Original article

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Diaphragm dysfunction and weaning failure in the ventilated critically ill patient: A systematic review and meta-analysis

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Abstract

***Introduction*: Diaphragm dysfunction following mechanical ventilation is associated with weaning failure from the ventilator in critically ill patients, resulting in a bad prognosis and increased mortality. We conducted a systematic review and meta-analysis to measure the risk of diaphragm dysfunction on weaning failure.**

***Methods*: We searched Pubmed, Embase, Cochrane, and Scopus databases without restriction to publication date. The clinical question was "is diaphragm dysfunction associated with weaning failure and increased weaning time in patients with >24 hours positive pressure mechanical ventilation?" The primary outcome was weaning failure, and the secondary outcome was weaning time. Risk Of Bias In Non-randomised Studies - of Interventions (ROBINS-I) was used to assess study quality and the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach was used to assess the certainty of evidence.**

***Results*: The search string yielded 164 studies. Twenty-one studies were collected for full text and appraised thoroughly following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline. Four studies with similar clinical questions were included in the systematic review. ROBINS-I showed that the studies have a low to medium risk of bias. GRADE showed a moderate to a high level of certainty evidence. Pooled odds ratio (OR) showed diaphragm dysfunction was closely associated with weaning failure (156 patients), OR 3.27 (CI95% 1.34-8.02) but loosely associated with weaning time (188 patients), mean weaning time difference of 3.12 (CI95% -0.09-6.33) hours.**

***Conclusion*: Diaphragm dysfunction as a complication of mechanical ventilation should be addressed carefully in critically ill patients since it is associated with weaning failure.**

Key words: Diaphragm dysfunction, mechanical ventilation, weaning failure.

Introduction

Critical illness is a life-threatening process that results in morbidity and mortality. Mechanical ventilation (MV) is a life-saving intervention for critically ill patients. (1) However, complications following MV have been issued since the beginning of the practice. The use of controlled MV causes diaphragm dysfunction (DD), referred to as ventilator-induced diaphragm dysfunction, through a series of pathways involving reduced protein synthesis and increased protein degradation. (2-4)

Diaphragm dysfunction has been reported to be responsible for weaning failure with an incidence of 23-80%, difficult weaning, prolonged intensive care unit (ICU) stay, prolonged duration of MV, and increased mortality. (5-8) However, the magnitude effect of this issue has not been known. Weaning failure is defined as the inability to liberate a patient from the ventilator. (9) Finding the cause of weaning difficulty is important to minimize the rates of extubation failure and prolonged ventilation that inevitably promotes DD and lead to more weaning failure. We performed a systematic review of the clinical trials to identify the effect of DD on wean-

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ing failure and weaning time. The clinical question was "is diaphragm dysfunction associated with weaning failure and increased weaning time in patients with >24 hours positive pressure mechanical ventilation?".

Method

Search strategy and selection criteria

This study was conducted in adherence to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement. The literature search was performed on Pubmed, Embase, Cochrane, and Scopus databases without restriction on publication date. The following keywords and their variations: "mechanical ventilation", "diaphragm dysfunction", and "weaning failure" were entered (**Appendix 1**). We assessed all relevant literature from clinical trial groups with the same clinical question as ours. We excluded any animal or pediatric studies (<18 years). Two reviewers (DPS and DL) independently screened the articles for eligibility by going through the titles and abstract. Both DPS and DL worked independently. Any conflicts were resolved by consensus or by a third reviewer (YWHG). All search in all databases was conducted on January 1st, 2022.

Data collection

Data were independently collected by DPS and DL independently with a predefined extraction form. The form included study characteristics (study design, setting, year of publication), patient characteristics (number of patients, age, sex, comorbidities, baseline characteristics before assessment of DD), physiologic parameters during MV, method of DD assessment, and outcome (weaning failure, weaning time). If the main outcome were not reported, the reviewers would contact the author to collect unpublished data. The outcome domain was adapted to the clinical question.

Assessment of risk of bias and certainty of the evidence

The Risk Of Bias In Non-randomised Studies - of Interventions (ROBINS-I) tools for assessing bias risk in non-randomized trials were used to assess studies for quality. (10) DPS and DL assessed the risk of bias of all studies independently. If they yielded a different conclusion regarding the study, YWHG independently would assess the debated study. We assessed statistical heterogeneity using the I^2 statistics, the chi-squared test, and visual inspection of the forest plots. The Grading of Recommendations, Assessments, Developments, and Evaluations (GRADE) approach was used to assess the certainty of evidence. (11)

Primary outcome

The primary outcome was weaning failure, defined as failure to pass a spontaneous-breathing trial or the need for reintubation within 48 hours following extubation. The primary outcome was categorized as dichotomous variables with yes/no for weaning failure, with an odds ratio (OR) as the effect measure. The secondary outcome was weaning time (hours), defined as the time spent in partial support modes such as pressure support or continuous positive airway pressure, with mean and standard deviation as the effect measure. Studies that were eligible for primary and secondary outcome synthesis were defined after tabulating the outcome of each study. Data conversion for weaning times that were not in hours was performed.

Statistical analysis

Revman 5 software was used for statistical analysis and to generate a pooled result for meta-analysis. The fixed effect model was used if the heterogeneity test showed homogenous data, while the random effect model was used otherwise. We pooled the number of events (weaning failure) in DD and no DD group for the dichotomous variable to generate a pooled risk ratio. For a continuous variable, we pooled the mean weaning time of each literature to generate mean differences. Subgroup analysis would be performed if the data showed any significantly different groups.

Results

Study details and demographic

The search string yielded 164 studies from searched databases. After omitting all reviews, case reports, and observational studies, 131 studies were available for screening. After removing duplicate studies, 41 studies were screened through title and abstract. Twenty-one studies were collected for the full text and appraised thoroughly following the PRISMA guideline. Four studies with a similar clinical question as ours were then included in a systematic review and meta-analysis (**Figure 1**). One study did not publish data in a dichotomous variable for weaning failure, so it was not included in the data pooling for that outcome. One hundred and fifty-six patients were collected for primary outcome pooling and 188 patients for secondary outcome pooling. Study details and pooled patient demographic are summarized in **Table 1**. The risk of bias assessment is shown in **Table 2**. It was concluded that the studies

had a low to medium risk of bias. Certainty level of evidence showed the studies had a moderate to a high level of certainty (**Appendix 2**).

Primary and secondary outcomes

One hundred fifty-six patients (3 studies) were included in the meta-analysis for the primary outcome (**Figure 2**). The heterogeneity test showed homogenous data. Consequently, the fixed effect model was used in the analysis. The pooled odds ratio of weaning failure was 3.27 (CI95% 1.34-8.02). The direction of the effect favored no diaphragm dysfunction. Diaphragm dysfunction was associated with weaning failure. For secondary outcomes, 188 patients (4 studies) were included in the meta-analysis (**Figure 3**). The heterogeneity test showed heterogeneous data, and a random effect model was used in the analysis. The weaning time pooled mean difference was 3.12 (CI95% -0.09-6.33) hours. There was a low association between diaphragm dysfunction and longer weaning time. Sensitivity analysis was not conducted.

Discussion

This systematic review and meta-analysis of clinical trials examined the effect of mechanical ventilation on diaphragm dysfunction that led to weaning failure and prolonged weaning time. Diaphragm dysfunction is defined as the loss of diaphragmatic force-generating capacity. (9) As the primary respiratory muscle, dysfunction of the diaphragm can be associated with respiratory symptoms in the more severe cases-failure. Mechanical ventilation could induce DD through pathways involving reduced protein synthesis and increased protein degradation. (2-4) Weaning failure is defined as failure to pass a spontaneous-breathing trial (SBT) or the need for reintubation within 48 hours following extubation. As an estimation, 40% of the duration of mechanical ventilation is dedicated to the process of weaning. (12) SBT assesses the patient's breathing ability while receiving minimal ventilator support.

This meta-analysis showed that DD was associated with weaning failure. The pooled odds ratio of weaning failure was 3.27 (CI95% 1.34-8.02). Previous observational studies supported this. (1,13-15) Several underlying mechanisms of MV cause DD have been reported, although some are still debatable and share no direct link. (2) Weaning failure is linked to increased MV time, leading to further and worsening diaphragm dysfunction, and the cycle keeps repeating. Our meta-analysis also showed that, although related, DD was not strongly associated with increased weaning time. The pooled mean difference in weaning time was 3.12 (CI95% -0.09-6.33) hours between DD and no DD groups. It could be inferred that DD could make the weaning process more difficult. These two findings can also show that failure is just right there waiting for patients with DD, even if a patient is successfully weaned from a ventilator (with a short weaning time).

There were several limitations of the studies involved in this meta-analysis. The studies included data needed to synthesize this meta-analysis. However, the studies were initially intended to answer a different research question. Kim 2011, (16) Mariani 2015, (17) and McCool 2020 (18) tried to illustrate the use of ultrasound to diagnose DD and the effect on MV weaning. Moon 2021 (19) measured dynamic inhomogeneity of aeration along the vertical axis of the lung to predict weaning failure regardless of DD. No study had an identical research question to our clinical question for our systematic review and meta-analysis. This could happen since highlighting the ultrasound function was as important as the presented data. For many years, DD has been difficult to diagnose. It used to involve biopsies of the diaphragm muscle postmortem. (20,21) The advancement of ultrasound for ICU bedside examination has risen in the last decade, and studies have been revolving around this topic. (19,22,23)

Limitations concerning review processed were a limited number of eligible studies. We found only four studies with a medium number of participants. This might not result in high power meta-analysis. Unpublished data were not sought mainly since we did not have the appropriate tool to collect unpublished data. Sensitivity analysis was not performed because we did not find too many intertwined data that might have influenced the pooled result. The main baseline characteristics were similar.

The management of DD should be approached by implementing a preventive and curative strategy. (5) Prevention can be done by stratifying patients' risk for DD before enrolling them in MV and making an appropriate clinical judgment to use MV on critically ill patients. (24) MV is associated with increased oxidative stress in the diaphragm. (25) This finding may suggest the growing role of pharmacologic agents such as antioxidants to lower oxidative stress and theophylline to reverse the reduction of transdiaphragmatic pressure resulting from resistive loaded breathing. (26) To this date, few studies have reported management of ventilator-induced DD. Future research is needed to prevent and treat DD

related to weaning failure.

Conflict of interest
The authors declare no conflict of interest concerning the review. The authors financially supported the study. There was no other party or sponsorship.

Disclosure
This publication complies with the ethical standard laid down in the 1964 Declaration of Helsinki.

Table 1. Study details and pooled patient demographic

Study	Study design	Setting	Number of patient[#]	Age[*]	Sex[ƒ]	Comorbidities[#]	Baseline characteristics before MV	Physiologic parameters during MV	Method of DD assessment	Outcome
Kim 2011 (16)	Prospective clinical trial	Medical ICU of Asan Medical Center, a university-affiliated, tertiary referral center in Seoul Korea, October 2008-March 2009	82	66 (11)	Male 50 (61)	Diabetes (10) Hypertension (11) COPD (9) Hypothyroidism (2) CABG (2) ARDS (4)	(not reported)	(not reported)	Ultrasound with the patient in a supine position. Ultrasound DD was diagnosed if an excursion was <10 mm or negative	DD Weaning failure[#]: 20/24 Weaning time[*]: 16.7 (14) No DD Weaning failure[#]: 34/58 Weaning time[*]: 4.5 (3)
Mariani 2015 (17)	Prospective interventional cohort study	ICU of the Centre Hospitalier de Versailles (Mignot site, Le Chesnay, France), November 2012-May 2013	34	64.6 (14.8)	Male 21 (62)	COPD (9) Diabetes (9) CVD (5) Cerebral insult (10) AKI (2)	(not reported)	(not reported)	Ultrasound dysfunction was defined as a diaphragmatic excursion of 11 mm or less in 2D mode and of 10 mm or less on the right and 11 mm or less on the left in M-mode.	DD Weaning failure[#]: 2/13 Weaning time[*]: 14.3 (7.8) No DD Weaning failure[#]: 0/21 Weaning time[*]: 12.1 (6.4)

McCool 2020 (18)	Prospective, randomized, controlled stuy	Brown University teaching hospital's ICU	32	55.8 (14.8)	Male 17 (53.1)	(not reported)	(not reported)	(not reported)	Diaphragm thickness (tdi) was measured at end-expiration and end-inspiration. Diaphragm dysfunction was defined as 4tdi% <30%.	DD Weaning time*: 2.38 (2.16) No DD Weaning time*: 0.96 (1.46)
Moon 2021 (19)	Prospective, randomized study	Medical ICU of Asan Medical Center, a university-affiliated, tertiary referral center in Seoul Korea, November 2018-April 2019	40	71 (12)	29 (72)	Diabetes (15) Hypertension (20) Arrythmia (7) CHF (6) Pneumonia (13) Chronic lung disease (23) Solid cancer (16) Hematology malignancy (6) Cirrhosis (4) CKD (11) Sepsis (14)	(not reported)	(not reported)	Ultrasound with the patient in a supine posistion. Ultrasound DD was diagnosed if an excursion was <10 mm or negative	DD Weaning failure#: 5/16 Weaning time*: 5 (4) No DD Weaning failure#: 4/24 Weaning time*: 4.5 (3)

Legend: MV=mechanical ventilation; DD=diaphragmatic dysfunction; ICU=intensive care unit; COPD=chronic obstructive pulmonary disease; CABG=coronary artery bypass graft; ARDS=acute respiratory distress syndrome; CVD=cerebrovascular disease; AKI=acute kidney injury; CHF=chronic heart failure; CKD=chronic kidney disease. *mean (SD); #n; ſn (%).

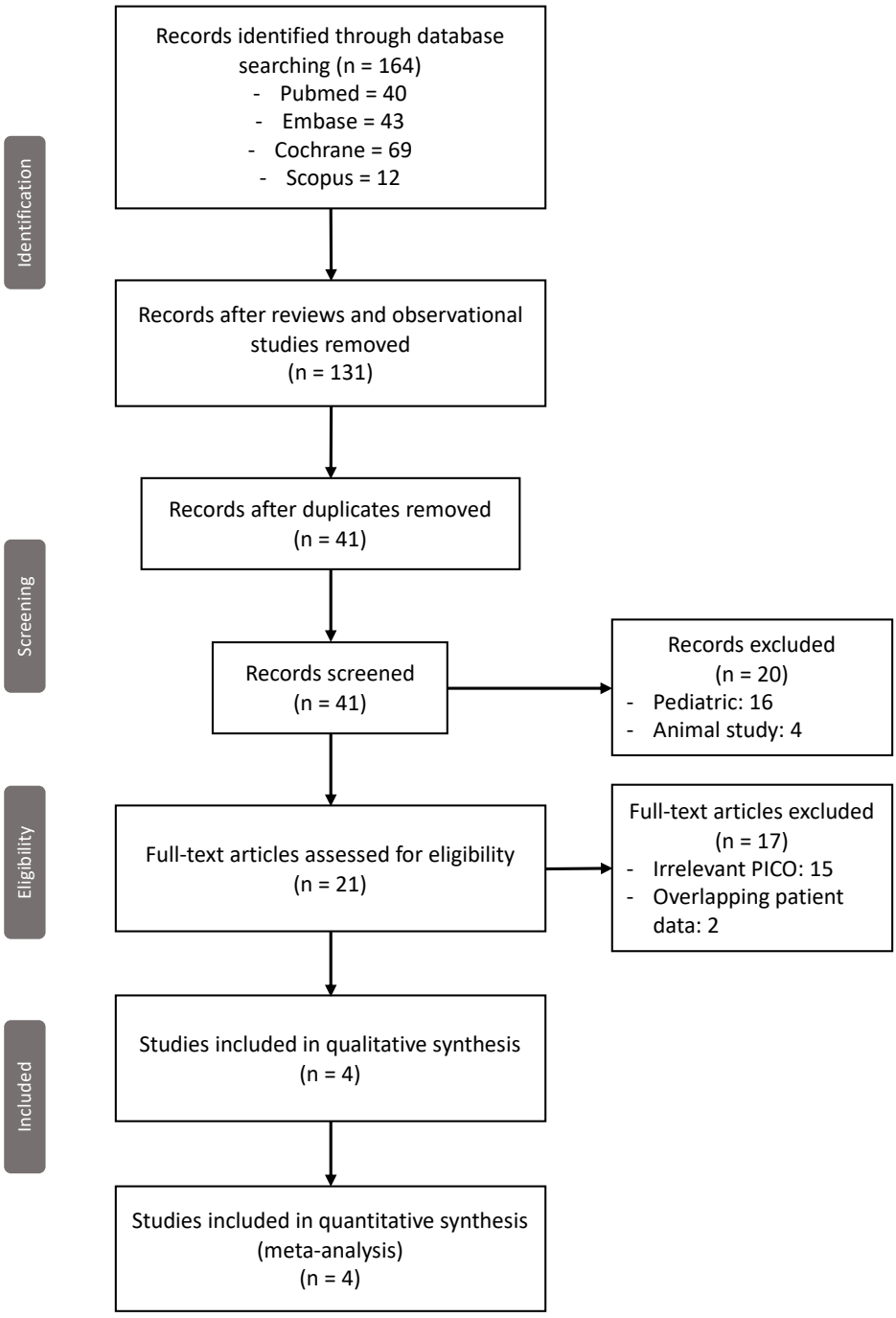
Table 2. Risk of bias assessment with ROBINS-I tool

Author/ year	Kim 2011	Mariani 2015	McCool 2020	Moon 2021
Bias due to confounding	?	?	+	+
Bias in selection of participants into the study	+	+	+	+
Bias in classification of interventions	?	?	+	+
Bias due to deviations from intended interventions	+	+	+	+
Bias due to missing data	+	+	+	+
Bias in measurement of outcomes	+	+	+	+
Bias in selection of reported result	?	+	+	?
Overall bias	?	?	+	+

+	Low risk of bias
?	Moderate risk of bias
x	High risk of bias
!	Critical risk of bias

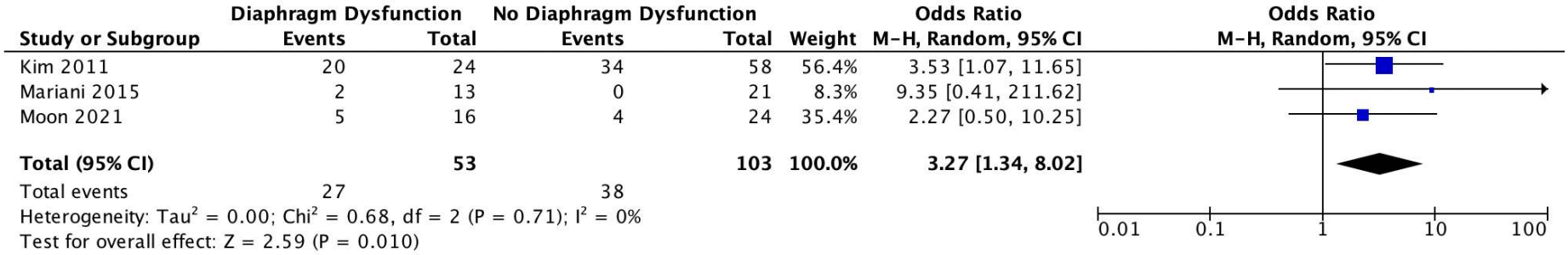
Legend: ROBINS-I=Risk Of Bias In Non-randomised Studies - of Interventions.

Figure 1. PRISMA flowchart



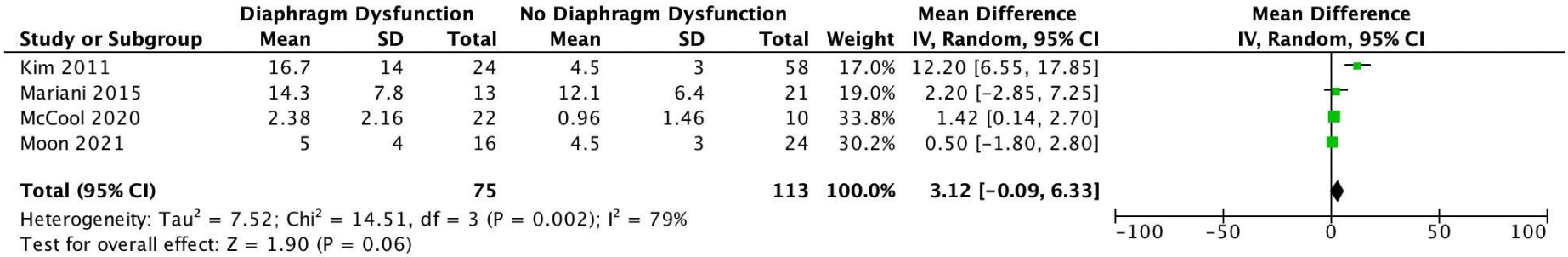
Legend: PRISMA=Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PICO=Patient, Intervention, Comparison, and Outcome.

Figure 2. The pooled odds ratio of weaning failure between diaphragm dysfunction and no dysfunction group



Legend: M-H=Mantel-Haenszel; CI=confidence interval; df=degree of freedom.

Figure 3. The pooled mean difference of weaning time between diaphragm dysfunction and no dysfunction group



Legend: SD=standard deviation; IV=weighted mean difference; CI=confidence interval; df=degree of freedom.

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Appendix 1

Pubmed

1.	"diaphragm dysfunction"[Title/Abstract] OR "diaphragm failure"[Title/Abstract] OR "diaphragm atrophy"[Title/Abstract] OR "diaphragm weakness"[Title/Abstract] OR "diaphragm thinning"[Title/Abstract]	903
2.	"mechanical ventilation"[Title/Abstract] OR "ventilatory support"[Title/Abstract] OR "artificial respiration"[Title/Abstract]	57,670
3.	“weaning failure"[Title/Abstract] OR "weaning difficulty"[Title/Abstract] OR "reintubation"[Title/Abstract] OR "prolonged weaning"[Title/Abstract]	3,344
4.	#1 AND #2 AND #3	40

Embase

1.	'diaphragm dysfunction':ab,ti OR 'diaphragm failure':ab,ti OR 'diaphragm atrophy':ab,ti OR 'diaphragm weakness':ab,ti OR 'diaphragm thinning':ab,ti	938
2.	'artificial ventilation':ab,ti OR 'mechanical ventilation':ab,ti OR 'ventilatory support':ab,ti	91,432
3.	'weaning failure':ab,ti OR 'weaning difficulty':ab,ti OR 'prolonged weaning':ab,ti OR reintubation:ab,ti OR 're intubation':ab,ti	5,882
4.	#1 AND #2 AND #3	43

Cochrane

1.	(diaphragm dysfunction):ti,ab,kw OR (diaphragm failure):ti,ab,kw OR (diaphragm atrophy):ti,ab,kw OR (diaphragm weakness):ti,ab,kw OR (diaphragm thinning):ti,ab,kw	544
2.	(mechanical ventilation):ti,ab,kw OR (artificial ventilation):ti,ab,kw OR (ventilatory support):ti,ab,kw	18,520
3.	(weaning failure):ti,ab,kw OR (weaning difficulty):ti,ab,kw OR (prolonged weaning):ti,ab,kw OR (reintubation):ti,ab,kw	2,068
4.	#1 AND #2 AND #3	69

Scopus

1.	TITLE-ABS ("diaphragm dysfunction") OR TITLE-ABS ("diaphragm atrophy") OR TITLE-ABS ("diaphragm failure") OR TITLE-ABS ("diaphragm weakness") OR TITLE-ABS ("diaphragm thinning")	634
2.	TITLE-ABS ("mechanical ventilation") OR TITLE-ABS ("artificial ventilationy") OR TITLE-ABS ("ventilatory support")	64,030
3.	TITLE-ABS ("weaning failure") OR TITLE-ABS ("weaning difficulty") OR TITLE-ABS ("prolonged weaning") OR TITLE-ABS ("reintubation")	3,269
4.	#1 AND #2 AND #3	12

Appendix 2

Grading of Recommendations, Assessments, Developments, and Evaluations (GRADE) approach for assessing the certainty of the evidence

Certainty assessment							Effect	Certainty
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other consideration		
Diaphragm Dysfunction								
4	Clinical trials	Not serious	Not serious	Not serious	Not serious		Important	High certainty
Weaning failure								
3	Clinical trials	Not serious	Not serious	Not serious	Not serious		Important	High certainty
Weaning time								
4	Clinical trials	Not serious	Serious	Not serious	Not serious	Different time units	Important	Moderate certainty

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