Can J Anesth/J Can Anesth (2023) 70:1516–1526
https://doi.org/10.1007/s12630-023-02539-7

REPORTS OF ORIGINAL INVESTIGATIONS

Tracheostomy *versus* prolonged intubation in moderate to severe traumatic brain injury: a multicentre retrospective cohort study

Comparaison de la trachéotomie et de l'intubation prolongée en cas de traumatisme craniocérébral modéré à grave : une étude de cohorte rétrospective multicentrique

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Received: 9 August 2022 / Revised: 29 January 2023 / Accepted: 16 February 2023 / Published online: 28 July 2023

Abstract

Purpose *Tracheostomy is a surgical procedure that is commonly performed in patients admitted to the intensive care unit (ICU). It is frequently required in patients with moderate to severe traumatic brain injury (TBI), a subset of patients with prolonged altered state of consciousness that may require a long period of mechanical respiratory assistance. While many clinicians favour the use of early tracheostomy in TBI patients, the evidence in favour of this practice remains scarce. The aims of our study were to evaluate the potential clinical benefits of tracheostomy versus prolonged endotracheal intubation, as well as whether the timing of the procedure may influence outcome in patients with moderate to severe TBI.*

Methods *We conducted a retrospective multicentre cohort study based on data from the provincial integrated trauma system of Quebec (Québec Trauma Registry). The study population was selected from adult trauma patients*

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s12630-023-02539-7.

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hospitalized between 2013 and 2019. We included patients 16 yr and older with moderate to severe TBI (Glasgow Coma Scale score < 13) who required mechanical ventilation for 96 hr or longer. Our primary outcome was 30-day mortality. Secondary outcomes included hospital and ICU mortality, six-month mortality, duration of mechanical ventilation, ventilator-associated pneumonia, ICU and hospital length of stay as well as orientation of patients upon discharge from the hospital. We used propensity score covariate adjustment. To overcome the effect of immortal time bias, an extended Cox shared frailty model was used to compare mortality between groups.

Results *From 2013 to 2019, 26,923 patients with TBI were registered in the Québec Trauma Registry. A total of 983 patients who required prolonged endotracheal intubation for 96 hr or more were included in the study, 374 of whom underwent a tracheostomy and 609 of whom remained intubated. We observed a reduction in 30-day mortality (adjusted hazard ratio, 0.33; 95% confidence interval, 0.21 to 0.53) associated with tracheostomy compared with prolonged endotracheal intubation. This effect was also seen in the ICU as well as at six months. Tracheostomy, when compared with prolonged endotracheal intubation, was associated with an increase in the duration of mechanical respiratory assistance without any increase in the length of stay. No effect on mortality was observed when comparing early vs late tracheostomy procedures. An early procedure was associated with a reduction in the duration of mechanical respiratory support as well as hospital and ICU length of stay.*

Conclusion *In this multicentre cohort study, tracheostomy was associated with decreased mortality when compared with prolonged endotracheal intubation in patients with moderate to severe TBI. This effect does not appear to be modified by the timing of the procedure. Nevertheless, the generalization and application of these results remains limited by potential residual time-dependent indication bias.*

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Résumé

Introduction *La trachéotomie est une intervention chirurgicale communément pratiquée chez les personnes admises à l'unité de soins intensifs (USI). Elle est fréquemment requise chez les patient·es victimes d'un traumatisme craniocérébral (TCC) modéré à grave, un sous-groupe présentant une altération prolongée de l'état de conscience qui peut nécessiter une longue période d'assistance respiratoire mécanique. Bien que bon nombre de cliniciens et cliniciennes soient favorables à l'utilisation d'une trachéotomie précoce chez cette patientèle, les données probantes en faveur de cette pratique restent insuffisantes. Les objectifs de notre étude étaient d'évaluer l'effet de la trachéotomie par rapport à l'intubation endotrachéale prolongée, ainsi que si le moment où la procédure est effectuée pouvait influencer cet effet, chez les personnes ayant subi un TCC modéré à grave.*

Méthodes *Nous avons effectué une étude de cohorte rétrospective multicentrique basée sur le système provincial intégré de traumatologie du Québec (Registre des traumatismes du Québec). La population de l'étude a été sélectionnée parmi les patient·es adultes victimes de traumatismes hospitalisé·es entre 2013 et 2019. Nous avons inclus les patient·es âgé·es de 16 ans et plus présentant un TCC modéré à grave (score sur l'échelle de coma de Glasgow [GCS] < 13) ayant nécessité une assistance respiratoire mécanique pendant 96 h ou plus. Notre critère d'évaluation principal était la mortalité à 30 jours. Les critères d'évaluation secondaires comprenaient la mortalité hospitalière et à l'USI, la mortalité à 6 mois, la durée d'assistance respiratoire mécanique, les pneumonies acquises en lien avec l'assistance respiratoire mécanique, les durées de séjour à l'USI et à l'hôpital ainsi que l'orientation des patient·es à leur sortie de l'hôpital. Nous avons utilisé un score de propension pour l'ajustement des covariables. Pour corriger l'effet du biais du temps immortel, un modèle de régression de la fragilité partagée de Cox étendu a été utilisé pour estimer la mortalité entre les groupes.*

Résultats *De 2013 à 2019, 26 923 personnes victimes de TCC ont été inscrites dans le Registre des traumatismes du Québec. Un total de 983 patient·es ayant nécessité une intubation endotrachéale prolongée de 96 h ou plus ont été inclus·es dans l'étude, dont 374 ont subi une trachéotomie et 609 sont resté·es intubé·es. Nous avons observé une réduction de la mortalité à 30 jours (aHR : 0,33 [0,21 − 0,53]) associée à la trachéotomie en comparaison à l'intubation endotrachéale prolongée. Cet effet a également été observé à l'USI ainsi qu'à 6 mois. La trachéotomie, comparée à l'intubation endotrachéale*

prolongée, était associée à une augmentation de la durée d'assistance respiratoire mécanique sans augmentation de la durée de séjour. Aucun effet sur la mortalité n'a été observé en comparant les procédures de trachéotomie précoces et tardive. Une procédure précoce a été associée à une réduction de la durée d'assistance respiratoire mécanique ainsi que la durée de séjour à l'USI et à l'hôpital.

Conclusion *Dans cette étude de cohorte multicentrique, nous avons observé que la trachéotomie est associée à une diminution de la mortalité en comparaison à l'intubation endotrachéale prolongée chez la patientèle ayant subi un TCC modéré ou grave. Cet effet ne semble pas modifié par le moment de la procédure durant l'hospitalisation. La généralisation et l'application de ces résultats restent toutefois limitées par un biais d'indication résiduel potentiel.*

Keywords critical care medicine · outcome · timing · tracheostomy · traumatic brain injury

Tracheostomy is one of the most frequent surgical interventions performed in critically ill patients requiring mechanical ventilation.[1] Tracheostomy facilitates pulmonary hygiene, increases patient comfort, reduces the use of sedatives, and shortens the duration of mechanical ventilation.[2,3] While many physicians favour the use of early tracheostomy in critically ill patients requiring prolonged mechanical ventilation, evidence supporting this practice is limited. In the general intensive care unit (ICU) population, the clinical benefits of early tracheostomy remain unclear despite numerous studies.[4,5]

Among patients with moderate to severe traumatic brain injury (TBI), the rate of tracheostomy is particularly high, as prolonged altered level of consciousness may necessitate prolonged mechanical ventilation.[6,7] Previous studies assessing the effects of early tracheostomy in this population have generated conflicting results,[8,9] so current practices regarding early tracheostomy in TBI patients vary considerably among centres.[7,10] Most studies are single centre or have important methodological limitations.[8] Two systematic reviews of patients with severe TBI did not observe a mortality benefit of early compared with late tracheostomy and/or prolonged intubation.[8,11] Only two small randomized clinical trials underpowered for clinically significant outcomes have been conducted.[12,13] The quality of the evidence is therefore very low. The aim of our study was to evaluate the effects of tracheostomy compared with prolonged intubation in critically ill patients with moderate or severe TBI in a comprehensive and integrated provincial trauma system.

Methods

Ethics

Our study was approved by the research ethics board of the CHU de Québec – Université Laval (#2020–148; Quebec City, QC, Canada). Our manuscript was written in compliance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.[14]

Study design and population

We conducted a retrospective multicentre cohort study on adult trauma patients ($\geq$ 16 yr old) admitted to a level I or II trauma centre in the province of Québec from 1 April 2013 to 31 March 2019 with moderate to severe TBI. Moderate to severe TBI was defined by a Glasgow Coma Scale (GCS) score of < 13 requiring mechanical respiratory assistance for $\geq$ 96 hr in the ICU. We excluded patients who became organ donors. We also excluded patients with pre-existing tracheostomy and patients admitted to burn units. We identified patients with TBI using Abbreviated Injury Scale (AIS) codes.

Study data

We extracted data from the Québec Trauma Registry. The registry was designed to include data from the entire province of Québec, Canada (population 8.5 million).[15,16] The Québec Trauma Registry includes data from 59 trauma centres, five of which are level I centres including two pediatric centres, five of which are level II centres, 21 of which are level III centres, and 28 of which are level IV centres. Participation in the registry is mandatory for all designated trauma centres.[17] Trauma centres all have a common data dictionary including standardized definitions of in-hospital complications. Information on patient demographics, injury characteristics, procedures, and outcomes are entered into the registry by trained data coders dedicated to coding registries using a standardized protocol. The registry data quality assurance program is enforced by data encoders locally and centrally after data transmission. The Québec Trauma Registry is centralized at the Québec Ministry of Health and Social Services where data quality control is managed using systematic audit and periodic validation conducted to identify aberrant data. Multiple strategies are employed to ensure the reliability of data; these include supervision by a data

coordinator, annual training, an electronic forum to respond to coding inquiries, and thrice-yearly meetings with clinicians and database experts.

We collected demographic data (age, sex, comorbidities), context of trauma (including mechanism of injury, external cause of trauma, burns, and spinal cord injury), and physiologic parameters and relevant events of the episode of care (including hypotension [arterial blood pressure < 90 mm Hg], hypoxemia [$SaO_2 < 90\%$], and cardiac arrest). Traumatic brain injury characteristics (initial GCS, intracranial hemorrhage including subarachnoid hemorrhage, subdural hematoma, epidural hematoma, cerebral edema, diffuse traumatic cerebral injury, etc.) were also extracted. We extracted information on surgical interventions occurring during the episode of care and the designation level of the hospital where the patient was treated.

Outcomes

Our primary outcome was 30-day mortality. Secondary outcomes were ICU mortality, six-month mortality, duration of mechanical ventilation, ICU length of stay, hospital length of stay, ventilator-acquired pneumonia, and discharge destination (home, rehabilitation centre, short-term care facility, and long-term care facility).

Statistical analysis

Logistic regression was used to model the odds of tracheostomy given a set of potential confounding variables, to estimate a propensity score. The potential confounding variables were selected based on literature as well as clinical relevance (Electronic Supplementary Material [ESM] eAppendix 1). Variables known to be outcome predictors from the Lab IMPACT model were also included.[18] The propensity score was used as an adjustment variable in all analysis models and restricted cubic splines were used to ensure the relationships with outcomes were correctly specified (ESM eAppendices 2 and 3).[19,20]

To address immortal time bias, the associations between all outcomes and exposure of tracheostomy were analyzed following two types of models and methodologies. First, we estimated adjusted hazard ratios (aHR) using extended Cox shared frailty regression, with tracheostomy modelled as a time-varying exposure.[21,22] Second, we used a Cox shared frailty regression model with landmark time methodology,[23] whereby analysis is restricted to patients who survived until the median time to tracheostomy (12 days). Multilevel Poisson regression was used to estimate the association between exposure and ventilator-acquired pneumonia, with mechanical ventilation duration modelled as an offset. A random intercept on trauma centre was used to account for potential clustering. Results from this analysis were compared with the results from the extended Cox shared frailty regression model.[21]

For lengths of stay and duration of mechanical ventilation, the worst outcome methodology was used[24] in addition to previous modelling strategies. Deceased patients were censored at the longest observed lengths of stay or longest mechanical ventilation duration. The reported adjusted measure of association (1/aHR) estimates the multiplicative inverse of being discharged alive from the hospital or the ICU. A value below one for 1/aHR indicates that exposed patients had fewer events than unexposed patients implying a shorter ICU or hospital length of stay or a shorter duration of mechanical ventilation. In contrast, a value above one indicates a longer stay or duration of mechanical ventilation among exposed patients. Discharge destination was analyzed using a multinomial model with a random effect for sites among patients surviving to discharge.

We used the Markov Chain Monte Carlo method with a noninformative single chain to simulate missing values on GCS scores (10.4%), systolic blood pressure (8.2%), and blood oxygen saturation (8.1%) for 18.7% of missing data patterns. Thereby, 25 imputed datasets were finally generated to achieve a better precision of the confidence intervals.[25] The imputation model contained all independent and dependent variables used in the models. Besides analysis on imputed datasets, sensitivity analyses of complete cases were also performed.

Subgroups and sensitivity analyses

In patients who had a tracheostomy, we performed a subgroup analysis to assess the effect of early (< 10 days of mechanical ventilation) *vs* late tracheostomy (≥ 10 days of mechanical ventilation) on all outcomes.

Sensitivity analysis for patients with better prognosis on mortality to test the hypothesis of an inherent indication bias using a Cox shared frailty regression model. Analyses were conducted for patients under 65 yr of age, patients with GCS > 4, and patients with no history of chronic obstructive pulmonary disease. Sensitivity analyses were conducted *a posteriori* to evaluate the effect of early tracheostomy on the duration of mechanical ventilation and ICU and hospital length of stay after the procedure was performed (using the time of tracheostomy as T_0).

All analyses were conducted using SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Patient characteristics

From 2013 to 2019, 26,923 patients with TBI were recorded in the Québec Trauma Registry. Of those, 3,411 had a moderate or severe TBI. Overall, our cohort of TBI patients requiring prolonged intubation for 96 hr or more included 983 patients (Fig. 1, Table 1). The median [interquartile range] duration of mechanical ventilation was 10 [6–15] days. Three hundred and seventy-four patients (38.1%) underwent a tracheostomy and 609 (61.9%) remained intubated (Fig. 1). Among patients who underwent a tracheostomy, 141 had an early tracheostomy (< 10 days) and 233 a late tracheostomy ($\geq$ 10 days). The median time to the tracheostomy procedure was 12 days. Most patients who underwent prolonged intubation for a TBI were discharged from the hospital to a rehabilitation unit (Fig. 2). Missing data was 10.4% for the GCS score, 8.2% for hypotension, and 8.1% for hypoxemia for a total of 18.7% variables with at least one missing variable.

Tracheostomy versus prolonged intubation

Results from the time-dependent Cox regression model showed decreased mortality at 30 days in patients with tracheostomy compared with those who underwent prolonged intubation (aHR, 0.33; 95% confidence interval, 0.21 to 0.53). These results were consistent in the ICU and at six months (Table 2). No difference was observed in the risk of ventilator-acquired pneumonia, ICU length of stay, and hospital length of stay, or duration of mechanical ventilation. We also observed no difference in the orientation at discharge. No significant differences were noted between results obtained from the time-related Cox models and the Cox shared frailty models with a landmark time analysis method (ESM eAppendices 4 and 5).

Early versus late tracheostomy

We observed no difference in mortality (at 30 days, in the ICU, or in hospital) with the timing of the tracheostomy procedure (early *vs* late) (Table 3). Nevertheless, an early tracheostomy was associated with a shorter duration of mechanical ventilation and ICU length of stay but not of hospital length of stay. We observed no effect on the incidence of ventilator-acquired pneumonia or on the

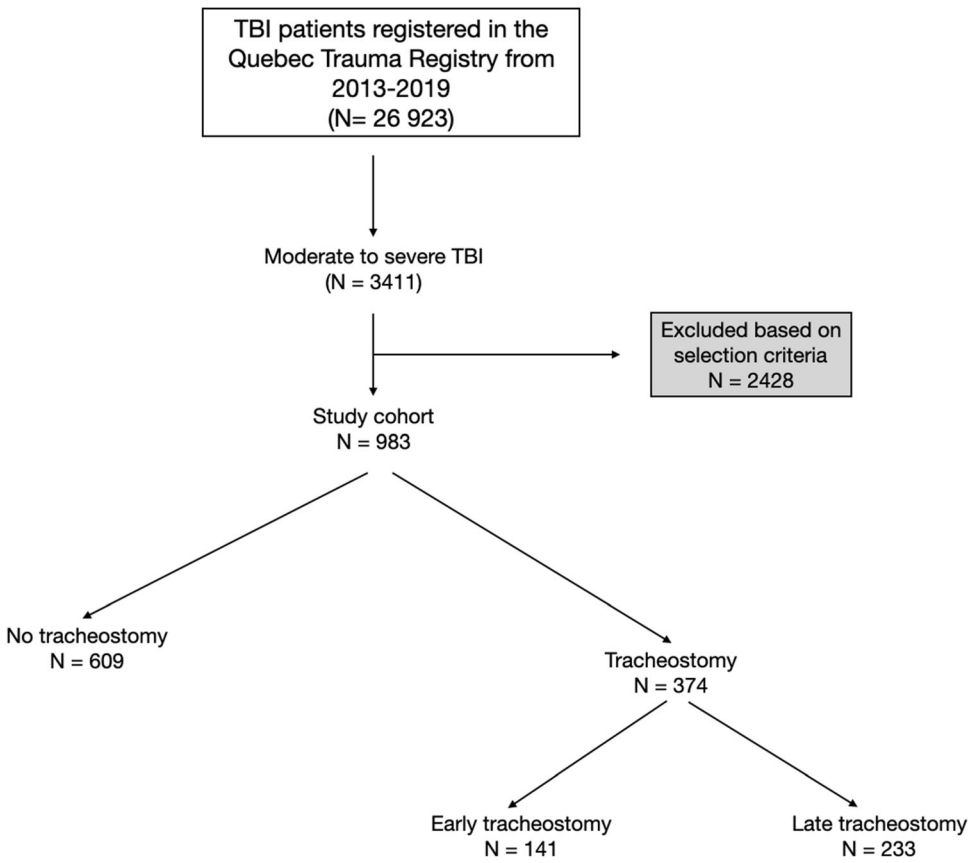

Fig. 1 Flow diagram of participants
TBI = traumatic brain injury

orientation of patients at discharge. Comparable results were observed when using a time-dependent Cox model on complete cases (ESM eAppendix 6).

Sensitivity analyses

Sensitivity analyses for patients with better prognosis showed a greater effect on ICU mortality, 30-day mortality, and six-month mortality compared with the overall cohort (ESM eAppendix 7).

In the early *vs* late tracheostomy analysis, when modifying T_0 for the time of tracheostomy, the difference in the duration of mechanical ventilation, ICU length of stay, and hospital length of stay was no longer observed (ESM eAppendix 8).

Discussion

In our multicentre retrospective cohort study performed in a regionalized provincial trauma system, we observed lower mortality at all time-points evaluated in patients who underwent a tracheostomy procedure compared with prolonged intubation. The procedure was, however, not associated with the incidence of ventilator-acquired pneumonia, duration of mechanical ventilation, or ICU and hospital length of stay. The lower mortality observed was not associated with the timing of the tracheostomy.

Our results are comparable to those observed in a previous retrospective cohort study that compared tracheostomy with prolonged intubation in patients with severe TBI.[26] In a recent multicentre cohort study of critically ill patients with mild, moderate, or severe TBI, patients who had a tracheostomy during their ICU stay had a lower GCS score on admission and were more likely to have an intracranial pressure monitor installed.[7] In this study, 96 patients (7%) died following a decision to withdraw life-sustaining therapies; only 10% of those patients had a tracheostomy. These observations raise the point that our results, as well as those from prior studies, may be limited by an inherent indication bias.[27] To test this hypothesis, we performed sensitivity analyses in patients with a relatively more favourable prognosis that showed minimal differences compared with the results from the whole cohort. On the other end, we observed a greater mortality benefit than previous studies did. The inclusion of moderate to severe TBI compared with only severe TBI in most studies may partially explain these differences. In addition, despite an optimal risk adjustment, patients with an unfavourable prognosis may have been overrepresented in the prolonged intubation group, thus potentially increasing an observed effect of tracheostomy on mortality. Although we cannot conclude that there are no residual indication biases explaining the results, it could reflect the lack of adjustment for other relevant confounders, especially time-varying confounders. Indeed, a major limitation of our study is the lack of adjustment for other significant confounders not available in our database, such as intracranial pressure and pupillary reactivity. Because of the retrospective design of our study, we could not assess the shared decision-making process between clinicians and patients on the decision to proceed with a tracheostomy in the context of a prolonged intubation. The usefulness of a tracheostomy may be limited in the context of a very unfavourable prognosis (greater risk of death) or a very favourable prognosis (greater risk of a more rapid extubation). There is evidence that patients with an unfavourable prognosis are often overrepresented in cohorts of patients with "prolonged intubation."[26,28] In our study, this may be partly reflected by the significantly higher ICU mortality compared with the 30-day and six-month mortality, as noted in a previous study.[26] Despite our study design and risk-adjusted analyses considering potential survival bias, our results on mortality may reflect an uncorrected indication bias.

Results from our subgroup analysis, showing no difference on mortality associated with early tracheostomy compared with late tracheostomy, are consistent with those of previous studies[6] and systematic reviews of trials and cohort studies.[8,11] The fact that we did not observe a difference in mortality in the early tracheostomy group may be explained by specific features related to TBI patients compared with other critically ill populations. Previous studies have shown that tracheostomy may increase intracranial pressure.[28,29] They highlighted the hypothesis that the intervention could be associated with secondary cerebral injuries if performed within a suboptimal window. Furthermore, the belief that an early tracheostomy may improve outcomes could lead to some unnecessary procedures.[30]

As opposed to the results of a previous systematic review of randomized clinical trials in patients with acute brain injury, we observed no effect of the timing of the tracheostomy on mortality.[30] Differences in study populations may explain these findings; while our study was strictly limited to critically ill patients with moderate and severe TBI, this review included a mixed population of critically ill patients with acute brain injury. Differences in level-of-care decisions and mortality in non-TBI populations may also explain these findings. Our results showing no difference in the risk of ventilator-acquired pneumonia associated with an early tracheostomy compared with a late procedure are also not aligned with those from previous studies. In a single retrospective cohort study,[6] a decreased risk of ventilator-acquired pneumonia with early tracheostomy was observed, which was also

Table 1 Demographic data

Characteristics	No tracheostomy $N = 609$	Tracheostomy $N = 374$	P value	Early tracheostomy $N = 141$	Late tracheostomy $N = 233$	P value	Overall $N = 983$
Age (yr), median [IQR]	56 [35–69]	47 [28–60]	< 0.001	46 [29–60]	48 [28–60]	0.81	52 [32–67]
Age categories (yr), *n*/total *N* (%)							
< 55	289/609 (47.5%)	239/374 (63.9%)	< 0.001	90/141 (63.8%)	149/233 (63.9%)	0.99	528/983 (53.7%)
55–64	117/609 (19.2%)	65/374 (17.4%)		25/141 (17.7%)	40/233 (17.2%)		182/983 (18.5%)
65–74	107/609 (17.6%)	32/374 (8.6%)		13/141 (9.2%)	19/233 (8.1%)		139/983 (14.1%)
75–84	75/609 (12.3%)	32/374 (8.6%)		11/141 (7.8%)	21/233 (9.0%)		107/983 (10.9%)
≥ 85	21/609 (3.4%)	6/374 (1.6%)		2/141 (1.4%)	4/233 (1.7%)		27/983 (2.7%)
Female sex, *n*/total *N* (%)	155/609 (25.5%)	81/374 (21.7%)	0.18	32/141 (22.7%)	49/233 (21.0%)	0.71	236/983 (24.0%)
Comorbidities, *n*/total *N* (%)							
Cirrhosis	15/609 (2.5%)	5/374 (1.3%)	0.22	3/141 (2.1%)	2/233 (0.9%)	0.37*	20/983 (2.0%)
Renal insufficiency	10/609 (1.6%)	4/374 (1.1%)	0.46	2/141 (1.4%)	2/233 (0.9%)	0.63*	14/983 (1.4%)
Diabetes	103/609 (16.9%)	45/374 (12.0%)	0.04	14/141 (9.9%)	31/233 (13.3%)	0.33	148/983 (15.1%)
Cardiac	74/609 (12.2%)	26/374 (6.9%)	0.01	9/141 (6.4%)	17/233 (7.3%)	0.74	100/983 (10.2%)
Pulmonary	60/609 (9.9%)	32/374 (8.6%)	0.50	8/141 (5.7%)	24/233 (10.3%)	0.12	92/983 (9.4%)
Neurologic	18/609 (2.9%)	7/374 (1.9%)	0.29	3/141 (2.1%)	4/233 (1.7%)	1.00*	25/983 (2.5%)
HIV	2/609 (0.3%)	1/374 (0.3%)	1.00*	0/141 (0.0%)	1/233 (0.4%)	1.00*	3/983 (0.3%)
Hypotension	27/609 (4.5%)	15/374 (4.1%)	0.75	5/141 (3.6%)	10/233 (4.4%)	0.72	42/983 (4.3%)
Hypoxemia	9/609 (1.5%)	6/374 (1.7%)	0.87	0/141 (0.0%)	6/233 (2.6%)	0.09	15/983 (1.6%)
TBI severity, *n*/total *N* (%)							
GCS, median [IQR]	6 [3–7]	6 [3–8]	0.90	6 [3–8]	5 [3–7]	< 0.001	6 [3–8]
≤ 8	498/609 (81.8%)	309/374 (82.6%)	0.74	109/141 (77.3%)	200/233 (85.8%)	0.03	807/983 (82.1%)
9–12	111/609 (18.2%)	65/374 (17.4%)		32/141 (22.7%)	33/233 (14.2%)		176/983 (17.9%)
Mechanism of injury, *n*/total *N* (%)							
MVC	275/609 (45.2%)	195/374 (52.1%)	< 0.001	66/141 (46.8%)	129/233 (55.4%)	0.17	470/983 (47.8%)
Fall from own height	79/609 (13.0%)	18/374 (4.8%)		8/141 (5.7%)	10/233 (4.3%)		97/983 (9.9%)
Fall more than own height	157/609 (25.8%)	71/374 (19.0%)		25/141 (17.7%)	46/233 (19.7%)		228/983 (23.2%)
Penetrating	11/609 (1.8%)	11/374 (2.9%)		7/141 (5.0%)	4/233 (1.7%)		22/983 (2.2%)
Other blunt	87/609 (14.3%)	79/374 (21.1%)		35/141 (24.8%)	44/233 (18.9%)		166/983 (16.9%)
Cranial injury AIS severity, *n*/total *N* (%)							
≤ 2	35/609 (5.8%)	10/374 (2.7%)	0.003	2/141 (1.4%)	8/233 (3.4%)	0.11	45/983 (4.6%)
3	123/609 (20.2%)	55/374 (14.7%)		27/141 (19.2%)	28/233 (12.0%)		178/983 (18.1%)
4	115/609 (18.9%)	61/374 (16.3%)		26/141 (18.4%)	35/233 (15.0%)		176/983 (17.9%)
≥ 5	336/609 (55.2%)	248/374 (66.3%)		86/141 (61.0%)	162/233 (69.5%)		584/983 (59.4%)
Extracranial injury (AIS ≥ 3), *n*/total *N* (%)							
Facial/neck	44/609 (7.2%)	48/374 (12.8%)	0.003	31/141 (22.0%)	17/233 (7.3%)	< 0.001	92/983 (9.4%)
Thoracic/abdominal	234/609 (38.4%)	182/374 (48.7%)	0.002	65/141 (46.1%)	117/233 (50.2%)	0.44	416/983 (42.3%)
Spine	50/609 (8.2%)	48/374 (12.8%)	0.02	18/141 (12.8%)	30/233 (12.9%)	0.98	98/983 (10.0%)
Upper/lower extremities	88/609 (14.4%)	63/374 (16.8%)	0.31	22/141 (15.6%)	41/233 (17.6%)	0.62	151/983 (15.4%)
Others	6/609 (1.0%)	1/374 (0.3%)	0.26*	0/141 (0.0%)	1/233 (0.4%)	1.00*	7/983 (0.7%)
Intracranial bleed, *n*/total *N* (%)							
SAH	408/609 (67.0%)	277/374 (74.1%)	0.02	104/141 (73.8%)	173/233 (74.2%)	0.92	685/983 (69.7%)
SDH	413/609 (67.8%)	270/374 (72.2%)	0.15	102/141 (72.3%)	168/233 (72.1%)	0.96	683/983 (69.5%)
EDH	73/609 (12.0%)	50/374 (13.4%)	0.52	20/141 (14.2%)	30/233 (12.9%)	0.72	123/983 (12.5%)
Cerebral edema	197/609 (32.3%)	140/374 (37.4%)	0.10	50/141 (35.5%)	90/233 (38.6%)	0.54	337/983 (34.3%)
Diffuse cerebral injury	167/609 (27.4%)	158/374 (42.2%)	< 0.001	52/141 (36.9%)	106/233 (45.5%)	0.10	325/983 (33.1%)
Surgery, *n*/total *N* (%)							
None	85/609 (14.0%)	18/374 (4.8%)	< 0.001	3/141 (2.1%)	15/233 (6.4%)	0.04	103/983 (10.5%)
Cranial	347/609 (57.0%)	220/374 (58.8%)		78/141 (55.3%)	142/233 (61.0%)		567/983 (57.7%)
Extracranial	177/609 (29.0%)	136/374 (36.4%)		60/141 (42.6%)	76/233 (32.6%)		313/983 (31.8%)

*Fisher' exact test

AIS = abbreviated injury scale; EDH = epidural hematoma; GCS = Glasgow Coma Scale; HIV = human immunodeficiency virus; IQR = interquartile range; MVC = motor vehicle collision; SAH = subarachnoid hemorrhage; SDH = subdural hematoma; TBI = traumatic brain injury

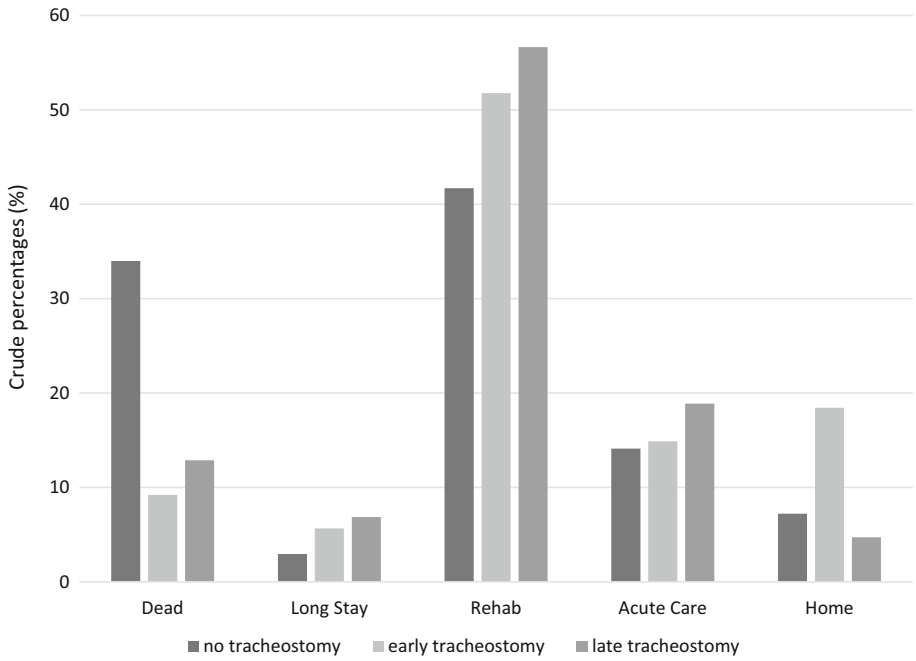

Fig. 2 Status at hospital discharge
Rehab = rehabilitation

Table 2 Outcomes based on the tracheostomy status (tracheostomy *vs* prolonged intubation)

	Unadjusted analysis		Adjusted analysis	
	HR (95% CI)	*P* value	aHR (95% CI)	*P* value
ICU mortality	0.14 (0.07 to 0.27)	< 0.001	0.15 (0.08 to 0.29)	< 0.001
30-day mortality	0.27 (0.17 to 0.42)	< 0.001	0.33 (0.21 to 0.53)	< 0.001
6-month mortality	0.37 (0.26 to 0.53)	< 0.001	0.46 (0.32 to 0.67)	< 0.001
	RR (95% CI)		aRR (95% CI)	
Ventilator-acquired pneumonia	0.83 (0.66 to 1.03)	0.09	0.81 (0.64 to 1.01)	0.07
	1/HR (95% CI)		1/aHR (95% CI)	
Mechanical ventilation duration	0.96 (0.83 to 1.12)	0.62	1.07 (0.91 to 1.25)	0.41
ICU length of stay	1.07 (0.93 to 1.23)	0.35	1.09 (0.94 to 1.26)	0.26
Hospital length of stay	0.83 (0.71 to 0.96)	0.01	0.91 (0.78 to 1.07)	0.26

aHR = adjusted hazard ratio; aRR = adjusted relative rate; CI = confidence interval; HR = hazard ratio; ICU = intensive care unit; RR = relative rate

observed in two systematic reviews including two small randomized clinical trials as well as retrospective cohort studies.[8,11] The fact that early tracheostomy is performed during the very acute phase of care, a period where patients are at increased risk of ventilator-acquired pneumonia, may help to explain these findings. Differences in the definition of early and late tracheostomy between studies may also contribute to this finding. Furthermore, we showed that early tracheostomy was associated with a shorter duration of mechanical ventilation, ICU stay, and hospital stay—an effect consistently observed in previous studies and systematic reviews.[6,8,11] Our sensitivity analysis using time of tracheostomy as T_0 reinforced that the potential effect on reducing duration of mechanical ventilation, ICU stay, and hospital stay happens before the procedure is performed. Nevertheless, a potential residual indication bias regarding the timing of the tracheostomy could still be present.

Our study has several strengths starting with its multicentre design within an integrated and comprehensive trauma system in the second largest Canadian province. The use of robust statistical methods, including the use of a time-dependent Cox-model with covariate adjustment including major prognostic indicators, is also an important strength. Our study also has limitations. Residual confounders may still be present,

Table 3 Outcomes based on the timing of the tracheostomy (early *vs* late)

	Unadjusted analysis		Adjusted analysis	
	HR (95% CI)	*P* value	aHR (95% CI)	*P* value
ICU mortality	1.26 (0.39 to 4.03)	0.70	1.25 (0.38 to 4.06)	0.65
30-day mortality	1.52 (0.65 to 3.54)	0.32	1.46 (0.61 to 3.47)	0.33
6-month mortality	0.85 (0.44 to 1.63)	0.64	0.96 (0.49 to 1.88)	0.91
	RR (95% CI)		aRR (95% CI)	
Ventilator-acquired pneumonia	0.96 (0.68 to 1.35)	0.82	1.10 (0.78 to 1.56)	0.61
	1/HR (95% CI)		1/aHR (95% CI)	
Mechanical ventilation duration	0.49 (0.39 to 0.61)	< 0.001	0.53 (0.42 to 0.67)	< 0.001
ICU length of stay	0.54 (0.44 to 0.67)	< 0.001	0.57 (0.46 to 0.71)	< 0.001
Hospital length of stay	0.75 (0.60 to 0.93)	< 0.001	0.81 (0.64 to 1.02)	0.08

aHR = adjusted hazard ratio; aRR = adjusted relative rate; CI = confidence interval; HR = hazard ratio; ICU = intensive care unit; RR = relative rate

and we cannot exclude a potential residual indication bias since the decision to perform the tracheostomy was not protocolized. Although we used well-known prognostic indicators for the severity of the TBI that could impact the decision to perform the procedure, potential confounding variables such as the presence of increased intracranial pressure and pupillary reactivity were not available. Furthermore, long-term functional outcomes—such as the extended Glasgow Outcome Scale, a standard long-term outcome in critically ill patients with TBI—were not collected in our dataset. The use of a different definition than < 10 days of mechanical ventilation to define early tracheostomy could also be challenged. Nevertheless, a recent systematic review in nonneurologically ill patients did not observe a differential effect based on the definition of early tracheostomy.[31] Lastly, the duration of sedation, which has previously been shown to be shorter in patients with early tracheostomy,[32] could not be evaluated in our study since the data were not collected in the Québec Trauma Registry dataset. Nevertheless, the observed effect on the duration of mechanical ventilation and ICU length of stay, outcomes bearing a greater clinical significance, is likely associated with a shorter duration of sedation.

Conclusion

In critically ill patients with TBI, tracheostomy was associated with lower mortality than prolonged intubation was. Whether performed early or later, the timing of tracheostomy was not associated with differences in mortality. The level of evidence supporting these results remains limited by potential residual confounders, including level-of-care decisions. A well-designed multicentre randomized clinical trial in patients with moderate to severe TBI is needed to inform clinician decision-making and practice guidelines related to the indication and optimal timing of tracheostomy.

Author contributions *Noémie Villemure-Poliquin* and *Alexis F. Turgeon* contributed to all aspects of this manuscript, including study conception and design; acquisition, analysis and interpretation of data; critical revision of the manuscript for important intellectual content; and drafting the manuscript. *Olivier Costerousse*, *Paule Lessard Bonaventure*, *Nathalie Audet*, *François Lauzier*, *Lynne Moore*, and *Ryan Zarychanski* contributed to the interpretation of data and the critical revision of the manuscript for important intellectual content.

Disclosures None of the authors of this manuscript have conflicts of interest to declare.

Funding statement This work was funded by a Foundation Scheme Grant (#148443) from the Canadian Institutes of Health Research (CIHR). The funder had no role in the design and conduction of the study. Dr. Villemure-Poliquin and Dr. Lessard Bonaventure are recipients of training awards from the Fonds de la Recherche du Québec – Santé (FRQS). Drs Lauzier and Moore are recipients of a research salary support award from FRQS. Dr. Zarychanski is supported by the Lyonel G. Israels Research Chair in Hematology, University of Manitoba. Dr. Turgeon is the chairholder of the Canada Research Chair in Critical Care Neurology and Trauma.

Editorial responsibility This submission was handled by Dr. Patricia S. Fontela, Associate Editor, *Canadian Journal of Anesthesia/Journal canadien d'anesthésie.*

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