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TRACHEOSTOMY PRACTICE AND TIMING IN TRAUMATIC BRAIN-INJURED PATIENTS: A CENTER-TBI STUDY

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KEYWORDS: Traumatic Brain Injury, Tracheostomy, Mechanical ventilation, Outcome

ABSTRACT

Purpose: Indications and optimal timing for tracheostomy in traumatic brain-injured (TBI) patients are uncertain. This study aims to describe the patients' characteristics, timing, and factors related to the decision to perform a tracheostomy and differences in strategies among different countries and assess the effect of the timing of tracheostomy on patients' outcomes.

Methods: We selected TBI patients from CENTER-TBI, a prospective observational longitudinal cohort study, with an intensive care unit stay ≥ 72 h. Tracheostomy was defined as early (≤ 7 days from admission) or late (> 7 days). We used a Cox regression model to identify critical factors that affected the timing of tracheostomy. The outcome was assessed at 6 months using the extended Glasgow Outcome Score.

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Results: Of the 1358 included patients, 433 (31.8%) had a tracheostomy. Age (hazard rate, HR = 1.04, 95% CI = 1.01–1.07, $p = 0.003$), Glasgow coma scale ≤ 8 (HR = 1.70, 95% CI = 1.22–2.36 at 7; $p < 0.001$), thoracic trauma (HR = 1.24, 95% CI = 1.01–1.52, $p = 0.020$), hypoxemia (HR = 1.37, 95% CI = 1.05–1.79, $p = 0.048$), unreactive pupil (HR = 1.76, 95% CI = 1.27–2.45 at 7; $p < 0.001$) were predictors for tracheostomy. Considerable heterogeneity among countries was found in tracheostomy frequency (7.9–50.2%) and timing (early 0–17.6%). Patients with a late tracheostomy were more likely to have a worse neurological outcome, i.e., mortality and poor neurological sequels (OR = 1.69, 95% CI = 1.07–2.67, $p = 0.018$), and longer length of stay (LOS) (38.5 vs. 49.4 days, $p = 0.003$).

Conclusions: Tracheostomy after TBI is routinely performed in severe neurological damaged patients. Early tracheostomy is associated with a better neurological outcome and reduced LOS, but the causality of this relationship remains unproven.

Introduction

Tracheostomy can facilitate weaning in long-term ventilated patients, potentially shortening the duration of mechanical ventilation and intensive care unit (ICU) stay, and reducing complications from prolonged tracheal intubation, such as ventilator-associated pneumonia (VAP) and tracheal lesions [1]. In patients who require ICU care after a TBI, the main indications for tracheostomy include failure to wean invasive mechanical ventilation, absence of protective airway reflexes, impairment of respiratory drive, and difficulties in managing secretions [2]. The proportion of TBI patients who might benefit from a tracheostomy, and the most appropriate timing for the procedure [3] are still undefined, and relevant biases confound the limited, mainly retrospective, available data on this issue. Moreover, policies and clinical practice vary among different centres, and the optimal indications for tracheostomy remain uncertain [4].

Conventionally, tracheostomies performed in the first week are classified as early, while tracheostomies performed later than 7 days are defined as late [5]. The ideal timing for a tracheostomy is uncertain since the evidence on the advantages of early over late tracheostomy is conflicting, and no real differences in mortality have been identified between early and late tracheostomy so far [6, 7].

To obtain insights into tracheostomy in patients who had suffered a TBI, we analysed data from the ICU stratum of the CENTER-TBI study [8]. This study aims to describe the characteristics of those TBI patients who undergo a tracheostomy and the current state of its timing; to identify the factors involved in performing the procedure and the different strategies between countries, and to assess the effect of the timing on patients' outcome.

Take-home message

Tracheostomy after TBI is commonly performed in the most severe neurological damaged patients. Early tracheostomy is associated with shorter ICU length of stay and with a trend of a better outcome.

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Methods

The Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI study, registered at clinicaltrials.gov NCT02210221) is a longitudinal prospective collection of TBI patient data across 65 centres in Europe between December 19, 2014, and December 17, 2017, as previously described [8, 9]. The Medical Ethics Committees approved the CENTER- TBI study in all participating centres, and we obtained informed consent according to local regulations.

We performed a pre-planned analysis focusing on tracheostomy practice in the CENTER-TBI cohort during the ICU stay (ESM1). The project was preregistered on the CENTER-TBI proposal platform in December 2018 and approved by the CENTER-TBI proposal review committee (ESM Document 1) before starting the analysis.

This report complies with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines (ESM Table S1).

For this analysis, the inclusion criteria were:

- A clinical diagnosis of TBI with an indication for a brain Computed Tomography scan (CT);
- Presentation to the hospital within 24 h (hrs) post-injury;
- ICU admission with a length of stay (LOS) ≥ 72 h.

Exclusion criteria were:

- Death in the first 72 h;
- Short ICU LOS (< 72 h).

These exclusion criteria were defined to exclude patients in whom tracheostomy was never likely to have been considered, either because of extremely severe injury and rapid death, or those in whom the injury was not severe enough.

DATA COLLECTION

Detailed data were collected on pre-injury factors and patient's characteristics, injury details, Glasgow coma scale (GCS), pre-hospital care, clinical care, post-acute care, and outcome, with a total of over 2500 unique data fields, with many fields collected serially over time (e.g., physiological variables in the ICU stratum). Hypoxemia was defined as a documented partial pressure of oxygen (PaO_2) < 8 kPa (60 mmHg), oxygen saturation (SaO_2) < 90%, or both; hypotension was defined as a documented systolic blood pressure < 90 mmHg.

OBJECTIVES

The aim of this study is threefold:

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1. Describe the patients' characteristics and timing of tracheostomy in TBI patients;

2. Identify the factors related to the decision to perform a tracheostomy and differences in strategies among different countries;

3. Assess the effect of the timing of tracheostomy on patients' outcomes.

OUTCOMES

The primary endpoint was the patients' functional outcome assessed by the Extended Glasgow Outcome Score (GOSE) at 6 months. An unfavourable outcome was defined as GOSE ≤4, which takes into account both poor neurological outcome and mortality together. All responses were obtained by study personnel from patients or from a proxy (where impaired cognitive capacity prevented patient interview), during a face-to-face visit, by telephone interview, or by postal questionnaire at 6 months (range 5-8 months) after injury [10]. All outcome evaluators had received training in the use of the GOSE. We also registered mortality at 6 months, and the ICU and hospital LOS.

STATISTICAL ANALYSIS

Continuous variables are described with median and interquartile range (IQR), or mean and standard deviation (SD), as appropriate, and categorical data were reported as absolute and relative frequencies. The nature of the variables guided the choice of the test for the comparison among groups.

FACTORS RELATED TO THE DECISION TO PERFORM A TRACHEOSTOMY

A Cox regression model was used to identify the key factors that affected the decision and timing of tracheostomy during ICU stay. Time origin was ICU admission, and patients who did not receive the procedure were censored at discharge from ICU or at death, whichever occurred first. A frailty term was included to account for centre-specific effects. Variables significant in the univariate analysis, and others judged clinically relevant, were initially identified, and the selection of the covariates for the final model (including age, GCS, pupillary reactivity, hypoxemia, thoracic, and facial trauma) was based on the likelihood ratio test (LRT) and Akaike Information Criterion (AIC). Assumptions regarding the proportionality of the hazards and the linearity of effects were investigated using the Schoenfeld test and the Martingale residuals, respectively [11]. For variables violating the proportional hazards assumption, the time dependence of the effect was adjusted by including a term for the interaction of the variable and time [11].

COUNTRY AND CENTRE DIFFERENCES

The country- and centre-specific incidence rate of late, early, and no tracheostomy was estimated from a proportional odds model, adjusting for patient characteristics associated with a tracheostomy, and including a random intercept for country and centre. The median odds ratio (MOR) was also calculated as a measure of variability between centres [12].

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OUTCOMES

The role of timing of tracheostomy on different outcomes was explored on the subset of patients who underwent a tracheostomy. The time to the procedure was evaluated both as a discrete (i.e., days from ICU admission) and as a categorical variable (i.e., ≤ 7 vs. > 7 days) [4]. A logistic regression model was applied to the odds of an unfavourable GOSE (GOSE ≤ 4), while we performed a Cox model on the 6-month mortality from ICU admission, with patients contributing to the risk set from the day of tracheostomy. Death from any cause was the event of interest, and patients alive at 6 months from ICU admission were censored. A linear regression model was used for the evaluation of LOS in both ICU and hospital. LOS was calculated from ICU admission (and from tracheostomy) to discharge or death in ICU, with a sensitivity analysis that excluded patients who died in ICU or hospital. All analyses were adjusted for known outcome predictors in the Core IMPACT model (i.e., age, GCS at arrival, and pupillary reactivity) [13].

MISSING VALUES

We used a multivariate imputation by chained equations in all the multivariable models to deal with missing values in the predictors, generating 50 imputed datasets [14]. Analyses on complete cases were also performed to check consistency in the results. Model diagnostics were performed in all the imputed datasets, and final decisions were taken based on the findings of the majority of datasets.

All the tests conducted were two-sided with a significance level of 5%. The analyses were conducted in R (version 3.5.2, R Core Team, 2019) [15].

Results

Of the 2138 consecutive patients requiring ICU care, 1358 (from 19 countries and 54 centres) had an ICU LOS ≥ 72 h. Of these, 433 subjects (31.8% of the study cohort, 20.2% of the overall ICU population) underwent a tracheostomy and were included in the analysis (ESM Figure S1). Details regarding the screening and enrolment process are described in the main CENTER-TBI manuscript [9].

PATIENTS' CHARACTERISTICS

Patients' characteristics at ICU admission are summarized in Table 1 (both overall and stratified by whether or not they received a tracheostomy). Patients who received or did not receive a tracheostomy were similar in terms of age, sex, pre-injury American Society of Anaesthesiologists' physical status (ASAPS) score, mechanism of injury, and pre-injury clinical history. Patients receiving tracheostomy more frequently had lower median GCS at arrival (median 5 vs. 8, p < 0.001), and abnormal pupillary reactivity (at least one unreactive pupil in 27.6% vs. 15.2%, p < 0.001). Moreover, patients who underwent tracheostomy had a higher rate of early hypoxemia (19.5% vs. 13.0%, p = 0.004), early hypotension (21.1% vs. 12.0%, p <0.001) and higher Injury Severity Score (ISS; mean of 38.4 vs. 33.5, p <0.001) due to more extra-cranial traumatic injury

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(67.2% vs. 56.8%, $p < 0.001$), especially facial (29.6% vs. 22.7%, $p = 0.008$) and thoracic trauma (47.6% vs. 36.6%, $p < 0.001$).

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Table 1. *Features at admission and during ICU stay in patients who received and did not receive tracheostomy and the overall population*

Characteristic	No tracheostomy (*n*	Tracheostomy (*n* = 433)	*P* value	Overall (*n* = 1358)	*n* missing
At admission					
Age(years),median (I-III quartiles)	50 (29-65)	45 (29-63)	0.102	49 (29-64)	0
Age ≥ 65 years, n (%)	232 (25.1)	99 (22.9)	0.413	331 (24.4)	
Sex: male, *n* (%)	677 (73.2)	333 (76.9)	0.163	1010 (74.4)	0
Race: Caucasian, *n* (%)	799 (97.3)	377 (95.9)	0.260	1176 (96.9)	144
Pre-injury ASAPS, *n* (%)			0.235		75
Normal healthy patient	489 (56.7)	257 (61.2)		746 (58.1)	
Patient with mild systemic	278 (32.2)	126 (30)		404 (31.5)	
Patient with severe systemic	96 (11.1)	37 (8.8)		133 (10.4)	
Cause of injury, *n* (%)			0.229		58
Road traffic accident	401 (45.7)	215 (50.8)		616 (47.4)	
Incidental fall	360 (41)	148 (35)		508 (39.1)	
Violence/assault	33 (3.8)	18 (4.3)		51 (3.9)	
Suicide attempt	15 (1.7)	11 (2.6)		26 (2)	
Other	68 (7.8)	31 (7.3)		99 (7.6)	
ISS, mean (SD)	33.45 (14)	38.40 (14.6)	< 0.001	35.05 (14.4)	21
ISS ≥	552 (61)	305 (70.6)	0.001	857 (64.1)	
Alcohol involved, *n* (%)	245 (30.2)	102 (27.6)	0.392	347 (29.4)	177
Drug abuse, *n* (%)	28 (3.9)	31 (9.4)	0.001	59 (5.6)	303
Hypoxemia: yes or suspected, *n*	111 (13)	78 (19.5)	0.004	189 (15.1)	105
Hypotension: yes or suspected, *n*	102 (12)	86 (21.1)	< 0.001	188 (14.9)	97
Severity TBI, *n* (%)			< 0.001		85
Mild	264 (30.6)	53 (12.9)		317 (24.9)	
Moderate	144 (16.7)	64 (15.6)		208 (16.3)	
Severe	454 (52.7)	294 (71.5)		748 (58.8)	
Pupillary reactivity, *n* (%)			< 0.001		82
Both reactive	732 (84.8)	299 (72.4)		1031 (80.8)	
One reactive	52 (6)	42 (10.2)		94 (7.4)	
Both unreactive	79 (9.2)	72 (17.4)		151 (11.8)	
GCS, median (I-III quartile)	8 (3-13)	5 (3-9)	< 0.001	7 (3-12)	85
Any extra-cranial injury, *n* (%)	525 (56.8)	291 (67.2)	< 0.001	816 (60.1)	0
Facial trauma, *n* (%)	210 (22.7)	128 (29.6)	0.008	338 (24.9)	0
Thoracic trauma, *n* (%)	339 (36.6)	206 (47.6)	< 0.001	545 (40.1)	0
In ICU					
Cranial surgery, *n* (%)	364 (39.8)	261 (60.4)	< 0.001	625 (46.4)	11
Extra-cranial surgery, *n* (%)	236 (25.8)	227 (52.5)	< 0.001	463 (34.3)	10
Reintubation, *n* (%)	65 (7.3)	50 (11.7)	0.010	115 (8.7)	40
Ventilator acquired pneumonia, *n*	127 (14)	149 (34.5)	< 0.001	276 (20.6)	16
ICP monitor, *n* (%)	478 (52.4)	351 (81.1)	< 0.001	829 (61.6)	12
Respiratory failure, *n* (%)	220 (24.2)	207 (47.8)	< 0.001	427 (31.8)	15
Antibiotics used, *n* (%)	724 (83.7)	401 (94.8)	< 0.001	1490 (74.4)	0

ASAPS American Society of Anaesthesiologists' Physical Status, *ICP* intracranial pressure, *ISS* injury severity score, *TBI* Traumatic Brain Injury

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During their ICU stay, patients receiving tracheostomy more frequently underwent the placement of an intracranial pressure (ICP) monitoring device (81.1% vs. 52.4, p <0.001), and suffered from ventilator acquired pneumonia (VAP; 35.5% vs. 14.0%, $p < 0.001$), and respiratory failure (47.8% vs. 24.2%, $p < 0.001$) (Table 1). Of the 1358 patients included in the study, 96 (7%) received a withdrawal of treatment: 86 (9.3%) were not tracheotomised, and 10 (2.3%) had undergone a tracheostomy.

TIMING OF TRACHEOSTOMY

The median (IQR) time to tracheostomy of the 433 patients was 9 (5-14) days from ICU admission, with 30 (6.9%) of the patients receiving tracheostomy on the day of ICU admission and the last procedure performed after 39 days in ICU (ESM Figure S2 and Figure S3). Details on the characteristics of the tracheotomised patients are reported separately for early (180 patients, 41.6%) and late (253 patients, 58.4%) procedures in Table 2. Patients receiving early tracheostomies were older (30.6% vs. 17.4% aged ≥ 65 years, $p = 0.002$), with a higher incidence of hypoxemia (24.4% vs. 16.1%, $p = 0.054$) and hypotension (25.9% vs. 17.6%, $p = 0.059$) in the pre-hospital and emergency department settings, and had facial injuries (34.4% vs. 26.1%, $p = 0.076$). Patients receiving a late tracheostomy had a higher rate of ventilator-associated pneumonia (39.7% vs. 27.2%, $p = 0.01$), and respiratory failure (52.2% vs. 41.7%, $p = 0.039$).

FACTORS RELATED TO THE DECISION TO PERFORM A TRACHEOSTOMY

The results of the Cox regression model for the tracheostomy procedure are reported in Table 3. Age had a statistically significant impact, indicating a 4% increase in the hazard of tracheostomy for each 5 year increase in age (HR = 1.04, 95% CI = 1.01-1.07, $p = 0.003$). The hazard for requiring a tracheostomy was significantly lower in patients with GCS > 8 vs. those with GCS ≤ 8 ($p < 0.001$) and the HR increased linearly after ICU admission, with the HR at 1, 7 and 15 days from admission calculated as 1.51 (95% CI = 1.09-2.10), 1.70 (95% CI = 1.22-2.36), and 1.98 (95% CI = 1.42-2.75), respectively. The effect of pupillary reactivity was also not constant in time, and the HR estimates indicate that patients with at least one unreactive pupil have a higher hazard ($p < 0.001$) as compared to those with both reacting pupils, with an HR at 1, 7 and 15 days from admission of 1.63 (95% CI = 1.17-2.27), 1.76 (95% CI = 1.27-2.45) and 1.96 (95% CI = 1.41-2.72). The hazard of tracheostomy was 1.24 times higher in patients with thoracic trauma as compared to those without (95% CI = 1.01-1.52, $p = 0.020$), while the two timing groups did not show a significant difference in the incidence of facial trauma (HR = 1.24, 95% CI = 1.00-1.53, pLRT = 0.0714, and $p = 0.149$). Finally, hypoxemia was associated with an increased hazard of undergoing a tracheostomy (HR = 1.37, 95% CI = 1.05-1.79, $p = 0.048$). The findings of the model on complete cases were consistent (ESM Table S2).

COUNTRY AND CENTRE DIFFERENCES

We observed a considerable heterogeneity among countries in the decision to perform a tracheostomy (with adjusted tracheostomy rates ranging from 7.9 to 50.2%) and in the timing for tracheostomy (with the incidence of late tracheostomy ranging from 7.9 to 32.6%, and early tracheostomy from 0 to 17.6%) (Fig. 1a). Furthermore, individual centres within the same country

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showed different adjusted percentages of early vs. late tracheostomy (Fig. 1b). In the vast majority of centres, a delayed procedure was more likely to happen than an early one, and only in two institutions, the policy was to opt exclusively for an early strategy. Moreover, the variability in the centre-specific rate of late tracheostomy was more pronounced than the early rate. The crude rates observed at country and centre levels are shown in ESM Figure S4. We used the MOR to quantify between-centre differences and found that even after correction for patient characteristics, there was a 2.2-fold difference in the odds of tracheostomy between centres with the highest and lowest tracheostomy rates.

OUTCOMES

The univariate analyses (ESM Table S3) showed no significant effect of early vs. late tracheostomy on ICU mortality, 6-month mortality, or 6-month GOSE (p = 0.399, *p* = 0.735, and *p* = 0.197, respectively). However, patients who received a late tracheostomy had a statistically significant longer mean LOS in ICU (19.6 vs. 26.7 days, *p* <0.001) and in hospital (38.5 vs. 49.4 days, *p* = 0.003) when measured from the point of ICU admission. These differences were abolished when LOS was measured from tracheostomy (mean LOS in ICU for early vs. late tracheostomy: 14.8 days vs. 12.5 days, *p* = 0.045; mean LOS in hospital: 13.1 days vs. 34.7 days, *p* = 0.915).

Table 2. *Features at admission and during ICU stay for early and late tracheostomy*

Characteristic	Early tracheostomy (*n* =	Late tracheostomy (*n* = 253)	*P* value	*n* missing
Age (years), median (I-III quartiles)	48.5 (31-67)	44.0 (28-59)	0.024	0
Age ≥ 65 years *n* (%)	55 (30.6)	44 (17.4)	0.002	
Sex: male, *n* (%)	139 (77.2)	194 (76.7)	0.987	0
Pre-injury ASAPS, *n* (%)			0.948	13
Normal healthy patient	105 (60.3)	152 (61.8)		
Patient with mild systemic disease	53 (30.5)	73 (29.7)		
Patient with severe systemic disease	16 (9.2)	21 (8.5)		
Previous TBI, *n* (%)	12 (7.5)	15 (6.5)	0.833	42
Use of anticoagulants, *n* (%)	9 (5.2)	8 (3.3)	0.465	18
Use of antiplatelets' drugs, *n* (%)	18 (10.5)	19 (7.8)	0.449	18
Hypoxemia: Yes or Suspected, *n* (%)	40 (24.4)	38 (16.1)	0.054	33
Hypotension: Yes or Suspected, *n* (%)	44 (25.9)	42 (17.6)	0.059	25
Cardiovascular history, *n* (%)	45 (25.6)	52 (21.1)	0.343	11
ISS, mean (SD)	38.3 (14.8)	38.5 (14.5)	0.896	1
ISS ≥	128 (71.1)	177 (70.2)	0.929	
Severity of TBI, *n* (%)			0.863	22
Mild	22 (13.1)	31 (12.8)		
Moderate	28 (16.7)	36 (14.8)		
Severe	118 (70.2)	176 (72.4)		
Cause of injury, *n* (%)			0.511	10
Road traffic accident	90 (51.4)	125 (50.4)		
Incidental fall	56 (32)	92 (37.1)		
Suicide attempt	7 (4)	4 (1.6)		
Violence/assault	8 (4.6)	10 (4.0)		
Other	14 (8)	17 (6.9)		

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Alcohol involved, *n* (%)	39 (25.7)	63 (28.9)	0.570	63
Drugs involved, *n* (%)	13 (9.5)	18 (9.3)	1.000	102
Pupillary reactivity, 4 (%)			0.675	20
Both reactive	120 (70.6)	179 (73.7)		
One reactive	17 (10)	25 (10.3)		
Both unreactive	33 (19.4)	39 (16)		
GCS, median (I-III quartile)	5.50 (3-10)	5 (3-9)	0.934	22
Any extra-cranial injury, *n* (%)	121 (67.2)	170 (67.2)	1.000	0
Facial trauma, *n* (%)	62 (34.4)	66 (26.1)	0.076	0
Thoracic trauma, *n* (%)	84 (46.7)	122 (48.2)	0.825	0
Cranial surgery, *n* (%)	102 (56.7)	159 (63.1)	0.212	1
Extra-cranial surgery, *n* (%)	96 (53.3)	131 (52)	0.858	1
Reintubation, *n* (%)	13 (7.4)	37 (14.8)	0.029	1
Days with tracheostomy, median (I-III	12.0 (6.8-18.3)	12.0 (6-20)	0.795	0
Tracheostomy at discharge from hospital, *n*	96 (53.3)	131 (51.8)	0.825	0
Intubated, *n* (%)	173 (96.6)	246 (97.2)	0.948	1
Ventilator-associated pneumonia, *n* (%)	49 (27.2)	100 (39.7)	0.010	1
ICP monitoring, *n* (%)	138 (76.7)	213 (84.2)	0.065	0
Cardiac arrest, *n* (%)	25 (13.9)	29 (11.5)	0.545	0
Respiratory failure, *n* (%)	75 (41.7)	132 (52.2)	0.039	0
Marshall score, *n* (%)			0.757	77
1	7 (4.9)	10 (4.7)		
2	67 (46.9)	87 (40.8)		
3	16 (11.2)	28 (13.1)		
4	1 (0.7)	5 (2.3)		
5	1 (0.7)	1 (0.5)		
6	51 (35.7)	82 (38.5)		
Antibiotics used, *n* (%)	159 (90.3)	242 (98)	0.001	10
H_2 Receptor antagonist used, *n* (%)	40 (22.7)	87 (35.2)	0.008	10
Neuromuscular blockade used, *n* (%)	78 (44.3)	140 (56.7)	0.016	10
PPI used, *n* (%)	108 (61.4)	147 (59.5)	0.778	10
Prokinetics used, *n* (%)	89 (50.6)	148 (59.9)	0.070	10
Sedation used, *n* (%)	170 (96.6)	243 (98.4)	0.385	10
Steroids used, *n* (%)	42 (23.9)	83 (33.6)	0.040	10

ASAPS American Society of Anaesthesiologists' Physical Status, *GCS* glasgow coma scale, *ICP* intracranial pressure, *ISS* injury severity score, *PPI* proton-pump inhibitor, *TBI* Traumatic Brain Injury.

Table 3. *Results of the Cox regression model for tracheostomy*

Variables	**HR (95% CI)**				
	All days	***P* value**	**At day 1**	**At day 7**	**At day 15**
Age (5 years)	1.04 (1.01-1.07)	0.003			
Thoracic trauma: yes vs.	1.24 (1.01-1.52)	0.020			
Facial trauma: yes vs. no	1.24 (1.00-1.53	0.149			
Hypoxemia: yes vs. no	1.37 (1.05-1.79)	0.048			
GCS > 8 vs. GCS < 8[a]		< 0.001^	1.51 (1.09-2.10)	1.70 (1.22-2.36)	1.98 (1.42-2.75)
Pupillary: 1-2 unreactive vs. 2 reacting[b]		< 0.001^	1.63 (1.17-2.27)	1.76 (1.27-2.45)	1.96 (1.41-2.72)

Significant random effect for center ($p < 0.001$)

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GCS glasgow coma scale, SE standard error

^p value of the test for the overall effect: main effect + interaction of the main effect with time

[a] The coefficients (SE) of the model for the main effect is 0.395 (0.178) and for the interaction with time is 0.019 (0.013)

[b] The coefficients (SE) of the model for the main effect is 0.474 (0.178) and for the interaction with time is 0.013 (0.013)

Fig. 1. Left panel (**a**). Percentage distribution of the decision to perform tracheostomy or not in each country (in blind). Only countries that have at least 20 patients admitted in ICU are reported alone; the remaining are grouped. Right panel (**b**). Percentage of early vs. late tracheostomy by centre with at least five tracheostomies. Centres within the same country have the same colour and a mass proportional to centre size. The bisector line is also reported. Results are adjusted for confounding factors.

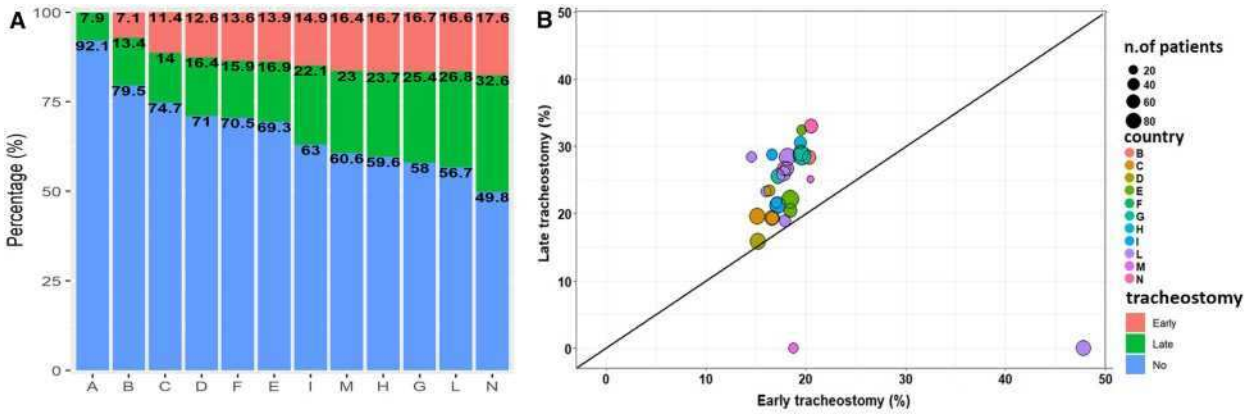

Table 4. *Results of the multivariable models on outcomes at 6 months or in ICU*

	GOSE < 5 at 6 months			Mortality at 6 months			LOS in ICU			LOS in hospital		
	OR	95% CI	*P* value	HR	95% CI	*P* value	Coeff.	SE	*P* value	Coeff.	SE	*P* value
Model 1												
Intercept	0.13	0.05–0.31	< 0.001				21.38	2.79	< 0.001	40.96	5.93	< 0.001
Age (years)	1.04	1.03–1.05	< 0.001	1.06	1.04–1.07	< 0.001	− 0.04	0.04	0.345	− 0.09	0.09	0.287
GCS ≤ 8 vs. GCS > 8	1.96	1.16–3.28	0.006	1.35	0.78–2.34	0.280	0.14	1.73	0.937	− 0.51	3.67	0.889
Pupils: 1–2 unreactive vs. 2 reactive	2.15	1.23–3.76	0.004	2.30	1.38–3.80	0.001	0.13	1.78	0.942	4.10	3.78	0.279
Late vs. early tracheostomy	1.69	1.07–2.67	0.018	1.22	0.73–2.03	0.442	6.89	1.58	< 0.001	11.45	3.35	< 0.001
Model 2												
Intercept	0.11	0.05–0.27	< 0.001				19.91	2.76	< 0.001	38.55	5.89	< 0.001
Age (years)	1.04	1.03–1.06	< 0.001	1.06	1.04–1.08	< 0.001	− 0.03	0.04	0.399	− 0.09	0.09	0.324
GCS ≥ 8 vs. GCS < 8	1.96	1.16–3.29	0.0065	1.30	0.76–2.24	0.339	0.06	1.71	0.974	− 0.65	3.64	0.859
Pupils: 1–2 unreactive vs. 2 reactive	2.12	1.21–3.71	0.0042	2.44	1.47–4.06	< 0.001	0.02	1.75	0.992	3.91	3.74	0.296
Days waiting for tracheostomy	1.04	1.01–1.07	0.006	1.06	1.03–1.08	< 0.001	0.52	0.09	< 0.001	0.86	0.19	< 0.001

The influence of the timing of tracheostomy was evaluated with a categorical variable (Model 1) and as a discrete variable (Model 2)

CI confidence interval, *Coeff.* coefficient, *HR* hazard ratio, *LOS* length of stay, *OR* odds ratio, *SE* standard error.

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The adjusted regression analyses demonstrated an association between an early tracheostomy and a better neurological outcome captured by the GOSE (Table 4). Patients with a late tracheostomy were more likely to have a worse neurological outcome (Model 1: OR = 1.69, 95% CI = 1.07-2.67, p = 0.018), and the analysis using day to tracheostomy as a continuous variable (Model 2) showed that every day of delay in performing tracheostomy was associated with an OR of 1.04 for unfavourable outcome (95% CI = 1.01-1.07, p = 0.006). The multivariable Cox analysis on mortality at 6 months found that tracheostomy performed after 1 week was not associated with a significant increase of the hazard of mortality (HR = 1.22, 95% CI = 0.73-2.03; p = 0.442). However, Model 2 showed that each increase of a day in the timing of tracheostomy was associated with a 6% increase in the hazard of mortality (HR = 1.06, 95% CI = 1.03-1.08, p <0.001). Late tracheostomy in Model 1 was associated with an increase in the mean ICU LOS of 6.9 days (95% CI = 3.7-9.9, p <0.001), and an increase in hospital LOS of 11.45 days (95% CI = 4.88-18.02, p < 0.001); each 2 days deferral in tracheostomy was associated with a 1-day increase in ICU LOS, and a 2 day increase in hospital LOS. LOS after tracheostomy in ICU was shorter in the late tracheostomy group (— 2.33 days, p = 0.04), while the hospital LOS was similar between the two groups (ESM Table S5). Similar results were obtained when excluding ICU deaths (data not shown). Sensitivity analyses on all the outcomes considering complete data gave consistent results (ESM Table S4).

Discussion

At our knowledge, this analysis based on prospective observational data from CENTER-TBI [8] is the most extensive assessment of the practice of tracheostomy in TBI patients, across centres and countries in Europe. Our main findings are:

- Tracheostomy is commonly performed in TBI patients in ICU, and is most frequently undertaken after the first week in ICU;
- The likelihood of receiving a tracheostomy increases significantly with age, the severity of neurological injury (expressed as lower GCS and pupillary abnormalities), extra-cranial injury (particularly thoracic trauma), and early secondary insults (such as hypoxemia);
- There are significant variations in tracheostomy rates across countries and centres in Europe;
- When assessed as a discrete variable, later tracheostomies are associated with an increase in unfavourable outcome and LOS.

We found that tracheostomy was frequent amongst TBI patients in the ICU. The procedure was undertaken in 31.8% of our study cohort, which is more frequent than in studies in general ICU cohorts, where past literature reports rates of about 10% [16, 17]. This increased need for tracheostomy in the TBI population is attributable to a higher rate of extubation failure and the need for pro-longed protection of the airways secondary to neurological injury. In general ICU patients, tracheostomy is most commonly performed after 14 days from admission [17, 18], with only a quarter of tracheostomies delivered on or before day 7 [16]. In contrast, only 26% of our TBI

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cohort underwent tracheostomy later than 14 days from admission, and in 41%, tracheostomy was undertaken before day 7.

The risk of receiving a tracheostomy was related to the severity of the neurological injury, quantified using GCS and pupillary reactivity at admission, and the presence of early secondary insults (such as hypoxemia). Non-neuro- logical drivers of the decision to perform a tracheostomy include age and the occurrence of thoracic trauma, which may adversely affect respiratory weaning and extubation success. While the effect of non-neurological factors and hypoxemia on the risk of receiving tracheostomy was constant over time, the Cox model indicated that both GCS and pupillary reactivity had a time-dependent effect, with an increased impact on the HR of tracheostomy with increasing time from admission. These findings suggest that both the initial severity of the neurological injury and probably its trajectory, play a role in the decision process. The result that the median time to tracheostomy was 9 days post-admission probably reflects a change in treatment targets. In the initial phase, the aim is to manage acute intracranial emergencies, and tracheostomy at this stage could increase intracranial pressure and adversely affect the outcome. Once this phase is complete, cessation of sedation, weaning from ventilator support, and initiation of rehabilitation become key treatment targets. This timing of tracheostomy also prevents the use of the procedure in patients with lesser severities of injury, who might achieve successful extubation, and in those who have a rapidly progressive course and succumb early to their injuries. This process of selection still leads to tracheostomy at an earlier stage than commonly observed in non-TBI patients but allows the selection of a cohort most likely susceptible to the potential benefits of the procedure on the patients' outcomes [19, 20], by dealing with ongoing failure to protect the airway and the consequent risk of extubation failure [21-24].

However, the approach to tracheostomy was by no means uniform across ICUs that contributed to CENTER-TBI. We found substantial between-country and between-centre differences in the incidence and timing of tracheostomy, which persisted even after adjustment for covariates. Our results suggest that the current, local medical practices influence the decision to perform a tracheostomy, along with the ethical and legal implications context, clinical expertise, and costs relating to the procedure and equipment, replicating past findings in the general ICU population [16, 17, 25].

The literature suggests that early tracheostomy may potentially reduce hospital stay, duration of mechanical ventilation and mortality rates [7, 19, 26, 27]. In a propensity-matched cohort study on TBI patients, early tracheostomy (≤ 7 days) was associated with shorter mechanical ventilation duration (10 vs. 16 days, RR = 0.70, 95% CI = 0.66-0.75), ICU and hospital LOS (RR = 0.75, CI = 0.66-0.75, and RR = 0.80, 95% CI = 0.74-0.86), but did not affect mortality [28]. While the results of a Cochrane meta-analysis in general ICU patients [5] showed a possible mortality benefit from a tracheostomy, our data replicate smaller studies that specifically addressed TBI. Khalili et al. [20] found that, in a cohort of 152 TBI patients, early tracheostomy resulted in lower ICU and hospital LOS (46.6 vs. 38.6 days, p =0.048; and 34.9 vs. 26.7 days, p = 0.003, respectively), but did not affect mortality. A meta-analysis by McCredie et al. [7] concluded that early tracheostomy might reduce

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the long-term mortality, duration of mechanical ventilation, and LOS. However, waiting longer, i.e., excluding patients probably improving or dying for brain damage, leads to fewer tracheostomy and similar short-term outcomes.

Each increase of 1 day in tracheostomy timing was significantly associated with a 4% increase in the risk of an unfavourable outcome with a 6% increase in the hazard of death. While this association may suggest a benefit from an earlier tracheostomy, we should be cautious about assigning causality to this association, since there may be competing confounds. Patients with more severe injury may have had a more prolonged need for therapies directed toward limiting the intracranial damage evolution (thus delaying tracheostomy) or might have a worse expected outcome (leading to a higher number of attempts to withhold tracheostomy).

In our cohort, patients who received late tracheostomy had a statistically significant longer mean LOS in ICU (by nearly 1 week) and in hospital (by about 11 days), with each 2 days deferral in tracheostomy associated with about 1 and 2 days' increase in LOS in ICU and hospital, respectively. In this direction also goes the interval between tracheostomy and discharge from ICU, which is shorter in the "later tracheostomy" group, along with the information that withdrawal of treatment is more frequent in patients without tracheostomy. Mortality in the ICU of tracheotomised patients was minimal (ESM figure S3).

LIMITATIONS

Although we used robust statistical methods and covariate adjustment, unidentified residual confounders may have affected our analyses. Moreover, although CENTER- TBI banked detailed data on many aspects of injury, clinical care, and outcome, some key characteristics, such as those related to mechanical ventilation and respiratory complications, were not recorded. The observational nature of our study only allows us to report associations and cannot test the causal relationships between factors and tracheostomy practice.

Conclusions

Patients with TBI undergo a tracheostomy, more often than in general ICU populations. Several patient- and injury-related factors are associated with the decision to perform a tracheostomy in this group of patients. How-ever, an analysis that adjusts for these covariates still shows substantial between-centre differences, which probably reflect inadequate evidence, a lack of consensus, and the absence of strong guidelines in this setting. The later performance of tracheostomy is associated with increased LOS and worse functional neurological outcome, but the causality of this relationship remains unproven. Randomized controlled trials exploring the effect of tracheostomy and its timing on patients' out-comes are warranted.

Abbreviations

ASAPS: American Society of Anaesthesiologists' physical status score; CENTER- TBI: Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury; CI: Confidence interval; CT: Computed tomography; ESM: Electronic supplementary material; GCS: Glasgow coma scale; GOSE: Extended Glasgow Outcome Score; HR: Hazard ratio; HRS: Hours; ICP: Intracranial pressure; ICU:

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Intensive care unit; IQR: Interquartile range; ISS: Injury severity score; LOS: Length of stay; MOR: Median odds ratio; OR: Odds ratio; PaO_2: Partial pressure of oxygen; RR: Relative risk; SaO_2: Oxygen saturation; SD: Standard deviation; TBI: Traumatic Brain Injury; TV: Tidal volume; VAP: Ventilator-associated pneumonia.

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Authors' contributions

GC ideated and supervised the project, participated in the data analysis, drafted the manuscript, and the supplementary tables, discussed the findings with all the authors, collected the COIs. CR ideated the project, participated in the data analysis, drafted the manuscript, and the supplementary tables. FG and SG analysed the data, drafted the manuscript, and the supplementary tables. CI was an active part of the manuscript drafting and revision. DM proofread the manuscript to ensure its compliance with standard scientific English' rules. All co-authors gave substantial feedback on the manuscript and approved the final version of it. This article is reported as per Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines (www.strobe-statemenent.org) (Electronic supplementary material ESM 1).

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Compliance with ethical standards

CONFLICTS OF INTEREST

GC is Editor-in-Chief of Intensive Care Medicine. GC reports grants, personal fees as Speakers' Bureau Member and Advisory Board Member from Integra and Neuroptics; personal fees from Nestle and UCB Pharma, all outside of the submitted work. DKM reports grants from the European Union and UK National Institute for Health Research, during the conduct of the study; grants, personal fees, and non-financial support from GlaxoSmithKline; personal fees from Neurotrauma Sciences, Lantmaanen AB, Pressura, and Pfizer, outside of the submitted work. The other authors declare that they have no competing interests.

AVAILABILITY OF DATA AND MATERIALS

The data supporting the findings in the study are available upon reasonable request from the corresponding Author (GC) and are stored at https://cente r-tbi.incf.org/_5cf8e3d1c3b0d43708ebef42. Imaging data can be found at https://center-tbi.incf.org/_5cf4dbd0560bb01102b6b28e, data on vitals values at https://center-tbi.incf.org/_5cf4dce9560bb01102b6b28f, while data regarding medications can be found at https://center-tbi.incf.org/_5cf4de0d56 0bb01102b6b291.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The Medical Ethics Committees of all participating centers approved the CENTER-TBI study, and informed consent was obtained according to local regulations.

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