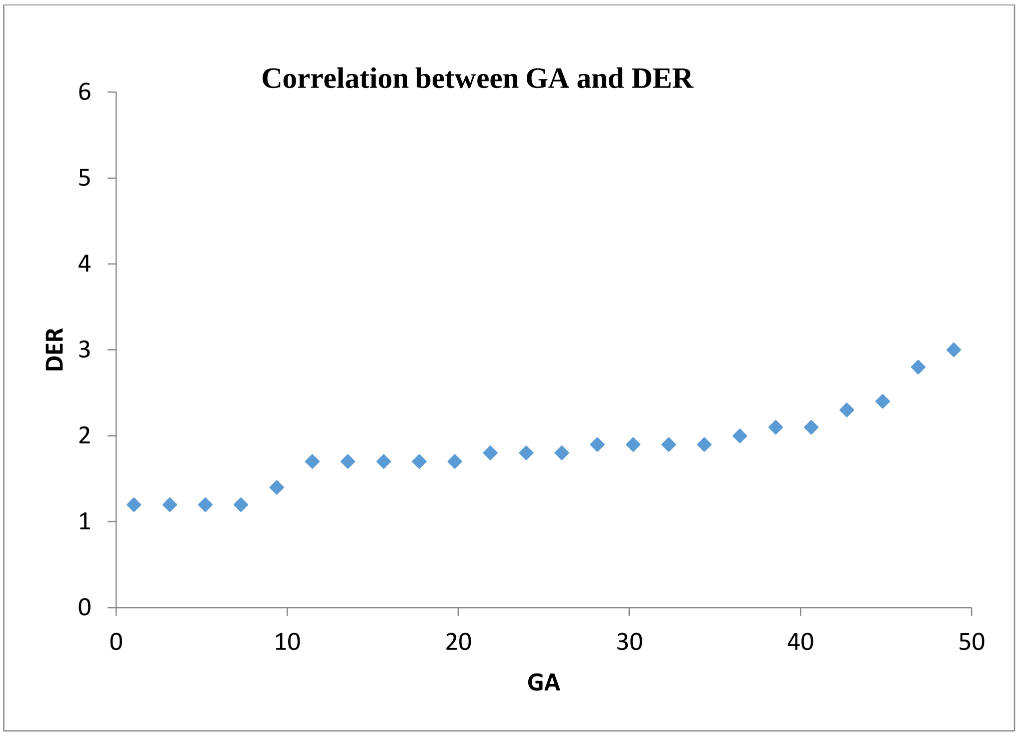


Figure (4b): Linear regression between GA and DER.

Results of multiple regression analysis using the diaphragmatic excursion on the right side was used as dependent variable and gestational age, weight, gender, disease type, PIP, and PEEP as independent variables were shown in table 6.

Table (6): Multiple regression analysis for factors affecting DER

Variable	Coefficients	P-value
Intercept	-0.12	0.98
Weight	-0.73	0.17
FW	0.06	0.35
PIP	-0.17	0.05
PEEP	0.180	0.33
GA	0.20	0.13
Gender	0.09	0.79
Cause	0.14	0.27

Sensitivity and specificity: Receiver operating characteristic (ROC) curve demonstrated an excellent sensitivity and specificity in detecting weaning failure in Full and preterm neonates whether using DEL or DER as presented in figures 5a and 5b.

Table (7): Cut off values for detection of weaning failure in Full term neonates:

Variable	Full term			Preterm	
AUC	Sensitivity	Specificity	AUC	Sensitivity	Specificity
DER (2.7)	100%	90%	DER (2.4)	70%	85%
DEL (2.55)	60%	90%	DEL (3.3)	70%	85%

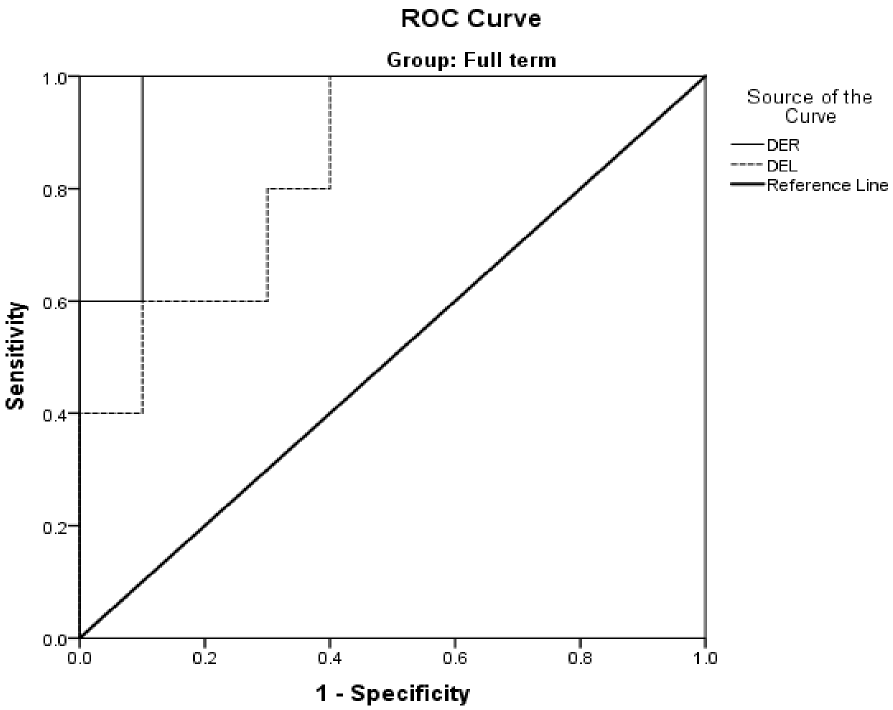


Figure (5a): Sensitivity and specificity of weaning failure in Full term neonates in pre-term neonates.

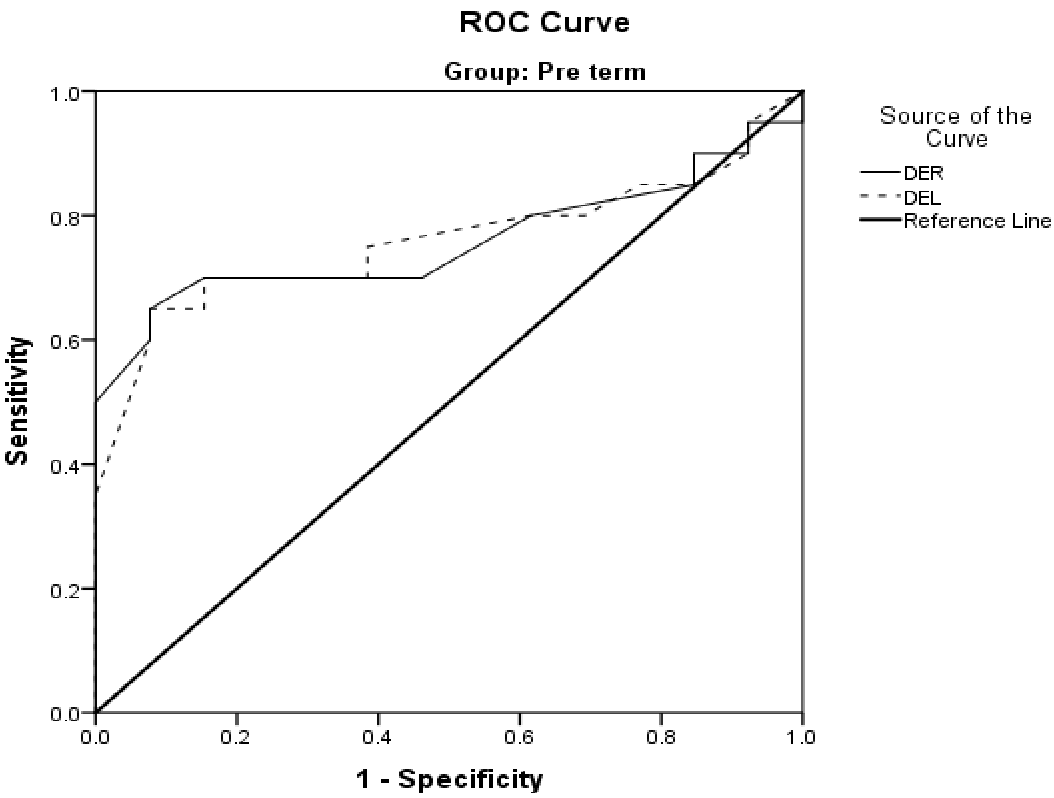


Figure (5b): Sensitivity and specificity of weaning failure.

AUC for DEL= 0.84, AUC for DER=0.96 AUC for DEL= 0.76, AUC for DER=0.75

DISCUSSION

Weaning from MV is a major problem up to fifth to half of preterm have weaning failure[14] which is similar to our study as 52 % of all neonates were reintubated. Diaphragmatic assessment using ultrasound is considered now as a modality for diagnosis of diaphragmatic dysfunction [12]. Appropriate timing for examination of the diaphragmatic function by ultrasound was reported before extubation from ventilator[14]. Nevertheless, our study results did not reveal any significant difference between measuring right or left diaphragmatic excursion before or after extubation.

The right and left diaphragmatic excursion were reported as 2.3± 0.37mm and 2±0.53mm; respectively[25]. This comes in the line with our study results where the level at which weaning failure was detected in full term neonates was 2.7, 2.5 mm while in preterm was 2.4, 3.3 mm on right and left diaphragmatic excursion; respectively (p value >0.05).

In our study, studying diaphragmatic excursion in MV neonates revealed an excellent cut off value predicting weaning failure in full-term. While, in preterm neonates, the cut off values predicting weaning failure was slightly less specific and sensitive. Similarly, **Bahgat *et al.*** [25] had revealed a right diaphragmatic excursion of 2.75mm and a left diaphragmatic excursion of 2.45mm with nearly similar predictability using ROC curve in pre-term neonates.

Of note, our study has matched another where total ventilation days were longer in babies with weaning failure compared to those with successful weaning (7 days vs. 9 days); respectively (*p*=0.05).

Regarding GA, it is well known that age is negatively correlated with excursion in deep breathing, and that females have less diaphragmatic excursion than male [26]. While in our study no difference in sex was detected yet, a significant difference between full-term and pre-term neonates was detected which matches the study results of **Bahgat *et al.*** [25]. In the contrary, **Johnson *et al.***[27] have revealed that diaphragmatic atrophy in intubated critically ill children have occurred rapidly and irrespectively of age.

The risk factors associated with diaphragmatic dysfunction have been extensively studied. Our study revealed that lower gestational age, presence of RDS, longer period on MV and higher ventilator setting (high PIP, PEEP and RR) were associated with deteriorated diaphragmatic function. Similarly, diaphragm dysfunction was associated with difficult weaning, and prolonged duration of mechanical ventilation[16].

In our study, the mortality rate in the successful weaning group was 4.3% in full term and 8.7% in preterm, while in weaning failure group it was 8% and 24% in full-term and preterm respectively, which matches with the results of other studies [25, 27].

CONCLUSION

Bedside ultrasound can predict weaning failure through measuring right or left diaphragmatic excursion in full term and preterm neonates.

RECOMMENDATION

Consensus protocol using diaphragmatic US with clinical parameters should be recommended for proper evaluation of each case before starting weaning to avoid weaning failure. Further controlled trials are required for the assessment of lung ultrasound with diaphragmatic and cranial sonar to be added to full clinical, laboratory parameters to create more specific criteria for weaning from ventilators.

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Author contribution: Authors contributed equally in the study.

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