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REVIEW

Early *versus* late tracheostomy for traumatic brain injury: a systematic review and meta-analysis

Pietro BERTINI [1] *, Alberto MARABOTTI [2, 3], Gianluca PATERNOSTER [4], Fabio SANGALLI [5], Diego COSTANZO [1], Alessandro ISIRDI [1], Matteo ROMANI [1], Niccolò CASTELLANI NICOLINI [1], Giulia BRIZZI [1], Michele CHECCHI [2], Fabio GUARRACINO [1]

[1]Department of Anesthesia and Critical Care Medicine, Azienda Ospedaliero-Universitaria Pisana, Pisa, Italy; [2]Department of Surgical, Medical and Molecular Pathology and Critical Care Medicine, University of Pisa, Pisa, Italy; [3]Intensive Care Unit and Regional ECMO Referral Center, Azienda Ospedaliero-Universitaria Careggi, Florence, Italy; [4]Division of Cardiac Resuscitation, Cardiovascular Anesthesia and Intensive Care, San Carlo Hospital, Potenza, Italy; [5]Anesthesia and Intensive Care, ASST Valtellina e Alto Lario, Milan, Italy

*Corresponding author: Pietro Bertini, Cardiothoracic and Vascular Anesthesia and Intensive Care, Department of Anesthesia and Critical Care Medicine, Azienda Ospedaliero Universitaria Pisana, Via Roma 67, 56124 Pisa, Italy. E-mail: pietro.bertini@gmail.com

ABSTRACT

INTRODUCTION: Tracheostomy is the most frequent bedside surgical procedure performed on patients with traumatic brain injury who require mechanical ventilation. To compare the effects of early tracheostomy *vs.* late tracheostomy on the duration of mechanical ventilation in patients with traumatic brain injury, we carried out a systematic review and meta-analysis.

EVIDENCE ACQUISITION: MEDLINE, Scopus, Web of Science, and Cochrane were searched from inception to 17th October 2022. Eligible clinical trials and observational studies reporting early *versus* late tracheostomy in TBI were searched. Two reviewers extracted data and independently assessed the risk of bias. The duration of mechanical ventilation was the primary outcome.

EVIDENCE SYNTHESIS: We pooled standardized mean differences and risk differences for random effects model. A total of 368 studies were retrieved and screened. Nineteen studies were selected, including 6253 patients. Mean time for early tracheostomy and late tracheostomy procedures was 6±2.9 days and 17±10.7 days, respectively. Early tracheostomy was associated with shorter mechanical ventilation duration (SMD=-1.79, 95% CI -2.71; -0.88) and fewer ventilator associated pneumonia (RD=-0.11, 95% CI -0.16; -0.06) when compared with late tracheostomy. Moreover, intensive care unit (ICU) (SMD=-1.64, 95% CI -2.44; -0.84) and hospital (SMD=-1.26, 95% CI -1.97; -0.56) length of stay were shorter when compared with late tracheostomy.

CONCLUSIONS: The findings from this meta-analysis suggest that early tracheostomy in severe TBI patients contributes to a lower exposure to secondary insults and nosocomial adverse events, increasing the opportunity of patient's early rehabilitation and discharge.

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KEY WORDS: Tracheostomy; Meta-analysis; Traumatic brain injury; Critical care; Intensive care units.

Introduction

Traumatic brain injury (TBI) is a complex illness that can cause temporary or permanent abnormalities in physical, cognitive, or psychosocial functioning due to both direct and indirect neurological damage. The main sources of injury include assaults, falls, and car crashes.[1] The anticipated global incidence of TBI is 939 cases per 100,000 people, however this number is much higher in North America (1299 cases per 100,000 people) and Europe (1012 cases per 100,000 people).[2] A further 69 million individuals will experience TBI each year, with an additional 5.48

million experiencing severe TBI (73 cases per 100,000 people annually).[3] This illustration highlights the epidemiological and monetary costs of TBI. Initiatives that reduce hospital costs while maintaining the caliber of service are essential to ensuring financial viability and improving patient care. Tracheotomy and tracheostomy are two terms that can be used interchangeably, although the first refers to the surgical dissection and the opening of the anterior wall of the trachea while the second refers to a percutaneous way of blunt dissection using a Seldinger's technique. For seriously ill patients requiring protracted mechanical ventilation (MV), tracheostomy can reduce complications from prolonged tracheal intubation (*i.e*. ventilation associate pneumonia [VAP]), tracheal lesions and MV duration.[4, 5] In 1989 the first consensus conference on artificial airways recommended endotracheal intubation when the estimated intubation time was shorter than 10 days while tracheostomy when was longer than 21 days.[6] In 2017 guidelines for tracheostomy in critical care patients stated that the only advantage of early tracheostomy (ET) was the reduction of the duration of MV (Grade 1B).[5] Conversely, a recent Bayesian analysis of a systematic review comparing early versus late tracheostomy (LT) demonstrated that the risk of all adverse clinical outcomes was reduced for ET.[7] Consequently, the debate on the timing of tracheostomy is still very active, even more in the TBI population. In TBI patients, tracheostomy is needed in case of failure to maintain a patent upper airway, impairment of respiratory drive, and difficulties in managing secretions. However, tracheostomy indication largely depends on the possibility of neurological recovery. The timing of tracheostomy should be balanced between the risk of a prolonged intubation in a patient with poor neurological recovery and the risk of an early tracheostomy in a patient with a rapid neurological recovery, exposing him only to procedure-related risks. This work aims to compares the impact of ET, a relatively low-cost and minor surgical procedure, with LT on the hospitalization outcomes of TBI patients based on the aforementioned presumptions.

A graphical abstract is provided in Supplementary Digital Material 1 (Supplementary Figure 1).

Evidence acquisition

This systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement's recommendations. The review protocol was published in the International Prospective Register of Systematic Reviews PROSPERO and is available at https://www.crd.yorl.ac.uk/PROSPERO under registration number CRD42022296258.

Search strategy

The literature search was carried out by two authors using MEDLINE, Scopus, Web Of Science, Cochrane Library Databases. The search terms included the following search string ((Early OR Late) AND (Tracheostomy OR (Tracheal Tube) OR (Tracheotomy)) AND ((Traumatic Brain Injury) OR TBI OR (Head injury)) throughout October 17th, 2022. Search limitations were not applied. The PRISMA flow diagram is shown in Figure 1. A supplementary search of the USA National Institutes of Health Registry (clinicaltrials.

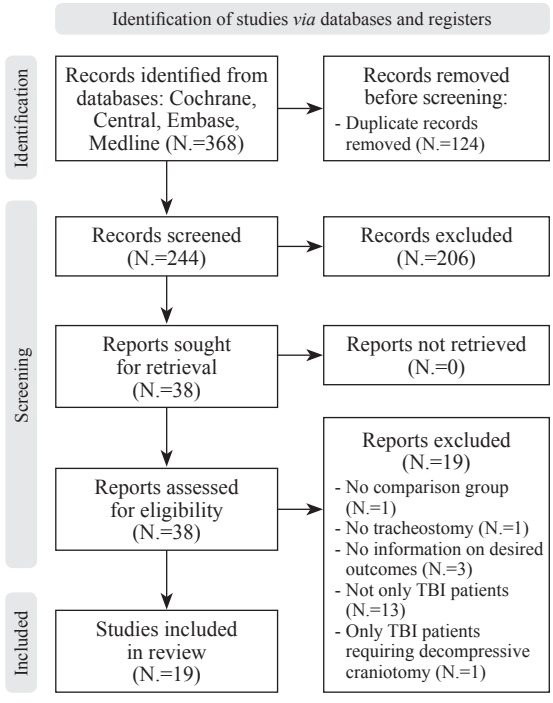

Figure 1.—PRISMA flow diagram.

gov) to screen for ongoing clinical trials using the term "Traumatic Brain Injury" and "tracheostomy" yielded seven results, only three studies pertaining to our purpose (Figure 1).

Eligibility criteria

We looked at all studies that mentioned tracheostomy for TBI in critically ill patients. The ET group was defined as the intervention group. LT was considered the control group.

Study selection and data extraction

We examined the abstracts and all of the titles. Studies and duplicate articles that were irrelevant were removed. To choose the final reports, all pertinent abstracts in their entirety were collected and double-checked. The information from the included studies was compiled and summarized in regard to the objective(s) of the study(s), design, length, sample size, inclusion and exclusion criteria, interventions, comparators, pertinent definitions, indication and timing of tracheostomy, outcomes, results, limitations, and conclusions. The main outcomes were MV duration and pneumonia caused by ventilation (VAP). The incidence of deep vein thrombosis (DVT), length of stay in the intensive care unit (ICU), and hospital expenses were all included as secondary outcomes in addition to mortality. The GRADE approach was used to evaluate the caliber of the evidence for the primary outcomes (Grading of Recommendations Assessment, Development, and Evaluation) based on five primary criteria: 1) risk of bias; 2) indirectness; 3) publication bias; 4) inconsistency; and 5) imprecision.[8] The degree of certainty associated with each outcome in the body of evidence was rated as high, moderate, low, or extremely low. A number of factors affected the evaluation, including publication bias, indirectness, inconsistency, and bias risk.[9]

Risk of bias assessment

The Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool was used to assess the validity of the observational studies.[10] Using the seven-category ROBINS-I approach, the degree of bias was rated as low, moderate, serious, major risk, or no information. The methodological quality of the accepted papers was evaluated separately by two reviewers, with disagreements being settled by discussion with a third reviewer. The revised Cochrane risk of bias tool for randomized trials was used to assess the validity of randomized trials.[11]

Data synthesis and analysis

Continuous variables were analyzed for primary and secondary outcomes: standardized mean difference (SMD) with 95% confidence intervals (CI) was calculated, and a pooled estimate, was computed weighting SMDs according to the variance and the number of participants in the study.[12] For categorical data, risk differences (RD) were estimated with 95% CI. In the initial stage, both of the individual study statistics and combinations of them were carried out. Then, the random-effects model was used. The investigation of additional variables, overall impact size, and the presence of heterogeneity were all part of the analysis. Visual assessment of forest plots, CI, and its minimum or no overlap were used to determine inconsistency among studies. The dichotomous primary outcome measures were subjected to sensitivity analysis. Studies were removed and replaced based on sample size or methodologic issues to ensure that the overall result, i.e. OR and conclusions, was not influenced. Sensitivity analysis is carried out performing the meta-analysis first by including all studies and then by removing studies one at the time and examining the overall effect; that is, to see if the overall outcome and findings were not influenced[13] (Supplementary Digital Material 2: Supplementary Tables I-X, Supplementary Figure 2-28). Because of the variety of studies and demography, we did not expect a similar impact size, and we predicted high heterogeneity. Therefore, a priori use of the random-effects model[14] was decided using the metafor package for R[15] and R-Studio Version 1.3 for macOS. Type II errors are less likely with this approach. Effects estimates are given as squares for each study, while proportions with their 95% confidence intervals are presented as horizontal lines. The I^2 and the chi-square test were employed to determine study heterogeneity. Heterogeneity was categorized as low (25%) moderate (50%) or high (75%).[16] The methodology outlined by Hozo *et al.* was used to estimate mean and standard de-

viation in studies that only reported median and interquartile range.[17] Effect estimates and their associated 95% Cis were used to summarize the findings. Visual inspection of the funnel plot indicated publication bias, which was then tested using Egger's test.[18] Publication bias was suspected when the P value was less than 0.05.

Evidence synthesis

A total of 368 records were screened as a consequence of the literature search, and 124 articles were screened after duplicates removal. 38 full-text papers were evaluated for eligibility after studies that did not fulfill the inclusion criteria were excluded (Figure 1). Nineteen papers were eliminated from the analysis, leaving 19 studies comprising 6253 patients.[19-37] For missing data, all corresponding authors were contacted; none gave further information. No pertinent ongoing randomized trials were identified. Patient's and study protocol characteristics are summarized in Table I and II.[19-37]

Tracheostomy time frames varied across studies, a more detailed description of time-points is in Supplementary Digital Material 2.

All the studies were at risk of bias due to confounding which affected the overall judgment of bias for the two primary outcomes VAP and MV (Supplementary Digital Material 2).

Evidence synthesis

Duration of mechanical ventilation

The duration of MV was analyzed in 11 studies[20, 22, 24, 26, 27, 30, 31, 34-37] including 2484 patients:

TABLE I.—*Characteristics of the five randomized controlled studies and the fourteen cohort studies comparing early vs late tracheostomy for traumatic brain injury ordered by publication year.*[19-37]

Study	Year	N. patients	Design	Country	Setting	Protocol
Sugerman[19]	1997	67	Randomized	USA	3 groups of patients: head trauma; non-head trauma and critically ill non-trauma	Early tracheostomy (day 3 – day 5) *vs.* continued endotracheal intubation (if tracheostomy necessary for airway control, it was performed between day 10 and day 14)
Bouderka[20]	2004	62	Randomized	Morocco	Isolated head injury with admission GCS ≤8. Randomization at day 5	Early tracheostomy (5th-6th day after admission) *vs.* prolonged endotracheal intubation
Barquist[21]	2006	60	Randomized	USA	Traumatic brain injury with GCS <4 with a negative brain computed tomography (CT) or a GCS >9 with a positive head CT. Randomization before day 8	Early tracheostomy (before day 8) *vs.* late (> day 28)
Ahmed[22]	2007	55	Non-randomized	USA	Traumatic brain injury with admission GCS ≤8 and expected survival >3 days	Early tracheostomy (≤ day 7) *vs.* late (> day 7)
Rizk[23]	2011	3104	Non-randomized	USA	Patients with evidence of traumatic head injury and admission GCS ≤8. Exclusion for isolated head injury and length of ICU stay <72 h	Early tracheostomy (≤ day 7) *vs.* late (> day 7)
Wang[24]	2012	66	Non-randomized	Taiwan	Traumatic brain injury with admission GCS ≤8	Early tracheostomy (≤ day 10) *vs.* late (> day 10)
Huang[25]	2013	38	Non-randomized	Taiwan	Traumatic brain injury requiring decompressive craniectomy. Exclusion for death in the first 7 days after trauma.	Early tracheostomy (≤ day 10 after decompressive craniectomy) *vs.* late (> day 10 after decompressive craniectomy)
Alali[26]	2014	1142	Non-randomized	Canada	Traumatic brain injury with head AIS score ≥3. Exclusion for severe injuries in other body regions, penetrating trauma or directives to withhold life-sustaining interventions	Early tracheostomy (≤ day 8) *vs.* late (> day 8)
Dunham[27]	2014	24	Randomized	USA	Blunt trauma with admission GCS ≤8. Randomization at day 3	Early tracheostomy (day 3-5) *vs.* late (day 10-14 if endotracheal extubation was not imminent)

(To be continued)

TABLE I.—*Characteristics of the five randomized controlled studies and the fourteen cohort studies comparing early vs late tracheostomy for traumatic brain injury ordered by publication year.*[19-37] *(continues).*

Study	Year	N. patients	Design	Country	Setting	Protocol
Siddiqui[28]	2015	100	Non-randomized	Pakistan	Isolated traumatic brain Injury with admission GCS <8	Early tracheostomy (≤ day 7) *vs.* late (> day 7)
Khalili[29]	2017	152	Non-randomized	Iran	Trauma with admission GCS < 8. Exclusion for patients died before day 10	Early tracheostomy (≤ day 6) *vs.* late (> day 6). Tracheostomy only with surgical technique.
Shibahashi[30]	2017	91	Non-randomized	Japan	Traumatic brain injury with AIS score >4. Exclusion for severe chest injury and intubation for upper airway obstruction.	Early tracheostomy (≤72 h) *vs.* late (>72 h)
Roushdy[31]	2018	87	Randomized	Egypt	Post traumatic head-injuries with admission GCS <8. Randomization at day 7 based on "willingness"	Early tracheostomy (< day 7) *vs.* late (> day 8). Tracheostomy only with surgical technique
Elkbuli[32]	2019	150	Non-randomized	USA	2 groups of patients: trauma with brain injury and trauma without brain injury	Three sub-groups: early tracheostomy (from day 0 to 3) *vs.* middle (from day 4 to 7) *vs.* late (> day 7). In the TBI group sub-analysis for 3 GCS groups (GCS <8; GCS 8-12; GCS 13-15)
Lu[33]	2019	98	Non-randomized	China	Traumatic brain injury with admission GCS ≤8. Exclusion for patients died within 3 days after admission	Early tracheostomy (≤ day 3) *vs.* late (> day 3)
Mclaughlin[34]	2019	242	Non-randomized	USA	Pediatric (<15 years) traumatic brain injury with head AIS score ≥3, requiring mechanical ventilation for >48 h and without severe chest, neck or face injury	Early tracheostomy (≤ day 14) *vs.* late (≥ day 15)
Sheehan[35]	2019	127	Non-randomized	USA	Pediatric (<16 years) traumatic brain injury with head AIS score >3	Early tracheostomy (< day 7) *vs.* late (≥ day 7)
Robba[36]	2020	433	Non-randomized	Europe (multicentric)	Traumatic brain injury with ICU length of stay ≥72 h. Exclusion for patients died in the first 72 h	Early tracheostomy (≤ day 7) *vs.* late (> day 7).
Ismail[37]	2021	155	Non-randomized	Malaysia	Severe traumatic brain injury with head AIS score ≥4 and without severe chest and/or cervical injury	Early tracheostomy (≤ day 3) *vs.* late (> day 3)

GCS: Glasgow Coma Scale; AIS: Abbreviated Injury Score.

TABLE II.—*Summary of baseline patients' characteristics and outcome of the nineteen included studies.*

Characteristics	ET	LT
N. of participants	3042	3211
Sex, male	2118/2739	2130/2888
Mean age (years)	43±14.2	42±15.7
Time to tracheostomy (days)	6.4±2.94	17.3±10.72
GCS	5.5±1.40	5.6±1.14
DVT	22/232	39/287
VAP	515/1329	769/1540
Mortality	394/2970	253/3128
Mean ICU LOS (days)	16±5.4	24±7.9
Mean Hospital LOS (days)	34±10.5	43±11.5
Duration of MV (days)	11±4.1	17±6.0
Costs (thousands of $)	132.84±142.02	191.81±158.31

GCS: Glasgow Coma Scale; DVT: deep vein thrombosis; VAP: ventilator-associated pneumonia; ICU: Intensive Care Unit; LOS: length of stay; MV: mechanical ventilation; ET: early tracheostomy; LT: late tracheostomy.

1142 patients were in the ET group, while 1142 were in the LT group. A standardized mean difference (SMD) of -1.79 (95% CI, -2.71; -0.88) was reported for ET with respect to LT (P<0.001, I^2=98.16%; P of heterogeneity <0.001); a meta-regression found no statistical differences between RCT and non-RCT (QM=3.47, P=0.06) (Figure 2). An Egger's Test (z=1.81; P=0.07) showed symmetry in the funnel plot indicating low risk of bias (Figure 3).

Ventilator associated pneumonia

VAP events were investigated in 15 studies[19-22, 24, 26-30, 32-36] including 2869 patients (1329 *vs.* 1540; RD=-0.11 [95% CI, -0.16; -0.06];

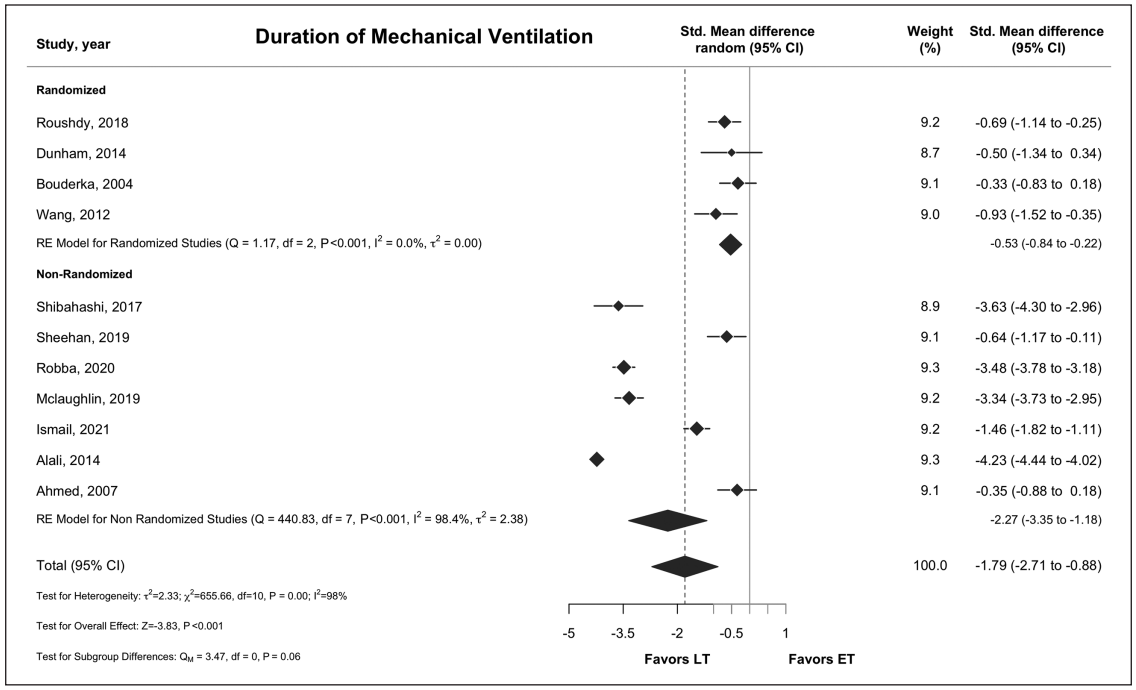

Figure 2.—Forest plot displaying the random-effect pooled estimates of 11 studies analyzing 2484 patients. MV duration was significantly lower in the ET group compared to controls SMD of -1.79 (95% CI, -2.71; -0.88) was reported for LT with respect to ET (P<0.001, I²=98.16%; P of heterogeneity 0.002).[20, 22, 24, 26, 27, 30, 31, 34-37]

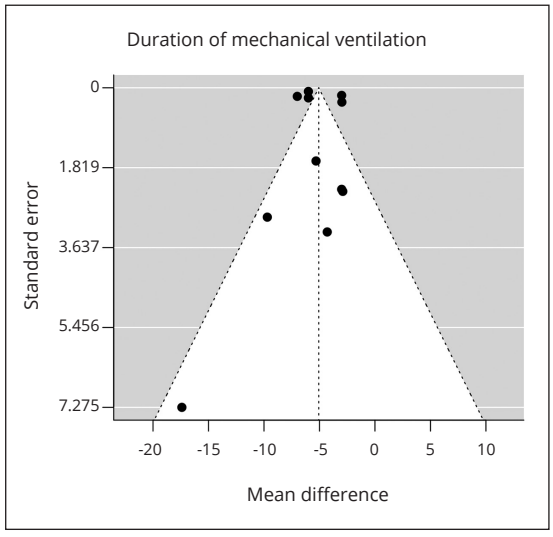

Figure 3.—Funnel plot displaying symmetry for the MV duration outcome indicating low risk of bias.

P<0.001, I²=40.77%; P of heterogeneity 0.094). A meta-regression found a statistical difference between RCT and non-RCT (QM=8.84, P=0.00) (Figure 4). An Egger's Test (z=-0.12; P=0.903) indicated reduced risk of bias as shown in the funnel plot (Figure 5).

ICU length of stay

ICU LOS was explored in 12 studies[19, 22, 24-26, 29, 30, 33-37] including 2666 patients: 1193 patients were in the ET group, while 1193 were in the LT group. A SMD of -1.64 (95% CI, -2.44; -0.84) was reported (P<0.001, I²=98.17%; P of heterogeneity <0.001) (Figure 6). An Egger's Test (z=0.54; P=0.587) indicated low risk of bias as demonstrated in the funnel plot (Supplementary Digital Material 2).

Hospital length of stay

Hospital LOS was analyzed in 10 studies[22, 24-26, 29, 30, 33-36] including 2444 patients: 1086 patients were in the ET group, while 1086 were in the LT group. A SMD of -1.26 (95% CI, -1.97; -0.56) was described; P<0.001, I²=97.67%; P of heterogeneity <0.001) (Figure 7). An Egger's Test (z=0.50; P=0.62) indicated symmetry in the funnel plot (Supplementary Digital Material 2).

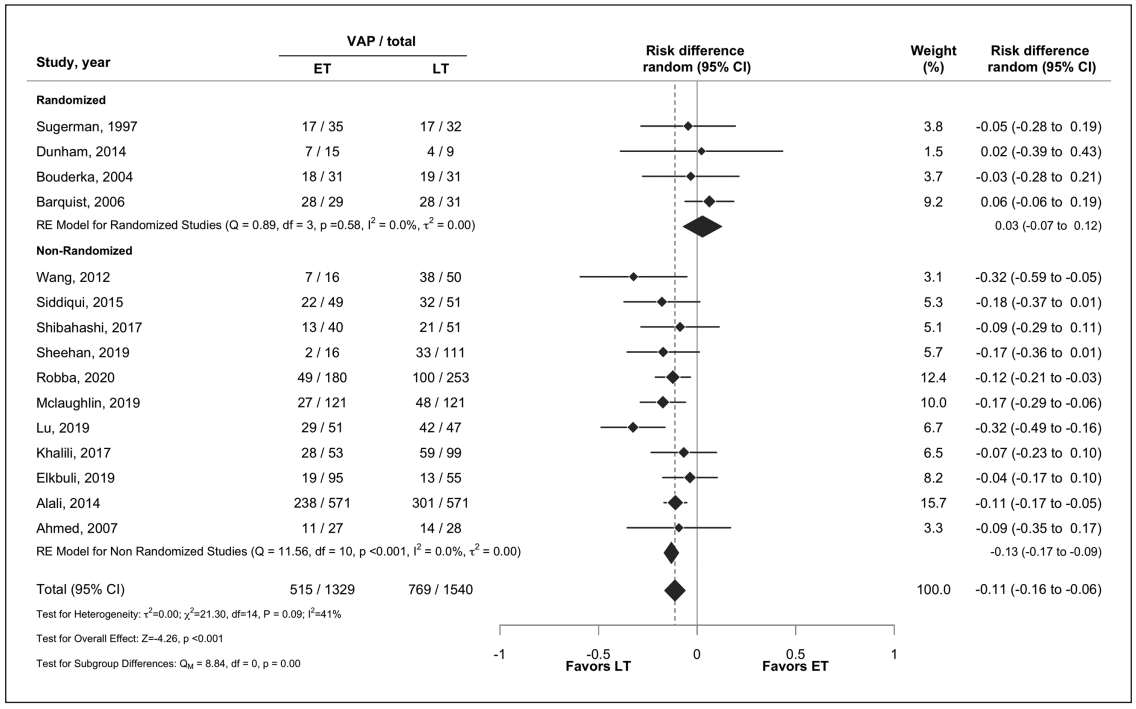

Figure 4.—Forest plot displaying the random-effect pooled estimates of 15 studies analyzing 2869 patients. VAP cases were significantly lower in the ET group compared to controls (RD=-0.11 [95% CI, -0.16; -0.06]; P<0.001, I^2=40.77%; P of heterogeneity 0.094).[19-22, 24, 26-30, 32-36]

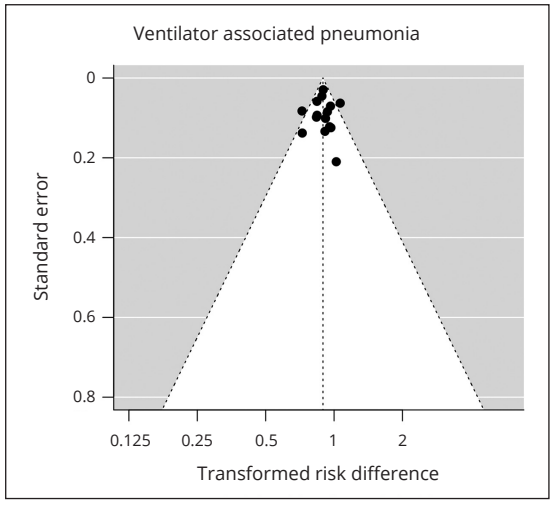

Figure 5.—Funnel plot displaying symmetry for the VAP outcome indicating low risk of bias.

Deep vein thrombosis

DVT was analyzed in three studies[32, 34, 35] including 519 patients: 232 patients were in the ET group, while 287 were in the LT group. LT was associated with an increase of DVT compared to ET (RD=-0.08 [95% CI, -0.14; -0.03]; P=0.0025, I^2=0.00%; P of heterogeneity 0.5499) (Supplementary Digital Material 2).

Costs

Costs were investigated in three studies[22, 30, 33] including 244 patients: 118 patients were in the ET group, while 118 were in the LT group. A SMD of - 1.18 (95% CI, -1.69; -0.67) was reported for ET with respect to LT (P=0.00, I^2=70.60%; P of heterogeneity 0.028) (Supplementary Digital Material 2).

Mortality

Mortality was analyzed in 18 studies[19-36] including 6098 patients. A statistical difference in mortality was found between the LT and ET groups. Overall, 394 of 2970, patients died in the ET group, while 253 of 3128 patients died in the LT group (RD=0.03 [95% CI, 0.00-0.06]; P=0.033, I^2=46.61%; P of heterogeneity 0.0025). A meta-

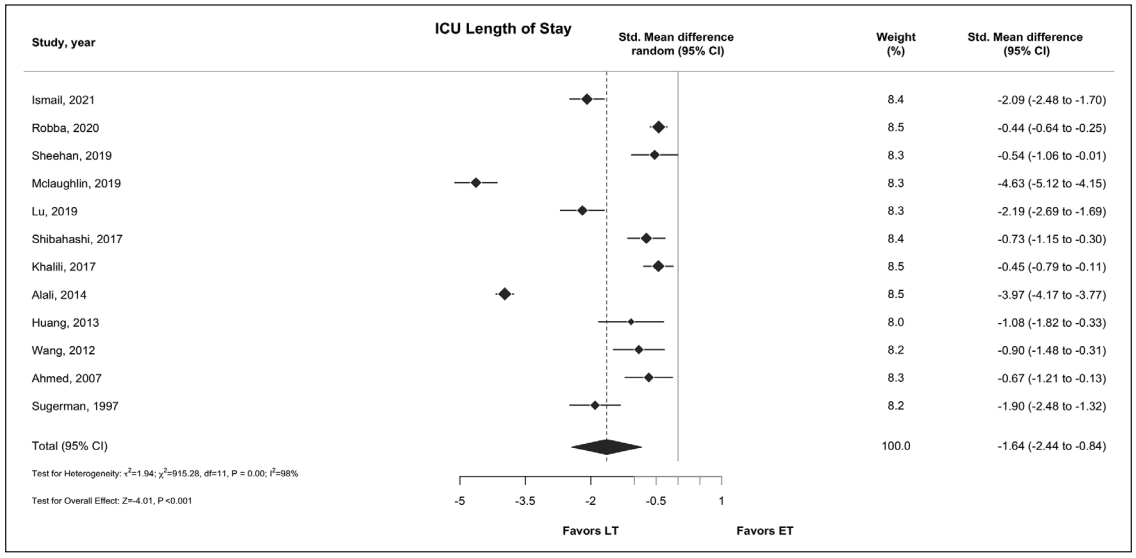

Figure 6.—Forest plot displaying the random-effect pooled estimates of 12 studies analyzing 2666 patients. ICU LOS duration was significantly lower in the ET group compared to controls (SMD=-1.64, 95% CI, -2.44; -0.84) was reported for LT with respect to ET (P<0.001, I^2=98.17%; P of heterogeneity <0.001).[19, 22, 24-26, 29, 30, 33-37]

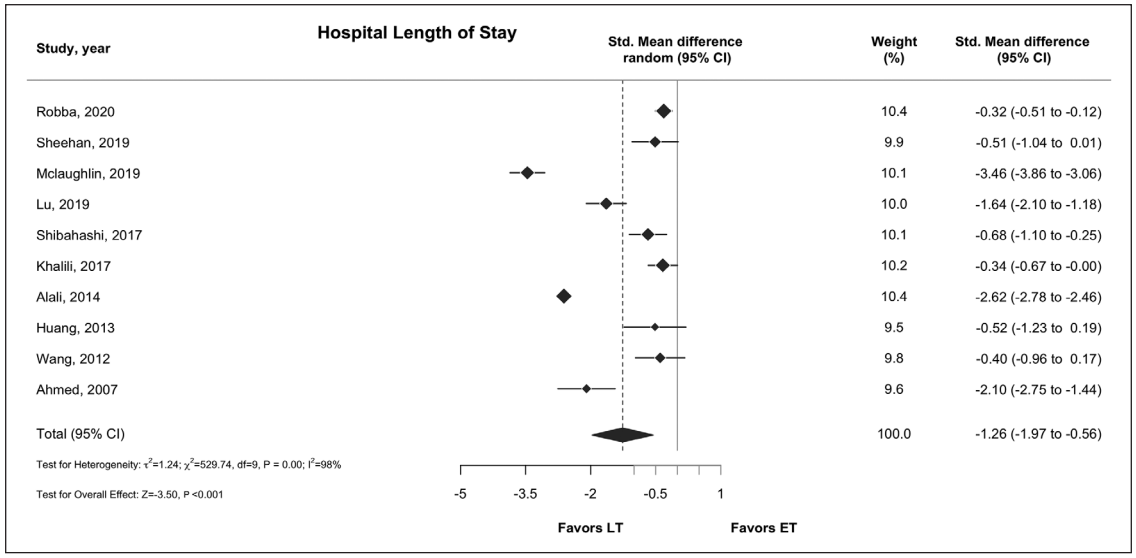

Figure 7.—Forest plot displaying the random-effect pooled estimates of 10 studies analyzing 2444 patients. Hospital LOS duration was significantly shorter in the ET group compared to controls (SMD=-1.26, 95% CI, -1.97; -0.56) was reported for LT with respect to ET (P<0.001, I^2=97.67%; P of heterogeneity <0.001).[22, 24-26, 29, 30, 33-36]

regression found no statistical differences between RCT and non-RCT (QM=1.35, P=0.25) (Supplementary Digital Material 2).

Discussion

We found early tracheostomy reduced MV duration and VAP. In addition, ET shortened ICU and hospital LOS. However, ET demonstrated an increase in overall mortality.

A recent systematic review reported nine studies[38] with results consistent with our investigation. A previous meta-analysis[39] was published in 2021 and show significant efficacy of ET in reducing VAP occurrence and MV length. Our

study added several published studies based on the previous meta-analyses with a larger sample size of 6253 patients, which allowed for better statistical efficacy and allowed subgroup analyses to verify our results' robustness.

Tracheostomy has become a routine procedure in ICU patients,[40, 41] contributing to patient comfort and movement, assisting with tracheal secretion mobilization, and supporting the suspension or reduction of sedative administration.[42, 43] It carries the same dangers and repercussions as any other procedure, including long-term airway injury, such as tracheomalacia, bleeding, and tracheal stenosis.[43] However, in comparison to the procedure's benefits, the occurrence of the aforementioned dangers is low.[44, 45] In severe TBI, patients are required to rely on long-term MV to reduce secondary insult causes[46] (as hypoxemia and hypercapnia). This prediction may lead to the insertion of a tracheostomy, with the goal of improving airway management.[42, 47] ET produced excellent outcomes in middle-aged persons with severe neurological conditions, as demonstrated by several investigations.[41, 42, 45] Regardless of the patients' neurologic assessments, the ET group had fewer ventilation days than the LT group, which may lead to a reduction in VAP exposure,[48] this result nonetheless, comes from only very few non randomized studies with substantial weight and short confidence intervals, while most of the studies included (and all the RCTs) have wide confidence intervals, resulting in not significant difference. Furthermore, the analysis of SMD revealed a substantial magnitude intervention effect (as defined by Cohen)[49, 50] for reducing MV duration. According to current evidence[51] MV raises the risk of VAP in TBI patients by 10% per day. As a result, ET might have a big impact on those patients. According to our analysis, LT was also associated with an increase of DVT compared to ET, although this was only reported by three studies,[32, 34, 35] highlighting the difficulty to draw significant conclusions, this evidence could be reflecting the reduction of mobilization, the increased need for sedation, paralyzing agents and the delayed active physiotherapy in this group of subjects. Our findings also show that ET patients had a shorter ICU and hospital stay, as well as a medium intervention effect,[49] indicating the treatment's importance in patient recovery from hemodynamic instability and ventilator weaning.[52, 53] After completing the weaning from MV, a patient is more likely to be discharged from the ICU and then from the hospital, reducing both lengths of stay.[41, 53] In the real-world setting of TBI's global epidemiologic impact,[54, 55] resource optimization and the availability of ICU beds and staff[56] are critical. The economic impact of ET and LT could be further examined in only three studies in this systematic review. The ET group had lower mean costs than the LT group, highlighting the possibility that ET could be used as a treatment option to improve indirect and direct cost control. However, based on our meta-analysis conducted on a relatively small sample size, no conclusive statements of this sort can be made. Despite this, tracheostomy is already linked to lower direct expenses[57-59] due to shorter hospital stays and lower infection treatment costs (patients may be at higher risk of infection due to the MV and/or ICU environment). When compared to LT patients[60] ET patients had a total cost savings of $ 4316.00. (average weighted costs in ICU). Moreover, ET has also been shown by Liu and Rudmik[61] to be more cost-effective than LT. Beyond tracheostomy, MV in critical trauma patients had a daily mean incremental cost of $ 1522.00 per patient per day.[62] The median in-hospital expenditures for severe TBI patients receiving MV treatment were estimated to be $ 55,267.00 per patient.[63] Despite the benefits listed, there is significant debate on the matter. Cox *et al.*[64] found that tracheotomy increases the proportion of patients with chronic load, which contributes to higher costs outside the hospital. Nonetheless, opting out of tracheostomy creates a significant ethical quandary, and the existing statistics do not support such a decision. The majority of our studies did not include data on the patient's overall health after their stay in the hospital.

Tracheostomy and mortality

Although prior findings suggest that mortality rate was not different between the LT and ET groups,[48, 57, 65-67] our analysis revealed a significantly higher mortality in the ET group. To provide an explanation, first we need to acknowledge that critical care trials often turn out to be neutral

and even when positive results are published, they display a low fragility index.[68] This adds evidence to the controversial role of mortality as primary outcome in critical care trials:[69] the high heterogeneity of critical illnesses and their treatments, and the inability to evaluate attributable mortality are all able to jeopardize the results of studies. Furthermore, ethical consideration is obliged: mortality should be replaced by a functional outcome because survival alone may not be sufficiently satisfactory. A deepen discussion on this issue is beyond the scope of our analysis but, it seems clear the need to review the role of mortality as a reliable outcome in studies on severely ill patients. Second, we examined the epidemiological implications of this finding. The outcome "mortality" is subjected to a bias in observational studies: the "immortal time" bias.[70] Immortal time is a period in which, by the design of the study, death cannot occur.[71] In fact, those who receive LT later should be alive for the period before exposure. In contrast, patients who received ET have a larger time window to "die." This bias creates a spurious beneficial effect of the late intervention over the early one. This issue is strongly increased when "early" deaths are common, as in TBI. Critical care literature is full of examples of "immortal time" bias and how to deal with it.[72, 73] It appears obvious that simply restricting the population of studies to those surviving a certain period or excluding the period from ICU admission to the exposure cannot be longer accepted, as it eliminates "immortal time" bias creating, in turn, a "selection" bias. A debate on "immortal time" bias in tracheostomy timing has flourished after the publication of Robba *et al.*[36] where, in secondary analysis, they demonstrate the presence of immortal bias.[74, 75] We agree to consider the timing of tracheostomy as a discrete variable (the evaluation of days "waiting" for a tracheostomy). In conclusion, in the light of the dark side of "mortality" as a reliable outcome, the intrinsic risk of "immortality bias" and the evidence of all the other outcomes favorable in the early approach, we feel we can encourage an ET approach.

Strengths of the study

To our knowledge, this review is the latest analysis of the most recent evidence on the topic. This meta-analysis aims to review the effect of ET *versus* LT on VAP and MV in TBI as the primary outcomes. The results are consistent with a previous meta-analysis[39] and show significant efficacy of ET in reducing VAP, length of MV as well as ICU and Hospital LOS. Compared with previous meta-analyses, this study collected data from a larger number of patients 3042 received an ET, while 3122 did have LT, for a total of 6253 patients studied. This strengthens the statistical data provided by the work. The funnel plots for all ten analyses were symmetrical, reducing the risk of reporting bias.

Limitations of the study

This study has some limitations. The studies analyzed were RCT, observational, retrospective, and single-center. The sample sizes of some studies are small. Patient selection resulted in a heterogeneous population relative to indications for primary outcomes. In addition, tracheostomy protocols were not specified in all studies and differed significantly between some centers. The variable timing used to designate tracheostomy as an early intervention, which has been questioned in other research,[76, 77] makes it difficult to determine the treatment's optimal timing for greatest benefit. According to the largest randomized controlled trial comparing early and late tracheostomy in a mixed ICU cohort,[77] 65% of patients assigned to the late group did not need one, highlighting the ongoing difficulty, even among experts and despite validated prediction scores, in accurately predicting the need for a tracheostomy. In neurological patients, predicting extubation failure is not substantially different. Also, the magnitude of the effect related to the timing of tracheostomy on prognosis is probably not so pronounced, and meta-analysis on observational, retrospective or single-center papers add few data on the topic. Besides, several elements of the research populations were found to be heterogeneous throughout the studies. Clinical heterogeneity in both therapy groups is a cause of heterogeneity, as are insufficient analyses, discrepancies in evaluating patient outcomes, and the lack of a systematic report. As a result, the papers included in this meta-analysis did not apply consistent diagnostic procedures for VAP assess-

ment or offer a single tracheostomy approach, which added to the heterogeneity. In reference studies, especially the observational investigations, we could identify a risk of bias due to their favor of ET. If they applied equal weight to all of their findings — they should have raised a high cautionary note to the ET intervention. Finally, the overall increased risk of bias, which may influence intervention effect evaluation, indicates a lack of organized randomized trials, as shown in earlier ET *versus* LT meta-analyses,[78] where outcomes could not be merged due to higher risk of bias. Furthermore, a successful treatment should be defined by decreased patient exposure to nosocomial events, acceptable survival rates, and improved patient functional status following treatment. All these aspects increase confounding factors and the risk of bias. Because of the limitations of the study, the results and conclusions should be interpreted with caution.

Future studies and prospect

Recruitment is underway for one interesting randomized controlled trial called Biper (Brain-injured Patients Extubation Readiness Study) (NCT04080440) which more researchers may be able to learn from, but whose aim was not the same as ours. To validate the superiority of one precise timing of airway management in such a difficult clinical state, more research, particularly multicenter RCTs, is required to gather more information regarding the different outcomes of TBI patients receiving ET compared to those receiving LT.

Conclusions

An ET approach may help reduce the length of MV, the risk of VAP and ICU and Hospital LOS. However, further studies are needed to overcome the limitations described and more clearly determine ET's efficacy in this clinical setting.

Key messages

- Early tracheostomy reduced mechanical ventilation duration and ventilator associated pneumonia in patients suffering from traumatic brain injury.
- Early tracheostomy shortened intensive care unit and hospital length of stay.
- In our meta-analysis, early tracheostomy demonstrated an increase in overall mortality and this could be related to the risk of "immortality bias" commonly seen in the critical care domain.
- Further investigations are needed to overcome the highlighted limitations and clearly demonstrate early tracheostomy's efficacy in this critical care setting.

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