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# Diaphragmatic ultrasonography for predicting ventilator weaning

## A meta-analysis

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**Abstract**

**Background:** Weaning failure is common in mechanically ventilated patients. Whether ultrasound can predict weaning outcome remains controversial. This meta-analysis was performed to assess the accuracy of diaphragmatic ultrasonography for predicting reintubation within 48 hours of extubation.

**Methods:** Literature search was performed in PubMed, Embase, and Cochrane Library to identify all the relevant papers, published in English up to July 16, 2017. Eligible studies were included if data were in adequate details to rebuild 2 × 2 contingency tables. Methodological quality of the included studies was evaluated using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) in Review Manager 5.3. The sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), diagnostic odds ratio (DOR), and summary receiver operating characteristic (SROC) curve were pooled using the fixed or random effects model, meanwhile, the heterogeneity was evaluated using Cochran *Q* test and $I^2$ statistics in Meta-DiSc 1.4. Publication bias was assessed using Deeks funnel plot in Stata 12.0.

**Results:** Thirteen studies with 742 subjects were included in this meta-analysis. The pooled sensitivities for diaphragm excursion (DE) and diaphragm thickness fraction (DTF) were 0.786 and 0.893, and the pooled specificities were 0.711 and 0.796, respectively. The area under curve (AUC) for DE and DTF were 0.8590 and 0.8381. The DORs for DE and DTF were 10.623 and 32.521. No publication bias was observed among these studies.

**Conclusions:** Diaphragmatic ultrasonography is a promising tool for predicting reintubation within 48 hours of extubation. However, due to heterogeneities among the included studies, large-scale studies are warranted to confirm our findings.

**Abbreviations:** AUC = area under curve, CI = confidence interval, DE = diaphragm excursion, DOR = diagnostic odds ratio, DTF = diaphragm thickness fraction, NLR = negative likelihood ratio, PImax = maximum inspiratory pressure, PLR = positive likelihood ratio, QUADAS = Quality Assessment of Diagnostic Accuracy Studies, RSBI = rapid shallow breathing index, SBT = spontaneous breathing test, SROC = summary receiver operating characteristic, VE = minute ventilation, VT = tidal volume.

**Keywords:** diagnosis, diagnostic accuracy, diaphragmatic displacement, diaphragmatic thickening, mechanical ventilator weaning, ultrasonography, ventilator weaning

## 1. Introduction

After the recovery of underlying conditions, most patients can be weaned from the mechanical ventilation successfully, given that they have sufficient gas exchange, good neurological and muscular status, and hemodynamic stability. However, weaning failure, defined as the requirement of invasive or noninvasive mechanical ventilation within 48 hours after extubation,[1] is extremely common. About 20% of mechanically ventilated patients confront weaning failure and require reintubation.[2] Weaning failure is associated with prolonged mechanical ventilation and ICU stay, as well as increased hospital mortality[2,3] ranging between 40% and 50%.[4] Delay in weaning from ventilator increases the inherent risks of mechanical ventilation, such as barotrauma, ventilator-associated pneumonia, and ventilator-induced diaphragmatic atrophy.[5] Thus, patients should be weaned from mechanical ventilation once they are able to cope with the respiratory load to avoid diaphragmatic dysfunction and infection, as well as to decrease the length of ICU and hospital stay.[6,7]

Current guidelines for weaning[8,9] recommend spontaneous breathing trial (SBT) as a tool to predict weaning outcome. However, 13% to 26% of patients who are extubated following a successful SBT need to be reintubated within 48 hours.[10,11] Many other weaning parameters have been used to predict weaning failure, including rapid shallow breathing index (RSBI), minute ventilation (VE), and maximum inspiratory pressure (PImax), but none has shown great prognostic accuracy.[2,12]

The diaphragm is the principal respiratory muscle. With an excursion of 1 to 2 cm, the diaphragm provides nearly 75% of the

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resting pulmonary ventilation, while during the forced breathing, its amplitude is up to 7 to 11 cm.[13] However, the diaphragm is vulnerable to damage from hypotension, hypoxia, and sepsis, all of which are very common in critically ill patients.[14,15] While in surgical patients, diaphragm dysfunction is often caused by acute insults such as trauma or surgical procedures. In addition, mechanical ventilation itself can decrease the force of the diaphragm and induce diaphragmatic dysfunction, named as ventilator-induced diaphragmatic dysfunction.[16,17] Many studies have shown that diaphragm dysfunction might lead to weaning failure and long-term mechanical ventilation.[18–21] Diaphragm dysfunction is responsible for a number of pulmonary complications, including atelectasis and pneumonia, which are risk factors for extubation failure. Hence, an early diagnosis of diaphragm dysfunction (before extubation) is mandatory to avoid weaning failure.

In recent years, diaphragmatic ultrasonography has emerged as a safe, no radiation, bed-side tool for assessment of diaphragm function and prediction of weaning outcome.[19] It provides both morphological and functional information in real time. Furthermore, it allows repeated measurements over time. Several ultrasound techniques, such as B-mode and M-mode, have been used to assess diaphragm sonographic predictors: diaphragm excursion (DE), which measures the distance that the diaphragm is able to move during the respiratory cycle, and diaphragm thickness fraction (DTF), which is the ratio between the difference in thickness from inspiration and expiration divided by the thickness on expiration [(Tinsp – Texp)/Texp].[22,23] DTF and DE during respiration reflect diaphragm function and are similar to "thickening fractions and motion amplitude" of the heart. Diaphragm thickness measured at end inspiration correlates with maximal inspiratory pressure[24] and the change in diaphragm thickness during respiration is strongly related to lung volume.[25]

However, the results are still controversial. For instance, some studies reported that DE and DTF had high sensitivity and specificity in predicting weaning outcome,[26,27] while others had opposite results.[28,29] To gain a more reliable conclusion, we performed this meta-analysis to summarize the overall performance of DE and DTF on predicting reintubation within 48 hours of extubation.

## 2. Methods

We carried out this systematic review following a predefined protocol, which was published in the International Prospective Register for Systematic Reviews with the registration number CRD42017072593. As it is a meta-analysis of the previous works of literature, approval of the ethics committee was not required.

### 2.1. Literature search

A comprehensive and systematic literature search was conducted by 2 independent researchers (CL and XL) in PubMed, Embase, and Cochrane Library up to July 16, 2017, using the following terms: "Ventilator Weaning," "Respirator Weaning," "Mechanical Ventilator Weaning," "Ultrasonography," "Ultrasound Imaging," "Diaphragm," "Diaphragmatic displacement," "Diaphragmatic thickening," "Sensitivity and Specificity," "Diagnosis," and "Diagnostic accuracy." In addition, the reference lists of the included studies were hand-screened to find potentially related papers.

### 2.2. Study selection

Studies that met the following criteria were included: participants aged ≥18 years; focused on ability or accuracy of diaphragmatic ultrasonography on predicting weaning outcome; published in English; provided sufficient data to calculate true-positive, false-positive, false-negative and true-negative numbers; defined weaning failure as the requirement of mechanical ventilation within 48 hours after extubation; protocols[30] and conference proceedings published as abstracts[31,32] were excluded.

### 2.3. Data extraction and quality assessment

Two researchers (CL and XL) independently carried out a primary screening of studies based on the titles and abstracts, then they conducted an examination of full texts in accordance with the eligibility criteria. Data were abstracted from included studies, including first author, year of publication, study period, location, setting, study design, target patient, number of patients, age, gender, patient position, the delay between diaphragmatic ultrasonography and weaning, cutoff value, right or left hemidiaphragm, machine and probe, probe position, number and skills of operator. Study quality was assessed by QUADAS-2,[33] which consisted of 4 domains: patient selection, index test, reference standard, flow and timing. A third author (HC) was invited to resolve any discrepancies between the 2 researchers.

### 2.4. Statistical analysis

Review Manager 5.3 (Cochrane Collaboration, Oxford, England) was used for quality assessment. Meta-DiSc 1.4 (Romany Cajal Hospital, Madrid, Spain) and Stata 12.0 (Stata Corporation, College Station, TX) were used for analysis. Sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), and diagnostic odds ratio (DOR) were pooled independently. The threshold effect was tested using Spearman correlation analysis. Heterogeneity was judged by Cochran *Q* test and $I^2$ statistics. If significant heterogeneity existed ($P < .05$ or $I^2 > 50\%$), the random effect model was used to calculate the pooled effect size; otherwise, the fixed effect model was applied.[34] Source of heterogeneities was detected by meta-regression analysis. Sensitivity analysis was also performed by removing the trials one by one to find the source of heterogeneities and evaluate the reliability of the results. Probable publication bias was estimated by Deeks funnel plot.

## 3. Results

### 3.1. Literature search

The process of literature search and selection is shown in Figure 1. Forty-two papers were obtained according to the search strategy, then 5 duplicates were removed. After screening for the titles and abstracts, 23 papers were excluded due to the irrelevant contents. Among the remaining articles, 8 were excluded because of reviews (n = 5), abstracts (n = 2), and protocol (n = 1). Finally, 6 studies[1,23,27,29,35,36] and 7 hand-screened studies,[22,26,28,37–40] which met the selected criteria, were included in our meta-analysis.

### 3.2. Characteristics and qualities of included studies

Thirteen prospective observational trials, with 742 adult participants, were included in the final meta-analysis and

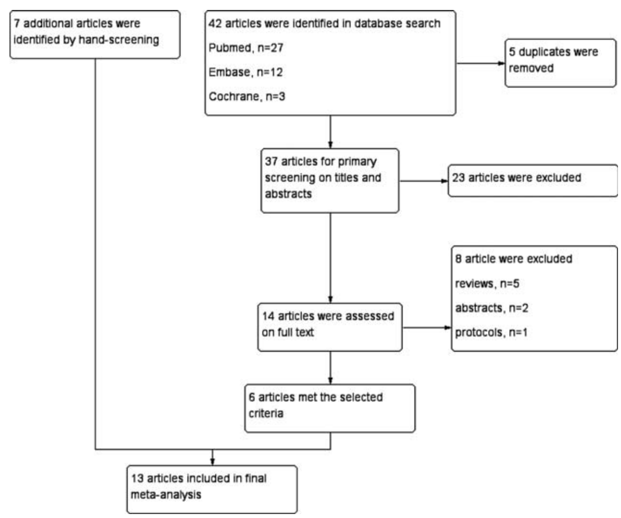


**Figure 1.** The flowchart of literature search and selection.

systematic review. These studies, published between 2011 and 2017, were from different countries, such as Egypt, France, Greece, Italy, Korea, and the USA. Nine studies reported data for DE (n=469), while 8 studies for DTF (n=485). Most of the studies were conducted in ICU, while 3 studies[26,28,38] took place in the respiratory ICU, 1 study[22] was conducted in a high dependency unit. Usually ultrasounds were performed on patients during the SBT,[1,22,23,26,28,35–38] 3 studies[29,39,40] had ultrasounds carried out before SBT, and only 1[27] had it done after SBT. Most studies reported DE or DTF during the resting breath, while only 2 studies[22,29] reported maximal DE or DTF during the forced breath. Ultrasounds and measurements were conducted in the supine position in 4 studies,[23,26,37,40] but another 9 studies[1,22,27–29,35,36,38,39] have performed the procedure in the semi-recumbent position. The ultrasound beam was directed to the diaphragmatic dome in 6 studies,[23,26,28,29,36,40] While 2 studies[22,35] observed the zone of apposition of the muscle. The characteristics of eligible studies are presented in Table 1. The methodological qualities of included studies were evaluated according to QUADAS-2. The results of quality assessment are shown in Figure 2.

### 3.3. Predicting value of DE and DTF on weaning outcome

The threshold effect was estimated using the Spearman correlation coefficient. No threshold effect was detected in DE (Spearman correlation coefficient: −0.234, $P=.544$) and DTF (Spearman correlation coefficient: 0.144, $P=.734$), therefore, a further combined analysis could be performed. The sensitivities of DE were homogeneous ($P=.075$, $I^2=44.0\%$), thus, the fixed effect model was used and the pooled specificity of DE was 0.786 [95% confidence interval (CI): 0.734–0.832]. Due to significant heterogeneity in sensitivities of DTF ($P=.009$, $I^2=62.6\%$), the random effect model was used and the pooled sensitivity of DTF was 0.893 (95% CI: 0.854–0.924). Similarly, because of significant heterogeneity in specificities of DE ($P=.000$, $I^2=76.3\%$), the random effect model was used and the pooled specificity of DE was 0.711 (95% CI: 0.637–0.777); however, the specificities of DTF were homogeneous ($P=.075$, $I^2=45.6\%$), thus, the fixed effect model was used and the pooled specificity of DTF was 0.796 (95% CI: 0.723–0.857). Significant heterogeneities were detected in NLRs of DE ($P=.015$, $I^2=57.9\%$) and DTF ($P=.029$, $I^2=55.2\%$), so the random effect model was performed, the pooled NLRs of DE and DTF were 0.287 (95% CI: 0.190–0.435) and 0.157 (95% CI: 0.094–0.259). Owing to significant heterogeneity in PLRs of DE ($P=.000$, $I^2=84.6\%$), the random effect model was used, and the pooled PLR of DE was 2.854 (95% CI: 1.474–5.527); conversely, PLRs of DTF were not heterogeneous ($P=.393$, $I^2=4.8\%$), the fixed effect model was applied, and the pooled PLR of DTF was 4.257 (95% CI: 3.113–5.822). Moreover, owing to heterogeneity ($P=.003$, $I^2=65.2\%$) in DORs of DE, the random effect model was used, and the pooled DOR of DE was 10.623 (95% CI: 4.169–27.068). On the contrary, the DORs of DTF exhibited consistency ($P=.127$, $I^2=37.9\%$), therefore, the fixed effect model was used and the combined DOR of DTF was 32.521 (95% CI: 18.618–56.807). The diagnostic performances of DE and DTF on weaning outcome are presented in Table 2 and Figure 3. The summary receiver operating characteristic (SROC) curve was applied to evaluate the comprehensive diagnostic performance. Figure 4 shows the SROC curves, with area under curve (AUC) of 0.8590 for DE and 0.8381 for DTF, indicating the high level of overall accuracy. Fagan nomogram, presented in Figure 5, was also used to analyze the diagnostic value of DE and DTF on weaning outcome.

In our meta-analysis, significant heterogeneities were observed. Meta-regression analysis was carried out to find the source of heterogeneities, however, due to the small number of included studies, no significant result was found in target patient (the difficult weaning patient or not), sample size (N≥50 or not), index test (maxDE/maxDTF during the forced breath or DE/DTF during the resting breath) and timing of index test (before/during SBT or after extubation). The results of meta-regression analysis are presented in Table 3. Sensitivity analysis, exhibited in Table 4, was also performed to explore the source of heterogeneities. After removing the trials one by one, the results remained consistent; however, the heterogeneities between studies were not significantly decreased, thus, additional large-scale trials are needed to confirm the findings of this study.

### 3.4. Publication bias

Publication bias was evaluated by Deeks funnel plot. Shown in Figure 6, the slope coefficient was −5.345298 and −32.12883, the associated $P$-value was $P=.782$ and $P=.054$, respectively, indicating no evidence of publication bias.

## 4. Discussion

Diaphragmatic ultrasonography has gained more and more attention from clinicians all over the world. As it is a noninvasive, painless and convenient bedside method, it might provide more accurate and reliable information regarding the prediction of weaning outcome.[41,42] However, the findings of related studies are inconsistent and lack statistical power, and the clinical significances of DE and DTF still remain controversial. Lerolle et al[18] demonstrated that DE correlated well with transdiaphragmatic pressure and suggested that DE could reflect diaphragmatic dysfunction. On the contrary, Umbrello et al[43] believed that DTF rather than DE was a reliable index of respiratory effort and diaphragmatic contractile function.

In our meta-analysis, the pooled sensitivities for DE and DTF were 0.786 and 0.893, and the pooled specificities were 0.711

**Table 1**

**Characteristics of included studies.**

| Study | Period | Location | Setting | Design | Patient | N | Age | Gender, m/f | Patient position | Delay between diaphragmatic ultrasound and weaning | Cutoff | Right or left hemidiaphragm | Machine | Probe | Probe position | Number and skills of operator |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Ali and Mohamad[41] | June 2013 to June 2015 | Egypt | ICU | Prospective | Patients who were invasively mechanically ventilated | 60 | 54 | 45/15 | Supine | Within 24 h before extubation | DE > 1.5 cm; DTF > 30% | Right | Echo Blaster 128 Kit | 4 and 10 MHz probe | Diaphragmatic dome | N/A |
| Baess et al[28] | January to June 2015 | Egypt | General and respiratory ICU | Prospective | Patients who were planned for weaning | 30 | 59.17 | 15/15 | Semi-recumbent | During the SBT or the PS trial | DE > 1 cm; DTF ≥ 30% | Right | Philips Healthcare, Andover, MA | 2–4 MHz phased array probe | Diaphragmatic dome | Physicians |
| Blumhof et al[40] | July 2014 to August 2015 | Philadelphia, USA | ICU | Prospective | Patients mechanically ventilated for greater than 24 h | 52 | 62 | 26/26 | Semi-recumbent | Within 48 h before extubation | DTF > 20% | Right | Sonosite M-Turbo, FujiFilm, Tokyo, Japan | 7.5–10 MHz transducer | N/A | Trained clinicians |
| Carrie et al[29] | December 2014 to April 2015 | France | ICU | Prospective | Patients who met the criteria for first SBT after at least 48 h of mechanical ventilation | 67 | 66 | 37/30 | Semi-recumbent | Before the start of SBT | maxDE > 2.7 cm | Right | Vivid S5TM ultrasound machine (GE Healthcare, Wauwatosa, WI) | 4 MHz cardiac probe | Diaphragmatic dome | Two experts |
| Dinino et al[35] | N/A | USA | Medical ICU | Prospective | Patients who were ready for SBT | 63 | 66 | 31/32 | Semi-recumbent | Within the first 5 min of the SBT or the PS trial | DTF ≥ 30% | Right | LOGIQ Book, GE Healthcare, Waukesha, WI | 7–10 MHz linear ultrasound probe | Zone of apposition of the diaphragm | Well-trained operator |
| Farghaly and Hasan[39] | April 2015 to November 2015 | Egypt | Respiratory ICU | Prospective | Patients with underlying pulmonary disease causing ARF who had successfully passed the SBT | 54 | SG, 65 FG, 62.5 | 31/23 | Semi-recumbent | Obtained at 30 min of a 2 h SBT | DE ≥ 10.5 mm; DTF ≥ 34.2% | N/A | Samsung Medison Sono Ace R3 ultrasound system | 7 and 3.5 MHz | N/A | Two experts |
| Fayed et al[38] | N/A | Egypt | ICU | Prospective | COPD patients | 112 | 62.61 | 97/15 | Supine | During the SBT | rightDTF > 29%; leftDTF > 24% | Both | Mindray DP-20 | 10 MHz linear transducer | N/A | N/A |
| Ferrari et al[22] | December 2009 to December 2011 | Turin, Italy | High dependency unit | Prospective | Patients who failing one or more attempts of weaning, met the criteria for a SBT | 46 | 64.6 | 34/12 | Semi-recumbent | During SBT | maxDTF > 36% | Right | Esaote MyLab 40 ultrasound system | 10 MHz linear ultrasound probe | Zone of apposition of the diaphragm | Well-trained researchers |
| Flevari et al[1] | June to December 2014 | Athens, Greece | Adult ICU | Prospective | Critically ill patients with difficult and/or prolonged weaning, met the criteria for SBT | 27 | 65 | 13/14 | Semi-recumbent | During SBT | leftDE ≥ 7 mm; rightDE > 10 mm | Right and left | N/A | 5 MHz vector transducer | N/A | N/A |
| Kim et al[23] | October 2008 to March 2009 | Seoul, Korea | Medical ICU | Prospective | Consecutive patients who required mechanical ventilation for 48 h, met the criteria for a SBT | 82 | 66 | 50/32 | Supine | At the start of SBT | leftDE ≥ 12 mm; rightDE ≥ 14 mm | Right and left | Esaote ultrasound machine (Esaote MyLab 30CV, Genoa, Italy) | 3.5 MHz ultrasound probe | Diaphragmatic dome | One well trained expert |
| Osman and Hashim[27] | August 2015 to august 2016 | Cairo, Egypt | ICU | Prospective | Patients in different ICU with various reason for ventilation, met the traditional weaning criteria | 68 | 56 | N/A | Semi-recumbent | After extubation | DE > 10 mm; DTF > 28% | N/A | Logic E9 (GE) and Honda electronics HS-2100 Portable ultrasound machine | 3.5 MHz convex probe and 9–11 MHz linear probe | N/A | N/A |
| Saeed et al[37] | November 2012 to October 2014 | Cairo, Egypt | Respiratory ICU | Prospective | COPD patients who were prepared for extubation | 30 | 59 | N/A | Supine | During SBT | DE > 1.1 cm | N/A | Mindray DP 1100 ultrasound machine | 3.5C (bandwidth 2–5 MHz) convex phased array probe | Diaphragmatic dome | N/A |
| Spadaro et al[36] | July 2014 to March 2015 | Ferrara, Italy | ICU | Prospective | Patients requiring mechanical ventilation for more than 48 h who were ready to perform a SBT | 51 | 65 | 31/20 | Semi-recumbent | During SBT, after 30 min from the beginning of the SBT, before reconnecting to the ventilator in the case of SBT failure | DE > 14 mm | Right and left | Sonosite M-Turbo; Sonosite Inc., Bothell, WA | 3.5–5 MHz convex ultrasound probe | Diaphragmatic dome | One well-trained intensivist |

ARF = acute respiratory failure, COPD = chronic obstructive pulmonary disease, DE = diaphragm excursion, DTF = diaphragm thickness fraction, FG = failed group, ICU = intensive care unit, m/f = male/female, N = number, N/A = not available, PS = pressure support, SBT = spontaneous breathing test, SG = successful group.

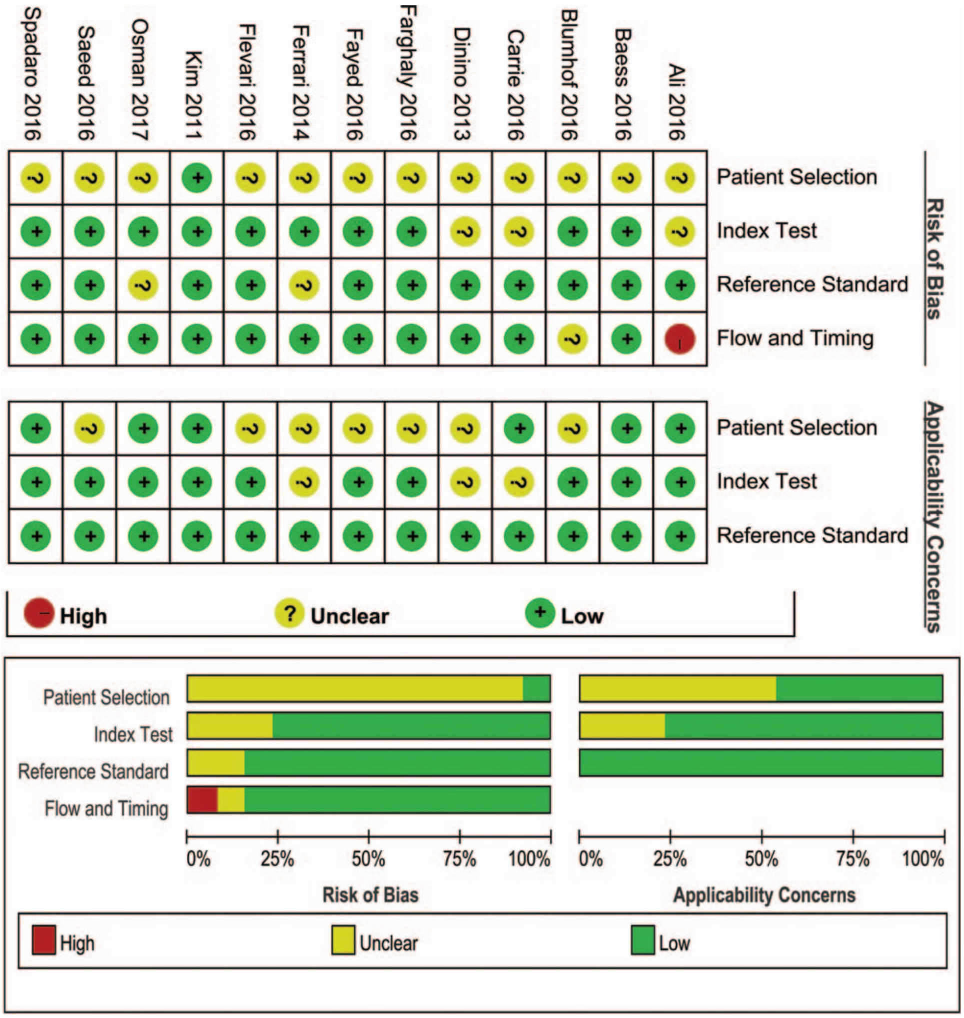


**Figure 2.** The methodological quality of included studies.

and 0.796, respectively. The SROC curve and the AUC were used to assess the overall diagnostic performance. The AUC for DE and DTF were 0.8590 and 0.8381, respectively. Our data indicate a satisfactory diagnostic accuracy in predicting extubation outcome. The DOR was also analyzed to evaluate the diagnostic accuracy. The DOR is the ratio between PLR and NLR, the larger the DOR is, the greater the diagnostic accuracy is. In this meta-analysis, the DORs for DE and DTF were 10.623 and 32.521, illustrating a high diagnostic accuracy.

Our data suggest a lower sensitivity and specificity for DE as compared to DTF in predicting weaning outcome. DTF reflects the active contraction of the diaphragm during the mechanical ventilation,[44] whereas DE is primarily related to the inspired volume,[45] regardless of whether it depends on the muscle effort or the ventilatory support. Therefore, DTF should be measured to estimate the diaphragm function in patients undergoing mechanical ventilation, while DE is meaningful in the absence of the ventilatory support. Moreover, diaphragm dysfunction is

**Table 2**

**The diagnostic performance of DE and DTF on weaning outcome.**

| Parameter | DE (95% CI) | DTF (95% CI) |
|---|---|---|
| SEN | 0.786 (95% CI: 0.734–0.832)* | 0.893 (95% CI: 0.854–0.924)† |
| SPE | 0.711 (95% CI: 0.637–0.777)† | 0.796 (95% CI: 0.723–0.857)* |
| PLR | 2.854 (95% CI: 1.474–5.527)† | 4.257 (95% CI: 3.113–5.822)* |
| NLR | 0.287 (95% CI: 0.190–0.435)† | 0.157 (95% CI: 0.094–0.259)† |
| DOR | 10.623 (95% CI: 4.169–27.068)† | 32.521 (95% CI: 18.618–56.807)* |
| AUC | 0.8590 | 0.9064 |

AUC = area under the curve, CI = confidence interval, DE = diaphragm excursion, DOR = diagnostic odds ratio, DTF = diaphragm thickness fraction, NLR = negative likelihood ratio, PLR = positive likelihood ratio, SEN = sensitivity, SPE = specificity.

* Fixed effect model was used.

† Random effect model was used.

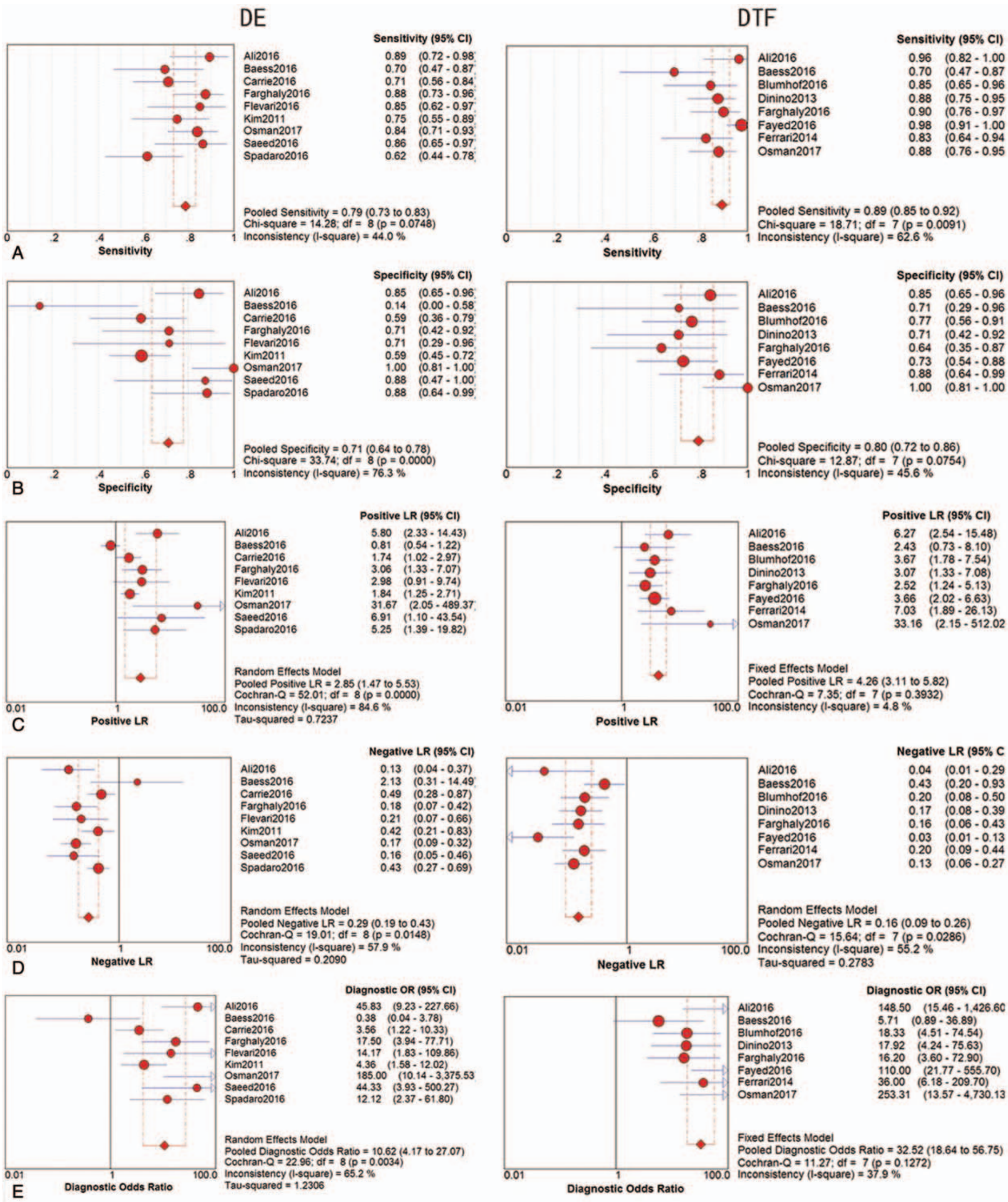


**Figure 3.** The diagnostic performance of DE and DTF on weaning outcome: (A) sensitivity, (B) specificity, (C) PLR, (D) NLR, (E) DOR. CI = confidence interval, DE = diaphragm excursion, DOR = diagnostic odds ratio, DTF = diaphragm thickness fraction, NLR = negative likelihood ratio, PLR = positive likelihood ratio.

the main cause of weaning failure, but not the only one, it is essential to contextualize the information derived from diaphragmatic ultrasound with clinical and laboratory data, as well as information obtained from other imaging technologies such as X-ray, CT scans, and echocardiography.

RSBI and VE, widely used in clinical practices, are the weaning parameters that measure the volume generated by all the respiratory muscles without especially assessing the contribution of the diaphragm.[23] Under the circumstance of diaphragm dysfunction, the diaphragm motion is inhibited and the accessory muscles take on a greater role in the production of tidal volume (VT).[46,47] Therefore, diaphragm dysfunction can be disguised by the compensatory action of other respiratory muscles during SBT.[30] However, the accessory muscles are weaker and more fatigable than the diaphragm, so the compensatory effect cannot be sustained for a long time.[48,49] Thus, weaning failure may

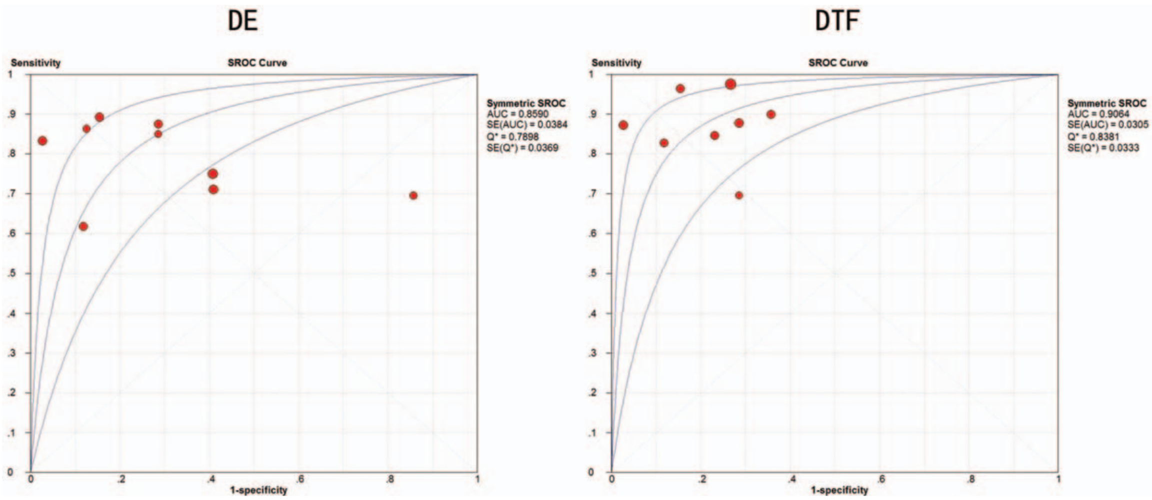


**Figure 4.** Summary receiver operating characteristic curves of DE and DTF on weaning outcome. DE = diaphragm excursion, DTF = diaphragm thickness fraction, SROC = summary receiver operating characteristic.

occur despite an initially acceptable RSBI and VT.[35] Spadaro et al[36] reported many patients failed the weaning attempt, though RSBI was much lower than the threshold predicting weaning failure described in the paper by Yang and Tobin.[50] Poor endurance is an important cause of failed weaning. DE and DTF reflect the ability of the diaphragm to generate inspiratory volume, hence, the true diaphragmatic contribution to VT.[43] There are other traditional ways to evaluate diaphragm dysfunction, such as fluoroscopy, electrical or magnetic phrenic nerve stimulation, and trans-diaphragmatic pressure measurement. However, all of these methods possess serious shortcomings, for instance, ionizing radiation, high cost, difficult

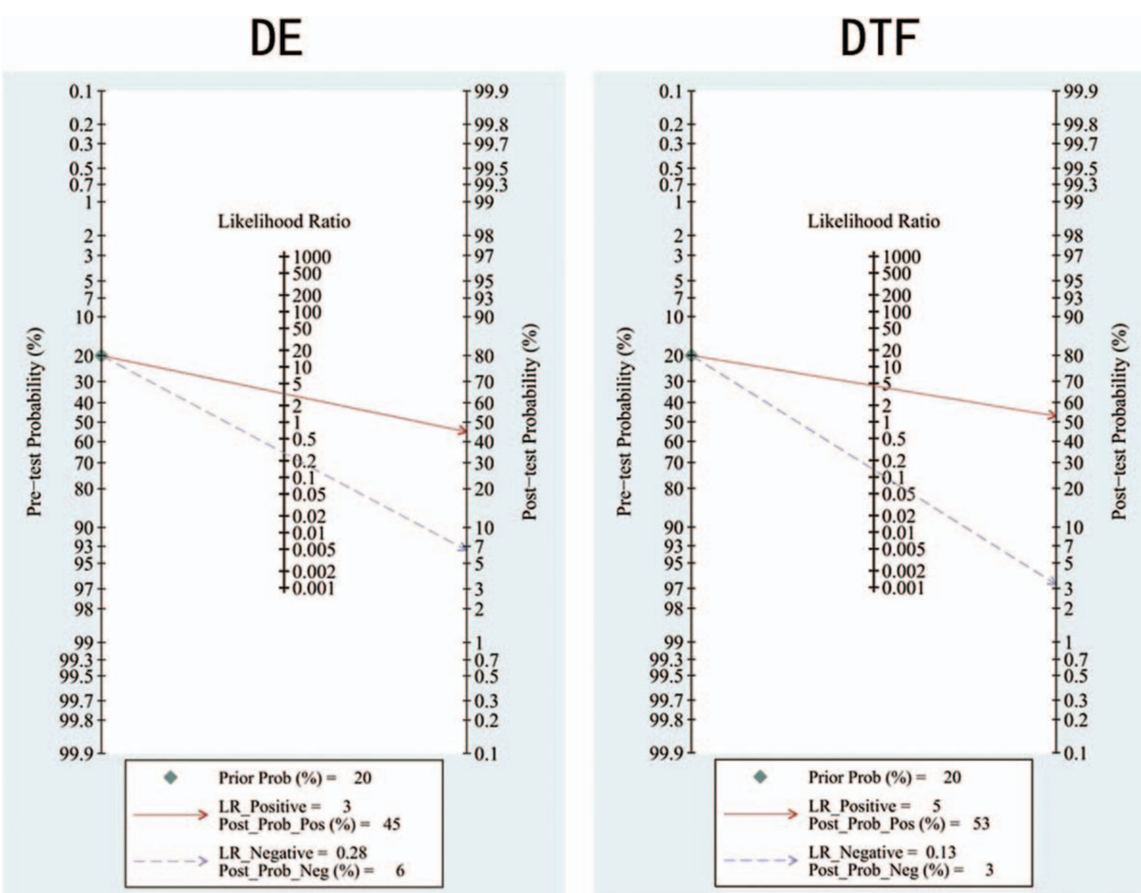


**Figure 5.** Fagan nomograms of DE and DTF on weaning outcome. DE = diaphragm excursion, DTF = diaphragm thickness fraction, LR = likelihood ratio.

**Table 3**

**Possible sources of heterogeneity (meta-regression analysis).**

| Index test | Covariate | Coefficient | *P* | RDOR |
|---|---|---|---|---|
| DE | Target patient (the difficult weaning patient or not) | 1.041 | .3977 | 2.83 |
| | Sample size (N ≥ 50 or not) | −0.223 | .8502 | 0.80 |
| | Index test (maxDE/maxDTF in the forced breath or DE/DTF in the resting breath) | −1.098 | .3710 | 0.33 |
| | Before/during SBT or after extubation | 1.216 | .5949 | 3.37 |
| DTF | Target patient (the difficult weaning patient or not) | 1.060 | .2005 | 2.89 |
| | Sample size (N ≥ 50 or not) | 1.153 | .3927 | 3.17 |
| | Index test (maxDE/maxDTF in the forced breath or DE/DTF in the resting breath) | 0.419 | .7846 | 1.52 |
| | Before/during SBT or after extubation | 3.819 | .0883 | 45.56 |

DE = diaphragm excursion, DTF = diaphragm thickness fraction, N = number, RDOR = relative diagnostic odds ratio, SBT = spontaneous breathing test.

**Table 4**

**The diagnostic performance of DE and DTF after omitting each trial (sensitivity analysis).**

| Index tests | Study excluded | SEN (95% CI)/$I^2$ | SPE (95% CI)/$I^2$ | DOR (95% CI)/$I^2$ | PLR/NLR |
|---|---|---|---|---|---|
| DE | Ali and Mohamad[41] | 0.775 (0.719–0.824)/41.0% | 0.687 (0.605–0.761)/77.2% | 8.58 (3.320–22.170)/61.3% | 2.541/0.311 |
| | Baess et al[28] | 0.794 (0.740–0.841)/46.8% | 0.735 (0.661–0.800)/70.1% | 13.673 (5.826–32.086)/55.9% | 3.211/0.269 |
| | Carrie et al[29] | 0.800 (0.744–0.848)/44.4% | 0.728 (0.650–0.798)/78.2% | 12.966 (4.500–37.360)/64.7% | 3.270/0.261 |
| | Farghaly and Hasan[39] | 0.772 (0.715–0.823)/41.0% | 0.711 (0.634–0.780)/79.3% | 10.031 (3.500–28.754)/68.1% | 2.876/0.305 |
| | Flevari et al[1] | 0.781 (0.727–0.829)/49.0% | 0.711 (0.636–0.778)/79.3% | 10.411 (3.717–29.157)/69.2% | 2.871/0.295 |
| | Kim et al[23] | 0.790 (0.736–0.838)/50.2% | 0.765 (0.678–0.838)/75.5% | 12.632 (4.225–37.767)/66.5% | 3.316/0.270 |
| | Osman and Hashim[27] | 0.775 (0.717–0.826)/46.9% | 0.677 (0.598–0.750)/66.1% | 8.616 (3.502–21.201)/62.0% | 2.492/0.315 |
| | Saeed et al[37] | 0.780 (0.725–0.828)/47.5% | 0.703 (0.627–0.772)/78.4% | 9.342 (3.520–24.793)/66.7% | 2.652/0.305 |
| | Spadaro et al[36] | 0.809 (0.755–0.855)/17.8% | 0.692 (0.614–0.764)/77.1% | 10.609 (3.679–30.588)/69.2% | 2.662/0.264 |
| DTF | Ali and Mohamad[41] | 0.886 (0.845–0.920)/63.9% | 0.786 (0.704–0.854)/51.4% | 28.403 (15.931–50.640)/33.7% | 4.036/0.170 |
| | Baess et al[28] | 0.908 (0.870–0.938)/47.1% | 0.800 (0.726–0.862)/52.3% | 39.908 (22.127–71.976)/25.9% | 4.402/0.120 |
| | Blumhof et al[40] | 0.897 (0.857–0.929)/66.9% | 0.802 (0.721–0.867)/52.9% | 36.376 (19.621–67.437)/44.4% | 4.356/0.147 |
| | Dinino et al[35] | 0.896 (0.854–0.929)/67.7% | 0.804 (0.728–0.867)/ 51.1% | 35.648 (19.278–65.919)/44.1% | 4.465/0.150 |
| | Farghaly and Hasan[39] | 0.892 (0.850–0.925)/67.9% | 0.812 (0.736–0.873)/ 45.0% | 35.898 (19.489–66.123)/43.2% | 4.632/0.154 |
| | Fayed et al[38] | 0.865 (0.816–0.905)/30.5% | 0.811 (0.731–0.877)/ 50.0% | 27.035 (14.895–49.069)/27.2% | 4.491/0.161 |
| | Ferrari et al[22] | 0.899 (0.859–0.931)/65.7% | 0.785 (0.706–0.851)/ 49.5% | 32.132 (17.832–57.899)/46.5% | 4.079/0.147 |
| | Osman and Hashim[27] | 0.895 (0.853–0.929)/67.8% | 0.769 (0.688–0.837)/ 0.0% | 27.672 (15.568–49.185)/32.7% | 3.745/0.158 |

CI = confidence interval, DE = diaphragm excursion, DOR = diagnostic odds ratio, DTF = diaphragm thickness fraction, NLR = negative likelihood ratio, PLR = positive likelihood ratio, SEN = sensitivity, SPE = specificity.

execution, invasiveness, and inconvenience.[22] What is more, transportation of critical patients to the radiology department is difficult and dangerous.

Similar systemic reviews and meta-analyses have been published recently[8,51]; however, the inclusion criteria, reference standard and major clinical endpoints of these meta-analyses are different from our study. Our study focuses on diaphragmatic ultrasound for predicting weaning failure within 48 hours after extubation in adults, which makes it much more specific and reliable. In addition, the latest trials are included in our paper, so the results are more powerful.

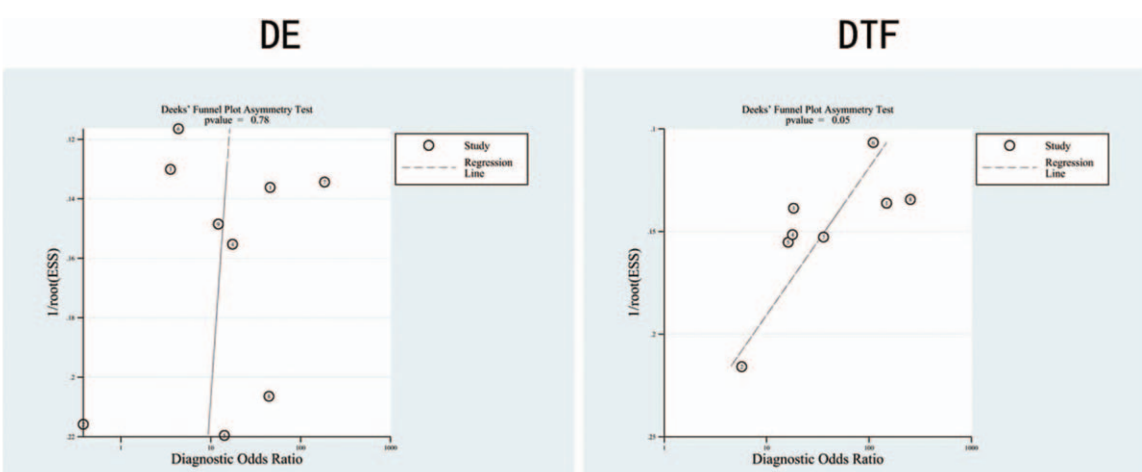


**Figure 6.** Deeks funnel plots for publication bias.

In this meta-analysis, significant heterogeneities were observed. However, sensitivity analysis showed the result of this meta-analysis was robust and reliable. Although meta-regression analysis was performed, we could not explore the source of potential heterogeneities due to the limited number of included studies. It is generally known that the measuring result could deviate as the position of probe changes. Moreover, DE may differ relying on the posture, demonstrating higher values when patients are supine than seated.[52] In addition, DTF may vary as STB progresses owing to diaphragmatic fatigue, that is to say, an early test would show lower accuracy to predict weaning failure. In our meta-analysis, with a coefficient of 3.819 and RDOR of 45.56, the timing of measurement was very nearly significant. Therefore, the exact position of probe, patient posture and the timing of ultrasound should be considered as factors that need to be solved in future studies. Moreover, we might hold that the accuracy of diaphragmatic ultrasound on predicting weaning outcome depends on the number and experience of the operators. Despite being an observer-reliant technique, the available evidence shows that both DTF and DE are replicable measures.[53,54]

In addition, we were also concerned about the effect of publication bias because positive results were more likely to be published. However, Deeks funnel plot indicates no publication bias in our meta-analysis.

There are some limitations in our meta-analysis. First, only articles published in English were included. Second, the influence of gender was not considered, since the excursion and thickness fraction were larger in men than in women. Third, the number of included studies was small and may not have fully assessed the diagnostic accuracy and could not find the source of heterogeneities. Thus, further large-scale studies are needed to investigate the diagnostic accuracy of DE and DTF.

## 5. Conclusion

Despite the limitations mentioned above, the results of our meta-analysis indicated that diaphragmatic ultrasonography may be a reliable, noninvasive and convenient way to predict reintubation within 48 hours of extubation. However, due to significant heterogeneities among the included studies, clinicians should be aware of the utilities and limitations of this tool. Additional high-quality, large-scale studies are required.

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## Author contributions

Conceived and designed the experiments: CL. Performed the experiments: CL, XL, HC. Analyzed the data: CL. Contributed reagents/materials/analysis tools: CL, XL, HC, HH, GW, ZW. Wrote the manuscript: CL.
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**Writing – original draft:** Caifeng Li.
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