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Prospective study: Diaphragmatic thickness as a predictor index for weaning from mechanical ventilation

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1. Introduction

For patients undergoing mechanical ventilation, timing is critical for proper weaning from the procedure; if this is performed prematurely complications can include increased cardiovascular and respiratory stress, CO_2 retention and hypoxemia [1,2]. However, unnecessary delay in weaning can also cause a number of side-effects [3-5]. Weaning outcomes have been assessed by several indices. Variables such as minute ventilation, Pao_2/Fio_2, rapid shallow breathing index and static compliance have all been used, with variable predictive values [6].

Previous studies have proved that diaphragmatic dysfunction is one of the main etiologies of difficult weaning, because the diaphragm progressively weakens with mechanical ventilation [7,8]. Methods used to assess diaphragm function, such as fluoroscopy, phrenic nerve stimulation, measurement of trans-diaphragmatic pressure and dynamic magnetic resonance imaging of the diaphragm, all have limitations. These include ionizing radiation exposure, low availability, invasiveness and necessity for patient transportation. Conversely, the use of ultrasound is safe, non-invasive, avoids radiation side-effects, and is available at the bedside [9].

The aim of this study was to assess whether the diaphragmatic thickening fraction measured by ultrasound can be used as a predictive index for weaning from mechanical ventilation.

The primary outcome of this study was determining the rate of successful weaning. Secondary outcomes included assessing the correlation between the duration of mechanical ventilation and the length of ICU stay according to the diaphragmatic thickening fraction.

2. Methods

This prospective, blind, observational study was performed at Tanta University Hospitals, Egypt, with approval from the institutional ethical committee, code 2833/10/14 (written informed consent was obtained from the relatives of all participants). The patients enrolled in this study were referred to our intensive care unit and placed on mechanical ventilation. All patient data was confidential, with secret codes and a private file for each patient, and used only for the current research.

Inclusion criteria for the study were as follows: adult patients >18 years old, who were eligible for weaning from mechanical ventilation as indicated by:

a) Evidence of reversal, or control, of the underlying cause of respiratory failure.
b) No significant abnormal physiology
c) Evidence of low ventilatory support determined by

1. $Fio_2 < 0.5$, PEEP = 5 cm H_2O, $PaO_2/FiO_2 > 200$ and static compliance ≥30 ml/cm H_2O.
2. Spontaneous respiratory rate < 35 cycles/min.
3. Haemodynamic stability with the absence of vasopressors and/or inotropes.
4. Being alert without sedation.

We excluded pregnant patients, those with surgical incisions likely to interfere with ultrasound examination, and those with diaphragmatic paralysis (that is, the paralyzed side of the diaphragm exhibiting abnormal paradoxical movement, i.e., moving in a cranial direction during inspiration) [10].

2.1. Study design

All patients who met the inclusion criteria and had a spontaneous respiratory rate of <25 cycles/min were enrolled in the study. Patients with a spontaneous respiratory rate ≥ 25 cycles/min were kept on pressure support until the spontaneous rate fell to <25 cycles/min, and then enrolled in the study and given a spontaneous T-piece breathing trial. Ultrasound assessment of the diaphragm was conducted during the first five to ten minutes of the initial spontaneous breathing trial. The clinician performing the ultrasound was not responsible for deciding whether the patient should be extubated or not. Also, the clinician deciding on the necessity for extubation was blinded to the results of the ultrasound assessment of diaphragmatic shortening. During the

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spontaneous breathing trial, the patients were assessed for RSBI, Pao_2/Fio_2, minute ventilation and static compliance.

2.1.1. Weaning outcomes

Successful weaning was defined as sustained spontaneous breathing >48 h after extubation; failed weaning was defined as a need for reintubation within 48 h, being terminally extubated, or requiring tracheostomy.

The criteria used to indicate a failure of the spontaneous breathing trial were: a change in mental status, onset of discomfort, diaphoresis, respiratory rate (RR) > 35 breaths/min, hemodynamic instability (heart rate > 140, systolic blood pressure > 180 or < 90 mmHg) [11] or signs of increased difficulty breathing.

2.1.2. Technique of diaphragmatic evaluation by ultrasound

The patients were lying in the semi-recumbent position, with the head of the bed elevated at an angle between 30 and 45°. Ultrasound was performed using Philips ultrasound (model CX_{50}), equipped with a high frequency linear probe (10–15 MHz). The diaphragm was visualized by placing the transducer perpendicular to the chest wall in the mid-axillary line between the 8th and 10th intercostal spaces, to observe the zone of apposition of the muscle 0.5 to 2 cm below the costo-phrenic sinus. Then the probe was directed medially, cephalad and dorsally, so that the ultrasound beam reached the posterior third of the corresponding hemi-diaphragm perpendicularly.

Assessing the posterior region of the diaphragm is logical, as the posterior region of the diaphragm is usually 40% more contractile compared with the anterior region [12]. However, the anterior window is often obscured by stomach and bowel gas, impeding the signal, and the direction of the ultrasound beam may not fall perpendicular to the craniocaudal axis. If the angle of the ultrasound beam exceeds 20° from the perpendicular line, the measurements may be inaccurate [13]. The two-dimensional (2D) mode was used initially to obtain the best approach and select the exploration line; the M-mode was then used to display the motion of the anatomical structures along the selected line. The diaphragm was imaged as a structure with three distinct layers, including two parallel echoic lines (the diaphragmatic pleura and the peritoneal membrane) and a hypoechoic structure between them (the muscle itself) (Fig. 2). In the frozen M-mode image, the distance from the middle of the pleura line to the middle of the peritoneal line is the diaphragm thickness.

Several images of the diaphragm were captured and stored, including at least three at the point of maximum thickening at total lung capacity (TLC), and at least three at minimum thickening at residual volume (RV), and the mean of the three measurements was recorded.

2.1.3. Data collection and measurement

The following information was collected for each registered patient: demographic data, the primary reasons for ICU admission, RSBI, Pao_2/Fio_2, minute ventilation and static compliance. Then, the diaphragmatic thickness fraction (DTF) was calculated as a percentage using the following formula: (thickness at end inspiration – thickness at end expiration/thickness at end expiration). The Δtdi% for each patient represented the mean of three breaths. Images were obtained within the first five minutes of the SB trial using T-piece. The duration of mechanical ventilation and length of ICU stay were also recorded.

2.2. Statistical methods

2.2.1. Sample size

The sample size was calculated using the Epi-Info software statistical package created by the World Health Organization and Centres for Disease Control and Prevention, Atlanta, Georgia, USA, version 2002. The sample size was calculated at $N = 64$ as a result of 95% confidence interval, 80% power of the study and a hypothetical percentage of expected outcome in the treatment group of 95% compared with 78% for the control groups [14].

Statistical presentation and analysis was conducted using SPSS V.24. Quantitative data were expressed using range, mean and standard deviation, while qualitative data were expressed using frequency and percentage. An unpaired *t*-test was used for the comparison of parametric data (RR and duration of mechanical ventilation) between the two groups, and the *U* test was used for comparison between both groups regarding BMI, age, compliance and length of ICU stay. Modified chi-square test for small numbers was used for comparison between the two groups regarding qualitative data (sex). *P* value <.05 was considered statistically significant. Agreement of the different predictors with the outcome was used and expressed in sensitivity, specificity, positive predictive value and negative predictive value. Receiver operating characteristic curve (ROC) was used to denote the diagnostic performance of the test, where area under the curve >80% denoted good performance and area in the region of 100% denoted the best performance of the test. Youden index was used in conjunction with the ROC curve. Net reclassification improvement index (NRI) was calculated, and Pearson correlation was used to detect correlation between parameters.

3. Results

The present study included 65 patients; 51 were successfully weaned after the first breathing trial, while the remaining 14 failed to be weaned (Fig. 1). Six of the fourteen patients did not complete the spontaneous breathing trial, two required non-invasive ventilation, and the remaining six required reintubation within 48 h of extubation. We classified the patients included in the study into two groups: successful weaning, and failed weaning. There was no statistically significant difference between both groups with regard to demographic data (age, sex and BMI) (Table 1). Etiology of respiratory failure in the patient population is shown in Table 1.

Pao_2/Fio_2 ratio, minute ventilation (litres/min), static compliance (ml/cm H_2O) and DTF (%) in the successful weaning group were significantly higher than those in the failed weaning group, as $P < .05$ (Table 1). RSBI (breaths/min/L) in the successful weaning group was significantly lower than that in the failed weaning group (Table 1). The receiver operating characteristic (ROC) curve (Fig. 3) was used to assess the diagnostic accuracy of previous predictors in predicting success of weaning. A cut-off value was taken to give the best sensitivity and specificity for each parameter (Table 2). Sensitivity was 94% for DTF, which is significantly higher than the sensitivity of RSBI ($P < .042$), which was 90%. The Pao_2/Fio_2 ratio had the same sensitivity (94%) compared with DTF, which had the highest positive predictive value (94%). Specificity of DTF was 78%, which was the highest specificity for all indexes. The areas under the ROC curves for each index are shown in Table 2, and the curves of weaning indexes are shown in Fig. 3. The areas under the DTF curves were significantly larger than those under the RSBI curve ($P < .03$). Comparison of the ROC curves using the Youden index showed 0.72 for the DTF curve, which was higher than that of the curves of other indexes. The net reclassification improvement index was calculated to quantify how well DTF reclassifies patients in weaning prediction compared with RSBI; the result was 0.107.

Length of ICU stay and duration of mechanical ventilation in failed weaning patients showed a statistically significant increase in comparison to the length of ICU stay in successful weaning patients. A good negative correlation between DTF and RSBI was observed (rho = −0.61, $P = .0001$), with good positive correlation between DTF and Pao_2/Fio_2 ratio (rho = 0.63, $P > .0001$). Also, a positive correlation between DTF and static compliance was observed (rho = 0.53, $P = .001$), while a negative correlation was observed between DTF, length of ICU stay (rho = −0.30, $P = .014$) and duration of mechanical ventilation (rho = −0.39, $P = .001$) (Fig. 4).

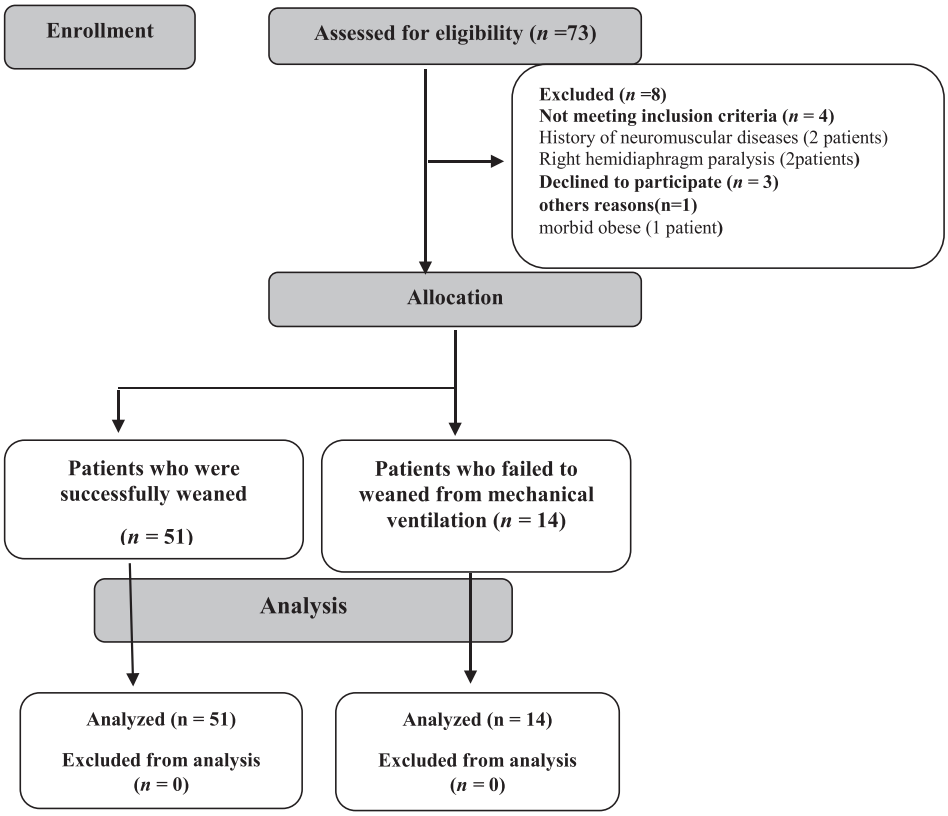

Fig. 1. Patient flowchart summarizing enrollment, allocation, follow-up and analysis in the study protocol.

4. Discussion

DTF was better than RSBI with regard to sensitivity and specificity. DTF was also superior in the exclusion of weaning failure because of its higher negative predictive value. A correct DTF of more than, or equal to, 30% was most accurate in predicting successful weaning with a sensitivity of 94% and a specificity of 78%, as reported by the studies of DiNino et al. [15] and Ali et al. [16]. They found that a cut-off value of 30% or more for diaphragmatic thickness was a good predictor of weaning success, with PPV of 91% and NPV of 63% in DiNino et al., and a sensitivity of 97.3%, specificity of 85.2%, PPV of 94.4%, NPV of 90.6% and accuracy of 91.9% in Ali E. R. et al., were predictors of extubation success.

Furthermore, the results of this study were comparable to those of other studies [17-19]. Ferrari et al. [20] found that a cut-off value of 36% was associated with successful weaning, with a PPV and NPV of 92% and 75%, respectively. Moreover, Samanta et al. [21] studied diaphragmatic ultrasound and found that the DTF cut-off was more than, or equal to, 25.5%, with AUC of 0.91 and sensitivity and specificity of 97% and 81%, respectively. Other studies by Blumhof et al. [22] and Jung et al. [23] demonstrated that right DTFs of >20% were associated with weaning success and better ICU outcomes.

Despite the different cut-off values of these studies, most authors agreed that DTF was a better weaning predictor than RSBI. The superiority of DTF over RSBI during SBT may be attributed to the importance of the diaphragm's contribution to tidal volume (VT). The RSBI is an integrative function of respiratory load and respiratory muscle capacity; the function of all inspiratory muscles, including the diaphragm and accessory inspiratory muscles, reflects RSBI. If the diaphragm is failing, the accessory inspiratory muscles will compensate to preserve VT, and the presence of diaphragm weakness may be masked by the increased work of the other inspiratory muscles (thoracic cage muscles) to VT. Because these muscles are easily fatigued, they will be unable to sustain adequate ventilation [15].

A systematic review and meta-analysis study performed by Llamas-Álvarez et al. [24] concluded that DTF is a modest predictor of weaning outcome in the general population of critically-ill patients. DTF is related to weaning success because many respiratory mechanisms are related to diaphragmatic muscle. Minas et al. [25] concluded that a positive, but not yet statistically significant, correlation was found between the respiratory muscle pressure and the thickening ratio of the diaphragm.

Table 1
Demographic data of included patients, etiology of respiratory failure and different weaning predictors.

Variables	Successful weaning	Failed weaning	P value
Sex			
Males	31	9	0.812
Females	20	5	
Age (years)	43.49 ± 12.88	40.85 ± 14.28	0.51
Body mass index (Kg/m^2)	23.84 ± 1.55	24.5 ± 1.72	0.18
Diagnosis			
Posttraumatic	10 (18.86%)	2 (14.28%)	
Postoperative	11 (20.75%)	2 (14.28%)	
COPD	3 (5.66%)	0 (0.00%)	
ARDS	6 (11.32%)	3 (21.42%)	
Toxic or metabolic coma	7 (13.20%)	2 (14.28%)	0.67
Post cardiac arrest	2 (3.77%)	2 (14.28%)	
Septic shock	5 (9.43%)	2 (14.28%)	
Pneumonia	5 (9.43%)	0 (0.00%)	
Stroke	2 (3.77%)	1 (07.14%)	
RSBI(breaths/min/L)	79.58 ± 20.36	102.39 ± 17.07	0.0003*
Pao_2/Fio_2 ratio	352.86 ± 63.79	251.85 ± 36.32	0.0001*
Minute ventilation (liter/min)	8.82 ± 2.07	7.11 ± 1.31	0.0005*
Static compliance (ml/cm H_2O)	52.49 ± 11.34	40.85 ± 10.78	0.001*
DTF (%)	49.48 ± 12.50	27.83 ± 9.95	0.0001*
Duration of MV(days)	5.98 ± 2.57	9.35 ± 3.49	0.0001*
Length of ICU stay(days)	8.64 ± 3.09	12.35 ± 3.31	0.0001*

* significant if $P < .05$.

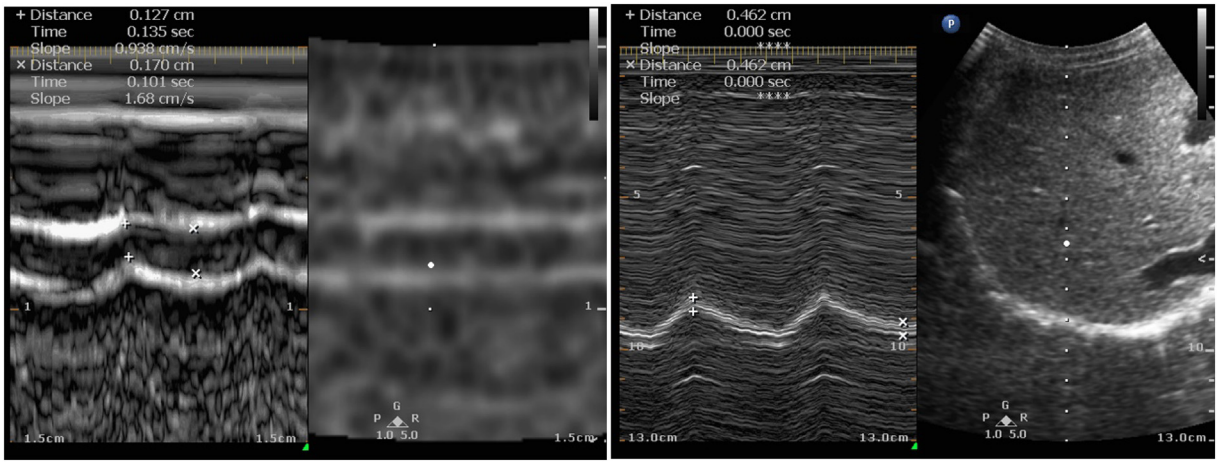

Fig. 2. Diaphragmatic ultrasound; 2D and m-modes.

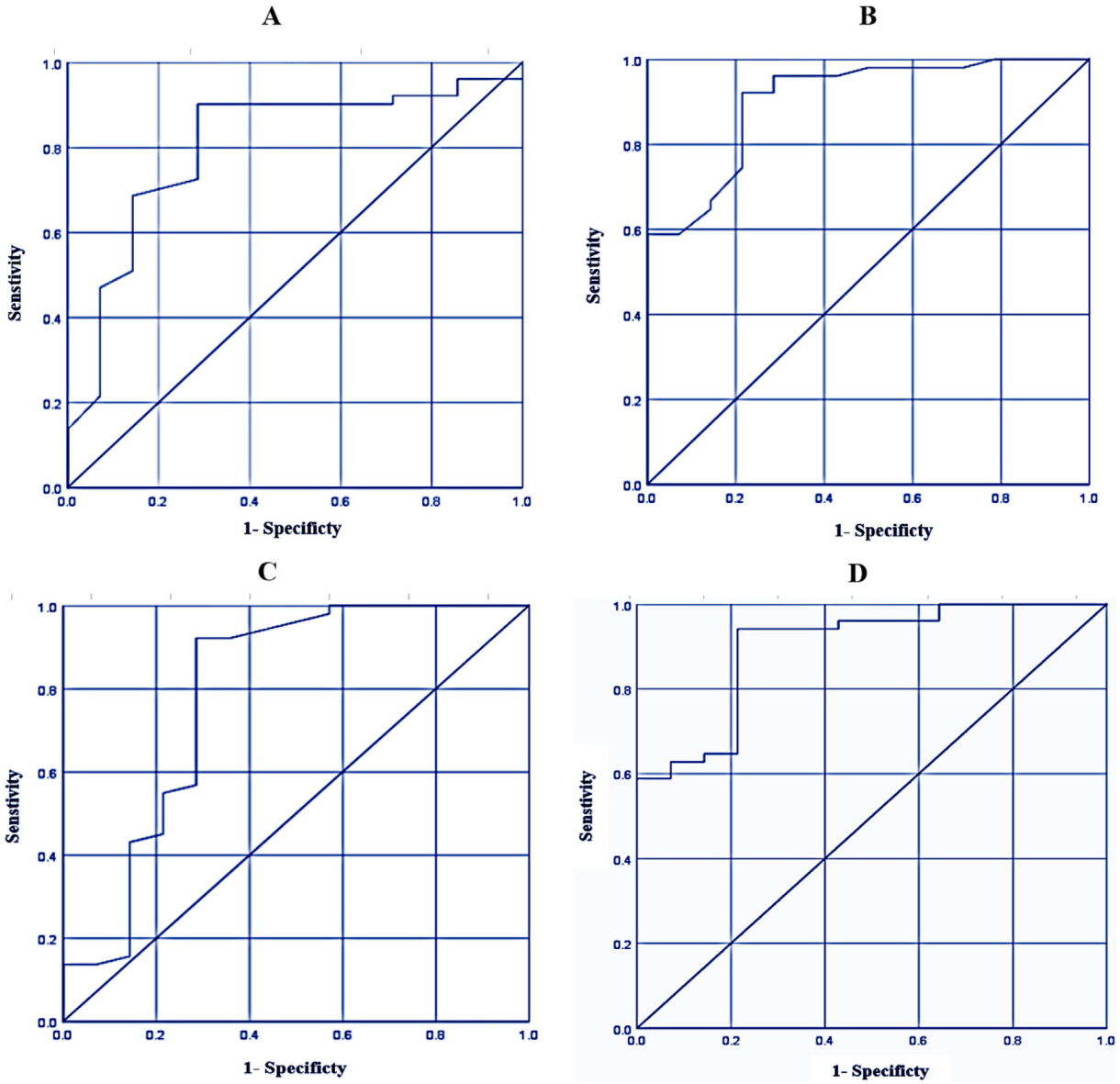

Fig. 3. ROC curve of weaning predictors. A. ROC curve of RSBI (AUC 0.80), B. ROC curve of PaO_2/FiO_2(AUC 0.90), C. ROC curve of static compliance, (AUC 0.79) D. ROC curve of DTF(AUC 0.89). AUC, area under the curve; ROC, receiver operating characteristic, RSBI, rapid shallow breathing index, DTF, diaphragmatic thickness fraction, Pao_2/Fio_2, partial pressure of arterial oxygen/fraction of inspired oxygen.

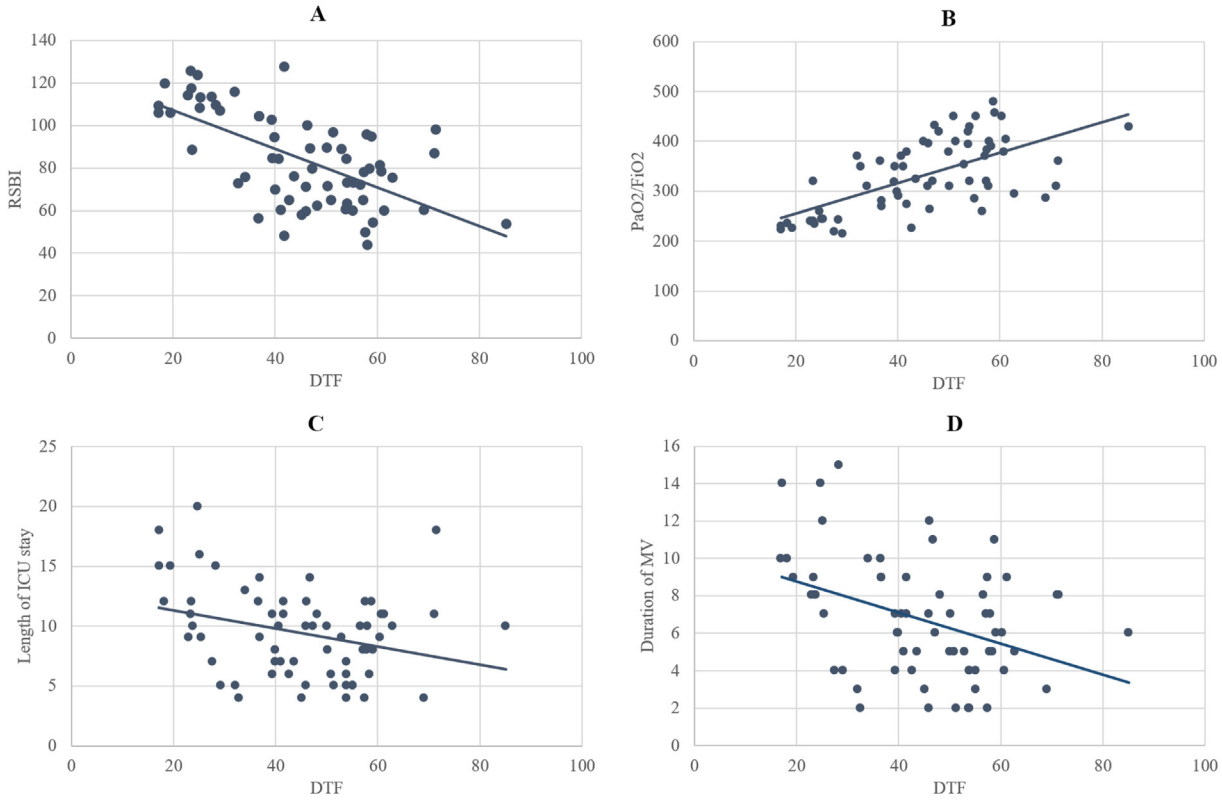

Fig. 4. A, correlation of DTF with RSBI B, correlation of DTF with Pao_2/Fio_2, C, correlation of DTF with length of ICU stay D, correlation of DTF with duration of mechanical.

A positive correlation was found between DTF and static compliance and Pao2/Fio2 ratio, while it had a negative correlation with RSBI, duration of mechanical ventilation and length of hospital stay. These findings match the Ferrari et al. [20] study, in which DTF showed a high significant correlation with the other parameters, including arterial blood gases and respiratory mechanics – mainly the RSBI and maximal inspiratory pressure, which was similar to other studies [26,27].

Regarding the duration of mechanical ventilation and length of ICU stay, there was a significant difference between the two groups, and these finding are in agreement with Dubé et al. [17] and Ferrari et al. [20]. The same results were found in Ali E. R. et al.'s [16] study, in which diaphragmatic dysfunction was significantly more frequent in patients with prolonged MV than those with shorter MV duration. These results also match Grosu et al.'s [3] study, which revealed that the duration of MV significantly predicted decreases in diaphragmatic thickness and strength. In accordance with the current study, Jaber et al. [28] concluded that the period of controlled mechanical ventilation should be kept short. This study showed high significance regarding PaO_2/Fio_2, meaning that Pao_2/Fio_2 is a good predictor of weaning success, with sensitivity of 94% and specificity of 71%. Barbosa e Silva et al.'s [29] study supported our results and proved that Pao2/Fio2 ratio is a good predictor of weaning success, with a high sensitivity of 0.97. Good correlation between DTF and Pao2/Fio2 ratio was observed. The present study results were in agreement with Davis et al.'s [30] and Zhu et al.'s [31] studies that found higher hypoxia and decreased PaO_2 associated with more diaphragmatic dysfunction (DD), and this was confirmed by profound reduction in diaphragmatic blood flow in VIDD. It is, therefore, speculated that reduced oxygen delivery may lead to the formation of reactive oxygen species with consecutive triggering of proteolytic cascades and enhanced oxidative stress [31]. We also found a positive correlation with static compliance and a negative correlation with RSBI. To our knowledge, no study has reported such findings before.

In disagreement with our results, the study of Holtzhausen et al. [32] mentioned that a thin diaphragm may be more resistant to fatigue and have better endurance than a thicker diaphragm. They found that in healthy individuals, stronger inspiratory muscles were correlated with poorer endurance. Their explanation was that under certain conditions, such as disease, disuse or specific training, respiratory muscle fibres can alter their properties to adapt to these conditions.

Table 2
Comparison between the validity of measured parameters with significance between the two groups.

Item	DTF	RSBI	PaO_2/FiO_2	Static compliance
Cut-off	30	105	250	40
Sensitivity %	94	90	94	92
CI	83.8–98.8	78.6–96.7	86.5–99.5	81.1–97.8
Specificity %	78	71	71	64
CI	49.2–95.3	41.9–91.6	41.9–91.6	41.9–91.6
PPV %	94	92	92	90
NPV %	78	66	76	69
AUC %	89	80	90	79
CI	79–95	68–89	80–96	67–88
Youden index (J)	0.72	0.61	0.65	0.56

PPV: positive predictive value, NNP: negative predictor value, AUC: area under the curve, CI: 95% confidence interval.

5. Conclusion

In this study a thickening fraction of the right diaphragm (measured by ultrasound) of more than, or equal to, 30%, was slightly better than RSBI regarding sensitivity and specificity, and was successful in predicting weaning outcomes with reductions in failed extubation, duration of mechanical ventilation and length of ICU stay.

Authors contribution

Salah El-din I. Alsherif: The idea of the research and the final approval of the manuscript.

Wafaa M. Abdelwahed: Conduct the study, data collection, analysis of the data and preparation of the manuscript.

Mohamed S. Abd Elghafar: Design of the study,supervising the conduct of the study and revision of the manuscript.

Yasser M, Amr: Revision of the manuscript.

Mohamed A. Eltomey: Supervising and approval of ultrasound work.

Conflicts of interest

The authors declare that they have no conflict of interest.

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