New modalities in evaluation of respiratory muscle weakness during weaning from mechanical ventilation in patients with acute exacerbation of COPD

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ABSTRACT

Background: The rapid shallow breathing index (RSBI), the diaphragmatic displacement (DD) and diaphragmatic thickening fraction (DTF) are considered accurate weaning predictors. This study was conducted to investigate new promising tools that predict successful and failed weaning of COPD patients from the ventilatory support. The diaphragmatic rapid shallow breathing index (D-RSBI), which is the ratio between respiratory rate (RR) and the diaphragmatic displacement (DD) is a new promising tool to predict weaning outcome. **Aim of work:** The aim of this study was to compare the ability of the traditional RSBI and D-RSBI and D-BLI (DD/ B line score) to predict successful weaning in ready-to-wean COPD patients. **Methods:** We performed a prospective cohort observational study. The study included 100 patients admitted to the Critical Care Department, Faculty of medicine; Cairo University with acute exacerbation of COPD and intubated for more than 48 hours. **Results:** A total of 66 (66%) patients had successful weaning trial, while 34 (34%) patients failed the weaning trial from which 10 patients had failed SBT from the start and 24 patients were reintubated within 48 hours of extubation. The cutoff value of the new composite parameter (D-BLI) for successful weaning is greater than or equal to 1.48 with (AUC= 0.992), with sensitivity and specificity of 95% and 95%, respectively. The cut-off value of D-RSBI for failed weaning from mechanical ventilation was > 1.7 breaths/min/mm showed 100% sensitivity and 97% specificity (AUC=0.996). The cut-off value of RSBI for failed weaning from mechanical ventilation was > 73.5 breaths/min/L showed 80% sensitivity and 100% specificity (AUC=0.957). There is a strong positive correlation between D-RSBI and RSBI (r = 0.678) (P = < 0.001). **Conclusion:** D-RSBI (RR/DD) and D-BLI (DD/B line score) were more promising tools than classic RSBI in predicting the weaning outcome. However, further larger studies are needed to validate these results.

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is the fourth leading cause of death causing more than 6% of all deaths globally. [1]

Weaning patients from mechanical ventilation is a questioning task because unduly delay can lead to further complications. Mechanical ventilation can be terminated as soon as the underlying cause for acute respiratory failure has been resolved.[2]

Weaning failure is defined as the failure to pass a spontaneous breathing trial or the need for reintubation within 48 hours following extubation. Around 25% of the intubated patients present with difficulty in liberation from mechanical ventilation, despite established weaning protocols. [3]

Reasons for failure to initiate spontaneous ventilation after a period of ventilatory stay include oxygenation failure and respiratory muscle dysfunction, brain troubles, cardiac illness, and endocrine disorders. [4]

Diaphragmatic dysfunction remains the main cause of weaning difficulty. Its incidence ranges from 33 to 95%. Diaphragmatic dysfunction among hospitalized patients is commonly credited to critical illness polyneuropathy and myopathy. [5, 6]

PATIENTS AND METHODS

This was a prospective observational cohort study on adult patients who were admitted to the Critical Care Department, Cairo university hospital over a period of fifteen months starting from February 2021 to May 2022.

The study was approved by faculty of Medicine – Cairo University, Medical Ethics Committee.

Patients

All chronic obstructive pulmonary disease (COPD) patients who required invasive mechanical ventilation for more than 48 h and planned for liberation from ventilatory support after improvement of the underlying cause of respiratory failure, were included in the study after obtaining an informed written consent from the patient's legal guardians.

Exclusion criteria were: Inability to obtain appropriate windows, patients under 18 years old, Hemodynamically unstable patients, on moderate or high doses of vasopressors, the presence of thoracotomy, pneumothorax, or pneumomediastinum, neuromuscular disease or use of Neuromuscular blocking agents within 48h before the study and advanced malignancy or advanced heart failure.

Methods

All patients were subjected to the following:

1. Detailed history taking, Detailed clinical examination, Laboratory investigations (Complete blood count, Coagulation profile, Arterial blood gases, Liver and renal functions and serum electrolytes), bedside twelve leads ECG and chest x-ray.

2. Ultrasonography: Each diaphragm was evaluated by the curvilinear and linear ultrasound probes of Siemens Acuson X300 PE ultrasound machine (probes of 2-5 and 5-10 MH frequency) **(Fig. 1)**.

Figure (1): Siemens Acuson X300 PE ultrasound machine

Diaphragmatic thickness fraction

The diaphragm was imagined by placing the probe perpendicular to the chest wall, in the eighth or ninth intercostal space, between the anterior axillary and the midaxillary lines 1 to 2cm below the costophrenic sinus [7].

The patient was then instructed to perform full inspiration to total lung capacity (TLC) and then to exhale to residual volume (RV).

The diaphragm was thickened maximally during inspiration. Several images of the diaphragm were stored, including at least three at the point of maximum thickening at TLC and at least three at minimum thickening at RV [8].

Images were obtained within the first hour of the SBT to identify the diaphragm and measure its thickness.

On each frozen M-mode image; the diaphragm thickness was measured from the middle of the pleural line to the middle of the peritoneal line. Then, DTF was calculated as percentage from the following formula: Maximum inspiratory thickness – Maximum expiratory thickness / Maximum expiratory thickness (**Fig. 2)** [9].

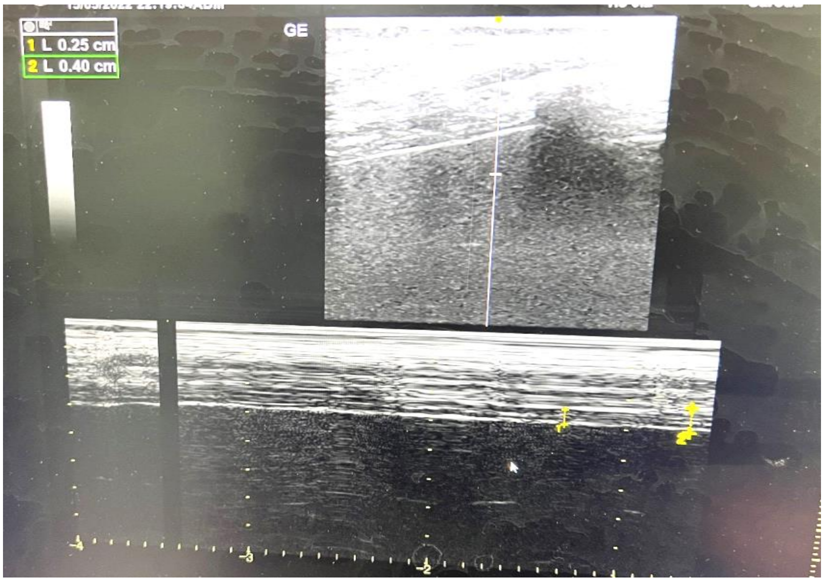

Fig. (2): Measurement of diaphragmatic thickness by B-Mode and M-Mode ultrasound. A representative ultrasound image of a patient's diaphragm at end-expiration (1) and end-inspiration (2). The distance between the diaphragmatic pleura and peritoneal pleura (the two echoic lines)

Diaphragmatic excursion (DE):
The diaphragmatic excursion was then measured through ultrasound using a low frequency curvilinear probe (2-5 MHz) placed in the subcostal area, between the mid-clavicular and anterior axillary lines, using the liver as acoustic window. Transducer was directed medially, cranially, and dorsally [10].
The mean DE was calculated in mm after recording the maximal displacements in three breathing cycles. All measurements were performed in the supine position during quiet breathing [11].
B line index:
B line index (BLI) was performed using a (2-4MHz) Linear probe**.** This score arises from the transformation of lung ultrasound patterns into numeric values, which are assigned according to the worst ultrasound pattern observed for a given chest region. Four lung ultrasound patterns were defined: Presence of A lines or fewer than two separated B lines (N), Multiple, well-defined B lines (B1 lines), Multiple fused B lines (B2 lines) and Lung consolidation (C), the presence of a tissue pattern characterized by dynamic air bronchograms [12].
N=0, B1 lines=1, B2 lines=2, C= 3.
The final score, ranging from 0 to 36, is the sum of the values, from 0 to 3, allocated to the BLI. Each intercostal space of upper and lower parts of the anterior, lateral, and posterior regions of the left and right chest wall was carefully examined according to the consensus conference recommendations for point of-care LUS [13].
3. Cardiac ultrasound
Cardiac functions measurement was done using the cardiac probe of Siemens Acuson X300 PE Ultrasound Machine.
Standard heart chambers quantification and estimation of Ejection fraction were obtained by parasternal long axis and four chamber views [14].
Tricuspid annular plane systolic excursion **(TAPSE)** was used to estimate systolic right ventricular function. It was obtained by placing the M-mode cursor over the lateral part of the tricuspid valve annulus in the apical four-chamber view. It was measured as the distance from the annulus to the apex at end diastole minus that distance at end systole [15].
4. Mechanical ventilation parameters: Measurement of respiratory rate (RR) and tidal volume (VT) during the SBT and calculation of Rapid shallow breathing index which is the ratio of respiratory rate to tidal volume (RR/VT), P peak, P plateau, FIO_2, PaO2/FiO_2 and PEEP and cause and duration of mechanical ventilation.
5. The diaphragmatic rapid shallow breathing index (D-RSBI)
The respiratory rate (RR) was divided by the diaphragmatic displacement (DD), which was described as the D-RSBI [16].
6. New scores for prediction of weaning outcomes: We performed preliminary logistic regression analysis of the different variables for 40 patients (derivation sample) to identify a new score for prediction of successful weaning from mechanical ventilation. Another more simplified tool was proposed by dividing diaphragmatic excursion over B line score, a new and promising assessment tool to predict weaning outcome named diaphragmatic B line index (**D-BLI).**
Both curves were evaluated by area under curve of ROC analysis. The best cut off was identified as the value having the highest Youden index [17]. The two newly derived scores were applied on a new 60 patients (validation sample).
Primary 0utcome parameters included: Successful weaning: defined as a state in which a patient was able to maintain his or her own breathing for 48 hours without any level of ventilator support. weaning failure: Weaning failure was diagnosed if failed SBT or if the patient was extubated but needed mechanical ventilation (invasive or non-invasive) or died within the following 48h [18-19].
Secondary outcome parameters included: Mortality, Length of hospital stay and Ventilation days
Statistical analysis: Data were coded and entered using the statistical package for the Social Sciences (SPSS) version 28 (IBM Corp., Armonk, NY, USA). Data was summarized using mean, standard deviation, median, minimum, and maximum in quantitative data and using frequency (count) and relative frequency (percentage) for categorical data. Comparisons between quantitative variables were done using the non-parametric Mann-Whitney test [20]. For comparing categorical data, Chi square (χ2) test was performed. Exact test was used instead when the expected frequency is less than 5 [21]. Correlations between quantitative variables were done using Spearman correlation coefficient [22]. ROC curve was constructed with area under curve analysis performed to detect best cutoff value of different parameters for detection of weaning failure. Logistic regression was done to detect independent predictors of weaning success [17]. P-values less than 0.05 were considered statistically significant. The sensitivity of a test (also called the true positive rate) is defined as the proportion of people with the disease who will have a positive result. The specificity of a test (also called the True Negative Rate) is the proportion of people without the disease who will have a negative result [17].

RESULTS

The study population was subdivided into two groups; successful and failed weaning groups where 66 patients weaned successfully from mechanical ventilation while 34 patients had failed weaning trial, from which 10 patients had failed SBT from the start.

24 patients were extubated then reintubated within 48 hours in the follow up period from which five patients had successful another weaning trial and another five patients were preceded to tracheostomy while fourteen patients were deceased. **Table (1)**

Table (1): Weaning outcome for studied patients.

Item	Number (40)	Percentage
Weaned	66	66%
Failed (SBT)	10	10%
Failed weaning then successful another trial	5	5%
Failed weaning then Tracheostomy	5	5%
Failed weaning then deceased	14	14%

Table (2) shows no statistically significant differences in preweaning parameters between weaning success and weaning failure groups as regard all demographic and clinical characteristics of the studied patients except for **LT sided heart failure, RT sided heart failure, pulmonary HTN and pneumonia** (P = < 0.001, < 0.001, < 0.001 and 0.004) respectively as pneumonia and heart failure was higher in the failed weaning groups.

A statistically significant difference was found between each of **SOFA, APACHE II scores** and weaning results, was found higher in the failed weaning groups (P = <0.001, <0.001) respectively

Table 2: Demographic and clinical characteristics of all studied patients

variables	All (n = 100)	Weaning success (n = 66)	Weaning failure (n = 34)	P value
Age (years)	65 ± 13	66 ± 11	62 ± 16	0.338
Male	67 (67)	41 (62.2)	26 (38.8)	0.148
Female	33 (33)	25 (75.8)	8 (24.2)	
Smokers	39 (39)	23 (59)	16 (41)	0.236
SOFA score	2.97 ± 2.01	2.08 ± 1.53	4.18 ± 2.12	<0.001
APACHE II	12.34 ± 5.60	9.8 ± 4.5	17.2 ± 4.11	<0.001
Comorbidities				
HTN	27(27%)	20 (74.1%)	7 (25.9%)	0.300
DM	27(27%)	15 (55.6%)	12 (44.4%)	0.180
RT sided Heart failure	22(22%)	5 (22.7%)	17 (77.3%)	< 0.001
Pulmonary HTN	20(20%)	3 (15%)	17 (85%)	< 0.001
LT sided Heart failure	30(30%)	11 (36.7%)	19 (63.3%)	< 0.001
Pneumonia	77(77%)	45 (58.4%)	32 (41.6%)	0.004
Hypothyroidism	20(20%)	10 (50%)	10 (50%)	0.091
COPD years	4.13 ± 2.53	3.30 ± 1.78	5.74 ± 2.99	< 0.001
Days of ICU stay	21.73 ± 12.50	26.26 ± 9.50	18.85 ± 13.15	< 0.001
Days of MV	5.96 ± 3.94	5.48 ± 4.01	6.88 ± 3.67	0.007

A statistically significant difference was found between **PaO_2/FiO_2, RR, VT,** and **RSBI** with weaning outcome, (P = < 0.001, < 0.001, < 0.001 and < 0.001) respectively.

There was no statistically significant difference between **P plateau** with weaning outcome (P = 0.110)

A statistically significant difference was found between each of **DTF**, **DE, B line lung score, TAPSE,** and **D-RBSI** and weaning outcome P = (< 0.001, < 0.001, < 0.001, < 0.001 and < 0.001) respectively in the study groups. **DTF, DE** and **TAPSE** was found higher in the successful weaning groups while **B line lung score** and **D-RBSI** was found lower in the successful weaning groups.

Table (3) shows the ventilatory and sonographic parameters among all the studied population.

variables	All (n = 100)	Weaning success	Weaning failure	P value

		(n = 66)	(n = 34)	
Ventilatory parameters				
PaO_2/FiO_2	284.94± 39.16	298.6± 26	258.3 ± 46	< 0.001
RSBI	63.57 ± 20.61	51.5± 11.3	86.9 ± 13	< 0.001
RR	26.38 ± 5.02	24±4	30.8±3.5	< 0.001
VT (ml)	436.70 ± 76.08	478± 54.7	356.5± 37.7	< 0.001
Pplateau(cmH2O)	17.13 ± 2.14	17.29± 1.7	16.8±2.76	0.110
Chest ultrasound and echographic parameters				
DTF (%)	0.48 ± 0.25	0.57 ± 0.22	0.30 ± 0.18	<0.001
Excursion(mm)	17.14 ± 5.48	19.74 ± 4.8	12 ± 2.26	<0.001
B line lung score	10.39 ± 4.18	8.48 ± 3.15	14.09 ± 3.38	<0.001
D-RBSI (breaths/min/mm)	1.70 ± 0.84	1.21 ± 0.29	2.64 ± 0.74	<0.001
TAPSE (mm)	1.93 ± 0.34	2.08 ± 0.26	1.65 ± 0.30	<0.001

Table (4) reports the overall results of the ROC analysis referring to the available weaning predictors: D-RSBI, RSBI, DD, RR, DTF and B line score. D-RSBI resulted in the parameter with the best diagnostic accuracy (AUROC = 0.99; P < 0.0001). A cutoff of D-RSBI >1.7 breaths/min/mm yielded 100 % sensitivity, 97 % specificity. Figure 7 shows strong positive correlation between RSBI and D-RSBI (R^2 = 0.892; P < 0.001).

Table 4: ROC curve for prediction of failed weaning by different parameters

Test Result Variable(s)	Cut off	Sensitivity	Specificity	P value	AUC	Asymptotic 95% Confidence Interval	
						Lower Bound	Upper Bound
DE	<15.5	94.1%	93.9%	< 0.001	0.947	0.897	0.997
DTF	<29%	67.6%	98.5%	< 0.001	0.848	0.757	0.938
B line score	11.5	79%	88%	< 0.001	0.899	0.829	0.970
RR	25.5	100%	62%	< 0.001	0.888	0.826	0.950
RSBI	73.5	80	100	< 0.001	0.957	0.908	1.006
D-RSBI	1.7	100	97	< 0.001	0.996	0.987	1.005

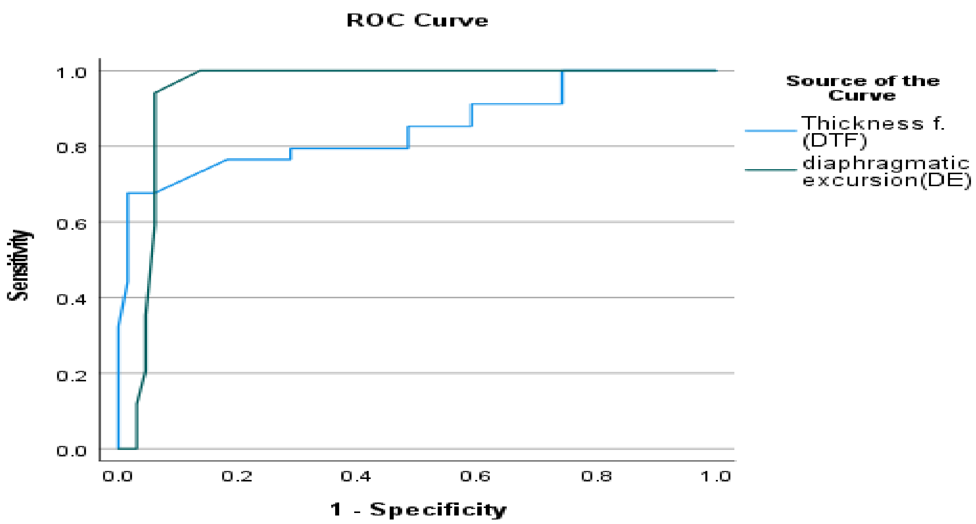

Figure 3: ROC curve for prediction of failed weaning by DTF and DE

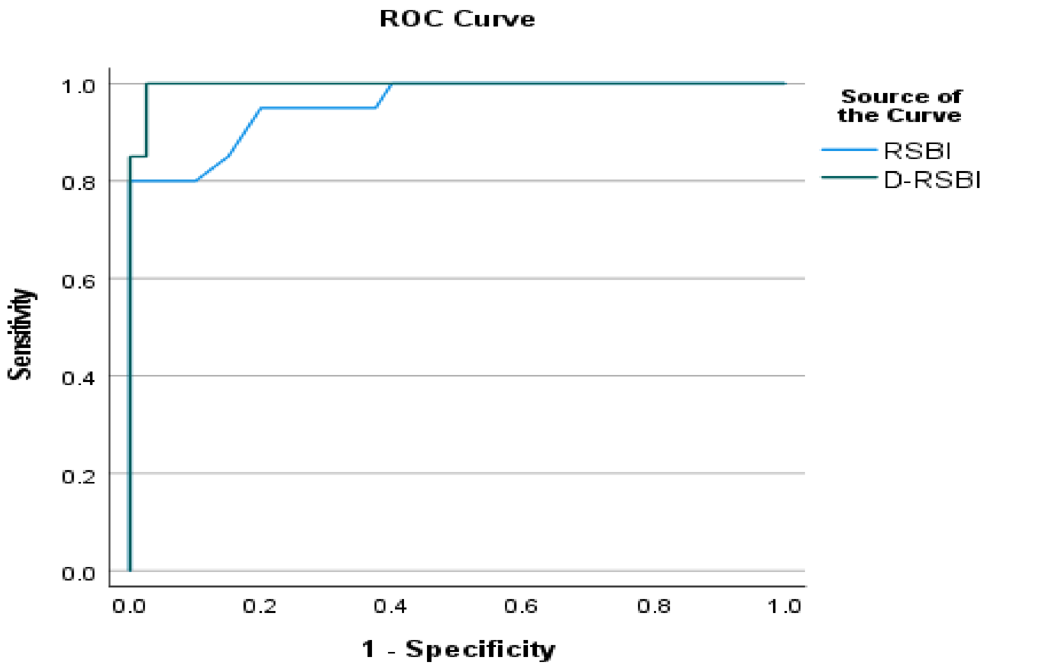

Figure 4: ROC curve for prediction of failed weaning by RSBI and D-SBI.

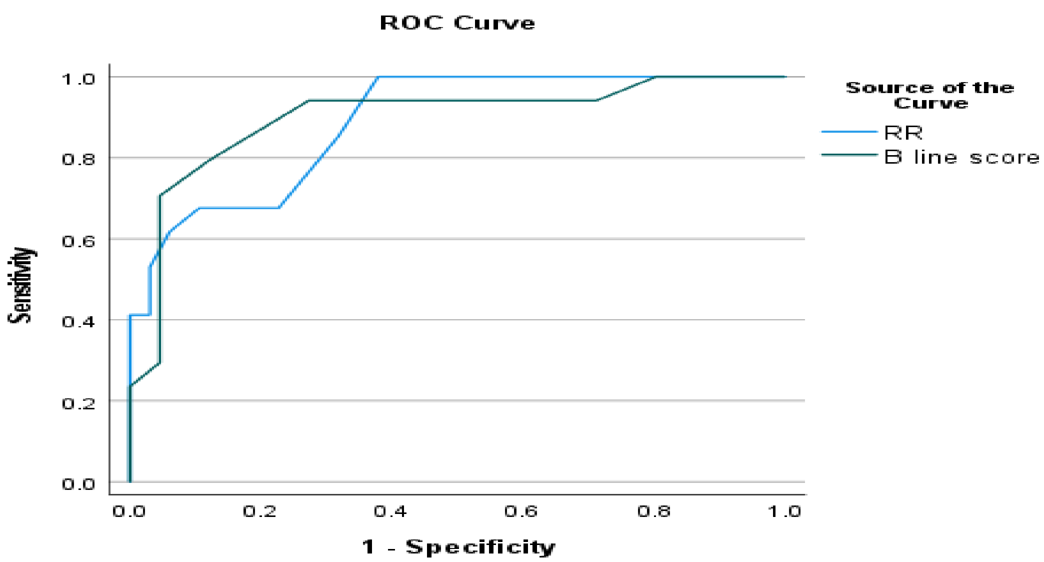

Figure 5: ROC curve for prediction of failed weaning by RR and B line score

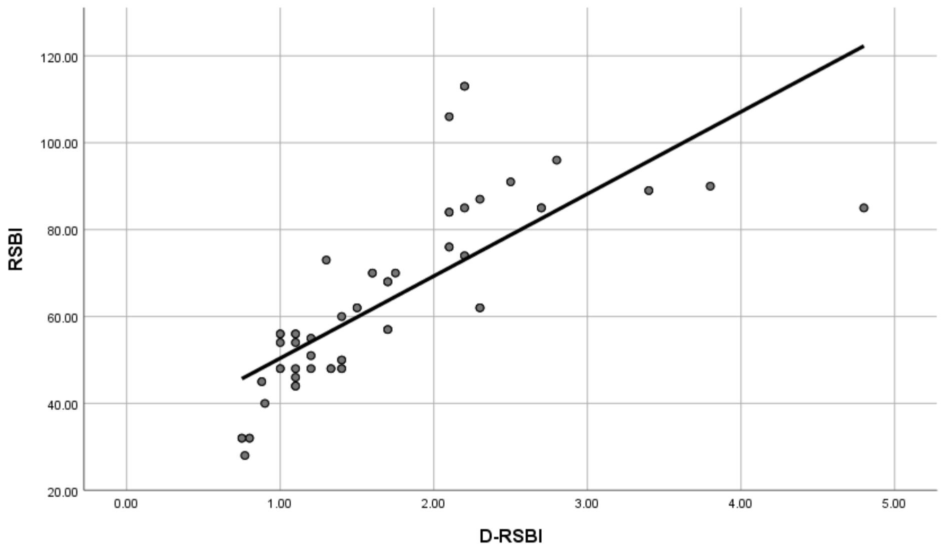

Figure 6: Correlation between D-RSBI and RSBI

New scores for prediction of weaning outcomes

BLI-d validation analysis for Dn anderivatio:

A – Derivation sample: Two new scores were derived by preliminary logistic regression including B line score and diaphragmatic excursion for prediction of weaning outcomes.

The derived Diaphragmatic B line index (D-BLI) was derived from the following equation:

Derived D-BLI= -0.255– (0.504*B line score) + (0.592* Diaphragmatic excursion)

Diaphragmatic B line index (D-BLI) was a new simplified score proposed by dividing diaphragmatic excursion over B line score (DD/B line score).

At a cut off **4** of derived **D-BLI**, its sensitivity to predict the successful weaning was 88% and its specificity was 100 % (AUC=0.981) while at a cut off **1.48** of **D-BLI**, its sensitivity to predict the successful weaning was 88% and its specificity was 100 % (AUC=0.980) **[Table 5 & Figure 7].**

Tale (5): ROC curve for prediction of succcessful weaning (derivation sample)

Test Result Variable(s)	Cut off	Sensitivity	Specificity	P value	AUC	Asymptotic 95% Confidence Interval	
						Lower Bound	Upper Bound
Derived D-BLI	4	88%	100 %	<0.001	0.981	0.949	1.000
D-BLI	1.48	88%	100%	<0.001	0.980	0.946	1.000

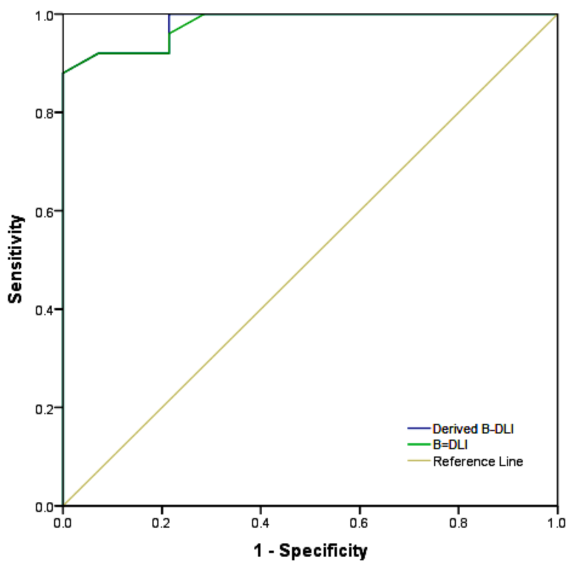

Figure 7: ROC curve for prediction of successful weaning (derivation sample)

B – Validation sample:
Both scores were applied to a new 60 patients by the validation sample. At a cut off **4** of derived **D-BLI**, its sensitivity to predict the successful weaning was 90% and its specificity was 100 % (AUC=0.998) while at a cut off **1.48** of **D-BLI**, its sensitivity to predict the successful weaning was 95% and its specificity was 95 % (AUC=0.992) **[Table 6 & Figure 8].**

Tale (6): ROC curve for prediction of successful weaning (validation sample)

Test Result Variable(s)	Cut off	Sensitivity	Specificity	P value	AUC	Asymptotic 95% Confidence Interval	
						Lower Bound	Upper Bound
Derived D-BLI	4	90%	100 %	<0.001	0.998	0.991	1.000
D-BLI	1.48	95%	95%	<0.001	0.992	0.979	1.000

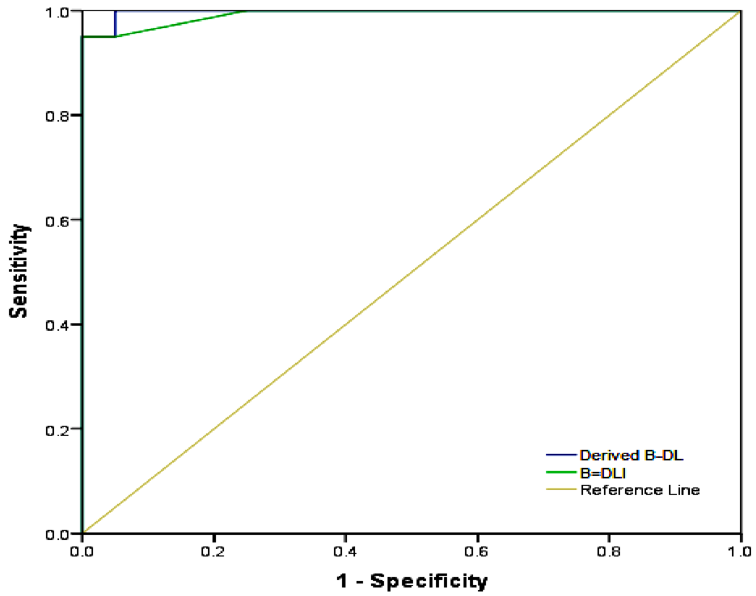

Figure 8: ROC curve for prediction of successful weaning (validation sample)

DISCUSSION
Weaning from mechanical ventilation can be defined as the way of gradually liberating the patient from ventilatory mechanics [2]. Mechanical ventilation can be discontinued in roughly 75% of mechanically ventilated patients whose underlying reason of respiratory failure has been resolved. Patients failing the weaning trial displayed higher length of ICU and hospital stay and mortality [23, 24].
The rapid shallow breathing index (RSBI) is one of the most widely used indices to predict weaning outcome. Delayed weaning failure is likely since the accessory muscles are more fatigable than the diaphragm [25].
The standard RSBI could be outfitted by replacing the tidal volume (VT) with diaphragmatic excursion (DE). The new talented index was named the diaphragmatic-RSBI (D-RSBI) [16]. The diaphragmatic rapid shallow breathing index (D-RSBI), which is the ratio between respiratory rate (RR) and diaphragmatic excursion (DE), is a new encouraging tool to predict weaning outcome [26].
There were no statistically significant differences in preweaning comorbidities were detected between weaning success and weaning failure groups, except for pneumonia and heart failure (P=0.004, < 0.001) respectively.
In the same context, there was no statistically significant differences in pre-weaning comorbidities in **Spadaro et al.,** [16] and **Mowafy et al.,** [27] except for sepsis as a reason for initiating mechanical ventilation (P = 0.035 and 0.008) respectively.
Our results showed that **DE** was significantly higher [19.7 mm (9–27) vs. 12 mm (7–16) respectively] in the successful weaning group compared to the failed one. The cut-off points of **DE** that can predict failed weaning was < 15.5 mm at end of inspiration.

This was close to the cut-off point of **Farghaly et al.,** [28] which was < 11 mm and **Kim et al.,** [29] < 17.9 mm.

Different results of DE may be due to differences in posture, showing higher values when patients are supine versus seated, also diaphragmatic ultrasound requires the use of high frequency probes and different operators meaning that slight variations in measurement between observers can substantially affect the result [30, 31].

Our results showed that the cut-off point of **RSBI** for failed weaning from mechanical ventilation was > 73.5 breaths/min/L showed 80% sensitivity and 100 % specificity (AUC=0.957).

In the same context, the other cut off points were **Goharani et al.,** [32] ≥ 85 breaths/min/L showed 95% sensitivity and 90% specificity (AUC=0.910), **Spadaro et al.,** [16] ≥ 62 breaths/min/L showed 52% sensitivity and 97% specificity (AUC=0.720), **Banerjee et al.,** [33] ≥ 104 breaths/min/L showed 100% sensitivity and 100% specificity (AUC=0.996) and **Soliman et al.,** [34] ≥ 71 breaths/ min/L showed 80% sensitivity and 70% specificity (AUC=0.815), and all were associated with a failed SBT.

This was so far from the cutoff value of 105 breaths/ min/L originally described by **Yang and Tobin,** [25] to predict weaning failing attempts.

Our results showed that the cut-off point of **D-RSBI** for failed weaning from programmed ventilation was > **1.7** breaths/min/mm showed 100% sensitivity and 97% specificity (AUC=0.996).

In the same context, the other cut off points were **Spadaro et al.,** [16] >1.3 breaths/min/mm yielded 94.1 % sensitivity, 64.7 % specificity (AUC=0.890), **Chengfen et al.,** [35]]>1.42 showed 91% sensitivity and 82% specificity (AUC=0.830), **Walaa et al.,** [26] >1.9 showed 82% sensitivity and 93% specificity (AUC=0.970) and **Zaytoun et al.,** [36] > 1.6 breaths/min/mm showed 86% sensitivity and 93% specificity (AUC=0.895), and all were associated with a failed SBT.

Several other studies have documented a wide range of predictive values for **RSBI** and **D-RSBI**, which could reflect Differences in methodology **Banerjee et al.,** [33] all the measurements have taken after 20 min of giving SBT and **Spadaro et al.,** [16] spontaneous ventilation through a T-tube was done with the FiO_2 set at the same level used during mechanical ventilation, variable inspiratory efforts, severity of illness at ICU admission, metabolic conditions, and duration of MV [25,37,38].

Our results showed that the cut-off point of derived diaphragmatic B line index **(derived D-BLI)** (obtained from the derivation sample on 40 patients then applied on new 60 patient as a validation sample) for successful weaning from mechanical ventilation was > 4 showed 90% sensitivity and 100 % specificity (AUC=0.998). Our results showed that the cut-off point of diaphragmatic B line index (**D-BLI)** (a new simplified score proposed by dividing diaphragmatic excursion over B line score, DD/B line score) for successful weaning from mechanical ventilation was > 1.48 showed 95% sensitivity and 95 % specificity (AUC=0.992).

There was no significant difference between statistically derived score (derived **D-BLI**) and our simple score (**D-BLI)** in sensitivity or specificity. **D-BLI** is an ideal promising and talented index should reflect all pathophysiological pathways that may lead to weaning failure, including excessive mechanical workload imposed on the respiratory muscles and impaired diaphragmatic function which was reflected by diaphragmatic excursion. Weaning induced cardiac failure, lung consolidative patches and reduced ability to keep the alveoli opened which was expressed by B line score.

It was proclaimed that different SBTs affected the outcome of weaning. PSV may be associated with lower weaning failure rates and T-tube may be related to a shorter weaning duration [39].

Limitations In this study could be summarized in: Patient population, our study was done on COPD patients. More clinical trials needed to be done on different clinical situations. A single physician performed the US. Nutritional status of the patients was not assessed which may affect muscle power. Being a single center study. Small derivation sample size for D-BLI for early prediction of failed weaning

CONCLUSIONS

D-RSBI (RR/DD) and D-BLI (DD/B line score) is a new, promising tools for prediction of weaning failure from mechanical ventilation.

Further studies on larger patient populations are required to validate the diagnostic accuracy of the D-RSBI and D-BLI for clinical prediction of weaning outcome.

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