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The impact of tracheotomy timing in critically ill patients undergoing mechanical ventilation: A meta-analysis of randomized controlled clinical trials with trial sequential analysis

Ruohui Wang [a,1], Changkun Pan [b,1], Xiaokun Wang [c], Feng Xu [d], Shuang Jiang [e*], Ming Li [f*]

[a] Department of ICU, The First Affiliated Hospital, Heilongjiang University of Chinese Medicine, Harbin, China
[b] Department of ICU, Jiamusi Tumour Hospital, Jiamusi, China
[c] Department of neurology, The Second Affiliated Hospital of Harbin Medical University, Harbin, China
[d] Department of Respiratory and Critical Care Medicine, The Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China
[e] Department of ICU, Jiamusi Hospital of Chinese Medicine, Jiamusi, China
[f] Department of ICU, The Second Affiliated Hospital of Harbin Medical University, Harbin, China

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ABSTRACT

Background: The optimal timing of tracheotomy in critically ill ventilated patients remains controversial.
Objectives: The objective of this meta-analysis was to assess tracheotomy timing for critically ill ventilated patients and determine the outcomes' reliability.
Methods: We searched PubMed, Embase, and the Cochrane Library for randomized controlled trials.
Results: Compared with late tracheotomy, early tracheotomy presented a lower incidence of ventilator-associated pneumonia (VAP), shorter duration of mechanical ventilation (MV), and shorter intensive care unit (ICU) stay. However, trial sequential analysis (TSA), a kind of cumulative meta-analysis, indicated that the evidence was unreliable and inconclusive.
Conclusions: The Findings suggest that early tracheotomy seems to be associated with a lower incidence of VAP, shorter duration of MV, shorter duration of sedation, and shorter ICU stay. However, the apparent benefits revealed in traditional meta-analysis contrast with the post-TSA results. More fully powered, randomized controlled trials focused on the outcomes of tracheotomy are highly warranted.

Introduction

Experts recommend tracheotomy to avoid serious oropharyngeal and laryngeal injury resulting from prolonged translaryngeal intubation. However, patients suffer serious complications when undergoing both open and percutaneous tracheotomy procedures or after, including pneumothorax, hemorrhage, tracheal displacement, tracheal stenosis and fistula formation.[1] In critically ill patients receiving mechanical ventilation (MV), tracheotomy also has accepted benefits, such as easier nursing care, improved comfort, a more secure tube with increased patient mobility, allowance of speech, oral nutrition and early weaning from MV.[2]

Despite these apparent advantages, the optimal timing (early verse late) for tracheotomy in critically ill patients requiring MV remains unclear. Conventional practice has maintained that patients who need MV should undergo tracheotomy only after they have proven incapable of being extubated after a typical period of 10 to 14 days.[3] Moreover, an increasing number of clinical studies suggest that early tracheotomy is associated with better outcomes than late tracheotomy, such as lower in mortality, reduced incidence of ventilator-associated pneumonia (VAP), shortened ventilator use, and shortened ICU length of stay.[4–8] This has been evaluated in a limited number of trials, and the results have been inconclusive.[9–14]

Two previous meta-analyses also reported different outcomes between early tracheotomy and late tracheotomy for critically ill patients receiving MV.[15,16] The two studies analyzed randomized trials and they showed no survival benefits between early and late tracheotomy, concordant with our meta-analysis. The study by Siempos et al showed early tracheotomy was associated with a lower incidence of VAP than late tracheotomy, also concordant with our meta-analysis.[16] Wang et al study showed that the timing of the tracheotomy did not significantly alter the clinical outcomes including incidence of VAP, ventilator use, and ICU length of stay, distinct from our meta-analysis.[15] The objective of the

* Corresponding authors.
E-mail address: jiangshuang7799@sohu.com (S. Jiang), liminghyd@sohu.com (M. Li).
[1] R.W. and C.P. contributed equally to this work.

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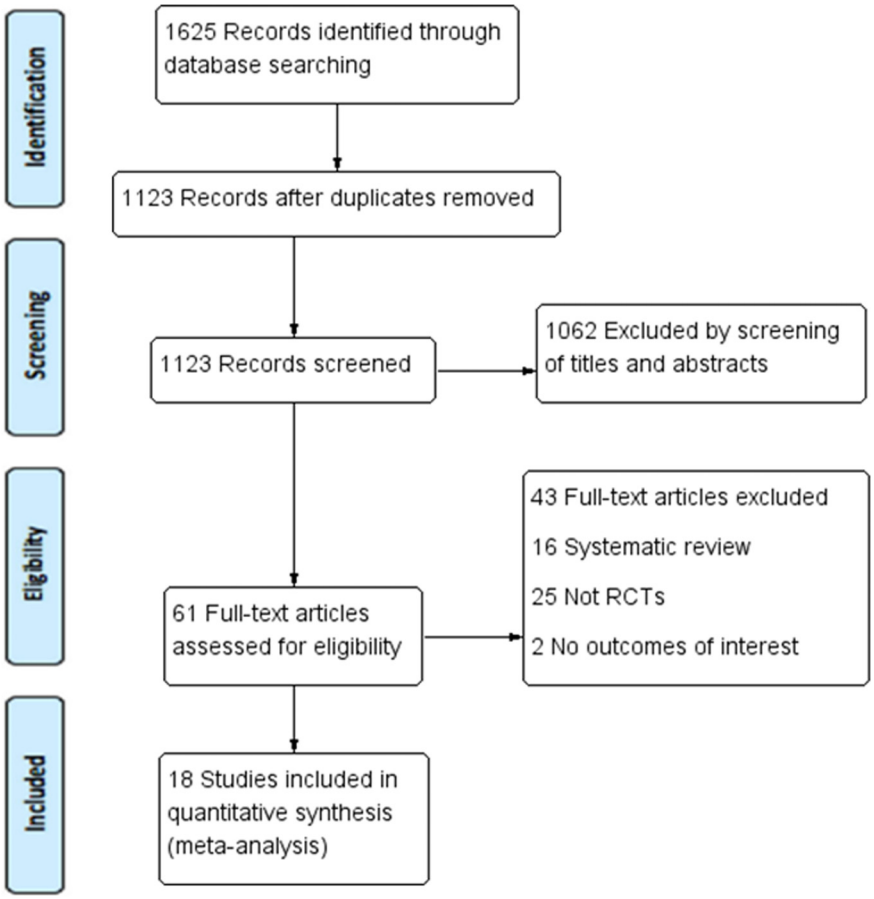

Fig. 1. Study flow diagram.

Table 1
Characteristics included in the meta-analysis

Study, year	Country	Setting	[a]Time of tracheostomy		Number of patients		Disease Severity	
			Early	Late	Early	Late	Early	Late
Dunham, 1984	USA	Trauma center	3–4	14	34	40	NR	NR
Rodriguez, 1990	USA	Surgical ICU	≤7	≥8	51	55	APACHE II score: 10 ± l	APACHE II score: 10 ± l
Sugerman, 1997	USA	Medical center	3–5	≥10–14	127	28	APACHE II score: 66 ± 3	APACHE II score: 55 ± 3
Saffle, 2002	USA	Burn ICU	2–3	≥14	21	23	NR	NR
Bouderka, 2004	Morocco	Trauma ICU	5–6	Prolonged intubation	31	31	SAPS: 5 ± 2	SAPS: 6 ± 4
Rumbak, 2004	USA	Medical ICU	≤2	14–16	60	60	APACHE II score: 27 ± 4	APACHE II score: 26 ± 3
Barquist, 2006	USA	Trauma center	≤7	≥29	29	31	APACHE II score: 12 ± 3	APACHE II score: 13 ± 5
Blot, 2008	France	Medical-surgical ICU	≤4	Prolonged intubation	61	62	APACHE II score: 47 ± 14	APACHE II score: 43 ± 15
Saboori, 2009	Iran	ICU	≤4	≥10	20	20	NR	NR
Terragni, 2010	Italy	ICU	6–8	≥13	209	210	SAPS: 51 ± 9	SAPS: 50 ± 9
Trouillet, 2011	France	Postcardiac surgery ICU	6–8	≥13	109	197	APACHE II score: 47 ± 12	APACHE II score: 46 ± 11
Bylappa, 2011	India	ICU	5–7	8–15	22	22	NR	NR
Zheng, 2012	China	Surgical ICU	3	15	58	61	APACHE II score: 20 ± 2	APACHE II score: 20 ± 3
Koch, 2012	Germany	Surgical, neurosurgical, and neurologic ICUs	≤4	≥6	50	50	APACHE II score: 21 ± (12–31)	APACHE II score: 22 ± (6–11)
Young, 2013	UK	General and cardiothoracic critical care units	≤4	≥10	451	448	APACHE II score: 20 ± 7	APACHE II score: 20 ± 6
Bösel, 2013	Germany	Neurological/neurosurgical ICUs	≤3	7–14	30	30	APACHE II score: 17 ± (13–19)	APACHE II score: 16 ± (11–19)
Diaz-Prieto, 2014	Spain	All consecutive ICU	<8	>14	245	244	APACHE II score: 20 ± (5–40)	APACHE II score: 19 ± (4–38)
Mohamed, 2014	Egyp	ICU	≤10	>10	20	20	APACHE II score: 22.75 ± 7	APACHE II score: 24.35 ± 8

ICU: Intensive care unit. NR: not reported. APACHE: Acute Physiology and Chronic Health Evaluation. SAPS: Simplified Acute Physiology Score.
[a] Day of tracheostomy placement after translaryngeal intubation.

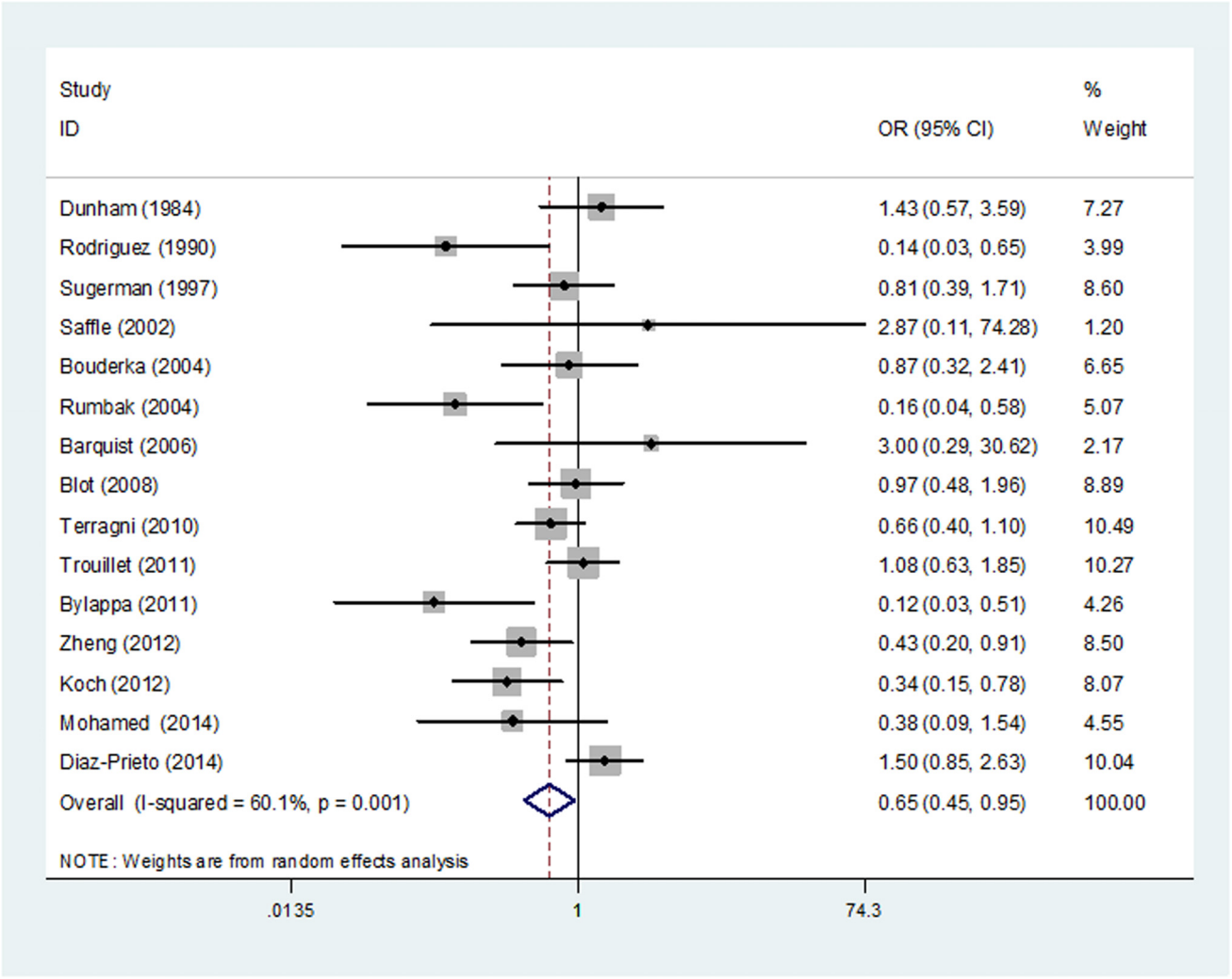

Fig. 2. Forest plot showing the impact of early tracheotomy on incidence of VAP compared to late tracheotomy. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article).

present study is to update the evidence to systematically evaluate the effects and safety related to the timing of tracheotomy on important clinical outcomes in critically ill patients receiving MV. To assess the reliability of the results, we also used trial sequential analyses (TSA), a kind of cumulative meta-analysis, to correct for the increased risk of random errors with trial sequential monitoring boundaries.

Materials and methods

Data sources and searches

We conducted the meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA statement).[17] Without language restrictions, we searched the PubMed, EMBASE, and Cochrane databases from 1984 to September 2017 identify potentially relevant studies. We used a combination of search terms related to (1) tracheotomy or tracheotomy; and (2) critically ill patients (e.g. “critical ill”, “critically ill”, “ICU”, and “emergency”). The reference lists of all selected studies were also manually searched to identify additional eligible studies.

Study selection

Two of the authors reviewed and extracted studies. Any disagreements were resolved by consensus with a third author if necessary. Studies were included if they met several criteria: (1) the inclusion of a study population with mechanically ventilated patients, (2) an intervention that includes early tracheotomy for the treatment of critically ill patients receiving MV compared to late tracheotomy, and (3) the report of at least one of the following outcomes: VAP, length of ICU stay, mortality, duration of sedation, and duration of MV. There is no consensus on the definition of early and late tracheotomy. Times of early tracheotomy were defined as being done during the first week after translaryngeal intubation. Times of late tracheotomy were defined as being done any time after the first week of mechanical ventilation.

Study quality assessment

Two of the authors assessed the risk of bias in the individual trials using the Cochrane risk of bias tool for randomized clinical trials.[18]

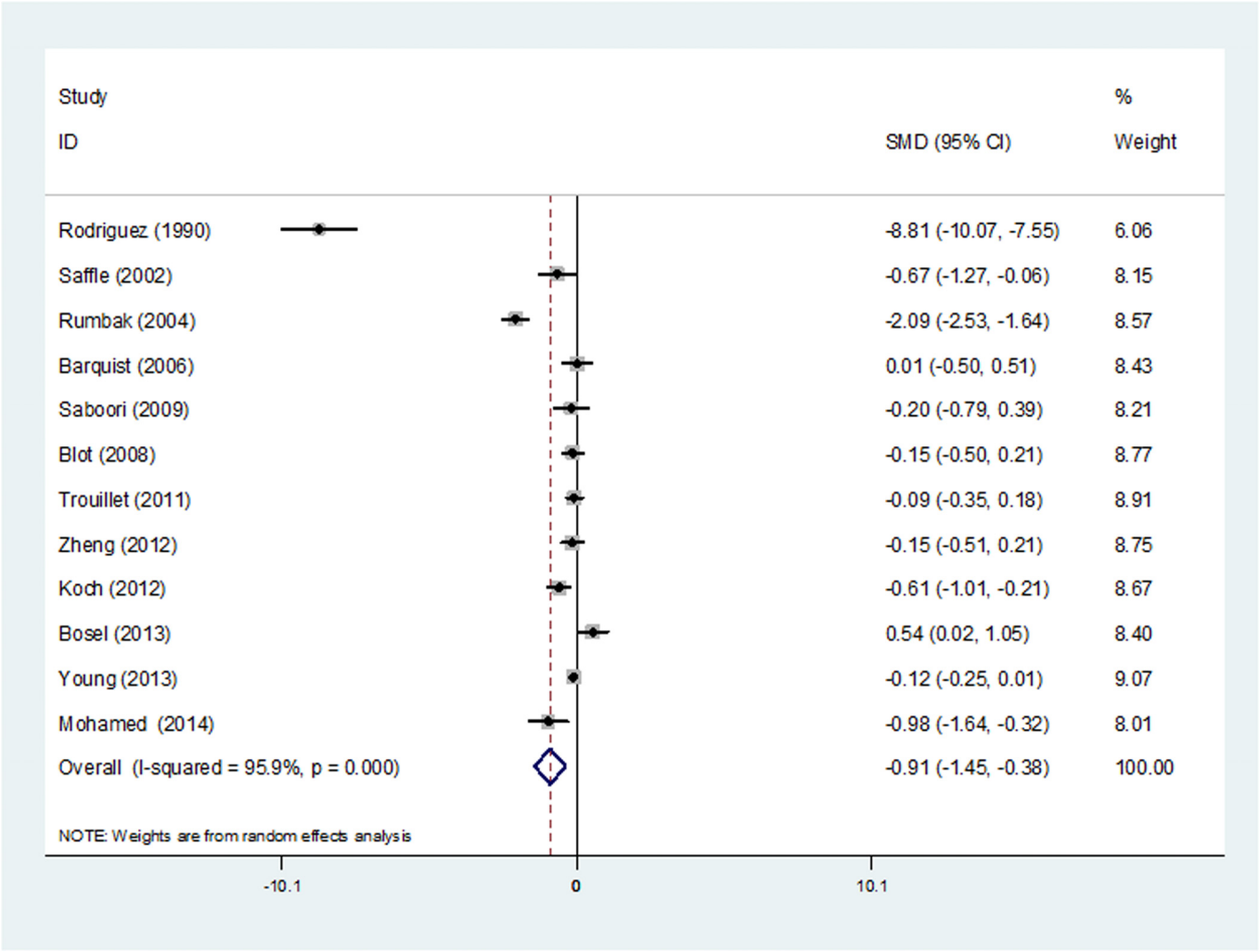

Fig. 3. Forest plot showing the impact of early tracheotomy on duration of mechanical ventilation compared to late tracheotomy. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article).

Using this tool, the quality of each article was assessed in the following domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, or other bias. Any divergence was resolved by a third author if necessary. Reviewers were not blinded to journal, author, or institution of publication.

Statistical analysis

We used STATA 12.0 (Stata Corporation, College Station, Texas) for statistical analyses. The differences between the two times of tracheotomies (early verse late) were calculated as the odds ratio (OR) for dichotomous outcomes and the standardized mean difference (SMD) for continuous outcomes, both with the 95% confidence interval (CI). Heterogeneity was assessed by the Cochran Q-statistic and the I^2 statistic. A P value lower than 0.10 together with an I^2 value higher than 50% was used to indicate significant heterogeneity. I^2 values of less than 50% represented acceptable between-study heterogeneity, and the fixed-effects model was selected. Otherwise, the random-effects model was selected.[19,20] Sensitivity analysis after excluding one study at a time was performed to assess the stability of the results. Publication bias was determined using a funnel plot and assessed by Egger's test.

Trial sequential analysis

With the type I errors resulting from an increased risk of random errors (false positive or false negative outcomes), we carried out TSA (TSA software version 0.9 Beta; Copenhagen Trial Unit, Copenhagen, Denmark) to adjust the pooled estimates for the information size accrued till date. We calculated required information size (RIS) for our meta-analysis, and used this monitoring boundary as a way of determining whether the evidence in our meta-analysis was reliable and conclusive, as suggested by a recent meta-analysis.[21]

Results

Trial identification and characteristics

The literature search yielded 1625 records through the database search, and 18 RCTs fulfilling the inclusion criteria were eligible for the final analysis.[4–14,22–28] The 18 RCTs included 3200 patients from 12 countries. An overview of the study selection process is presented in Fig. 1, and the main characteristics of the included studies are shown in Table 1. An assessment of each risk of bias is presented in Supplemental Figure 1.

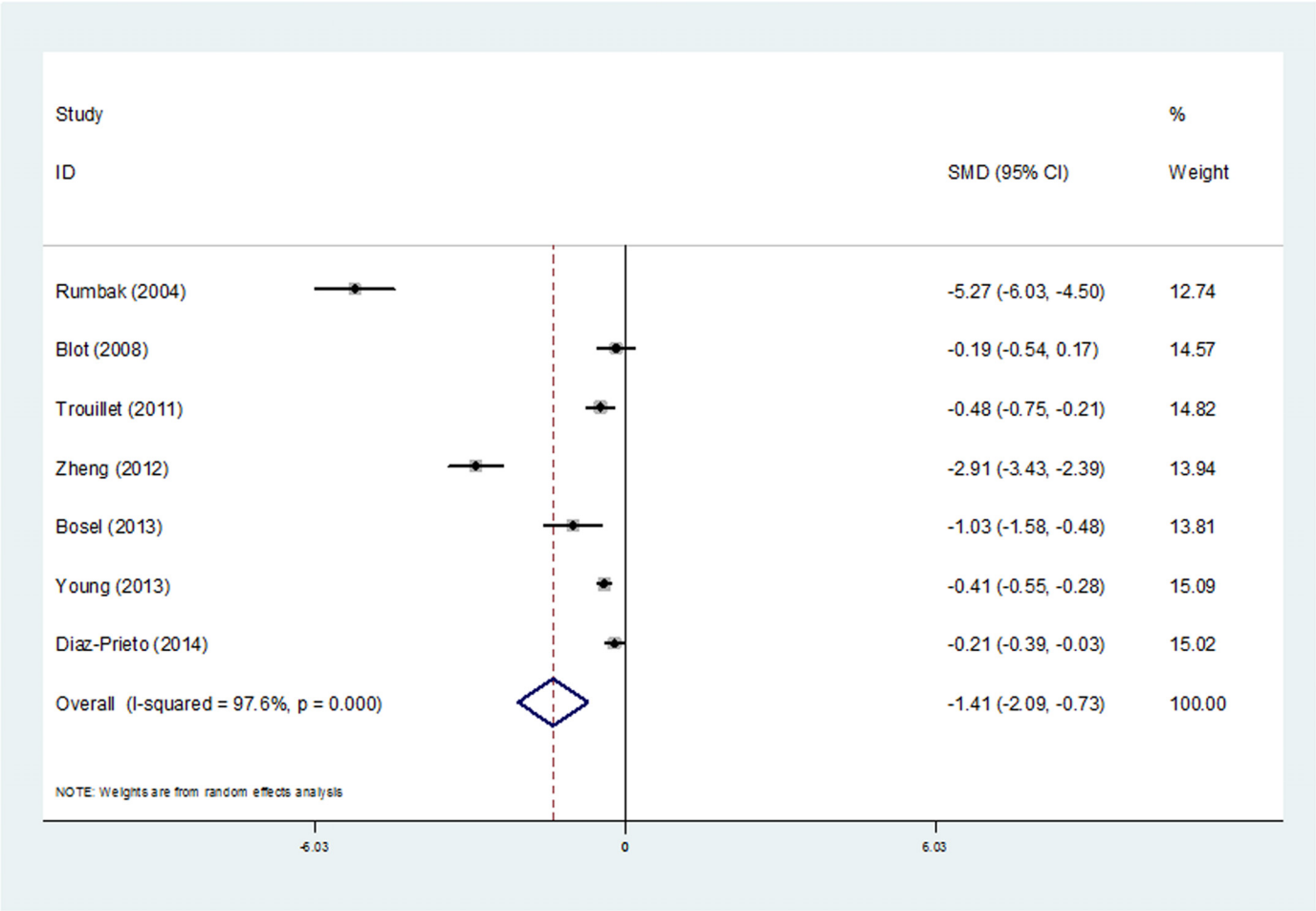

Fig. 4. Forest plot showing the impact of early tracheotomy on duration of sedation compared to late tracheotomy. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article).

Of the 18 trials included in the meta-analysis, 15 reported VAP,[4–14,22,23,25,26] 12 reported the duration of MV,[4,5,7,8,10,12,13,23,24,26–28] 7 reported the duration of sedation,[5,7,14,23,26–28] 11 reported the length of ICU stay,[4,5,7,8,11,13,14,25–28] and 15 reported all-cause mortality.[4,5,7,8,10–14,22,23,25–28]

Meta-analysis results

Timing of tracheotomy on ventilator-associated pneumonia

Fifteen of the eighteen studies reported on the incidence of VAP. We pooled the manually calculated OR for the effect of timing (early versus late) of the tracheotomy on the incidence of VAP (Fig. 2). Compared with late tracheotomy, the pooled analysis showed that early tracheotomy was associated with lower incidence of VAP (OR 0.65, (95% CI, 0.45–0.95); $P = 0.025$). Subgroup analyses showed that compared with late tracheotomy, early tracheotomy was associated with the incidence of VAP benefit in trials with underlying risk of mortality lower than 20% and patients in Asia. To correct for random error and repetitive testing of sparse data, TSA was calculated with $\alpha = 0.05$ and $\beta = 0.20$ (power 80%). The required diversity-adjusted information size based on the intervention effect was suggested by the included trials using a random-effects model with a relative risk reduction of 5.99% and 38.5% event rate for late tracheotomy. TSA showed that the Z value of all 15 trials did not cross the sequential monitoring boundary, and the accumulated amount of information was not up to the optimal information size (information size required 6141 patients), indicating that the cumulative evidence was unreliable and inconclusive (Fig. 6A).

A funnel plot for VAP analysis was shown in Supplemental Fig. 2A, and we detected no evidence of publication bias ($P = 0.200$). We therefore conducted sensitivity analyses to explore potential sources of heterogeneity. The results were unchanged by the elimination of any study (Supplemental Fig. 2B).

Effects of tracheotomy timing on duration of mechanical ventilation, duration of sedation, and length of ICU stay

Twelve trials reported the duration of MV as an outcome, which was shorter with early tracheotomy than with late tracheotomy (SMD −0.91, (95% CI, −1.45 to −0.38); $P = 0.001$) (Fig. 3). Duration of MV remained lower in patients given early tracheotomy than in those given late tracheotomy in the subgroup of trials with underlying risk of mortality equal to or greater than 20% and patients in USA and Africa. Data from seven trials indicated that early tracheotomy was associated with a shorter duration of sedation compared with late tracheotomy (SMD −1.41, (95% CI, −2.09 to −0.73); $P < 0.001$) (Fig. 4). Duration of sedation was lower in patients given

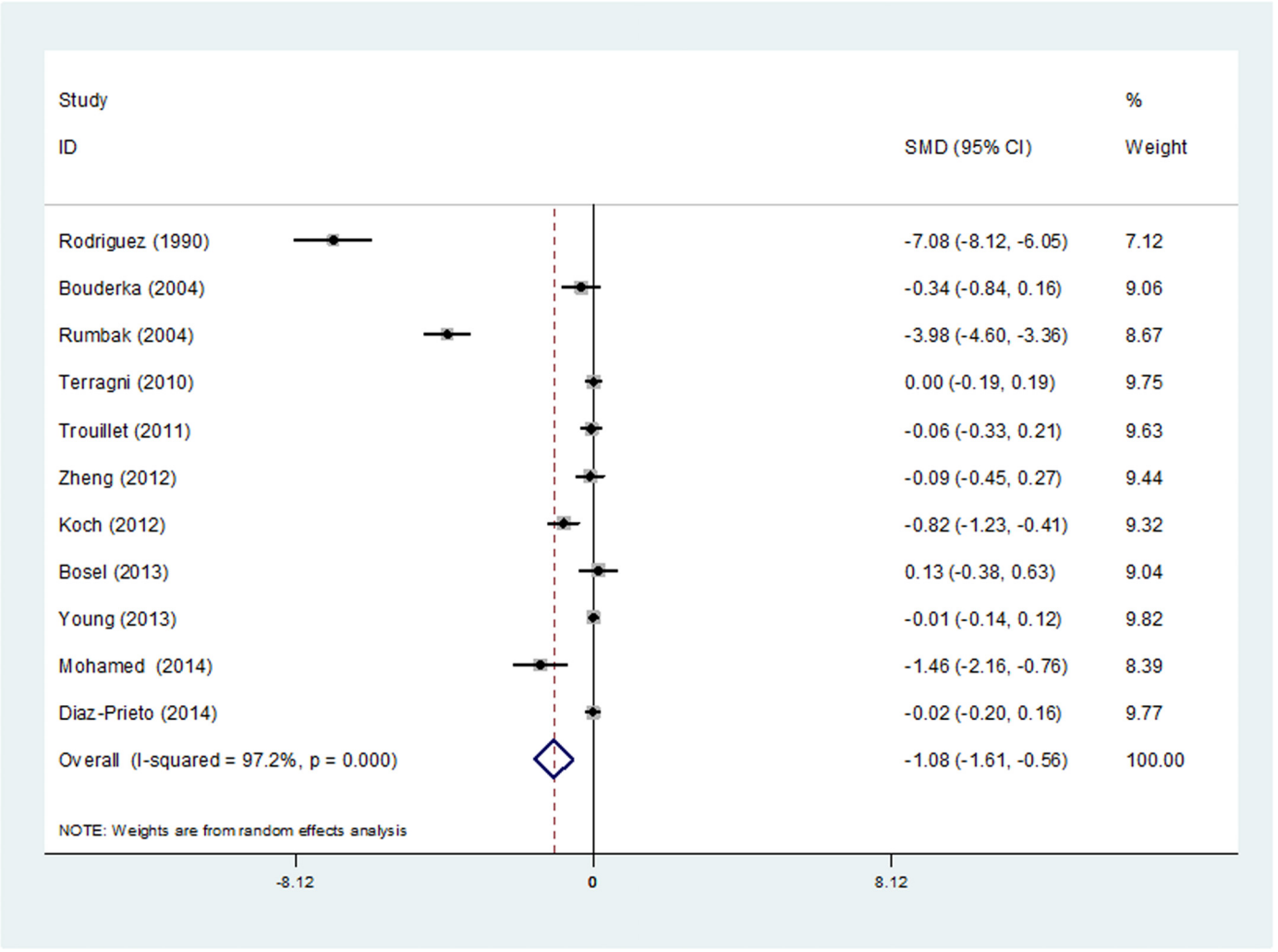

Fig. 5. Forest plot showing the impact of early tracheotomy on length of ICU stay compared to late tracheotomy. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article).

early tracheotomy than in those who had late tracheotomy in any subgroup. The length of ICU stay was assessed in 11 studies and was shorter with early tracheotomy than with late (SMD −1.08, (95% CI, −1.61 to −0.56); $P < 0.001$) (Fig. 5). Findings from subgroup analyses suggested that the effect of early tracheotomy on the length of ICU stay was lower with underlying risk of mortality equal to or greater than 20% and patients in USA. TSA analyses for the duration of MV, duration of sedation, and length of ICU stay were presented in Fig. 6B, C, and D, respectively. The calculations indicated that the optimal information sizes needed to detect reliable effects were 4701, 4212, and 6155 patients. Furthermore, for these outcomes, the Z curve crossed the conventional boundary but not the trial sequential monitoring boundary, which indicated sufficient and conclusive evidence.

Funnel plots for the duration of MV, duration of sedation, and length of ICU stay were presented in Supplemental Figs. 2A, 3A, and 4A, respectively. We detected no evidence of publication bias ($P = 0.081$, $P = 0.055$, and $P = 0.013$). Sensitivity analyses were also carried out to determine the influence of each study on the pooled SMD, and the statistical findings were not materially altered by the elimination of any study (Supplemental Figs. 2B, 3B, and 4B).

Timing of tracheotomy on all-cause mortality

Fig. 7 shows the pooled OR of ICU mortality, hospital mortality, and 28-, 30-, 60-, and 90-day mortality. We did not find any significant difference (early versus late tracheotomy) in either ICU mortality (OR 0.85, (95% CI, 0.68–1.06); $P = 0.139$), hospital mortality (OR 0.85, (95% CI, 0.69–1.04); $P = 0.116$), 28-day mortality (OR 0.79, (95% CI, 0.66–0.96); $P = 0.018$), 60-day mortality (OR 0.96, (95% CI, 0.59–1.56); $P = 0.874$), or 90-day mortality (OR 0.87, (95% CI, 0.63–1.21), and

Discussion

The main finding of the present study is that early (versus late) tracheotomy is associated with shorter duration of sedation. Subgroup analysis found that the benefits of early tracheotomy on duration of sedation are in any subgroup by region and baseline risk of

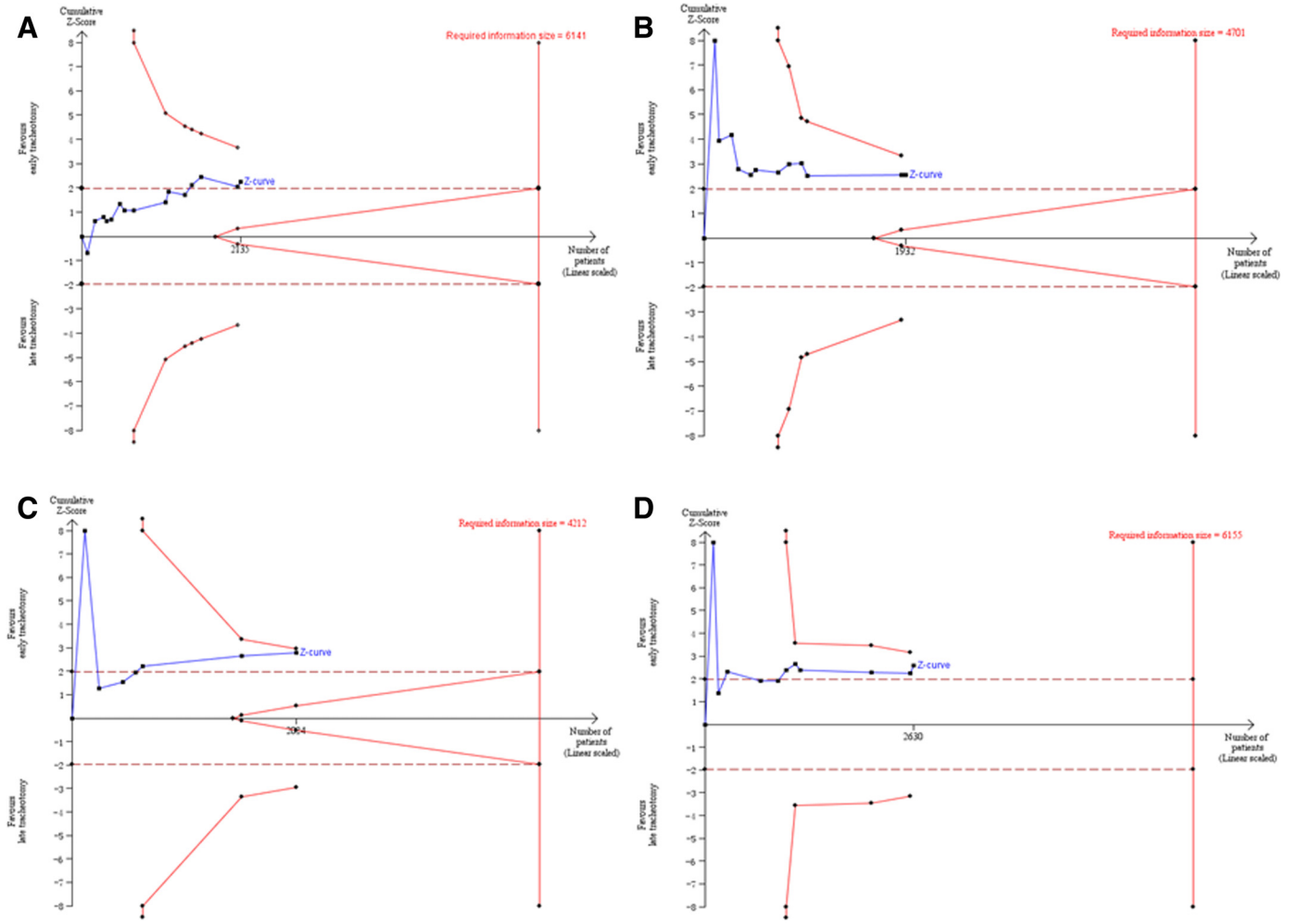

Fig. 6. Trial sequential analyses on (A) incidence of VAP, (B) duration of MV, (C) duration of sedation, and (D) length of ICU stay.

mortality. Thus, duration of sedation may have more impact due to the early tracheotomy. Also, early tracheotomy was associated with a lower risk of VAP, shorter duration of MV, and shorter ICU stay than late tracheotomy. However, the robust TSA aimed at detecting a significant difference indicated a lack of firm evidence for these clinical outcomes. Furthermore, there were no differences regarding all-cause mortality including ICU mortality, hospital mortality and 28-, 30-, 60-, and 90-day mortality.

The development of the percutaneous dilatation technique has allowed physicians to perform tracheotomy at the bedside rather than in the operating room, which has dramatically increased the number of procedures performed.[29] Early tracheotomy may be considered when the clinical impression is that the patient requires prolonged MV and tracheotomy would prevent one or more complications of prolonged intubation including increased patient discomfort, the need for sedation or the risk of pneumonia.[30] Although there was Initially enthusiastic support for early tracheotomy to improve patient outcomes, repeated studies have been unable to reproduce such robust benefits.[13,14,26,31] It is difficult to clarify objective criteria to foresee whether patients will require prolonged ventilatory support and therefore a tracheotomy. Physicians base their decision to perform tracheotomy on subjective clinical criteria that occur as the patient progresses and on the opinions of the patient's relatives.[14] Several studies have also emphasized the difficulty in selecting the time of tracheotomy for mechanically ventilated patients.[22,23] Some reports have proposed scoring systems for predicting prolonged intubation, which may provide a basis for future research on the benefits of early tracheotomy.[32]

The timing of tracheotomy has always been a subject of debate, and previous meta-analyses have conflicting findings.[15,16] To confirm the effect of the timing of tracheotomy, we expanded the previous meta-analysis by including additional RCTs with full published text. We also found that sensitivity analyses did not alter the pooled results, thus providing evidence of the robustness of our findings. Although the main findings of our meta-analysis supported early tracheotomy for some clinical outcomes, we further applied TSA to provide a more conservative estimate of whether our meta-analysis established sufficient and conclusive evidence.

This study has several limitations. First, eight of the 18 RCTs included had a sample size of < 100 patients, and only four RCTs had a sample size >200 patients, which might have resulted in overestimation of the effect size. Second, there is heterogeneity in several of the analyses. Third, differences in definitions of the timing of tracheotomy and critically ill patients in the included trials might account

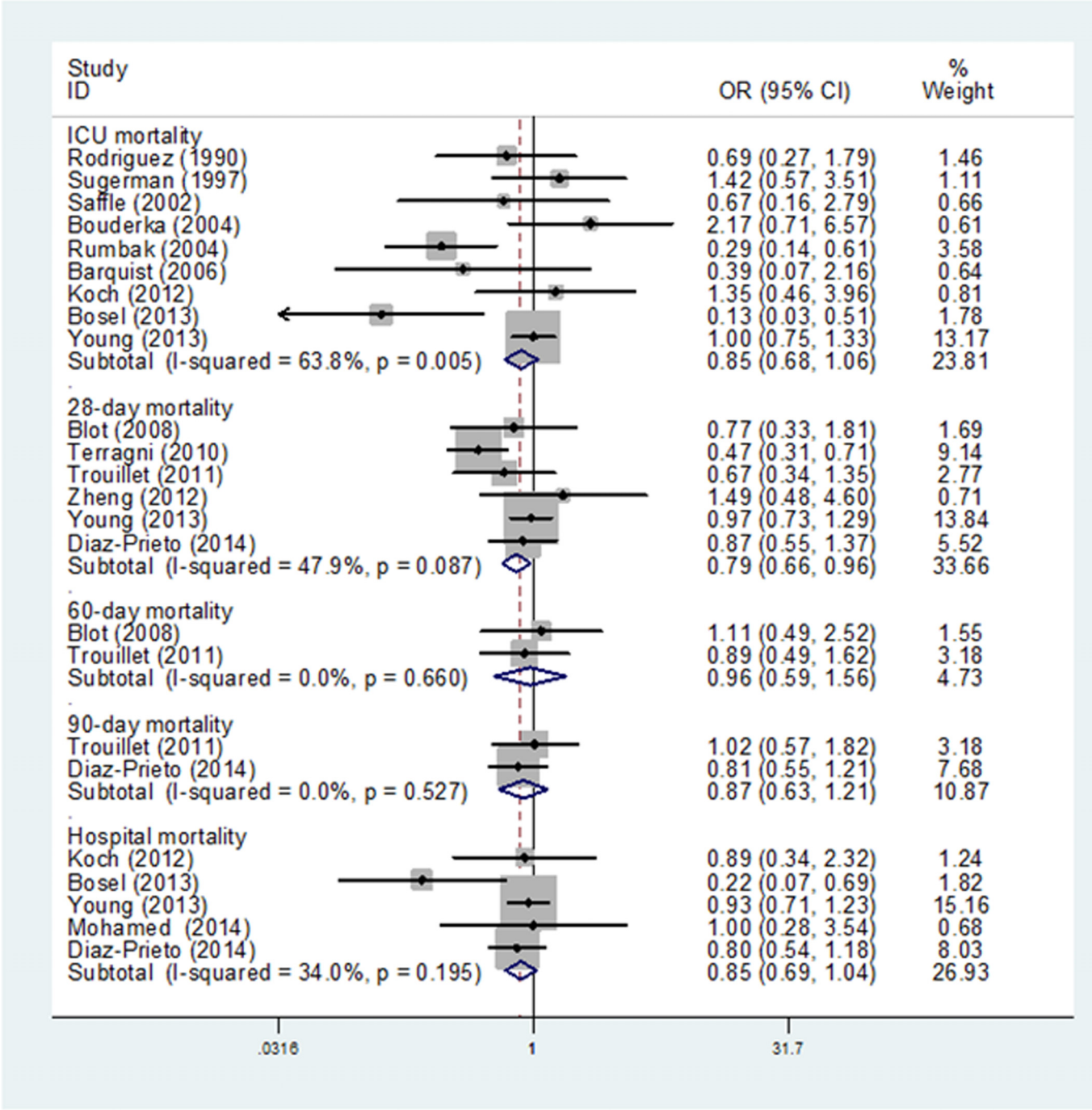

Fig. 7. Forest plot showing the impact of early tracheotomy on mortality compared to late tracheotomy. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

for the observed heterogeneity. The presence of heterogeneity is a critical factor in guiding doctors to choose the timing of tracheotomy. Fourth, the cost-effectiveness of the timing of tracheotomy was not evaluated in this study, because such information was not available in all studies included. Fifth, we have tried to locate unpublished data, but failed. This should be taken into careful consideration when evaluating the results of the present analysis.

In summary, this updated meta-analysis reveals that early tracheotomy seems to be associated with a significantly lower risk of VAP, shorter duration of MV, shorter duration of sedation, and shorter ICU stays than late tracheotomy. However, the apparent benefits observed in these clinical outcomes do not persist after TSA. Furthermore, there is a non-significant trend toward reductions in all-cause mortality. Thus, more powered, randomized controlled trials on this subject are highly warranted. (Table 2).

Table 2
Subgroup analyses ventilator-associated pneumonia, duration of mechanical ventilation, duration of sedation, and length of ICU stay

	Ventilator-associated pneumonia		Duration of mechanical ventilation		Duration of sedation		Length of ICU stay	
	OR (95% CI)	*P*-value	SMD (95% CI)	*P*-value	SMD (95% CI)	*P*-value	SMD (95% CI)	*P*-value
Subgroup analyses by region								
USA	0.63 (0.25 to 1.62)	0.34	−2.8 (−5.13 to −0.48)	0.018	−5.27 (−6.03 to −4.5)	<0.0001	−5.50 (−8.54 to −2.46)	<0.0001
Europe	0.85 (0.55 to 1.32)	0.469	−0.12 (−0.35 to 0.12)	0.325	−0.39 (−0.57 to −0.21)	<0.0001	−0.09 (−0.26 to 0.07)	0.276
Asia	0.26 (0.08 to 0.91)	0.035	−0.17 (−0.47 to 0.14)	0.291	−2.91 (−3.43 to −2.39)	<0.0001	−0.09 (−0.45 to 0.27)	0.617
Africa	0.66 (0.29 to 1.50)	0.316	−0.98 (−1.64 to −0.32)	0.003	/	/	−0.87 (−1.97 to −0.23)	0.12
Subgroup analyses by baseline risk of mortality								
≥20%	0.72 (0.45 to 1.13)	0.154	−1.33 (−2.12 to −0.54)	0.001	−1.13 (−1.75 to −0.52)	<0.0001	−1.25 (−1.86 to −0.64)	<0.0001
<20%	0.55 (0.31 to 0.99)	0.048	−0.27 (−0.62 to 0.09)	0.142	−2.91 (−3.43 to −2.39)	<0.0001	−0.45 (−1.16 to −0.26)	0.217

Conflicts of interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

Funding source

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Ethics

No ethics approval required.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.hrtlng.2018.09.005.

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