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CHEST

Original Research

CRITICAL CARE

The Timing of Tracheotomy in Critically Ill Patients Undergoing Mechanical Ventilation

A Systematic Review and Meta-analysis of Randomized Controlled Trials

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Background: **The objective of this study was to systematically review and quantitatively synthesize all randomized controlled trials (RCTs), comparing important outcomes in ventilated critically ill patients who received an early or late tracheotomy.**

Methods: **A systematic literature search of PubMed, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Embase, the Cochrane Central Register of Controlled Trials, the National Research Register, the National Health Service Trusts Clinical Trials Register, and the Medical Research Council UK database was conducted using specific search terms. Eligible studies were RCTs that compared early tracheotomy (ET) with either late tracheotomy or prolonged endotracheal intubation in critically ill adult patients.**

Results: **Seven trials with 1,044 patients were analyzed. ET did not significantly reduce short-term mortality (relative risk [RR], 0.86; 95% CI, 0.65-1.13), long-term mortality (RR, 0.84; 95% CI, 0.68-1.04), or incidence of ventilator-associated pneumonia (RR, 0.94; 95% CI, 0.77-1.15) in critically ill patients. The timing of the tracheotomy was not associated with a markedly reduced duration of mechanical ventilation (MV) (weighted mean difference [WMD], −3.90 days; 95% CI, −9.71-1.91) or sedation (WMD, −7.09 days; 95% CI, −14.64-0.45), shorter stay in ICU (WMD, −6.93 days; 95% CI, −16.50-2.63) or hospital (WMD, 1.45 days; 95% CI, −5.31-8.22), or more complications (RR, 0.94; 95% CI, 0.66-1.34).**

Conclusions: **The present meta-analysis suggested that the timing of the tracheotomy did not significantly alter important clinical outcomes in critically ill patients. The duration of MV and sedation, as well as the long-term outcomes of ET in mechanically ventilated patients, should be evaluated in rigorously designed and adequately powered RCTs in the future.**

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Abbreviations: ET = early tracheotomy; LT = late tracheotomy; MV = mechanical ventilation; PTI = prolonged translaryngeal intubation; RCT = randomized controlled trial; RR = relative risk; VAP = ventilator-associated pneumonia; WMD = weighted mean difference

Tracheotomy is a frequently performed surgical procedure in critically ill patients.[1] For patients who require prolonged mechanical ventilation (MV), replacement of translaryngeal intubation with a tracheotomy is often considered.[2] Generally accepted benefits of tracheotomy (relative to prolonged translaryngeal intubation [PTI]) include greater airway security, improved patient comfort, better oral hygiene, and easier nursing care.[3-5] However, tracheotomy is not risk free. Complications related to tracheotomy include bleeding, wound infection, tracheal stenosis, and occasionally death.[6-8] Recent evidence suggests that the percutaneous dilatational technique is increasingly the first choice for ICU tracheotomy, compared with the open surgical technique.[9,10] However, the optimal timing (early vs late) of the tracheotomy in critically ill patients requiring prolonged MV remains unclear.[11,12]

A meta-analysis published by Griffiths et al[13] in 2005 indicated that early tracheotomy (ET) shortened the

duration of MV and length of ICU stay in patients who required prolonged MV. Since then, several other randomized controlled trials (RCTs) have been published on the topic.[14,15] Consequently, we conducted an updated systematic review and meta-analysis of RCTs on the timing of tracheotomies to investigate the effect of ET vs either PTI or PTI followed by late tracheotomy (LT) on important clinical outcomes in critically ill patients.

Materials and Methods

Search Strategy

In reporting our results, we followed the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses.[16] Relevant articles in all languages were identified by searching PubMed, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Embase, the Cochrane Central Register of Controlled Trials, the National Research Register, the National Health Service Trusts Clinical Trials Register, and the Medical Research Council UK database (up to July 10, 2011). Electronic searches were performed using Exploded Medical Subject Headings and the appropriate corresponding keywords: "tracheostomy," "tracheotomy" AND "critical care," "critical illness," "intensive care," "critically ill." We restricted the findings of the previous searches using a highly sensitive search strategy recommended by the Cochrane Collaboration for identifying RCTs.[17] We also checked the reference lists of RCTs and previous meta-analyses identified by the previous searches to include other potentially eligible trials.

Two authors independently included RCTs in the analysis if they compared ET with either PTI or PTI followed by LT in critically ill adult patients. ET was defined as a tracheotomy performed up to 7 days after initiation of translaryngeal intubation and MV. LT was any time thereafter. Agreement regarding trial inclusion was assessed using the Cohen κ statistic.[18]

Data Extraction

Two authors independently extracted the following data: study design (ie, date, location, and sample size), patient characteristics, study methodology (ie, inclusion/exclusion criteria, weaning protocol, tracheotomy technique, method of randomization, and analysis method), intervention (ie, definitions of ET and LT), and main outcomes. If data needed clarification or were not presented in the publication, we contacted the original authors. Extracted data were entered into Microsoft Office Excel 2007 (Redmond, Washington) and were checked by the third author. Any disagreement was resolved by discussion. The quality of trials was assessed with the method recommended by the Cochrane Collaboration for assessing risk of bias.[19]

The primary outcomes were short-term mortality and incidence of ventilator-associated pneumonia (VAP). Secondary outcomes included long-term mortality, duration of MV, duration of sedation, length of ICU stay, length of hospital stay, and complications. Short-term mortality referred to hospital mortality or mortality within 90-day follow-up after admission. Long-term mortality referred to mortality between hospital discharge and at least 1 year follow-up thereafter. Complications were defined as events related to tracheotomy or PTI that were life threatening, required an intervention, or resulted in prolonged hospitalization.

Statistical Analysis

Analyses were on an intention-to-treat basis. Differences were expressed as relative risks (RRs) with 95% CIs for dichotomous outcomes, and weighted mean differences (WMDs) with 95% CIs for continuous outcomes. A fixed-effect model was used, and a random-effects model was used in the case of significant heterogeneity (P value of χ^2 test $< .10$ and $I^2 > 50\%$). Potential sources of heterogeneity were identified by sensitivity analyses conducted by omitting one study in each turn and investigating the influence of a single study on the overall pooled estimate. Publication bias was assessed by visually inspecting a funnel plot. A P value $< .05$ was considered statistically significant. All statistical analyses were performed using Review Manager, version 5.0 (RevMan; The Cochrane Collaboration; Oxford, England).

Results

Study Identification

The comprehensive search yielded a total of 1,212 relevant publications, and the abstracts were obtained for all citations (Fig 1). Seven RCTs with a total of

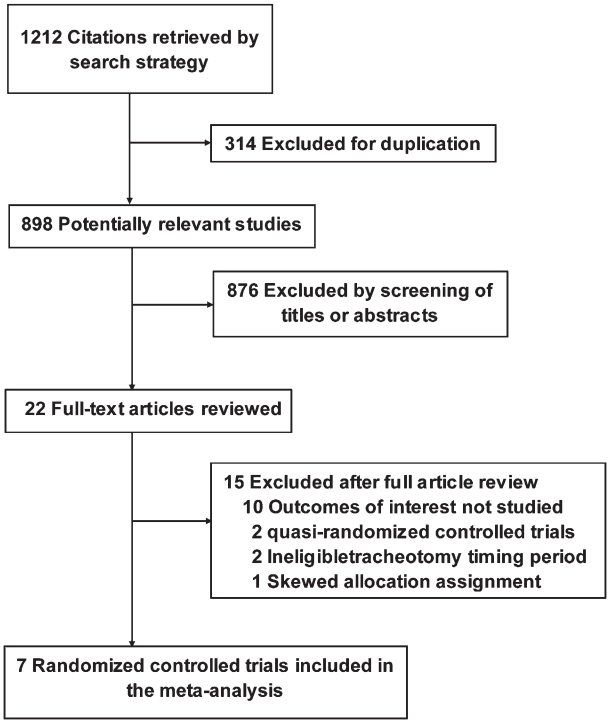

Figure 1. Flowchart of study selection.

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Table 1—*Characteristics of Included Trials*

Study/Year	Intensive Care Setting	Timing of Tracheotomy		Mean Age, y		Disease Severity	Weaning Control	Tracheotomy Information	VAP Definition	Intention-to-Treat Analysis
		Early	Late	Early	Late					
Saffle et al[20]/2002	Burn ICU	Next available operative day	14 d after burn injury	44.5 ± 19.7	51.3 ± 19.2	Not reported	Yes	Performed in the operating room, mostly using surgical technique	CDC criteria	Yes
Bouderka et al[21]/2004	Units for head injury patients	5-6 d after admission	Prolonged endotracheal intubation	41.1 ± 17.5	40 ± 19	SAPS score: Early: 5.4 ± 1.5 Late: 6 ± 3.8	No	Not reported	CDC criteria	Implied
Rumbak et al[4]/2004	3 Medical ICUs	0-2 d after initiation of MV	14-16 d after initiation of MV	63 ± 10.4	63 ± 9.3	APACHE II score: Early: 27.4 ± 4.2 Prolonged: 26.3 ± 2.6	Yes	Percutaneous dilational tracheotomy procedure	Clinical features with positive protected specimen brushes or BAL cultures	Yes
Barquist et al[14]/2006	Trauma center	Before 8 d of admission	After 28 d after admission	53.7 ± 21.5	49.9 ± 18.3	APACHE II score: Early: 12.1 ± 3.2 Late: 13.1 ± 5.1	Yes	Performed both at the bedside and in the operating room	CDC criteria	Yes
Blot et al[15]/2008	25 Medical-surgical ICUs	Before 4 d of initiation of MV	After 14 d of initiation of MV	55 (19-88)[a]	58 (20-88)[a]	SAPS II score: Early: 50 (17-103)[a] Late: 50 (15-96)[a]	Yes	Most often performed at the bedside using a surgical technique	Clinical features with positive cultures of pulmonary secretion samples	Yes
Terragni et al[22]/2010	12 ICUs	6-8 d after endotracheal intubation	13-15 d after endotracheal intubation	61.8 ± 17.4	61.3 ± 16.8	SAPS II score: Early: 51.1 ± 8.7 Late: 49.7 ± 8.6	Yes	Performed at the bedside using percutaneous techniques	Using the simplified CPIS. CPIS > 6 was considered to indicate the presence of VAP	Yes
Trouillet et al[23]/2011	Postcardiac surgery ICU	Before 5 d after surgery	15 d after initiation of MV	64.1 ± 13.3	66.0 ± 12.4	SAPS II score: Early: 47.2 ± 12.4 Late: 45.8 ± 11.4	Yes	Performed at the bedside using percutaneous techniques	Clinical features with positive BAL cultures	Yes

Data are presented as mean ± SD unless indicated otherwise. APACHE = Acute Physiology and Chronic Health Evaluation; CDC = Centers for Disease Control and Prevention; CPIS = Clinical Pulmonary Infection Score; MV = mechanical ventilation; SAPS = Simplified Acute Physiologic Score; VAP = ventilator-associated pneumonia.
[a]Median (range).

1,044 patients met the inclusion criteria.[4,14,15,20-23] The Cohen κ statistic for agreement on study inclusion was 0.92.

Among the seven trials, three were conducted in North America,[4,14,20] three in Europe,[15,22,23] and one in North Africa.[21] Three trials were multicenter studies.[4,15,22] All trials were published in English. The mean age of the patients ranged from 40 to 66 years. The selected trials examined various populations in critical care units, including medical,[4] medical-surgical,[15,22] trauma,[14] head injury,[21] burn,[20] and post-cardiac surgery patients.[23] The definitions of VAP differed across the trials, among which three[14,20,21] used Centers for Disease Control and Prevention criteria,[24] three required microbiologic confirmation,[4,15,23] and the remaining one used the simplified Clinical Pulmonary Infection Score.[22] Tracheotomy techniques were reported in six trials,[4,14,15,20,22,23] including surgical procedure, percutaneous dilational procedure, or both, and were performed at the bedside, operating room, or both. Six of the included seven trials reported the weaning protocols.[4,14,15,20,22,23] Details of the included trials are summarized in Table 1.

Among all the selected trials, randomized sequence and allocation sequence concealment were conducted adequately. Because of the nature of the intervention of the tracheotomy, physicians could not be blinded to the randomization arm, and the objective outcomes (eg, mortality) were not likely to be influenced by lack of blinding. Blinded fashion was clearly stated in the adjudication of VAP in two trials.[15,22] The numbers and reasons for withdrawal/dropout were reported in all trials. Two trials[14,20] were defined as having other sources of bias because one was stopped early after the first interim analysis[14] and the other had a baseline imbalance after adequate randomization.[20] An overview of the risk of bias is shown in Table 2.

Primary Outcomes

Data on primary outcomes were available from all seven trials (N = 1,044) (Table 3). ET did not significantly reduce short-term mortality (RR, 0.86; 95% CI, 0.65-1.13; $P = .28$; P for heterogeneity = .09; $I^2 = 45\%$) (Fig 2) or incidence of VAP (RR, 0.94; 95% CI, 0.77-1.15; $P = .54$; P for heterogeneity = .0009; $I^2 = 74\%$) (Fig 3).

Secondary Outcomes

Two trials (n = 443)[22,23] reported data on long-term mortality. No significant difference was detected (RR, 0.84; 95% CI, 0.68-1.04; $P = .10$; P for heterogeneity = .52; $I^2 = 0\%$) (Fig 4). Information on duration of MV and sedation was available for four trials (n = 442)[4,20,21,23] and two trials (n = 336),[4,23] respectively. ET did not significantly shorten the duration of MV (WMD, −3.90 days; 95% CI, −9.71-1.91; $P = .19$; P for heterogeneity < .0001; $I^2 = 86\%$) (Fig 5), or sedation (WMD, −7.09 days; 95% CI, −14.64-0.45; P for heterogeneity < .00001; $I^2 = 98\%$) (Fig 6). Data on length of ICU (n = 396)[4,23] and hospital (n = 260)[20,23] stay were available for two trials, respectively. ET was not associated with a shorter length of ICU (WMD, −6.93 days; 95% CI, −16.50-2.63; $P = .16$; P for heterogeneity = .001; $I^2 = 91\%$) (Fig 7) or hospital (WMD, 1.45 days; 95% CI, −5.31-8.22; $P = .67$; P for heterogeneity = .97; $I^2 = 0\%$) (Fig 8) stay. Five trials[4,15,21-23] (n = 744) reported data on complications. No significant difference was detected (RR, 0.94; 95% CI, 0.66-1.34; $P = .74$; P for heterogeneity = .66; $I^2 = 0\%$) (Fig 9).

Sensitivity Analyses and Publication Bias

Tests for heterogeneity identified the trial by Rumbak et al[4] as having outlying results. Exclusion of this trial resolved the heterogeneity, but did not change the results (short-term mortality: RR, 0.94; 95% CI, 0.77-1.15; $P = .54$; incidence of VAP: RR. 1.01; 95% CI, 0.89-1.14; $P = .93$; duration of MV: WMD, −1.84 days; 95% CI, −4.86-1.19; $P = .23$). For the meta-analysis of ET on short-term mortality, there was no evidence of significant publication bias by inspection of the funnel plot (Fig 10).

Discussion

Our meta-analysis suggested that ET did not significantly reduce short- or long-term mortality or incidence of VAP in critically ill patients. In addition, the

Table 2—*Assessing Risk of Bias*

Study/Year	Sequence Generation	Allocation Concealment	Blinding	Incomplete Outcome Data Addressed	Selective Outcome Reporting	Free of Other Bias
Saffle et al[20]/2002	Yes	Yes	No	Yes	Yes	No
Bouderka et al[21]/2004	Yes	Yes	No	Yes	Yes	Yes
Rumbak et al[4]/2004	Yes	Yes	No	Yes	Yes	Yes
Barquist et al[14]/2006	Yes	Yes	No	Yes	Yes	No
Blot et al[15]/2008	Yes	Yes	Yes	Yes	Yes	Yes
Terragni et al[22]/2010	Yes	Yes	Yes	Yes	Yes	Yes
Trouillet et al[23]/2011	Yes	Yes	No	Yes	Yes	Yes

Table 3—*Summary of Results of Included Trials*

Study/Year	Patients, No.		Short-term Mortality, No. (%)		Pneumonia, No. (%)		Long-term Mortality, No.		Duration of MV, Mean ± SD		Duration of Sedation, Mean ± SD		Length of ICU Stay, Mean ± SD		Length of Hospital Stay, Mean ± SD		Complications, No.	
	ET	LT	ET	LT	ET	LT	ET	LT	ET	LT	ET	LT	ET	LT	ET	LT	ET	LT
Saffle et al[20]/2002	21	23	4 (19.0)	6 (26.1)	21 (100)	22 (95.7)			35.5 ± 20.62	31.4 ± 24.94	…	…	…	…	58.4 ± 28.87	57.3 ± 38.37	…	…
Bouderka et al[21]/2004	31	31	12 (38.7)	7 (22.6)	18 (58.1)	19 (61.3)	…	…	14.5 ± 7.3	17.5 ± 10.6	…	…	…	…	…	…	9/31	8/31
Rumbak et al[4]/2004	60	60	19 (31.7)	37 (61.7)	3 (5.0)	15 (25.0)	…	…	7.6 ± 4.0	17.4 ± 5.3	3.2 ± 0.4	14.1 ± 2.9	4.8 ± 1.4	16.2 ± 3.8	…	…	5/60	4/60
Barquist et al[14]/2006	29	31	2 (6.9)	5 (16.1)	28 (96.6)	28 (90.3)	…	…	…	…	…	…	…	…	…	…	…	…
Blot et al[15]/2008	61	62	21 (34.4)	20 (32.3)	30 (49.2)	31 (50.0)	…	…	14(2-60)[a]	16(3-60)[a]	…	…	…	…	…	…	15/40	23/42
Terragni et al[22]/2010	209	210	55 (26.3)	66 (31.4)	30 (14.4)	44 (21.0)	72/144	85/148	…	…	…	…	…	…	31(17-49)[b]	32(18-59)[b]	16/145	11/119
Trouillet et al[23]/2011	109	107	33 (30.3)	32 (29.9)	50 (45.9)	47 (43.9)	12/76	17/75	17.9 ± 14.9	19.3 ± 16.9	6.4 ± 5.9	9.6 ± 7.3	23.9 ± 21.3	25.5 ± 22.2	39.0 ± 27.0	37.5 ± 26.9	1/109	1/107

ET = early tracheotomy; LT = late tracheotomy. See Table 1 legend for expansion of other abbreviations.

[a]1-60 d duration, median (range), $P = .64$.

[b]Mean (interquartile range).

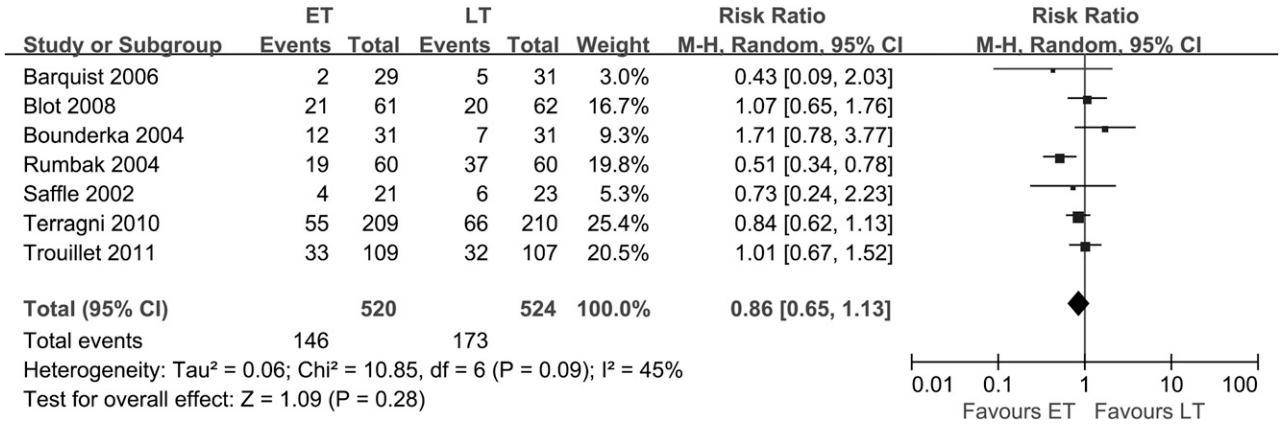

FIGURE 2. Comparison of the short-term mortality between the ET group and the LT group. df = degrees of freedom; ET = early tracheotomy; LT = late tracheotomy; M-H = Mantel-Haenszel.

present study showed that ET was not associated with a markedly reduced duration of MV or sedation, shorter stay in ICU or hospital, or more complications.

Differences between the current meta-analysis and a previous one by Griffiths et al[13] should be noted. In their meta-analysis,[13] five trials with a total of 406 patients were included, among which two trials were quasi-randomized, thereby producing a potential for selection bias. Because of the nature of the intervention of tracheotomy, physicians could not be blinded to the randomization arm. Therefore, true randomization adopted in assigning patients becomes a more crucial factor to warrant the internal validity of a trial. In our meta-analysis, the inclusion criteria were strictly restricted to RCTs, and thus seven RCTs with a total of 1,044 patients were finally included.

Our meta-analysis indicated that ET did not significantly shorten the duration of MV or length of ICU stay, which was different from the results of Griffiths et al.[13] Among the included trials, only two[4,21] reported a significantly shorter duration of MV in the ET group. However, Bouderka et al[21] did not describe their weaning methods, which raises concern about the validity of their finding of shorter MV with ET, because it was certainly possible that physicians were more aggressive in their weaning attempts once tracheotomy was performed.[5] In the study by Rumbak et al,[4] although the weaning protocol was described, the mean duration of MV in the ET group exceeded the mean length of ICU stay, whereas it did not in the LT group, which might be because of earlier transfer out of the ICU, while still on MV. This earlier transition of patients in the ET group to a lower-level care area might cause a potential bias between the two groups. Therefore, based on the relatively high-quality trials included, our meta-analysis calls into question Griffiths et al's[13] findings of a shorter duration of MV and length of ICU stay with ET.

The anticipated benefits of tracheotomy included improved patient comfort due to reduced oropharyngeal and laryngeal stimulation, which might in turn shorten duration of sedation.[25] In a retrospective study, Nieszkowska et al[26] first reported that

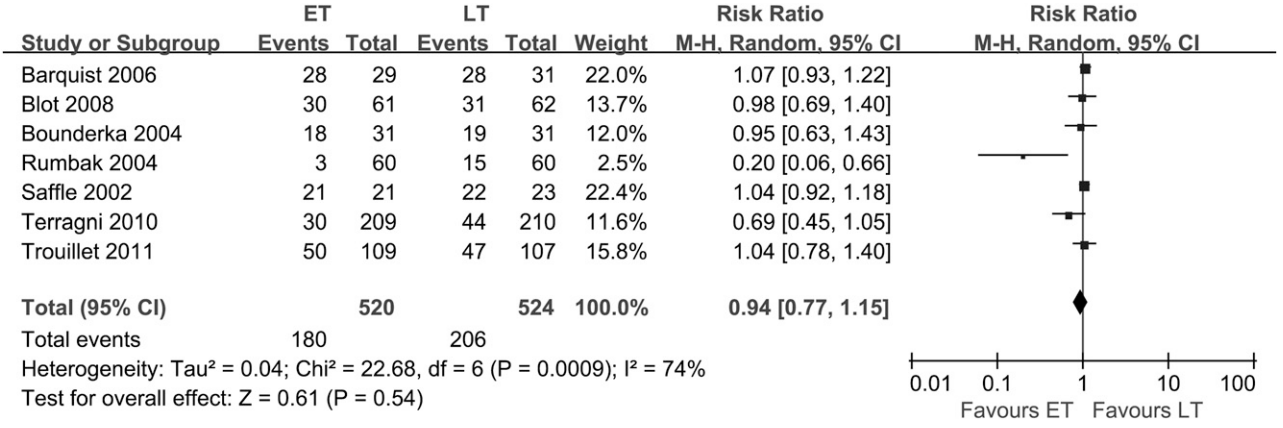

FIGURE 3. Comparison of the incidence of ventilator-associated pneumonia between the ET group and the LT group. See Figure 1 legend for expansion of abbreviations.

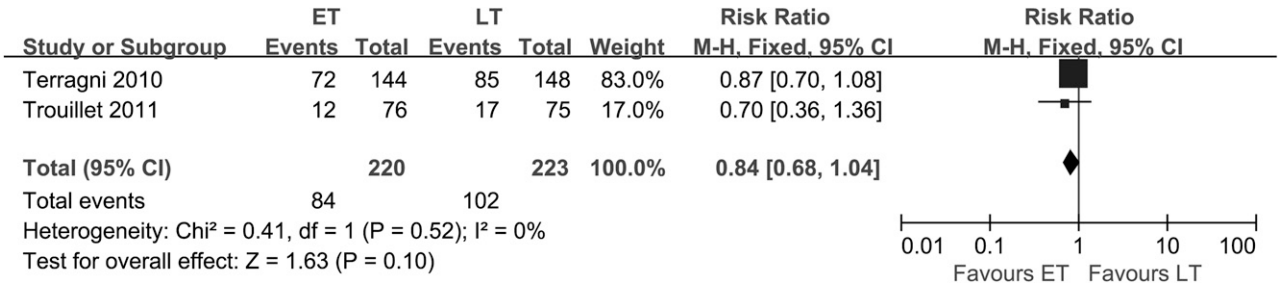

FIGURE 4. Comparison of the long-term mortality between the ET group and the LT group. See Figure 1 legend for expansion of abbreviations.

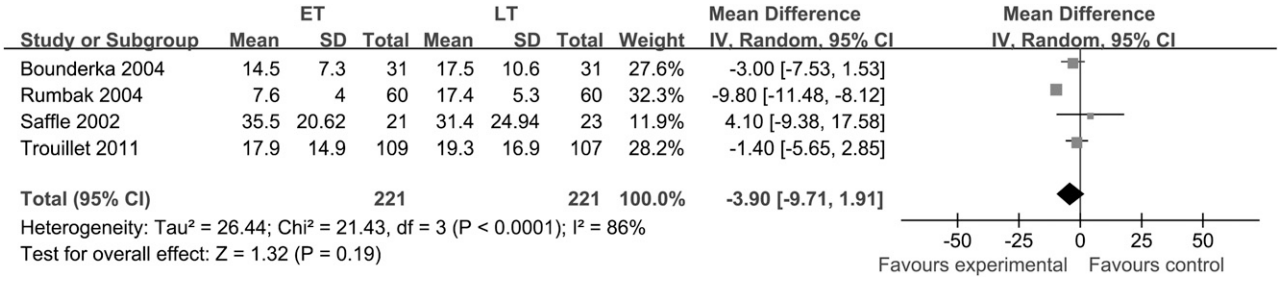

FIGURE 5. Comparison of the duration of mechanical ventilation between the ET group and LT group. See Figure 1 legend for expansion of abbreviations.

tracheotomized mechanically ventilated patients required less IV sedative administration, spent less time heavily sedated, and achieved more autonomy earlier. However, another retrospective study, by Veelo et al,[27] suggested that no reduction in sedation requirements was observed after tracheotomy. In the present study, pooled analysis did not indicate a statistically significant reduction in the duration of sedation ($P = .07$), although both trials[4,23] demonstrated a significantly shorter duration of sedation in the ET group. To date, because of the limited number of RCTs investigating the outcome of duration of sedation, it is difficult to draw a firm conclusion about it.

Despite being a commonly performed procedure, tracheotomy is not risk free. In a retrospective study, Goldenberg et al[28] reported a major complication rate of 4.3%, with 0.7% mortality, related to tracheotomy. In the present study, pooled analysis suggested no significant difference regarding complications between the ET group and the control group (RR, 0.94; 95% CI, 0.66-1.34; $P = .74$). Besides balancing the benefits and risks of tracheotomy, a major concern is the ability to identify early which patients require prolonged MV. This issue was highlighted by Terragni et al's[22] study showing that a significant number of patients (43.3%) in the LT group improved to the extent that tracheotomy was not required. There had been attempts to produce a formula to help identify which burn patients would require long-term ventilation.[29] However, such a formula applicable to the general population had yet to be produced and validated.[30]

So far, little is known about the long-term outcomes of ET. Among the included trials, Terragni et al[22] reported that no difference was detected regarding

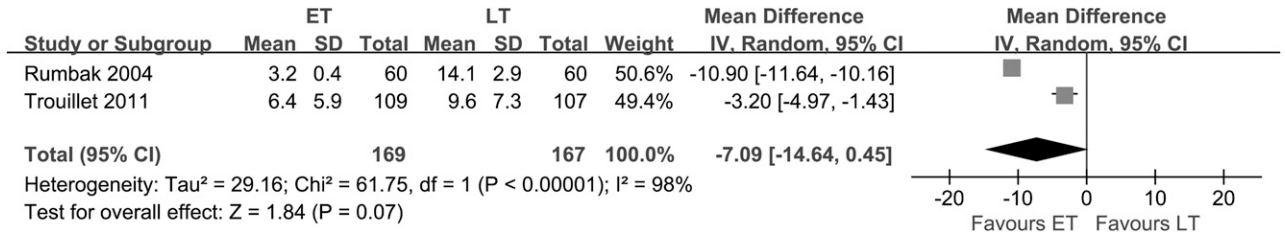

FIGURE 6. Comparison of the duration of sedation between the ET group and the LT group. See Figure 1 legend for expansion of abbreviations.

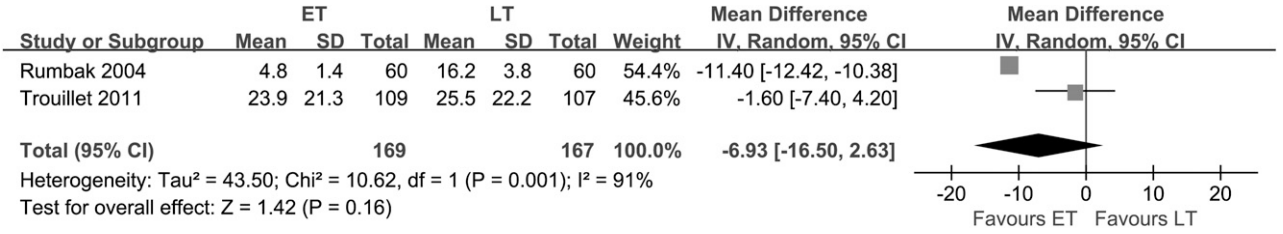

FIGURE 7. Comparison of the length of ICU stay between the ET group and the LT group. See Figure 1 legend for expansion of abbreviations.

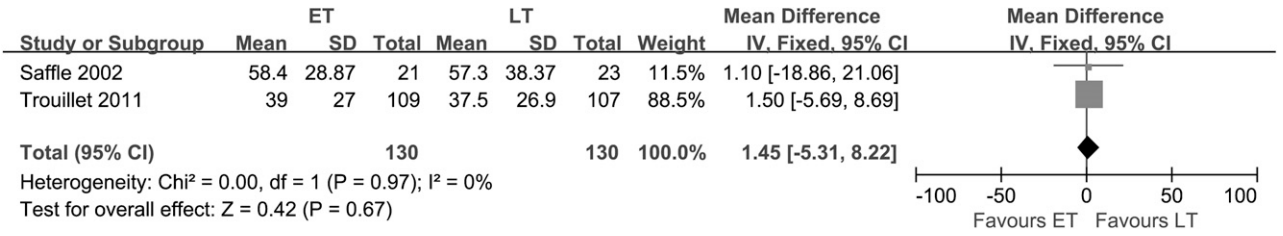

FIGURE 8. Comparison of the length of hospital stay between the ET group and the LT group. See Figure 1 legend for expansion of abbreviations.

the need for a long-term care facility after hospital discharge ($P = .92$) or 1-year mortality ($P = .25$). Trouillet et al[23] reported no significant difference in activities of daily living ($P = .52$), anxiety ($P = .87$), depression ($P = .45$), posttraumatic stress disorder ($P = .78$), or mortality ($P = .49$) after a median follow-up of 873 days. Our pooled analysis also suggested no significant difference in long-term mortality (RR, 0.84; 95% CI, 0.68-1.04; $P = .10$). Therefore, RCTs powered to address the long-term costs related to ET are warranted in future.

The Intensive Care Society of the United Kingdom recently completed a large, multicenter, randomized trial, the TracMan trial (N = 909).[31] The full TracMan results await publication but provisional results have been presented in a conference. Of note, the TracMan results presented were consistent with the findings of our meta-analysis.[32]

There are several limitations to the present study. First, the geographic regions covered included North America (United States), Europe (France and Italy), and North Africa (Morocco). Therefore, our results limited generalizability to other regions (for example, Asia and Latin America). Second, there was considerable heterogeneity among the included trials. The targeted population varied greatly. The adopted definitions of ET and LT differed: ET from day 2 to day 8 after intubation; LT from day 14 to day 28 after intubation. Therefore, because of considerable heterogeneity, as well as the limited number of RCTs regarding some outcomes (eg, duration of MV and sedation, length of stay in ICU, and hospital), caution should be taken when interpreting the results. Finally, although there was no evidence of potential bias by inspection of the funnel plots, it is possible that RCTs not identified for this

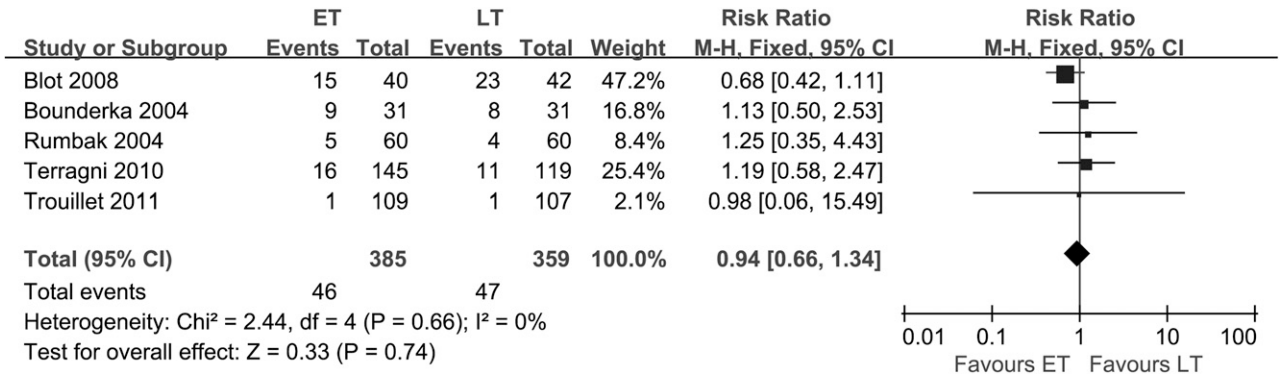

FIGURE 9. Comparison of the complications between the ET group and the LT group. See Figure 1 legend for expansion of abbreviations.

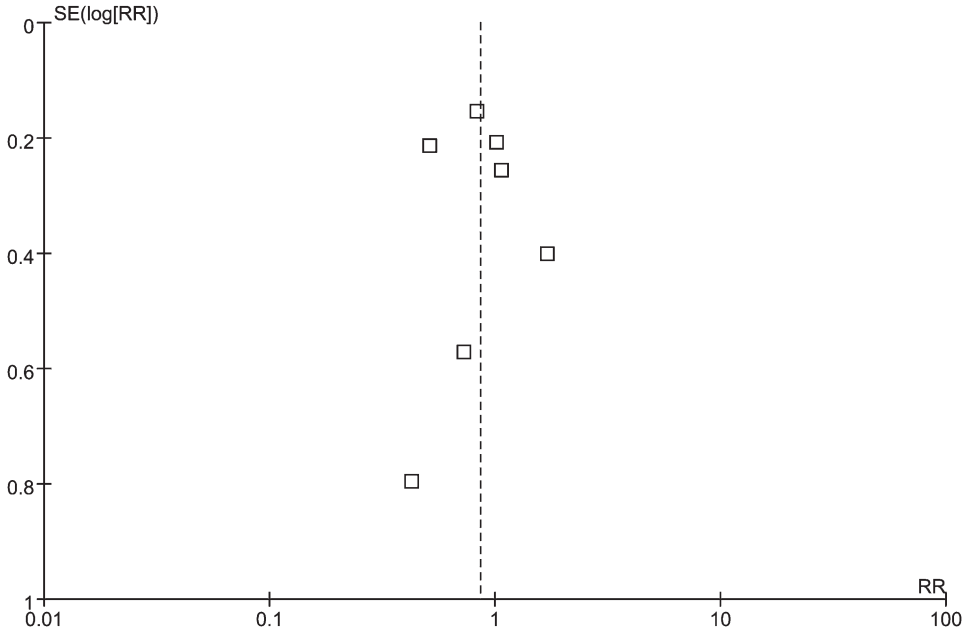

FIGURE 10. Funnel plot for the short-term mortality between the ET group and the LT group. RR = relative risk.

review could have had an impact on the pooled effect estimates.

CONCLUSIONS

Our meta-analysis suggested that the timing of tracheotomy did not significantly alter important clinical outcomes in critically ill patients. A sensitive and validated formula to identify early those who need prolonged MV in the global increasing population of intubated critically ill patients is warranted. In addition, the duration of MV and sedation, as well as the long-term costs of ET in mechanically ventilated patients, should be evaluated in rigorously designed and adequately powered RCTs in the future.

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Author contributions: Drs Li and Deng had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Dr Wang: contributed to the definition of inclusion and exclusion criteria, electronic and manual search of the literature, drafting and revision of the manuscript, study design, and analysis and interpretation of the data.
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Dr Li: contributed to the study design; interpretation of the results; and writing, revision, and approval of the manuscript.
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