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ORIGINAL ARTICLE

Effect of Timing of Tracheotomy on Clinical Outcomes: an Update Meta-analysis Including 11 Trials

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Key words: intensive care unit; artificial respiration; tracheotomy; Meta-analysis

Objective To estimate the relative effect of early *vs.* late tracheotomy on clinical end-points in unselected intensive care unit (ICU) patients undergoing mechanical ventilation.

Methods We searched electronic databases (up to February 27, 2013) for both randomized control trials and observational studies satisfying the predefined inclusion criteria.

Results We retrieved 11 reports of studies including a total of 13 705 patients. Early tracheotomy was associated with significant reductions in mortality [33.3% *vs.* 36.3%; relative risk (RR); 0.92; 95% confidence interval (CI): 0.88, 0.97; I^2 : 29%], length of ICU stay (mean difference: -6.55 days; 95% CI: -8.19, -4.90; I^2 : 98%) and duration of mechanical ventilation (mean difference: -6.53 days; 95% CI: -11.43, -1.63; I^2 : 100%). However, as compared with late tracheotomy, early tracheotomy did not reduce the incidence of hospital pneumonia (21.9% *vs.* 21.0%, RR: 0.85; 95% CI: 0.68, 1.06; I^2 : 67%).

Conclusions Early tracheotomy can reduce length of ICU stay, duration of mechanical ventilation and mortality but has no influence on hospital pneumonia when compared with late tracheotomy. Once the decision has been made about tracheotomy, clinical physicians should not hesitate to perform the procedure.

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THE reasons of artificial airway for most of critically ill patients were mainly due to prolonged mechanical ventilation (MV) or airway protection, such as neurological patients. Comparing with endotracheal intubation, tracheotomy enhanced patient comfort and had shorter intensive care unit (ICU) or hospital stay, which may have supportive data. The other possible advantages of procedure were lowering airway resistance, improving pulmonary toilet and fewer lung infection, benefit for oral feeding, which might

also be associated with less sedative administration.^{1, 2}

Percutaneous dilatation tracheotomy (PDT) with or without bronchoscopic control has been used widely and increasingly because it is easy and convenient implementation since 1985.³⁻⁵ Comparing the method of tracheotomy itself, in spite of surgical or percutaneous techniques, the timing of tracheotomy was more important in terms of the outcomes. But the appropriate time of diverting artificial airway from translaryngeal endotracheal intubation to tracheotomy remained controversial, and also there was no consensus in the literature about what should be considered as an early tracheotomy.

In 1989, The National Association of Medical Directors

of Respiratory Care has published a recommendation based on only expert opinion that tracheotomy should be performed in patients who still required artificial ventilation 21 days after admission.⁶ But the clinicians often made the selection for tracheotomy timing according to their individual favors in fact. In the two retrospective observational studies, median time from onset of MV to tracheotomy was 12 days.^{7, 8} In the past decade well designed observational studies or randomized control trials (RCTs) have been completed gradually, so it was necessary to pull all studies available together and find the exact answer again. Without a large Meta-analysis, the question of whether early tracheotomy should be considered after MV could not be well addressed. Thus, we conducted a Meta-analysis of results of studies available comparing different time of tracheotomy on clinical impact and exploring the potential benefit of early tracheotomy on adult patients admitted to ICU who required prolonged MV.

MATERIALS AND METHODS

Search source and strategy

A systematic Medline and PubMed database search was performed (up to February 27, 2013). Furthermore, other databases were also checked including the China National Knowledge Internet, EMBASE, J-STAGE, the Cochrane Library (Cochrane Central Register of Controlled Trials), International Pharmaceutical Abstracts, ISI Web of Science, Global Health, and the grey literature (SIGLE) databases.

The following key literatures were used to search studies of interest: [tracheotomy] AND [artificial respiration OR mechanical ventilation] with no restriction or subheadings. The reference lists of all retrieved literatures were checked for other potentially relevant citations.

Selection criteria

Studies were included in the present Meta-analysis if they met all the following criteria: (1) critically ill patients enrolled underwent MV; (2) they compared early tracheotomy with late tracheotomy or prolonged endotracheal intubation; (3) they were written in English. Both RCTs and observational studies were included to increase sample size, population coverage, and statistical power. Identification of early tracheotomy was according to individual definition.

Quality assessment and data extraction

We assessed the quality of the studies included with a well-established scale developed by Jadad *et al.*⁹ The range of possible scores were 0-5. The two authors selected trials according to the inclusion criteria independently and blindly.

Then they assessed trial quality independently and extracted information from published reports by using a standardized protocol and reporting form: study design, first author's first name, year of publication, number of enrolled patients, timing of tracheotomy, events of end-points. If there were several mortality endpoints, we selected the longer follow-up results. For example, in the ICU mortality, hospital mortality, 90-day mortality, or one-year mortality, we chose one-year mortality as the final endpoint event. Diagnosis criteria of hospital pneumonia depended on respective definition. Disagreement was resolved by discussion and arbitration by the third author (Lian-di Li) if necessary.

Statistical analysis

RevMan 5.0.25 software, developed by the Cochrane Collaboration (<http://www.cc-ims.net/revman>), was used for the Meta-analysis. The heterogeneity between selected articles was tested with use of I^2 and *chi-square* tests. We applied the fixed-effects model when there was no statistically significant difference between the results and the random-effects was applied when there was a significant difference. The publication bias was evaluated by using funnel plots and the fail-safe number (N_{fs}). Any calculated N_{fs} value smaller than the number of observed studies indicated publication bias that might influence the Meta-analysis results. We calculated the $N_{fs0.05}$ according to the formula $N_{fs0.05} = (\sum Z/1.64)^2 - k$, where k is the number of reports of studies included in the Meta-analysis. $P < 0.05$ was considered as significant.

RESULTS

Through the MEDLINE electronic database search, a total of nine RCTs were found and three of them were excluded because the patients enrolled did not receive MV.¹⁰⁻¹⁸ Figure 1 summarizes the selection of reports of eligible clinical trials. Seven retrospective observational studies were found and five of them were included.¹⁹⁻²³ The other two retrospective studies conducted by Combes Alain and Arabi Yaseen M were excluded because they compared tracheotomy and non-tracheotomy and the average time of procedure was 12 days.^{7, 8} A total of 13 705 subjects were enrolled in the studies, of which 1034 were from six RCTs^{11-13, 15, 17, 18} and 12 671 from five observational studies.¹⁹⁻²³ The quality assessment, detailed characteristics of subjects, and therapy information of the eligible studies are given in Table 1.

No heterogeneity with regard to mortality outcome was found in ten studies ($P > 0.39$, and $I^2 = 1\%$), so a fixed effects model was used for analysis for this variable. However, heterogeneity was found in terms of hospital acquired pneumonia, length of ICU

stay, and duration of MV, so a random effects model was then used for their analysis.

We could compare data for four clinical end-points. The

risk of mortality, length of ICU stay, and duration of MV differed between early tracheotomy group and late tracheotomy group (Figs. 2, 3, 4).

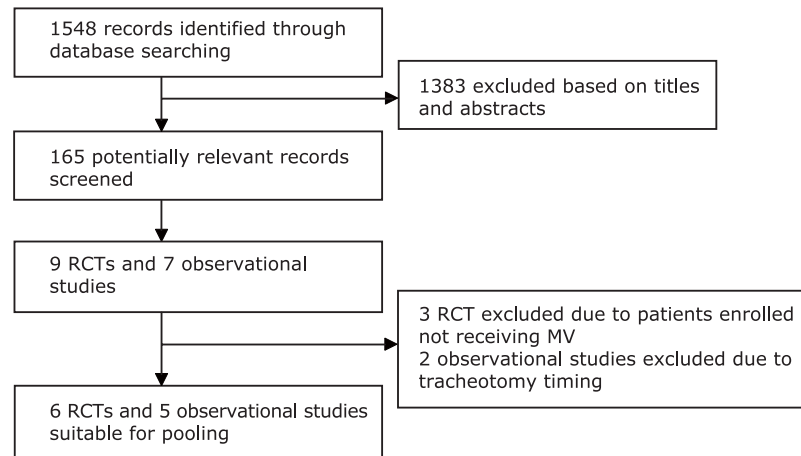


Figure 1. Flowchart of literature selection process.

RCT: randomized controlled trial; MV: mechanical ventilation.

Table 1. Chief characteristics of studies included in the Meta-analysis

Study	Year of publication	Study design	Quality assessment (Jadad score)	Number of cases	Mean age (yrs)	Number of men	Timing of tracheotomy		Study population	Available end-points	Type of tracheotomy procedure
							Early	Late/EI			
Sugerman <i>et al</i> ¹¹	1997	Multicenter RCT	3/5	112	NA	NA	3-5 days	Prolonged EI	Trauma and non-trauma critically ill patients requiring MV	ICU LOS, mortality, pneumonia	PDT or open surgery
Saffle <i>et al</i> ¹²	2002	Single center RCT	3/5	44	48	NA	<4 days	>14 days	Burn patients requiring MV	Mortality, LOS, DMV	Open surgery
Rumbak <i>et al</i> ¹³	2004	Single center RCT	3/5	120	63	54	2 days	14-16 days	MV	Mortality, DMV, ICU LOS, pneumonia	PDT
Blot <i>et al</i> ¹⁵	2008	Multicenter RCT	3/5	123	57	72	4 days	Prolonged EI	Unselected ICU patients requiring MV	Mortality, DMV, LTC, infection complication	NA
Terragni <i>et al</i> ¹⁷	2010	Multicenter RCT	3/5	419	62	67	6-8 days	13-15 days	MV	VAP, hospital LOS, mortality, VFD	NA
Trouillet <i>et al</i> ¹⁸	2011	Single center RCT	3/5	216	65	66	Immediate early	15 days	MV after cardiac surgery	ICU and hospital LOS, DMV, VAP, VFD	PDT
Moller <i>et al</i> ¹⁹	2005	Multicenter retrospective		185	52	62	<7 days	>7 days	Surgical ICU patients requiring MV	ICU and hospital LOS, DMV, VAP	PDT or open surgery
Flaatten <i>et al</i> ²⁰	2006	Single center retrospective		461	53	NA	<6 days	>6 days	ICU patients	DMV, ICU/hospital LOS, mortality	PDT or open surgery
Scales <i>et al</i> ²¹	2008	Retrospective cohort		10 927	62	60	≤10 days	>10 days	ICU patients requiring MV	ICU LOS, DMV, mortality	NA
Zagli <i>et al</i> ²²	2010	Single center retrospective		506	55	71	≤3 days	>3 days	Emergency ICU patients requiring MV	VAP, DMV, ICU and hospital LOS, mortality	PDT
Tong <i>et al</i> ²³	2012	Single center retrospective		592	68	52	≤7 days	>7 days	Non-trauma ICU patients	DMV, ICU/hospital LOS, mortality, VAP	PDT or open surgery

NA: not available; EI: endotracheal intubation; ICU: intensive care unit; LOS: length of stay; PDT: percutaneous dilational tracheotomy; DMV: duration of mechanical ventilation; LTC: laryngeal and tracheal complication; VAP: ventilator-associated pneumonia; VFD: ventilator-free days.

Primary endpoints

Mortality was the primary endpoint event and reviewed for ten trials.^{11-13, 15, 17, 18, 20-23} The risk of mortality in early tracheotomy group was significantly lower than that in late tracheotomy [33.3% vs. 36.3%, respectively; relative risk (RR): 0.92, 95% confidence interval (CI): 0.88, 0.97; $P=0.004$; Fig. 2, Table 2]. To exclude impact of potential confounding factors related to mortality, we analyzed each cluster of exposed and not exposed patients to allow an accurate estimation (Table 3). Study design and time of tracheotomy influenced the outcome of mortality. Observational study, performing the procedure and PDT had more possibility to induce the positive results.

Secondary endpoints

Secondary endpoints were length of ICU stay, duration of MV and hospital pneumonia. The length of ICU stay reviewed seven trials^{11-13, 18, 19, 22, 23} in the early tracheotomy group was shorter than that in the late group (mean difference: -6.55 days; 95% CI: -8.19, -4.90; $P<0.00001$; Fig. 3, Table 2). The duration of MV reviewed six trials^{12, 13, 18, 19, 22, 23} in the early tracheotomy group was also shorter comparing the late tracheotomy group (mean difference: -6.53 days; 95% CI: -11.43, -1.63; $P=0.009$; Fig. 4, Table 2). There was no significant difference on hospital acquired pneumonia between

early tracheotomy and late tracheotomy in nine trials (21.9% vs. 21.0%; RR: 0.85, 95% CI: 0.68, 1.06; $P=0.15$; Fig. 5, Table 2).^{11-13, 15, 17, 18, 21-23}

Sensitivity / subgroup analyses

In the sensitivity analyses, removal of the largest study²¹ produced no substantial alterations in pooled RRs in terms of mortality (data not shown).

The between-study heterogeneity was explained in part by the variability in study design, type of technique and time of tracheotomy, which had not been well addressed by sensitivity analyses. So we performed subgroup analyses respectively with regard to the end-point of mortality (Table 3).

Publication bias

The funnel plot of the publication bias of the ten trials in terms of mortality events (Fig. 6). The funnel plot showed no publication bias for studies included in the Meta-analysis in terms of mortality. We calculated the $N_{fs0.05}$ for each end-point event and found the $N_{fs0.05}$ values for length of ICU stay ($N_{fs0.05}=9619$), duration of MV ($N_{fs0.05}=12\ 114$), hospital pneumonia ($N_{fs0.05}=22$) and mortality ($N_{fs0.05}=46$) to be greater than the number of studies included in the Meta-analysis.

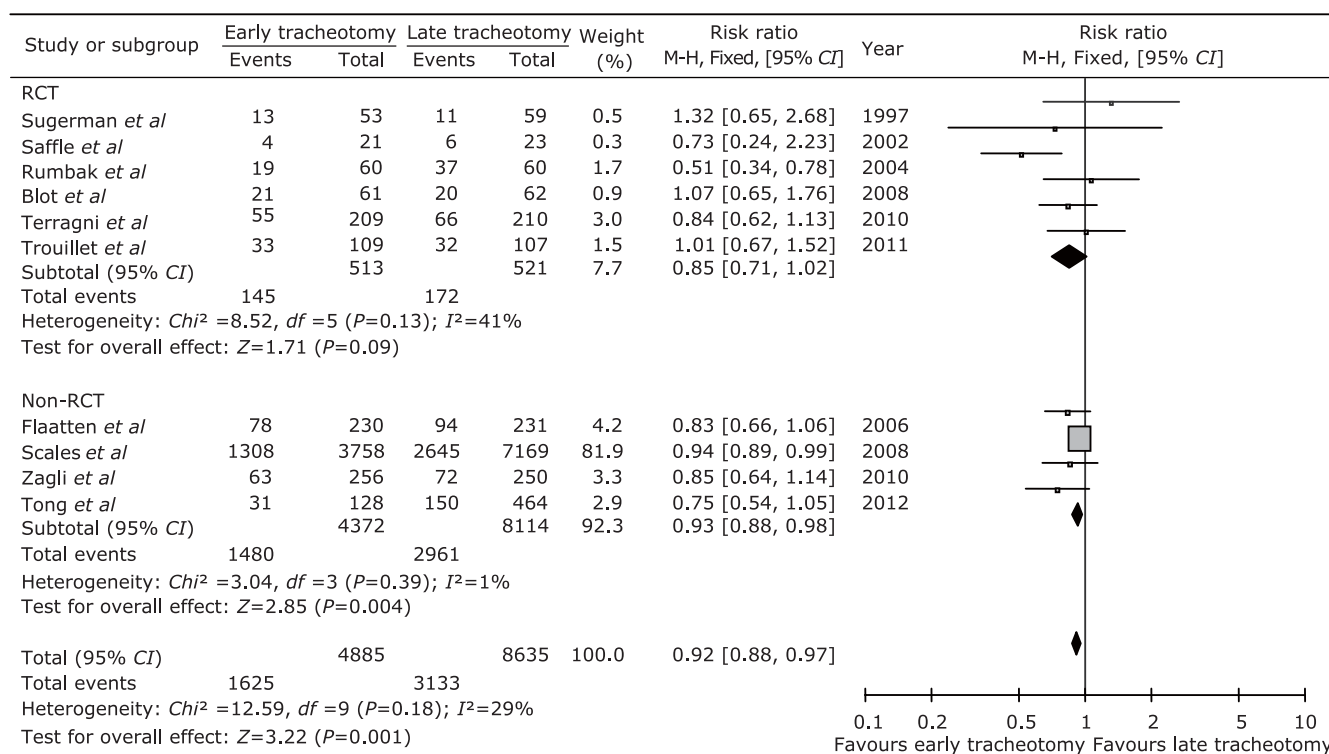


Figure 2. Meta-analysis of 6 RCT and 4 observational studies estimating the impact of early tracheotomy on mortality event comparing late tracheotomy.

CI: confidence interval.

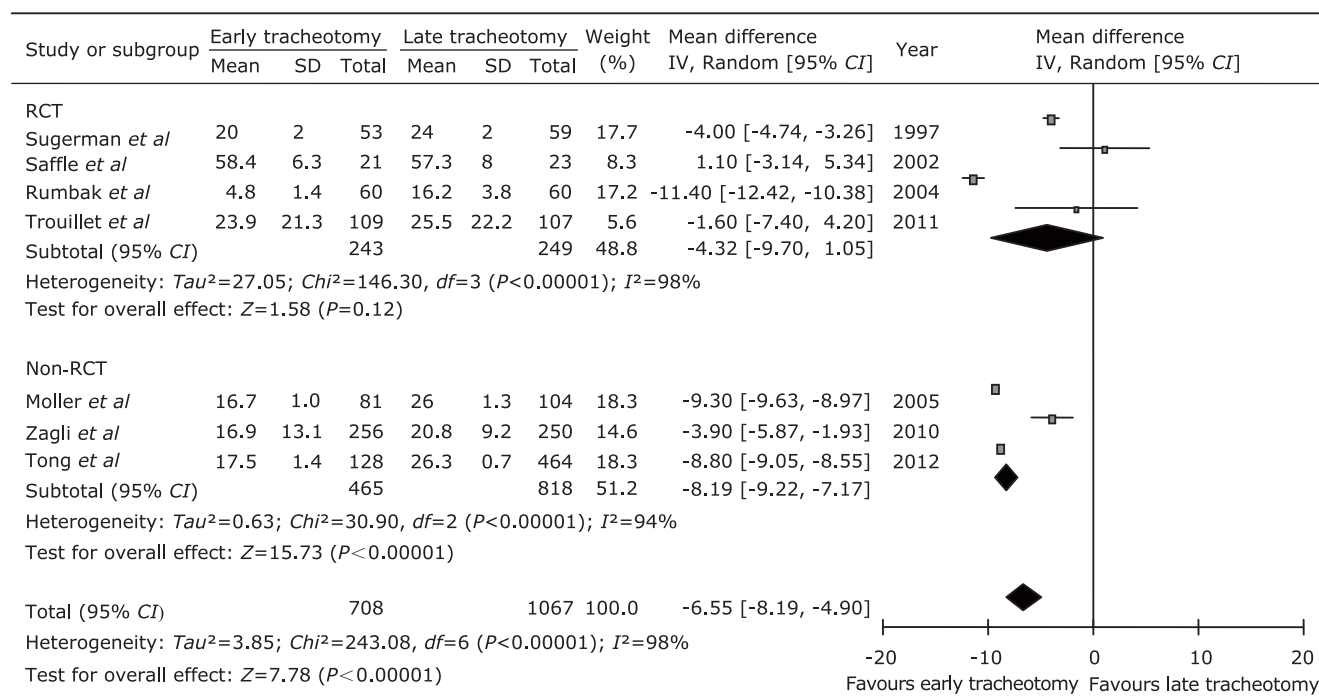


Figure 3. Meta-analysis of 4 RCT and 3 observational studies estimating the impact of early tracheotomy on length of ICU stay comparing late tracheotomy.

SD: standard deviation; IV: inverse variance.

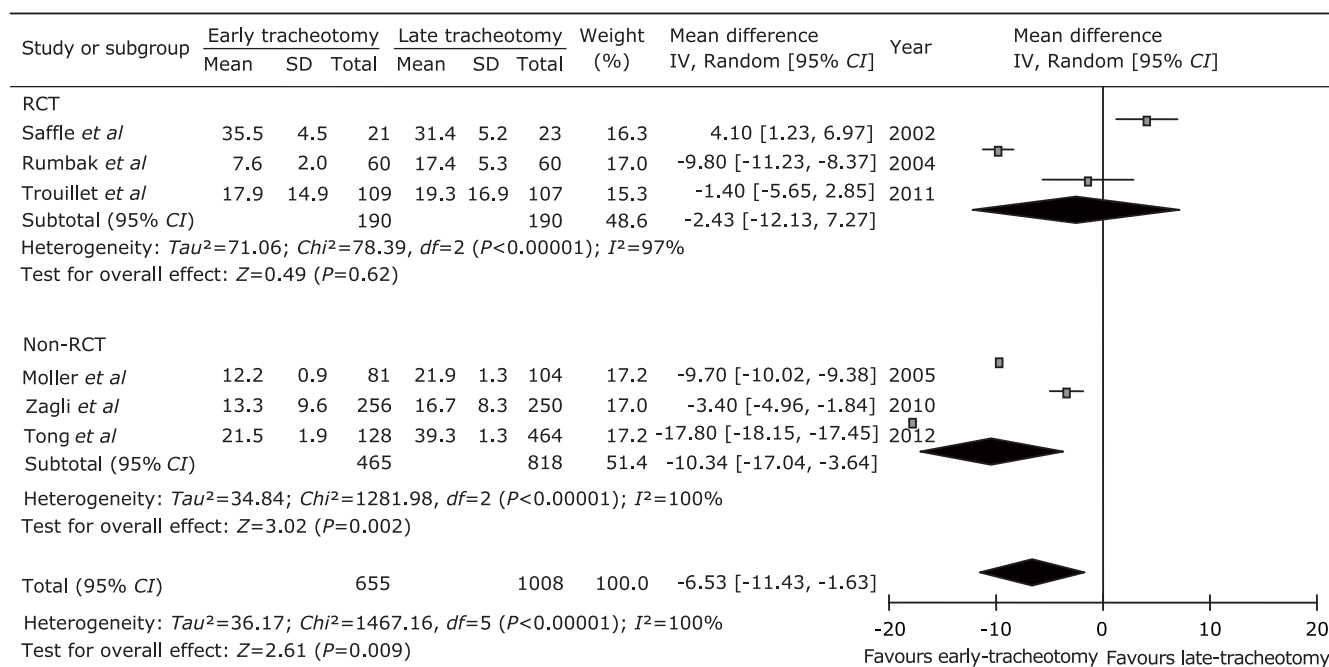


Figure 4. Meta-analysis of 3 RCT and 3 observational studies estimating the impact of early tracheotomy on duration of MV comparing late tracheotomy.

Table 2. Meta-analysis of risk of clinical endpoint events

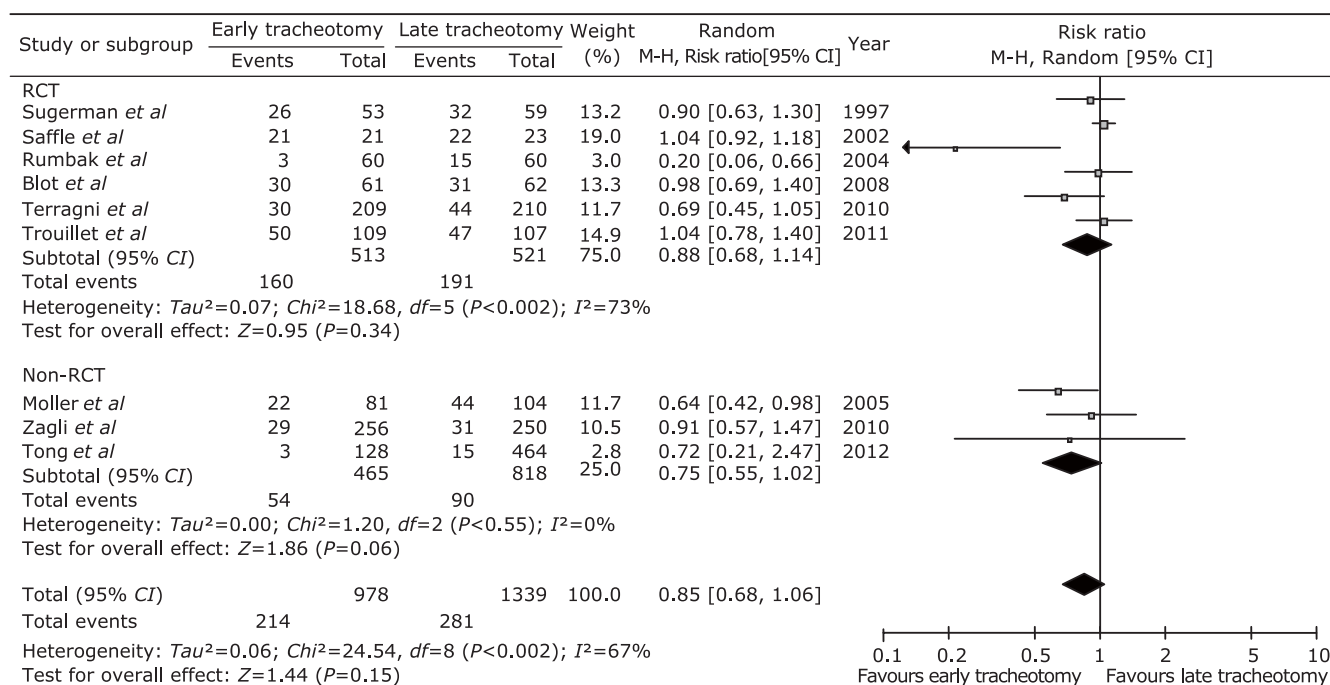
Events	References		Events/Total		OR (95% CI)	P value	I ² (%)	Heterogeneity P value
	RCTs	Observational studies	Early tracheotomy	Late tracheotomy				
ICU/hospital mortality	11-13, 15, 17, 18	20-23	1625/4885	3133/8635	0.92 (0.88, 0.97)	0.001	29	0.180
Rate of hospital acquired pneumonia	11-13, 15, 17, 18	19, 22, 23	214/978	281/1339	0.85 (0.68, 1.06)	0.150	67	0.002
Duration of MV	12, 13, 18	19, 22, 23	655	1008	-6.53 (-11.43, -1.63)	0.009	100	<0.00001
Length of ICU stay	11-13, 18	19, 22, 23	708	1067	-6.55 (-8.19, -4.90)	<0.00001	98	<0.00001

OR: odds ratio.

Table 3. Subgroup analyses with regard to the risk of mortality

Category	Number of studies	References	Number of patients	RR (95% CI)	P value	I ² (%)	Heterogeneity P value
Adjustment for study design							
RCTs	6	11-13, 15, 17, 18	1034	0.85 (0.71-1.02)	0.09	41	0.13
Observational studies	4	20-23	12 486	0.93 (0.88-0.98)	0.004	1	0.39
Adjustment for type of technique							
PDT	3	13, 18, 22	842	0.80 (0.65-0.98)	0.03	65	0.06
Open surgery/PDT	3	11, 20, 23	1165	0.83 (0.69-1.00)	0.05	0	0.37
Open surgery	1	12	44	0.73 (0.24-2.23)	0.58		
Adjustment for time of early tracheotomy							
≤4 days	6	11-13, 15, 18, 22	1077	0.86 (0.72-1.04)	0.11	53	0.08
5-7 days	3	17, 20, 23	1516	0.93 (0.88-0.98)	0.004	5	0.37
<10 days	1	21	10 927	0.94 (0.89-0.99)	0.03		

PDT: percutaneous dilation tracheotomy; RR: relative risk.

**Figure 5.** Meta-analysis of 6 RCT and 3 observational studies estimating the impact of early tracheotomy on hospital acquired pneumonia event comparing late tracheotomy.

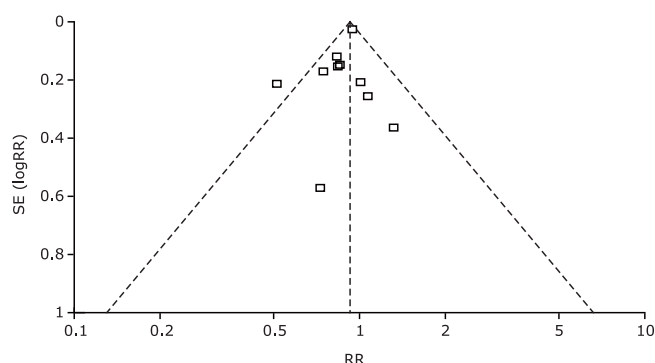


Figure 6. Funnel plot of publication bias in terms of mortality.

DISCUSSION

Our Meta-analysis pooled all RCTs and observational studies together for analysis and revealed that early tracheotomy not only reduced duration of MV and length of ICU stay, but also decreased the incidence of overall mortality which considerably differed with the previous Meta-analysis results. In 2005 Griffiths and his colleagues found in a Meta-analysis that an earlier tracheotomy had some advantages such as reduced duration of artificial ventilation and length of stay in adult patients undergoing artificial ventilation, but the hospital mortality and pneumonia did not differ between early and late-tracheotomy.²⁴ Wang *et al*²⁵ also found negative results about outcomes of early tracheotomy. While in our analysis, there was significant difference with regard to mortality and this was the most interesting discovery. Our study enrolled larger sample of subjects including 13 705 patients which enlarged the accuracy of results. The six of all ten trials including in our analysis published after 2005, so in a way the trials enrolled were advanced and well designed, and also represented the new status. RCTs were generally lower sample and well designed, but that was the idealization which hardly easily being performed in fact. Observational studies commonly had larger subject samples and reflected real clinical status. The decision of procedure often depends on clinical team' discussion and judgment. In this analysis, observational studies had more positive results. Subgroup analysis performed subsequently in terms of mortality showed that early tracheotomy had a trend of decreased mortality in six RCTs trials, and in observational studies including four trials showed an absolute advantage of reducing mortality.

Another favorable outcome well being recognized was lower duration of MV and length of ICU stay, which also mean reduced ICU resources and cost-saving. Several physiologic factors explained why early tracheotomy may

facilitate weaning, such as reduced dead space, less airway resistance, decreased work of breathing, better secretion removal by suctioning, less likelihood of tube obstruction, and better glottic function. Clinicians' behavior also affected discontinuation of respiratory support when encountered different patients of prolonged endotracheal intubation or tracheotomy, and the more rapid weaning were often seen in the latter.^{2, 26}

We found that incidence of hospital pneumonia was not affected by tracheotomy itself or time of that, which was in accordance with the previous three Meta-analyses reports.^{24, 25, 27} Performing a tracheotomy itself may potentially lead to an increased incidence of pneumonia because it destroyed the structure and protection role of natural airway. In ICU circumstance, frequent invasive handling or contaminating air by pathogenic microorganism may counteract the benefit of tracheotomy such as pulmonary toilet or convenient nursing care. Other possible complications regarding tracheotomy included incision bleeding, laryngeal or tracheal injury, increased nursing care, *et al*. However, these outcomes mentioned above were not assessed because of unsatisfactory data collection. Several studies paying attention to these problems found that there were significant more oral-labial and laryngeal damages in the prolonged translaryngeal intubation patients.^{11, 13}

Generally performing a tracheotomy was considered as early tracheotomy if the procedure occurred < 7 days after artificial ventilation, but the exact time remained debated. Subgroup analyses for timing of tracheotomy showed us that more earlier procedure (<4 days) did not show additional benefits and 5-7 days after MV may be an appropriate time for patients in whom weaning and extubation was not likely before day 14 (Table 3).¹

The main limitation of the present study was heterogeneity. Although both RCTs and observational study were enrolled together to enlarge the sample of study, which also resulted significant heterogeneity. Apart from this, another heterogeneity was that we studied targeted population included trauma, burn, medical, and surgery patients, which may mask some specific benefits and limit generalizability of results. Finally, there was different definition about early tracheotomy which varied greatly from immediate to day 8 after intubation. Considering items mentioned above, interpretation of results should be cautioned.

Our Meta-analysis results may be significant and helpful for ICU physicians when considering this procedure. Further investigation focusing on subgroup-specific population, for instance, neurological critically ill patients, should be advocated.

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