Prediction of extubation outcome in critically ill patients: a systematic review and meta-analysis

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Abstract

Background: Extubation failure is an important issue in ventilated patients and its risk factors remain a matter of research. We conducted a systematic review and meta-analysis to explore factors associated with extubation failure in ventilated patients who passed a spontaneous breathing trial and underwent planned extubation. This systematic review was registered in PROPERO with the Registration ID CRD42019137003.

Methods: We searched the PubMed, Web of Science and Cochrane Controlled Register of Trials for studies published from January 1998 to December 2018. We included observational studies involving risk factors associated with extubation failure in adult intensive care unit patients who underwent invasive mechanical ventilation. Two authors independently extracted data and assessed the validity of included studies.

Results: Sixty-seven studies (involving 26,847 participants) met the inclusion criteria and were included in our meta-analysis. We analyzed 49 variables and, among them, we identified 26 factors significantly associated with extubation failure. Risk factors were distributed into three domains (comorbidities, acute disease severity and characteristics at time of extubation) involving mainly three functions (circulatory, respiratory and neurological). Among these, the physiological respiratory characteristics at time of extubation were the most represented. The individual topic of secretion management was the one with the largest number of variables. By Bayesian multivariable meta-analysis, twelve factors were significantly associated with extubation failure: age, history of cardiac disease, history of respiratory disease, Simplified Acute Physiologic Score II score, pneumonia, duration of mechanical ventilation, heart rate, Rapid Shallow Breathing Index, negative inspiratory force, lower PaO2/FiO2 ratio, lower hemoglobin level and lower Glasgow Coma Scale before extubation, with the latest factor having the strongest association with extubation outcome.

Conclusions: Numerous factors are associated with extubation failure in critically ill patients who have passed a spontaneous breathing trial. Robust multiparametric clinical scores and/or artificial intelligence algorithms should be tested based on the selected independent variables in order to improve the prediction of extubation outcome in the clinical scenario.
Background
As mechanical ventilation is associated with complications (e.g., ventilator-associated pneumonia) [1], the optimal time to wean patients from mechanical ventilation is a critical goal to achieve in intensive care unit (ICU) [2]. The decision to extubate is therefore usually taken as soon as a patient meet predefined weaning criteria and successfully pass a spontaneous breathing trial (SBT) [3]. Nevertheless, in 10–20% of patients who pass a spontaneous breathing trial and undergo planned extubation, extubation failure still occurs.

Extubation failure is usually defined as the need for reintubation within hours or days after a planned extubation. The time considered varies from 24 h [4, 5] until any time during the hospital stay [6, 7]. Extubation failure is associated with an overall increase in the duration of mechanical ventilation, a greater need for tracheostomy, higher medical costs and a 25–50% increased mortality rate [8–12]. There is some evidence that extubation failure is not just a marker of a more severe illness, but independently affects patients survival regardless of underlying illness severity [9, 13].

Unfortunately, the pathophysiology of extubation failure is not yet fully understood and a simple tool for predicting extubation failure is not available. Some studies suggested that the use of standardized weaning protocols reduced the total time of mechanical ventilation [14, 15] but the parameters that should be included in weaning protocols still remain controversial. Considering the complications associated with both a too early and delayed liberation from mechanical ventilation, the identification of robust risk factors for extubation failure would be extremely helpful in order to optimize the weaning process.

We therefore decided to conduct a systematic review of the literature and a meta-analysis to search risk factors associated with extubation failure, in adult critically ill patients who passed a SBT and underwent a planned extubation.

Methods
Search strategy and selection criteria
We performed this study in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [16]. We searched PubMed, Web of Science and Cochrane controlled register of trials (CENTRAL) to identify articles on risk factors for extubation failure from January 1998 to December 2018. We used the following search algorithm: (extubation) AND (success OR failure OR factor OR predictor OR prediction OR risk OR score OR outcome OR mortality OR reintubation OR intensive care unit).

We included all studies that evaluated any risk factors for extubation failure in adult (at least 18 years old) ICU patients under invasive mechanical ventilation. We excluded studies in children and animals and studies not written in English. References of all selected articles were scanned for additional relevant manuscripts. This study was registered in the International Prospective Register of Systematic Reviews (PROSPERO) database (Registration Number CRD42019137003). Ethical approval was not required.

Data analysis
After the removal of the duplicates, two authors (FT, JM) independently screened titles and abstracts to obtain relevant articles for full text review. We obtained the full text of all potentially relevant studies and the authors independently decided for final inclusion in the review. We also reviewed the references of relevant articles to avoid missing any studies. Any disagreement was resolved by consensus or discussion with a third reviewer (AMD).

The review authors independently extracted data. The following data were recorded from each selected study: year of publication, study design, baseline characteristics of the population (age, comorbidities), severity scores on ICU admission and stay [Severity Acute Physiologic Score (SAPS), Acute Physiology and Chronic Health Evaluation (APACHE)], medications, characteristics of the SBT, definition of extubation failure, risk factors associated with extubation failure (respiratory, cardiovascular, neurologic, laboratory parameters) and primary outcome (extubation failure). We further excluded risk factors with excessive missing data (reported in less than 10% of studies; see Additional file 1: Table S1 in the additional material). Study quality was assessed in terms of risk of bias using the QUIPS tool for prognostic studies (Cochrane), rating the potential risk of bias as high, moderate or low for each of six domains, namely study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding, statistical analysis and reporting. Two authors (FT, JM) independently assessed the risk of bias, implying a third author in case of disagreement (AMD).
Statistical analysis

We conducted a meta-analysis of observational prospective and retrospective studies. Data were summarized using medians and interquartile ranges (IQRs) or mean ± standard deviation (SD) were appropriate [17]. For binary variables, the odds ratio (OR) with 95% confidence interval (CI) was calculated for extubation failure. For continuous variables, we calculated the mean difference with 95% CI between extubation success and extubation failure groups. A natural log transformation of OR (lnOR) was derived from crude OR (for binary variables) [18, 19] and from standardized mean differences (for continuous variables) [19] in a symmetric scale, from minus infinity, to infinity, with zero defining no effect [18], to allow comparison between categorical and numeric variables.

We adopted the inverse variance method for developing weights for individual study effects. We quantified heterogeneity using $I^2$ and $Q$ statistics, with values greater than 50% regarded as being indicative of moderate-to-high heterogeneity [20]. We used a random effect model to assess the population average mean difference and 95% CI or OR and 95% CI for all the risk factors for extubation failure. In order to measure the dispersion of the pooled effect across study settings, we generated predictions intervals [21].

We performed prespecified subgroup analyses according to the type of ICU patients, e.g., medical, surgical, mixed, neurological or other type of ICU. A heatmap was created to present lnOR (scaled to adjust for extreme values) for each variable according to ICU type. We conducted a sensitivity analysis including only studies referring to the most used definition of extubation failure (death or reintubation within 48 h from extubation), to explore if it changed the significance of the results. Another sensitivity analysis focused on studies referring to death or reintubation (whatever the delay).

A multivariable meta-analysis of multiple factors was secondarily performed with variables significantly associated with extubation outcome, using effect sizes as lnOR [22] and the altmeta package for R [23, 24]. Among related significant univariate factors, only the most statistically robust (as per the lnOR), yet clinically relevant were entered into the models in order to minimize the effect of collinearity. Individual study effects and pooled effects were visualized through forest plots.

Publication biases were assessed graphically through funnel plot asymmetry [25]. Data were pooled and analyzed using Review Manager (Cochrane TC. Review Manager 5.3. Cph Nord Cochrane Cent, 2008) with a two-sided significance level of 5%, and R 3.1.2 (The R Foundation for Statistical Computing, Vienna, Austria).

Results

Studies

We identified a total of 12,921 references from our searches (Fig. 1). After removing 4833 duplicates, we screened the titles and abstracts of 8088 articles, of which 7927 were excluded. The full texts of 161 studies were reviewed and 94 were excluded. Thus, we included 67 studies in the narrative review, and 66 studies were included in the quantitative synthesis. Of the 67 studies included in the review, 50 were prospective observational studies [4–6, 9, 12, 13, 26–69] and 17 were retrospective studies [7, 70–85]. Fifty-seven studies were monocentric and ten were multicentric. Studies took place in medical ($n=19$), surgical ($n=9$), mixed ($n=28$) and neurological ($n=11$) ICUs.

We included 67 studies involving 26,847 participants in the meta-analysis. The type of SBT and the definition of extubation failure varied among the included studies (Table 1). SBT types included: multiple choice for SBT ($n=15$, with 4 studies allowing CPAP and 14 studies allowing T-tube), low pressure support with low positive end expiratory pressure ($n=30$, flow-by ($n=1$), standard pressure support ventilation ($n=1$), proportional assist ventilation ($n=1$) and automatic tube compensation with low PEEP ($n=1$). Extubation failure was defined either as death or reintubation within hours to days after extubation (24 h, 48 h, 72 h or 7 days in 4, 30, 14 and 5 studies, respectively), or as the reinstitution of any mechanical ventilation after extubation, either invasive or noninvasive with a curative indication (10 studies).

Risk factors for extubation failure

Among the 49 variables analyzed, we found 26 variables significantly associated with extubation outcome, distributed into three domains [comorbidities ($n=5$), acute disease severity ($n=6$) and characteristics at time of extubation ($n=15$)] (Table 2, Fig. 2) involving mainly three functions [respiratory ($n=16$), circulatory ($n=3$) and neurological ($n=1$)]; see Additional file 1: Fig. S1 in the additional material).

Comorbidities

We found a higher risk of extubation failure in older patients. Chronic obstructive respiratory disease, history of chronic cardiac or respiratory disease were associated with a higher risk of extubation failure as well. In contrast, a higher body mass index was associated with successful extubation.

Acute disease severity

Patients who failed extubation also differed from patients who succeeded in terms of acute disease severity, with higher values of SAPS II and APACHE II score in the
former group. Acute heart failure, COPD exacerbation and pneumonia were the reasons for intubation significantly associated with a higher risk of extubation failure. Duration of mechanical ventilation before extubation was longer in patients with extubation failure.

Characteristics at the time of extubation
These variables involved the following physiological systems: (1) respiratory: related to secretion management (cough, cough peak flow, maximal expiratory pressure, presence of moderate to abundant secretions, negative
inspiratory force), ventilation pattern [respiratory rate and tidal volume before extubation, rapid shallow breathing index (RSBI) after one minute from the SBT start, RSBI before extubation] and oxygenation (SaO2, PaO2 and PaO2/FiO2 before extubation, hemoglobin on the day of extubation); (2) cardiovascular (heart rate before extubation); and (3) neurological (Glasgow Coma Scale before extubation). The individual topic of secretion management was the one with the largest number variables (five).

Subgroup analysis
Subgroup analyses according to the type of ICU are presented in Additional file 1: Fig. S2 and Table S2 in the additional material. Among the 49 variables analyzed, 30 were significantly associated with extubation outcome in at least one ICU type. Eight factors were significant in the majority of ICU types (at least three among the five types), including age, SAPS II score, duration of mechanical ventilation before extubation, heart rate, respiratory rate, RSBI, PaO2 before extubation and cough peak flow. Duration of mechanical ventilation had the broadest association across ICU types (4/5 types), while cough peak flow had the strongest association across ICU types (Additional file 1: Fig. S2).

Sensitivity analysis
Due to the heterogeneity among studies in terms of definition of extubation failure, we performed an exploratory sensitivity analysis restricted to studies where extubation failure was defined as death or reintubation, whatever the delay (57 out of 67 included in the meta-analysis): the vast majority of variables identified by crude analysis (23) remained significant, while only three were not (see Fig. 2, and Additional file 1: Table S3 in the additional material). Another sensitivity analysis was restricted to studies where extubation failure was defined as death or reintubation within 48 h (30 articles out of 67 included in the meta-analysis): 15 variables remained significant while eleven were not, including factors related to cough and tracheal secretions (see Fig. 2, and Additional file 1: Table S4 in the additional material).

Multivariable analysis
The 26 variables significantly associated with extubation outcome were assessed using a multivariable analysis for multiple factors (Additional file 1: Fig. S3 in the additional material). Twelve variables (age, history of cardiac disease, history of respiratory disease, SAPS II score, duration of mechanical ventilation, pneumonia, heart rate, RSBI, negative inspiratory force, lower PaO2/FiO2, lower Glasgow Coma Scale and lower hemoglobin level before extubation) were retained in the final model (Fig. 3). Glasgow Coma Scale (GCS) before extubation had the strongest independent association with extubation outcome.

Quality
Included studies differed in their methodological quality (Fig. 4, and Additional file 1: Fig. S4 in the additional material). High risk of bias was related to the study

**Table 1** Type of spontaneous breathing trial and definition of extubation failure

| Variable | Number of studies (%)
|----------|----------------------|
| Spontaneous breathing trial | |
| T piece | 15 (22.4%) |
| Low pressure support with zero-end expiratory pressure | 6 (9.0%) |
| Continuous positive airway pressure | 3 (4.5%) |
| Other | 33 (49.3%) |
| Not available | 10 (14.8%) |
| Duration of SBT | |
| 30 min | 12 (17.9%) |
| 60 min | 8 (11.9%) |
| 120 min | 13 (19.4%) |
| Variable* | 21 (31.3%) |
| Not available | 12 (17.9%) |
| Definition of SBT failure | |
| Respiratory rate | 43 (64.2%) |
| Increased breathing work or distress signs | 31 (46.9%) |
| Arterial oxygen saturation | 39 (58.2%) |
| PaO2 | 8 (11.9%) |
| PaCO2 | 10 (14.9%) |
| Tidal volume or minute ventilation or RSBI | 11 (16.4%) |
| Heart rate | 36 (53.7%) |
| Arterial pressure or introduction of vasopressor drug | 36 (53.7%) |
| Neurological criteria | 38 (56.7%) |
| Not available | 20 (29.9%) |
| Definition of extubation failure | |
| Death or reintubation | |
| Within 24 h | 4 (6.0%) |
| Within 48 h | 30 (44.8%) |
| Within 72 h | 14 (20.9%) |
| Within 7 days | 5 (7.5%) |
| At any time until discharge or death | 4 (6.0%) |
| Reintubation or curative non-invasive mechanical ventilation | 10 (14.9%) |

SBT spontaneous breathing trial, PaO2 partial pressure of oxygen, PaCO2 partial pressure of carbon dioxide, RSBI Rapid Shallow Breathing Index, * from 30 min to 12 h
| Variables                                      | n  | N               | Statistical method | Effect estimate [95%CI] |
|------------------------------------------------|----|-----------------|--------------------|------------------------|
| Age*                                          | 59 | 23,426          | Mean difference    | 3.43 [2.44, 4.41]      |
| APACHE II score*                               | 33 | 15,696          | Mean difference    | 1.63 [0.92, 2.35]      |
| Body mass index*                               | 13 | 8483            | Mean difference    | −0.64 [−1.21, −0.08]   |
| Male sex                                       | 52 | 22,093          | Odds ratio         | 0.90 [0.76, 1.07]      |
| SAPS II*                                       | 15 | 7159            | Mean difference    | 4.20 [2.75, 5.65]      |
| History of cardiac disease*                    | 16 | 7298            | Odds ratio         | 1.35 [1.12, 1.64]      |
| History of respiratory disease*                | 11 | 6303            | Odds ratio         | 1.49 [1.18, 1.87]      |
| COPD*                                         | 12 | 1984            | Odds ratio         | 1.60 [1.16, 2.21]      |
| Acute heart failure*                           | 11 | 3947            | Odds ratio         | 1.40 [1.04, 1.89]      |
| ARDS                                          | 9  | 2842            | Odds ratio         | 1.13 [0.75, 1.69]      |
| COPD exacerbation*                             | 18 | 4183            | Odds ratio         | 1.26 [1.01, 1.58]      |
| Glasgow Coma Scale before ext.*               | 13 | 5933            | Mean difference    | −0.75 [−1.06, −0.43]   |
| Pneumonia*                                     | 17 | 3692            | Odds ratio         | 1.48 [1.21, 1.81]      |
| Albumin                                       | 9  | 5481            | Mean difference    | −0.21 [−0.43, 0.02]    |
| Hemoglobin*                                    | 18 | 7277            | Mean difference    | −0.54 [−0.72, −0.35]   |
| PaCO2 before ext.                              | 34 | 12,328          | Mean difference    | 0.81 [−0.02, 1.64]     |
| PaO2 before ext.*                              | 22 | 9677            | Mean difference    | −8.02 [−12.39, −3.66]  |
| PaO2/FiO2 before ext.*                         | 30 | 11,960          | Mean difference    | −19.38 [−26.92, −11.84]|
| SaO2 before ext.*                              | 7  | 1893            | Mean difference    | −0.44 [−0.87, −0.01]   |
| Duration of MV before ext.*                    | 46 | 19,775          | Mean difference    | 1.03 [0.62, 1.43]      |
| Respiratory rate before ext.*                  | 27 | 15,178          | Mean difference    | 1.86 [1.19, 2.54]      |
| RSBI*                                         | 44 | 20,301          | Mean difference    | 8.51 [6.20, 10.81]     |
| RSBI after 1 min SBT*                          | 8  | 1606            | Mean difference    | 10.26 [3.68, 16.84]    |
| Tidal volume before ext.*                      | 25 | 12,070          | Mean difference    | −28.69 [−44.61, −12.78]|
| Heart rate before ext.*                        | 20 | 9848            | Mean difference    | 2.99 [1.49, 4.49]      |
| Maximal expiratory pressure*                   | 9  | 12,183          | Mean difference    | −10.22 [−17.70, −2.73] |
| Negative inspiratory force*                    | 14 | 13,448          | Mean difference    | 5.30 [3.11, 7.48]      |
| Cough*                                         | 7  | 3337            | Odds ratio         | 0.33 [0.16, 0.66]      |
| Cough peak flow*                               | 8  | 1041            | Mean difference    | −27.50 [−38.95, −16.04]|
| Moderate/abundant secretions*                  | 7  | 2248            | Odds ratio         | 1.98 [1.14, 3.43]      |
| Acute respiratory failure                      | 7  | 1249            | Odds ratio         | 1.43 [0.88, 2.32]      |
| Coma                                           | 8  | 2742            | Odds ratio         | 0.77 [0.57, 1.03]      |
| Creatinine                                     | 9  | 5422            | Mean difference    | 0.11 [−0.06, 0.29]     |
| Diastolic blood pressure before ext            | 9  | 1651            | Mean difference    | −1.03 [−2.57, 0.50]    |
| Diabetes                                       | 15 | 5976            | Odds ratio         | 1.27 [0.96, 1.69]      |
| FiO2 during SBT*                               | 11 | 7818            | Mean difference    | 0.00 [−0.00, 0.01]     |
| Glasgow Coma Scale upon admission              | 14 | 9113            | Mean difference    | −0.28 [−0.57, 0.00]    |
| History of hypertension                        | 8  | 998             | Odds ratio         | 1.09 [0.78, 1.52]      |
| Mean arterial pressure before ext              | 7  | 5161            | Mean difference    | −0.95 [−2.36, 0.45]    |
| Minute ventilation before ext                  | 17 | 14,383          | Mean difference    | 0.00 [−0.34, 0.34]     |
| Neurologic diagnosis                           | 9  | 3357            | Odds ratio         | 1.19 [0.76, 1.87]      |
| PEEP during SBT*                               | 11 | 7214            | Mean difference    | 0.05 [−0.00, 0.01]     |
| pH before ext*                                 | 27 | 11,392          | Mean difference    | −0.00 [−0.01, 0.00]    |
| Postoperative respiratory failure              | 7  | 2713            | Odds ratio         | 1.01 [0.69, 1.48]      |
| SBP before ext*                                | 13 | 5240            | Mean difference    | −0.41 [−1.95, 1.13]    |
| Sepsis                                         | 7  | 2903            | Odds ratio         | 1.17 [0.92, 1.48]      |
| Shock                                          | 8  | 1722            | Odds ratio         | 0.87 [0.50, 1.50]      |
| Steroids                                       | 7  | 3674            | Odds ratio         | 0.84 [0.58, 1.24]      |
| Trauma                                         | 7  | 4916            | Odds ratio         | 0.83 [0.63, 1.09]      |
participation in eight studies [47, 57, 78–82, 85], to study attrition in one study [33], to prognostic factor measurement in one study [7], to the outcome measurement in two studies [29, 77] and to study confounding in five studies [27, 65, 78, 81, 85]. The remaining studies had low or unclear risk of bias for each of the six domains.

**Discussion**

To the best of our knowledge, we herein report the first meta-analysis on factors associated with extubation failure. By multivariable analysis, twelve factors were significantly associated with extubation failure: age, history of cardiac disease, history of respiratory disease, SAPS II score, duration of mechanical ventilation, pneumonia, heart rate, RSBI, negative inspiratory force, lower PaO₂/FiO₂, lower hemoglobin level before extubation and lower Glasgow Coma Scale before extubation, with the latest factor having the strongest independent association with extubation outcome.

**Definition of extubation failure**

An important information that comes out from our systematic review is that there is lack of standardization about the definition of extubation failure. It was defined as death or reintubation within a time interval that varies from 24 h to 7 days and in some studies, it also comprised the need for curative noninvasive ventilation after extubation. This leads to a risk of bias in evaluating...
the prognostic factors for extubation failure. For this reason, we performed a sensitivity analysis considering only studies where extubation failure was defined as death or reintubation within 48 h, since this is the most used definition. In this sensitivity analysis, the majority (15 out of 26) of factors identified by the crude analysis remained significant. However, cough, cough peak flow and secretions were no longer associated with extubation outcome when considering a 48 h delay. Alteration of cough and/or excessive secretions may act as major cause of delayed reintubation. These findings, and the increasing use of prophylactic non-invasive ventilation and high flow oxygen after extubation, may suggest the
use of death or reintubation within a seven-day delay to define extubation failure in future studies [86].

Risk factors for extubation failure
As highlighted in the present work, many factors may contribute to extubation failure in a given critically ill patient, suggesting an individual pathophysiological approach. The topic of secretion management was the one with the largest number of variables (five) significantly associated with extubation failure, pointing out that it should be carefully evaluated before extubation. The assessment of the “upper airway patency”, in terms of amount of secretions and the ability to clear them through an effective cough, has been increasingly used in the literature, even though these parameters are difficult to measure in an objective and standardized way. Cough peak flow is a parameter that has been proposed in the last few years to overcome this problem, but our multivariable analysis suggests negative inspiratory pressure as a relevant indicator.

Although the majority of statistically significant variables from our meta-analysis were related to the respiratory function (16 variables), the circulatory (three variables) and neurological (one variable) functions were also involved, with Glasgow Coma Scale having the strongest association with extubation outcome by multivariable analysis. These results are consistent with the plurality of often-intertwined mechanisms of extubation failure. Thus, restricting the clinical reasoning to the spectrum of a few variables related to the respiratory function may weaken the decisional process of liberation from mechanical ventilation. Robust multiparametric clinical scores and/or artificial intelligence algorithms should be tested based on the selected variables in order to improve the prediction of extubation outcome in the clinical scenario.

Strengths and limitations
Strengths of our study include the wide period of assessment and selection process. One limitation is the lack of standardization in the definition of extubation failure. However, we performed a sensitivity analysis using the most accepted definition. Another limitation is that, due to the lack of data, we could not analyze the postextubation stridor, which is considered a rare but important risk factor for extubation failure. Finally, we may have missed other potentially important factors since we chose to analyze only parameters evaluated in at least 10% of included studies.

Conclusion
We performed a systematic review and meta-analysis of a wide population of critically ill patients, finding 26 and 12 risk factors for extubation failure in patients who have successfully passed a spontaneous breathing trial by univariate and multivariable analysis, respectively. These factors were related to age, comorbidities, acute disease severity and physiological characteristics at the time of extubation. To further explore these factors and their combination, a unique definition of extubation failure is needed. An automated algorithm incorporating these factors would probably be very useful to inform the decisional process of extubation.

Abbreviations
APACHE: Acute physiology and chronic health evaluation; ARDS: Acute respiratory distress syndrome; BMI: Body mass index; CI: Confidence interval; COPD: Chronic Obstructive Pulmonary Disease; FiO2: Fraction of inspired oxygen; GCS: Glasgow Coma Scale; ICU: Intensive care unit; IQRs: Interquartile ranges; MEP: Maximal expiratory pressure; MV: Mechanical ventilation; NIF: Negative inspiratory force; OR: Odds ratio; PaCO2: Partial pressure of carbon dioxide in the arterial blood; PaO2: Partial pressure of oxygen in the arterial blood; PEEP: Positive end expiratory pressure; RSBI: Rapid shallow breathing index; SaO2: Oxygen saturation in the arterial blood; SAPS: Severity acute physiologic score; SBT: Spontaneous breathing trial; SD: Standard deviation.

Supplementary Information
The online version contains supplementary material available at https://doi.org/10.1186/s13054-021-03802-3.

Additional file 1: Table S1. Variables excluded because of missing data.

Figure S1. Forest plots for variables statistically significantly associated with extubation failure. Table S2. Subgroup analyses by intensive care unit type. Figure S2. Heatmap of natural log transformation of odd ratios (LnOR) for extubation failure, according to ICU type. Table S3. Sensitivity analysis focusing on studies defining extubation failure as death or reintubation, whatever the delay. Table S4. Sensitivity analysis focusing on studies defining extubation failure at 48 h. Figure S3. Individual risk of bias in the included studies. Figure S4. Forest plot for the 26 variables significantly associated with extubation failure, assessed by multivariate meta-analysis for multiple factors.

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Authors’ contributions
AMD, FT and JM designed the meta-analysis. FT and JM searched for the articles, screened titles and abstracts and extracted data. AMD, FT and SG performed statistical analysis and interpretation of data. AWT, GC and MA contributed to the conception of the study. FT and AMD drafted the manuscript, and FT, SG, JM, GC, AWT, MA and AMD revised it for important intellectual content; all authors read and approved the final manuscript.

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Declarations

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Not applicable.

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Competing interests
The authors declare that they have no competing interests.

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