

The effect of tracheostomy timing during critical illness on long-term survival*

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Background: Tracheostomy is common in intensive care unit patients, but the appropriate timing is controversial.

Objective: To determine whether earlier tracheostomy is associated with greater long-term survival.

Design: Retrospective cohort analysis.

Setting: Acute care hospitals in Ontario, Canada (n = 114).

Patients: All mechanically ventilated intensive care unit patients who received tracheostomy between April 1, 1992 and March 31, 2004, excluding extreme cases (<2 or ≥28 days) and children (<18 yrs).

Measurements: For crude analyses, tracheostomy timing was classified as early (≤10 days) vs. late (>10 days) with mortality measured at multiple follow-up intervals. Proportional hazards analyses considered tracheostomy as a time-dependent variable to adjust for measurable confounders and possible survivor treatment bias. We used stratification, propensity score, and instrumental variable analyses to adjust for patient differences.

Results: A total of 10,927 patients received tracheostomy during the study, of which one-third (n = 3758) received early and

two-thirds late (n = 7169). Patients receiving early tracheostomy had lower unadjusted 90-day (34.8% vs. 36.9%; $p = 0.032$), 1 yr (46.5% vs. 49.8%; $p = 0.001$), and study mortality (63.9% vs. 67.2%; $p < 0.001$) than patients receiving late tracheostomy. Multivariable analyses treating tracheostomy as a time-dependent variable showed that each additional delay of 1 day was associated with increased mortality (hazard ratio 1.008, 95% confidence interval 1.004–1.012), equivalent to an increase in 90-day mortality from 36.2% to 37.6% per week of delay (relative risk increase 3.9%; number needed to treat, 71 patients to save one life per week delay).

Limitations: This analysis provides guidance regarding timing but not patient selection for tracheostomy.

Conclusions: Physicians performing early tracheostomy should not anticipate a large potential survival benefit. Future research should concentrate on identifying which patients will receive the most benefit. (Crit Care Med 2008; 36:2547–2557)

KEY WORDS: tracheostomy; critical care; respiration; artificial; mortality; proportional hazards models

Tracheostomy is a common procedure in intensive care unit (ICU) patients, and relatively affordable if physicians choose a percutaneous approach (1, 2). Between 2% and 11% of ICU patients requiring mechanical ventilation receive a tracheostomy (3–

5), accounting for about 26% of all ventilator days and up to 14% of all hospital days (6). Tracheostomy can help patient well-being by reducing laryngeal irritation, lowering respiratory tract resistance, improving pulmonary toilet, enhancing patient communication, and decreasing the requirements for sedation (7). However, the procedure is associated with complications including stomal hemorrhage, site infections, pneumomediastinum, pneumothorax, tracheomalacia, tracheoesophageal fistula, and catastrophic arterial fistula (8–10).

Controversy surrounds the optimal timing of tracheostomy. Surveys from France and the United Kingdom, for example, documented variability for both the timing and the indications for tracheostomy (11, 12). The National Association of Medical Directors of Respiratory Care strongly recommends performing tracheostomy in all patients receiving mechanical ventilation 21 days after ICU admission (13). In contrast, guidelines created jointly by the American Association for Respiratory Care, the American College

of Chest Physicians, and the American College of Critical Care Medicine make no specific recommendations about tracheostomy timing, but suggest that the procedure should be considered if the patient will require prolonged ventilator assistance (14).

Some small observational studies of tracheostomy suggest possible advantages with earlier treatment, including more rapid weaning from mechanical ventilation and shorter length of ICU stay (15–17). However, these analyses are limited by their single hospital sampling. Larger retrospective analyses with more careful matching of patients showed no effect of timing on mortality (18). None of these studies accounted for possible survivor treatment bias, akin to many other analyses in the literature (19, 20). The effect of survivor treatment bias is to favor interventions that occur late following the start of follow-up (21). Unfortunately, all previous retrospective studies, which failed to incorporate the tracheostomy procedure as a time-dependent variable, would tend to favor late tracheostomy, because patients in

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the “early” group are considered at risk of dying before patients in the “late” group have received the procedure. Survivor treatment bias can be addressed using proportional hazards modeling incorporating time-dependent variables for retrospective studies.

The largest meta-analysis of randomized controlled trials ($n = 5$) evaluating the impact of tracheostomy timing on mortality collectively involved 406 patients and observed substantial heterogeneity because of variable definitions of early (range, 2–7 days) and late (range, 8–16 days or not specified) tracheostomy (22). Each study examined a different specific patient population [head injury (23), trauma (24), postoperative (25), medical (26), and burns (27)]. Performance of early tracheostomy did not significantly change mortality [0.27 vs. 0.37; relative risk 0.79 (95% confidence interval [CI] 0.45–1.39), but reduced the total duration of artificial respiration by about 8.5 days (95% CI 1.7–15.3) and ICU length of stay by about 15.3 days (95% CI 6.1–24.6).

The healthcare system in Ontario provides a unique opportunity to study survival outcomes after tracheostomy in ICU patients across multiple study centers for a broad population across multiple subgroups. The large sample size available also enables measurement of small mortality differences. We used these databases to evaluate the association of tracheostomy timing with survival of mechanically ventilated patients. Our study question was “Does earlier tracheostomy lead to improved long-term survival among ICU patients receiving mechanical ventilation?”

METHODS

Setting. The Ontario health databases and methods for characterizing patients have been previously validated and are described in the Appendix (28–30). The accrual period for this study was April 1, 1992 to March 31, 2004, representing all available years. We excluded patients receiving tracheostomy within the first 48 hrs of mechanical ventilation to avoid patients requiring the procedure to treat emergency airway obstruction or to complete another surgical procedure. Patients receiving tracheostomy 28 days or more after initiation of mechanical ventilation were also excluded to create a more homogeneous cohort and avoid biases related to outlier patients. We also performed secondary analyses using a cohort of all patients who received a first episode of mechanical ventilation during 1992 to 2004 (described in the Appendix).

Timing. We considered tracheostomy timing as a continuous variable measured as

number of days between initiation of mechanical ventilation and tracheostomy procedure. For crude comparisons, tracheostomy timing was also categorized according to two time periods termed “early” and “late.” Tracheostomies were considered early if the procedure occurred ≤ 10 days after mechanical ventilation (but not within 2 days). Tracheostomies were considered late if the procedure occurred > 10 days after mechanical ventilation (but < 28 days). Ten days was selected in advance as a cut-point because the median time to tracheostomy in observational studies has varied between 9 and 14 days (5–7) and one prominent set of guidelines recommends limiting endotracheal intubation to patients requiring < 10 days of mechanical ventilation (13). We also explored other thresholds by characterizing timing as very early (< 7 days) or very late (> 15 days).

Outcome. The primary outcome was the hazard of dying after initiation of mechanical ventilation as measured using a proportional hazards model considering tracheostomy as a time-dependent variable. The end of the observation period was March 31, 2005, so that all survivors were followed for at least 1 yr and at most 13 yrs (median 6.4 yrs). For secondary analyses, we also considered 90-day and 1-yr mortality. Frequency of death was analyzed using the chi-square test. Life tables were constructed to create Kaplan-Meier survival curves. We measured the following as secondary end points: time from tracheostomy to discontinuation of mechanical ventilation, total length of ICU stay, and ventilator-free days at 28 and 180 days (31, 32).

Statistics. We used three analytical techniques to adjust for multiple possible biases (see Appendix). First, we used multivariable proportional hazards analyses considering tracheostomy as a time-dependent variable to adjust for measured confounders and correct for survivor treatment bias. Second, we incorporated an instrumental variable (physician practice pattern quartile) into the survival analyses to account for physician preferences regarding tracheostomy timing. This instrumental variable was created by classifying each physician into quartiles according to their median time to tracheostomy in relation to their peers. Third, we repeated our proportional hazards analyses in a matched cohort assembled using a propensity score to compensate for measured patient differences that might influence decisions regarding tracheostomy timing. More information regarding these analyses is available in the Appendix.

All p values were two-tailed and computed using SAS software (version 8.02, SAS Institute, Cary, NC). The study was approved by the ethics committee of the Sunnybrook Health Sciences Centre. Analyses were conducted using confidentiality safeguards at the Institute for Clinical Evaluative Sciences in Ontario.

RESULTS

During the 12-yr study period 14,782 patients received a tracheostomy in 114 hospitals. Overall, 3238 were conducted < 2 days after the initiation of mechanical ventilation in the ICU and 617 patients had the procedure performed 28 days or more after mechanical ventilation. This yielded 10,927 patients for analysis (Table 1). A slight increase in the number of tracheostomies was apparent over time (1992–1993, $n = 697$; 2003–2004, $n = 991$) representing an average increase of 2% per year ($p = 0.005$). The mean age of patients was 62 yrs (SD 16) and the majority (60%) were men. Neurologic compromise was common, occurring in 31% of the cohort. One-third of patients (3758; 34%) received early (≤ 10 days from mechanical ventilation) and two-thirds (7169; 66%) received late (> 10 days) tracheostomy (Table 2).

Early vs. Late Tracheostomy. Patients receiving late tracheostomy tended to be older (63 yrs vs. 60 yrs, $p < 0.001$), more likely to have a history of cardiac disease (15% vs. 11%, $p < 0.001$), and had greater median numbers of physician visits during the 3 yrs preceding the ICU admission (77 vs. 71; $p < 0.001$). Conversely, patients receiving late tracheostomy were less likely to have a neurologic disorder (28% vs. 36%; $p < 0.001$) or traumatic injury (14% vs. 21%; $p < 0.001$). Patients in both groups were similar for other demographic and clinical characteristics including neighborhood income quintile and Deyo-adapted Charlson comorbidity index (33–35).

Crude Analyses. Overall 7219 (66.1%) patients died during the study period. Patients receiving early tracheostomy, compared with patients receiving late tracheostomy, had lower cumulative mortality at 90 days [1309 (34.8%) vs. 2647 (36.9%); $p = 0.03$], 1 yr [1749 (46.5%) vs. 3572 (49.8%); $p = 0.001$], and during the entire study period [2403 (63.9%) vs. 4816 (67.2%); $p < 0.001$]. This mortality advantage persisted during extended follow-up (Fig. 1). The crude mortality differences associated with early tracheostomy were insignificant when intermediate time frames (days 7, 8, 9 vs. days 10, 11, 12) were considered [90-day mortality 614 of 1108 (35.7%) vs. 744 of 1273 (36.9%); $p = 0.44$] but became accentuated when patients receiving very early (< 7 days) were compared with those receiving very late (> 15 days) tracheostomy [90-day mortality 459 of 1411 (32.5%) vs. 1388 of 2367 (37.0%); $p < 0.001$].

Table 1. Characteristics of patients receiving tracheostomy^a

	Early Tracheostomy (n = 3758)	Late Tracheostomy (n = 7169)	p
Index hospitalization			
Age—mean (SD)	60 (17)	63 (15)	<0.001
Sex—female (%)	1429 (38)	2996 (42)	<0.001
Surgical (%)	1486 (40)	3625 (51)	<0.001
Trauma (%)	774 (21)	978 (14)	<0.001
Neurological (%)	1349 (36)	1986 (28)	<0.001
Central nervous system (%)	1158 (31)	1605 (22)	<0.001
Peripheral nervous system (%)	263 (7.0)	514 (7.2)	0.741
Past hospitalizations			
Medical history			
Cardiac (%)	410 (11)	1079 (15)	<0.001
Respiratory (%)	263 (7.0)	428 (6.0)	0.036
Gastrointestinal (%)	45 (1.2)	112 (1.6)	0.128
Trauma (%)	550 (15)	1055 (15)	0.910
Neighborhood income quintile ^b			0.684
First quintile (%)	912 (24)	1709 (24)	
Second quintile (%)	816 (22)	1577 (22)	
Third quintile (%)	700 (19)	1331 (19)	
Fourth quintile (%)	597 (16)	1104 (15)	
Fifth quintile (%)	538 (14)	1098 (15)	
Urban (%)	6235 (88)	9494 (88)	0.806
Physician claims in preceding 3 yrs— median (IQR)	71 (29–129)	77 (37–138)	<0.001
Hospitalizations in preceding 3 yrs— median (IQR)	0 (0–2)	1 (0–2)	<0.001
Hospital days in preceding 3 yrs— median (IQR)	0 (0–14)	2 (0–16)	0.012
Hospital admission to ICU admission (d)—median (IQR)	0 (0–3)	0 (0–3)	0.0002
Charlson comorbidity index—median (IQR)	1 (0–2)	1 (0–2)	<0.001

^aNumbers in parentheses represent standard deviation (SD), percent (%), or interquartile range (IQR) where indicated; ^bIncome data were missing for 5% of the sample.

Table 2. Tracheostomy time characteristics^a

	Early Tracheostomy	Late Tracheostomy	p
Mechanical ventilation to tracheostomy (days)—median (IQR)	7 (5–9)	16 (13–19)	<0.001
ICU admission to tracheostomy (days)—median (IQR)	8 (5–9)	16 (13–20)	<0.001
Hospitalization to tracheostomy (days)—median (IQR)	9 (7–11)	18 (15–23)	<0.001
Hospitalization to ICU admission (days)—median (IQR)	0 (0–3)	0 (0–3)	<0.001
Mechanical ventilation after tracheostomy (days)—median (IQR)	7 (2–19)	13 (6–27)	<0.001
Mechanical ventilation, total (days)—median (IQR)	14 (10–26)	30 (22–45)	<0.001
Ventilator-free days to day 28—mean (SD)	9.7 (8.8)	3.0 (4.6)	<0.001
Ventilator-free days to day 180—mean (SD)	94.2 (80.9)	81.2 (74.6)	<0.001
Duration of follow-up (yrs)—median (IQR)	6.6 (4.0–9.3)	6.2 (3.6–9.2)	0.005

^aNumbers in parentheses represent interquartile range (IQR) or standard deviation (SD) where indicated.

The survival advantage associated with early (≤ 10 days) vs. late (> 10 days) tracheostomy in different subgroups is shown in Figure 2 (90-day mortality) and in Figure A1 (1-yr mortality; Appendix). The benefit of early tracheostomy persisted across multiple subgroups, although the CIs often overlapped the null

effect. The largest inconsistency was that patients with a previous cardiac history seemed to do poorer with early tracheostomy compared with late tracheostomy [increase in relative risk of death at 90 days 0.135 (95% CI 0.003–0.285)].

We also performed secondary crude analyses using a cohort of all 298,066

patients who received a first episode of mechanical ventilation in Ontario during 1992 to 2004. A total of 2995 of these patients received tracheostomy ≥ 2 days but ≤ 10 days and were still alive on day 10. These patients were then compared with 14,975 patients who were still alive and requiring mechanical ventilation after day 10 but who had not yet received a tracheostomy. Compared with this latter group, patients receiving early tracheostomy had lower cumulative mortality at 90 days [953 (31.8%) vs. 7009 (46.8%) $p < 0.0001$; odds ratio (OR) 0.530, 95% CI 0.488–0.577], 1 yr [1295 (43.2%) vs. 7966 (53.2%), $p < 0.0001$; OR 0.670, 95% CI 0.619–0.725], and during the entire study period [1824 (60.9%) vs. 10,152 (67.8%), $p < 0.0001$; OR 0.740, 95% CI 0.682–0.802]. In a multivariable model adjusting for age, sex, neurologic diagnosis, trauma diagnosis, number of previous hospitalizations, total hospital days during the preceding 3 yrs, Deyo-adapted Charlson comorbidity index, history of cardiac disease, and history of respiratory disease, the group of patients receiving early tracheostomy had lower mortality at 90 days (OR 0.618, 95% CI 0.565–0.676) and at 1 yr (OR 0.814, 95% CI 0.745–0.888), but not during the entire study period (OR 0.995, 95% CI 0.906–1.094; median duration of follow-up 1.64 yrs and 0.49 yrs, respectively).

ICU Length of Stay and Treatment. Patients receiving early tracheostomy had more ventilator-free days than patients receiving late tracheostomy at 28 days (mean 9.7 vs. 3.0; $p < 0.001$) and at 180 days (mean 94.2 vs. 81.2; $p < 0.001$). Patients receiving early tracheostomy had faster weaning from mechanical ventilation following the procedure [median 7 (interquartile range 2–19) vs. 13 (interquartile range 6–27); $p < 0.001$].

Proportional Hazards Model. The univariate proportional hazard model treating time to tracheostomy (days) as a time-dependent function yielded a hazard ratio (per day of delay) for death during the study period of 1.019 (95% CI 1.015–1.023, $p < 0.0001$). The multivariable model adjusted for the following covariables: age, sex, Deyo-adapted Charlson comorbidity index, number of previous hospitalizations during preceding 3 yrs, trauma admission, history of respiratory disease, and history of cardiac disease. This model yielded a more modest hazard ratio of 1.008 (95% CI 1.004–1.012, $p < 0.0001$) for each additional day that the procedure was delayed, equivalent to a

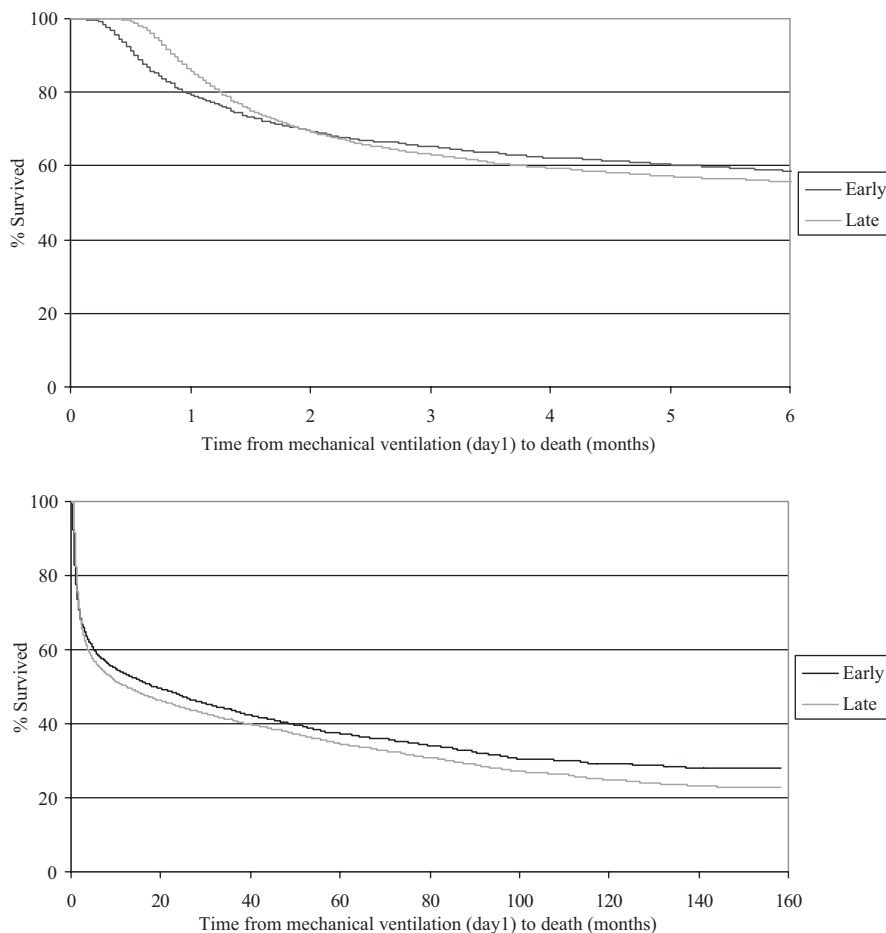


Figure 1. Survival of tracheostomized patients after initiation of mechanical ventilation. Graph is Kaplan-Meier plot showing survival. y-axis is percentage of patients surviving after tracheostomy during ICU admission. x-axis is time after initiation of mechanical ventilation. The lower panel is a reproduction of the upper panel with the time axis extended. Note that survivor treatment bias is most evident in upper graph.

hazard ratio of 1.06 (95% CI 1.04–1.09) for a delay of 7 days. An approach that retained all covariates listed in Table 1 yielded a marginally higher hazard ratio of 1.011 (95% CI 1.007–1.015, $p < 0.0001$) for each additional 1-day delay. We repeated the primary multivariable analysis but measuring 90-day mortality to test the stability of this estimate over the short term; this approach yielded a somewhat greater hazard ratio per day of delay of 1.018 (95% CI 1.012–1.024, $p < 0.0001$).

Instrumental Variable Analysis. Physician practice pattern quartile was strongly associated with individual patients' time to tracheostomy, but no clear trend was seen for this variable and patient survival at 90 days (Appendix). Inclusion of the instrumental variable into our unadjusted and multivariable proportional hazard models yielded nearly identical results favoring early tracheostomy

with an unadjusted hazard ratio per day of delay on mortality during study period of 1.019 (95% CI 1.015–1.024, $p < 0.0001$) and at 90 days of 1.029 (95% CI 1.022–1.035, $p < 0.0001$); adjusted hazard ratio per day of delay on mortality during study period of 1.010 (95% CI 1.005–1.014, $p < 0.0001$) and at 90 days of 1.020 (95% CI 1.014–1.027, $p < 0.0001$).

Propensity Score Matched Cohort. The analyses of tracheostomy timing using a propensity score matched cohort yielded findings that were similar to our primary results and are reported in the Appendix.

DISCUSSION

We analyzed 10,927 mechanically ventilated patients receiving tracheostomy over more than a decade and found that earlier tracheostomy compared with later

tracheostomy was associated with a modest survival benefit. Patients having the procedure between 2 and 10 days of mechanical ventilation had lower 90-day (34.8% vs. 36.9%) and 1-yr mortality (46.5% vs. 49.8%) than patients receiving tracheostomy between days 10 and 28. This observation was consistent during long-term follow-up and across multiple subgroups. Weaning from mechanical ventilation occurred more quickly and ventilator-free days were also greater in the early tracheostomy group.

Univariate survival analyses typically consider patients' risk of dying after the start of a treatment. This approach can lead to survivor treatment bias favoring those receiving late tracheostomy because no deaths can occur before the tracheostomy. We also believe that the early group might have less favorable prognoses owing to unmeasured factors that influenced physicians' decisions to expedite the procedure. Indeed, patients receiving early tracheostomy were more likely to have a trauma or neurologic diagnosis, and physicians might have judged these patients to be prone to weaning failure. The purpose of the time-dependent multivariable proportional hazards model is to attenuate possible survivor treatment bias and adjust for measurable confounders. This approach showed that delays were associated with increased mortality risk equivalent to 90-day mortality increases from 36.2% to 37.6% (relative risk increase 3.9%; number needed to treat, 71 patients to save one life per week delay). Time-dependent bias could also cause crude comparisons of other outcomes, such as ventilator-free days or duration of mechanical ventilation, to appear worse for the late tracheostomy group. Unfortunately, these continuous end points are not easily analyzed using conventional modeling techniques to study the effects of time-dependent variables.

We believe using proportional hazards modeling and treating time to tracheostomy as a time-dependent variable is an appropriate statistical model, but this model requires several assumptions. The violated assumption of proportional hazards (Fig. 1) was addressed through a time-dependent variable, yet we have no easy way to prove that all other covariates considered in our model conform to the proportional hazards assumption. Other assumptions of the model include that censoring is noninformative, death times are independent of each other, and the

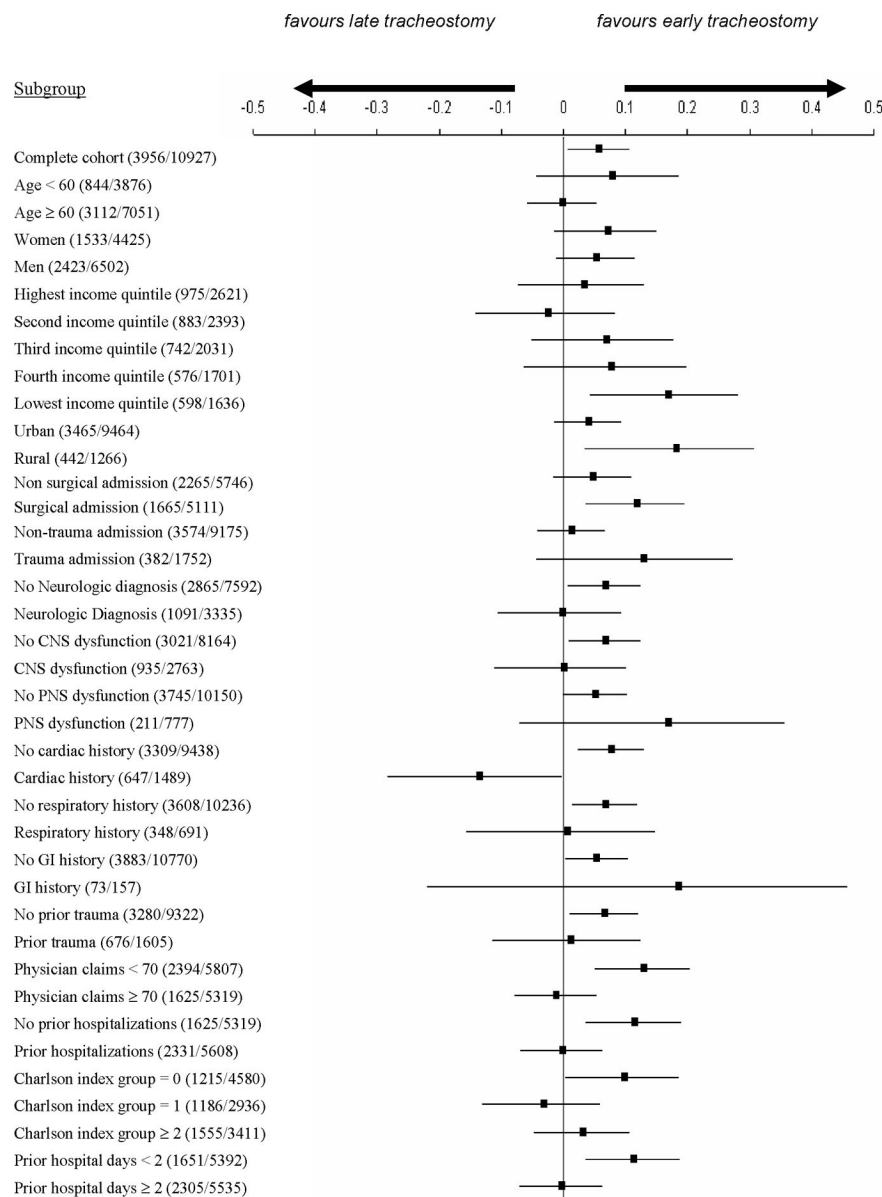


Figure 2. Relative reduction in risk of death at 90 days. Relative risk of death for patients receiving early tracheostomy (≤ 10 days after mechanical ventilation) compared with patients receiving late tracheostomy (> 10 days after mechanical ventilation). An x-axis value of 0 denotes the null effect, where risk with early tracheostomy equals risk with late tracheostomy. Values to the right of 0 indicate a relative risk reduction in favor of early tracheostomy. Baseline risk in each analysis shown in parentheses as total number of deaths and total sample size. Complete cohort analysis appears at the top, showing a 5.7% relative reduction in the risk of death at 90 days for patients receiving early tracheostomy compared with late tracheostomy (95% CI 0.5%–10%). CNS, central nervous system; PNS, peripheral nervous system; GI, gastrointestinal. Physician claims refers to number of physician claims during previous 3 yrs. Previous hospitalizations refers to number of hospitalizations during previous 3 yrs. Prior hospital days refers to total number of hospital days during previous 3 yrs.

hazard is continuous. To satisfy the last assumption, tied survival times are not possible and censoring is assumed to occur after all the deaths. Our data contained some tied survival times, but the results did not change depending on whether the Breslow, Efron, exact or discrete likelihood estimation methods were applied (36).

The appropriateness of using survival methods, including the proportional hazards model, for ICU outcome studies has been questioned because patients do not benefit if their survival is only transiently prolonged. In these situations, survival analysis techniques could lead to incorrect inferences about benefit (37). We do not believe these concerns apply to our

observations for the following reasons: patients were followed over a decade, so that relative changes are based on an extended baseline; we measured total mortality rather than ICU mortality or other short-term end point; the results of the proportional hazards model were congruent with analyses censoring survival at 90-days; the mortality findings persisted over the entire observation period, and only a minority of patients were still hospitalized at the end of follow-up.

The decision to perform tracheostomy involves consideration of multiple factors, including patient characteristics, ICU diagnosis, severity of illness, comorbidities, response to treatment, overall hospital course, and physician judgment. Our database does not contain such nuances, but we attempted to adjust for unmeasured confounders using stratification, instrumental variable analyses, and propensity matching. Each of these approaches yielded results that favored early tracheostomy. However, it is still possible that patients receiving early tracheostomy are systematically different from those receiving late tracheostomy in ways that are not considered in these analyses. We took precautions to analyze the data considering multiple assumptions and variable clinical situations, but unmeasured confounders might have favored patients receiving early tracheostomy.

Early tracheostomy may confer several advantages. A tracheostomy tube is more comfortable than an endotracheal tube and may thereby decrease requirements for sedation, and facilitate earlier recovery from mechanical ventilation (7, 38). This idea is supported by the finding of increased ventilator-free days among the early tracheostomy group. Earlier weaning also may help prevent complications such as ventilator-associated pneumonia (25,39,40) and ventilator-induced lung injury (41, 42). Similar to others (43), we also observed reduced ICU length of stay with early tracheostomy, which might protect patients against complications such as decubitus ulcers (44, 45), venous thromboembolism (46), or catheter-related bloodstream infections (47). The relative contribution of each of these factors in explaining our observations is unknown.

The main limitation of our research is that it offers guidance on timing but not patient selection for tracheostomy (48, 49). Although our study suggests that there may be a small long-term survival benefit associated with earlier tracheostomy, we can only speculate on the mechanism. We

observed lower crude mortality in patients receiving early tracheostomy compared with a cohort of patients who were ventilated for 10 days without receiving the procedure, but this comparison is risky because we are unable to adjust for nuances that influence physicians' decision to not perform the procedure. We reasoned that each patient in our cohort had an indication for tracheostomy, and that the biggest determinant affecting differences in timing of a few days would be physician judgment. However, it is possible that reasons for performing the procedure still varied during these short intervals. Our health databases do not contain nuances to explain how many patients were considered for tracheostomy yet eventually survived without receiving the procedure. Providing early tracheostomy to all eligible patients might cause some patients to receive the procedure that might have eventually been successfully managed with primary extubation.

This is the largest study of tracheostomy in ICU patients to date. The strengths include the broad selection criteria and long follow-up. The observed benefits with early tracheostomy support previous studies, but the small magnitude of the observed effect suggests that enormous sample size might be required to mount a randomized clinical trial. We know of two anticipated trials of early vs. late tracheostomy that will examine mortality as a primary end point, including Tracman (MREC 04/MRE00/43; target sample size 1208 patients) and Blot (ClinicalTrials.gov NCT00127621; completed, 468 patients). Our results imply that these randomized trials will not detect a mortality difference and are unlikely to provide information about long-term survival. Until more studies become available, we recommend that physicians consider performing tracheostomy somewhat earlier to achieve the established benefits of the procedure and not in anticipation of a large potential survival benefit.

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APPENDIX

Technical Details on Methods and Analyses. Herein, we elaborate on the methods of our study, including the identification and characterization of patients; identification of ICU admissions; analyses of all mechanically ventilated patients; and development of our analytical approaches including our multivariable proportional hazards model, our instrumental variable model, and creation of (and results from) our propensity score matched cohort.

Identification of Patients. Our study involved the following Ontario health databases: the Ontario Health Insurance Plan database, the Canadian Institute for Health Information Discharge Abstract Database, and the Registered Persons Database. These databases have been validated and used extensively in previous research. It has been estimated that services received outside of Ontario comprise <0.5% of all procedures performed for Ontario residents (1). Although some patients may be lost to follow-up because of migration out of the province, studies in other populations suggest that this occurs infrequently (<3%) (2). Furthermore, the most recent Statistics Canada census (2006) estimated that over a 5-yr period only 185,785 (1.6%) of Ontario citizens migrated outside of the province, and 566,710 (4.9%) Ontario citizens migrated outside of Canada (3).

We identified all Ontario adults (age \geq 18 yrs) who received tracheostomy in the ICU using the Ontario Health Insurance Plan database, which contains fee-for-service claims for services provided by physicians to Ontario residents (4, 5). If multiple tracheostomies were performed on the same patient, we only considered the first procedure. The study period was from April 1, 1992, to March 31, 2005, representing all years available for analyses.

Characterization of Patients. Patients receiving tracheostomy were linked to the Canadian Institute for Health Information Discharge Abstract Database to obtain demographic, administrative, and clinical data for hospital care in Canada. Individuals were also linked to the Registered Persons Database, which contains vital statistics on Canadian citizens. These databases have been used extensively in past research (6, 7). The admission containing the most recent discharge date was retained when multiple

records had the same healthcare number, admission date, and date of birth. If duplicate records were identical for health care number and admission date, the record associated with the most recent discharge date was retained. If discharge dates were also identical, one of the records was randomly deleted. If patients were transferred between hospitals, we only focused on the hospital admission during which the tracheostomy procedure was performed.

Identification of ICU Admission. We identified admissions to ICU using codes in the Ontario Health Insurance Plan database according to a previously described algorithm (8) and focused on the ICU admission corresponding to the tracheostomy procedure date. Patients were excluded if they were not in the ICU on the day of tracheostomy or if they were not receiving mechanical ventilation. ICU length of stay was calculated by counting the number of sequential ICU codes appearing on subsequent days following the first day of ICU. When ICU codes were interrupted by >1 day we assumed the patient had been discharged then readmitted to ICU, and this subsequent readmission was considered the same ICU stay. ICU procedures were identified using the Ontario Health Insurance Plan database. Mechanical ventilation was identified using a previously described algorithm (9).

Analyses of All Mechanically Ventilated Patients. We also performed secondary crude analyses using a cohort of all 298,066 patients who received a first episode of mechanical ventilation during 1992 to 2004. Of these, 3103 received a tracheostomy \geq 2 days but \leq 10 days. Only 108 of these early tracheostomy patients died before day 10 and were excluded from subsequent analyses (leaving 2995 early tracheostomy patients). These patients were then compared with 14,975 patients who were still alive and requiring mechanical ventilation after day 10 but who had not yet received a tracheostomy. Among this latter group, 4371 patients received a tracheostomy >10 days but <20 days after mechanical ventilation, and 913 patients received tracheostomy >20 days but <28 days. The results of these crude comparisons are reported in the main article.

We also constructed a multivariable logistic regression model to adjust for patient factors that were associated with the risk of death following 90 days, 1 yr, and during the entire study. We forced into this model

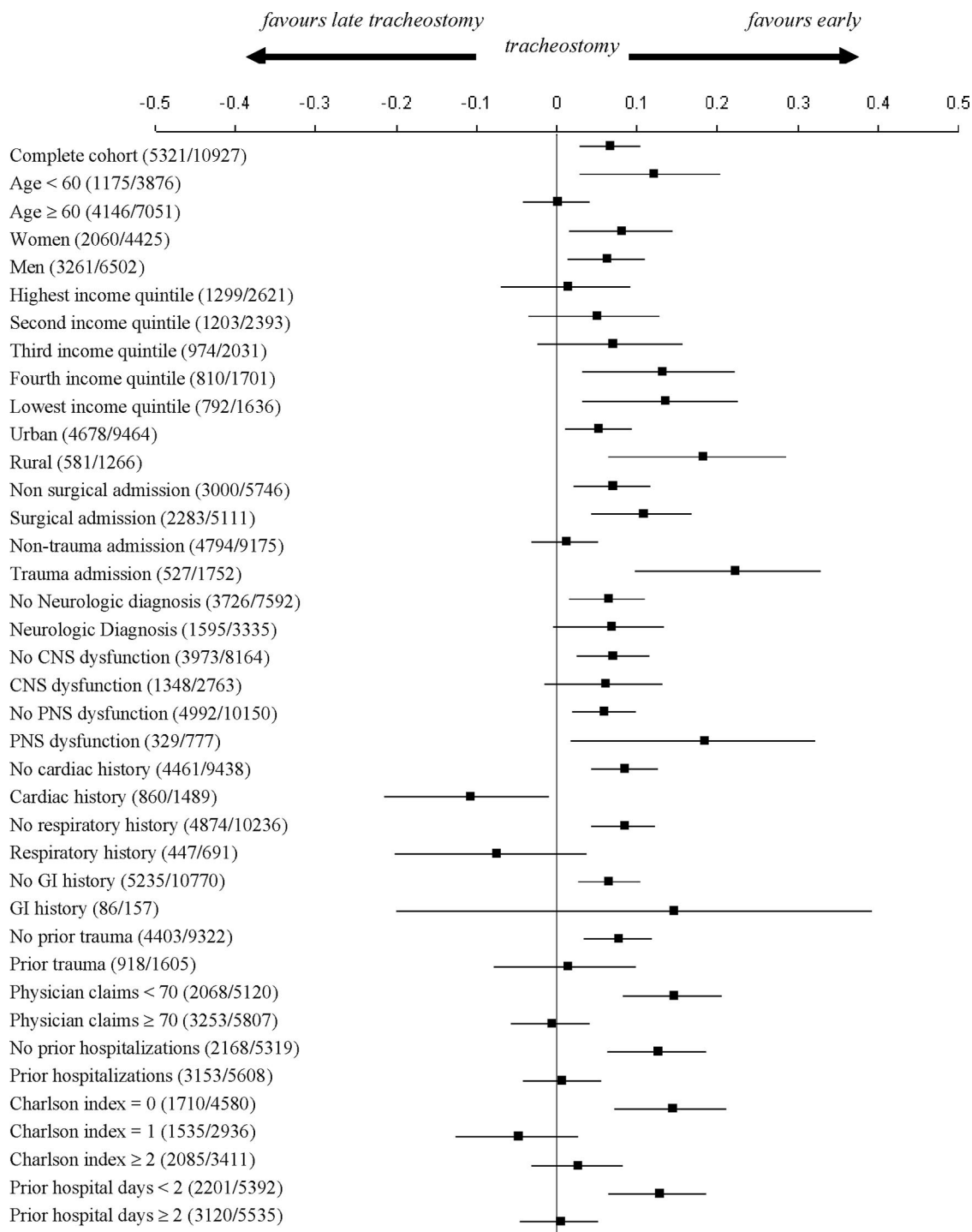


Figure A1. Relative reduction in risk of death at 1 yr following early vs. late tracheostomy among prespecified subgroups. Relative risk of death for patients receiving early tracheostomy (≤ 10 days after mechanical ventilation) compared with patients receiving late tracheostomy (> 10 days after mechanical ventilation). An x-axis value of 0 denotes the null effect, where risk with early tracheostomy equals risk with late tracheostomy. Values to the right of 0 indicate a relative risk reduction in favor of early tracheostomy. Baseline risk in each analysis shown in parentheses as total number of deaths and total sample size. Complete cohort analysis appears at the top, showing a 6.6% relative reduction in the risk of death at 365 days for patients receiving early tracheostomy compared with patients receiving late tracheostomy (95% confidence interval 2.6%–10%). *CNS*, central nervous system; *PNS*, peripheral nervous system; *GI*, gastrointestinal. Physician claims refers to number of physician claims during previous 3 yrs. Previous hospitalizations refers to number of hospitalizations during previous 3 yrs. Prior hospital days refers to total number of hospital days during previous 3 yrs.

identical covariates as in the main multivariable analysis (described below). The results of these adjusted analyses comparing patients receiving tracheostomy ≥ 2 days

but ≤ 10 days to those patients who were still requiring mechanical ventilation after 10 days without a tracheostomy are reported as odds ratios.

Accounting for Survivor Treatment Bias Using Proportional Hazards Modeling. Our primary analysis considered tracheostomy timing as a time dependent

(delayed entry) variable in a proportional hazards model to reduce the potential for survivor treatment bias when considering its effect on mortality (10–13). This approach was analogous to that used in early studies of heart transplantation (14–18). For example, a patient would enter the model as a step function on the day of tracheostomy but, once entered, the hazard of dying for that patient would be estimated indexed to time since initiation of mechanical ventilation. This approach ensured that hazard ratios are not distorted based on comparisons before the patient's tracheostomy procedure.

Adjustments Using Multivariable Models. We constructed our multivariable proportional hazards time-dependent model by forcing tracheostomy timing (days) into the models and then including all candidate covariables appearing in Table 1. Using a backward-selection strategy at a significance level of $p = 0.05$, the following variables were retained in the final model: age, sex, neurologic diagnosis, trauma diagnosis, number of previous hospitalizations, total hospital days during the preceding 3 yrs, Deyo-adapted Charlson comorbidity index (19–21), history of car-

diac disease, and history of respiratory disease. We excluded total hospital days during the preceding 3 yrs because of colinearity with number of previous hospitalizations (Pearson correlation coefficient 0.68, $p < 0.0001$; interaction term $p < 0.0001$). The analyses were repeated considering tracheostomy timing as a quadratic and cubic function to test for nonlinear relationships. We used the exact likelihood estimation method to handle tied death times (10).

We generated bootstrap CIs to evaluate the degree of uncertainty associated with parameter estimates produced by our multivariable proportional hazards time-dependent model (22). We sampled 10,927 observations randomly from our study cohort with replacement to obtain a bootstrap dataset and then calculated the bootstrap version of the parameter estimates produced by our multivariable model. This process was repeated 1000 times to obtain an estimate of the bootstrap distribution. Using this approach, the mortality risk of 1.008 (95% CI 1.004–1.013) associated with delaying tracheostomy for one additional day was

nearly identical to that obtained in our primary analysis.

Instrumental Variable Model. We created an instrumental variable to adjust for physician preferences regarding tracheostomy timing. Instrumental variable analysis is a technique used in econometrics and sometimes extended to health services research (23–28). The methodology relies on an instrumental variable that is associated with a patient's likelihood of receiving an intervention but that is independent of the outcome of this treatment. Theoretically, this instrumental variable can adjust for both known and unknown factors that relate to the likelihood of receiving an intervention. In this study, we classified each physician into quartiles according to their median time to tracheostomy in relation to their peers (quartiles for median time to tracheostomy: 9, 13, 17 days). This instrumental variable (physician practice pattern quartile) representing physician practice pattern was incorporated into our proportional hazards regression models. Patient characteristics according to physician quartile for median tracheostomy timing are shown in Table A1.

Table A1. Characteristics of patients receiving tracheostomy—instrumental variable analysis^a

	Physician with Median Time to Tracheostomy ≤9 days (1st Quartile), n = 1081	Physician with Median Time to Tracheostomy 9 days to ≤13 days (2nd Quartile), n = 5073	Physician with Median Time to Tracheostomy 13 days to ≤17 days (3rd Quartile), n = 3885	Physician with Median Time to Tracheostomy >17 days (4th Quartile), n = 888
Mean time to tracheostomy—days (SD)	8.8 (4.8)	12 (5.4)	15 (5.5)	19 (5.6)
Death at 90 days	426 (39)	1762 (35)	1451 (37)	317 (36)
Index hospitalization				
Age—mean (SD)	61 (17)	62 (16)	62 (16)	64 (15)
Sex—female (%)	435 (40)	2051 (40)	1579 (41)	360 (41)
Trauma (%)	204 (19)	873 (17)	570 (15)	105 (12)
Neurological (%)	360 (33)	1634 (32)	1145 (29)	196 (22)
Central nervous system (%)	301 (28)	1359 (27)	953 (25)	150 (17)
Peripheral nervous system (%)	79 (7.3)	380 (7.5)	266 (6.8)	52 (5.9)
Past hospitalizations				
Medical history				
Cardiac (%)	117 (11)	376 (13)	540 (14)	156 (18)
Respiratory (%)	70 (6.5)	300 (5.9)	270 (7.0)	51 (5.7)
Gastrointestinal (%)	11 (1.0)	65 (1.3)	63 (1.6)	18 (2.0)
Trauma (%)	173 (16)	704 (14)	604 (16)	124 (14)
Neighborhood income quintile				
First quintile (%)	259 (24)	1208 (24)	932 (24)	222 (25)
Second quintile (%)	269 (25)	1097 (22)	832 (21)	195 (22)
Third quintile (%)	223 (21)	939 (19)	717 (19)	152 (17)
Fourth quintile (%)	160 (15)	791 (16)	604 (16)	146 (17)
Fifth quintile (%)	119 (11)	770 (15)	617 (16)	130 (15)
Missing (%)	51 (4.7)	268 (5.3)	183 (4.7)	43 (4.8)
Urban (%)	917 (87)	4369 (88)	3463 (90)	745 (85)
Physician claims in previous 3 yrs—median (IQR)	69 (29–126)	74 (34–132)	77 (35–140)	76 (39–134)
Hospitalizations in previous 3 yrs—median (IQR)	0 (0–2)	0 (0–2)	1 (0–2)	1 (0–2)
Hospital days in previous 3 yrs—median (IQR)	0 (0–15)	0 (0–14)	2 (0–16)	4 (0–20)
Charlson comorbidity index—median (IQR)	1 (0–2)	1 (0–2)	1 (0–2)	1 (0–2)
Hospital admission to ICU (days)—median (IQR)	0 (0–3)	0 (0–3)	0 (0–3)	0 (0–4)

^aNumbers in parentheses represent standard deviation (SD), percent (%), or interquartile range (IQR) where indicated.

Table A2. Propensity matched subcohort^a

	Early Tracheostomy	Late Tracheostomy
Index hospitalization		
Age—mean (SD)	60.4 (17.0)	60.2 (16.4)
Sex—female (%)	1419 (38)	1391 (37)
Trauma (%)	754 (20)	727 (20)
Neurological (%)	1325 (36)	1316 (35)
Surgical (%)	1485 (40)	1474 (40)
Past hospitalizations		
Medical history		
Cardiac (%)	408 (11)	433 (12)
Respiratory (%)	261 (7.0)	271 (7.3)
Gastrointestinal (%)	45 (1.2)	44 (1.2)
Trauma (%)	542 (15)	551 (15)
Neighborhood income quintile ^a		
First quintile (%)	902 (24)	890 (24)
Second quintile (%)	807 (22)	807 (22)
Third quintile (%)	690 (19)	712 (19)
Fourth quintile (%)	589 (16)	605 (16)
Fifth quintile (%)	535 (14)	500 (14)
Missing (%)	193 (5.2)	202 (5.4)
Urban (%)	3223 (87)	3218 (87)
Physician claims (OHIP) during preceding 3 yrs—median (IQR)	71 (30–130)	69 (31–127)
Hospitalizations during preceding 3 yrs—median (IQR)	0 (0–2)	0 (0–2)
Hospital days during preceding 3 yrs—median (IQR)	0 (0–15)	0 (0–15)
Charlson comorbidity index group		
Charlson Index = 0 (%)	1656 (45)	1641 (44)
Charlson Index = 1 (%)	989 (27)	999 (27)
Charlson Index ≥ 2 (%)	1071 (29)	1076 (29)
Hospital admission to ICU admission (days)—median (IQR)	0 (0–3)	0 (0–3)

^aNumbers in parentheses represent standard deviation (SD), percent (%), and interquartile range (IQR) where indicated.

OHIP, Ontario Health Insurance Plan.

The physician quartile containing median times to tracheostomy between 9 and ≤13 days had the most patients (n = 5073) and the quartile containing median times >17 days had the least patients (n = 888). There was no clear trend for this instrumental variable on patient mortality at 90 days (range, 35% for second quartile to 39% for first quartile). The results obtained from our multivariable proportional hazards model incorporating the instrumental variable are presented in the main article.

Propensity Score Model. We developed a propensity score to account for patient differences that might influence decisions regarding tracheostomy timing (29–31). This multivariable logistic regression model was constructed to predict likelihood, or propensity score, for receiving early (≤10 days) vs. late (>10 days) tracheostomy using all baseline characteristics listed in Table A1. A 1:1 matching technique assigned each patient in the early group to a propensity-matched control in the late group (32). This procedure sorts all patients according to propensity scores, and then matches each case (early group) to the

control (late group) having the closest propensity score (within 0.2 SD). If multiple controls match to a case, one control is selected at random. Once a case has been matched, that match is not reconsidered. Suitable matches could not be found for 42 (1.1%) of patients in the early cohort. Our final propensity-matched cohort was well-balanced for all available patient characteristics (Table A2). We then repeated our proportional hazards regression models using this propensity score matched cohort, analyzed across five strata of propensity scores.

Characteristics of the propensity-matched cohort are shown in Table A2. Patients in the propensity-matched cohort receiving early tracheostomy had more ventilator-free days than the late group at 28 days (9.7 vs. 3.3; $p < 0.001$) and at 180 days (94.0 vs. 85.9; $p < 0.001$). We applied our proportional hazards analyses treating tracheostomy as a time-dependent variable to this propensity-matched cohort. Using this approach, the unadjusted hazard ratio for each additional day of delay was 1.012 (95% CI 1.007–1.017, $p < 0.0001$) for total mortality during the study period and 1.021

(95% CI 1.014–1.029, $p < 0.0001$) for 90-day mortality. Similar results were obtained for the multivariable proportional hazards model incorporating the other covariates [hazard ratio for mortality during study period 1.010 (95% CI 1.005–1.016, $p < 0.0001$)] and for 90-day mortality 1.019 (95% CI 1.012–1.027, $p < 0.0001$).

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