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TITLE PAGE

Association between spontaneous breathing trial methods and reintubation in adult critically ill patients: A systematic review and network meta-analysis of randomized controlled trials

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Short title: Network meta-analysis of different SBT methods

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Abbreviations list

CPAP, Continuous Positive Airway Pressure
HFO, High Flow Oxygen
ICU, Intensive care unit
PAV+, Proportional Assist Ventilation
PEEP, Positive End-Expiratory Pressure
PSV, Pressure support ventilation
RCT, Randomized Controlled Trial
SBT, Spontaneous breathing trial

Conflict of interest

All the authors declare no conflict of interest.

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Guarantor

AC and SS had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Authors' contributions

MI, SS, VFT and AC gave substantial contributions to the conception and design of the work; MI, SS and AC drafted the manuscript; MI, SS, VFT and AC collected the data; SS performed the analysis with contributions from MI, VFT and AC. All the authors (MI, SS, VFT, NL, EB, AG, AC) gave substantial contribution to interpretation of data for the work, revised critically the manuscript for important intellectual content, gave the final approval of the version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Other contributions

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Abstract

Background

Reintubation is associated with higher risk of mortality. There is no clear evidence on the best spontaneous breathing trial (SBT) method to reduce the risk of reintubation.

Research Question

Are different methods of conducting SBT in critically ill patients associated with different risk of reintubation compared to T-tube?

Study Design and Methods

We conducted a systematic review and Bayesian network meta-analysis of randomized controlled trials (RCTs) investigating the effects of different SBT methods on reintubation. We surveyed PubMed, MEDLINE, CINAHL and CENTRAL databases from inception to 26th January 2024. The Surface Under the Cumulative Ranking curve (SUCRA) was used to determine the likelihood that an intervention was ranked as the best. Pairwise comparisons were also investigated by frequentist meta-analysis. Certainty of the evidence was assessed according to the GRADE approach.

Results

A total of 22 RCTs were included, for a total of 6196 patients. The network included nine nodes, with 13 direct pairwise comparisons. About 71% of the patients were allocated to T-tube and PSV-ZEEP, with 2135 and 2101 patients, respectively. The only intervention with a significantly lower risk of reintubation compared to T-tube was high flow oxygen (HFO) (RR 0.23, CrI 0.09 to 0.51, moderate quality evidence). HFO was associated with the highest probability of being the best intervention for reducing the risk of reintubation (81.86%, SUCRA 96.42), followed by continuous positive airway pressure (11.8%, SUCRA 76.75).

Interpretation

HFO SBT was associated with a lower risk of reintubation in comparison to other SBT

methods. The results of our analysis should be considered with caution due to the low number of studies that investigated HFO SBT, and potential clinical heterogeneity related to co-interventions. Further trials should be performed to confirm the results on larger cohorts of patients and assess specific subgroups.

Registration

CRD42023449264

Keywords list

Spontaneous breathing trial; weaning; reintubation; extubation; high flow oxygen; intensive care unit; network meta-analysis

INTRODUCTION

Spontaneous breathing trials (SBT) are used to assess whether patients are ready for extubation once clinical criteria for weaning have been assessed and reached[1]. The rationale behind performing a SBT is to simulate the work of breathing that the patient will face after the extubation and assess its effects on cardiorespiratory function. The ideal SBT should help confirming the identification of patients ready for spontaneous breathing and limiting the occurrence of reintubation. Although the failure of a SBT is partly based on objective criteria, a high grade of variation is due to the clinical assessor. Notably, extubation failure *per se* is associated with higher risk of mortality, independently of severity of disease and clinical condition[1,2].

T-piece and minimally supported ventilation have been widely investigated as SBT methods[3] and guidelines exist on SBTs and weaning process [4]. However, the best SBT method is far from being definitively known. Indeed, the published studies are heterogenous in terms of duration of the SBT, proportion of use of post-extubation respiratory support, weaning protocols prior to the SBT. Moreover, the false negative of any SBT method would

reasonably never be quantified, as ethical reasons impede to extubate a patient who failed an SBT, even in the context of a clinical trial. Ongoing research witnesses that improvements in predicting extubation outcomes are still needed[5]. Furthermore, novel methods of performing SBT, such as high-flow oxygen through dedicated devices, have been recently proposed [6], and the efficacy remains uncertain. A network meta-analysis can be the best statistical method to summarize the effects of more than two interventions towards the same outcome, and to quantitatively consider indirect evidence [7]. The aim of this systematic review and network meta-analysis was to evaluate the association between different methods of SBT and the risk of subsequent reintubation in critically ill patients.

METHODS

The protocol of this systematic review was prospectively registered in PROSPERO international database (CRD42023449264). The reporting follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for network meta-analysis (PRISMA-NMA)[8]. The PRISMA-NMA checklist is available at **e-Appendix 1.**

We conducted a systematic search on PubMed, MEDLINE, the Cumulative Index to Nursing and Allied Health Literature (CINAHL), and the Cochrane Central Register of Controlled Trials (CENTRAL) databases, from inception to 26th January 2024. We searched for randomized controlled trials (RCTs) investigating the effectiveness of SBT methods (I), in comparison to other SBT methods or extubation without SBT (C), towards the outcome of reintubation (O) in adult critically ill patients (P). The search strategy is available at **e-Appendix 2**. After removal of duplicates, all the records were screened from title and abstract by two investigators (MI, VFT), blindly. A third investigator (SS) periodically surveyed other sources using the snowballing method. Relevant records were selected for review of full-text, and they were finally included if two investigators (MI, VFT) agreed on

their eligibility. In case of disagreements, eligibility was assessed through consensus between the two investigators, or by arbitration with a third investigator (AC). Nonrandomized studies and studies comparing different weaning strategies from mechanical ventilation but not specifically focusing on SBT methods were excluded. Abstracts and conference proceedings were excluded. Studies focusing on pediatric populations were also excluded. Studies with unclear reporting of all the inclusion criteria and whose authors did not reply to requests for clarifications were excluded. Duplicate removal and the screening process were performed with the aid of the web-based software *Rayyan*[9].

The primary outcome was reintubation, defined as the proportion of patients reintubated within 72 hours after extubation. The choice of the timepoint for this outcome was based on the evidence supporting its clinical relevance and association with risk of mortality[10]. In case this timepoint was not available, we collected the data on primary outcome at the closest timepoint reported by the authors. Additional outcomes of interest were extubation rate after the first or initial successful SBT, ICU mortality, ICU length of stay and duration of invasive mechanical ventilation.

Data extraction from the included studies was performed in duplicate (MI, VFT) and using a standardized electronic data extraction form, through the platform *RedCap*[11]. We collected study data including study design and setting, patients' characteristics, characteristics of the interventions and comparison and outcome measures. In case of doubt on data interpretation, we contacted the corresponding authors via email for clarifications. No SBT types were clustered or merged for the purpose of our analysis and data were collected as reported by the authors.

Two authors independently (MI, VFT) performed the assessment of risk of bias using the Rob2 tool[12] for the primary outcome (i.e. reintubation). Discrepancies were solved via consensus among four authors (MI, SS, VFT and AC). Domains per study were evaluated

according to Cochrane handbook indications. Visualization was performed by using the Robvis tool[13]. The bias in the measurement of the outcome was rated according to the information reported by study authors as criteria for reintubation, since it was likely present in all the included studies. Indeed, masking was not possible, and reintubation is an outcome that may reflect decisions made by the treating physicians, prone to subjectivity. High risk of bias was assigned to this domain when criteria for reintubation were not a-priori declared in detail. In the case of pre-specified criteria for reintubation, the studies were judged at some concerns for this domain, considering that the open-label design of the studies could have influenced clinical decisions.

We evaluated the certainty of evidence using the GRADE approach for network meta-analysis[14]. For the primary outcome, we rated the certainty of each comparison as either high, moderate, low, or very low based on risk of bias, reporting bias, indirectness, imprecision, heterogeneity, incoherence (difference between direct and indirect effect). We decided to use the null as the threshold for imprecision assessment. We used the CINeMA tool[15] for the analysis and the reporting of the confidence as suggested by Cochrane (https://cinema.ispm.unibe.ch/#). This assessment was performed by one author (AC) and then validated by consensus among other authors (MI, SS, VFT, AC).

Statistical analysis

We performed a Bayesian random-effects network meta-analysis. The geometry of the network was graphically summarized in a network plot. The generalized linear models we adopted to perform the network meta-analyses were based on noninformative a priori distributions[16,17]. We also performed a secondary analysis under the JAGS (Just Another Gibbs Sampler) models for the random-effect analyses **(e-Appendix 3).** We estimated the effect sizes of dichotomous outcomes as risk ratios and the effect sizes of continuous outcomes as mean differences. We expressed the precision of effect sizes using the 95% credibility intervals. In case of multi arm trials, each arm was treated according to its

intervention as a standalone intervention for the network meta-analysis. The distribution of treatment ranks was based on the effect size estimates from the network meta-analysis and the desirability of each outcome. Then, the hierarchy of treatments was summarized using the surface under the cumulative ranking curve (SUCRA), which reflects the level of confidence in a treatment outperforming all alternative treatments. The Surface Under the Cumulative Ranking curve (SUCRA) presents numerically the overall ranking for each intervention, ranging from 0 to 100%, coinciding with the bottom and the top ranks, respectively. Heterogeneity was assessed using the I^2 statistic and publication bias was assessed visually with a funnel plot. In the case of arms with zero events, appropriate sub analyses were conducted excluding the intervention with zero events for the considered outcome. Pairwise comparisons were also investigated by random-effects frequentist pairwise meta-analysis. All the analyses were conducted by one author (SS) by means of codes in the R programming language (The R Foundation for Statistical Computing) run through the Integrated Development Environment RStudio (RStudio Team, RStudio: Integrated Development for R. RStudio, Inc.) with input by other authors (MI, VFT, AC). The packages used for Bayesian network meta-analysis were "BUGSnet" and its dependencies “rjags" and "coda," while the “meta” package was used to perform pairwise frequentist meta-analysis of selected direct comparisons [18–22]. A mortality analysis including all studies presenting zero events was performed with the netmeta R-package[21].

RESULTS

We retrieved 2552 records. A total of 22 RCTs were finally included in the meta-analysis, for a total of 6196 patients [3,6,23–41]. The inclusion and exclusion process is presented in **Figure 1**, as a PRISMA flow diagram. The **e-Table 2** summarizes the reasons for exclusion of studies assessed from full-text. The characteristics of the included studies are presented in **Table 1**. All the studies were conducted in single center, except for 6 multicenter studies. Of note, the only multi-national study was conducted in 1997[28] in 27

ICUs from Spain, Argentina, Brazil and Venezuela. A high variability was found in terms of duration of SBTs across the studies, with median duration ranging from 30min to 120min. The interventions investigated by the included studies were i) T-piece, ii) “PSV+-PEEP”: Pressure support ventilation (PSV) with positive end-expiratory pressure (PEEP), iii) “PSV-ZEEP”: Pressure support ventilation (PSV) without positive end-expiratory pressure (PEEP), iv) Continuous positive airway pressure (CPAP), v) CPAP with Automatic Tube Compensation (ATC), vi) High flow oxygen (HFO) through dedicated device, vii) Proportional Assist Ventilation (PAV+). The majority of the studies compared two arms of interventions, but three studies compared three arms of interventions. The results of risk of bias assessment for the primary outcome are graphically presented as appropriate in **e-Appendix 2, e-Figure 1.** The main reasons for studies judged as “some concerns” or “high risk of bias” were related to the randomization process, to the measurement of the outcome and to the selection of reported results.

Additional results from the sensitivity analysis of the primary outcome conducted under different a priori distributions are available at **e-Appendix 3 (e-Figure 8 and e-Figure 9)**.

Reintubation

Twenty trials[3,6,23–30,32–35,37–41] reported the outcome of reintubation for 5970 patients. The network plot for the primary outcome is available at **Figure 2.** The network included nine nodes, with 13 direct pairwise comparisons. About 71% of the included patients were allocated to T-tube and PSV-ZEEP, with 2135 and 2101 patients, respectively.

HFO was associated with the highest probability of being the best intervention for reducing the risk of early reintubation (81.86%, SUCRA 96.42), followed by CPAP (11.8%, SUCRA 76.75), PAV+ (3.8%, SUCRA 57.65), ATC+CPAP (2.29%, SUCRA 57.25), ATC (0.03%, SUCRA 30.62), PSV-PEEP (0%, SUCRA 40), PSV-ZEEP (0%, SUCRA 37.7), T-

tube (0%, SUCRA 27.48), and no SBT (0%, SUCRA 26.13) see **Figure 3, panel a**. The only intervention with a statistically lower risk of reintubation compared to T-tube was HFO (RR 0.23, CrI 0.09 to 0.51, moderate quality evidence). The forest plot showing the risk ratios of the different interventions compared to T-piece are presented in **Figure 3, panel b.** We estimated the median number needed to treat for HFO at 10.56 (CrI 8.93 to 16.6), when compared to T-tube, 7.84 (CrI 7.1 to 14.2), when compared to PSV-ZEEP, and 8.3 (CrI 6.94 to 13), when compared to PSV-PEEP.

HFO was associated with a lower risk of reintubation when compared at pairwise analysis to T-tube SBT (RR=0.29 95% C.I. 0.106 to 0.792, p-value=0.034; I^2=0, Q=0.62, degree of freedom=2, n=386 patients) (**Figure 4, panel a**). The individual study results grouped by treatment comparisons are available at **e-Appendix 2, e-Figure 2**.

We also analyzed the pairwise comparisons between PSV and T-piece and we found no statistically significant associations between the interventions and the outcome of reintubation (See **Figure 4, panel b and c**).

The evaluation of the certainty of evidence for all the comparisons is reported in **e-Table 2**. The confidence rating was judged as moderate due to downgrading for risk of bias in 7 comparisons (HFO vs No SBT, HFO vs PSV-PEEP, HFO vs T-Tube, HFO vs. ATC, HFO vs. PSV-ZEEP, PSV-ZEEP vs. T-Tube, PSV-PEEP vs. PSV-ZEEP) and as low for further downgrading for imprecision in all other comparisons.

The examination of leverage plots for both the random-effects model and the "inconsistency model" revealed no evidence of overall inconsistency. This was proved by the superior performance of our meta-analysis generalized linear model, as indicated by the lower values of DIC (66.74 vs. 69.47), Dres (37.12 vs. 37.98), pD (29.62 vs. 31.48, **e-Appendix 3, e-Figure 10, panel a and b).** Global and local incoherence were also

investigated using the CINeMA tool, ruling out any concerns (Global test χ2 statistic: 6.039, 6 degrees of freedom, P value: 0.419; **e-Appendix 2, e-Table 2**). We also conducted a nodesplit analysis for this outcome, that is available at **e-Appendix 3, e-Table 3.**

No signs of publication bias were identified at funnel plot visualization for the analysis of studies on HFO (Egger's test b = -3.399, CI -5.32 to -1.48.; t = 2.23; p-value = 0.268) (**e-Appendix 2, e-Figure 3).**

Secondary outcomes

Extubation after first SBT

All the included studies reported the outcome of first SBT success rate. SBT with ATC+CPAP was associated with the highest probability (34.26%) of being the first-ranked intervention with a SUCRA of 58.25. Of note, HFO had a lower probability of being ranked as the best but a better overall SUCRA score (77.3). HFO had also a significantly lower risk of failure at first SBT in comparison to T-tube (RR 0.48, CrI 0.21 to 0.99). All the other interventions presented a wide credibility interval crossing the median line and no significant effect on the risk of initial SBT failure, in comparison with T-tube (SUCRA 24.93), as shown by the league plot at **e-Appendix 2, e-Figure 4**. Upon inspection of the leverage plots, the inconsistency model showed slightly more dispersed data points and a marginally superior residual deviance. The nodesplit analysis revealed signs of local inconsistency for three comparisons: PSV-PEEP vs. PSV-ZEEP (p = 0.0324), PSV-PEEP vs. T-tube (p = 0.0007), PSV-ZEEP vs. T-tube (p = 0.0838**, e-Appendix 3, e-Table 4**)

Overall duration of mechanical ventilation

The results of the analysis are presented in **e-Appendix 2, e-Figure 5.** Based on 5 studies reporting the outcome of 731 patients, CPAP was estimated to be the best intervention in reducing the overall duration of mechanical ventilation with a SUCRA of 74.7.

However, considering the effect size estimations, no interventions were associated with a statistically evident effect on this outcome. The plots of consistency and inconsistency models were indistinguishable, as the evidence for each comparison was collected alternatively from either direct or indirect evidence **(e-Appendix 3, e-Figure 12)** Results of the nodesplit analysis are available at **e-Appendix 3, e-Table 5** for this outcome.

ICU mortality

Nine studies assessed the outcome of ICU mortality. The results of the analysis are presented in **e-Appendix 2, e-Figure 6**. PAV+ was the best-ranked intervention with a SUCRA score 99.81. As the only study allocating patients to PAV+ reported no ICU mortality, a sub analysis was performed excluding the PAV+ intervention[42]. This sub-analysis showed that ATC had the highest probability of being the best intervention (SUCRA 79.69, RR 0.53 CrI 0.15 to 1.62). No interventions had a statistically evident effect on ICU mortality. We also performed a random-effects frequentist network meta-analysis using a 0.5 continuity correction for a single arm presenting 0 events (PAV+) (**e-Appendix 3, e-Figure 13**). This meta-analysis showed no statistically discernible effects of any treatment in comparison to T-tube SBT. The precision of effect size estimation was too low to generate any estimated effect in favor of this intervention. Leverage plots of consistency and inconsistency models were substantially overlapping, while the nodesplit analysis detected no signs of local inconsistency **(e-Appendix 3, e-Figure 14** and **e-Table 6)**

Intensive care unit length of stay

The analysis for the outcome ICU length of stay was based on 12 studies reporting the outcome for 5158 patients and its results are presented in the **e-Appendix 2, e-Figure 7**, with a SUCRA ranking suggesting ATC (SUCRA 66.37) as the best intervention but no statistically discernible effect among the interventions. Leverage plots of consistency and

inconsistency models and results of nodesplit analysis are available at **e-Appendix 3, e-Figure 15** and **e-Table 7** for this outcome.

DISCUSSION

The main finding of this Bayesian network meta-analysis was that HFO SBT might reduce the risk of reintubation, when compared to other methods of performing SBT or to direct extubation without SBT. This result was concordant in both the direct and indirect evidence, the outcome of reintubation was judged of critical relevance and the certainty of the evidence supporting this specific finding was moderate. However, the results of our analysis should be taken with caution, as the only three studies[6,33,34] investigating HFO were single-center RCTs, including a total of 482 patients, with a small event rate for the outcome reintubation and judged at "high risk of bias"[33,34] or "some concerns"[6].

The results indicate the need for further studies on the role of HFO as SBT method. Indeed, HFO might also be associated with a higher success rate at the first attempt of SBT compared with T-tube, thus potentially overcoming the historical dilemma of choosing between methods with potentially low reintubation rate but low success rate (eg. T-Piece) and methods with potentially high success rate but with high reintubation rate (eg. PSV)[3]. Scientific community has largely debated that "minimal ventilator settings" could aid reducing the load of breathing in patients more vulnerable to extubation failure, and the actual recommendations supports SBT with inspiratory pressure support (5-8 cmH_2O) for SBT[4].

However, no clear superiority or inferiority of PSV has been demonstrated over T-piece[3] and our results are in line with available literature. Indeed, a recent pairwise meta-analysis has shown that PSV SBTs were not associated with increased risk of reintubation[43]. Difference exists with our analysis, as the authors also included children and perioperative patients, merged the interventions into a pairwise comparison between PSV and other techniques despite adopting a network design and lastly updated the search in 2023. These

differences can explain why, despite temporally close, our results showed a benefit of HFO not previously detected by other meta-analysis. Another recent network meta-analysis compared ATC to different methods of SBTs, assessing SBT and extubation outcomes[44]. The authors found ATC as the method associated with the highest probability of extubation success, but none of the included studies had HFO-SBT as intervention or comparator [44].

Our analysis did not show any discernible effect of interventions on the secondary outcomes and overall, our results suggest that SBT is probably not able to determine an effect on such clinical outcomes *per se*, but it must be put in context with clinical care (e.g. post-extubation protocols of care, extent of organs failure)[45]. On the other hand, the clinical impact estimated by our results is to prevent one reintubation in ten or nearly 7 extubated patients if the decision is taken upon HFO SBT versus T-tube or PSV.

The estimated superiority of HFO SBT found by our analysis can be interpreted considering its increased use as post-extubation support[46]. Indeed, an SBT with HFO may more faithfully simulate the real work of breathing that patients will face after extubation, in comparison with other SBT methods, given that they will receive HFNO as post-extubation respiratory support. On the other hand, this can limit the external validity of the HFO estimated superiority, as specifically discussed by Fossat et al., declaring a high rate of HFNO use after extubation in their RCT[6].

High flow oxygen applied through nasal cannula (HFNC) may reduce reintubation in critically ill adults after extubation, in comparison with conventional oxygen therapy, through its flow-related effects including the delivery of heated and humidified air flow[27]. However, the device adopted to perform SBT with HFO is the one dedicated to tracheostomy cannulas (HFO-T). Such device determines smaller airway pressures (i.e. average up to 1.2 mmHg) in tracheostomized patients compared to HFNO, resulting more similar to HFNO applied during spontaneous respiration in patients keeping mouth open[47]. Such limited effects have been attributed to the small expiratory resistance to flow offered by the tracheal stoma, and

preclinical studies confirmed a better performance of the device when an increased expiratory resistance is applied[48]. Further data are needed to explore the physiological effects of HFO applied to endotracheal tube during an SBT.

It must be also considered that the efficacy of an SBT method goes along with the clinical assessors' sensitivity in assessing the results of the SBT, leading to the final decision to extubate the patient. The increasing experience of ICU physicians with HFO devices could have thus also led to its estimated superiority over other methods.

Our analysis has limitations. The results are based on aggregated data reported by the included trials, and we were unable to explore the effects of the different SBT techniques on patients at high risk of reintubation or extubation failure, since only two studies [3,6] specifically focused on this population. Most studies were judged at high risk of bias, and this led to a downgrading of the certainty rating. Another potential limitation lies in the heterogeneous application of both prophylactic and therapeutic non-invasive respiratory supports in the included studies, not considered in our analysis. Indeed, we could only speculate that the HFO-SBT estimated superiority may depend on a high rate of HFNO use after extubation, but no subgroup analysis could be performed on patients receiving HFNO after extubation, due to lack of data granularity on post-extubation support. We also did not assess the impact of resuming mechanical ventilation after the SBT and prior to extubate the patients[49,50], to avoid high heterogeneity of our analysis. Moreover, we decided not to consider the duration of SBT to further split the nodes of the interventions and to accept the increased heterogeneity as there is currently no evidence of superiority between the two most frequent durations adopted (i.e. 30min and 120min)[10]. Indeed, we could not consider different levels of pressure support or flow rate due to scarce reporting in the included studies. All these factors are part of the condition under which the SBT was performed, and they have likely varied among included studies. We cannot exclude that these factors may act as effect modifiers in the association between SBT method and reintubation. We could not explore

the association of risks with specific covariates such as age or cardiorespiratory comorbidities, and duration of SBT because the risk of ecological fallacy was considered too high to perform metaregression analyses[51]. The generalized linear models we adopted to perform the network meta-analyses were based on noninformative a priori distributions, letting the actual data affect in a more significant measure the posterior parameters, i.e., the size effect[17]. According to our sensitivity analysis, it is likely that different priors (and design for its selection) may change the results of the association between the interventions and reintubation. Finally, the majority of the included studies (18 out of 23) were rated at overall high risk of bias. The main reason for this decision was related to the lack of detailed information on the criteria for reintubation. We were unable to perform meta-analysis considering studies at moderate or low risk of bias only, as this analysis would have resulted in a disconnected network. Our judgments should be considered as conservative, underlying the subjectivity intrinsically connected to the clinical decision to reintubate. As insights for future research, further studies evaluating the effectiveness of intervention aimed at reducing the risk of reintubation should put specific attention to mitigating this bias (i.e. details on reintubation criteria).

However, our analysis and the findings also have strengths. First, we prospectively registered the protocol and adopted a rigorous and reproducible methodology. In addition, we included RCTs only. Moreover, the statistical discernibility of the results for the primary outcome reintubation was confirmed in both the mixed treatment network meta-analysis and the frequentist pairwise meta-analysis.

INTERPRETATION

Available evidence suggests that HFO SBT was associated with a lower risk of reintubation in comparison to other SBT methods. Heterogeneity in the conditions under which the SBT is performed and the use of prophylactic and therapeutic non-invasive

respiratory supports after extubation may potentially change these findings. Further high-quality trials should be performed to confirm this result and to evaluate specific subgroups of patients or patient clusterization (e.g. based on post-extubation support). Physiological studies should also explore the mechanisms behind the estimated benefit of applying high flow oxygen through an endotracheal tube during a spontaneous breathing trial.

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536 **Table 1. Characteristics of the included studies**
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Author, Country (Year)	Study design	Population	Intervention	Comparison	Primary outcome	Overall Risk of Bias
Cekmen, Turkey (2011)[23]	Single-center RCT	40 adult patients admitted to ICU and mechanically ventilated for > 48 h	SBT with CPAP, PEEP ≤5 cmH_2O, FiO_2 ≤0.4	SBT with T-piece with 4 L/min of Oxygen	Successful weaning, defined as the ability to maintain spontaneous breathing for 48h after extubation	High risk
Chittawatanarat, Thailand (2018)[24]	Single-center RCT	520 adult patients admitted to ICU and mechanically ventilated for > 12 h	Up to 2 h of SBT with PSV, inspiratory pressure 5-7 cmH_2O, PEEP 5 cmH_2O, FiO_2 0.4, expiration triggered at 25% of peak inspiratory flow rate	Up to 2 h of SBT with T-piece with oxygen flow at 10-15 L/min	Outcomes: success of the first SBT and reintubation	High risk
Cohen, Israel (2009)[26]	Single-center RCT	180 adult patients admitted to ICU and mechanically ventilated for > 24 h	1-hour SBT with CPAP, 5 cmH_2O, with ATC 100%, FiO_2 <0.5	1-hour SBT with PSV, pressure support 7 cmH_2O, PEEP 5 cmH_2O, FiO_2 <0.5	Ability to maintain spontaneous, unassisted breathing for more than 48h after extubation	High risk
Cohen, Israel (2006)[25]	Single-center RCT	99 adult patients admitted to ICU and mechanically ventilated for > 24 h	1-hour SBT with CPAP of 5 cmH_2O, with inspiratory ATC 100%, FiO_2 set at the same level required before SBT	1-hour SBT with CPAP of 5 cmH_2O, FiO_2 set at the same level required before SBT	Successful extubation, defined as the ability to maintain spontaneous breathing for 48h after extubation	High risk
El-Shahat, Egypt (2015)[27]	Single-center RCT	166 adult patients admitted to respiratory ICU with respiratory	30-120 min of SBT with rapid decline of PS from 15 cmH_2O to 8 cmH_2O. If failed, subsequent SBT conducted with gradually	30-120min of SBT with ATC set at 100%. Flow-triggering set at 3 l/min, peak end	Weaning duration And successful extubation	High risk

		disorders and mechanically ventilated for > 1d	lowered PS (by 2–4 cmH2O). Flow-triggering set at 3 l/min, peak end expiratory pressure at 0–5 cmH_2O and FiO_2 ≤ 0.4	expiratory pressure at 0–5 cmH_2O and FiO_2 ≤ 0.4		
Esteban, Spain, Argentina, Brazil and Venezuela (1997)[28]	Multi-center RCT	484 adult patients admitted to ICU and mechanically ventilated for > 48h	120-min SBT with PSV, pressure support of 7 cmH_2O	120-min SBT with T-tube	Successful extubation without reintubation within 48 h after extubation	High risk
Farid, Pakistan (2021)[29]	Multi-center RCT	48 adult patients admitted to ICU and mechanically ventilated for ≥ 24 h	30-min SBT with PSV	120-min SBT with T-tube	Outcomes: Extubation, reintubation and mortality	High risk
Figueroa-Casas, USA (2010)[30]	Single-center RCT	118 adult patients admitted to ICU and mechanically ventilated for ≥ 24h	30-min of SBT with CPAP of 5 cmH_2O, FiO2 as previously set	30-min SBT with PEEP of 5 cmH_2O, ATC 100%, FiO_2 as previously set	Duration of weaning, defined as the number of days from first SBT to extubation	Some concerns
Fossat, France (2021)[6]	Single-center RCT	106 adult patients admitted to ICU, at high risk for weaning failure, with a chronic pulmonary and/or cardiac disease and mechanically ventilated for > 24h	30-min SBT with HFO set at 60 L/min for all patients and the FiO_2 was set at the same level while on the ventilator. The connection between the HFO device and the tube was made with the tracheotomy connection device	30-min SBT with T-piece with oxygen flow, calculated as minute ventilation multiplied by the FiO_2 as displayed by the ventilator before SBT	Proportion of patients alive and free of invasive ventilation at 7 days after first SBT	Some concerns

Haberthür, Switzerland (2002)[31]	Single-center RCT	90 adult patients admitted to ICU with acute respiratory failure and mechanically ventilated for > 24h	• 120-min SBT with ATC and PEEP 5cmH2O • 120-min SBT with PSV 5 cmH_2O and PEEP 5 cmH_2O	120-min SBT with T-tube	Outcomes: Successful extubation, unsuccessful extubation, predicted as being not extubatable	High risk
Koh, Korea (2000)[32]	Single-center RCT	42 adult patients admitted to ICU and mechanically ventilated for > 3 days	Immediate extubation without SBT	60-min SBT with T-tube	Outcomes: success rate and reintubation rate	High risk
Lee, South Korea (2022)[33]	Single-center RCT	108 adult patients admitted to ICU and mechanically ventilated for > 12h	30-60min SBT with high flow oxygen 60L/min, FiO_2 0.4. The connection between the HFO device and the tube was made with the tracheotomy connection device	30-60min SBT with T-tube with 8L/min flow and FiO_2 of 0.4	Rate of weaning failure on day 2, defined as either the failure of SBT within 72h after the first SBT or the need for reintubation or death within 48h following extubation	High risk
Liu, China (2019)[34]	Single-center RCT	268 adult patients admitted to ICU and mechanically ventilated for ≥ 48h	• 120-min SBT with PSV 7 cmH_2O • 120-min SBT with high flow oxygen at 40L/min	120-min SBT with T-tube	Outcomes: passing rate, duration of MV, reintubation rate and mortality	High risk
Matić, Croatia (2004)[35]	Single-center RCT	260 adult patients admitted to ICU and mechanically ventilated for > 48h	120-min SBT with PSV 8 cmH_2O	120-min SBT with T-tube	Outcomes: successful extubation, failure of extubation, duration of weaning and MV, reintubation, life-threatening complications, ICU LOS and ICU mortality	High risk

Matić, Croatia (2006)[36]	Single-center RCT	136 adult patients with COPD, admitted to ICU and mechanically ventilated for > 24h	120-min SBT with PSV (from 18cmH_2O to 5 cmH_2O)	120-min SBT with T-tube	Outcomes: successful extubation, duration of weaning and MV, reintubation, ICU LOS and ICU mortality	High risk
Pellegrini, Brazil (2018)[37]	Multi-center RCT	190 adult patients with COPD, admitted to ICU and mechanically ventilated for ≥ 48h	30-min SBT with PSV 10 cmH_2O while maintaining the PEEP and FiO_2 previously adjusted to achieve an arterial saturation of at least 92%	30 minutes T-connector, which continuously supplied humidified oxygen to achieve a saturation of at least 92% in the absence of positive pressure	MV duration, defined as the interval between the intubation and successful extubation (48h without invasive ventilation), death on MV or tracheostomy	High risk
Subirà, Spain (2019)[38]	Multi-center RCT	1153 adult patients admitted to ICU and mechanically ventilated for ≥ 24h	30-min SBT with PSV 8 cmH_2O, PEEP 0 cmH_2O, FiO_2 unchanged from previous mechanical ventilation	120-min SBT with T-piece	Successful extubation, defined as remaining free of invasive mechanical ventilation 72 hours after the first SBT	Some concerns
Teixeira, Brazil (2015)[39]	Single-center RCT	160 adult patients admitted to ICU and mechanically ventilated ≥ 24h	• SBT with PSV 7 cmH_2O • SBT with PAV+, with adjusted support to a comfortable range (0.3-0.7 J/L)	SBT with T-piece with supplemental oxygen, adjusted to maintain SpO_2 at 92%	Outcomes: successful extubation and reintubation within 48h	High risk
Thille, France (2022)[3]	Multi-center RCT	983 adult patients admitted to ICU, mechanically ventilated for > 24h and at high-	1-hour SBT with PSV 8 cmH_2O, and FiO_2 ≤ 0.4, no PEEP. Reconnection before extubation if success of SBT	1-hour SBT with T-piece at a flow rate of up to 6 liters per minute, corresponding to FiO_2 ≤ 0.4. Reconnection	Number of ventilator free days, defined as total time alive and without invasive mechanical ventilation from the initial SBT through day 28	Some concerns

		risk of reintubation		before extubation if success of SBT		
Vats, India (2016)[40]	Single-center RCT	40 adult patients admitted to ICU and mechanically ventilated for > 48h	SBT with PSV 7 cmH_2O and deep breathing exercises	SBT with T-tube circuit and deep breathing exercises	Outcomes: successful extubation and reintubation	High risk
Wang, China, (2014)[41]	Single-center RCT	121 adult patients admitted to ICU and mechanically ventilated for > 48h	1-hour SBT with PSV 7 cmH_2O	Immediate extubation without SBT	Outcomes: successful extubation and reintubation	High risk
Hernández Martínez, Spain, (2024)[52]	Multi-center RCT	884 adult patients admitted to ICU, mechanically ventilated for > 24 h, diagnosed with hypoxemic respiratory failure, requiring $FiO_2 \geq 50\%$ and PEEP ≥ 10 cmH_2O for ≥ 8 h and judged at low or intermediate risk for extubation failure	30-min SBT with PSV 8 cmH_2O, PEEP 5 cmH_2O. Reconnection before extubation if success of SBT	30-min SBT with PSV 5 cmH_2O, PEEP 0 cmH_2O. Reconnection before extubation if success of SBT	Time to extubation, defined as time from randomization to extubation	Some concerns

The table shows the characteristics of the included studies, as reported by the authors.
Data are presented as frequencies, percentages and median [IQR] or mean ± SD, as appropriate.
ICU, intensive care unit; LOS, length of stay; MV, mechanical ventilation; RCT, randomized controlled trial; SBT, spontaneous breathing trial

FIGURE LEGENDS

Figure 1: PRISMA flow diagram

The diagram shows the process of inclusion and exclusion of records as per PRISMA statement.

Figure 2: Network plot for the primary outcome

The figure shows the network plot on the quantitative analysis conducted on the primary outcome. Each node corresponds to an intervention or comparison and the edges represent the direct comparisons between them. The size of the node is proportional to the number of patients allocated to the intervention, while the edge width is based on the number of studies directly comparing the two interventions.

Figure 3: SUCRA and forest plot for the primary outcome

The figure shows the SUCRA plot (panel a) and forest plot (panel b) showing the results of network meta-analysis for the primary outcome.

Figure 4: Forest plots showing the results of pairwise analyses for the primary outcome

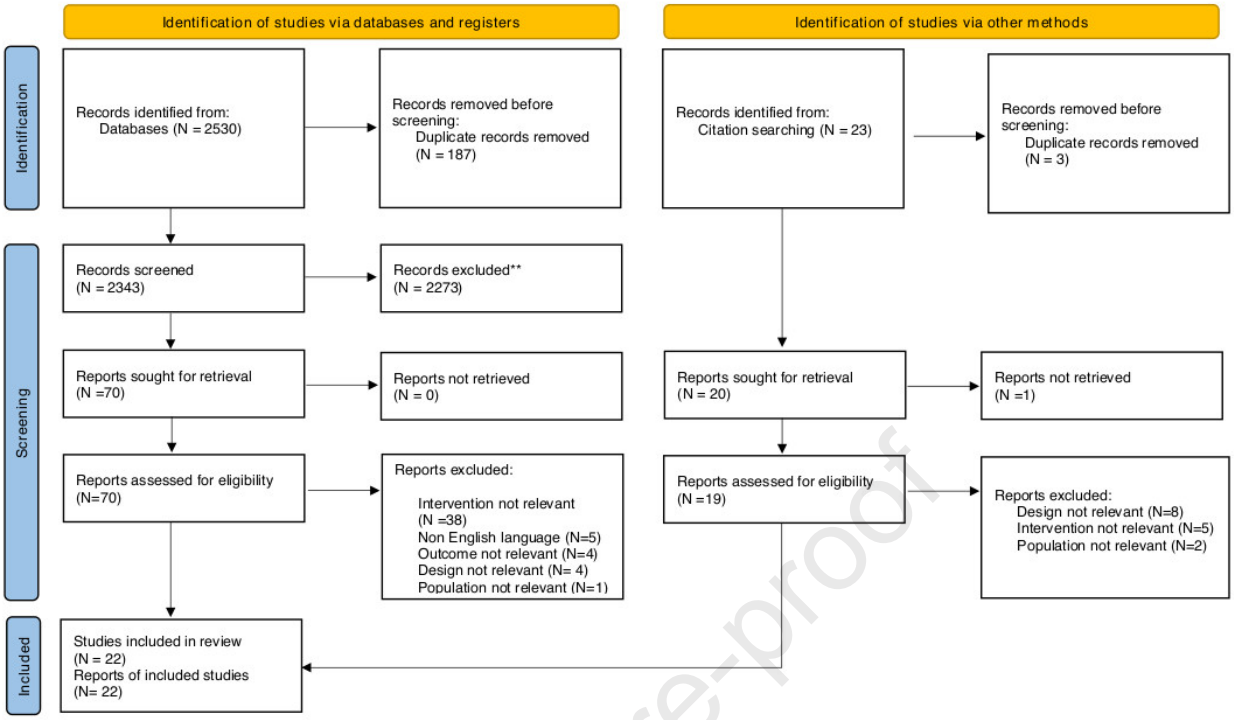
The figure shows the forest plots reporting the results of the pairwise comparisons between HFO and T-tube (panel a), HFO and PSV-PEEP (panel b) and HFO and PSV-ZEEP (panel c).

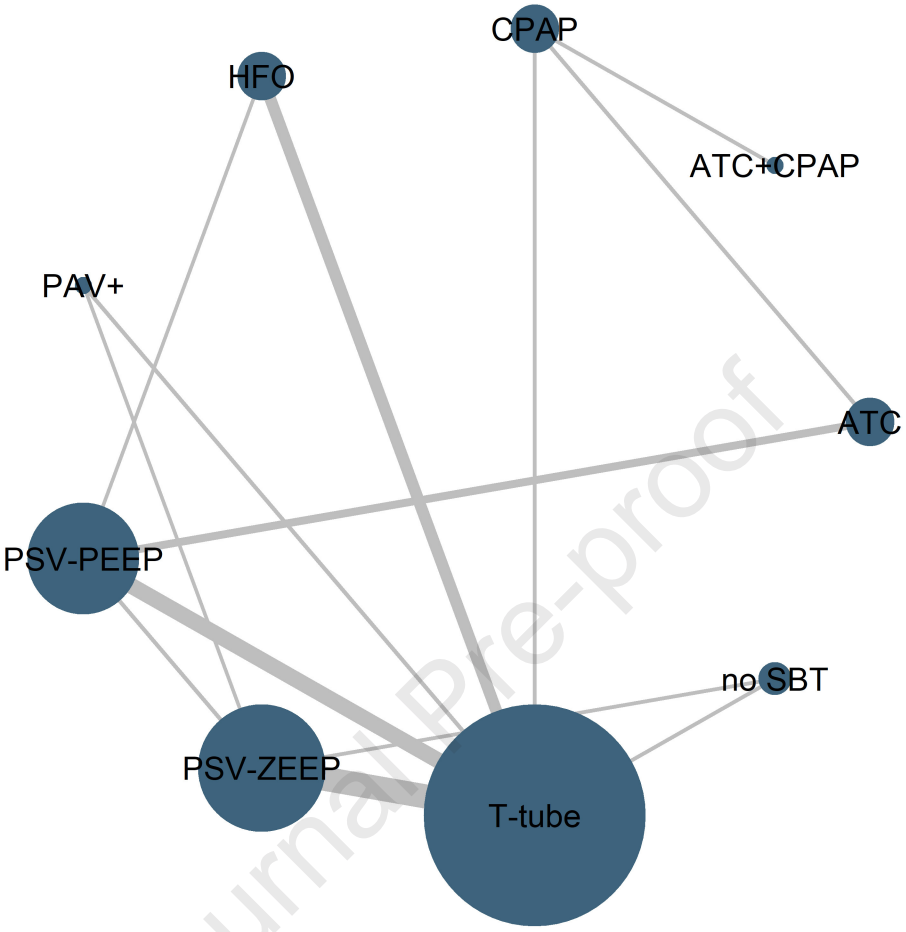
Take-Home Point pullout

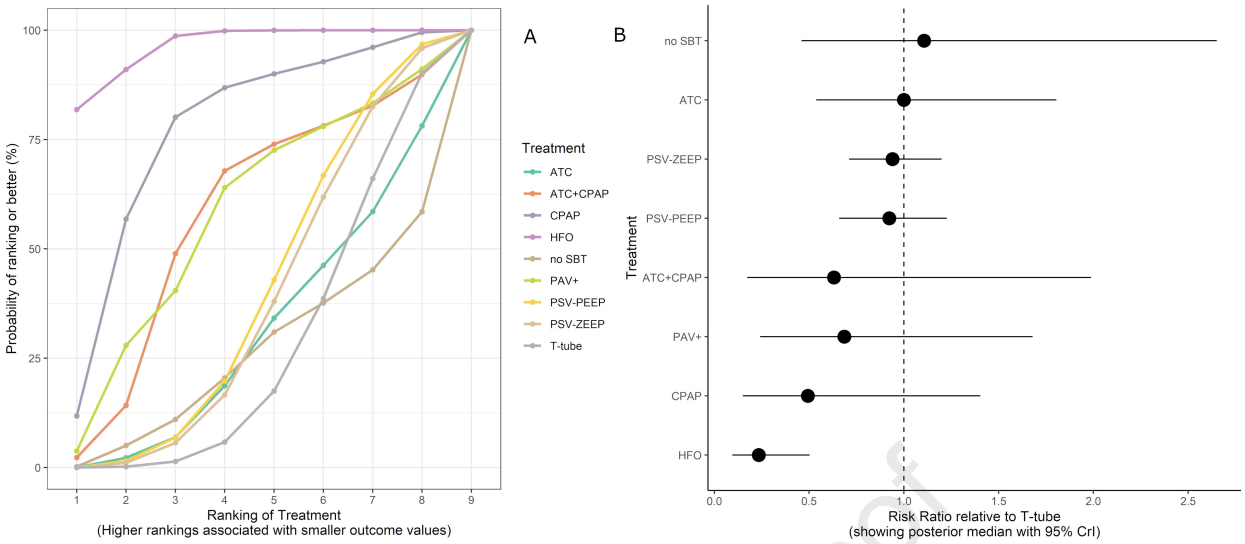
- Research question: Are different methods of conducting SBT in critically ill patients associated with different risk of reintubation?
- Results: The network meta-analysis showed that the only intervention with a statistically lower risk of reintubation compared to T-tube was high flow oxygen (HFO) (RR 0.23, CrI 0.09 to 0.51, moderate quality evidence). HFO was associated with the

highest probability of being the best intervention for reducing the risk of early reintubation (81.86%, SUCRA 96.42).

- Interpretation: Further high-quality trials should be performed to confirm this result and to evaluate specific subgroups of patients or patient clusterization (e.g. based on post-extubation support). Physiological studies should also explore the mechanisms behind the estimated benefit of applying high flow oxygen through an endotracheal tube during a spontaneous breathing trial.







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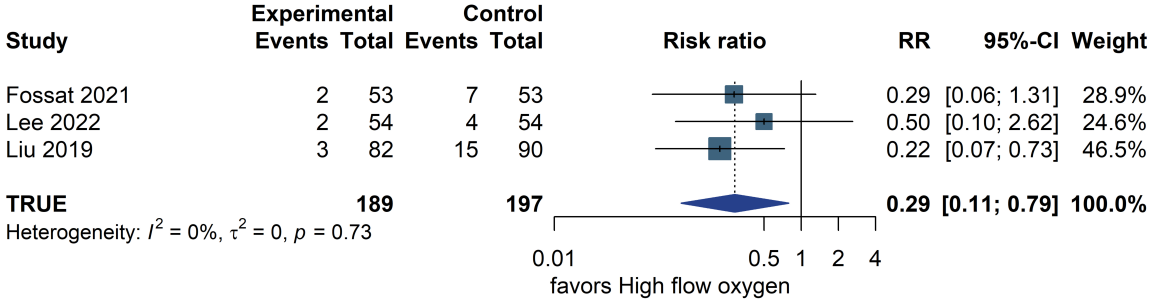

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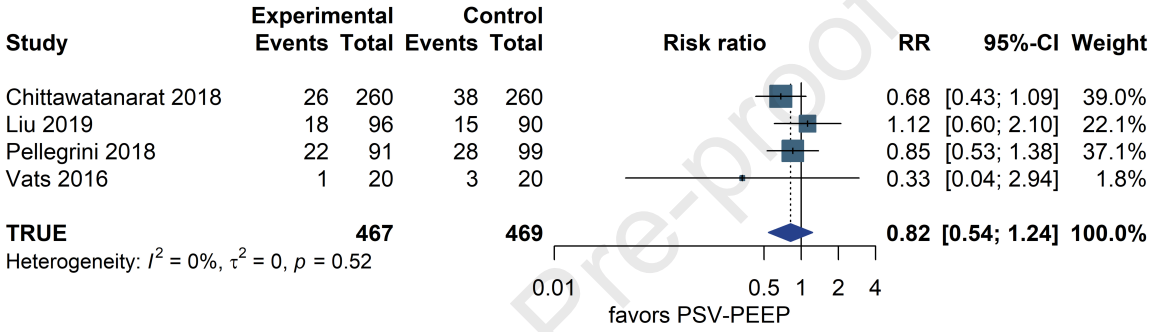

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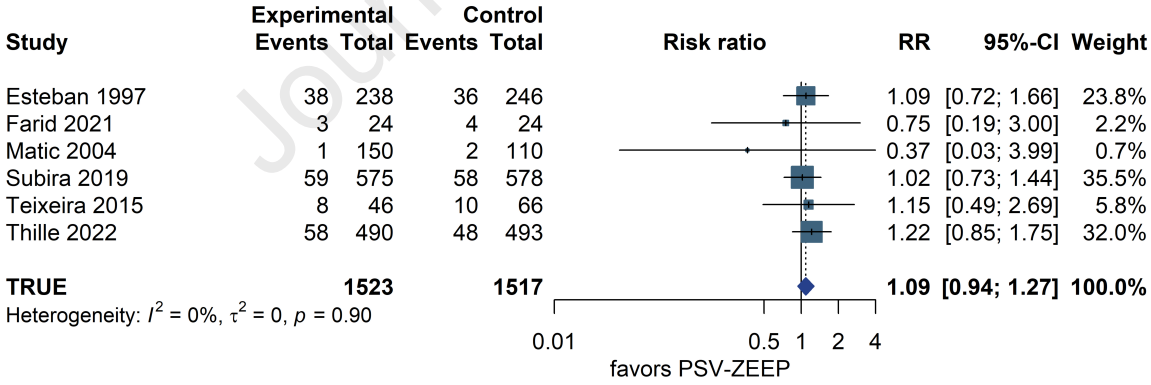


e-Appendix 1 to:

Association between spontaneous breathing trial methods and reintubation:

A systematic review and network meta-analysis of randomized controlled trials

LIST OF CONTENTS

PRISMA NMA Checklist of Items to Include When Reporting A Systematic Review Involving a Network Meta-analysis

Section/Topic	Item #	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review *incorporating a network meta-analysis (or related form of meta-analysis).*	Title page
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: **Background:** main objectives **Methods:** data sources; study eligibility criteria, participants, and interventions; study appraisal; and *synthesis methods, such as network meta-analysis.* **Results:** number of studies and participants identified; summary estimates with corresponding confidence/credible intervals; *treatment rankings may also be discussed. Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyses for brevity.* **Discussion/Conclusions:** limitations; conclusions and implications of findings. **Other:** primary source of funding; systematic review registration number with registry name.	1-2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known, *including mention of why a network meta-analysis has been conducted.*	2
Objectives	4	Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists and if and where it can be accessed (e.g., Web address); and, if available, provide registration information, including registration number.	3
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. *Clearly describe eligible treatments included in the treatment network, and note whether any have been clustered or merged into the same node (with justification).*	3-4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	3
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	e-Appendix 2

Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable,	3-4

		included in the meta-analysis).	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4
Geometry of the network	**S1**	Describe methods used to explore the geometry of the treatment network under study and potential biases related to it. This should include how the evidence base has been graphically summarized for presentation, and what characteristics were compiled and used to describe the evidence base to readers.	5
Risk of bias within individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	4
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). *Also describe the use of additional summary measures assessed, such as treatment rankings and surface under the cumulative ranking curve (SUCRA) values, as well as modified approaches used to present summary findings from meta-analyses.*	5
Planned methods of analysis	14	Describe the methods of handling data and combining results of studies for each network meta-analysis. This should include, but not be limited to: • *Handling of multi-arm trials;* • *Selection of variance structure;* • *Selection of prior distributions in Bayesian analyses; and* • *Assessment of model fit.*	5-6
Assessment of Inconsistency	**S2**	Describe the statistical methods used to evaluate the agreement. of direct and indirect evidence in the treatment network(s) studied. Describe efforts taken to address its presence when found.	5-6
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	5-6
Additional analyses	16	Describe methods of additional analyses if done, indicating which were pre-specified. This may include, but not be limited to, the following: • Sensitivity or subgroup analyses; • Meta-regression analyses; • *Alternative formulations of the treatment network; and* • *Use of alternative prior distributions for Bayesian analyses (if applicable).*	5

RESULTS†			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6 and Figure 1
Presentation of network structure	**S3**	Provide a network graph of the included studies to enable visualization of the geometry of the treatment network.	Figure 2
Summary of network geometry	**S4**	Provide a brief overview of characteristics of the treatment network. This may include commentary on the abundance of trials and randomized patients for the different interventions and pairwise comparisons in the network, gaps of evidence in the treatment network, and potential biases reflected by the network structure.	7 and caption of Figure 2
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment.	e-Figure 1
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: 1) simple summary data for each intervention group, and 2) effect estimates and confidence intervals. *Modified approaches may be needed to deal with information from larger networks.*	e-Figure 2
Synthesis of results	21	Present results of each meta-analysis done, including confidence/credible intervals. *In larger networks, authors may focus on comparisons versus a particular comparator (e.g. placebo or standard care), with full findings presented in an appendix. League tables and forest plots may be considered to summarize pairwise comparisons.* If additional summary measures were explored (such as treatment rankings), these should also be presented.	7-9
Exploration for inconsistency	**S5**	Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency and inconsistency models, *P* values from statistical tests, or summary of inconsistency estimates from different parts of the treatment network.	8, e-Figure 3, e-Table 2
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies for the evidence base being studied.	8
Results of additional analyses	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression analyses, *alternative network geometries studied, alternative choice of prior distributions for Bayesian analyses*, and so forth).	9
DISCUSSION			
Summary of evidence	24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy-makers).	10-12
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias). *Comment on the validity of the assumptions, such as transitivity and consistency. Comment*	10-12

		on any concerns regarding network geometry (e.g., avoidance of certain comparisons).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	12
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. This should also include information regarding whether funding has been received from manufacturers of treatments in the network and/or whether some of the authors are content experts with professional conflicts of interest that could affect use of treatments in the network.	Title page

e-Appendix to:

Association between spontaneous breathing trial methods and reintubation in adult critically ill patients: A systematic review and network meta-analysis of randomized controlled trials

LIST OF CONTENTS

Search strategy

CINAHL

((spontaneous breathing trial OR t tube OR t-piece OR ventilation weaning) NOT (neonate OR neonatal OR premature OR preterm OR newborn OR infant OR child)) AND (controlled trial or randomized controlled trial)

CENTRAL

#1 MeSH descriptor: [Ventilator Weaning] explode all trees
#2 ("spontaneous breathing trial"):ti,ab,kw OR ("T-tube"):ti,ab,kw OR ("T-piece"):ti,ab,kw OR ("SBT"):ti,ab,kw
#3 ("CPAP"):ti,ab,kw OR ("continuous positive airway pressure"):ti,ab,kw OR ("continuous positive pressure ventilation"):ti,ab,kw
#4 MeSH descriptor: [Child] explode all trees
#5 (newborn):ti,ab,kw
#6 (neonate*):ti,ab,kw
#7 (#1 AND (#2 OR #3)) NOT (#4 OR #5 OR #6) in Trials (Word variations have been searched)

Pubmed
("Ventilator Weaning"[MeSH Terms] OR "ventilator weaning/methods"[MeSH Major Topic] OR "ventilator weaning/instrumentation"[MeSH Major Topic] OR (("spontaneous"[All Fields] OR "spontaneously"[All Fields]) AND ("breath"[All Fields] OR "breathe"[All Fields] OR "breathed"[All Fields] OR "breathes"[All Fields] OR "breathings"[All Fields] OR "breaths"[All Fields] OR "respiration"[MeSH Terms] OR "respiration"[All Fields] OR "breathing"[All Fields]) AND ("clinical trials as topic"[MeSH Terms] OR ("clinical"[All Fields] AND "trials"[All Fields] AND "topic"[All Fields]) OR "clinical trials as topic"[All Fields] OR "trial"[All Fields] OR "trial s"[All Fields] OR "trialed"[All Fields] OR "trialing"[All Fields] OR "trials"[All Fields])) OR "SBT"[All Fields] OR (("weaning"[MeSH Terms] OR "weaning"[All Fields] OR "weaned"[All Fields] OR "weanings"[All Fields] OR "weans"[All Fields]) AND ("clinical trials as topic"[MeSH Terms] OR ("clinical"[All Fields] AND "trials"[All Fields] AND "topic"[All Fields]) OR "clinical trials as topic"[All Fields] OR "trial"[All Fields] OR "trial s"[All Fields] OR "trialed"[All Fields] OR "trialing"[All Fields] OR "trials"[All Fields])) OR "T-piece"[All Fields])

Pubmed Medline

("Ventilator Weaning"[MeSH Terms] OR "ventilator weaning/methods"[MeSH Major Topic] OR "ventilator weaning/instrumentation"[MeSH Major Topic] OR (("spontaneous"[All Fields] OR "spontaneously"[All Fields]) AND ("breath"[All Fields] OR "breathe"[All Fields] OR "breathed"[All Fields] OR "breathes"[All Fields] OR "breathings"[All Fields] OR "breaths"[All Fields] OR "respiration"[MeSH Terms] OR "respiration"[All Fields] OR "breathing"[All Fields]) AND ("clinical trials as topic"[MeSH Terms] OR ("clinical"[All Fields] AND "trials"[All Fields] AND "topic"[All Fields]) OR "clinical trials as topic"[All Fields] OR "trial"[All Fields] OR "trial s"[All Fields] OR "trialed"[All Fields] OR "trialing"[All Fields] OR "trials"[All Fields])) OR "SBT"[All Fields] OR (("weaning"[MeSH Terms] OR "weaning"[All Fields] OR "weaned"[All Fields] OR "weanings"[All Fields] OR "weans"[All Fields]) AND ("clinical trials as topic"[MeSH Terms] OR ("clinical"[All Fields] AND "trials"[All Fields] AND "topic"[All Fields])

OR "clinical trials as topic"[All Fields] OR "trial"[All Fields] OR "trial s"[All Fields] OR "trialed"[All Fields] OR "trialing"[All Fields] OR "trials"[All Fields])) OR "T-piece"[All Fields]) NOT (infant*[Title/Abstract] OR baby-led[Title/Abstract] OR newborn*[Title/Abstract] OR neonate*[Title/Abstract] OR (animal[Title/Abstract] OR animals[Title/Abstract] OR canine*[Title/Abstract] OR dog[Title/Abstract] OR dogs[Title/Abstract] OR feline[Title/Abstract] OR hamster*[Title/Abstract] OR lamb[Title/Abstract] OR lambs[Title/Abstract] OR mice[Title/Abstract] OR monkey[Title/Abstract] OR monkeys[Title/Abstract] OR mouse[Title/Abstract] OR murine[Title/Abstract] OR pig[Title/Abstract] OR pigs[Title/Abstract] OR piglet*[Title/Abstract] OR porcine[Title/Abstract] OR primate*[Title/Abstract] OR rabbit*[Title/Abstract] OR rats[Title/Abstract] OR rat[Title/Abstract] OR rodent*[Title/Abstract] OR sheep*[Title/Abstract] OR calf[Title/Abstract] OR calves[Title/Abstract] OR veterinar*[Title/Abstract]) NOT (human*[Title/Abstract] OR patient*[Title/Abstract])) NOT (preterm[Title/Abstract] OR infant*[Title/Abstract] OR baby-led[Title/Abstract] OR newborn*[Title/Abstract] OR neonate*[Title/Abstract]) AND (“randomized controlled trial”[Publication Type] OR “controlled clinical trial”[Publication Type]

e-Table 2. Studies excluded from full text with reasons for exclusion

N.	First Author	DOI / PMID	Year	Title	Reason for exclusion
1	Medrinal C.	10.1186/s13054-023-04597-1	2023	Transcutaneous electrical diaphragmatic stimulation in mechanically ventilated patients: a randomized study	Intervention not relevant
2	Vaschetto R.	10.1186/s13063-023-07560-1	2023	A pragmatic, open-label, multi-center, randomized controlled clinical trial on the rotational use of interfaces vs standard of care in patients treated with noninvasive positive pressure ventilation for acute hypercapnic respiratory failure: the ROTAtional-USE of interface STUDY (ROTA-USE STUDY)	Intervention not relevant
3	Zhang L	10.26355/eurrev_202307_32961	2023	Effectiveness of remimazolam besylate combined with alfentanil for fiberoptic bronchoscopy with preserved spontaneous breathing: a prospective, randomized, controlled clinical trial	Intervention not relevant
4	Zhang B	10.1111/crj.13618	2023	An investigation on the respiratory mechanics of mechanically ventilated patients during spontaneous breathing trials with enhanced low-level pressure support ventilation	Randomized crossover design
5	Lim HC	10.5811/westjem.2021.4.51108	2021	Randomised Controlled Trial Assessing Head Down Deep Breathing Method Versus	Intervention not relevant

				Modified Valsalva Manoeuvre for Treatment of Supraventricular Tachycardia in the Emergency Department	
6	Thille AW	10.1164/rccm.202106-1452OC	2021	Beneficial Effects of Noninvasive Ventilation after Extubation in Obese or Overweight Patients: A Post Hoc Analysis of a Randomized Clinical Trial	Intervention not relevant
7	Thille AW	10.1186/s13054-021-03621-6	2021	Non-invasive ventilation versus high-flow nasal oxygen for postextubation respiratory failure in ICU: a post-hoc analysis of a randomized clinical trial	Intervention not relevant
8	Hadfield DJ	10.1186/s13054-020-02923-5	2020	Neurally adjusted ventilatory assist versus pressure support ventilation: a randomized controlled feasibility trial performed in patients at risk of prolonged mechanical ventilation	Intervention not relevant
9	Thille AW	10.1001/jama.2019.14901	2019	Effect of Postextubation High-Flow Nasal Oxygen With Noninvasive Ventilation vs High-Flow Nasal Oxygen Alone on Reintubation Among Patients at High Risk of Extubation Failure: A Randomized Clinical Trial	Intervention not relevant
10	Perkins GD	10.3310/hta23480	2019	Protocolised non-invasive compared with invasive weaning from mechanical ventilation for adults in intensive care: the Breathe RCT	Intervention not relevant
11	Perkins GD	10.1001/jama.2018.13763	2018	Effect of Protocolized Weaning With Early Extubation to Noninvasive Ventilation vs Invasive Weaning on Time to Liberation From Mechanical Ventilation Among Patients With Respiratory Failure: The Breathe Randomized Clinical Trial	Intervention not relevant
12	Ferreira	10.1186/s12890-017-0484-5	2017	Neurally Adjusted Ventilatory Assist (NAVA) or Pressure Support Ventilation (PSV) during spontaneous breathing trials in critically ill patients: a crossover trial	Randomized crossover design
13	Frat JP	10.1097/CCM.0000000000002818	2018	Predictors of Intubation in Patients With Acute Hypoxemic Respiratory Failure Treated With a Noninvasive Oxygenation Strategy	Intervention not relevant

14	Celli P	10.1016/j.transproceed.2014.06.046	2014	Adaptive support ventilation versus synchronized intermittent mandatory ventilation with pressure support in weaning patients after orthotopic liver transplantation	Intervention not relevant
15	Burns KE	10.1186/1745-6215-10-81	2009	Wean Earlier and Automatically with New technology (the WEAN study): a protocol of a multicentre, pilot randomized controlled trial	Intervention not relevant
16	Dongelmans DA	10.1213/ane.0b013e318190c49f	2009	Weaning automation with adaptive support ventilation: a randomized controlled trial in cardiothoracic surgery patients	Intervention not relevant
17	Thille AW	10.1007/s00134-008-1121-9	2008	Reduction of patient-ventilator asynchrony by reducing tidal volume during pressure-support ventilation	Intervention not relevant
18	Esteban A	10.1056/NEJMoa032736	2004	Non-invasive positive-pressure ventilation for respiratory failure after extubation	Intervention not relevant
19	Girault C	PMID: 14743096	2003	VENISE: Non-invasive ventilation during mechanical ventilation weaning in chronic respiratory failure patients. A prospective randomised controlled and multicenter trial	Non English language
20	Girault C	10.1097/01.CCM.0000063284.92122.0E	2003	Mechanical effects of airway humidification devices in difficult to wean patients	Intervention not relevant
21	Reissman HK	10.1007/s001340000725	2000	Continuous positive airway pressure facilitates spontaneous breathing in weaning chronic obstructive pulmonary disease patients by improving breathing pattern and gas exchange	Randomized crossover design
22	Guerin C	10.1007/s001340051339	2000	Effect of PEEP on work of breathing in mechanically ventilated COPD patients	Intervention not relevant
23	Marelich GP	10.1378/chest.118.2.459	2000	Protocol weaning of mechanical ventilation in medical and surgical patients by respiratory care practitioners and nurses: effect on weaning time and incidence of ventilator-associated pneumonia	Intervention not relevant
24	Girault C	10.1164/ajrccm.160.1.9802120	2012	Noninvasive ventilation as a systematic extubation and	Intervention not relevant

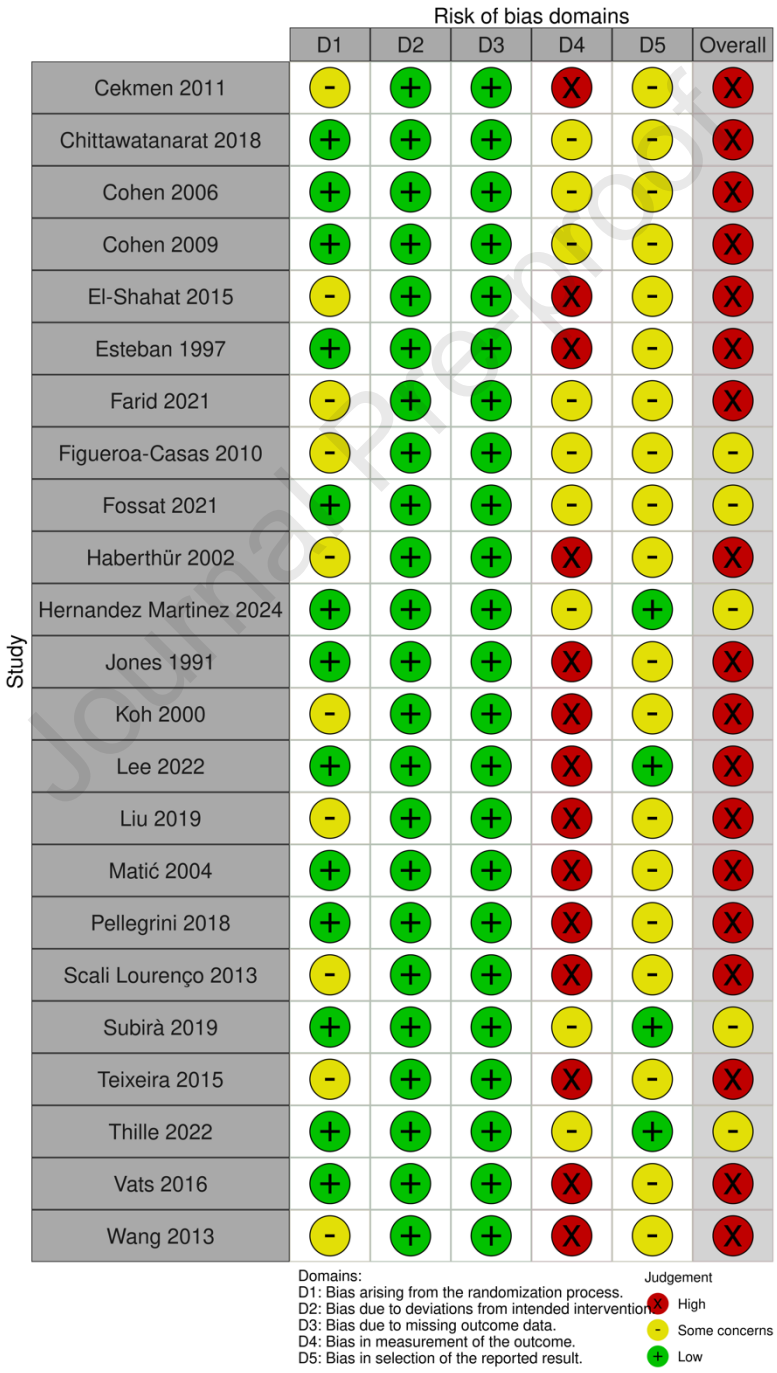
				weaning technique in acute-on-chronic respiratory failure: a prospective, randomized controlled study	
25	Esteban A	10.1056/NEJM199502093320601	1995	A comparison of four methods of weaning patients from mechanical ventilation. Spanish Lung Failure Collaborative Group	Intervention not relevant
26	Koller W	PMID: 6359947	1983	Weaning postoperative artificial respiration in cardiac surgery patients, CPAP versus ZEEP	Non English language
27	Feeley TW	10.1016/s0140-6736(75)90719-9	1975	Positive end-expiratory pressure in weaning patients from controlled ventilation. A prospective randomised trial	Intervention not relevant
28	Dos Santos	10.1016/j.jcrc.2010.05.032	2011	Energy expenditure during weaning from mechanical ventilation: is there any difference between pressure support and T-tube?	Randomized Crossover design
29	Mahul	10.1186/s13054-016-1457-4	2016	Spontaneous breathing trial and post-extubation work of breathing in morbidly obese critically ill patients.	Randomized Crossover design
30	Dadam	10.1016/j.chest.2021.02.064	2021	The Effect of Reconnection to Mechanical Ventilation for 1 Hour After Spontaneous Breathing Trial on Reintubation Among Patients Ventilated for More Than 12 Hours: A Randomized Clinical Trial.	Intervention not relevant
31	Brault	10.1186/s13054-022-04063-4	2022	The PROMIZING trial enrollment algorithm for early identification of patients ready for unassisted breathing.	Intervention not relevant
32	Jones DP	10.1378/chest.100.6.1655	1991	Positive end-expiratory pressure vs T-piece. Extubation after mechanical ventilation	Outcome not relevant
33	Duan J	10.1097/ta.0b013e318249a0d5	2012	Protocol-directed versus physician-directed weaning from noninvasive ventilation: The impact in chronic obstructive pulmonary disease patients.	Intervention not relevant
34	Molina-Saldarriaga FJ	10.1016/j.medin.2010.03.007	2010	Spontaneous breathing trial in chronic obstructive pulmonary disease: continuous positive airway pressure (CPAP) versus T-piece	Non English language
35	Yin C	10.3760/cma.j.issn.2095-	2018	Comparison of the effect of	Non English

		4352.2018.10.006		CPAP+PPS mode and CPAP+ASB mode in weaning on acute exacerbation of chronic obstructive pulmonary disease patients	language
36	Sassoon CS	10.1164/ajrccm/143.3.469	1991	Pressure-time product during continuous positive airway pressure, pressure support ventilation, and T-piece during weaning from mechanical ventilation	Intervention not relevant
37	Koksal GM	10.1186/cc2413	2004	The effects of different weaning modes on the endocrine stress response	Intervention not relevant
38	Bailey CR	10.1111/j.1365-2044.1995.tb06092.x	1995	The role of continuous positive airway pressure during weaning from mechanical ventilation in cardiac surgical patients	Outcome not relevant
39	Thille AW	10.1136/bmjopen-2020-042619	2020	T-piece versus pressure-support ventilation for spontaneous breathing trials before extubation in patients at high risk of reintubation: protocol for a multicentre, randomised controlled trial (TIP-EX)	Wrong design - Protocol
40	Guntzel Chiappa	10.1111/crj.12363	2017	Spontaneous breathing trial in T-tube negatively impact on autonomic modulation of heart rate compared with pressure support in critically ill patients	Outcome not relevant
41	Ma YM	PMID: 20450635	2010	The effect of spontaneous breathing trial on weaning from ventilators	Non English language
42	Fernandez MM	10.1007/s00134-017-4911-0	2017	Reconnection to mechanical ventilation for 1 h after a successful spontaneous breathing trial reduces reintubation in critically ill patients: a multicenter randomized controlled trial	Intervention not relevant
43	Guerin C.	10.1186/s13613-019-0611-y	2019	Low-pressure support vs automatic tube compensation during spontaneous breathing trial for weaning	Randomized crossover design
44	El Batanouny M.	10.1016/j.ejcdt.2017.07.002	2017	Use of automatic tube compensation (ATC) for weaning from mechanical ventilation in acute respiratory failure	Intervention not relevant
45	Teixeira C.	10.1590/s1806-37132012000300012	2012	Impact of a mechanical ventilation weaning protocol on the extubation failure rate in difficult-to-wean patients	Intervention not relevant

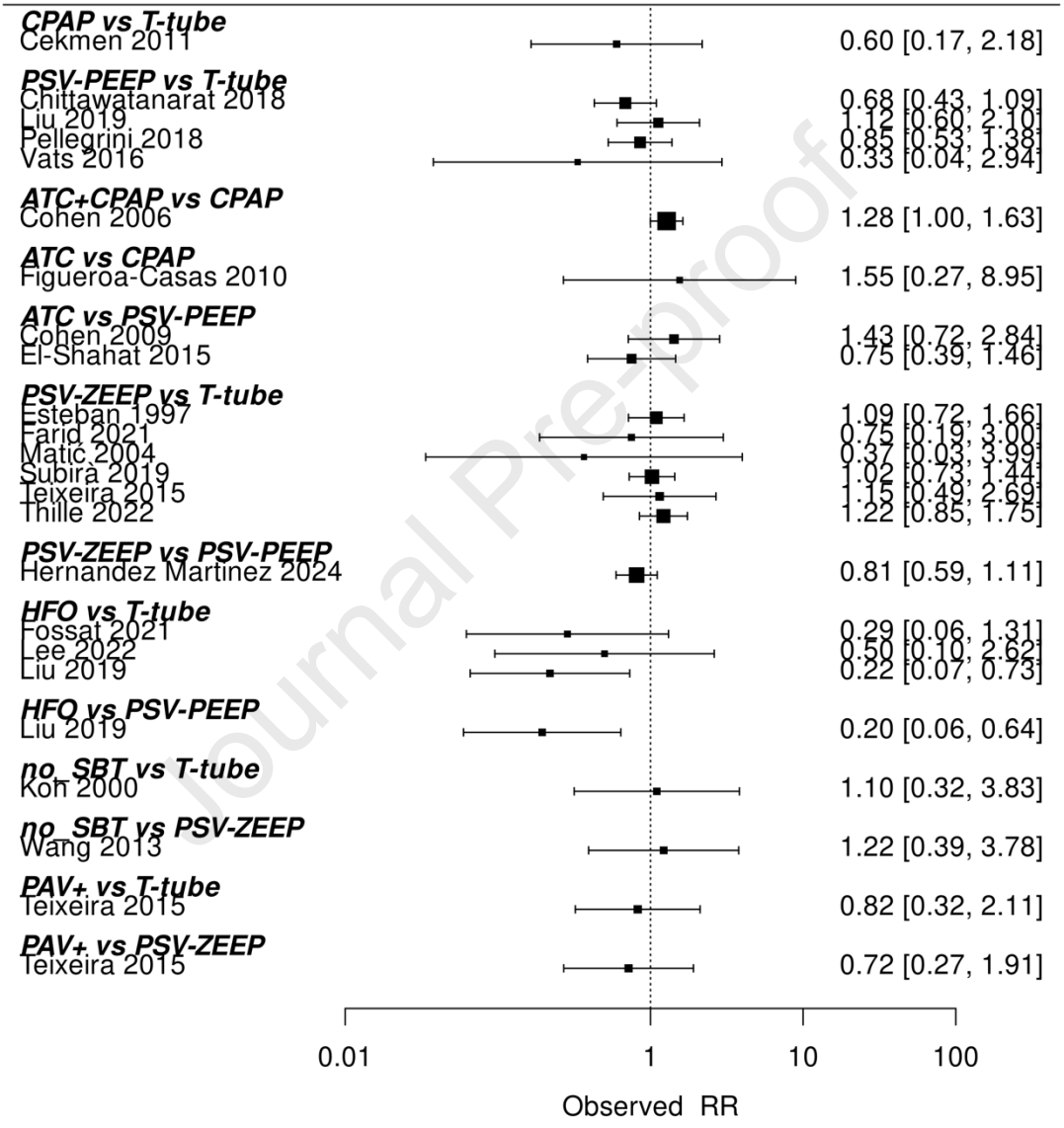
46	Raurich JM	PMID: 18655738	2008	Hypercapnia test as a predictor of success in spontaneous breathing trials and extubation	Intervention not relevant
47	Perren A	10.1007/s00134-002-1353-z	2022	Protocol-directed weaning from mechanical ventilation: clinical outcome in patients randomized for a 30-min or 120-min trial with pressure support ventilation	Wrong design
48	Tomlinson JR	10.1378/chest.96.2.348	1989	A prospective comparison of IMV and T-piece weaning from mechanical ventilation	Intervention not relevant
49	Perren A	10.1007/s00134-010-1984-4	2010	Patients' prediction of extubation success	Intervention not relevant
50	Kuhlen R	10.1017/S0265021503000024	2003	Breathing pattern and workload during automatic tube compensation, pressure support and T-piece trials in weaning patients	Intervention not relevant
51	Esteban A	10.1164/ajrccm.159.2.9803106	1999	Effect of spontaneous breathing trial duration on outcome of attempts to discontinue mechanical ventilation. Spanish Lung Failure Collaborative Group	Intervention not relevant
52	Alia I	10.1186/cc4996	2000	Weaning from mechanical ventilation	Intervention not relevant
53	Brochard L	10.1164/ajrccm.150.4.7921460	1994	Comparison of three methods of gradual withdrawal from ventilatory support during weaning from mechanical ventilation	Intervention not relevant
54	Scali Lourenço I.	10.5935/1678-9741.20130075	2013	Pressure support-ventilation versus spontaneous breathing with "T-Tube" for interrupting the ventilation after cardiac operations	Outcome not relevant
55	Chopin C	10.1007/BF01723368	1989	Carbon dioxide mandatory ventilation (CO2MV): a new method for weaning from mechanical ventilation. Description and comparative clinical study with I.M.V. and T. tube method in COPD patient	Intervention not relevant
56	Hoffman LA	PMID: 12526235	2003	Effect of tracheal gas insufflation during weaning from prolonged mechanical ventilation: a preliminary study	Intervention not relevant
57	Vitacca M	10.1164/ajrccm.164.2.2008160	2001	Comparison of two methods for weaning patients with chronic obstructive pulmonary disease requiring mechanical	Intervention not relevant

				ventilation for more than 15 days	
58	Schifelbain LM	10.1590/s1807-59322011000100019	2011	Echocardiographic evaluation during weaning from mechanical ventilation	Intervention not relevant
59	Duan J	10.1213/ANE.0b013e31825c7dba	2012	Dual-mode weaning strategy for difficult-weaning tracheotomy patients: a feasibility study	Population not relevant
60	Burns KEA	10.1097/CCM.0000000000003722	2019	Frequency of Screening for Weaning From Mechanical Ventilation: two Contemporaneous Proof-of-Principle Randomized Controlled Trials	Intervention not relevant
61	Rieder Mde	10.1590/s1807-59322009000500006	2009	Short-term effects of positive expiratory airway pressure in patients being weaned from mechanical ventilatioN	Intervention not relevant
62	El-beleidy ASE	10.1155/2013/871376	2013	Automatic Tube Compensation versus Pressure Support Ventilation and Extubation Outcome in Children: A Randomized Controlled Study	Population not relevant
63	Esteban A	10.1378/chest.106.4.1188	1994	Modes of mechanical ventilation and weaning: A national survey of Spanish hospitals	Randomized crossover design
64	El Batanouny M	10.1016/j.ejcdt.2017.07.002	2017	Use of automatic tube compensation (ATC) for weaning from mechanical ventilation in acute respiratory failure	Wrong design - Non Randomized Trial
65	Soo Jin Na	10.1186/s12931-022-01942-w	2022	Comparison between pressure support ventilation and T-piece in spontaneous breathing trials.	Wrong design - Non Randomized Trial
66	Magnet FS	10.1007/s00063-019-0599-y	2019	The spontaneous breathing trial is of low predictive value regarding spontaneous breathing ability in subjects with prolonged, unsuccessful weaning.	Wrong design - Non Randomized Trial
67	Zhang	10.1097/MAJ.0000000000000286	2014	Comparison of pressure support ventilation and T-piece in determining rapid shallow breathing index in spontaneous breathing trials	Population not relevant

e-Figure 1. Traffic lights plot of risk of bias assessment for the primary outcome
The figure shows the results of risk of bias assessment performed with Rob2 tool. Judgement of high, some concerns or low risk of bias were assigned according to Cochrane guidance.



e-Figure 2. Individual study results grouped by treatment comparisons
The figure shows the observed RR along with their CI for each included study, grouped by treatment comparisons



e-Table 2. GRADE assessment of certainty of evidence

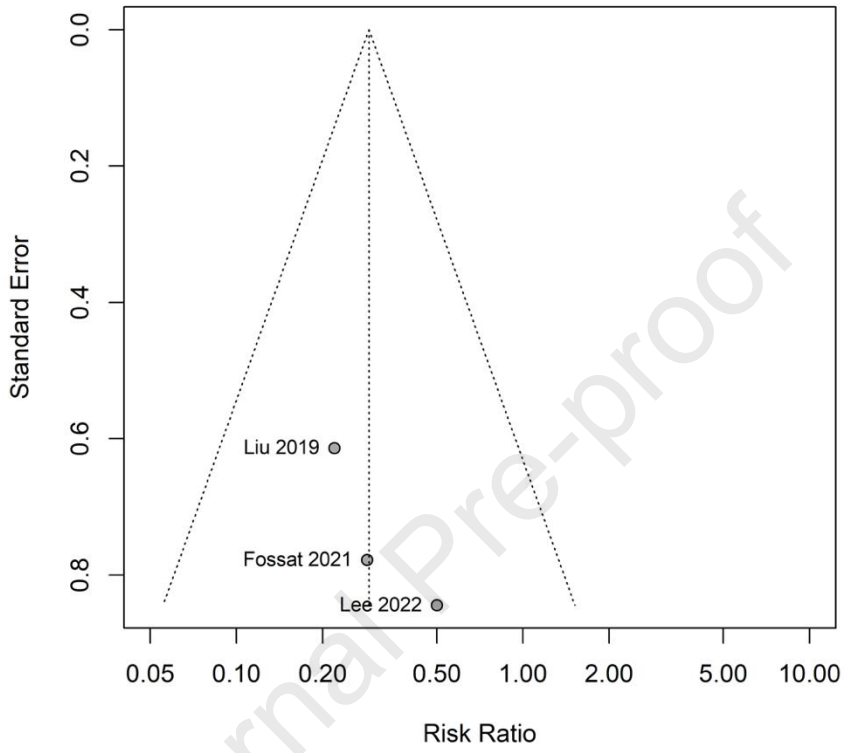
The table shows the results of GRADE assessment of certainty of evidence per each comparison, as performed using the CINeMA tool

Comparison	Number of studies	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating	Reason(s) for downgrading
ATC:CPAP	1	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
ATC:PSV-PEEP	2	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
ATC+CPAP:CPAP	1	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
CPAP:T-tube	1	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
HFO:PSV-PEEP	1	Major concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate	["Within-study bias"]
HFO:T-tube	3	Major concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate	["Within-study bias"]
PAV+:PSV-ZEEP	1	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
PAV+:T-tube	1	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
PSV-PEEP:PSV-ZEEP	1	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Within-study bias","Imprecision"]
PSV-PEEP:T-tube	4	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
PSV-ZEEP:T-tube	6	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	["Within-study bias","Imprecision"]
No SBT:PSV-ZEEP	1	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
No SBT:T-tube	1	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
ATC:ATC+CPAP	0	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
ATC:HFO	0	Major concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate	["Within-study bias"]
ATC:PAV+	0	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
ATC:PSV-ZEEP	0	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
ATC:T-tube	0	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
ATC:no_SBT	0	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
ATC+CPAP:HFO	0	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
ATC+CPAP:PAV+	0	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]

ATC+CPAP:PSV-PEEP	0	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
ATC+CPAP:PSV-ZEEP	0	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
ATC+CPAP:T-tube	0	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
ATC+CPAP:no_SBT	0	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
CPAP:HFO	0	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
CPAP:PAV+	0	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
CPAP:PSV-PEEP	0	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
CPAP:PSV-ZEEP	0	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
CPAP:No SBT	0	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
HFO:PAV+	0	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
HFO:PSV-ZEEP	0	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate	["Within-study bias"]
HFO:No SBT	0	Major concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate	["Within-study bias"]
PAV+:PSV-PEEP	0	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
No SBT:PAV+	0	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]
No SBT:PSV-PEEP	0	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	["Within-study bias","Imprecision"]

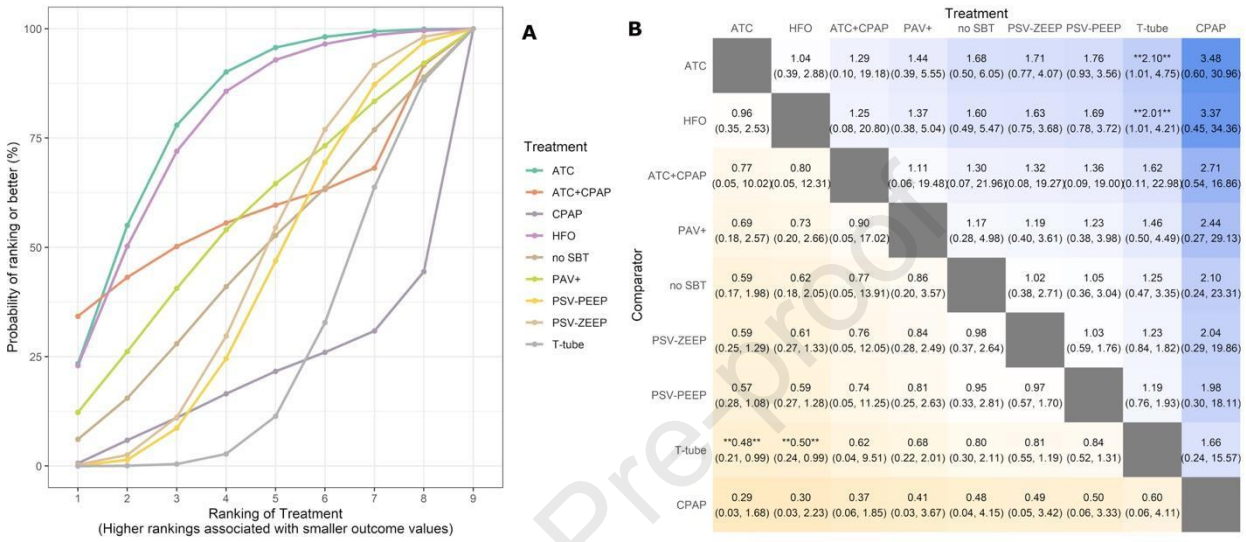
e-Figure 3. Funnel plot for the analysis of studies on HFO

The figure shows the funnel plot for the analysis of studies on HFO investigating visual signs of publication bias.



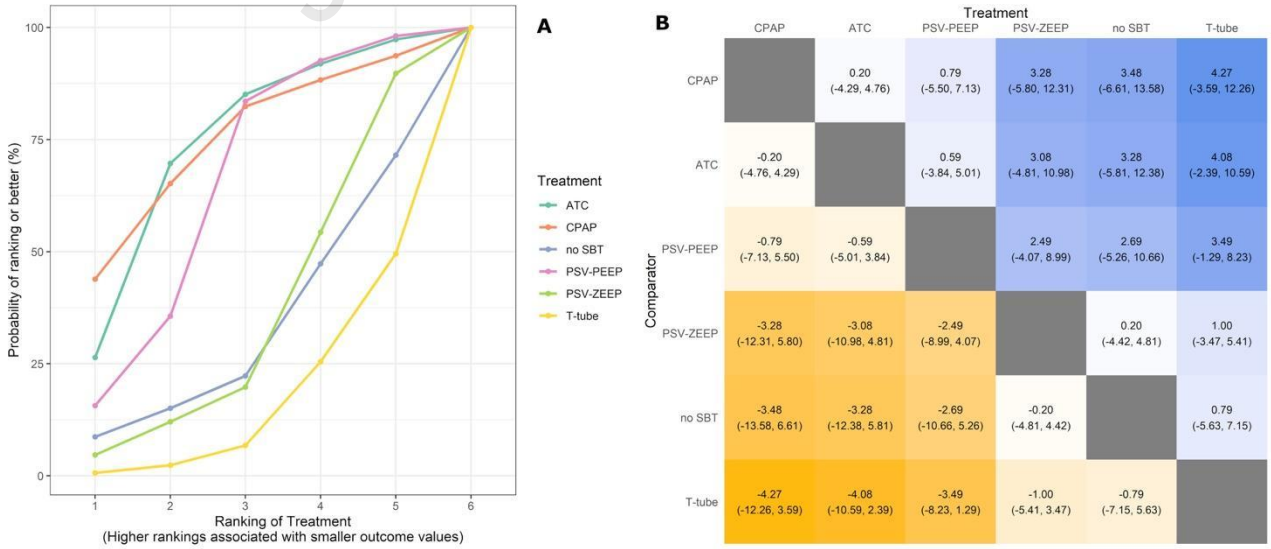
e-Figure 4. SUCRA and league plot for the outcome of extubation after first SBT

The figure shows the SUCRA plot (panel a) and league plot (panel b) showing the results of analysis on outcome of extubation after first SBT



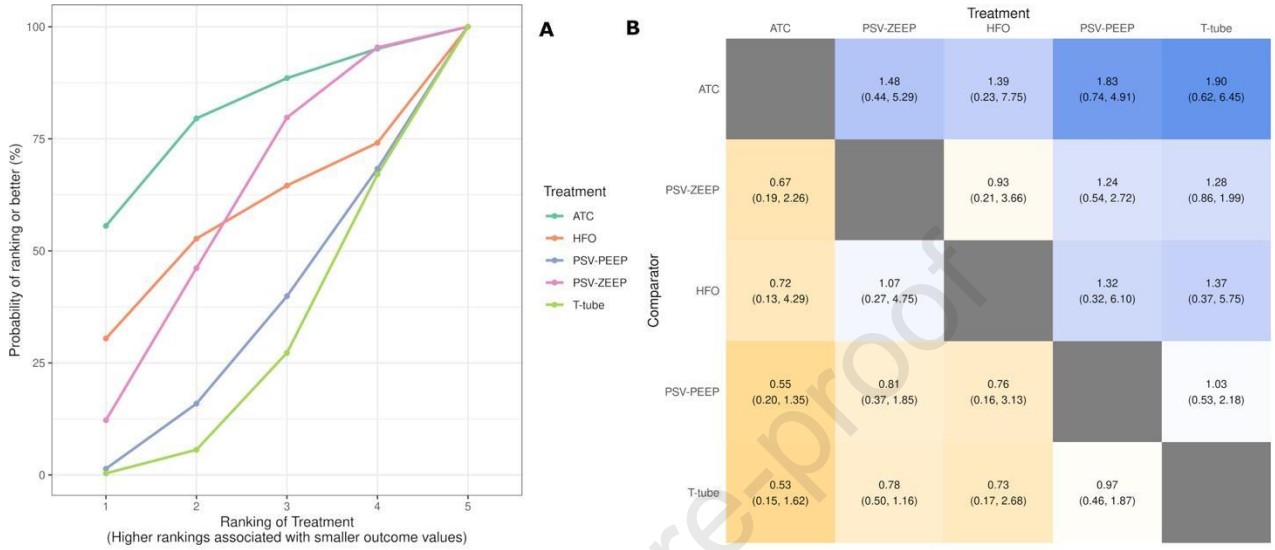
e-Figure 5. SUCRA and league plot for the outcome of overall duration of mechanical ventilation

The figure shows the SUCRA plot (panel a) and league plot (panel b) showing the results of analysis on outcome of overall duration of mechanical ventilation



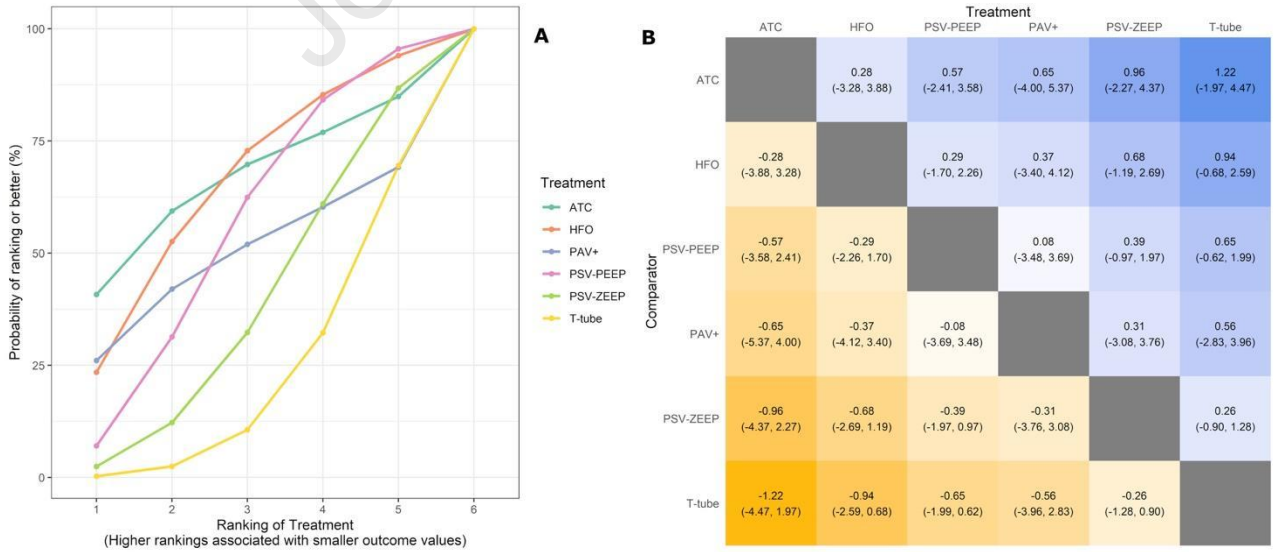
e-Figure 6. SUCRA and league plot for the subanalysis on outcome of ICU mortality excluding the PAV+ intervention

The figure shows the SUCRA plot (panel a) and league plot (panel b) showing the results of for the subanalysis on outcome of ICU mortality excluding the PAV+ intervention.



e-Figure 7. SUCRA and league plot for the outcome of ICU length of stay

The figure shows the SUCRA plot (panel a) and league plot (panel b) showing the results of analysis on outcome of ICU length of stay



e-Appendix 3 to:

Association between spontaneous breathing trial methods and reintubation:

A systematic review and network meta-analysis of randomized controlled trials

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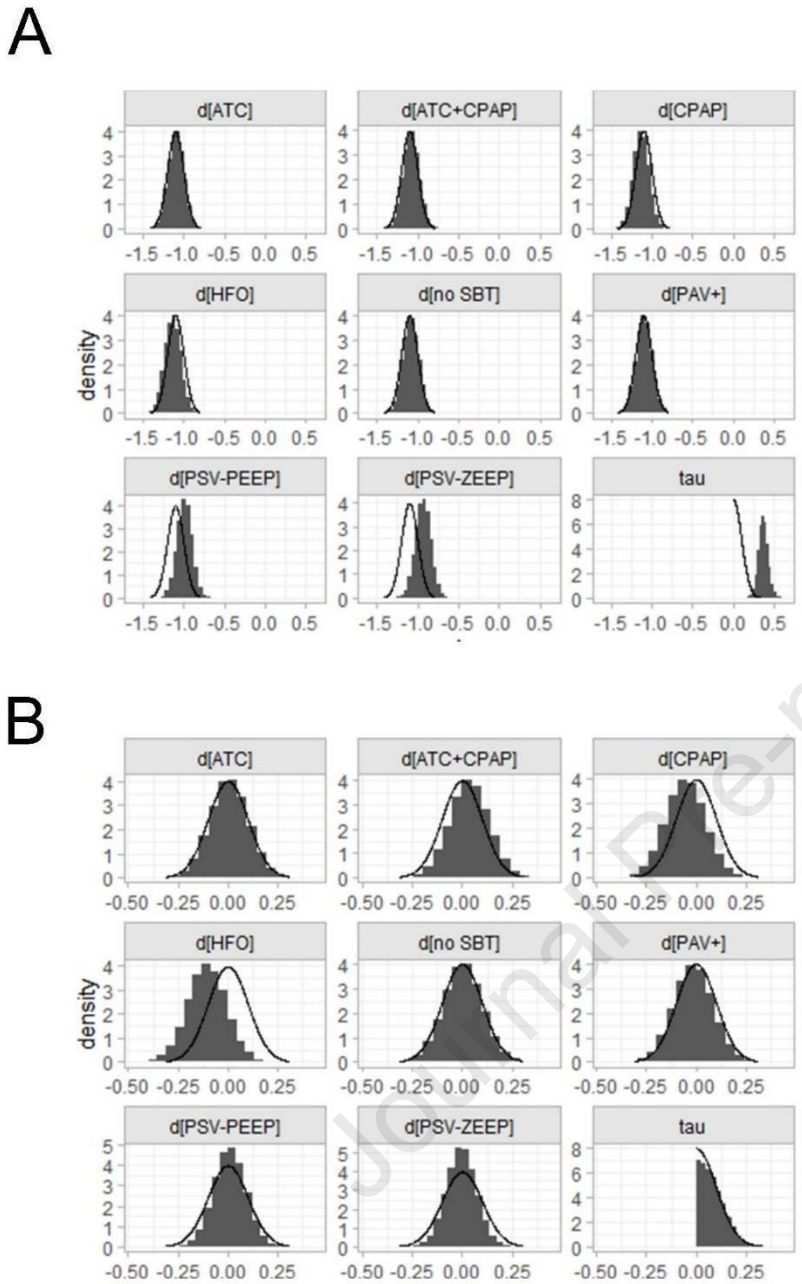
Results of the secondary analysis conducted under the JAGS models

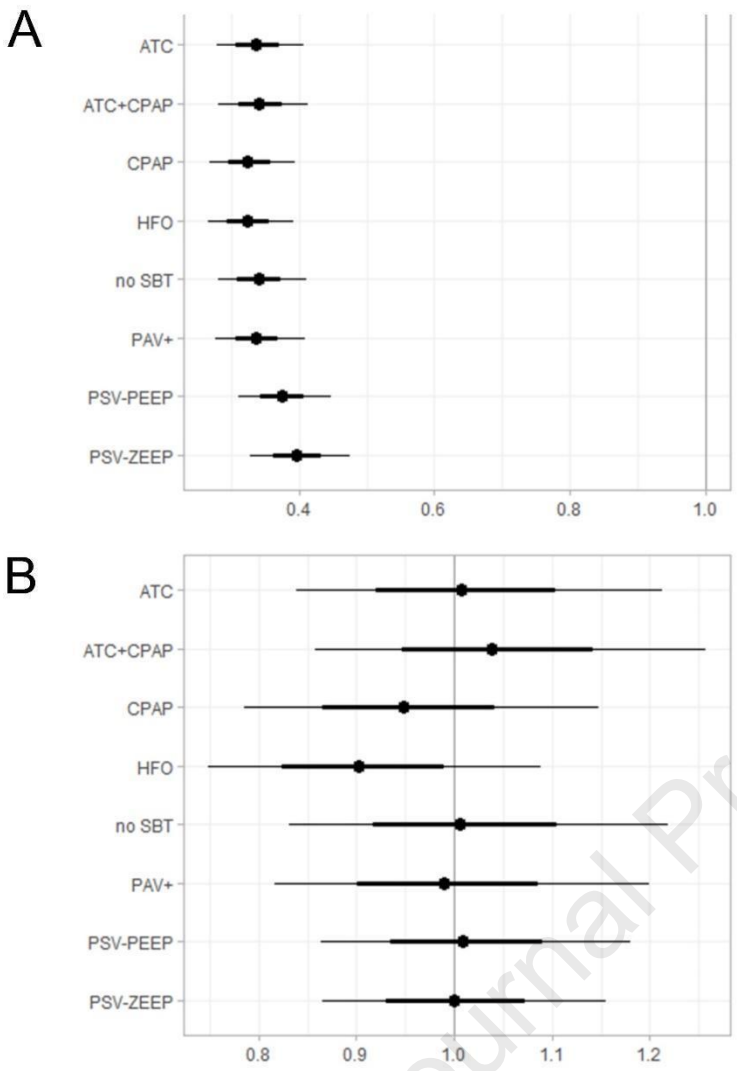
We conducted a sensitivity analysis of reintubation under different a priori distributions, simulating two scenarios using the R package multinma (Phillippo DM, Dias S, Ades AE, Belger M, Brnabic A, Schacht A, Saure D, Kadziola Z, Welton NJ (2020). “Multilevel Network Meta-Regression for population-adjusted treatment comparisons.” Journal of the Royal Statistical Society: Series A (Statistics in Society), 183(3), 1189-1210. doi:10.1111/rssa.12579; Phillippo DM (2023). *multinma: Bayesian Network Meta-Analysis of Individual and Aggregate Data*. doi:10.5281/zenodo.3904454, R package version 0.7.0, https://dmphillippo.github.io/multinma/). The first scenario was centered on a moderate effect size with a small standard deviation and heterogeneity. The second scenario was centered on a null difference with a small standard deviation and minimal heterogeneity. In the first scenario, all treatments had a statistically discernible effect in comparison to T-tube, while in the second one, none reached statistical evidence.



e-Figure 8. Prior and posterior distributions for the two models of the sensitivity analysis

This picture displays the posteriori results (solid histogram) for two distinct models, along with the a priori distribution (line). On the x-axis is represented the magnitude of the effect size, d, of the comparison between the treatment and the T-tube as the reference comparator measured in logOR, while on the y-axis is represented the probability density, in order to visualize the effect of the priors on the allocation of credibility on the different effect sizes. In the upper panel A, we plotted a first model associated with an expectation of a moderate-sized effect and characterized by the model with a normal prior for the intercept centered at 0 logOR with a standard deviation

of 5, a normal prior for the treatment effect size with a mean of -1.1 logOR and a standard deviation of 0.1, and a normal prior for the heterogeneity of the effect size centered at 0 logOR with a standard deviation of 0.1. In the lower panel B, we represented a second model associated with an expectation of a null effect and designed with a normal prior for the intercept centered at 0 logOR with a standard deviation of 5, a normal prior for the treatment effect size centered at 0 logOR with a standard deviation of 0.1, and a normal prior for the heterogeneity of the effect size with a mean of 0 logOR and a standard deviation of 0.1.



e-Figure 9. Forest plots of the two models designed for the sensitivity analysis with T-tube as the reference comparator.
Panel A model with informative prior centered at -1.1 log OR; panel B with informative prior centered at the null effect.

3. JAGS Models

Reintubation

```
# Random effects model for multi-arm trials

model {
  # *** PROGRAM STARTS ***
```

```
# Arm-based trials
for (i in 1:ns_a) {  # LOOP THROUGH STUDIES

  w[i,1] <- 0  # adjustment for multi-arm trials is zero for control arm
  delta[i,1] <- 0  # treatment effect is zero for control arm

  for (k in 1:na_a[i]) {  # LOOP THROUGH ARMS
    rhat[i,k] <- p[i,k] * n[i,k]  # expected value of the numerators
    dev_a[i,k] <- 2 * (
      r[i,k] * (log(r[i,k]) - log(rhat[i,k])) +
      (n[i,k] - r[i,k]) * (log(n[i,k] - r[i,k]) - log(n[i,k] - rhat[i,k]))
    )  # Deviance contribution

    # model for linear predictor
    r[i,k] ~ dbin(p[i,k], n[i,k])  # binomial likelihood
    log(p[i,k]) <- mu[i] + delta[i,k]
  }

  resdev_a[i] <- sum(dev_a[i, 1:na_a[i]])

  for (k in 2:na_a[i]) {  # LOOP THROUGH ARMS
    # trial-specific LOR distributions
    delta[i,k] ~ dnorm(md[i,k], taud[i,k])

    # mean of LOR distributions, with multi-arm trial correction
    md[i,k] <- d[t_a[i,k]] - d[t_a[i,1]] + sw[i,k]

    # precision of LOR distributions (with multi-arm trial correction)
    taud[i,k] <- pow(sigma2, -1) * 2 * (k-1) / k

    # adjustment, multi-arm RCTs
    w[i,k] <- (delta[i,k] - d[t_a[i,k]] + d[t_a[i,1]])

    # cumulative adjustment for multi-arm trials
    sw[i,k] <- sum(w[i, 1:(k-1)]) / (k-1)
  }
}

# Contrast-based trials
resdev_c <- 0

totresdev <- sum(resdev_a[], resdev_c[])
d[1] <- 0  # treatment effect is zero for reference treatment

for (i in 1:ns_a) {
```

```
    mu[i] <- log(p.base[i])  # priors for all trial baselines
    p.base[i] ~ dunif(0, 1)
  }

  for (k in 2:nt) {
    d[k] ~ dnorm(0, (1.50913739288213 * 15)^(-2))
  }

  sigma ~ dunif(0, 1.50913739288213)
  sigma2 <- sigma^2
  tau <- pow(sigma, -2)
}

# Treatment key
# 1: T-tube
# 2: ATC
# 3: ATC+CPAP
# 4: CPAP
# 5: HFO
# 6: no SBT
# 7: PAV+
# 8: PSV-PEEP
# 9: PSV-ZEEP
```

Extubation

```
# Random effects model for multi-arm trials

model {
  # *** PROGRAM STARTS ***

  # Arm-based trials
  for (i in 1:ns_a) {  # LOOP THROUGH STUDIES

    w[i,1] <- 0  # adjustment for multi-arm trials is zero for
control arm
    delta[i,1] <- 0  # treatment effect is zero for control arm

    for (k in 1:na_a[i]) {  # LOOP THROUGH ARMS
      rhat[i,k] <- p[i,k] * n[i,k]  # expected value of the
numerators
      dev_a[i,k] <- 2 * (
        r[i,k] * (log(r[i,k]) - log(rhat[i,k])) +
        (n[i,k] - r[i,k]) * (log(n[i,k] - r[i,k]) - log(n[i,k] -
rhat[i,k]))
      )  # Deviance contribution

      # model for linear predictor
      r[i,k] ~ dbin(p[i,k], n[i,k])  # binomial likelihood
      log(p[i,k]) <- mu[i] + delta[i,k]
    }

    resdev_a[i] <- sum(dev_a[i, 1:na_a[i]])

    for (k in 2:na_a[i]) {  # LOOP THROUGH ARMS
      # trial-specific LOR distributions
      delta[i,k] ~ dnorm(md[i,k], taud[i,k])

      # mean of LOR distributions, with multi-arm trial correction
      md[i,k] <- d[t_a[i,k]] - d[t_a[i,1]] + sw[i,k]

      # precision of LOR distributions (with multi-arm trial
correction)
      taud[i,k] <- pow(sigma2, -1) * 2 * (k-1) / k
```

```
      # adjustment, multi-arm RCTs
      w[i,k] <- (delta[i,k] - d[t_a[i,k]] + d[t_a[i,1]])

      # cumulative adjustment for multi-arm trials
      sw[i,k] <- sum(w[i, 1:(k-1)]) / (k-1)
    }
  }

  # Contrast-based trials
  resdev_c <- 0

  totresdev <- sum(resdev_a[], resdev_c[])
  d[1] <- 0  # treatment effect is zero for reference treatment

  for (i in 1:ns_a) {
    mu[i] <- log(p.base[i])  # priors for all trial baselines
    p.base[i] ~ dunif(0, 1)
  }

  for (k in 2:nt) {
    d[k] ~ dnorm(0, (2.53161293719395 * 15)^(-2))
  }

  sigma ~ dunif(0, 2.53161293719395)
  sigma2 <- sigma^2
  tau <- pow(sigma, -2)
}

# Treatment key
# 1: T-tube
# 2: ATC
# 3: ATC+CPAP
# 4: CPAP
# 5: HFO
# 6: no SBT
# 7: PAV+
# 8: PSV-PEEP
# 9: PSV-ZEEP
```

Intensive care unit length of stay

```
# Random effects model for multi-arm trials

model {
  # *** PROGRAM STARTS ***

  # Arm-based trials
  for (i in 1:ns_a) {  # LOOP THROUGH STUDIES

    w[i,1] <- 0  # adjustment for multi-arm trials is zero for control arm
    delta[i,1] <- 0  # treatment effect is zero for control arm

    for (k in 1:na_a[i]) {  # LOOP THROUGH ARMS
      prec[i,k] <- pow(se[i,k], -2)
      dev_a[i,k] <- (y[i,k] - theta_a[i,k]) * (y[i,k] - theta_a[i,k]) *
prec[i,k]  # Deviance contribution

      # model for linear predictor
      y[i,k] ~ dnorm(theta_a[i,k], prec[i,k])
      theta_a[i,k] <- mu[i] + delta[i,k]
    }

    resdev_a[i] <- sum(dev_a[i, 1:na_a[i]])

    for (k in 2:na_a[i]) {  # LOOP THROUGH ARMS
      # trial-specific LOR distributions
      delta[i,k] ~ dnorm(md[i,k], taud[i,k])

      # mean of LOR distributions, with multi-arm trial correction
      md[i,k] <- d[t_a[i,k]] - d[t_a[i,1]] + sw[i,k]

      # precision of LOR distributions (with multi-arm trial correction)
      taud[i,k] <- pow(sigma2, -1) * 2 * (k-1) / k

      # adjustment, multi-arm RCTs
      w[i,k] <- (delta[i,k] - d[t_a[i,k]] + d[t_a[i,1]])

      # cumulative adjustment for multi-arm trials
      sw[i,k] <- sum(w[i, 1:(k-1)]) / (k-1)
    }
  }

  # Contrast-based trials
  resdev_c <- 0

  totresdev <- sum(resdev_a[], resdev_c[])
  d[1] <- 0  # treatment effect is zero for reference treatment

  for (i in 1:ns_a) {
```

```
    mu[i] ~ dnorm(0, (2 * 15)^(-2))
  }

  for (k in 2:nt) {
    d[k] ~ dnorm(0, (2 * 15)^(-2))
  }

  sigma ~ dunif(0, 2)
  sigma2 <- sigma^2
  tau <- pow(sigma, -2)
}

# Treatment key
# 1: T-tube
# 2: ATC
# 3: HFO
# 4: PAV+
# 5: PSV-PEEP
# 6: PSV-ZEEP
```

Overall duration of mechanical ventilation

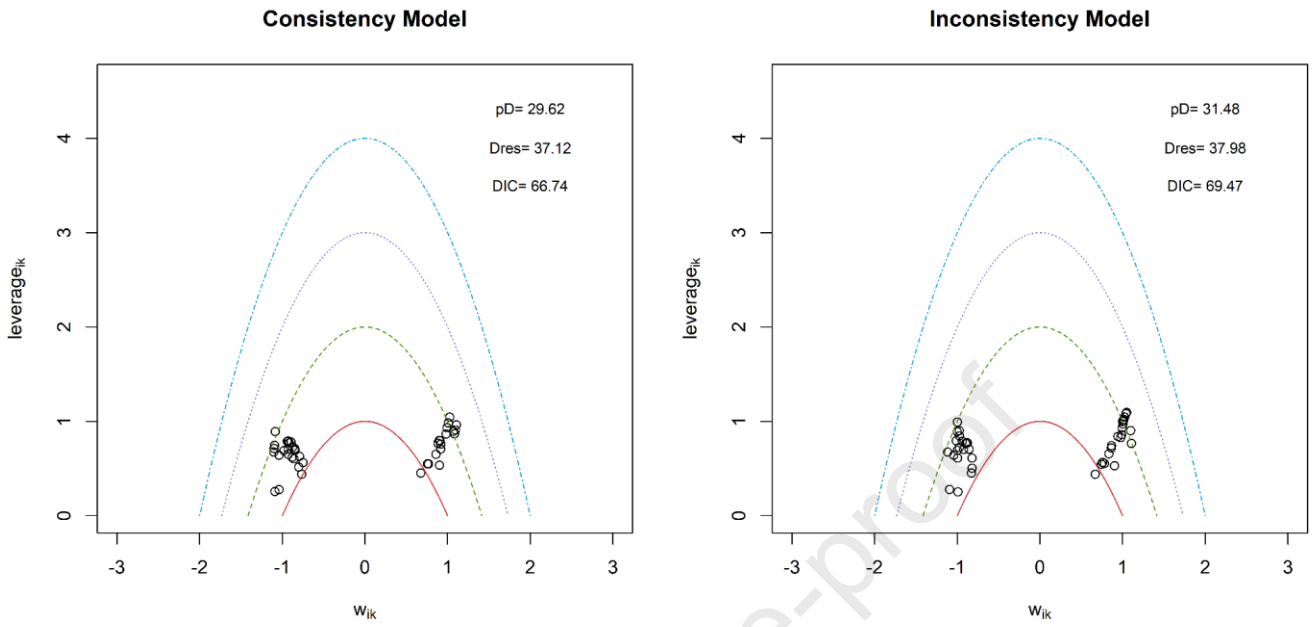
```
# Random effects model for multi-arm trials

model {
  # *** PROGRAM STARTS ***

  # Arm-based trials
  for (i in 1:ns_a) {  # LOOP THROUGH STUDIES

     w[i,1] <- 0  # adjustment for multi-arm trials is zero for control arm
     delta[i,1] <- 0  # treatment effect is zero for control arm

     for (k in 1:na_a[i]) {  # LOOP THROUGH ARMS
     prec[i,k] <- pow(se[i,k], -2)
     dev_a[i,k] <- (y[i,k] - theta_a[i,k]) * (y[i,k] - theta_a[i,k]) *
prec[i,k]  # Deviance contribution

     # model for linear predictor
     y[i,k] ~ dnorm(theta_a[i,k], prec[i,k])
     theta_a[i,k] <- mu[i] + delta[i,k]
     }

     resdev_a[i] <- sum(dev_a[i, 1:na_a[i]])

     for (k in 2:na_a[i]) {  # LOOP THROUGH ARMS
     # trial-specific LOR distributions
     delta[i,k] ~ dnorm(md[i,k], taud[i,k])

     # mean of LOR distributions, with multi-arm trial correction
     md[i,k] <- d[t_a[i,k]] - d[t_a[i,1]] + sw[i,k]

     # precision of LOR distributions (with multi-arm trial correction)
     taud[i,k] <- pow(sigma2, -1) * 2 * (k-1) / k

     # adjustment, multi-arm RCTs
     w[i,k] <- (delta[i,k] - d[t_a[i,k]] + d[t_a[i,1]])

     # cumulative adjustment for multi-arm trials
     sw[i,k] <- sum(w[i, 1:(k-1)]) / (k-1)
     }
  }

  # Contrast-based trials
  resdev_c <- 0

  totresdev <- sum(resdev_a[], resdev_c[])
  d[1] <- 0  # treatment effect is zero for reference treatment
```

```
  for (i in 1:ns_a) {
     mu[i] ~ dnorm(0, (3.51 * 15)^(-2))
  }

  for (k in 2:nt) {
     d[k] ~ dnorm(0, (3.51 * 15)^(-2))
  }

  sigma ~ dunif(0, 3.51)
  sigma2 <- sigma^2
  tau <- pow(sigma, -2)
}

# Treatment key
# 1: T-tube
# 2: ATC
# 3: CPAP
# 4: no SBT
# 5: PSV-PEEP
# 6: PSV-ZEEP
```

Mortality

```
# Random effects model for multi-arm trials

model {
  # *** PROGRAM STARTS ***

  # Arm-based trials
  for (i in 1:ns_a) {  # LOOP THROUGH STUDIES

     w[i,1] <- 0  # adjustment for multi-arm trials is zero for control arm
     delta[i,1] <- 0  # treatment effect is zero for control arm

     for (k in 1:na_a[i]) {  # LOOP THROUGH ARMS
     rhat[i,k] <- p[i,k] * n[i,k]  # expected value of the numerators
     dev_a[i,k] <- 2 * (
     r[i,k] * (log(r[i,k]) - log(rhat[i,k])) +
     (n[i,k] - r[i,k]) * (log(n[i,k] - r[i,k]) - log(n[i,k] - rhat[i,k]))
     )  # Deviance contribution

     # model for linear predictor
     r[i,k] ~ dbin(p[i,k], n[i,k])  # binomial likelihood
     log(p[i,k]) <- mu[i] + delta[i,k]
     }

     resdev_a[i] <- sum(dev_a[i, 1:na_a[i]])

     for (k in 2:na_a[i]) {  # LOOP THROUGH ARMS
     # trial-specific LOR distributions
     delta[i,k] ~ dnorm(md[i,k], taud[i,k])

     # mean of LOR distributions, with multi-arm trial correction
     md[i,k] <- d[t_a[i,k]] - d[t_a[i,1]] + sw[i,k]

     # precision of LOR distributions (with multi-arm trial correction)
     taud[i,k] <- pow(sigma2, -1) * 2 * (k-1) / k

     # adjustment, multi-arm RCTs
     w[i,k] <- (delta[i,k] - d[t_a[i,k]] + d[t_a[i,1]])

     # cumulative adjustment for multi-arm trials
     sw[i,k] <- sum(w[i, 1:(k-1)]) / (k-1)
     }
  }

  # Contrast-based trials
  resdev_c <- 0

  totresdev <- sum(resdev_a[], resdev_c[])
  d[1] <- 0  # treatment effect is zero for reference treatment
```

```
  for (i in 1:ns_a) {
      mu[i] <- log(p.base[i])  # priors for all trial baselines
      p.base[i] ~ dunif(0, 1)
  }

  for (k in 2:nt) {
      d[k] ~ dnorm(0, (2.08502295151803 * 15)^(-2))
  }

  sigma ~ dunif(0, 2.08502295151803)
  sigma2 <- sigma^2
  tau <- pow(sigma, -2)
}

# Treatment key
# 1: T-tube
# 2: ATC
# 3: HFO
# 4: PAV+
# 5: PSV-PEEP
# 6: PSV-ZEEP
```



e-Figure 10. Global inconsistency for the reintubation outcome

The figure shows the consistency (panel a) and inconsistency model (panel b) for the primary outcome.

Nodesplit analysis

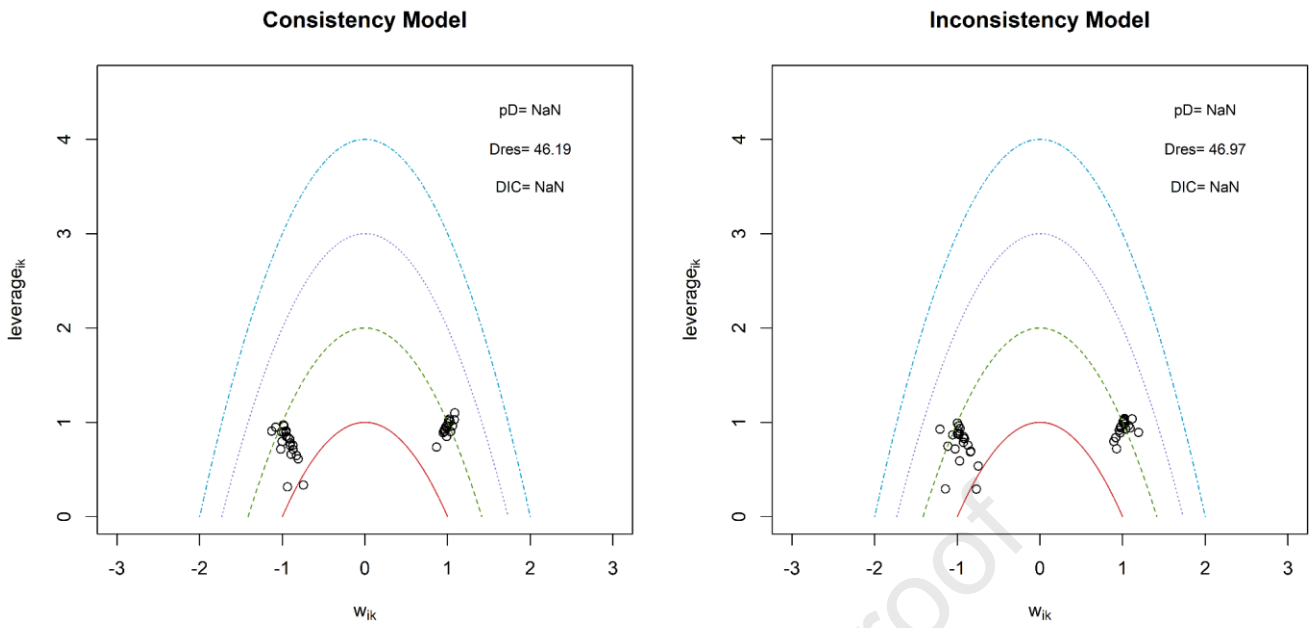
Reintubation within 72 hours

Comparison	k	nma	direct	indir.	RoR	z	p.value
ATC vs. ATC+CPAP	0	1.29	.	1.29	.	.	.
ATC vs. CPAP	1	1.64	1.55	1.70	0.91	-0.08	0.9376
ATC vs. HFO	0	3.65	.	3.65	.	.	.
ATC vs. no SBT	0	0.87	.	0.87	.	.	.
ATC vs. PAV+	0	1.31	.	1.31	.	.	.
ATC vs. PSV-PEEP	2	1.02	1.02	0.94	1.09	0.08	0.9376
ATC vs. PSV-ZEEP	0	1.02	.	1.02	.	.	.
ATC vs. T-tube	0	1.01	.	1.01	.	.	.
ATC+CPAP vs. CPAP	1	1.28	1.28	.	.	.	.
ATC+CPAP vs. HFO	0	2.84	.	2.84	.	.	.
ATC+CPAP vs. no SBT	0	0.68	.	0.68	.	.	.
ATC+CPAP vs. PAV+	0	1.02	.	1.02	.	.	.
ATC+CPAP vs. PSV-PEEP	0	0.79	.	0.79	.	.	.
ATC+CPAP vs. PSV-ZEEP	0	0.79	.	0.79	.	.	.
ATC+CPAP vs. T-tube	0	0.79	.	0.79	.	.	.
CPAP vs. HFO	0	2.23	.	2.23	.	.	.
CPAP vs. no SBT	0	0.53	.	0.53	.	.	.
CPAP vs. PAV+	0	0.80	.	0.80	.	.	.
CPAP vs. PSV-PEEP	0	0.62	.	0.62	.	.	.

CPAP vs. PSV-ZEEP	0	0.62	.	0.62	.	.	.
CPAP vs. T-tube	1	0.62	0.60	0.66	0.91	-0.08	0.9376
HFO vs. no SBT	0	0.24	.	0.24	.	.	.
HFO vs. PAV+	0	0.36	.	0.36	.	.	.
HFO vs. PSV-PEEP	1	0.28	0.20	0.38	0.51	-0.80	0.4257
HFO vs. PSV-ZEEP	0	0.28	.	0.28	.	.	.
HFO vs. T-tube	3	0.28	0.29	.	.	.	.
no SBT vs. PAV+	0	1.50	.	1.50	.	.	.
no SBT vs. PSV-PEEP	0	1.17	.	1.17	.	.	.
no SBT vs. PSV-ZEEP	1	1.17	1.22	1.11	1.10	0.11	0.9094
no SBT vs. T-tube	1	1.16	1.10	1.21	0.91	-0.11	0.9094
PAV+ vs. PSV-PEEP	0	0.78	.	0.78	.	.	.
PAV+ vs. PSV-ZEEP	1	0.78	0.72	.	.	.	.
PAV+ vs. T-tube	1	0.77	0.82	.	.	.	.
PSV-PEEP vs. PSV-ZEEP	1	1.00	1.23	0.76	1.61	1.99	0.0463
PSV-PEEP vs. T-tube	4	0.99	0.82	1.33	0.62	-2.01	0.0440
PSV-ZEEP vs. T-tube	6	0.99	1.09	0.69	1.59	1.98	0.0480

Legend: comparison - Treatment comparison k - Number of studies providing direct evidence nma - Estimated treatment effect (RR) in network meta-analysis direct - Estimated treatment effect (RR) derived from direct evidence indir. - Estimated treatment effect (RR) derived from indirect evidence RoR - Ratio of Ratios (direct versus indirect) z - z-value of test for disagreement (direct versus indirect) p-value - p-value of test for disagreement (direct versus indirect)

e-Table 3. Nodesplit analysis for the reintubation outcome



e- Figure 11. Global inconsistency for the extubation outcome

Nodesplit analysis

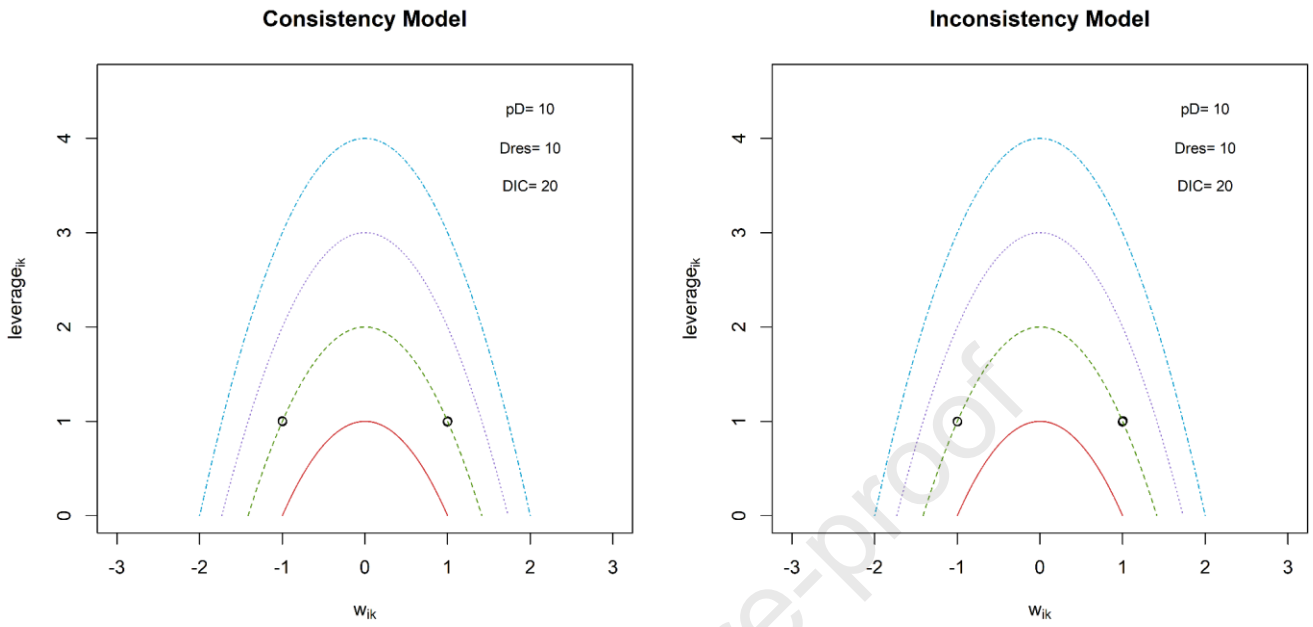
Extubation after successful SBT

Comparison	k	nma	direct	indir.	RoR	z	p.value
ATC vs. ATC+CPAP	0	0.50	.	0.50	.	.	.
ATC vs. CPAP	1	0.16	0.08	0.54	0.15	-0.74	0.4603
ATC vs. HFO	0	0.94	.	0.94	.	.	.
ATC vs. no_SBT	0	0.64	.	0.64	.	.	.
ATC vs. PAV+	0	0.70	.	0.70	.	.	.
ATC vs. PSV-PEEP	3	0.57	0.59	0.09	6.59	0.72	0.4702
ATC vs. PSV-ZEEP	0	0.61	.	0.61	.	.	.
ATC vs. T-tube	1	0.51	0.48	0.54	0.88	-0.15	0.8820
ATC+CPAP vs. CPAP	1	0.31	0.31	.	.	.	.
ATC+CPAP vs. HFO	0	1.87	.	1.87	.	.	.
ATC+CPAP vs. no_SBT	0	1.28	.	1.28	.	.	.
ATC+CPAP vs. PAV+	0	1.39	.	1.39	.	.	.
ATC+CPAP vs. PSV-PEEP	0	1.15	.	1.15	.	.	.
ATC+CPAP vs. PSV-ZEEP	0	1.21	.	1.21	.	.	.
ATC+CPAP vs. T-tube	0	1.03	.	1.03	.	.	.
CPAP vs. HFO	0	5.97	.	5.97	.	.	.
CPAP vs. no_SBT	0	4.06	.	4.06	.	.	.
CPAP vs. PAV+	0	4.44	.	4.44	.	.	.
CPAP vs. PSV-PEEP	0	3.65	.	3.65	.	.	.

CPAP vs. PSV-ZEEP	0	3.87	.	3.87	.	.	.
CPAP vs. T-tube	1	3.28	1.00	6.78	0.15	-0.74	0.4603
HFO vs. no_SBT	0	0.68	.	0.68	.	.	.
HFO vs. PAV+	0	0.74	.	0.74	.	.	.
HFO vs. PSV-PEEP	1	0.61	0.51	0.77	0.66	-0.50	0.6202
HFO vs. PSV-ZEEP	0	0.65	.	0.65	.	.	.
HFO vs. T-tube	3	0.55	0.56	.	.	.	.
no_SBT vs. PAV+	0	1.09	.	1.09	.	.	.
no_SBT vs. PSV-PEEP	0	0.90	.	0.90	.	.	.
no_SBT vs. PSV-ZEEP	1	0.95	1.20	0.79	1.52	0.41	0.6789
no_SBT vs. T-tube	1	0.81	0.68	1.04	0.66	-0.41	0.6789
PAV+ vs. PSV-PEEP	0	0.82	.	0.82	.	.	.
PAV+ vs. PSV-ZEEP	1	0.87	0.69	.	.	.	.
PAV+ vs. T-tube	1	0.74	0.93	.	.	.	.
PSV-PEEP vs. PSV-ZEEP	1	1.06	0.47	1.60	0.29	-2.14	0.0324
PSV-PEEP vs. T-tube	5	0.90	1.12	0.34	3.30	3.40	0.0007
PSV-ZEEP vs. T-tube	7	0.85	0.75	1.72	0.44	-1.73	0.0838

Legend: comparison - Treatment comparison k - Number of studies providing direct evidence nma - Estimated treatment effect (RR) in network meta-analysis direct - Estimated treatment effect (RR) derived from direct evidence indir. - Estimated treatment effect (RR) derived from indirect evidence RoR - Ratio of Ratios (direct versus indirect) z - z-value of test for disagreement (direct versus indirect) p-value - p-value of test for disagreement (direct versus indirect)

e-Table 4. Nodesplit analysis for the extubation outcome



e- Figure 12. Global inconsistency for the overall duration of mechanical ventilation outcome

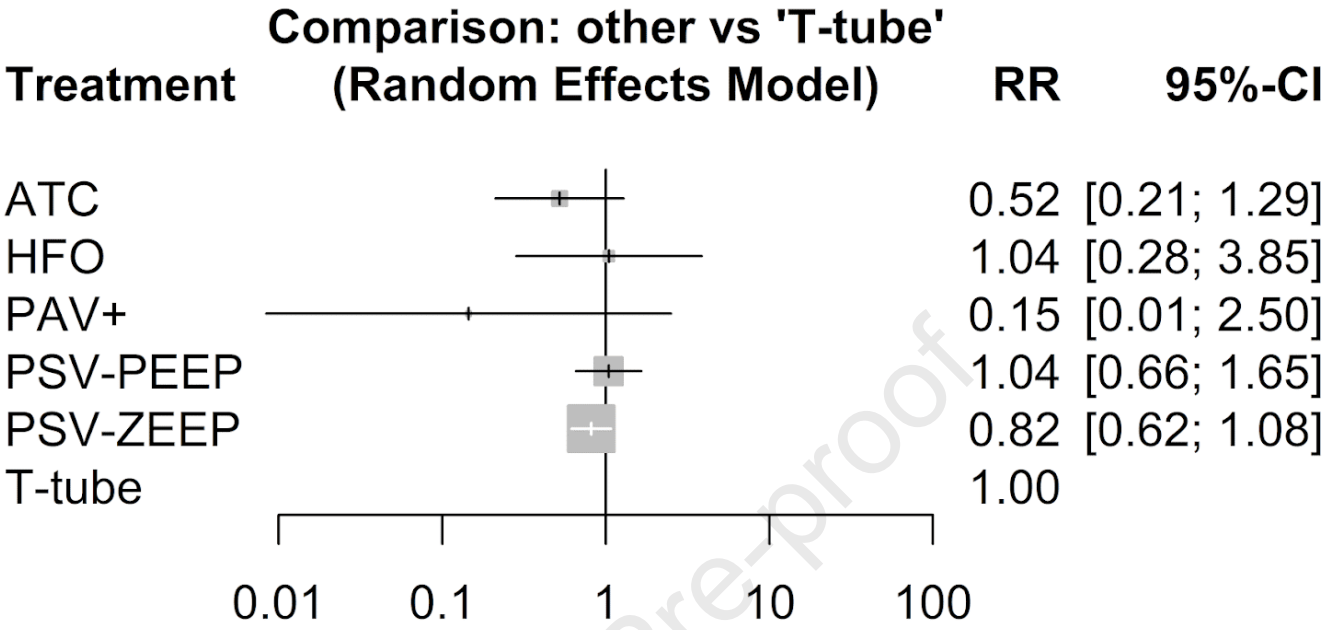
Nodesplit analysis

Duration of mechanical ventilation

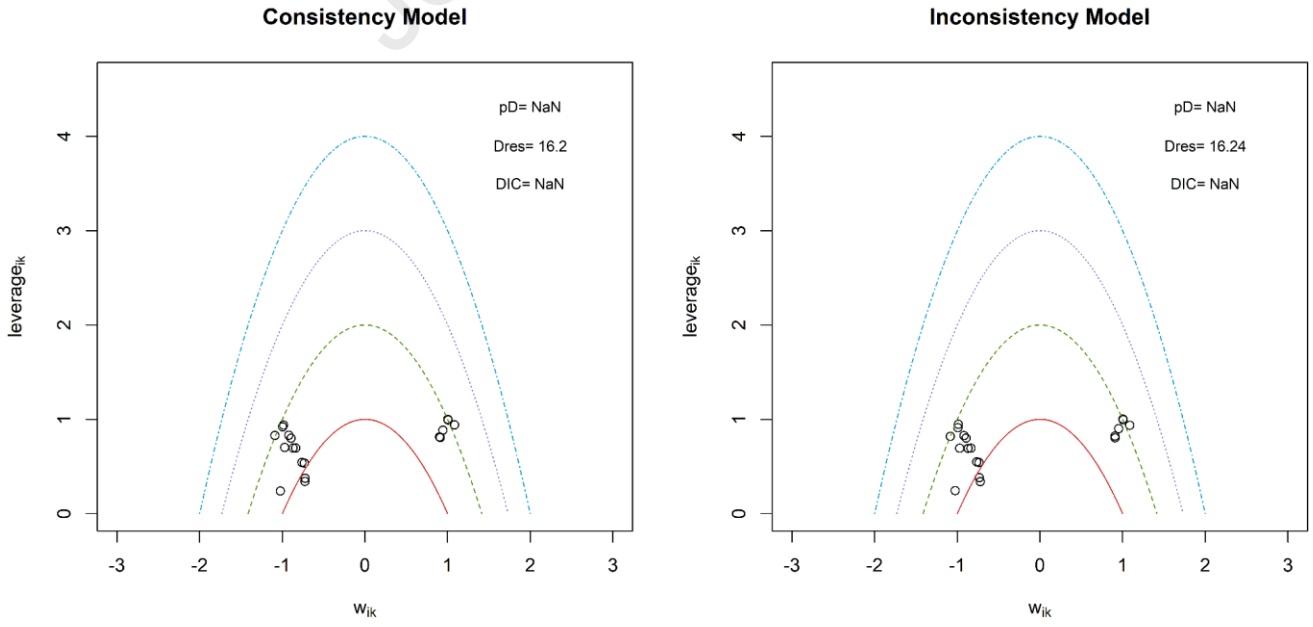
Comparison	k	nma	direct	indir.	RoR	z	p.value
ATC vs. CPAP	1	1.22	1.22	.	.	.	
ATC vs. no_SBT	0	0.04	.	0.04	.	.	.
ATC vs. PSV-PEEP	1	0.55	0.55	.	.	.	
ATC vs. PSV-ZEEP	0	0.05	.	0.05	.	.	.
ATC vs. T-tube	0	0.02	.	0.02	.	.	.
CPAP vs. no_SBT	0	0.03	.	0.03	.	.	.
CPAP vs. PSV-PEEP	0	0.45	.	0.45	.	.	.
CPAP vs. PSV-ZEEP	0	0.04	.	0.04	.	.	.
CPAP vs. T-tube	0	0.01	.	0.01	.	.	.
no_SBT vs. PSV-PEEP	0	15.03	.	15.03	.	.	.
no_SBT vs. PSV-ZEEP	1	1.22	1.22	.	.	.	
no_SBT vs. T-tube	0	0.45	.	0.45	.	.	.
PSV-PEEP vs. PSV-ZEEP	0	0.08	.	0.08	.	.	.
PSV-PEEP vs. T-tube	1	0.03	0.03	.	.	.	
PSV-ZEEP vs. T-tube	1	0.37	0.37	.	.	.	

Legend: comparison - Treatment comparison k - Number of studies providing direct evidence nma - Estimated treatment effect (RR) in network meta-analysis direct - Estimated treatment effect (RR) derived from direct evidence indir. - Estimated treatment effect (RR) derived from indirect evidence RoR - Ratio of Ratios (direct versus indirect) z - z-value of test for disagreement (direct versus indirect) p-value - p-value of test for disagreement (direct versus indirect)

e-Table 5. Nodesplit analysis for the overall duration of mechanical ventilation outcome



e- Figure 13. Forest plot for the mortality outcome frequentist analysis with continuity correction



e- Figure 14. Global inconsistency for the ICU mortality outcome

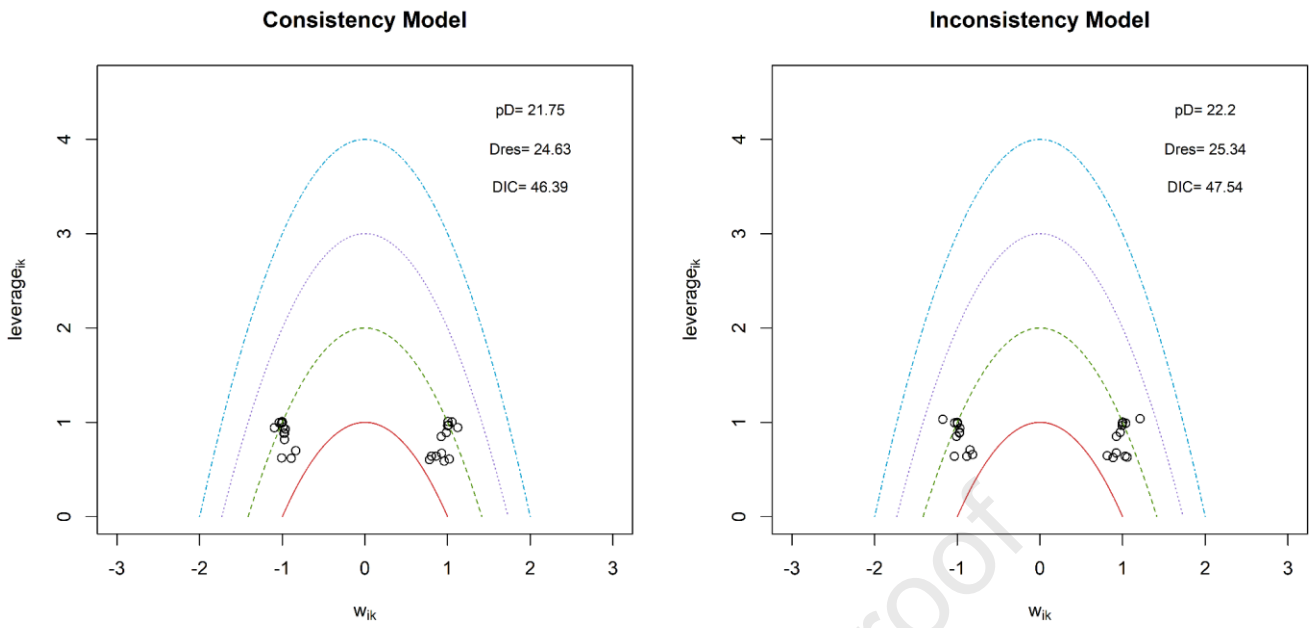
Nodesplit analysis

Mortality

Comparison	k	nma	direct	indir.	RoR	z	p.value
ATC vs. HFO	0	0.51	.	0.51	.	.	.
ATC vs. PAV+	0	3.71	.	3.71	.	.	.
ATC vs. PSV-PEEP	1	0.52	0.52	.	.	.	.
ATC vs. PSV-ZEEP	0	0.66	.	0.66	.	.	.
ATC vs. T-tube	0	0.54	.	0.54	.	.	.
HFO vs. PAV+	0	7.25	.	7.25	.	.	.
HFO vs. PSV-PEEP	1	1.01	1.17	0.96	1.22	0.15	0.8835
HFO vs. PSV-ZEEP	0	1.28	.	1.28	.	.	.
HFO vs. T-tube	2	1.05	1.03	.	.	.	.
PAV+ vs. PSV-PEEP	0	0.14	.	0.14	.	.	.
PAV+ vs. PSV-ZEEP	1	0.18	0.32	.	.	.	.
PAV+ vs. T-tube	1	0.15	0.12	.	.	.	.
PSV-PEEP vs. PSV-ZEEP	0	1.27	.	1.27	.	.	.
PSV-PEEP vs. T-tube	2	1.04	1.04	.	.	.	.
PSV-ZEEP vs. T-tube	5	0.82	0.82	.	.	.	.

Legend: comparison - Treatment comparison k - Number of studies providing direct evidence nma - Estimated treatment effect (RR) in network meta-analysis direct - Estimated treatment effect (RR) derived from direct evidence indir. - Estimated treatment effect (RR) derived from indirect evidence RoR - Ratio of Ratios (direct versus indirect) z - z-value of test for disagreement (direct versus indirect) p-value - p-value of test for disagreement (direct versus indirect)

e-Table 6. Nodesplit analysis for the ICU mortality outcome



e- Figure 15. Global inconsistency for the intensive care length of stay outcome

Nodesplit analysis

Length of Intensive Care Unit stay

Comparison	k	nma	direct	indir.	RoR	z	p.value
ATC vs. HFO	0	0.75	.	0.75	.	.	.
ATC vs. PAV+	0	0.53	.	0.53	.	.	.
ATC vs. PSV-PEEP	1	0.57	0.57	.	.	.	.
ATC vs. PSV-ZEEP	0	0.39	.	0.39	.	.	.
ATC vs. T-tube	0	0.29	.	0.29	.	.	.
HFO vs. PAV+	0	0.70	.	0.70	.	.	.
HFO vs. PSV-PEEP	1	0.75	0.37	1.06	0.35	-0.51	0.6098
HFO vs. PSV-ZEEP	0	0.52	.	0.52	.	.	.
HFO vs. T-tube	3	0.39	0.40	.	.	.	.
PAV+ vs. PSV-PEEP	0	1.07	.	1.07	.	.	.
PAV+ vs. PSV-ZEEP	1	0.74	0.67	.	.	.	.
PAV+ vs. T-tube	1	0.56	0.61	.	.	.	.
PSV-PEEP vs. PSV-ZEEP	1	0.69	0.47	0.96	0.49	-0.57	0.5687
PSV-PEEP vs. T-tube	3	0.52	0.58	0.33	1.78	0.43	0.6656
PSV-ZEEP vs. T-tube	5	0.76	0.68	1.92	0.36	-1.35	0.1780

Legend: comparison - Treatment comparison k - Number of studies providing direct evidence nma - Estimated treatment effect (RR) in network meta-analysis direct - Estimated treatment effect (RR) derived from direct evidence indir. - Estimated treatment effect (RR) derived from indirect evidence RoR - Ratio of Ratios (direct versus indirect) z - z-value of test for disagreement (direct versus indirect) p-value - p-value of test for disagreement (direct versus indirect)

e-Table 7. Nodesplit analysis for the intensive care unit length of stay outcome