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Systematic Review and Meta-Analysis of Early versus Late Tracheostomy on Risk of Ventilator-associated Pneumonia

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An abstract of a thesis submitted to the Faculty of the Rollins School of Public Health of Emory University in partial fulfillment of the requirements for the degree of Master of Public Health in Hubert Department of Global Health, 2017

Abstract

Systematic Review and Meta-Analysis of Early versus Late Tracheostomy on Risk of Ventilator-associated Pneumonia

By

Bayan Ali Shekiri

Objective

To compare the effect of early tracheotomy (ET) and late tracheotomy (LT) on ventilator-associated pneumonia (VAP) incidence and mortality in critically ill patients who received mechanical ventilation.

Method

We searched PubMed, Web of science and the Cochrane Central Register of Controlled Trials. We included randomized controlled trials (RCTs) and observational studies, which compared ET with LT in critically ill patients. Meta-analyses using the random-effects model were conducted for ventilator-associated pneumonia (VAP) and mortality.

Results

A total of 16 studies involving 2542 patients (895 in the ET group and 1647 in the LT group) were included in this analysis. Qualitative analyses show Early tracheotomy could reduce the VAP incidence and reduce the mortality. The meta-analysis showed that there is no significance difference between the ET and LT in the VAP and mortality incidence.

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Introduction

Ventilator-associated pneumonia (VAP) is a lung infection that develops in hospitalized patients with mechanical ventilation (MV). It develops after at least 48 hours of MV. Associated with increased morbidity and mortality, it's the leading cause of death among all causes of hospital-acquired infections (HAI). According to Hunter (2012), the mortality rate attributable to VAP is 27% in ordinary cases, but it has been as high as 43% when the causative agent was antibiotic resistant [19]. In other instances, it has increased the length of stay of patients in the ICU or hospitals. As a result, the cost to patients rises, leaving many bankrupt after medication.

Intubation with the translaryngeal endotracheal tube is the main way to put a patient under MV. Prolonged intubation of critically ill patients often develop VAP. Bassi, *et* al. (2014) indicated that VAP develops as the endotracheal tube allows oropharyngeal contamination to pass freely into the lower segments of the lungs [17].

Tracheostomy is an invasive procedure to replace the endotracheal tube. The procedure has numerous advantages for the patient; the most obvious being that it reduces the adverse effects of the endotracheal. Placing a tracheostomy leads to a less airway dead space and lower airway resistance, both of which have the potential of reducing the work of breathing. Further, it is associated with decreasing need for analgesics and sedatives, both of which have side effects. Other benefits include avoiding oropharyngeal and laryngeal lesions, making oral feeding for the patient possible, as well as making nursing care to patients more comfortable [18]. As with any invasive procedure, there is risk of complications such as bleeding, infections along the path of surgery, subcutaneous emphysema, pneumothorax, and tracheal stenosis [20].

Nevertheless, comparing tracheostomy to prolonged translaryngeal intubation, the benefits of it greatly outweigh the side effects, making it preferable.

Recent studies demonstrate that early tracheostomy can reduce the duration of patient's ventilation, further reducing the time of stay in the ICU and thus reducing the chances of developing VAP. Early tracheostomy is defined as done in the first few days of intubation, as the risk of the VAP is greater at the first week of ventilation, mostly before the 10th day of MV. Late tracheostomy is done anytime after that. Although the endotracheal tube is a risk factor for VAP, the optimum timing of tracheostomy is not defined in critically ill patients who need prolonged intubation. There are studies in various settings of early tracheotomy; most established that differences in timing of the tracheostomy led to different outcomes. Depending on the time of the tracheostomy, the effect on patients may be different. These studies do not invalidated the potential of early tracheostomy to reduce chances of VAP. They put these findings into question. To large extent, the specific potential benefits of optimal timing for conducting the tracheostomy, especially concerning reducing the chances of VAP in the critically ill patients who are in need of a longer period of intubation, is not yet fully established [18].

With inconclusive results, various researchers have conducted multiple studies to determine the relationship between VAP and tracheostomy. Most systematic reviews have been conducted on critically ill patients enrolled only in RCTs.

This study aims to systematically review and evaluate the effect of tracheostomy as identified in RCTs, case control and retrospective cohort to determine if tracheostomy reduces the chances of developing VAP along with reduced mortality.

Methodology

Search strategy and selection

This study was conducted with guidance from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. This was not human subject's research, so IRB review was not required (a note of exemption was received from Emory University). Searching published articles in PubMed, the Web of Science, and Cochrane Central Register of Controlled Trials were done with no date restrictions. The search was limited to human subjects and studies only published in English. These study designs were included: randomized control trials, prospective, retrospective, observational, and case-control studies. Studies were selected to meet these inclusion criteria: 1- critically ill adult patients; 2- intervention to be assessed is early tracheostomy versus late tracheostomy; 3 - the primary outcome of interest is to measure VAP incidence related to both ET and LT. Secondary outcomes was the mortality incidence. Only studies comparing early and late tracheostomy were included; they should have VAP as a primary or secondary outcome. Excluded were those studies involving other than human subjects, articles in different languages, and subjects < 18 years of age. Reports or descriptive studies were also excluded.

Search terms and synonyms identified by Medical Subject Heading (MeSH) were used to find relevant articles in PubMed, Web of Science, and the Cochrane Central Register of Controlled Trials databases:

1- "Tracheostomy" OR "Tracheotomy"

2- "Critically ill" OR "Critical" OR "ICU" OR "Intensive care"

3- “Ventilator-associated pneumonia” OR “hospital-acquired pneumonia” OR “device-related pneumonia” OR “VAP”

Data extraction and analysis

Relevant data were extracted and summarized from eligible studies: author name, publication year, study design, ICU type, early tracheostomy definition, late tracheostomy definition, VAP definition, and outcomes (Table1). Outcomes were manually extracted from studies (proportion of VAP in early tracheostomy groups, proportion of VAP in late tracheostomy groups and mortality incidence) (Table 2). Meta-analyses using the random-effects model were conducted for ventilator-associated pneumonia and mortality.

Table 1 Summary characteristics of included studies for systematic review of early versus late tracheostomies on ventilators, 2017

Study	Type	Setting (ICUι)	ET◊ (days of MV•)	LT♦ (days of MV)	VAP°	Outcomes
Nseir *et* al., 2007 [1]	Retrospective Observational	Surgical	1–7	After 7	CDCτ Criteria	VAP, Mortality
Ahmed *et* al., 2007 [2]	Retrospective Observational	Surgical	1–7	After 7	Clinical features with positive BALɘ cultures	VAP, Mortality
Schneider *et* al., 2009 [3]	Retrospective Observational	Adult	1–7	After 7	Clinical features with positive BAL cultures	VAP, Mortality
Terragni *et* al., 2010 [4]	Randomized Controlled Trial	Multiple	6–8	13–15	Modified CPISε	VAP
Koch *et* al., 2012 [5]	Randomized Controlled Trial	Multiple	1-6	After 6	Modified CPIS	VAP, Mortality
Wang *et* al., 2012 [6]	Retrospective Observational	Surgical	1-10	After 10	Clinical features with positive BAL cultures	VAP, Mortality
Zheng *et* al., 2012 [7]	Randomized Controlled Trial	Surgical	1-3	At day 15	Modified CPIS	VAP, Mortality
Tong *et* al., 2012 [8]	Retrospective Observational	Multiple	1–7	After 7	Not reported	VAP, Mortality
Dunham *et* al., 2014 [9]	Randomized Controlled Trial	Adult	3-5	10-14	Clinical features with positive BAL cultures	VAP, Mortality
Correia *et* al., 2014 [10]	Retrospective Observational	Adult	1–7	After 7	Clinical features with positive BAL cultures	VAP, Mortality
Jeon *et* al., 2014 [11]	Retrospective Observational	Surgical	1-10	After 10	CDC Criteria	VAP, Mortality
Mohamed *et* al., 2014 [12]	Randomized Controlled Trial	Adult	1-10	After 10	Not reported	VAP, Mortality
Gessler *et* al., 2015 [13]	Retrospective Observational	Neurologic	1–7	8–20	Not reported	VAP, Mortality
Hyde *et* al., 2015 [14]	Retrospective Observational	Adult	1–5	After 5	Clinical features with positive BAL cultures	VAP, Mortality
Magdić Turković *et* al., 2016 [15]	Retrospective Observational	Surgical	1–7	After 7	Modified CPIS	VAP, Mortality
Khalili *et* al., 2017 [16]	Retrospective observational	Adult	1–6	After 6	CDC Criteria	VAP, Mortality

ɘ BAL= bronchoalveolar lavage ι ICU= intensive care unit • MV=mechanical ventilation ° VAP= ventilator-associated pneumonia ε CPIS= Clinical Pulmonary Infection Score τ CDC= Centers for Disease Control and Prevention ◊ ET=early tracheotomy ♦LT= late tracheotomy

Table 2 Summary of the outcomes for systematic review of early versus late tracheostomies on ventilators, 2017

Study	Patients N.		VAP° N (%)		VAP P value	Mortality N(%)		Mortality P value
	ET◊	LT♦	ET	LT		ET	LT	
Nseir *et* al., 2007 [1]	49	128	9 (18)	42 (32)	0.041	7 (14%)	66 (51%)	0.001
Ahmed *et* al., 2007 [2]	27	28	11(41%)	14 (50%)	0.59	4 (15%)	1 (4%)	0.19
Schneider *et* al., 2009 [3]	43	115	10 (23.3%)	60 (52.2%)	<0.001	9 (20.9%)	37 (32.2%)	0.168
Terragni et al., 2010 [4]	209	210	30 (14.4%)	44 (21.0%)	0.07	NA	NA	NA
Koch *et* al., 2012 [5]	50	50	19 (38%)	32 (64%)	Not reported	10(20%)	11(22%)	0.81
Wang *et* al., 2012 [6]	16	50	7 (44%)	38 (76%)	0.04	2 (12%)	4 (8%)	0.63
Zheng *et* al., 2012 [7]	58	61	17 (29.3%)	30 (49.2%)	0.027	8 (13.8%)	6 (9.8%)	0.551
Tong *et* al., 2012 [8]	128	464	3 (2%)	15 (3%)	0.61	31 (24%)	150 (32%)	0.08
Dunham *et* al., 2014 [9]	15	9	7 (46.7%)	4 (44.4%)	0.69	0 (0.0%)	0 (0.0%)	> 0.05
Correia *et* al., 2014 [10]	18	101	1 (5.6)	44 (43.6)	0.001	2 (11.1%)	25 (24.8%)	0.36
Jeon *et* al., 2014 [11]	39	86	2 (5%)	16 (18.6%)	0.056	2 (5%)	6 (7%)	1
Mohamed *et* al., 2014 [12]	20	20	4 (20%)	8 (40%)	0.167	8 (40%)	8 (40%)	1.000
Gessler *et* al., 2015 [13]	39	109	19(48.7%)	75 (68.8%)	0.03	3(7.7%)	8(7%)	0.93
Hyde *et* al., 2015 [14]	53	53	18 (34%)	34 (64%)	0.0019	6 (12%)	4 (8%)	0.49
Magdić Turković *et* al., 2016 [15]	78	64	27 (45%)	33 (55%)	0.06	21 (27%)	20 (31%)	0.704
Khalili *et* al., 2017 [16]	53	99	28 (52.8)	59 (59.6)	0.492	10 (18.9%)	18 (18.2%)	>0.99
Total	895	1647	238(26.6%)	548 (33%)		123 (18%) out of 686	364 (25.3%) out of 1437	

◊ ET=early tracheotomy ♦LT= late tracheotomy ° VAP= ventilator-associated pneumonia

Results

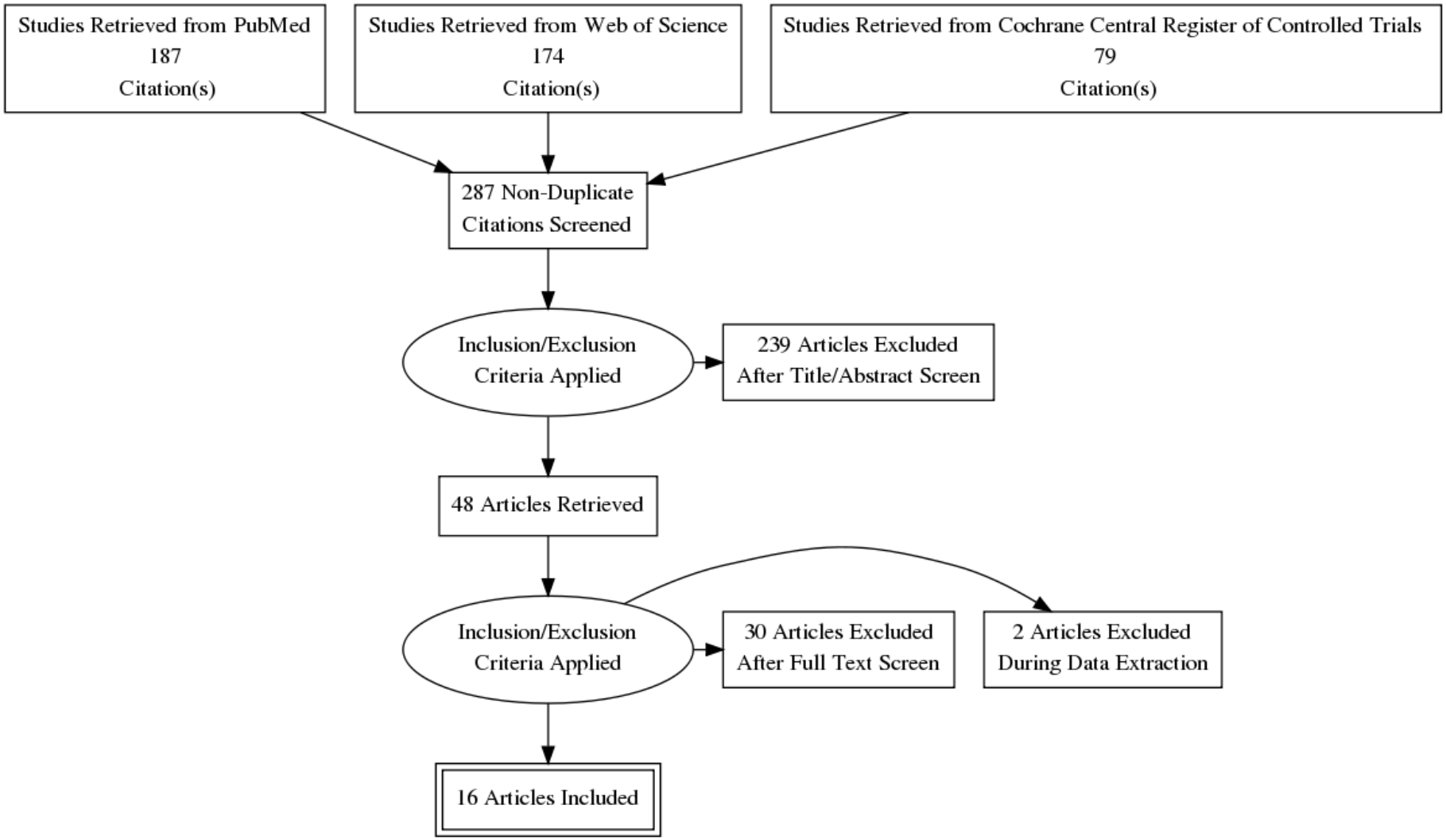
Study selection

Electronic searches done in PubMed, Web of Science, and the Cochrane Central Register of Controlled Trials yielded 440 articles. Screened by abstract, we excluded 390 that were duplicates or not related. Full text screening of the remaining 48 resulted in 30 not meeting the eligibility criteria. Two were excluded during the data extraction because of no comparison between early and late tracheostomy. Therefore, 16 studies were included in the final analyses (Figure 1).

Study Characteristics

Of the 2542 patients enrolled, 895 were assigned to the early tracheostomy group and 1647 were assigned to late tracheostomy group (Table 1). These 16 studies included randomized controlled trials, retrospective analysis, and prospective case-control studies. All patients were critically ill and admitted to the ICU due to various conditions (e.g., surgery or trauma). All had VAP as a primary or secondary outcome. One study reported only VAP as an outcome, two reported VAP and mortality; the rest reported VAP and mortality.

Figure 1 Selection process for Systematic Review of Early versus Late Tacheostomies on Ventilators, 2017



Primary outcome, Ventilator-Associated Pneumonia

All of the sixteen studies reported and evaluated the incidence of ventilator-associated Pneumonia. Out of 895 patients assigned to early tracheostomy, there was 238 (26.6%) patient diagnosed with VAP. While from the 1647 patients assigned to late tracheostomy there were 548 (33%) were diagnosed with VAP. From these results, we can see that the incidence of VAP was lower in the early tracheostomy group vs. late tracheostomy group (26.6% vs. 33%).

We used a random effect model to do the statistical meta-analysis. Through eyeball test looking to the forest plot at studies level, we can see that there are 4 studies [2] [3] [5] [14] that their 95% confidence interval did not overlap the null value. That mean the early tracheostomy was significantly difference in decreasing the VAP rate. Comparing to the rest of the studies where their confidence intervals overlapped the null value, there were no statistical significance. However, statistically overall at meta-analysis level, it was not significantly different (RR = 0.98; 95% CI = 0.72–1. 32; P = 0.88) with statistical evidence of heterogeneity among all studies (I-squared = 88.7%) (Table 3) (Figure 2)

Table 3 Summary of Meta-Analysis estimate for VAP outcome, 2017

Study	RR	[95% Conf. Interval]		% Weight
Nseir *et* al., 2007 [1]	1.569	0.828	2.972	6.05
Ahmed *et* al., 2007 [2]	0.503	0.383	0.661	7.76
Schneider *et* al., 2009 [3]	0.284	0.217	0.371	7.78
Terragni *et* al., 2010 [4]	1.230	0.919	1.648	7.69
Koch *et* al., 2012 [5]	0.579	0.461	0.728	7.91
Wang *et* al., 2012 [6]	1.558	0.698	3.480	5.23
Zheng *et* al., 2012 [7]	1.348	0.883	2.055	7.13
Tong *et* al., 2012 [8]	1.297	0.457	3.686	4.17
Dunham *et* al., 2014 [9]	0.982	0.570	1.692	6.54
Correia *et* al., 2014 [10]	6.807	0.936	49.509	1.82
Jeon *et* al., 2014 [11]	2.808	0.741	10.642	3.18
Mohamed *et* al., 2014 [12]	1.500	0.636	3.538	4.97
Gessler *et* al., 2015 [13]	1.304	0.804	2.114	6.84
Hyde *et* al., 2015 [14]	0.515	0.422	0.628	8.00
Magdić Turković *et* al., 2016 [15]	1.221	0.889	1.676	7.59
Khalili *et* al., 2017 [16]	1.083	0.745	1.576	7.35
D+L pooled RR	0.977	0.722	1.323	100.00

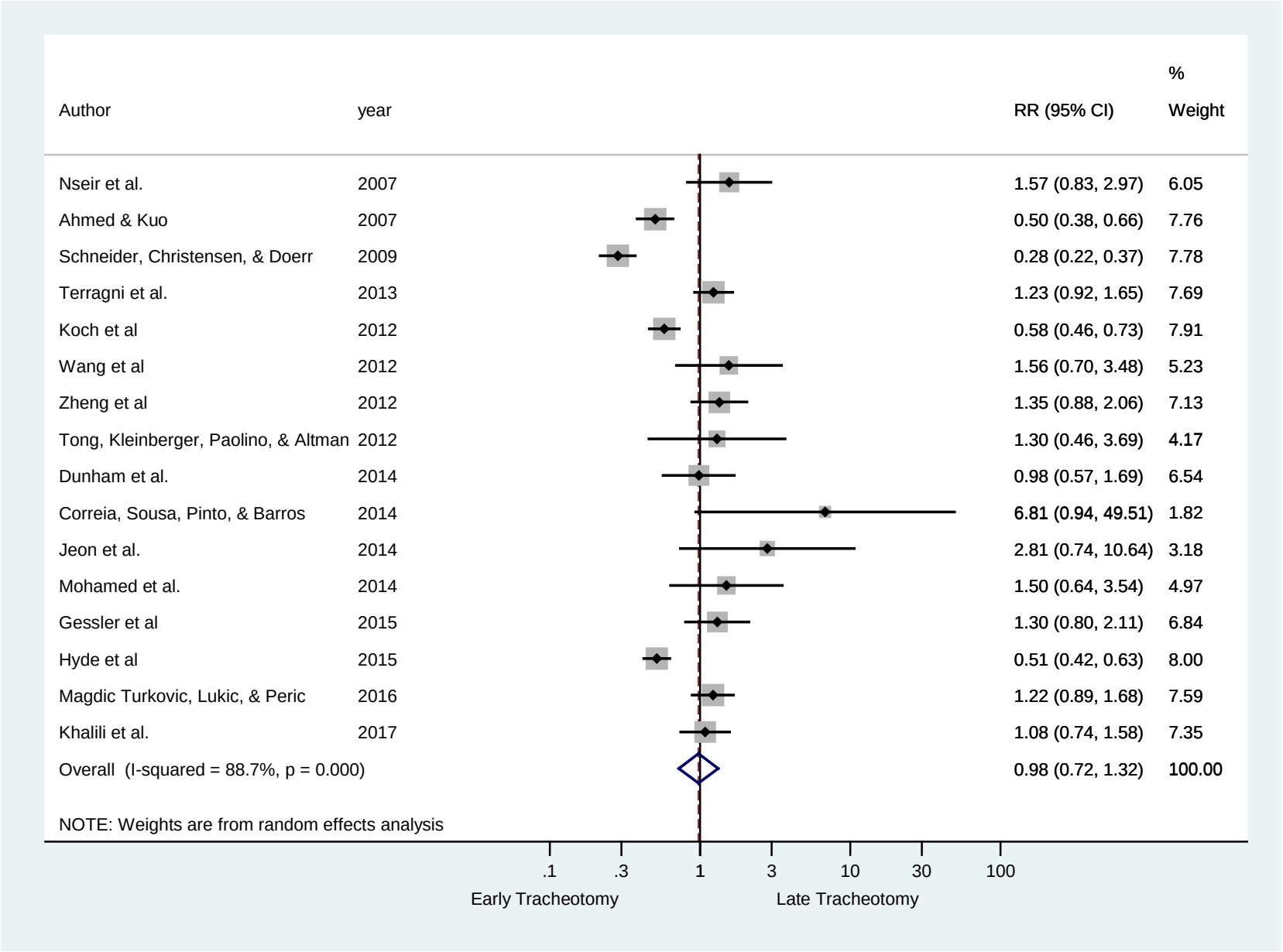
Heterogeneity chi-squared = 132.90 (d.f. = 15) p = 0.000

I-squared (variation in RR attributable to heterogeneity) = 88.7%

Estimate of between-study variance Tau-squared = 0.2881

Test of RR=1 : z= 0.15 p = 0.881

Figure 2 Forest Plot for Incidence of VAP in Early versus Late Tracheostomy, 2017



Secondary outcome, Mortality

Fifteen studies evaluated mortality among early tracheostomy and late tracheostomy patients. There were 123 (18%) patient died from total 686 patients assigned to early tracheostomy and 364 (25.3%) of 1437 patients died in the late tracheostomy group. From these results, we can see that the mortality incidence was lower in the early tracheostomy group vs. late tracheostomy group (18% vs. 25.3%).

Random effect model was used to do the statistical meta-analysis. Through visual examination to the forest plot at studies level, we can see that there are 4 studies [2] [3] [5] [14] that their 95% confidence interval did not overlap the null value. That mean the early tracheostomy was significantly difference in decreasing the mortality rate in these studies. In the other side there was one study significantly decreasing mortality rate in the late tracheostomy group [1]. Comparing to the rest of the studies where their confidence intervals overlapped the null value, there were no statistical significance. However, statistically overall at meta-analysis level, there was not quit significant difference between the two groups (RR = 0.79; 95% CI = 0.59–1. 04; P = 0.09) with statistical evidence of heterogeneity among all studies (I-squared = 84.8%) (Table 4) (Figure 3).

Table 4 Summary of Meta-Analysis estimate for Mortality outcome, 2017

Study	RR	[95% Conf. Interval]		% Weight
Nseir *et* al., 2007 [1]	2.887	1.373	6.072	6.12
Ahmed *et* al., 2007 [2]	0.507	0.383	0.671	9.58
Schneider *et* al., 2009 [3]	0.280	0.216	0.363	9.70
Koch *et* al., 2012 [5]	0.512	0.417	0.629	10.01
Wang *et* al., 2012 [6]	0.727	0.217	2.437	3.62
Zheng *et* al., 2012 [7]	0.853	0.523	1.392	8.04
Tong *et* al., 2012 [8]	1.262	0.885	1.801	9.06
Correia *et* al., 2014 [10]	2.042	0.504	8.280	2.96
Jeon *et* al., 2014 [11]	1.248	0.365	4.262	3.54
Mohamed *et* al., 2014 [12]	1.000	0.560	1.786	7.33
Gessler *et* al., 2015 [13]	0.966	0.355	2.631	4.56
Hyde *et* al., 2015 [14]	0.833	0.485	1.431	7.63
Magdić Turković *et* al., 2016 [15]	0.559	0.478	0.654	10.24
Khalili *et* al., 2017 [16]	0.976	0.568	1.679	7.62
Dunham *et* al., 2014 [9]	(Excluded)			
Terragni *et* al., 2010 [4]	(Excluded)			
D+L pooled RR	0.785	0.591	1.043	100.00

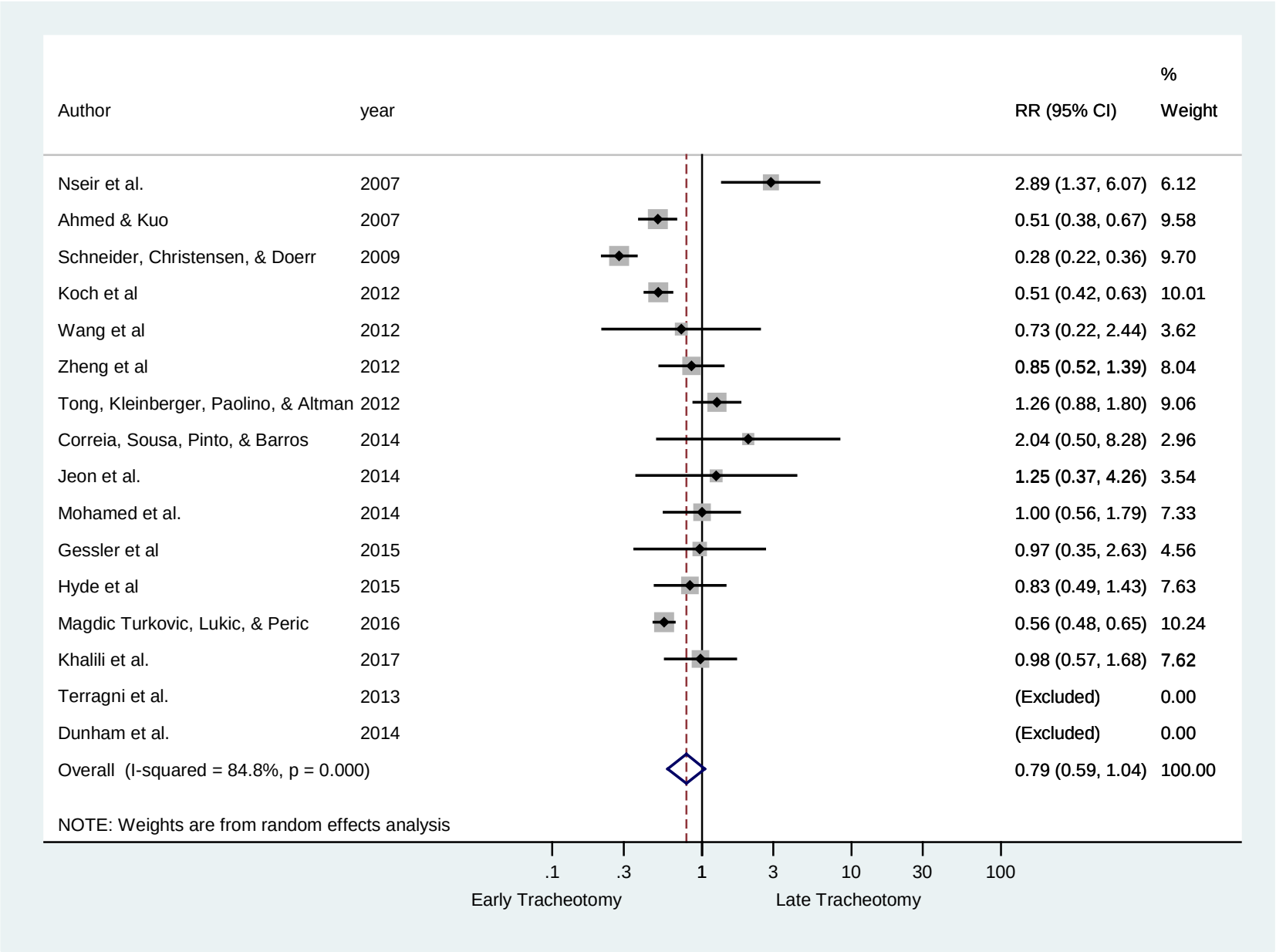
Heterogeneity chi-squared = 85.46 (d.f. = 13) p = 0.000

I-squared (variation in RR attributable to heterogeneity) = 84.8%

Estimate of between-study variance Tau-squared = 0.1980

Test of RR=1 : z= 1.67 p = 0.095

Figure 3 Forest Plot for Incidence of Mortality in Early versus Late Tracheostomy, 2017



Publication Bias assessment

To explore the apparent associations between the effect size and study size (Publication bias) for the Ventilator associated pneumonia outcome and Mortality outcome, graphical approach and statistical tests were employed. Funnel plots presented at (Figure 4) and (Figure 5) can be interpreted to be asymmetric which is an indication that the smaller studies tend to give results emphasizing the effect of late tracheostomy. The contour plot distinguished between publication bias and other causes of asymmetry. The plot revealed that smaller studies were found not only in the areas of statistical significance which is given by the shaded area but also in area of non-significance which is given by the white area.

Heterogeneity investigation:

To examine the magnitude and statistical significance of the relationship between the observed effect size of the study and the size of the studies, the Egger's meta-regression model were estimated and the result also confirm that the smaller studies tend to give different results compared to larger studies as the confidence interval of the intercept is considerably wide.

Also, the trim-and-fill method was applied, though the assumption which states that the asymmetry funnel plot is solely caused by publication bias cannot be established in this report.

Figure 4 Funnel plot for VAP incidence in Early versus Late Tracheostomy, 2017

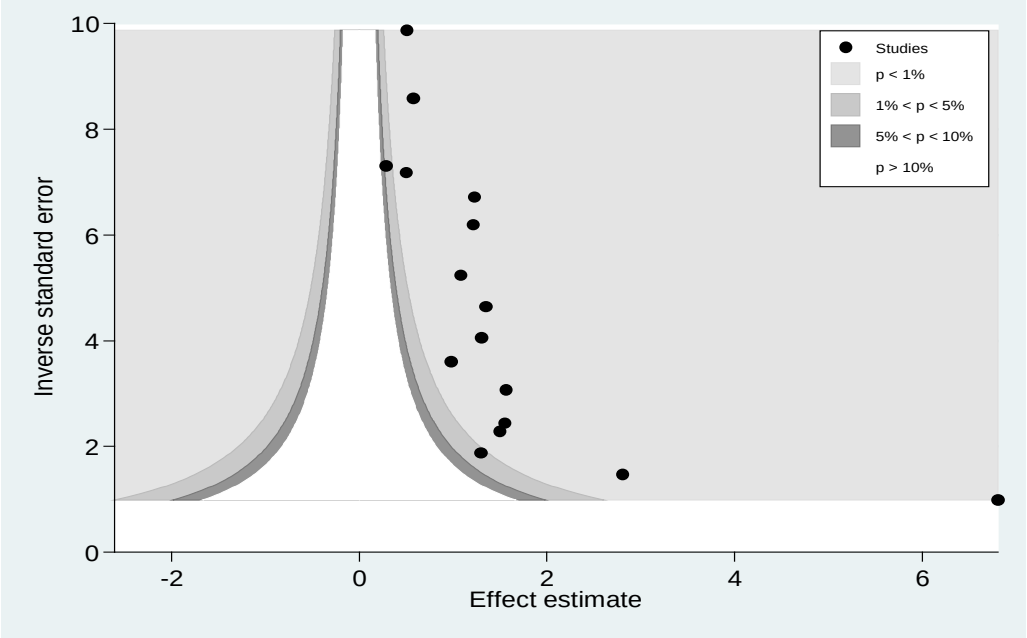
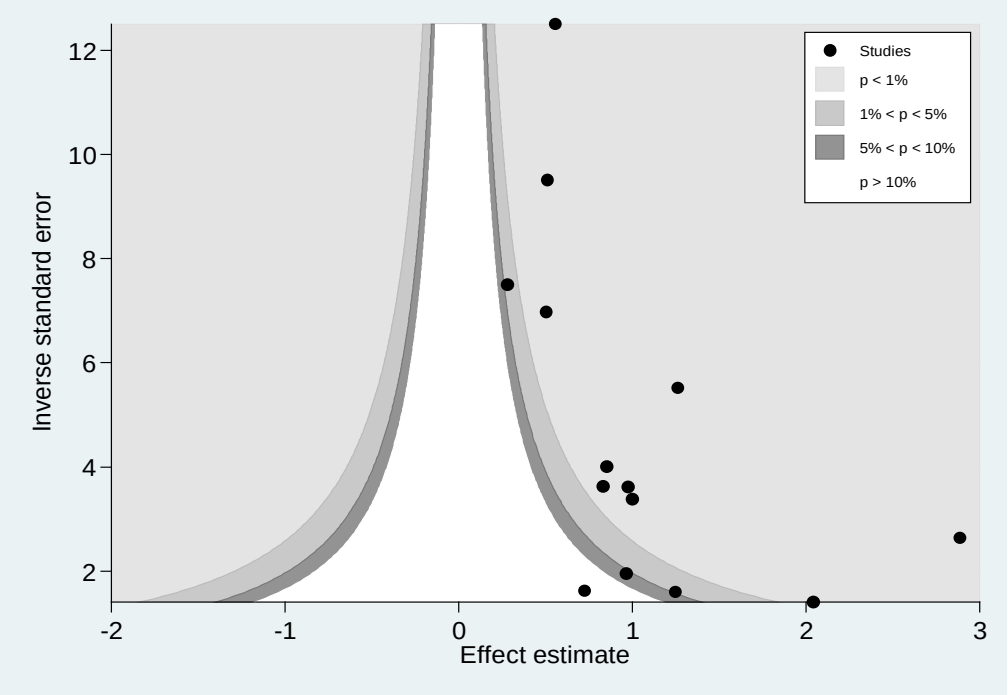


Figure 5 Funnel plot for Mortality incidence in Early versus Late Tracheostomy, 2017



Discussion

There have been six meta-analyses [23-28] of RCTs and one meta-analysis of observational studies [29] published to show the relationship of the tracheostomy timing on clinical prognosis of the patients. All of them are comparing the early tracheostomy with late tracheostomy or prolonged intubation and assessing the effect of tracheostomy timing on mortality, VAP, length of ICU stays and other outcomes.

Our study was the first study that pulled data from both observational and randomized controlled trials together to assess the impact of tracheostomy timing effect on clinical prognosis of critically ill patients. In our study, we identified 16 studies that compared the effect of ET and LT among critically ill patients who received mechanical ventilation. Narrative review and meta-analyses were conducted to estimate the overall VAP incidence and mortality incidence in both groups. The narrative analysis shows that the incidence of VAP and mortality could be reduced with the performance of early tracheostomy.

Meta-analyses for two RCTs [23] [25] and the meta-analysis for observational studies [29] show that Early tracheostomy has significant benefit in reducing the mortality and length of ICU stay, but it does not influence VAP. The rest of meta-analyses [24] [26] [27] [28] shows that the incidence of VAP was not statistically different between ET and LT in VAP incidence and Mortality which was similar to our study results.

This study has several limitations. The definition of early tracheostomy and late tracheostomy were different among the studies. Also, the diagnostic criteria of VAP

were different, and some of the studies didn't report it. One of the considered limitation is the heterogeneity level. Also, it was possible that we didn't retrieve all published articles, but by performing the search many times, we minimize that risk.

Conclusion

Over the years, Patient clinical outcomes based on the timing of tracheotomy, especially when considering the incidence of ventilator-associated pneumonia, mortality, and time of hospitalization, outcomes have been controversial. Early tracheostomy has shown benefits over late tracheostomy in our narrative review and some of other studies. Intensive care physician should consider the tracheostomy timing cautiously.

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