

# The predictive value of diaphragm ultrasound for weaning outcomes in critically ill children

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## Research article

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# Abstract

**Background:** Multiple studies have shown that diaphragmatic ultrasound can better predict the outcome of weaning in adults. However, there are few studies focusing on children, leading to a lack of sufficient clinical evidence for the application of diaphragmatic ultrasound in children. The purpose of this study is to investigate the predictive value of diaphragm ultrasound for weaning outcomes in critically ill children.

**Methods:** The study included 50 cases whose mechanical ventilation (MV) time was >48 h, and all eligibles were divided into either the weaning success group (n = 39) or the weaning failure group (n = 11). Diaphragm thickness, diaphragmatic excursion (DE), and diaphragmatic thickening fraction (DTF) were measured in the zone of apposition. The maximum inspiratory pressure (P<sub>I</sub>max) was also recorded.

**Results:** The ventilatory treatment time (P = 0.002) and length of PICU stay (P = 0.013) in the weaning failure group was longer than the success group. Cut-off values of diaphragmatic measures associated with successful weaning were  $\geq 21\%$  for DTF with a sensitivity of 0.82 and a specificity of 0.81, whereas it was  $\geq 0.86$  cmH<sub>2</sub>O/kg for P<sub>I</sub>max with a sensitivity of 0.51 and a specificity of 0.82. The linear correlation analysis showed that DTF had significant correlation with P<sub>I</sub>max in children (P = 0.003).

**Conclusions:** Diaphragm ultrasound has great value in predicting the weaning outcome of critically ill children. DTF and P<sub>I</sub>max presented better performance than other diaphragmatic parameters. However, DE has limited value in predicting weaning outcomes of children with MV.

## Introduction

Mechanical ventilation (MV) technology is widely used in paediatric critical care. About 30% of children in the paediatric intensive care unit (PICU) receive MV support.<sup>[1]</sup> However, MV support is not the end of the treatment, and the ultimate goal is to help patients wean off of MV support. An international consensus conference on weaning from MV in 2007 proposed that weaning should be categorized into three groups: simple weaning, difficult weaning, and prolonged weaning.<sup>[2]</sup> A multicentre study has shown that 10% of patients with MV had a difficult weaning duration of more than 1 day and less than 1 week, and 9% had a prolonged weaning duration of 1 week or more.<sup>[3]</sup> Failure to wean (FTW) is generally defined as difficult and prolonged weaning. FTW has significantly worse clinical outcomes. Studies have shown that FTW is an independent risk factor for mortality in ICU patients and prolonged length of ICU stay, and it is also associated with the occurrence of intensive care unit-acquired weakness (ICU-AW) and ventilator-induced diaphragmatic dysfunction (VIDD).<sup>[4-6]</sup> Therefore, weaning from mechanical ventilation represents a crucial step for every patient. The optimal timing of weaning can shorten the duration of MV and reduce complications. Weaning predictors – such as rapid shallow breathing index (RSBI), airway occlusion pressure 0.1 s (P<sub>0.1</sub>), maximum inspiratory pressure (P<sub>I</sub>max), and the weaning index – have been used to improve the rate of successful weaning in adult studies.<sup>[7-9]</sup> Unfortunately, in terms of weaning success in children, there is an insufficient amount of data to suggest the usefulness of predictors being superior to clinical judgment.<sup>[10]</sup>

As a new technology in recent years, diaphragm ultrasound allows for the direct visualisation of the diaphragmatic function of patients,<sup>[11-13]</sup> which has the advantages of being noninvasive, rapid, and easy to perform at the bedside. Therefore, it is suitable for application in patients with MV in ICU.<sup>[12, 13]</sup> Multiple adult studies have shown that diaphragmatic ultrasound can better predict the outcome of weaning, which has great value on guiding weaning in patients with MV.<sup>[14-16]</sup> However, there are few studies of diaphragmatic ultrasound in the field of paediatric critical medicine, leading to diaphragmatic ultrasound data being insufficient. In addition, the respiratory physiology and anatomical characteristics of children are different from that of adults. Therefore, the conclusions of adult studies may not be applicable to children, and more studies in children are needed to confirm the effectiveness of diaphragmatic ultrasound in predicting the outcome of weaning. This paper is the first study to investigate the predictive value of diaphragm ultrasound for weaning outcomes in critically ill children.

## Methods

### Patients

This prospective study was conducted in the paediatric intensive care unit of First Hospital of Jilin University, Changchun, China. Study subjects included 61 consecutive patients between January 2019 and May 2019, who were aged less than 18 years. The institutional ethics committee of the hospital approved the study protocol (ChiCTR1800020196). The parents or guardians of the eligible children provided written informed consent. An information sheet was provided for the parents or guardians of the participants.

All children who received mechanical ventilation support for  $\geq 48$  h and met standard criteria for weaning readiness (improvement in the cause of primary disease,  $P_{aO_2}/F_{iO_2} > 200$ , positive end-expiratory pressure (PEEP)  $\leq 5-10$  cm H<sub>2</sub>O,  $F_{iO_2} \leq 50\%$ , and hemodynamically stable in the absence of vasopressors) were included in the study.<sup>[17]</sup> If the child experienced a known neuromuscular disease (such as amyotrophic lateral sclerosis, Guillain-Barre, or myasthenia gravis), cervical spinal cord injury, pneumothorax, death during mechanical ventilation, or if there was an unwillingness of the parents or guardians to participate in the study, then that child was excluded from the study.

### Study Design

All eligibles underwent the spontaneous breathing test (SBT), which was performed using pressure support trials with a pressure support (8 cm H<sub>2</sub>O) and 5 cm H<sub>2</sub>O PEEP using Drager Evita 4 ventilator for 30 min (Patients who cannot tolerate spontaneous breathing tests during observation time were classified as weaning failed groups).<sup>[2]</sup> Ultrasound measurements and P<sub>I</sub>max were taken at the fifth minute after the start of SBT. The patient passed the SBT if the exhaled tidal volume was equal to or above 5 mL/kg of the ideal body weight, and if the respiratory rate remained within the targeted range for age (<6 months 20–50 breaths/min; 6 months – 2 yr. 15–45 breaths/min; 2 yr. – 5 yr. 15–40 breaths/min; >5 yr. 10–35

breaths/min).<sup>[18]</sup> All patients accepted the Venturi inside the mask for oxygen therapy after passing the SBT. Successful weaning was defined as the ability to maintain spontaneous breathing for >48 h.

## **Plmax Measurement**

The measurement of Plmax was occluding the airway at end expiration through a unidirectional valve, and maintained for approximately 10 breaths or 20 s.<sup>[19]</sup> Finally, the maximum negative pressure displayed by the ventilator was recorded. Body weight(BW) is known as the predictor of Plmax in healthy children<sup>[20]</sup> therefore, we standardised Plmax value by varying BW(Plmax/BW).

All patients were placed in a semi-recumbent position with the head of the bed at a 30-degree angle. Two experienced sonographers performed ultrasound measurements by using the same portable ultrasound machine (Mindray, M7 series, China), and the evaluators were blinded to the results of the SBT prior to measurement. In the present study, only the right hemidiaphragm was measured because the right hemidiaphragm was more feasible and repeatable compared with the left hemidiaphragm.<sup>[21]</sup> Diaphragm thickness (Tdi) was measured by using a 10 MHz linear probe at the zone of apposition at the right eighth or ninth intercostal space, which is between the anterior axillary and the midaxillary lines. The direction of the ultrasound probe was perpendicular to the diaphragm. At this position, the diaphragmatic ultrasound image was a hypoechoic structure between two echoic lines (the diaphragmatic pleura and the peritoneal membrane) in the B-mode (Fig. 1). In the same position, M-mode ultrasonography was used to measure resting Tdi at end-expiration (Tdi-exp) and end-inspiration (Tdi-insp), respectively (Fig. 2). The Tdi measurement was the inner edge of the peritoneal membrane to the inner edge of the diaphragmatic pleura. The calculation formula of diaphragmatic thickening fraction (DTF) was  $(Tdi-insp - Tdi-exp) / Tdi-exp$ . For the measurement of diaphragmatic excursion (DE), a 5 MHz probe was placed at the junction of the right mid-clavicle line and the right subcostal margin, where the probe direction paralleled the diaphragmatic movement. The diaphragmatic movement toward the probe during inspiration was recorded as an upward motion of the M-mode tracing, and the movement was opposite during expiration. In a breathing cycle, the amplitude of DE was the maximum point that moved vertically downward to the lowest point in M-mode (Fig. 3).<sup>[22, 23]</sup> The DE was continuously measured for 3 times in free breathing, and then the average was taken. DE and BW have significant positive correlations in children<sup>[24]</sup>. Therefore, we standardised DE by varying BW(DE/BW).

## **Statistical Analysis**

Analyses were carried out using IBM SPSS Statistics for Windows, Version 22.0 (IBM Corp, Armonk, NY). Depending on whether distribution was normal or non-normal, continuous variables were described as mean  $\pm$  SD or median (interquartile range). Categorical variables were described as n(%). Continuous variables were compared with Student's t-test or Mann-Whitney U test. Depending on sample size, categorical variables were compared with Chi-squared test or Fisher's exact test. The correlation analyses were conducted using the Pearson method to test the relationship between DTF, Plmax, and DE. To determine the best cut off for DE, DTF and Plmax to predict weaning success, the area under the receiver

operating characteristic (ROC) curve was calculated. For all final comparisons, a p-value less than or equal to 0.05 was considered statistically significant.

## Results

### Sample Characteristics

61 patients underwent mechanical ventilation support during the study period. Eleven cases were excluded: ten cases passed away during mechanical ventilation, and one case had pneumothorax. Finally, 50 patients met the inclusion criteria. Eligibles were divided into either the weaning success group (n = 39) or weaning failure group (n = 11) (Figure 4).

All patient characteristics are summarized in Table 1. Ventilatory treatment time ( $P = 0.002$ ) and length of PICU stay ( $P = 0.013$ ) in the weaning failure group was significantly longer than the success group. Three cases passed away occurred after 48 hours of successful extubation in the failure group, the in-hospital mortality was 27.3% (3/11), and there was one died in the success group. The DTF ( $P < 0.001$ ) and was significantly higher in the weaning success group than the failure group. However, it should be noted that there were no differences in Tdi, DE or PImax between the weaning success and failure groups (Table 2).

### Diaphragmatic parameters and PImax predict the value of weaning success

Of the 39 patients who were categorized as having successful weaning, 32 had a DTF of  $\geq 21\%$ . Of the 11 who failed weaning, 9 had a DTF  $< 21\%$ . The resulting positive predictive value (PPV) and negative predictive value (NPV) was 94% and 56%, respectively. 20 cases with PImax  $\geq 0.86$  cmH<sub>2</sub>O/kg in the 39 patients who were successfully weaning, and 9 cases had a DE  $< 0.86$  cmH<sub>2</sub>O/kg of the 11 who failed weaning, had a resulting PPV and NPV of 91% and 32%, respectively.

An ROC curve was used to assess the diagnostic accuracy of DTF, DE and PImax in predicting weaning success. A cut-off value of DTF  $\geq 21\%$  was associated with weaning success with a sensitivity of 82% and a specificity of 81%. A cut-off value of PImax  $\geq 0.86$  cmH<sub>2</sub>O/kg was associated with weaning success with a sensitivity of 51% and a specificity of 82%, as shown in Table 3. The area under the ROC curve for DTF was 0.89 (95% confidence interval [0.78 to 0.99]) (Supplemental Figure 1A), and for PImax it was 0.70 (95% confidence interval [0.52 to 0.88]) (Supplemental Figure 1B). DE has limited value in predicting weaning success ( $P = 0.20$ ). The area under the ROC curve for DE was 0.63 (95% confidence interval [0.43 to 0.83])

### Correlation analysis within DTF, PImax, and DE

A Pearson linear correlation analysis was performed within DTF, PImax, and DE (Supplemental Table 1). The results showed that DTF had significant correlation with PImax ( $r = 0.410$ ,  $P = 0.003$ ). The same analysis was also performed between DTF and DE. The results showed that there was significant correlation between DTF and DE ( $r = 0.380$ ,  $P = 0.006$ ).

## Discussion

This paper is the first study to investigate the predictive value of diaphragm ultrasound for weaning outcomes in critically ill children. The findings of this study demonstrate that the DTF of patients in the group of weaning failure were significantly lower than those in the successful group, which is consistent with the results of previous study,<sup>[21, 25, 26]</sup> indicating that the patients with weaning failure generally had diaphragmatic dysfunction (DD). At the same time, the study also demonstrates that the duration of MV in the failed group was significantly longer than that in the successful group, suggesting that the prolonged MV had promoted the occurrence of DD. Respiratory muscle weakness in critically ill patients was associated with difficulty in weaning from mechanical ventilation.<sup>[27]</sup> Therefore, monitoring diaphragm function during SBT was important for predicting the outcomes of weaning.

Among the 50 patients within the present study, the rate of weaning success was 78% (39/50), and the rate of weaning failure was 22% (11/50), which was lower than the previous study (30%).<sup>[28]</sup> The areas under the ROC curve of DTF and P<sub>I</sub>max for patients with weaning success were 0.89 and 0.70, respectively. An optimal cut-off value for predicting weaning success of DTF and P<sub>I</sub>max were 21% and 0.86 cmH<sub>2</sub>O/kg. The results of the present study showed that DTF  $\geq$  21% was associated with weaning success with a sensitivity of 0.82 and a specificity of 0.81, and P<sub>I</sub>max  $\geq$  0.86 cmH<sub>2</sub>O/kg was associated with weaning success with a sensitivity of 0.51 and a specificity of 0.82. Both have good value for predicting weaning success of children, but the predictive value of DTF is better than that of P<sub>I</sub>max. A study by Ferrari established that a DTF of 36% predicted successful weaning in patients requiring long-term ventilator support.<sup>[29]</sup> Farghaly et al. have showed that DTF%  $\geq$  34.2% was associated with successful extubation.<sup>[23]</sup> The results of the above studies are all adults, and the results of the present study (DTF  $\geq$  21%) are lower than the above studies. The main reasons for consideration are as follows: the thickness and strength of human skeletal muscle fibres vary with age, and the diaphragm is a skeletal muscle that also conforms to this physiological change,<sup>[24]</sup> thus the DTF of children will be less than that of adults. In addition, the majority of patients in adult studies were elderly chronic obstructive pulmonary disease (COPD) patients, whose diaphragmatic muscle fibres had a chronic oxidative remodelling process,<sup>[30]</sup> leading to diaphragm compensatory ability weakness. Accordingly,<sup>[30]</sup> more extensive contraction was needed to meet the ventilation. Further, most patients for studies that focus on children suffered mostly from acute respiratory diseases such as severe pneumonia and laryngitis – whose diaphragm had no chronic oxidative remodelling process and had good compensatory ability. The above may be the main reasons for the differences found between the results of the present study and those of adults.

P<sub>I</sub>max is often used in the assessment of respiratory muscles, which can indirectly react to inspiratory muscle strength. The study conducted by Ferrari et al.<sup>[29]</sup> demonstrated that P<sub>I</sub>max was positively correlated with DTF in adults with mechanical ventilation ( $r = 0.71$ ,  $P < 0.05$ ). Ueki et al.<sup>[31]</sup> have provided a similar result ( $r = 0.82$ ,  $P < 0.01$ ). Our study has also found that the significant linear correlation between DTF and P<sub>I</sub>max. And it should be noted that we need to standardise P<sub>I</sub>max value by varying BW.

However, the predictive value of P<sub>I</sub>max in children was not better as adults<sup>[32]</sup>. In the process of measuring P<sub>I</sub>max, it was determined that the cooperation of children was significantly lower than that of adults, resulting in insufficient inspiratory effort. In addition, P<sub>I</sub>max is the result of a combination of all inspiratory muscles, though the development of intercostal muscles and sternocleidomastoid muscles in children was immature.<sup>[33]</sup> The above factors will reduce the predictive value of P<sub>I</sub>max in children.

There are several limitations in this study. First, a relatively small population was studied. Especially since 11 patients failed to wean, the ability to predict weaning success within the present study was not sufficiently provided. Second, DE has better value of predicting weaning outcome in adults. But in our study, DE had limited value in predicting weaning outcomes, although we standardised DE by varying BW. This may due to the size of sample. Third, because there is currently no reference value of DTF in children, it is unknown whether the initial diaphragmatic function of the enrolled children within the present study is abnormal or not. Finally, though diaphragmatic endurance is also important for weaning from mechanical ventilation, the present study only assesses the diaphragm muscle strength. Therefore, the diaphragmatic time-tension index and other indicators can be used to explore the relationship between diaphragmatic endurance and weaning outcome.

## Conclusion

Diaphragm ultrasound has great value in predicting the weaning outcome of critically ill children. DTF and P<sub>I</sub>max showed better performance in predicting weaning outcomes than other diaphragmatic parameters. However, DE has limited value on predicting weaning outcomes in children with MV.

## Abbreviations

PICU: pediatric intensive care unit; MV: mechanical ventilation; PCIS: pediatric critical illness score; ICU-AW: intensive care unit-acquired weakness; FTW: failure to wean; VIDD: ventilator-induced diaphragmatic dysfunction; RSBI: rapid shallow breathing index; P<sub>0.1</sub>: airway occlusion pressure 0.1 s; P<sub>I</sub>max: maximum inspiratory pressure; SBT: spontaneous breathing test; T<sub>di</sub>: diaphragm thickness; DTF: diaphragmatic thickening fraction; DE: diaphragmatic excursion; VT: tidal volume; PPV: positive predictive value; NPV: negative predictive value; AUC: area under curve; IQR: interquartile range; SD: Standard Deviation; PEEP: positive end-expiratory pressure; COPD: chronic obstructive pulmonary disease; BW: body weight

## Declarations

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### Funding:

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### **Availability of data and materials:**

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

### **Authors' contributions:**

Yang Xue conceived the study design and data collection. Zhen Zhang participated in the study design. Chu-Qiao Sheng performed statistical analyses. Yu-Mei Li participated in literature search. Fei-Yong Jia reviewed the manuscript. All authors interpreted the data, contributed to the intellectual content, reviewed the manuscript, and approved the final version.

### **Ethics approval and consent to participate**

The study was approved by the institutional ethics committee of the hospital, the First Hospital of Jilin University (ChiCTR1800020196). The parents or guardians of the eligible children provided written informed consent. An information sheet was provided for the parents or guardians of all the participants.

### **Consent for publication**

Not applicable.

### **Competing interests**

The authors declare that they have no competing interests.

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the first weaning trial. *Respir Care* 2011; 56(5): 716-717. 29. Ferrari G, G De Filippi, F Elia, et al. Diaphragm ultrasound as a new index of discontinuation from mechanical ventilation. *Crit Ultrasound J* 2014; 6(1): 8. 30. Zhang Y, Gao J, Luo Y, et al. The effect of various durations of cigarette smoke exposure on muscle fibre remodeling in rat diaphragms. *Biomed Pharmacother* 2019; 117:109053. 31. Ueki J, PF De Bruin, and NB Pride. In vivo assessment of diaphragm contraction by ultrasound in normal subjects. *Thorax* 1995; 50(11): 1157-1161. 32. Bruton, Anne. A pilot study to investigate any relationship between sustained maximal inspiratory pressure and extubation outcome. *Heart & Lung* 2002; 31(2): 0-149. 33. Yang X, PF Xu, L Shan, et al. Advances in respiratory assessment and treatment in children undergoing invasive mechanical ventilation. *Zhong guo Dang Dai Er Ke Za Zhi* 2019; 21(1): 94-99.

## Tables

**Supplemental Table 1. linear correlation between DTF and PImax, DE**

Factors	DTF	
	<i>r</i>	<i>P</i>
DE	0.380	0.006
PImax	0.410	0.003

**DTF** = diaphragmatic thickening fraction; **DE** = diaphragmatic excursion; **PImax** = maximum inspiratory pressure

**Table 2. Weaning indexes of all patients**

Weaning indexes	Weaning success	Weaning failure	<i>P</i>
	Group(n=39)	Group(n=11)	
DTF%(mean±SD)	30.93±11.23	15.98±6.65	<b>&lt;0.001</b>
DE, mm/kg(mean±SD)	0.74±0.75	0.45±0.32	0.23
Tdi at end inspiration, mm/kg(mean±SD)	1.07±0.88	1.08±0.62	0.97
Tdi at end expiration, mm/kg(mean±SD)	0.79±0.61	0.91±0.49	0.59
PImax, cmH <sub>2</sub> O/kg(mean±SD)	0.91±0.56	0.56±0.49	0.07

**DTF**= diaphragmatic thickening fraction, **DE**= diaphragmatic excursion, **Tdi**= diaphragm thickness

**PImax**= maximum inspiratory pressure

**Table 3. DTF and PImax**

Parameters	Sensitivity(%)	Specificity(%)	PPV(%)	NPV(%)	AUC
DTF $\geq$ 21%	82	81	94	56	0.89
PImax $\geq$ 0.86cmH <sub>2</sub> O/kg	51	82	91	32	0.70

**PPV**= positive predictive value, **NPV**= negative predictive value, **AUC**= area under curve

## Supplemental Figure

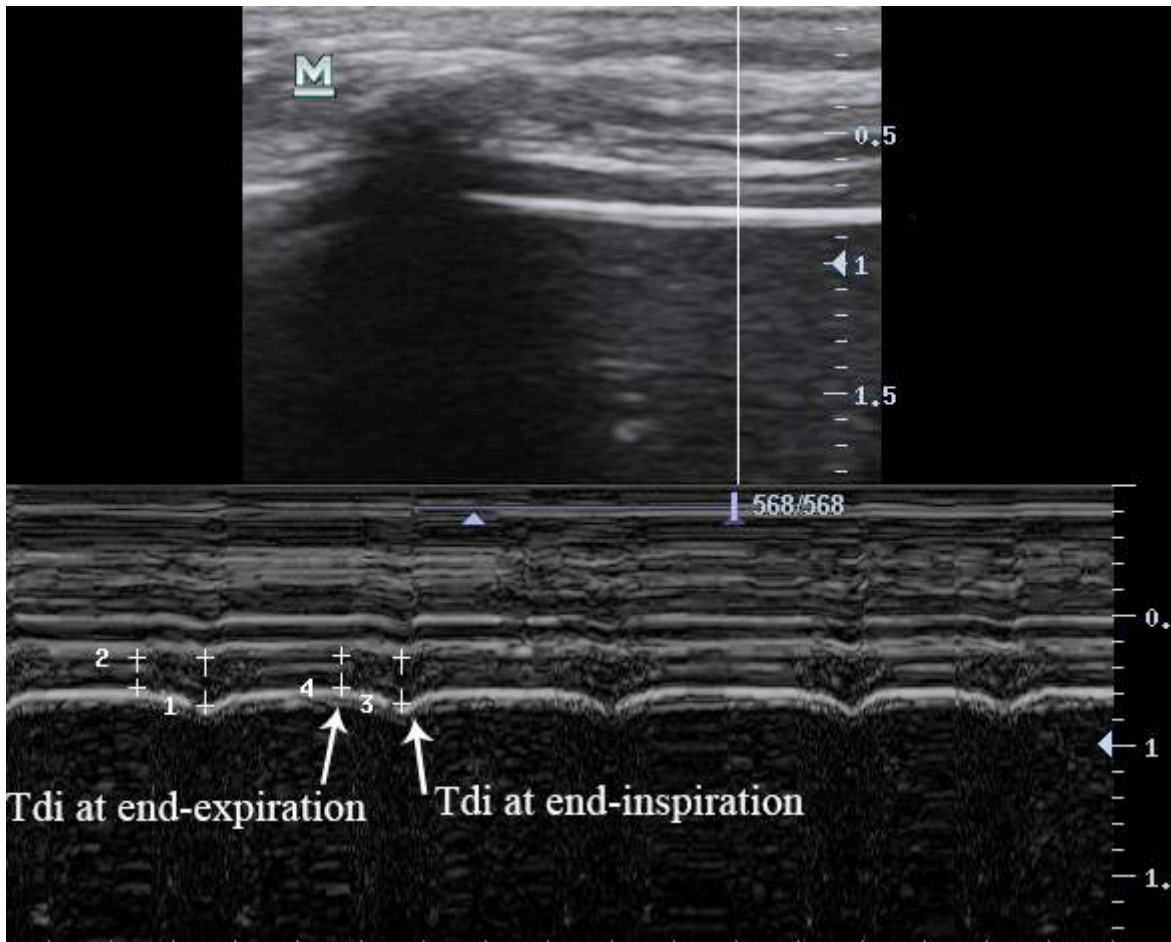
**Supplemental Figure 1A** Area under receiving operating characteristic curve for DTF% to predict weaning success. The optimum cut-off value of DTF% was  $\geq$ 21% with an AUC of 0.89 (95% CI [0.78 to 0.99]); **1B** Area under receiving operating characteristic curve for DE to predict weaning success. The optimum cut-off value of DE was  $\geq$ 8.40 mm with an AUC of 0.77 (95% CI [0.64 to 0.91]).

## Figures



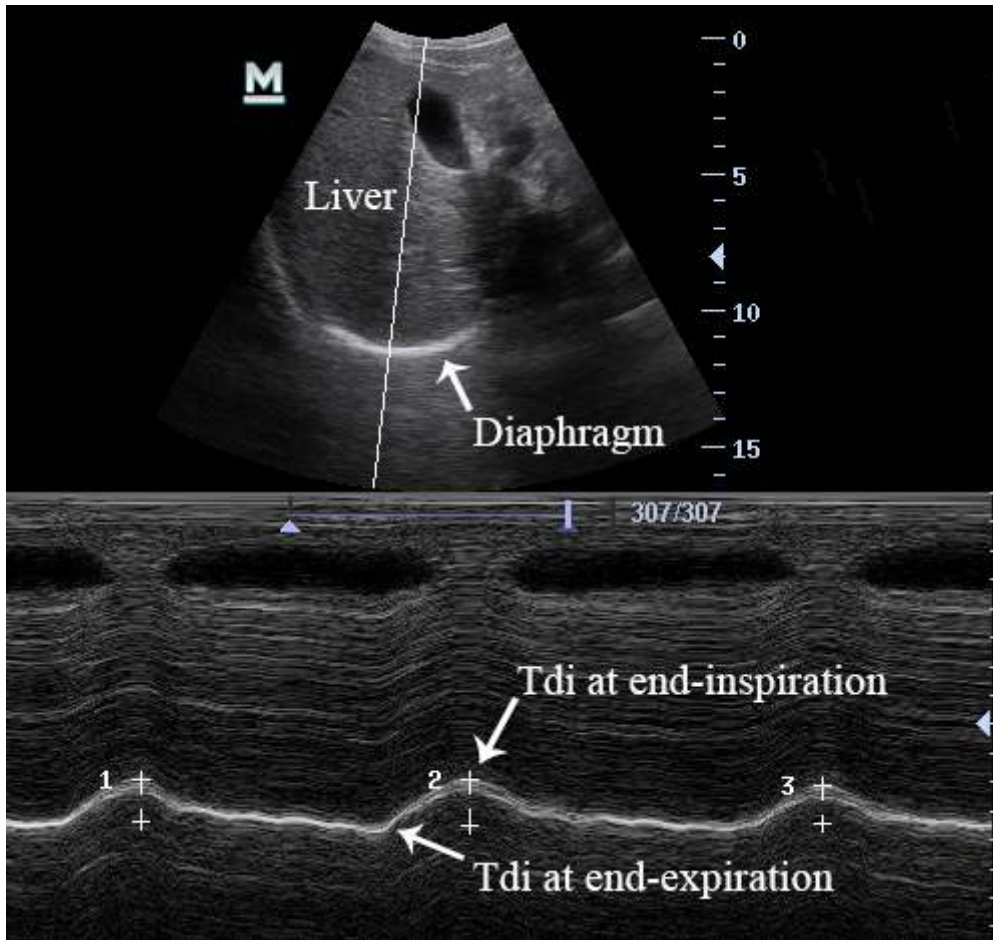
Figure 1

Ultrasound B-mode using a 10 MHz probe in the zone of apposition.



**Figure 2**

Ultrasound M-mode using a 10 MHz probe in the zone of apposition.



**Figure 3**

Ultrasound assessment of diaphragm diaphragmatic excursion in M-mode.

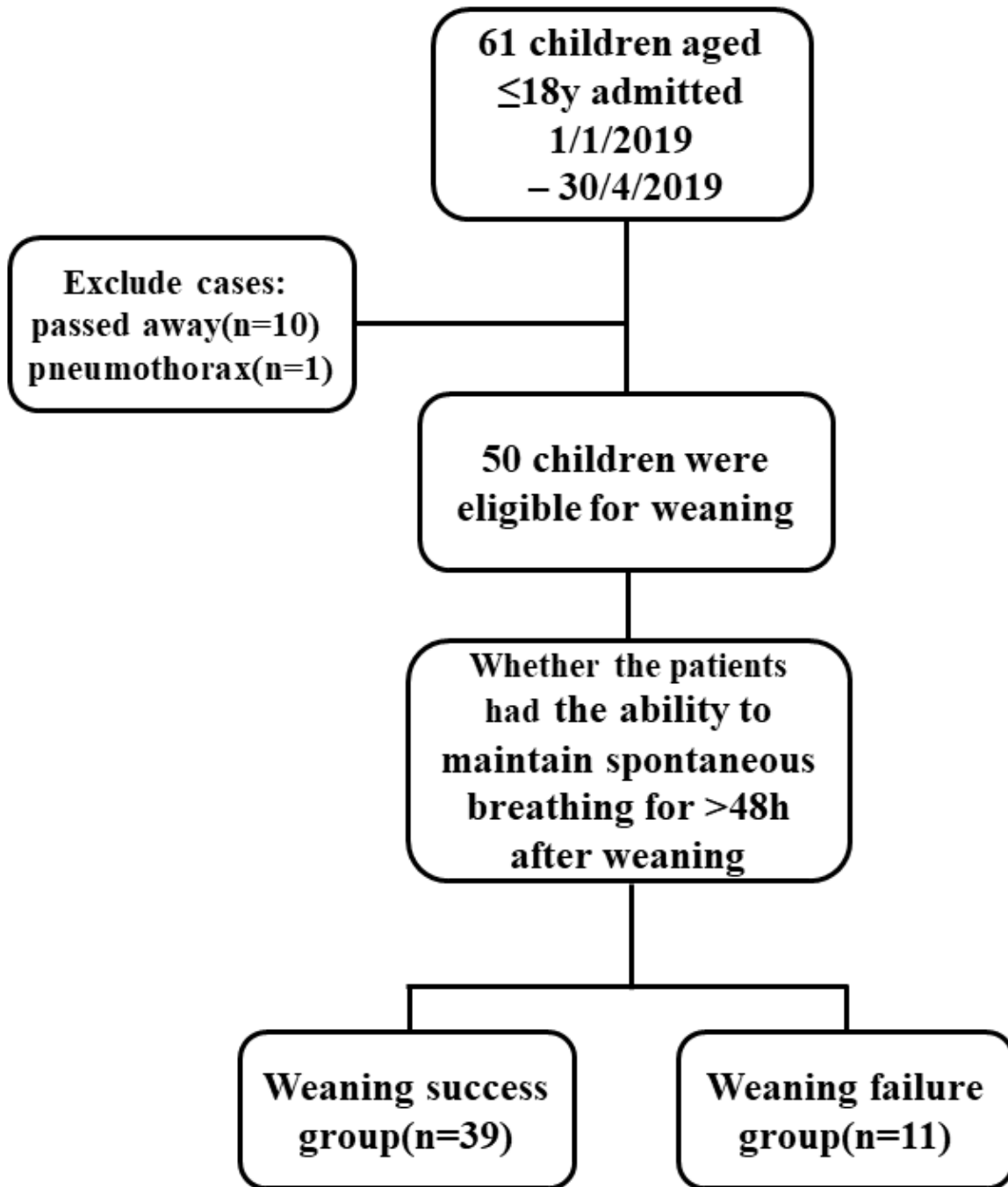
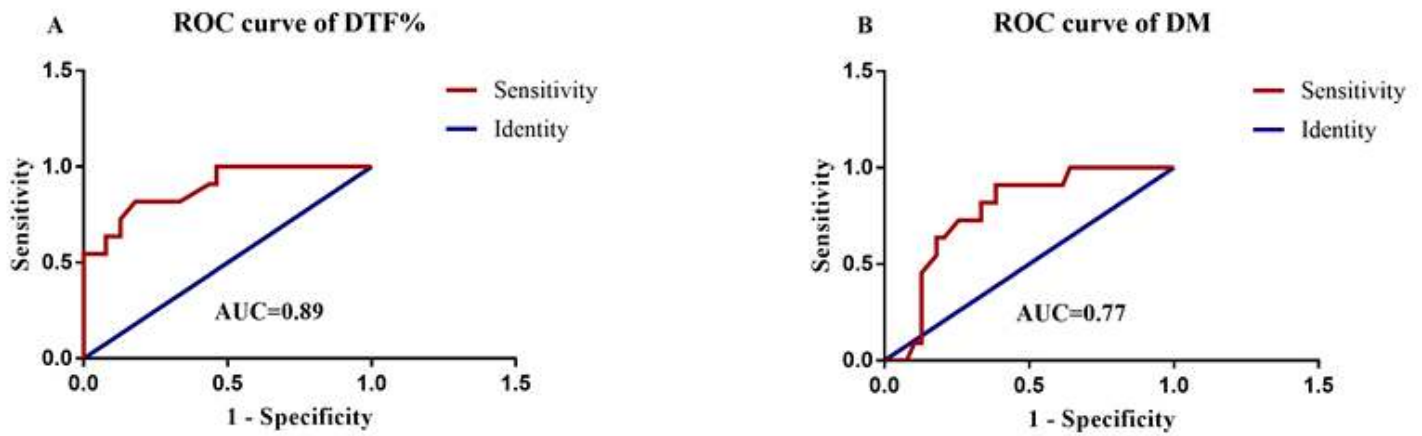


Figure 4

Flow chart of this study.



**Figure 5**

5A Area under receiving operating characteristic curve for DTF% to predict weaning success. The optimum cut-off value of DTF% was  $\geq 21\%$  with an AUC of 0.89 (95% CI [0.78 to 0.99]); 5B Area under receiving operating characteristic curve for DE to predict weaning success. The optimum cut-off value of DE was  $\geq 8.40$  mm with an AUC of 0.77 (95% CI [0.64 to 0.91]).

## Supplementary Files

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