EUROPEAN RESPIRATORY *journal*

FLAGSHIP SCIENTIFIC JOURNAL OF ERS

Early View

Original article

ICU outcomes can be predicted by non invasive muscle evaluation: a meta-analysis

Clément Medrinal, Yann Combret, Roger Hilfiker, Guillaume Prieur, Nadine Aroichane, Francis-Edouard Gravier, Tristan Bonnevie, Olivier Contal, Bouchra Lamia

Please cite this article as: Medrinal Cément, Combret Y, Hilfiker R, *et al*. ICU outcomes can be predicted by non invasive muscle evaluation: a meta-analysis. *Eur Respir J* 2020; in press (https://doi.org/10.1183/13993003.02482-2019).

ICU outcomes can be predicted by non invasive muscle evaluation: a meta-analysis.

Clément Medrinal[1,2], Yann Combret[2,3], Roger Hilfiker[4], Guillaume Prieur[1,2,3], Nadine Aroichane[5], Francis-Edouard Gravier[1,6], Tristan Bonnevie[1,6], Olivier Contal[7*], Bouchra Lamia[1,8,9*].

*The authors contributed equally.

Author Affiliations:

Clément Medrinal, PhD, [1]Normandie Univ, UNIROUEN, EA3830-GRHV, 76 000 Rouen, France; Institute for Research and Innovation in Biomedicine (IRIB), 76 000 Rouen, France and [2]Groupe Hospitalier du Havre, Intensive Care Unit department, avenue Pierre Mendes France 76290 Montivilliers, France.

Yann Combret, Msc, [2]Groupe Hospitalier du Havre, Intensive Care Unit department, avenue Pierre Mendes France 76290 Montivilliers, France and [3]Research and Clinical Experimentation Institute (IREC), Pulmonology, ORL and Dermatology, Louvain Catholic University, Brussels 1200, Belgium.

Roger Hilfiker, Statistician, [4]University of Applied Sciences and Arts Western Switzerland Valais (HES-SO Valais-Wallis), School of Health Sciences, Leukerbad, Switzerland.

Guillaume Prieur, Msc, [1]Normandie Univ, UNIROUEN, EA3830-GRHV, 76 000 Rouen, France; Institute for Research and Innovation in Biomedicine (IRIB), 76 000 Rouen, France and [2]Groupe Hospitalier du Havre, Intensive Care Unit department, avenue Pierre Mendes France 76290 Montivilliers, France and [3]Research and Clinical Experimentation Institute

(IREC), Pulmonology, ORL and Dermatology, Louvain Catholic University, Brussels 1200, Belgium.

Nadine Aroichane, PT, [5]School of Physiotherapy, Rouen University Hospital, Rouen, France.

Francis-Edouard Gravier, Msc, [1]Normandie Univ, UNIROUEN, EA3830-GRHV, 76 000 Rouen, France; Institute for Research and Innovation in Biomedicine (IRIB), 76 000 Rouen, France and [6]ADIR Association, Bois-Guillaume, France.

Tristan Bonnevie, Msc [1]Normandie Univ, UNIROUEN, EA3830-GRHV, 76 000 Rouen, France; Institute for Research and Innovation in Biomedicine (IRIB), 76 000 Rouen, France and [6]ADIR Association, Bois-Guillaume, France.

Olivier Contal, PhD, [7]University of Applied Sciences and Arts Western Switzerland (HES-SO), avenue de Beaumont, 1011, Lausanne, Switzerland.

Bouchra Lamia, [1]Normandie Univ, UNIROUEN, EA3830-GRHV, 76 000 Rouen, France; Institute for Research and Innovation in Biomedicine (IRIB), 76 000 Rouen, France and [8]Groupe Hospitalier du Havre, Pulmonology department, avenue Pierre Mendes France 76290 Montivilliers, France and [9]Pulmonology, Respiratory Department, Rouen University Hospital, Rouen, France.

Corresponding author:

Clément Medrinal, Intensive Care Unit department, Groupe Hospitalier du Havre, 76290 Montivilliers. medrinal.clement.mk@gmail.com

Abstract

Background The relationship between muscle function in critically ill patients assessed using bedside techniques and clinical outcomes has not been systematically described. We aimed to evaluate the association between muscle weakness assessed by bedside evaluation and mortality or weaning from mechanical ventilation, and the capacity of each evaluation tool to predict outcomes.

Methods Five databases (PubMed, EMBASE, CINAHL, Cochrane library, Science Direct) were searched from January 2000 to December 2018. Data were extracted and random effects meta-analyses were performed.

Results Sixty studies were analysed, including 4382 patients. ICU-related muscle weakness was associated with an increase in overall mortality with odds ratios ranging from 1.2 [95% CI 0.60 to 2.40] to 4.48 [95% CI 1.49 to 13.42]. Transdiaphragmatic twitch pressure had the highest predictive capacity for overall mortality, with a sensitivity of 0.87 [95%CI 0.76 to 0.93] and a specificity of 0.36 [95%CI 0.27-0.43]. The area under the curve (AUC) was 0.74 [95%CI 0.70 to 0.78]. Muscle weakness was associated with an increase in mechanical ventilation weaning failure rate with an odds ratio ranging from 2.64 [95% CI 0.72 to 9.64] to 19.07 [95% CI 9.35 to 38.9]. Diaphragm thickening fraction had the highest predictive capacity for weaning failure with a sensitivity of 0.76 [95%CI 0.67 to 0.83] and a specificity of 0.86 [95%CI 0.78 to 0.92]. The AUC was 0.86 [95%CI 0.83 to 0.89].

Conclusion ICU-related muscle weakness detected by bedside techniques is a serious issue associated with a high risk of death or prolonged mechanical ventilation. Evaluating diaphragm function should be a clinical priority in the ICU.

Systematic Review Registration: PROSPERO 2019 [CRD42019122081]

Keywords: Intensive care Unit, Muscles weakness, Mechanical Ventilation

Introduction

ICU-acquired weakness (ICU-Aw) is a frequent complication of hospitalisation in intensive care. It includes limb muscle weakness[1, 2], diaphragm dysfunction[3], and global respiratory muscle weakness. Muscle weakness is multifactorial with sepsis, multi-organ failure, mechanical ventilation and pre-admission status being the main risk factors.[4, 5] Muscle weakness is currently diagnosed by a clinical examination involving a voluntary manual muscle strength test graded, for example, by the Medical Research Council (MRC) Scale.[6, 7]

Muscle weakness is often associated with a poor prognosis: dysfunction of the diaphragm or respiratory muscle weakness can both prolong the duration of mechanical ventilation and cause a failure to be weaned from it.[3] Furthermore, limb muscle weakness reduces physical capacity, functional ability, and autonomy, [8] and for that reason early identification of muscle weakness is essential.[9] This is challenging, however, since voluntary muscle strength can currently only be tested in patients who are both awake and cooperative. One study, for example, showed that only 25% of eligible patients could be evaluated with the MRC scale; the others could not because of their neurological status.[7] Several authors have highlighted the need for better bedside-tools for the identification of muscle weakness.[4, 9, 10] Non-invasive methods that evaluate diaphragm contractility and function have been proposed, such as magnetic phrenic nerve stimulation,[11] neuromuscular or diaphragm ultrasonography.[12, 13] Although such tools show promise, issues remain that need resolution before they can be routinely used. Firstly, their clinical relevance has not been validated; data regarding the relationships between muscle function and critical outcomes are needed for each test. Secondly, their routine clinical use is limited since no evaluation of

diagnostic capacity has yet been undertaken in a large representative sample of critically ill patients.

Thirdly, we do not know which of these tests is the most applicable for predicting patient outcomes.

The first aim of this systematic review and meta-analysis, therefore, was to identify and determine the clinical relevance of currently available, non-invasive, bedside muscle weakness evaluation tools by analysing the relationship between these methods and critical outcomes such as mortality and ventilator weaning failure. The second aim was to determine the capacity of each evaluation tool to predict the critical outcomes.

Method

The systematic review was carried out in accordance with the Meta-analysis of Observational Studies in Epidemiology (MOOSE) [14] and our protocol registered in PROSPERO [CRD42019122081]. In January 2019 the following five databases were searched for publications in either English, French or Spanish dating between January 2000 and December 2018: PubMed, EMBASE, CINAHL, the Cochrane Library, and Science Direct; the reference lists of all included articles were also searched for possible articles.

The search strategy involved combining keywords from the three domains: the condition studied (i.e. muscle weakness), the evaluation tool used, and the outcome(s) measured. MeSh search terms for condition were: “critically ill patient” or “ICU-acquired weakness” or “diaphragm dysfunction” or “respiratory weakness”, MeSh search terms for the evaluation tool were: “diaphragmatic ultrasound” or “transdiaphragmatic twitch pressure” or “phrenic nerve stimulation” or “maximal inspiratory pressure” or “handgrip dynamometer” or “handheld dynamometer” or “medical research council score” or “neuromuscular ultrasound”

and MeSh search terms for outcomes were: “mortality” or “mechanical ventilation weaning” or “extubation” or “mechanical ventilation”.

Screening and study selection

The aim of the review was to evaluate the impact of muscle weakness on one or more of the following “critical outcomes”: total mortality, mortality in ICU, mortality in hospital, weaning from mechanical ventilation, duration of mechanical ventilation and/or insertion of a tracheostomy. The capacity of each evaluation tool to predict each of the critical outcomes was also evaluated. A student physiotherapist (NA) supervised by a senior physiotherapist (CM) screened titles and abstracts for potential eligibility. A second senior physiotherapist (YC) also screened the studies (independently from NA and CM). Finally, CM and YC compared their results to determine which studies should be included or excluded. Any disagreements were resolved following discussion with a third senior reviewer (GP).

Observational cohort studies that compared the impact of limb and/or respiratory muscle weakness on critical outcomes in patients with and without weakness were included. Studies were excluded if patient strength was evaluated after discharge from ICU or if a prior intervention had been undertaken that might have influenced muscle weakness or critical outcomes or if muscle weakness was assessed by electromyography. As a result, letters were included but randomised control studies, retrospective analyses and conference abstracts were all excluded.

Data extraction

Two independent reviewers (CM and YC) extracted the data from each study using a standardized extraction form that included the patients’ conditions, clinical outcomes, the evaluation tool and how it was used to evaluate muscle strength (Table 1). All data were

checked for accuracy by NA supervised by GP. Any missing data were requested from article authors by email and, if there was no reply, another email was sent each month for three months. Of the 26 authors contacted, 13 provided additional essential information; they have been included as "contributors".[5, 8, 11, 13, 15–23]

If several evaluation tools were used in the same article, then data were extracted for each tool individually.[3, 5, 15–17, 21, 24–29] When two articles reported the same cases [5, 13] care was taken to avoid double-counting (e.g. Ptrstim). In these cases, clarity was sought from the authors. Groups of patients that did not match the review question were excluded from the analysis [18].

The definitions provided in each article for the diagnosis of muscle weakness and "weaning failure" from mechanical ventilation (i.e. where either extubation or spontaneous breathing failed) were used. If raw data was received from an author for a tool that had not been fully described in the original article (e.g. cut-off values were missing) we determined the cut-off value based on values in the literature. This was only required for maximal inspiratory pressure (MIP) and MRC scores (respectively 25cmH_2O and 48/60).

Risk of bias assessment

Two reviewers (CM and YC) independently assessed the risk of bias for each study included in the meta-analyses in two stages: 1) bias was assessed for each outcome using the Quality in Prognosis Studies tool (QUIPS) [30] and 2) bias relating to the predictive capacity of each tool for mortality and weaning failure using the Quality Assessment of Diagnostic Accuracy Studies criteria (QUADAS-2).[31] Any disagreements were resolved following discussion with a third senior reviewer (GP).

Meta-Analysis

To analyse the association between each of the tests used to diagnose muscle weakness, random effects meta-analyses were performed using the DerSimonian & Laird method for binary outcomes, with odds ratios and their corresponding 95% confidence intervals calculated using the Hartung-Knapp-Sidik Jonkman method.[32] Standardized mean differences (Hedges' g) were calculated using a random effects model and the REML estimation method for the continuous outcomes. To assess heterogeneity, we used I^2 to express the amount of variability in the effect-estimates that is due to the differences between studies (above chance), H^2 to express the relative excess in Q over its degree of freedom; and τ^2 for the variance of the effect sizes. To evaluate a small study effect, we used funnel plots to evaluate asymmetry, and Harbord's test in situations where at least ten studies were included in a meta-analysis (a modification of Egger's test) to assess the hypothesis that smaller studies tend to show larger effects. Sensitivity and specificity were calculated based on true positive, false positive, false negative and true negative values and are presented as a forest plot of sensitivity and specificity. A hierarchical summary receiver operating characteristic curve (HSROC) [33] was plotted and sensitivity and specificity were pooled in the bivariate model.[34] Because there were no covariates in the analysis, these two methods represent different parametrizations of the same model.[35]

Results

Characteristics of the studies included in the systematic review

The search generated 6713 records. After screening abstracts and titles, 87 potentially eligible papers were downloaded for full-text review. Of these, 46 were included (Figure 1).[3, 5, 8, 11, 13, 15–29, 36–61] Some of these 46 articles evaluated more than one diagnostic test, therefore the final analysis included evaluation data from 60 separate studies on a total of 4392 patients (Figure 1). The main characteristics of each of the 60 studies are shown in Table

1. Of the 60 studies, 23 evaluated respiratory muscle strength using diaphragm ultrasound (1390 patients),[3, 13, 15–18, 24, 26–28, 36–48] 6 used transdiaphragmatic twitch pressure (292 patients) [3, 5, 11, 13, 49, 50] and 13 used MIP (709 patients) [3, 15–17, 25–28, 51–55]. A further fourteen graded limb muscle strength using the MRC score (1656 patients) [5, 8, 15, 19–21, 25, 29, 56–61] and 4 used the handgrip test (335 patients).[21–23, 29]

The majority of studies were European (52%), but several studies were from North America (20%), North-Africa (13%), Asia and South America (15%). The mean age of all the patients included was 61.8 ±5.5 years with a male/female ratio of 60/40. In this worldwide population, the prevalence of patients with muscle weakness was 47%. 41% had diaphragm weakness, 49% had a global respiratory muscle weakness and 50% had limb muscle weakness.

Risk of bias analysis

QUIPS

Of the 6 domains of the QUIPS, the "study confounding" domain included the highest number of studies with a high "risk of bias": 39% had a risk of bias for mortality or ventilator weaning (53%) Only 51% of the studies specifically reported that they evaluated the impact of muscle weakness on mortality and 53% evaluated the impact on weaning. The figures for the bias analyses are available in the supplemental data (Figures E1, E2, E3, E4, E5).

QUADAS-2

The majority of studies had a low "risk of bias" according to the QUADAS-2 tool. The "flow and timing" component contained a high number of "unclears" because the time that elapsed between the measurements and patient death was infrequently specified.

The “patient selection” domain in the “applicability” section contained a higher number of studies classified with a “high” risk of bias for mortality and weaning because of several that focused on specific pathologies such as chronic obstructive pulmonary disease or difficult-to-wean patients. Details of the bias for each evaluation and the figures for the bias analysis for the predictive capacity of each tool itself are available in the supplemental data (Figure E6 and Figure E7).

Small study bias

For overall mortality with versus without diagnosed weakness, the analysis for the MRC Score showed funnel plot asymmetry but no statistical evidence of a small study effect (p value from Harbord’s test p=0.7454). Too few studies were available to evaluate this bias for the other outcomes (Figure E8).

For weaning failure with versus without diagnosed weakness, the outcomes “Diaphragm ultrasound, Diaphragm excursion”, “Diaphragm ultrasound, Diaphragm thickening fraction”, and “Maximal Inspiratory Pressure” showed funnel plot asymmetries but no statistical evidence of a small study effect (p values from Harbord’s tests p=0.22, p=0.77, p=0.56). Too few studies were available to evaluate small study effects for the other tests (Figure E9).

For intensive care unit mortality, the meta-analysis for the MRC Score showed funnel plot asymmetry but no statistical evidence of a small study effect (p value from Harbord’s test p=0.83). Too few studies were available for the other outcomes to test small study effects (Figure E10).

For hospital mortality, too few studies were available for each test to formally evaluate small study effects (Figure E11).

Impact of muscle weakness on mortality and predictive capacity

Thirty-three studies (2974 patients) evaluated mortality [3, 5, 8, 11, 13, 15–21, 23, 29, 38, 39, 41, 47, 50, 55, 56, 58–61]: muscles weakness was strongly associated with an increase in overall mortality with odds ratios ranging from 1.2 [95% CI 0.60 to 2.40] using diaphragm ultrasound (decrease in diaphragm thickness) to 4.48 [95% CI 1.49 to 13.42] using maximal inspiratory pressure. Heterogeneity (I^2) ranged from 18% to 55%. The results are shown in Figure 2. Muscle weakness evaluated by daphragm thickening fraction, Transdiaphragmatic twitch pressure, MRC and Handgrip tools was associated with an increase in mortality in patients both in ICU and in hospital. MIP was not statistically associated with ICU mortality (Figure E12 and Figure E13).

The sensitivity, specificity and area under the curve (AUC) for the predictive capacity of each tool are presented in Table 2. Studies were grouped according to the tool used and the measurement carried out. It was not possible to evaluate the sensitivity, specificity or AUC of diaphragm thickness,[18] or force measured by the handgrip test because the minimum required number of evaluations (at least four) was not met. Overall, the predictive capacities of transdiaphragmatic twitch pressure, diaphragm thickening fraction and MIP were higher than those of MRC score or diaphragm excursion. Transdiaphragmatic twitch pressure had the highest predictive capacity for overall mortality, with a sensitivity of 0.87 [95%CI 0.76-0.93], a specificity of 0.36 [95%CI 0.27-0.43] and an AUC of 0.74 [95%CI 0.70-0.78]. The Receiver Operating Characteristics (ROC) curves and the predictive capacity of mortality in ICU and in the hospital are presented in the supplemental data (Figure E14, E15, E16, E17). Individual sensitivity and specificity values for each study are shown in the in the supplemental data (Figure E18).

Impact of muscle weakness on mechanical ventilation weaning and predictive capacity

The 41 studies that evaluated the impact of muscle weakness on mechanical ventilation weaning and the capacity of muscle weakness to predict difficult weaning or failure to wean included a total of 2514 patients.[3, 5, 15–18, 22–24, 26–28, 36–40, 42–46, 48, 51–55, 59, 60, 62] Muscle weakness was strongly associated with an increase in mechanical ventilation weaning failure rate with an odds ratio ranging from 2.64 (95% CI 0.72 to 9.64) using MRC score to 19.07 (95% CI 9.35 to 38.9) using diaphragm thickening fraction (Figure 3). Heterogeneity (I^2) ranged from 2% to 75%.

The sensitivity, specificity and area under the curve (AUC) of the prediction of weaning failure are presented in Table 2. Only diaphragm thickening fraction, diaphragm excursion and MIP could be analysed. Diaphragm thickening fraction had the highest predictive capacity for weaning failure with a sensitivity of 0.76 [95%CI 0.67-0.83], a specificity of 0.86 [95%CI 0.78-0.92] and an AUC of 0.86 [95%CI 0.83-0.89]. The sensitivity and specificity for each study are shown in the supplemental data (Figure E19).

Impact of muscle weakness on other outcomes.

As can be seen in Figure E20 and Figure E21, muscle weakness was often associated with a longer duration of mechanical ventilation (range of standardised mean difference across studies from -0.18 to 3.47) and a longer ICU length of stay (range of standardised mean difference across studies from -0.34 to 2.6), however there was substantial heterogeneity. Weakness was only associated with the incidence of tracheostomy using the Handgrip test.

Discussion

This systematic review included the largest sample of patients with ICU-Aw to date and evaluated all currently available non-invasive “bedside” tests. The results of this study have allowed the following conclusions to be drawn:

1. Respiratory or limb muscle weakness was associated with an increase in the rate of mortality, a failure to wean from artificial ventilation as well as an increased duration of both mechanical ventilation and length of stay in ICU.
2. Short term outcomes (mortality in ICU or weaning failure) were better predicted by tools that specifically evaluated diaphragm function than other tools.
3. The capacity to predict long-term outcomes was lower than for short-term outcomes.
4. There was significant heterogeneity among the measurement protocols and cut-off scores used.

The results of this meta-analysis showed that diaphragm function evaluated during a spontaneous breathing trial is a good indicator for the prediction of mortality in ICU and weaning failure. Poor diaphragm function (measured using transdiaphragmatic twitch pressure or ultrasound) was more strongly associated with an increased risk of mortality in ICU and failure to wean from mechanical ventilation than manual muscle testing. These results therefore suggest that in the initial stages of care, whilst the patient is in ICU and ventilated, evaluations of muscle strength should focus on the respiratory muscles in order to predict such critical outcomes. We suggest that diaphragm function should be closely monitored to detect patients with a high risk of poor clinical outcomes. The advantage of tools that evaluate respiratory muscle function is that they do not always require patient cooperation if the measurement is not maximal and can therefore be performed early, facilitating a faster diagnosis and commencement of treatment.

Phrenic magnetic stimulation is uncommon and difficult to use in routine clinical practice at the bedside, due to the equipment required, however diaphragm ultrasound and MIP are readily carried out and rapidly provide similar information for clinicians. Nevertheless, it is important to note that phrenic magnetic stimulation can be performed on admission to ICU,

independently from the mode of ventilation, in contrast with diaphragm thickening fraction which is greatly influenced by the type of ventilation. Dubé et al. reported that the diaphragm thickening fraction was well correlated with magnetic stimulation of the phrenic nerves at the time of transfer to pressure support ventilation. However, it was not correlated during assisted, controlled ventilation, possibly due to passive lung inflation and the reduction in respiratory effort.[13] Even if the relationship between MIP and diaphragm function is weaker, we suggest that patients with a low MIP should also be closely monitored since MIP had an AUC>0.70 for all the critical mortality and weaning failure outcomes investigated.[63]

In our analysis, it was not possible to pool the sensitivity and specificity of the MRC scale and the handgrip test in order to predict weaning failure. Nevertheless, individual results suggested that weaning failure could not be accurately predicted by those tools and that the capacity of the MRC scale to predict ICU mortality was low. However, for longer-term mortality, the predictive capacity of the MRC scale was similar to that of the diaphragm thickening fraction and MIP. The MRC scale, which requires no equipment but involves patient cooperation could be more relevant and easier to evaluate later, following transfer to the general ward to evaluate limb muscle function and to determine appropriate rehabilitation strategies[64, 65].

At this time, therefore, systematic screening for muscle weakness appears pertinent and useful to optimise the treatment of critically ill patients. Moreover, our results highlight the need for the urgent consideration of any therapeutic or preventive interventions aiming at mitigating the effects of ICU-aw and respiratory muscle dysfunction. Although risk factors for the development of muscle weakness have been established,[5] few preventative strategies or cures currently exist. One strategy is to maintain spontaneous ventilation as far as possible under mechanical ventilation, such as has been demonstrated in animal studies with applying

a diaphragm protective ventilation.[66–68] Sedation can be concomitantly adapted in order to permit intensive early rehabilitation in ICU.[69, 70] However, several recent studies demonstrated that intensive rehabilitation in critically ill patients did not produce better results than standard, moderate intensity rehabilitation.[71–74] Another study found that active mobilising exercises did not reduce patient mortality, despite increased muscle strength and walking ability.[75] Similar results were found in studies of inspiratory muscle training (IMT) in ventilated patients[76, 77]: IMT improves MIP and reduces weaning duration in ventilated patients but does not appear to modify the total duration of mechanical ventilation and does not influence mortality. The modalities of application of this treatment and the effects on clinical outcomes remain to be specified.[78] Nevertheless, it should be noted that none of the aforementioned research evaluated rehabilitation in patients with ICU-Aw. An important finding of this study is that respiratory and limb muscle weakness is an international-wide health issue for patients in ICU, with a global prevalence of 47% meaning that one in two patients have an increased risk of mortality. Moreover, an increased rate of mechanical ventilation weaning failure, increased duration of mechanical ventilation and longer ICU stays as a result of ICU-Aw considerably increase the cost of care per patient (+30%).[8] Results from this meta-analysis support the need for an urgent evaluation of rehabilitation for both respiratory and limb muscle weakness in patients with ICU-Aw.

To our knowledge, this is the first study to evaluate the clinical relevance of all data published within the last decade that described non-invasive, bedside tests for use in ICU. The only currently available tool that could not be evaluated was neuromuscular ultrasound as no studies were found, either published or unpublished, that evaluated its clinical use. The pooled sample set of these articles resulted in analysis of the largest sample of patients with ICU-Aw studied to date. The review included research drawn from international sources, and missing

data were recovered from the authors. From these data, several key outcomes were evaluated, and the risk of bias was analysed for each outcome.

We consider the limitations of this review to be the following: firstly, evaluation of the impact of muscle weakness on mortality was not always the main aim of all articles, which may have led to confounding factors in the observations. Secondly, although it was not explicitly studied here, it is supposed that the relationship between muscle function evaluation and patient mortality is also likely to be influenced by the time since diagnosis, as well as the care pathway followed by the patient following discharge from ICU.[79, 80] Moreover, little is currently known about the development or the reversibility of muscle weakness. Thirdly, due to limited data it was impossible to undertake a pooled analysis of sensitivity and specificity since the studies used different cut-offs for the same outcome. Thus, in order to increase the external validity of our results, standardization of the timing and modalities of muscle evaluation in ICU is needed. Fourthly, the number of studies of the handgrip test was insufficient for analysis of its predictive capacity. Fifthly, there is currently a lack of information regarding the increase in diaphragm thickness as reported by Goligher et al, which represents a type of diaphragm injury. Finally, we were unfortunately unable to analyse all existing data for MIP, a test that is frequently reported in the literature. Despite efforts to obtain extra data for clarification from authors, only 3 [15–17] provided individual MIP values.

Conclusion

The results of this study allow firm conclusions to be drawn regarding the clinical relevance and utility of tools for the early diagnosis of muscle weakness. Muscle weakness during ICU is a serious issue associated with high rates of mortality and so we suggest that respiratory muscle function should be evaluated as a priority in ICU, preferably via the measurement of

diaphragm thickening fraction using ultrasound. Patients found to have muscle weakness should then be closely monitored. Further studies are urgently needed to evaluate if rehabilitation could reduce mortality rate specifically in patients with ICU-Aw.

Acknowledgment

Collaborators

Naeem Ali, University Hospital, Division of Pulmonary, Critical Care, and Sleep Medicine, 168 Doan Hall, 410 W 10th Avenue, Columbus, OH 43210, United States. Provide data and information for the conduct and analysis of the work.

Cédric Carrié, Critical Care Department, Centre Hospitalier Robert Boulin, 33500 Libourne, France. Provide data and information for the conduct and analysis of the work.

Guillaume Cottereau, Physiotherapy and Rehabilitation Department, Hôpital Antoine-Béclère, Clamart, France. Provide data and information for the conduct and analysis of the work.

Alexandre Demoule, Groupe Hospitalier Pitié-Salpêtrière Charles Foix, Service de Pneumologie, Médecine Intensive et Réanimation (Département R3S), AP-HP, INSERM, UMRS1158 neurophysiologie respiratoire expérimentale et clinique, Sorbonne Université, Paris, France. Provide data and information for the conduct and analysis of the work and critical revision of the manuscript for important intellectual content.

Martin Dres, Sorbonne University, Experimental and Clinical Neurophysiology, National Institute for Health and Medical Research (INSERM, UMRS-1158; M.D.) the Pneumology and Intensive Care Department, Pitie Salpetriere Hospital, F-75013, (A.D.), Paris, France. Provide data and information for the conduct and analysis of the work and critical revision of the manuscript for important intellectual content.

Bruno Pierre Dubé, Département de Médecine, Service de Pneumologie, Centre Hospitalier de l'Université de Montréal (CHUM), Montréal, Canada, Centre de Recherche du Centre Hospitalier de l'Université de Montréal, Montreal, QC, Canada. Provide data and information for the conduct and analysis of the work and critical revision of the manuscript for important intellectual content.

Ewan Goligher, Interdepartmental Division of Critical Care Medicine, University of Toronto, Toronto, Canada, Department of Medicine, Division of Respirology, University Health Network, Toronto, Canada and Toronto and General Hospital Research Institute, 585 University Ave., 11-PMB Room 192, Toronto, ON, M5G 2N2, Canada. Provide data and information for the conduct and analysis of the work.

Greet Hermans, Department of Cellular and Molecular Medicine, KU Leuven, Leuven, Belgium and Medical Intensive Care Unit, University Hospitals Leuven, Leuven, Belgium. Provide data and information for the conduct and analysis of the work.

Aliae Mohamed Hussein, Chest Department, Faculty of Medicine, Assiut University, Assiut, 71515, Egypt. Provide data and information for the conduct and analysis of the work.

Savino Spadaro, Department of Morphology, Experimental Medicine and Surgery, Section of Anaesthesia and Intensive Care, Arcispedale Sant' Anna, University of Ferrara, Ferrara, Italy. Provide data and information for the conduct and analysis of the work.

Eva María Tenza-Lozano, Physician, Intensive Care Specialist, Intensive Care Unit of the General University Hospital of Elche, Spain. Provide data and information for the conduct and analysis of the work.

Luuk Wieske, Department of Neurology, Amsterdam UMC, University of Amsterdam, Amsterdam Neuroscience, Amsterdam, The Netherlands. Provide data and information for the conduct and analysis of the work.

Esther Witteveen, Department of Intensive Care, Amsterdam University Medical Centers, Amsterdam, The Netherlands and Laboratory of Experimental Intensive Care and Anesthesiology (L·E·I·C·A), Amsterdam University Medical Centers, Amsterdam, The Netherlands. Provide data and information for the conduct and analysis of the work.

Author Contribution

Guarantor: Clément Medrinal

Study concept and design: Medrinal, Combret, Prieur, Contal, Lamia

Acquisition of data: All authors

Analysis and interpretation of pooled data: Medrinal, Combret, Hlifiker, Prieur, Gravier, Bonnevie, Contal, Lamia

Drafting of the manuscript: Medrinal, Combret, Hilfiker, Prieur

Critical revision of the manuscript for important intellectual content: All authors

Statistical analysis of pooled data: Hilfiker

Conflicts of interest and financial disclosure: No conflicts of interest in regards with the subject of the manuscript.

Data Access, Responsibility, and analysis: Clément Medrinal had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Data sharing: The study specific summary data included in the meta-analysis can be obtained from the corresponding author: Clément Medrinal ; medrinal.clement.mk@gmail.com.

References

1. Tennilä A, Salmi T, Pettilä V, Roine RO, Varpula T, Takkunen O. Early signs of critical illness polyneuropathy in ICU patients with systemic inflammatory response syndrome or sepsis. *Intensive Care Med.* 2000; 26: 1360–1363.

2. De Jonghe B, Sharshar T, Lefaucheur J-P, Authier F-J, Durand-Zaleski I, Boussarsar M, Cerf C, Renaud E, Mesrati F, Carlet J, Raphaël J-C, Outin H, Bastuji-Garin S, Groupe de Réflexion et d'Etude des Neuromyopathies en Réanimation. Paresis acquired in the intensive care unit: a prospective multicenter study. *JAMA* 2002; 288: 2859–2867.

3. Jung B, Moury PH, Mahul M, de Jong A, Galia F, Prades A, Albaladejo P, Chanques G, Molinari N, Jaber S. Diaphragmatic dysfunction in patients with ICU-acquired weakness and its impact on extubation failure. *Intensive Care Med.* 2016; 42: 853–861.

4. Kress JP, Hall JB. ICU-Acquired Weakness and Recovery from Critical Illness. *N. Engl. J. Med.* 2014; 370: 1626–1635.

5. Dres M, Dubé B-P, Mayaux J, Delemazure J, Reuter D, Brochard L, Similowski T, Demoule A. Coexistence and Impact of Limb Muscle and Diaphragm Weakness at Time of Liberation from Mechanical Ventilation in Medical Intensive Care Unit Patients. *Am. J. Respir. Crit. Care Med.* 2017; 195: 57–66.

6. Fan E, Cheek F, Chlan L, Gosselink R, Hart N, Herridge MS, Hopkins RO, Hough CL, Kress JP, Latronico N, Moss M, Needham DM, Rich MM, Stevens RD, Wilson KC, Winkelman C, Zochodne DW, Ali NA, ATS Committee on ICU-acquired Weakness in Adults, American Thoracic Society. An official American Thoracic Society Clinical Practice guideline: the diagnosis of intensive care unit-acquired weakness in adults. *Am. J. Respir. Crit. Care Med.* 2014; 190: 1437–1446.

7. Hough CL, Lieu BK, Caldwell ES. Manual muscle strength testing of critically ill patients: feasibility and interobserver agreement. *Crit. Care Lond. Engl.* 2011; 15: R43.

8. Hermans G, Van Mechelen H, Clerckx B, Vanhullebusch T, Mesotten D, Wilmer A, Casaer MP, Meersseman P, Debaveye Y, Van Cromphaut S, Wouters PJ, Gosselink R, Van den Berghe G. Acute outcomes and 1-year mortality of intensive care unit-acquired weakness. A cohort study and propensity-matched analysis. *Am. J. Respir. Crit. Care Med.* 2014; 190: 410–420.

9. Latronico N, Herridge M, Hopkins RO, Angus D, Hart N, Hermans G, Iwashyna T, Arabi Y, Citerio G, Wesley Ely E, Hall J, Mehta S, Puntillo K, Van den Hoeven J, Wunsch H, Cook D, Dos Santos C,

Rubenfeld G, Vincent J-L, Van den Berghe G, Azoulay E, Needham DM. The ICM research agenda on intensive care unit-acquired weakness. *Intensive Care Med.* 2017; 43: 1270–1281.

10. Jolley SE, Bunnell AE, Hough CL. ICU-Acquired Weakness. *Chest* 2016; 150: 1129–1140.

11. Demoule A, Jung B, Prodanovic H, Molinari N, Chanques G, Coirault C, Matecki S, Duguet A, Similowski T, Jaber S. Diaphragm dysfunction on admission to the intensive care unit. Prevalence, risk factors, and prognostic impact-a prospective study. *Am. J. Respir. Crit. Care Med.* 2013; 188: 213–219.

12. Puthucheary ZA, Rawal J, McPhail M, Connolly B, Ratnayake G, Chan P, Hopkinson NS, Phadke R, Padhke R, Dew T, Sidhu PS, Velloso C, Seymour J, Agley CC, Selby A, Limb M, Edwards LM, Smith K, Rowlerson A, Rennie MJ, Moxham J, Harridge SDR, Hart N, Montgomery HE. Acute skeletal muscle wasting in critical illness. *JAMA* 2013; 310: 1591–1600.

13. Dubé B-P, Dres M, Mayaux J, Demiri S, Similowski T, Demoule A. Ultrasound evaluation of diaphragm function in mechanically ventilated patients: comparison to phrenic stimulation and prognostic implications. *Thorax* 2017; 72: 811–818.

14. Stroup DF. Meta-analysis of Observational Studies in EpidemiologyA Proposal for Reporting. *JAMA* 2000; 283: 2008.

15. Carrie C, Gisbert-Mora C, Bonnardel E, Gauche B, Biais M, Vargas F, Hilbert G. Ultrasonographic diaphragmatic excursion is inaccurate and not better than the MRC score for predicting weaning-failure in mechanically ventilated patients. *Anaesth. Crit. Care Pain Med.* 2017; 36: 9–14.

16. Spadaro S, Grasso S, Mauri T, Dalla Corte F, Alvisi V, Ragazzi R, Cricca V, Biondi G, Di Mussi R, Marangoni E, Volta CA. Can diaphragmatic ultrasonography performed during the T-tube trial predict weaning failure? The role of diaphragmatic rapid shallow breathing index. *Crit. Care Lond. Engl.* 2016; 20: 305.

17. Tenza-Lozano E, Llamas-Alvarez A, Jaimez-Navarro E, Fernández-Sánchez J. Lung and diaphragm ultrasound as predictors of success in weaning from mechanical ventilation. *Crit. Ultrasound J.* 2018; 10: 12.

18. Goligher EC, Dres M, Fan E, Rubenfeld GD, Scales DC, Herridge MS, Vorona S, Sklar MC, Rittayamai N, Lanys A, Murray A, Brace D, Urrea C, Reid WD, Tomlinson G, Slutsky AS, Kavanagh BP, Brochard LJ, Ferguson ND. Mechanical Ventilation-induced Diaphragm Atrophy Strongly Impacts Clinical Outcomes. *Am. J. Respir. Crit. Care Med.* 2018; 197: 204–213.

19. Wieske L, Dettling-Ihnenfeldt DS, Verhamme C, Nollet F, van Schaik IN, Schultz MJ, Horn J, van der Schaaf M. Impact of ICU-acquired weakness on post-ICU physical functioning: a follow-up study. *Crit. Care Lond. Engl.* 2015; 19: 196.

20. Witteveen E, Sommers J, Wieske L, Doorduin J, van Alfen N, Schultz MJ, van Schaik IN, Horn J, Verhamme C. Diagnostic accuracy of quantitative neuromuscular ultrasound for the diagnosis of intensive care unit-acquired weakness: a cross-sectional observational study. *Ann. Intensive Care* 2017; 7: 40.

21. Ali NA, O'Brien JM, Hoffmann SP, Phillips G, Garland A, Finley JCW, Almoosa K, Hejal R, Wolf KM, Lemeshow S, Connors AF, Marsh CB, Midwest Critical Care Consortium. Acquired

weakness, handgrip strength, and mortality in critically ill patients. *Am. J. Respir. Crit. Care Med.* 2008; 178: 261–268.

22. Cottereau G, Dres M, Avenel A, Fichet J, Jacobs FM, Prat D, Hamzaoui O, Richard C, Antonello M, Sztrymf B. Handgrip Strength Predicts Difficult Weaning But Not Extubation Failure in Mechanically Ventilated Subjects. *Respir. Care* 2015; 60: 1097–1104.

23. Mohamed-Hussein AAR, Makhlouf HA, Selim ZI, Gamaleldin Saleh W. Association between hand grip strength with weaning and intensive care outcomes in COPD patients: A pilot study. *Clin. Respir. J.* 2018; 12: 2475–2479.

24. Dres M, Goligher EC, Dubé B-P, Morawiec E, Dangers L, Reuter D, Mayaux J, Similowski T, Demoule A. Diaphragm function and weaning from mechanical ventilation: an ultrasound and phrenic nerve stimulation clinical study. *Ann. Intensive Care* 2018; 8: 53.

25. Tzanis G, Vasileiadis I, Zervakis D, Karatzanos E, Dimopoulos S, Pitsolis T, Tripodaki E, Gerovasili V, Routsi C, Nanas S. Maximum inspiratory pressure, a surrogate parameter for the assessment of ICU-acquired weakness. *BMC Anesthesiol.* 2011; 11: 14.

26. Flevari A, Lignos M, Konstantonis D, Armaganidis A. Diaphragmatic ultrasonography as an adjunct predictor tool of weaning success in patients with difficult and prolonged weaning. *Minerva Anestesiol.* 2016; 82: 1149–1157.

27. Saeed A, El Assal G, Ali T, Hendawy M. Role of ultrasound in assessment of diaphragmatic function in chronic obstructive pulmonary disease patients during weaning from mechanical ventilation. *Egypt. J. Bronchol.* 2016; 10: 167.

28. Jiang J-R, Tsai T-H, Jerng J-S, Yu C-J, Wu H-D, Yang P-C. Ultrasonographic evaluation of liver/spleen movements and extubation outcome. *Chest* 2004; 126: 179–185.

29. Lee JJ, Waak K, Grosse-Sundrup M, Xue F, Lee J, Chipman D, Ryan C, Bittner EA, Schmidt U, Eikermann M. Global muscle strength but not grip strength predicts mortality and length of stay in a general population in a surgical intensive care unit. *Phys. Ther.* 2012; 92: 1546–1555.

30. Hayden JA, van der Windt DA, Cartwright JL, Côté P, Bombardier C. Assessing bias in studies of prognostic factors. *Ann. Intern. Med.* 2013; 158: 280–286.

31. Whiting PF, Rutjes AWS, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, Leeflang MMG, Sterne JAC, Bossuyt PMM, QUADAS-2 Group. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Ann. Intern. Med.* 2011; 155: 529–536.

32. IntHout J, Ioannidis JPA, Borm GF. The Hartung-Knapp-Sidik-Jonkman method for random effects meta-analysis is straightforward and considerably outperforms the standard DerSimonian-Laird method. *BMC Med. Res. Methodol.* 2014; 14: 25.

33. Rutter CM, Gatsonis CA. A hierarchical regression approach to meta-analysis of diagnostic test accuracy evaluations. *Stat. Med.* 2001; 20: 2865–2884.

34. Reitsma JB, Glas AS, Rutjes AWS, Scholten RJPM, Bossuyt PM, Zwinderman AH. Bivariate analysis of sensitivity and specificity produces informative summary measures in diagnostic reviews. *J. Clin. Epidemiol.* 2005; 58: 982–990.

35. Harbord RM, Deeks JJ, Egger M, Whiting P, Sterne JAC. A unification of models for meta-analysis of diagnostic accuracy studies. *Biostat. Oxf. Engl.* 2007; 8: 239–251.

36. Abbas A, Embarak S, Walaa M, Lutfy SM. Role of diaphragmatic rapid shallow breathing index in predicting weaning outcome in patients with acute exacerbation of COPD. *Int. J. Chron. Obstruct. Pulmon. Dis.* 2018; 13: 1655–1661.

37. Khan MT, Munawar K, Hussain SW, Qadeer A, Saeed ML, Shad ZS, Qureshi MSS, Abdullah A. Comparing Ultrasound-based Diaphragmatic Excursion with Rapid Shallow Breathing Index as a Weaning Predictor. *Cureus* 2018; 10: e3710.

38. Kim WY, Suh HJ, Hong S-B, Koh Y, Lim C-M. Diaphragm dysfunction assessed by ultrasonography: influence on weaning from mechanical ventilation. *Crit. Care Med.* 2011; 39: 2627–2630.

39. Mariani LF, Bedel J, Gros A, Lerolle N, Milojevic K, Laurent V, Hilly J, Troché G, Bedos JP, Planquette B. Ultrasonography for Screening and Follow-Up of Diaphragmatic Dysfunction in the ICU: A Pilot Study. *J. Intensive Care Med.* 2016; 31: 338–343.

40. Theerawit P, Eksombatchai D, Sutherasan Y, Suwatanapongched T, Kiatboonsri C, Kiatboonsri S. Diaphragmatic parameters by ultrasonography for predicting weaning outcomes. *BMC Pulm. Med.* 2018; 18: 175.

41. Ali ER, Mohamad AM. Diaphragm ultrasound as a new functional and morphological index of outcome, prognosis and discontinuation from mechanical ventilation in critically ill patients and evaluating the possible protective indices against VIDD. *Egypt. J. Chest Dis. Tuberc.* 2017; 66: 339–351.

42. Baess A, Abdallah T, Emara D, Hassan M. Diaphragmatic ultrasound as a predictor of successful extubation from mechanical ventilation: thickness, displacement, or both? *Egypt. J. Bronchol.* 2016; 10: 162.

43. Blumhof S, Wheeler D, Thomas K, McCool FD, Mora J. Change in Diaphragmatic Thickness During the Respiratory Cycle Predicts Extubation Success at Various Levels of Pressure Support Ventilation. *Lung* 2016; 194: 519–525.

44. DiNino E, Gartman EJ, Sethi JM, McCool FD. Diaphragm ultrasound as a predictor of successful extubation from mechanical ventilation. *Thorax* 2014; 69: 423–427.

45. Farghaly S, Hasan AA. Diaphragm ultrasound as a new method to predict extubation outcome in mechanically ventilated patients. *Aust. Crit. Care Off. J. Confed. Aust. Crit. Care Nurses* 2017; 30: 37–43.

46. Ferrari G, De Filippi G, Elia F, Panero F, Volpicelli G, Aprà F. Diaphragm ultrasound as a new index of discontinuation from mechanical ventilation. *Crit. Ultrasound J.* 2014; 6: 8.

47. Lu Z, Xu Q, Yuan Y, Zhang G, Guo F, Ge H. Diaphragmatic Dysfunction Is Characterized by Increased Duration of Mechanical Ventilation in Subjects With Prolonged Weaning. *Respir. Care* 2016; 61: 1316–1322.

48. Osman AM, Hashim RM. Diaphragmatic and lung ultrasound application as new predictive indices for the weaning process in ICU patients. *Egypt. J. Radiol. Nucl. Med.* 2017; 48: 61–66.

49. Hermans G, Agten A, Testelmans D, Decramer M, Gayan-Ramirez G. Increased duration of mechanical ventilation is associated with decreased diaphragmatic force: a prospective observational study. *Crit. Care Lond. Engl.* 2010; 14: R127.

50. Supinski GS, Callahan LA. Diaphragm weakness in mechanically ventilated critically ill patients. *Crit. Care Lond. Engl.* 2013; 17: R120.

51. Alvisi R, Volta CA, Righini ER, Capuzzo M, Ragazzi R, Verri M, Candini G, Gritti G, Milic-Emili J. Predictors of weaning outcome in chronic obstructive pulmonary disease patients. *Eur. Respir. J.* 2000; 15: 656–662.

52. Bruton A. A pilot study to investigate any relationship between sustained maximal inspiratory pressure and extubation outcome. *Heart Lung J. Crit. Care* 2002; 31: 141–149.

53. De Jonghe B, Bastuji-Garin S, Durand M-C, Malissin I, Rodrigues P, Cerf C, Outin H, Sharshar T, Groupe de Réflexion et d'Etude des Neuromyopathies en Réanimation. Respiratory weakness is associated with limb weakness and delayed weaning in critical illness. *Crit. Care Med.* 2007; 35: 2007–2015.

54. de Souza LC, Guimarães FS, Lugon JR. The timed inspiratory effort: a promising index of mechanical ventilation weaning for patients with neurologic or neuromuscular diseases. *Respir. Care* 2015; 60: 231–238.

55. Medrinal C, Prieur G, Frenoy É, Robledo Quesada A, Poncet A, Bonnevie T, Gravier F-E, Lamia B, Contal O. Respiratory weakness after mechanical ventilation is associated with one-year mortality - a prospective study. *Crit. Care Lond. Engl.* 2016; 20: 231.

56. Brunello A-G, Haenggi M, Wigger O, Porta F, Takala J, Jakob SM. Usefulness of a clinical diagnosis of ICU-acquired paresis to predict outcome in patients with SIRS and acute respiratory failure. *Intensive Care Med.* 2010; 36: 66–74.

57. De Jonghe B, Bastuji-Garin S, Sharshar T, Outin H, Brochard L. Does ICU-acquired paresis lengthen weaning from mechanical ventilation? *Intensive Care Med.* 2004; 30: 1117–1121.

58. Dinglas VD, Aronson Friedman L, Colantuoni E, Mendez-Tellez PA, Shanholtz CB, Ciesla ND, Pronovost PJ, Needham DM. Muscle Weakness and 5-Year Survival in Acute Respiratory Distress Syndrome Survivors. *Crit. Care Med.* 2017; 45: 446–453.

59. Medrinal C, Prieur G, Frenoy É, Combret Y, Gravier FE, Bonnevie T, Poncet A, Robledo Quesada A, Lamia B, Contal O. Is overlap of respiratory and limb muscle weakness at weaning from mechanical ventilation associated with poorer outcomes? *Intensive Care Med.* 2017; 43: 282–283.

60. Diaz Ballve LP, Dargains N, Urrutia Inchaustegui JG, Bratos A, Milagros Percaz M de L, Bueno Ardariz C, Cagide S, Balestrieri C, Gamarra C, Paz D, Rotela E, Muller S, Bustos F, Aranda Castro R, Settembrino E. Weakness acquired in the intensive care unit. Incidence, risk factors and their association with inspiratory weakness. Observational cohort study. *Rev. Bras. Ter. Intensiva* 2017; 29: 466–475.

61. Sharshar T, Bastuji-Garin S, Stevens RD, Durand M-C, Malissin I, Rodriguez P, Cerf C, Outin H, De Jonghe B. Presence and severity of intensive care unit-acquired paresis at time of awakening are associated with increased intensive care unit and hospital mortality*: *Crit. Care Med.* 2009; 37: 3047–3053.

62. Ali ER, Mohamad AM. Diaphragm ultrasound as a new functional and morphological index of outcome, prognosis and discontinuation from mechanical ventilation in critically ill patients and evaluating the possible protective indices against VIDD. *Egypt. J. Chest Dis. Tuberc.* 2017; 66: 339–351.

63. Moons KGM, Altman DG, Vergouwe Y, Royston P. Prognosis and prognostic research: application and impact of prognostic models in clinical practice. *BMJ* 2009; 338: b606.

64. Schweickert WD, Pohlman MC, Pohlman AS, Nigos C, Pawlik AJ, Esbrook CL, Spears L, Miller M, Franczyk M, Deprizio D, Schmidt GA, Bowman A, Barr R, McCallister KE, Hall JB, Kress JP. Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. *Lancet Lond. Engl.* 2009; 373: 1874–1882.

65. Chao P, Shih C-J, Lee Y-J, Tseng C-M, Kuo S-C, Shih Y-N, Chou K-T, Tarng D-C, Li S-Y, Ou S-M, Chen Y-T. Association of postdischarge rehabilitation with mortality in intensive care unit survivors of sepsis. *Am. J. Respir. Crit. Care Med.* 2014; 190: 1003–1011.

66. Sassoon CSH, Zhu E, Caiozzo VJ. Assist-control mechanical ventilation attenuates ventilator-induced diaphragmatic dysfunction. *Am. J. Respir. Crit. Care Med.* 2004; 170: 626–632.

67. Futier E, Constantin J-M, Combaret L, Mosoni L, Roszyk L, Sapin V, Attaix D, Jung B, Jaber S, Bazin J-E. Pressure support ventilation attenuates ventilator-induced protein modifications in the diaphragm. *Crit. Care Lond. Engl.* 2008; 12: R116.

68. Schepens T, Dres M, Heunks L, Goligher EC. Diaphragm-protective mechanical ventilation. *Curr. Opin. Crit. Care* 2019; 25: 77–85.

69. Jolley SE, Moss M, Needham DM, Caldwell E, Morris PE, Miller RR, Ringwood N, Anders M, Koo KK, Gundel SE, Parry SM, Hough CL, Acute Respiratory Distress Syndrome Network Investigators. Point Prevalence Study of Mobilization Practices for Acute Respiratory Failure Patients in the United States. *Crit. Care Med.* 2017; 45: 205–215.

70. Medrinal C, Combret Y, Prieur G, Robledo Quesada A, Bonnevie T, Gravier FE, Dupuis Lozeron E, Frenoy E, Contal O, Lamia B. Comparison of exercise intensity during four early rehabilitation techniques in sedated and ventilated patients in ICU: a randomised cross-over trial. *Crit. Care Lond. Engl.* 2018; 22: 110.

71. Moss M, Nordon-Craft A, Malone D, Van Pelt D, Frankel SK, Warner ML, Kriekels W, McNulty M, Fairclough DL, Schenkman M. A Randomized Trial of an Intensive Physical Therapy Program for Patients with Acute Respiratory Failure. *Am. J. Respir. Crit. Care Med.* 2016; 193: 1101–1110.

72. Wright SE, Thomas K, Watson G, Baker C, Bryant A, Chadwick TJ, Shen J, Wood R, Wilkinson J, Mansfield L, Stafford V, Wade C, Furneval J, Henderson A, Hugill K, Howard P, Roy A, Bonner S, Baudouin S. Intensive versus standard physical rehabilitation therapy in the critically ill (EPICC): a multicentre, parallel-group, randomised controlled trial. *Thorax* 2018; 73: 213–221.

73. Fossat G, Baudin F, Courtes L, Bobet S, Dupont A, Bretagnol A, Benzekri-Lefèvre D, Kamel T, Muller G, Bercault N, Barbier F, Runge I, Nay M-A, Skarzynski M, Mathonnet A, Boulain T. Effect of In-Bed Leg Cycling and Electrical Stimulation of the Quadriceps on Global Muscle Strength in Critically Ill Adults: A Randomized Clinical Trial. *JAMA* 2018; 320: 368.

74. Morris PE, Berry MJ, Files DC, Thompson JC, Hauser J, Flores L, Dhar S, Chmelo E, Lovato J, Case LD, Bakhru RN, Sarwal A, Parry SM, Campbell P, Mote A, Winkelman C, Hite RD, Nicklas B,

Chatterjee A, Young MP. Standardized Rehabilitation and Hospital Length of Stay Among Patients With Acute Respiratory Failure: A Randomized Clinical Trial. *JAMA* 2016; 315: 2694–2702.

75. Tipping CJ, Harrold M, Holland A, Romero L, Nisbet T, Hodgson CL. The effects of active mobilisation and rehabilitation in ICU on mortality and function: a systematic review. *Intensive Care Med.* 2017; 43: 171–183.

76. Bissett BM, Leditschke IA, Neeman T, Boots R, Paratz J. Inspiratory muscle training to enhance recovery from mechanical ventilation: a randomised trial. *Thorax* 2016; 71: 812–819.

77. Elkins M, Dentice R. Inspiratory muscle training facilitates weaning from mechanical ventilation among patients in the intensive care unit: a systematic review. *J. Physiother.* 2015; 61: 125–134.

78. Vorona S, Sabatini U, Al-Maqbali S, Bertoni M, Dres M, Bissett B, Van Haren F, Martin AD, Urrea C, Brace D, Parotto M, Herridge MS, Adhikari NKJ, Fan E, Melo LT, Reid WD, Brochard LJ, Ferguson ND, Goligher EC. Inspiratory Muscle Rehabilitation in Critically Ill Adults. A Systematic Review and Meta-Analysis. *Ann. Am. Thorac. Soc.* 2018; 15: 735–744.

79. Ferrante LE, Pisani MA, Murphy TE, Gahbauer EA, Leo-Summers LS, Gill TM. Factors Associated with Functional Recovery among Older Intensive Care Unit Survivors. *Am. J. Respir. Crit. Care Med.* 2016; 194: 299–307.

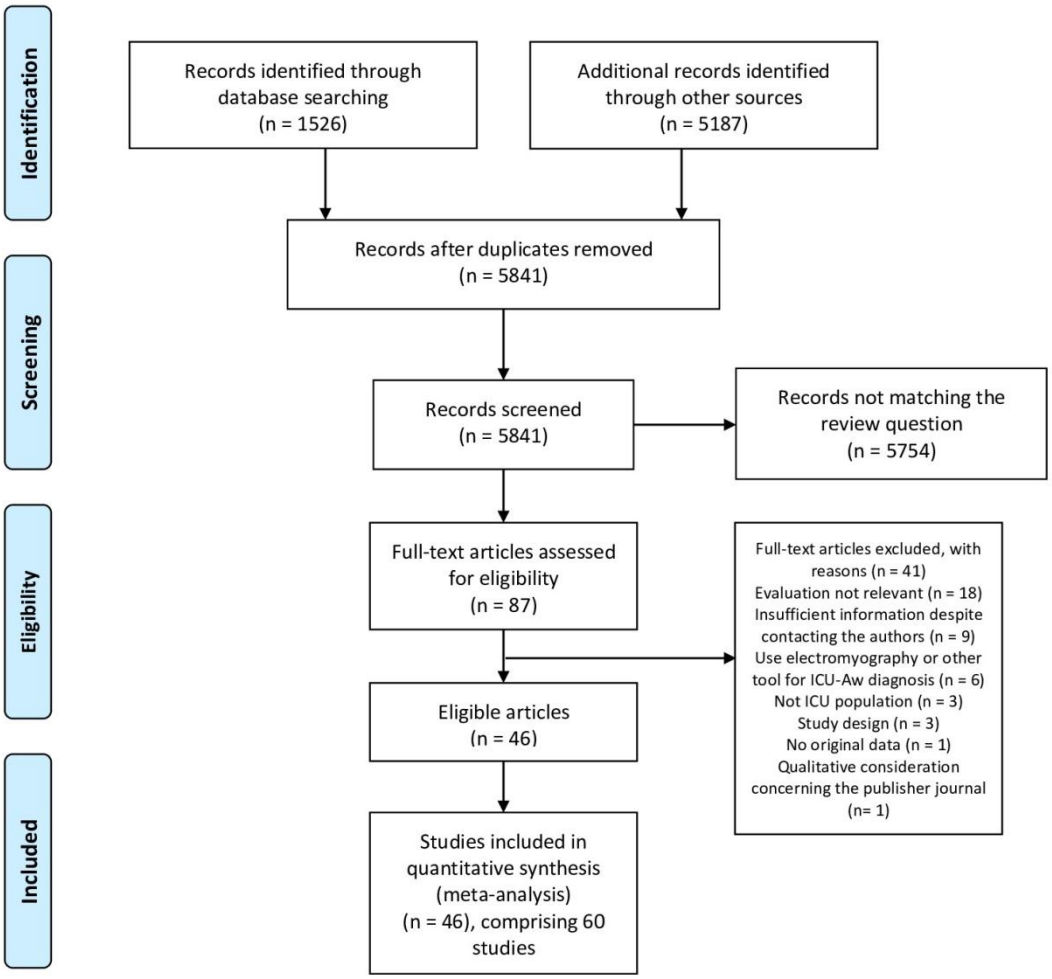
80. Herridge MS, Chu LM, Matte A, Tomlinson G, Chan L, Thomas C, Friedrich JO, Mehta S, Lamontagne F, Levasseur M, Ferguson ND, Adhikari NKJ, Rudkowski JC, Meggison H, Skrobik Y, Flannery J, Bayley M, Batt J, Santos CD, Abbey SE, Tan A, Lo V, Mathur S, Parotto M, Morris D, Flockhart L, Fan E, Lee CM, Wilcox ME, Ayas N, et al. The RECOVER Program: Disability Risk Groups and 1-Year Outcome after 7 or More Days of Mechanical Ventilation. *Am. J. Respir. Crit. Care Med.* 2016; 194: 831–844.

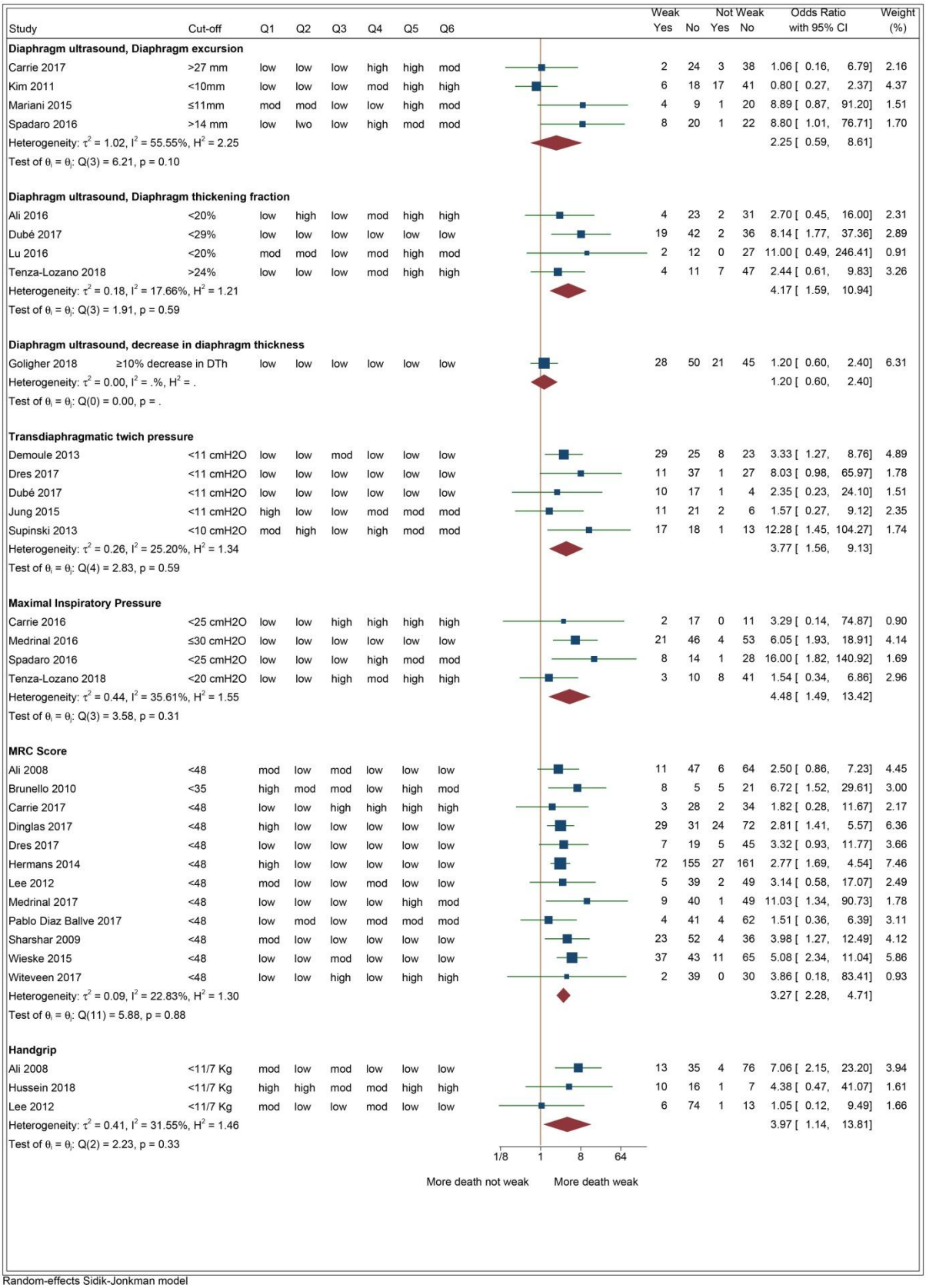
Figures legend

Figure 1 Flowchart for study identification and selection

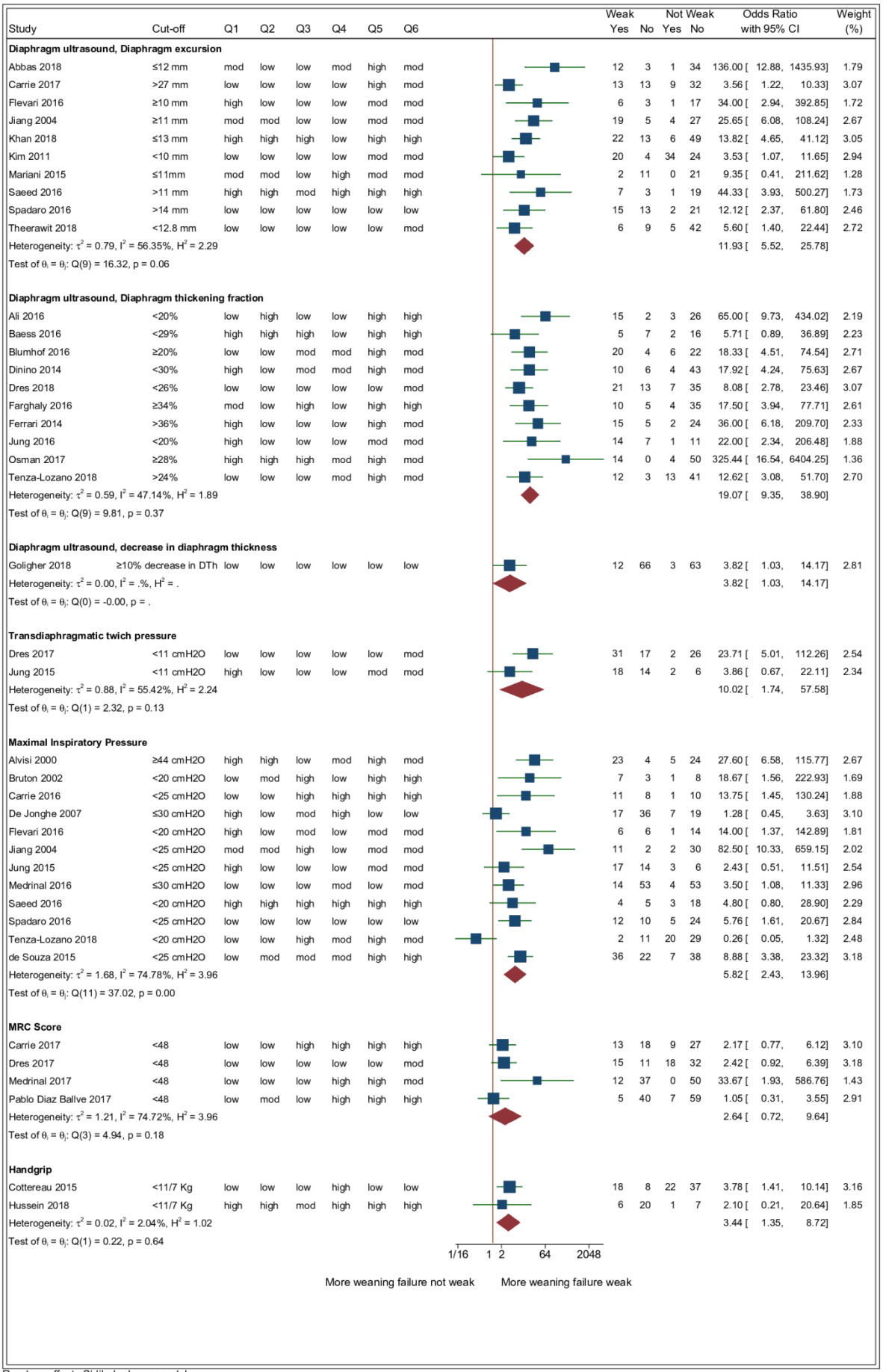
Figure 2 Odds ratios for overall mortality with versus without a diagnosed weakness. Q represents the different Quality in Prognosis Studies tool (QUIPS) items. Q1=Study participation ; Q2=Study attrition ; Q3=Pronostic factor measurment ; Q4=Outcome measurment ; Q5=Study confounding ; Q6=Statistical analysis and reporting

Figure 3 Odds ratios for weaning failure with versus without a diagnosed weakness. Q represents the different Quality in Prognosis Studies tool (QUIPS) items. Q1=Study participation ; Q2=Study attrition ; Q3=Pronostic factor measurment ; Q4=Outcome measurment ; Q5=Study confounding ; Q6=Statistical analysis and reporting


Identification
Screening
Eligibility
Included
Records identified through database searching (n = 1526)
Additional records identified through other sources (n = 5187)
Records after duplicates removed (n = 5841)
Records screened (n = 5841)
Records not matching the review question (n = 5754)
Full-text articles assessed for eligibility (n = 87)
Full-text articles excluded, with reasons (n = 41)
Evaluation not relevant (n = 18)
Insufficient information despite contacting the authors (n = 9)
Use electromyography or other tool for ICU-Aw diagnosis (n = 6)
Not ICU population (n = 3)
Study design (n = 3)
No original data (n = 1)
Qualitative consideration concerning the publisher journal (n= 1)
Eligible articles (n = 46)
Studies included in quantitative synthesis (meta-analysis) (n = 46), comprising 60 studies



Random-effects Sidik-Jonkman model



Random-effects Sidik-Jonkman model

Table 1. Characteristics of studies included in the meta-analysis

First Author (name and year)	Country	N	Population	Measurments and cut-off value	Time and condition of measure
Diaphragm Ultrasound					
Abbas 2018	Egypt	50	COPD under MV > 48h	EXdi (≤12mm)	During First SBT on a T-tube
Carrie 2017	France	67	Patients under MV > 48h	EXdi (>27 mm)	During first SBT : PS : 7/Pep :0 cmH_2O
Flevari 2016	Greece	27	Patients with difficult and prolonged weaning	EXdi (≥10mm)	During SBT on a T-tube
Jiang 2004	Taiwan	55	Patients under MV	EXdi (≥11 mm)	During SBT on a T-tube
Khan 2018	Pakistan	90	Patients under MV > 48h	EXdi (≤13 mm)	During SBT
Kim 2011	Korean	82	Patients under MV > 48h	EXdi (<10mm)	During SBT
Mariani 2015	France	34	Patients under MV > 7 days	EXdi (≤11mm)	During SBT on a T-tube
Saeed 2016	Egypt	30	COPD under MV	EXdi (>11 mm)	During SBT
Spadaro 2016	Italy	51	Patients under MV > 48h	EXdi (>14 mm)	During First SBT on a T-tube
Theerawit 2018	Thailand	62	Patients under MV	EXdi (<12,8mm)	At the end of SBT on a T-tube
Ali 2016	Egypt	60	Patients under MV > 72h	TFdi (<20%)	Not specified
Baess 2016	Egypt	30	Patients under MV	TFdi (<29%)	During SBT
Blumhof 2016	USA	52	Patients under MV > 24h	TFdi (≥20%)	During SBT by pressure support
Dinino 2014	USA	63	Patients under MV	TFdi (<30%)	Prior to the first SBT : PS : 5/Pep :5 cmH_2O
Dres 2018	France	76	Patients under MV > 24h	TFdi (<26%)	Prior to the first SBT
Dubé 2017	Canada	99	Patients under MV > 24h	TFdi (<29%)	During Pressure Support Ventilation
Farghaly 2016	Egypt	54	Patients with pulmonary disease under MV	TFdi (≥34%)	During SBT : PS : 8/Pep :0 cmH_2O
Ferrari 2014	Italy	46	Patients on PSV with a tracheostomy tube	TFdi (>36%)	During SBT without MV
Jung 2016	France	40	Patients with ICU-Aw under MV > 48h	TFdi (<20%)	During SBT (T-tube or PS : 7/Pep :0 cmH_2O
Lu 2016	China	41	Patients with difficult and prolonged weaning	TFdi (<20%)	During SBT : PS : 5/Pep :3 cmH_2O
Osman 2017	Egypt	68	Patients under MV	TFdi (≥28%)	During SBT without MV
Tenza-Lozano 2018	Spain	69	Patients under MV > 24h	TFdi (>24%)	During SBT
Goligher 2018	Canada	144*	Patients under MV	≥10% decrease in DTh	Daily on weekdays until extubation
Transdiaphragmatic twich pressure					
Demoule 2013	France	85	Patients under MV > 48h	Ptrstim (<11 cmH20)	Within 24 hours of intubation

Dres 2017	France	76	Patients under MV > 24h	Ptrstim (<11 cmH20)	Prior to the first SBT
Dubé 2017	Canada	32*	Patients under MV > 24h	Ptrstim (<11 cmH20)	During Pressure Support Ventilation
Hermans 2010	Netherlands	10	Patients under MV	TwPdi (<10 cmH20)	Not specified
Jung 2015	France	40	Patients with ICU-Aw under MV > 48h	Ptrstim (<11 cmH20)	During SBT (T-tube or PS : 7/Pep :0 cmH_2O
Supinski 2013	USA	49	Patients under MV > 24h	TwPdi (<10 cmH20)	Not specified
Maximal Inspiratory Pressure					
Alvisi 2000	Italy	56	COPD patients	MIP (≥44 cmH2O)	During SBT on a T-tube
Bruton 2002	UK	19	Patients with ICU-Aw under MV > 48h	MIP (<20 cmH20)	Within 12 h before extubation
Carrie 2016	France	30	Patients under MV > 48h	MIP (<25 cmH20)†	Not specified
De Jonghe 2007	France	79	Patients under MV > 7 days	MIP (≤30 cmH2O)	The day of awakening
De Souza 2015	Brazil	103	Patients under MV > 24h	MIP (<25 cmH20)	Prior SBT
Flevari 2016	Greece	27	Patients with difficult and prolonged weaning	MIP (<20 cmH20)	During SBT on a T-tube
Jiang 2004	Taiwan	55	Patients under MV	MIP (<25 cmH20)	During SBT on a T-tube
Jung 2015	France	40	Patients with ICU-Aw under MV > 48h	MIP (<25 cmH20)†	During SBT (T-tube or PS : 7/Pep :0 cmH_2O
Medrinal 2016	France	124	Patients under MV > 24h	MIP (≤30 cmH2O)	During SBT : PS : 7/Pep :0 cmH_2O
Saeed 2016	Egypt	30	COPD under MV	MIP (<20 cmH20)	During SBT
Spadaro 2016	Italy	51	Patients under MV > 48h	MIP (<25 cmH20)	During First SBT on a T-tube
Tenza-Lozano 2018	Spain	69	Patients under MV > 24h	MIP (<25 cmH20)†	Not specified
Tzanis 2011	Greece	33	ICU stay >7 days	MIP (<36 cmH2O)	48 h after the discontinuation of sedation
MRC Score					
Ali 2008	USA	128	Patients under MV > 5 days	MRC <48/60	When patients was awake and attentive
Brunello 2010	Switzerland	39	Patients under MV > 48h	MRC <35/60	Not specified
Carrie 2017	France	30	Patients under MV > 48h	MRC <48/60	Prior to the first SBT
De Jonghe 2004	France	95	Patients under MV > 7 days	MRC <48/60	The day of awakening
Dinglas 2017	USA	156	ARDS patients	MRC <48/60	Prior to hospital discharge
Dres 2017	France	76	Patients under MV > 24h	MRC <48/60	Prior to the first SBT
Hermans 2014	Netherlands	415	ICU stay >8 days	MRC <48/60	When patients was awake and attentive
Lee 2012	USA	95	ICU stay >48h	MRC <48/60	When patients was awake and attentive
Medrinal 2017	France	99	Patients under MV > 24h	MRC <48/60	During SBT : PS : 7/Pep :0 cmH_2O
Pablo Diaz Ballve 2017	Argentina	111	Patients under MV > 24h	MRC <48/60	When patients was awake and attentive
Sharshar 2009	France	115	Patients under MV > 7 days	MRC <48/60	When patients was awake and attentive
Tzanis 2011	Greece	33	ICU stay >7 days	MRC <48/60	level of consciousness adequate for order
Wieske 2015	Netherlands	156	Patients under MV > 48h	MRC <48/60	as soon as patients were awake

Witeveen 2017	Netherlands	71	Patients under MV > 48h	MRC <48/60	as soon as patients were awake
Handgrip test					
Ali 2008	USA	128	Patients under MV > 5 days	11kg and 7Kg	When patients was awake and attentive
Cottereau 2015	France	85	Patients under MV > 48h	11kg and 7Kg	Prior to the SBT
Lee 2012	USA	95	ICU stay >48h	11kg and 7Kg	When patients was awake and attentive
Hussein 2018	Egypt	34	COPD under MV > 48h	11kg and 7Kg	24h after recovery from sedation

* Sample size differences between the original article and the analyse due to group of patient exclusion to avoid double-counting [13] or because it does not match the review question [18]. † Represent studies with undetermined cut-off value ; COPD, Chronic obstructive pulmonary disease ; MV, Mechanical ventilation ; EXdi, Diaphragm excursion ; PS, Pressure support ; Pep, positive expiratory pressure ; SBT, Spontaneous breathing trial ; TFdi, Diaphragm thickening fraction ; ICU-Aw, Intensive care unit acquired weakness ; DTh, Diaphragm thickeness ; Ptrstim, Transdiaphragmatic twich pressure (measured by tracheal pressure) ; TwPdi, Transdiaphragmatic twich pressure (measured by the substraction of abdominal pressure and oesophageal pressure) ; MIP, Maximal inspiratory pressure ; MRC, Medrical research council score ; ARDS, Acute respiratory distress syndrome.

Table 2. Summary estimates of the performance bedsides methods for muscles weakness evaluation for predict critical outcomes

Outcome and measurment	Number of studies	Sensitivity (95% CI)	Specificity (95% CI)	Area under the curve (95% CI)	Likelihood ratio (95% CI)	
					Positive	Negative
Overall Death						
Diaphragm excursion	4	0.59 [0.27 to 0.85]	0.62 [0.54 to 0.70]	0.64 [0.59 to 0.68]	1.60 [0.9 to 2.6]	0.65 [0.30 to 1.41]
Diaphragm thickening fraction	4	0.71 [0.41 to 0.90]	0.64 [0.49 to 0.77]	0.71 [0.67 to 0.75]	2.00 [1.50 to 2.70]	0.45 [0.21 to 0.97]
Transdiaphragmatic twich pressure	5	0.87 [0.76 to 0.93]	0.36 [0.27 to 0.43]	0.74 [0.70 to 0.78]	1.36 [1.15 to 1.61]	0.36 [0.19 to 0.68]
Maximal Inspiratory Pressure	4	0.79 [0.41 to 0.95]	0.61 [0.44 to 0.75]	0.71 [0.67 to 0.75]	2.01 [1.56 to 2.6]	0.34 [0.11 to 1.05]
MRC Score	12	0.70 [0.62 to 0.77]	0.57 [0.52 to 0.63]	0.68 [0.63 to 0.72]	1.64 [1.47 to 1.84]	0.52 [0.42 to 0.63]
ICU Death						
Transdiaphragmatic twich pressure	4	0.88 [0.76 to 0.94]	0.34 [0.23 to 0.48]	0.85 [0.82 to 0.88]	1.33 [1.08 to 1.64]	0.36 [0.16 to 0.77]
MRC Score	10	0.78 [0.65 to 0.87]	0.54 [0.48 to 0.59]	0.66 [0.61 to 0.70]	1.68 [1.48 to 1.91]	0.41 [0.26 to 0.64]
Hospital Death						
Diaphragm excursion	4	0.56 [0.21 to 0.86]	0.62 [0.54 to 0.69]	0.63 [0.58 to 0.67]	1.50 [0.80 to 2.80]	0.71 [0.30 to 1.65]
Diaphragm thickening fraction	4	0.71 [0.41 to 0.90]	0.64 [0.49 to 0.77]	0.71 [0.67 to 0.75]	2.00 [1.50 to 2.70]	0.45 [0.21 to 0.97]
Maximal Inspiratory Pressure	4	0.80 [0.40 to 0.96]	0.60 [0.42 to 0.75]	0.71 [0.67 to 0.75]	1.33 [1.08 to 1.64]	0.36 [0.16 to 0.77]
MRC Score	9	0.75 [0.67 to 0.82]	0.57 [0.51 to 0.63]	0.71 [0.67 to 0.75]	1.74 [1.52 to 2]	0.43 [0.32 to 0.57]
Weaning failure						
Diaphragm excursion	10	0.76 [0.61 to 0.87]	0.80 [0.73 to 0.85]	0.84 [0.81 to 0.87]	5.50 [3.40 to 9.00]	0.28 [0.20 to 0.38]
Diaphragm thickening fraction	10	0.76 [0.67 to 0.83]	0.86 [0.78 to 0.92]	0.86 [0.83 to 0.89]	3.70 [2.70 to 5.10]	0.30 [0.17 to 0.52]
Maximal Inspiratory Pressure	12	0.76 [0.61 to 0.86]	0.66 [0.54 to 0.77]	0.77 [0.73 to 0.80]	2.30 [1.6 to 3.3]	0.36 [0.21 to 0.62]

CI, Confidence interval ; MRC, Medical research council ; ICU, Intensive care unit.

Electronical Supplemental Figures Legend

Figure E1 Methodological quality assessment according to the QUIPS for overall mortality

Figure E2 Methodological quality assessment according to the QUIPS for mechanical ventilation weaning failure

Figure E3 Methodological quality assessment according to the QUIPS for mechanical ventilation duration

Figure E4 Methodological quality assessment according to the QUIPS for Intensive care unit length of stay

Figure E5 Methodological quality assessment according to the QUIPS for tracheostomy

Figure E6 Methodological quality assessment according to the QUADAS-2 for overall mortality

Figure E7 Methodological quality assessment according to the QUADAS-2 for mechanical ventilation weaning failure

Figure E8 Funnel plot of studies assessing overall mortality

Figure E9 Funnel plot of studies assessing weaning

Figure E10 Funnel plot of studies assessing ICU mortality

Figure E11 Funnel plot of studies assessing Hospital mortality

Figure E12 Odds ratios for intensive care unit mortality with versus without a diagnosed weakness. Q represents the different Quality in Prognosis Studies tool (QUIPS) items. Q1=Study participation ; Q2=Study attrition ; Q3=Pronostic factor measurment ; Q4=Outcome measurment ; Q5=Study confounding ;Q6=Statistical analysis and reporting

Figure E13 Odds ratios for hospital mortality with versus without a diagnosed weakness. Q represents the different Quality in Prognosis Studies tool (QUIPS) items. Q1=Study participation ; Q2=Study attrition ; Q3=Pronostic factor measurment ; Q4=Outcome measurment ; Q5=Study confounding ;Q6=Statistical analysis and reporting

Figure E14 Hierarchical summary receiver operating characteristic (HSROC) curve of diaphragm thickening fraction, diaphragm excursion, transdiaphragmatic twitch pressure, maximal inspiratory pressure and MRC score for overall mortality prediction and confidence ellipse around the optimal summary value

Figure E15 Hierarchical summary receiver operating characteristic (HSROC) curve of transdiaphragmatic twitch pressure and MRC score for ICU mortality prediction and confidence ellipse around the optimal summary value

Figure E16 Hierarchical summary receiver operating characteristic (HSROC) curve of diaphragm thickening fraction, diaphragm excursion, maximal inspiratory pressure and MRC

score for hospital mortality prediction and confidence ellipse around the optimal summary value

Figure E17 Hierarchical summary receiver operating characteristic (HSROC) curve of diaphragm thickening fraction, diaphragm excursion and maximal inspiratory pressure for mechanical ventilation weaning failure prediction and confidence ellipse around the optimal summary value

Figure E18 Forest plot of sensitivity and specificity in studies that measure overall mortality

Figure E19 Forest plot of sensitivity and specificity in studies that measure mechanical ventilation weaning failure

Figure E20 Standardized mean difference in mechanical ventilation duration (days) with and without weakness

Figure E21 Standardized mean difference in ICU length of stay (days) with and without weakness

Online Supplement

ICU outcomes can be predicted by non invasive muscle evaluation : a meta-analysis.

Clément Medrinal[1,2], Yann Combret[2,3], Roger Hilfiker[4], Guillaume Prieur[1,2,3], Nadine Aroichane[5], Francis-Edouard Gravier[1,6], Tristan Bonnevie[1,6], Olivier Contal[7*], Bouchra Lamia[1,8,9*].

Oline Figures

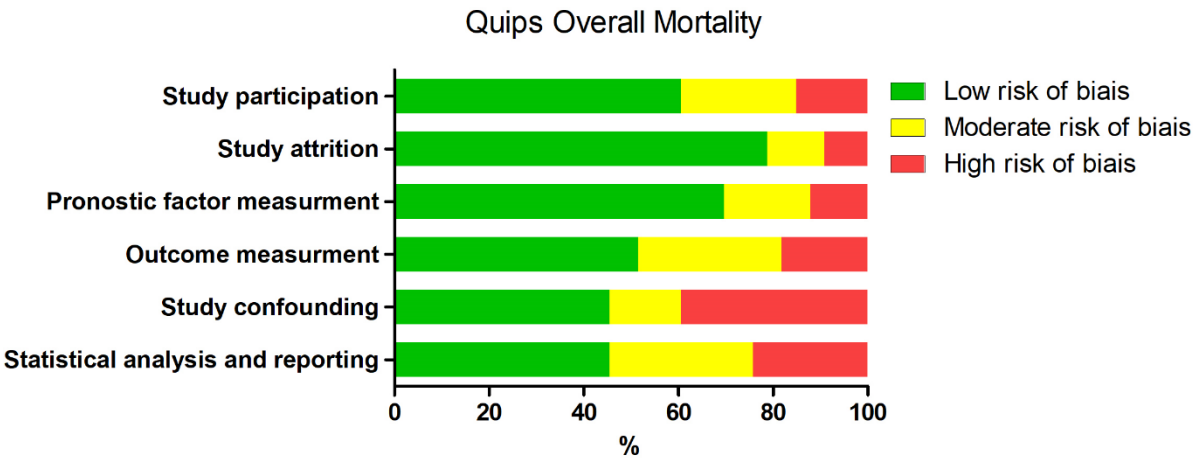


Figure E1 Methodological quality assessment according to the QUIPS for overall mortality

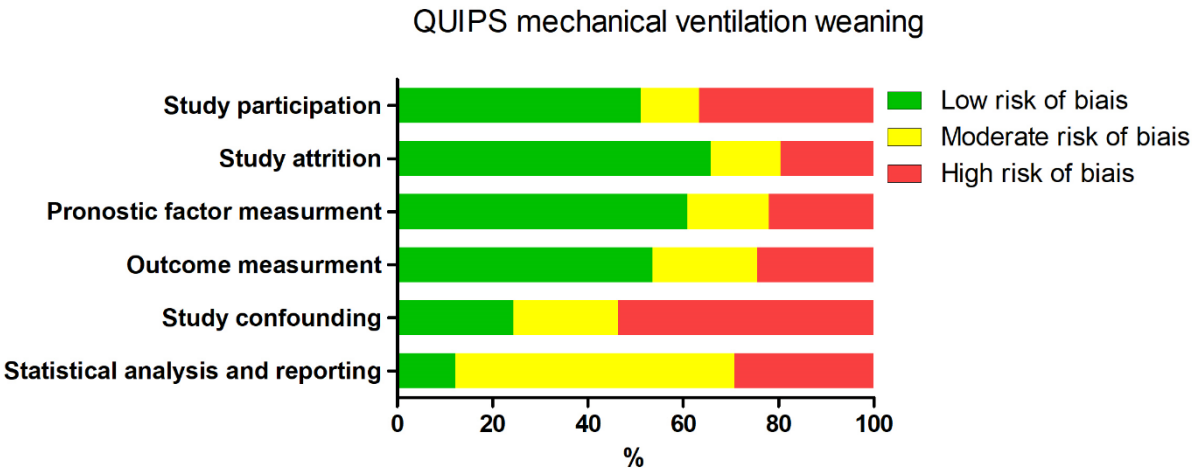


Figure E2 Methodological quality assessment according to the QUIPS for mechanical ventilation weaning failure

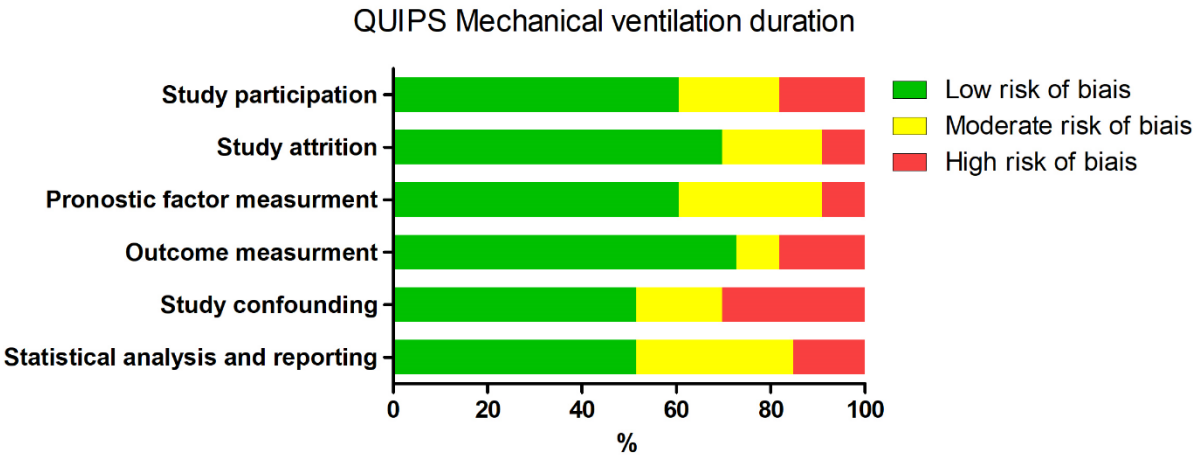


Figure E3 Methodological quality assessment according to the QUIPS for mechanical ventilation duration

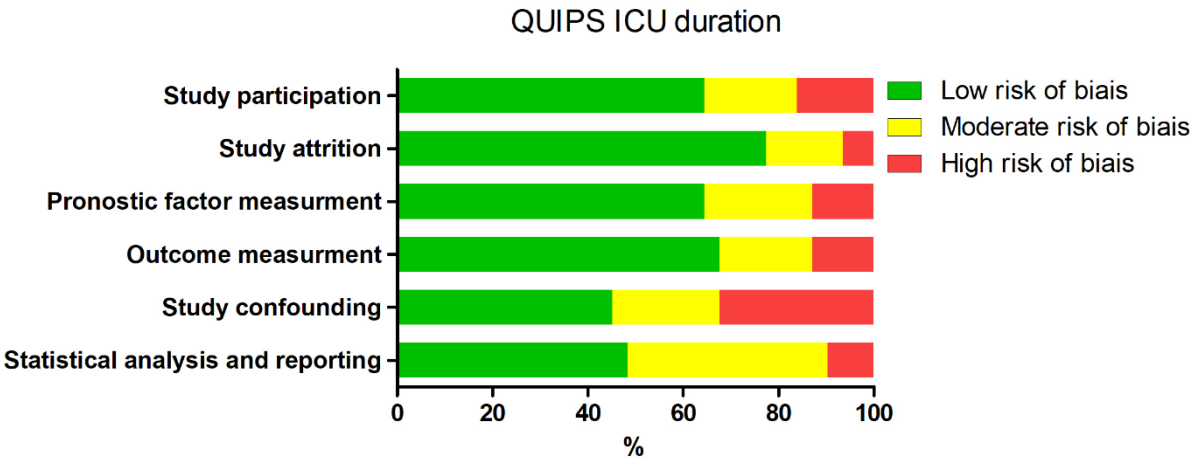


Figure E4 Methodological quality assessment according to the QUIPS for Intensive care unit length of stay

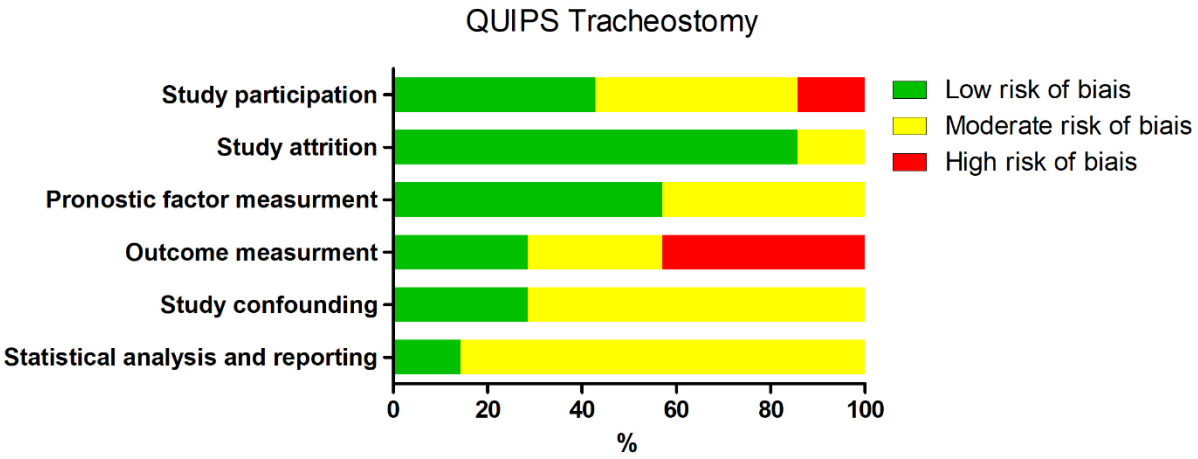


Figure E5 Methodological quality assessment according to the QUIPS for tracheostomy

QUADAS

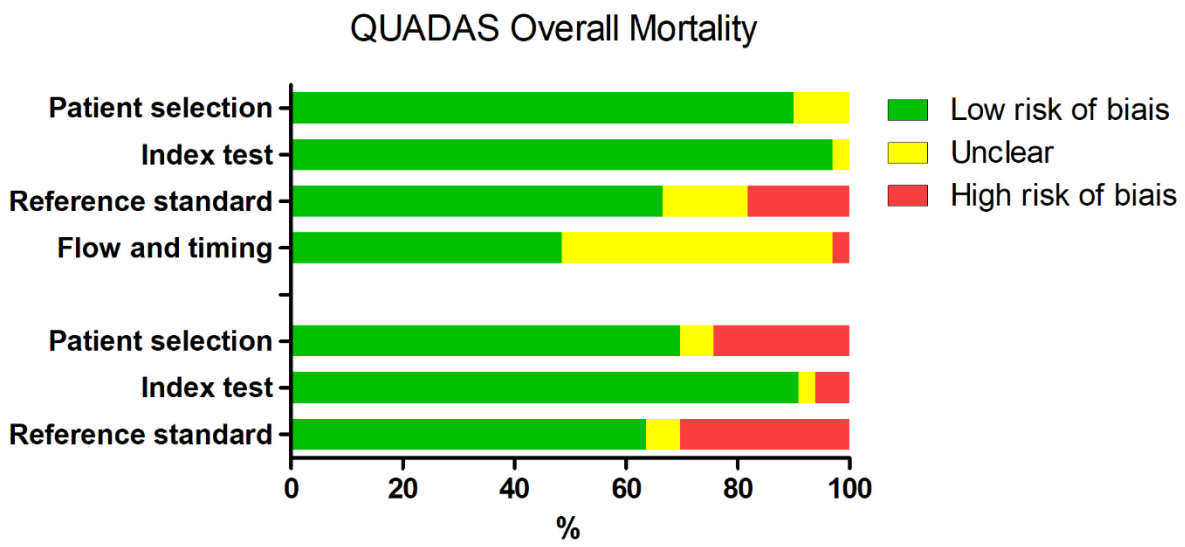


Figure E6 Methodological quality assessment according to the QUADAS-2 for overall mortality

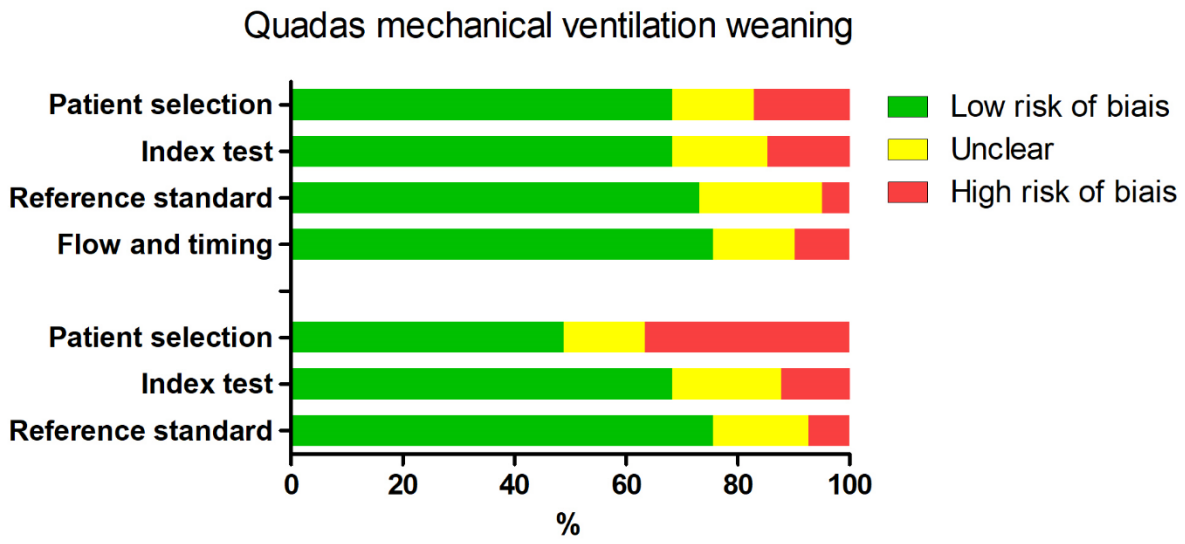


Figure E7 Methodological quality assessment according to the QUADAS-2 for mechanical ventilation weaning failure

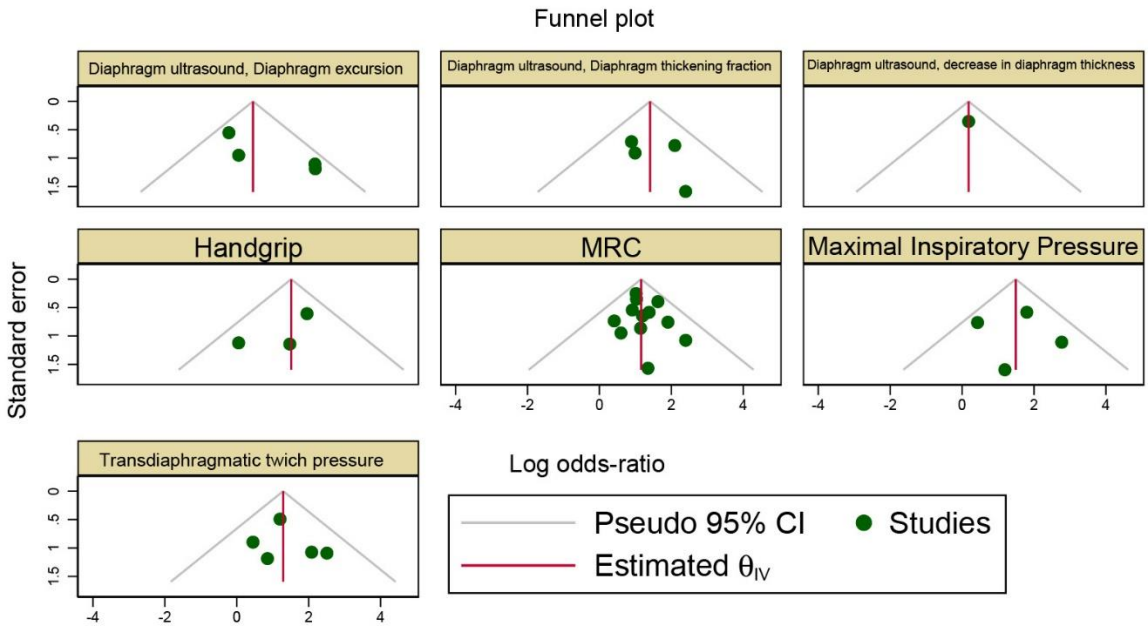


Figure E8 Funnel plot of studies assessing overall mortality

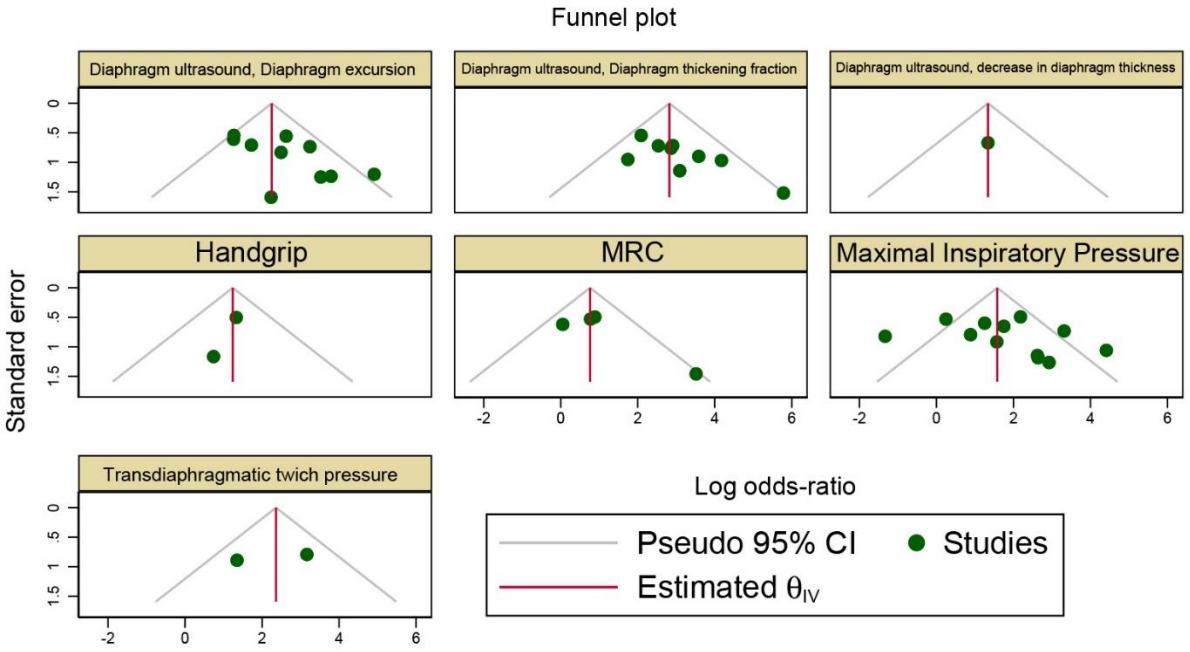


Figure E9 Funnel plot of studies assessing weaning

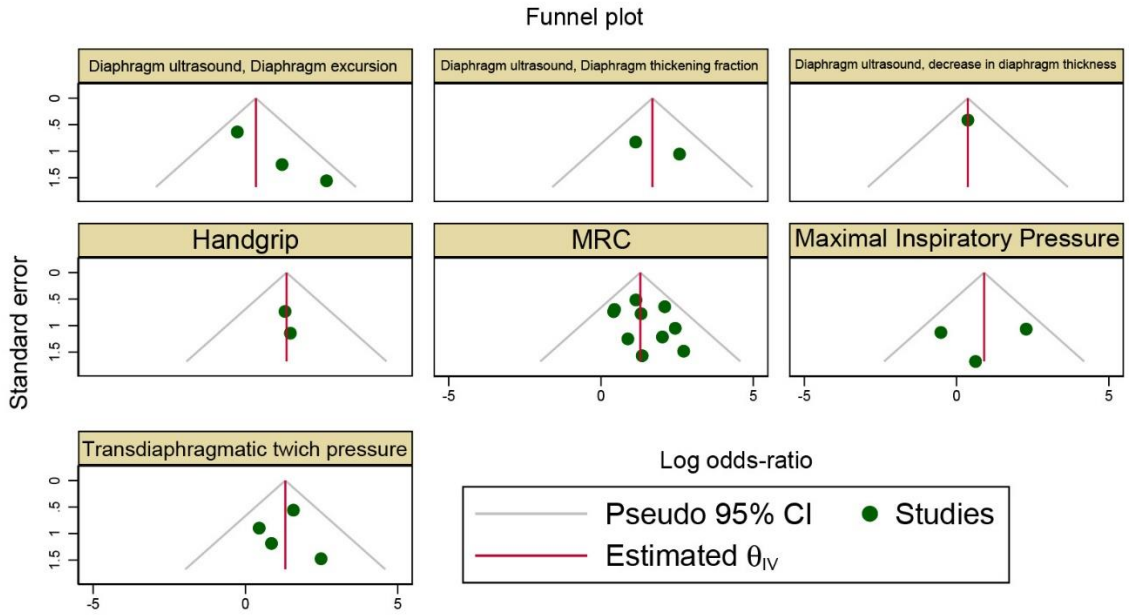


Figure E10 Funnel plot of studies assessing ICU mortality

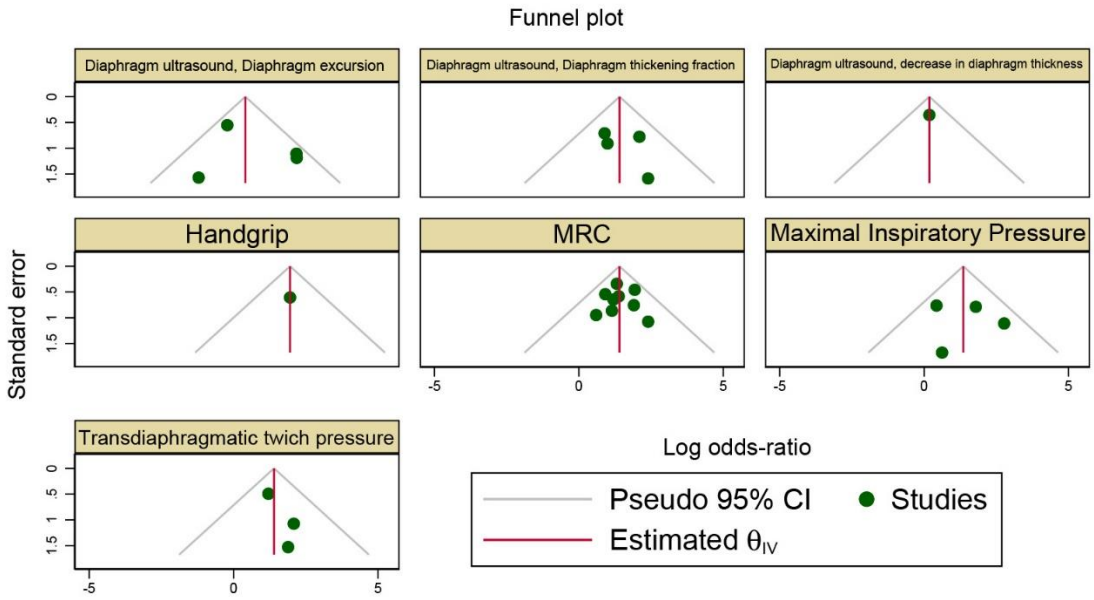


Figure E11 Funnel plot of studies assessing Hospital mortality

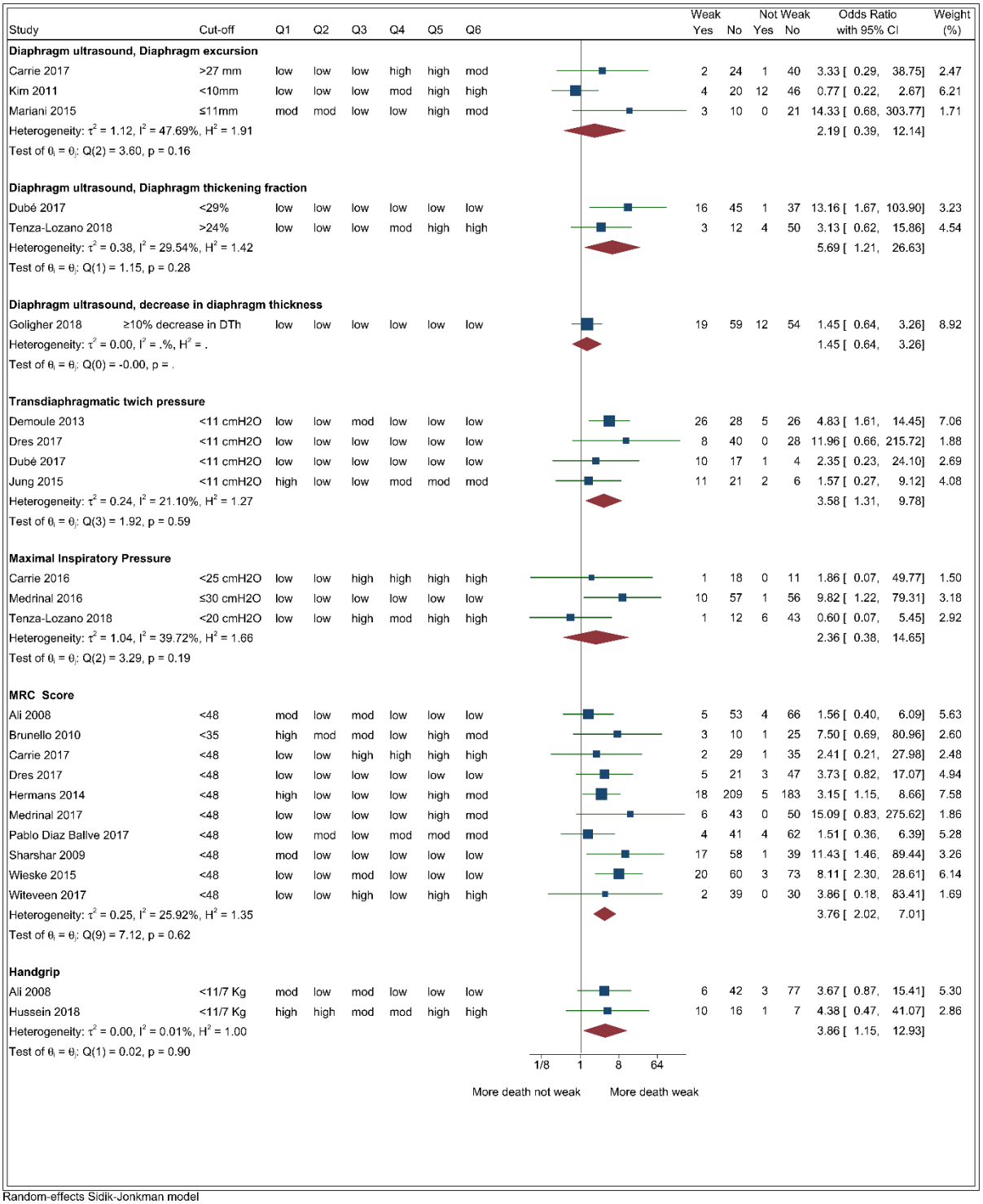


Figure E12 Odds ratios for intensive care unit mortality with versus without a diagnosed weakness. Q represents the different Quality in Prognosis Studies tool (QUIPS) items. Q1=Study participation ; Q2=Study attrition ; Q3=Pronostic factor measurment ; Q4=Outcome measurment ; Q5=Study confounding ;Q6=Statistical analysis and reporting

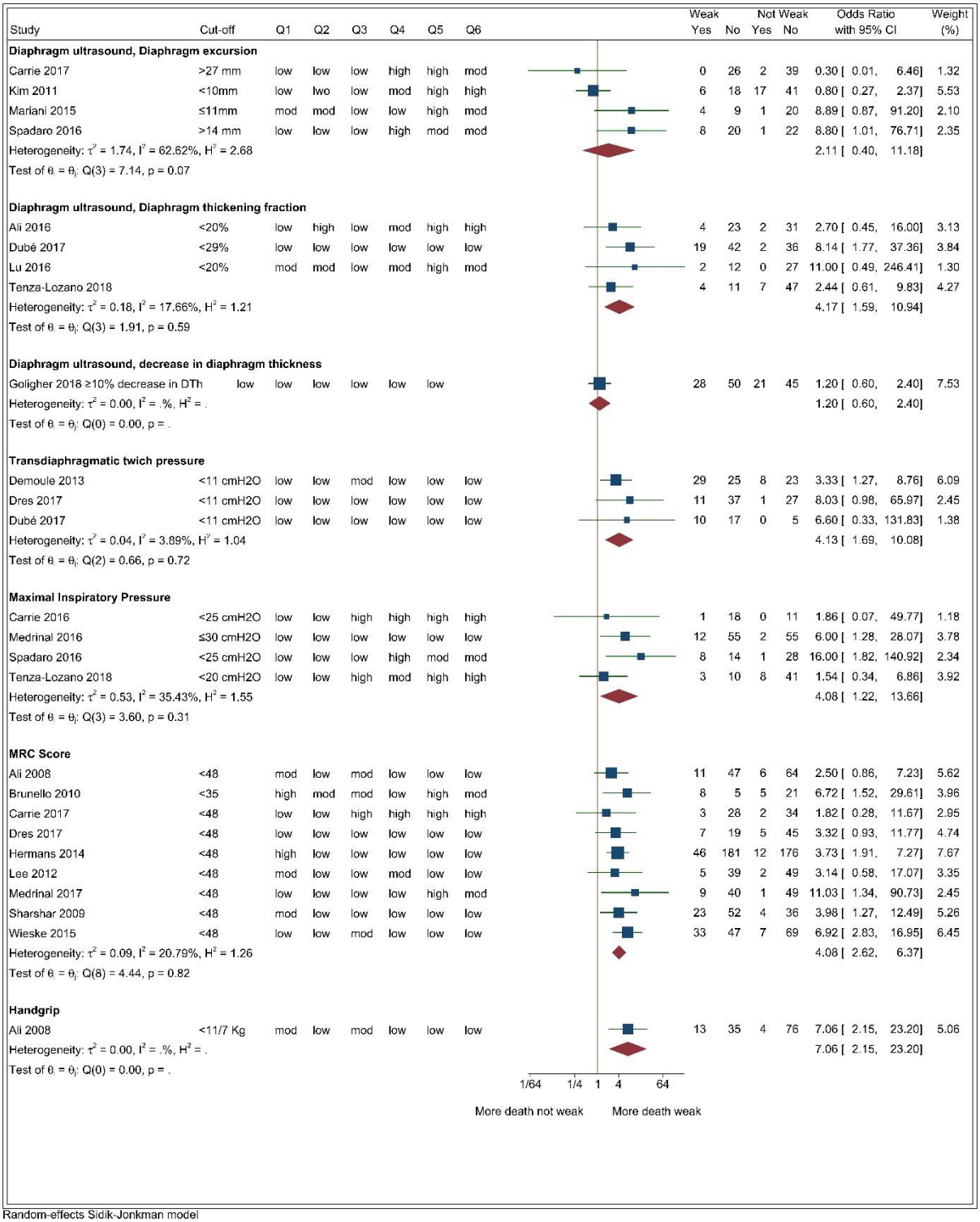


Figure E13 Odds ratios for hospital mortality with versus without a diagnosed weakness. Q represents the different Quality in Prognosis Studies tool (QUIPS) items. Q1=Study participation ; Q2=Study attrition ; Q3=Pronostic factor measurment ; Q4=Outcome measurment ; Q5=Study confounding ;Q6=Statistical analysis and reporting

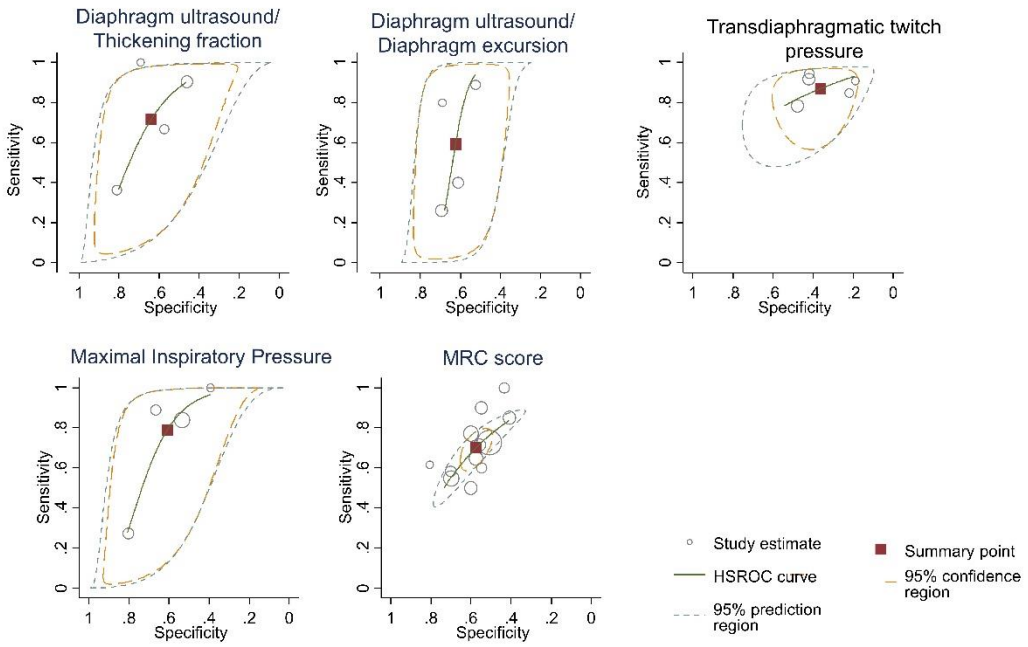


Figure E14 Hierarchical summary receiver operating characteristic (HSROC) curve of diaphragm thickening fraction, diaphragm excursion, transdiaphragmatic twitch pressure, maximal inspiratory pressure and MRC score for overall mortality prediction and confidence ellipse around the optimal summary value

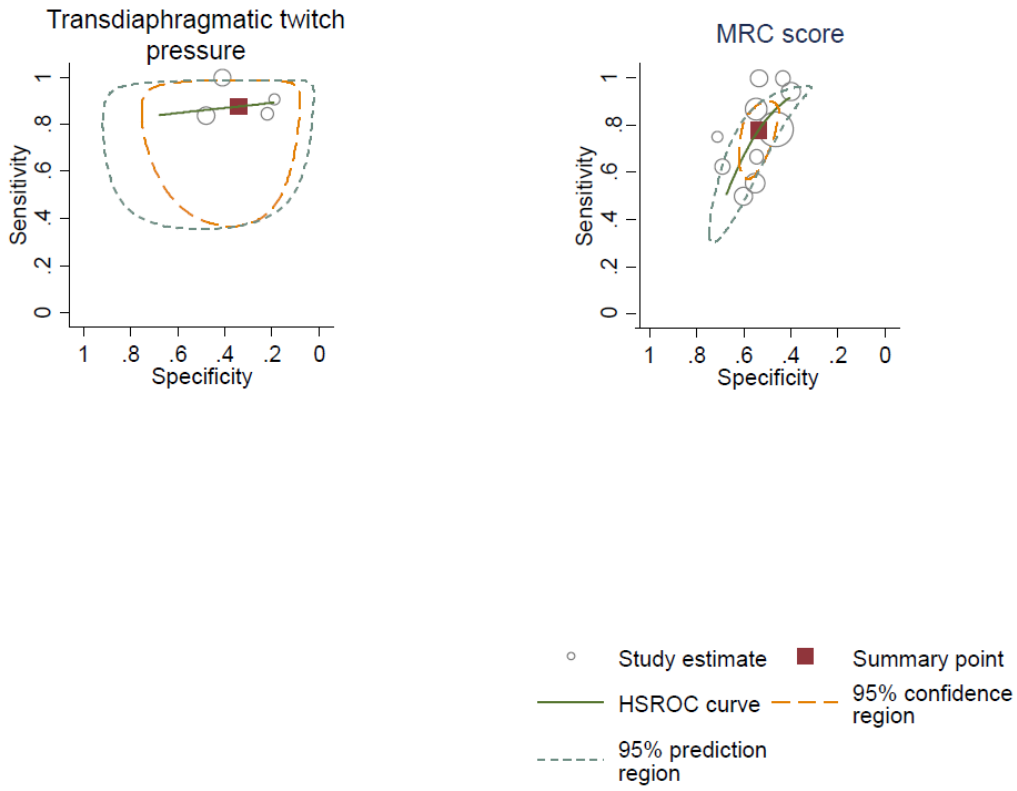


Figure E15 Hierarchical summary receiver operating characteristic (HSROC) curve of transdiaphragmatic twitch pressure and MRC score for ICU mortality prediction and confidence ellipse around the optimal summary value

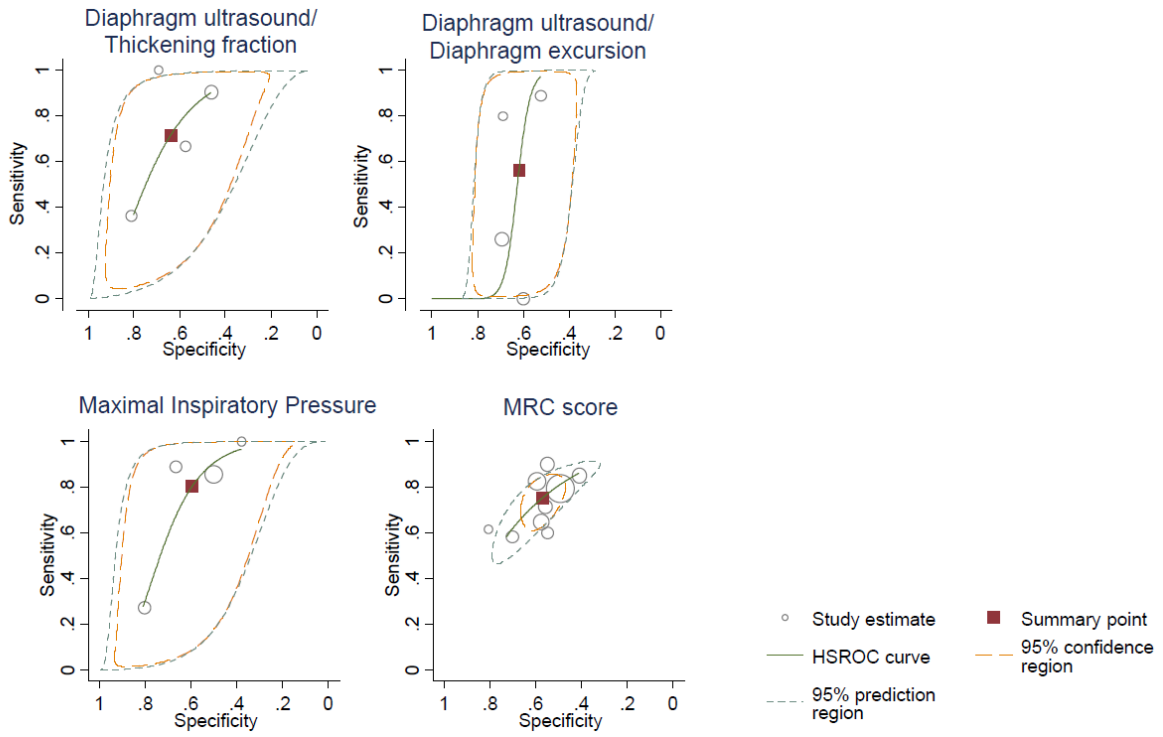


Figure E16 Hierarchical summary receiver operating characteristic (HSROC) curve of diaphragm thickening fraction, diaphragm excursion, maximal inspiratory pressure and MRC score for hospital mortality prediction and confidence ellipse around the optimal summary value

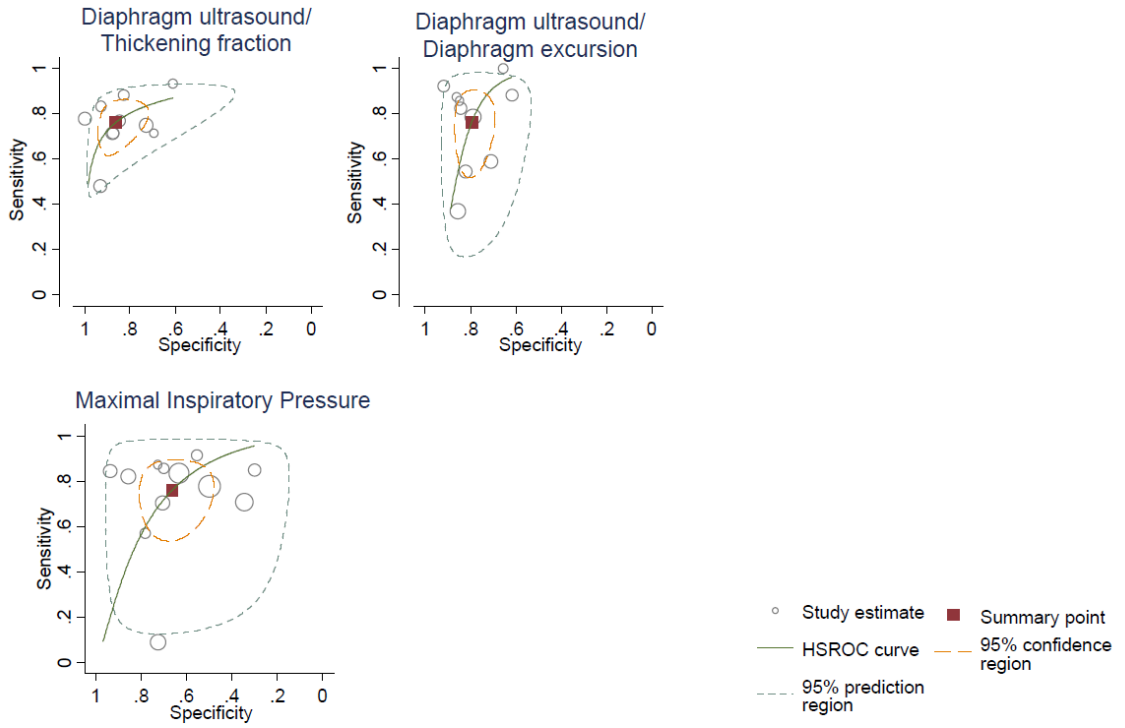


Figure E17 Hierarchical summary receiver operating characteristic (HSROC) curve of diaphragm thickening fraction, diaphragm excursion and maximal inspiratory pressure for mechanical ventilation weaning failure prediction and confidence ellipse around the optimal summary value

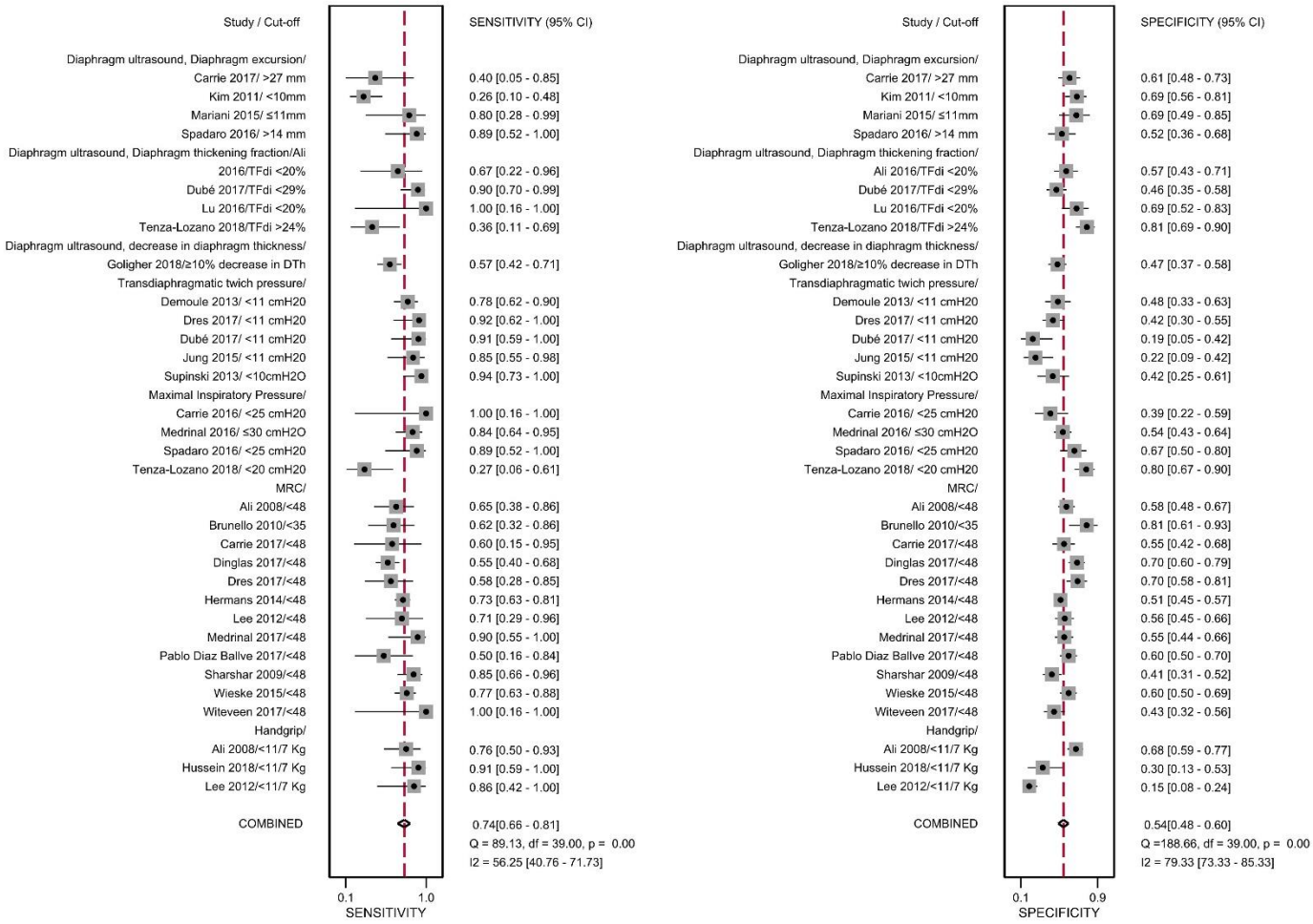


Figure E19 Forest plot of sensitivity and specificity in studies that measure overall mortality

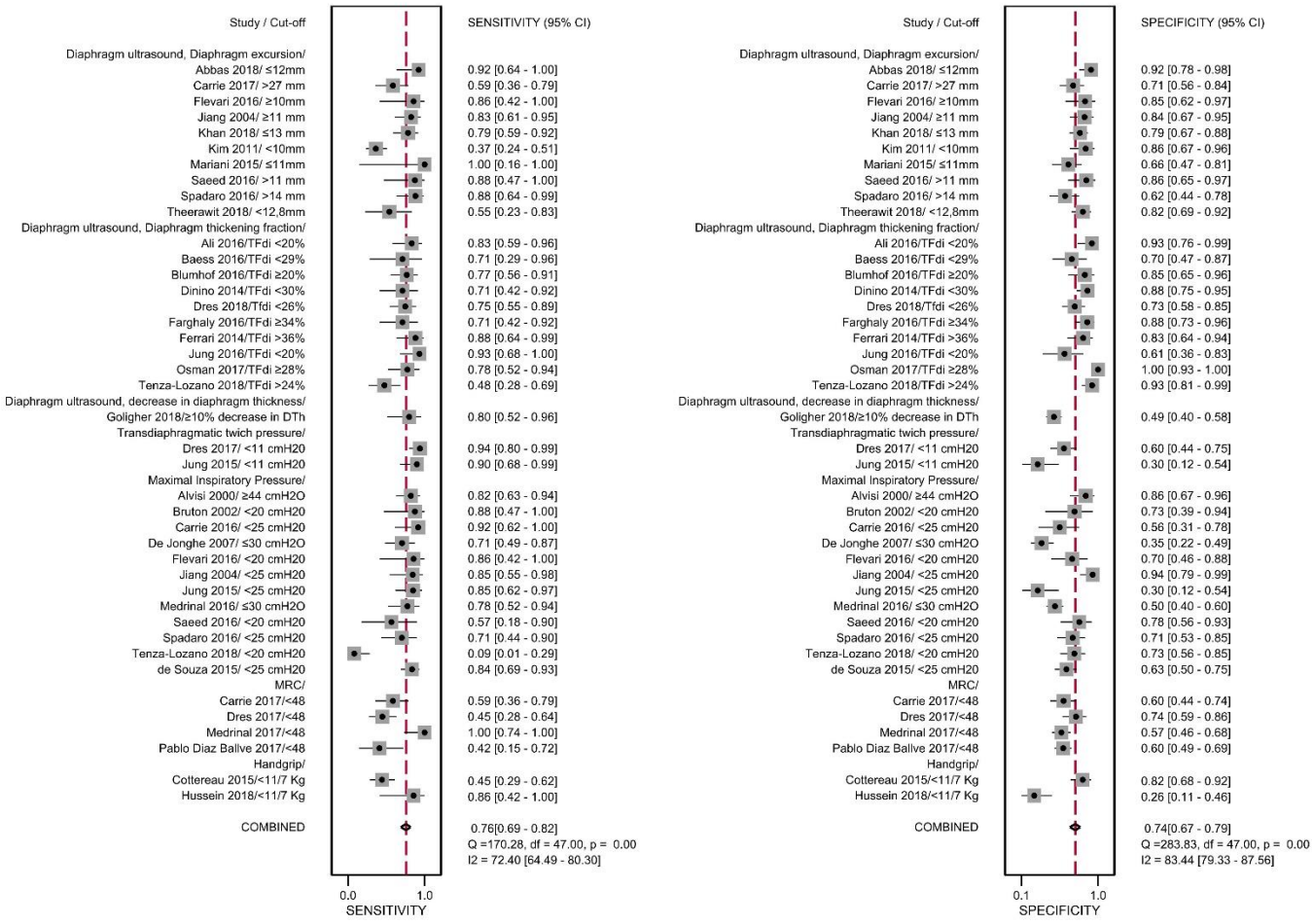


Figure E20 Forest plot of sensitivity and specificity in studies that measure mechanical ventilation weaning failure

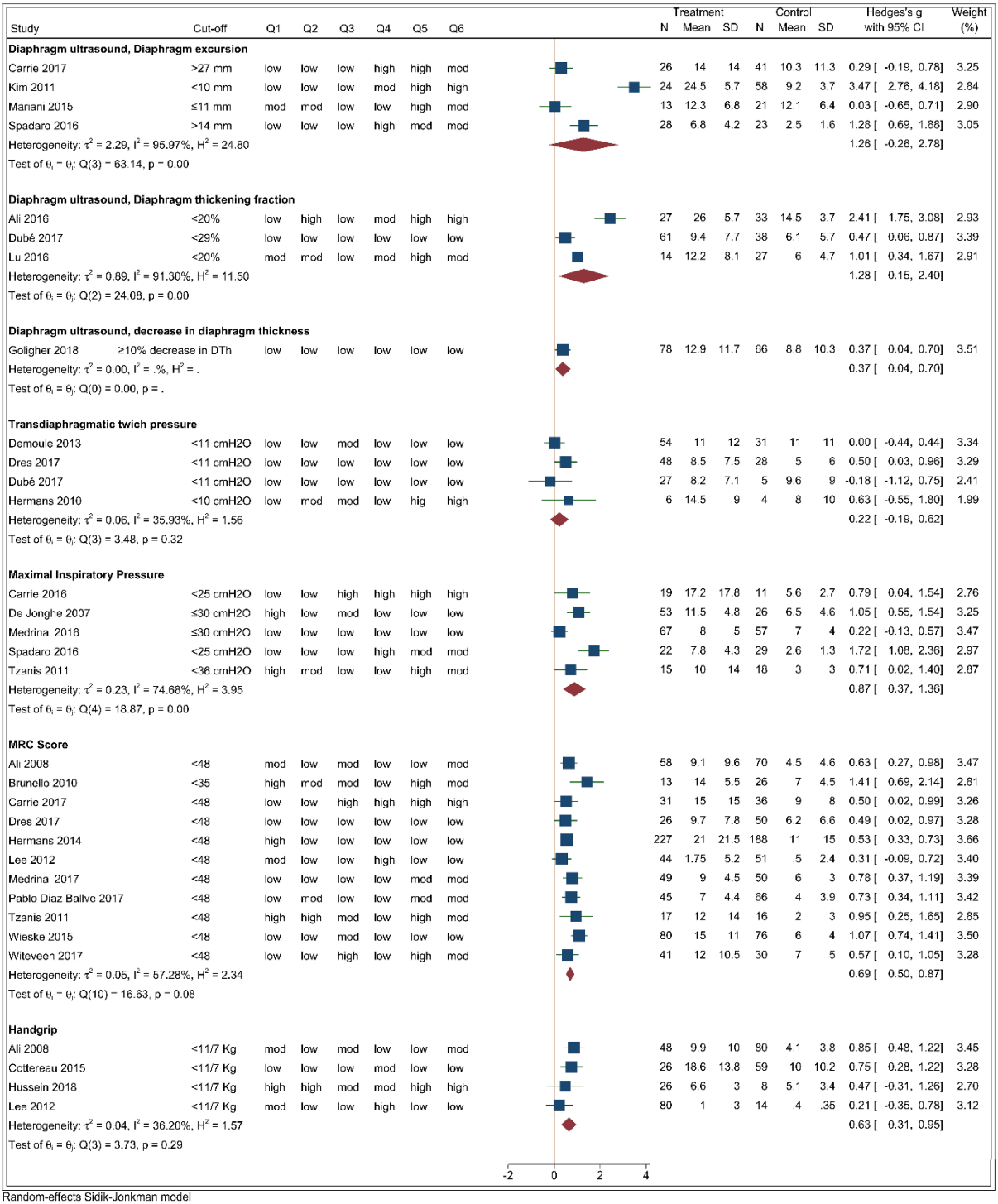


Figure E21 Standardized mean difference in mechanical ventilation duration (days) with and without weakness

Online Supplement

ICU outcomes can be predicted by non invasive muscle evaluation : a meta-analysis.

Clément Medrinal[1,2], Yann Combret[2,3], Roger Hilfiker[4], Guillaume Prieur[1,2,3], Nadine Aroichane[5], Francis-Edouard Gravier[1,6], Tristan Bonnevie[1,6], Olivier Contal[7*], Bouchra Lamia[1,8,9*].

Online table

Table E1. Excluded studies with reasons

Reason for exclusion	First author	Year of publication	Journal	Article Title
Evaluation not relevant	Baldwin CE	2014	Physical Therapy	Alterations in respiratory and limb muscle strength and size in patients with sepsis who are mechanically ventilated.
	Buscher	2015	Anesthesia and Intensive Care	Assessment of diaphragmatic function with cervical magnetic stimulation in critically ill patients.
	Cartwright MS	2013	Muscle Nerve	Quantitative neuromuscular ultrasound in the intensive care unit.
	Cattapan SE	2003	Thorax	Can diaphragmatic contractility be assessed by airway twitch pressure in mechanically ventilated patients?
	Chlan LL	2015	American Journal of Critical Care	Peripheral muscle strength and correlates of muscle weakness in patients receiving mechanical ventilation.
	Goligher EC	2015	American Journal of Respiratory and Critical Care Medicine	Diaphragm Thickness during Mechanical Ventilation. Impact of Inspiratory Effort.
	Hough CL	2011	Critical Care	Manual muscle strength testing of critically ill patients: feasibility and interobserver agreement.
	Jaber S	2011	American Journal of Respiratory and Critical Care Medicine	Rapidly progressive diaphragmatic weakness and injury during mechanical ventilation in humans.
	Lerolle N	2009	Chest	Ultrasonographic diagnostic criterion for severe diaphragmatic

				dysfunction after cardiac surgery.
	Mills GH	2001	British Journal of Anesthesia	Tracheal tube pressure change during magnetic stimulation of the phrenic nerves as an indicator of diaphragm strength on the intensive care unit.
	Parry SM	2015	Journal of Critical Care	Ultrasonography in the intensive care setting can be used to detect changes in the quality and quantity of muscle and is related to muscle strength and function.
	Sánchez Solana L	2018	Enfermeria Intensiva	Acquired neuromuscular dysfunction in the intensive care unit.
	Schepens T	2015	Critical Care	The course of diaphragm atrophy in ventilated patients assessed with ultrasound: a longitudinal cohort study.
	Valette X	2015	Intensive Care Medicine	Diaphragmatic dysfunction at admission in intensive care unit: the value of diaphragmatic ultrasonography.
	Watson AC	2001	Critical Care Medicine	Measurement of twitch transdiaphragmatic, esophageal, and endotracheal tube pressure with bilateral anterolateral magnetic phrenic nerve stimulation in patients in the intensive care unit.
	Wieske L	2013	Intensive Care Medicine	Autonomic dysfunction in ICU-acquired weakness: a prospective observational pilot study.
	Wieske L	2014	PloS One	Early prediction of intensive care unit-acquired weakness using easily available parameters: a prospective observational study.
	Zambon M	2016	Critical Care Medicine	Mechanical Ventilation and Diaphragmatic Atrophy in Critically Ill Patients: An Ultrasound Study.
Insufficient information despite contacting the authors	Bien UDS	2015	Journal of Physical Therapy Science	Maximum inspiratory pressure and rapid shallow breathing index as predictors of successful ventilator weaning.
	Connolly BA	2013	Critical Care	Clinical predictive value of manual muscle strength testing during critical illness: an observational cohort study.
	De Jonghe B	2002	JAMA	Paresis acquired in the intensive care unit: a prospective multicenter study.
	Luo L	2017	BMC Pulmonary Medicine	Different effects of cardiac and diaphragm function assessed by ultrasound on extubation outcomes in difficult-to-wean patients: a cohort study.
	Pirompanich P	2018	Journal of Intensive Care Medicine	Use of diaphragm thickening fraction combined with rapid shallow breathing index for predicting success of weaning from mechanical

				ventilator in medical patients.
	Qing Q	2018	Journal of Thoracic Disease	Using twitch tracheal airway pressure, negative inhale forced pressure, and Medical Research Council score to guide weaning from mechanical ventilation.
	Samanta S	2017	Journal of Intensive Care Medicine	Diaphragm thickening fraction to predict weaning-a prospective exploratory study.
	Supinski GS	2016	Critical Care	Correlation of maximal inspiratory pressure to transdiaphragmatic twitch pressure in intensive care unit patients.
	Savi A	2012	Journal of Critical Care	Weaning predictors do not predict extubation failure in simple-to-wean patients.
Use electromyography or other tool for ICU-Aw diagnosis	Angel MJ	2007	Canadian Journal of Neurological Science	Neuromuscular function in survivors of the acute respiratory distress syndrome.
	Guarneri B	2008	Journal of Neurology Neuro surgery and Psychiatry	Long-term outcome in patients with critical illness myopathy or neuropathy: the Italian multicentre CRIMYNE study.
	Jansen D	2018	Critical Care	Estimation of the diaphragm neuromuscular efficiency index in mechanically ventilated critically ill patients.
	Khan J	2006	Neurology	Early development of critical illness myopathy and neuropathy in patients with severe sepsis.
	Nordine T	2007	Revue Neurologique	The predominance of myopathy as a cause of intensive-care-unit-acquired paralysis: the diagnostic value of direct muscle stimulation
	Young GB	2004	Critical Care	A stronger approach to weakness in the intensive care unit.
Not ICU Population	Adler D	2014	American Journal of Respiratory and Critical Care Medicine	Does inspiratory muscle dysfunction predict readmission after intensive care unit discharge?
	Palkar A	2018	Lung	Serial Diaphragm Ultrasonography to Predict Successful Discontinuation of Mechanical Ventilation.
	Semmler A	2013	Journal of Neurology	Long-term neuromuscular sequelae of critical illness.
Study design	Herridge MS	2014	American Journal of Respiratory and Critical Care Medicine	ICU-acquired weakness, morbidity, and death.
	Liu Y-Y	2018	Experimental Biology and	Ventilator-induced diaphragm dysfunction in critical illness.

			Medicine	
	Schefold JC	2010	Journal of Cachexia and Sarcopenia Muscle	Intensive care unit-acquired weakness (ICUAW) and muscle wasting in critically ill patients with severe sepsis and septic shock.
No original data	Demoule A	2016	Annals of Intensive Care	Patterns of diaphragm function in critically ill patients receiving prolonged mechanical ventilation: a prospective longitudinal study.
Qualitative consideration concerning the publisher journal	Fayed	2016	Journal of American Science	Use of Ultrasound to Assess Diaphragmatic Thickness as a Weaning Parameter in Invasively Ventilated Chronic Obstructive Pulmonary Disease Patients